STUDIES IN ORGANIC SYNTHESES:
ODORINE, ODORINOL AND CARBAZATE OXIDATION.

A Thesis

Submitted to the Faculty of Graduate Studies in

Partial Fulfillment of the Requirement of the Degree

of Doctor of Philosophy

by

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ABSTRACT

A synthesis of the natural products odorine ((+)-(E,2S,2′R)-2-methyl-N-[1′-(1"-oxo-3"-phenylprop-2"-enyl)pyrrolidin-2′-yl]butamide) and odorinol ((+)-(E)-2-hydroxy-2-methyl-N-[1′-(1"-oxo-3"-phenylprop-2"-enyl)pyrrolidin-2′-yl]butamide) is described in Part 1. In Part 2 several carbazates are synthesized and their oxidation studied as a possible means of reducing (deoxygenating) alcohols.

Odorine and odorinol were synthesized by constructing the amide bond between unstable 1-cinnamoyl-2-prolidinyl-amine and an activated form of 2-methylbutanoic acid or 2-hydroxy-2-methylbutanoic acid. Dicyclohexylcarbodiimide was a suitable reagent for activation but only afforded the two amides in low yields. However, odorine was obtained in good yield if 2-methylbutanoic acid chloride was used. The analogous activation of the hydroxy acid as 5-methyl-5-ethyl-1,3,2-dioxathiolan-4-one-2-oxide failed. Numerous other reagents were found to give little or none of the wanted product.

The amine was prepared by the acid cleavage of several carbamates prepared in turn from N-cinnamoylproline by modified Curtius or Hofmann reactions. These latter reactions were found to proceed in low yields due to the decomposition of the intermediate isocyanates. Racemization occurred readily in the carbamates and in odorine preventing the preparation of optically pure

odorine. The compounds are characterized by proton magnetic resonance (300 MHz), carbon-13 magnetic resonance, infrared and mass spectrometry techniques, and by their optical rotations.

In part 2, several carbazates are prepared using 1H-benzotriazole-1-carbonyl chloride, a general reagent except for bulky alcohols and alcohols which can act as good leaving groups.

The oxidation of methyl carbazate is investigated with numerous oxidants, and the gaseous and non-gaseous products are analyzed by gas chromatography. Barium manganate is used extensively because of the clean products it affords. Phenyl, benzyl and 2-phenylethyl carbazates are also briefly investigated. There is no evidence of the cyclic rearrangement to form the alkane, nitrogen and carbon dioxide suggested in the literature. Instead, the results point to the formation of the alkoxy- and aryloxycarbonyl radicals which undergo the expected reactions.

There is evidence for the thermodynamically unfavored decarbonylation reaction of the alkoxycarbonyl radicals presumably due to the coordination to a metal. The formate obtained is suggested to be from the rearrangement of an intermediate diazene.

ACKNOWLEDGEMENTS

This thesis is dedicated to my parents who through their continued support made it possible.

I would like to thank Dr. Norman R. Hunter for his unending advice, guidance, and encouragement throughout the course of this work.

I also express by appreciation to the other members of my advisory committee: Drs. D. M. McKinnon, P. L. Loewen, and especially Dr. J. L. Charlton.

Thanks to Kirk Marat for obtaining the proton (90 and 300 MHz) and carbon-13 spectra, and to Wayne Buchannon for the numerous mass spectra he obtained.

I acknowledge Dr. M. Zafar Khan who carried out parallel experiments on the synthesis of odorine and odorinol.

Finally, I thank the Natural Sciences and Engineering Research Council Canada for a postgraduate scholarship, and the Faculty of Graduate Studies, University of Manitoba for a graduate fellowship.

ABBREVIATIONS AND CONVENTIONS

- The numbers representing chemical structures are underlined.
- The numbers representing equations are given in square brackets.
- References are given in parentheses.
- Ac = acyl
- Ar = aryl
- Et = ethyl
- Me = methyl
- Ph = phenyl
- In the nmr spectra: b = broad
  d = doublet
  m = multiplet
  s = singlet
  t = triplet
- In the ir spectra: b = broad
  m = medium intensity
  s = strong intensity
  w = weak intensity

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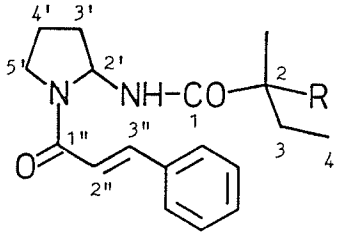
PART 1.

ODORINE, ODORINOL.

INTRODUCTION

Massy-Westropp and coworkers have isolated two new nitrogeneous compounds along with several new tetracyclic triterpenes from the extracts of the leaves from Aglaia odorata Lour. (Meliaceae), a small tree found predominantly in Thialand, Malaysia, China and the Philippines (1). The aqueous extract from the roots and leaves of this plant was used by the Thai people as a heart stimulant and febrifuge (a medicine efficacious in reducing or removing fever). These workers have named the two compounds odorine and odorinol, and have identified them (1,2) by chemical and spectroscopic means to be: (+)-(E,2S,2′R)-2-methyl-N-[1′-(1"-oxo-3"-phenylprop-2"-enyl)pyrrolidin-2′-yl]butamide (1a) and (+)-(E)-2-hydroxy-2-methyl-N-[1′-(1"-oxo-3"-phenylprop-2"-enyl)pyrrolidin-2′-yl]butamide (2). The absolute configuration of odorinol has not been determined.



1 R=H a) 2S, 2′R (+)-odorine

b) 2R, 2′S (-)-odorine

2 R=OH odorinol

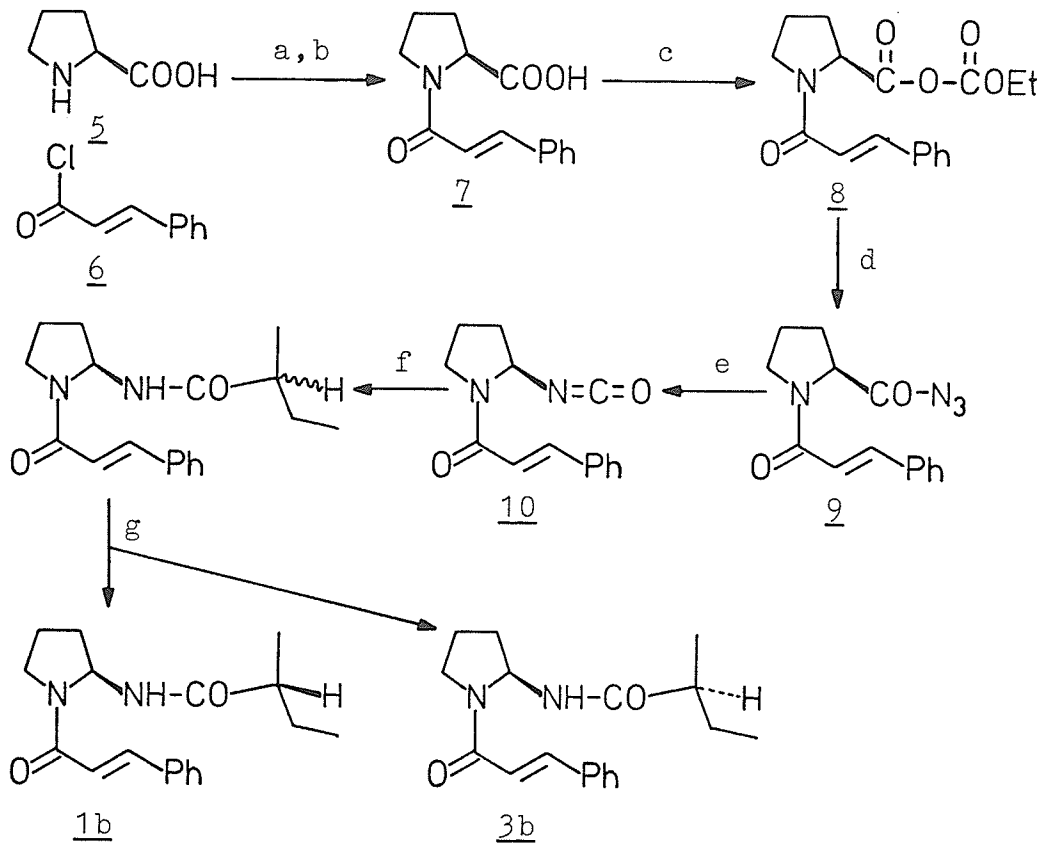
Connolly and coworkers have also isolated these two compounds from the leaves of Aglaia roxburghiana

(Meliaceae) (3); these workers have given 1a the trivial name roxburghilin. For convenience, 1 and 2 will be referred to as odorine and odorinol and the diastereomers as epiodorine (3) and epiodorinol (4).

The structures of odorine and odorinol were assigned from the spectroscopic data and the stereochemistry of odorine was determined by chemical means (2). The configuration at C2 in natural (+)-odorine (1a) was determined by acid hydrolysis and by measuring the optical rotation of the 2-methylbutanoic acid liberated. The optical rotation was dextrorotatory which corresponds to the S configuration in the acid (4) and thus also at C2 in (+)-odorine.

The chirality on the ring at C2′ was determined by the synthesis from L-proline (5) which has the S-configuration (Scheme 1). N-Cinnamoyl proline (7), prepared by a Schotten-Baumann reaction (60%), was reacted with ethyl chloroformate to give a mixed anhydride 8 that was converted into the acid azide 9 with aqueous sodium azide (87%). Warming caused 9 to rearrange into the isocyanate 10 which was not isolated but reacted further with 2-butylmagnesium bromide at low temperature (58%). The Curtius rearrangement, for example 9 to 10, is known to occur with retention of configuration (5).

Due to the racemic nature of the Grignard reagent a mixture of odorine and epiodorine was obtained. High performance liquid chromatography (hplc) was used to



(-)-odorine (-)-epiodorine

(3a = (+)-epiodorine)

SCHEME 1. a: 1N NaOH, 0°C; b: acidification; c: 1.1EtOOCCl, 1.1TEA, THF, 90 min. -20°C; d: 1.1NaN_3, H_2O, 30 min. -20°C; e:THF, 30 min. reflux; f: 1.2BrMgCH(Me)Et, THF, 2 h -78°C then 14 h at room temperature; g: hplc.

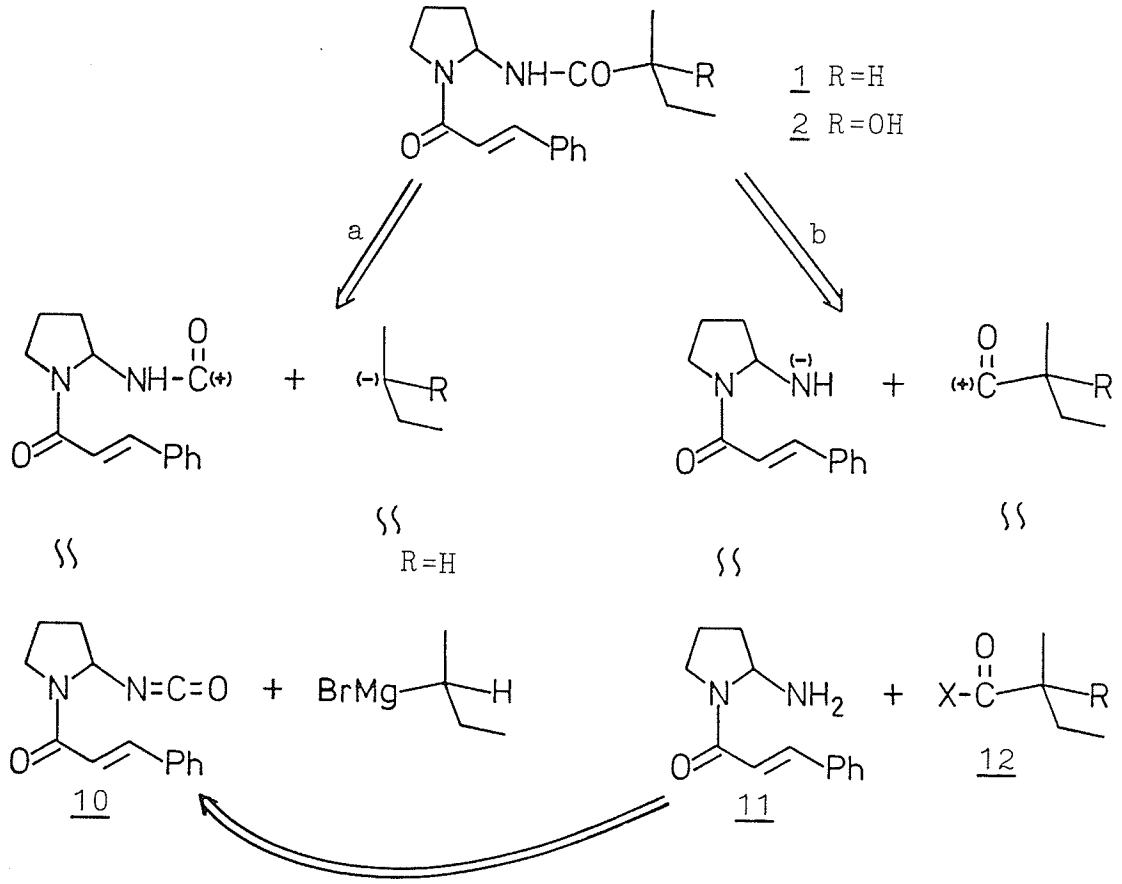
separate these diastereomers which were both found to be levorotatory. A comparison of the melting points and the spectroscopic properties with that of natural (+)-odorine allowed (-)-odorine (1b) and (-)-epiodorine (3b) to be assigned. Hydrolysis of this (-)-odorine afforded (-)-R-2-methylbutanoic acid while (-)-epiodorine yielded the acid

of the opposite (S) configuration. Thus the synthetic (−)-odorine was (2R,2′S) and so the natural (+)-odorine must be (2S,2′R). The 2",3"-dihydrocompound was also prepared by the analogous route and the hydrolysis yielded the same results for the configuration at the two chiral centers.

The absolute configuration of odorinol (2) could presumably also be determined in the same manner. However, the presence of the tertiary hydroxy group obviously makes the synthesis more complicated.

It was of interest to see if a synthesis could be developed that would allow optically pure odorine and odorinol to be prepared free from the epimers. If the general structure of these compounds is examined, the obvious bond to disconnect would be the amide bond (Scheme 2, path b) resulting in an amine 11 and an activated acid derivative 12. The amine could be prepared by the hydrolysis of the isocyanate 10. If these two components could be obtained optically pure and could be coupled without racemization then our goal could be achieved.

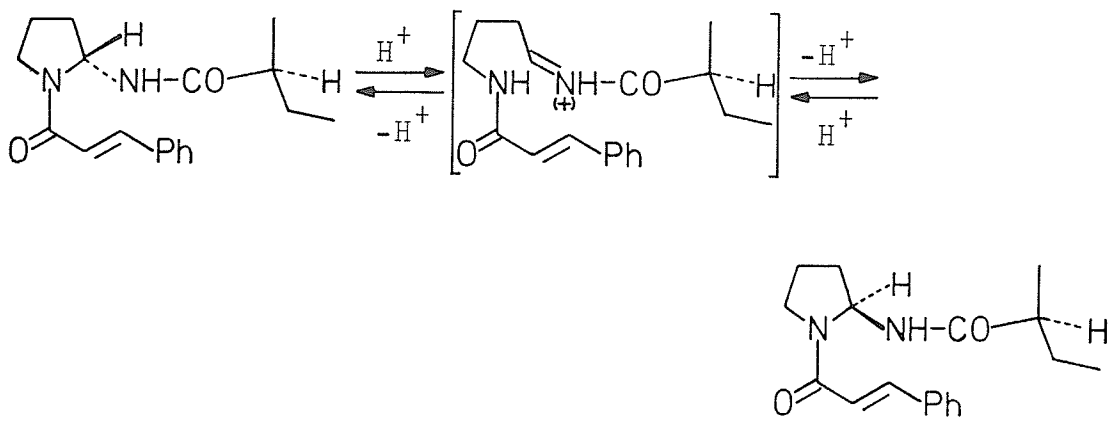
Many methods are known for the preparation of amide bonds under a variety of conditions (6). Some of these methods also allow for the formation of such bonds in the presence of an unprotected hydroxy group. The problem here is the stability of the free amine 11. Related N-CH-N compounds are known to be somewhat labile. In fact, odorine itself isomerized on standing in chloroform or in the presence of acid but was stable when free from acid



SCHEME 2. The Disconnection of Odorine and Odorinol.

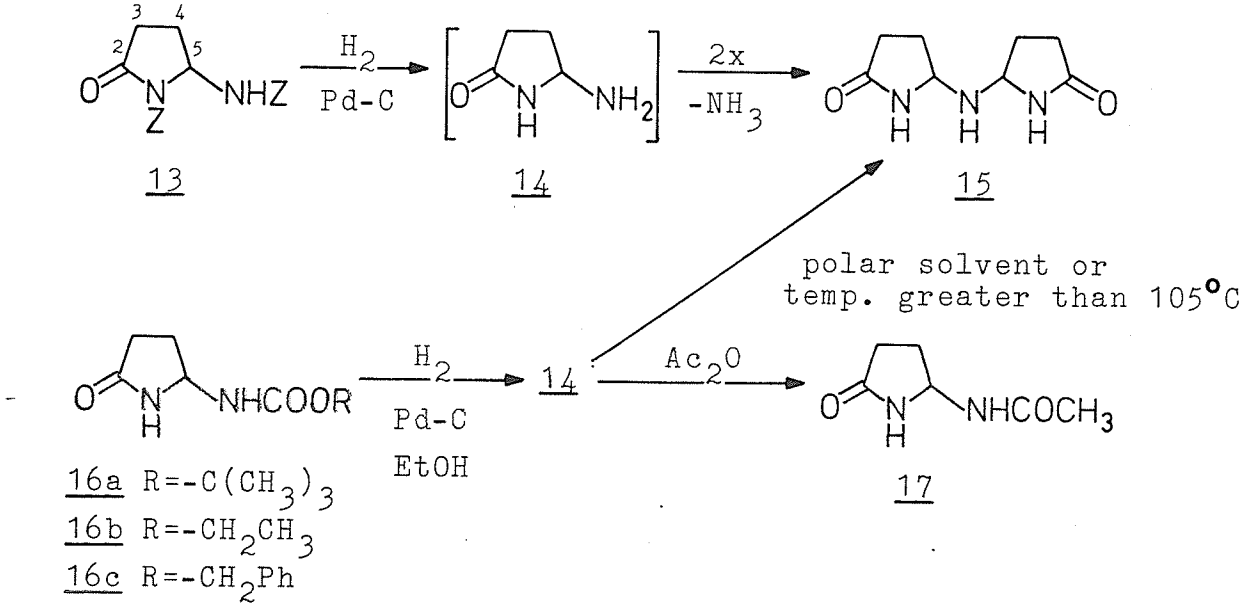
(2,3). This isomerization can be explained by the formation of an intermediate ring opened ion as shown in Scheme 3. Literature precedents for other N-CH-N compounds are also known.

A search of the literature has not revealed any work on 2-aminopyrrolidines but the related 5-amino-2-pyrrolidinone system has been prepared by Japanese workers (7). These workers found that the catalytic hydrogenation of racemic 13 with Pd-C did not afford the expected amine 14 but the secondary amine 15 instead. However, the amine



SCHEME 3. The Acid Catalyzed Isomerization of Odorine.

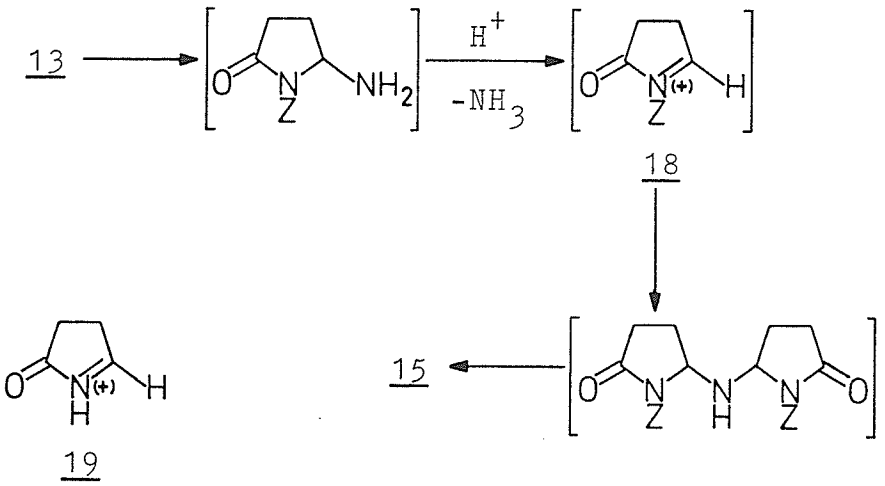
14 was obtained in quantitative yield from three different carbamates (16a,b,c) when the 1-position was unsubstituted. This amine was stable enough to be recrystallized from benzene and acetylation afforded the amide 17



SCHEME 4.

quantitatively. Decomposition to 15 occurred, however, in polar solvent or at elevated temperature (>105°C).

The inability to isolate 14 from 13 can be rationalized by Scheme 5. Cleavage of the benzyloxy-carbonyl group presumably occurred first at the 5 position giving, after loss of ammonia, the ion 18. This iminium ion was probably more stable than the unsubstituted ion 19 which would be formed by ammonia loss from 14.

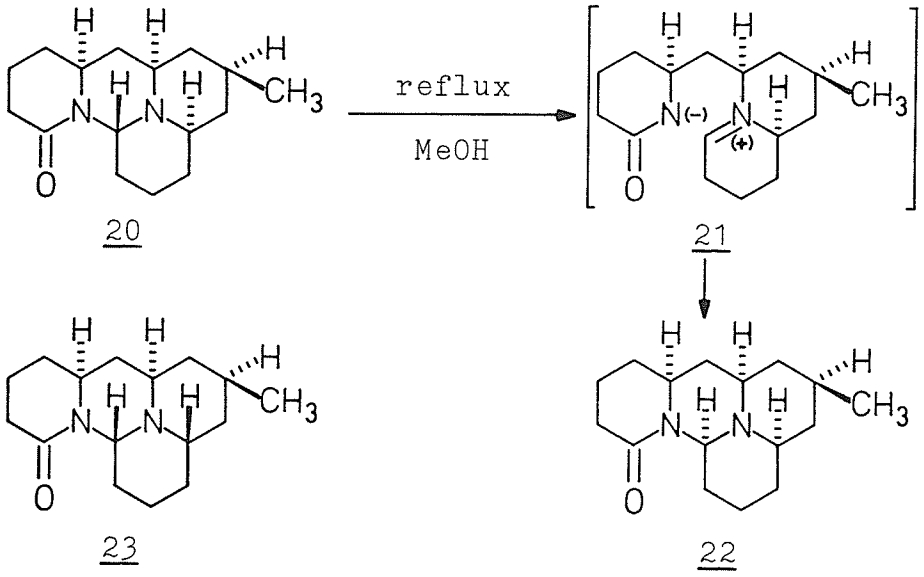


SCHEME 5.

In contrast to this work, Willson and Goodman (8) have prepared the optically active (S)-5-amino-2-pyrrolidinone (14) by the hydrogenation of 13 in ethyl acetate using 10% Pd/C. This amine 14 and the carbamate 13 were characterized by infrared spectroscopy, and high resolution nmr and mass spectroscopy but the data and experimental details including the specific rotation were not given. One must conclude that the amine 14 is not very stable and

its stability depends on the exact experimental conditions used in its preparation. One may also expect the 1-cinnamoyl-2-pyrrolidinylamine(11) to behave similarly.

The lability of another N-CH-N compound has been reported by Ayer and coworkers (9). Allocernuine (20), when refluxed in methanol, was isomerized to epiallocernuine (22) presumably via the zwitterionic intermediate 21.



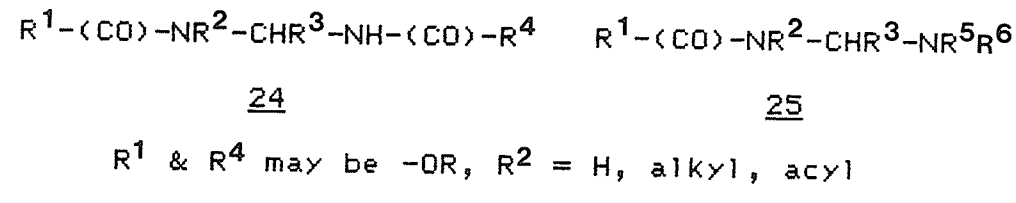
20 21 23 22

SCHEME 6. The Isomerization of Allocernuine.

Relief of steric strain was postulated to be the driving force for this isomerization since the isomer cernuine (23) was found not to isomerize in this way. Also, unlike cernuine, allocernuine underwent reductive cleavage under mild conditions.

The lability of the compounds 24 and 25, among others,

has allowed them to be used as electrophilic reagents in the α-amidoalkylation of various nucleophiles at carbon (10).

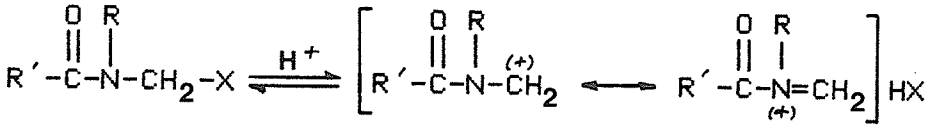


24 25

R^1 & R^4 may be -OR, R^2 = H, alkyl, acyl

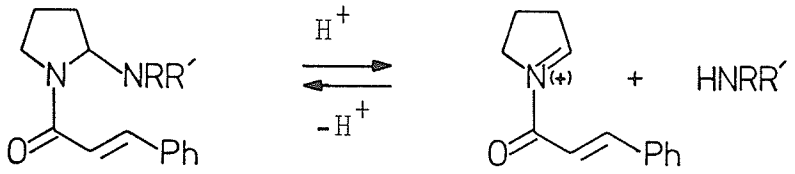
For these compounds this reaction usually takes place under acidic conditions which can vary in severity from concentrated sulfuric acid and hot polyphosphoric acid to refluxing glacial acetic acid or dilute phosphoryl chloride at room temperature.

The mechanism is believed to involve an intermediate with carbonium-ammonium ion character (Scheme 7). The extent of the ionization will depend on the reaction conditions. In very strong acids of high dielectric constant, appreciable dissociation probably occurs but this will be unlikely in acid-catalyzed reactions in media of low dielectric constant. Here, the reaction with weak nucleophiles probably involves either tight ion pairs or incipient carbonium ions formed by an S_N1 process.

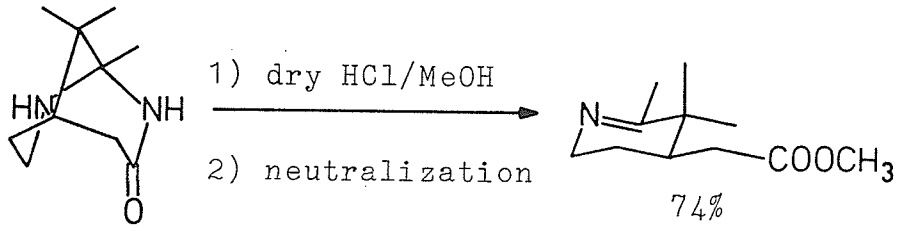


SCHEME 7.

While these extreme conditions will obviously not be used in the synthesis of odorine, under acidic conditions there may be a similar tendency for some degree of dissociation which could result in racemization and possibly decomposition.

[1] 

A related reaction has been discovered in this laboratory (11). The bicyclic compound 26, the product of the Schmidt reaction on camphor, was stable in concentrated sulfuric acid but underwent ring-opening on heating with dry HCl in methanol. In this case, the amide moiety seems to be the better leaving group in contrast to what was found for 25 (Scheme 7).

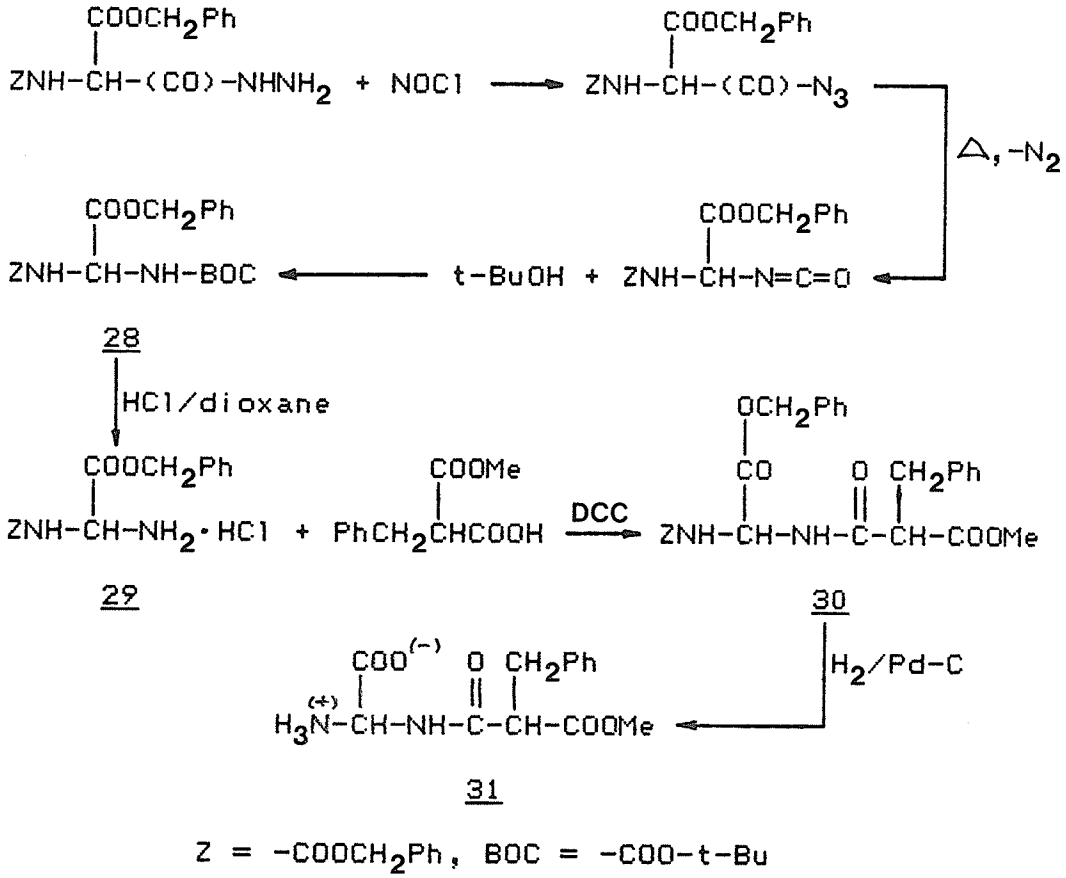
[2] 

26 27

Although the amine 11 can be expected to be unstable, other reports suggest that under the proper conditions it may be stable enough to serve as an intermediate if

immediately reacted further.

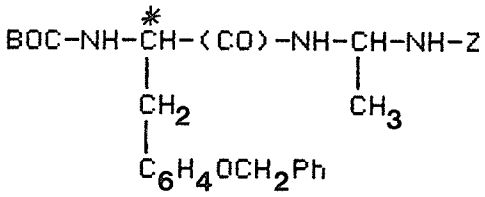
Goodman and coworkers (12) in their synthetic work on understanding the molecular basis for sweet taste have synthesized racemic 31 by the route shown (Scheme 8). The t-butyloxycarbonyl group was selectively removed from 28 with HCl/dioxane and the resulting salt 29 was immediately coupled with 2-benzylmalonic acid monomethyl ester using dicyclohexylcarbodiimide (DCC, a brief discussion of this coupling reagent follows).



Z = $-COOCH_2Ph$, BOC = $-COO-t-Bu$

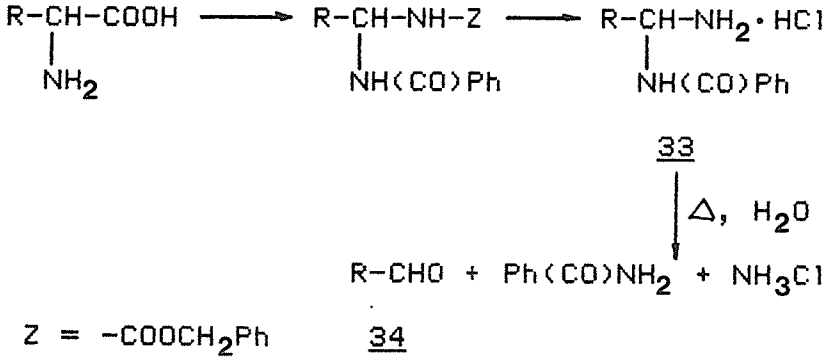
SCHEME 8.

Similarly the optically active N-(t-butyloxycarbonyl-O-benzyl-L-tyrosyl)-N′-benzyloxycarbonyl-α,α-diaminoethane (32) was prepared in 60% yield from the corresponding hydrazide. This compound was crystalline, mp 170°C, $[\alpha]_D^{21}$ -17.86°(C = 2.01 g/100 mL, DMF).



32

This synthesis is related to work by Bergmann and Zervas (13) on the stepwise degradation of polypeptides. They used a similar method to prepare the amine 33 which on boiling in water afforded the corresponding aldehyde plus ammonium chloride and benzamide.

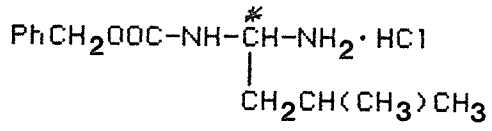


Z = $-COOCH_2Ph$ 34

SCHEME 9.

In the case of optically active amino acids, all the compounds up to and including the amine 33 were found to

retain their optical activity. For example, they reported that 35, as a 5% solution in methanol, had a specific rotation of $[\alpha]_D^{22}$-47°.

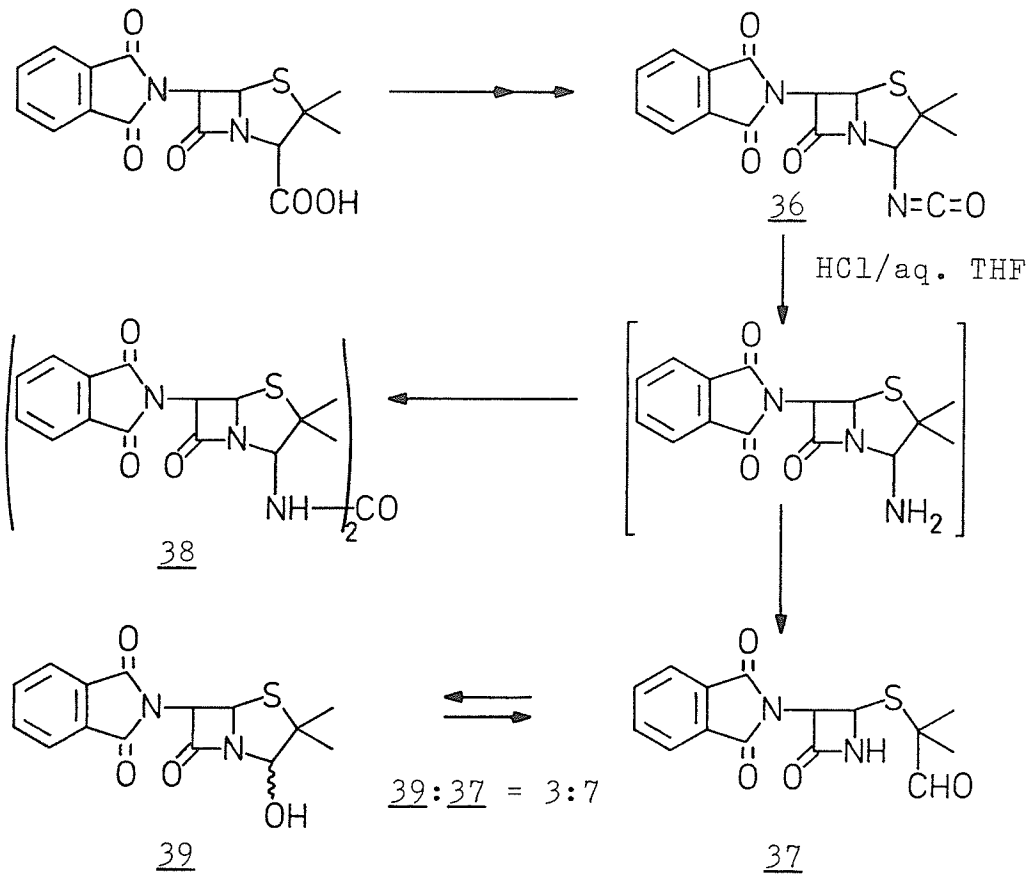


35

As mentioned previously, the chiral amine 11 is most conveniently prepared from the isocyanate 10 derived from N-cinnamoylproline (7) through a Curtius type reaction. Isocyanates can be directly hydrolyzed by acid to the amine hydrochloride. However, the yields are usually lower than if the hydrolysis is carried out indirectly via the carbamate formed by the reaction of the isocyanate with an alcohol.

The exact conditions required to cleave these carbamates depends on the nature of the alcohol used. Moreover, the conditions must be anhydrous since, as seen in the work of Bergmann and Zervas, the amine 11 is likely to undergo further hydrolysis.

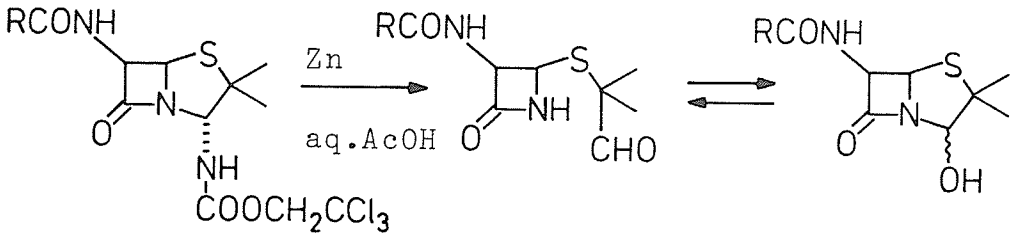
Sheehan (16) has used such aqueous conditions to cleave the 3,4-bond in a penicillin derivative without hydrolyzing the β-lactam moiety. 2,2-Dimethyl-6-phthalimido-3-penamyl isocyanate (36) was treated with one equivalent of HCl in aqueous THF under dilute conditions affording the aldehyde 37 in 75-80% yield and the urea 38



SCHEME 10.

in about 10-15% yield. When Heusler (15) carried out this hydrolysis on two slightly different isocyanates, cleavage of the β-lactam ring also occurred. This further cleavage was avoided if the hydrolysis was carried out indirectly through the carbamates 40a,b using zinc and aqueous acetic acid. Indirect hydrolysis also prevented the formation of urea that is always formed in the direct hydrolysis.

The optimum carbamate to use in the synthesis of odorine and odorinol was difficult to propose before investigation. While 5-amino-2-pyrrolidinone (14) was prepared by reductive cleavage of the benzyloxycarbonyl

[3] 

40a R=-CH_2OPh

40b R=-CH_2Ph

group, these conditions have been found to reduce the cinnamoyl group present in odorine and odorinol (1,2,3). It appeared best to introduce the N-cinnamoyl group immediately since it was a required substituent in the final product and it would at the same time act as a protecting group for the ring nitrogen. Most conditions for the cleavage of a carbamate group, other than hydrogenolysis, involve acidic conditions (17). As seen, the t-butyloxy (BOC) and benzyloxycarbonyl (Z) groups are popular protecting groups that are acid labile. It was thought that if a strong acid was used the amine 11 would be stable enough as the salt to be immediately reacted further, after neutralization, with an activated form of the acid.

The formation of amide bonds has been well studied and numerous reagents have been reported in the literature. This topic has been covered by many articles (6) but a very brief discussion will be given here.

Normally the formation of an amide bond involves the activation of the acid component in some manner.

[4] $R\text{-}NH_2 + X\text{-}(CO)\text{-}R' \longrightarrow R\text{-}NH\text{-}(CO)\text{-}R' + HX$

One of the simplest ways of activation is by an acid chloride (X = Cl). This method is no longer popular due to the high reactivity and thus the many side-reactions that can occur including the high susceptibility of activated amino acids to racemize. However, it has been recently reported that this high reactivity is required in the formation of amide bonds that are sterically hindered (18).

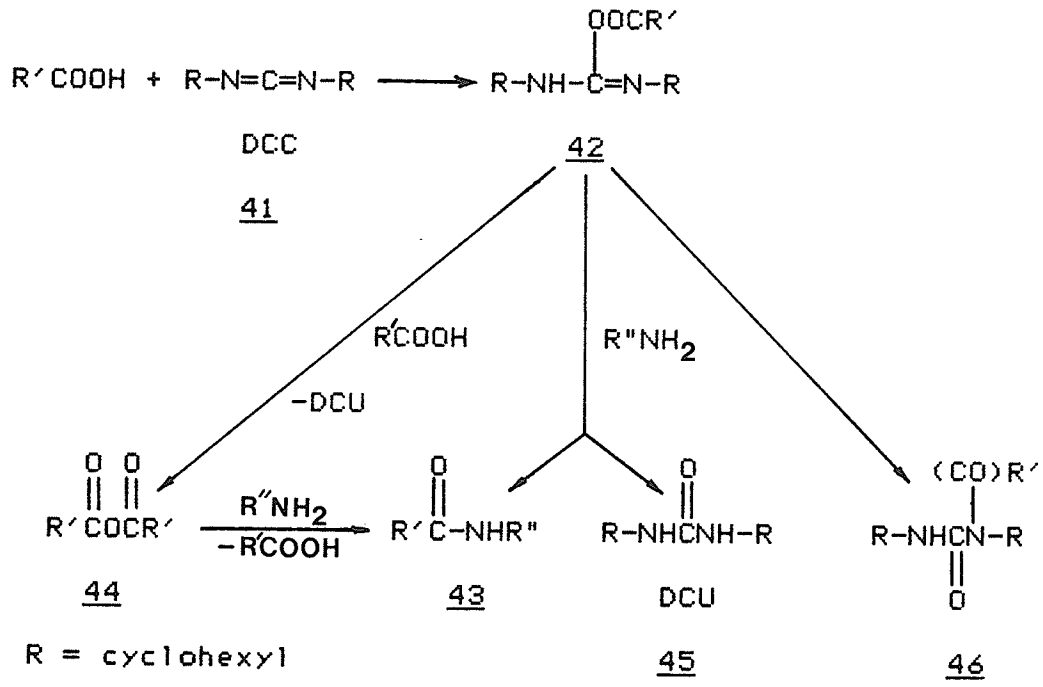
Traditionally the carbonylazide method ($X = N_3$) has been the safest way of fragment condensation due to the low degree of racemization with amino acids and the minimal side-chain protection required. However, carbonylazides are unstable and numerous side-products can be formed due, for example, to the Curtius rearrangement to isocyanates and subsequent reaction of the isocyanates.

One of the most common coupling reagents used today is dicyclohexylcarbodiimide (DCC, 41), a highly reactive compound which usually gives good yields within a short time. Normally, an equimolar amount of DCC is added to an equimolar amount of the acid and amine in an organic solvent such as methylene chloride, ethyl acetate or dimethyl formamide (DMF) at $0^{\circ}C$.

The mechanism involves the formation of an O-acylisourea 42 as the reactive intermediate (Scheme 11). This intermediate can either react directly with the amine to form the amide 43 or with the acid to form a symmetrical

anhydride 44 which then acylates the amine.

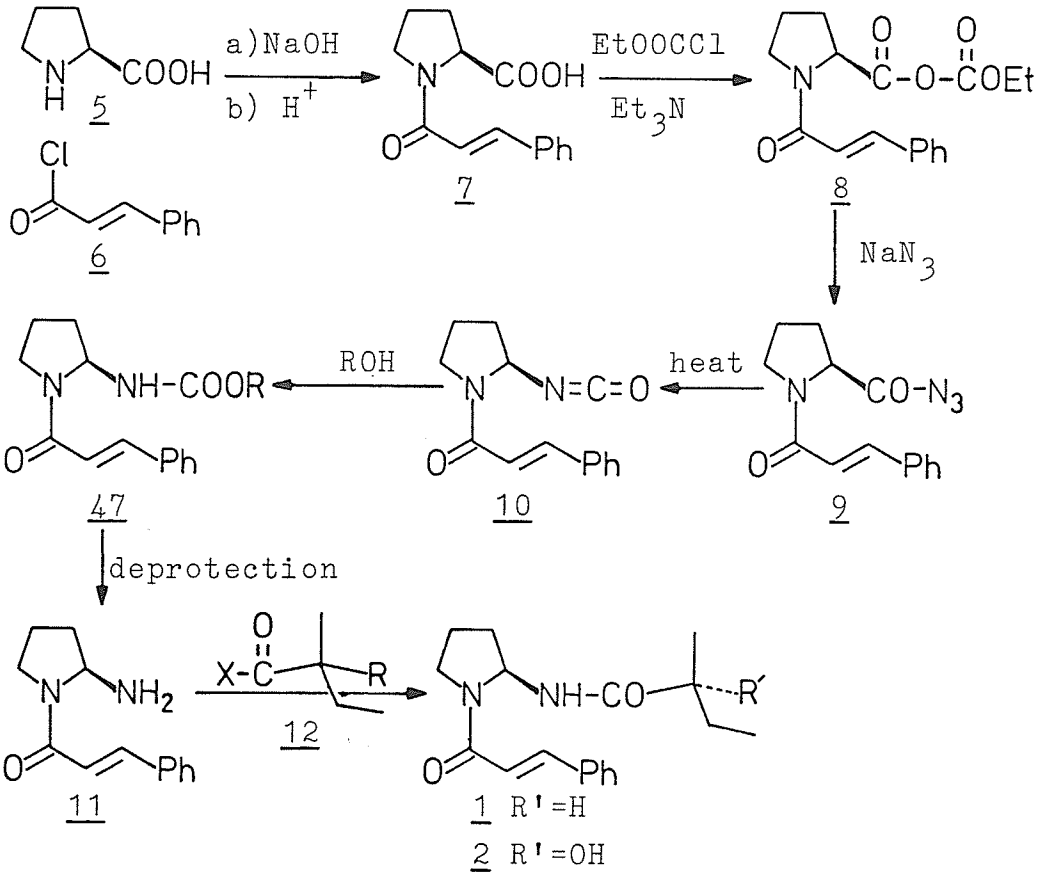
In both cases, the by-product is dicyclohexylurea (DCU, 45). Often the O-acylisourea is found to undergo O->N acyl migration forming an N-acylurea side-product 46 which is unreactive towards amines. This side-product and the DCU by-product are sometimes difficult to remove from the product amide due to their similar solubilities. DCC has also been successfully used with compounds having unprotected hydroxy groups and thus may be useful for the synthesis of odorinol.



SCHEME 11.

Thus, the overall objective of our research was to find the best method of preparing racemic odorine and odorinol via the amine 11 and an activated form of the

corresponding acid 12 (Scheme 12). The amine would be prepared by the deprotection of a suitable carbamate derivative. We planned on synthesizing a series of these protected amines including the t-butyl, benzyl and 4-methoxybenzyl (anisyl) carbamates by reacting the isocyanate 10 with the appropriate alcohol. In turn the isocyanate would be prepared from N-cinnamoylproline using the modified Curtius or an equivalent reaction.



SCHEME 12. Proposed Synthesis of Odorine and Odorinol.

The activated acids 12 to be investigated included the acid azide, chloride and the O-acylisourea formed by the reaction with DCC. When the optimum synthesis is devised it could then be used to prepare the optically pure compounds.

DISCUSSION

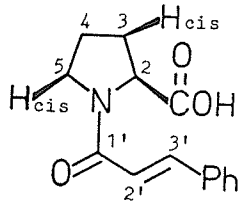
This investigation can be divided into three sections, the preparation of the various carbamates 47, the cleavage of these carbamates to give the intermediate amine 11 usually as a salt and the coupling step to yield odorine or odorinol.

Preparation of the Carbamates

The starting material, (E,S)-N-cinnamoylproline (7), was prepared by a Schotten-Baumann reaction (19) from L-proline (5) and t-cinnamoyl chloride (6). Later we found that this method was also used by Massy-Westropp and coworkers in their synthesis of odorine (2). In addition to the expected signals, the high resolution ^1H nmr of this material had small peaks that were probably due to the presence of a second rotamer about the amide bond (20). From the areas one can estimate that approximately 5% of the acid was present as this second rotamer. This and several other ^1H nmr spectra are reproduced in the experimental section.

Another feature of this spectrum was the deshielding effect observed in the pyrrolidine ring protons. These protons appear as two groups, the two protons at H5 (3.5-4.0 ppm) and the four protons at H3 and H4 (1.9-2.6 ppm). One proton from each of these groups is deshielded slightly presumably by the proximity to the carboxylic acid group. (Figure 1) (21,22). The two protons cis to this group at H3 and H5 on the ring are likely closer to and could lie in

the deshielding cone of the carbonyl. This feature was also observed in the high resolution ^{1}H nmr spectra of the compounds prepared from this compound. The ^{13}C spectral assignments are tabulated in the appendix.

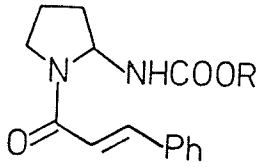


7

FIGURE 1.

The carbamates (also called urethanes) initially of interest were the 1,1-dimethylethyl 48 (t-butyl) and phenylmethyl 49 (benzyl) carbamates (Table 1). The t-butyloxycarbonyl (BOC) and benzyloxycarbonyl (Z) groups are very common protecting groups for amines and can be rapidly cleaved with acids (18). A related, even more acid labile compound also investigated was the 4-methoxyphenylmethyl 50 (anisyl) carbamate. The carbamates 49 and 50 were prepared from the acid 7 by the reaction of the corresponding alcohols with the isocyanate 10 (Scheme 13). Due to the possible dehydration of t-butyl alcohol, the t-butyl carbamate 48 was prepared by another route. The carbamates 51 and 52 were similarily prepared by the reaction of the isocyanate with 2-phenylthioethanol and 2-phenylsulfonylethanol.

TABLE 1. Preparation of the Carbamates.

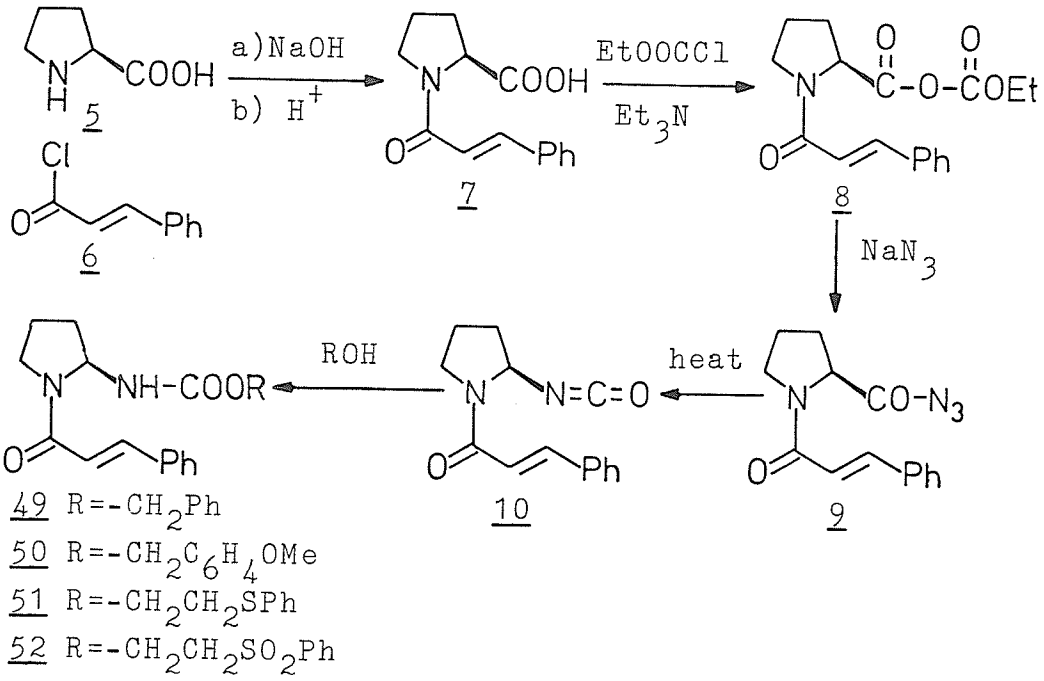


R	% Yield	Comments
Modified Curtius Reaction		
$-CH_2Ph$[b]	26 (34)[a]	
49		
$-CH_2C_6H_4OMe$[b]	23 (33)[a]	Ether 56 also isolated (4%)
50		
$-CH_2CH_2SPh$	25	
51		
$-CH_2CH_2SO_2Ph$	*	
52		
Using DPPA		
$-C(CH_3)_3$	-	Allophanate 71 major
48		product (36%)
$-CH_2C_6H_4OMe$	27	As a 1:1 mixture with
52		the allophanate 72 (24%)
Using LTA		
$-C(CH_3)_3$	39	
48		

* Decomposed on column chromatograpy.

[a]Corrected for recovered N-cinnamoylproline (7).

[b]With dimethyltin dichloride catalyst.

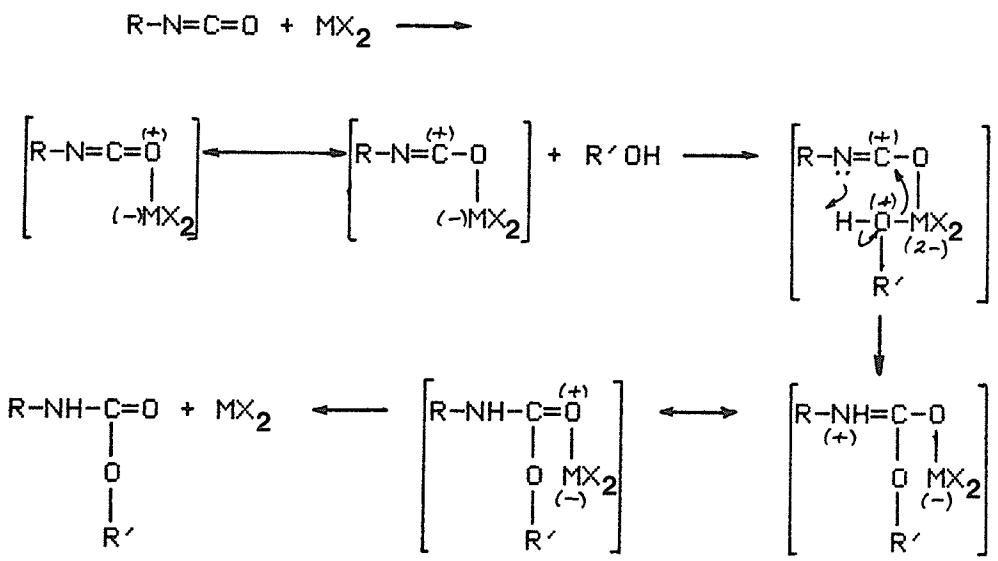


SCHEME 13. Preparation of the Carbamates.

Weinstock's procedure (23) was used to prepare the isocyanate 10 and later we found that Massy-Westropp also followed this procedure. This involved reacting (E,S)-cinnamoylproline (7) with ethyl chloroformate to give a mixed anhydride 8. Treatment with aqueous sodium azide afforded the corresponding acid azide 9 which had completely rearranged to the isocyanate 10 on refluxing 20 min in toluene or 45 min in benzene. Reaction of this isocyanate with dry alcohol to give the carbamate was complete after several hours of refluxing in benzene or toluene.

To increase the rate of carbamate formation a small amount of dimethyltin dichloride, approximately 0.01 equivalents, was used in later reactions. With this

catalyst, the reaction was complete after approximately 1 hour at room temperature or 15 minutes at reflux in benzene or toluene. Such reactions between alcohols and isocyanates are known to be catalyzed by tertiary amines and very effectively by tin compounds (24). Scheme 14 indicates a possible mechanism for the catalysis by such metal compounds. The coordination allows the hydroxyl to enter on the same side as the metal and also act as a proton donor. This can explain the large catalytic effect these metals can have. It is also possible that the metal may instead first coordinate to the alcohol and then to the isocyanate.



SCHEME 14.

The Catalysis of the Isocyanate-Alcohol Reaction.

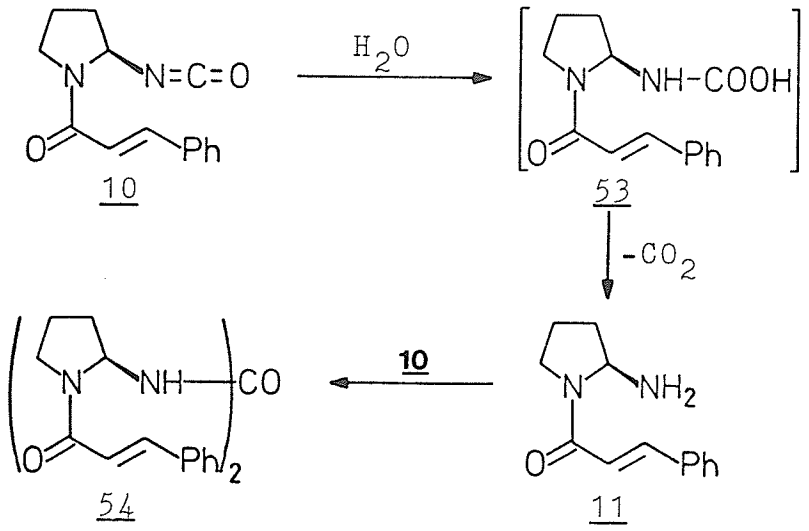
Such tin catalysts have also been reported to increase the relative rate of reaction of isocyanates with alcohols

vs. water. Normally, without such a catalyst the reaction of isocyanates with water is faster than with an alcohol. Thus the hydrolysis of the isocyanate by fortuitous traces of water and the formation of urea (see later) should be decreased with such a catalyst. One would then also expect an improved yield of carbamate. However, we found that while the catalyst did greatly increase the reaction rate the yield of carbamate was unchanged.

The products of these reactions were not very pure and usually flash chromatography (25) was required to isolate the pure carbamate although recrystallization could be used with the benzyl carbamate 49.

The 4-methoxybenzyl carbamate 50 obtained when the chromatography was carried out with ethyl ether was optically active, $[\alpha]_D^{26}$ -41^o while the material obtained when ethyl acetate was used as a mobile phase was largely racemized, $[\alpha]_D^{19}$ -2^o. The trace of acetic acid present in the ethyl acetate may be the cause of this racemization. This racemization indicated that the carbamates were stereochemically unstable which could make the synthesis of optically pure odorine and odorinol via the amine difficult.

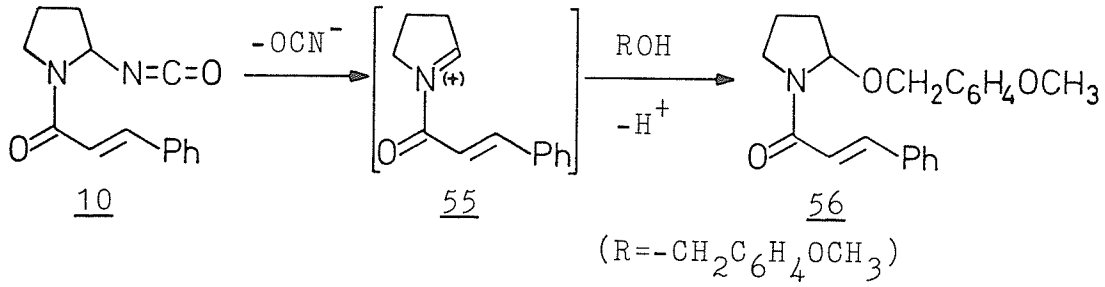
The isolated yields of the carbamates were always rather low (ca. 25-35%) no matter what modification was used. While the urea 54 from the hydrolysis of the isocyanate 10 was also formed to a varying extent, this could not account for all of the material.



SCHEME 15.

Hydrolysis and Urea Formation from the Isocyanate 10.

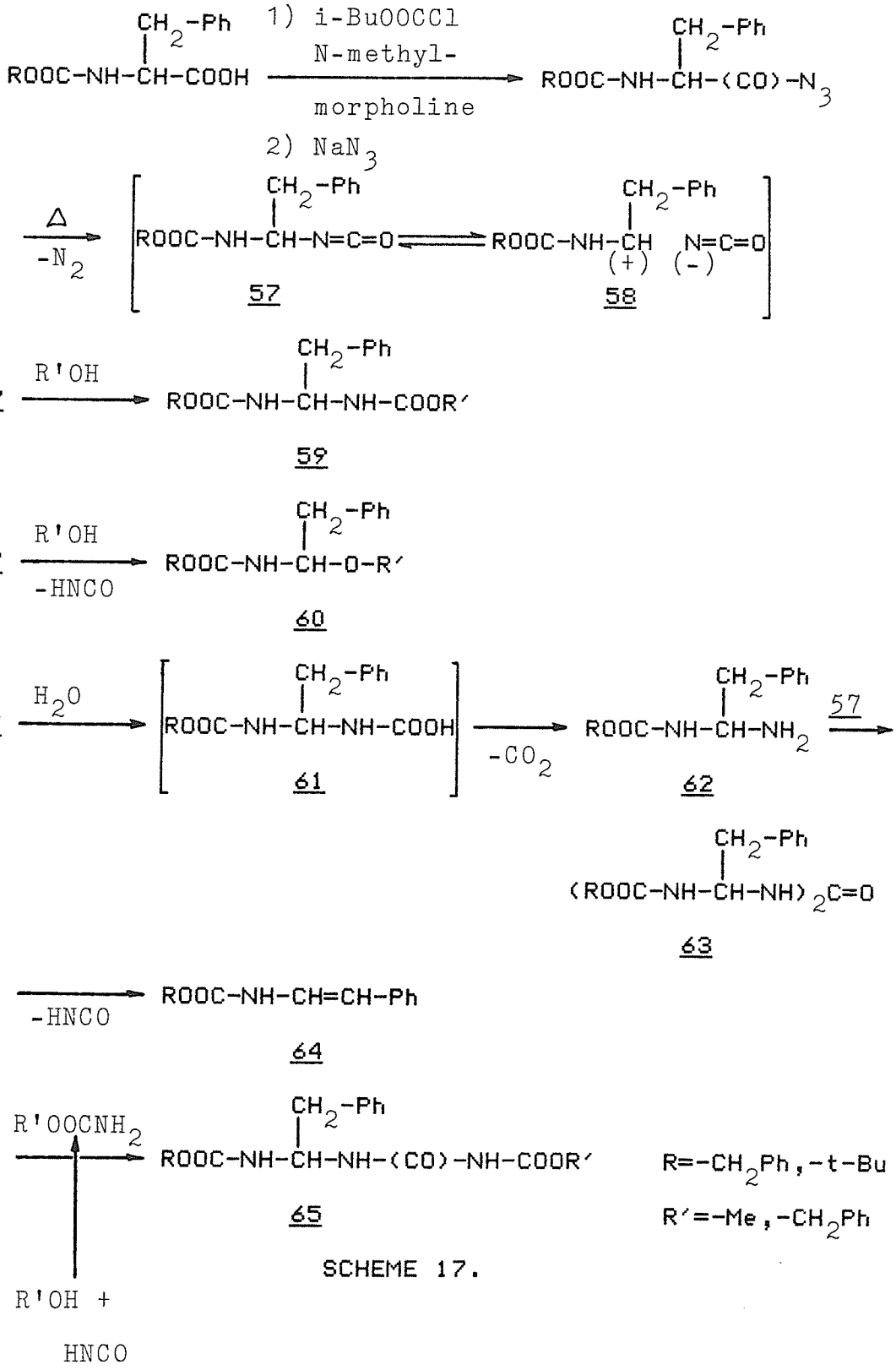
Another faster running compound was also found to be present in the product mixture but in most cases it decomposed during isolation. However, in the reaction with 4-methoxybenzyl alcohol this side-product was isolated as an oil which was contaminated with and/or decomposing to 4-methoxybenzyl alcohol and so was difficult to purify. The spectroscopic properties of this material were consistent with (E)-1-(1'-oxo-3'-phenylprop-2'-enyl)-2-(4-methoxyphenylmethoxy)-pyrrolidine (56), the ether formed by the loss of the isocyanate ion from 10 and further reaction with 4-methoxybenzyl alcohol (ca. 4% yield). This ether could be isolated when ethyl ether was used as the mobile phase in the chromatography but not with ethyl acetate. The trace of acetic acid in the ethyl acetate may be causing 56 to decompose when this solvent was used.



SCHEME 16. Ether Formation.

Such ether formation from the isocyanate-alcohol reaction has been reported by Goodman and coworkers (26). These workers wished to optimize the yield of another N-CH-N carbamate 59 and investigated the role that different amounts of alcohol played. With a large excess of alcohol, a complex mixture of products was formed. For example, the reaction of the isocyanate 57 with a 20 fold excess of methanol afforded not only the expected carbamate 59 but also four other products: 60, 63, 64 and 65 (Scheme 17). The ready loss of the isocyanate ion can explain the occurrence of these compounds.

It was suggested that the ether 60 was formed by the displacement of the isocyanate ion by the alcohol as postulated above. The well-known reaction of isocyanates with water would have resulted in the urea 63 while the elimination of isocyanic acid would form the alkene 64, a styrene derivative. Reaction of the liberated isocyanate ion with the alcohol followed by further reaction with 57 would yield the allophanate 65.


ROOC-NH-CH-COOH
CH2-Ph
1) i-BuOOCCl
N-methyl-
morpholine
2) NaN3
ROOC-NH-CH-(CO)-N3
Δ
-N2
ROOC-NH-CH-N=C=O
57
ROOC-NH-CH (+) N=C=O (-)
58
R'OH
ROOC-NH-CH-NH-COOR'
59
-HNCO
ROOC-NH-CH-O-R'
60
H2O
ROOC-NH-CH-NH-COOH
61
-CO2
ROOC-NH-CH-NH2
62
(ROOC-NH-CH-NH)2C=O
63
ROOC-NH-CH=CH-Ph
64
R'OOCNH2
ROOC-NH-CH-NH-(CO)-NH-COOR'
65
R'OH +
HNCO
R=-CH2Ph, -t-Bu
R'=-Me, -CH2Ph

SCHEME 17.

Dissociation and re-association of the isocyanate, 57 and 58, could also occur but this would result in racemic carbamate 59. Goodman found no racemic carbamate either in the presence of high or low ratio of alcohol to isocyanate 57. The carbamate 59 was found to be stable to decomposition after formation; it was recovered unchanged from refluxing methanol after 12 hours.

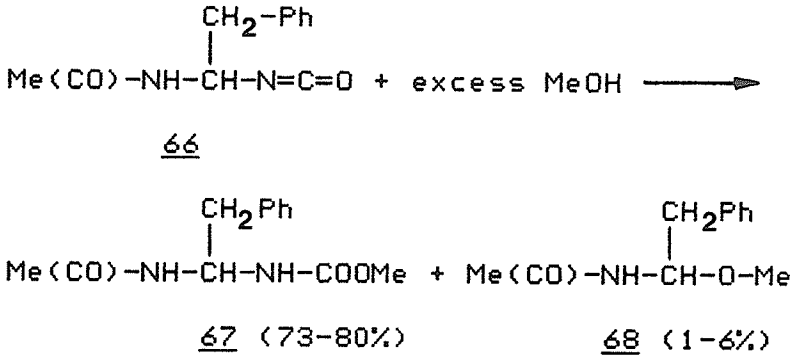
As indicated in the table, less alcohol increased the amount of carbamate at the expense of the other compounds. The authors could not explain the different ratio of products obtained with methanol and benzyl alcohol.

TABLE 2. Product Distribution in the Reaction of Isocyanate 57 with Various Amounts of Alcohol.

57	R'OH (equiv)	59	60	65	63	64
R=$PhCH_2$-	MeOH (20)	49%	9%	5%	1%	6%
	MeOH (2)	65	-	2	-	-
=t-Bu-	MeOH (20)	29	44	12	-	-
	MeOH (2)	45	-	4	-	-
	$PhCH_2OH$ (10)	18	18	20	-	-
	$PhCH_2OH$ (2)	31	-	18	-	-

When an acetyl group instead of a carbamate group was present in the isocyanate 66, 67 was found to be the main product (73-80%) and only a trace amount of 68 (1-6%) was formed even under acid and base catalysis and with a large excess of methanol. This is another example of the

lability of N-CH-N compounds and how this lability depends on the structure and the presence of other functional groups.

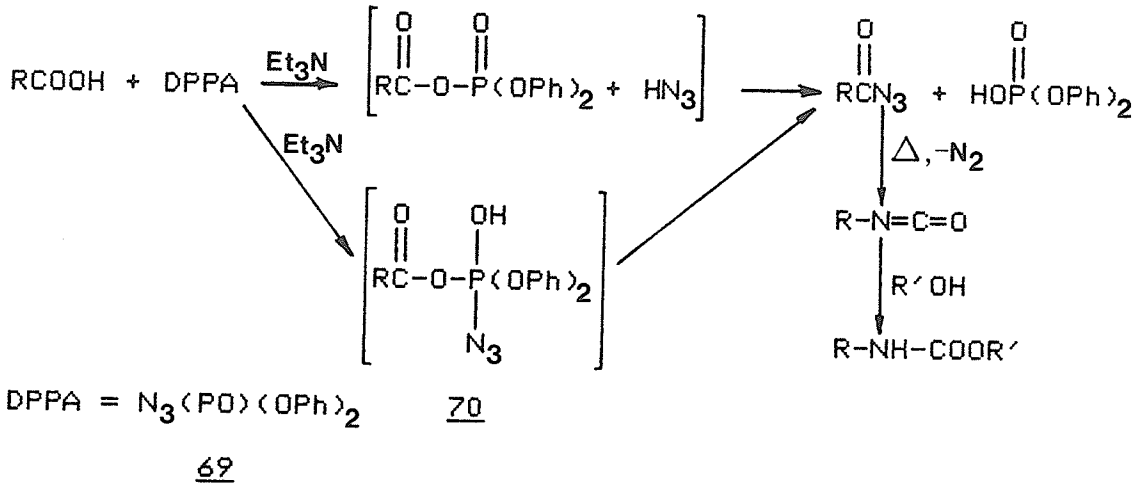
[5] 

66

67 (73-80%) 68 (1-6%)

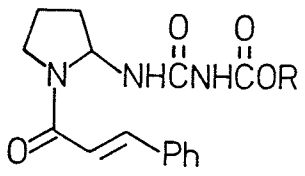
Diphenyl phosphorazidate (DPPA, 69) has been reported to be a new convenient reagent that can be used for a Curtius-like reaction (27). A carboxylic acid in the presence of an alcohol and triethylamine (TEA) can be converted to a carbamate in a single step with this reagent. The mechanism involves the formation of a mixed carboxylic-phosphoric anhydride 70 which then yields an acid azide (Scheme 18). Further reaction proceeds as described earlier for the Curtius reaction. This reagent was investigated to determine if it would increase the yield of carbamate.

We refluxed N-cinnamoylproline (7) with DPPA and TEA in t-butyl alcohol, and purified the product by flash chromatography yielding a mixture of the t-butyl carbamate 48 and an unknown compound. Recrystallization of this material afforded a crystalline compound with a ^1H nmr



SCHEME 18.

spectrum very similar to that of the carbamate 48. The ^{13}C and ir spectra indicated the presence of two carbonyl groups. The ms of this unknown was also very similar to that of the pure carbamate but it had a parent ion at 43 mass units higher than that of the carbamate. Therefore, the unknown was assigned the structure of the allophanate 71 (36% yield) from the incorporation of an additional isocyanate unit similar to the earlier observation of Goodman (26).



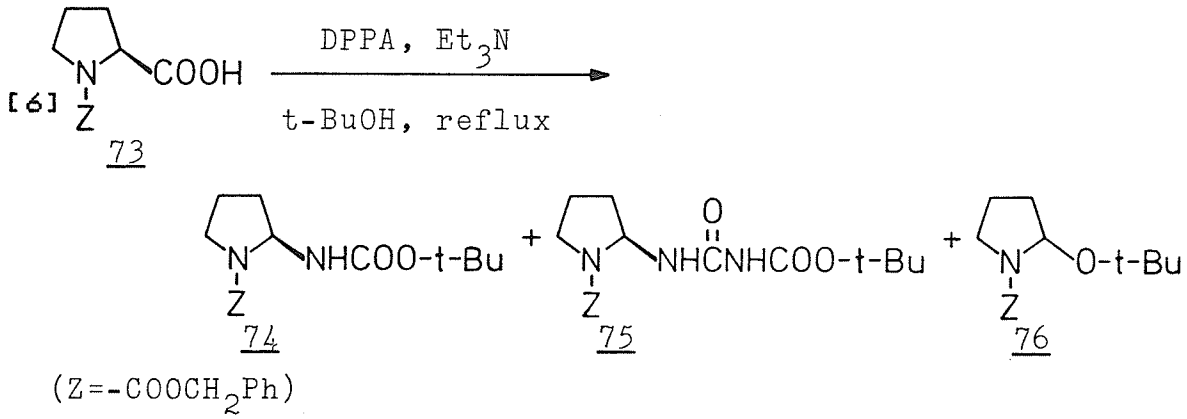
71 R=-t-Bu

72 R=-$CH_2C_6H_4OCH_3$

Similarly, the reaction of the acid 7 with p-methoxybenzyl alcohol and DPPA in dry benzene followed by column chromatography afforded a colorless oil which was found to be an approximately 1:1 mixture of the carbamate 50 and allophanate 72 (ca. 27 and 24% yield, respectively).

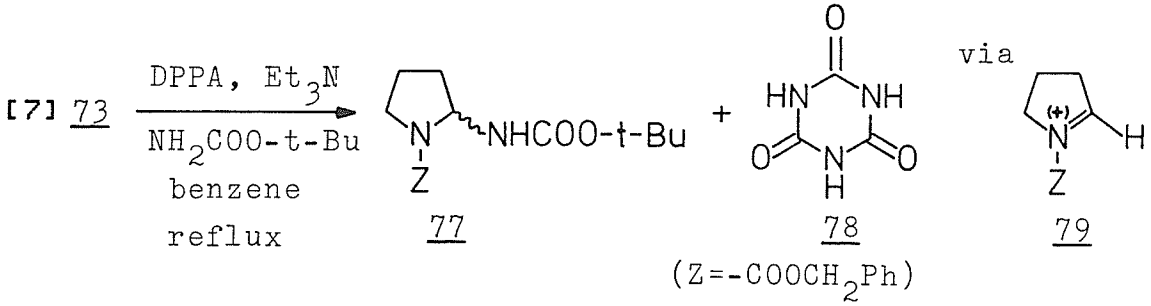
For some compounds better yields were reported when this reaction was carried out in two steps instead of one. Thus, the isocyanate 10 was formed first by refluxing the N-cinnamoylproline and DPPA in dry benzene and then p-methoxybenzyl alcohol was added. However, this modification did not improve the reaction and a mixture was again obtained.

Yamada and coworkers (28) have reported similar observations on the reaction of DPPA with (S)-N-benzyloxycarbonylproline (73). In fact, the t-butyl carbamate 74 was isolated in only 5% yield with the allophanate 75 being the major product (35%); both these compounds were optically active.



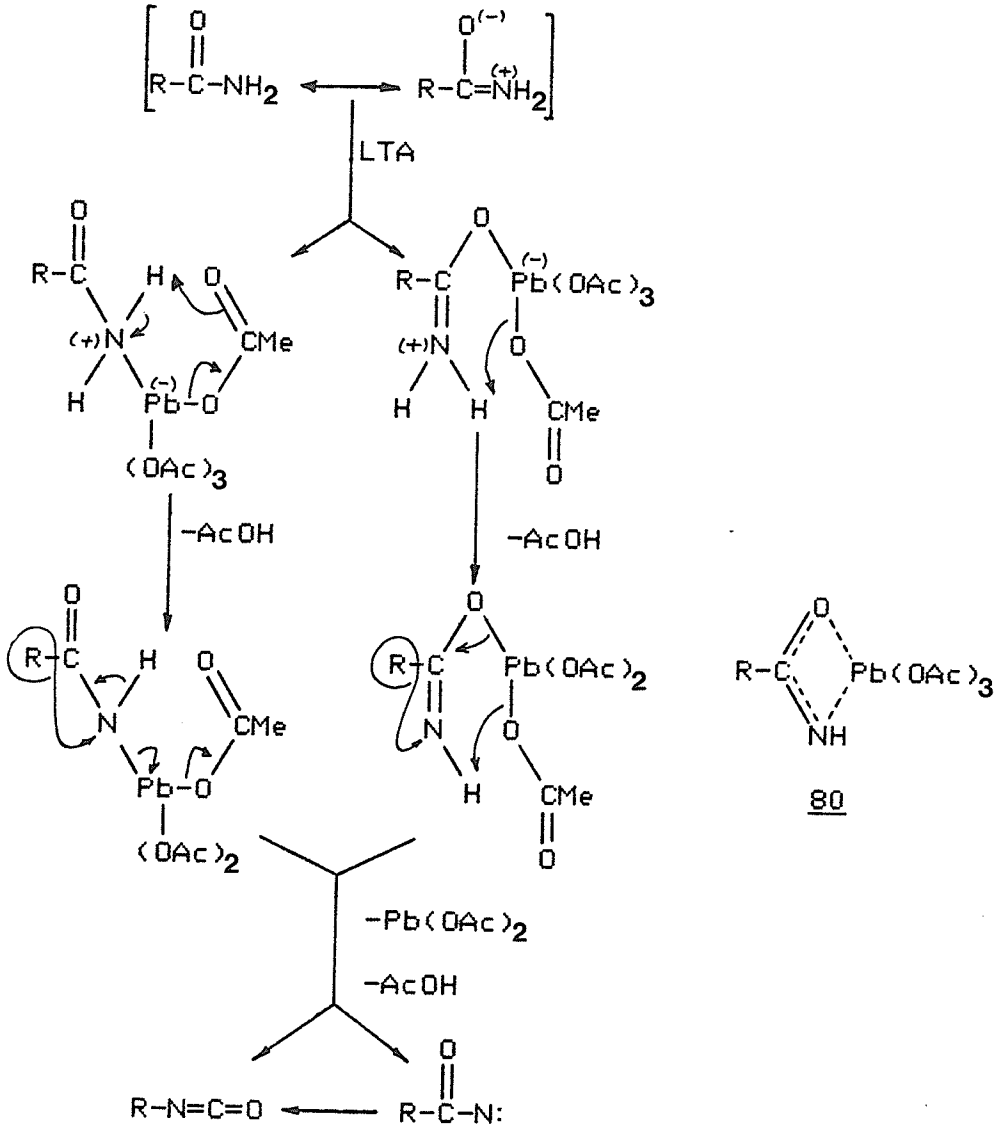
Even the Curtius reaction on this compound was found to give the allophanate 75 as the major product (33%) with the expected carbamate 74 produced in only 14% yield. Goodman and coworkers (26) have repeated this reaction and have also identified the formation of the ether 76 which was not stable even when stored at -4°C under nitrogen.

Yamada repeated this reaction in the presence of t-butyl carbamate instead of t-butyl alcohol and found that racemic carbamate 77 was the major product (66%) along with cyanuric acid 78 (12%). In this case the formation of the allophanate 75 was suppressed by the addition of the t-butyl carbamate to the intermediate immonium ion 79 to give the racemic carbamate 77. If direct displacement of the isocyanate ion occurred inversion of configuration and not the observed racemization would have taken place. The more nucleophilic t-butyl carbamate must favor the loss of the isocyanate ion rather than formation of the allophanate 74.



Carboxylic acids can be rearranged to isocyanates via the acid amide using the Hofmann reaction (29). Normally this reaction is carried out with bromine under strongly

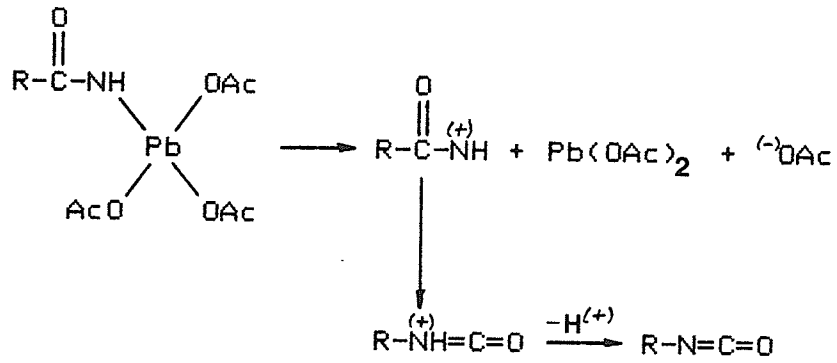
basic conditions, conditions which are too vigorous for sensitive molecules. Baumgarten (30) and Beckwith (31) have reported that amides can also be rearranged by treatment with lead tetraacetate (LTA) in a Hofmann-like reaction. The suggested mechanism is indicated in Scheme 19.



SCHEME 19.

Formation of Carbamates by the LTA Oxidation of Amides.

The suggested intermediate complex $RCONHPb(OAc)_3$ likely exists in a symmetrical form 80 where the lead atom is bonded to both the oxygen and nitrogen atoms. A discrete nitrene intermediate may be involved although there is no experimental evidence for its existence. It has also been suggested that the reaction may proceed via a nitrenium ion (Scheme 20). Baumgarten and coworkers have found that this oxidative rearrangement proceeds with retention of configuration like the Hofmann (29), Curtius (5) and other related reactions.



SCHEME 20.

By carrying out the oxidation in the presence of an alcohol, the corresponding carbamate can be formed directly. The preparation of a carbamate followed by hydrolysis to give the amine was found to be preferred over direct hydrolysis of the isocyanate since the indirect method usually afforded the amine in better yields. Baumgarten has found t-butyl alcohol to be the preferable reaction solvent although benzyl alcohol was also suitable.

One of the disadvantages of this reaction is that in some cases the LTA may oxidize the alcohol faster than the amide.

We investigated this reaction to see if it would improve the yield of the carbamate. The (S)-N-cinnamoylproline amide (81) was prepared from the acid 7 by the method of Roberts and coworkers (32) again using ethyl chloroformate and triethylamine followed by reaction with dry ammonia gas. This amide was refluxed with LTA in dry t-butyl alcohol and the reaction mixture was purified by flash chromatography affording the t-butyl carbamate 48 in 39% yield. A trace of the t-butyl allophanate 71 was also detected by ms and nmr.

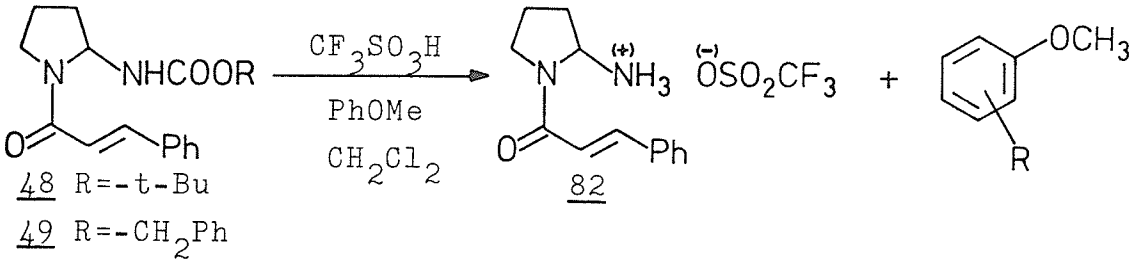
Again the low yield of the carbamate must be due to decomposition of the intermediate isocyanate 10. This carbamate 48 was also found to be stereochemically unstable; the crude optically active material from the column chromatography racemized to a large extent on recrystallization from ether/pentane. This facile racemization again suggested that acid cleavage would cause extensive racemization and so not allow the amine 11 to be prepared in an optically active form.

Thus, the preparation of the carbamates do not proceed in very good yields because the intermediate isocyanate has a tendency to decompose by the loss of the isocyanate ion. Low yields were observed with both the modified Curtius reaction and the direct reaction of DPPA with N-

cinnamoylproline. A slightly better but still rather low yield of t-butyl carbamate was obtained by the LTA reaction on N-cinnamoylproline amide in the presence of t-butyl alcohol. Of course this synthesis required the amide to be first prepared. The unstable ether 56 was isolated as a by-product in the Curtius reaction with p-methoxybenzyl alcohol and the allophanates 71 and 72 in the DPPA reaction. These carbamates were found to undergo facile racemization which indicated that optically pure odorine and odorinol may not be obtained by this route.

The Cleavage of the Carbamates

As already mentioned, t-butyl, benzyl, and p-methoxybenzyl carbamates can be cleaved with strong acids. Trifluoromethanesulfonic acid (triflic acid, TFMSA) (33) is one of the strongest acids known and can cleave various acid-labile amino protecting groups quantitatively within 3-60 minutes at room temperature (34,35). The t-butyloxy-carbonyl group (BOC) is cleaved within 3-5 minutes and the benzyloxycarbonyl group (Z) usually within 15 minutes. The literature procedure involves excess triflic acid (5-10 equivalents) and methylene chloride or trifluoroacetic acid (TFA) as a solvent. Anisole (1.5-3 equivalents) is used as a scavenger to suppress the possible alkylation reaction. This alkylation may be due to the generation of the t-butyl and benzyl cations or more likely due to the formation of the t-butyl and benzyl trifluoromethanesulfonates.

[8] 

We investigated the cleavage of carbamates by strong acids since it seemed to be a promising method of obtaining the amine 11 as a salt without decomposition and while still possibly retaining the optical activity. Early in our investigations, the deblocking was carried out in neat anisole without any other solvent but later methylene chloride was used. To simplify purification, most of the anisoles were removed by quickly extracting the cleaved product with dry pentane. The t-butyl and benzyl carbamates 48 and 49, respectively, were found to be smoothly cleaved under all of these conditions.

The 4-methoxybenzyloxycarbonyl group (Z(OMe)) is more acid labile than the benzyloxycarbonyl (Z) protecting group due to the electron releasing methoxy group. Thus, the Z(OMe) group can be cleaved with trifluoroacetic acid at 0°C while the Z protecting group remains untouched under these conditions (36). Indeed, we found the p-methoxybenzyl carbamate 50 in methylene chloride was readily cleaved by TFA again in the presence of anisole to prevent the alkylation reaction.

Other alkoxycarbonyl protecting groups are known that

can be cleaved under various non-acidic conditions (17). For instance, the 2-(4-tolyl)sulphonylethyl carbamates are cleaved with strong inorganic bases (37), conditions however which are too vigorous for sensitive molecules. The corresponding 2-(4-tolyl)sulphonylethyl esters have been smoothly cleaved under mild, neutral conditions with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene at room temperature (38). One would expect this DBN fragmentation also to be applicable to the cleavage of the carbamates.

Because these mild conditions seemed promising, we also prepared such a carbamate by the reaction of the corresponding alcohol with the isocyanate 10 from the Curtius reaction. Since 2-(4-tolyl)sulfonylethanol was unavailable the 2-phenylsulfonylethanol was used instead. Since the crude product from this reaction was found to decompose on column chromatography the 2-phenylthioethyl analogue was first prepared and then oxidized with potassium peroxymonosulfate. The 2-phenylsulphonylethyl carbamate 52 was indeed found to be cleaved by DBN but the free amine 11 seemed to decompose since no odorine could be isolated when this crude amine was treated with 2-methylbutanoic acid and DCC (see later).

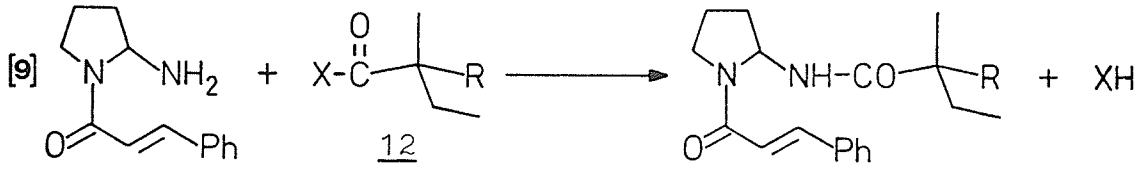
Carbamates can also be cleaved under mild, nonaqueous conditions by using iodotrimethylsilane or chlorotrimethyl-silane and sodium iodide which generates the former reagent in situ (39). Both reagents were found to cause extensive decomposition in initial investigations and so this method

was not pursued further.

Thus, the t-butyl and benzyl carbamates 48 and 49, respectively, were readily cleaved with TFMSA while the p-methoxybenzyl analogue 50 was easily cleaved with TFA and these seemed to be the most promising methods of generating the amine 11.

The Coupling Reactions

Several methods of coupling the 1-cinnamoyl-2-pyrrolinylamine (11) with 2-methylbutanoic acid (83) and 2-hydroxy-2-methylbutanoic acid (84) were investigated to see which would give the optimum yields. Obviously not every one of the numerous methods available could be examined, only some of the representative methods which seemed promising were tried.



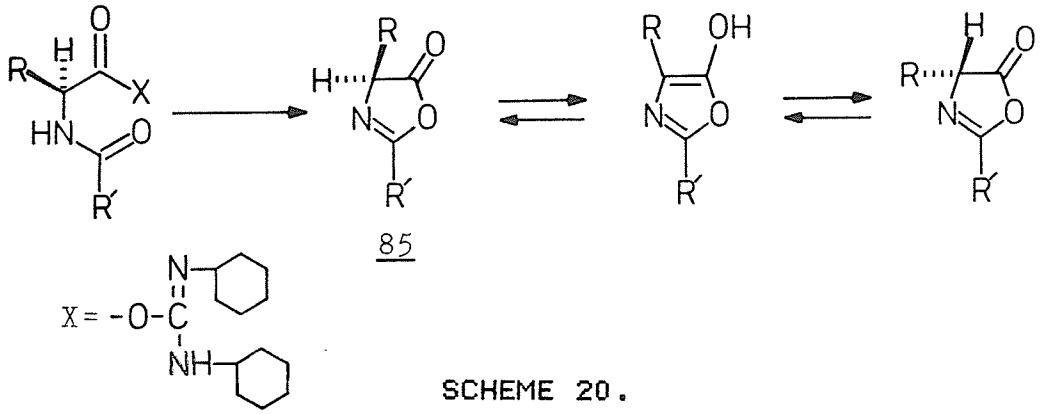
11 12 1 R=H 2 R=OH

Dicyclohexylcarbodiimide (DCC) (41) is one of the most common reagents available for the preparation of amide bonds (40,41) and so was the logical first reagent to investigate. We cleaved the t-butyl carbamate 48 with TFMSA, treated the resulting salt with 2-methylbutanoic acid, DCC and TEA, and obtained odorine (1) and epiodorine (3) in 25% yield after chromatography. With the anisyl carbamate 50 in which TFA was employed in the cleavage, 1 and 3 were obtained in ca. 17% yield.

The analogous DCC coupling of the amine 11 from the benzyl carbamate 49 with the hydroxy acid 84 afforded odorinol (2) and epiodorinol (4) but only in 11% yield.

The lower yield in this case must be due to some involvement of the hydroxy group in the coupling reaction. One does not expect the hydroxy acid to undergo self-condensation under such conditions since the amine nitrogen is much more nucleophilic than the hydroxyl group. The presence of the hydroxy group in the intermediate acylisourea may increase the steric bulk enough to slow the attack of the amine by a significant amount and thus decrease the yield of odorinol. Dipole-dipole repulsion between the attacking nitrogen atom and the hydroxy oxygen atom may also contribute to a decrease in the rate of attack.

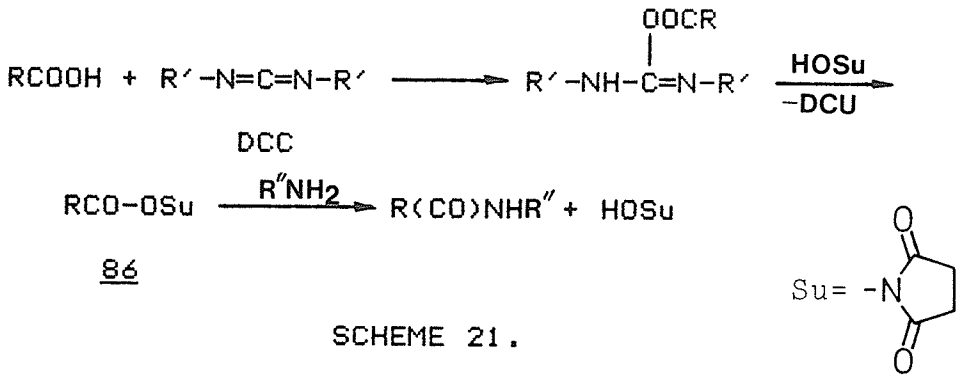
One of the disadvantages of DCC is that when the carboxylic group of acylamino acids, for example, is activated, racemization can occur via oxazolone 85 formation (6a).



SCHEME 20.

This racemization can be reduced if the reaction is carried out in the presence of N-hydroxysuccinimide (HOSu) (42) or other such compounds. These additives form highly

active esters 86 with the carboxylic acid component which then react rapidly with amines. Racemization is reduced because of the fast formation and consumption of the active esters. It was thought that the fast reaction of such a highly active ester might also increase the yield of odorine and odorinol.



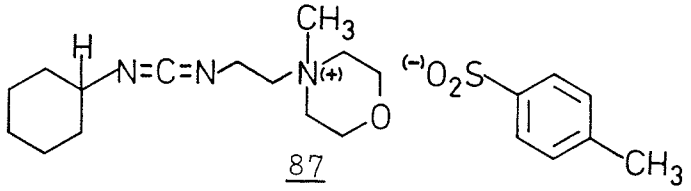
SCHEME 21.

We repeated the DCC coupling reaction with added N-hydroxysuccinimide but the yield of odorinol (2) and epiodorinol (4) decreased to 4%. The N-hydroxysuccinimide and 2-methylbutanoic acid (83) were then first coupled using DCC to form a mixture of the N-hydroxysuccinimide ester and the 2-methylbutanoic acid anhydride. Reaction of this mixture and the amine 11 generated from the anisyl carbamate 50 produced very little odorine. The reason for this decrease in the yield was not clear. It appears that in this case, the O-acylisourea was a more active acylating agent than the N-hydroxysuccinimide ester or the anhydride.

The N,N′-dicyclohexylurea (DCU) (45) by-product and the acylurea (46) from the rearrangement of the

intermediate O-acylisourea (42) (Scheme 11) were difficult to separate from the odorine and odorinol because of their similar solubilities. Column chromatography was required to purify the odorine and odorinol from this reaction. The ureas were usually not isolated since they were strongly held by the silica gel.

Water-soluble diimides might reduce these purification problems since the ureas formed from these reagents could simply be washed out of the product mixture. Thus the water-soluble 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-p-toluenesulfonate (87) (43) was briefly examined.



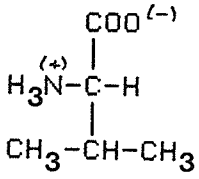
87

As a model system, the coupling of 2-hydroxy-2-methylbutanoic acid (84) with aniline using this reagent was investigated. The non-nucleophilic aniline was used because it was believed it would mimic the steric hindrance present in the amine 11. However, the recrystallized yield of the N-phenyl-2-hydroxy-2-methylbutamide was only 15%. Another model compound, 2-phenylsulfonylethyl N-phenylcarbamate, was cleaved with DBN and the liberated aniline treated with 2-hydroxy-2-

methylbutanoic acid (84) and the water soluble diimide 87 but again very little of the N-phenyl-2-hydroxy-2-methylbutamide was obtained. Similarly, the 2-phenylsulfonylethyl carbamate 82 afforded no odorinol and epiodorinol. The amine 11 may be decomposing under these conditions since even with DCC no odorine was obtained from this compound.

The low yields of odorine and odorinol observed could be due to a number of reasons but steric hindrance was likely an important factor. Both the amine 11 and the carboxylic acids 83 and 84 have rather large, bulky groups attached to them. The intermediate O-acylisourea 42 from the reaction of the acid with DCC may be sufficiently hindered toward nucleophilic attack by the amine 11 so that rearrangement to the unreactive N-acylurea 46 would be favored. This hindered nucleophilic attack may also make the decomposition of the amine 11 an important contributing reaction. A significant amount of the acid anhydride may also be preferentially formed and this seems to be relatively unreactive towards the amine.

Examples of such steric hindrance in peptide synthesis have been reported (44). For instance, the amino acids valine (88) and isoleucine (89) have bulky side chains because of the branching at the β-carbon atom. It has been found that the nucleophilic attack by amines is severely hindered in the activated carbonyl derivatives of these compounds. This results in a low rate of acylation and



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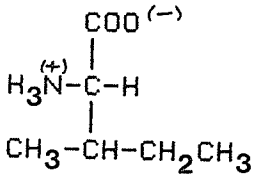
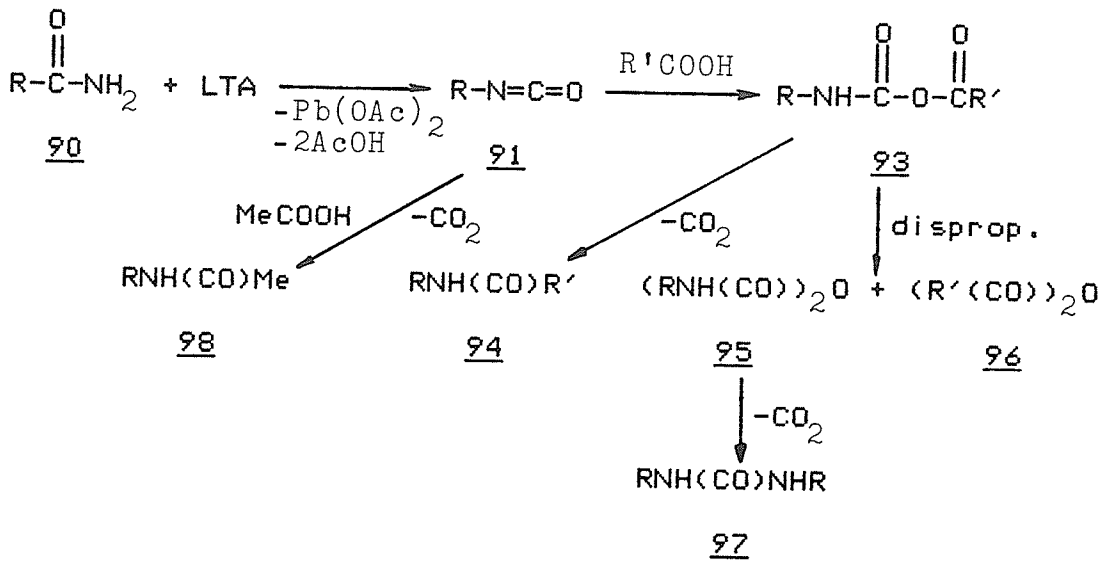


89

causes competing processes to become important which may result in considerable amounts of by-products. In the DCC coupling, the O→N migration can become important and significant amounts of N-acylurea can be formed especially when weak nucleophiles are involved. N-Acylurea is usually present as a side-product in such reactions but normally only in small amounts. A similar formation of acylurea tends to occur when the carboxylic group of proline (3) is activated with DCC. The O→N migration is pronounced in dimethylformamide, less so in methylene chloride.

Beckwith and coworkers (31) have reported that such a coupling reaction can be carried out by the LTA oxidation of primary amides in the presence of a carboxylic acid. The mechanism involves the interaction of the carboxylic acid 92 with the isocyanate 91 formed from the amide 90 by the earlier discussed mechanism (Scheme 19) leading to a mixed anhydride intermediate 93 (Scheme 22). This mixed anhydride can now lose carbon dioxide to form the acylamine 94 or disproportionate to give the symmetrical anhydride 95 and 96. Loss of carbon dioxide from 95 results in the urea 97. The product distribution of this reaction depends on the experimental conditions and the structure of the



SCHEME 22.

compounds. However, one can usually expect the formation of some urea 97 and also acetylamine 98 from the acetic acid present in the LTA.

When we treated 1-cinnamoyl-2-pyrrolinylcarboxamide (81) with LTA in the presence of 2-methylbutanoic acid (83) no odorine was detected and the urea 54 was the major product. Similarly, the reaction of 2-methylbutanoic acid (83) with the preformed isocyanate 10 also resulted in the urea 54 as the major product and so this reaction was not pursued further.

Activation of a carboxylic acid as an acid azide is one of the classical methods used in peptide chemistry for preparing amide bonds. As discussed earlier, DPPA is a convenient reagent that can be used to prepare such an azide. Reaction with DPPA at a higher temperature causes rearrangement to the isocyanate but at lower temperatures

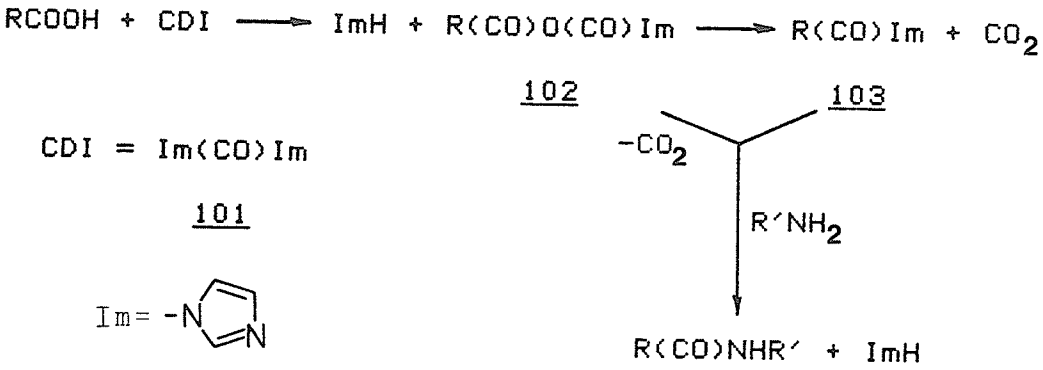
the intermediate acid azide can form an amide bond with an amine (45). Thus, 2-methylbutanoic acid (83) was treated with DPPA/TEA in dimethylformamide for 23 hours at room temperature and then reacted with the amine 11 generated from the anisyl carbamate 50. However, only a trace of odorine was obtained.

Diethylphosphoryl cyanide (DEPC, 99) is a reagent similar to DPPA which can be used to prepare the acyl nitrile 100 from carboxylic acids in situ (46). Amines and carboxylic acids which are difficult to couple with other reagents can be coupled in good yields with this reagent (47). However, we could not obtain any odorine with this compound and so this method was not investigated any further.

[10] $RCOOH + DEPC + TEA \longrightarrow \underset{\underline{100}}{R(CO)CN} + (EtO)_2POOH \cdot TEA$

$DEPC = \underset{\underline{99}}{(EtO)_2(PO)CN}$

Carboxylic acids have also been activated as N-acyl-imidazoles 103 as imidazole is a good leaving group. These compounds can be conveniently prepared by treating the acid with 1,1'-carbonyldiimidazole (CDI, 101) (48). However, only a trace of odorine was obtained from the reaction of 2-methylbutanoic acid (83) with CDI in dry DMF followed by the amine 11 generated from the anisyl carbamate 50.



SCHEME 23.

One of the simplest ways a carboxylic acid can be activated is as an acid chloride. This method has been used in peptide syntheses (18) but it suffers from some drawbacks (6a).

In some initial investigations, we treated the amine 11 generated from the anisyl carbamate 50 with acetyl chloride and TEA at 0°C. A 1:1 mixture of the acetamide and the diacylated compound, an imide, were obtained in a clean reaction with a good yield.

[11] $R(CO)Cl + NH_2\text{-}R' \xrightarrow[-HCl]{} R(CO)NHR' \xrightarrow[-HCl]{RCOCl} (R(CO))_2NR'$

We repeated the reaction with 2-methylbutanoic acid chloride (104) and again had a clean reaction with a good mass balance. However, the product was found to be a mixture of odorine (1), epiodorine (3) and the trifluoroacetamide 105. The proportion of 1 and 3 vs. 105 was found to depend on the temperature and the order of addition (Table 3). The optimum yield was obtained when

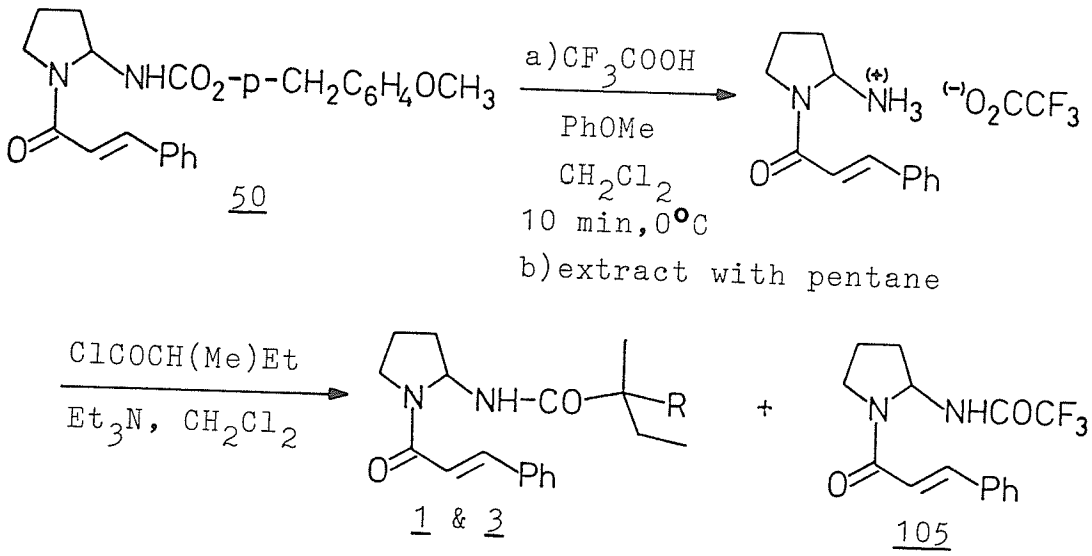


TABLE 3. The Preparation of Odorine using 2-Methylbutanoic Acid Chloride.

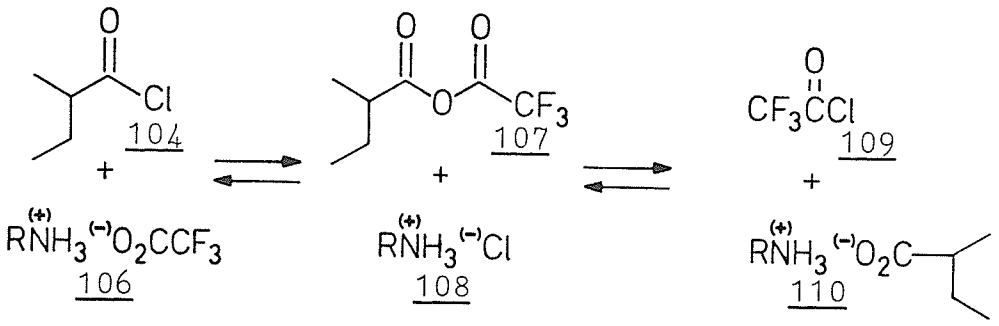
Acid Chloride 104 (equiv)	TEA (equiv)	Temp[b] (°C)	Products 1&3:105
3.0 (1st)[a]	3.1 (2nd)[a]	0	1:1
2.7 (1st)	7.0 (2nd)	-77	105 main product
2.5 (2nd)	6.7 (1st)	-77	amine precipitates.
3.0 (1st)	7.7 (2nd)	-23	3:1
3.0 (2nd)	8.0 (1st)	-23	6:1
3.0 (2nd)	7.5 (1st)	-23	8:1 (ca. 22% 1&3 recrst.)

[a]Order of addition. [b]Coupling temperature.

the reaction was carried out in a dry-ice/carbon tetrachloride bath (ca. -23°C) and when the TEA was added first followed by the acid chloride. At the lower temperature of a dry-ice/acetone bath, the amine 11

precipitated out of solution and after warming to room temperature the trifluoroacetamide 105 was the main product.

The occurrence of the trifluoroacetamide 105 can be rationalized by the formation of the mixed anhydride 107.

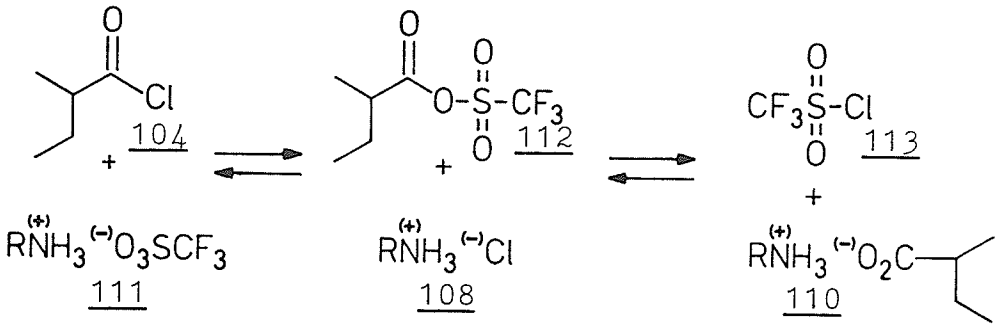


SCHEME 25.

One would expect the formation of 108 and thus also 107 to be favored since it is the salt of the strongest base (RNH_2) and the strongest acid (HCl) in the system. Instead of such thermodynamic control the formation of the mixed anhydride may be due to the kinetically controlled attack of trifluoroacetate ion. The trifluoroacetyl chloride 109 should not be present to any great extent and so would not be important in the formation of 105. The reaction of the mixed anhydride 107 with the amine 11 can take place at either carbonyl. The trifluoromethyl carboxylate would be the better leaving group but nucleophilic attack at the other carbonyl would be favored on grounds of less steric hindrance.

The cleavage of the carbamates with trifluoromethane-

sulfonic acid would avoid the formation of the trifluoroacetamide 105. Even if the corresponding mixed anhydride 112 is formed, acetylation should only occur since the trifluoromethanesulfonate anion is such a very good leaving group. Trifluoromethanesulfonic-carboxylic anhydrides of the type 112 have been found to be some of the most powerful acylating agents known (49).



SCHEME 26.

Benzene and other non-activated arenes are smoothly acylated by such mixed anhydrides without any Friedel-Crafts catalyst. Indeed, when we cleaved the t-butyl carbamate 48 with this reagent and treated the amine salt with 2-methylbutanoyl chloride (104) and TEA, odorine (1) and epiodorine (3) were obtained in a good yield (61%).

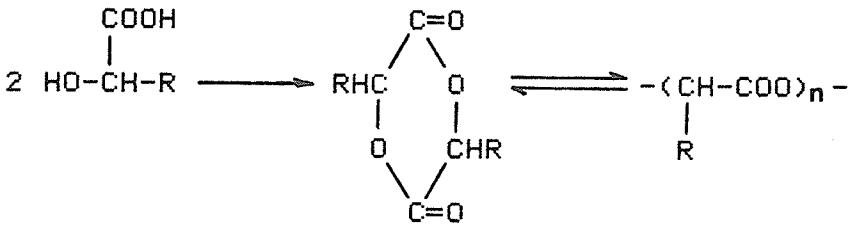
Massy-Westropp (1) found natural (+)-odorine (1a) had a specific rotation of $[\alpha]$ +72.6° while the material isolated by Connolly (3) had undergone partial racemization, $[\alpha]$ +34°. The synthetic (-)-odorine (1a) and (-)-epiodorine (9b) prepared by the former workers (2) were reported to have specific rotations of $[\alpha]$ -20° and -2°;

respectively. Again, partial racemization occurred with the odorine and so most likely also with the epiodorine.

In our synthesis, if no racemization takes place a 1:1 mixture of (-)-odorine and (-)-epiodorine was expected since racemic 2-methylbutanoic acid (83) was used. If one assumes such a 1:1 mixture has an optical rotation which is approximately the average of the two compounds then we would expect a specific rotation of at least $[\alpha]$ -10^{0}. However, the product of our reaction was optically inactive within experimental error and so complete racemization must have occurred. While some of this racemization may have taken place during the preparation of the carbamates, most likely occurred in the acid cleavage of these carbamates. Thus, this method could obviously not be used to prepare the optically active odorine as planned. Enough acid may be present to racemize the amine 11 and/or odorine by a ring-opening mechanism (Scheme 3).

Since the acid chloride method afforded odorine and epiodorine in a good yield, although racemic, a similar means of activation was also investigated for the synthesis of odorinol. Here the introduction of a hydroxy group complicates the synthesis.

α-Hydroxy acids can undergo self-condensation to give both lactides 114, dimeric 6-membered cyclic esters, and linear polymers 115 (50). Normally one would also expect a similar cyclization and/or polymerization from such hydroxy acids on attempting to form the acid chloride. Obviously,



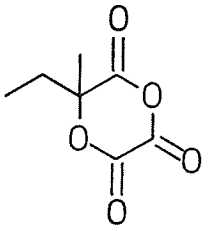
114 115

SCHEME 27.

if the hydroxy group was protected, these self-condensation reactions could not occur. Since the hydroxy group in 2-hydroxy-2-methylbutanoic acid (84) is hindered, it was hoped that under mild conditions the acid chloride could be prepared as an intermediate and immediately further reacted with the amine.

One reagent that can form acid chlorides under mild conditions is oxalyl chloride. This compound has been used to smoothly prepare acid chlorides in methylene chloride at 0°C (18). The crude acid chlorides from this reaction are usually quite clean since only volatile by-products are formed, and these by-products, the excess oxalyl chloride, and the solvent can simply be removed under vacuum.

Model couplings were carried out with 2-hydroxy-2-methylbutanoic acid (84) and aniline using this reagent but only a trace of the wanted amide was formed, and very little material was recovered from the reaction. It is possible that a cyclic carbonate 116 was formed similar to the known anhydrocarboxylate 117 (51). Related cyclic compounds can be prepared from substituted ureas and oxalyl



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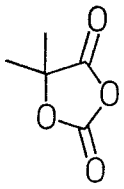
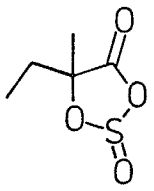


117

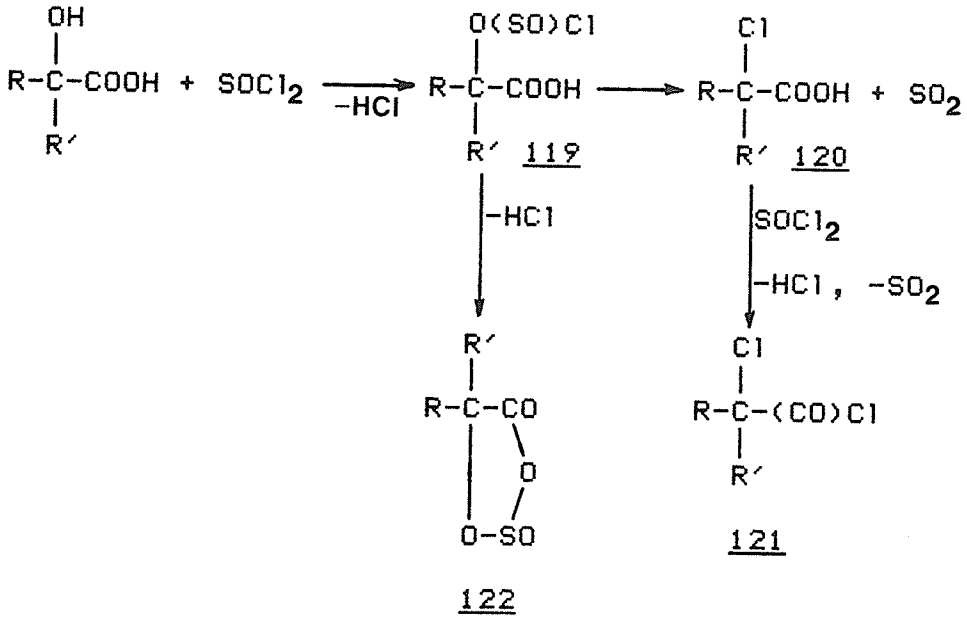
chloride (52). This compound could then undergo nucleophilic attack leading to the incorporation of the oxalyl group and not the formation of the wanted amide.

A similar cyclic compound has been prepared by the reaction of a hydroxy acid with thionyl chloride (51). Thus, treatment of 2-hydroxy-2-methylbutanoic acid with thionyl chloride at 0°C has been reported to form the anhydrosulphite 118, more formally named 5-methyl-5-ethyl-1,3,2-dioxathiolan-4-one-2-oxide (53). These cyclic compounds undergo polymerization and have been reported to react with amines and alcohols to give amides and esters, respectively, although they have not been used synthetically.



118

This cyclic compound seemed to be a promising method of activation while at the same time avoiding the need to separately protect the hydroxy group. We prepared the anhydrosulfite 118 according to a literature procedure (54) and investigated the reaction with aniline as a model. However, none of the N-phenyl-2-hydroxy-2-methylbutamide could be isolated. Similarly the amine 11 from the t-butyl carbamate 48 yielded no odorinol, ie., no incorporation of the 2-hydroxy-2-methylbutyl group occurred. The anhydrosulfite had the correct boiling point and ir spectrum but the ms was more complex than expected (53). These compounds are known to hydrolyze very rapidly so that hydrolysis and decomposition/polymerization may simply have occurred in the reaction mixture.



SCHEME 28.

An important side-reaction in the preparation of these anhydrosulfites is the formation of a chloro-acid chloride 121. This chloride has a boiling point similar to that of the anhydrosulfite and so purification by fractional distillation is difficult (53). However, even if this were a major product one would then expect the chloro analogue of odorinol to be formed and this was not observed.

Thus the synthesis of odorinol seems to require the initial protection of the hydroxy group. Vigorous conditions for protecting the 2-hydroxy-2-methylbutanoic acid must be avoided since dehydration could occur; cis-2-methylbut-2-enoic acid (angelic acid) has been prepared by the dehydration of this acid at 150-190°C. Once the appropriate protecting group has been introduced, the synthesis of odorinol would follow that of odorine requiring only an additional deprotection step at the end. Since the optically pure odorinol could not be prepared due to rapid racemization further investigations were not carried out.

CONCLUSION

Odorine and odorinol, as a mixture with their epimers, could indeed be prepared by the formation of the amide bond.

The required amine 11, as a salt, was prepared by the acid cleavage of a suitable carbamate; trifluoromethanesulfonic acid (TFMSA) was used to cleave the t-butyl 48 and benzyl 49 carbamates while the p-anisyl carbamate 50 was cleaved with trifluoroacetic acid (TFA). Both reactions were carried out in methylene chloride at 0°C in the presence of excess anisole to suppress the possible alkylation of the aromatic ring present in the cinnamoyl group.

The benzyl, anisyl and also 2-phenylthioethyl 51 carbamates were prepared by the reaction of the appropriate alcohol with the isocyanate 10 which in turn was prepared in high yield from N-cinnamoylproline using a modified Curtius reaction. This isocyanate-alcohol reaction was found not to proceed in high yields (23-26%) presumably due to the decomposition of the isocyanate 10 by loss of the isocyanate ion. With anisyl alcohol, the ether 56 formed by such a loss and further reaction with the anisyl alcohol was identified by spectroscopic means but could not be isolated in pure form due to its instability (ca. 4% yield). Dimethyltin dichloride was found to effectively catalyze the reaction of the isocyanate 10 with alcohols but without any increase in the yields. The t-butyl

carbamate 48 was prepared in slightly higher yields (39%) from N-cinnamoylproline amide by treatment with lead tetraacetate (LTA) in t-butanol.

Carbamates have also been directly prepared in a one-pot reaction from a carboxylic acid and alcohol using diphenyl phosphorazidate (DPPA). However, treatment of N-cinnamoylproline with DPPA in t-butanol afforded the t-butyl allophanate 71 as the major product (36%). The formation of this compound can be explained by the reaction of the intermediate isocyanate 10 with the isocyanate ion followed by further reaction with t-butanol. The analogous reaction with anisyl alcohol afforded a mixture of the anisyl carbamate 50 and the anisyl allophanate 72 (ca. 27 and 24%, respectively) which could not be separated.

Several methods were investigated to couple the amine 11 with 2-methylbutanoic acid (83) or 2-hydroxy-2-methylbutanoic acid (84). In these reactions the free amine was liberated from the freshly prepared amine salt with triethylamine and immediately reacted with the appropriately activated acid.

The common coupling reagent dicyclohexylcarbodiimide (DCC, 41) afforded odorine and its epimer in 17-25% yield while odorinol and its epimer were obtained in 11% yield. The addition of N-hydroxysuccinimide which forms highly active esters in the DCC coupling reaction decreased the yields of both odorine and odorinol. A better yield of odorine (61%) was obtained when the acid was activated as

an acid chloride, ie. using 2-methylbutanoyl chloride (104).

Odorinol could not be prepared from the corresponding hydroxy acid chloride presumably due to a self-condensation reaction. The cyclic sulfoxide compound, 5-methyl-5-ethyl-1,3,2-dioxathiolan-4-one-2-oxide (118), seemed to be a promising method of both activating the acid group while at the same time protecting the hydroxy group. However, the reaction of this compound and the amine 11 did not afford any odorinol. Thus, the synthesis of odorinol by the formation of the amide bond via the acid chloride would require the protection of the hydroxy group in the 2-hydroxy-2-methylbutanoic acid (84) and such protection was not examined in this investigation.

Numerous other coupling methods were also investigated but all were found to give either no or poorer yields of odorine or odorinol. These coupling agents included the water-soluble carbodiimide 1-cyclohexyl-3-(2-morpholino-ethyl)carbodiimide metho-p-toluenesulfonate (87), DPPA, diethylphosphoryl cyanide (DEPC, 99), and 1,1'-carbonyl-diimidazole (CDI, 101). Both the wanted Hofmann rearrangement and coupling have been achieved in the literature in a one-pot reaction by the treatment of an amide with LTA in the presence of an acid. However, no odorine could be detected when N-cinnamoylproline amide (81) was treated with LTA in the presence of 2-methyl-butanoic acid instead the urea 54 was only isolated.

The N-cinnamoyl proline carbamates were found to racemize very easily either during their preparation or on purification by recrystallization or column chromatography. Similarly, the odorine and epiodorine mixture from the acidic cleavage of the carbamates and the acid chloride coupling was found to be racemic, i.e. the amine 11 or the odorine must racemize under these conditions. Thus, this route cannot be used to prepare the optically pure compounds due to the facile isomerization at the C2 position of the pyrrolidine ring.

EXPERIMENTAL

General

The solvents used were usually certified A.C.S. (Fisher) and when necessary were dried by distillation from an appropriate drying agent (19, 55) and stored over dried molecular sieves (4 or 5 Å, Davison supplied by Fisher). Anhydrous magnesium sulfate (Fisher certified) was used as a drying agent for extraction solvents. The phenylthioethanol used was prepared in this laboratory according to a literature procedure (56). The commercial suppliers of the chemicals used infrequently are listed in the experimental where they were used, the source of the chemicals used more often follow: Aldrich-p-methoxybenzyl alcohol, dicyclohexyl carbodiimide (DCC), ethyl chloroformate, trifluoroacetic acid, trifluoromethanesulfonic acid; Fisher-anisole (certified), benzyl alcohol (certified), sodium azide (purified), triethylamine (TEA); PCR Incorp.-dimethyltin dichloride.

Flash chromatography according to the method of Still (25) was carried out on silica gel 60, 230-400 mesh (E. Merck). Analytical thin layer chromatography (tlc) was done on silica gel F254 pre-coated on plastic sheets to a thickness of 0.2 mm (E. Merck) and was visualized with iodine or shortwave ultraviolet light.

A Kern full-circle polarimeter was used to determine the specific rotation. The angle of rotation was measured immediately after making the solution with at least 6 pairs

of readings made for each sample. Each such pair of measurements were the two readings determined by approaching the point of uniform adumbration from each side with the analyzer. The error was estimated as the sum of one standard deviation for the zero and the angle of rotation reading.

^{1}H nuclear magnetic resonance spectra were normally obtained on a Varian Anaspect EM 360 spectrometer at 60 MHz. Other spectra were measured on a Bruker WH 90 (90.02 MHz for ^{1}H and 22.63 MHz for ^{13}C) or a Bruker AM 300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C). Unless otherwise indicated, the solvent used was chloroform-d with tetramethylsilane as an internal standard (Aldrich). Mass spectra were recorded on a Finnigan 1015 spectrometer; the assignments rationalize the fragments observed and are by no means definite. The infrared spectra were measured on a Pye Unicam SP1000 spectrophotometer calibrated with a polystyrene film (0.05 mm thickness). Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario.

(E,S)-N-(1'-Oxo-3'-phenylprop-2'-enyl)pyrrolidine-2-carboxylic Acid (7) (2)

((S)-N-Cinnamoylproline)

L-Proline (28.01 g, 0.243 mol, Aldrich 99+%) was dissolved in 1 N NaOH (200 mL) and cooled with stirring in an ice-bath to 0°C. Phenolphthalein indicator solution (1% in ethanol, 2 drops) was introduced and trans-cinnamoyl chloride (6) (50.92 g, 0.306 mol) was added dropwise over 60 min with the concurrent addition of 2 N NaOH (125 mL) to maintain basicity. During the addition the temperature was maintained at 0-2°C.

After the addition was complete, the reaction was stirred another 1 h in the ice-salt bath; an additional portion of 2 N NaOH (25 mL) had to be added to maintain basicity. The unreacted acid chloride was filtered-off and the reaction acidified to Congo-red (pH 3-5) with 10% HCl (150 mL). The white, sticky mass that formed was carefully crushed, stirred another 30 min in the reaction mixture, removed by filtration, rinsed with cold water and allowed to dry.

The crude acid (60.28 g, 101%, mp 184.5-189.0°C) was recrystallized from chloroform (350 mL) affording 51.20 g (86%) pure (S)-N-cinnamoylproline (7) in 4 crops, mp (first crop) 187.5-189.5°C; lit. mp 184-185°C (2).

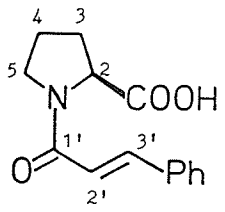
$[\alpha]_D^{21}$ -74±4° (C=1.015 g/100 mL, ethanol, 2 dm cell)

Further recrystallization from ethanol afforded crystals of mp 185.5-187.5°C.

$[\alpha]_D^{21}$ -72±4° (C=1.008g/100 mL, ethanol, 2 dm cell)

lit. $[\alpha]_D^{24}$ -72°(ethanol) (2)

^{1}H nmr at 300 MHz; a small amount of a second rotamer (5%) was present:



δ 1.94-2.16 ppm	(m, 3H, 1xH3, 2xH4)	
2.54-2.61	(m, 1H, 1xH3)	
3.64-3.74	(m, 1H, 1xH5)	
3.74-3.82	(m, 1H, 1xH5)	
4.60-4.65	(m, 0.06H, H2)	
4.72-4.76	(m, 0.94H, H2)	
6.60	(d, J 15 Hz, 0.05H, H2′)	
6.72	(d, J 15.4 Hz, 0.95H, H2′)	
7.31-7.43	(m, 3H, aromatic)	
7.48-7.59	(m, 2H, aromatic)	
7.72	(d, J 15 Hz, ca. 0.04H, H3′)	
7.83	(d, J 15.4 Hz, ca. 0.96H, H3′)	

ir (chloroform):

$\bar{\nu}$ 979 cm^{-1}	(m)	=C-H out-of-plane bend
1605	(m)	C=C stretch
1645	(s)	-(C=O)-N stretch
1757	(s, broadened)	-(C=O)-OH stretch
2425-3645	(w, v.broad)	-OH stretch

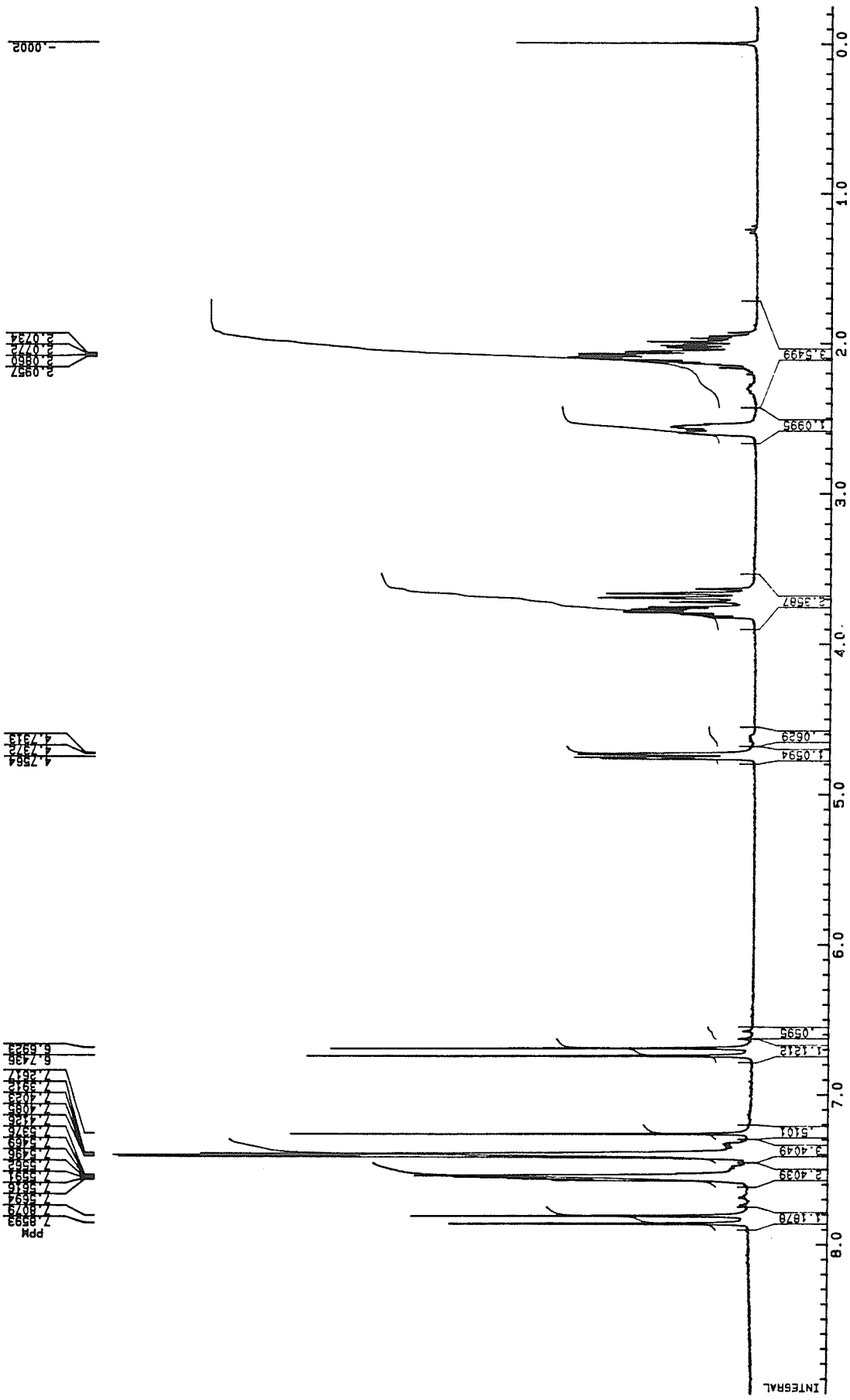


FIGURE 2. (S)-N-Cinnamoylproline (7).

ms:

m/z		
245		M+
201		-44, -CO
172		Ph-CH=CH-(CO)-$NC_2H_4^+$
131	base	Ph-CH=CH-C=O$^+$
103		Ph-CH=CH$^+$
91		$C_7H_7^+$
77		$C_6H_5^+$
70		$C_4H_8N^+$

(E,S)-N-(1'-Oxo-3'-phenylprop-2'-enyl)pyrrolidine-2-carbamide (81) (32)

((S)-N-Cinnamoylproline Amide)

Triethylamine (TEA) (13.27 g, 0.131 mol) was added to a stirred suspension of (S)-N-cinnamoylproline (7) (32.02 g, 0.131 mol) in methylene chloride (250 mL) at room temperature when a clear solution was formed. This solution was cooled to -7°C with an ice/salt bath and ethyl chloroformate (14.35 g, 0.132 mol) was added over 15 min while the temperature was kept at or less than 0°C. After stirring a further 30 min at -5 to 0°C, ammonia gas (Matheson), dried with a trap containing NaOH pellets, was added over 75 min. Initially, heat was evolved and the reaction warmed from -5 to +2°C. Later in the addition the temperature remained at -5°C indicating the reaction was largely complete. The mixture was stirred an additional 2 h at room temperature and was filtered in two portions on

two Buchner funnels.

The crude product in the filtrate was dissolved in chloroform (175 mL), washed with 10% K_2CO_3 (2x20 mL), 10% HCl (2x20 mL), saturated NaCl solution (2x20 mL), and dried. The precipitate in the Buchner funnels were combined, extracted with chloroform (150 mL), filtered, washed as above and dried. The tlc (EtOAc) indicated both solutions contained mainly the amide along with some unidentified impurities. After concentration, the cream-colored solid was recrystallized from hot chloroform/benzene affording 22.89 g (72%) (S)-N-cinnamoylproline amide (81) in several crops, mp 164.0-165.0°C.

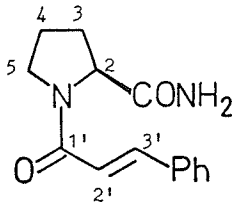
$[\alpha]_D^{21}$ -221±4° (C=1.007 g/100 mL, chloroform, 2 dm cell)

Further recrystallization from hot chloroform/benzene did not have a large effect, mp 163.5-164.5°C.

$[\alpha]_D^{20}$ -219±4° (C=1.012 g/100 mL, chloroform, 2 dm cell)

Analysis for $C_{14}H_{16}N_2O_2$; calculated: C 68.83, H 6.60, N 11.47%; found: C 69.63, 69.20; H 7.02, 6.90; N 11.41, 11.28%.

^{1}H nmr at 300 MHz; a second rotamer was present (ca. 15%):



δ1.82-2.33 ppm	(m,	3H, 1xH3, 2xH4)
2.43-2.51	(m,	1H, 1xH3)
3.60-3.69	(m,	1H, 1xH5)
3.72-3.82	(m,	1H, 1xH5)
4.51-4.54	(m,	0.15H, H2)
4.73-4.77	(m,	0.85H, H2)
5.59	(b,	0.85H, 1xNH)
5.98	(b,	0.15H, 1xNH)
6.45	(b,	ca. 0.15H, 1xNH)
6.59	(d,	J 15.3 Hz, 0.15H, H2′)
6.76	(d,	J 15.5 Hz, 0.85H, H2′)
7.24	(b,	1H, 1xNH)
7.33-7.42	(m,	3H, aromatic)
7.45-7.57	(m,	2H, aromatic)
7.74	(d,	J 15.5 Hz, 1H, H3′)

ir (chloroform):

$\bar{\nu}$ 979 cm^{-1}	(m)	=C-H out-of-plane bend
1576-1616	(s,broadened)	N-H bend, C=C stetch
1651	(s)	-(C=O)-N stetch
1697	(s)	-(C=O)-NH stetch
3345	(m,b)	-NH stretch
3495	(m,sharp)	-NH stretch

ms:

m/z 244	M+	
227	-17,	-OH
215	-29,	-CHO

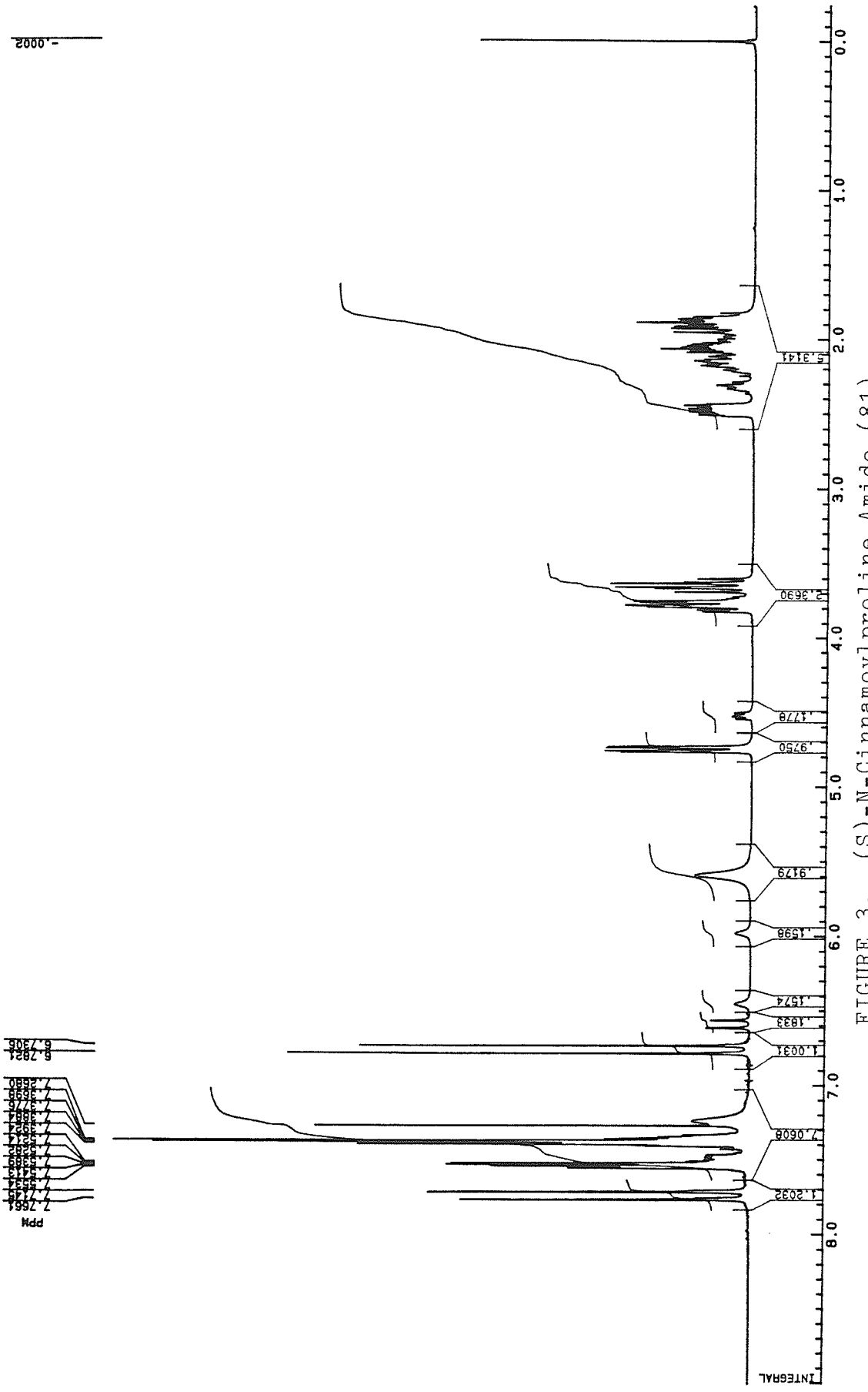


FIGURE 3. (S)-N-Cinnamoylproline Amide (81).

200		$Ph-CH=CH-(CO)-NC_4H_7^+$
131	base	$Ph-CH=CH-C=O^+$
103		$Ph-CH=CH^+$
77		$C_6H_5^+$
70		$C_4H_8N^+$

(E,2S)-[1-(1'-Oxo-3'-phenylprop-2'-enyl)-2-pyrrolidinyl]-carbamic Acid, 1,1-Dimethyl Ethyl Ester (48) (30)
(t-Butyl Carbamate)

(S)-N-Cinnamoylproline amide (81) (8.00 g, 32.7 mmol) was dissolved in dry t-BuOH (200 mL) with warming and lead tetraacetate (LTA) (16.01 g, 36.1 mmol, Aldrich, stored over conc. H_2SO_4) was added in one portion. The reaction was immediately immersed in a hot wax bath (ca. 130°C) and stirred. After 1 h reflux, the reaction was allowed to cool and was concentrated on a rotary evaporator.

The residue was extracted with ether (3x50 mL), filtered, washed with 10% HCl (25 mL), 10% K_2CO_3 (3x25 mL), saturated NaCl solution (25 mL) and dried. On concentration, 8.32 g of a light yellow solid was obtained. The aqueous washings were re-extracted with chloroform (3x25 mL), washed with 10% HCl (20 mL), 10% K_2CO_3 (2x20 mL), saturated NaCl solution (20 mL) and dried. Removal of the solvent afforded 3.98 g white solid.

Some of the crude product (5.66 g) was purified by flash chromatography on silica gel using ether/EtOAc (1:1) or EtOAc affording 1.84 g (39%) t-butyl carbamate (48), mp

159.0-169.0°C.

$[\alpha]_D^{21}$ -26±3° (C=1.022 g/100 mL, chloroform, 2 dm cell)

The ms had a peak due to the parent ion at m/z 316 and also a small signal at m/z 359 due to the t-butyl allophanate 71.

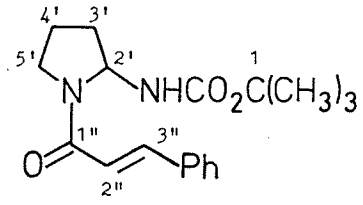
Recrystallization from ether/pentane yielded fine white crystals, mp 181.5-183.5°C, which had undergone extensive racemization:

$[\alpha]_D^{21}$ -1±6° (C=1.264 g/100 mL, chloroform, 1 dm cell)

Analysis for $C_{18}H_{24}N_2O_3$; calculated: C 68.33, H 7.65, N 8.85%; found: C 68.58, H 7.99, N 8.32%. A trace of allophanate was still found to be present.

^{1}H nmr at 300 MHz:

δ1.42 ppm	(s, 9H, 3xMe)
1.69	(s, 3xMe, allophanate impurity)
1.81-2.10	(m, 3H, 1xH3′, 2xH4′)
2.10-2.29	(m, 1H, 1xH3′)
3.43-3.52	(m, 1H, 1xH5′)
3.68-3.74	(m, 1H, 1xH5′)
5.13-5.16	(m, 1H, H2′)
5.83-5.89	(m, 1H, NH)
7.10	(d, J 15.2 Hz, 1H, H2")



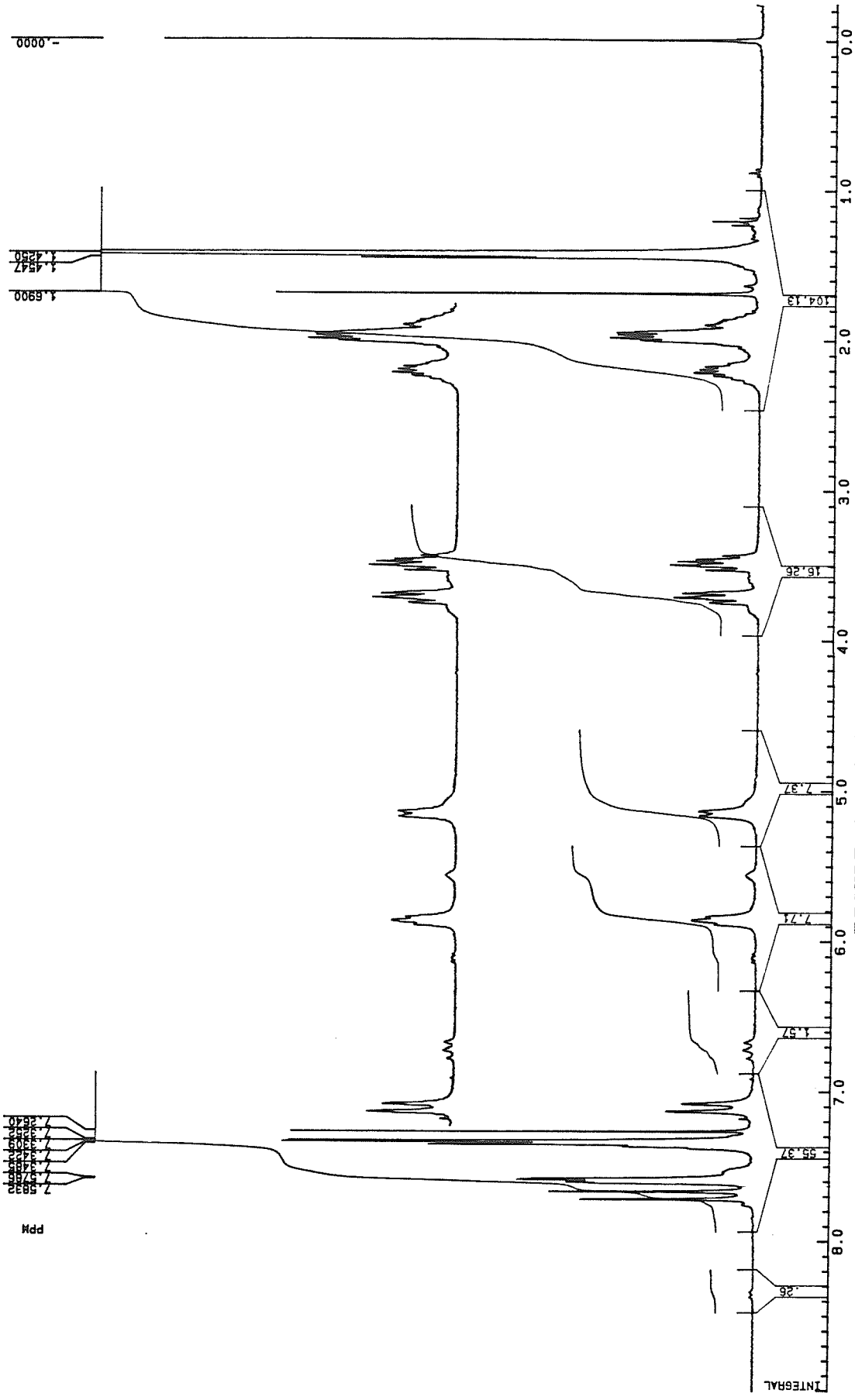


FIGURE 4. t-Butyl Carbamate 48.

7.30-7.38 (m, 3H, aromatic)

7.50-7.64 (m, 2H, aromatic)

7.69 (d, J 15.4 Hz, 1H, H3")

ir (chloroform):

$\bar{\nu}$ 1160 cm^{-1} (s) C-O stretch

1510 (m) Amide II

1611 (s) C=C stetch

1655 (s) -(C=O)-N stetch

1714 (s) -NH-(C=O)-O- stetch

3345 (w,b) N-H stretch

3455 (m,sharp) N-H stretch

ms:

m/z			
	359	(0.3%)	allophanate
	316	(4.2)	M+
	303	(0.7)	359-56, $-Me_2C=CH_2$
	260	(36.3)	316-56, $-Me_2C=CH_2$
	216	(3.3)	$Ph-CH=CH-(CO)-(NC_4H_7)-NH_2^+$
	215	(6.4)	$Ph-CH=CH-(CO)-(NC_4H_7)-NH^+$
	200	(16.4)	$Ph-CH=CH-(CO)-NC_4H_7^+$
	199	(32.9)	$Ph-CH=CH-(CO)-NC_4H_6^+$
	131	(100.0)	$Ph-CH=CH-C=O^+$
	103	(39.0)	$Ph-CH=CH^+$
	91	(3.2)	$C_7H_7^+$
	85	(16.4)	$(C_4H_7N)-NH_2^+$
	77	(19.9)	$C_6H_5^+$
	70	(25.3)	$C_4H_8N^+$
	57	(65.1)	Me_3C^+

(E,2S)-[1-(1'-Oxo-3'-phenylprop-2'-enyl)-2-pyrrolidinyl]-carbamic Acid, Phenylmethyl Ester (49) (23)

(Benzyl Carbamate)

N-Cinnamoylproline (Z) (9.66 g, 39.4 mmol) was suspended in acetone (50 mL) and cooled in an ice/salt bath (ca. 1°C). A solution of TEA (4.42 g, 43.7 mmol) in acetone (40 mL) was added over 4 min resulting in a homogeneous solution. Ethyl chloroformate (4.74 g, 43.7 mmol) in acetone (50 mL) was then added dropwise over 35 min while the temperature was maintained at -1 to -3°C. After stirring an additional 15 min, a cold aqueous solution of sodium azide (5.14 g, 7.91 mmol, in 50 mL water) was slowly added over 45 min (-1 to -3°C).

The reaction was stirred another 15 min and then was poured onto cold water (200 mL) in a separatory funnel. After extraction with cold toluene (4x100 mL), the combined organics were washed with a cold saturated solution of NaCl (4x100 mL) and dried.

Unreacted acid (2.20 g, 8.70 mmol) precipitated from the acidified (50 mL 10% HCl) aqueous layer on standing overnight.

The ir of the organic solution was consistent with the expected acid azide:

ir(film):

$\bar{\nu}$ 1614 cm^{-1}	(s)	C=C
1657	(s)	-CH=CH-(CO)-N

1725	(s)	$-(\underline{C=O})-N=N=N$
2132	(s)	$-N=\overset{(+)}{N}=\overset{(-)}{N}$

Rearrangement to the isocyanate was complete after heating the toluene solution for 30 min with a hot water bath:

ir(film):

$\bar{\nu}$ 1616 cm^{-1}	(s)	C=C
1660	(s)	$-CH=CH-(\underline{C=O})-N$
2242	(s)	-N=C=O

On cooling in an ice bath (3°C), benzyl alcohol (4.28 g, 39.6 mmol) in dry benzene (15 mL) was added followed by dimethyltin dichloride (102 mg, 0.463 mmol) and the mixture was allowed to warm to room temperature with stirring. After 1 h no more isocyanate was present as indicated by ir:

ir(film):

$\bar{\nu}$ 1542 cm^{-1}	(m)	amide II
1593	(s)	C=C
1649	(s)	$-CH=CH-(\underline{C=O})-N$
1710	(s)	$-NH-(\underline{C=O})-O-$

The reaction was allowed to stand overnight, washed with a saturated solution of NaCl (3x150 mL), dried and

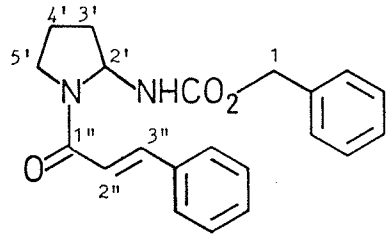
concentrated to ca. 100 mL. The product was precipitated with pentane (25 mL), redissolved in hot benzene (225 mL) and the insoluble urea 54 filtered-off (0.28 g, 3%, 4% corrected for recovered acid, mp 235.0-237.0°C). On cooling, 3.32 g (24%, 31% corrected) benzyl carbamate 49 was obtained in two crops, mp 144.5-146.5°C. Further carbamate (0.28 g, total 3.60 g, 26%, 34% corrected) was obtained by concentrating the original benzene solution and recrystallizing the residue from benzene/hexanes, mp 144.0-147.0°C.

$[\alpha]_D^{22}$ -2±5°(C=1.006 g/ 100 mL, chloroform, 2 dm cell)

An analytical sample was further recrystallized from hot benzene, mp 146.5-148.0°C. Analysis for $C_{21}H_{22}N_2O_3$; calculated: C 71.98, H 6.33, N 7.99%; found: C 72.75, 72.83, H 6.96, 6.71, N 7.79, 7.93%. If 1/6 mole of benzene was included in the crystals then the expected analysis for $C_{22}H_{23}N_2O_3$ is C 72.91, H 6.40, N 7.71%.

^{1}H nmr:

δ 2.00 ppm (b, 4H, 2xH3', 2xH4')
3.50 (b, 2H, 2xH5')
5.12 (s, 1H, $-C\underline{H}_2-Ph$)
5.17 (s, 1H, $-C\underline{H}_2-Ph$)
5.57-6.02 (v.b, 1H, H2')
6.28-6.67 (v.b, 1H, -NH-, exchangeable with D_2O)



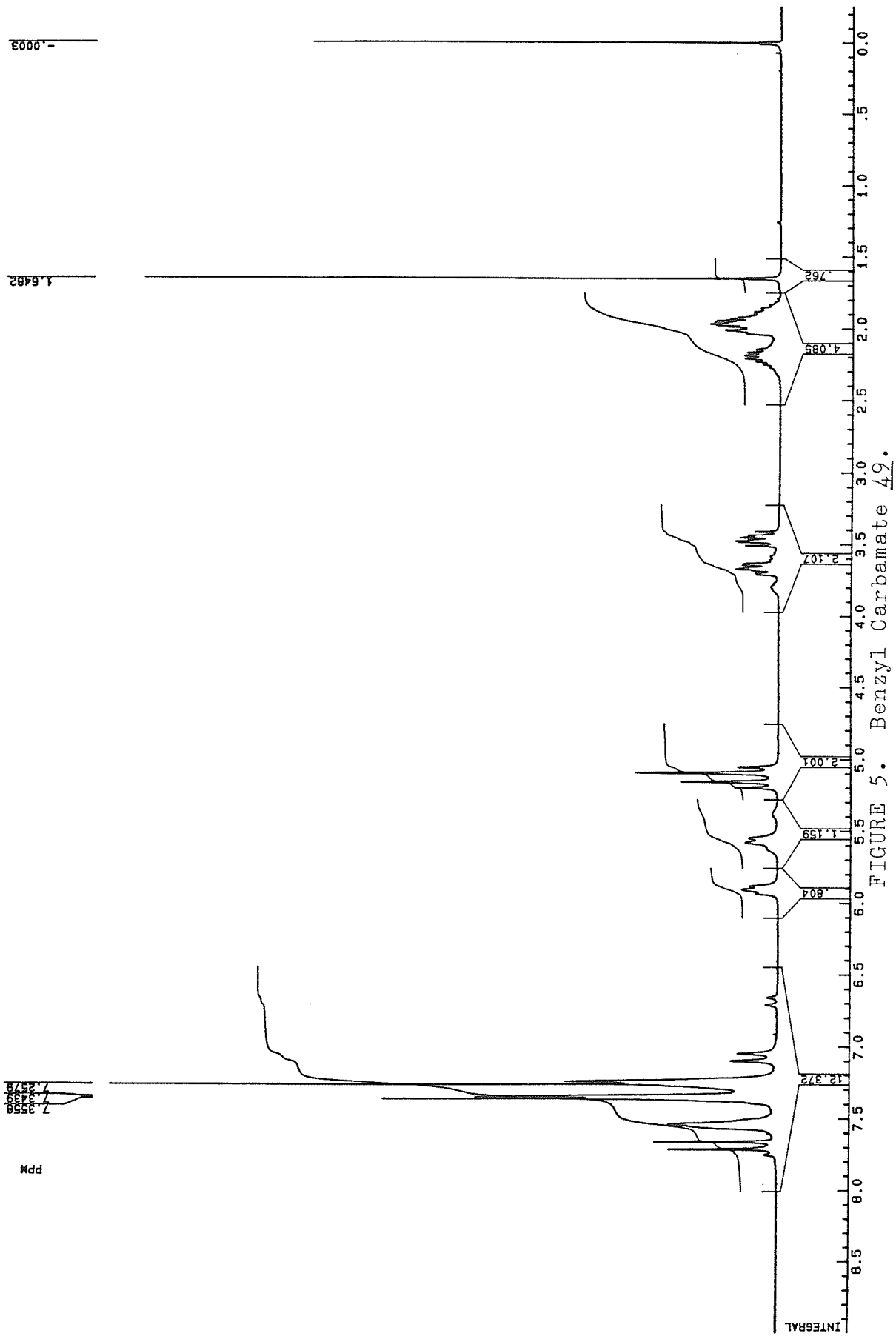


FIGURE 5. Benzyl Carbamate 49.

7.17-7.55 (m, 11H, H2", aromatic)

7.68 (d, J 15 Hz, 1H, H3")

ir (chloroform):

$\bar{\nu}$ 1505-1543 cm^{-1} (m) Amide II

1610 (s) C=C stetch

1663 (s) -(C=O)-N stetch

1720 (s) -NH-(C=O)-O- stetch

3305 (w, v.b) N-H stretch

3455 (m) N-H stretch

ms:

m/z			
	350	(13.3%)	M+
	259	(4.4)	-91, $-C_7H_7$
	215	(5.6)	$Ph-CH=CH-(CO)-(NC_4H_7)-NH^+$
	199	(24.4)	$Ph-CH=CH-(CO)-NC_4H_6^+$
	131	(60.0)	$Ph-CH=CH-C=O^+$
	108	(10.0)	$C_7H_8O^+$
	107	(7.8)	$C_7H_7O^+$
	103	(28.9)	$Ph-CH=CH^+$
	91	(48.9)	$C_7H_7^+$
	79	(21.1)	$C_6H_9^+$
	78	(100.0)	$C_6H_8^+$
	77	(46.7)	$C_6H_7^+$

(E,2S)-[1-(1'-Oxo-3'-phenylprop-2'-enyl)-2-pyrrolidinyl]-carbamic Acid, 4-Methoxyphenylmethyl Ester (50) (23) (p-Methoxybenzyl Carbamate)

(S)-N-Cinnamoylproline (7) (10.00 g, 40.8 mmol) was suspended in acetone (50 mL), cooled in an ice bath (3°C), and a solution of TEA (4.55 g, 45.0 mmol) in acetone (40 mL) was quickly added over 3 min with stirring resulting in a homogeneous solution. NaCl was added to the bath and the temperature was maintained at 0-3°C while ethyl chloroformate (4.90 g, 45.1 mmol) in acetone (50 mL) was added over 35 min. After stirring an additional 35 min, an aqueous solution of sodium azide (5.38 g, 82.8 mmol, in 50 mL water) was slowly added (35 min, -1 to 3°C).

The reaction was stirred another 30 min then poured onto ice-cold water (200 mL) in a separatory funnel and extracted with cold toluene (4x100mL). The combined organics phases were divided into 2 portions, washed with cold water (2x50 mL), cold saturated NaCl solution (3x50 mL), recombined and dried in a refrigerator.

Unreacted 7 (3.11 g, 12.7 mmol) was recovered from the aqueous layer by acidification with 10% HCl (50 mL) and extraction with ether (2x100 mL) and chloroform (100 mL).

An ir of the toluene solution showed the presence of an acid azide group:

ir(film):

$\bar{\nu}$ 1605 cm^{-1} C=C

1652 $-(\underline{C=O})-CH=CH-$

1719 $-(\underline{C=O})-N=N=N$

2125 $-N=\overset{(+)}{N}=\overset{(-)}{N}$

The filtered solution was refluxed on a steam bath for 20 min after which the rearrangement to the isocyanate was found to be complete:

ir(film):

$\bar{\nu}$ 1612 cm^{-1} C=C

1656 $-(\underline{C=O})-CH=CH-$

2235 $-N=C=O$

On cooling, p-methoxybenzyl alcohol (5.65g, 40.9 mmol) in dry benzene (25 mL) was added followed by dimethyltin dichloride (103 mg, 0.469 mmol). After a 20 min reflux period, the reaction was found to be complete as shown by the absence of the isocyanate group:

ir(film):

$\bar{\nu}$ 1613 cm^{-1} C=C

1651 $-(\underline{C=O})-CH=CH-$

1711 $-NH-(\underline{C=O})-O-$

On standing overnight, the solvent was removed and the residue was extracted with pentane (2x50 mL) to remove some of the residual toluene and p-methoxybenzyl alcohol affording

12.36 g of a yellow oil. This material was then warmed at 70-100°C for 1 h while under high vacuum (0.1-0.2 mm Hg) to remove any remaining alcohol; 11.13 g of a yellow oil remained.

Some of this crude material (7.44 g) was purified by flash chromatography on silica gel using ethyl acetate/ petroleum ether (10:1). This purified material was washed with 10% Na_2CO_3 solution to remove the residual acetic acid from the ethyl acetate.

p-Methoxybenzyl carbamate 50 was obtained as an off-white solid 2.35 g (23%, 33% corrected for recovered acid), mp 123.0-128.0°C. The optical rotation indicated racemization had occurred:

$[\alpha]_D^{19}$ -2±4° (C=1.054 g/100 mL, chloroform, 2 dm cell)

Further recystallization from hot benzene yielded material with mp 129.0-131.5°C.

An analytical sample was further recrystallized from benzene, mp 98-108°C. The nmr indicated approximately one mole of benzene had been included in the crystals. This solvent of crystallization was removed (apparently) by warming in a drying pistol under high vacuum, mp 130.0-131.5°C. Analysis for $C_{22}H_{24}N_2O_4$; calculated: C 69.46, H 6.36, N 7.36%; found: C 72.86, 72.78; H 7.04, 6.78; N 6.60, 6.57%. The expected analysis for $C_{27}H_{29}N_2O_4$ if 5/6

mole of benzene was present in the crystals is: C 72.79, H 6.56, N 6.29%.

^{1}H nmr:

δ1.98 ppm	(b, 4H, 2xH3′, 2xH4′)
3.58	(b, 3H, 2xH5′)
3.72	(s, 3H, -O-Me)
5.03	(s, 1H, $-CH_2-Ph$)
5.10	(s, 1H, $-CH_2-Ph$)
5.88	(b, 1H, H2′)
6.30	(b.d, J 9 ca. Hz, 1H, NH)
6.47-6.88	(m, 2H, aromatic)
7.03	(d, J 15 Hz, 1H, H2")
7.23-7.55	(m, 7H, aromatic)
7.72	(d, J 15 Hz, 1H, H3")

ir(chloroform):

$\bar{\nu}$ 1519 cm^{-1}	(s)	Amide II
1614	(s)	C=C stretch stretch
1653	(s)	-(C=O)-CH=CH- stretch
1719	(s)	-NH-(C=O)-O- stretch
3450	(w)	N-H stretch

ms:

m/z 380	M+
336	-44, $-CO_2$
319	-61, $-CO_2$, $-NH_3$
259	-121, $-MeO-(C_6H_4)-CH_2$
249	$MeO-(C_6H_4)-CH_2-O(CO)-NH-(C_4H_7N)^+$

242	$Ph-CH=CH-(CO)-(NC_4H_7)-N=C=O^+$
215	$Ph-CH=CH-(CO)-(NC_4H_7)-NH^+$
200	$Ph-CH=CH-(CO)-NC_4H_7^+$
189	$MeO-(C_6H_4)-(C_5H_7N)^+$
181	$MeO-(C_6H_4)-CH_2-O(CO)-NH_2^+$
148	$Ph-CH=CH-(CO)-NH_3^+$
138	$MeO-(C_6H_4)-CH_2-OH^+$
137 base	$MeO-(C_6H_4)-CH_2-O^+$
131	$Ph-CH=CH-C=O^+$
121	$MeO-(C_6H_4)-CH_2^+$
103	$Ph-CH=CH^+$
91	$C_7H_7^+$
85	$(C_4H_7N)-NH_2^+$
77	$C_6H_5^+$
70	$C_4H_8N^+$

The early fractions from the column chromatography were found to contain p-methoxybenzyl alcohol plus an unknown material which decomposed on standing in the ethyl acetate solution.

The reaction was repeated under similar conditions and the acid Z (20.00 g, 81.5 mmol) afforded 30.23 g of a light golden liquid. Flash chromatography using ethyl ether on a portion of this crude material (27.13 g) yielded 6.96 g (25%) p-methoxybenzyl carbamate 50, and 1.70 g of the unknown compound. No attempt was made to recover any of the starting material Z in the aqueous solution.

The carbamate 50 was identical to the earlier described material except it was found to have a higher specific rotation:

$[\alpha]_D^{26}$ -41±4° (C=1.218 g/100 mL, chloroform, 2 dm cell)

In this case, the unknown did not decompose and was further purified by removing the remaining p-methoxybenzyl alcohol with a micro-distillation apparatus under high vacuum. An oil bath was used to slowly heat the material up to 100°C while at 0.05-0.1 mm Hg. Under the identical conditions the carbamate also did not distill and was recovered unchanged.

The residue was found to be consistent with the ether (E)-1-(1'-oxo-3'-phenylprop-2'-enyl)-2-(4-methoxyphenyl-methoxypyrrolidine (56), (4% yield).

The ^{1}H nmr spectrum of this material was found to change slightly in different solvents:

^{1}H nmr ($CDCl_3$):

δ1.97 ppm	(b, 4H, 2xH3, 2xH4)
3.60	(b, 2H, 2xH5)
3.77	(s, 3H, -OMe)
4.48	(s, 1H, 1x-OCH_2-Ph)
4.67	(s, 1H, 1x-OCH_2-Ph)
5.38	(b, 0.7H, H2)
5.83	(b, 0.3H, H2)

6.45-6.93, 7.40-7.50 (m, 9H, aromatic)

7.72 (d, J 15 Hz, 1H, H2′)

7.77 (d, J 15 Hz, 1H, H3′)

^{1}H nmr (C_6D_6):

δ 1.20-2.00 ppm (v.b, 4H, 2xH3, 2xH4)

3.35 (s, 3H, -OMe)

3.65 (b, 2H, 2xH5)

4.25 (s, 1H, 1x-OCH_2-Ph)

4.92 (s, 1H, 1x-OCH_2-Ph)

5.05 (b, 0.7H, H2)

5.95 (b, 0.3H, H2)

6.65-7.50 (m, 9H, aromatic, H2′)

8.10 (d, J 15 Hz, 1H, H3′)

ir(chloroform):

$\bar{\nu}$ 1613 cm^{-1} (s) CH=CH

1654 (s) -N-(C=O)-CH=CH

ms

m/z			
	216	(0.8%)	$Ph-CH=CH-(CO)-(NC_4H_7O)^+$
	200	(5.6)	$Ph-CH=CH-(CO)-NC_4H_7^+$
	138	(66.0)	$Me-O-(C_6H_4)-CH_2OH^+$
	137	(46.0)	$Me-O-(C_6H_4)-CH_2O^+$
	131	(36.0)	$Ph-CH=CH-C=O^+$
	121	(50.0)	$Me-O-(C_6H_4)-CH_2^+$
	109	(86.0)	$Me-O-C_6H_6^+$
	107	(40.0)	$C_7H_7O^+$
	105	(19.8)	$C_7H_5O^+$
	103	(24.0)	$Ph-CH=CH^+$

86	(4.4)	$C_4H_8NO^+$
84	(6.4)	$C_4H_6NO^+$
77	(100.0)	$C_6H_5^+$

Rinsing the column with methanol yielded 6.43 g (38%) of a compound which was recrystallized from methanol and found to be (E,2S)-[1,3-di-[1-(1'-oxo-3'-phenylprop-2'-enyl)-2-pyrrolidinyl]]urea (54). Analysis for $C_{27}H_{30}N_4O_3$; calculated: C 70.72, H 6.59, N 12.22%; found: C 71.06, H 6.77, N 11.91%.

The ^{1}H nmr at 300 MHz of 54 had features similar to those observed in the related compounds but was more complex. This unexpected complexity may be due to hindered rotation about the amide and urea bonds.

ir(chloroform):

$\tilde{\nu}$ 1556-1574	cm^{-1}(m)	Amide II
1601	(s)	C=C stretch
1654	(s)	NH-(C=O)-NH, N-(C=O)-CH=CH- stretch
3265-3465	(w)	N-H stretch

ms:

m/z 458		M+
327		-131, -Ph-CH=CH-C=O
258		$Ph-CH=CH-(CO)-(NC_4H_7)-NH-(CO)-NH^+$
242		$Ph-CH=CH-(CO)-(NC_4H_7)-N=C=O^+$
215		$Ph-CH=CH-(CO)-(NC_4H_7)-NH^+$
200		$Ph-CH=CH-(CO)-NC_4H_7^+$

131 base $Ph-CH=CH-C=O^+$

103 $Ph-CH=CH^+$

91 $C_7H_7^+$

85 $C_4H_8N^+$

77 $C_6H_5^+$

A similar yield of carbamate was obtained when no tin catalyst was added but the benzene solution had to be refluxed for ca. 4 h for the the isocyanate peak to completely disappear.

(E,2S)-[1-(1'-Oxo-3'-phenylprop-2'-enyl)-2-pyrrolidinyl]-carbamic Acid, 2-Phenylthioethyl Ester (51) (23)

(2-Phenylthioethyl Carbamate)

2-Phenylthioethyl carbamate 51 was prepared via the analogous route used above but with no tin catalyst. Flash chromatography (2:1 chloroform/ ether) afforded pure 51 (25%) as an oil which solidified on standing, mp 104-114°C. Recrystallization from benzene/pentane afforded a colorless solid, mp 114.5-116.0°C.

^1H nmr:

δ 2.05 ppm (b, 4H, H3', H4')

3.08 (t, J ca. 6 Hz, 2H, $-C\underline{H}_2-S-Ph$)

3.62 (b, 2H, H5')

4.28 (t, J ca. 6 Hz, 2H, $-(C=O)O-C\underline{H}_2-$)

5.90 (b, 2H, H2', NH)

7.22-7.67 (m, 11H, aromatic, H2")

7.80 (d, J 15 Hz, 1H, H3")

ir(chloroform):

$\bar{\nu}$ 1606 cm^{-1} (s) C=C stretch

1651 (s) C=O stretch

1722 (s) -NH-(C=O)-O- stretch

3315 (w,v.b) N-H stretch

3445 (w,sharp) N-H stretch

ms:

m/z 154 $Ph-S-CH_2CH_2OH^{+\cdot}$

131 $Ph-CH=CH-C=O^{+}$

123 $Ph-S-CH_2^{+}$

110 $PhSH^{+\cdot}$

109 PhS^{+}

87 $C_4H_{11}N_2^{+}$

85 $C_4H_9N_2^{+}$

83 base $C_4H_7N_2^{+}$

(E,2S)-[1-(1'-Oxo-3'-phenylprop-2'-enyl)-2-pyrrolidinyl]-carbamic Acid, 2-Phenylsulfonylethyl Ester (52, 2-Phenylsulfonyl Carbamate), via Oxidation of the 2-Phenylthioethyl Carbamate (51) (59)

2-Phenylthioethyl carbamate 51 (222 mg, 0.560 mmol) was dissolved in methanol (30 mL) and cooled in an ice-salt bath. An aqueous solution of Oxone® (525 mg, 1.71 mmol $KHSO_5$, Aldrich, in 1 mL water) was added by pipet and rinsed in with another portion of water (1 mL). After 5

min in the cold, the reaction was stirred another 4 h at room temperature.

A tlc (EtOAc) after 10 min indicated that most of the sulfide had been oxidized to the sulfoxide or the sulfone. Oxidation was complete after ca. 3.5 h and the reaction was diluted with water (50 mL), extracted with chloroform (3x20 mL), washed with water (2x20 mL), saturated NaCl solution (2x20 mL) and dried.

Removal of the solvent afforded 240 mg (100%) of 2-phenylsulphonylethyl carbamate 52 as a white foam, mp 40-60°C which contains trace impurities of the sulfide and sulfoxide by tlc (EtOAc).

^{1}H nmr:

δ1.92 ppm	(b, 4H, 2xH3′, 2xH4′)
3.14-3.50	(m, 4H, 2xH5′, $-CH_2-SO_2-Ph$)
4.22	(t, J 5.5 Hz, 2H, $-(CO)O-CH_2-O$)
5.25-5.75	(v.b, 1H, H2′)
6.02	(b.d, J 9.5 Hz, 1H, NH)
6.68	(b.d, J 14.5 Hz, 1H, H2")
6.95-7.46	(m, 11H, aromatic, H3")

ir(chloroform):

$\bar{\nu}$ 1150 cm^{-1}	(s)	SO symmetric stretch
1323	(s)	SO asymmetric stretch
1609	(s)	C=C stretch
1651	(s)	-(C=O)-CH=CH- stretch
1725	(s)	-NH-(C=O)-O- stretch

3315 (w,v.b) N-H stretch

3445 (w,sharp) N-H stretch

The ms indicates some epoxidation may have occurred.

ms:

m/z		
	231	$Ph-(C_2H_2O)-(CO)-(NC_4H_7)-NH^+$
	215	$Ph-CH=CH-(CO)-(NC_4H_7)-NH^+$
	199	$Ph-CH=CH-(CO)-NC_4H_6^+$
	131	$Ph-CH=CH-C=O^+$
	121	$Ph-CH_2CH_2-O^+$
	119	$Ph-CH=CH-O^+$
	117 base	$Ph-C=C=O^+$
	103	$Ph-CH=CH^+$
	84	$(NC_4H_7)-NH^+$

Diphenylphosphoryl Azide (69, DPPA) (45)

Diphenylchlorophosphate (40.0 mL, 51.8 g, 0.193 mol, Sigma) was added to a stirred solution of sodium azide (14.00 g, 0.215 mol) in acetone (100 mL) at room temperature. After stirring for 5 h, the opaque white solution was allowed to stand overnight. The white solid was filtered-off and the filtrate concentrated affording a light yellow liquid (53.46 g).

This crude product was distilled under vacuum through a Vigreux column (10 cm) affording 36.58 g (69%) of DPPA (69) as a colorless liquid, bp 140-165°C at 0.10-0.15 mm; lit. bp 157°C at 0.17 mm (45).

ir(neat):

$\bar{\nu}$ 691 cm^{-1}	(m)	C-H out-of-plane bend
974	(s)	C-O
1167	(s)	P-O-C
1190	(s)	P-O-C
1212	(s)	P-O-C
1278	(s)	P=O
1306	(s)	P=O
1494	(s)	C=C aromatic
1594	(s)	C=C aromatic
2170	(s)	$-N=\overset{(+)}{N}=\overset{(-)}{N}$
3080	(w)	C-H aromatic

ms:

m/z	326	(1.3%)	$(PhO)_3P=O^+$ impurity
	275	(64.1)	M+
	247	(1.3)	-28, $-N_2$
	233	(2.6)	-42, $-N_3$
	224	(5.1)	$PhO-(P=O)(N_3)_2^+$ impurity
	182	(5.1)	$PhO-(P=O)-N_3^+$
	170	(7.7)	$PhO-(P-N)(O)_2^+$
	154	(25.6)	$PhO-(P=O)-N^+$
	140	(21.8)	$PhO-P=O^+$
	94	(28.2)	$PhOH^+$
	91	(15.4)	$C_7H_7^+$
	77	(100.0)	$C_6H_5^+$
	65	(74.4)	$C_5H_5^+$

63 (20.5) $O{=}P{=}O^{+}$

Reaction of (E,2S)-1-(1′-Oxo-3′-phenylprop-2′-enyl)-2-pyrrolidine-2-carboxylic Acid (7) and t-Butyl Alcohol with DPPA (69) (27,45)

DPPA (69) (0.9 mL, 1.1 g, 4.2 mmol) followed by TEA (0.6 mL, 0.4 g, 4.3 mmol) was added by syringe to N-cinnamoylproline (7) (1.04 g, 4.24 mmol) in t-BuOH (20.16 g, 0.27 mol). The solution was refluxed 10 h while being monitored by tlc (EtOAc); the reaction was found to be complete after 3 h.

After dilution with methylene chloride (40 mL), the solution was washed with water (3x20 mL), 10% Na_2CO_3 (20 mL), 10% HCl (20 mL), water (2x20 mL), saturated NaCl solution (20 mL) and dried.

Removal of the solvent afforded 1.71 g semi-solid. Recrystallization from methylene chloride yielded 223 mg (15%) of a white powder, mp 191.5-193.0°C, which was found to be (E,2S)-[[[1-(1′-oxo-3′-phenylprop-2′-enyl)-2-pyrrolidinyl]amino]carbonyl]carbamic acid, 1,1-dimethyl-ethyl ester (71, t-butyl allophanate).

^{1}H nmr:

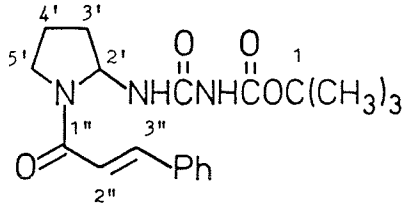
δ 1.45 ppm (s, 9H, 3xMe)

1.83-2.33 (b, 4H, 2xH3′, 2xH4′)

3.62-3.90 (b, 2H, 2xH5′)

5.97-6.35 (v.b, 1H, H2′)

7.18-7.72 (m, 8H, NH, H2", H3", aromatic)



ir(chloroform):

$\bar{\nu}$1156 cm^{-1}	(s)	C-O
1553	(m)	Amide II
1608	(m)	C=C
1645	(m)	N-(C=O)-CH=CH-
1694-1713 & 1730	(s)	N-(C=O)-NH-(C=O)-
3340	(w,broadened)	N-H stretch
3450	(w,sharp)	N-H stretch

ms:

m/z 359		M+.
303		-56, $-Me_2C=CH_2$
285		-74, $-Me_2C=CH_2$, $-H_2O$
259		$Ph-CH=CH-(CO)-(NC_4H_7)-NH-(CO)-NH_2^+$
242		$Ph-CH=CH-(CO)-(NC_4H_7)-N=C=O^+$
228		$(NC_4H_7)-NH-(CO)-NH-COOCMe^+$
215		$Ph-CH=CH-(CO)-(NC_4H_7)-N^+$
200		$Ph-CH=CH-(CO)-NC_4H_7^+$
199		$Ph-CH=CH-(CO)-NC_4H_6^{+\cdot}$
172		$(NC_4H_7)-NH-(CO)-NH-COOH^+$
131	base	$Ph-CH=CH-C=O^+$
128		$(NC_4H_7)-NH-(CO)-NH_2^+$
103		$Ph-CH=CH^+$

The reaction was repeated on 5.00 g (20.4 mmol) N-cinnamoyl proline (Z) with a shorter reflux period (2.5 h); work-up afforded 9.37 g of a golden oil. Flash

chromatography (4:1 EtOAc:petroleum ether) on a portion of this material (0.81 g) afforded 0.44 g of a mixture of t-butyl carbamate (48) and (E,2S)-[[[1-(1'-oxo-3'-phenyl-prop-2'-enyl)-2-pyrrolidinyl]amino]carbonyl]carbamic acid, 1,1-dimethylethyl ester (71, t-butyl allophanate) as a viscous oil. Recrystallization from methylene chloride/ carbon tetrachloride afforded 230 mg (36%) t-butyl allophanate 71, mp 185.0-187.0°C.

Reaction of (S)-N-Cinnamoylproline (7) and 4-Methoxyphenylmethanol with DPPA (27,45)

DPPA (69) (4.4 mL, 5.62 g, 20.4 mmol) and TEA (2.9 mL, 2.10 g, 20.8 mmol) were added with a syringe to a mixture of N-cinnamoylproline (7) (5.00 g, 20.4 mmol) and p-methoxybenzyl alcohol (2.83 g, 20.5 mmol) in dry benzene (55 mL). The reaction was refluxed for 2.5 h and monitored by tlc (EtOAc).

After cooling, the reaction was diluted with methylene chloride (100 mL), washed with 10% Na_2CO_3 (30 mL), 10% HCl (30 mL), water (2x30 mL), saturated NaCl solution (30 mL) and dried. Removal of the solvent yielded 10.14 g of a yellow oil.

A portion of this crude material (0.86 g) was purified by flash chromatography using EtOAc/petroleum ether (4:1) as the mobile phase. This afforded 0.30 g of a colorless oil that was one spot by tlc (4:1 EtOAc/petroleum ether) but found to be a mixture of p-methoxybenzyl carbamate (50) and (E,2S)-[[[1-(1'-oxo-3'-phenylprop-2'-enyl)-2-pyrrolidinyl]amino]carbonyl]carbamic acid, 4-methoxyphenylmethyl ester (72, p-methoxybenzyl allophanate), approximately 1:1 by nmr (27% and 24% yield, respectively).

^{1}H nmr:

δ 1.67-2.23 ppm (b, 4H, 2xH3', 2xH4')

3.18-3.90 (b, 2H, 2xH5')

3.70 & 3.75 (s, 3H, -OMe)

4.92-5.18 (s, 2H, $-CH_2-$)

5.67-6.25 (b, 1H, H2′)

6.52-7.93 (m, 12H, H2", H3", aromatic)

ir (chloroform):

$\bar{\nu}$	1453-1553 cm^{-1}	(m)	Amide II
	1616	(s)	C=C stretch
	1655	(s)	N-(C=O)-CH=CH- stretch
	1710-1730	(s)	-(C=O)-O- stretch
	3350	(w)	N-H stretch
	3450	(m)	N-H stretch

ms:

m/z	217	$Ph-CH=CH-(CO)-(NC_4H_7)-NH_3^+$
	201	$PH-CH=CH-(CO)-NC_4H_8^+$
	200	$PH-CH=CH-(CO)-NC_4H_7^+$
	199	$PH-CH=CH-(CO)-NC_4H_6^+$
	138	$MeO-(C_6H_4)-CH_2OH^+$
	131	$PH-CH=CH-C=O^+$
	121	$MeO-(C_6H_4)-CH_2^+$
	103	$PH-CH=CH^+$
	91	$C_7H_7^+$
	88	$C_4H_{12}N_2^+$
	86	$C_4H_{10}N_2^+$
	84 base	$C_4H_8N_2^+$

2-Methylbutanoic Acid (83) (60)

An aqueous solution of $KMnO_4$ (140.34 g, 0.888 mol, Fisher) in water (2550 mL) was added over 80 min to a cold, stirring mixture of 2-methylbutanol (60.03 g, 0.681 mol, Aldrich) and Na_2CO_3 (17.58 g, 0.166 mol, Fisher) in water (175 mL) while the temperature was maintained at or less than 10°C. The reaction was then stirred at room temperature overnight.

After filtering through a medium-porosity sintered glass funnel, the solution was concentrated to 600 mL, covered with ether (50 mL), acidified with 10% H_2SO_4 (200 mL), and extracted with ether (2x100 mL). Potassium chloride was added to the aqueous layer which was then extracted with ether (100 mL). Additional 10% H_2SO_4 (100 mL) was added and the solution was re-extracted (2x200 mL ether). The combined ethereal extracts were dried and concentrated affording 61.08 g (88%) crude acid.

Vacuum distillation yielded 40.31 g (58%) clear, colorless 2-methylbutanoic acid (83), bp 101.0-106.5°C/45-50 mm; lit. bp 177°C or ca. 90°C/50 mm (61).

^{1}H nmr:

δ 1.00 ppm (t, J 7 Hz, 3H, 3xH4)

1.22 (d, J 8 Hz, 3H, 2-Me)

1.35-1.98 (m, 2H, 2xH3)

1.98-2.70 (m, 1H, H2)

10.2 (s, 1H, -COOH)

ir (neat):

$\bar{\nu}$ 1230 cm^{-1} (s) C-O stretch

1720 (s) C=O stretch

3000 (m) O-H stretch

ms:

m/z 102 M+

87 -15, -Me

74 -28, $-CH_2=CH_2$, McLafferty Rearrangement

57 -45, -COOH

2-Methylbutanoyl Chloride (104) (57)

Redistilled thionyl chloride (9.0 mL, 15.0 g, 0.13 mol, Fisher reagent) was brought to a gentle reflux with a steam-heated water-bath and 2-methylbutanoic acid (83) (10.03 g, 98.2 mmol) was added dropwise over 30 min. After refluxing for 75 min, the reaction was allowed to cool and the crude acid chloride was distilled directly out of the reaction flask. The clear, colorless liquid (9.56 g, 81%) was collected at 100-119°C.

The crude product was redistilled through a 10 cm Vigreux column affording 6.20 g (52%) 2-methylbutanoyl chloride (104), bp 109-114°C; lit. 117°C (62).

ir (neat):

$\bar{\nu}$ 1711 cm^{-1} (w) -(C=O)-OH impurity from hydrolysis

1799 (s) -(C=O)-Cl

ms:

m/z			
	120,122	(0.4%, 0.2%, Ratio 2.17)	M+
	105,107	(1.2, 0.5, Ratio 2.63)	-15, -Me
	102	(1.0)	$EtCH(Me)COOH^{+}$
	92,94	(17.8, 5.7, Ratio 3.15)	$EtCH(Me)Cl^{+}$
	85	(30.2)	$EtCH(Me)-C{=}O^{+}$
	57	(98.4)	$CH(Me)Et^{+}$
	43	(100.0)	$C_3H_7^{+}$

Expect $^{35}Cl/^{37}Cl$ = 100/32.5 = 3.08, experimental error was probably the cause of the observed deviation from this value.

Diethylphosphoryl Cyanide (99, DEPC) (46, 63)

Cyanogen bromide (10.01 g, 0.0945 mol, Fisher reagent) was added in portions to stirred triethyl phosphite (14.27 g, 0.0859 mol, Eastman practical) in an ice/methanol bath. After 1.5 h in the bath, the reaction was stirred at room temperature for 1.5 h, warmed 0.5 h with a heating mantle and allowed to stand overnight at room temperature.

The reaction was distilled under vacuum yielding 11.89 g (85%) of a light yellow liquid, bp 59°C/23 mm - 101°C/16 mm. Redistillation through a 10 cm Vigreux column afforded 8.52 g (61%) DEPC (99) as a colorless liquid, bp 123-127°C/23-24 mm; lit. bp 103-104°C/20 mm or ca. 108°C/24 mm (63).

ir (neat):

$\bar{\nu}$ 1171	cm^{-1}	(m)	P-OEt
1310		(s)	P=O
2075		(w)	-N=C: impurity
2200		(s)	-C-N

ms:

m/z 164		M+1
162		M-1
148		-15, -Me
136		-27, -HCN
134		-29, -Et
120		-43, -HCN, -O
108	base	-55, -CN, -Et
91		-72, -OEt, -HCN
83		$P(O-H)_4^+$
82		$(P=O)(O-H)_3^+$
81		$P(O)_2(O-H)_2^+$
65		$HO-P-OH^+$
55		$Et-CN^+$

Odorine (1) and Epiodorine (3) from p-Methoxybenzyl Carbamate (50) using DCC Coupling (41)

Trifluoromethanesulfonic acid (0.75 mL, 1.3 g, 8.5 mmol) was quickly added with a syringe to a stirring solution of p-methoxybenzyl carbamate (50) (380 mg, 1.20 mmol) and anisole (280 mg, 2.59 mmol) in methylene chloride

(3 mL) at room temperature. After 2 min at room temperature and 5 min in an ice/salt bath, water (1.0 mL), 2-methylbutanoic acid (83) (180 mg, 1.76 mmol) and TEA (1.2 mL, 0.87 g, 8.6 mmol) were added followed by a solution of DCC (450 mg, 2.18 mmol) in methylene chloride (2 mL). The reaction was stirred for 15 min and then allowed to stand 25 h at ca. -5°C.

The product mixture was diluted with methylene chloride (30 mL), filtered, washed with 5% HCl (10 mL), 5% $NaHCO_3$ (10 mL), water (2x10mL), saturated KCl solution (10 mL), and dried. The solvent was removed, the residue redissolved in methylene chloride (20 mL), and the solution was filtered and reconcentrated yielding 650 mg yellow semi-solid.

Flash chromatography on silica gel using chloroform/absolute ethanol (24:1) afforded 90 mg (25%) odorine (1) and epiodorine (3) as a white solid. The tlc (24:1 chloroform/ethanol) demonstrated that this material consisted of two very closely running compounds. The spectroscopic properties of this material were identical to that from a later preparation which proceeded in a higher yield.

Odorine (1) and Epiodorine (3) from p-Methoxybenzyl Carbamate (50) using DCC Coupling (41)

p-Methoxybenzyl carbamate (50) (833 mg, 2.19 mmol) was dissolved in anisole (6.00 g, 55.5 mmol) and cooled in an

ice/salt bath. To this stirring solution was then added trifluoroacetic acid (2.0 mL, 3.0 g, 26 mmol) with a syringe. After 15 min the excess acid was removed on a rotary evaporator, the residue was extracted with pentane (3x30 mL) and was reconcentrated.

This mixture was diluted with methylene chloride (2 mL) and cooled in a liquid nitrogen/carbon tetrachloride bath (ca. -23°C). 2-Methylbutanoic acid (83) (277 mg, 2.71 mmol) was then added followed by TEA (326 mg, 3.22 mmol) and DCC (586 mg, 2.84 mmol). After stirring for 35 min, the reaction was stored overnight in a freezer at ca. -5°C.

The product mixture was then diluted with methylene chloride (50 mL), filtered, shaken with glacial acetic acid (2 mL) to decompose the excess DCC, and washed with 10% HCl (10 mL), 10% Na_2CO_3 (10 mL), water (2x10 mL), saturated NaCl solution (10 mL), and dried.

Removal of the solvent afforded 610 mg semi-solid which was purified by flash chromatography on silica gel using ether/chloroform (10:1). The odorine (1) and epiodorine (3), 110 mg (17%) mp 157.5-161.5°C, had the expected spectroscopic properties (see later).

Odorine (1) and Epiodorine (3) from p-Methoxybenzyl Carbamate (50) and 2-Methylbutanoyl Chloride (104) (18)

p-Methoxybenzyl carbamate (50) (367 mg, 0.965 mmol) and anisole (0.33 g, 3.05 mmol) was dissolved in dry methylene chloride (3.0 mL), cooled in an ice/salt bath and

trifluoroacetic acid (0.40 mL, 0.59 g, 5.2 mmol) was added with a syringe.

After stirring for 10 min, the solution was concentrated without heating, the residue was extracted with dry pentane (6 mL) and the residual pentane was removed on a rotary evaporator. The salt, as an oil, was diluted with dry methylene chloride (21 mL), cooled in a dry-ice/carbon tetrachloride bath, and a syringe used to add TEA (1.0 mL, 0.73 g, 7.2 mmol) and 2-methylbutanoyl chloride (104) (0.35 mL, 0.35 g, 2.9 mmol).

After 30 min, additional methylene chloride (50 mL) was added and the solution was washed with 10% HCl (20 mL), 10% Na_2CO_3 (20 mL), saturated NaCl solution (2x20 mL) and dried. The tlc (10:1 ether:chloroform) indicated that this solution was mainly odorine (1) and epiodorine (3) contaminated with a small amount of (E)-N-[1-(1'-oxo-3'-phenylprop-2'-enyl)-2-pyrrolidinyl]trifluoroacetamide (105) (by comparison with a known sample). After removal of the solvent, the residue was triturated with dry pentane (3x20 mL) affording 0.28 g yellow solid. Recrystallization from hot benzene yielded 63 mg (22%) odorine (1) and epiodorine (3), mp 154.5-161.0°C with the same properties as the material from a later preparation which proceeded in a higher yield.

The trifluoroacetamide 105 was isolated from another such reaction and was found to be racemic with the following properties:

^{1}H nmr:

δ 2.17 ppm	(b, 4H, 2xH3′, 2xH4′)
3.48	(b, 2H, 2xH5′)
5.95-6.25	(b, 1H, H2′)
6.72	(d, J 15 Hz, 1H, 2")
7.37	(m, 5H, aromatic)
7.68	(d, J 15 Hz, 1H, H2")
8.83-9.08	(b, 1H, NH)

ir (chloroform):

$\bar{\nu}$ 1161-1236 cm^{-1}	(s) C-F stretch
1553	(w) amide II
1613	(s) C=C stretch
1655	(s) N-(C=O)-CH=CH- stretch
1715-1725	(s) NH-(C=O)-CF stretch
3185-3505	(w) N-H stretch

ms:

m/z	312	(2.6%)	M+
	243	(1.3)	-69, $-CF_3$
	215	(1.3)	-97, $-(CO)CF_3$
	200	(2.6)	$Ph-CH=CH-(CO)-NC_4H_7^+$
	199	(8.0)	$Ph-CH=CH-(CO)-NC_4H_6^+$
	181	(8.0)	$(NC\ H\ )-NH-(CO)-CF_3^+$
	131	(100.0)	$Ph-CH=CH-C=O^+$
	103	(78.7)	$Ph-CH=CH^+$
	97	(1.3)	$CF_3-C=O^+$

91	(4.0)	$C_7H_7^+$
86	(14.7)	$C_4H_9N_2^+$
77	(60.0)	$C_6H_5^+$
69	(20.0)	F_3C^+

Odorine (1) and Epiodorine (3) from t-Butyl Carbamate (48) and 2-Methylbutanoyl Chloride (104) (18)

t-Butyl carbamate (48) (404 mg, 1.28 mmol) and anisole (425 mg, 3.93 mmol) were dissolved in methylene chloride (5 mL) and treated at room temperature with trifluoromethane sulfonic acid (0.35 mL, 594 mg, 3.96 mmol). After stirring for 5 min, most of the solvent was removed on a rotary evaporator with gentle heating and the golden oil was extracted with dry pentane (3x3 mL) to remove most of the anisole and t-butyl anisoles.

Methylene chloride (5 mL) was added to this oil which did not dissolve and the two layers were cooled in an ice/salt bath. A syringe was used to add 2-methylbutanoyl chloride (104) (0.35 mL, 347 mg, 2.88 mmol) and TEA (1.10 mL, 799 mg, 7.89 mmol) to this mixture. On swirling the oil slowly dissolved and a homogeneous solution was obtained. After stirring 1 h at room temperature, the solution was diluted with methylene chloride (100 mL), washed with 10% HCl (2x20 mL), 10% K_2CO_3 (2x20 mL), saturated NaCl solution and dried.

The tlc (EtOAc) of the product showed mainly two

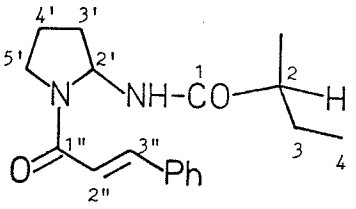
overlapping spots due to odorine (1) and epiodorine (3) with a faster running spot due to anisoles.

The crude product was purified by flash chromatography on silica gel eluting with EtOAc:ether (1:1). In an attempt to separate the diastereomers, the fractions due to the wanted product were combined in two portions, a faster running (top) fraction and a slower running (bottom) band. The top fraction afforded 169 mg (44%) of a light yellow solid, mp 170.5-173.5°C, and the bottom 64 mg (17%) of a light yellow solid, mp 180.0-181.0°C. High resolution ^{1}H nmr spectroscopy showed the top fraction was an essentially equal mixture of diastereomers while partial separation had occurred with the bottom fraction (an approximately 3:1 mixture). Further separation was not attempted.

The top fraction was found to be racemic, a levorotatory rotation was expected if racemization had not occurred. Recrystallization of the top fraction from benzene afforded odorine (1) and epiodorine (3) as a white powder, mp 175.5-177.0°C. Analysis for $C_{18}H_{24}N_2O_2$; calculated: C 71.97, H 8.05, N 9.33%; found: C 71.63, H 8.14, N 8.74%.

^{1}H nmr at 300 MHz:

δ 0.79 & 0.90 ppm (t, J 7.5 Hz, 3H, 3xH4)
1.06 & 1.15 (d, J 7 Hz, 3H, 2-Me)
1.35-1.49 & 1.57-1.75 (m, 2H, 2xH3)
1.62 (s, impurity)



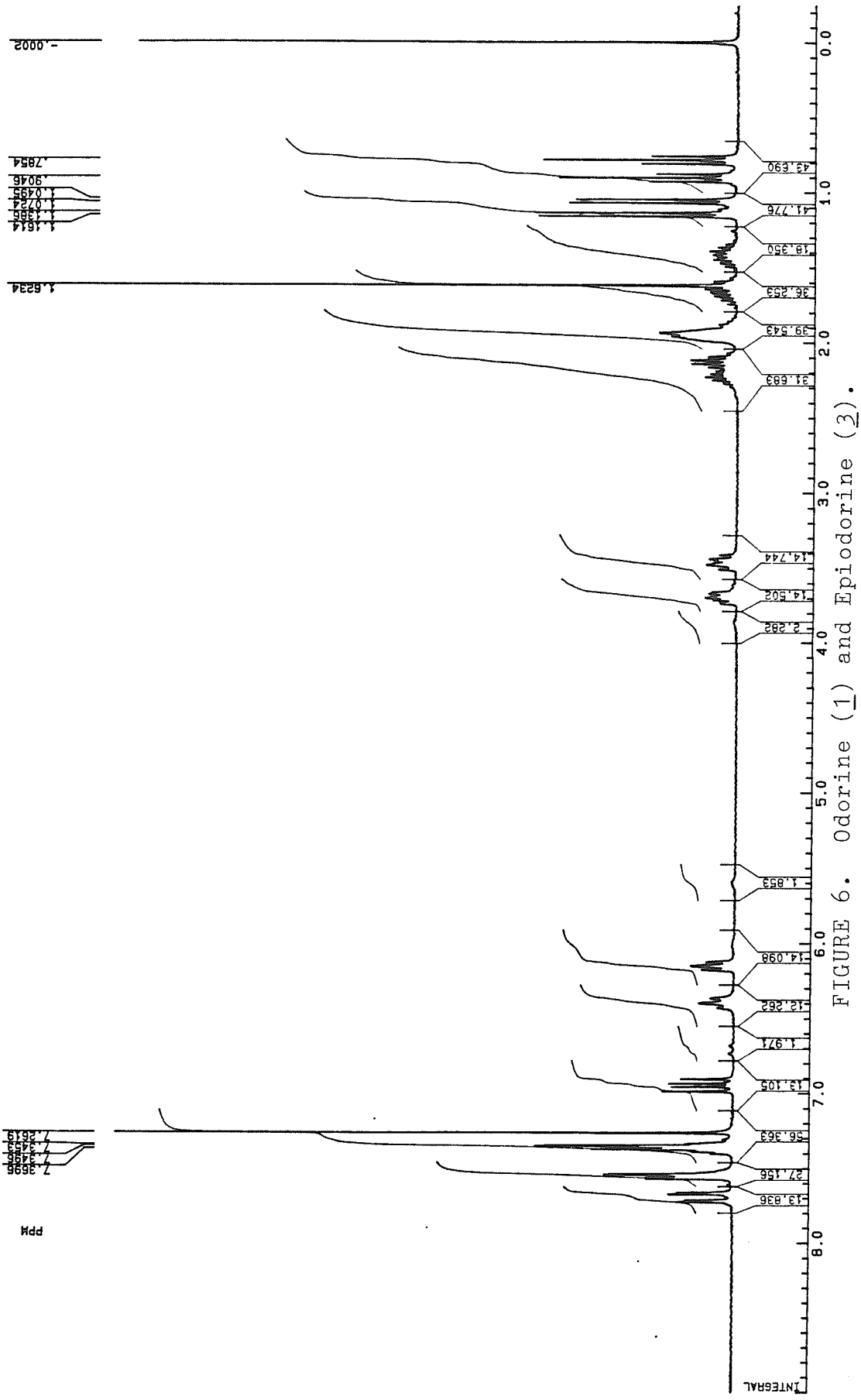


FIGURE 6. Odorine (1) and Epiodorine (2).

1.86-2.01	(m, 3H, 1xH3′, 2xH4′)
2.07-2.29	(m, 2H, 1xH3′, H2)
3.41-3.51	(m, 1H, 1xH5′)
3.66-3.74	(m, 1H, 1xH5′)
6.15	(t, broadened, J 7.6 Hz, 1H, H2′)
6.40	(t, broadened, J 9.4 Hz, 1H, NH)
6.93 & 6.96	(d, J 15.4 Hz, 1H, H2")
7.33-7.40	(m, 3H, aromatic)
7.54-7.57	(m, 2H, aromatic)
7.69 & 7.70	(d, J 15.4 Hz, 1H, H3")

ir (chloroform):

$\bar{\nu}$ 1505-1545 cm^{-1}	(m)	Amide II
1607	(s)	NH, C=C stretch
1651	(s)	N-(C=O)-CH=CH stretch
1667	(s)	NH-(C=O)-C stretch
3300	(m)	N-H stretch
3450	(w)	N-H stretch

ms:

m/z	300	(7.7%)	M+
	216	(3.3)	$Ph-CH=CH-(CO)-(NC_4H_7)-NH_2^+$
	215	(14.5)	$Ph-CH=CH-(CO)-(NC_4H_7)-NH^+$
	200	(6.5)	$Ph-CH=CH-(CO)-NC_4H_7^+$
	199	(24.6)	$Ph-CH=CH-(CO)-NC_4H_6^+$
	169	(36.2)	$NC_4H_7-NH-(CO)-CH(Me)Et^+$
	131	(72.5)	$Ph-CH=CH-C=O^+$
	103	(29.7)	$Ph-CH=CH^+$
	91	(2.5)	$C_7H_7^+$

85	(100.0)	$C_4H_9N_2^+$ or $OC-CH(Me)Et^+$
83	(89.9)	$C_4H_7N_2$
77	(15.2)	$C_6H_5^+$
70	(10.9)	$C_4H_7N^+$
57	(22.6)	$CH(Me)Et^+$

2-Hydroxy-2-methylbutanoic Acid (84) (64)

An aqueous solution of sodium metabisulfite (190.10 g, 1.00 mol, Fisher, equivalent to 2.00 mol sodium bisulfite, 240 mL water) was added over 0.5 h to a vigorously stirred mixture of methyl ethyl ketone (108.53 g, 1.51 mol, Fisher technical), sodium cyanide (78.50 g, 1.60 mol, Fisher certified reagent), and cracked-ice (ca. 250 g). During the addition, the temperature was maintained at 30-40°C and when complete the reaction was cooled to 0°C with a dry-ice/acetone bath.

The top layer was decanted affording 81.9 g (55%) crude cyanohydrin which was hydrolyzed by heating with concentrated HCl (200 mL) for 8 h at 90-100°C. Upon cooling to room temperature, anhydrous sodium sulfate (50 g, Fisher certified) was added and the reaction cooled further with a dry-ice/acetone bath (ca. -25°C).

The reaction mixture was filtered, extracted with ether (3x150 mL), and dried. Removal of the solvent afforded 25.82 g (14%) white solid which was triturated with petroleum ether (700 mL) yielding 19.47 g (11%) 2-

hydroxy-2-methylbutanoic acid (84), mp 71.5-72.5°C; lit. mp 72.5°C (62).

^{1}H nmr:

δ 0.93 ppm	(t, J 7 Hz, 3H, 3xH4)	
1.48	(s, 3H, 2-Me)	
1.68	(q, J 7 Hz, 2H, 2xH3)	
6.40	(b, 2H, -OH, COOH)	

ir (Nujol):

$\bar{\nu}$ 1244 cm^{-1}	(s)	C-O stretch
1728	(s)	C=O stretch
3460	(m)	O-H stretch

ms:

m/z 119		M+1
103		-15, -Me
101		-17, -OH
90		-28, $-CH_2=CH_2$, McLafferty rearrangement
89		-29, -Et
73	base	-45, -COOH
57		$Et-C=O^+$
55		$CH_2=CH-C=O^+$
45		$COOH^+$
43		$Me-C=O^+$
29		Et^+

Odorinol (2) and Epiodorinol (4) from Benzyl Carbamate (49) using DCC (41)

Triflic acid (0.90 mL, 1.5 g, 10.2 mmol) was quickly

added to a stirring solution of benzyl carbamate (49) (0.50 g, 1.43 mmol) and anisole (0.32 g, 2.96 mmol) in methylene chloride (5 mL). The reaction was stirred for 5 min at room temperature and then 5 min in an ice/salt bath. To this cold solution was added water (1 mL), 2-hydroxy-2-methylbutanoic acid (84) (0.21 g, 1.78 mmol), TEA (1.40 mL, 1.02 g, 10.0 mmol) and a solution of DCC (0.45 g, 2.18 mmol) in methylene chloride (2 mL). After 0.5 h, the mixture was stored overnight (ca. 23 h) in a freezer at ca. -5°C.

The reaction was diluted with methylene chloride (40 mL), filtered, washed with 5% HCl (10 mL), 5% $NaHCO_3$ (10 mL), water (2x10 mL), saturated KCl solution (10 mL) and dried. The solvent was removed, the residue redissolved in methylene chloride, the solution was filtered, and reconcentrated affording 580 mg yellow semi-solid. Flash chromatography on silica gel using chloroform/absolute ethanol (24:1) afforded 50 mg (11%) odorinol (2) and epiodorinol (4) in three fractions. The first fraction was essentially one diastereomer while the other two fractions were a mixture with the other diastereomer present in excess.

^{1}H nmr at 300 MHz:

0.91 ppm	(t, J 7.5 Hz, 3H, 3xH4)
1.35	(s, 3H, 2-Me)
1.58-1.70	(m, 2H, 3xH3)

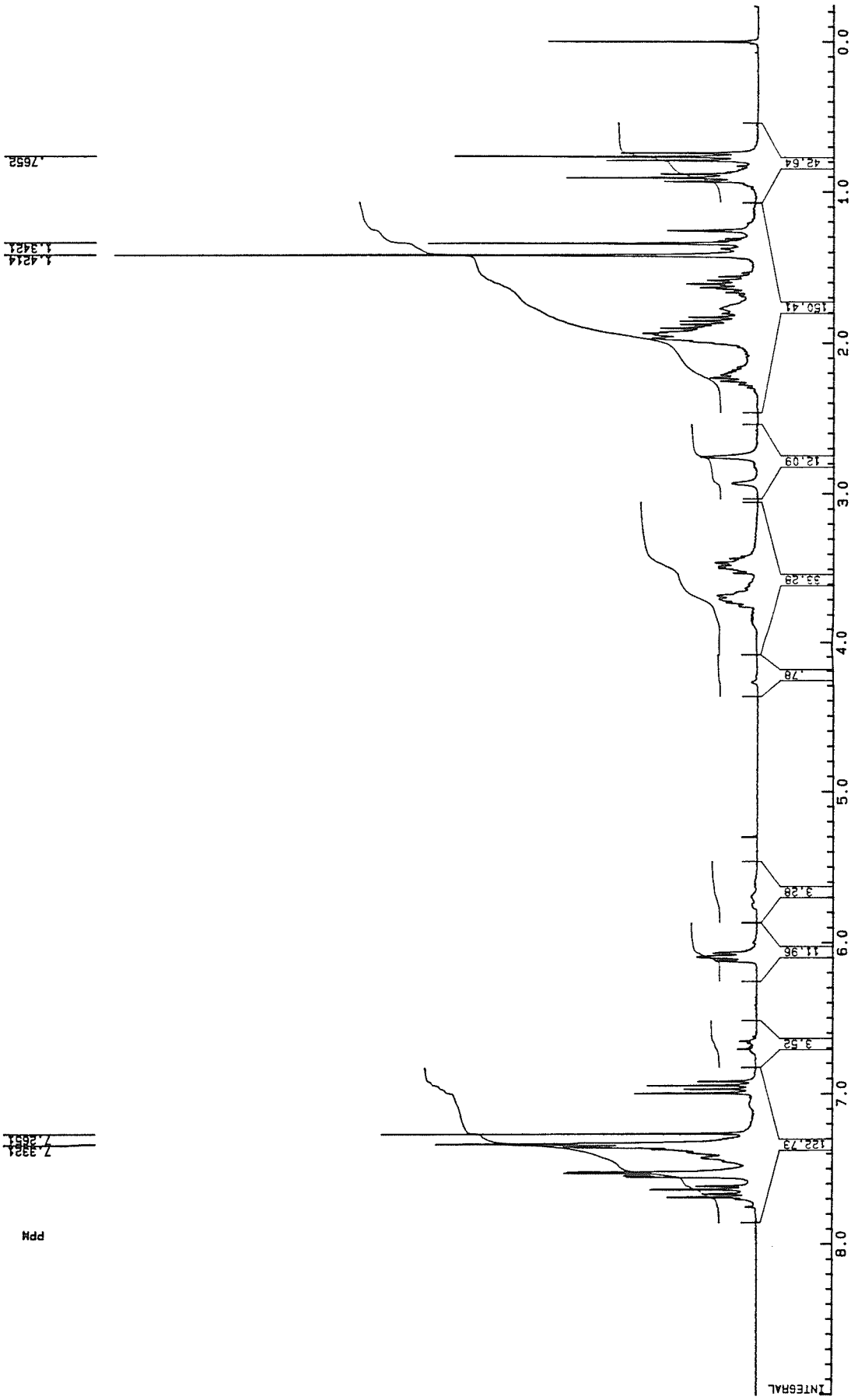


FIGURE 7. Odorinol (2) and Epiodorinol (4).

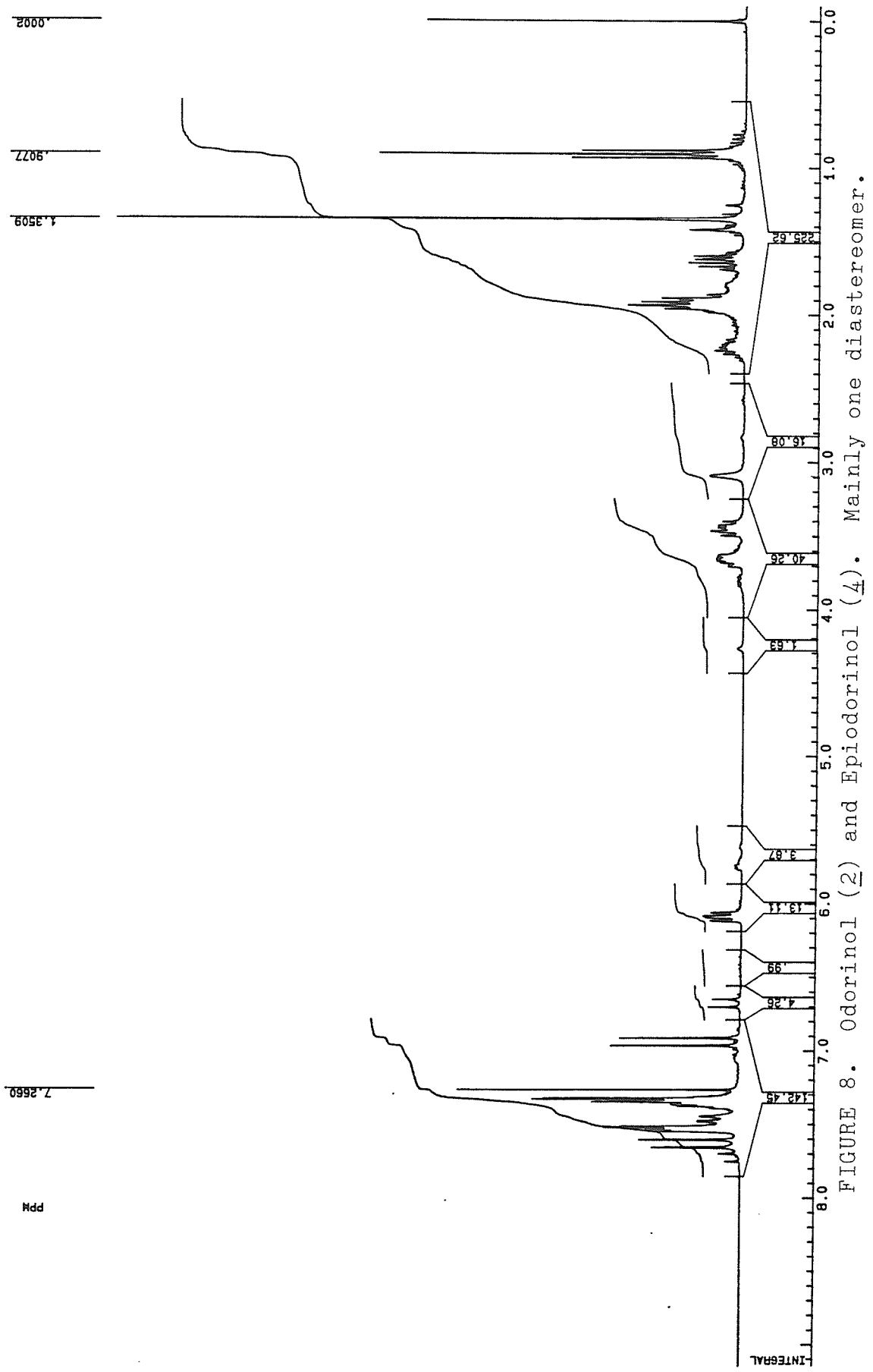
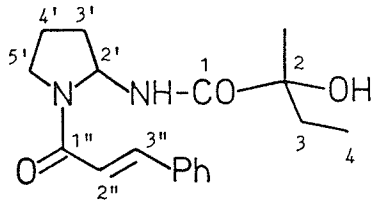


FIGURE 8. Odorinol (2) and Epiodorinol (4). Mainly one diastereomer.

1.77-2.02		(m, 3H, 1xH3′, 2xH4′)
2.15-2.31		(m, 1H, 1xH4′)
3.10		(s, 1H, OH)
3.40-3.49		(m, 1H, 1xH5′)
3.60-3.70		(m, 1H, 1xH5′)
6.06-6.12		(m, 1H, H2′)
6.68		(d, J 15 Hz, 0.21H, H2")
6.93		(d, J 15 Hz, 0.79H, H2")
7.31-7.56		(m, 6H, NH, aromatic)
7.62		(d, J 15 Hz, 0.82H, H3")
7.73		(d, J 15 Hz, 0.18H, H3")



ir (chloroform):

$\tilde{\nu}$ 1514	cm^{-1}	(s)	Amide II
1608		(s)	C=C stretch
1663		(s)	C=O stretch
3425		(s)	-OH stretch

ms:

m/z 316		(0.7%)	M+
244		(0.7)	-72, $-Et(Me)C=O^+$
217		(5.2)	$Ph-CH=CH-(CO)-(NC_4H_7)-NH_3^+$
215		(1.5)	$Ph-CH=CH-(CO)-(NC_4H_7)-NH^+$
201		(10.4)	$Ph-CH=CH-(CO)-NC_4H_8^+$
200		(7.5)	$Ph-CH=CH-(CO)-NC_4H_7^+$
199		(8.2)	$Ph-CH=CH-(CO)-NC_4H_6^+$
185		(5.2)	$(NC_4H_7)-NH-(CO)-C(Me)(OH)Et^+$
131		(100.0)	$Ph-CH=CH-C=O^+$
103		(49.3)	$Ph-CH=CH^+$

86	(10.4)	$C_4H_{10}N_2^{+\cdot}$
85	(9.0)	$C_4H_9N_2^{+}$
84	(11.9)	$C_4H_8N_2^{+\cdot}$ or $Me-CH=CH(Me)C=O^{+\cdot}$
77	(31.3)	$C_6H_5^{+}$
73	(19.4)	$Et(Me)(OH)C^{+}$

Odorinol (2) and Epiodorinol (4) from Benzyl Carbamate (49) using DCC and N-Hydroxysuccinimide (42)

Trifluoromethanesulfonic acid (0.90 mL, 1.5 g, 10.2 mmol) was added to a stirring solution of benzyl carbamate (49) (0.50 g, 1.43 mmol) and anisole (0.36 g, 3.33 mmol) in methylene chloride (5 mL). After 5 min at room temperature, the reaction was cooled 5 min in a dry-ice/carbon tetrachloride bath (ca. -23°C). To this solution was then added TEA (1.40 mL, 1.02 g, 10.0 mmol), 2-hydroxy-2-methylbutanoic acid (84) (0.20 g, 1.69 mmol), N-hydroxysuccinimide (0.33 g, 2.85 mmol, Sigma) in anhydrous dimethoxyethane (4 mL), and a solution of DCC (0.45 g, 2.18 mmol) in anhydrous dimethoxyethane (2 mL). After 1 h at -23°C, the reaction was stirred at room temperature for 24 h.

The filtered solution was concentrated, redissolved in methylene chloride (30 mL), glacial acetic acid (1mL) was added and the solution was washed with 10% Na_2CO_3 (10 mL), 5% HCl (10 mL), water (2x10 mL), saturated KCl solution (10 mL) and dried. Removal of the solvent afforded 920 mg of a

light yellow semi-solid. Flash chromatography on silica gel using chloroform:absolute ethanol (24:1) resulted in 20 mg (4%) odorinol (2) and epiodorinol (4) with the expected properties.

Odorinol (2) and Epiodorinol (4) from p-Methoxybenzyl Carbamate (50) using DCC (41)

p-Methoxybenzyl carbamate (50) (801 mg, 2.11 mmol) and anisole (3.00 g, 27.7 mmol) was dissolved in methylene chloride (3 mL) and cooled in an ice/salt bath. To this cool, stirred solution was added trifluoroacetic acid (2.0 mL, 3.0 g, 26 mmol). After 10 min the solvent was removed and the residue was extracted with pentane (3x25 mL).

The salt, as an oil, was diluted with methylene chloride (2 mL) and cooled in a dry-ice/carbon tetrachloride bath. To this stirred solution was added 2-hydroxy-2-methylbutanoic acid (84) (378 mg, 3.20 mmol), TEA (327 mg, 3.23 mmol) and DCC (673 mg, 3.26 mmol). After 1.5 h in the bath, the reaction was stored overnight at ca. -5°C.

In the work-up, the product mixture was diluted with methylene chloride (50 mL), filtered, shaken with glacial acetic acid (2 mL) to decompose the excess DCC, and washed with 10% HCl (10 mL), 10% Na_2CO_3 (10 mL), water (2x10 mL), saturated NaCl solution (10 mL) and dried.

Removal of the solvent afforded 900 mg of a semi-solid

material that was purified by flash chromatography on silica gel using ether/chloroform (10:1) as the solvent. The crude odorinol (2) and epiodorinol (4) (53 mg, 8%, mp 192.5-198.0°C) was triturated affording 13 mg (2%) white solid, mp 214-221°C, with the expected properties.

5-Methyl-5-ethyl-1,3,2-dioxathiolan-4-one-2-oxide (118)(54)
(2-Hydroxy-2-methylbutanoic Acid Anhydrosulfite)

Distilled thionyl chloride (10.0 mL, 16.7 g, 0.140 mmol, Fisher reagent) was cooled with an ice/salt bath to ca. -3°C and 2-hydroxy-2-methylbutanoic acid (84) (4.00 g, 33.9 mmol) was quickly added in one-portion with stirring. After 15 min, the reaction was connected to the house-vacuum via a Drierite trap and stirred for 7 h at -2 to +5°C. There was a slow foaming as gas was slowly released. The mixture, while still connected to the house-vacuum, was stored overnight in a refrigerator at 5°C and then allowed to slowly warm to room temperature.

The excess thionyl chloride was removed with warming under vacuum using a water aspirator and the crude product was distilled under vacuum affording 4.02 g (72%) 2-hydroxy-2-methylbutanoic acid anhydrosulfite (118) as a yellow liquid, bp 67-84°C/ 15-16 mm; lit. 60-61°C/9 mm or ca. 70°C/15 mm (54).

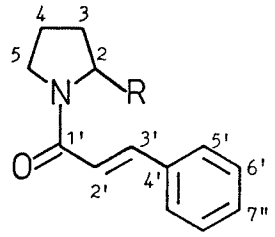
ir neat:

1251 cm	(s)	S=O
1726	(m)	C=O acid impurity due to hydroysis
1814	(v.s)	C=O

The ms was found to be complex probably due to the rapid hydrolysis that occurs.

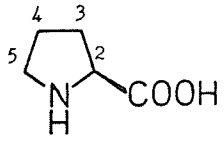
APPENDIX

The ^{13}C nmr spectral assignments are tabulated in this section. These spectra were assigned using the reported spectrum of odorine (1a) and epiodorine (3b) as a reference and with some simple additivity rules (65,66). For easy comparison, the spectra were divided into two parts, the N-cinnamoyl pyrrolidine ring and the functional group at the C2 position of the ring. Some of the compounds were numbered in a slightly different manner so that a uniform system could be used throughout this section.



123

As expected, the shifts of the pyrrolidine ring were very similar to that reported for proline (67).



C2	C3	C4	C5	COOH
61.1	29.2	23.9	46.0	174.1 ppm

The shifts calculated for the alkene carbons of cinnamic acid and ester are listed below together with the literature values for cinnamic acid (68).

		C2	C3
HOOC-CH=CH-Ph	calc.	116.3	144.3 ppm
	found	119.1	145.1
ROOC-CH=CH-Ph	calc.	118.3	142.3

One would expect the corresponding alkene carbons of N-cinnamoyl proline (7) and the other derivatives to also fall in this region and indeed two such signals were observed (Table 5). Massy-Westropp and coworkers (1) have also reported two signals at 118.2 and 143.0 ppm for natural (+)-odorine (1a) but incorrectly assigned these to C3′ and C2′, respectively (Table 6).

The unambigious assignment of the aromatic ring of the cinnamoyl group was more difficult. Since no substituent data was available for the -CH=CH-COOH group, the substituent effect was based on $-CH=CH_2$ and the resulting values calculated for styrene are shown in Table 4. The substituted carbon atom was predicted to occur the furthest downfield followed by the meta, para and ortho carbons, in that order. The assignment of the latter three carbons was tentative since they had such similar chemical shifts.

Most of the signals due to the functional group could be easily assigned. However, some overlap occurred with the benzyl 49 and anisyl 50 carbamates. The calculated values for benzyl alcohol and benzyl acetate, models for the carbamate group, are listed in Table 4. Again the

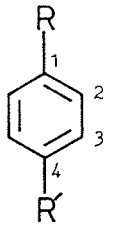
substituted aromatic carbon was shifted the furthest downfield and so was easy to assign in the benzyl carbamate 49. The ortho, meta and para carbons were all predicted to have very similar shifts and so could not be unambigiously assigned.

Similarly the substituted aromatic carbons of anisyl alcohol and anisyl acetate are shifted downfield and so stand out clearly in the spectrum of anisyl carbamate 50. The unsubstituted aromatic carbons fall in the same region found for the unsubstituted aromatic carbons of the cinnamoyl group and could not be assigned (Table 5).

The C2 of the 2-hydroxy-2-methylbutanoyl group in odorinol (2) and epiodorinol (4) was not observed (Table 6) and was probably buried under the chloroform-d signal at ca. 76.6, 77.0 and 77.5 ppm. The C2 of 2-hydroxy-2-methyl-butanoic acid (84) was found at 75.16 ppm.

The chemical shifts of the t-butyl 71 and anisyl 72 allophanates were found to be very similar to the carbamates as expected (Table 7). An extra peak which could not be assigned was found at 152-155 ppm in the anisyl carbamate/allophanate mixture.

TABLE 4. Calculated Chemical Shifts of Substituted Benzenes.



R (R′)	C1	C2	C3	C4		
$-CH=CH_2$ (H)	138.0[a,b]	126.5	128.7	128.0	CH CH_2	135.5 112.0
$-CH_2OH$ (H)	140.8[a] 140.5[b]	127.1 127.5	127.1 128.5	127.1 127.5	CH_2	64.5
$-CH_2O(CO)Me$ (H)	136.2[a]	128.5	128.5	128.5	CH_2	66.1
$-CH_2OH$ (OMe)	133.1[a,b]	128.1	112.7	158.5	CH_2 Me	64.5 54.1
$-CH_2OOCCMe$ (OMe)	128.5[a]	129.5	114.1	159.9	CH_2 Me	66.1 54.1

[a] Ref. 65.
[b] Ref. 66.

TABLE 5. Observed Chemical Shifts of N-Cinnamoyl Pyrrolidine Derivatives.[a]

	Z	81	48	49	50
Main skeleton					
C4	24.84	24.98 (22.86 17%)	21.63	21.49	21.38
C3	27.35	27.31 (32.07 14%)	34.72	34.61	34.52
C5	47.85	47.52 (47.19 15%)	45.81	45.87	45.82
C2	60.50	59.76 (61.36 16%)	64.41	65.03	65.02
C2′	116.52	117.87 (117.51 16%)	118.60	118.27	118.40
C5′	128.26	128.10	128.34	128.19 128.26	128.21 128.48
C7′	128.97	128.89	128.68	128.52 128.82	128.76
C6′	130.48	130.03	129.60	129.73	129.75
C4′	134.53	134.91 (134.69 21%)	135.24	135.13	135.15
C3′	145.11	143.37 (143.65 13%)	142.50	142.88	142.64
C1′	167.77	166.15	165.82	165.87	165.78
Functional group					
R	COOH	$CONH_2$	NHCOOt-Bu	$NHCOOCH_2Ph$	$NHCOOCH_2Ar$
C=O	172.31	173.69 (175.09 14%)	154.44	155.10	155.27
C1			80.23	66.89	66.49
C2			28.23	136.19	113.83
C3 & C4				*	*
C5				*	159.49
OMe					55.15

[a] The numbers in parentheses represent the chemical shift of a minor rotamer and the percent height relative to the corresponding peak of the major rotamer.

* These signal(s) overlap with the cinnamoyl aromatic ring.

TABLE 6. Reported and Observed Chemical Shifts of Odorine and Odorinol.[a]

	1a	3b	1 & 3	2 & 4	
Main skeleton					
C4	21.8	21.7	21.64	21.81	
C3	34.6	34.6	34.55 (34.65 88%)	34.64	
C5	46.1	46.2	46.11	46.04	
C2	62.8	62.7	62.71 (62.60 97%)	62.40	
C2′	118.2	118.2	118.05	118.12	
C5′	128.2	128.3	128.29	128.25	
C7′	128.8	128.8	128.84	128.80	
C6′	129.8	129.9	129.90	129.76	
C4′	135.4	134.9	134.87	134.97	
C3′	143.0	142.9	142.98 (142.85 71%)	142.80	
C1′	166.2	165.9	165.79	165.75	
Butanoyl group		$-\overset{1}{C}(CH_3)(R)\overset{2}{C}H_2\overset{3}{C}H_3$ R = H, OH			hydroxy acid
C1	175.9	175.7	175.58	174.43	181.91
C4	11.8	12.0	11.89	7.77	7.85
2-Me	17.4	17.4	17.33 (17.57 62%)	26.27	25.42
C3	27.1	27.3	27.22 (27.01 84%)	33.09	32.91
C2	43.3	43.1	43.15	*	75.16

[a] The figures in parentheses represent the chemical shift of the diastereomer and the percent height relative to the corresponding peak.

* This signal was hidden by the chloroform-d signal.

TABLE 7. A Comparison of the Chemical Shifts of the Carbamates and Allophanates.

	48	71	50	50 & 72
Main skeleton				
C4	21.63	21.77	21.38	21.36 21.57
C3	34.72	34.59	34.52	34.45
C5	45.81	45.89	45.82	45.83
C2	64.41	63.23	65.02	63.40 65.06
C2′	118.60	118.47	118.40	118.46
C5′	128.34	128.22	128.21 128.48	126.86 128.17
C7′	128.68	128.71	128.76	128.49 128.73
C6′	129.60	129.59	129.75	129.72 130.19
C4′	135.24	135.29	135.15	135.15
C3′	142.50	142.78	142.64	142.60 142.85
C1′	165.82	165.83	165.78	165.80
Functional group				
R	NHCOOt-Bu	NHCONHCOOt-Bu	NHCOOAr	NHCOOAr NHCONHCOOAr
C=O	154.44	152.47 153.20	155.27	152.26 154.27 155.47
C1	28.37	28.03	66.49	66.47 67.81
C2	80.23	83.24	113.83	113.82 114.01
C3 & C4			*	*
C5			159.49	159.47 159.92
OMe			55.15	55.14

* These signal(s) overlap with the cinnamoyl aromatic ring.

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PART 2.

CARBAZATE OXIDATION.

INTRODUCTION

The selective replacement of the hydroxyl group by hydrogen is an increasingly important transformation in organic chemistry. Deoxy compounds often have higher biological activity than the corresponding hydroxy precursors which are more readily deactivated by enzymatic action (1). Efficient methods of deoxygenation also allow the use of carbohydrates as cheap starting materials in the synthesis of complex compounds; the so-called chiro-economic synthesis (2).

Many methods have been and are constantly being developed for the reduction (deoxygenation) of alcohols (3). One of the oldest involves heating the alcohol with hydrogen iodide and phosphorus for several hours at 150-240°C in a sealed tube (4). These conditions are obviously too extreme to be used with most complex molecules although it has the potential of becoming a useful method for the conversion of cellulose to hydrocarbons for use as a fuel (5).

For the purpose of this discussion, deoxygenation can be divided into two categories depending on if the alcohol is or is not activated by the presence of a stabilizing group. Activated alcohols, for example tertiary, allylic, benzylic, α-keto, can be deoxygenated directly and relatively specifically by a number of methods. These include hydrogenolysis, reduction with metal hydrides, dissolving metal and electrochemical reactions.

Activated		Unactivated
tertiary	$RR'R''C-OH$	$R-(CH_2)_n-OH$
allylic	$RR'C=CH-CH_2-OH$	
benzylic	$Ph-CH_2-OH$	
α-keto	$R-(CO)-CH(OH)-R'$	

direct & relatively specific methods of deoxygenation

examples:

-hydrogenolysis (H_2/catalyst)

-metal hydrides ($LiAlH_4$,$AlHCl_3$)

-dissolving-metal

-electrochemical

indirect methods of deoxygenation

formation of a reactive derivative

examples:

-oxidation to aldehyde or ketone & Wolff-Kishner or Clemmensen reduction

-dehydration & hydrogenation

-conversion to halide or sulfonate & displacement with hydride

SCHEME 1.

Convential Methods for the Deoxygenation of Alcohols.

Unactivated alcohols can normally only be reduced indirectly through some type of 'reactive' derivative. The methods used include the oxidation to a ketone or aldehyde and reduction by a Wolff-Kishner (hydrazine/base) or

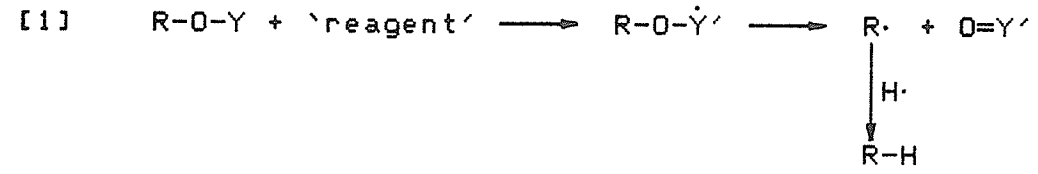
Clemmensen reaction (HCl/Hg-Zn), and dehydration and hydrogenation especially for tertiary alcohols. However, the most common technique is to convert the alcohol into the corresponding halide or sulfonate and then displace these good leaving groups with hydride.

Such nucleophilic displacement reactions are useful with simple, sterically unhindered alcohols but complex, polyfunctional compounds with sterically hindered hydroxy groups pose problems. In these ionic reactions, the reactants and intermediates are highly solvated and S_N displacement reactions only take place in low yields if at all due to steric hindrance and dipole repulsion. Rearrangements and eliminations are also common side reactions when carbocations are intermediates.

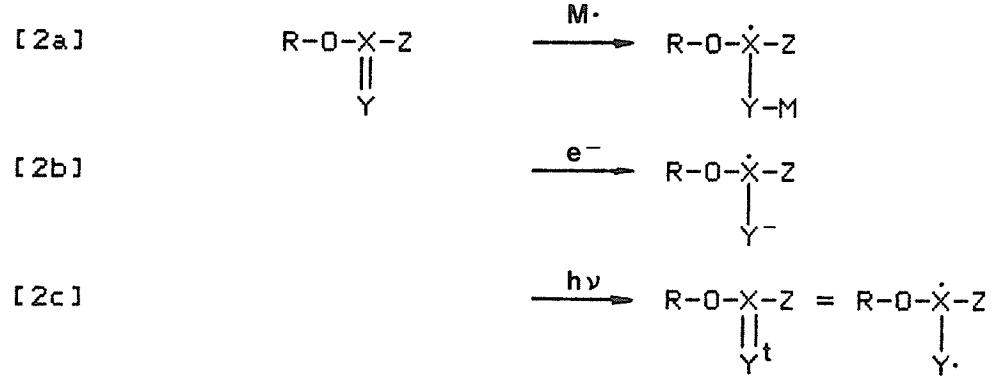
Neutral reactions avoid these difficulties and radical type reactions have been successfully used in the deoxygenation of complex alcohols. Radicals are less susceptible to steric factors since they are not solvated and can be produced under neutral conditions. A complete review on the radical deoxygenation of alcohols by Hartwig has recently appeared in the literature and a brief outline will be given here (6).

Radical deoxygenations involve the homolytic cleavage of a C-O bond in a suitable derivative of the alcohol. This is carried out by first converting this derivative to a radical by some means which then fragments by β-cleavage forming an alkyl radical. Abstraction of a hydrogen atom

from a suitable donor then produces the hydrocarbon.

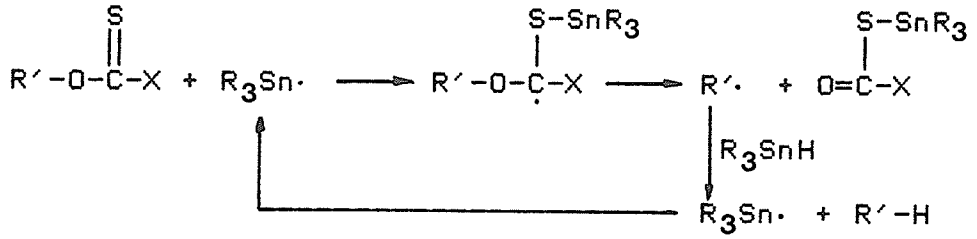


Activation is usually as a carbonyl derivative and the radical can be produced in three general ways; by the addition of a radical [2a], electron transfer [2b] or the photochemical excitation of this group to a triplet state [2c]:



The Barton-McCombie reaction is one of the most familiar and useful of these reactions (7). Here an O-alkylthiocarbonyl compound is reacted with a trialkyltin radical which is capable of forming a stable bond to sulfur (Scheme 2). Fragmentation forms the radical on carbon with the conversion of the C=S to a C=O bond being the driving force of this cleavage. Abstraction from a hydrogen atom donor, in this case a trialkyltin hydride,

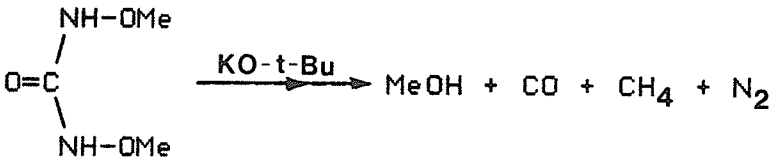
affords the reduced alcohol.



SCHEME 2. The Barton-McCombie Reaction.

While many neutral methods of deoxygenation are now available, new reactions are always of interest since they may have unique properties.

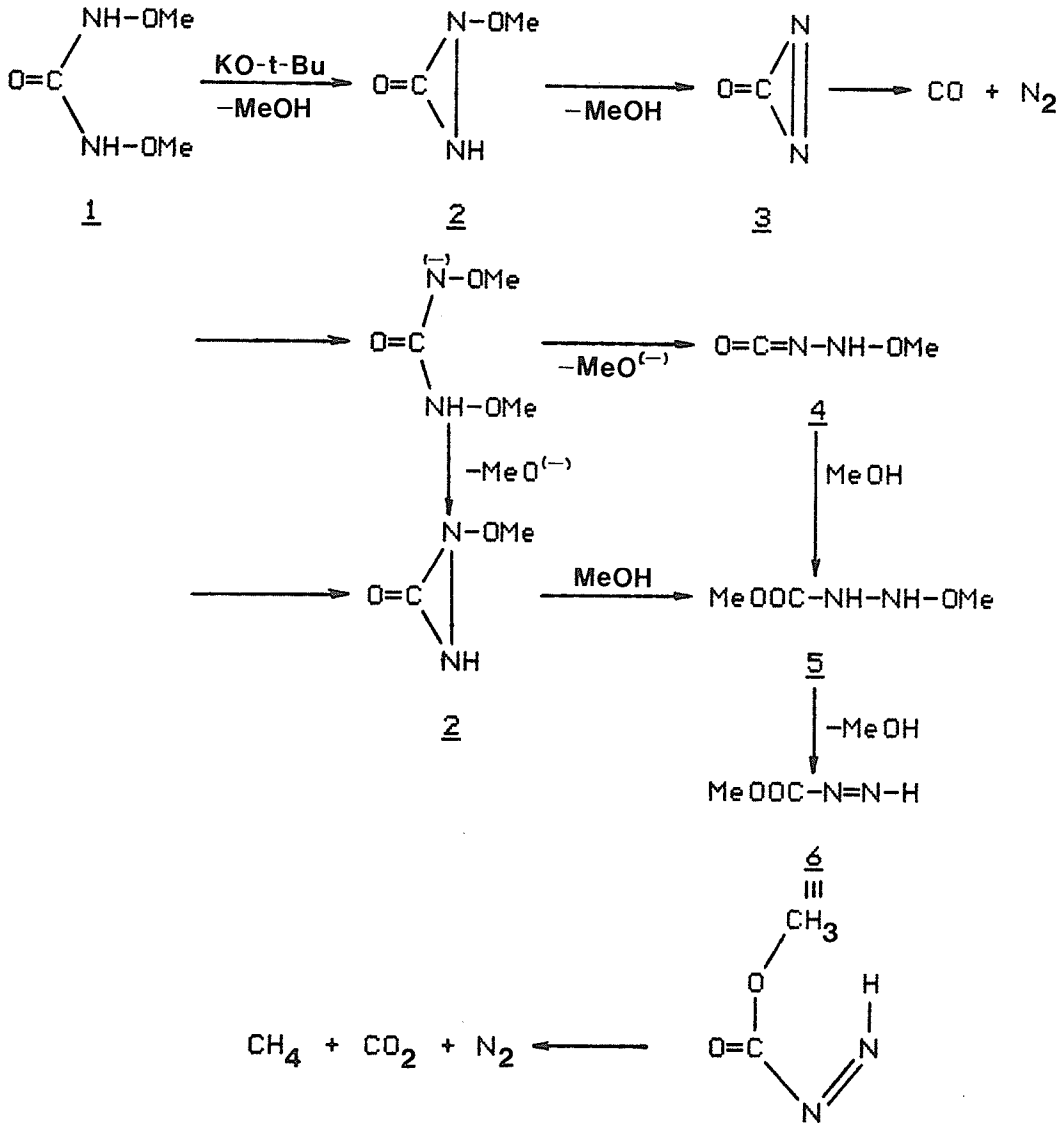
Ohme and Preushof have discovered a reaction that has the potential of becoming another such method of deoxygenation (8). These workers published a report in 1970 on the mechanism of hydrazine formation from urea. Among their findings they reported that N,N′-dimethoxyurea (1), in contrast to other ureas, does not form a hydrazine on treatment with potassium t-butoxide. Instead methanol, carbon monoxide and methane were formed presumably along with nitrogen.

[3] 

1

Apparently the carbon monoxide came from the

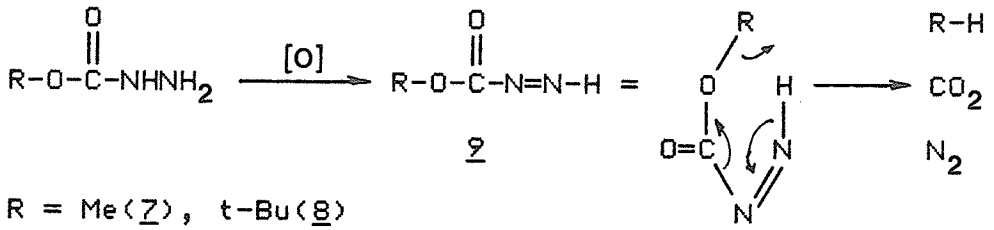
decomposition of the diazirinone 3 formed by cyclization and loss of two moles of methanol (Scheme 3). This was analogous to earlier work of Ohme and coworkers on the base decomposition of N,N′-dichlorourea to carbon monoxide and nitrogen (9), and of N,N′-dimethoxysulfamide to sulfur dioxide and nitrogen (10).



SCHEME 3. The Decomposition of N,N′-Dimethoxyurea.

A cyclic rearrangement of the diazene 6 (also called a diimine or diimide) was suggested to have been the source of the methane. The proposed mechanism involved the loss of methanol from the urea 1 to form an isocyanate 4 in a Hofmann-like rearrangement or the formation of an intermediate three-membered ring 2, a diaziridinone. Other N-substituted ureas have been observed by these workers to rearrange by these two pathways on treatment with hypochlorite. When possible, the major pathway was found to be via the isocyanate (8). Further reaction with methanol would form the methyl 2-methoxycarbazate (1-methoxyhydrazine-2-carboxylic acid methyl ester, 5) which would be the source of the diazene 6 on elimination of methanol.

To further establish this mechanism, methyl and t-butyl carbazate (7 and 8, respectively) were oxidized with chromium (IV) oxide, potassium permanganate and alkaline potassium ferricyanide. According to these workers, methane and iso-butane were formed in all cases independent of the solvent. The rearrangement of the diazene 9 was again suggested to be the source of these hydrocarbons (Scheme 4). No other details accompany these qualitative results but nitrogen and carbon dioxide are also presumably formed. One can only speculate if any carbon monoxide was a product of this oxidation.

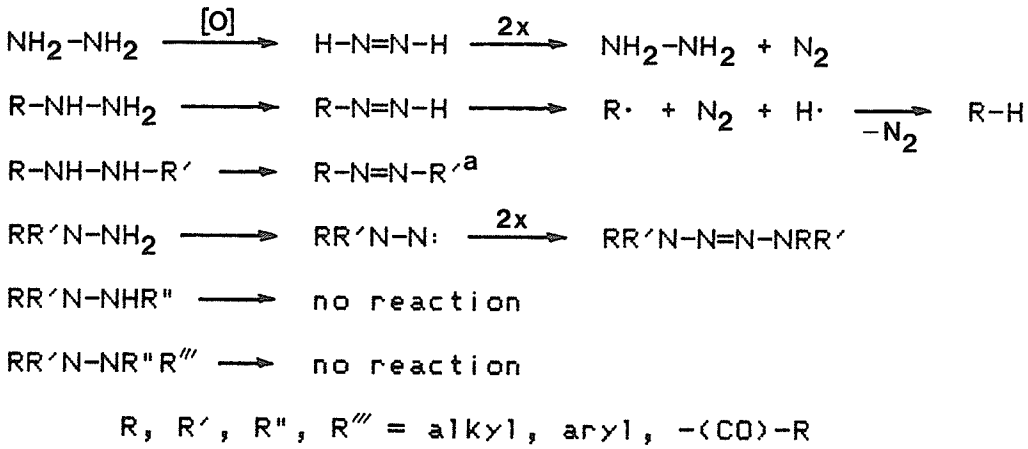


R = Me(7), t-Bu(8)

[O] = CrO_3, $KMnO_4$, alkaline $K_3Fe(CN)_6$

SCHEME 4. Proposed Oxidative Decomposition of Carbazates.

Much work has been reported on the oxidation of hydrazine and its derivatives (11). Azo compounds are usually formed by this oxidation if the substitution on the hydrazine allows it. The stability of the resulting compounds depends on the reaction conditions and the substituents on the azo compound. Scheme 5 gives a brief, simplified outline of the initial products obtained by the oxidation of various types of hydrazines.



R, R′, R", R‴ = alkyl, aryl, -(CO)-R

[a]Hydrogen peroxide and peroxy compounds can cause slow further oxidation to azoxy compounds.

SCHEME 5. General Oxidation Pattern of Various Hydrazines.

Considerable related work has been carried out on the oxidation of acid hydrazides. At the turn of this century, Curtius found that acid hydrazides were oxidized by iodine to the corresponding diacylhydrazines (12):

[4] $$R(CO)NHNH_2 \xrightarrow{I_2} R(CO)NHNH(CO)R$$

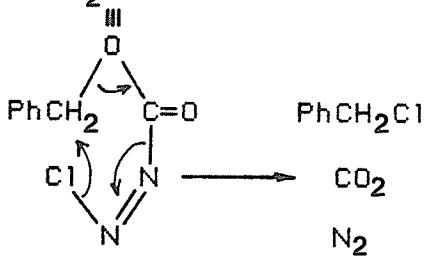
Many years later, Carpino found that treatment of an acid hydrazide in nitromethane or methylene chloride with hydrogen chloride gas followed by chlorine formed the acid chloride in good yields (13):

[5] $$R(CO)NHNH_2 \xrightarrow{HCl} R(CO)NHNH_3Cl \xrightarrow[48\text{-}79\%]{2Cl_2} R(CO)Cl + N_2 + 4HCl$$

Benzyl carbazate hydrochloride did not afford the expected benzyl chloroformate but benzyl chloride instead (76%). Under the reaction conditions (ice-bath temperature) the benzyl chloroformate was stable toward the loss of carbon dioxide. Carpino suggested the benzyl chloride was formed because of the special geometry that could be achieved by the intermediate from the oxidation. He proposed a chloroazo compound 10 which could decompose through a six-membered cyclic transition state.

[6] $PhCH_2OOCNHNH_3Cl + 2Cl_2 \xrightarrow{//} PhCH_2OOCCl + N_2 + 4HCl$

$\longrightarrow PhCH_2OOC\text{-}N{=}N\text{-}Cl$



10

The acid chlorides formed from the other hydrazide hydrochlorides are presumably also formed via the chloroazo compound 11 by an undetermined mechanism.

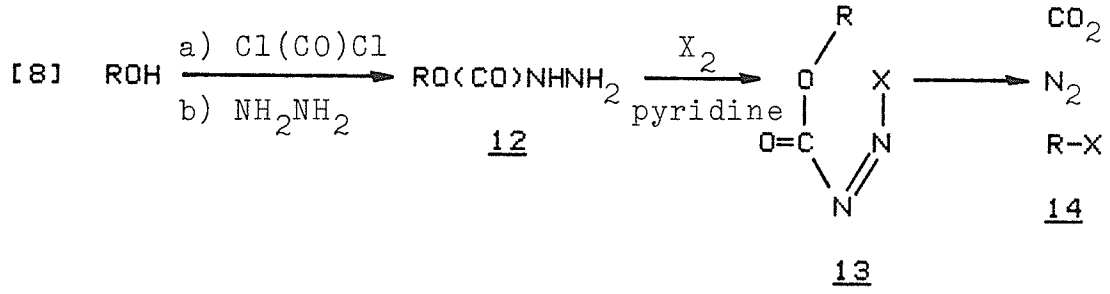
[7] $R(CO)NHNH_3Cl + 2Cl_2 \xrightarrow[-4HCl]{} R(CO)N{=}NCl \longrightarrow R(CO)Cl + N_2$

11

The initial formation of the hydrochloride salt must prevent the production of the diacylhydrazine by decreasing the nucleophilicity of the hydrazine group. This would hinder reaction of the unoxidized hydrazide with the acid chloride or an intermediate of the oxidation. Such intermediates have in fact been found to have acylating properties. Wolman and coworkers have reported the formation of amide bonds under similar oxidative conditions (14). An acid hydrazide in the presence of an amine was treated with various oxidizing agents, including halogens, forming the amide in good yields. Presumably the hydrazide was preferentially oxidized to a diazonium salt or azo intermediate which then reacted with the amine to

form the amide bond with the evolution of nitrogen. The diacylhydrazine was formed by acylation of the unreacted hydrazine when no amine was present and to a small extent in its presence. This method was used by these workers to prepare several peptides.

Clive and Denyer have also investigated the oxidation of hydrazine derivatives, in this case carbazates 12, with a positive source of halogen [8] (15). They too suggest the formation of a haloazo intermediate 13 which could fragment in various ways including the above mentioned pericyclic process forming an alkyl halide 14 plus carbon dioxide and nitrogen.



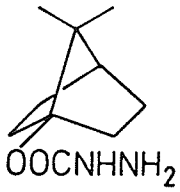
Adamantyl carbazate (15) afforded fair yields of the corresponding bromide and iodide on treatment with N-bromosuccinimide (NBS) and N-iodosuccinimide (NIS), respectively, but none of the chloride was obtained with N-chlorosuccinimide (NCS). Cyclohexyl carbazate (16) was oxidized under similar conditions and a substantial amount of the trans-1,2-dibromocyclohexane was obtained in addition to the cyclohexyl bromide. The dibromide was

probably formed from cyclohexene which may arise via the carbonium ion or by elimination in the azo intermediate. Thus this replacement of the $-OOC-NHNH_2$ group by halogen is limited to compounds where olefin formation is difficult.

This reaction can also be used to carry out a substitution at a bridgehead position. Thus 1-iodoapocamphane was obtained in 39% yield from the oxidation of 1-apocamphanyl carbazate (17) with iodine-pyridine. Normal nucleophilic substitution is very difficult at the bridgehead position of the bicyclo[2,2,1]heptyl system.

TABLE 1. Oxidation of Alkyl Carbazates with a Positive Source of Halogen.

R	Oxidant	%Yield R-X
adamantyl(17)	NBS[a]	49%
	NIS[b]	63
	NCS[c]	--
cyclohexyl(16)	NBS	42[d]
	NIS	39
1-apocamphyl(17)	I_2/pyr[e]	39



17

[a]N-Bromosuccinimide. [b]N-Iodosuccinimide. [c]N-Chlorosuccinimide. [d]1,2-Dibromocyclohexane also formed (38%). [e]Pyridine.

Thus the six-membered pericyclic rearrangement has been suggested to occur with both hydrogen and halogen as nucleophiles, structures 9 and 13.

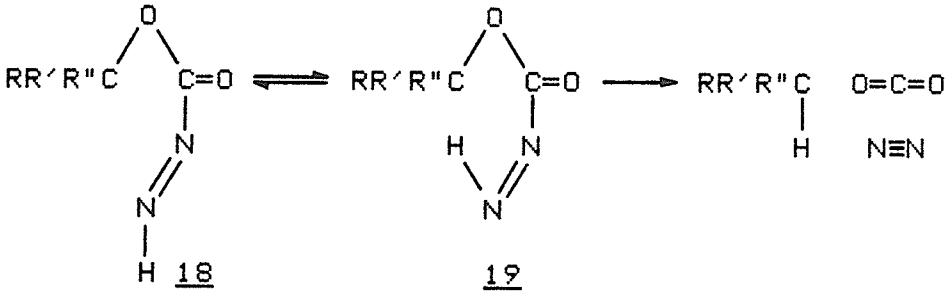
Let us examine this suggested rearrangement of the diazenes 9 and 13 in more detail. Such a rearrangement can be considered in terms of Baldwin's rules for ring closure (16). These rules examine the geometry of the transition state for intramolecular ring closure to see if a reaction will be 'favored' or 'disfavored'. If the transition state cannot be attained without serious distortion of the normal bond angles or distances then ring closure will occur only with difficulty or not at all and the reaction is then 'disfavored'. While the cyclic rearrangement under consideration is strictly not a ring-closure the same geometric constraints should be required. Baldwin, in fact, has applied these rules to a similar rearrangement (16).

These rules are based on the geometry required for nucleophilic attack at a carbon atom. For a tetrahedral carbon, as in this case, the optimum direction of approach by the nucleophile is backside attack opposite the leaving group at an angle of 180° resulting in the inversion of the carbon center. This is the well-known Walden inversion of the S_N2 reaction. According to Baldwin's nomenclature the rearrangement under consideration is a 6-Endo-Tet reaction: a six-membered ring is being formed or in this case a six-membered transition state, the bond being broken as a

result of the nucleophilc attack is part of the 'ring' being formed (endo), and the electrophilic carbon is tetrahedral. Such reactions are disfavored according to the empirical rules developed by Baldwin.

The same conclusion can be reached if one simply inspects a model of this azo intermediate; the optimum geometry for inversion at the carbon atom cannot be easily attained.

It should be noted that azo compounds exist as both the cis and the more stable trans isomers (19 and 18, respectively) (17). Obviously only the cis structure is suitable for the rearrangement.



SCHEME 6.

Disubstituted trans-azo compounds can be isomerized photolytically to the less stable cis-azo compounds some of which can thermally reisomerize back to the trans isomer (18). The parent compound (diazene) is believed to be a mixture of the cis and trans isomers which can rapidly equilibrate (19). Therefore it is likely that the diazenes 18 and 19 also exist as an equilibrium mixture so that the

necessary cis isomer will be present in the reaction mixture.

Baldwin's rules also only apply when the nucleophilic atom is a first row element of the periodic table. The larger atom radii and bond distances of the atoms of the second row may remove the geometric restraints of a disfavored ring closure. Thus the cyclic rearrangement of of the haloazo compound 13 suggested by Clive and Denyer may in fact be favored for bromine and iodine. The reason no adamantyl chloride was obtained could be due to the smaller chlorine atom which cannot attain the proper geometry. However, this is inconsistent with the formation of the benzyl chloride observed by Carpino.

Another constraint given by Baldwin is that these rules apply only for ring closures in which inversion of the carbon atom occurs. Thus, "these Rules may not apply to concerted electrocyclic processes in which geometric changes other than inversions are often observed" (16).

Both rearrangements are calculated to be exothermic from the energies of the bonds made and broken (Table 2). Since the change in entropy is expected to be positive, the reaction will be favored thermodynamically. Of course this gives no indication of the rate at which this reaction will proceed, i.e., if there is an accessible low-energy pathway that the reaction can follow.

Thus, there is some question whether the cyclic rearrangement proposed by Ohme and Preushof is actually

occurring in the oxidation of carbazates. However, as long as a hydrocarbon is formed then this reaction could still be used as a method of deoxygenating alcohols. The reaction may proceed by a different mechanism, for example by a stepwise fragmentation or an intramolecular reaction.

TABLE 2. Enthalpy Change Associated with the Rearrangement of the Diazene.[a]

$RR'R''C\underline{-}O\text{-}(CO)\underline{-}N{=}N\underline{-}X \longrightarrow RR'R''C\underline{-}X + O\underline{=}C{=}O + N\underline{\equiv}N$

X=H

Bonds broken:		Bonds formed:	
$C\text{-}O_\sigma$	80	$C\text{-}O_\pi$	100
$C\text{-}N_\sigma$	75	$N\text{-}N_\pi$	125
N-H	95 /250	C-H	95 /320

$-\Delta H = +320-250 = +70$ kcal/mol

X=Halogen

Bonds broken:		Bonds formed:	
$C\text{-}O_\sigma$	80	$C\text{-}O_\pi$	100
$C\text{-}N_\sigma$	75	$N\text{-}N_\pi$	125
N-Cl, -Br, -I	ca.60[b] /215	C-Cl	82 /307
		-Br	69 /294
		-I	53 /278

$-\Delta H = +(278 \text{ to } 307)-215 = +(63 \text{ to } 92)$ kcal/mol

[a]Ref. 20. [b]Ref. 21.

For this oxidation to become a convenient method of deoxygenation we also required a convenient, general synthesis of carbazates. Carbazates have been prepared in numerous ways all of which involve the displacement of a good leaving group from a carbonate derivative (Table 3). We were interested in a method of preparation that would involve the treatment of the alcohol with a reagent to form the carbonate derivative which then could be reacted further with hydrazine to yield the carbazate. As seen

TABLE 3. Literature Preparations of Carbazates.[b]

$$RO(CO)X + NH_2NH_2{}^{a} \longrightarrow RO(CO)NHNH_2 + HX$$

X=	R= , % Yield						
	Me	Et	Ph	Bz	t-Bu	1-Ad	Other
Cl	45(49)[c,20]			(89-93)[c,21]		62[23]	
				46(76)[c,22]			
OR	90-95[24]	90[24,32]	58[25,32]	73[27,28]			Ref.26,34
	90[25]			(46)[c,29]			
				71[32]			
OEt							Ref.32
OCH_2Ph					64[27]		
OPh					89-97[31]		
$OC_6H_4NO_2$[d]					72[32]	47[23]	
OC_6Cl_5					72[33]		Ref.35
SMe					72-86[34]	60[23]	
Im[e]					82[35]		

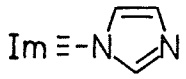
[a] May be hydrate. [b] References are indicated. [c] As salt. [d] 4-Nitrophenyl. [e] Imidazole.

above phosgene is the simplest reagent but it is inconvenient to use because of its toxicity and low boiling point. A nontoxic, stable crystalline reagent would be much nicer to work with.

1,1′-Carbonyldiimidazole (CDI, 20) prepared by the reaction of phosgene with imidazole is such a reagent (38). Alcohols and phenols react with CDI under the influence of heat or a catalyst to give an 1-alkoxy- or 1-aryloxy-carbonyl imidazole (21).

[9] CDI + ROH $\xrightarrow[-\text{ImH}]{}$ Im-CO-OR $\xrightarrow[-\text{ImH}]{R'NH_2}$ ROOC-NHR′

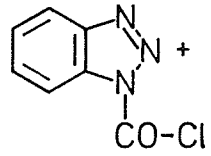
20 21

CDI = Im-CO-Im. Im ≡ 

The sodium salt of the alcohol or of imidazole can be used as a catalyst and then the reaction is exothermic and proceeds at room temperature. Excess alcohol must be avoided, except in the case of t-butanol, since this will result in further reaction and the formation of the carbonate. The t-butyl carbonate is formed only on extended heating, six hours at 65°C, in the presence of one of the above mentioned catalysts. The alkoxycarbonyl imidazole compounds react quickly with the nucleophilic hydrazine to form the corresponding carbazates.

A similar compound, 1H-benzotriazole-1-carbonyl chloride (BTCOCl) (22), has been described by Butula and

coworkers (39). BTCOCl is a crystalline low melting solid prepared by the reaction of excess phosgene with benzotriazole (BTH). This compound reacts with alcohols and phenols without a catalyst to give 1-alkoxy- or 1-aryloxycarbonyl benzotriazoles (23) which are more stable to hydrolysis and alcoholysis than the imidazole analogs. Unreacted material was recovered after heating such compounds in ethanol (96%) for five hours (40). This stability could be advantageous especially if these compounds are to be isolated. These compounds will, however, react quickly with strong nucleophiles like amines, hydrazines and semicarbazides. Butula and coworkers have prepared 2-phenyl ethylcarbazate by this method but have not applied this synthesis to the preparation of unsubstituted carbazates (40).

[10]  + ROH $\xrightarrow{-HCl}$ BT-CO-OR $\xrightarrow[-BTH]{R'NH_2}$ ROOC-NHR′

BTCOCl, 22 23

Thus we set out to see if BTCOCl could be used as a general reagent for the preparation of carbazates. We then investigated the behaviour of several carbazates under various oxidative conditions. Initial investigations were carried out on benzyl carbazate (24) and more detailed work was done on methyl (7), phenyl (25), benzyl (26) and 2-phenylethyl carbazate (27). We hoped to confirm the work

of Ohme and Preushof that the hydrocarbons are produced by the oxidative treatment of these carbazates. By optimizing the conditions we then intended to maximize the yield of the hydrocarbon. It was also hoped that we could shed more light on the mechanism of this reaction.

RESULTS

The results are presented in two sections: the preparation of the carbazates and the oxidation of these carbazates.

Preparation of the Carbazates

As discussed above, we were interested in using 1-benzotriazole carbonyl chloride (BTCOCl, 22) as a general reagent for the preparation of the carbazates. The synthesis of the commercially unavailable BTCOCl has been described by Butula and coworkers but only on a one gram scale which is not very useful when it is to be used as a reagent in multigram preparations (39). Therefore, it was important to develop a large scale synthesis of this compound which proceeds in high yield.

As a starting point, the two slightly different preparations described by these workers were simply scaled-up. Thus, phosgene gas (96.5 g, 0.420 mol) was added over 1.5 h to a solution of benzotriazole (BTH, 50.02 g, 0.420 mol) in toluene (1 L) at 60°C and then stirred another 2 h at this temperature. However, in addition to the wanted BTCOCl (44%), a large amount of benzotriazole hydrochloride (BTH.HCl, 46%) and some 1,1'-carbonyldibenzotriazole (CODBT, 9%) was obtained.

A scale-up of the other preparation afforded a higher yield of BTCOCl. Thus, BTH (100.0 g, 0.839 mol) suspended in ether (1.5 L) was slowly added to phosgene (208.5 g, 2.12 mol) in benzene (800 mL) at room temperature. A

quantitative yield of crude BTCOCl was obtained and recrystallization afforded the pure compound as a white solid in 94% overall yield.

This preparation was inconvenient however because of the large amount of solvents required due to the low solubility of BTH in ether and other organic solvents. We then tried adding solid BTH to a solution of phosgene in anhydrous toluene but again obtained a large amount of the salt (37%) along with the wanted product (63%). However, this salt could be avoided simply by using ether as the solvent in this latter preparation. Thus, solid BTH (25.03 g, 0.210 mol) was added to phosgene (45.9 g, 0.464 mol) in cool ether (500 mL) and stirred overnight affording 31.12 g (98%) crude BTCOCl. This crude material was found to be suitable for further reaction but could be purified by recrystallization from dry pentane. The ether must dissolve a small amount of the salt which then dissociates to HCl and free BTH and undergoes further reaction.

In the presence of triethylamine (TEA), BTCOCl reacted readily with most alcohols and phenols affording the crystalline 1-alkoxy- or 1-aryloxycarbonylbenzotriazole in good yields (Table 4). However, this reaction was slow with hindered alcohols, for example borneol and isoborneol reacted completely only after long reaction times affording oils which were difficult to purify. Distillation was not attempted with these compounds since these benzotriazole derivatives may be explosive; BTH has exploded in a large-

scale distillation (41). 1-Adamantanol did not react with BTCOCl at all and was recovered unchanged even after prolonged reaction times.

[11] $ROH + BTCOCl \xrightarrow[-TEA\cdot HCl]{TEA} ROOCBT \xrightarrow{NH_2NH_2} ROOCNHNH_2 + BTH$

TABLE 4. Preparation of Carbazates using BTCOCl.

R	% Yield ROOCBT		% Yield $ROOCNHNH_2$[a]		% Yield BTH
	crude	recryst	crude	recryst	recovered
$PhCH_2CH_2-$	97	70	--	69	41
$PhCH_2-$	--	85	--	79	50
Ph-[c]	--	84	--	14	76
$2,3\text{-}Me_2C_6H_3-$	91	72	68	36[b]	--
$2,6\text{-}Me_2C_6H_3-$	88	75	--	--	--
$CH_3(CH_2)_{11}-$	96	54	89	62[b]	--
$c\text{-}C_6H_{11}-$	89	30	74	36[b]	--

[a]Anhydrous hydrazine was used unless otherwise indicated. [b]Hydrazine hydrate was used. [c]Carbohydrazide also isolated (25%).

The 1-alkoxy- and 1-aryloxycarbonylbenzotriazoles reacted smoothly with hydrazine hydrate or anhydrous hydrazine at room temperature affording the corresponding crude carbazates in high yield. However, some difficulty was encountered in separating the BTH by-product from the carbazates due to the similar solubility properties these two compounds have. Both compounds are basic and so both

dissolve in aqueous acids to some extent. Most of the BTH could however be separated from the carbazate by extracting the slightly acidic BTH with aqueous base. The drawback of this base washing was that it was found to decrease the isolated yields of the carbazates, especially the low molecular weight ones because of their slight water solubilities.

Although hydrazine hydrate and anhydrous hydrazine both afforded the carbazates, the cleaner products were obtained when anhydrous hydrazine was used. Under these anhydrous conditions some of the BTH by-product precipitates out of solution leaving less behind in solution to be washed out. When the hydrazine hydrate was used no such precipitate was obtained and the crude carbazate was found to contain more BTH. In this situation some of the BTH must dissolve in the small residual aqueous layer while a considerable proportion remains behind in the organic layer.

The yield of phenyl carbazate from this method was found to be rather low (14%, Table 4). Carbohydrazide was also isolated (25%) in this reaction and a large amount of BTH was recovered (76%). A similar low yield of this carbazate was also obtained from the commercially available phenyl chloroformate (29%, Table 5). In contrast, benzyl and 1-adamantyl carbazate (25) were both obtained in fair yields from the corresponding chloroformate (68 and 78%, respectively). The loss of the phenolate ion must be

competing with the loss of the benzotriazole and chloride ions. It has in fact been used as a leaving group in the preparation of t-butyl carbazate from t-butyl phenyl carbonate (Table 3).

[12] $ROOCCl + 2NH_2NH_2 \longrightarrow ROOCNHNH_2 + NH_2NH_2{\cdot}HCl$

TABLE 5. Preparation of Carbazates via the Chloroformate[a]

R	%Yield
Ph-	29
$PhCH_2$-	68
1-Ad-	78

[a] Anhydrous hydrazine.

Oxidation Studies

Initial investigations were carried out with the commercially available benzyl carbazate which was treated with various oxidants under the typical conditions used with these reagents. It was immediately evident that this reaction was more complicated than expected since numerous compounds were formed and in no case was there any evidence by nmr of the formation of any toluene. Table 6 outlines the results from some of these experiments.

Some of these unexpected results were likely due to the method used to carry out these oxidations, ie. the addition of the oxidant to the relatively concentrated benzyl carbazate solution. Under these conditions high

TABLE 6. The Oxidation of Benzyl Carbazates.

Oxidant[a] (equiv.)	Exptl. Conditions	Products[b] (%Yield)
H_5IO_6[d,42] (1.5)	anhyd.ether 1h at 20°C	Bz-I (-)[c,f] PhCHO (trace)
$K_3Fe(CN)_6$[e,43] (3.0)	5% $NaHCO_3$/CHCl 2h at 20°C	PhCHO (trace)
$Hg(OAc)_2$[g,44] (2.0)	water 1h at 20°C	$(BzOOCNN)_2Hg$
$Pb(OAc)_4$[g,45] (2.5)	$CHCl_3$ 2h at 20°C	$BzOOCCH_3$ (65%)
MnO_2[d,g,46] (2.5)	pet.ether/$CHCl_3$ 1h at 20°C	Bz-Bz (ca.40%)
$C_5H_5NH^+ClCrO_3^-$[d,47] (1.5)	$CHCl_3$ 1.5h at 20°C	Bz-Bz (ca.10%) BzOOCNHN=CHPh(28,ca.25%) PhCHO (ca.20%)
$BaMnO_4$[48] (9.7)	$CHCl_3$ 2h at 20°C	Bz-Bz (ca.40%) BzOOCNHN=CHPh(ca.25%) PhCHO (ca.35%)

[a] References are indicated. [b] Identified by ^1H nmr.

[c] Bz = benzyl. [d] One unidentified compound also formed.

[e] Two unidentified compounds also formed. [f] Decomposes with the formation of iodine. [g] No benzaldehyde detected.

concentrations of unreacted carbazates, intermediates and products would be present in the reaction favoring the formation of bimolecular products. This would account for the observed formation of the 2-benyzloxycarbonyl benzaldehyde hydrazone. The bibenzyl was most reasonably formed by the dimerization of the resonance stabilized benzyl radical (49).

Since most of these oxidations gave rather complex mixtures another approach was required which would give a less complex product mixture. We concentrated on the use of barium manganate ($BaMnO_4$) since this mild, fairly selective oxidant was convenient to use and resulted in fairly clean product mixtures in the oxidation of the benzyl carbazate (48).

According to Ohme and Preushof the oxidation of methyl carbazate should afford methane, carbon dioxide and nitrogen (8). Some of the other possible products that can be envisioned include ethane (by analogy to the formation of bibenzyl), carbon monoxide, methanol, formaldehyde and formic acid. Since most of the potential products are gases, if the composition of the evolved gas is analyzed then the course of the reaction should be fairly easy to determine.

We followed this method of attack and developed a method of collecting and analyzing the gas produced by the oxidation of methyl carbazate. The apparatus used consisted of a two-necked Erlenmeyer flask fitted with a

pressure equalizing addition funnel and connected through a gas-bulb to an inverted graduated cylinder. In a reaction, the flask was loaded with the oxidant and solvent, and the carbazate solution was placed in the addition funnel. When an elevated temperature was required the reaction flask was placed in a hot wax bath at the appropriate temperature. The carbazate solution was then added dropwise to the stirring oxidant solution (or suspension) and the evolved gas passed through the gas-bulb into the inverted graduated cylinder (oxidation method A).

Later slight improvements were made resulting in oxidation method B. These included thermostatting the addition funnel and reaction flask at 40°C, and collecting the evolved gas over brine in a closed graduated cylinder. This cylinder had a leveling bulb attached to it so that the pressure in the cylinder could be equilibrated with atmospheric pressure. The temperature selected was somewhat arbitrary; this temperature was easy to attain with the apparatus at hand. A slightly elevated temperature was needed since some of the carbazates were found to have a rather low solubility in the organic solvents at room temperature and so this elevated temperature prevented precipitation.

The evolved gas was analyzed by gas chromatography (gc) initially on columns of 5 A molecular sieves and Porapak Q® (analysis method A), and later on 5 A molecular sieves and Chromosorb 102® columns (analysis method B).

These two methods also differed in the way the instrument response was calibrated. In method A pure gases were used giving calibration factors which corrected the areas of the peaks for the different response of the gases. In method B calibration was with mixtures of the gas of interest in another gas, usually nitrogen, yielding equations that gave the percentage of the gas directly from its peak area. With a knowledge of the volume of the gas, its composition, and assuming all the methyl carbazate had been oxidized, the percent yield of each gas could then be determined.

To confirm the work of Ohme and Preushof we oxidized methyl carbazate with potassium ferricyanide, potassium permanganate, and chromium trioxide under the usual aqueous conditions used with these oxidants (Table 7). However, no methane could be detected even though nitrogen was produced in almost quantitative yields so that at least in terms of the hydrazine group 'complete' oxidation must have been occurring.

A large amount of carbon dioxide (61-64%) was the only other gas detected with chromium trioxide under neutral or acidic conditions. Under neutral conditions the oxidation with potassium permanganate resulted in only a low yield (7%) of carbon dioxide which was increased tenfold when the reaction was carried out in the presence of dilute sulfuric acid. Hydroxide ion is produced with this oxidant under such neutral conditions resulting in the formation of the carbonate ion and thus decreasing the amount of carbon

TABLE 7. The Oxidation of Methyl Carbazate.[a]

Expt. No.	Oxidant (mmol)	Solvent[b]	Temp. (°C)	Time Addn. (min)	Analysis Method	Percent Yield (Error) Corrected N_2	Percent Yield (Error)[c] CH_4	CO	CO_2
Aqueous Conditions									
1	$KMnO_4$ (17.3)	water	22	22	B	94.7(8.8)	0	0	6.3(0.8)
						93.9(10.0)	0	0	7.1(0.9)
2	$KMnO_4$ (7.59)	toluene[i] 10% H_2SO_4	22	50	B	81.9(5.9)	0	0	71.8(5.5)
						80.2(6.8)	0	0	73.4(5.6)
3	CrO_3 (9.30)	water	22	15	B	96.7(7.1)	0	0	61.5(4.6)
						94.1(6.9)	0	0	64.2(4.8)
4	CrO_3[j] (7.50) 10% H_2SO_4	water toluene	22	16	B	107.9(7.1)	0	0	59.8(4.2)
						106.7(7.3)	0	0	61.0(4.3)
5[e]	$K_3Fe(CN)_6$ (22.6) KOH (47.2)	water	22	27	B	102.6(8.0)	0	3.6(0.7)	0
						102.4(8.0)	0	3.7(0.7)	0
Barium manganate in anhydrous aromatic solvents									
6[e,k]	$BaMnO_4$ (17.6)	toluene[m]	reflux (111)	135	A	78.8(7.8)	1.9(0.3)	19.3(2.4)	44.7(5.2)
7[d]	$BaMnO_4$ (17.6)	toluene	reflux (111)	27	B	75.9(5.5)	2.5(0.4)	16.0(2.7)	31.9(2.4)
8[n]	$BaMnO_4$ (17.4)	toluene	reflux (111)	20	B	54.8(5.0)	3.8(0.5)	16.3(2.7)	14.5(1.5)
9[d]	$BaMnO_4$ (16.9)	toluene	22	72	B	91.7(7.1)	1.8(0.6)	5.1(0.9)	18.3(1.7)
						90.5(7.4)	1.9(0.6)	5.3(1.0)	19.2(1.8)
10[e]	$BaMnO_4$ (17.5)	toluene PhSH[o] (7.79)	reflux (111)	28	B	27.8(5.2)	1.1(0.3)	7.9(2.2)	2.0(0.4)
11[l]	$BaMnO_4$ (17.4)	p-xylene	reflux (138)	105	A	113.6(22.1)	6.8(0.8)	4.7(0.6)	15.6(2.2)
12[d]	$BaMnO_4$ (17.9)	mesitylene[p]	reflux (165)	60	A	97.2(14.9)	12.9(1.1)	6.4(1.1)	21.8(3.6)
13	$BaMnO_4$ (17.4)	mesitylene Ph_2CH_2[q] (11.9)	reflux (165)	72	A	107.2(15.6)	17.2(1.3)	6.5(1.0)	25.0(2.6)

TABLE 7. (continued).

Expt. No.	Oxidant (mmol)	Solvent[b]	Temp. (°C)	Time Addn. (min)	Analysis Method	Percent Yield (Error) Corrected N_2	CH_4	CO	CO_2
14[e]	$BaMnO_4$ (19.7)	mesitylene Ph_2CH_2[f] (12.1)	reflux (165)	42	A	105.1(13.6)	18.0(1.5)	8.5(1.6)	28.7(3.5)
15[g]	$BaMnO_4$ (17.9)	decalin Ph_2CH_2[f] (11.9)	reflux (196)	30	A	74.0(8.6)	12.6(1.2)	10.0(2.3)	38.3(6.3)
16[h]	$BaMnO_4$ (17.7)	tetralin	reflux (208)	40	A	107.8(12.5)	2.7(0.3)	14.3(1.8)	0.9(0.1)
17[d]	$BaMnO_4$ (56.6)	tetralin	reflux (208)	5	A	84.2(8.0)	10.6(1.0)	10.9(1.3)	8.4(1.1)
18[f]	$BaMnO_4$ (18.0)	tetralin	22	45	B	61.6(9.1)	0	0	5.3(0.8)
19[f]	$BaMnO_4$ (18.5)	tetralin	120-125	20	B	79.8(8.7)	4.5(0.7)	5.3(1.6)	6.3(1.0)
20[e]	$BaMnO_4$ (17.6)	tetralin	140-144	15	B	73.8(7.3)	6.6(1.1)	8.3(1.3)	8.3(1.0)
21[d]	$BaMnO_4$ (17.5)	tetralin	174-179	14	B	83.3(8.5)	12.1(1.3)	9.0(1.7)	14.0(1.3)
22[e]	$BaMnO_4$ (18.1)	tetralin	188-197	8	B	93.9(8.6)	15.4(1.5)	7.5(1.3)	20.9(2.0)
Various oxidants in aromatic solvents									
23[d]	PTD[f] (17.1)	toluene	reflux (111)	31	B	ca. 58.8	0	0	trace
24[d]	$Hg(OAc)_2$ (17.8)	tetralin	141-146	24	B	84.9(7.3)	2.5(0.4)	32.4(4.3)	8.3(0.8)
25[d]	HgO (17.5)	tetralin	149-152	28	B	104.2(9.8)	2.4(0.5)	5.8(0.9)	8.4(1.5)
26[d]	LTA (17.5)	toluene	reflux (111)	24	B	78.7(6.4) 77.8(5.9)	1.9(0.4) 2.0(0.4)	0 0	60.5(4.6) 61.3(4.6)
27[d]	PCC[t] (16.8)	toluene	reflux (111)	20	B	79.6(7.1) 74.0(6.0)	3.9(0.9) 4.3(1.0)	7.4(1.4) 8.3(1.6)	35.1(2.9) 39.3(3.3)
28[f]	PDC[u] (16.9)	toluene	reflux (111)	32	B	101.0(9.0) 91.0(7.8)	0.5(0.3) 0.6(0.3)	12.4(2.1) 14.7(2.5)	39.2(2.9) 46.7(3.4)

TABLE 7. (continued).

Expt. No.	Oxidant (mmol)	Solvent[b]	Temp. (°C)	Time Addn. (min)	Analysis Method	Percent Yield (Error) Corrected N_2	Percent Yield (Error)[c] CH_4	CO	CO_2
29[v]	H_5IO_6 (16.7)	toluene	reflux (111)	63	B	99.9(8.2) 93.9(7.9)	0 0	4.2(0.6) 4.4(0.7)	89.0(5.9) 94.8(6.3)

[a] Except as noted 0.50 g (5.55 mmol) methyl carbazate used.
[b] The methyl carbazate was normally dissolved in 75 mL solvent and added dropwise to the oxidant in 50 mL of the same solvent.
[c] Corrected yields are given when the reaction was carried out under helium; correction for the leakage of air was not possible when the reaction was flushed with argon.
[d] 0.51 g (5.66 mmol) methyl carbazate consumed.
[e] 0.52 g (5.77 mmol) methyl carbazate consumed.
[f] 0.53 g (5.88 mmol) methyl carbazate consumed.
[g] 0.38 g (4.22 mmol) methyl carbazate consumed.
[h] 0.55 g (6.11 mmol) methyl carbazate consumed.
[i] Potassium permanganate in 10% H_2SO_4 (15 mL) and toluene (35 mL).
[j] Oxidant mixture consisted of 15.0 mL of 5% CrO_3 in 10% H_2SO_4 and 35 mL toluene.
[k] Ethane also produced, 0.9(0.1)%.
[l] Ethane also produced, 0.15(0.02)%.
[m] Methyl carbazate was dissolved in 50 mL toluene.
[n] Freshly prepared according to literature procedure, not as active as commercial material.
[o] PhSH (0.8 mL, 0.86 g, 7.79 mmol) added with carbazate, 3.67 g PhSSPh (94%) recovered from reaction.
[p] Methyl carbazate was dissolved in 100 mL mesitylene.
[q] Ph_2CH_2 added with carbazate.
[r] Ph_2CH_2 present with oxidant.
[s] PTD = 4-phenyl-1,2,4-triazoline-3,5-dione.
[t] PCC = pyridinium chlorochromate.
[u] PDC = pyridinium dichromate.
[v] Residue from reaction fairly clean, contains α, o- and p-iodotoluene (ca. 1:4:5.2).

dioxide collected (50).

The above two reactions carried out in the presence of acid, experiments 2 and 4, were two-phase oxidations with toluene as the second phase. It was hoped that some product could be recovered from the organic layer on the completion of the reaction. However, no material was found when the toluene was removed on a rotary evaporator showing that no high molecular weight products were formed under

these aqueous conditions.

In the oxidation with potassium ferricyanide/potassium hydroxide, the usual combination with this reagent (43), no carbon dioxide was detected and instead carbon monoxide (4%) was the only gas found along with the nitrogen. This suggested a different mechanism with this oxidant.

In initial experiments under very dilute aqueous conditions, the oxidation with potassium permanganate also formed a small amount of ethane together with nitrogen and carbon dioxide but again no methane was detected.

Thus, the rearrangement proposed by Ohme and Preushof does not in fact seem to take place. The formation of ethane under dilute conditions suggests the dimerization of the methyl radical as in the formation of the bibenzyl. If the methyl radical is an intermediate then in the presence of a hydrogen atom donor methane should be formed.

We repeated the oxidations in anhydrous toluene in which the methyl group can act as a source of the hydrogen atom forming the resonance stabilized benzyl radical (Table 7). Most of these studies involved barium manganate since it gave clean reaction products and it is known not to oxidize the benzylic position under the conditions used (48).

As can be seen in the table, a large amount of nitrogen was produced in most cases again indicating an essentially complete oxidation of the carbazate. Varying ratios of both carbon dioxide and carbon monoxide were

usually also evolved with the former normally produced in the larger amount. Under these anhydrous conditions a small amount of methane was also usually detected. In a few oxidations very small quantities of ethane were also found.

Thus, in contrast to the report of Ohme and Preushof the solvent does play a role and seems to be acting as a hydrogen atom donor. Presumably the yield of methane could be increased further by using an even better hydrogen atom donor. However, good hydrogen donors are normally incompatible with oxidizing agents, ie. they would be oxidized by these reagents instead of acting as a hydrogen atom donor. Thiols have been used as such donors (51) and when we repeated the reaction adding thiophenol (1.3 equivalents) with the carbazate we obtained a lower yield of all the gases. The near quantitative yield of diphenylsulfide (PhSSPh, 94%, recrystallized) recovered from the reaction seems to indicate that the thiophenol was being oxidizing faster than or competitively with the carbazate as expected.

We also investigated the temperature effect by carrying out the oxidation in refluxing p-xylene and mesitylene. The results are summarized in Table 7 and in the Diagram 1. As might be expected the increase in temperature tended to increase the yield of nitrogen and also increased the methane evolved while decreasing the yield of ethane. Interestingly, the yield of carbon

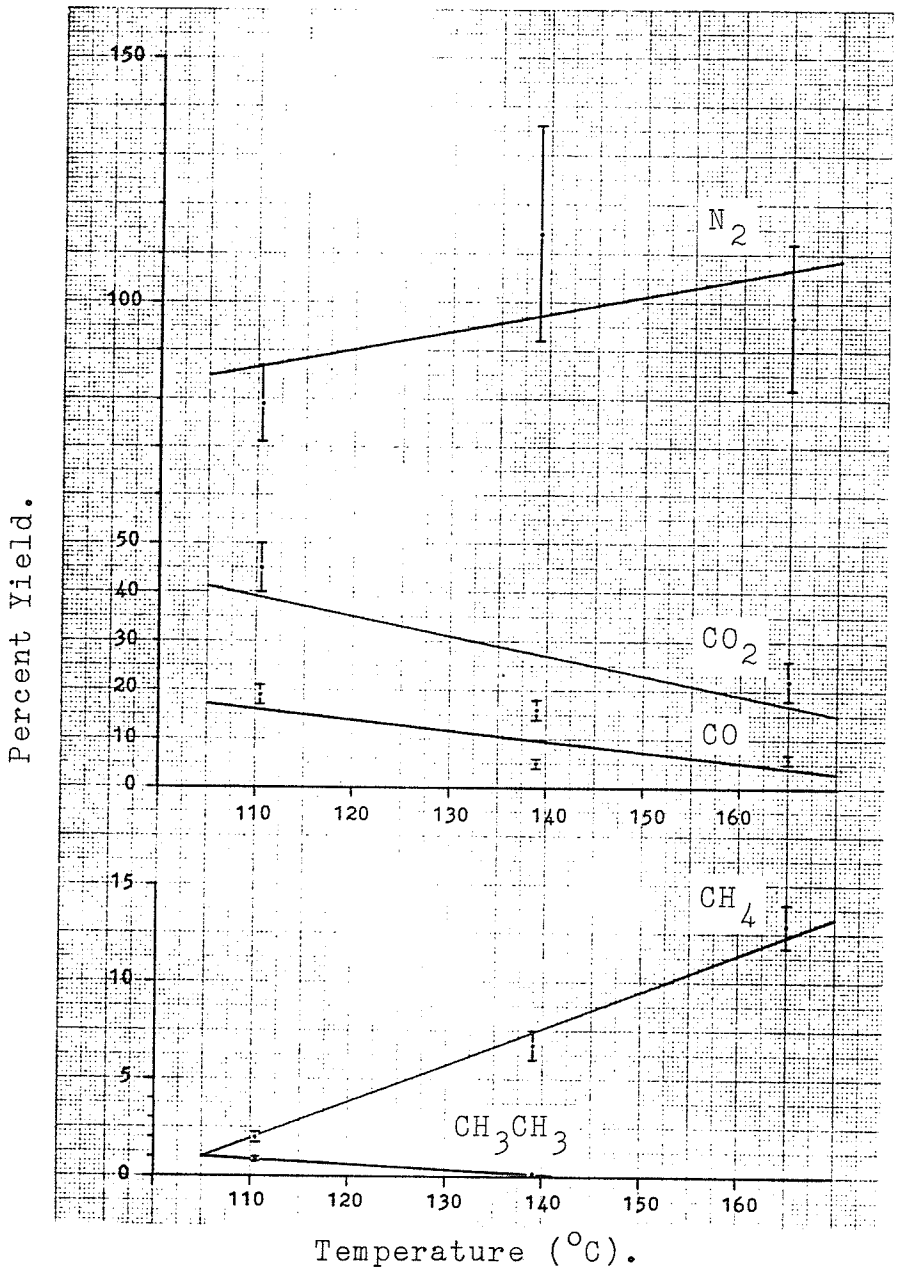


DIAGRAM 1. Methyl Carbazate Oxidation.
Barium Manganate in Various Solvents at Reflux.
(111°C=toluene, 138°C=p-xylene, 165°C=mesitylene.)

dioxide and carbon monoxide both decreased with this increase in temperature. One might have expected an increase in all the gases except ethane with an increase in temperature because of a more complete reaction and or

decomposition.

The oxidation in mesitylene was also repeated in the presence of diphenylmethane an even better hydrogen atom donor (52). As expected the largest increase in the yield of methane was obtained when this additive was present in the reaction mixture (experiment 14) rather than being added with the methyl carbazate (experiment 13). The higher concentration of diphenylmethane under the former conditions increases the probability of the methyl radical encountering the added hydrogen atom donor under these conditions.

Since the change in the solvents may have some effect on the results observed we also studied the temperature effect in tetralin. This is a good hydrogen atom donor (52) and has a high boiling point so it can be used over a wide range of temperatures. Table 7 and Diagram 2 summarize the results. Here an increase in the temperature resulted in the expected increase in the yields of all the gases. It should also be noted that at the higher temperatures the yield of methane and carbon dioxide were approximately equal. In the other solvents the yield of methane was usually considerably less than that of the carbon dioxide. As was usual with this oxidant the yield of carbon monoxide was always less than or equal to that of the carbon dioxide. Again, large quantities of nitrogen were produced except at the low temperatures. As shown on the graph the carbon dioxide and methane seemed to

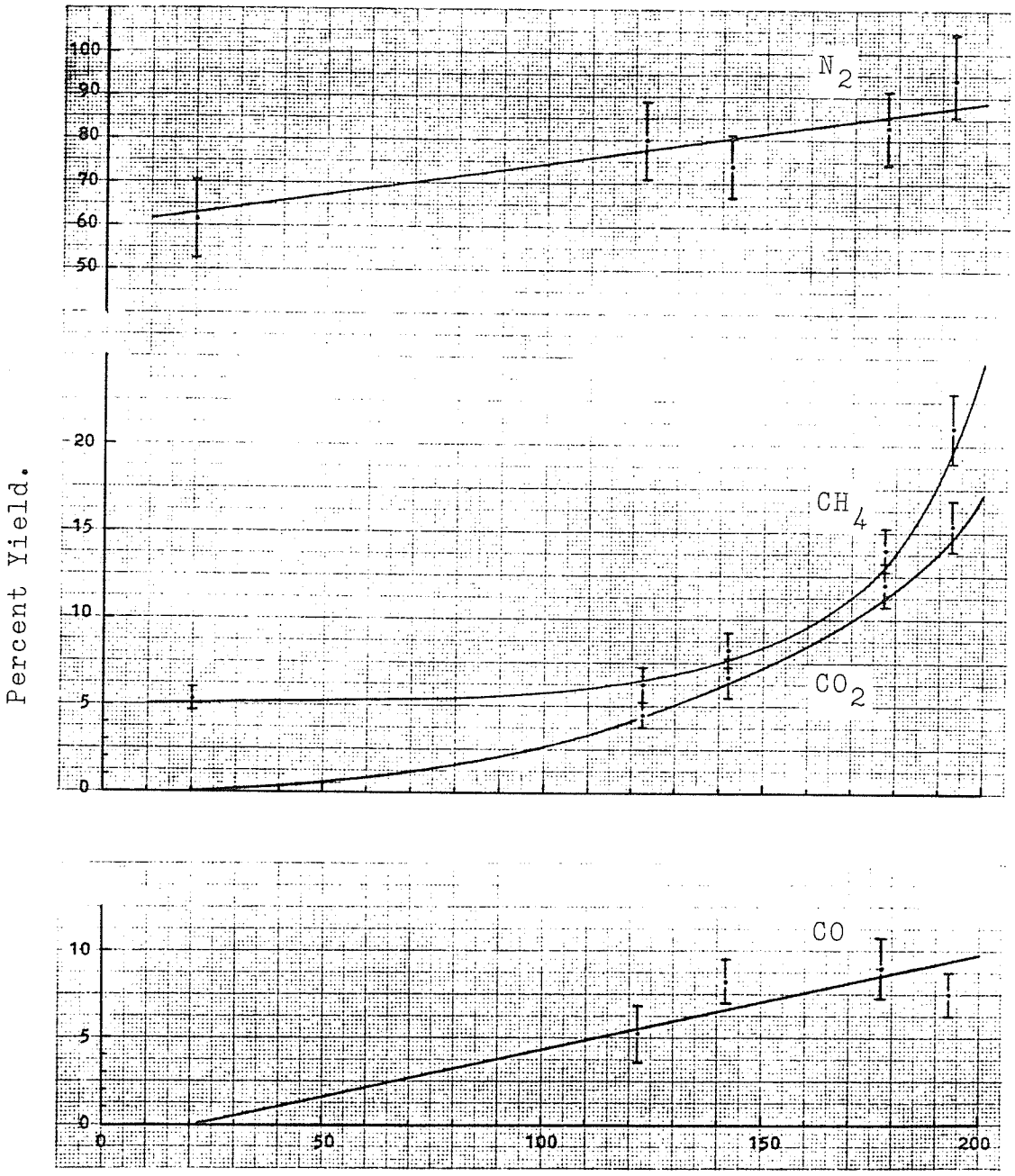


DIAGRAM 2. Methyl Carbazate Oxidation. Barium Manganate in Tetralin at Various Temperatures.

increase exponentially with temperature while the nitrogen and carbon monoxide increased linearly.

Table 7 also lists some of the other oxidants investigated in toluene and tetralin. Most afforded yields of gases similar tothose obtained from the barium manganate oxidations. However, the lead tetraacetate (LTA) oxidation (experiment 26) afforded no carbon monoxide even though a large amount of carbon dioxide was produced. A near quantitative yield of carbon dioxide was obtained with the periodic acid but no methane was produced (experiment 29).

These oxidations normally evolved near quantitative yields of nitrogen while the methane, carbon dioxide and carbon monoxide produced were usually much less than the theoretical amounts. Therefore, other nongaseous products must also be formed to account for this poor mass-balance. Thus, we repeated some of these oxidations in benzene and also analyzed the product solution by gas chromatography. Benzene was chosen as a solvent because we were hoping to trap the intermediate(s) with this molecule and fewer products can be anticipated in this solvent as compared to toluene. These reactions were carried out at 40°C with a thermostatted bath according to oxidation method B and the results are listed in Table 8.

The distribution of gases from the oxidation with barium manganate in benzene (experiments 31 and 32) was similar to that obtained in toluene (experiment 7). The warm carbazate solution (40°C) was also added to the

TABLE 8. Oxidation of Methyl Carbazate in Benzene.[a]

Expt. No.	Oxidant (mmol)	Time Addn. (min)	[toluene] $\times 10^{-4}$M (mg/L)	Percent Yield (Error)[b] Corrected Percent Yield (Error) N_2	CH_4	CO	CO_2	%Yield (Error) PhCOOMe $(PhCH_2)_2$ PhMe
30[c]	$BaMnO_4$ (33.6)	38	2.1 (19)	84.5(5.9) 84.0(5.8)	1.0(0.3) 1.0(0.3)	6.9(1.6) 7.0(1.7)	17.7(1.3) 18.1(1.4)	13.2(0.4)[d,e] ca.0.61 ca.0.16
31	$BaMnO_4$ (33.5)	54	1.7 (16)	89.5(5.2) 89.0(5.2)	0 0	17.3(2.0) 17.5(2.0)	23.9(1.4) 24.2(1.4)	14(2) ca.0.2 ca.0.4
32	$BaMnO_4$ (33.4)	56	4.4 (41)	94.2(3.9) 93.5(3.8)	0.6(0.2) 0.6(0.2)	12.7(1.9) 13.0(1.9)	25.9(1.8) 26.4(1.9)	13.2(0.4) 0.24(0.02) 0.46(0.09)
33	HgO (yellow) (33.4)	45[f]	1.7 (16)	71.4(4.6) 71.3(4.7)	0.6(0.2) 0.6(0.2)	0 0	1.8(0.2) 1.9(0.3)	1.66(0.04) 0 0
34	MnO_2 (115.4)	90	1.7 (16)	101.7(5.0) 100.8(4.5)	0 0	16.4(1.8) 16.7(1.8)	33.9(2.2) 34.5(2.2)	0.45(0.03) 0 ca.0.11
35	$KMnO_4$ (34.0)	144	1.7 (16)	ca.20	trace	0	trace	2.6(0.1)[e] ca.0.02 ca.0.03

[a] Methyl carbazate (1.00 g, 11.1 mmol) oxidized according to oxidation method B in benzene (100 mL) at 40 C with the oxidant in the same solvent (50 mL). The system was flushed with helium.
[b] Gas analysis by Method B.
[c] Reaction flask at room temperature.
[d] Diphenyl also identified, ca. 0.03%.
[e] One unidentified compound present in low concentration.
[f] Slow reaction, stirred another 180 min to ensure reaction was complete.

oxidant suspension at room temperature (experiment 30) and this was found to decrease the yield of all the gases except methane which increased slightly. The gc analysis of the product solution showed that methyl benzoate was the main product from all three experiments (13-14%). Small amounts of bibenzyl (0.2-0.6%) and toluene (0.2-0.5%) were

also identified. Toluene was present as a trace impurity in the benzene ($2-4x10^{-4}$M, 16-41 mg/L) to start with but a small amount were also produced by this reaction. Diphenyl and an unidentified product was also found in very low yields in the room temperature reaction (experiment 30). We attempted to analyze for methanol and methyl formate, other likely products, but these compounds could not be determined since they eluted with the solvent peak. We also analyzed for but could not detect any dimethyl oxalate.

Hydrazine compounds have been extensively oxidized with yellow mercuric oxide and manganese dioxide (11). We prepared these oxidants according to the literature procedures (53, 46) and repeated the oxidation in benzene. The mercuric oxide was found to react slowly and lower yields of nitrogen and carbon dioxide were obtained while no carbon monoxide was evolved. The low yield of methane was similar to that obtained from the barium manganate oxidations. Methyl benzoate was the only compound detected in the reaction mixture and in lower yields (ca. 2%). In contrast, the manganese dioxide seemed to be more active and afforded a more complete oxidation since the yield of nitrogen was quantitative. The yields of carbon dioxide and carbon monoxide were also higher than that from the barium manganate oxidation but no methane was produced. Again, methyl benzoate was the main compound in the reaction mixture but it was present in a very small

quantity (0.5%); a trace of toluene was also detected (ca. 0.1%).

The oxidation of methyl carbazate in benzene was also investigated with potassium permanganate. As expected, the oxidation was incomplete because of the low solubility of this reagent in benzene. Nitrogen was the only gas detected together with small amounts of methyl benzoate (3%) and trace amounts of bibenzyl (ca. 0.02%) and toluene (ca. 0.03%).

Methyl benzoate, the main compound found in these reaction mixtures, was likely formed by the aromatic substitution of the methoxy carbonyl radical (MeOOC·) or carbonium ion ($MeOOC^{(+)}$) on benzene, the solvent. This intermediate would be formed by the oxidation of the hydrazine moiety of the methyl carbazate and the eventual loss of nitrogen. To further study the nature of this aromatic substitution we repeated the oxidations in a mixed solvent, toluene/benzene and chlorobenzene/benzene. By determining the distribution of the isomeric benzoates and the relative yields of these substituted methyl benzoates vs. methyl benzoate one should be able to distinguish between a radical or ionic mechanism.

Both solvent mixtures afforded the typical mixture of gases obtained with the oxidation with barium manganate; a near quantitative yield of nitrogen (86-96%), some carbon dioxide (20-24%), less carbon monoxide (11-13%), and little or no methane (0-2%) (Table 9). Again, the main product in

TABLE 9. Oxidation of Methyl Carbazate in Mixed Solvents.[a,b]

Expt. No.	$BaMnO_4$ mmol	Time Addn. (min)	Ratio[d] Solvent Peaks After/ Before (Error)	Percent Yield (Error)[c] Corrected N_2	CH_4	CO	CO_2	%Yield (Error) PhCOOMe o-ArCOOMe m-ArCOOMe p-ArCOOMe
Toluene/benzene (equal volume)								
36	33.7	24	1.004	87.3(4.3)	1.2(0.3)	12.0(2.5)	21.7(1.8)	4.02(0.18)[e]
			(0.003)	86.1(5.8)	1.3(0.3)	12.4(2.6)	22.4(1.8)	3.00(0.11)
								1.29(0.05)
								0.92(0.03)
37	33.5	35	1.025	90.7(4.9)	1.5(0.3)	10.6(1.2)	20.2(1.5)	4.32(0.08)[f]
			(0.015)	90.2(4.9)	1.6(0.3)	10.7(1.2)	20.4(1.6)	3.19(0.13)
								1.45(0.13)
								0.93(0.05)
38	33.6 $Cu(OAc)_2 \cdot H_2O$ 11.3	60	1.007	90.5(3.8)	1.3(0.2)	16.1(2.0)	24.5(1.1)	2.14(0.29)[g]
			(0.008)	90.2(3.9)	1.3(0.2)	16.2(2.0)	24.6(1.1)	2.12(0.24)
								0.77(0.13)
								0.45(0.05)
Chlorobenzene/benzene (equimolar)								
39	33.3	73	1.007	95.6(4.7)	0	13.0(2.1)	24.3(1.3)	4.92(0.14)
			(0.030)	95.5(5.2)	0	13.1(2.1)	24.3(1.3)	2.59(0.15)
								1.61(0.16)
								1.05(0.12)

[a] Methyl carbazate (1.00 g, 11.1 mmol) oxidized according to oxidation method B in 100 mL solvent at 40°C with the oxidant in the same solvent.
[b] The system was flushed with helium.
[c] Gas analysis by analysis method B.
[d] Ratio of solvent peak areas after to before:
$[A(Ph\text{-}X)_{after} / A(Ph\text{-}H)_{after}] / [A(Ph\text{-}X)_{before} / A(Ph\text{-}H)_{before}]$
[e] Bibenzyl also formed, 0.158(0.007)%.
[f] Bibenzyl also formed, 0.17(0.02)%.
[g] Bibenzyl also formed, 0.11(0.01)%.

the product mixture was methyl benzoate (4-5%) and the isomeric substituted methyl benzoates (ca. 5%). The presence of the meta isomer in relatively large quantities together with other considerations indicated that the reaction proceeded by a radical mechanism, ie. homolytic aromatic substition was taking place (see the following discussion). A small amount of bibenzyl was the only other

identifiable compound in the toluene/benzene oxidation. Very small quantities of other unidentified compounds were present in both reactions. We compared the ratio of the two solvent peaks before and after the reaction to see if there was any preferential evaporation of the two solvents; none was detectable.

The toluene/benzene oxidation was also carried out in the presence of cupric acetate; copper (II) salts are effective radical oxidants (54). A similar distribution of gases was obtained from this reaction although the yields of carbon dioxide and carbon monoxide were both slightly higher. A similar distribution of benzoates was also obtained but in lower yields.

The oxidation of three larger carbazates (phenyl, benzyl and 2-phenylethyl carbazate; 25, 26 and 27, respectively) were also investigated to determine what influence these various groups had on the compounds formed in this reaction. As seen above the low molecular weight of the other possible products from the oxidation of methyl carbazate makes their analysis difficult. Again, large amounts of nitrogen were obtained from all three compounds, and no methane or ethane was expected or detected in these oxidations (Table 10). The phenyl carbazate afforded a large amount of carbon monoxide (34%) and only a low yield of carbon dioxide (4%) while the situation was reversed with the benzyl analogue (2 and 44%, respectively).

TABLE 10. Oxidation of Large Molecular Weight Carbazates.[a]

Expt.	Oxidant (mmol)	Solvent	Temp. (°C)	Time Addn. (min)	Percent Yield (Error)[b] Corrected Percent Yield (Error) N_2	CH_4	CO	CO_2
Phenyl carbazate								
40	$BaMnO_4$	benzene	40	78	74.0(3.3)	0	33.0(3.6)	3.5(0.3)
	(33.3)				73.4(3.7)	0	33.5(3.7)	3.5(0.3)
Benzyl carbazate								
41	$BaMnO_4$	benzene	40	64	90.0(3.1)	0	2.1(0.7)	43.8(1.8)
	(33.5)				89.5(3.5)	0	2.1(0.7)	44.2(1.9)
Phenylethyl carbazate								
42	$BaMnO_4$	benzene	40	50	82.3(6.1)	0	3.6(1.0)	14.5(0.7)
	(33.8)				81.0(3.6)	0	3.9(1.1)	15.5(0.8)
43	$BaMnO_4$	methylene	40	120	85.5(4.1)	0	4.0(0.6)	19.9(1.6)
	(33.5)	chloride			84.9(4.7)	0	4.2(0.7)	20.5(1.7)

[a] Carbazate (11.1 mmol) oxidized according to oxidation method B in benzene (100 mL) at 40°C with the oxidant in the same solvent (50 mL). The system was flushed with helium.
[b] Gas analysis by analysis method B.

The more typical although somewhat low yields of these two gases were found with the 2-phenylethyl carbazate (4% carbon monoxide and 21% carbon dioxide). Table 11 lists the main components of the product solutions of these oxidations. As can be seen quite a variety of compounds were formed.

2-Phenylethyl carbazate was also oxidized with barium manganate in methylene chloride and the main components of the product mixture were separated by preparative tlc. Along with the main product of 2-phenylethanol and the small amount of 2-phenylethyl formate another high melting compound was also isolated. Analysis by ^{1}H and ^{13}C nmr, ir and ms demonstrated that this compound was the dimer 29.

TABLE 11. Nongaseous Products from the Oxidation of Large Molecular Weight Carbazates.

$ROOCNHNH_2$	Products	%Yield (Error)
$R=Ph^{a,c}$	R-OH	27.6 (10.6)
	R-OOCR	9.7 (0.4)
	R-OOCH	3.1 (1.2)
$R=PhCH_2^{a,d}$	R-R	60.6 (2.8)
	Ph(C=O)H	13.9 (1.0)
	R-OH	8.5 (0.8)
	R-OOCH	1.5 (0.1)
	R-H	0.35 (0.07)
$R=PhCH_2CH_2^{a,e}$	R-OH	21.5 (0.5)
	R-OOCH	5.4 (0.1)
	R-OOCPh	4.03 (0.08)
	R-H	3.9 (0.4)
$R=PhCH_2CH_2^{b}$	R-OH	6
	R-OOCH	0.8
	dimer 29	0.6

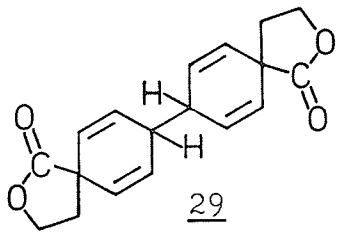
[a]Oxidation carried out with barium manganate in benzene at 40°C and analyzed by gc.

[b]Oxidation carried out in methylene chloride and products were separated by tlc.

[c]No Ph-Ph detected.

[d]No PhCOOH, $PhCH_2OOCPh$, Ph-Ph or $PhCH_2Ph$ detected.

[e]No $PhCH_2CH_2Ph$, Ph-Ph, $PhCH_2COOH$, $PhCH_2(CO)H$ or 3,4-dihydro-2(1H)-benzopyran-1-one detected.



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As shown in Table 6, a white solid was isolated when benzyl carbazate was treated with mercuric acetate in water. The nmr, ir, ms and x-ray fluorescence data were consistent with the organomercury complex $(PhCH_2OOCN{=}N)_2Hg$ (28). Treatment of methyl carbazate in a similar manner yielded much gas and a very small amount of an unstable product which again was found to contain mercury by ms. Oxidation of adamantyl carbazate (15) afforded an unstable semi-solid consistent with the organomercury AdOOCNNHgOAc (30). Exchange of the acetate group for bromide with sodium bromide seemed to cause the loss of nitrogen and the formation of AdOOCHgBr (31, 55).

DISCUSSION

As in the previous section, the discussion is divided into two sections dealing with the preparation of the carbazates and the oxidation studies.

Preparation of the Carbazates

We developed an efficient means of preparing BTCOCl on a large scale by adding solid BTH to phosgene in ether at room temperature. This reagent reacted readily with unhindered alcohols and phenols to give good yields of the corresponding 1-alkoxy- and 1-aryloxycarbonylbenzotriazoles. Treatment of these compounds with hydrazine afforded the corresponding crude carbazates in good yields. However, some difficulty was encountered on trying to separate the wanted carbazate from the BTH by-product. These two compounds have similar solubility properties but the BTH could be removed with only a slight loss of carbazate by extraction with base.

Preparation of carbazates by this method was also limited to alcohols which could not act as good leaving groups. For example, 1-phenoxybenzotriazole was found to lose the phenoxy group in competition with the benzotriazole in the reaction with hydrazine affording a low yield of phenyl carbazate. Thus, this method could not be used to prepare, for example, nitrophenyl carbazates.

Oxidation Studies

Since initial studies on benzyl carbazates afforded complex results we decided to study the oxidation of methyl

carbazate by analyzing the gases given off by this reaction.

Methodology

Mixtures of the permanent gases (hydrogen, oxygen-argon, nitrogen, carbon monoxide and carbon dioxide), methane and ethane can be analyzed by gas chromatography (gc). These gases can be separated isothermally using two columns or with one column if temperature programming is used (56). Analysis was carried out isothermally since a gc with the required thermal conductivity detector and temperature programming was not available.

A Molecular Sieve 5A or 13X column will separate hydrogen, oxygen-argon (elute together), nitrogen, methane and carbon dioxide, in that order. Since carbon monoxide (and water) is absorbed by the Molecular Sieve, a second column for this gas is also required. Commonly used is a solid adsorbent of a porous polyaromatic polymer such as Chromosorb 102®, a styrene divinylbenzene polymer, or Porapak Q®, an ethylvinylbenzene-divinylbenzene polymer (56,57). On these columns hydrogen, oxygen-argon, nitrogen and carbon monoxide elute as a single peak followed by peaks corresponding to methane, carbon dioxide and ethane, in that order.

There are some limitations to the use of Molecular Sieve columns. The above mentioned absorption of water and carbon dioxide will cause gradual deactivation which can decrease retention times and peak separations (resolution),

and may alter the order of elution. Hydrocarbons heavier than methane have excessively long retention times or are absorbed by this packing again leading to deactivation of the column. Thus, the Molecular Sieve column should be protected from these compounds as much as possible to retard premature deactivation.

Alternative methods of analyzing such mixtures of gases are also available but the gc method was the most convenient and flexible (58).

We used two slightly different methods, analysis methods A and B, to analyze the gas evolved from the oxidations with the latter employing some slight improvements over the former. Both systems had the 5A Molecular Sieve column in common while method A used a column of Porapak Q® and method B used Chromosorb 102®. In method A the instrument response was calibrated by injecting various volumes of the pure gases of interest. Linear regression was used to fit the best line of peak area to volume and the area that corresponded to 0.5 mL was used as the calibration factor for that particular gas. In the other method the instrument was calibrated using known mixtures of the gas of interest in nitrogen or argon. Again linear regression was used to fit these points to a line of area vs. percentage of gas. Thus, in this system the absolute percentage of a particular gas could be determined from its area.

Since the total volume of gases collected and the relative proportions was known, it was possible to

calculate the yield of each gas assuming all of the carbazate had been oxidized.

The response factors of many different compounds for gc analyses have been tabulated (59). The literature values for the gases of interest and those determined by us are compared relative to a value of one for nitrogen in Table 12. In analysis method A the values for the Porapak Q® column are relative to a value of 0.85 for methane since the values on the two columns are unrelated. The factors on the Chromosorb 102® column in method B were calculated relative to both nitrogen (=1) and methane (=0.85) since the equations used were absolute.

TABLE 12. The Experimental and Literature Response Factors of the Gases Evolved by the Oxidation of Methyl Carbazate.

	Thermal Response				
	Nitrogen	Carbon Monoxide	Methane	Carbon Dioxide	Ethane
Literature[a,d]	42	42	35.7	48	51.2
Relative to:					
Nitrogen	1	1.00	0.85	1.14	1.22
Method A[a]					
Relative to:					
Nitrogen[e]	1	0.99	0.80	-	-
Methane[f]	-	-	0.85	1.43	1.36
Method B[b,c]					
Relative to:					
Nitrogen[e]	1(0.409)	1.15(0.125)	0.82(0.023)	-	-
Nitrogen[g]	-	-	0.67(0.004)	0.91(0.065)	1.05(-0.005)
Methane[g]	-	-	0.85(0.005)	1.15(0.082)	1.33(-0.006)

[a]True Response = (Peak Area)/(Thermal Response Value)
[b]True Response = (Peak Area)/(Thermal Response Value) + Correction
[c]The relative correction is indicated in brackets. [d]Ref. (59).
[e]On a column of Molecular Sieves, 5 A. [f]On a column of Porapak Q®.
[g]On a column of Chromosorb 102®.

It is somewhat difficult to compare the literature values and those from method A to the values from method B. The former two methods correct the peak areas with a line where the intercept was zero while in method B a nonzero intercept was used. However, except for nitrogen these intercepts were rather small. These response factors are in fair agreement with each other.

In analysis method B we could determine the amount of methane on both columns and these values were usually in good agreement with each other. The value with the smaller estimated error was used in the further calculations. In analysis method A methane was used to relate the values of both columns to each other and so could obviously not be used if no methane was present. This was the reason why method B was developed.

Ideally some gas should have been used as an internal standard in these analyses. All of the above mentioned common gases except hydrogen could be present in the gas collected from the oxidation of methyl carbazate. Hydrogen would not be a good gas to use as such an internal standard since it gives an abnormal response under the usual conditions used for analysis (56). However, since we were not interested in the absolute value of any gas but the relative amounts evolved we felt that the error would be small.

The oxidation of the methyl carbazate was carried out in a sealed system so that the evolved gas could be

collected. As in the gas analysis, two slightly different methods of oxidation were used as slight improvements were made (oxidation method A and B, respectively). In both these methods a solution of the carbazate was added dropwise to the stirring oxidant solution/suspension to ensure complete oxidation and minimize bimolecular products.

Initially, the reaction flask was heated with a wax bath at the appropriate temperature while the addition funnel was at room temperature (oxidation method A). The gas evolved by the reaction flowed through a gas-bulb and was collected over water in an inverted graduated cylinder. When the oxidation was complete the volume of gas collected was measured and the gas in the gas-bulb was analyzed by gc according to analysis method A.

Several problems were encountered with this procedure. At the elevated temperatures the temperature control was difficult causing a fluctuation in the volume of gas measured. Collecting the gas in the inverted graduated cylinder also led to inaccuracies because it was difficult to ensure that water level in and outside the cylinder were the same height causing the gas to be compressed or expanded. The evolved gases likely had some solubility in the water used and some of the gases may have been preferentially dissolved. The methyl and other carbazates were also found not to be very soluble at room temperature in the organic solvents used occassionally resulting in their precipitation in the addition funnel.

Thus, we developed oxidation method B which minimized these problems. Here both the addition funnel and reaction flask were thermostated at 40°C which was a convenient temperature to work at with the apparatus at hand. This elevated temperature eliminated the precipitation of the carbazates. The evolved gas in this method was collected over a brine solution in a closed graduated cylinder with attached leveling bulb. This minimized any absorption of the gases and allowed the pressure in the cylinder to be equalized to the atmospheric pressure.

Working with gases had some associated difficulties which made the analysis less accurate than under ideal conditions. As mentioned both the compressibility of gases and the volume change with temperature will lead to inaccuracies. There was also the possibility of absorption or selective absorption of the gases evolved in the fluids used. The estimated error in the percent yield of each gas was usually approximately 10% or less except for for small values which had larger associated errors.

It was also found that removing a sample from the gas-bulb for gc analysis resulted in some leakage of air and thus caused a change in the sample composition. This was most evident when the system was flushed with helium where sampling caused the oxygen peak to slowly increase in size. This effect was also augmented by the necessity of flushing the syringe with the collected gas before a sample was injected into the gc. The leakage could have been reduced

by first pressurizing the gas-bulb before sampling by injecting a small amount of the gas used to flush the system (argon or helium). This gas could also have been used to flush the syringe further decreasing the leakage. However, to be consistent throughout these changes were not incorporated and instead the leakage was minimized by another route.

All the analyses involved five injections made alternatively onto each column. However, only the first two injections on each column were used in the calculations to minimize the sampling error discussed above. The errors were estimated and carried through in the usual way; all the details are contained in the experimental section.

We attempted to repeat the oxidations as closely as possible so that the results were as reproducible as possible. The concentrations of the various carbazates were maintained the same throughout all the experiments. In initial experiments we found that less solvent in the reaction flask, ie. a more concentrated oxidant solution/ suspension, resulted in a more complete oxidation. It was found to be difficult to maintain the same rate of addition and stirring from experiment to experiment. Also the conditions of the oxidants were not easily determined beforehand and were used as is. All these factors could have some undetermined influence on the outcome of the oxidation.

Oxidation of Methyl Carbazate

The oxidation of methyl carbazate with potassium ferricyanide, potassium permanganate and chromium trioxide under the aqueous conditions presumably used by Ohme and Preushof did not afford any detectable amount of methane. Thus, the rearrangement proposed by these workers must not be occurring under these conditions. Methane, however, was obtained under anhydrous conditions with increasingly larger amounts formed as the hydrogen atom donating ability of the solvent was increased. This would seem to indicate the formation of the methyl radical which abstracts a hydrogen atom when possible to form methane. The formation of ethane under very dilute aqueous conditions where dimerization of the methyl radical presumably occurred was consistent with this explanation. Under most of the conditions used a large amount of nitrogen was produced. Carbon dioxide and carbon monoxide were normally also produced in smaller varying amounts with the former usually formed in the larger quantities.

The near quantitative yield of nitrogen indicated that the hydrazino group was essentially completely converted to nitrogen and was not incorporated to any significant extent in any other products. This reflects the mode of oxidation, ie. the slow addition of the carbazate to the stirring oxidant maintained a relatively low concentration of carbazate ensuring a complete oxidation as was desired.

Many studies have been carried out on the oxidation of

hydrazine and its derivatives (11). As indicated in the introduction, the oxidation of 1,2-disubstituted hydrazines under the appropriate conditions affords disubstituted diazene (azo) compounds that can usually be isolated. The oxidation of monosubstituted hydrazines is also thought to proceed through such azo compounds which, however, cannot be isolated because of their instability. A brief discussion of some of the investigations on these monosubstituted diazenes follows below in order to see what might be expected from the oxidation of the carbazates.

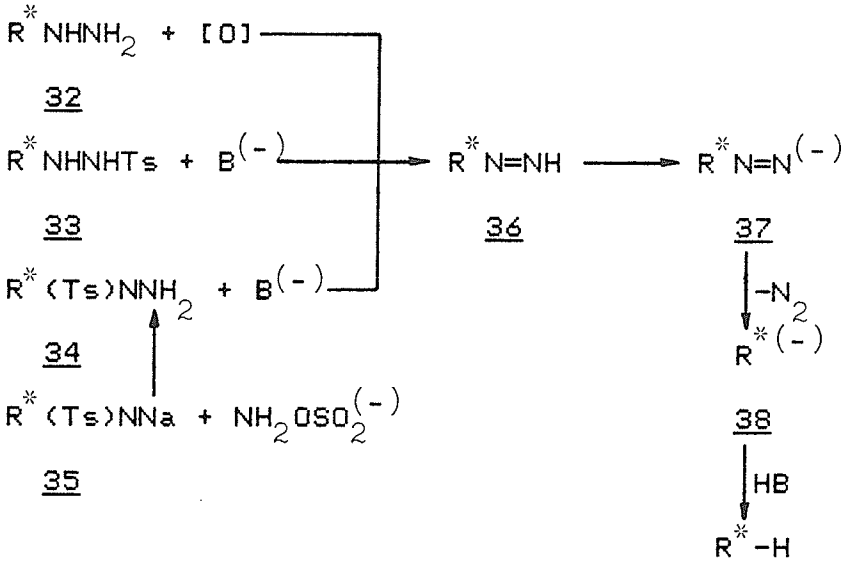
THE GENERATION OF DIAZENES FROM DISUBSTITUTED HYDRAZINES AND DERIVATIVES:

PREPARATION OF 2-PHENYL-2-BUTYLDIAZENE.

Cram and Bradshaw published an early thorough study on an alkyl diazene in 1963 (60). Using the "multiple origin criterion" they investigated the loss of nitrogen from optically active 2-phenyl-2-butyldiazene (36) generated in three different ways. This hypothesis states that a common set of products formed via different reactions from different starting materials should be formed via a common intermediate. In this investigation 2-phenylbutane (39) and nitrogen were formed from the oxidative cleavage of 2-phenyl-2-butylhydrazine (32), and the base cleavage of 1-(2-phenyl-2-butyl)-2-p-toluenesulfonylhydrazine (33) and 1-(2-phenyl-2-butyl)-1-p-toluenesulfonylhydrazine (34), Scheme 7.

Numerous oxidizing agents were examined and many were

found to give the desired conversion but potassium periodate was found to be the most practical over the range of solvents used. These solvents included t-butanol,



R^* = -CMe(Et)(Ph) Ts = p-$CH_3C_6H_4SO_2$-

SCHEME 7. The Multiple Origin Criterion.

ethanol, methanol, water and DMSO with and without the corresponding potassium salt as a base except for DMSO where potassium t-butoxide was used. The 2-phenylbutane was afforded in 13-63% yield at 100°C under these conditions. Halogens were also suitable oxidants but halogenation of the product occurred if the conditions were not carefully controlled. Olefin was the main product when oxygen was employed as the oxidant.

1-(2-Phenyl-2-butyl)-2-p-toluenesulfonylhydrazine (33) was cleaved under various basic conditions including: t-BuOK/t-BuOH (with and without water), n-BuOK/n-BuOH,

EtOK/EtOH, $HOCH_2CH_2OK/HOCH_2CH_2OH$, KOH/H_2O, t-BuOK/dioxane, and DMSO with t-BuOK and KOH (both with and without water). Usually the reaction was carried out at 100°C affording 2-phenylbutane in 21-83% yield.

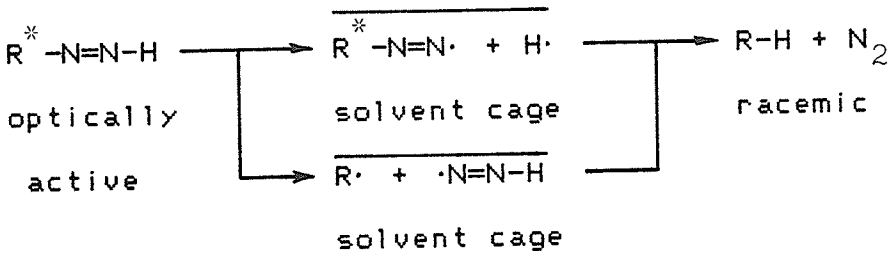
1-(2-Phenyl-2-butyl)-1-p-toluenesulfonylhydrazine (34) was formed in situ by treating the p-tosylsulfonamide of 2-phenyl-2-butylamine (35) and sodium hydroxide in ethanol/water at reflux with hydroxylamine-o-sulfonic acid. Most of the reagent was decomposed by the base to give sodium sulfate and hydroxylamine and so the reaction was not extensively investigated.

Even though these three compounds had different structures, each afforded 2-phenylbutane and nitrogen under the appropriate conditions. Under similar conditions these three starting materials also resulted in 2-phenylbutane with the same optical activity within experimental error. This suggested that there was at least one common intermediate and 2-phenyl-2-butyldiazene (36) was the most logical choice.

The stereochemical outcome of the oxidation of (+)-phenylhydrazine and the cleavage of (+)-1-(2-phenyl-2-butyl)-1-p-toluenesulfonylhydrazine depended on the base concentration in all the solvents tried. When no base was present complete racemization occurred while in the presence of some base retention (40-80%) and sometimes inversion (1-33%) occurred depending on the exact conditions. These observations suggest that 2-phenyl-2-

butyldiazene decomposes by two independent competing reactions one which is base-catalyzed and partially stereoselective, and the other which is not base-catalyzed and is non-stereoselective.

These workers suggested the most likely mechanism for the non-base catalyzed reaction involved a homolytic cleavage of either the C-N or N-H bond in the diazene 36 followed by the loss of nitrogen and the recombination of the radical pair formed within the solvent cage.



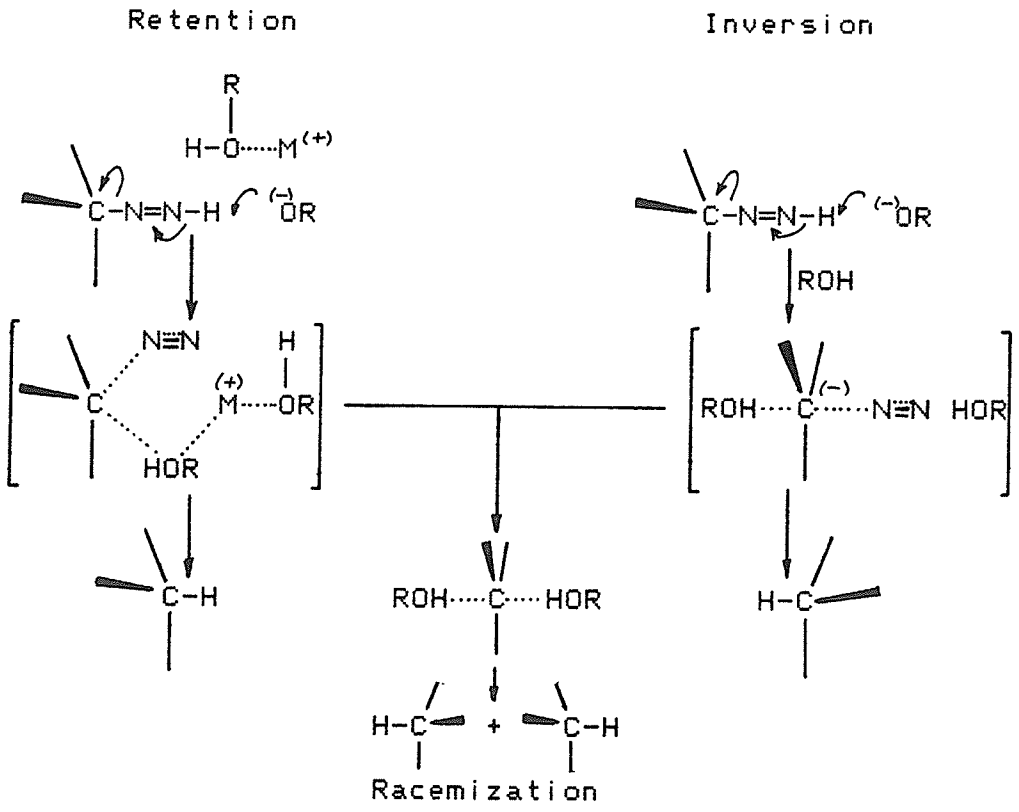
SCHEME 8.

The Non-base Catalyzed Non-stereoselective Reaction.

The base-catalyzed reaction exhibited a stereoselectivity and steric direction which depended on the type of solvent. There was a distinct correlation between the stereochemistry of this reaction and the dielectric constant of the solvent. However, the concentration of the proton donors, the acidity of the solvent and even the change from hydroxylic to nonhydroxylic solvents had only a minor effect on the stereochemistry. Thus, in solvents of low dielectric constant net retention occurred while net inversion was

observed in solvents of high dielectric constant. This suggested the 2-phenyl-2-butyl anion (38) was an intermediate and as with other reactions involving leaving groups the stereochemical fate of the carbanion depends on the detailed structure of its immediate environment.

Base abstraction of a proton from 36 generates the 2-phenyl-2-butyl anion (38) after loss of nitrogen in either a one-step or two step process, Scheme 9.



SCHEME 9. The Base-Catalyzed Decomposition of the Diazene.

In proton-donating solvents of low dielectric constant or in non-proton donating solvents the carbanion captures a proton before the species diffuse apart and retention

occurs. With more acidic solvents of higher dielectric constant the solvent participates from the backside. The carbanion is then hydrogen-bonded from the back-side and collapse results in the inverted product. In both situations, the carbanion can also become symmetrically solvated and then racemization occurs.

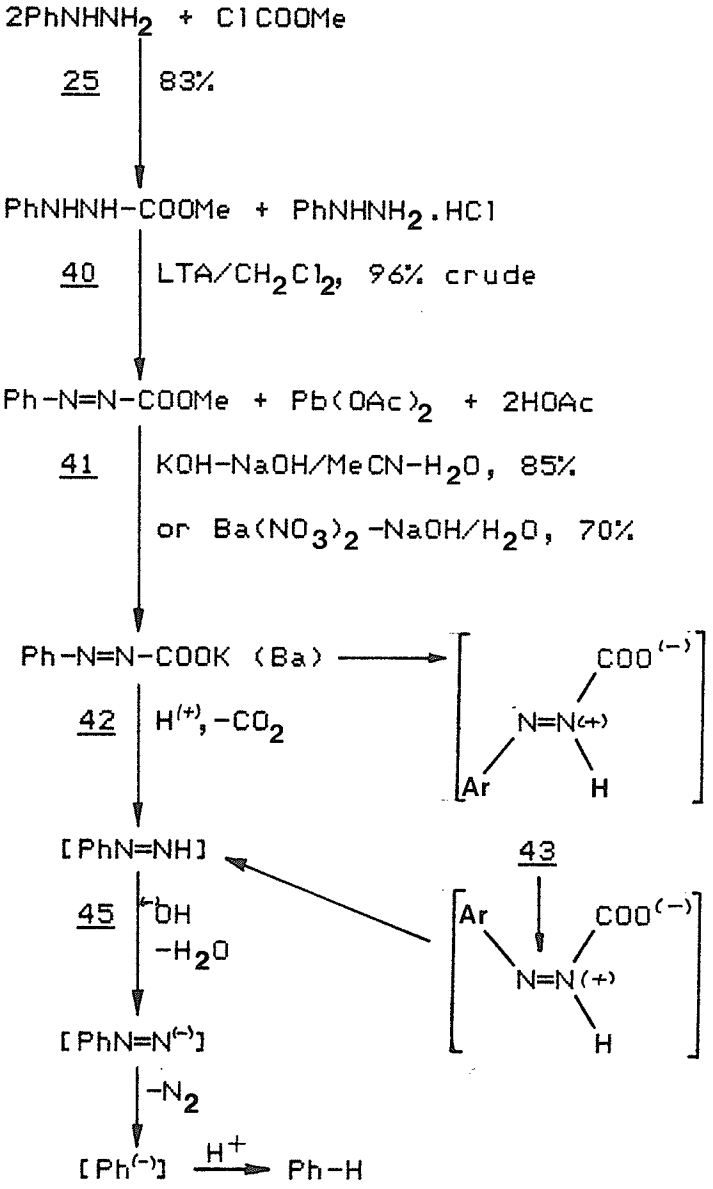
Thus, these workers hypothesized that the diazene was the most probable intermediate formed in the oxidation of the hydrazine 32 and this diazene could decompose homolytically or heterolytically in the presence of base.

THE PREPARATION OF PHENYLDIAZENE.

A monosubstituted diazene was first directly observed by Kosower and coworkers (61). Phenyldiazene was prepared by the decarboxylation of phenyldiazene carboxylic acid formed from the methyl ester 41 by hydrolysis. This methyl phenyldiazenecarboxylate was prepared by condensing phenyl hydrazine with methyl chloroformate followed by oxidation with LTA (Scheme 10). The ester was extremely rapidly hydrolyzed by base, and the potassium and barium salts 42 could be precipitated out of basic solution. These salts were decomposed by acid affording a large quantity of carbon dioxide (>90%). This decarboxylation was believed to proceed through the zwitterions 43 and 44.

The intermediate phenyldiazene was found to be very sensitive to oxygen yielding products of strong light absorption. Therefore, these workers devised procedures to generate the phenyldiazene in solution under anaerobic

conditions in an apparatus suitable for spectroscopic measurements. The uv spectrum of the phenyldiazene that they observed was similar to that of 1-methyl-2-phenyldiazene, Ph-N=N-Me.



SCHEME 10. The Preparation of Phenyldiazene.

Dilute solutions, approximately 1×10^{-9}M, of phenyldiazene were found to be moderately stable in aqueous

buffer with a half-life for disappearance of approximately 80,000s. Acetonitrile solutions were more stable probably due in part to the basicity of water; the half life was approximately 600,000s for a $1x10^{-4}$M solution. The most convenient preparation of phenyldiazene involved the protonation of a tetra-n-alkylammonium salt of phenyldiazenecarboxylic acid with triethylamine hydrochloride or another such amine hydrochloride. This reaction was possible because triethylamine (TEA) was found to have little effect on the stability of phenyldiazene in acetonitrile. Concentrations up to $7x10^{-2}$ M could be prepared in this way.

To confirm the structure phenyldiazene was reduced to phenylhydrazine by diazene (diimide) formed in situ. The uv spectrum of this phenylhydrazine was virtually identical with that of authentic hydrazine.

[13] $2TEA\cdot HCl + KOOC-N=N-COOK \longrightarrow HN=NH + 2TEA + 2KCl + 2CO_2$

[14] $PhN=NH + HN=NH \longrightarrow PhNHNH_2 + N_2$

Early preparations of phenyldiazene involved the generation of fairly dilute acetonitrile solutions followed by concentration by the codistillation with acetonitrile. These solutions could not be concentrated to much more than 10^{-3}M because the rate at which the diazene disappeared increased with concentration and thus pure diazene could not be isolated. The rate of disappearance of 2-

phenyldiazene-1-d, Ph-N=N-D, was found to be much lower than that of phenyldiazene. Thus, the hydrogen transfer must be associated with the rate-limiting step with an isotope effect of k_H/k_D 4-5.

The disappearence of phenyldiazene was found to be a bimolecular reaction with benzene (60-80%) and nitrogen (ca. 80%) formed as the major products with minor amounts of hydrazobenzene (ca. 15%) and diphenyl (ca. 0.2%).

[15] $2PhN{=}NH \rightarrow PhH + N_2 + PhNHNHPh + PhPh +$ other products

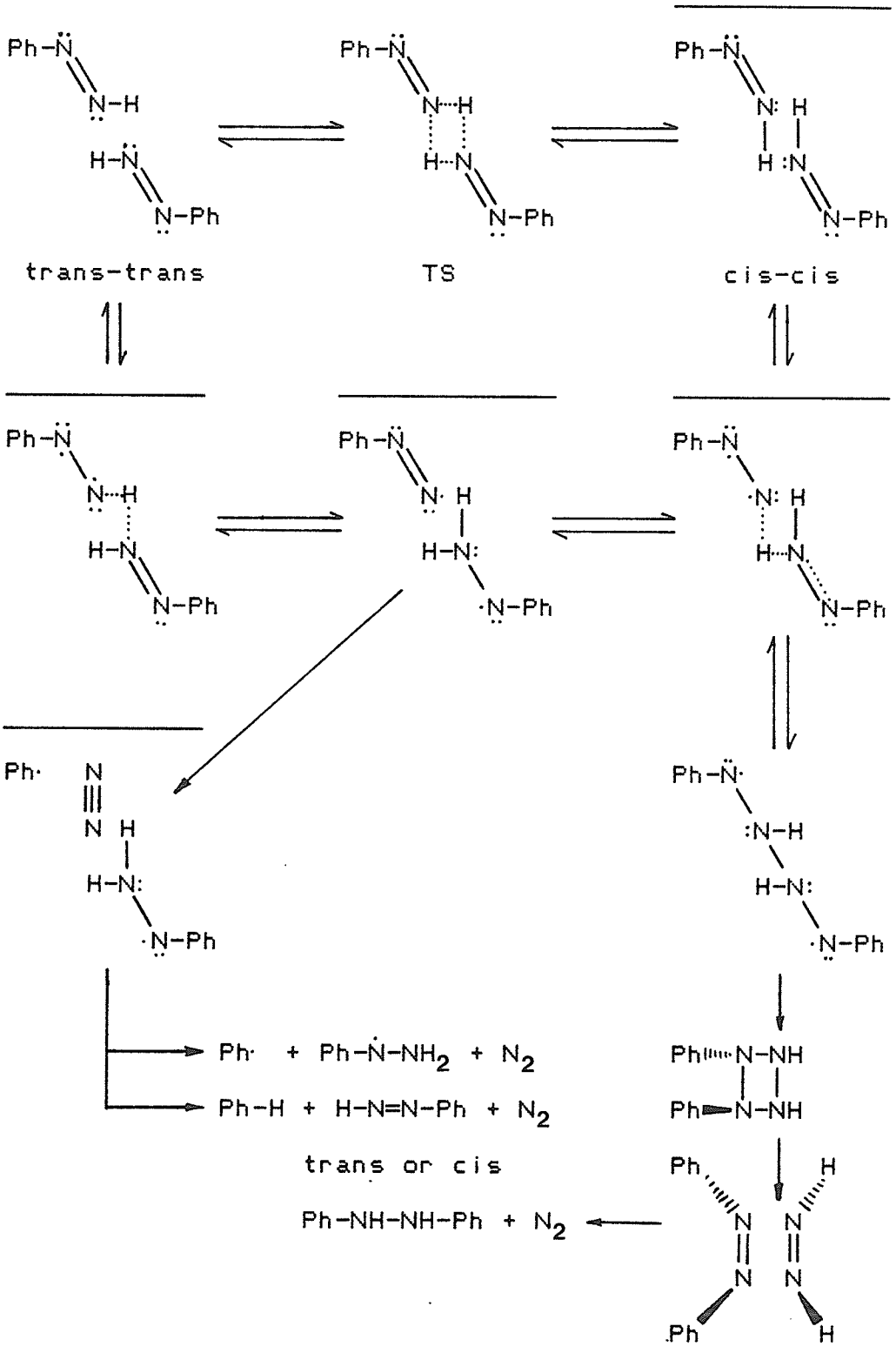
With Ph-N=N-D the yield of nitrogen and benzene both decreased (>45% and 56%, respectively) and the extent of deuteration was only 73%. Therefore some of the hydrogen acquired in the formation of the benzene must not come from the phenyldiazene. These products were not extensively examined because relatively small quantities were produced, the product mixture was complex (up to ten spots by tlc) and some of these products were sensitive to air.

Phenyldiazene was assigned to have the trans structure on the basis of the low absorption intensity of the longest wavelength band. The rate constant for the bimolecular rearrangement trans to cis estimated as between 10^{-3} and 10^{-7} L/mole-s. The reverse process, cis to trans, would be faster by the amount corresponding to the difference in the stabilities of the two isomers. Experimentally the rate constant for the disappearance was found to be 2×10^{-2}

L/mole-s within the range estimated for the bimolecular trans to cis rearrangement. Because of this similarity Kosower postulated this rearrangement was an important, perhaps rate-limiting, step in the bimolecular disappearance of phenyldiazene.

A change in solvent was found to have little effect and the product composition was not greatly influenced by a change in the initial concentration of phenyldiazene. These observations suggest a neutral reaction mechanism and that the products are determined within a solvent cage. A radical reaction was likely since a clean, well-defined set of products was not observed and Ph-N=N-D failed to give benzene-d quantitatively. The breaking of the N-H bond must be a rate-limiting step because of the observed isotope effect.

The proposed mechanism is shown in Scheme 11. The first step is the bimolecular conversion of trans to cis phenyldiazene. Hydrogen transfer then occurs in the solvent cage from one cis-phenyldiazene to another generating two radicals. This is facilitated by the conversion of one of these molecules to a species with significant triplet contribution. Loss of nitrogen and abstraction of hydrogen in the cage by the phenyl radical forms benzene and cis- or trans-phenyldiazene.



*Horizontal lines indicate a solvent cage.

SCHEME 11. Mechanism for the Decomposition of Phenyldiazene

Dissociation from the solvent cage is also possible and further reactions include the addition of phenyl radicals to phenyldiazene forming 1,2-diphenylhydrazine, [16] or the phenylhydrazine from the phenylhydrazino radical [17].

[16] $Ph\cdot + H\text{-}N{=}N\text{-}Ph \longrightarrow Ph\text{-}NH\text{-}\dot{N}\text{-}Ph \xrightarrow{+H\cdot} Ph\text{-}NH\text{-}NH\text{-}Ph$

[17] $Ph\text{-}\dot{N}\text{-}NH_2 + H\cdot \longrightarrow Ph\text{-}NH\text{-}NH_2$

Of interest here is the rapid reaction of phenyldiazene with oxygen. On exposure to air phenyldiazene rapidly disappeared forming benzene as the major product. Kosower proposed oxygen initiates a free-radical chain reaction related to the oxidation of aldimines to nitriles (61).

[18] $Ph\text{-}N{=}N\text{-}H + O_2 \longrightarrow Ph\text{-}N{=}N\cdot + \cdot OOH$

[19] $Ph\text{-}N{=}N\cdot \longrightarrow Ph\cdot + N$

[20] $Ph\cdot + Ph\text{-}N{=}N\text{-}H \longrightarrow Ph\text{-}H + Ph\text{-}N{=}N\cdot$

[21] $\cdot OOH + Ph\text{-}N{=}N\text{-}H \longrightarrow Ph\text{-}N{=}N\cdot + H_2O_2$

[22] $2R\cdot \longrightarrow R\text{-}R$ (termination reactions)

The treatment of phenyldiazene with sodium hydroxide (0.1N) produced benzene (79±8%) and confirmed the often postulated decomposition of the diazene intermediate under basic conditions.

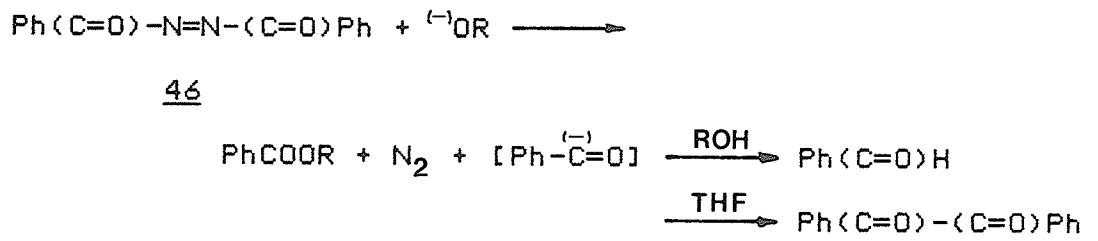
[23] $Ph\text{-}N{=}N\text{-}H + OH^{(-)} \longrightarrow Ph\text{-}H + N_2 + H_2O$

Other substituted phenyldiazenes and alkyldiazenes were also studied by these workers (61). Most reacted quickly with oxygen forming the corresponding hydrocarbon as the major product. Thus, the sensitivity to oxygen is a property of all monsubstituted diazenes. Only 4-nitrobenzene was found to undergo a slower such reaction forming 4,4′-dinitrohydrazobenzene as the major product (63%) and nitrobenzene in only 30-35% yield. This anomaly must be due to the stabilizing effect of the nitro group on radicals. The nitro group is extremely effective in stabilizing free-radicals generated at positions next to the benzene ring, for example accounting for the stability of the diphenylpicrylhydrazyl radical (62). It is thought that with this group addition instead of abstraction occurs in the cis triplet-cis ground state transition state, Scheme 11. Closure and loss of diazene would form 1,2-bis(4-nitrophenyl)diazene which could be reduced by the diazene leading to the observed products.

The very rapid hydrolysis of alkyl and arylazoformates by acids and bases has been further investigated by Hegarty and Tuohey(63).

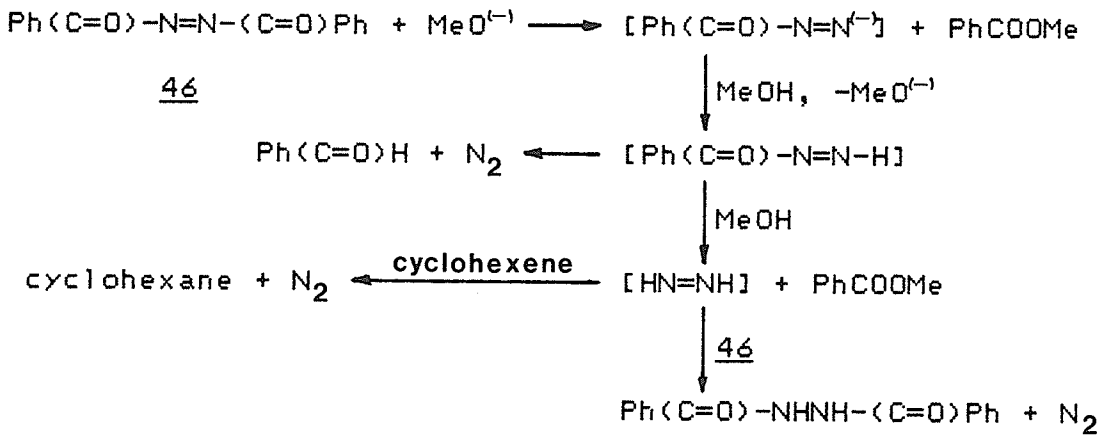
THE REACTION OF DIBENZOYLDIAZENE WITH ALKOXIDE.

Bumgardner and coworkers have investigated the analogous reaction of alkoxide ion with dibenzoyldiazene (46) in an attempt to produce the benzoyl anion(64). In protic media, benzaldehyde was the expected product from this intermediate while benzil was expected in aprotic media.



SCHEME 12. The Expected Decomposition of Dibenzoyldiazene.

In methanol substantial amounts of dibenzoylhydrazine (41%) and only a small amount of benzaldehyde (2-4%) was formed indicating the benzoyl anion was not formed. The postulated mechanism is shown below.

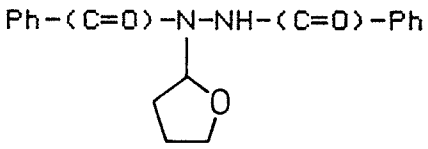


SCHEME 13. Decomposition of Dibenzoyldiazene in Methanol.

The benzoyldiazene was an intermediate formed from the diazene anion and can react further with alkoxide to form diazene or undergo decomposition to benzaldehyde and nitrogen. This decomposition could occur via a bimolecular reaction as described by Kosower and Huang (61) for phenyldiazene or as in the McFadyen-Stevens reaction (see later). Unreacted dibenzoyldiazene would be reduced by

diazene to form the isolated dibenzoylhydrazine. In the presence of cyclohexene, the yield of dibenzoylhydrazine was reduced (36%) and cyclohexane was formed supporting this pathway.

Different products were formed in the aprotic solvent tetrahydrofuran (THF). These products included tribenzoylhydrazine, benzoic acid, a trace of benzil and compound 47 which indicated that the solvent was involved in the reaction.



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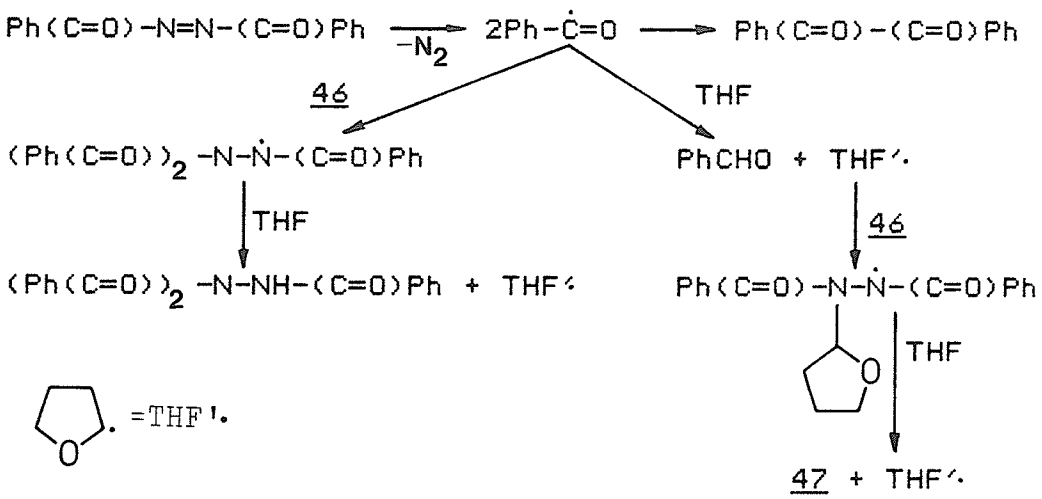
No 1,2-dibenzoylhydrazine was formed indicating benzoyldiazene was not an intermediate. The proposed radical pathway is shown in Scheme 14; the abstraction of the α-hydrogen in THF is an important process in certain radical reactions. The methoxide ion was believed to take part in an electron-transfer reaction which may account for the rate enhancement with increasing methoxide concentration.

Thus, there was no evidence for a benzoyl anion intermediate in either protic or aprotic solvents. Of interest to us was the apparent formation of benzoyldiazene in methanol which can lose nitrogen to form benzaldehyde.



SCHEME 14. Decomposition of Dibenzoyldiazene in THF.

THE ALCOHOLYSIS OF 1-PHENYL-2-BENZOYLDIAZENE.

Nicholson and Cohen have earlier studied the rapid acid and base catalyzed alcoholysis of thermally stable azo compounds such as 1-phenyl-2-benzoyldiazene (Ph-N=N-(C=O)Ph, 48) and 1-phenyl-2-carbethoxydiazene (Ph-N=N-COOEt, 49) (65).

When the methanolysis of 1-phenyl-2-benzoyldiazene was carried out in the presence of benzene, carbon tetrachloride, nitrobenzene, naphthalene and acrylonitrile substantial amounts of bibenzyl, chlorobenzene, the isomeric nitrobibenzyls, the isomeric phenylnaphthalenes and polyacrylonitrile, respectively, were formed. This was unequivocal evidence for the intermediacy of the phenyl radical. The methanolysis of low concentrations (<0.01 M) of 48 in the absence of such additives lead to a large yield of nitrogen (ca. 90%), methyl benzoate and a moderate

yield of benzene. At higher concentrations (ca. 0.1 M) the diphenyl benzoylhydrazines, the products of the addition of phenyl and hydrogen radicals to 1-phenyl-2-benzoyldiazene were also formed at the expense of the other compounds.

The acid- or base-catalyzed methanolysis of 1-phenyl-2-benzoyldiazene presumably leads initially to methyl benzoate and phenyldiazene.

[24] $Ph(C{=}O)\text{-}N{=}N\text{-}Ph + MeOH \xrightarrow{H^+(OH^-)} PhCOOMe + PhN{=}NH\ (PhN{=}N^-)$

This reaction does not proceed to completion at moderate initial concentrations of 48 (ca. 0.1) since a competitive reaction forms substantial amounts of 1,2-diphenyl-1-benzoylhydrazine and 1,1-diphenyl-2-benzoylhydrazine.

[25] $Ph(C{=}O)\text{-}N{=}N\text{-}Ph + MeOH \xrightarrow{H^+(OH^-)} Ph(C{=}O)\text{-}NHNPh_2 + Ph(C{=}O)N(Ph)NHPh$

As the concentration of 1-phenyl-2-benzoyldiazene was increased both the yield of methyl benzoate and benzene decreased from 85 and 60% to approximately 40 and 12%, respectively.

This methanolysis was found to be more effectively catalyzed by ferric ions than by acids or bases. Ferric nitrate catalyzed the methanolysis of 1-phenyl-2-benzoyldiazene (0.07 M) and approximately 80% of the ferric ions were reduced to ferrous ions based on initial diazene.

This oxidizing agent increased the yield of methyl benzoate to 81-87% and of benzene to 65-70% which were at least as high as those found in the absence of added oxidant but at an initial concentration of 46 of an order of magnitude lower. The yields of the products when the reaction was carried out in the presence of the above additives was also increased. Thus, the oxidizing agent must have increased the yield of the intermediate phenyl radical.

The intermediate phenyldiazene seems to be largely oxidized by the ferric ions to the phenyldiazene radical which then loses nitrogen to form the phenyl radical. Most of the phenyl radical then abstracts a hydrogen atom to form benzene or can react with an additive if present.

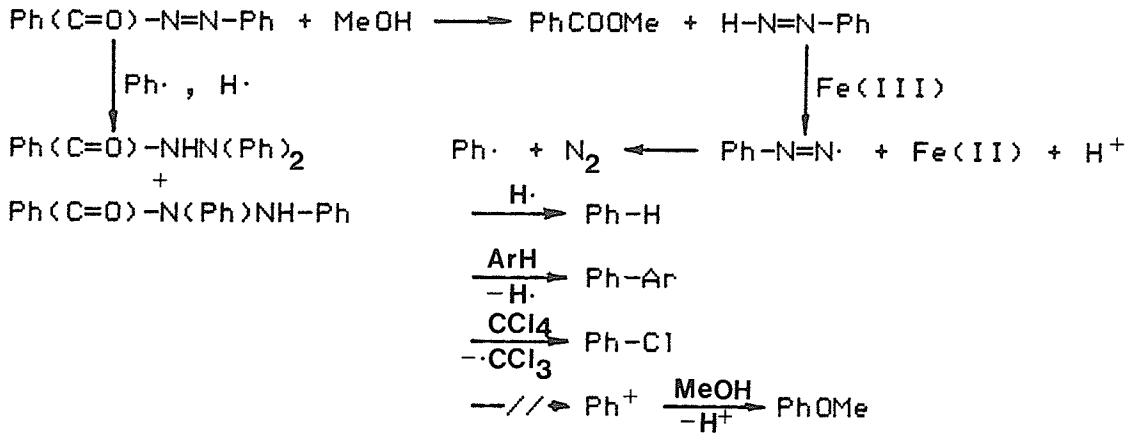
[26] $PhN{=}NH + Fe(III) \longrightarrow PhN{=}N\cdot + Fe(II) + H^{+}$

[27] $PhN{=}N\cdot \longrightarrow Ph\cdot + N_2$

A small fraction of phenyldiazene and phenyl radical may add to 1-phenyl-2-benzoyldiazene since the methyl benzoate was not produced in a quantitative yield and the yield of benzene was less than that of methyl benzoate. The ferric ion did not oxidize the phenyl radical to any substantial amount since only low yields of anisole (ca. 5%) were formed.

An outline of the proposed mechanism is given below. The correspondence in the yield of methyl benzoate with that of ferrous ion indicates the phenyldiazene was not

oxidized by a chain reaction.



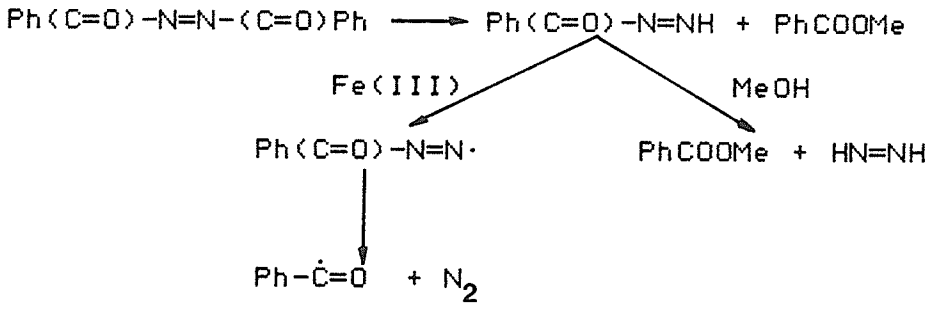
SCHEME 15. Decomposition of 1-Phenyl-2-benzoyldiazene.

The phenylhexadienyl type radicals which are the initial products of the arylation reaction were probably not converted quantitatively to the biaryls and so do not reflect the total yield of the phenyl radical. Chlorobenzene was formed in 71% yield when the reaction was carried out in the presence of carbon tetrachloride. This was a high yield when compared to the 78% yield of methyl benzoate from this experiment. This latter figure was the maximum possible yield of phenyl diazene and phenyl radical. Thus, 90% of the phenyldiazene was converted to chlorobenzene and the small remainder appeared as benzene. This high yield of phenyl radical must also occur in the absence of additives where benzene was the major product. Here most of the benzene must result from the abstraction of hydrogen from methanol by the phenyl radical.

The ferric nitrate catalyzed methanolysis was also

found to polymerize acrylonitrile very effectively. Thus, the ferric ions must act as a Lewis acid and again increased the yield of the phenyl radical leading to more polymer than when hydrogen chloride was used (25 vs. 16% yield, respectively).

Dibenzoyldiazene (Ph(C=O)-N=N-(C=O)Ph, 50) was found to give very little polymer (ca. 1%) on acid-catalyzed methanolysis but again ferric nitrate lead to an increase. Acid catalyzed methanolysis probably forms benzoyldiazene (Ph(C=O)-N=NH) which decomposes to diazene, a poor source of hydrogen atoms. The ferric ions probably also lead to the formation of benzoyldiazene which was then oxidized by these ions to the the benzoyldiazene radical. Decomposition forms nitrogen and the benzoyl radical which could initiate polymerization.



SCHEME 16. The Decomposition of Dibenzoyldiazene.

Of special interest to us, diethyl azodicarboxylate (EtOOC-N=N-COOEt) was found to cause polymerization both in the presence of acid and ferric ion. Presumably this proceeds through EtOOCN=NH, and the radicals EtOOCN=N· and

EtOOC· which were more effectively formed in the presence of the oxidant. In the absence of an added oxidant 51 may itself act as the oxidant forming the free radical although less efficiently.

Thus, in the oxidation of phenyldiazene the intermediate phenyldiazene is likely further oxidized to the phenyldiazene radical (Ph-N=N·) which loses nitrogen to form the observed phenyl radical instead of undergoing direct thermal decomposition to nitrogen, and the phenyl and hydrogen radicals. Analogous oxidation of other monosubstituted hydrazines also probably occurs via the corresponding monosubstituted diazene which is oxidized further forming nitrogen and the corresponding free radical in high yields.

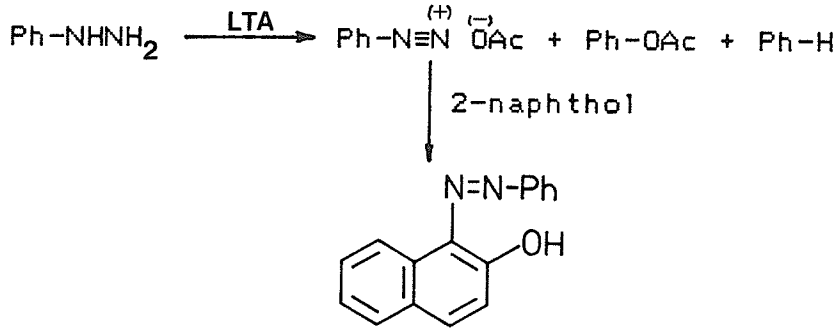
[28] $R\text{-}NHNH_2 \xrightarrow{[O]} R\text{-}N{=}N\text{-}H \xrightarrow{[O]} R\text{-}N{=}N\cdot \xrightarrow[-N_2]{[O]} R\cdot$

THE GENERATION OF DIAZENES BY THE OXIDATION OF MONOSUBSTITUTED HYDRAZINES:

THE LTA OXIDATION OF PHENYLHYDRAZINE.

Aylward has studied the oxidation of phenylhydrazine with lead tetraacetate (LTA) in several different solvents, and has found the products varied both with temperature and solvent (45a).

The main product from the oxidation at -75°C in methylene chloride was the benzenediazonium ion (46%), characterized as its derivative with 2-naphthol, along with small amounts of phenyl acetate (5%) and benzene (4%).

[29] 

Phenylation of the solvent occurred when the reaction was carried out in benzene, chlorobenzene or nitrobenzene at room temperature (Table 13). The distribution of the isomeric bibenzyls formed was largely unaffected by the molar ratio of the reactants and the order of mixing, with only a 3-4% difference observed. The average distribution of the ortho:meta:para isomers were found to be 61.4:25.1:13.5 % and 60.2:10.3:29.5 % for the chlorobiphenyls and nitrobiphenyls, respectively. The

yields were only slightly affected by carrying the reaction out under nitrogen.

TABLE 13. Oxidation of Phenylhydrazine with LTA at 20°C.

Solvent	% Yield				
	Ph-H	Ph-Ph	PhN=NPh	Ph-OAc	Ph-Y
methylene chloride	ca.60	ca.1	ca.3	0-3	0-5[a]
benzene	-	26-37	ca.5	0-2	-
chlorobenzene	18-26	1	ca.2	ca.1	ca.37[b]
nitrobenzene	27-30	1	ca.2	ca.1	36-41[c]

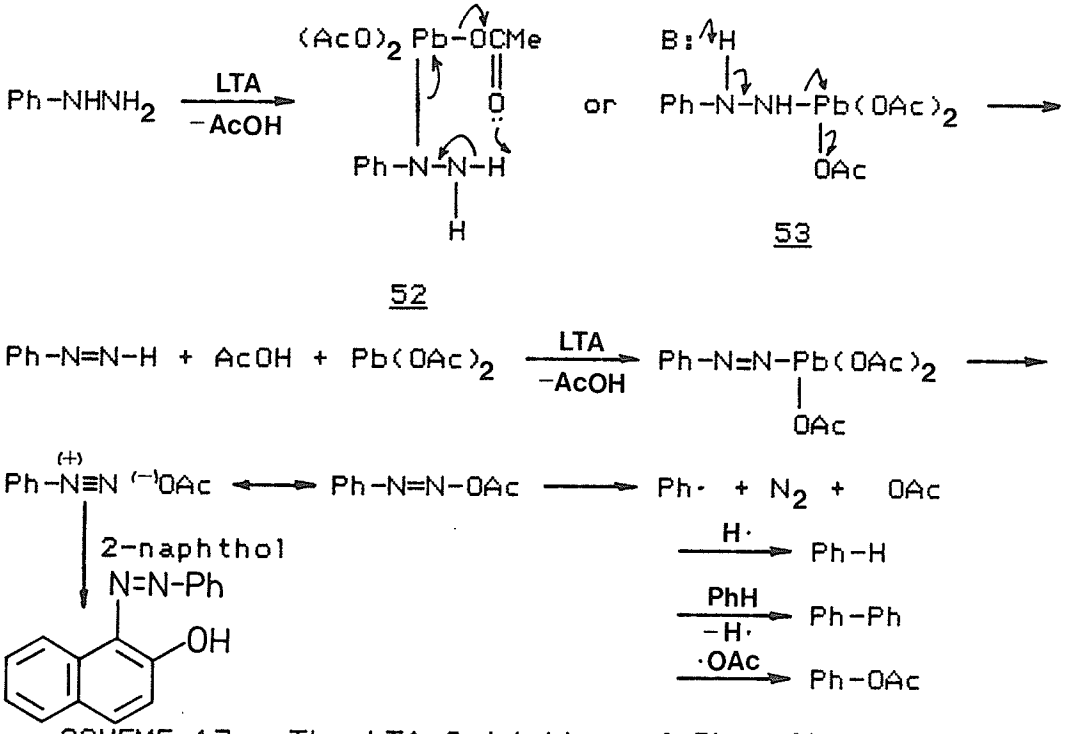
[a] Y = Cl. [b] Y = C_6H_5Cl. [c] Y = $C_6H_5NO_2$.

The products and their distribution suggested the intermediacy of a phenyl radical. In methylene chloride the phenyl radical abstracted a hydrogen or chlorine atom to form benzene and chlorobenzene as the major and minor products. Aromatic homolytic substitution occurred along with hydrogen abstraction in aromatic solvents, forming the isomeric biaryls as well as benzene. The distribution of these isomers corresponds very well with other reactions which form the phenyl radical (see later).

Phenyldiazene has been suggested to undergo unimolecular decomposition forming the phenyl radical but without much evidence. As seen above, other workers have suggested that phenyldiazene is further oxidized in the presence of the ferric ion or oxygen to form the phenyl

radical. Here the phenyl radical was not formed by the action of oxygen on phenyldiazene since when the reaction was carried out under nitrogen the yield of products decreased only slightly.

The mechanism suggested by the authors is shown below as Scheme 17.

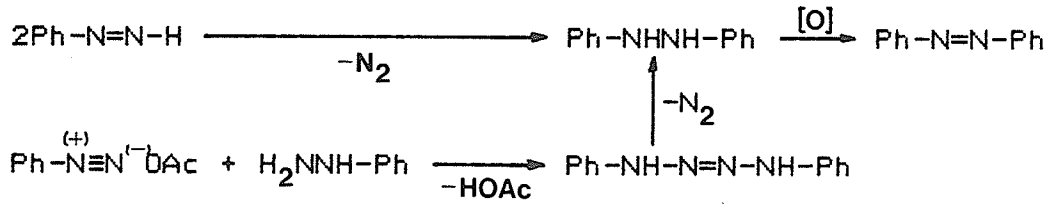


SCHEME 17. The LTA Oxidation of Phenylhydrazine.

In the reaction with LTA the phenylhydrazine could undergo substitution on either nitrogen. However, the substituted position is the more likely site since this is the more nucleophilic position, for example arylhydrazines are alkylated with simple alkylating agents at this position provided the aryl group does not carry electron withdrawing groups (66). Again phenyldiazene was likely an

intermediate and was further oxidized to the benzenediazonium ion (benzeneazoacetate) which was stable at low temperatures but decomposed at room temperature to the phenyl radical. The equilibrium between the diazonium ion and the azoacetate is well documented, and the decomposition of benzeneazoacetate is similar to the decomposition of N-nitroacetanilide and the Gomberg reaction (45a).

The fairly high yield of benzene obtained when the oxidation was carried out in aromatic solvents could be due to hydrogen abstraction by phenyl radicals from the initial LTA complex 52 or 53, or from the methyl groups present. The azobenzene likely arises from the oxidation of hydrazobenzene. This compound could be formed by the bimolecular decomposition of phenyldiazene or by the attack of the diazonium ion on phenyldiazene and the loss of nitrogen from the resulting tetrazene.



SCHEME 18. Formation of Azobenzene.

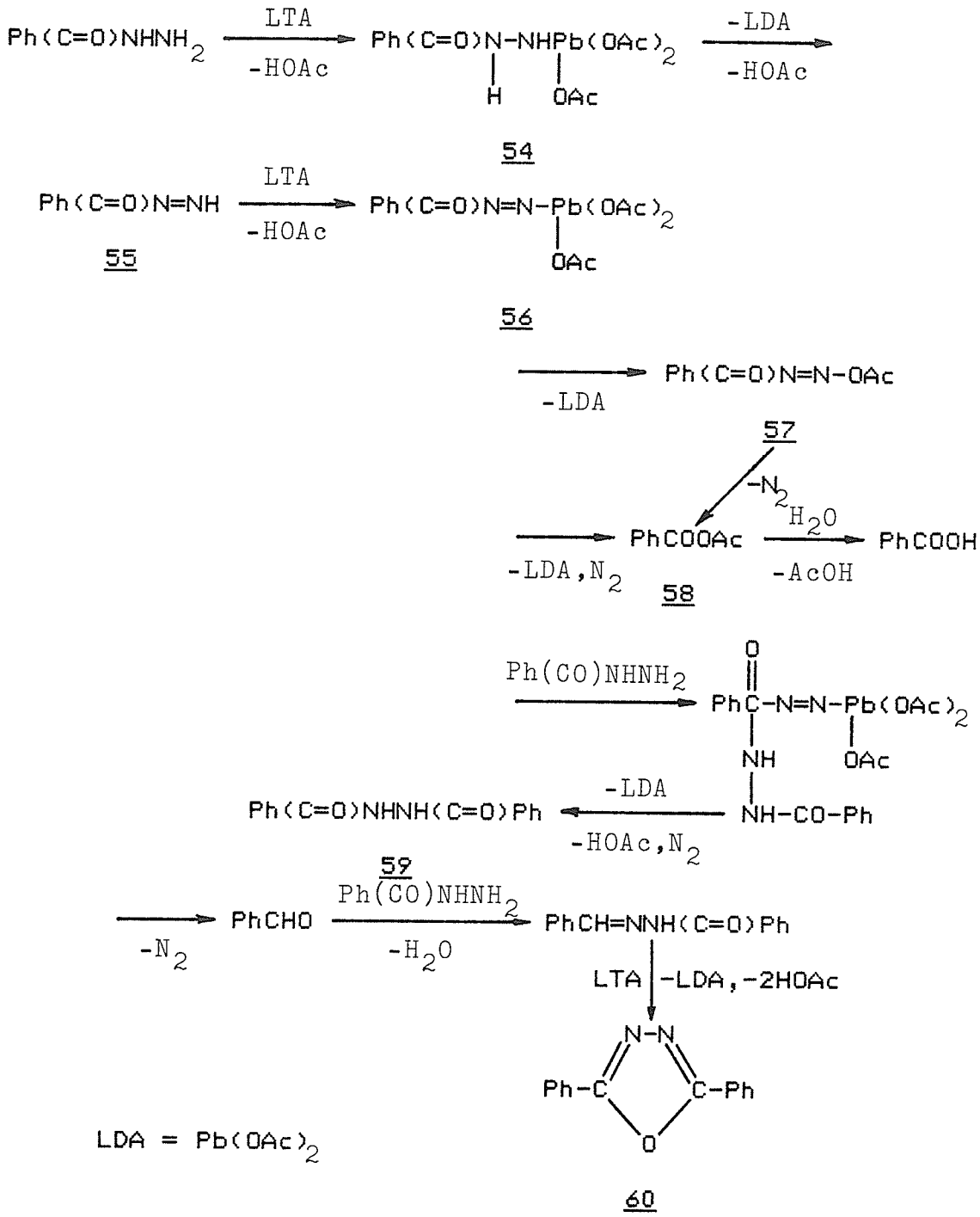
THE LTA OXIDATION OF ARYLHYDRAZIDES.

Aylward and Norman have also investigated the oxidation with LTA of arylhydrazides (67). In their work, benzhydrazide was slowly added to excess LTA (2.5 mol) in

benzene at room temperature, and the evolution of nitrogen began immediately and stopped within 2 minutes after the addition was complete. After hydrolytic work-up, benzoic acid was isolated (90%) and a small amount of benzophenone (0.6%) was found by gc. The 4-chloro-, 4-methyl-, and 4-methoxybenzhydrazides also gave the corresponding acids in high yields under the same conditions. However, with the 4-nitro derivative the evolution of nitrogen was barely perceptible at room temperature but the reaction was complete after approximately 2 h at 60°C.

Benzoic acid was also obtained in high yield when benzhydrazide was oxidized in methylene chloride, methanol or anisole. Small quantities of 4-methoxybenzophenone and methyl benzoate were found by gc when the reaction was carried out in anisole and methanol. In contrast, 4-nitrobenzhydrazide afforded the corresponding methyl ester as the major product in methanol.

When LTA (1.25 mol) was slowly added to benzhydrazide in acetic acid or benzene, the yield of benzoic acid was reduced and significant amounts of 1,1′-dibenzoylhydrazine and tribenzoylhydrazine were isolated. Analysis of the oxidation in benzene by gc before hydrolytic work-up showed the presence of acetic and benzoic anhydride which were both absent after work-up. Thus, these workers suggested the mixed anhydride Ph(C=O)-O-(C=O)Me was the likely initial oxidation product and that this disproportionated to the symmetrical anhydrides.



SCHEME 19. The LTA Oxidation of Benzhydrazide.

Oxidation probably occurs by a mechanism similar to that proposed above for the oxidation of phenylhydrazine. A hydrazine-LTA complex 54 was suggested, again with

coordination through the more nucleophilic nitrogen atom, which eliminates acetic acid to form the diazene 55. This is consistent with the slower oxidation of 4-nitrobenzhydrazide and 1,1'-diacylhydrazine in which the nucleophilicity is reduced.

The diazene is likely further oxidized via another organolead (IV) complex 56 to give the mixed anhydride 58. As in the oxidation of phenylhydrazine, benzoylazoacetate (57) could also be an intermediate.

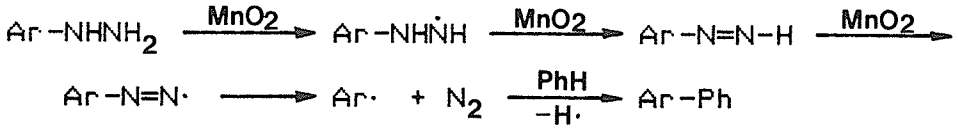
To minimize the further oxidation of the expected diazene intermediate these workers slowly added a dilute LTA solution to a dilute solution of the benzhydrazide in methylene chloride. The main product obtained from this modification was 1,1'-dibenzoylhydrazine (59, 58%) together with small amounts of benzaldehyde (1%) and 2,5-diphenyloxadiazole (60, 3%). The oxadiazole was demonstrated to be formed under these conditions from benzaldehyde and benzylhydrazide via the benzaldehyde benzoylhydrazone. These results were consistent with the intermediacy of the acyldiazene 55. Moreover, in the presence of TEA the yield of oxadiazole was increased (9%) consistent with an increase in the formation of benzaldehyde by the base-catayzed elimination from the diazene via a McFadyen-Stevens type reaction (see below).

Under these conditions where the hydrazide was in excess for most of the reaction, nucleophilic attack by the hydrazide on 56 or an equivalent could compete leading to

the 1,1'-diacylhydrazine 59. Further reaction of this compound would form the observed triacylhydrazine.

THE OXIDATION OF ARYLHYDRAZINES WITH MANGANESE DIOXIDE.

Bhatnagar and George have examined the oxidation of several arylhydrazines in benzene with manganese dioxide (46a). From the oxidation of phenyl-, 4-nitrophenyl- and 2,4,6-trichlorophenylhydrazine they have isolated biphenyl (26%), 4-nitrobiphenyl (50%) and 2,4,6-trichlorobiphenyl (39%). They also suggest the formation of the aryl radical via the further oxidation of the intermediate diazene.



SCHEME 20. The Proposed Oxidation of Arylhydrazines with Manganese Dioxide.

THE OXIDATION OF HYDRAZIDES WITH COPPER(II).

Tsuji and coworkers have oxidized hydrazides with stoichiometric amounts of copper(II) and also with oxygen in the presence of catalytic amounts of copper(II) (68). Under suitable conditions in the presence of water, alcohol or amine the corresponding carboxylic acid, ester or amide, respectively, can be prepared in high yields under mild conditions.

The formation of these compounds suggests an intermediate acyl cation, nucleophilic attack by water, alcohols and amines yielding the observed compounds.

The intermediate acyl cation would be produced by the stepwise 4-electron oxidation of the hydrazide by four moles of copper(II), an one electron oxidant (Scheme 20). Oxygen reoxidizes the copper(I) to copper(II) and so allowed the oxidation to be carried out with a catalytic amount of copper(II) when oxygen was bubbled through the reaction mixture. Presumably, the diazene was an intermediate again which underwent further oxidization through the acyl radical finally yielding the acyl cation. Radicals are very efficiently oxidized by copper(II) (54).

$$R(C{=}O)\text{-}NHNH_2 + 2CuXY \longrightarrow R(C{=}O)\text{-}N{=}N\text{-}H + 2CuX + 2HY$$

$$R(C{=}O)\text{-}N{=}N\text{-}H + CuXY \longrightarrow R(C{=}O)\text{-}N{=}N\cdot + CuX + HY$$

$$R(C{=}O)\text{-}N{=}N\cdot \longrightarrow R\text{-}\dot{C}{=}O + N_2$$

$$R\text{-}\dot{C}{=}O + CuXY \longrightarrow R\text{-}\overset{(+)}{C}{=}O + CuX + Y^{(-)}$$

$$R\text{-}\overset{(+)}{C}{=}O + Y^{(-)} \longrightarrow R(C{=}O)\text{-}Y$$

$$Y = OH,\ OR,\ NR_2.$$

SCHEME 21. The Oxidation of Hydrazides with Copper(II).

THE OXIDATION OF HYDRAZINES WITH mTFBSP.

Hoffman and Kumar have oxidized a series of hydrazines with m-(trifluoromethyl)benzenesulfonyl peroxide (mTFBSP, $(m\text{-}CF_3C_6H_4SO_2O)_2$) with results similar to those obtained with other oxidants (69).

A solution of mTFBSP in methylene chloride was slowly added to a solution of the aryl hydrazine at -78°C then exposed to air forming the corresponding hydrocarbon in

good yields (47-73%). Excess hydrazine was required since two equivalents of m-(trifluoromethyl)benzenesulfonic acid were generated by the reaction.

[30] $3Ar\text{-}NHNH_2 \xrightarrow[CH_2Cl_2,-78^{\circ}]{\text{a) mTFBSP}\ \text{b) air}} Ar\text{-}H + 2ArNHNH_3^{(+)}Ar'SO_3^{(-)} + N_2$

Ar = Ph, p-MeC_6H_4, p-Cl-C_6H_4

A diazene was implicated as a primary oxidation product by several observations. In order to get satisfactory yields of the hydrocarbon the reaction mixture had to be exposed to the atmosphere (oxygen). As mentioned above, monosubstituted diazenes are rapidly oxidized by oxygen to give the hydrocarbon. Thus, the diazene was likely the primary oxidation product and this was oxidized to a significant extent by oxygen to the hydrocarbon. Also, the arylazo compound was always detected in the product mixture by tlc and in the oxidation of phenylhydrazine azobenzene (4.7%) was isolated. This compound could arise from the known bimolecular decomposition of aryldiazenes which give the hydrocarbon and the hydrazo compound.

[31] $2R\text{-}N{=}N\text{-}H \longrightarrow R\text{-}H + 1/2R\text{-}NHNH\text{-}R + N_2$

Further oxidation of the hydrazobenzene by mTFBSP, confirmed experimentally, would result in the azobenzene

(70%).

When the oxidation of phenylhydrazine was carried out with 2 equivalents of mTFBSP the phenyl diazonium ion was formed as shown by the 2-naphthol diazonium coupling product (23%) and the conversion to chlorobenzene by cuprous chloride (25%). Presumably the diazene was oxidized further under these conditions. These results are similar

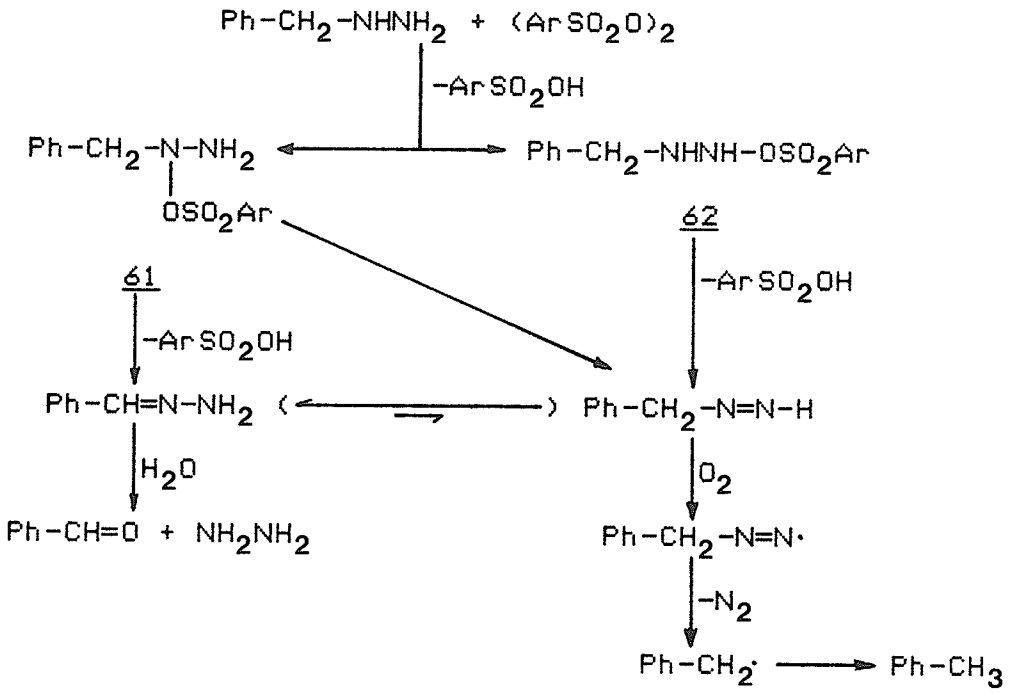
[32] $4PhNHNH_2 + 2(ArSO_2O)_2 \longrightarrow \overset{(+)}{PhN{\equiv}N}\ ArSO_3^{(-)} + 3PhNH\overset{(+)}{N}H_3ArSO_3^{(-)}$

to those reported by Aylward with LTA discussed above and Back's work with benzeneseleninic acid and anhydride (70).

The mechanism of the oxidation cannot be definitely determined from this study. However, the mechanism suggested for the oxidation of benzylhydrazine which gave toluene (51%) and benzaldehyde (25%) is outlined below.

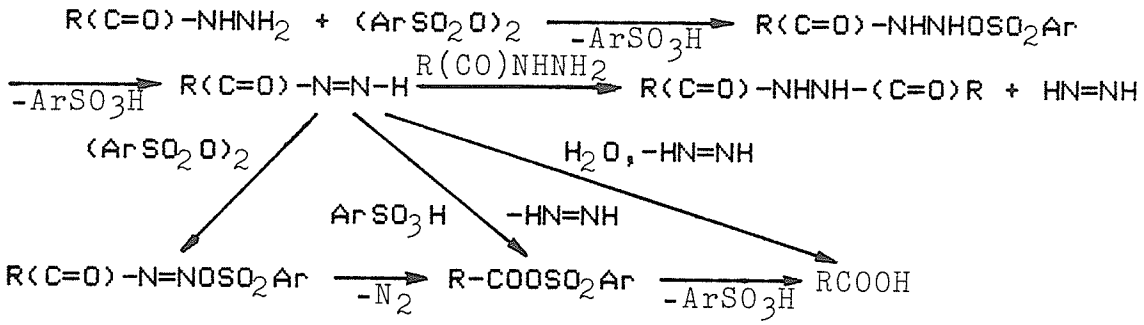
Benzhydrazine can react with mTFBSP to give two N-substituted compounds 61 and 62. Again the internal nitrogen is more nucleophilic and substitution is more likely at this position. Elimination in 61 can then proceed via two routes leading to a hydrazone or a diazene. Due to the higher acidity of the N-H bond the diazene would be favored kinetically while the more stable hydrazone would be favored thermodynamically. Tautomerization of the diazene to the hydrazone could occur but usually such reactions require strong acids or bases, or free radical initiators. Toluene is the product expected from the

further decomposition of the diazene while the benzaldehyde is likely formed by the hydrolysis of the hydrazone.



SCHEME 22. The mTFBSP Oxidation of Benzylhydrazine.

These workers have also oxidized hydrazides with mTFBSP. Hydrazides were less reactive than hydrazines but reacted smoothly at 25°C to give high yields of the corresponding diacylhydrazines. A small amount of the carboxylic acid was detected in all cases by tlc and was isolated for benzylhydrazide. Again the diazene was the likely intermediate. These are known to be good acylating agents and thus reaction with unreacted starting material will result in the observed product.



SCHEME 23. The mTFBSP Oxidation of Acid Hydrazides.

The carboxylic acid was probably formed via the mixed anhydride formed by further oxidation or reaction with arenesulfonate. Direct hydrolysis of the diazene was not likely since moisture was excluded. These results are similar to those with the oxidation with selenium oxidants (70), LTA (71) and halogens (72).

Related to these oxidations is a method of preparing aromatic aldehydes. This involves the base-catalyzed oxidation of monoacylhydrazines using potassium ferricyanide (the Kalb-Gross reaction) or sodium metaperiodate (73).

[33] $Ar(C=O)NHNH_2 + [O] \longrightarrow Ar(C=O)N=NH \longrightarrow ArCHO + N_2$

$[O] = K_3Fe(CN)_6, NaIO_4$

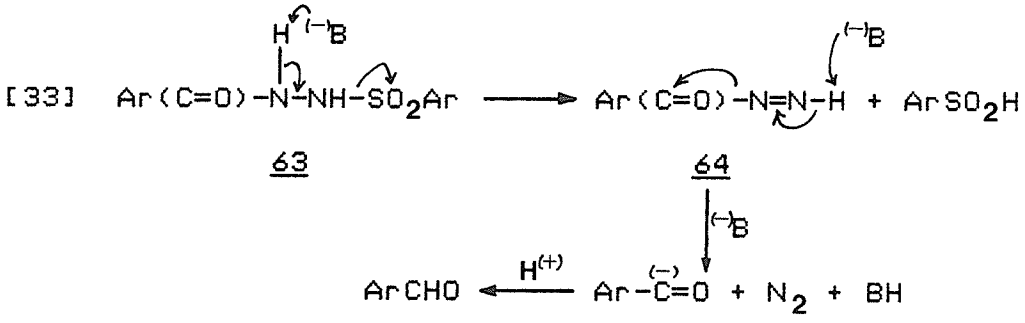
As seen above, the formation of benzaldehyde from dibenzoyldiazene apparently also proceeds through such a diazene.

THE GENERATION OF DIAZENES BY THE ELIMINATION FROM HYDRAZINE DERIVATIVES:

THE MCFADYEN-STEVENS REACTION.

In the related McFadyen-Stevens reaction, an aldehyde is formed when arylbenzenesulfonylhydrazines 63 undergo base-catalyzed thermal decomposition in ethylene glycol at 160°C with the loss of nitrogen and sulfinate (74). McFadyen and Stevens have suggested that a diazene 64 and an acyl anion 65 are intermediates formed as a result of successive bimolecular eliminations.

In both reactions the yield of aldehyde is increased by the presence of electron-donating groups in the 2 or 4 position of the aroylhydrazide moiety while electron withdrawing groups in these positions decrease the yield of

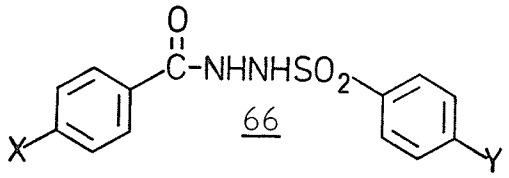


[33]

63 64

aldehyde leading instead to symmetrical diarylhydrazides.

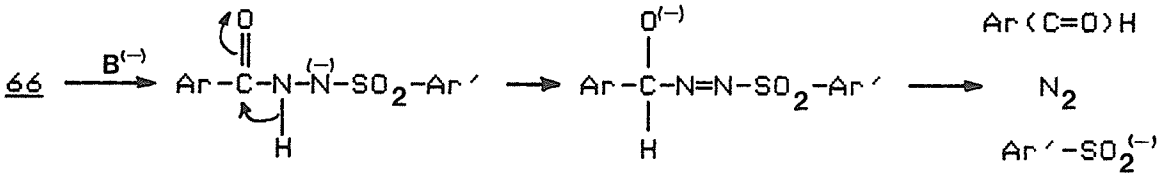
The similarity between these two reactions suggest that both occur by a common intermediate. With the formation of the sulfinate ion it was suggested that electron-withdrawing substituents Y in the 4 position of the benzenesulfonyl group in 66 might facilitate the elimination step and thus increase the yield of the aldehyde.



66

However, when 1-(4-substituted benzenesulfonyl)-2-(3-methylthiazole-5-carbonyl)hydrazines were subjected to these conditions, the yield of 3-methylthiazole-2-aldehyde was found to decrease with the 4-substituents MeO>H>Br>NO . Thus, electron-donating groups in both positions X and Y in 66 enhanced the yield of aldehyde.

Other workers have suggested that the reaction involves the rapid abstraction of a proton from the sulfonamide nitrogen and the resulting anion 67 undergoes a 1,2-hydride shift which would be promoted when Y is electron-donating(74). Decomposition of the resulting sulfonylazoalkoxide ion 68 would give the aldehyde, nitrogen and the arylsulfinate ion.



SCHEME 24. Suggested Mechanism for the McFadyen-Stevens Reaction.

Under the early standard reaction conditions this procedure was only applicable to the preparation of aromatic and heterocyclic aldehydes. This was found to be due to the excess of base (5 equivalents) causing the base-catalyzed attack on the α-hydrogen atom of aliphatic aldehydes and their loss due to condensation reactions. Later, it was found that aliphatic aldehydes could be obtained if they lacked such an α-hydrogen atom, for example pivalaldehyde, or if the reaction period was shortened by using flash pyrolysis techniques. Later improvements to the McFadyen-Stevens reaction included the use of a relatively aprotic solvent and one equivalent of base or the sodium salt of the mixed hydrazide without additional base. Additional base with either of the latter two modifications was found not to increase the yield of aldehyde.

Craig and coworkers have confirmed the anticipated differences in the acidities of the N-1 and N-2 protons of these compounds (74). Solubility tests and nmr studies have shown that the N-1 protons of 1-benzenesulfonyl-2-arylhydrazines are more acidic as expected. This fact was not consistent with the initial mechanism proposed by McFadyen-Stevens, [33].

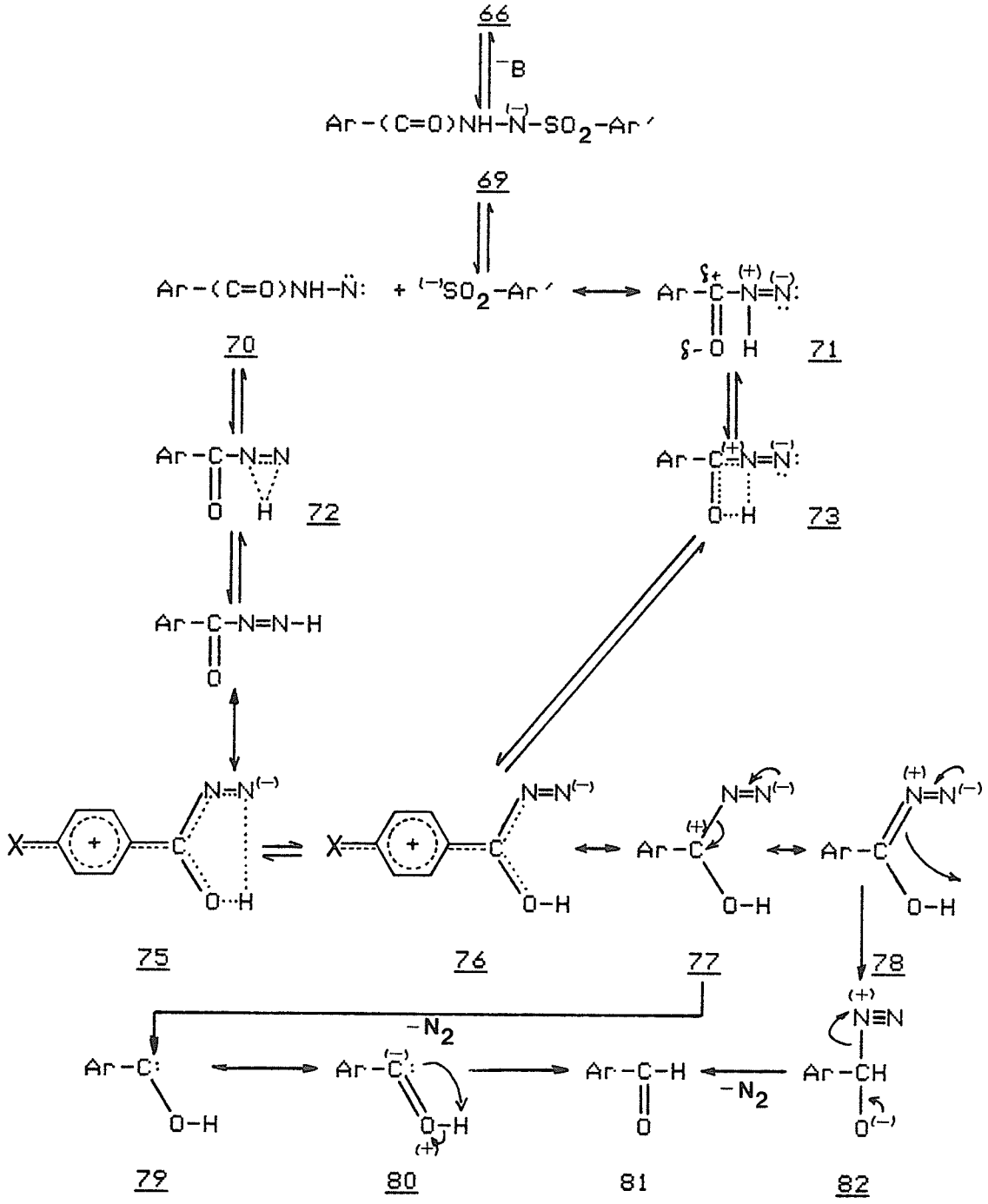
To further elucidate the mechanism the kinetics of solution thermolysis have been studied for several such compounds. In the presence of 1 equivalent of sodium carbonate the thermolysis at 160^{o}C in diethyl carbitol

followed first-order kinetics. The preformed sodium salts of the hydrazides showed the same rate data. Thus, the reaction follows first-order kinetics with respect to the anion of the hydrazide.

The reaction was found to be accelerated by electron-donating and retarded by electron-withdrawing para substituents X. The ρ value of -1.38 from a Hammett plot implies that the greatest electron density at the reaction site is the most rate accelerating. This suggests the hydrogen is transferred to the carbon as a hydrogen ion and not as a hydride ion. Varying the para substituent Y also showed the same trend but the effect was very small.

The sodium salt of the dideuteriohydrazide (66, X=OMe, Y=H) formed the corresponding 1-deuterioaldehyde at a much slower rate for the first-order reaction with an isotope effect k_H/k_D=2.28 at 160°C. The corresponding isotope effect k_H/k_D that would be observed for the McFadyen-Stevens reaction at 25°C was calculated to be approximately 4.5. Therefore, the N-H bond is clearly broken in the rate-determining step.

The mechanism proposed by Craig and coworkers is shown in Scheme 25. The anion of the acylhydrazide 69 is the reacting species and would be formed by the extremely rapid proton abstraction from 66. At the high reaction temperature, cleavage of the anion occurs quickly forming the benzoylaminonitrene 70 and the benzenesulfinate ion. This nitrene could then form a 5-membered transition state



SCHEME 25 .

Craig's Mechanism for the McFadyen-Stevens Reaction.

75 in equilibrium with the highly resonance stabilized ylide 76. This rearrangement could occur by insertion of the nitrene 70 into the N-H bond to give the diazene intermediate 74. Alternatively, rearrangement could occur by the 4-membered transition state 73. Irreversible loss of nitrogen from the mesomer 77 forms the hydroxyphenylcarbene 79 and hydrogen migration results in benzaldehyde (81).

In the dipolar mesomeric form 80 it can be seen that charge repulsion will exist between the negative carbene atom and the negative charge induced at C-1 of the benzene ring by an electron-donating substituent at C-4, eg. -OMe. Rapid reaarrangement to the aldehyde will relieve this charge repulsion.

Benzaldehyde could also be formed from the 1-hydroxy-1-phenyldiazoalkane 78 by tautomerization to 82 followed by loss of nitrogen.

The elimination of the benzenesulfinate ion must be a fast step since if it were rate-determining there would be no deuterium isotope effect because no N-H bond is broken in this step. Also, if it were rate-determining then the nature of the para substituent Y would have a profound effect on the rate of the reaction which was not observed. A rate-determining step would also have to be regarded as irreversible. To test the reversibility the reaction was repeated with the sodium salt of 66, X=OMe and Y=H, in the presence of 5 molar equivalents of sodium p-toluene-

sulfinate and was stopped after 3 minute reaction time. Analysis of the reaction mixture showed the presence of 7% of 66, X=OMe and Y=Me, demonstrating that the elimination must be reversible.

The reaction rates were found to vary only slightly in solvents of widely different chemical nature, ie. very similar yields of aldehyde were obtained using diethyl carbitol, ethylene glycol, DMSO, DMF or dimethylacetamide. This agrees with typical findings for thermolysis reactions in which nitrenes are involved where the solvent presumably only solvates the transition state. Thus, with a nitrene mechanism involving only neutral intermediates the reaction rate should not be greatly effected by a change in the solvent as was observed.

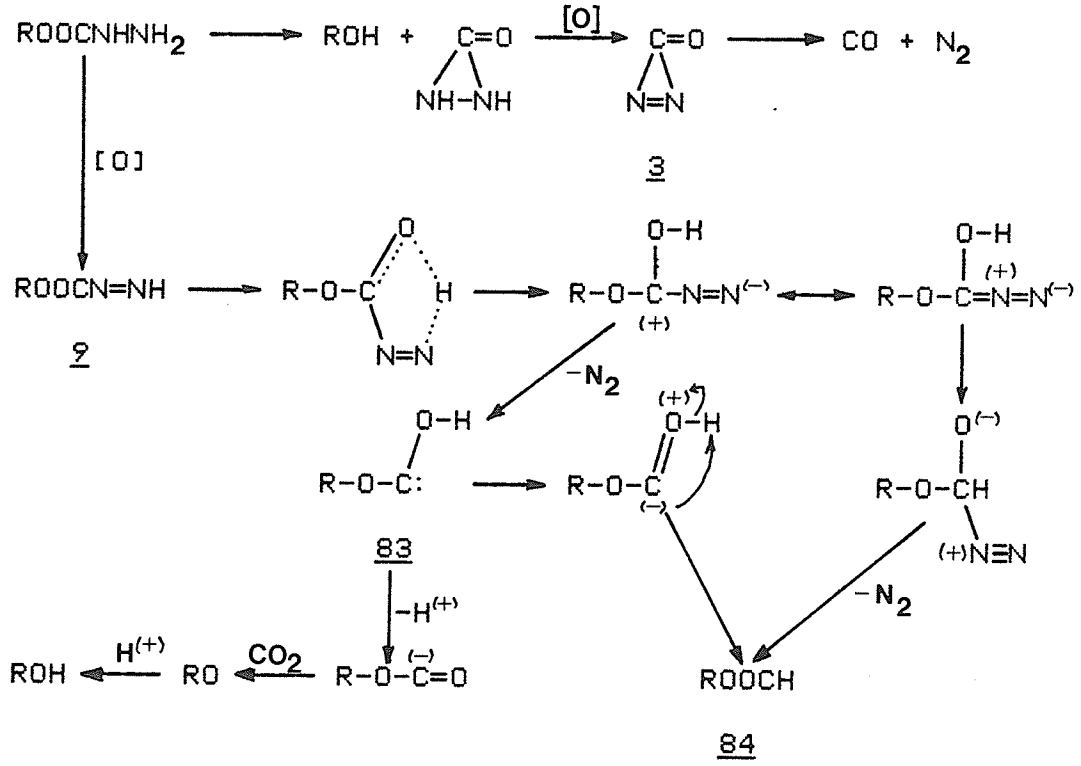
Presumably in the base-catalyzed oxidation of monoacylhydrazine with potassium ferricyanide and sodium metaperiodate, the diazene is formed which then decomposes via a similar route. Thus, under the proper conditions acyldiazenes can probably undergo rearrangement leading to reduction and the formation of an aldehyde.

These different methods all generate the azo group and the products obtained all have similar properties. Thus, these products reflect the reactivity of the azo moiety rather than the method of generation or the nature of the oxidant. Under our oxidative conditions it seems reasonable that a diazene is formed from the carbazates as postulated by Ohme and Preushof. However, it is likely

that further oxidation to an azo radical occurs. Loss of nitrogen from this azo radical is the obvious pathway of decomposition leading to the formation of an alkoxy or aryloxycarbonyl radical.

[34] $ROOC\text{-}NHNH_2 \xrightarrow{[O]} ROOC\text{-}N{=}N\text{-}H \xrightarrow{[O]} ROOC\text{-}N{=}N\cdot \xrightarrow[-N_2]{} ROOC\cdot$

It is also possible that proton transfer from nitrogen to oxygen could occur in the diazene 9 before further oxidation takes place as proposed by Craig and coworkers for the McFadyen-Stevens reaction. Two routes are again available in which further rearrangement could occur both leading to the formate ester 84.



SCHEME 26. Possible Oxidative Pathway of Carbazates.

It may also be possible that the carbene 83 could lose a proton followed by carbon monoxide forming the alcohol. Formation of the aziridinone and oxidation to 3 would also lead to the alcohol and carbon monoxide as proposed by Ohme and Preushof (see Scheme 3).

THE REACTIONS OF ALKOXY- AND ARYLOXYCARBONYL RADICALS.

Alkoxy- and aryloxycarbonyl radicals have been formulated as reaction intermediates, spectroscopically detected and studied, and their reactions have been investigated in both the gas- and liquid-phase. In spite of this wide study there are still ambiguities in the literature concerning these reactive intermediates.

There is no published study on the radicals formed by the oxidation of carbazates. However, the radicals prepared by this route should have properties similar to those prepared from other compounds and so should behave similarly. As discussed above, Nicholson and Cohen suggest that diethyl azodicarboxylate (EtOOCN=NCOOEt) undergoes methanolysis in the presence of both mineral acids and ferric ion to form the diazene EtOOCN=NH and then the radicals EtOOCN=N· and EtOOC· (65). Some of the previous work on alkoxycarbonyl radicals are discussed below and indicate what products may be expected from the oxidation of carbazates.

THE REDUCTION OF CHLOROFORMATES.

The reduction of chloroformates is believed to proceed through alkoxycarbonyl radicals. Kuivila and Walsh first reported that benzyl chloroformate when treated at room temperature for 2 weeks with tri-n-butyltin hydride gave a mixture of benzyl formate (61%) and toluene (39%) (75).

[35] $ROOCCl + (n\text{-}Bu)_3SnH \longrightarrow ROOCH + RH + (n\text{-}Bu)_3SnCl$

Ethyl chloroformate on the other hand only underwent 5% reduction after 3 h at 80°C. Complete reduction occurred however in the presence of 1.6 mole % AIBN (azobisisobutyronitrile) forming only ethyl formate and tri-n-butyltin chloride.

Beak and Moje have also studied this reduction (76). Benzyl chloroformate when treated 22 h at 36°C with tri-n-butyltin hydride in hexane afforded toluene (22%) with a very small amount of benzyl formate (<1%) and no "significant amount" of benzyl alcohol. Increasing the amount of hydride or the concentration was found to increase the formate at the expense of the toluene. This reaction did not proceed via the benzyl chloride since there was no significant conversion to this compound under the reaction conditions (a maximum of 4%). Cyclohexyl chloroformate under similar conditions afforded only cyclohexyl formate and less than 1% cyclohexane.

Both these groups suggest the reaction proceeds via the alkoxycarbonyl radical, Scheme 27. Beak and Moje claim that such radicals are thermodynamically disposed to fragment to carbon dioxide and the carbon radical but have an appreciable activation energy to decomposition. The rate of this fragmentation depends of the stability of the radical formed. Thus, the decomposition is facile with benzyl chloroformate since the resonance stabilized benzyl radical is formed. The ethyl and cyclohexyl radicals are not as stable and so the fragmentation will be slower.

[36] $Z\cdot + MH \longrightarrow ZH + M\cdot$ Initiation

[37] $M\cdot + ROOCX \longrightarrow ROOC\cdot + MX$

[38] $ROOC\cdot \longrightarrow R\cdot + CO_2$

[39] $ROOC\cdot \longrightarrow RO\cdot + CO$

[40] $ROOC\cdot + MH \longrightarrow ROOCH + M\cdot$

[41] $R\cdot + MH \longrightarrow RH + M\cdot$

[42] $RO\cdot + MH \longrightarrow ROH + M\cdot$

Typical initiators (Z·):

AIBN (azobisisobutyronitrile)

$Me_2C(CN)-N=N-C(CN)Me_2 \longrightarrow 2Me_2\dot{C}-CN + N_2$

t-Butyl peroxide

$t\text{-}BuO\text{-}O\text{-}t\text{-}Bu \longrightarrow 2t\text{-}BuO\cdot$

Typical hydrides (MH): $(n\text{-}Bu)_3SnH$, $(n\text{-}Pr)_3SiH$

SCHEME 27. The Reduction of Chloroformates with Hydrides.

Jackson and Malek have also investigated the reduction of chloroformates (77). These workers have employed an organosilicon hydride instead of an organotin hydride because the latter tend to reduce chloroformates to formates, ie. abstraction [40] competes effectively with fragmentation [38].

[43] $$RO_2CCl \xrightarrow[0.5\text{-}1.0(t\text{-}BuO)_2]{\text{2-4 } Pr_3SiH} R\text{-}H + CO_2 + (n\text{-}Pr)_3SiCl$$
$$4\text{-}24h \text{ at } 140^oC$$

Since the Si-H bond in organosilanes is stronger than the Sn-H bond in organotin hydrides, abstraction will be slower and fragmentation can compete favorably. The high yields

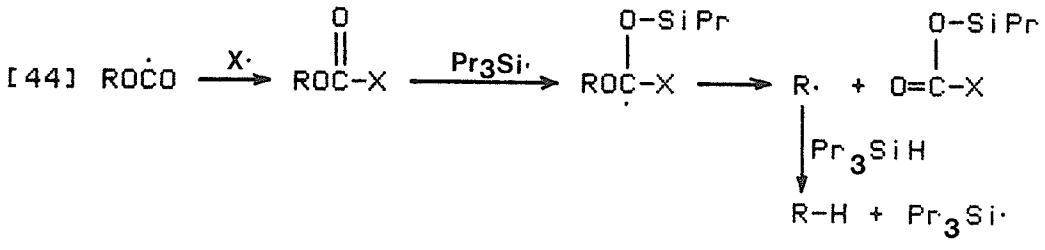
of the alkane with primary and secondary chloroformates indicates [39] and [40] do not compete significantly.

R	% Yield RH
n-octyl	85-92
cyclohexyl	91
cholestan-3β-yl	69
Et_3C-	18
$PhCH_2$-	11
Ph-	trace
$CH_3COCH_2CH_2CH_2$-	43-69

TABLE 14.

The Reduction of Chloroformates with Organosilanes.

The unusually large amount of t-butyl peroxide required appears not to be due to induced decomposition of the peroxide but due to a one-to-one reaction.



This pathway accounts for the large consumption of peroxide and silane while still affording a good yield of the alkane, R-H.

As shown in the table, very good yields of alkane were

obtained from primary and secondary alcohols while tertiary and benzylic alcohols and phenols afforded poor yields. The abstraction reaction [41] should be fast for all radicals R except for the t-butyl and benzyl radicals which are more stable. In contrast, the phenoxycarbonyl radical will undergo a slow fragmentation [38] and instead [39] will be favoured. This difference will be discussed in more detail below.

THE REDUCTION OF SELENOCARBONATES.

Pfenniger and coworkers have developed a related reduction based on selenocarbonates (78).

[45] $$ROH \xrightarrow{O{=}CCl_2} ROOCCl \xrightarrow[pyridine]{PhSeH} ROOCSePh \xrightarrow[initiator,heat]{1.5\ n\text{-}Bu_3SnH} ROOCH\ \&/or\ ROH\ \&/or\ RH$$

The product distribution from this reaction can be controlled by varying the temperature as shown in Table 15. The optimum temperature for the deoxy products is at 144°C, refluxing xylene. This method cannot be used to reduce phenols, eg. 88, because of the unwanted fragmentation of the intermediate phenoxycarbonyl radical. Although tertiary alcohols undergo reduction even at a low temperature these alcohols were converted into the mixed carbonates in low yields only.

Curiously this method not only forms the nor-alkane and the formate but also the alcohol. As seen above, the

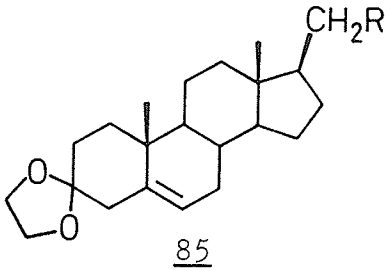
alcohol has not been reported as a product in similar reductions.

TABLE 15. The Reduction of Selenocarbonates.

Seleno-carbonate	Solvent[a]	Temp. °C	%Yield Product		
			Nor-alkane	Formate	Alcohol
85	Bz	80	18	62	20
	Tol	110	38	25	30
	Xyl	144	58	5	37
	TMB	164	66	25	7
	Bz	RT,hν	--	81	19
86	Bz	80	5	76	9
	Tol	110	39	42	14
	Xyl	144	73	16	11
	TMB	164	62	28	10
87	Bz	80	51	43	--
	Tol	110	75	16	6
	Xyl	144	90	4	5
	Bz	RT,hν	9	87	1
88[b]	Xyl	144	--	18	62
50	Bz	80	81	15	--

[a]Bz=benzene, Tol=toluene, Xyl=xylene, TMB=1,3,5,trimethylenebenzene (mesitylene).

[b]5% carbonate also produced.



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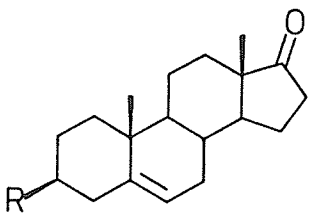

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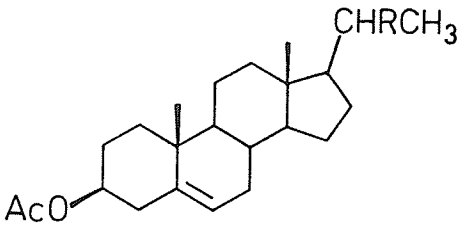

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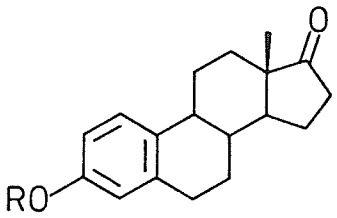

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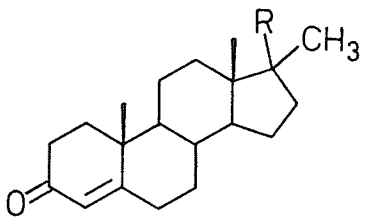


89

R=OOCSeC$_6$H$_5$

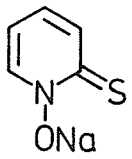
Pfenniger and coworkers have explained this by the loss of carbon monoxide from the alkoxycarbonyl radical.

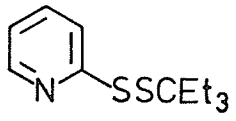
[39] $$ROOC\cdot \longrightarrow RO\cdot + CO$$

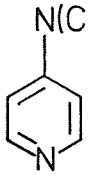
However, based on other investigations such a fragmentation is not expected except for when R is an aromatic group. This points to a different reaction or perhaps the influence of another reagent.

THE FRAGMENTATION OF MIXED OXALATE ESTERS.

Alkoxycarbonyl radicals have also been prepared through oxalic acid derivatives. Barton and Crich have recently described a method of deoxygenating alcohols by the radical induced fragmentation of a mixed oxalate ester (79).

[46] ROH + ClCOCOCl ⟶ ROOC-COCl + 

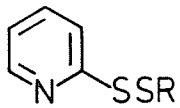
$\xrightarrow[\text{benzene, reflux 1h}]{2Et_3CSH,\ \text{trace DMAP}}$ RH + $2CO_2$ + 

DMAP = 

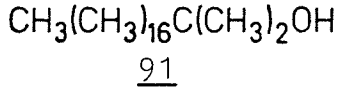
This method affords a good yield of the deoxy compound with tertairy alcohols but secondary alcohols do not give a very good conversion, Table 16. The formation of the formate from cholesterol (93) suggests that at least for secondary groups the two moles of carbon dioxide are not eliminated in a concerted process. Again, there was no evidence of the intermediate alkoxycarbonyl radical losing carbon monoxide.

TABLE 16. The Deoxygenation via Mixed Oxalate Esters.

ROH	% Yield RH	% Yield 81
91	81	72
92	70	67
93[a]	43	51


81

[a] In refluxing chlorobenzene (132°C). Formate (15%) also formed.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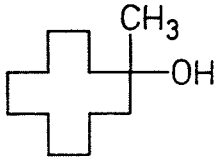
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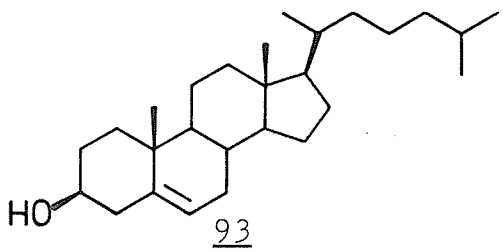
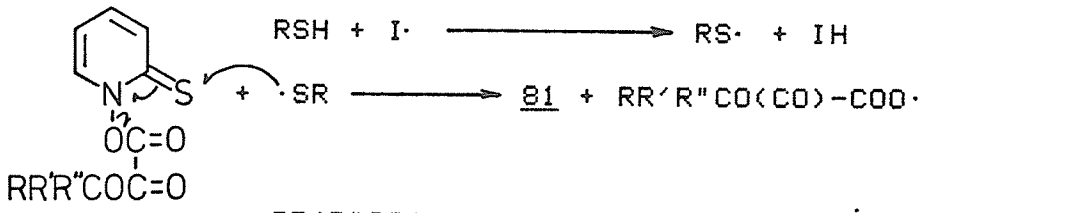

93

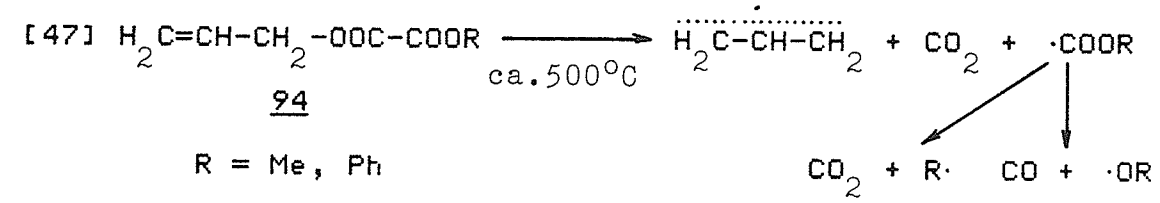


SCHEME 28.

The Radical Induced Fragmentation of a Mixed Oxalate Ester.

THE THERMOLYSIS OF ALLYL OXALATES.

The vapor-phase thermolysis of allyl methyl oxalate and allyl phenyl oxalate has been studied by Louw and coworkers, and they too have evidence for the intermediacy of alkoxy- and aryloxycarbonyl radicals (80). A flow system at 400-500°C and atmospheric pressure was used with excess toluene and nitrogen as diluents.



The thermal stablilities of both oxalates were found to be equal within a factor of two while dimethyl oxalate was essentially stable under the reaction conditions. Thus, the mere breaking of the central C-C bond was not involved in the thermolysis. The initial fragmentation

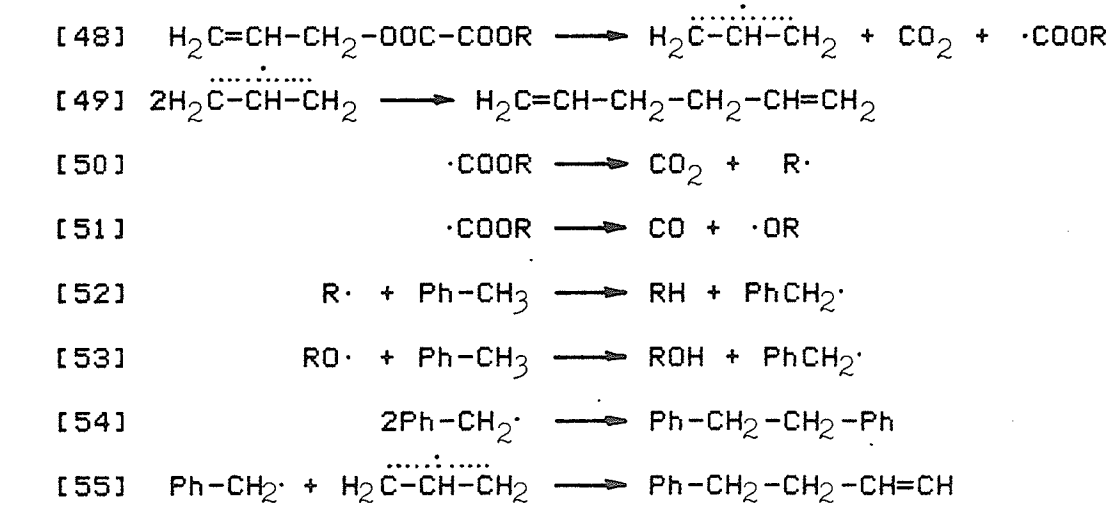
[48] was found to be the rate determining step. For the methyl compound, the ratio of carbon dioxide to carbon monoxide indicates that $k_{50} > k_{51}$. The phenol to benzene ratio for the allyl phenyl oxalate when run in m-xylene indicates that $k_{50} < k_{51}$ or $k_{51}/k_{50} > 80/0.3 =$ ca. 270.

TABLE 17.

Product Distribution in the Thermolysis of Allyl Oxalates.

R	% Yield[a]							
	CO	CO	RH	ROH	A-A[b]	A-B[c]	B-B[d]	Ph-H
Me[e]	190(10)	5-10	90(10)	-	6-20	30-60	15-35	5-15
Ph[f]	ca.100	ca.90	5-15	80-100	5-10	25-60	ca.25	5-15

[a] Based on converted ester. The error is given in the parentheses. [b] A-A=biallyl. [c] A-B=4-phenylbut-1-ene. [d] B-B=bibenzyl. [e] In toluene. In m-xylene <1% benzene and 5-10% toluene formed. [f] In toluene. In m-xylene 0.1-0.3% benzene and 5-10% toluene formed.



SCHEME 29. The Vapor-phase Thermolysis of Oxalate Esters.

The benzene and toluene formed when the reaction was carried out in toluene and xylene, respectively, were probably formed via a homolytic displacement reaction and not by hydrogen abstraction by the corresponding radical.

[56] $$H\cdot + Ar\text{-}X \longrightarrow Ar\text{-}H + X\cdot$$

$Ar = Ph,\ C_6H_4CH_3 \qquad X = Me,\ OOCCOO\text{-}C_3H_5$

Since $k_{50} > k_{51}$ for the methyl compound, the formation of the carbon monoxide from this compound was explained by a different pathway, Scheme 30. The small amount of acrolein that was detected was consistent with this explaination.

$$Me\cdot + H_2C{=}CH\text{-}CH_2\text{-}OOC\text{-}COOMe \longrightarrow CH_4 + H_2\dot{C}\text{-}\dot{C}H\text{-}CH\text{-}OOC\text{-}COOMe$$

$$\longrightarrow H_2C{=}CH\text{-}(CO)H + 2CO + \cdot OMe$$

$$CO \longleftarrow CH_2O + H_2O$$

SCHEME 30. The Formation of Carbon Monoxide.

Again, the alkoxycarbonyl radicals only lost carbon dioxide; there was very little evidence for the competitive loss of carbon monoxide. In contrast, loss of carbon monoxide is favored with phenoxycarbonyl radicals due to the stronger C-O bond in this radical.

THE HYPOIODITE REACTION.

Another related reaction is the photolysis of the alkyl half-esters of oxalic acid 95 in the presence of mercury(II) oxide-iodine reagent, the hypoiodite reaction.

Goosen and coworkers have studied this reaction and found a mixture of products but none of the alkane was formed by this reaction (81). The gas evolved from this reaction was analyzed for carbon dioxide with barium hydroxide by the formation of a precipitate of barium carbonate; the presence of carbon monoxide was not investigated.

In most cases the dialkyl oxalate and the alcohol were the main products with only low yields of the alkyl iodides formed, Table 18. In fact, no benzyl iodide was formed even though C-O cleavage would have formed the resonance-stabilized benzyl radical. Similarily, the t-butyl hydrogen oxalate yielded only t-butyl alcohol and di-t-butyloxalate but no iodide.

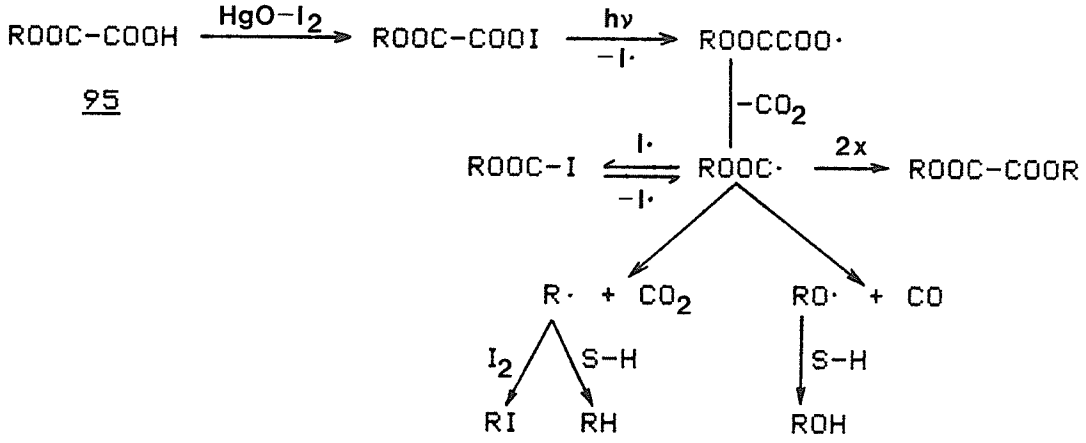
TABLE 18. The Hypoiodite Reaction.

95, R=	% Yield			
	$BaCO_3$	RI	$(ROOC)_2$	ROH
n-Bu	18	2	45	30
s-Bu	22	-	78	trace
t-Bu	33	-	50	50
1-Octadecanyl	56	-	75	3
Cyclohexyl	32	3	14	trace
Benzyl[a]	54	0	36	10
9-Triptycyl[b]	34	-	--	trace

[a]Benzaldehyde (39%) also formed. [b]9-Triptycyl iodoformate (55%) also formed. Triptycene = 9,10-o-benzeno-9,10-dihydroanthracene.

t-Butyl alcohol was found not to be formed via the iodide under the reaction conditions.

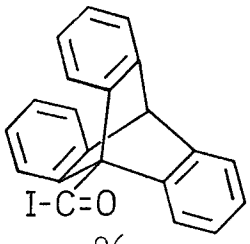
The dialkyl oxalates were probably formed by the dimerization of the alkoxycarbonyl radical, Scheme 31. This explanation is consistent with the formation of the mixed oxalate as well as the symmetrical diester when a mixture of two different hydrogen oxalates was used in the reaction.



SCHEME 31. The Hypoiodite Reaction.

The iodoformates were likely intermediates since when 9-triptycyl hydrogen oxalate was oxidized the iodoformate was isolated. Iodoformates have been reported to be unstable and the formation from the alkoxycarbonyl radical should be reversible. The stability of the 9-triptycyl iodoformate (96) may be due to steric hindrance or to the pi-interaction of the iodoformate group and the aromatic rings. The formation and stability of this iodoformate accounts for the absence of the di-9-triptycyl oxalate as a

product. Iodine must trap the intermediate radical before the dimerization can occur.



96

Unique to this study was the formation of the oxalate esters which were not usually observed. To account for the alcohol formed, Goosen and coworkers proposed that the alkoxycarbonyl radical fragments to the alkoxy radical and carbon monoxide but this explanation is unlikely based on other investigations. The unusual course of this reaction was likely due to the mercury(II) oxide-iodine reagent. Louw and coworkers suggest that the products observed may have been formed by the action of the hypoiodite reagent on ICOOR without involving free organic radicals (80). The formation of an organomercury compound can also explain some of the products formed (see below).

HYDROGEN ABSTRACTION FROM FORMATES.

Thynne and Grey have studied the abstraction of hydrogen atoms from methyl formate by the methoxyl radical between 120 and 185°C in the gas-phase (82). The thermal decomposition of gaseous dimethyl peroxide was the source of these methoxyl radicals. The course of the induced decomposition can be represented by the mechanism shown

below.

[57] $MeOOMe \longrightarrow 2MeO\cdot$

[58] $MeO\cdot + HCOOMe \longrightarrow MeOH + \cdot COOMe$

[59] $\cdot COOMe \longrightarrow CO_2 + Me\cdot$

[60] $Me\cdot + HCOOMe \longrightarrow CH_4 + \cdot COOMe$

[61] $MeO\cdot + Me\cdot \longrightarrow CH_4 + CH_2O$

[62] $MeO\cdot + Me\cdot \longrightarrow MeOMe$

[63] $2Me\cdot \longrightarrow Me\text{-}Me$

SCHEME 32. The Induced Decomposition of Methyl Formate.

The findings were consistent with the formation of the methoxycarbonyl radical, ·COOMe, and the quantitative decomposition to carbon dioxide and the methyl radical. Again, there was no evidence for the decarbonylation tion reaction. Similar results were obtained by Thynne for other formates (83).

Ausloos has found that methyl, ethyl, n-propyl and n-butyl formate will form the corresponding alcohol and carbon monoxide but only on photolysis at short wavelengths (<250nm) (84). When a β-hydrogen atom is present in the alkyl group an alkene and formic acid can also be formed.

[64] $HCOOR + h\nu \longrightarrow CO + HOR$

$\longrightarrow HCOOH + alkene$

Griller and Roberts have studied such alkoxycarbonyl

σ-radicals by electron spin resonance (esr)(85). A liquid mixture of di-t-butyl peroxide and formate were subjected to uv irradiation and the esr spectrum of the alkoxycarbonyl radical was observed. At the appropriate temperature the esr spectrum of the ethyl and t-butyl radical was also observed for ethyl and t-butyl formate. The mechanism suggested was very similar to that of Thynne and Grey (Scheme 32).

There was no evidence of the presence of the adamantyl radical with adamantyl formate although the alkoxycarbonyl radical was observed by esr. Presumably decarboxylation did occur but was accompanied by fast hydrogen abstraction leading to the chain decomposition of the formate.

[65] $$Ad\text{-}O\text{-}\dot{C}{=}O \longrightarrow Ad\cdot + CO_2$$

[66] $$Ad\cdot + Ad\text{-}O\text{-}CHO \longrightarrow Ad\text{-}H + Ad\text{-}O\text{-}\dot{C}O$$

Again there was no evidence for the loss of carbon monoxide from the alkoxycarbonyl radicals.

THE DECOMPOSITION OF AZOCARBOXYLATES.

Esr has also been used by Alberti and Hudson, and others to study the thermolysis and photolysis of azocarboxylates (86). The results were similar to those above and are consistent with the production of the alkoxycarbonyl radicals and loss of carbon dioxide by these radicals. Again there was no evidence for the decarbonylation of these alkoxycarbonyl radicals.

$$ROOC\text{-}N{=}N\text{-}COOR \xrightarrow{h\nu \text{ or } \Delta} 2ROOC\cdot + N_2$$

$$ROOC\cdot \longrightarrow R\cdot + CO_2$$

$$ROOC\cdot \longrightarrow\!\!\!\!\!/\!\!/ \longrightarrow RO\cdot + CO$$

R = Ethyl, t-Butyl

SCHEME 33. The Decomposition of Azocarboxylates.

Jones, Morris and Thynne came to similar conclusions on their gas-phase study of the thermal decomposition of dimethyl azodiformate (87). In this study esr was not used; instead the products were analyzed by mass spectroscopy.

Another more recent and very thorough investigation on the thermal decomposition of azocarboxylates has been carried out by Zabel and Trahanovsky (27). These workers studied the decomposition of methyl and phenyl triphenylmethylazocarboxylate (97a and 97b, respectively) at 60°C in benzene or cumene (isopropylbenzene).

$$Ph_3C\text{-}N{=}N\text{-}COOR$$

97a R=Me

97b R=Ph

They found that these compounds were useful for generating alkoxycarbonyl radicals under mild conditions. The results were again consistent with the conclusions made above.

As one would expect, the cleavage of the carbon-nitrogen bond between the trityl and azo groups in these compounds occurred at a relatively low temperature. The

stable trityl radical was formed with simultaneous or fast loss of a nitrogen molecule to form an alkoxycarbonyl radical. Table 19 lists the identified decomposition products from these compounds. The evolved gases were collected and analyzed by conventional gas analysis for carbon dioxide and carbon monoxide. Nitrogen was assumed to comprise the remainder of this gas.

TABLE 19. The Thermal Decomposition of Azocarboxylates.

Cmpd.	Solvent	Temp (°C)	% Yield CO_2	CO	N_2	101	98	102	103
97a[a]									
	benzene	60	0[b]	2.2	97.8	21	24	11	6.5
	cumene	60	-	-	-	20	28	14	3.6
97b[c]									
	benzene	75	0.1[b]	2.2	97.7	18	>11	>16	-

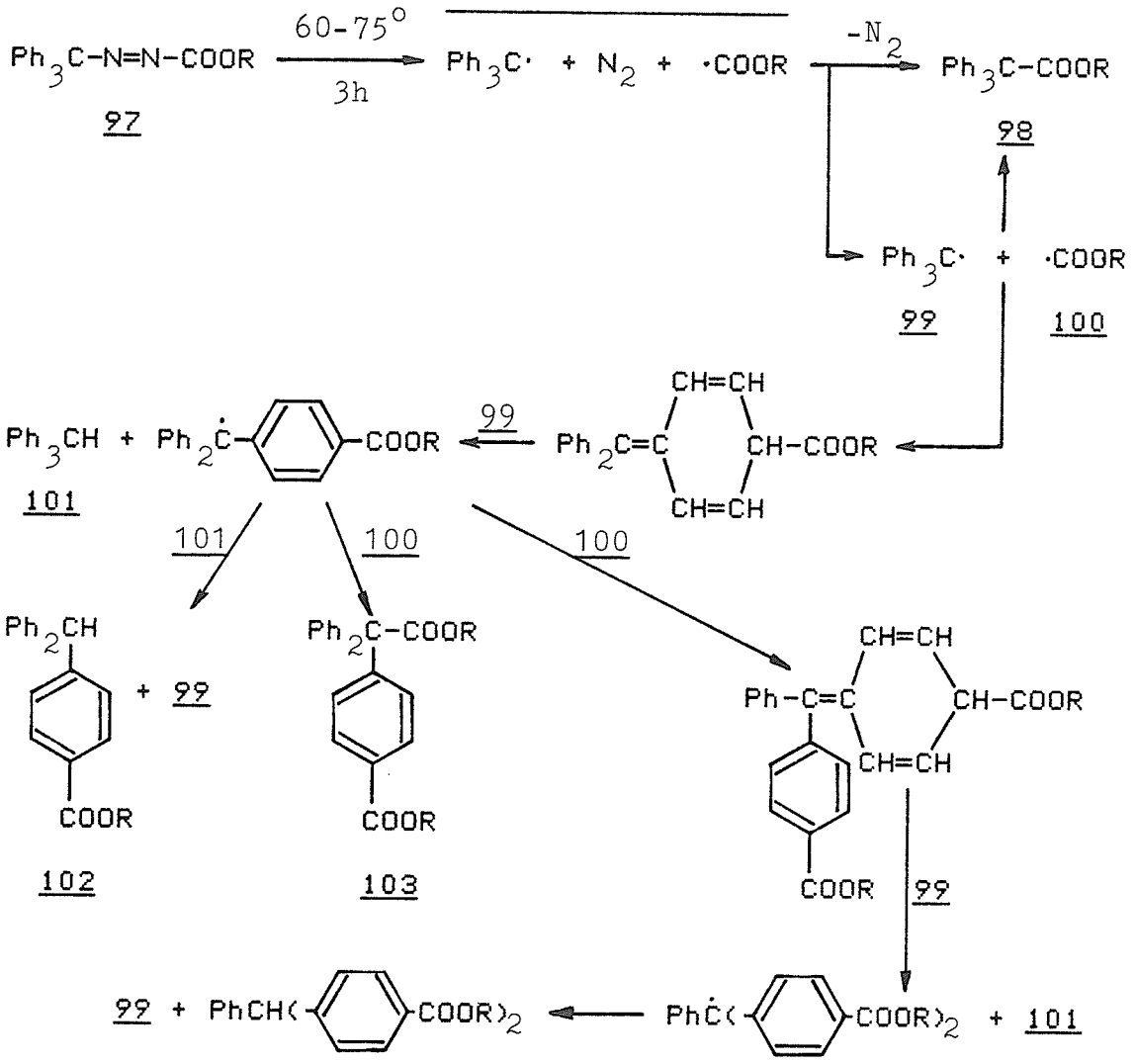
[a]No measureable amounts of MeOOCH, MeOOCPh, MeOOCCOOMe, MeOCOOMe or $MeOOCCMe_2Ph$. Half-life ca. 20 min. by nmr. [b]Maximum estimated yield. [c]No measureable amounts of PhOOCH, PhOOCPh, PhOOCCOOPh or PhOCOOPh. $PhCH(C_6H_4\text{-}COOPh)_2$ (104) also formed, 3.2%.

Although more than 95% of the theoretical amount of nitrogen was formed no decarboxylation and only a small amount of decarbonylation (maximum ca. 2%) could have taken place. This carbon monoxide was probably near the lower limit of detection and could not be determined with

certainty.

All of the products that contain the alkoxycarbonyl group can be explained by coupling reactions of the alkoxycarbonyl radical with a trityl or substituted trityl radical. Five other compounds also containing the trityl and/or alkoxycarbonyl groups were also isolated but could not be identified. A further complication to the analysis was the reaction of oxygen with the excess trityl radicals at the end of the reaction. This would explain the at least 20 distinct bands present in each reaction by tlc.

The most likely route to the products are shown below in Scheme 34. According to this mechanism tri- and tetracarboalkoxy compounds as well as compounds with ortho substituted carboalkoxy groups were also possible products and this would account for the complex mixtures observed. The failure to observe the expected decarboxylation may be due to the relatively high concentration of the very stable trityl radicals. These could be present in a sufficiently high concentration that the alkoxycarbonyl radicals were trapped before any other reactions could occur to any significant extent. The failure to detect oxalates may indicate that the coupling of two alkoxycarbonyl radicals is relatively slow due to an unfavorable polar effect or that these radicals may be rapidly trapped by the trityl radicals.



SCHEME 34. The Thermal Decomposition of Azocarboxylates.

CARBOALKOXYMERCURY COMPOUNDS.

Of related interest are the carbomethoxymercury compounds 105 and 106 prepared by the reaction of carbon monoxide with mercuric acetate and methanol.

[67] $Hg(OAc)_2 + CO + MeOH \underset{\Delta, H^{(+)}}{\rightleftharpoons} MeCOO\text{-}Hg\text{-}COOMe + MeCOOH$

105

$\downarrow KCl$

$Cl\text{-}Hg\text{-}COOMe + MeCOOK$

106

Halpern and Kettle have shown by nmr and ir that these salts have the structure indicated (55). Presumably these compounds are formed through the intermediate mercury carbonyl complex 107.

[68] $X\text{-}Hg\text{-}OMe + CO \longrightarrow \overset{CO}{\underset{\downarrow}{X\text{-}Hg\text{-}OMe}} \longrightarrow X\text{-}Hg\text{-}COOMe$

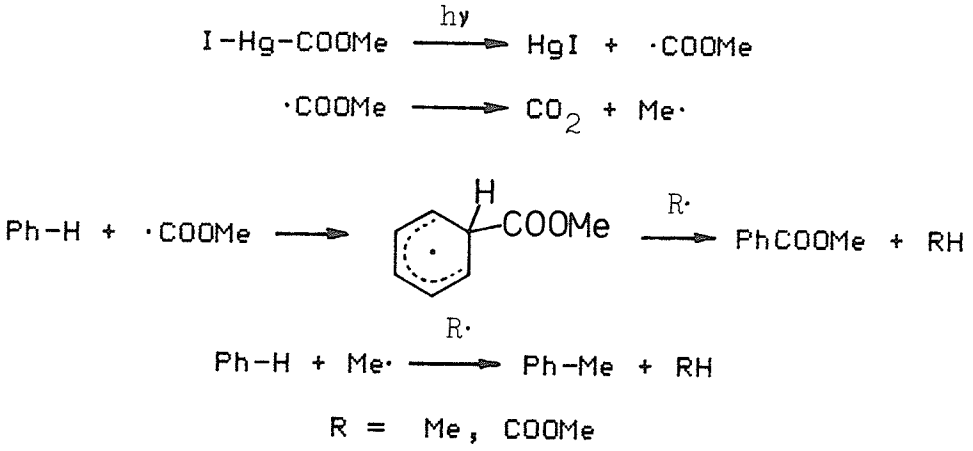
107

These organomercury compounds undergo acid decomposition by nucleophilic assistance leading to carbon monoxide, the alcohol and a mercuric salt (88).

[69] $Cl\text{-}Hg\text{-}COOMe + 3Cl^- \xrightarrow[DMSO]{CF_3COOH} HgCl_4^{2-} + CO + MeOH$

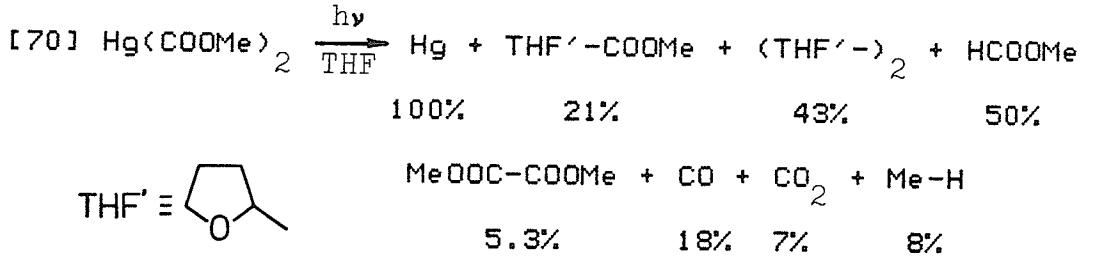
Fanta has studied some of the other reactions these carbomethoxymercuric salts undergo (89). Photolysis of a benzene solution for 6h at 6-10°C resulted in mercurous iodide (56%), methyl benzoate (21%), toluene (12%) and an unidentified compound. Presumably under these conditions the salt decomposes to the mercurous salt and the

methoxycarbonyl radical which can undergo further reaction.



SCHEME 35. The Photolysis of Carbomethoxymercuric Iodide.

The photolytic behaviour of related mercury compounds has also been investigated by Sakakibara and Odaira (90). These workers irradiated various mercury salts in THF with a low-pressure mercury lamp for 12 h under nitrogen at room temperature. The carbomethoxylation of the solvent was again taken as evidence for the formation of the carbomethoxy radical. The results for one salt investigated is shown below.



Other salts with different ligands result in a somewhat different distribution of products.

In this system considerable carbon monoxide was formed. As seen above in other studies, methoxycarbonyl radicals normally do not lose carbon monoxide. Photolysis may produce the methoxycarbonyl radicals in an excited state which may be expected to have different properties and decarbonylate. Or this may simply be a thermal effect with the mercury causing the loss by the reverse reaction used to form this compound [68].

The formation of the dimethyl oxalate should also be noted. Alkoxycarbonyl radicals usually do not dimerize in these systems and this may again be due to the presence of the mercury. The mercury may have a template effect causing the two methoxycarbonyl radicals to rapidly react with each other around the mercury atom before isomerization takes place. This would explain the formation of the dialkyl oxalate in the investigation of Goosen and coworkers on the hypoiodite reaction.

Our results from the oxidation of methyl carbazate are consistent with the formation and decomposition of the methoxycarbonyl radical. Oxidation likely proceeds via the diazene 6 to the azo radical which then readily loses nitrogen which was quantiatively formed in most cases.

[71] $$MeOOCNHNH_2 \xrightarrow{[O]} MeOOCN{=}NH \xrightarrow{[O]} MeOOCN{=}N\cdot \xrightarrow[-N_2]{[O]} MeOOC\cdot \longrightarrow Me\cdot + CO_2$$

The thermodynamically favored loss of carbon dioxide results in the methyl radical which can abstract a hydrogen atom from a suitable donor. As seen from the variation in the yield of methane with different solvents, the solvent can play an important role in donating a hydrogen atom by virtue of its high concentration. The methoxycarbonyl and methyl radicals can also react with the aromatic solvent present (homolytic aromatic substitution). This explains the formation of the methyl benzoate and toluene when the oxidation was carried out in benzene (Table 8).

While the methoxycarbonyl radicals are thermodynamically disposed towards loss of carbon dioxide there is evidence for an appreciable activation energy (see the Appendix). This explains the relatively large amount of methyl benzoate formed (13-14%) while only a trace of toluene was produced (ca. 0.1-0.4%) (Table 8).

The formation of bibenzyl is most reasonably explained by the dimerization of the resonance stabilized benzyl

radical. Hydrogen abstraction from the toluene impurity present in the benzene or from the toluene produced would afford this radical. A trace of diphenyl was also identified in one such reaction and is presumably formed by the dimerization of the phenyl radical (expt. 30). Since benzene is a poor hydrogen atom donor a very strong hydrogen abstracter is required to form the phenyl radical from it. Alkoxy radicals are such powerful hydrogen atom abstracters and thus the formation of the methoxy radical is a possible explanation (see below).

In most of these oxidations we were able to detect considerable amounts of carbon monoxide usually in lower yields than that of carbon dioxide. Decarbonylation of the ROOC· radical is only expected when R is an aromatic ring and this is consistent with the results from the oxidation of phenyl carbazate (33 and 3.5% carbon monoxide and carbon dioxide, respectively). As seen above in the literature examples there are only a few cases when such a decarbonylation has been proposed for cases when R is not an aryl group. These include Pfenniger's work on selenocarbonates (78) and Goosen's work on the hypoiodite reaction (81). Louw in his study on the vapor-phase thermolysis of allyl methyl oxalate has explained the small amount of carbon monoxide formed by another route (80).

A possible explaination is the coordination of the methoxycarbonyl radical to a metal.

[72] $$MeOOC\text{-}M\text{-} \rightleftharpoons MeO\text{-}\overset{\overset{CO}{\downarrow}}{M}\text{-}$$

Carbomethoxymercury compounds, for example 105 and 106, decompose on heating or on acid treatment forming carbon monoxide and methanol (55, 89). A similar reaction could take place in the presence of other metals. Alkoxycarbonyl transition metal complexes play an important role in the formation of various organic compounds (91). Iron and manganese among others are known to form such complexes (92).

The Oxidation of Phenyl, Benzyl and 2-Phenylethyl Carbazates.

The results from the oxidation of phenyl, benzyl and 2-phenylethyl carbazate were presented in Table 10 and 11. Again a large amount of nitrogen was formed and as expected no methane was formed. Presumably, the ROOC· radical was again formed and except for when R was phenyl loss of carbon dioxide was favored.

As expected for phenyl carbazate a large amount of phenol was formed. However, since no diphenyl could be detected the phenoxy radical must not abstract a hydrogen atom from benzene. Other sources of the hydrogen atom are present in the reaction mixture, for example unoxidized or partially oxidized carbazate, or the intermediate radical from the homolytic substitution on benzene. Phenol could also be formed together with aziridinone by a cyclization

type reaction as proposed by Ohme and Preushof (Scheme 26). While ca. 73% of the hydrazino group can be accounted for only 40-50% of the phenyl and carbonyl groups can be detected. Thus, other products must also be formed, and diphenyl hydrazinedicarboxylate (PhOOCNHNHCOOPh) and/or diphenyl azodicarboxylate (PhOOCN=NCOOPh) are possibilities. As seen above, carbonyl azo compounds are good acylating agents.

Since the phenoxycarbonyl radical has a high activation energy for loss of carbon monoxide, the formation of the relatively large amount of phenyl benzoate might be expected. However, the formation of the formate is unforeseen since benzene is a poor hydrogen atom donor. The phenoxycarbonyl radical could be abstracting a hydrogen atom from another source or the formate could be the result of a McFadyen-Stevens type reaction (Scheme 26).

In the oxidation of benzyl carbazate a large amount of bibenzyl is expected since the benzyloxycarbonyl radical should readily lose carbon dioxide to form the resonance stabilized benzyl radical and this was observed. A small fraction of these benzyl radicals may encounter a good hydrogen atom donor and afford the small amount of toluene detected. However, the formation of benzyl formate, and the relatively large amounts of benzyl alcohol and benzaldehyde was unexpected. One does not expect the benzyloxycarbonyl radical to exist in solution long enough to abstract a hydrogen atom and this is consistent with the

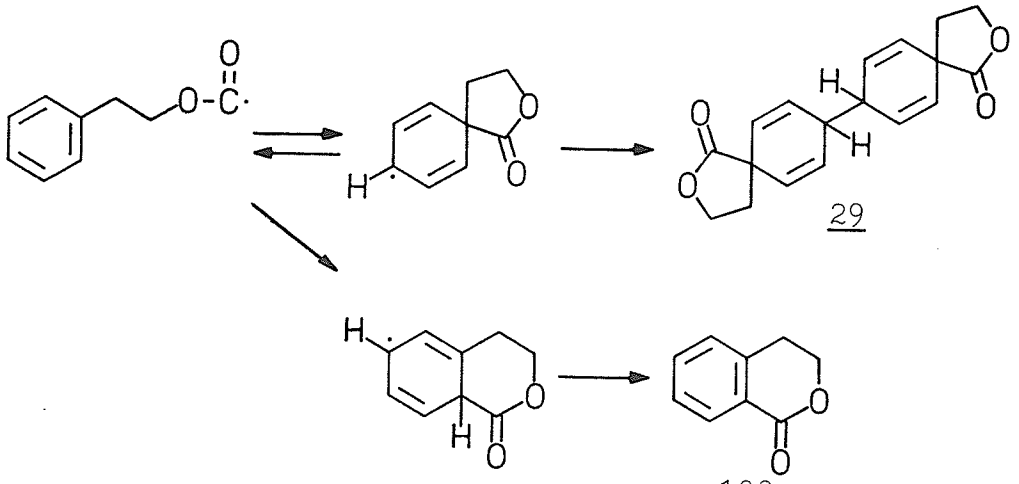
failure to detect any benzyl benzoate. Compare this with the work of Beak and Moje who obtained mainly toluene (22%) with only a very small amount of benzyl formate (<1%) and no "significant amount" of benzyl alcohol when they reduced benzyl chloroformate with tri-n-butyltin hydride, a very good hydrogen atom donor (76).

The formate is probably best explained by the McFadyen-Stevens reaction. Coordination of the benzyloxycarbonyl radical to the manganese atom could lead to the benzyloxy radical and carbon monoxide. Disproportionation would form benzaldehyde and benzyl alcohol, of which the latter which could be oxidized further by the oxidant present to more of the benzaldehyde. No diphenyl, diphenylmethane or benzoic acid were detected in the reaction mixture. Most of the hydrazino and benzyl groups can be accounted for but only ca. 50% of the carbonyl group can be traced. The carbon monoxide, carbon dioxide or the benzyloxycarbonyl group may be forming a stable metal complex. Both gases are known to form stable complexes with transition metals (93).

The oxidation of 2-phenylethyl carbazate will form the 2-phenylethyloxycarbonyl radical which again will have some stability because of an appreciable activation energy for the loss of carbon dioxide. This explains the relatively large amount of 2-phenylethyl benzoate detected. Any loss of carbon dioxide will yield the primary 2-phenylethyl radical which will readily abstract hydrogen to give

phenylethane. The 2-phenylethyl formate may be formed by the hydrogen abstraction by the 2-phenylethyloxycarbonyl radical or more likely via a McFadyen-Stevens type reaction. Again a large amount of alcohol was detected and this may be due to the decarbonylation reaction under the influence of the manganese atom. No bibenzyl, diphenyl, phenylacetaldehyde, phenylacetic acid or 3,4-dihydro-2(1H)-benzopyran-1-one (108) could be detected.

When this oxidation was conducted in methylene chloride, preparative tlc on the reaction mixture afforded 2-phenylethanol, 2-phenylethyl formate together with a high melting solid which was identified spectroscopically as the dimer 29.



Scheme 36.

Dimerization of the 2-Phenylethyloxycarbonyl Radical.

In benzene other reactions of the 2-phenylethyloxycarbonyl radical presumably occur to avoid the loss of the

aromaticity of the benzene ring.

A related cyclization and dimerization has been observed by Hey and coworkers (94). Julia has calculated that the analogous 5-membered spiro radical from the cyclization of the phenylbutyl radical is approximately 2.5 Kcal/mol less stable than the open chain radical while the 6-membered cyclized radical is approximately 6.2 Kcal/mol more stable (95). Thus, the formation of the spiro radical is kinetically controlled while the formation of the 6-membered ring is thermodynamically favored.

When methyl carbazate was oxidized with potassium permanganate, chromium trioxide and potassium ferricyanide in aqueous solution, presumably the conditions used by Ohme and Preushof, no methane was detectedeven though a near quantitative yield of nitrogen was obtained (Table 7). Carbon dioxide was the only other gas detected in the oxidation with potassium permanganate and chromium trioxide. However, no carbon dioxide was observed when potassium ferricyanide was used and instead a low yield of carbon monoxide was obtained. It seems that with the former two powerful oxidants oxidation proceeds past the methoxycarbonyl radical to the carbonium ion. Reaction with water would afford methylcarbonic acid which would decompose to carbon dioxide and methanol. Compare this with the work of Tsuji and coworkers on copper(II) discussed above (68).

[73] $ROOCNHNH_2 \xrightarrow[-N_2]{[O]} ROOC\cdot \xrightarrow{[O]} ROOC^{(+)} \xrightarrow[-H^{(+)}]{H_2O} ROCOOH \xrightarrow[-CO_2]{} ROH$

Obviously a different mechanism takes place with the ferric reagent. The methoxycarbonyl radical may form a complex with iron, as with mercury, some of which could decompose to methanol and carbon monoxide. Such iron complexes are known (91).

AROMATIC SUBSTITUTION BY THE METHOXYCARBONYL RADICAL.

As seen above the methoxycarbonyl radical, ·COOMe, can undergo homolytic substitution on aromatic systems. To investigate the electronic nature of these radicals Tiecco and coworkers have determined the relative rates and isomer distributions in such reactions (96). The polar nature and thus the nucleophilicity of carbon-centered radicals is known to be affected by the hybridization of the orbital carrying the unpaired electron.

In this study the methoxycarbonyl radicals were generated in three different ways: by the thermal decomposition of dimethyl azodicarboxylate [74], by the hydrogen abstraction from methyl formate [75], and by the thermal decomposition of methyl t-butylperoxyoxalate [76].

[74] $MeOOC-N=N-COOMe \xrightarrow{\Delta} MeOOC-N=N + \cdot COOMe$

[75] $t\text{-}BuO\cdot + HCOOMe \longrightarrow t\text{-}BuOH + \cdot COOMe$

$t\text{-}Bu\text{-}O\text{-}O\text{-}t\text{-}Bu \xrightarrow{h\nu,\ RT} t\text{-}BuO\cdot$

[76] $$t\text{-BuO-OOC-COOMe} \xrightarrow{\Delta} t\text{-BuO}\cdot + CO_2 + \cdot COOMe$$

In benzene these reactions formed the substitution product methyl benzoate in every case with isolated yields of 27, 19 and 17% for [74], [75] and [76], respectively. Small quantities of toluene were also detected presumably from the analogous substitution reaction by the methyl radical, [79]. This methyl radical could be formed by the decarboxylation of the methoxycarbonyl radical or by the fragmentation of the t-butoxy radical, [78] and [79], respectively. Diphenyl was also formed when the methoxycarbonyl radical was generated according to [75] and [76] but not from [74]. Presumably the t-butoxy radical abstracts a hydrogen atom from benzene and the resulting phenyl radical could react with benzene. Traces of bibenzyl from the dimerization of the benzyl radical were also present when these two methods were used.

[77] $$\cdot COOMe + PhH \xrightarrow[-H\cdot]{} PhCOOMe$$

[78] $$\cdot COOMe \longrightarrow CO_2 + Me\cdot$$

[79] $$t\text{-BuO}\cdot \longrightarrow Me\text{-}CO\text{-}Me + Me\cdot$$

[80] $$Me\cdot + PhH \xrightarrow[-H\cdot]{} PhMe$$

[81] $$t\text{-BuO}\cdot + PhH \longrightarrow t\text{-BuOH} + Ph\cdot$$

[82] $$Ph\cdot + PhH \xrightarrow[-H\cdot]{} Ph\text{-}Ph$$

[83] $$Ph\text{-}Me + R\cdot \longrightarrow RH + Ph\text{-}CH_2\cdot \xrightarrow{2x} Ph\text{-}CH_2\text{-}CH_2Ph$$

SCHEME 37. Reactions of the Methoxycarbonyl Radical in Aromatic Solvents.

The concentration of toluene was probably too low in [74] for any significant amount of bibenzyl to be formed. Bibenzyl was found to be the major product when these reactions were carried out in toluene.

Reactions [75] and [76] were also carried out in several different substituted benzenes, and in equimolar mixtures of these solvents and benzene. The decomposition of the azocarboxylate was not further employed as a source of the methoxycarbonyl radical since this reaction was found not to be as clean as the other two reactions. Other unidentified products were also formed.

Gas chromatography was used to determine the quantities of the isomeric methyl benzoates and methyl benzoate formed in these reactions. The distribution of these isomers shows the reactivity of the various nuclear positions and the total reactivity of these substituted benzenes relative to benzene. These methoxycarbonylbenzenes were obtained in only 10-20% yields depending on the aromatic solvent employed. These low yields are due to the concurrent reactions of the methoxycarbonyl radical, the most important of which is the decarboxylation reaction.

The results are collected in Table 20 together with the corresponding values for the phenylation reaction for comparison purposes.

TABLE 20. Isomeric Distribution[a] and Relative Reactivities[b] (K) of Substituted Benzenes (Ph-R) to the Methoxycarbonyl[c] and the Phenyl Radical.

R	COOMe					Ph			
	o-	m-	p-	K	%Yield[d]	o-	m-	p-	K
Me	56.0	26.9	17.1	1.45	10	60.9	25.1	14.0	1.58
CMe	0	64.7	35.3	0.73	13	23.3	51.2	25.5	0.72
Cl	46.8	34.2	19.0	0.85	11	50.0	32.0	18.0	1.0
Br	45.1	37.3	17.6	0.86	10	53.5	31.5	15.0	1.39
COOMe	35.1	17.9	47.0	2.2	16	57.0	17.5	25.5	1.77
COMe	40.0	0	60.0	2.3	15	58.0	13.1	28.9	2.2
CN	38.5	13.5	48.0	2.6	20	61.0	12.0	27.0	2.4
NO	77.4	0	22.6	3.8	21	63.0	10.0	27.0	2.94

[a]Determined by gc. [b]Relative to benzene. [c]Produced from methyl t-butylperoxyoxalate at 65°C. Photolysis of di-t-butyl peroxide in the presence of methyl formate at room temperature afforded similar results. [d]Determined from reactions carried out on a preparative scale.

Steric effects caused the degree of ortho substitution to be lower with the methoxycarbonyl radical than with the phenyl radical. The results also indicate a preference for relatively electropositive nuclear positions due to a low nucleophilicity of the radical. This is consistent with the much higher yields observed by Bernardi and coworkers in the homolytic substitution of protonated heteroaromatic

bases with alkoxycarbonylradicals (97). Thus, the behavior of the methoxycarbonyl radical is not significantly different from those of other carbon radicals with similar hybridization like the phenyl, vinyl and cyclopropyl radicals.

Similar results were obtained by Norman and coworkers on the homolytic substitution of benzene and anisole by the methoxycarbonyl radical generated by from monomethyl oxalate and LTA (98).

We also conducted the oxidation of methyl carbazate in toluene/benzene and chlorobenzene/benzene to determine the substitution pattern and thus further investigate the nature of the intermediate causing substitution. Our results were very similar to those of Tieco and coworkers (Table 21) except we found the relative reactivity of chlorobenzene was greater than that of benzene. Since the methoxycarbonyl radical is slightly nucleophilic, attack on the electron deficient chlorobenzene should be favored over attack on benzene. Similarily, the attack of the p-methoxyphenyl radical on chlorobenzene vs. benzene has a relative rate factor of K 1.92 (99).

A similar distribution and relative reactivity was obtained in the presence of copper(II) which is an efficient radical oxidant. However, the total percent yield of benzoates decreased and this must be due to the further oxidation of the methoxycarbonyl radical (see below).

TABLE 21.

Aromatic Substitution by the Methoxycarbonyl Radical.

Ph-R	Experimental					Literature[a]				
	Isomer Distn.(%)					Isomer Distn.(%)				
R=	o-	m-	p-	K	%Yield[b]	o-	m-	p-	K	%Yield[b]
Me[c]	57.6 (2.1)	24.8 (0.9)	17.7 (0.6)	1.55 (0.13)	9.23 (0.37)	56.0	26.9	17.1	1.45	10
	57.3 (3.2)	26.0 (1.4)	16.7 (0.9)	1.54 (0.12)	9.89 (0.39)					
	[d]63.5 (9.9)	23.1 (3.6)	13.5 (2.1)	1.87 (0.54)	5.48 (0.81)					
Cl	49.3 (4.0)	30.7 (2.5)	20.0 91.6)	1.07 (0.12)	10.17 (0.57)	46.8	34.2	19.0	0.85	11

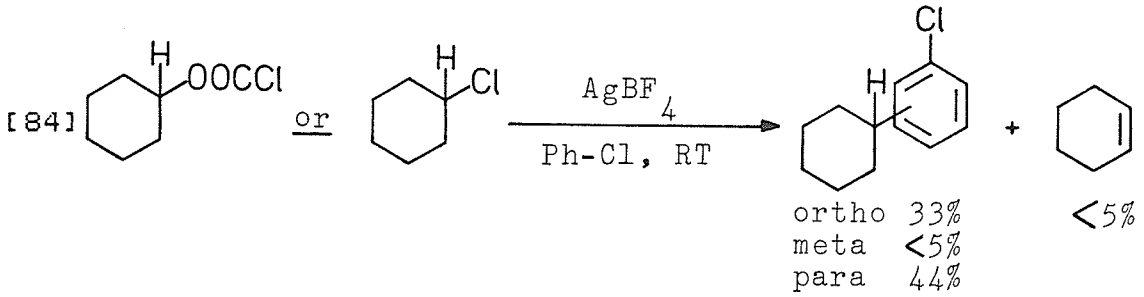
[a]Ref. (98). [b]Total yield of methylbenzoates.

[c]Corrected to be equimolar. [d]In the presence of $Cu(OAc)_2$.

These results conclusively prove that the methoxycarbonyl radical is being formed by the oxidation of the methyl carbazate. The low yields of the benzoates is similar to that when this radical is produced by other routes. Thus, the carbonium ion is not involved since much less of the meta isomer would be expected.

Beak and coworkers were interested in generating such carboxylium ions, $R-O-\overset{(+)}{C}=O$ (100). When they treated cyclohexyl chloroformate with an equimolar amount of silver fluoroborate in chlorobenzene at room temperature they

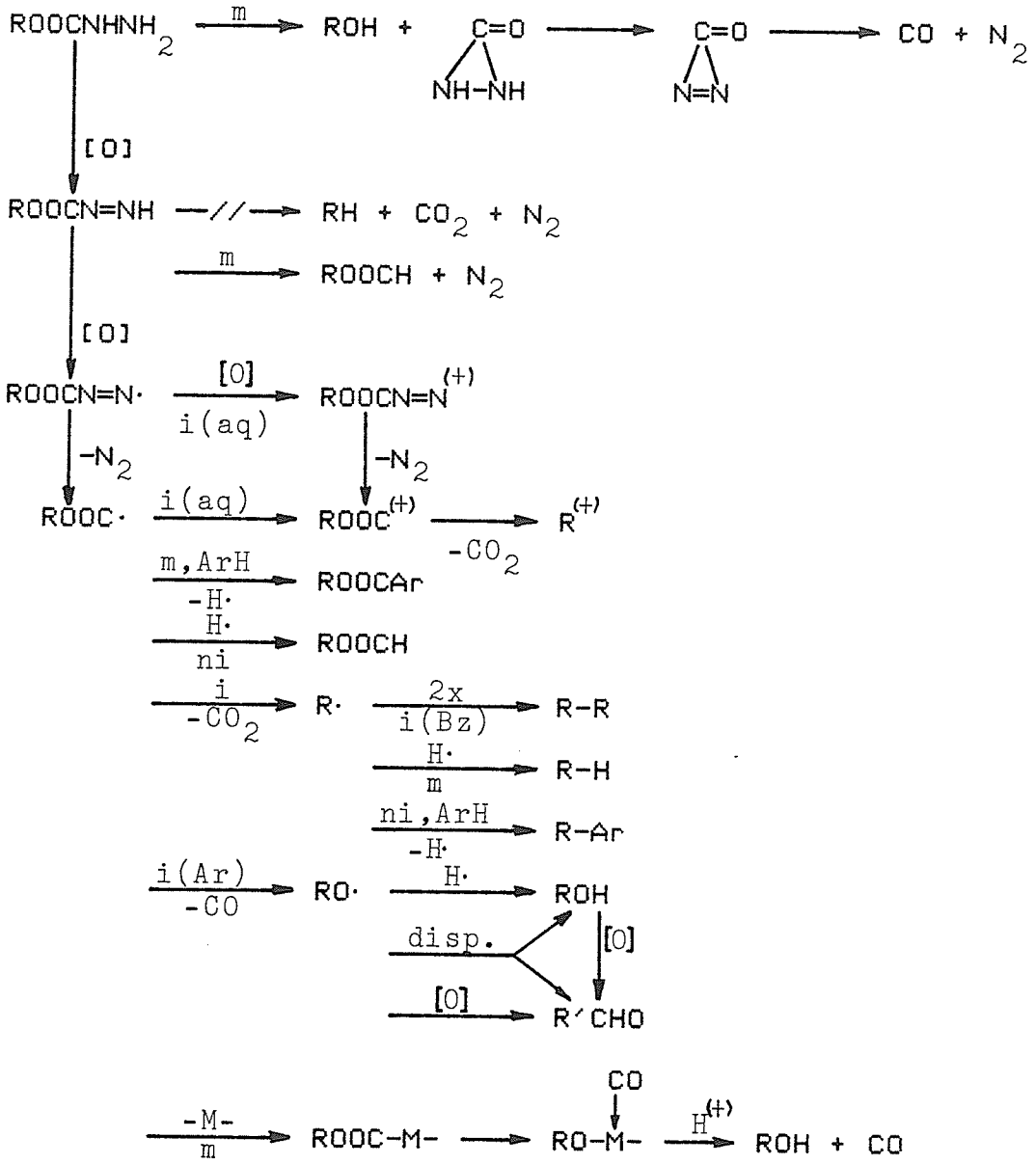
obtained o- and p-cyclohexylchlorobenzene (33 and 44%, respectively) with very little if any meta-substituted isomer and cyclohexene (less than 5% of each). Cyclohexyl chloride afforded the same products.



These reactions were rationalized by the intermediacy of the carboxylium ion which loses carbon dioxide forming the carbonium ion which then reacts with the solvent.

Similarly, alkyl chloroformates react with aromatic hydrocarbons in a Friedel-Crafts reaction to afford the alkylarene. However, aryl chloroformates do form the expected aryl esters of aromatic acids (101). Again, this is because loss of carbon dioxide from an aryl carboxylium ion is a high energy process.

The proposed mechanism for the oxidative decomposition of carbazates is given below.



SCHEME 38. The Oxidation of Carbazates.

m=minor. i(aq)=important in aqueous solutions with strong oxidants. ni=not important. i=important when R≠Ar. i(Bz)=important when R=benzyl. i(Ar)=important when R=Ar.

CONCLUSION

There was no evidence for the oxidative rearrangement of carbazates to the alkane proposed by Ohme and Preushof. Instead, the main reaction was found to be the formation of the alkoxy- or aryloxycarbonyl radical by the oxidation of the hydrazino group and the loss of nitrogen. These radicals underwent the expected reactions including the aromatic homolytic substitution of the solvent, and loss of carbon dioxide from the alkoxy- and of carbon monoxide from the aryloxycarbonyl radical. Conclusive proof of these radicals was the isomer distribution obtained in substituted aromatic solvents and the formation of the cyclized dimer 29 from 2-phenylethyl carbazate.

An unexpected large amount of carbon monoxide and alcohol was obtained from these oxidations. Since the decarbonylation reaction is favored only for the aryloxycarbonyl radicals this loss was proposed to be due to the coordination of the metal present in the oxidant.

The formation of the benzyl formate from the benzyl carbazate was suggested to arise via a McFadyen-Stevens type reaction.

EXPERIMENTAL

General

The solvents (Fisher, certified A.C.S.; except: mesitylene, Aldrich; p-xylene, Eastman) were purified and dried by distillation from anhydrous calcium chloride and were stored over dried Molecular Sieves (5 A, Davison supplied by Fisher). No drying agent was used in the distillation of chlorobenzene (Fisher, certified) and tetralin (Aldrich, 95%). Methyl carbazate (Aldrich) was purified by vacuum distillation and triethylamine (Fisher, reagent) was distilled from phthalic anhydride. The commercial benzyl carbazate used was from Eastman. Activated manganese dioxide, yellow mercuric oxide, 4-phenyl-1,2,4-triazoline-3,5-dione (PTD) and pyridinium chlorochromate (PCC) were prepared according to the literature procedures (46,53,102,47). The other oxidants were commercially available and were used as is: barium manganate, pyridinium dichromate (PDC), lead tetraacetate (LTA) (Aldrich); chromium trioxide, potassium ferricyanide, potassium permanganate (Fisher, certified A.C.S.), red mercuric oxide (Fisher); mercuric acetate (Matheson, Coleman and Bell, reagent A.C.S.); periodic acid (G. Frederick Smith Chemical Company, reagent).

The constant temperature bath was manufactured by Wilkens-Anderson Co. and the constant temperature circulator (Thermomix) used was from Bronwill Scientific, Inc.

Analytical thin layer chromatography (tlc) was done on silica gel F254 pre-coated on plastic sheets to a thickness of 0.2 mm (E. Merck) and was visualized with iodine or shortwave ultraviolet light. Preparative tlc was carried out on silica gel for tlc containing an ultraviolet indicator and calcium sulfate binder (DSF-5, Camag).

Gas chromatography (gc) was carried out on a BASIC gas chromatograph, Model 6500 (Carle Instruments, Inc.), with a 5 A Molecular Sieve and a Porapak Q® or Chromasorb 102® columns (see a later section for complete details), a Perkin-Elmer Sigma 2b with a SP-400 chlorophenyl column (6 ft, Supelco) with temperature programming from 40-200°C, or on a Hewlett Packard 5710A with a column consisting of Bentone 34 (5%) and diisodecyl phthalate (5%) on Chromosorb W (6 ft) at 130°C.

Melting points were measured with a Fisher-Johns melting point apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Anaspect EM 360 (^{1}H at 60 MHz), a Bruker WH 90 (90.02 MHz for ^{1}H and 22.63 MHz for ^{13}C) or a Bruker AM 300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C). Unless otherwise indicated, the solvent used was chloroform-d with tetramethylsilane (TMS) as an internal standard (Aldrich). Mass spectra (ms) were recorded on a Finnigan 1015 spectrometer; the assignments rationalize the fragments observed and are by no means definite. Abundances relative to the base peak of 100% were given

when all the peaks remained on scale. The infrared spectra (ir) were measured on a Pye Unicam SP1000 spectrometer calibrated with a polystyrene film (0.05 mm thickness). Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario.

PREPARATION OF STARTING MATERIALS

1H-Benzotriazole-1-Carbonyl Chloride (BTCOCl) (22)(39)

Anhydrous ether (500 mL) and a magnetic stirring bar were placed in a 1 L 3-necked round bottom flask. This was fitted with a gas inlet tube (sintered-glass diaphragm) and two ground glass stoppers. A rubber hose was attached to the inlet tube, clamped shut and the apparatus was weighed. One of the stoppers was now replaced with a Friedrich's condenser fitted with a drying tube and the flask was cooled in an ice-bath with stirring. Phosgene gas (Matheson) was slowly added from a lecture cylinder while the weight of this cylinder was monitored. The addition was stopped after ca. 1.75 h when a weight loss of 52.2 g was indicated; this would correspond to 0.528 mol of phosgene. The reaction flask was now returned to its original configuration and was reweighed. The new weight indicated that ca 45.9 g (0.464 mol) of phosgene had been absorbed; this was taken as the more accurate value neglecting the loss of ether during the charging process.

The reaction flask was removed from the bath and a 100 mL round bottomed flask containing benzotriazole (BTH) (25.03 g, 0.210 mol, Fisher reagent grade) was attached to it via a 15 cm Tygon tube, 2.5 cm in diameter. This solid BTH was slowly added with stirring to the cold, ethereal phosgene solution over 3.5 h. Complete dissolution did not occur and an opaque white suspension resulted. However, on stirring overnight at room temperature a clear, colorless

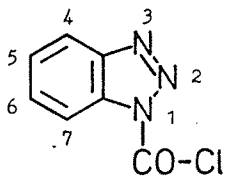
solution was obtained.

Phosgene indicator paper (103) demonstrated that phosgene was still present. The flask was flushed with nitrogen for 1 h and the entrained phosgene was decomposed by passing the nitrogen stream through a 20% solution of sodium hydroxide then into a drain which had water running into it. The reaction was then opened to the atmosphere and flushed with nitrogen for another 0.5 h. Phosgene indicator paper now only underwent a slight color change showing that only a small amount of phosgene was still present. The ether was carefully removed yielding 31.12 g (98.3%) of crude BTCOCl (22), mp 51.5-53.0°C. It was important that a sodium hydroxide trap was used on the rotary evaporator so that the final traces of phosgene present in the ether were removed and not released into the atmosphere.

This material may contain a trace amount of 1,1'-carbonyl dibenzotriazole (DBTCO) but was suitable for further reaction. Recrystallization from dry pentane afforded pure crystals of BTCOCl, mp 52.5-54.0°C; lit. mp 54-55°C (39).

^{1}H nmr at 300 MHz:

δ 7.57-7.62 ppm (m, 1H, H5 or H6)
7.72-7.78 (m, 1H, H5 or H6)
8.13-8.19 (m, 2H, H4, H7)



ir (chloroform):

$\bar{\nu}$1607 cm^{-1}	(w)	N=N stretch
1769	(s)	C=O stretch

ms:

m/z			
181,183	M+	Ratio	2.81
153,155	BT-Cl$^+$		2.91
146	BT-CO$^+$		
125,127	C_6H_4-N-Cl$^+$		2.70
119	BTH$^+$		
118	BT$^+$		
90 (base)	$C_6H_4N^+$		

The ratio of chlorine isotopes observed was within experimental error of the expected ratio of $^{35}Cl/^{37}Cl$ = 100/32.5 = 3.08.

General Procedure for the Preparation of 1-Alkoxy- and 1-Aryloxycarbonyl Benzotriazole

A solution of the alcohol or phenol (1-12 g) in dry benzene or toluene (10-100 mL) was added dropwise to a stirring solution of crude BTCOCl (1.0 equiv) and triethylamine (1.0 equiv) in dry benzene or toluene (10-120 mL) at room temperature. Cooling was used, if necessary, to maintain the reaction temperature at less than ca. 35°C and the progress of the reaction was followed by tlc.

After stirring at room temperature for 1-6 h the precipitate of triethylamine hydrochloride was filtered off on a Buchner funnel. The solvent was now either completely

removed on a rotary evaporator and the residue recrystallized from a suitable solvent or, if the product began to crystallize when the solution was concentrated, it was then filtered off. This procedure was repeated until no more material could be obtained in this way. The remainder of the solvent was then completely removed and the residue recrystallized or triturated with a suitable solvent.

1-(2-Phenylethoxycarbonyl)benzotriazole (109)

Distilled 2-phenylethanol (12.02 g, 0.0984 mol, Aldrich) in dry toluene (80 mL) was added dropwise over 0.4 h to a solution of crude BTCOCl (18.09 g, 0.0996 mol) and TEA (14.0 mL, 10.16 g, 0.100 mol) in dry toluene (100 mL). When the temperature had risen to 35°C the reaction was cooled with an ice-bath. Tlc (ether), after 1 h stirring at room temperature, indicated the reaction was essentially complete.

The reaction mixture was filtered after 6 h and 13.31 g (98.3%) TEA.HCl was obtained. The filtrate was concentrated as far as possible and the residual toluene removed by extracting with pentane (3x25 mL). The total crude yield was 25.45 g (96.8%) of an off-white solid, mp 42.5-47.0°C.

A portion of the crude product (1.05 g) was recrystallized from 1:1 ether:petroleum ether (50 mL) yielding 0.76 g (70.1%) of colorless crystals of 109, mp

47.0-49.5°C. Analysis for $C_{15}H_{13}N_3O_2$; calculated: C 67.40, H 4.90, N 15.72%; found: C 67.82, 67.87; H 5.11, 5.00; N 15.48, 15.41%.

^{1}H nmr at 90 MHz:

δ 3.24 ppm	(t, J 7.2 Hz, 2H,	$-C\underline{H}_2-Ph$)
4.82	(t, J 7.2 Hz, 2H,	$-COO-C\underline{H}_2-$)
7.22-7.72	(m, 7H, aromatic)	
7.97-8.20	(m, 2H, aromatic)	

ir (chloroform):

$\bar{\nu}$ 1607 cm^{-1}	(w)	N=N, C=C, stretch
1767	(s)	C=O stretch

ms:

m/z		
267		M+
239		-28, $-N_2$
194		-73, -COOH, N_2
163		BT-COOH$^+$
146		BT-CO$^+$
121		$PhCH_2CH_2O^+$
120		$PhCH_2CHO^+$
119		BTH$^+$
105	(base)	$PhCH_2CH_2^+$
104		PhCH=CH$^+$
91		$C_7H_7^+$
90		$C_6H_4N^+$
79		$C_6H_7^+$
77		$C_6H_5^+$

1-Benzyloxycarbonylbenzotriazole (110)

Distilled dry benzyl alcohol (9.06 g, 0.0838 mol, Shawinigan, reagent) in dry distilled benzene (80 mL) was dropwise added over 0.75 h to a stirring solution of crude BTCOCl (15.32 g, 0.0844 mol) and TEA (ca. 12.0 mL 8.71 g, 0.0860 mol) in dry benzene (100 mL). The reaction was allowed to warm to 30°C and was then cooled with a room temperature water bath.

Tlc (ether, and 1:1 petroleum ether:ether), after 1.25 h at room temperature, showed the reaction was essentially complete. After stirring for 5.6 h the white precipitate of TEA.HCl (11.14 g, 96.6%) was filtered off. The product was obtained by gradually removing the solvent and filtering off the resulting precipitate, mp 108.0-110.0°C; lit. 106-108°C, 107-108°C (39). The residue obtained upon removal of all the solvent was recrystallized from 1:1 benzene:petroleum ether affording material with mp 107.0-109.0 C. A total of 17.99 g (84.8%) 110 was obtained in this way.

^{1}H nmr at 90 MHz:

δ 5.63 ppm (s, 2H, $-CH_2-$)

7.34-7.74 (m, 7H, aromatic)

8.04-8.19 (m, 2H, aromatic)

ir (chloroform):

$\bar{\nu}$1600	cm^{-1}	(w) N=N, stretch
1612		(w) C=C, stretch
1771		(v.s) C=O, stretch

ms:

m/z	253	(5.0%)	M+
	180	(9.0)	-73, -COOH, $-N_2$
	119	(33.2)	BTH^+
	107	(20.8)	$PhCH_2O^+$
	91	(100.0)	$C_7H_7^+$
	79	(4.5)	$C_6H_7^+$
	78	(7.2)	$C_6H_6^+$
	77	(6.8)	$C_6H_5^+$

1-Phenyloxycarbonylbenzotriazole (111)

A solution of phenol (10.02 g, 0.106 mol, BDH) in dry distilled benzene (100 mL) was slowly added over 1.3 h to a stirring solution of BTCOCl (19.28 g, 0.106 mol) and TEA (10.79 g, 0.107 mol) in dry benzene (120 mL). The temperature was allowed to rise to 31°C whereupon the reaction was cooled with a water bath.

Tlc (1:1 petroleum ether:ether) seemed to indicate that the reaction was complete although it was difficult to distinguish between phenol and the product. After stirring for 1.7 h at room temperature the white precipitate of TEA.HCl was filtered off (13.88 g, 95.0%). Pure 111 (21.34 g, 84.0%) was obtained as a white solid on gradually

removing the benzene and filtering, mp 110.5-111.5°C; lit. 110-112°C, 109-110°C (39). The final residue on complete removal of the remainder of the solvent was triturated with benzene.

^{1}H nmr at 90 MHz:

7.36-7.78 ppm (m, 7H, aromatic)

8.12-8.24 (m, 2H, aromatic)

ir (chloroform):

$\bar{\nu}$ 1595 cm^{-1} (m) N=N, stretch

1601,1612 (w) C=C, stretch

1780 (v.s) C=O, stretch

ms:

m/z			
	239	(0)	No parent ion
	146	(100.0)	BT-CO$^+$
	118	(66.7)	BT$^+$
	94	(13.3)	PhOH$^+$
	90	(98.3)	$C_6H_4N^+$
	77	(33.3)	$C_6H_5^+$

1-(2,6-Dimethylphenyloxy)carbonylbenzotriazole (112)

2,6-Dimethylphenol (1.35 g, 11.1 mmol, Aldrich) in toluene (15 mL) was slowly added to a stirring solution of BTCOCl (2.06 g, 11.3 mmol) and TEA (ca. 1.6 mL, 1.16 g, 11.5 mmol) in toluene (10 mL) with stirring. Heat was evolved and after stirring for 1.5 h at room temperature the TEA.HCl was filtered off (1.47 g, 96.6%). After the

solvent was removed, the 2.59 g (87.7%) of crude product was recrystallized from ether (75 mL) yielding 2.20 g (74.5%) pure 112, mp 133.5-136.0°C.

Analysis for $C_{15}H_{13}N_3O_2$; calculated: C 67.40, H 4.90, N 15.72%; found: C 67.59, 67.82; H 5.18, 5.01; N 15.47, 15.51%.

^{1}H nmr at 90 MHz:

δ 2.32 ppm	(s, 6H,	2xMe)
7.18	(s, 3H,	aromatic)
7.47-7.80	(m, 2H,	aromatic)
8.14-8.26	(m, 2H,	aromatic)

ir(chloroform):

$\bar{\nu}$ 1603 cm^{-1}	(w)	N=N, stretch
1614	(w)	C=C, stretch
1773	(s)	C=O, stretch

ms:

m/z 267	(0.1%)	M+
239	(0.2)	-28, $-N_2$
223	(22.0)	-44, $-CO_2$
146	(92.8)	BT-CO$^+$
121	(17.2)	$(Me)_2C_6H_3O^+$
118	(83.5)	BT$^+$
90	(100.0)	$C_7H_6^+$
77	(30.9)	$C_6H_5^+$

1-(2,3-Dimethylphenyloxy)carbonylbenzotriazole (113)

To a stirring solution of BTCOCl (2.05 g, 11.3 mmol) and TEA (ca. 1.75 mL, 1.27 g, 12.5 mmol) in toluene (10 mL) was added dropwise a solution of 2,3-dimethylphenol (1.37 g, 11.2 mmol, Aldrich) in toluene (20 mL). Heat was evolved and after 2 h at room temperature the precipitate of TEA.HCl was filtered off (1.48 g, 95.9%). The solvent was completely removed and the crude ester (2.74 g, 91.4%) recrystallized from ether (30 mL) affording 2.15 g (71.7%) light gold crystals of 113, mp 126.0-128.0°C.

An analytical sample was further recrytallized from benzene/pentane, mp 128.0-129.5°C. Analysis for $C_{15}H_{13}N_3O_2$; calculated: C 67.40, H 4.90, N 15.72%; found: C 67.66, 67.42, 67.34; H 5.26, 5.21, 5.07; N 15.32, 15.24, 15.37%.

^{1}H nmr at 90 MHz:

δ 2.24 ppm	(s, 3H, 3-Me)
2.36	(s, 3H, 2-Me)
7.18	(s, 3H, aromatic)
7.46-7.79	(m, 2H, aromatic)
8.12-8.25	(m, 2H, aromatic)

ir (chloroform):

$\bar{\nu}$ 1602 cm^{-1}	(w)	N=N, stretch
1613	(w)	C=C, stretch
1771	(v.s)	C=O, stretch

ms:

m/s		
	267	M+
	239	-28, $-N_2$
	223	-44, CO_2
	146(base)	BT-CO$^+$
	121	$Me_2C_6H_3O^+$
	118	BT$^+$
	90	$C_7H_6^+$
	77	$C_6H_5^+$

1-Dodecyloxycarbonylbenzotriazole (114)

To a stirring solution of BTCOCl (2.03 g, 11.2 mmol, Matheson, Coleman and Bell) and TEA (ca. 1.6 mL, 1.16 g, 11.5 mmol) in dry toluene (10 mL) was dropwise added a solution of dodecanol (2.12 g, 11.4 mmol) in toluene (10 mL). The reaction was exothermic and the precipitate of TEA.HCl (1.45 g, 94.2%) was filtered off after stirring for 1.5 h at room temperature. The crude product (3.54 g, 95.5%) obtained on complete removal of the solvent was recrystallized from ether (30 mL) affording 2.00 g (54.0%) 114, mp 43.0-44.0°C.

An analytical sample was recrystallized from benzene/pentane, mp 45.0-45.5°C. Analysis for $C_{19}H_{29}N_3O_2$; calculated: C 68.85, H 8.82, N 12.68%; found: C 69.03, H 9.08, N 12.40%.

^{1}H nmr at 90 MHz:

δ 0.76-1.61 ppm (m, 21H, $-(CH_2)_9CH_3$)

1.78-2.11 (m, 2H, $-O-CH_2\underline{CH_2}-$)

4.62 (t, J 6.6 Hz, 2H, $-O-CH_2-$)

7.40-7.76 (m, 2H, aromatic)

8.08-8.19 (m, 2H, aromatic)

ir (chloroform):

$\bar{\nu}$ 1601 cm^{-1} (w) N=N, stretch

1613 (w) C=C, stretch

1771 (v.s) C=O, stretch

ms:

m/z			
	331	(14.6%)	M+
	303	(0.7)	-28, $-N_2$
	258	(0.9)	-73, -COOH, $-N_2$
	191	(3.6)	$C_6H_4N-COO-CH_2CH_2CH_2CH_3^+$
	146	(4.3)	$BT-CO^+$
	135	(24.6)	$C_6H_4N-COOH^+$
	119	(41.1)	BTH^+
	91	(42.9)	$C_6H_5N^+$
	90	(30.4)	$C_6H_4N^+$
	43	(100.0)	$C_3H_7^+$

<u>1-Cyclohexyloxycarbonylbenzotriazole (115)</u>

A solution of cyclohexanol (1.15 g, 11.5 mmol, Fisher) in toluene (10 mL) was added dropwise with stirring to BTCOCl (2.02 g, 11.1 mmol) and TEA (ca. 1.75 mL, 1.27 g, 12.5 mmol) in dry toluene (10 mL) at room temperature. The

reaction was exothermic and was worked-up after 1.5 h. The precipitate of TEA.HCl (1.45 g, 94.7%) was filtered off and 2.42 g (88.7%) of crude 115 was obtained on concentrating the filtrate. The crude product was purified by recrystallization from ether affording 0.82 g (30.1%) 115, mp 70.5-73.5°C.

An analytical sample was further recrystallized from benzene/pentane but the melting point was unaltered, mp 70.5-73.5°C. Analysis for $C_{13}H_{15}N_3O_2$; calculated: C 63.66, H 6.16, N 17.13%; found: C 64.08, 63.85; H 6.30, 6.40; N 16.81, 16.83%.

^{1}H nmr at 90 MHz:

δ 1.16-2.37 ppm	(m, 10H,	$-(CH_2)_5-$)
5.22	(m, 1H,	O-C<u>H</u>-)
7.36-7.75	(m, 2H,	aromatic)
7.98-8.19	(m, 2H,	aromatic)

ir (chloroform):

$\bar{\nu}$ 1603 cm^{-1}	(w)	N=N, stretch
1614	(w)	C=C, stretch
1763	(s)	C=O, stretch

ms:

m/z 245	(20.2%)	M+
200	(1.0)	-45, -COOH
164	(10.0)	BTH+H^+
146	(3.9)	BT-CO^+
136	(16.7)	$C_6H_5NCOOH^+$

135	(11.9)	$C_6H_4NCOOH^+$
119	(51.8)	BTH^+
99	(33.9)	$c\text{-}(C_6H_{11})\text{-}O^+$
91	(33.3)	$C_6H_5N^+$
90	(39.9)	$C_6H_4N^+$
83	(63.7)	$C_6H_{11}^+$
55	(100.0)	$C_4H_7^+$

General Procedure for the Preparation of Alkyl and Aryl Carbazates

A solution of the 1-alkoxy- or 1-aryloxycarbonyl-benzotriazole (5-20 g) in benzene (50-100 mL) was added dropwise with stirring to a mixture of hydrazine (Eastman, 95+%) or hydrazine hydrate (85%, Fisher, purified) (1.2-1.5 equiv) and benzene (50-100 mL) at room temperature over 1-2 h. The temperature was monitored to be certain that it did not rise over ca. 35°C; cooling was usually not necessary. The progress of the reaction was monitored by tlc. Normally the reaction was complete after 1-2 h at room temperature.

Work-up involved washing the reaction mixture with 10% sodium carbonate and water to remove the BTH and drying over anhydrous magnesium sulfate (Fisher, certified). If anhydrous hydrazine was used then some of the BTH could be recovered by neutralizing the combined basic extracts with 10% HCl and extracting with ether. This was not possible when the hydrate was used since the BTH dissolved in the residual aqueous hydrazine solution.

The solvent was then either completely removed and the crude carbazate recrystallized or the solution was concentrated until crystallization began and then filtered. This was repeated until no more material could be obtained in this manner. The solvent was then completely removed and the residue recrystallized or triturated with a suitable solvent.

For some small scale preparations neat hydrazine hydrate (85%, 1.3-1.5 equiv) was directly added to a stirring solution of the 1-alkoxy- or 1-aryloxycarbonyl-benzotriazole (1 g) in benzene or toluene (25 mL) at room temperature.

2-Phenylethyl Carbazate (27)

Crude 1-(2-phenylethyloxy)carbonylbenzotriazole (109) (10.02g, 0.0375 mol) in benzene (100 mL) was added over 1.7 h to a solution of anhydrous hydrazine (1.54 g, 0.0456 mol) in benzene (50 mL) at room temperature. After stirring for 2.25 h at room temperature the cream colored precipitate of crude BTH (1.50 g, 33.6%) was filtered-off.

The benzene solution was extracted with 10% potassium carbonate (5x10 mL), water (10 mL) and dried. Further BTH (0.35 g, 41.4% total) was recovered by acidifying the basic extracts with 10% sulfuric acid (50 mL) and reextracting with chloroform (3x10 mL).

A tlc (1:1 ether:petroleum ether) indicated that some BTH was still present in the benzene solution. The benzene was removed in portions on a rotary evaporator and the precipitate filtered-off affording 4.66 g (68.9%) pure 27, mp 90.0-91.0°C.

A sample for analysis was further purified by recrystallization from hot 1,1,1-trichloroethane, mp 90.0-90.5°C. Analysis for $C_9H_{12}N_2O_2$; calculated: C 59.99, H 6.71, N 15.55%; found: C 60.00, 60.20; H 7.01, 6.86;

N 16.09, 15.84%.

^{1}H nmr at 90 MHz:

δ 2.94 ppm	(t, J 7.0 Hz, 2H,	Ph-C$\underline{H}_2$-)
3.42	(s, 2H,	-NH_2)
4.33	(t, J 7.0 Hz, 2H,	-C$\underline{H}_2$-COO-)
6.00	(s, 1H,	-NH-)
7.16-7.31	(m, 5H,	aromatic)

ir (film from carbon tetrachloride):

$\bar{\nu}$ 1641 cm^{-1}	(s)	Amide II
1699	(s)	C=O stretch
3340	(s)	N-H stretch

ms:

m/z 180		M+
121		$PhCH_2CH_2O^+$
105(base)		$PhCH_2CH_2^+$
104		$PhCH{=}CH_2^+$
91		$C_7H_7^+$
79		$C_6H_7^+$
77		$C_6H_5^+$
65		$C_5H_5^+$
59		$O{=}C{=}NH{-}NH_2^+$

Benzylcarbazate (24)

1-Benzyloxycarbonylbenzotriazole (110) (4.82 g, 19.0 mmol) in benzene (100 mL) was added dropwise over 0.9 h to a stirred solution of anhydrous hydrazine (0.81 g, 24.0

mmol) in benzene (50 mL). The reaction was carried out in a cool water bath so the temperature remained at 18-25°C. When the addition was complete a light yellow precipitate of crude BTH was present and the reaction was stirred another 0.8 h at room temperature.

The BTH was filtered off (0.84 g, 37.0%) and the resultant solution was washed with 10% potassium carbonate (5x10 mL), saturated sodium chloride solution (10 mL) and dried. Tlc (1:1 petroleum ether:ether) indicated that this solution was essentially pure carbazate. A further 0.30 g BTH (50.2% total) was obtained on acidifying the combined basic extracts with 10% HCl (50 mL) and reextracting with chloroform (3x25 mL).

The washed benzene solution was concentrated (40 mL) and the white needles of benzyl carbazate were filtered off. Pentane was added to precipitate more product and the residue from complete removal of the solvent was recrystallized from benzene/pentane. The total yield of 24 was 2.50g (79.1%), mp 67.5-69.0°C; lit. mp 66.5-67°C (24).

^{1}H nmr at 90 MHz:

δ3.43 ppm	(s, 2H,	$-NH_2$)
5.14	(s, 2H,	$-CH_2-$)
6.11	(s, 1H,	-NH-)
7.35	(s, 5H,	aromatic)

ir (chloroform):

$\bar{\nu}$1635 cm^{-1}	(m)	Amide II
1731	(v.s)	C=O stretch
3370	(m)	N-H stretch
3470	(m)	N-H stretch

ms:

m/z	166	M+
	149	-17, $-NH_3$
	135	-31, $-N_2H_3$
	122	-44, $-CO_2$
	107	$Ph-CH_2O$
	105	Ph-CO or $Ph-CH_2N$
	91(base)	C_7H_7
	79	C_6H_7
	77	C_6H_5
	65	C_5H_5

Phenyl Carbazate (25)

1-Phenyloxycarbonylbenzotriazole (111) (20.00 g, 0.0836 mol) in benzene (200 mL) was added over 2.2 h to a stirred solution of anhydrous hydrazine (95+%, 3.40 g, 0.101 mol) in benzene (100 mL). The reaction temperature was maintained at 10-20°C with an ice bath.

After an additional 2.25 h at room temperature the yellow precipitate which had appeared was filtered-off affording 1.12 g (24.7%) of a cream-colored carbohydrazide, mp 157.5-159.0°C, lit. 153-154°C (104).

The filtered solution was washed with 10% sodium carbonate (5x50 mL), saturated sodium chloride solution (2x50 mL) and dried. The solvent was partially removed and the carbazate which had appeared was filtered-off. The solution was concentrated to dryness and the residue triturated with cold carbon tetrachloride yielding a total of 1.72 g (13.5%) of pure 25, mp 104.5-106.5°C; lit. 103-104°C (27). Low melting material (2.87 g) which had the smell of phenol was extracted into the solvent. Crude BTH (7.53 g, 75.6%) was recovered from the original organic layer.

Some decomposition of the phenyl carbazate occurred when it was recrystallized from hot carbon tetrachloride; trituration with this cold solvent was a better method of purification.

^{1}H nmr at 90 MHz:

δ3.87 ppm	(s, 2H,	$-NH_2$)
6.38	(s, 1H,	-NH-)
7.07-7.48	(m, 5H,	aromatic)

ir (chloroform):

$\bar{\nu}$1596 cm^{-1}	(m) C=C stretch
1635	(m) Amide II
1743	(v.s) C=O stetch
3365	(m) N-H stretch
3465	(m) N-H stretch

ms:

m/z		
	152	M+
	121	Ph-OOC$^+$
	94(base)	PhOH$^+$
	77	$C_6H_5^+$
	66	$C_5H_6^+$
	65	$C_5H_5^+$

2,3-Dimethylphenyl Carbazate (115)

Hydrazine hydrate (85%, ca. 0.33 g, 5.60 mmol) was reacted with 1-(2,3-dimethyl)phenyloxycarbonylbenzotriazole (113) (1.12 g, 4.19 mmol) in benzene (25 mL). After stirring for 1 h at room temperature the reaction was worked-up by washing with 2.5% sodium carbonate (3x5 mL), water (3x5 mL), reextracting the aqueous washings with chloroform (3x10 mL) and drying the combined organic layers. The solvent was evaporated, and carbon tetrachloride was added and removed three times.

The nmr indicated that BTH was still present so the crude material was washed again as above. The crude carbazate was obtained as a light orange solid (0.51 g, 67.5%). Recrystallization from pentane/ether (20 mL) afforded 0.27 g (35.8%) beige crystals of 115, mp 114.0-116.5°C.

An analytical sample was further recrystallized from pentane/benzene, mp 117.5-118.0°C. Analysis for $C_9H_{12}N_2O_2$; calculated: C 59.99, H 6.71, N 15.55%; found C

59.90, H 6.84, N 15.22%.

^{1}H nmr at 90 MHz:

δ 2.10 ppm	(s, 3H, 3-Me)	
2.29	(s, 3H, 2-Me)	
ca.3.23	(v.b, 2H, $-NH_2$)	
ca.6.37	(b, 1H, -NH-)	
6.91-7.12	(m, 3H, aromatic)	

ir (chloroform):

$\bar{\nu}$ 1633 cm^{-1}	(m)	Amide II
1744	(v.s)	C=O stretch
3360	(w)	N-H stretch
3460	(w)	N-H stretch

ms:

m/z	180	(15.9%)	M+
	122	(100.0)	$Me_2C_6H_3OH^+$
	107	(39.6)	$MeC_6H_3OH^+$
	91	(11.2)	$C_7H_7^+$
	77	(17.3)	$C_6H_5^+$

Dodecyl Carbazate (116)

Hydrazine hydrate (85%, ca. 0.30 g, 5.09 mmol) was reacted with 1-dodecyloxycarbonylbenzotriazole (114)(1.1 g, 3.32 mmol) in toluene (25 mL). After stirring for 1 h at room temperature the reaction was worked-up by washing with 2.5% sodium carbonate (3x5 mL), water (3x5 mL), the aqueous washings reextracted with chloroform (3x10 mL) and the

combined organics dried.

This solution was concentrated, and carbon tetrachloride was added and removed three times affording a white solid (1.07 g). A trace of BTH was still present by nmr so this crude material was washed again as above affording 0.72 g (88.8%) of a very light yellow solid. This crude carbazate was recrystallized from pentane (30 mL) yielding 0.50 g (61.7%) white crystals, mp 63.0-65.0°C.

An analytical sample was further recrystallized from benzene/pentane, mp 66.5-67.0°C. Analysis for $C_{13}H_{28}N_2O_2$; calculated: C 63.89, H 11.55, N 11.46%; found: C 63.91, H 11.77, N 11.07%.

^{1}H nmr at 90 MHz:

δ 0.76-1.01 ppm	(m, 3H, CH_3-)
1.14-1.74	(m, 20H, -$(CH_2)_{10}$-)
3.74	(s, 2H, -NH_2)
4.10	(t, J 6.4 Hz, 2H, -O-CH_2-)
5.94	(s, 1H, -NH-)

ir (chloroform):

$\bar{\nu}$ 1634 cm^{-1}	(m)	Amide II
1728	(s)	C=O
3370	(w)	N-H stretch
3475	(m)	N-H stretch

ms:

m/z 244	(16.5%)	M+
213	(1.9)	-31, -N_2H_3

185	(0.9)	$CH_3(CH_2)_{11}O^+$
171	(5.5)	$(CH_2)_{11}\ OH^+$
157	(4.1)	$(CH_2)_{10}\ OH^+$
143	(3.5)	$(CH_2)_9\ OH^+$
125,127,<u>129</u>	(0.6,1.7,3.5)	$(CH_2)_8\ OH^+$
111,113,<u>115</u>	(1.7,3.6,3.6)	$(CH_2)_7\ OH^+$
97,99,<u>101</u>	(3.4,6.1,4.6)	$(CH_2)_6\ OH^+$
83,85,<u>87</u>	(5.8,27.7,5.7)	$(CH_2)_5\ OH^+$
77	(56.6)	$HOOCNHNH_3^+$
76	(57.8)	$HOOCNHNH_2^+$
69,71,<u>73</u>	(15.7,50.6,8.1)	$(CH_2)_4\ OH^+$
55,57,<u>59</u>	(44.6,98.8,27.7)	$(CH_2)_3\ OH^+$
41,43,<u>45</u>	(61.4,100.0,7.7)	$CH_2CH_2\ OH^+$

<u>Cyclohexyl Carbazate (16)</u>

Hydrazine hydrate (85%, ca. 0.38 g, 6.45 mmol) was reacted with crude 1-cyclohexylcarbonylbenzotriazole (115) (1.09 g, 4.44 mmol) in toluene (25 mL). After 1 h the reaction was worked-up by washing the mixture with 2.5% sodium carbonate (3x10 mL), water (3x10 mL), the combined aqueous washings reextracted with chloroform (3x10 mL) and the organics dried.

After concentration, carbon tetrachloride was added and removed three times affording 0.52 g (74.0%) of a white solid. Recrystallization from pentane/ether (20 mL) yielded 0.25 g (35.6%) white crystals of <u>16</u>, mp 84.0-87.5°C.

A sample for analysis was further recrystallized from pentane/benzene, mp 89.5-92.0°C. Analysis for $C_7H_{14}N_2O_2$; calculated: C 53.15, H 8.92, N 17.71%; found: C 53.39, H 9.02, N 17.29%.

^{1}H nmr at 90 MHz:

δ 0.98-2.12 ppm	(m, 10H,	$-(CH_2)_5-$)
3.49	(s, 2H,	$-NH_2$)
4.47-4.87	(m, 1H,	-CH-O)
6.02	(s, 1H,	-NH-)

ir (chloroform):

$\bar{\nu}$ 1633 cm^{-1}	(s)	Amide II
1719	(v.s)	C=O
3360	(m)	N-H stretch
3465	(s)	N-H stretch

ms:

m/z 158		M+
114		-44, $-CO_2$
99		$c-C_6H_{11}O^+$
98		$c-C_6H_{10}O^+$
83 (base)		$c-C_6H_{11}^+$

Preparation of the Carbazates via the Chloroformate

1-Adamantyl Carbazate (15) (25)

Cold liquid phosgene (22.4 g, 0.226 mol, Matheson) was weighed into a 3-necked 500 mL round-bottomed flask containing dry benzene (100 mL) at room temperature. 1-

Adamantanol (5.00 g, 0.0328 mol, Aldrich, 99%) and freshly distilled dry pyridine (4.70 g, 0.0594 mol, Fisher, certified ACS) in dry benzene (125 mL) were added over 1 h to this stirred solution while the reaction temperature was maintained at less than 6°C with an ice-salt bath. A white precipitate of pyridinium hydrochloride was immediately formed and the adamantanol solution was rinsed in with an additional portion of dry benzene (50 mL).

The reaction was stirred at room temperature for 1.5 h, filtered, washed with ice-water (150 mL), dried over magnesium sulfate in a refrigerator, and gently concentrated on a rotary evaporator to ca. 100 mL. An ir run on a film obtained by allowing a few drops of the benzene solution to evaporate on a salt plate was consistent with 1-adamantyl chloroformate.

ir (film):

$\bar{\nu}$ 1147 cm^{-1} (s)

1790 (s)

The chloroformate solution was divided into two approximately equal portions and one portion was reacted further with hydrazine. Assuming the yield was quantitative then 0.0328 mol of the chloroformate should have been produced. According to the relative weights, the solution to be reacted then contained 0.0180 mol (3.86 g) of the chloroformate.

This chloroformate solution (ca. 0.0180 mol in 100 mL benzene) was added over 50 min to a stirred solution of anhydrous hydrazine (5.22 g, 0.163 mol, Eastman) in dry t-butanol (50 mL) using an ice/salt bath to maintain the temperature at less than 5°C. The solution was rinsed in with an additional portion of dry benzene (60 mL).

The reaction was worked-up after stirring for 2 h at room temperature. The mixture was concentrated to ca. 10 mL with mild heating, diluted with ether (200 mL) and water (20 mL), washed with 50 mL portions of water, 1% sodium carbonate, saturated sodium chloride solution, and dried. Pure white crystals of 1-adamantyl carbazate (15) (2.59 g, 68.4%) were obtained when the benzene was partially removed and the solution cooled in a freezer, mp 139.5-142.0°C; lit. mp 141-142°C (25).

The remainder of the chloroformate solution was similarly reacted with hydrazine hydrate (95+%, 4.10 g, ca. 0.128 mol) in dry t-butanol (40 mL) yielding 2.14 g (68.8%) 15.

An additional 0.66 g product was obtained by combining the mother liquors from both of the above reactions, concentrating and recrystallizing from ether/hexanes. The total yield was therefore 78.0% (5.39 g).

^{1}H nmr at 60 MHz:

δ 1.68-2.13 ppm (m, 15H, adamantyl)

3.70 (b, 2H, $-NH_2$)

5.57-6.20 (v.b, 1H, -NH-)

ir (chloroform):

$\bar{\nu}$ 1632 cm^{-1} (m) Amide II

1715 (s) C=O stretch

3370 (w) N-H stretch

3470 (m) N-H stretch

ms:

m/z		
210	(-)	No parent ion
166	(10.1%)	-44, $-CO_2$
152	(0.9)	AdOH $^+$
135	(100.0%)	Ad $^+$
107	(9.3)	$C_8H_{11}^+$
93	(23.0)	$C_7H_9^+$
79	(23.7)	$C_6H_7^+$
67	(10.5)	$C_5H_7^+$
55	(9.1)	$C_4H_7^+$
41	(11.6)	$C_3H_5^+$

Benzyl Carbazate (24) (23)

Benzyl chloroformate (ca. 14.92 g, 0.0874 mol, Aldrich) was added dropwise over 1.2 h to a stirred mixture of anhydrous hydrazine (95+%, 15.05 g, 0.446 mol, Eastman) and anhydrous ether (100 mL). The reaction temperature was maintained at -5 to 0°C with an ice/salt bath. The white precipitate which had formed redissolved on stirring another 1 h at room temperature to give two clear immiscible layers. After separation of these layers, the

top ethereal layer was washed with water (3x5 mL) and dried.

The solution was saturated with HCl gas and filtered affording 8.74 g (49.3%) of the benzyl carbazate salt as fine white shiny platelets, mp 166.0-169.5°C. These were dried under vacuum over phosphorus pentoxide, mp. 168.5-171.5°C; lit. mp 170.0-170.5°C (23). On concentrating the mother liquors, further material was obtained as the free carbazate 24 (2.77 g, 68.4% total), mp 66.0-69.0°C; lit. 66.5-67.0°C (23).

The salt (8.18 g, 0.0404 mol) was suspended in chloroform (100 mL) and cooled with an ice/salt bath. A solution of TEA (5.07 g, 0.0501 mol) in chloroform (25 mL) was added dropwise over 0.3 h while maintaining the temperature at -7 to -6°C. After an additional 1.5 h at room temperature the reaction was diluted with ether (135 mL) and the precipitate of TEA.HCl filtered-off (4.85 g, 87.2 %).

The filtered solution was concentrated to ca. 75 mL and petroleum ether (75 mL) added to cause the product to precipitate out. Further concentration of the mother liquors and addition of petroleum ether resulted in a quantitative yield of benzyl carbazate as a white solid (6.63 g, 98.8%), mp 66.5-68.0°C; lit. 66.5-67.0°C.

The benzyl carbazate had the identical spectroscopic properties as the material described earlier.

Phenyl Carbazate (25)

A solution of phenyl chloroformate (15.05 g, 0.0961 mol, Eastman) in anhydrous ether (100 mL) was added over 2 h to a stirred mixture of hydrazine (95+%, 16.06 g, 0.476 mol) in anhydrous ether while the temperature was maintained at -5 to 0°C with an ice/salt bath. The reaction was stirred an additional 0.5 h in the bath and 0.5 h at room temperature. Enough water (25 mL) then was added to dissolve the white precipitate which had formed and the layers were separated. The ethereal solution was washed with a small amount of water (3x5 mL) and dried. On treatment with dry HCl gas, 6.39 g (35.2%) phenyl carbazate hydrochloride was obtained. The mother liquors afforded 5.12 g (56.6%) of phenol.

The salt (2.02 g, 10.7 mmol) was suspended in chloroform (60 mL), cooled in an ice/salt bath and treated over 0.7 h with a solution of TEA (1.11 g, 11.0 mmol) in chloroform (20 mL) while the temperature was maintained at -7 to -10°C. Ether (100 mL) was added to precipitate the TEA·HCl (1.12 g, 76.0%) and ,after filtering, the solution was concentrated to ca. 40 mL. Diluting with pentane (50 mL) afforded 1.33 g (81.6%, 28.7% overall) of 25, mp 99.5-103.0°C; lit. 103-104°C (27).

Trituration of 0.50 g of the carbazate with carbon tetrachloride (2x10 mL) yielded 0.41 g (82.0%) of material with an unchanged mp. The phenyl carbazate had the expected spectroscopic properties, see earlier.

GENERAL METHOD OF OXIDATION

Two slightly different general methods of oxidation were used in this investigation. In method A the oxidation was carried out at various temperatures and the gases evolved were collected in an inverted cylinder while in method B a completely closed system was used and the reaction was done in a bath thermostated at 40°C

Method A

Oxidant, dry solvent (50 mL) and a magnetic stirring bar were placed in a two-necked Erlenmeyer flask (250 mL) which was fitted with a pressure-equalized addition funnel (125) and a condenser which was connected to a gas-bulb (167 mL) and a Firestone valve.

Distilled methyl carbazate (ca. 0.50 g, 5.55 mmol) was dissolved with warming in dry solvent (50-75 mL) in a round-bottomed flask (100 mL). This solution was then purged at least six times using the Firestone valve between argon (or helium) and the house vacuum; warming was used if necessary to keep the carbazate in solution. This solution was quickly transferred into the addition funnel mL) and the entire system including the gas-bulb was purged at least six times with stirring. A slow stream of argon (helium) was bubbled through the gas-bulb and out a delivery tube to completely flush the system. The reaction flask was then placed into a hot paraffin wax bath at the required temperature and was allowed to warm for ca. 5 min

with stirring.

The carbazate solution was added dropwise over 0.5-2.5 h and the evolved gas was collected in an inverted graduated cylinder (500 mL). The reaction mixture was then stirred another 10-20 min to ensure the oxidation was complete. Gas evolution normally began immediately, continued smoothly throughout the addition and ceased within minutes after the addition was complete. The gas-bulb was then isolated, the amount of gas collected measured and the reaction allowed to cool. The gas was analyzed by gc using one of the two methods described below.

Method B

Carbazate (11.1 mmol), dry solvent (100 mL) and a magnetic stirring bar were placed in a round-bottomed flask (250 mL) and was purged at least six times between the house-vacuum and helium with a Firestone valve to remove the air. Stirring and warming were used if necessary to dissolve the carbazate in the solvent while still under an atmosphere of helium. The round-bottomed flask was then removed from the system and was quickly stoppered.

Barium manganate (ca. 8.53 g, 33.3 mmol) and dry solvent (50 mL) were placed in a two-necked reaction flask (250 mL) which was fitted with a jacketed addition funnel and a condenser. To this condenser was attached a Firestone valve and a gas-bulb (167 mL) to which was

connected a closed graduated cylinder (900 mL) and a leveling bulb (1L). With the gas-bulb still closed the entire system was purged at least six times between helium and the house-vacuum using the Firestone valve.

The carbazate solution was then quickly poured into the addition funnel while helium was being flushed out and the system carefully and quickly purged another six times. Water flow through the jacket of the addition funnel and stirring were started. The height of the leveling bulb was adjusted so that the level of the saturated sodium chloride solution was just at the graduated cylinder. After the helium gas was shut-off at the pressure regulator, the excess pressure in the system was relieved by opening the screw valve on the Firestone valve several turns and then was closed.

The apparatus was allowed to equilibrate 5 min and then the carbazate solution was added dropwise. As soon as the first few bubbles of gas were collected in the gas cylinder the leveling bulb was lowered a few mm's. As the addition continued and the gas collected in the cylinder the leveling bulb was further lowered another two or three times so that the head pressure exerted by the leveling bulb was not excessive.

Usually the addition was complete after 1-2 h and the gas evolution normally stopped within minutes of this. Stirring was continued another 10-15 min to make sure that the oxidation was complete. The stopcock at the outlet of

the cylinder was then closed and the leveling bulb adjusted so that the levels in it and in the gas cylinder were equal. The stopcock was reopened and the levels were checked to confirm they were still equal. The gas-bulb was isolated and the volume of gas collected was measured.

After cooling the reaction flask in an ice bath, the barium salts were removed by filtering through a layer of magnesium sulfate in a Buchner funnel.

The gas in the gas-bulb was analyzed by gc according to method B and in some cases the solution was analyzed on another gc.

GC GAS ANALYSIS

The gas collected from the oxidation was analyzed by one of two slightly different methods, the main difference between the two was the way the calibration was carried out. A BASIC gas chromatograph, Model 6500 (Carle Instruments, Inc.) was used together with a Fisher Recordall 5000 Series two pen recorder.

Method A

-42/60 Molecular Sieve 5 A

Coast Engineering Laboratory; Formula 012467

4 ft x 1/8 in, stainless steel

Flow: 37 mL/min

-100/120 Porapak Q®

Waters Assoc., Inc.; Batch 869

4 ft x 1/8 in, stainless steel

Flow: 9 mL/min

Regulator Pressure: 13 psi

Column and Inlet Temperature: ambient

Carrier Gas: Helium

Detector: Thermal Conductivity

Attenuation: 1

Recorder: Y 0.01, Y 0.001

The molecular sieves were activated by heating for 20 h in a muffle furnace at 160-280°C and were allowed to cool in a desiccator. The gas flow was adjusted so as to optimize the resolution of a oxygen, nitrogen, methane and carbon dioxide mixture. Completely optimium flows could not be obtained since the head pressure to both columns could not be independently adjusted; one pressure was applied to both columns at the same time.

Before an analysis, the instrument was tested by injecting 3x0.5 mL samples of air with a 1 mL syringe into the molecular sieve column and then five times into the Porapak Q®column. If operation was satisfactory then the reaction gas was analyzed.

The analysis involved first flushing a 1 mL syringe with 3x1.0 mL of the reaction gas in a gas-bulb (167 mL). A 1 mL sample was then withdrawn, 0.5 mL flushed out and 0.5 mL quickly injected into the gc. Normally eight injections were made starting with the molecular sieve column and then alternating columns. The area of each peak from the recorder trace was estimated as the product of the

height and the width at half height ($A = H \cdot W_{1/2}$). Each area was corrected using a calibration factor determined using the pure gas (see below). As the gas in the gas-bulb was sampled, air was found to gradually leak into the system causing a gradual change in the peak areas. To minimize this variation, only the first two injections on each column were averaged and used in the further calculations; the error was estimated as half the difference between these two areas. A VisiCalc® program was used to calculate the yield of the gases as in the following example.

In a typical example, methyl carbazate was oxidized with barium manganate in refluxing p-xylene. The average area of the first two peaks of each gas and the estimated error are listed in the table. These areas were corrected by dividing by the appropriate calibration factor determined as described in the next section. For nitrogen:

$$\begin{aligned} \text{Area-Cor } N_2 &= (\text{area } N_2)/(\text{Cal}_{MS}(N_2)) \\ &= [3218(352.8)]/[138.07(4.454)] \\ &= [3218(10.96\%)]/[138.07(3.26\%)] \\ &= 23.31(14.22\%) \end{aligned}$$

The error in the corrected area was estimated to be the sum of the individual percent errors.

The results from both columns were related, area-rel, by dividing these corrected areas by the area of the

methane peak of the same column. Further division by the sum of these relative areas, including the methane only once, resulted in the relative yields of the gases, rel.yield.

In this reaction, 0.50(0.01)g or 5.55(2.0%)mmol carbazate was consumed and 193(5)mL gas was collected which corresponds to approximately:

$$n = PV/RT$$

$$= \frac{([745(5)/760]\ \text{atm})(193(5)\ \text{mL})}{(0.080562\ \text{l atm mol K})(295.0\ \text{K})}$$

$$= 7.816(3.25\%)\ \text{mmol}$$

When the atmospheric pressure was not measured it was estimated to be 745(5)mm Hg as was the case here.

From the amount of gas expected, the amount found and from the relative yield of nitrogen, the yield of nitrogen can finally be determined:

$$\text{Yield } N_2 = (\text{rel yield})(\text{mmol gas})/(\text{mmol carbazate})$$

$$= [80.66(14.22\%)][7.816(3.25\%)]/[5.55(2.00\%)]$$

$$= 113.6(19.47\%)$$

$$= 113.6(22.1)$$

For the ethane, a factor of two must be included since two molecules of methyl carbazate form two methyl radicals which result in one molecule of ethane.

TABLE 22. Gas Analysis by Method A.

	MS(N_2)	MS(CH_4)	PQ(CH_4)	MS(CO)	PQ(CO_2)	PQ(C_2H_6)
Area	3218	154.95	106.72	133.05	410.47	1.9
Error	352.8	20.55	3.68	4.95	14.57	0.1
Area-Cor	23.3069	1.4015	0.2230	0.9740	0.5087	0.0025
Error%	14.19	16.33	6.06	6.54	8.64	9.65
Area-Rel	16.6305	1	1	0.6950	2.2808	0.0111
Rel.Yield	80.66	4.85	4.85	3.37	11.06	0.05
Yield	113.60	6.83	6.83	4.75	15.58	0.15
Error	22.10	1.47	0.77	0.56	2.17	0.02

MS = Molecular Sieve column. PQ = Porapak Q® Column.

When the reaction was carried out under helium it was possible to correct for the leakage of air; helium is transparent to the analysis since it was also used as the carrier gas. Under these conditions the oxygen peak was found to gradually increase in each chromatogram. The ratio of the area of the nitrogen to oxygen peak in the initially run air samples were averaged. In the analysis of the collected gas the area of the oxygen peak was multiplied by this factor which should give the area of nitrogen due to air. Subtraction gave the corrected nitrogen areas which were averaged and the calculations were repeated as above. Usually there was very little leakage in the first two injections and so the corrected yields were very similar to uncorrected yields.

Calibration Factors for Method A

Various volumes of pure gas, 2 x 0.2, 0.4, 0.6, 0.8, and 1.0 mL, were injected as above into the applicable column and the areas determined. Linear regression was used to fit the best line of area vs. volume to the data including the origin. The area that corresponded to a volume of 0.5 mL was used as the calibration factor.

The calibration lines and the corresponding calibration factors were:

Molecular Sieves column:

$A_{MS}(N_2)$ = [262.566(7.042)][Vol mL] + 6.788(4.454)

$Cal_{MS}(N_2)$ = 138.071(4.454)

$A_{MS}(CH_4)$ = [211.004(5.362)][Vol mL] + 5.062(3.391)

$Cal_{MS}(CH_4)$ = 110.564(3.391)

$A_{MS}(CO)$ = [273.98596.094)][Vol mL] - 0.396(3.854)

$Cal_{MS}(CO)$ = 136.596(3.854)

Porapak Q® column:

$A_{PQ}(CH_4)$ = [913.894(19.762)][Vol mL] + 21.562(12.498)

$Cal_{PQ}(CH_4)$ = 478.509(12.498)

$A_{PQ}(CO_2)$ = [1490.909(64.943)][Vol mL] + 61.486(41.074)

$Cal_{PQ}(CO_2)$ = 806.940(41.074)

$A_{PQ}(C_2H_6)$= [1505.184(53.293)][Vol mL] + 14.695(33.706)

$Cal_{PQ}(C_2H_6)$ = 767.287(33.706)

Method B

-60/80 Molecular Sieve 5 A

Supelco, Inc.; Lot No. 478232

6 ft x 1/8 in, copper

Flow: 26.0 mL/min

-60/80 Chromosorb 102®

Supelco, Inc.; Lot No. 315

6 ft x 1/8 in, copper

Flow: 37.7 mL/min

Regulator Pressure: 30 psi

Column and Inlet Temperature: ambient

Carrier gas: Helium

Detector: Thermal Conductivity

Attenuation: 1

Recorder: Y 0.001, Y Integration Low

The molecular sieves were activated by heating for 4 h at 300-340°C in a muffle furnace then removed while still hot and allowed to cool in a desiccator. The gas flow through the gc was adjusted to optimize resolution using a sample of 3.0% methane in nitrogen. Here the 1 mL syringe was flushed with 3x0.2 mL of the gas collected from the reaction, this caused less leakage of air. Then 1 mL was withdrawn, 0.5 mL flushed out and the remaining 0.5 mL quickly injected into the gc. Ten such injections for each gas sample were made starting with the molecular sieve column and alternating columns.

The area corresponding to each peak was determined using the integration trace by the standard method. Again, only the first two injections were used in the calculations to minimize the effect of the leakage of air. A VisiCalc®

program was used to calculate the yield of gases using the calibration lines determined using authentic samples as described below.

A sample calculation follows. In a typical experiment, methyl carbazate was oxidized with barium manganate in equal volume benzene:toluene at 40°C under helium. On the molecular sieve column the area of the nitrogen peak was determined to be 360 and 363 counts or 361.5(1.5) counts. Thus, the percent composition of nitrogen was:

$$\% \ (N_2) = [361.5(1.5) + 21.67481]/[7.28291(0.10650)]$$
$$= [361.5(0.39\%) + 21.67481]/[7.28291(1.46\%)]$$
$$= 52.61(1.85)\%$$

The error in the calibration line was estimated as the standard deviation in the slope. Similarly, the percent of the other gases were calculated from the areas using the appropriate calibration curves (see later), no ethane was detected (Table 23). Since the concentration of methane could be determined with either column, the value with the lower percent error was used in the further calculations; here it was the value determined with the Chromosorb column. The relative yields were now determined by dividing the percent values by the sum of these percent values using only the one appropriate methane value.

TABLE 23. Gas Analysis by Method B.

	$MS(N_2)$	$MS(N_2)$ Corr.	$MS(CH_4)$	$C(CH_4)$	MS(CO)	$C(CO_2)$
Area	361.5	358	2.5	3.5	67	91.5
Error	1.5	2	0.5	0.5	2	0.5
%	52.6129	52.1323	0.5814	0.7399	9.3484	14.2392
%Error	1.85	1.99	18.41	16.42	10.09	2.24
Rel.Y	68.38		-	0.96	12.15	18.51
Yield	90.46		-	1.27	16.07	24.48
Error	3.82		-	0.24	2.00	1.13
Corrected						
Rel.Y		68.18	-	0.97	12.23	18.62
Yield		90.19	-	1.28	16.17	24.63
Error		3.93	-	0.24	2.02	1.14

MS = Molecular Sieve column. C = Chromosorb 102® column.

In this reaction 1.00(0.01)g or 11.10(1.0%)mmol methyl carbazate was consumed and 368(5)mL of gas was collected which corresponds to:

$$n = (PV)/(RT)$$

$$= \frac{[733.5(0.1)/760 \text{ atm}][368(5) \text{ mL}]}{(0.0820562 \text{ l atm mol K})(294.8 \text{ K})}$$

$$= 14.68(1.37\%) \text{ mmol}$$

Thus, the yield of nitrogen was:

$$\text{Yield } (N_2) = (\text{Rel Yield})(\text{mmol gas})/(\text{mmol carbazate})$$
$$= [68.38(1.85\%)][14.68(1.37\%)]/[11.10(1.0\%)]$$
$$= 90.43(4.22\%)$$
$$= 90.43(3.82)$$

GC Calibration B

Preparation of the Standard Gas Mixtures

A large gas-bulb (167 or 168 mL) was flushed with either nitrogen or argon. The gas of interest was withdrawn from a small (78 mL) gas-bulb while this gas was flowing through it and out through a bubbler. A suitably sized large syringe was flushed with 3x5 mL of this gas and then (n+5)mL was withdraw. Five mL of gas was flushed out and the volume required (n mL) was injected into the large gas-bulb allowing the displaced gas to flow out a bubbler connected at one end. At least 30 min were allowed to elapse for thorough mixing of the two gases to occur. These samples injected into the large gas-bulb were less than or equal to 45 mL since with greater volumes some of the injected gas was found to flow out with the displaced. The calculated concentrations would then be higher than the true value.

For a 167 mL bulb the percent concentration of gas would be:

$$\% \text{ Conc} = 100n/167$$

Therefore if 35 mL of nitrogen was injected into argon:

$$\% \text{ Conc} = 21.0 \% \text{ nitrogen in argon}$$

For higher concentrations a second injection of the gas of interest was necessary. Here the second injection of n′ mL would displace n′ mL of a mixture of gases so the concentration was calculated accordingly. The n′ mL injected displaced n′(n/167) mL of the gas of interest therefore the new volume of this gas in the bulb was:

$$n' + n - n'(n/167)$$

So the new concentration was:

$$\% \text{ Conc}' = 100(n' + n - n'(n/167))/167$$

Normally n′ = n, so:

$$\% \text{ Conc}' = 100(2n - n(n/167))/167$$
$$= 100(2n - n(\% \text{ Conc}/100))/167$$

For example if 2 x 35 mL nitrogen was injected into argon then:

% Conc' = 100(70 - 35(0.210))/167

= 37.5% nitrogen in argon

Various samples of gases were blended in this way and for each sample 5x0.5 mL injections made as described above. The corresponding area (counts) were determined from the integration trace on the recorder. Again there was a noticeable slow leakage of air and so only the first two injections of each sample was used to minimize this. Linear regression was used to fit these points including the origin to a line of area vs. percentage.

Nitrogen

Eight samples of nitrogen in argon (17.9, 21.0, 23.8, 26.9, 32.7, 37.3, 42.2, and 46.4%) plus pure nitrogen were run.

$A(N_2)$ = [7.28291(0.10650)]($\%N_2$) - 21.67481(4.69288)

Correlation Coefficient = 0.99819

Methane

Six samples of methane in nitrogen (2.99, 5.95, 11.90, 14.97, 17.86, and 20.8%) were used.

Molecular Sieve Column

$A_{MS}(CH_4)$ = [5.99753(0.24438)]($\%CH_4$) - 0.98702(3.27124)

Correlation Coefficient = 0.99099

Chromosorb Column

A_c (CH_4) = [4.91110(0.13063)]($\%CH_4$) - 0.133589(1.74865)

Correlation Coefficient = 0.99613

Carbon Dioxide

Six samples with nitrogen dilutant were run (2.99, 5.95, 8.98, 11.90 14.97, and 17.86%).

$A(CO_2) = [6.64606(0.11353)](\%CO_2) - 3.13427(1.26971)$

Correlation Coefficient = 0.99840

Ethane

Six mixtures with the same percent composition as the cabon dioxide were run.

$A(ethane)=[7.66487(0.13154)](\%C_2H_6) + 0.28913(1.47434)$

Correlation Coefficient = 0.99838

Carbon Monoxide

The same 6 percent compositions as for carbon dioxide were run.

$A(CO) = [8.37971(0.46935)](\%CO) - 7.65315(5.24915)$

Correlation Coefficient = 0.98318

INITIAL INVESTIGATIONS. METHYL CARBAZATE OXIDATION

In the initial investigations methyl carbazate (ca. 0.50 g, 5.55 mmol) was oxidized by method A in various solvents, with various oxidants and under various conditions. The gas collected was analyzed according to method A or B, Table 7.

OXIDATION AND COMPLETE ANALYSIS

The oxidations in this section were carried out according to general method B. The collected gas was analyzed by method B and the reaction solution was analyzed by gc on a column of SP-400, chlorophenyl.

Oxidation of Methyl Carbazate

a) In Benzene

Methyl carbazate was oxidized in benzene with barium manganate, yellow mercuric oxide, activated manganese dioxide and potassium permanganate. The details and results are given in Table 8.

The benzene solution was analyzed by gc using napthlene as an internal standard. Solutions of bibenzyl, dimethyl oxalate, diphenyl, methanol, methyl benzoate, methyl formate and toluene in benzene were used to identify and quantitate the major products formed. Methyl benzoate was found to be the major compound present with small amounts of toluene and bibenzyl also sometimes formed. Note the distilled benzene contained a trace impurity of toluene. The presence or absence of methanol and methyl

formate in the reaction mixture could not be determined since these compounds were found to elute with the solvent peak.

b) In Toluene/Benzene

Barium manganate was used to oxidize the methyl carbazate in toluene/benzene (equal volumes), Table 9. The reaction mixture was analyzed using adamantane as an internal standard. Solutions of bibenzyl, methyl benzoate, and ortho-, meta- and para-methyl toluate were used to identify and quantitate the major products formed. The para-methyl toluate was commercially available and the ortho and meta isomers were synthesized from the corresponding acids by a standard procedure (76 and 85% yields, respectively) (103).

At least six other unidentified compounds were also present in very low concentrations but further analysis was not attempted. The ratio of solvent peak areas before and after reaction was determined to confirm there was no preferential evaporation of the solvent.

c) In Chlorobenzene/Toluene

Methyl carbazate was oxidized with barium manganate in equimolar molar chlorobenzene/toluene, Table 9. The compounds formed were identified and quantitated with solutions of methyl benzoate, and ortho-, meta- and para-methyl chlorobenzoate in equimolar chlorobenzene/benzene. The three isomeric esters were prepared from the corresponding acids (2-, 3-, and 4-chlorobenzoic acid) by a

standard method (86, 79 and 82%, distilled, respectively)(103). The reaction mixture was analyzed with an internal standard of adamantane. Since the meta and para isomers were not separated under these conditions a column of 5% Bentone 34, 5% diisodecyl phthalate on Chromosorb W was also used.

The chlorobenzene solvent used contained two unidentified impurities in very low concentrations; these may have been dichloro- and trichlorobenzene. The reaction mixture was also found to contain two other compounds but in such low concentrations that further analysis was not attempted.

Oxidation of Phenyl Carbazate

Phenyl carbazate (1.67 g, 11.0 mmol) in dry benzene was added to a suspension of barium manganate over 78 min and then stirred another 11 min to ensure that oxidation was complete; 300(5) mL gas was collected, Table 10.

The benzene solution was analyzed using an internal standard of naphthalene. Solutions of diphenyl, phenol, phenyl benzoate and phenyl formate were used to identify and quantitate the products formed. The phenyl formate was prepared from phenol, dimethylformamide and phosphorus oxychloride according to a literature procedure (42% distilled yield) (105).

The compounds found and the percent yield were:

phenol	27.6(10.6)%
phenyl benzoate	9.7(0.4)%

phenyl formate 3.1(1.2)%

At least four other unidentified compounds were also present but in such low concentrations that further analysis was not attempted.

The phenol and phenyl formate could not be separated under these chromatographic conditions. However, in prepared mixtures most of the phenol was found to extracted by washing with a solution of potassium carbonate (10%) while most of the formate remained in solution. Thus, calibration solutions were prepared and the ratio of the phenol and the phenyl formate peak areas was determined before and after such washing. A portion of the reaction was washed in the identical manner and the ratio of areas before and after washing was measured. The proportion of phenol and phenyl formate was estimated with this information.

Oxidation of Benzyl Carbazate

Benzyl carbazate (1.84 g, 11.1 mmol) in dry benzene was added to barium manganate (8.58 g, 33.5 mmol) over 64 min and stirred another 10 min. Method B was used to analyze the gas collected 373(5 mL); the details are listed in Table 10.

The benzene was analyzed using naphthalene as an internal standard. Solutions of benzaldehyde, benzoic acid, benzyl alcohol, benzyl benzoate, benzyl formate, bibenzyl, diphenyl, diphenylmethane and toluene were used to identify and quantitate the products formed. The benzyl

formate was prepared from formic acid and benzyl alcohol by a standard procedure (49% yield, distilled) (103).

The products identified were:

bibenzyl	60.6(2.8)%
benzaldehyde	13.9(1.0)%
benzyl alcohol	8.5(0.8)%
benzyl formate	1.5(0.1)%
toluene	0.35(0.07)%

At least two other compounds were also present but in such low concentrations that further analysis was not carried out.

Oxidation of 2-Phenylethyl Carbazate

Phenyl carbazate (2.00 g, 11.1 mmol) in dry benzene was reacted with barium manganate (8.65 g, 33.8 mmol) over 50 min and stirred another 10 min to ensure the oxidation was complete. The analysis of the gas collected 270(5) mL is shown in Table 10.

The product solution was analyzed with adamantane as an internal standard. Solutions of bibenzyl, 3,4-dihydro-2(1H)-benzopyran-1-one, diphenyl, ethyl benzene, phenylacetaldehyde, phenylacetic acid, 2-phenylethanol, 2-phenylethyl benzoate and 2-phenylethyl formate were made to identify and quantitate the products formed.

The 2-phenylethyl formate and 2-phenylethyl benzoate were synthesized from the alcohols by a standard procedure (86 and 75% distilled yields, respectively) (103). The 3,4-dihydro-2(1H)-benzopyran-1-one (3,4-dihydroisocoumarin

or 1-isochromanone) was prepared from homophthalic acid by the methods of Grummitt and coworkers (106), and Bose and Chaudhury (107) (18% overall yield, not optimized). The phenylacetaldehylde was obtained as a mixture of four compounds by the PDC oxidation of the alcohol. One of these compounds was the 2-phenylethanol due to incomplete oxidation. The phenylacetaldehyde seemed to polymerize on standing. None of the these three unknown compounds were present in the reaction mixture of the 2-phenylethyl carbazate.

The compounds found and their percent yields were:

2-phenylethanol	21.5(0.5)%
2-phenylethyl formate	5.4(0.1)%
2-phenylethyl benzoate	4.03(0.08)%
ethyl benzene	3.9(0.4)%

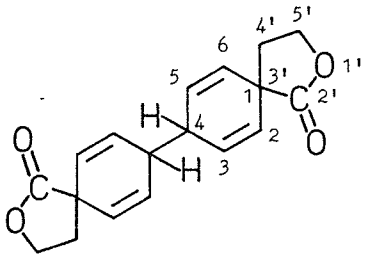
At least eight other compounds were also present but in such low yields that no further identification was carried out.

The oxidation was repeated in dry methylene chloride; a solution of 2-phenylethyl carbazate (2.00 g, 11.1 mmol) was added to barium manganate (8.58 g, 33.5 mmol) over 2 h and stirred another 10 min. No warm water was circulated through the jacket of the addition funnel because of the low boiling point of this solvent. The composition of the collected gas 299(5)mL is tabulated in Table 10.

The filtered methylene chloride solution was not analyzed by gc but instead the major components were

isolated. The solvent was removed affording 0.76 g of a light yellow semi-solid. Extraction with pentane (3x10 mL) afforded 0.13 g of a colorless liquid which consisted of nine compounds by tlc (1:1 petroleum ether:ether). 2-Phenylethanol (84 mg, 6%) and 2-phenylethyl formate (13 mg, 0.8%) were isolated from this mixture by preparative tlc (1:1 petroleum ether:ether).

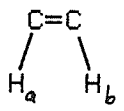
The material insoluble in the pentane was recrystallized from 1,1,1-trichloroethane (10 mL) affording ca. 10 mg of a brown solid, mp 207.5-210.0°C. The spectroscopic data were consistent with 4,4"-bi-[cyclohexadi-2,5-ene-1-spiro-3'-(tetrahydronfuran-2'-one)] (29), the dimer of the cyclized 2-phenylethoxycarbonyl radical (0.6% yield).

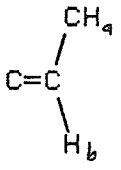


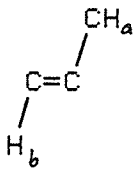
^{1}H nmr at 300 MHz:

δ 2.27 ppm	(t, J 6.9 Hz, 2H, 2xH4')
2.95	(m, 1H, H4)
4.37	(t, J 6.9 Hz, 2H, 2xH5')
5.71	(d of d, J 1.5, & 10.2 Hz, 2H, H2, H6)
6.03	(d of d, J 3.1, & 10.2 Hz, 2H, H3, H5)

Compare with the literature values of proton spin-spin-constants (108):







J_{ab} (Hz)	6-12	4-10	0-3
J_{ab} Typical	10	7	1.5

^{13}C nmr at 75.4 MHz:

37.77 ppm (C4′)

40.64 (spiro carbon, C1,3′ or C4)

45.75 (spiro carbon, C1,3′ or C4)

65.04 (C5′)

125.52 (C2 or C3)

130.00 (C2 or C3)

177.18 (C2′)

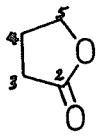
Compare with the literature value of γ-butyrolactone (108):

22.2 ppm (C4)

27.7 (C3)

68.6 (C5)

177.9 (C2)



ir (Nujol):

$\bar{\nu}$ 1022 cm^{-1} C-O stretch

1162 C-O stretch

1761 C=O stretch

Compare with the carbonyl stretch in γ-butyrolactone, 1770 cm^{-1}.

ms:

m/z		
	298	No parent ion
	254	-44, $-CO_2$
	167	$C_6H_5(COOH)(CH_2CH_2OH)^+$
	149	$Ph-CH_2CH_2OOC^+$ or $c-(C_2H_4OOC)C_6H_5^+$
	122	$Ph-CH_2CH_2OH^+$
	120	$Ph-CH_2CH=O^+$ or $Ph-CH=CH-OH^+$
	119	$Ph-CH=CH-O^+$
	117	$Ph-C\equiv C=O^+$
	105(base)	$PhCH_2CH_2^+$ or $Ph-CO^+$
	91	$C_7H_7^+$
	79	$C_6H_7^+$
	77	$C_6H_5^+$

APPENDIX

The thermodynamic properties of alkoxy- and aryloxycarbonyl radicals are summarized in this section.

The selectivity of the ROOC· thermolysis depends on the group R; for R=alkyl and allyl decarboxylation occurs ($k_A >> k_B$) while for R=phenyl decarbonylation takes place ($k_A << k_B$).

$$R\text{-}O\text{-}C{=}O \xrightarrow{A} R\cdot + CO_2$$
$$\xrightarrow{B} RO\cdot + CO$$

The phenyloxycarbonyl radical has a strong Ph-OCO bond and a weak PhO-CO bond due to the resonance stabilization of the phenoxy radical. The dissociation energy of the Ph-OCO bond was estimated to be ca. 16 kcal/mol stronger than that of the Me-OCO bond while the PhO-CO bond has been estimated to be ca. 18kcal/mol weaker than that of MeO-CO (80).

Alkoxycarbonyl radicals are also thermodynamically somewhat stable, ie. while thermodynamically disposed to fragment to carbon dioxide and a carbon radical there is an appreciable activation energy towards such a decomposition. These radicals are more stable to decarboxylation than the isomeric acyloxy radicals (85).

Some thermodynamic properties of various such radicals are listed below as well as those of the acyloxyradical for comparison purposes.

TABLE 24. The Enthalpies of Decomposition.

R	ΔH_α (kcal/mol)			ΔH_β (kcal/mol)		
Me	-15[a]	-11[b]	-10.9[c]	22[a]	25[b]	24.8[c]
Et	-14		-10.0	24		24.7
n-Pr			-6.3			26.4
i-Pr			-8.2			27.5
n-Bu			-3.2			28.5
Allyl	-26			25		
Ph	+1	-0.4		4	1.6	

[a] Ref. 80. [b] Ref. 77. [c] Ref. 82 and 83.

TABLE 25. The Gaseous Heats of Formation of ROOC .

R	ΔH_f° (kcal/mol)		
Me	-45,-43,-52[a]	-51.7,-53.6[b]	-55.8[b]
Et	-54,-57	-59.6,	-60.8
n-Pr		-65.8	-65.8
i-Pr		-68.9	-67.0
n-Bu		-71.9	-70.8
Allyl	-28		
Ph	-17,-19		

[a] Ref. 80. [b] Ref. 82 and 83.

TABLE 26. Activation Energy for Decarboxylation.

R	$E_{act.}$ (kcal/mol)
Me	18.5
n-Pr	12.7
Ph	23.9, 23

Ref. 77.

TABLE 27. Estimated Half-life of ROOC· at 140°C.

R	$t_{1/2}$ (s)
Me	2×10^{-4}
Ph	ca. 0.1
R(≠Ar)	$<2\times10^{-4}$

Ref. 77.

The rate constant for reaction A where R=t-Bu has been estimated to be 2.9×10^{5} s^{-1} at 60°C (85). For the decarboxylation of the acyloxy radical:

$$Me\text{-}COO\cdot \xrightarrow{C} Me\cdot + CO_2$$

the activation energy in solution has been estimated to 6.6 kcal/mol and the rate constant 1.6×10^{9} s^{-1} at 60°C (85).

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