AN INVESTIGATION OF THE MECHANISM AND PRODUCTS OF THE SCHMIDT REACTION ON CAMPHOR

A Thesis

Submitted to the Faculty of Graduate Studies in

Partial Fulfillment of the Requirements of the Degree

of Doctor of Philosophy

by

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CANADA

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ABSTRACT

An investigation of the Schmidt reaction on camphor is carried out. This investigation includes the structure elucidation of the products from this reaction and a detailed study of the mechanism which is proposed for this reaction.

To begin with, a thorough review of the literature about the mechanism of the Schmidt reaction on ketones is presented. Then, the Schmidt reaction on camphor is discussed. Some reactions are carried out towards the characterization of the major product, an aminolactam, which was obtained from the Schmidt reaction on camphor. The characterization of the product, an iminoester, from the 3%-methanolic-HCl methanolysis of the aminolactam is described. From such studies and further spectroscopic data obtained by proton magnetic resonance (400 MHz) and carbon-13 magnetic resonance techniques e.g., INEPT and carbon-proton shift mapping, the identity of the major product as 2,8-diaza-3-oxo-1,9,9-trimethylbicyclo[3.3.1] nonane is established. The characterization of three other minor products from the Schmidt reaction on camphor is discussed. The structure elucidation of the products from the methanolysis of an adduct, 2,8-diaza-3-oxo-1,8,9,9-tetramethylbicyclo[3.3.1]nonane, is also described.

In the second part, firstly the routes to the formation of the minor products from the Schmidt reaction on camphor are outlined. Secondly, a mechanism for the formation of the major product

(aminolactam) from this reaction is proposed and some work is carried out towards the establishment of this proposed mechanism, which includes: (a) synthesis of the proposed transient intermediates, (b) preparation of the aminolactam from the above mentioned intermediates, (c) preparation of the deuterated aminolactam from these intermediates, (d) spectroscopic studies of the sites and extent of the deuterium incorporation in the aminolactam.

An interesting compound, 2,4,6-tri(2'-hydroxy-2',3',3'-trimethyl-cyclopentylmethyl)-1,3,5-triazine, which is obtained during the synthesis of the above mentioned intermediates, is characterized.

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ABBREVIATIONS USED

- The numbers representing chemical structures are underlined.
- The references are given in parentheses ( ).
- d = doublet
- dd = double doublet
- ddd = " double doublet
- dddd = " double double doublet
- ddddd = " double double double doublet
- All Latin words, e.g., et al., are underlined.
- The unit for c (characterizing specific rotation) is g/100 ml.
- The assignment of the words 'Equation' (or 'eqn') and 'Scheme' to the chemical reaction(s) are not meant to represent different categories of chemical reaction(s).
- The word 'equation' is used in full when it is written at the bottom of the chemical reaction(s) that it represents and is used in an abbreviated form 'eqn' when it is written at the right side of the chemical reaction(s) that it represents.

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INTRODUCTION

A. THE SCHMIDT REACTION

There are actually three reactions called by the name SCHMIDT REACTION, involving the addition of hydrazoic acid (HN_3) to carboxylic acids, aldehydes and ketones, and alcohols and olefins in the presence of a strong mineral acid (1). The Schmidt reaction is suitable for the preparation of:

(a) Amines from carboxylic acids:

$$RCOOH + HN_3 \xrightarrow{H_2SO_4} RNH_2 + CO_2 + N_2 \qquad \text{eqn 1}$$

(b) Nitriles and formyl derivatives of amines from aldehydes:

$$RCHO + HN_3 \xrightarrow{H_2SO_4} RCN \text{ and } RNHCHO \qquad \text{eqn 2}$$

(c) Amides (and lactams) from ketones:

$$RCOR + HN_3 \xrightarrow{H_2SO_4} RCONHR + N_2 \qquad \text{eqn 3}$$

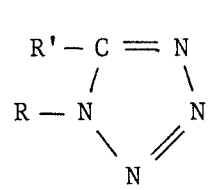
(d) Schiff's bases from olefins and alcohols:

$$R_2C = CR_2 + HN_3 \xrightarrow{H_2SO_4} R_2CHN = CR_2 + N_2 \qquad \text{eqn 4}$$

$$R\text{-}CHOH\text{-}R + HN_3 \xrightarrow{H_2SO_4} R\text{-}CH = N\text{-}R + H_2O + N_2 \qquad \text{eqn 5}$$

(e) Substituted tetrazoles by the use of excess hydrazoic acids on aldehydes, ketones and nitriles:

$$R\text{-}CO\text{-}R' + 2HN_3 \xrightarrow{H_2SO_4} \underset{\underline{A}}{\text{tetrazole}} \qquad \text{eqn 6}$$



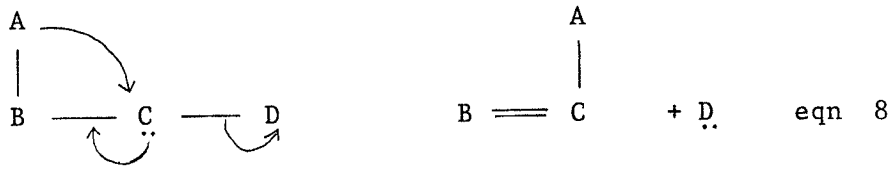
$$R\text{-}CN + 2HN_3 \xrightarrow{H_2SO_4} \underline{A},\ R' = NH_2 \qquad \text{eqn 7}$$

The mechanism for the formation of the above products, especially amides and lactams, will be discussed in detail in the Section D. Numerous studies that were carried out on the Schmidt reaction have been reviewed by Wolff (2), Smith (3), Banthorpe (4), Koldobski, et al. (5), and Krow (6).

B. RELATIONSHIP TO OTHER SEXTET REARRANGEMENTS

The Schmidt reaction with ketones belongs to a large group of reactions known as "sextet rearrangements". These rearrangements arise from a molecular cleavage accompanied by a structural change in one of the fragments. This change, a migration of a group from a neighboring atom, takes place so as to avoid the generation of an atom of a first period element with only a sextet of electrons in its valence shell. Whether the electron-deficient atom actually occurs as a discrete entity, or whether its formation is prevented by

migration in concert with the cleavage, cannot always be said, and all such cases are considered together:



eqn 8

A = migrating group

B = migration origin

C = migration terminus

D = leaving group

In most cases the migrating group leaves from a carbon atom. All the migrations occur between vicinal atoms.

These rearrangements may be classified according to the kind of atom at the migration terminus, as follows:

(a) Migration to carbon atom: the electron deficient carbon atom generated (the migration terminus) may be a carbene as in the rearrangement of ∝-diazoketones, or it may be a carbonium ion as in the Wagner-Meerwein and pinacolic rearrangements,

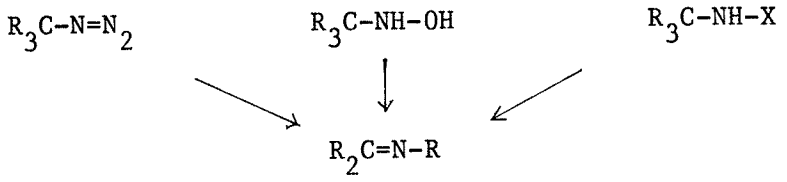
(b) Carbon to oxygen rearrangement, e.g. Baeyer-Villiger reaction,

(c) Carbon to nitrogen rearrangements.

According to Smith (7) the carbon to nitrogen rearrangements may be classified on the basis of the type of the migration origin, the migration terminus and the leaving group, as follows:

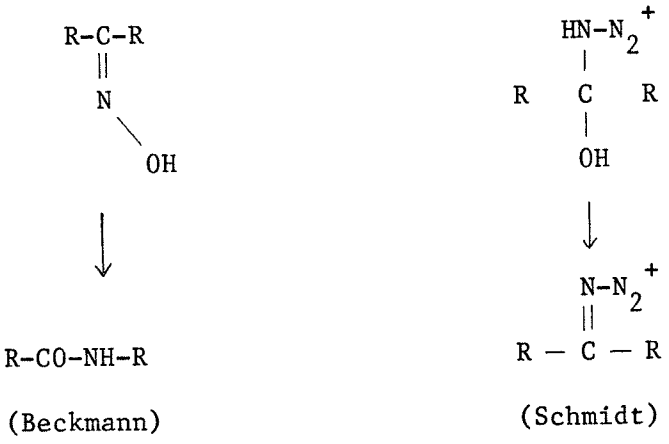
(a) Systems in which the carbon skeleton is saturated or aromatic; the functional groups that cleave so as to induce the migration from carbon to nitrogen are azides, hydroxylamines, and

haloamines (eqn 9) from which, respectively nitrogen, derivatives of hydroxyl or halides are cleaved in the initiating step.



eqn 9

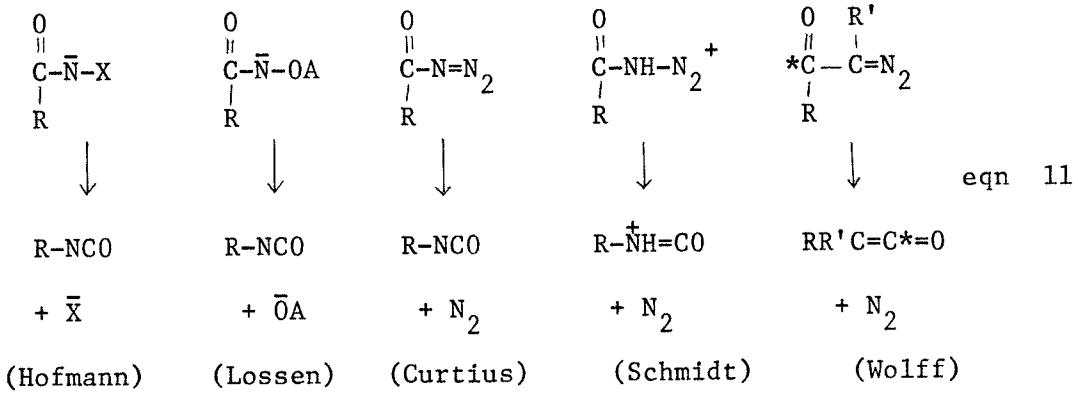
(b) Derivatives of ketones and aldehydes; the functional groups that cleave so as to induce the migration from carbon to nitrogen are oximes (the Beckmann rearrangement), and protonated azidohydrins or iminodiazonium ions (the Schmidt reaction). These derivatives of ketones respectively lose hydroxyl groups (protonated form, i.e. H_2O) and nitrogen in the initiating step.



eqn 10

(c) Carboxyl derivatives; N-haloamides (Hofmann), O-acyl-hydroxamic acids (Lossen), acylazides (Curtius), protonated acylazide (Schmidt), α-diazoketones (Wolff). In each of these reactions, a species is lost from an atom adjacent to a carbonyl group, and the

other carbonyl attached group migrates to the site of loss. It has been established (7) for many examples of all of these reactions that isocyanates (or ketenes) are the initial products. In practical syntheses, these substances undergo further reactions before a product is isolated. Isocyanates and ketenes react readily with all types of compounds having O-H or N-H functions yielding urethanes, ureas, esters or amides. Some of these intermediate species, e.g. acylazides and isocyanates have been isolated and identified (7,8), while the structure for other rearrangement species are deduced from secondary evidence and by analogy (7,9).



eqn 11

Although some features of the Schmidt reaction and Wolff rearrangement are different from the first three rearrangements, their mechanisms are so closely related that they are classified together with respect to mechanism. After having discussed the relationship of the Schmidt reaction to the above mentioned reactions, it would be worth mentioning that Fodor and Nagubandi (10) have also correlated the Schmidt reaction to the Von Braun, Beckmann, Bischler-Napieralski and Ritter reactions. These authors suggested that these reactions proceed through nitrilium salt intermediates.

C. REAGENTS FOR THE SCHMIDT REACTION

The key reagents that are required to carry out the Schmidt reaction are hydrazoic acid, sulphuric acid or some Lewis acid, an appropriate organic solvent, and a substrate.

Chloroform and benzene are the most common solvents used in the Schmidt reaction. Since chloroform is inert towards hydrazoic acid, it may be preferable to use it for dissolving hydrazoic acid or for dissolving the carbonyl substrate. But under most conditions benzene, which is relatively unreactive is just as satisfactory. Trichloroethylene (11a) and dioxane (11b) have also been used.

The most extensively used catalyst in the Schmidt reaction has been concentrated sulphuric acid. In dilute sulphuric acid the yield decreases sharply (11). Other catalysts (2) are hydrogen chloride, phosphorous oxychloride, phosphorous pentoxide, phosphorous pentachloride, thionyl chloride, ferric chloride, stannic chloride, sulfoacetic acid and other sulfonic acids, phosphoric acid, aluminum chloride, and ultraviolet light.

The reaction is exothermic and the temperature can be controlled either by the rate of addition of sulphuric acid or that of hydrazoic acid (or sodium azide) to the reaction mixture. In most cases the reaction with aldehydes and ketones is carried out with cooling of the reaction mixture in an ice bath. The best yields of amines from acids are obtained at 35°C to 50°C. Glycine is obtained in only 29% yield from malonic acid at 40°C, whereas the yield is 46% at 50°C

(12). Aniline is obtained in 85% yield from benzoic acid at 40°C, but the yield drops to 44% at the boiling point of chloroform (11).

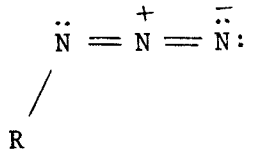
Hydrazoic acid can be used as a solution in an appropriate organic solvent. Alternatively, sodium azide can be used in the presence of sulphuric acid resulting in the in situ generation of hydrazoic acid. The in situ generation method has the advantage of eliminating one step and avoiding the isolation of very poisonous and volatile hydrazoic acid. However, higher yields of the products have been reported from the same starting material when free hydrazoic acid was used. d-$\alpha\gamma$-Diamino-n-butyric acid was obtained, from d-glutamic acid, in 41% and 33% yields when free hydrazoic acid and sodium azide were used respectively (12). In recent investigations the use of sodium azide directly has been favored because of the increased knowledge about the toxic and explosive properties of hydrazoic acid.

Hydrazoic acid is a colourless liquid, of sharp, irritating odor with a boiling point of about 37°C and a freezing point of -80°C. It is highly poisonous, its toxicity being the order of that of hydrogen cyanide. Concentrations in the air greater than 0.0005 mg/L evoke marked symptoms of intoxication (13). The toxic effects may be delayed with the symptoms appearing the day following the exposure. The main physiological effect is marked lowering in blood pressure with an accompanying rise in the rate of heart beat and respiration. It is thought that hydrazoic acid interferes with the oxidation-reduction processes of the human body (14). Pure hydrazoic acid is violently explosive (14). Heat, mechanical shock or exposure to

some reagents, e.g. conc. sulphuric acid, will decompose organic azides (15,16). As a result of decomposition, molecular nitrogen is formed and the process is accompanied by the release of large amounts of energy. In the absence of a solvent an explosion may occur. Hydrazoic acid is, therefore, used in dilute solution (4% to 6%) in which it is quite stable (2).

Since hydrazoic acid is the most important reagent required to carry out the Schmidt reaction, it is important to know more about it's physical chemistry. This knowledge would help in understanding the rearrangements involved in the reaction. The azide radical N_3 belongs to a group of inorganic radicals which have certain properties in common with the halogen atoms. Other members of this group are $C\bar{N}$, $\bar{N}CO$, $S\bar{N}$, etc. For this reason the corresponding compounds are called pseudohalides. In common with halogens they form either an anion $\bar{X}$ or a covalent bond R-X. Their acids (HX) are weaker than the hydrogen halides. The dissociation constant, Ka, of HN_3 is 2.04×10^{-5}M at 25°C (17). The reducing power of the halide and pseudohalide ions increases in the following order (18): $\bar{F}$, $\bar{N}CO$, $\bar{C}l$, $\bar{N}_3$, $\bar{B}r$, $SC\bar{N}$, $\bar{I}$. In this and other respects, the azido group shows a close resemblance to bromine.

Electronic structure (19): For covalent azides one can draw two "canonical structures" in keeping with the octet rule and the adjacent charge rule as follows:



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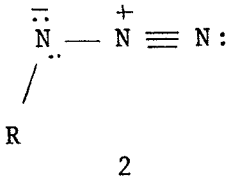


2

A simplified description of the valence states of the three nitrogen atoms is given below in Table 1 (only the L-shell orbitals are included).

Table 1. Valence states of nitrogen atoms in $HN_a N_b N_c$.

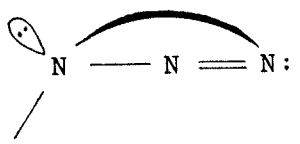
Atom	Lone pairs	δ Electrons	π Electrons
N_a	$(s_\delta p)^2$	$p\delta s'$ $p\delta s''$	py
N_b		sp sp	$(py)^2$, px
N_c	$(s)^2$	pz	py , px

The sp hybridization of the central N_b atom is responsible for the linear structure of the azido group. The nature of the δ bond may be summarized as follows:

$H\text{-}N_a$: $\delta H\text{-}p\delta s'$ (δH is a δ orbital of H)

$N_a\text{-}N_b$: $p\delta s''\text{-}sp$; $N_b\text{-}N_c$: sp-p (or sp-pδs)

A simple formula which conveys much information on the bonding in the azido group, where the arc represents the delocalized bond, is as follows:



Thus the central N atom is bound to its neighbors by two δ, one

localized $\pi(\pi_L)$ bond formed by the two px electrons from N_b and N_c, and one delocalized $\pi(\pi_D)$ bond. [The py orbitals of the three N atoms form three 'delocalized π' orbitals, one filled bonding, one filled non-bonding, and one vacant anti-bonding orbital (πy^*)]. The 16 electrons of the azido group (5 from each nitrogen and 1 from H) are distributed as follows: 6 in the three δ bonds; 4 in the two lone pairs (non-bonding electrons) (one pair in the 2s oribtal of N_c and the other in the $s\delta p$ hybrid of N_a); 2 in the π_L; and 4 in the two π_D orbitals (bonding, and non-bonding).

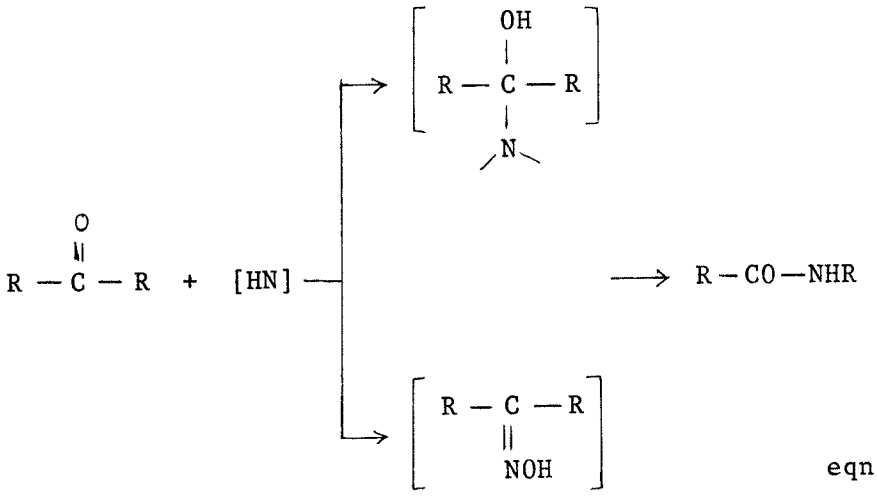
D. GENERAL MECHANISM OF THE SCHMIDT REACTION

(1) SCHMIDT'S VIEW:

In 1923, while studying the decomposition of hydrazoic acid by sulphuric acid, Karl F. Schmidt observed that benzene had an accelerating effect on the decomposition (2). The products that he obtained were either aniline sulphate or hydrazine sulphate depending on the temperature. As a result of this observation he postulated that "imine radical" NH was the species responsible and that it was produced as a result of the decomposition of HN_3 by sulphuric acid:

$$HN_3 \longrightarrow [HN<] + N_2$$
$$C_6H_6 + [HN<] \longrightarrow C_6N_5.NH_2$$
$$4[HN<] \longrightarrow 2[HN:NH] \longrightarrow N_2 + H_2N.NH_2 \qquad \text{eqn 12}$$

Considering the species [HN] as capable of adding to a reactive group, he added benzophenone to the mixture. He was convinced of the correctness of his hypothesis when he obtained a quantitative yield of benzanilide. The route to the formation of benzanilide was conceived as the formation of an adduct from the imine radical and benzophenone which rearranged, either directly or through an intermediate oxime, via a Beckmann type rearrangement, to the amide (21) (eqn 13):



eqn 13

This hypothesis was found to be erroneous, because:

(a) ketones were found to react readily at 0°C but hydrazoic acid is quite stable in sulphuric acid at this temperature; (b) the Schmidt reaction is catalysed by many other Lewis acid catalysts, as e.g. those mentioned above (page 6); and (c) oximes could not be intermediates, since the Beckmann rearrangement does not occur under the conditions where the Schmidt reaction takes place readily. Also, the oxime of ∝-hydrindone is unchanged by heating with conc. sulphuric acid at 100°C, whereas under the Schmidt reaction conditions ∝-hydrindone is smoothly converted into hydrocarbostyril at 40°C (22).

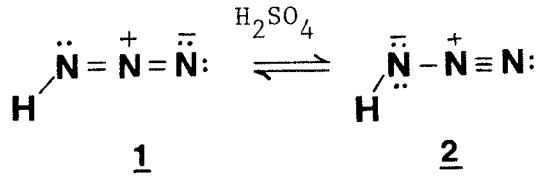
(2) EARLY TO RECENT VIEWS:

Oliveri-Mandala (23) criticized Schmidt's proposed mechanism, and suggested that the initial step is probably the addition of hydrazoic acid to the carbonyl group to form the corresponding azide, which would then decompose with loss of nitrogen to give the products obtained by Schmidt. Hurd (24) elaborated this proposed mechanism

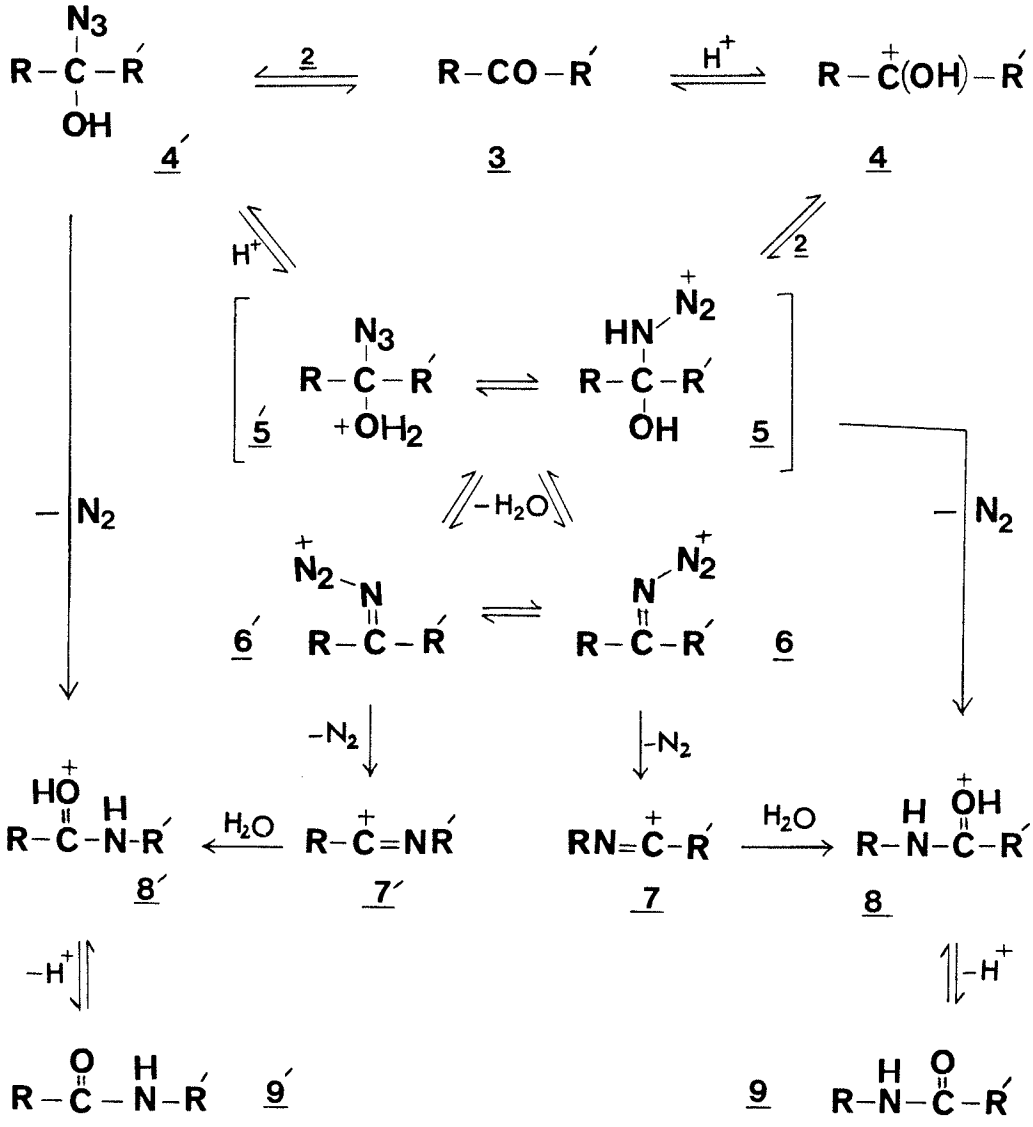
and suggested the activation of hydrazoic acid by conc. sulphuric acid to an active form 2 (see Scheme 1) which then adds to the carbonyl group. Briggs and Lyttleton (11a) obtained quantitative data from the decomposition of hydrazoic acid alone and from its action upon a series of substituted benzoic acids in the presence of conc. sulphuric acid which supported the Oliveri-Mandala's view. Later on this view was further elaborated (25-34 and the references therein) with the help of experimental data which included some kinetic evidence. Modern views of the mechanism of the Schmidt reaction on ketones are presented in Scheme 1. This mechanism explains the mode of formation of almost all the products from the Schmidt reaction, e.g., isomeric amides, tetrazoles, nitriles, and amines from ketones, aldehydes and carboxylic acids (see details later on). Scheme 1 is mainly derived from secondary evidence and analogy with related reactions. The overall mechanistic treatment which I have developed in Scheme 1 has two slightly different forms: (a) the direct conversion 5 → 8 (or 4' → 8') was suggested initially for carboxylic acids (26) and later on for ketones (34); and (b) the conversion through iminodiazonium ions 6 or 6' was suggested for ketones (3,27). These two views of the mechanism are widely accepted today.

Although this mechanism also explains the formation of products from the Schmidt reaction on bridged bicyclic ketones, the different factors involved during their rearrangement will be discussed separately later (cf. page 36).

Before an attempt is made to discuss the involvement of each step and the nature of intermediates, Scheme 1 can be summarized in the following way: (a) hydrazoic acid is activated by conc. sulphuric



1 2



SCHEME 1

acid and (b) it attacks the carbonyl compound (in a free or protonated form) to give the hydroazidohydrin 5 or azidohydrin 4', (c) intermediate 5 (or 4') either rearranges directly to 8(or 8') or dehydrates to iminodiazonium ion 6(or 6'), (d) the loss of nitrogen by the iminodiazonium ion is accompanied by the migration of the substituent (R or R') in the antiposition in relation to the diazogroup, (e) the iminocarbonium ion 7(or 7') arising under these conditions interacts with water or with any other nucleophile, forming the reaction product.

A detailed examination of the reaction mechanism is best made by examining the individual stages of the process, beginning with the state of the reactants in the reaction medium.

(a) Behaviour of ketones in strong acid solutions:

Ketones, which are typical weak organic bases, are protonated at the oxygen atom in strong acid solutions (25) such as conc. sulphuric acid (eqn 14). (Sulphuric acid, which is used in the Schmidt reaction in large excess relative to the ketone and the hydrazoic acid, serves also as the reaction medium).

$$RCOR' + H^+ \longrightarrow [RCOHR]^+ \qquad \text{eqn 14}$$

Hammett (35) and Stewart and Yates (36) determined spectrophotometrically the pKa values for some substituted and non-substituted acetophenones and showed that such compounds belong to the series of Hammett bases. Later on Dunn and Zalewski (37) found that

acetophenone and many other α,β-unsaturated aliphatic ketones (as well as aldehydes and carboxylic acids) can be satisfactorily described by the amide acidity function H_A introduced by Yates, Stevens and Katritzky (38). However, reinvestigations showed that protonation of acetophenone and some other aromatic ketones is better described by the H_0 Hammet function than by H_A (5,39). The protonation of aliphatic ketones has been less well studied. It has been found that the ionization constants of their conjugate acids are mainly in the range, pKa = -6 to -8 (5,39).

The simplified interpretation of the protonation of ketones in terms of equation 14 does not reflect all the essential features of the process. It has been stated (5) that the following equilibria are characteristic of certain ketones in solutions of strong inorganic acids:

$$S.sH_2O + H^+.xH_2O \rightleftharpoons S...H^+.nH_2O + (s+x-n)H_2O$$
$$S...H^+.nH_2O \rightleftharpoons SH^+ + nH_2O \qquad \text{eqn 15}$$

where S is the base (ketone). Therefore the results obtained in the study of the protonation of ketones refer to equilibria in equation 15 and not equation 14. Also equation 14 does not take into account the effect of the solvent. It has been suggested (40) that both forms of ketones (S and SH^+) are hydrated, and the protonation may best be represented as follows (5):

$$S.bH_2O + H^+.xH_2O \rightleftharpoons SH^+.mH_2O + (b+x-m)H_2O \qquad \text{eqn 16}$$

(b) Behaviour of HN_3 in strong acid solutions:

Hydrazoic acid is a weak inorganic acid which is protonated in strongly protogenic systems, as follows:

$$HN_3 + H^+ \rightleftharpoons [H_2N_3]^+ \qquad \text{eqn 17}$$

$$[H_2N_3]^+ + H^+ \rightleftharpoons [H_3N_3]^{++} \qquad \text{eqn 18}$$

In the two phase system of sulphuric acid and chloroform, the partition coefficient and hence the activity coefficient of the non-protonated form of HN_3 remain constant over the range 25% to 40% sulphuric acid (41). A sharp change in the partition coefficient was observed only in 78-85% sulphuric acid. This change is believed to be due to the protonation of hydrazoic acid (41). The ionization constant of $[H_2N_3]^+$ was found to be -6.21. The anomalous variation of the partition coefficient in sulphuric acid at higher concentrations (95%) made it impossible to characterize the second protonation process of HN_3 in terms of equation 18. Bak and Prestgard (41) estimated pKa = -10.1 for the acid $[H_3N_3]^{++}$.

Occasionally hydrochloric, polyphosphoric, trichloroacetic and trifluoroacetic acids are employed as catalysts in the Schmidt reaction. The reactions of ketones and hydrazoic acid in such media are analogous to those in sulphuric acid. However, here solvation effects play a greater role: in media of low acidity there is the possibility of formation of a hydrogen-bonded complex of the carbonyl compound with the media. When the Schmidt reaction is catalysed by Lewis acids, the reaction species is probably the

complex formed by the interaction of the ketone with the aprotic acid (5).

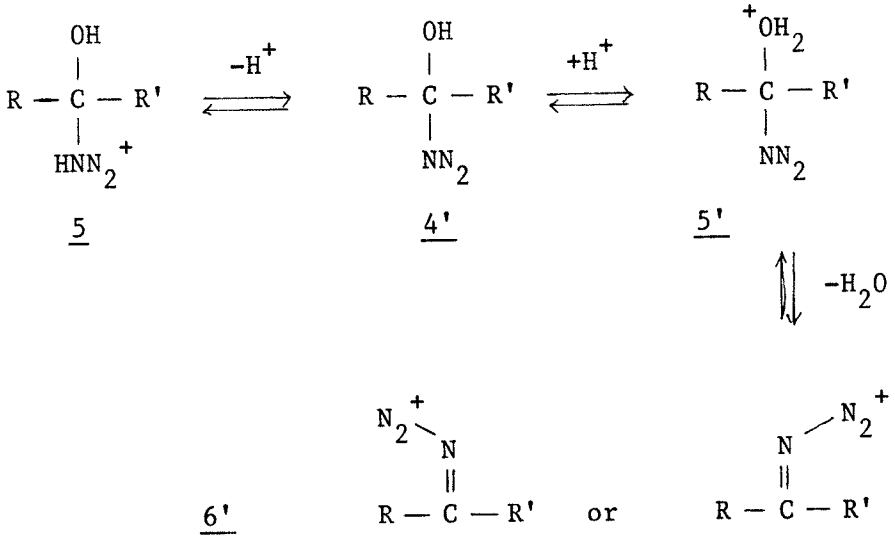
(c) Addition of hydrazoic acid to the carbonyl group:

Generally speaking, the addition of hydrazoic acid to the carbonyl compound depends on the electrophilicity of the carbon atom of the carbonyl group, and the nucleophilicity of hydrazoic acid. Protonation of ketones in aqueous sulphuric acid solutions with a sufficiently high acidity will appreciably increase the polarity of the carbonyl group, and therefore the electrophilicity of the carbonyl carbon, and will promote the addition of nucleophiles. Fikes and Shetcher (33,34) obtained 95% of amides (crude product) from the action of hydrazoic acid on alkyl cyclopropyl ketones in 83-89% sulphuric acid whereas in 50% sulphuric acid large amounts of unreacted ketones were recovered. However, in media with a high acidity ($H_0 > -9$) the rearrangement is retarded owing to a decrease of the non-protonated form of hydrazoic acid (5).

The order of reactivity of ketones has been observed to be: aliphatic ketones > alkylaryl ketones > benzophenones (27). This is the same order as the basicity of the carbonyl groups (43). Therefore, it has been suggested that the rate of reaction of ketones with hydrazoic acid is determined by their basicity (3). There is also the qualitative observation that sterically hindered ketones, such as tertiary alkyl ketones and ortho-substituted benzophenones, are sluggish compared to the analogous unhindered ketones and may

even be inert (3). In addition, the electronic and steric properties of the substituents also should control the reactivity of the carbonyl group. [Usually substituents with a +I or +M effect lead to an increase of the basicity of the ketone, but lowers its reactivity in relation to the nucleophilic agent. Conversely, substituents with a -I or -M effect reduce the basicity of the ketone, enhancing, at the same time, its reactivity towards nucleophiles (5).]

The interaction of hydrazoic acid with a ketone leads to the intermediate hydroazidohydrin 5 or azidohydrin 4'. Only in one case was an azidohydrin of the type 4' isolated (77% yield) and identified in the reaction of perfluorocyclobutanone with hydrazoic acid (42). An azidohydrin with a higher energy content than the starting compound would either tend to regenerate the starting ketone or form a stable iminodiazonium ion 6 (or 6') by dehydration. Dehydration is promoted by the following protolytic equilibria (5):



5 4' 5' 6' 6 eqn 19

It has been suggested that the energy content of 6(or 6') is lower than hydroxycarbonium ion 4 which promotes a shift of equilibrium in

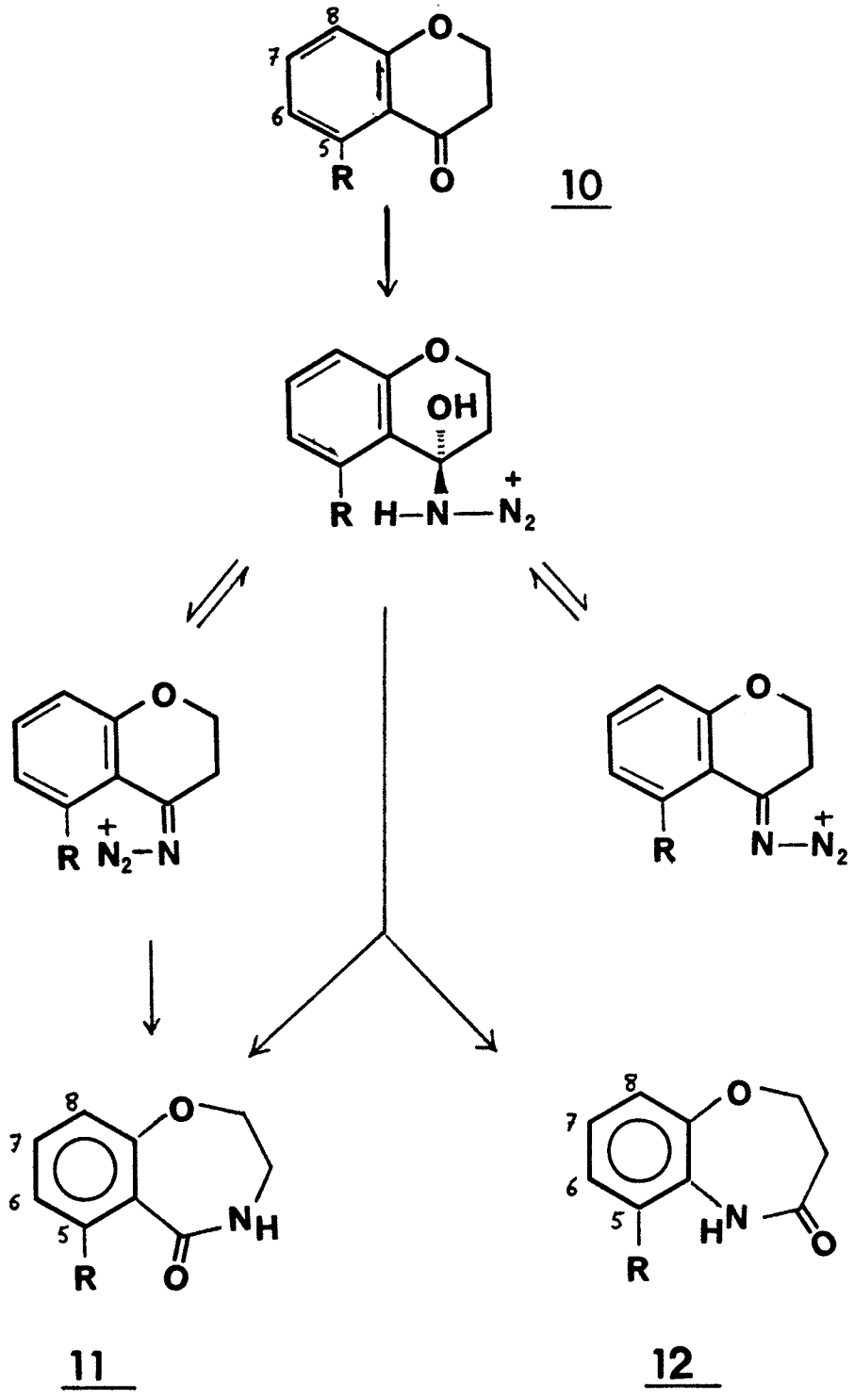
the forward direction.

A hydroazidohydrin also would tend to rearrange directly to 8 or 8' (cf Scheme 1).

(d) Direct rearrangement of the hydroazidohydrin to amides with loss of nitrogen:

Although in most cases the formation of isomeric amides has been justified by the involvement of isomeric iminodiazonium ions 6 and 6' and their stereospecific trans rearrangements (3,5,11a), there are a few cases where a direct rearrangement of the hydroazidohydrin, with loss of nitrogen, to amides is also suggested. In such cases it is believed that there is competition between the direct rearrangement of the hydroazidohydrin and the rearrangement through the iminodiazonium ions. Different factors, such as steric, electronic and acidity of the medium, are considered to favor one or the other kind of rearrangement.

Bhalerao and Thyagarajan (44) examined the mechanism of the Schmidt rearrangement in the conversion of chromanones 10 to 1,4- and 1,5-benzoxazepinones 11 and 12 respectively. They found that with substituents in the 6-, 7- or 8-positions of 10 (eqn 20), only electronic effects prevail resulting in the exclusive formation of 1,4-benzoxazepinones 11 through the involvement of the iminodiazonium ion. Steric effects come into play with increased bulk of substituents in the 5-position of 10. The relative population of the iminodiazonium ion having a cis configuration relative to the bulkier



EQUATION 20

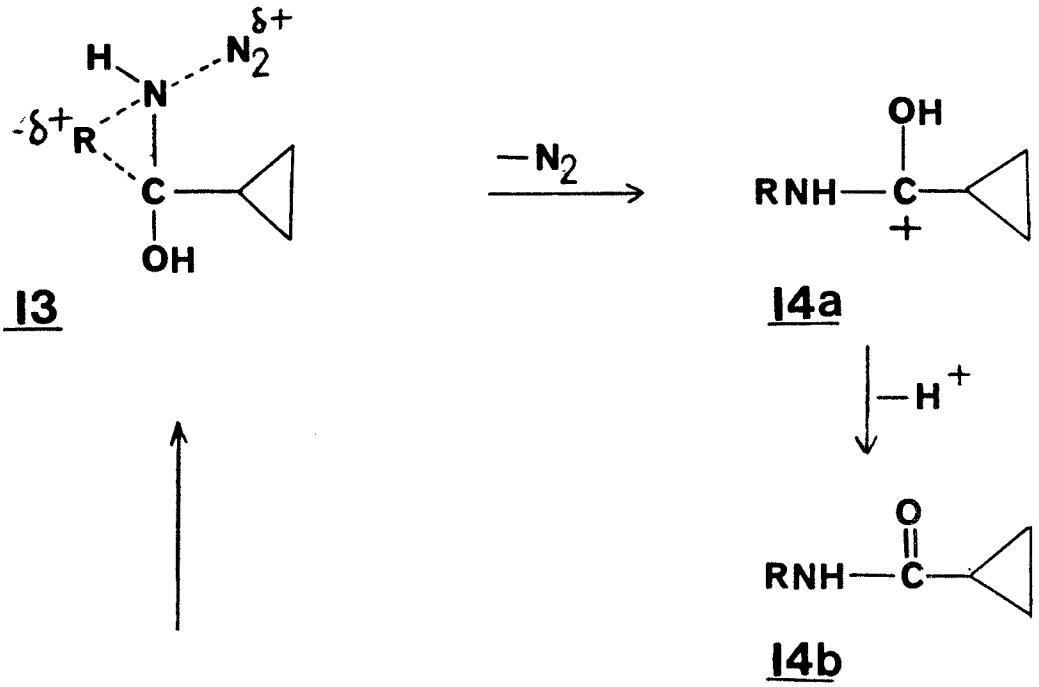
substituent at 5-position of the chromanones would be extremely low. In these cases 20-40% of the product from migration of the sterically non-favored alkyl bond was obtained via the direct rearrangement of the corresponding hydroazidohydrin. It was concluded that products could be derived either through the iminodiazonium ion or, when the latter was not sterically favoured, through the hydroazidohydrin.

Under similar conditions of the Schmidt reaction, DiMaio and Permutti (45) also have suggested the simultaneous action of two mechanisms: the direct rearrangement of hydroazidohydrin to the lactam, and rearrangements through the trans iminodiazonium ion accounting for 25% and 75% of the isomeric products respectively (vida infra).

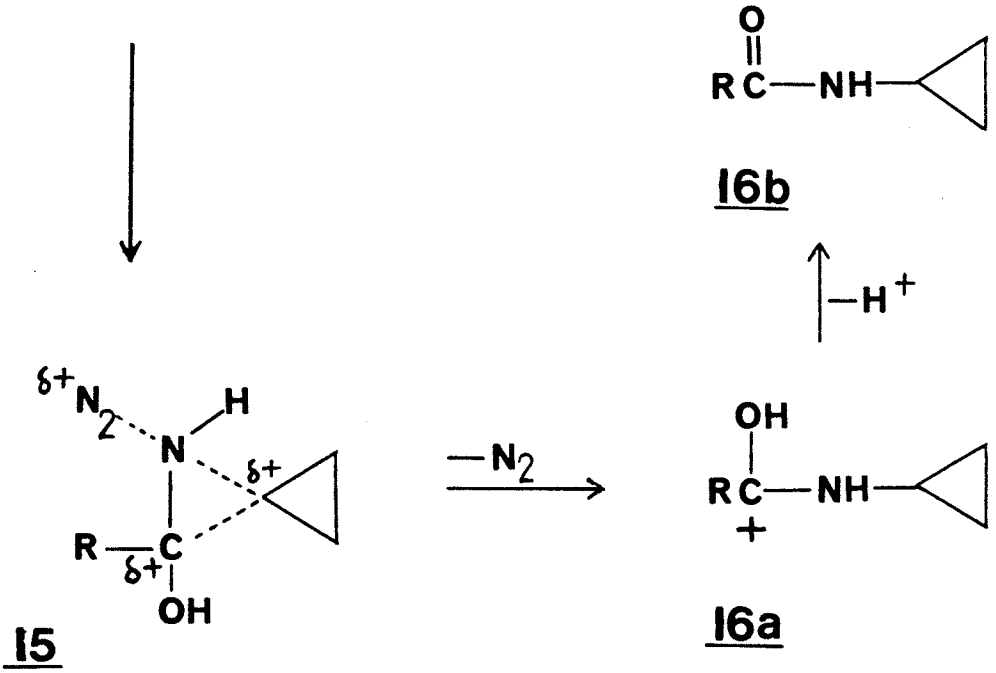
The ratios of isomeric amides 14b and 15b (eqn 21) from the reaction of alkyl cyclopropyl ketones with HN_3 are markedly influenced by the acidity of the reaction medium (see Table 2) (33,34).

Table 2. ALKYL/CYCLOPROPYL MIGRATION RATIOS IN SCHMIDT REACTIONS OF ALKYL CYCLOPROPYL KETONES

	R/cyclopropyl migration ratio (14b/16b)		
acid catalyst	R = Me	R = Et	R = i-Pr
89% H_2SO_4	27:73		
83% H_2SO_4	26:74	18:82	8:92
69% H_2SO_4	56:44	18:82	4:96
50% H_2SO_4	90:10	74:26	18:82
CCl_3CO_2H	73:27	74:26	52:48



HYDROAZIDOHYDRIN



EQUATION 21

Interesting evidence was presented (33,34) that the Schmidt reaction occurs via (1) collapse of syn- and anti-iminodiazonium ions in strong acid environments; in 83-89% sulphuric acid high proportions of cyclopropyl, rather than alkyl, migration occur (vida infra), and (2) the profound increase in alkyl migration as acid strength is reduced suggests that in 50% sulphuric acid and in trichloroacetic acid reactions occur predominantly by direct rearrangement of the hydroazidohydrin. To support the latter mechanism, Fikes and Shetcher (33,34) suggested that in the transition states 13 and 15 (eqn 21), due to the presence of both the OH and the cyclopropyl groups, considerable positive charge may reside on the migration origin, so that 13 and 15 would resemble products 14a and 16a respectively. Thus, alkyl migration, rather than cyclopropyl, may arise from stabilization of 13 (R = Me or Et) by cyclopropylcarbinyl resonance (34).

In contrast, at high acid strengths in which dehydration to syn- and anti-iminodiazonium ions is likely, there presumably is considerable positive charge at the migration terminus, which might be stabilized by cyclopropyl migration (vide infra).

The direct rearrangement of hydroazidohydrins with loss of nitrogen also accounts for the formation of amines from carboxylic acids. If R' in 5 (and therefore in 9), Scheme 1 (page 14), is hydroxyl, the intermediate carbamic acid (9 in this case) would instantaneously lose carbon dioxide in strong acids yielding the amine (2,11a,26).

(e) Stereochemistry of the Dehydration Step followed by Rearrangement:

Scheme 1 shows the possibility of geometrical isomerism of the intermediate iminodiazonium ions determining the products if trans migration applies in the Schmidt reaction as it does in the Beckmann rearrangement. In 1950 Smith and Horwitz (29) observed that p-substituted benzophenones gave a mixture of isomeric benzanilides in a ratio of 1:1 regardless of the nature of the p-substituent. These ratios were very much the same as those obtained from the Beckmann rearrangement of the equilibrated oximes (46). This relationship enabled them to postulate that an equilibrium exists between the isomeric iminodiazonium ions as it does between the isomeric oximes involved in the Beckmann rearrangement. The two isomeric iminodiazonium ions presumably equilibrate through the intermediate hydroazidohydrin 5 (and/or 5')(3). The ratios of the syn and anti-isomers in the equilibrium mixture are determined by the reaction conditions and also by electronic and steric factors.

Effects attributable to steric influence on the relative stabilities of the geometrically isomeric iminodiazonium ions were observed in a series of phenyl alkyl ketones (29):

$$C_6H_5COR \longrightarrow C_6H_5NH\text{-}COR + C_6H_5CO\text{-}NHR \qquad \text{eqn 22}$$

where R=Me, Et and isopropyl (eqn 22) and the ratio of the N-phenyl to N-alkyl amide is 95:5, 85:15 and 51:49 respectively. These ratios are consistent with the concept that the intermediate iminodiazonium

ion prefers a configuration in which steric interference with the diazo nitrogen is smallest.

It has been suggested (3) that in the rearrangement through the iminodiazonium ion, the rate determining step for the release of nitrogen might reasonably be the addition of HN_3, the dehydration of the hydroazidohydrin (5→6), or the rearrangement step (6→7) (Scheme 1, page 14). Only the latter step was assumed to be irreversible. By analogy with oximation, Smith (3) assumed that step 5→6 (and 5'→ 6') is slow and may be rate determining, and its reversal provides a path for equilibrium between the geometrical isomers 6 and 6'. If the rearrangement step 6→7 (and 6'→ 7') is faster than this equilibrium, then the relative populations of 6 and 6' will determine the product ratios. The populations of 6 and 6' are determined by the relative rates of 5→ 6 and 5'→ 6' dehydrations, therefore correlations of product ratios with steric effect must be considered in terms of the transition states for step 5→6 and 5'→ 6'. In other words, the ratios would be kinetically controlled. Again by analogy with oximation, Smith assumed that the transition states for step 5→ 6 (and 5'→ 6') sufficiently resemble the products 6 and 6' that one could approximate steric influences in the transition states by considering the same effects in these products. On this basis, the independence of the nature of para substituents shown by the products ratio 1:1 from benzophenones (vida supra) could be accounted for.

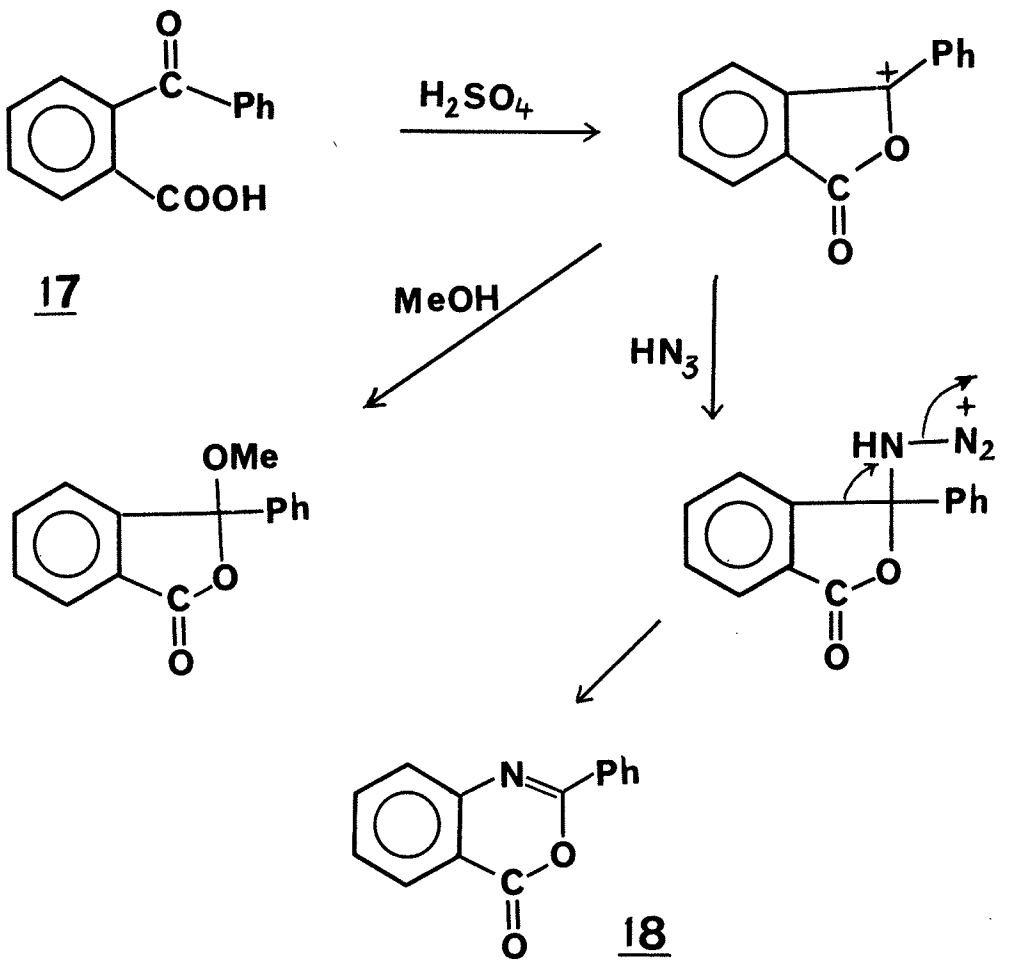
Let us consider the opposite possibility that step 6→7 (and 6'→ 7') is slower than the dehydration step, and thus rate determining. Equilibration between 6 and 6' would then be achieved continually while rearrangement is going on, so that the product

ratios would be determined by the relative rates of rearrangement (6 7 and 6' 7'); that is, migration aptitude would govern the product ratios. This analysis accomodates the bulk of the data which was available up to 1963 when Smith (3) published this analysis. But direct evidence for the importance of intrinsic migratory aptitudes in the rearrangement of aliphatic ketones is provided by the kinetic and product effects observed on reaction of 1-^{14}C acetone (31). Here the methyl group containing the heavy isotope migrated less readily than its isotopically normal partner. Steric effects on populations of intermediates in this case can be ruled out.

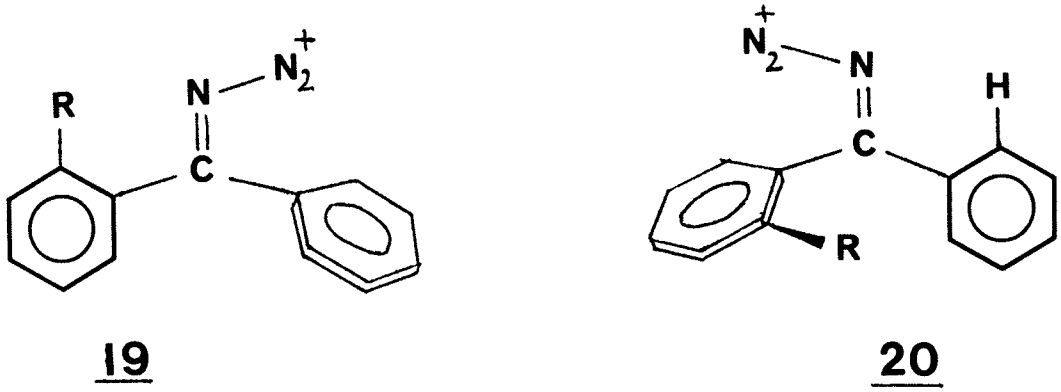
However, it would be very unlikely that the effects of electronic (migratory aptitude) and steric factors would occur in a "pure" form. The ratio of the amides formed is more likely to be affected by all the factors, only some of them will of course be decisive. The relations applicable to one series of ketones need not necessarily exist in another series. This assumption makes it more difficult to interpret the available data. The anomalous behaviour of some ketones observed may be associated with a possible change in the rates of individual stages as a function of the nature of the ketone and with the competing effect of electronic and steric factors on the structure of the iminodiazonium ion. For example, chemists were bewildered for some time by the anomalous behaviour of ortho-subsituted benzophenones (o-XC_6H_4COPh) where preferential migration of the unsubstituted phenyl ring has been observed. At the same time ortho-substituted acetophenones (o-$XC_6H_4COCH_3$) give rise to aryl migration products. Product analyses showed that predominant migration of the unsubstituted ring occurred when X was methyl,

ethyl, isopropyl or halogen, and similarly when ortho-substitution was located in a naphthyl ring such as that of 1-benzoylnaphthalene (32,47). However, when X was methoxy nearly equal proportions of the two rearrangement products were found, and when X was nitro or carboxy or phenyl there was predominant migration of the substituted ring. A correlation of products with either size or polarity of substituents was not possible. The behaviour of o-carboxylbenzophenone (o-benzoylbenzoic acid) 17 has been rationalized (48) on the grounds of reaction of the lactol form of the substrate and an oxazine 18 has been isolated from the reaction mixture (eqn 23).

A similar explanation has been proposed for the nitro compound and o-phenylbenzophenones (32). The remaining results can be convincingly explained (3,32) if it is appreciated that only one of the aromatic rings can be conjugated with the carbonyl group. This leads to the breakdown of the coplanarity of the system. The iminodiazonium ion derived from such compounds can exist as two steric isomers 19 and 20 (see next page). If the ortho-substituent promotes the conjugation of the substituted phenyl group to the iminodiazo (or carbonyl) group, conformation 19 predominates and preferential migration of the ortho-substituted ring is observed. When the substituent does not have an appreciable effect on the capacity of the phenyl group for conjugation, conformation 20 predominates and the migration of the unsubstitued ring is significant. The existence of the two steric isomers 19 and 20 also explains the different ortho-effects of ethyl and methoxy groups. They are sterically almost equivalent, but the methoxy group is more effectively conjugated with the phenyl group. The major product

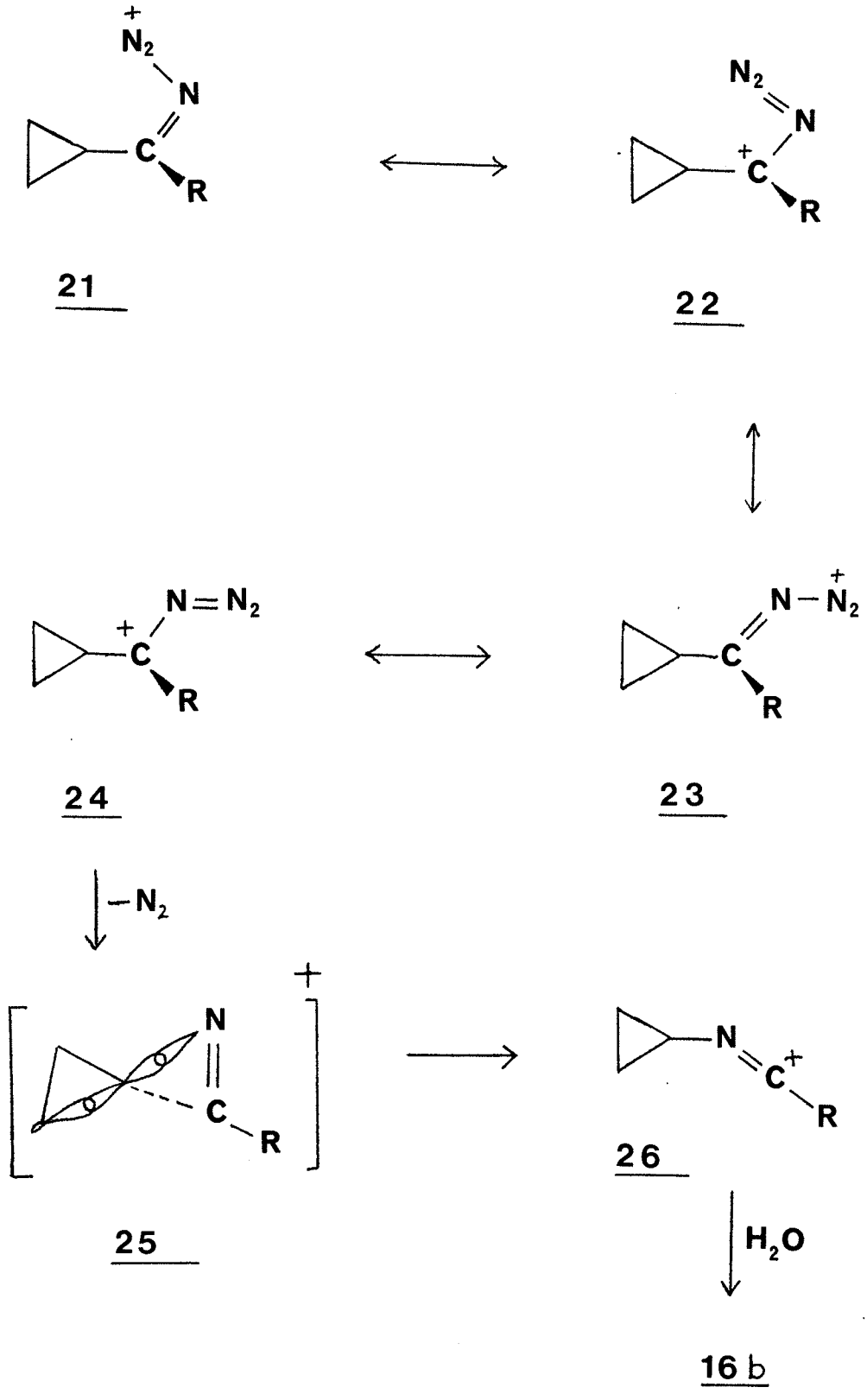

O
C
Ph
COOH
17
H_2SO_4
Ph
+
O
C
O
MeOH
HN_3
OMe
Ph
O
C
O
HN
+
N_2
Ph
O
C
O
N
Ph
O
C
O
18

EQUATION 23


R
N
N_2^+
C
19
N_2^+
N
H
C
R
20

(77-79%) obtained from o-ethylbenzophenone is N-phenyl-o-ethyl-benzamide, while o-methoxybenzophenone gives a 1:1 mixture of the isomeric amides (47).

It has been observed in some cases that the ratio of isomeric amides also depends on the nature of the medium. One case was mentioned previously (page 22). In this case the ratio of isomeric amides 14b and 16b formed from alkyl cyclopropyl ketones is markedly influenced by the acidity of the medium. The data in Table 2 (page 22) for the reactions of alkyl cyclopropyl ketones with hydrazoic acid (33,34) reveal several significant features. Noteworthy is the high proportion of cyclopropyl rather than alkyl migraton that occurs at high acid strengths. Furthermore, at all concentrations of sulphuric acid, the migration order for alkyl group (relative to cyclopropyl) is Me $>$ Et $>$ i-Pr. Such an order is unusual for Schmidt reactions of ketones; the usual migraton order, described by Smith (3), is i-Pr $>$ Et $>$ Me. It can also be seen from Table 2 that in 83% sulphuric acid the percent cyclopropyl migration increases as the steric bulk of the alkyl group opposite it in the starting ketone increases. This result is clearly contrary to the prediction that steric repulsions in the transiton states leading to iminodiazonium ions 21 and 23 (eqn 24) are responsible for the amide ratios. However, in 83% sulphuric acid the reactions may proceed via 21 and 23 which, if they equilibrate readily with each other, allow migratory aptitudes to determine the amide ratios. Fikes and Shetcher thought that the interconversions of 21 and 23 may occur rapidly because the double bond character of their imino linkages is greatly reduced as in 22 and 24 because of cyclopropylcarbinyl resonance.



EQUATION 24

Fikes and Shetcher (33,34) conceived that cyclopropyl, rather than alkyl, migration to positive nitrogen might occur because the cyclopropyl group in 23 can stabilize the transition state leading to cyclopropyl migration by delocalization of the bonds of the ring which are high in p character. Such stabilization might come about in either of two ways, by ring-edge participation or perhaps, more favourably, by participation of the back lobes of the cyclopropyl ring orbitals (C-1,2 and C-1,3) as in transition state 25. Fikes and Shetcher (33,34) also suggested that probably a combination of several factors may be responsible for the surprising migration order (relative to cyclopropyl) of Me > Et > i-Pr in 83% sulphuric acid, but it is difficult to distinguish among these factors.

Brackenridge (5,49) obtained interesting results in a study of the effect of the concentration of sulphuric acid on the ratio of isomeric amides in the case of substituted benzophenones. He observed that upon increase of the concentration of sulphuric acid from 88% to 99%, (therefore also increasing the polarity of the medium) there was a sharp change in the migration ratio. The transition state for the conversion from hydroazidohydrin to iminodiazonium ion will be more polar if (a) the medium is more polar, and (b) the meta-substituted phenyl ring (with an electronegative substituent) is in the anti position with respect to the diazo-group. The rate of dehydration of the hydroazidohydrin depends largely on the polarity of the solvent. Consequently with an increase of the polarity of the medium, the reaction will proceed via a polar transition state and, therefore, resulting in a considerable change in the ratio of the isomeric amides. It was also observed

that para-substituted benzophenones were almost insensitive to the effect of the medium.

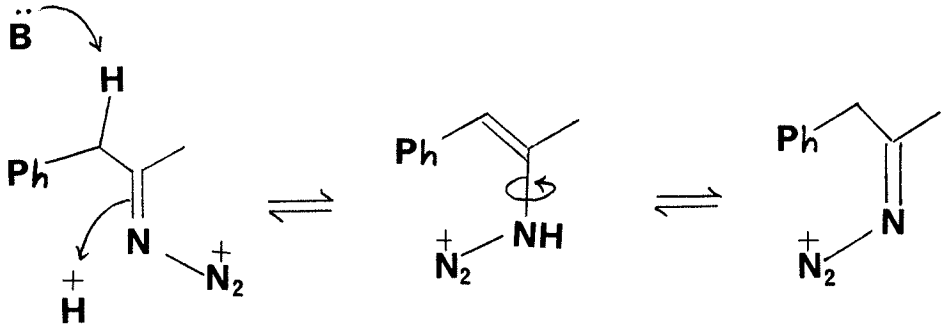
Although the solvent effects on the Schmidt reaction are poorly understood, recently some detailed studies (50) were carried out in order to understand such effects. It was found (50a) that the relative migratory aptitude of benzyl and alkyl groups in the reaction of arylpropanones and 2-arylcyclohexanones with hydrazoic acid depends on the the solvent, temperature, and nature of the substitutents in the aryl ring. At room temperature the amide ratio from benzyl to methyl migration in substituted phenylpropanone was 0.67 (50). The effect of temperature and solvent on this ratio is shown in Table 3.

It was found that reaction 'in benzene' occurred practically completely in the sulphuric acid phase and was very similar to that in polyphosphoric acid, whereas reaction in ether occurred in the organic phase and was much slower. In ether, methyl migration was favoured, and in polyphosphoric acid, benzyl migration was favoured. Increasing the temperature in both cases caused the reaction to be less selective. It was concluded (50a), "whereas the mechanism in ether is different to that in benzene, in neither case can the product ratio be explained on purely electronic or steric grounds". Ether is a better solvating agent for cations than benzene and, therefore, in ether the enthalpy of the iminodiazonium ions is lowered more than that of the transition states for their rearrangement, which have the charge more delocalized. This results in the enthalpy change (ΔH) for reaction in ether being larger than that in benzene and consequently the rate of amide formation is

slower and the lifetime of iminodiazonium ion larger, providing time for equilibration. This equilibrium is probably aided by the ether which acts as a base (see the structures below Table 3).

Table 3. BENZYL:METHYL GROUP MIGRATION RATIOS IN THE REACTION OF PHENYLPROPANONE WITH HYDRAZOIC ACID.

Solvent	Temp.(°C)	Ratio	Solvent	Temp.(°C)	Ratio
Ether	0	0.45	benzene	0	4.1
Ether	20	0.67	benzene	20	3.7
10% Benzene-ether	20	0.77	polyphosphoric acid	20	3.1
50% Benzene-ether	20	1.8	polyphosphoric acid	50	2.6
90% Benzene-ether	20	3.5	polyphosphoric acid	100	2.0



A few examples discussed above, and other mechanistic work cited in the literature show that there are two views regarding the equilibration of isomeric iminodiazonium ions 6 and 6' (Scheme 1, page 14): (a) equilibration via hydration and dehydration involving the hydroazidohydrin 5 (and/or 5'), and (b) rapid isomerization of 6 and 6'. There is no direct evidence presented in support of either view. However, recently Bach and Wolber (51) carried out some theoretical investigations of the barriers to nitrogen inversion in N-cyano- and N-diazoformimine. The inversion process, or lateral shift mechanism, for topomerization of the N-cyanoimine was calculated to be 14.5 kcal/mol while nitrogen inversion in the N-diazoimine was 28.2 kcal/mol. These observations mitigate against the above view (b) i.e. the involvement of rapid isomerization of 6 and 6'.

So far different factors were discussed that are considered to be responsible for the preferential migration of R or R' groups in the iminodiazonium ions 6 and 6'. However, the rearrangement process 6→7 (and 6'→7') is unequivocally considered to be a "concerted process", i.e. migration of the R or R' group and loss of nitrogen take place at the same time, and does not involve the "iminium ion" $RRC=N^+$. The latter would lead to essentially equal quantities of products of migration of each group as little discrimination would be expected for movements to such a reactive centre.

The other concomitant reactions leading to the formation of tetrazoles, nitriles and other cleavage products etc. will be discussed later (section E).

(3) MECHANISM OF REACTION OF CYCLIC AND BRIDGED BICYCLIC KETONES

The same mechanism, as described above in Scheme 1, is believed to operate during the Schmidt reaction on cyclic ketones (monocyclic, fused bicyclic, bridged bicyclic, and polycyclic ketones). Although the various factors considered to be responsible for the different ratios of isomeric amides account fairly satisfactorily for the experimental observation with open-chain ketones, the situation becomes more complex with cyclic and bicyclic ketones. The solvent and temperature effects may be the same in both cases, but the electronic and steric effect would operate in a much different fashion during the rearrangement processes in cyclic ketones due to the following strains in cyclic systems:

(a) Small angle strain in cyclic systems having 3,4 and even 5 membered rings.

(b) Non-bonded interactions due to the close proximity of non-bonded atoms.

(c) In medium size rings there would be one of the following types of strains:

(i) transannular interaction due to gauche conformations, or

(ii) Pitzer strain due to eclipsed conformations.

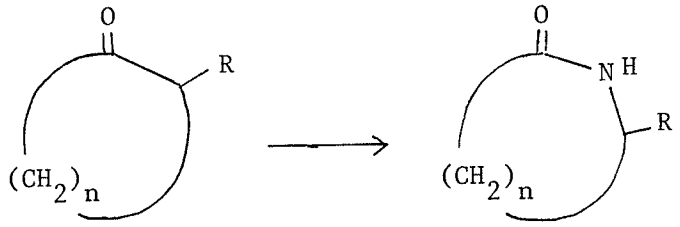
As a result of such strains the energy of the system would be relatively higher than that of the open-chain systems. Therefore the tendency for the release of energy due to strain would also direct the course of the reaction.

The Schmidt reaction on cyclic ketones, like the Beckmann rearrangement, leads mainly to the insertion of nitrogen into the

cyclic system and, therefore, results in ring enlargement. An interesting problem, common to many of such ring enlargement reactions, arises in the case of bicyclic systems in which the carbon atom (of the carbonyl group) involved is in the position alpha to the ring junction. In such cases, the direction of ring enlargement is mostly determined by the rule according to which the most substituted carbon atom migrates. Sometimes the products also correspond to migration of a less substituted atoms or a mixture of products is obtained.

Although a few examples of the Schmidt reaction on cyclic ketones can be found in the literature [e.g. (52)] prior to the report of the Schmidt reaction on norcamphor and cyclopentanonorcamphor by Elderfield and Losin in 1961 (53), most of the work in this area has been carried out since that date. Some of the cyclic systems which have been subjected to the Schmidt reaction include: (a) monocyclic ketones (52); (b) fused cyclic ketones (45,54); (c) bridged bicyclic ketones (6), e.g. bicyclo[2.2.1]heptanones (53,55), bicyclo[2.2.2]octanones (56), bicyclo[3.2.1]octanones (57) bicyclo[3.3.1]nonanones (58), bicyclo[3.3.2]decanones (59) and bicyclo[4.3.1]decanones (58e).

Shechter and Kirk (52a), observed that reaction of 2-alkyl-cyclopentanones 27a and 2-alkylcyclohexanones 27b (eqn 25) with hydrazoic acid and sulphuric acid resulted in migration of the 2-alkylmethylene group to yield 6-alkyl-2-piperidones 28a (63-83%) and 7-alkyl-2-ketohexamethylenimines 28b (58-87%) respectively. By analogy with the 2-alkylmethylene group migration during the Beckmann rearrangement of analogous oximes, they suggested that steric factors



eqn 25

27a, n=3

27b, n=4

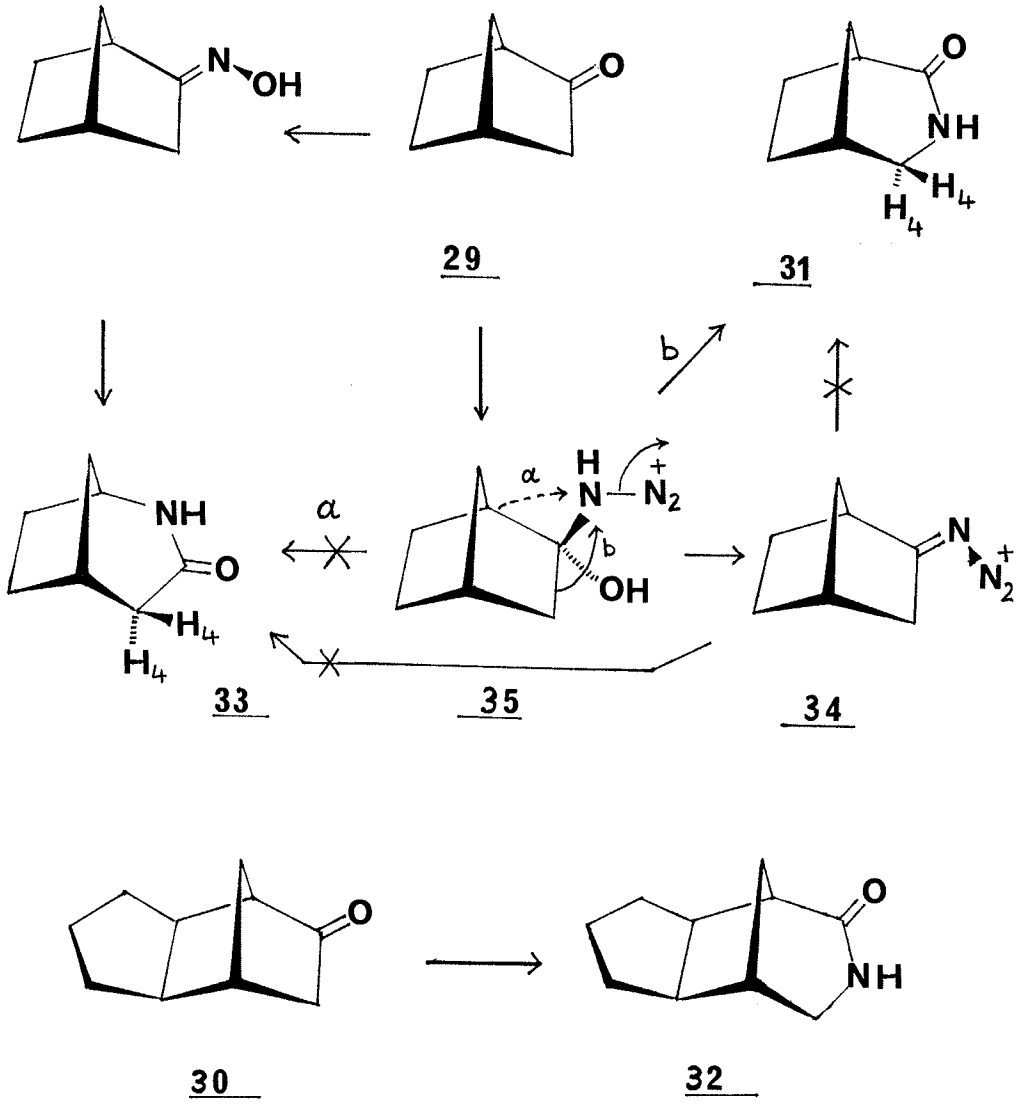
28a, n=3

28b, n=4

which influence the formation of the trans-oximino-2-alkylcyclo-alkanones are being manifested in reaction of 27 with hydrazoic acid.

It is generally assumed that steric as well as electronic factors are responsible for the migraton of the more substituted carbon (e.g. a bridgehead carbon) during ring enlargement reactions (45). However, this is not always true (60). For example, the well-known Baeyer-Villiger oxidation of camphor yields (61) only α-campholide; the "wrong" product from the point of view of electronic rules.

Elderfield and Losin (53) studied the behaviour of norcamphor 29 and cyclopentanonorcamphor 30 (Scheme 2) under conditions of the Schmidt reaction and the Beckmann rearrangement. Lactam 31, resulting from the unexpected methylene migration, was isolated in up to 30% yield from the Schmidt reaction on 29. (Similarly 30 gave lactam 32). Although the yields were low, the preference for soley methylene migration during the Schmidt reaction contrasts sharply with the preference for bridgehead methine migration to form lactam

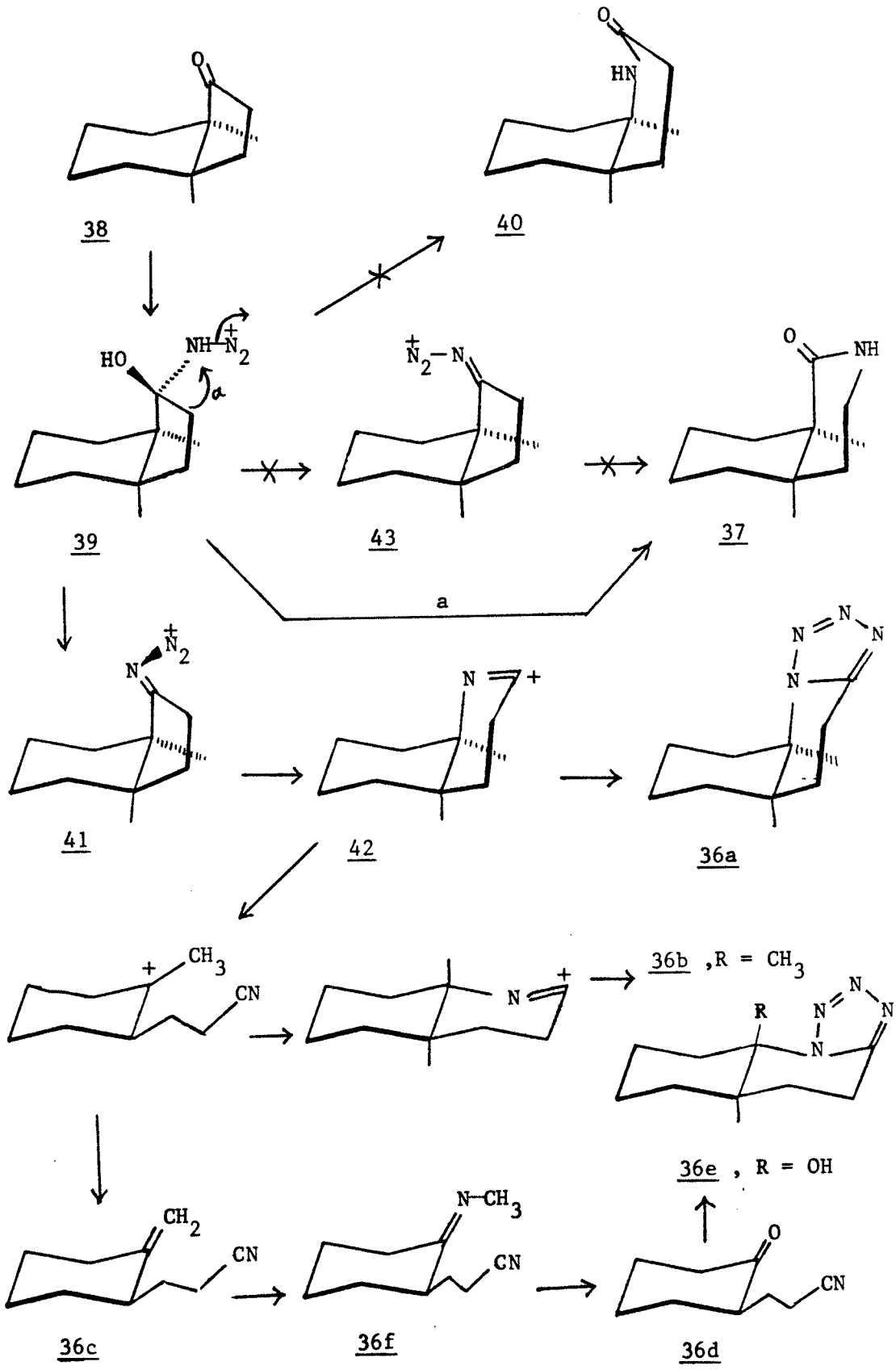


SCHEME 2

33 observed during the Beckmann rearrangement of the oxime of 29 (Scheme 2).

The earlier view of Smith, as discussed before, that iminodiazonium ions rearrange following the same rules as the Beckmann rearrangement of the corresponding oximes, and that identical products should result from either rearrangement, does not explain the above mentioned behaviour of norcamphor 29 and 30. Clearly, lactam 31 does not arise by the rearrangement of iminodiazonium ion 34, and perhaps, is formed by the direct rearrangement of the hydroazidohydrin 35. However, the latter rearrangement (Scheme 2, path b) would involve a less favourable boat transition state (62).

It was mentioned earlier (page 20) that Bhalerao and Thagarajan (44), and DiMaio and Permutti (45) independently suggested the simultaneous action of two mechanisms. The latter group in 1966 observed regioisomeric insertion products of the quinoline type 36a, 36b, 36c, 36d, 36e, and isoquinoline type 37 in 60% total yield from the Schmidt reaction on cis-8-methylhydrindan-1-one 38 (Scheme 3). The isoquinoline type lactam 37, the only lactam isolated, arose from methylene migration while the quinoline type products (36a-e) arose from migration of the more substituted ring-junction carbon atom. The first mechanism suggested was based upon a theory of relative boat-chair conformational energies which was also suggested by Murray, et al., (62) for the Baeyer-Villiger oxidation of camphor and the steroidal D-ring. It was assumed that the attack of hydrazoic acid on the ketone would take place from the convex side (63) of cis-8-methylhydrindan-1-one possessing the configuration 38. This would result in formation of the hydroazidohydrin intermediate



SCHEME 3

39. The synchronous rearrangement of 39 with loss of nitrogen would lead directly to lactam 37 via a transition state with an energetically favoured chair conformation. The more substituted ring-junction carbon migration of 39 to form lactam 40 would occur through a less favourable boat transition state.

The second mechanism for the Schmidt reaction of 38 was based upon a stereoelectronic control theory which accounts for the formation of quinoline type products. This theory involves stereospecific trans migration of the more substituted ring-junction carbon, with loss of nitrogen, in the iminodiazonium ion 41 which would be formed by dehydration of 39. This process would lead to iminimum cation 42 which, by the attack of excess hydrazoic acid, would yield tetrazole 36a. The iminium cation 42 could also ring open, recyclize, undergo further attack by hydrazoic acid and, thus, yield products 36b, 36c, 36d and 36e, as shown in Scheme 3. It was also argued that the iminodiazonium ion formed by the dehydration of 39 would exist only in conformation 41 and not in the conformation 43 because the corresponding oxime has OH trans to methyl and rearranges in trans manner to the lactam 40. This analogy was based on the assumption that 41 and the corresponding oxime are isosteric because $-N_2^+$ is bulkier than OH. According to this argument lactam 37 does not arise from iminodiazonium ion 43, and therefore it must arise directly from 39 through the energetically favored chair transition state (Scheme 3, path a).

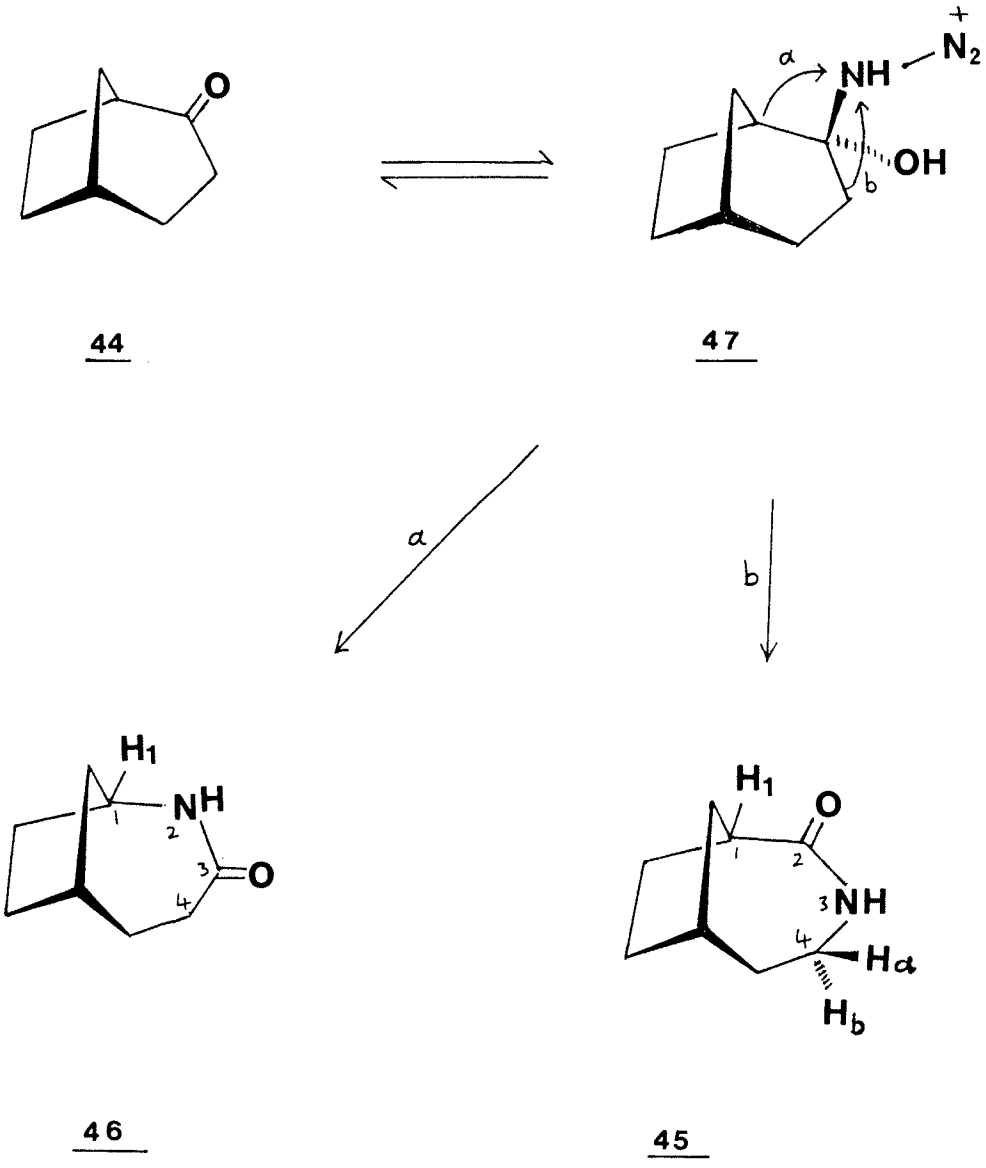
Krow (6) has argued that the boat-chair analysis is deceptive because it can not explain the formation of 3-azalactam 31 via methylene migration of hydroazidohydrin 35 (Scheme 2) which would be

generated from the exo attack of hydrazoic acid on norcamphor 29. In order to explain the formation of methylene migrated products, e.g. 3-azalactam 31, Sauers (64) suggested a localized torsional strain theory which will be discussed in the Results and Discussion, Part IIB).

Arya and Shenoy (57a) reported that hydrazoic acid/sulphuric acid treatment of bicyclo[3.2.1]octan-2-one 44 (eqn 26) also resulted only in methylene migrated 3-azalactam 45. Krow and Szczepanski (57a) recently repeated the experiment under the same conditions and found only 62:38 preference for 3-azalactam 45 over 2-azalactam 46, as determined by high resolution nmr. At 360 MHz the mixture of 46 and 45 shows clearly separated peaks at δ 3.63 (H_1) for 46 and at δ 2.92 (H_1), δ 3.33 (H_{4a}), and δ3.05 (H_{4b}) for 45.

Krow and Szczepanski (57a) suggested that lactams 45 and 46 arose by the direct rearrangement of the tetrahedral intermedate 47, and their ratio would be a function of the relative migratory aptitudes of the bridgehead and methylene carbons!

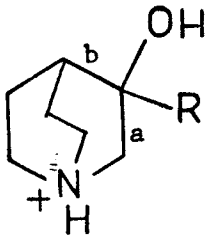
Paquette and Scott (56b) observed a consistent migratory aptitude manifested by 1-azabicyclic ketones under the Schmidt reaction conditions. (The Schmidt reaction was employed as a first step for the two step synthesis of α,β-unsaturated azalactams to be studied for transannular cyclization.) In intermediates such as 48a-c (Scheme 4), the strong electron-attracting characteristics of the protonated bridgehead-nitrogen atom are seen to reduce the migratory aptitude of the neighbouring carbon-carbon bond (labelled a) to the electron deficient hydroazide nitrogen. The operation of this inductive effect permits the alternative carbon-carbon bond (labelled b) to rearrange preferentially. The exclusive formation of



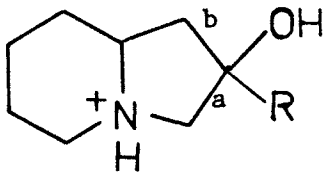
44 47

46 45

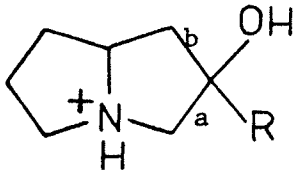
EQUATION 26



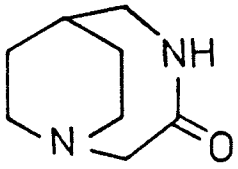
48a



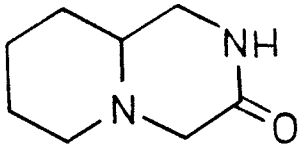
48b



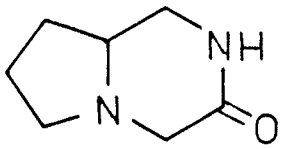
48c



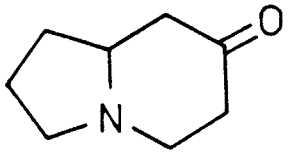
49a



49b



49c



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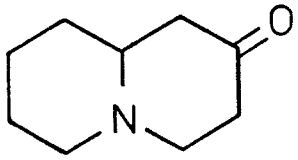

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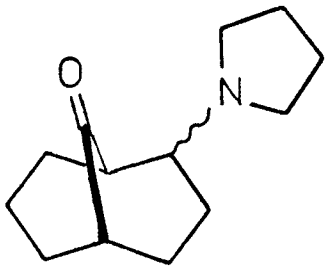


52

SCHEME 4

49a-c supports this idea. Introduction of an additional methylene group between the ring nitrogen and the carbonyl group can be expected to diminish substantially this inductive effect and in such examples the migratory aptitudes of the two bonds would be expected to exhibit less directional specificity. This prediction was supported by the behaviour of 50, 51 and 52. Compound 51 resulted in bond-a and bond-b migrated lactams while 50 and 52 (68f) resulted in only bond-a migrated lactams.

Sasaki and his colleagues (58a, 58d, 59 and 65) have extensively studied the Schmidt reaction on the rigid ring system of adamantane derivatives. They (58a) observed a remarkable catalyst-solvent effect on the product distribution during the Schmidt reaction on adamantan-2-one 53 (see Table 4).

Two reaction paths a and b (Scheme 5) were postulated for the Schmidt reaction on 53, but with predominant ring fission via path b. However, as shown in Scheme 5, hydroazidohydrin 54 was suggested to be the common intermediate for both paths. Based on several experimental facts, it was concluded that lactam 55 was produced mainly via a path involving intermediate 56. Path b involving 57 and 58, though possible, seemed not to be important for the lactam formation. The observed solvent effects on the product distribution could be explained by the solvent effect on the equilibrium between 54 and 57. On the basis of experimental evidence, it was suggested that tetrazole 59 did not arise from lactam 55 but that it might have arisen by the attack of excess hydrazoic acid on cation 58. By analogy with the Beckmann fission of oximes, it was suggested that the unsaturated nitrile 60 could be produced from 57 either via 58

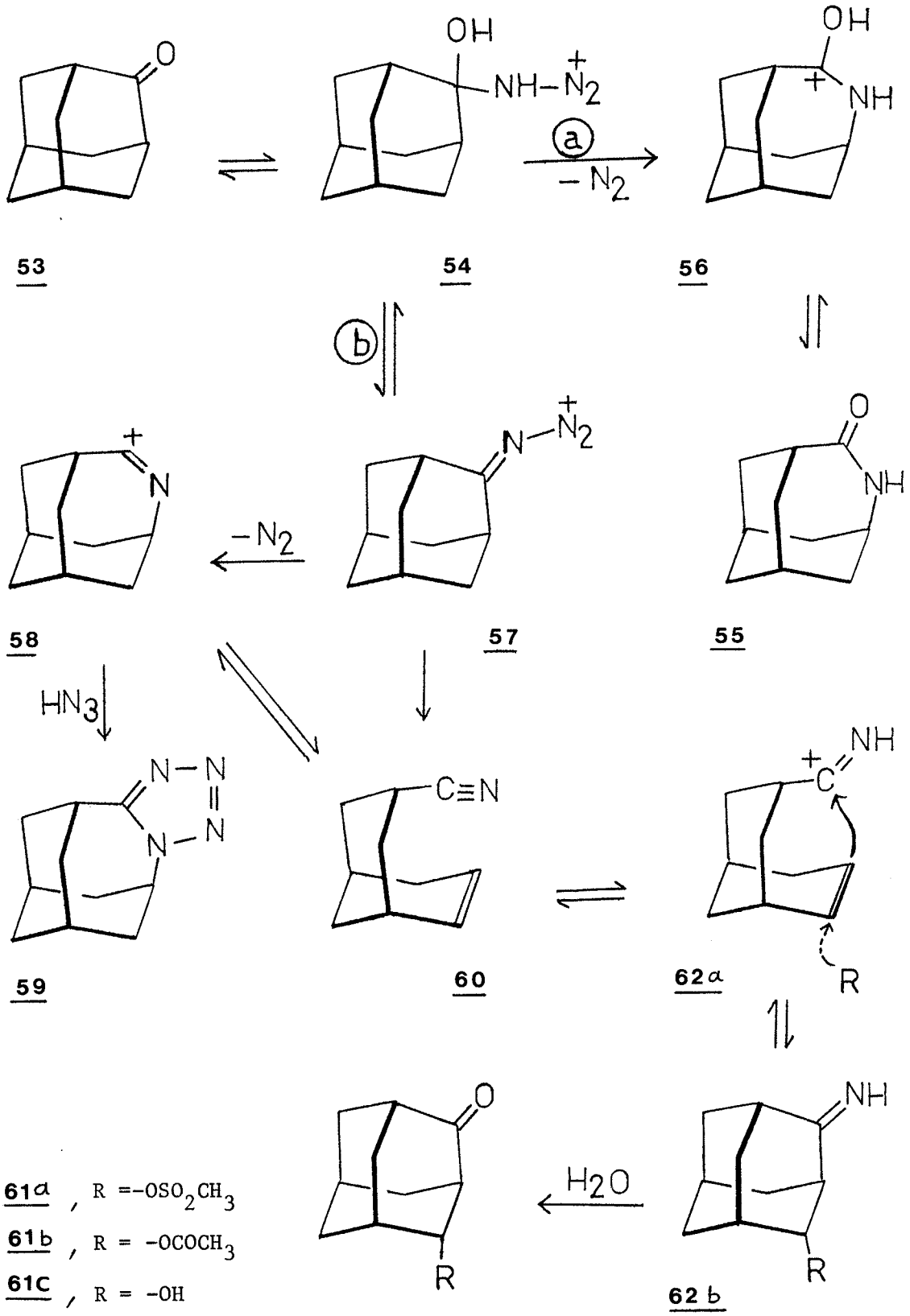
Table 4. SCHMIDT REACTION PRODUCTS OF ADAMANTAN-2-ONE 53 UNDER VARIOUS CATALYST-SOLVENT SYSTEMS[a].

Catalyst-solvent (v/v)	Reaction time (hr)	Products (yield, %)		
CH_3SO_3H	50	61a(88)	55(11)	
CH_3SO_3H-AcOH (3/4)	1	61a(3)	55(33)	60(61)
CH_3SO_3H-AcOH (1/1)	2.5	61a(5.5)	55(27)	60(57)
CH_3SO_3H-H_2O (8/3)	25.5	55(36)	60(54)	
CF_3COOH	3.2	55(59.5)	60(40.5)	
CCl_3COOH	1.3	55(53.5)	60(46.5)	
H_2SO_4-AcOH (1/1)	50	55(27.4)	61b(32.2)	61c(10)
AcOH(glacial)[b]	50			
CH_3SO_3H-AcOH[c] (1/4)	24	55(60)	60(36)	59(5)

a = Reactions were carried out using a small excess of NaN_3 at room temperature

b = Almost complete recovery of 53

c = 3.7 Molar ratio of NaN_3 to 53



53 54 56 58 57 55 59 60 62a 62b

SCHEME 5

or, more reasonably, directly by a concerted process. It was also demonstrated that 60 was a precursor of 4-substituted adamantan-2-one products 61a, 61b and 61c which were isolated during the Schmidt reaction on 53. The intermediates 62a and 62b were considered to be involved during the conversion of 60 to 61. The practical isolation of unsaturated nitrile 60 suggests that the Schmidt reaction on 53 involves the so-called fragmentation-recombination mechanism.

E. CONCOMITANT REACTIONS

So far only the major features of the mechanism of the Schmidt reaction have been discussed in detail. In this section side reactions, other than the formation of amides and lactams, shall be considered.

Side reactions leading to the formation of tetrazoles, aminotetrazoles, ureas, aminoethers and cleavage products such as nitriles are commonly observed during the Schmidt reaction. The occurrence of these side reactions depends upon the reaction condition and the properties of the substrates. Most of these side reactions derive from the iminodiazonium ion or the following stage, i.e., iminocation 7 and/or 7' (Scheme 1).

One of the important side reactions that is derived from the iminodiazonium ion stage is the fragmentation which produces a nitrile and another product arising from the ejected more stable cation. The formation of cleavage products is more common in cyclic systems having Baeyer ring-strain. Two such cases were already

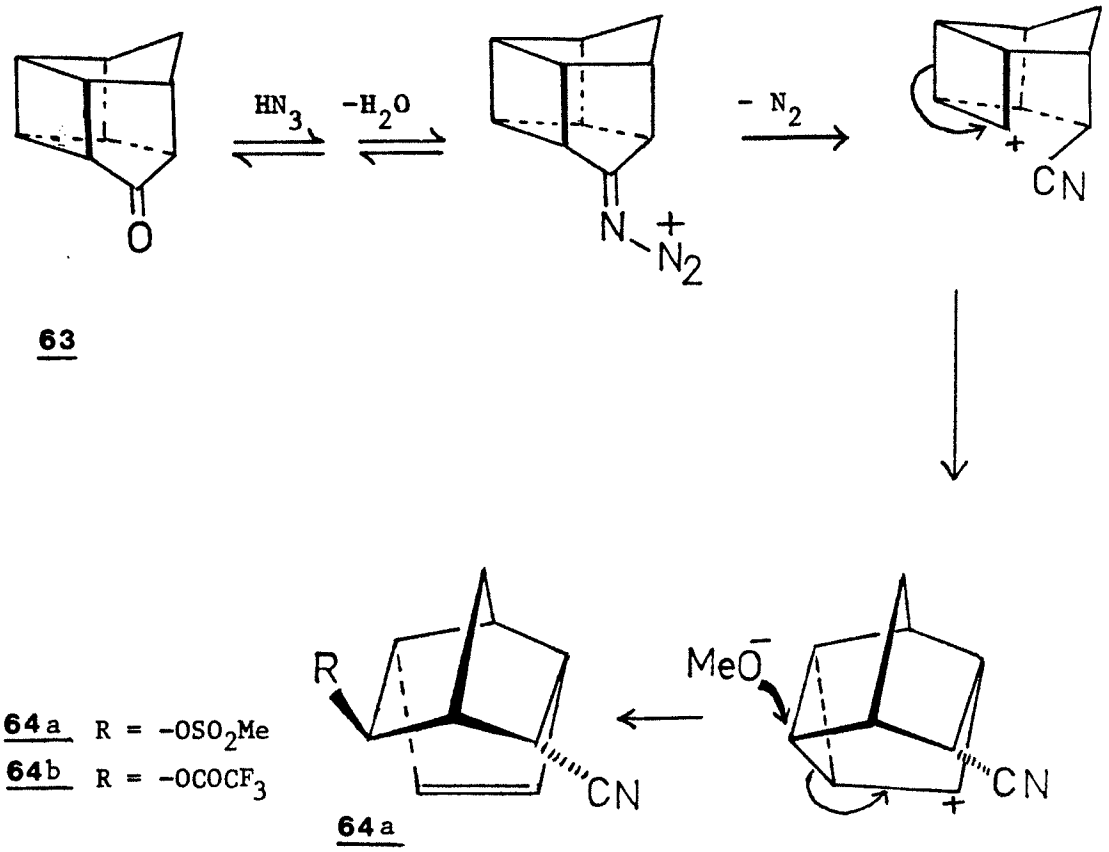
mentioned during the discussion of the Schmidt reaction on cis-8-methylhydrindan-1-one 38 (45) and adamantan-2-one 53 (58a).

Metha et al. (66) observed a novel regiospecific fragmentation process during the Schmidt reaction on 1,3-bishomocubanone 63 (eqn 27). The fragmentation was followed by carbonium ion rearrangements leading to brendane derivatives 64a and 64b. Reaction of 1,3-bishomocubanone 63 with sodium azide in (a) methanesulphonic acid (0-5°C, 1h) produced mesylate 64a in 45% yield, and (b) trifluoroacetic acid (0-5°C, 1h) produced acetate 64b as the major product. A reasonable mechanism proposed (66) for the genesis of exo-2-methanesulphonoxy-endo-9-cyanobrend-4-ene 64a from 63 is shown in equation 27.

Blaney et al. (58c) found that, upon treatment with sodium azide in cold methanesulphonic acid, diamantanone 65 underwent a Schmidt fragmentation-hydrolysis reaction to yield unsaturated acid 66 in 41% yield (eqn 28). The normal Schmidt rearrangement product which was considered to be a mixture of 67a and 67b, was also isolated in 50% yield.

Fragmentation products have also been isolated in considerable yields during the Schmidt reaction on t-butyl alkyl ketones (67) and 1-azabicyclo[2.2.2]octane-3-one (56c).

Aldehydes all undergo fragmentation to nitriles (3), although small to moderate amounts of formamides may be formed as well (eqn 29).



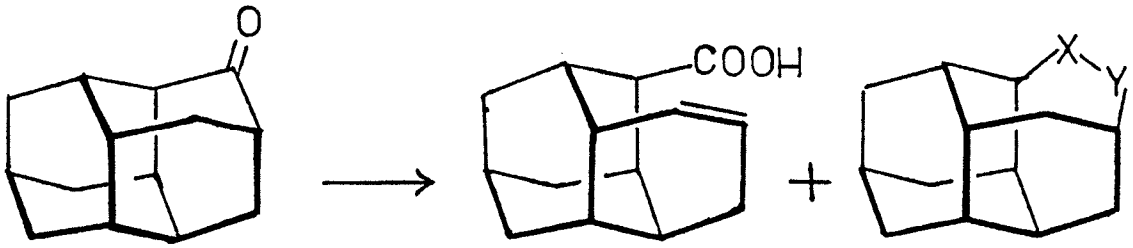
63

64a R = $-OSO_2Me$

64b R = $-OCOCF_3$

64a

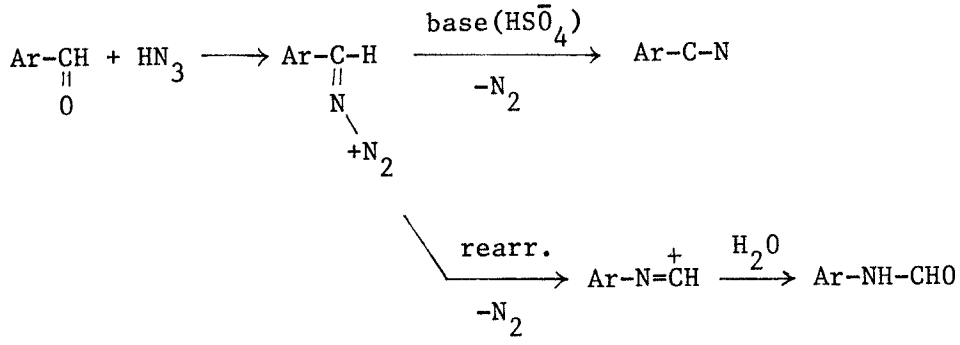
EQUATION 27



65 **66** **67a** X = C=O , Y = NH

67b Y = C=O , X = NH

EQUATION 28



eqn 29

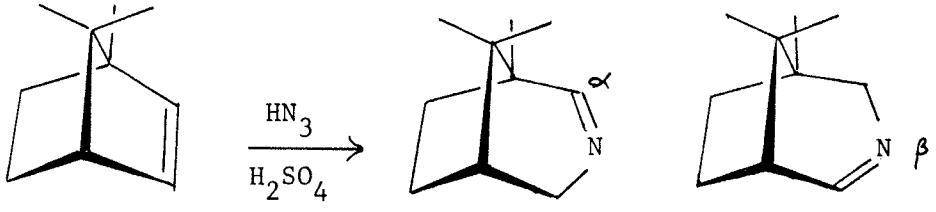
It was found (68) that reaction of p-substituted benzaldehydes (and benzoic acids) at low acidity affords mainly nitriles together with a small yield of formanilide, but that at high acidity these products were obtained in the opposite ratio.

It has been found (69) that α,β-unsaturated ketones, e.g. methyl vinyl ketones, yield 1,2-diketones. In such a case, attack of hydrazoic acid takes place at the β-olefinic carbon atom. On the other hand cinnamic acid (an α,β-unsaturated acid) yields mainly phenyl acetaldehyde and aniline as a by-product (2). Wolff has reviewed in detail the Schmidt reaction with organic acids (2).

The Schmidt reaction with olefinic compounds results in the formation of Schiff's bases. Sometimes the reaction does not stop at this stage and the Schiff's base hydrolyses to yield a ketone and an amine. For example, from amylene (2-methyl-2-propene) the products isolated after hydrolysis are acetone, methyl ethyl ketone, methyl amine, and ethyl amine. As shown in Scheme 3, the olefinic compound

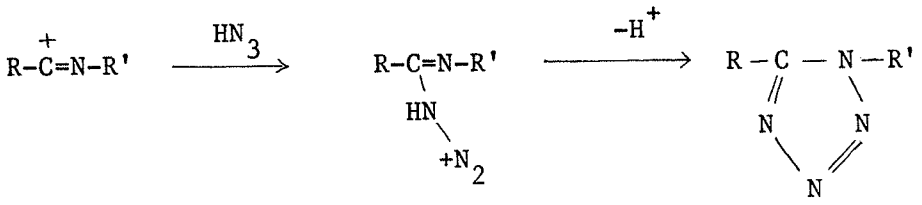
36c, isolated in only 3% yield during the Schmidt reaction on cis-8-methylhydrindan-1-one, underwent further Schmidt reaction to yield ketone 36d. The Schiff's base 36f could not be isolated (45). Conjugation with C=O, NO_2 or an azomethine linkage allows addition to occur more readily at the olefinic bond. Reaction of hydrazoic acid with cyclic olefinic compounds is a convenient method for ring enlargement. For example, cyclobutene yields cycloheximine, and camphene 68 yields a mixture of 50% of α- and 25% of β-N-dehydrocamphidine (2) (eqn 30).

One of the most important side reactions is the formation of tetrazoles which exhibit a high biological activity and are used as stimulators of cardiac activity (70). It is known that tetrazoles can not be obtained by further action of hydrazoic acid on the corresponding lactams or amides (3,45). Therefore, these tetrazoles must arise from an intermediate stage. It is now generally believed that tetrazoles are formed by the addition of one molecule of



68 eqn 30

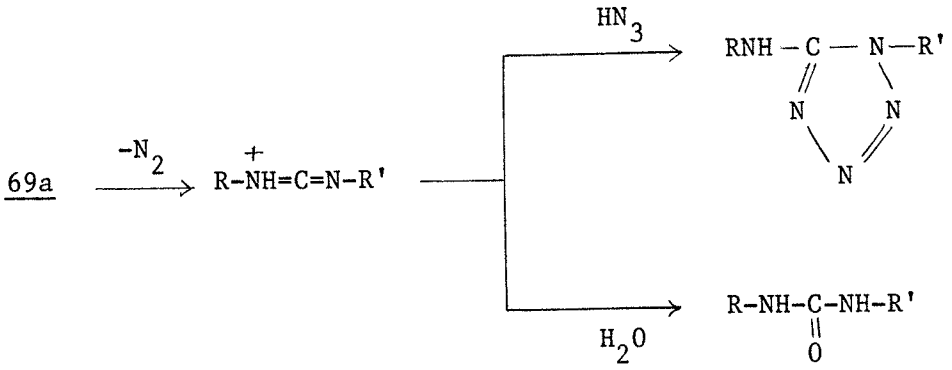
hydrazoic acid to an iminocarbonium ion 7' (Scheme 1)(3-7). The protonated imidoazide 69a (eqn 31), thus formed, should cyclize to tetrazole 69b according to the general principle that tetrazoles are formed when imidyl azides are prepared in other ways (71).



eqn 31

7' 69a 69b

The potential imidoazide 69a may lose nitrogen with formation of a carbodiimide which may convert into an aminotetrazole or urea as a result of secondary reaction with hydrazoic acid or with water (eqn 32).



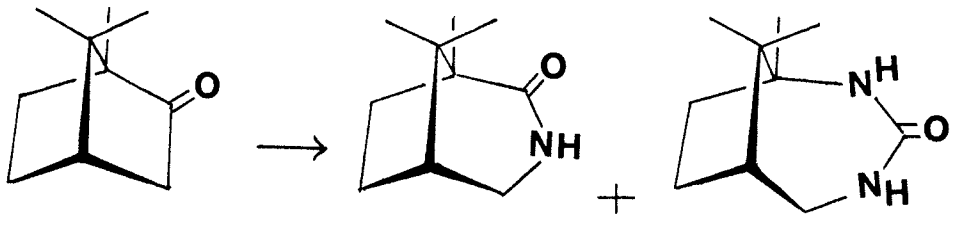
eqn 32

However, the formation of aminotetrazoles and urea during the Schmidt reaction takes place extremely rarely. In many cases (e.g. 45, 58a, 59, 72) the formation of tetrazoles as a by-product or as the sole

product during the Schmidt reaction has been observed.

Karl F. Schmidt in one of his patents (73) has reported that treatment of camphor 70 with excess hydrazoic acid in the presence of (a) antimonypentachloride-benzene, (b) tintetrachloride-sulphuric acid-benzene, and (c) 100% sulphuric acid-benzene, produced camphor tetrazole in 75%, 39% and 20% yields respectively. The product was identified by its elemental composition ($C_{10}H_{16}N_4$) and its melting point 242-43°C. The concurrent formation of other products was not reported!

Recently ApSimon and Hunter (55a), during the course of some investigations of N-nitrosamine photolysis, attempted to prepare α-camphidone 71 via the Schmidt reaction on camphor 70 (eq. 33). The reaction of camphor in chloroform with sodium azide (2.2 equivalents) in the presence of conc. sulphuric acid produced 71 in less than 1% yield. The major product of this reaction (30% yield) had melting point 178-180°C. Based on elemental analysis, mass, infrared and nuclear magnetic resonance spectroscopy the structure 72, a urea, was assigned to this major product.



eqn 33

70 **71** **72**

However, the structure 72 assigned to the new major product is suspect on the following basis:

(a) The formation of urea during the Schmidt reaction is very rare and has never been observed as more than a minor reaction (3,5). It has been encountered principally with ortho-substituted benzophenones (74)

(b) The melting point 178-180°C reported for this compound is low for ureas (75a)

(c) The infrared absorption at 1650 cm^{-1} is not characteristic of ureas (75a) but corresponds to amidic absorptions (75b).

The carbon-13 nuclear magnetic resonance spectrum, which will be discussed later (Results and Discussion Part ID), shows a downfield absorption at 173.8 ppm which is characteristic of amidic carbon but not of a urea carbon.

These facts led to the reinvestigation of the Schmidt reaction on camphor in detail and to the determination of the structures of the major, and minor products as well as the mechanisms leading to these products. The results of this investigation are described in the following sections.

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

The objective of this work was to study the Schmidt reaction on camphor. This study includes the characterization of all products from this reaction and a detailed study of the mechanism which is proposed for this reaction.

The results and discussion of this study will proceed in two parts as follows:

Part I. Structure elucidation: This includes the Schmidt reaction on camphor and the characterization of the products isolated, plus the characterization of the products obtained from some other reactions carried out towards the structure elucidation of the major product from the Schmidt reaction on camphor.

Part II. Mechanism: This involves a discussion of the mechanism established for the Schmidt reaction on camphor.

PART I. STRUCTURAL ELUCIDATION STUDIES

In this part of the results and discussion, first the Schmidt reaction on camphor will be discussed in detail. Secondly, the work carried out towards the structure elucidation of the major product from this reaction will be discussed in a chronological order. Also the work carried out towards the structure elucidation of minor products from the Schmidt reaction on camphor will be discussed.

The discussion will proceed as follows:

(A) The Schmidt reaction on camphor

(B) Reactions of the major product towards its characterization

(C) 3% Methanolic-HCl methanolysis of aminolactam

(D) Conclusion of the structure of aminolactam

(E) Products of addition reactions of aminolactam

(F) Other minor products from the Schmidt reaction on camphor

(G) 3% Methanolic-HCl methanolysis of N_8-methyl aminolactam and characterization of the products

A. THE SCHMIDT REACTION ON CAMPHOR

The Schmidt reaction on camphor was carried out on 0.05 mol to 0.4 mol of camphor. The most convenient scale in terms of handling was found to be 0.2 mol of camphor. The reaction was carried out in two ways: (a) Solid sodium azide was added slowly to the rapidly stirred mixture of camphor, chloroform and conc. sulphuric acid; or (b) Conc. sulphuric acid was added slowly to the rapidly stirred mixture of camphor, chloroform and sodium azide. In both cases the system consisted of two phases and vigorous stirring was required for an additional 3-4 h period at room temperature to complete the reaction. (Further stirring of the mixture for 16 h or 40 h at room temperature did not improve the yield). Identical work-up (see experimental) gave almost the same yields of a major product irrespective of the order of addition. The yield of this major product, a colorless crystalline substance (mp 180-181°C in a sealed tube), obtained from various trials ranged from 30-42%. (The optimum conditions discovered for the reaction are given in the experimental section). The reaction is exothermic and, therefore, the rate of addition of solid sodium azide or that of conc. sulphuric acid to the rest of the mixture was an important factor in determining the yield

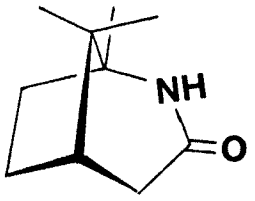
of the major product. Rapid addition of either reagent caused the release of volatile hydrazoic acid from the hot reaction mixture and, therefore, lowered the yield. Also the yields from the exothermic reaction were low when the temperature was controlled at room temperature or less, and in such cases a large amount of unreacted camphor was recovered. The reaction was carried out with 2.1 equivalents of sodium azide for one mole equivalent of camphor. The reaction starting with one mole equivalent each of sodium azide and camphor is reported elsewhere (55a). Sulphuric acid was used in large excess which also served as the reaction medium.

The major product was isolated after dilution and basification (to pH 10 with 20% aqueous sodium hydroxide solution) of the acid layer of the reaction mixture, followed by extraction with chloroform. Further adjustment of this basic aqueous layer to pH 13-14, followed by chloroform extraction did not yield any more of the major product. The major product could not be extracted with chloroform from neutral or acidic aqueous solution. Other minor products which were isolated in low yields will be discussed later.

The mass spectrum of the major product showed the molecular ion peak at m/z 182 which indicates an even number of nitrogen atoms in the molecule. The infrared spectrum showed N-H stretch of secondary amines at 3310 cm^{-1} and 3285 cm^{-1} and N-H stretch of amides at 3180 cm^{-1}, C=0 stretch of amide band I at 1662 cm^{-1} and amide band II at 1655-1640 cm^{-1} (76a-b). Proton nuclear magnetic resonance (90 MHz) spectrum showed two different deuterium exchangeable protons; one at δ 5.9 and the other at δ 1.6. The downfield absorption could be assigned to a secondary amidic proton and the upfield absorption

could be assigned to a secondary amine proton. Carbon-13 nuclear magnetic resonance (22.63 MHz) spectrum (broad band ^{1}H-decoupled) showed 10 carbon atoms. FT-polarization transfer (^{1}H-decoupled INEPT) technique (77) was used to assign the carbon-13 chemical shifts (in ppm) to CH, CH_2, CH_3 and quaternary carbon-atoms as follows: 71.8 (Cq), 37.9 (CH), 37.4 (CH_2), 35.9 (CH_2), 35.8 (Cq), 28.5 (CH_2), 24.0 (CH_3), 23.1 (CH_3), and 22.9 (CH_3); the chemical shift at 173.8 ppm was assigned to an amidic carbon-atom.

These analyses do not correspond to the structure of urea 72. They do not correspond to the normal Schmidt reaction products 71 or bridgehead-carbon migrated lactam 73 which would be expected to arise either via the direct rearrangement of the corresponding hydroazidohydrin or via the rearrangement of the corresponding iminodiazonium ions. The cleavage process of the bicyclic ring-system at the corresponding hydroazidohydrin or the iminodiazonium ion stage was, therefore, also considered. This cleavage process will be discussed in Part II of this section.



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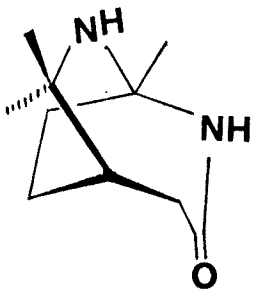
B. REACTIONS OF THE MAJOR PRODUCT TOWARDS ITS CHARACTERISATION

Based on the spectral data and a consideration of a possible mechanism (fragmentation-addition of HN_3-recyclization) the three structures 74, 75 and 76 were tentatively chosen as possible candidates for the major product of the Schmidt reaction on camphor (hereafter called the aminolactam). The rationalization of these choices, in mechanistic terms, as well as the consideration of other possible structures will be made in Part II.



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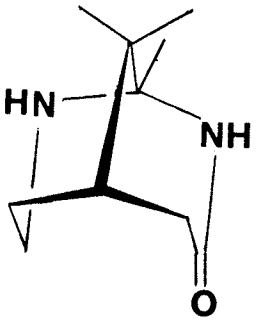

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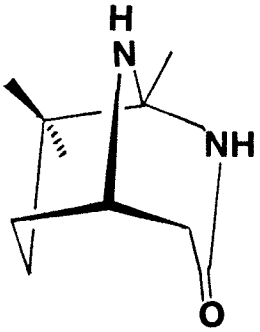

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At this stage, based on mass, infrared and nuclear magnetic resonance (90 MHz) spectra no clear distinction could be made between these three possible candidates 74, 75 and 76. However, it should be noted that each of them has a secondary amidic and a secondary amine function. In order to confirm that the major product contained an amidic nitrogen and an amine nitrogen (as in 74, 75 and 76), the following reactions were carried out.

(a) Stirring a benzene solution of the aminolactam and phenyl isocyanate at room temperature overnight gave a colorless, crystalline solid in 59% yield hereafter called N-(phenylcarbamoyl)-aminolactam 77. Its mass spectrum showed the molecular ion peak at m/z 301 indicating the addition of one molecule of phenyl isocyanate to the aminolactam. Its infrared and nuclear magnetic resonance spectra will be discussed later.

(b) Heating a methanol solution of the aminolactam and methyl iodide in a pressure bottle at 55-62°C for 3 days produced a colorless solid. Neutralization of this solid, after dissolving in water, followed by work-up, produced a colorless solid in 58% yield hereafter called N-methylaminolactam 78. The mass spectrum of 78 indicated the parent ion peak at m/z 196. This indicates that the methyl group has added to only one nitrogen atom. Its infrared and nuclear magnetic resonance spectra will be discussed later.

Alternately, a 2-propanol solution of the aminolactam and methyl iodide at room temperature overnight gave, after neutralization, a shiny, colorless solid in 37% yield. This product was shown to be identical to the above N-methylaminolactam 78 by tlc, and infrared, mass and nuclear magnetic resonance spectroscopy.

Reaction of the aminolactam in dichloromethane with Magic Methyl® (97% methyl fluorosulphonate) at room temperature for 1.5 h produced a white solid. Neutralization of this solid, by dissolving in 1N sodium hydroxide aqueous solution, followed by workup, produced a quantitative yield of a colorless solid. This solid was identified as the N-methylaminolactam 78.

(c) Reaction of the aminolactam in benzene with acetyl chloride in the presence of pyridine at room temeprature overnight, produced, after neutralization with aqueous HCl, the N-acetylated aminolactam 79 in low yield. Its mass spectrum indicated the parent ion peak at m/z 224.

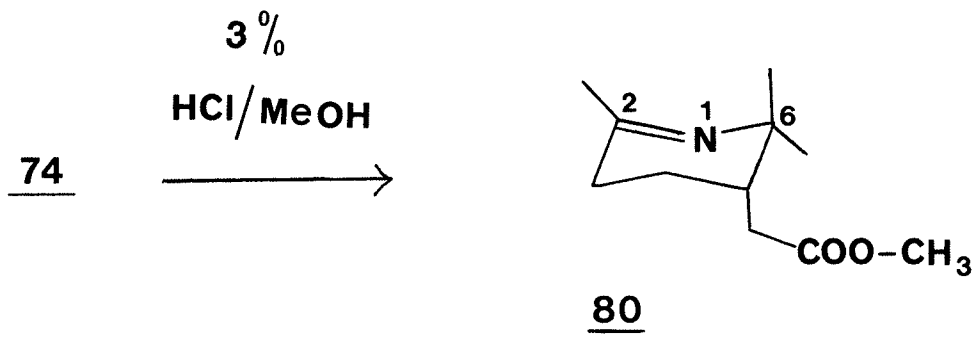
(d) The N-methylaminolactam 78 did not undergo further addition reactions with 2.5 equivalents of methyl iodide (a) in methanol in a pressure bottle at 60°C after 16 h, or (b) in 2-propanol at 80°C after 16 h.

The addition of the phenylcarbamoyl, methyl, and acetyl groups to only one nitrogen atom confirms that in the aminolactam there is one amine functionality and one amido group. [These results still do not differenciate between the structures 74, 75 and 76.]

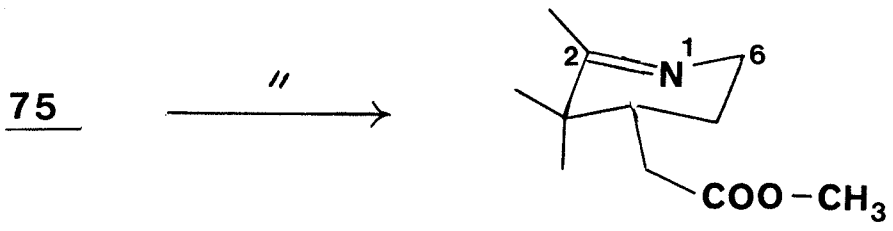
C. 3% METHANOLIC-HCl METHANOLYSIS OF AMINO LACTAM

It was envisaged that methanolysis (78) products of the aminolactams 74, 75 and 76 would be different from each other. Therefore, the identification of the product(s) obtained from such methanolysis of these aminolactam would help in identifying the parent compound.

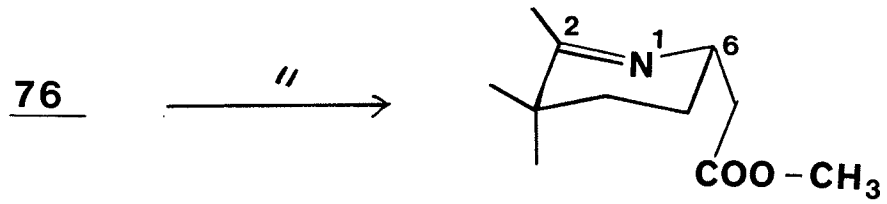
The aminolactam was mixed with 3% methanolic HCl [prepared by addition of acetyl chloride to methanol (78)] and heated under reflux for 3 days. The product obtained after work-up was a clear liquid, bp 85-90°C (0.4 mm Hg), 74% yield; tlc: one spot, R_f = 0.55 in chloroform-ethanol (10:1, v:v). High resolution mass spectrum indicated the parent ion peak (64.8%) at m/z 197.1419 as the exact mass for $C_{11}H_{19}NO_2$. Exact mass calculated for $C_{11}H_{19}NO_2$ is 197.1416. The infrared spectrum showed absorption for an imine functionality (C=N) at 1665 cm^{-1}(s), and for the ester group (-COO-R) at 1745 cm^{-1}(s). The presence of a methyl ester group ($-COO-CH_3$) was confirmed by the presence of the fragment ion (20.6%) in mass spectrum, at m/z 166.1232 for the elements $C_{10}H_{16}NO$ (see Table 7). This fragment ion arose from the molecular ion by the loss of $-OCH_3$ radical. Proton nuclear magnetic resonance (90 MHz) spectrum showed a singlet at δ 3.65 (3Hs) [$-COO-CH_3$], a double doublet at δ 1.91 (3Hs) [$-N=CR-CH_3$], and two singlets at δ 1.15 (3Hs) and δ 0.97 (3Hs). Based on this spectral information the possible structures envisaged were the iminoesters 80, 81 and 82 which would be produced under the reaction conditions from the aminolactams 74, 75 and 76 respectively (eqn 34).



80



81



82

EQUATION 34

The high resolution proton nuclear magnetic resonance (400 MHz) spectrum (Figure 1) of this 3% methanolic-HCl methanolysis product established the structure of the iminoester as 81. The chemical shifts, assigments and couplings are given in Table 5. The two protons H_{6a} and H_{6e} at the position alpha to N in 81 absorb respectively at δ 3.372 and δ 3.582, and each is coupled to H_{5a} and H_{5e} (see Table 5 for J values).

The iminoester 80 does not have proton(s) alpha to the N-atom, and iminoester 82 has only one axial proton at a position alpha to the N-atom. Another distinctive feature of the proton spectrum of 81 that would not be observed in the proton spectrum of 80 and 82, is long range coupling to the C-10 methyl. The C-10 methyl of 81 absorbs at δ 1.922 and is coupled to two protons at C_6 showing a double doublet [$^5J(Me, H_{6e})$ = 1.6 Hz and $^5J(Me,H_{6a})$ = 2 Hz]. The iminoesters 80 and 82 respectively would have no or one H-atom alpha to N. The values for chemical shifts and couplings in Table 5 are from the simulated spectrum using an AMDAL 470 computer (LAME-LAOCOON program). The experimental and simulated proton spectra are shown in Figure 2.

The carbon-13 nuclear magnetic resonance (regular broad-band ^1H-decoupled, and ^1H-decoupled INEPT) data and assignments are shown in Table 6 below.

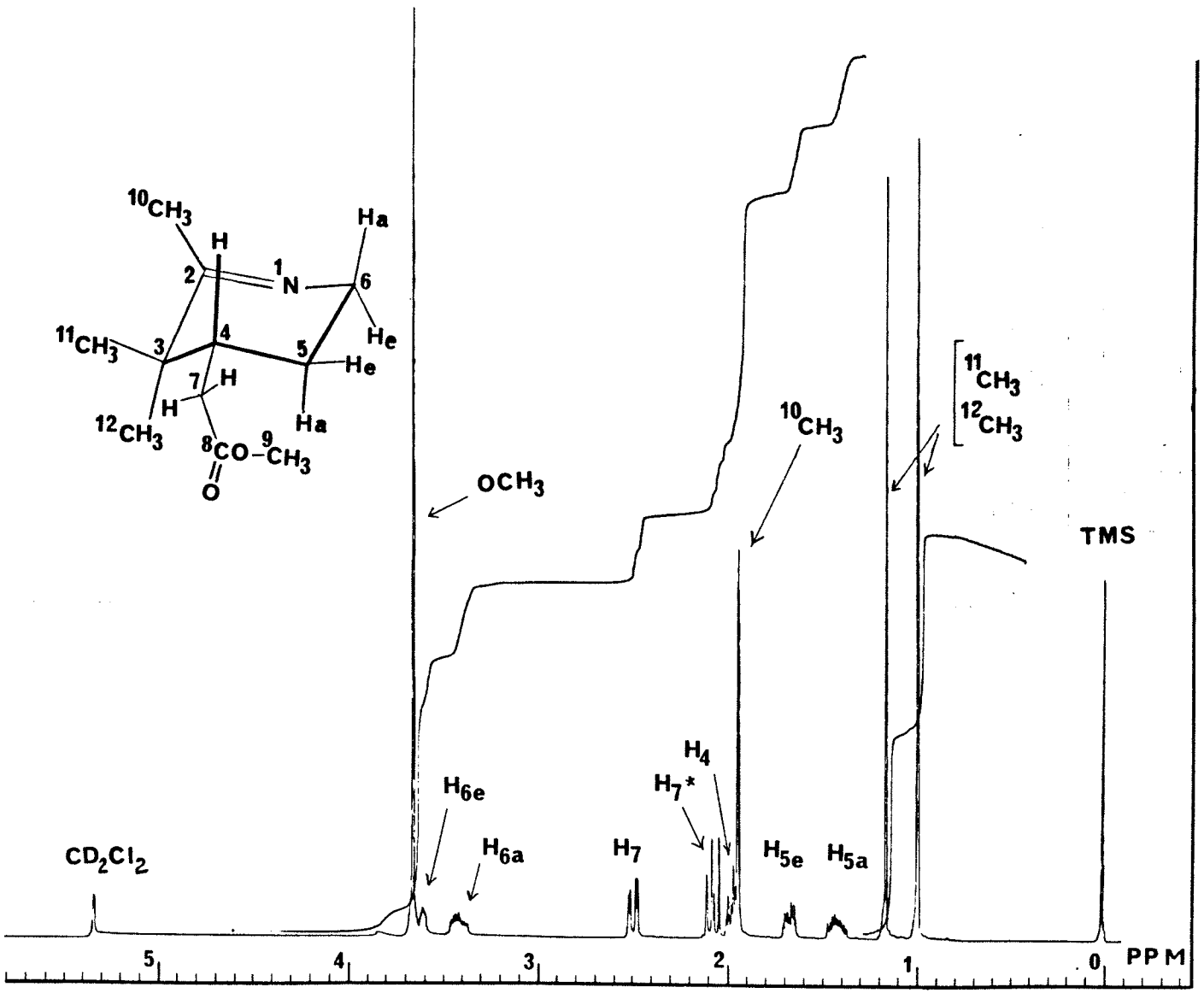


FIGURE 1. ^{1}H-nuclear magnetic resonance (400 MHz) spectrum of iminoester 81

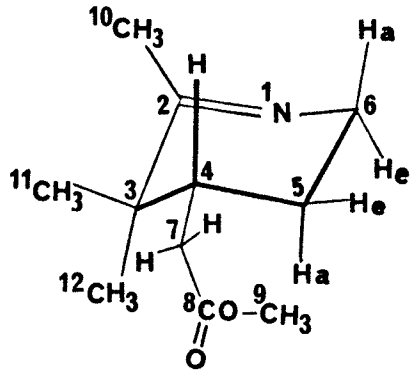


TABLE 5. DATA FROM THE ^{1}H-NMR (400 MHz) OF IMINOESTER 81 (CHEMICAL SHIFT IS DELTA RELATIVE TO TMS, SOLVENT CD_2Cl_2), (COUPLING ARE IN Hz)

CHEMICAL SHIFTS	ASSIGNMENTS	COUPLINGS
0.979	C-11 Me	---
1.147	C-12 Me	---
1.404	H_{5a}	$^{3}J(5a,4)=11.00$, $^{2}J(5a,5e)=-13.70$, $^{3}J(5a,6e)=5.50$, $^{3}J(5a,6a)=10.00$
1.642	H_{5e}	$^{3}J(5e,4)=3.80$, $^{2}J(5e,5a)=-13.70$, $^{3}J(5e,6e)=3.20$, $^{3}J(5e,6a)=5.50$
1.922	C-10 Me	$^{5}J(Me,6e)=1.60$, $^{5}J(Me,6a)=2.00$
1.942	H_4	$^{3}J(4,5a)=11.00$, $^{3}J(4,5e)=3.80$, $^{3}J(4,7)=3.80$, $^{3}J(4,7^{*})=11.00$
2.043	$H_{7}*$	$^{2}J(7^{*},7)=-15.00$, $^{3}J(7^{*},4)=11.00$
2.462	H_7	$^{2}J(7,7^{*})=-15.00$, $^{3}J(7,4)=3.80$
3.372	H_{6a}	$^{2}J(6a,6e)=-18.00$, $^{3}J(6a,5e)=5.50$, $^{3}J(6a,5a)=10.00$, $^{5}J(6a,Me)=2.00$
3.582	H_{6e}	$^{2}J(6e,6a)=-18.00$, $^{3}J(6e,5e)=3.20$, $^{3}J(6e,5a)=5.50$, $^{5}J(6e,Me)=1.60$
3.619	-OMe	---

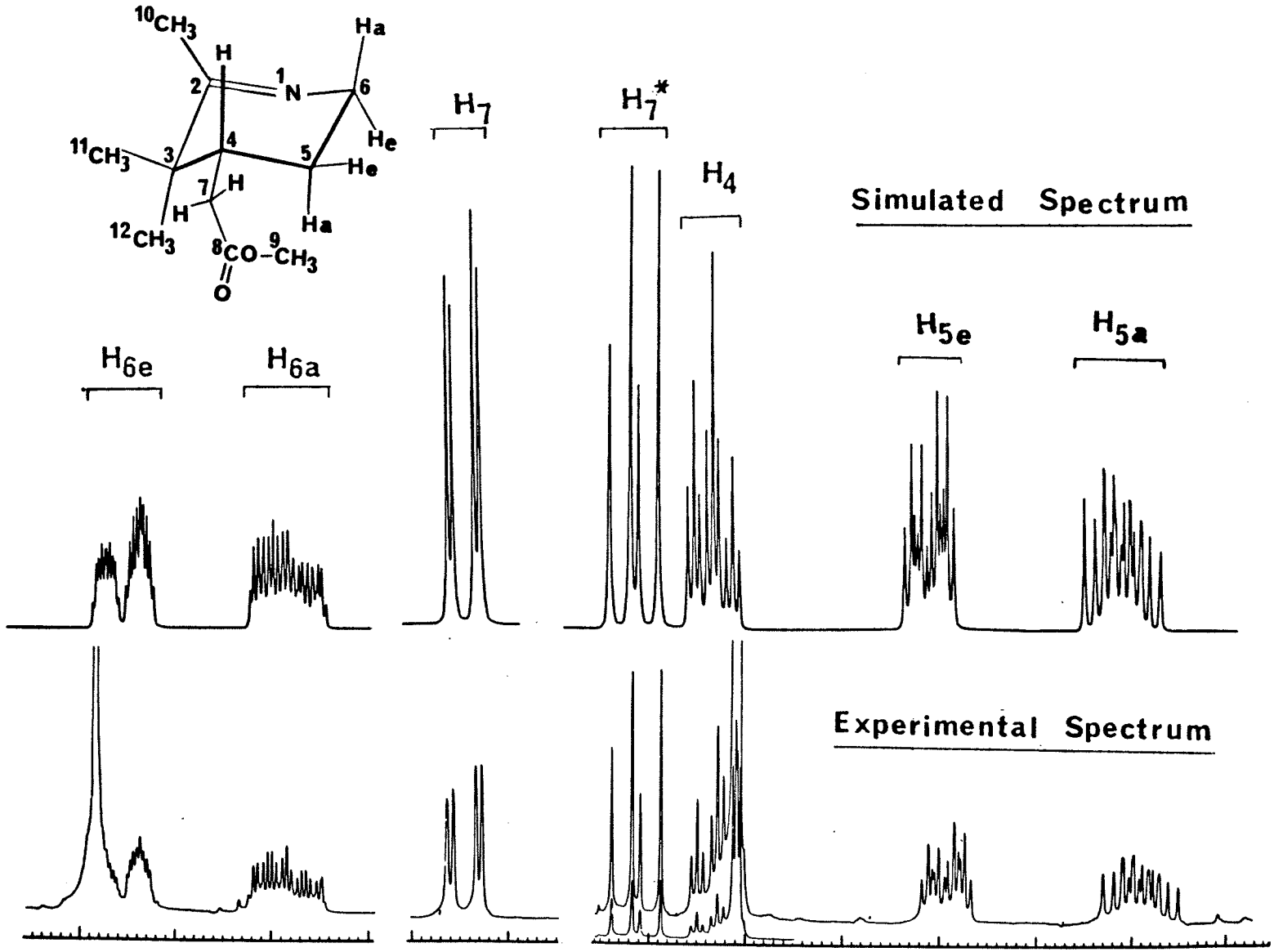


FIGURE 2. ^{1}H-nmr (400 MHz) spectra of iminoestar 81 ; top: simulated, bottom: experimental.

TABLE 6. THE CARBON-13 NMR DATA OF THE IMINOESTER 81.

Chemical shifts ppm	173.6	172.8	51.6	48.6	38.7[a]	35.4	25.3	24.4	22.6	21.0
^{1}H-decoupled INEPT	-	-	CH_3	CH_2	C_q and CH	CH_2	CH_3	CH_2	CH_3	CH_3
^{13}C-assign-	2 and 8		9	6	3 and 4	7	10	5	11 and 12	

a = Carbon-3 and 4 absorb at the same position in the broad-band ^{1}H-decoupled carbon-13 nuclear magnetic resonance spectrum. This was confirmed by the ^{1}H-decoupled INEPT technique which demonstrated the presence of a quaternary and a methine carbon absorbing at 38.66 ppm. The carbon-13 nuclear magnetic resonance spectra of the iminoester 81 are given in Figure 3.

The tentative mass spectral fragmentation mechanisms are presented in Scheme 6. The most abundant peaks with the % intensity and their elemental composition from the high resolution mass spectrum of the iminoester 81 are given in Table 7 below.

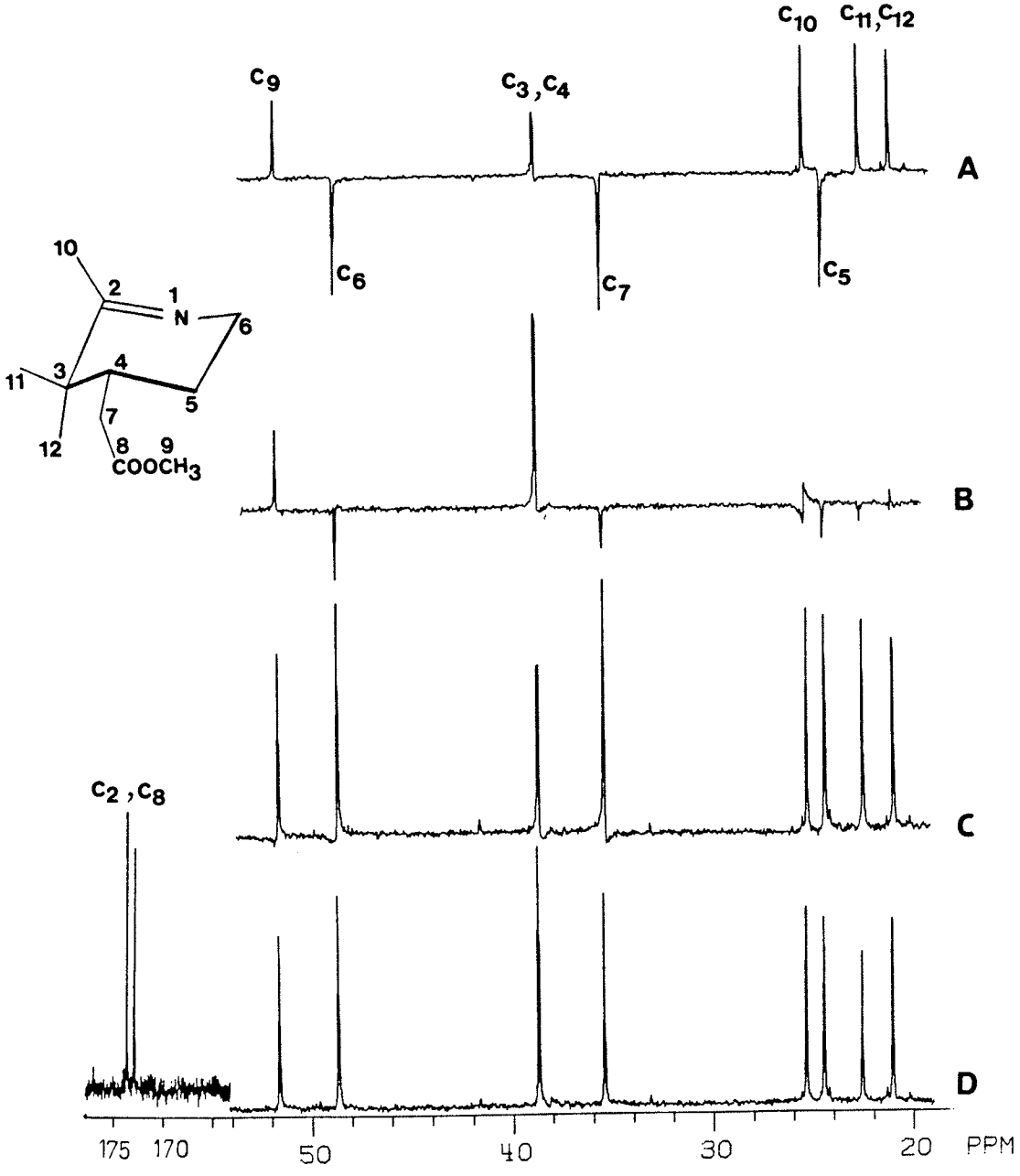
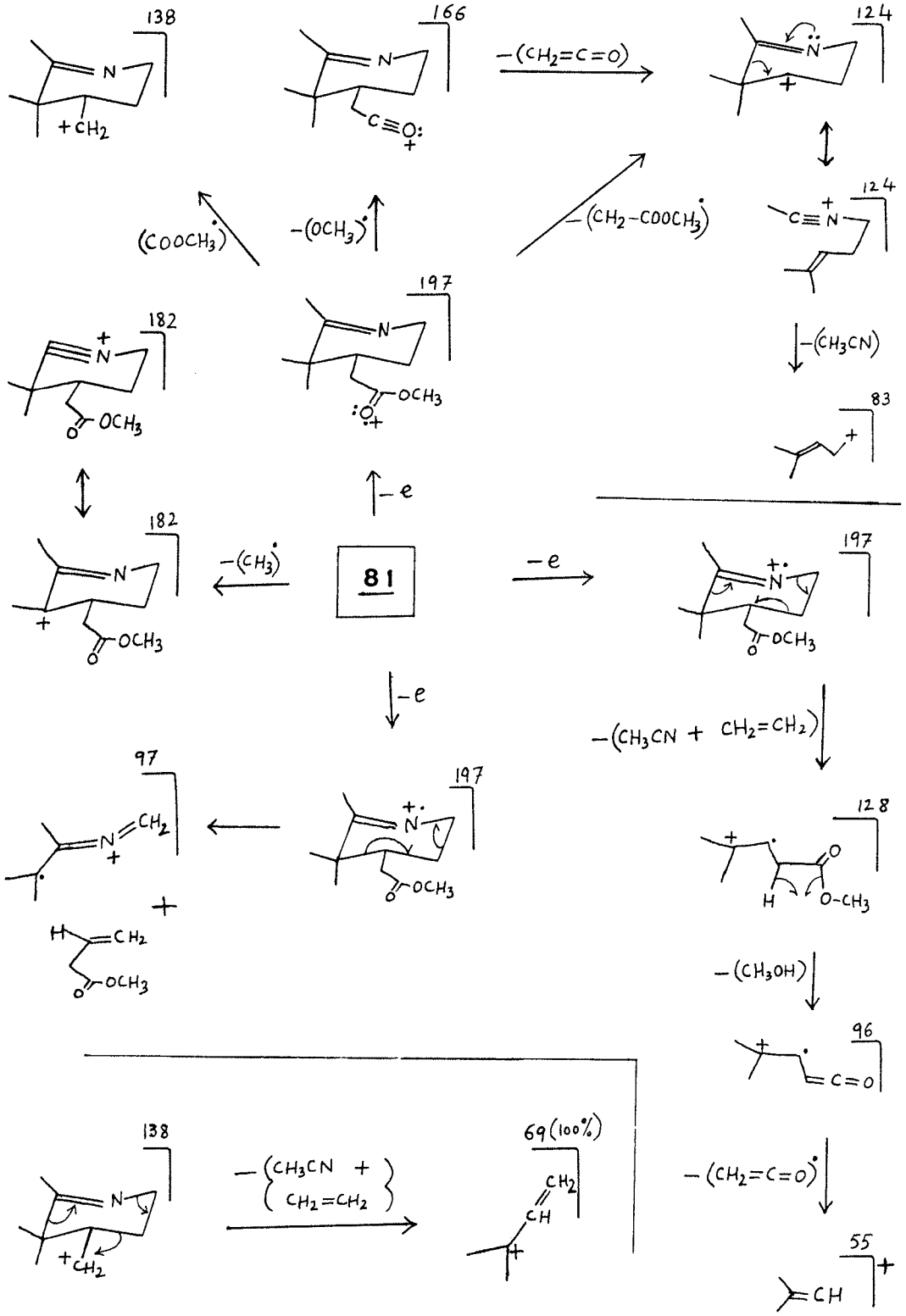


FIGURE 3. Carbon-13 nmr spectra of iminoester 81; A-C are INEPT spectra, A: CH_3 and CH are up ↑ and CH_2 are down ↓, B: CH are up ↑, C: all carbons except C_q are up↑, D: regular broand band ^1H-decoupled spectrum.

TABLE 7. THE HIGH RESOLUTION MASS SPECTRAL DATA OF THE IMINOESTER 81.

MEAS MASS[a]	% INT[a]	ELEMENTS[a]				FRAGMENTS
		C	H	N	O	
197.1419	64.82	11	19	1	2	$[M^+]$
182.1181	18.57	10	16	1	2	$(M^+)-(CH_3)$
166.1232	20.56	10	16	1	1	$(M^+)-(31)[(M^+)-(OCH_3)]$
138.1284	8.49	9	16	1	-	$(M^+)-(50)[(M^+)-(COO-CH_3)]$
128.0837	60.76	7	12	-	2	$(M^+)-(69)[(M^+)-(CH_3CN+CH_2=CH_2)]$
124.1127	60.63	8	14	1	-	$(M^+)-(73)[(M^+)-(-CH_2-COO-CH_3)]$
97.0903	28.76	6	11	1	-	$(M^+)-(100)[(CH_3)_2C-C(CH_3)=N-CH_2]^+$
96.0576	67.71	6	8	-	1	$(128)-(OCH_3),[(CH_3)_2C=CH-CH=C=O]^+$
83.0869	67.26	6	11	-	-	$(124)-(CH_3CN)[(CH_3)_2C=CH-CH_2-CH_2]^+$
69.0676	100.00	5	9	-	-	$(124)-(CH_3-CNCH_2)[(CH_3)_2C=CH-CH_2]^+$
68.0624	56.29	5	8	-	-	$(83)-(CH_3)[CH_3C=CH-CH_2]^+$
55.0573	62.38	4	7	-	-	$(96)-(CH=C=O)[(CH_3)_2C=CH]^+$

a = These values were obtained from the computer print out.



SCHEME 6. The tentative mass-spectral fragmentation mechanisms of iminoester 81

D. CONCLUSION OF THE STRUCTURE OF THE AMINOLACTAM

Because only compound 75 would give rise to the iminoester 81 (eqn 34), the structure of the aminolactam is, therefore, assigned to structure 75. This deduction of the structure of 75 was confirmed by the high resolution proton nuclear magnetic resonance (400 MHz) spectrum of the aminolactam (Figure 4). The chemical shifts, assignments and couplings are given in Table 8, where the values for chemical shifts and coupling constants are from the simulated spectrum using an AMDAL 470 computer (LAME-LAOCOON program). The experimental and simulated spectra of 75 are shown in Figure 5. No long range couplings of the three methyl groups, i.e. C-10, C-11 and C-12 to other protons could be assigned. However, the tentative assignments of these three methyl groups was based on the following reasoning: (a) the C-11 methyl group is very close to the deshielding zone of the carbonyl group, and, therefore, assigned to the most downfield absorption; (b) the C-12 methyl is attached to the quaternary carbon (C-1) which is bonded to two electronegative nitrogen atoms; therefore, the C-12 absorbtion is considered to be more downfield than the C-10 methyl absorption. The assignments of H_{7a}, H_{7e}, and H_5 and their couplings to other protons, as shown in Table 8, were also confirmed, at a later stage, by the high resolution proton nuclear magnetic resonance (400 MHz) spectra of the deuterated aminolactams. In these compounds, which will be discussed in detail in Part II, the positions H_{7a}, H_{7e} and H_5 were deuterated. The carbon-13 nuclear magnetic resonance (regular broad-band

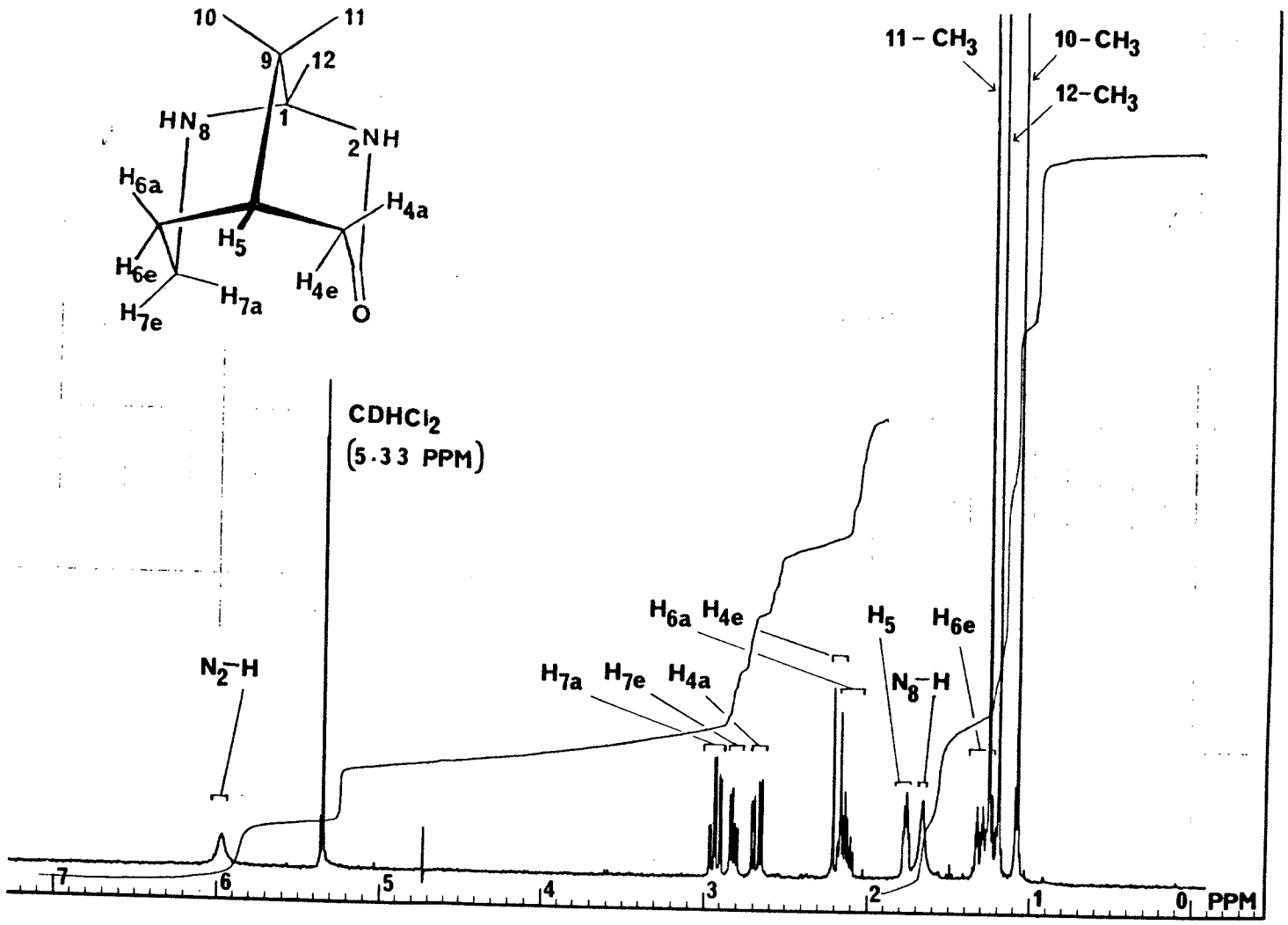


FIGURE 4. ^{1}H-nuclear magnetic resonance (400 MHz) spectrum of aminolactam 75 .

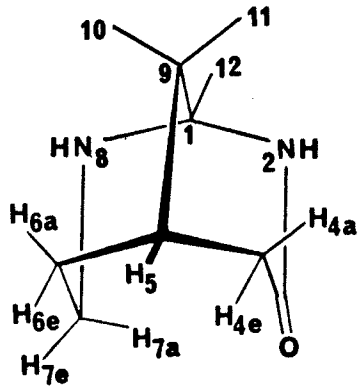


TABLE 8. DATA FROM THE ^{1}H-NMR (400 MHz) OF AMINOLACTAM 75 ;(CHEMICAL SHIFT IS DELTA RELATIVE TO TMS,SOLVENT CD_2Cl_2),(COUPLING ARE IN Hz)

CHEMICAL SHIFTS	ASSIGNMENTS	COUPLINGS
1.058	C-10 Me	----------
1.176	C-12 Me	----------
1.236	C-11 Me	----------
1.290	H_{6e}	$^{2}J(6e,6a)=-13.43$, $^{3}J(6e,5)=2.80$, $^{3}J(6e,7a)=4.00$, $^{3}J(6e,7e)=1.68$
1.642	N_8-H	----------
1.744	H_5	$^{3}J(5,4a)=7.00$, $^{3}J(5,6a)=4.02$, $^{3}J(5,6e)=2.80$, $^{4}J(5,7e)=0.62$, $^{3}J(5,4e)=0.50$(assigned)
2.116	H_{6a}	$^{2}J(6a,6e)=-13.43$, $^{3}J(6a,5)=4.02$, $^{4}J(6a,4a)=1.51$, $^{3}J(6a,7e)=5.82$, $^{3}J(6a,7a)=13.39$
2.169	H_{4e}	$^{2}J(4e,4a)=-18.63$, $^{3}J(4e,5)=0.5$(assigned)
2.655	H_{4a}	$^{2}J(4a,4e)=-18.63$, $^{3}J(4a,5)=7.00$, $^{4}J(4a,6a)=1.51$
2.799	H_{7e}	$^{2}J(7e,7a)=-12.49$, $^{3}J(7e,6a)=5.82$, $^{3}J(7e,6e)=1.68$, $^{4}J(7e,5)=0.62$
2.911	H_{7a}	$^{2}J(7a,7e)=-12.49$, $^{3}J(7a,6a)=13.39$, $^{3}J(7a,6e)=4.00$, + long range
5.95	N_2-H	----------

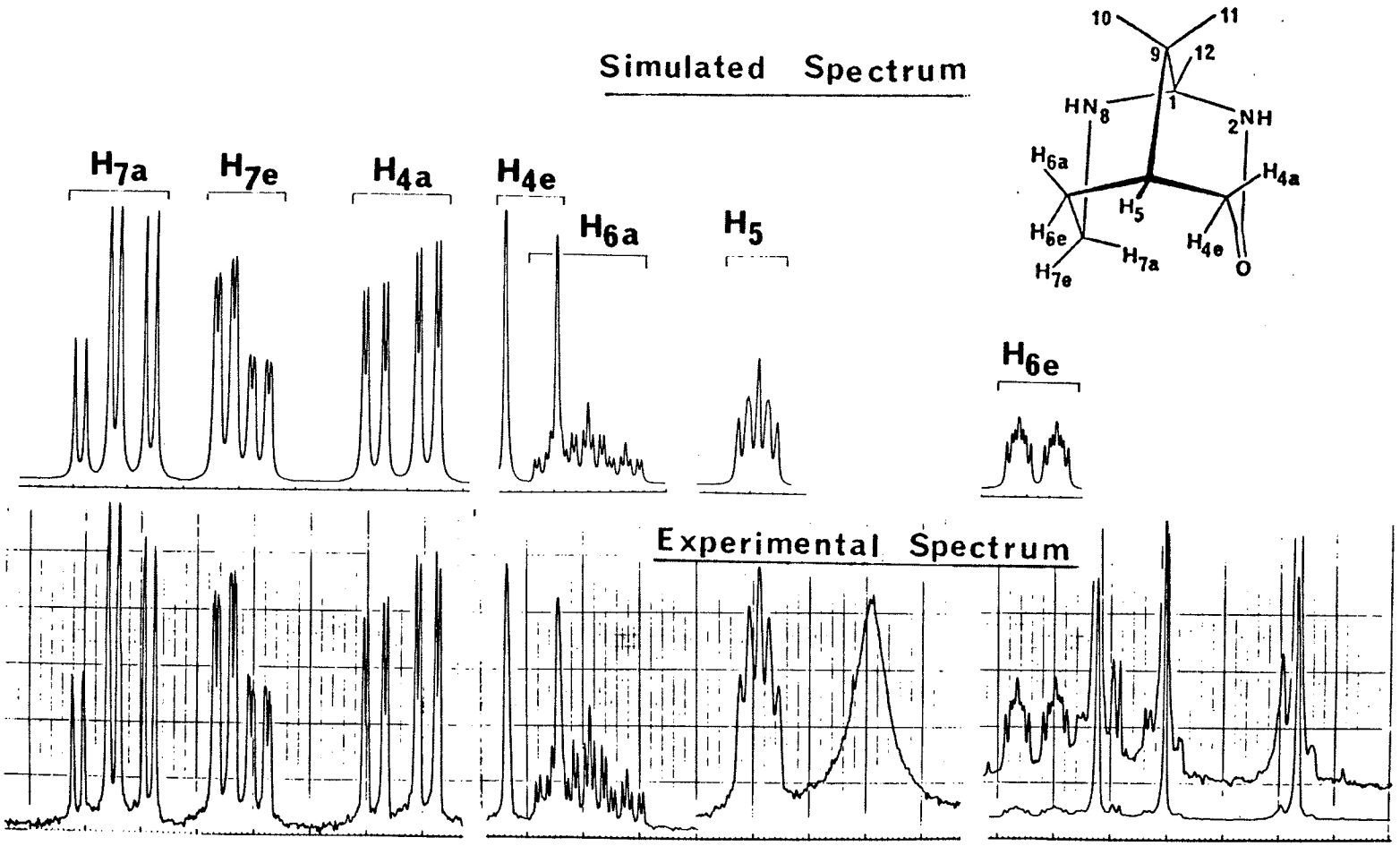


FIGURE 5. ^{1}H-nmr (400 MHz) spectra of aminolactam 75 ;
top: simulated spectrum, bottom: experimental spectrum.

^{1}H-decoupled, and ^{1}H-decoupled INEPT) data and assignments are shown in Table 9 below:

TABLE 9. THE CARBON-13 NMR DATA OF THE AMINOLACTAM 75.

Chemical Shifts (ppm)	173.8	71.8	37.9	37.4	35.9	35.8	28.5	23.9	23.1	22.9
^{1}H-decoupled INEPT	-	-	CH	CH_2	CH_2	C_q	CH_2	CH_3	CH_3	CH_3
^{13}C-Assignments	3	1	5	7 and 4		9	6	10, 11 and 12		

As shown in Table 9, the ^{1}H-decoupled INEPT technique could not be used to distinguish between the methylene-C_4 and the methylene-C_7 absorption. Carbon-proton shift mapping (see Figure 6) distinguished between these two methylene carbons. The downfield absorption at 37.4 ppm was assigned to C_7 and the upfield absorption at 35.9 ppm was assigned to C_4. The Carbon-13 nuclear magnetic resonance spectra of 75 are given in Figure 7.

The most abundant peaks with the % intensity and their elemental composition from the high resolution mass spectrum of the amino lactam 75 are given in Table 10 below.

TABLE-10. THE HIGH RESOLUTION MASS SPECTRAL DATA OF THE AMINOLACTAM 75

MEAS MASS[a]	% INT[a]	ELEMENTS[a]				FRAGMENTS
		C	H	N	O	
182.1420	100	10	18	2	1	$[M]^+$
167.1186	13.69	9	15	2	1	$(M^+)-(CH_3)$
139.1304	20.28		?			$(M^+)-(43),[(M^+)-(HN=C=O)]$
126.0794	21.65	6	10	2	1	$(167)-(41),[(167)-(CH_3-C=CH_2)^\cdot]$
125.0717	12.19	6	9	2	1	$(167)-(42),[(167)-(CH_3-CH=CH_2)]$
124.1122	11.14	8	14	1	0	$(167)-(43),[(167)-(HN=C=O)]$
114.0792	41.56	5	10	2	1	$(M^+)-(68),[(M^+)-(CH_2=C=C(CH_3)_2)]$
113.0715	20.43	5	9	2	1	$(114)-(H^\cdot)$
98.0970	38.52	6	12	1	0	$(139)-(41),[(139)-(-CH_2-CH=CH_2^\cdot)]$
82.0783	78.52	6	10	0	0	$(167)-(85)[CH_2=C(CH_3)-CH(CH_2)_2]^{\cdot+}$

a = These values were obtained from the computer print out.

The tentative mass spectral fragmentation mechanisms are presented in Scheme 7. The exact mass calculated for $C_{10}H_{18}N_2O$ is 182.1419 which is in excellent agreement with the observed value, i.e., 182.1420.

All these results confirm that the major product of the Schmidt reaction on camphor is the aminolactam 75 which is named as 2,8-diaza-3-oxo-1,9,9-trimethylbicyclo[3.3.1]nonane. This assignment of structure 75 to the aminolactam is further confirmed by

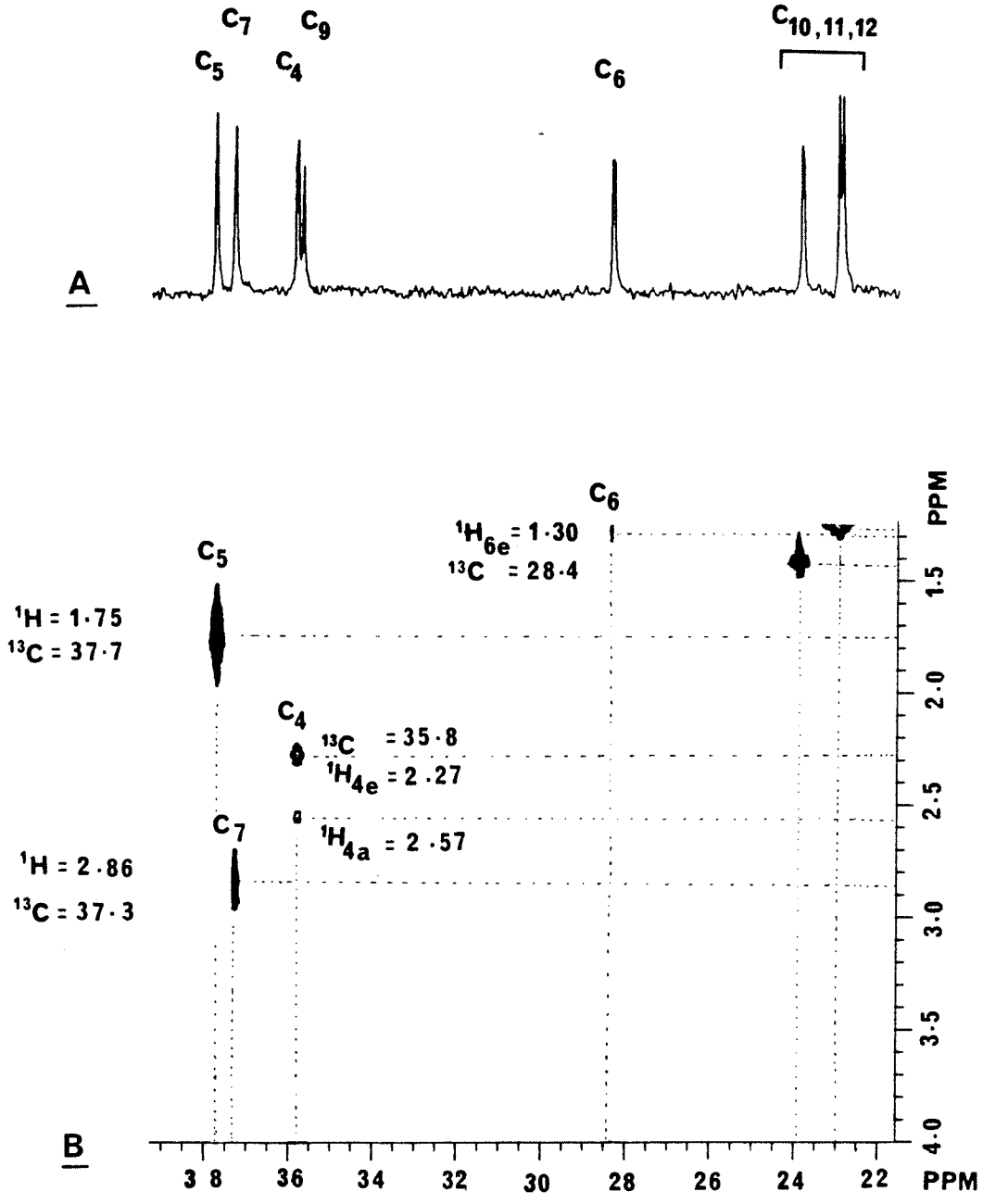


FIGURE 6. B: Carbon-Proton shift map of aminolactam 75 ;
A: ^{13}C-nmr spectrum; the down field absorption of C_1(at 71.8 ppm) and C_3(at 173.8 ppm) are not shown.

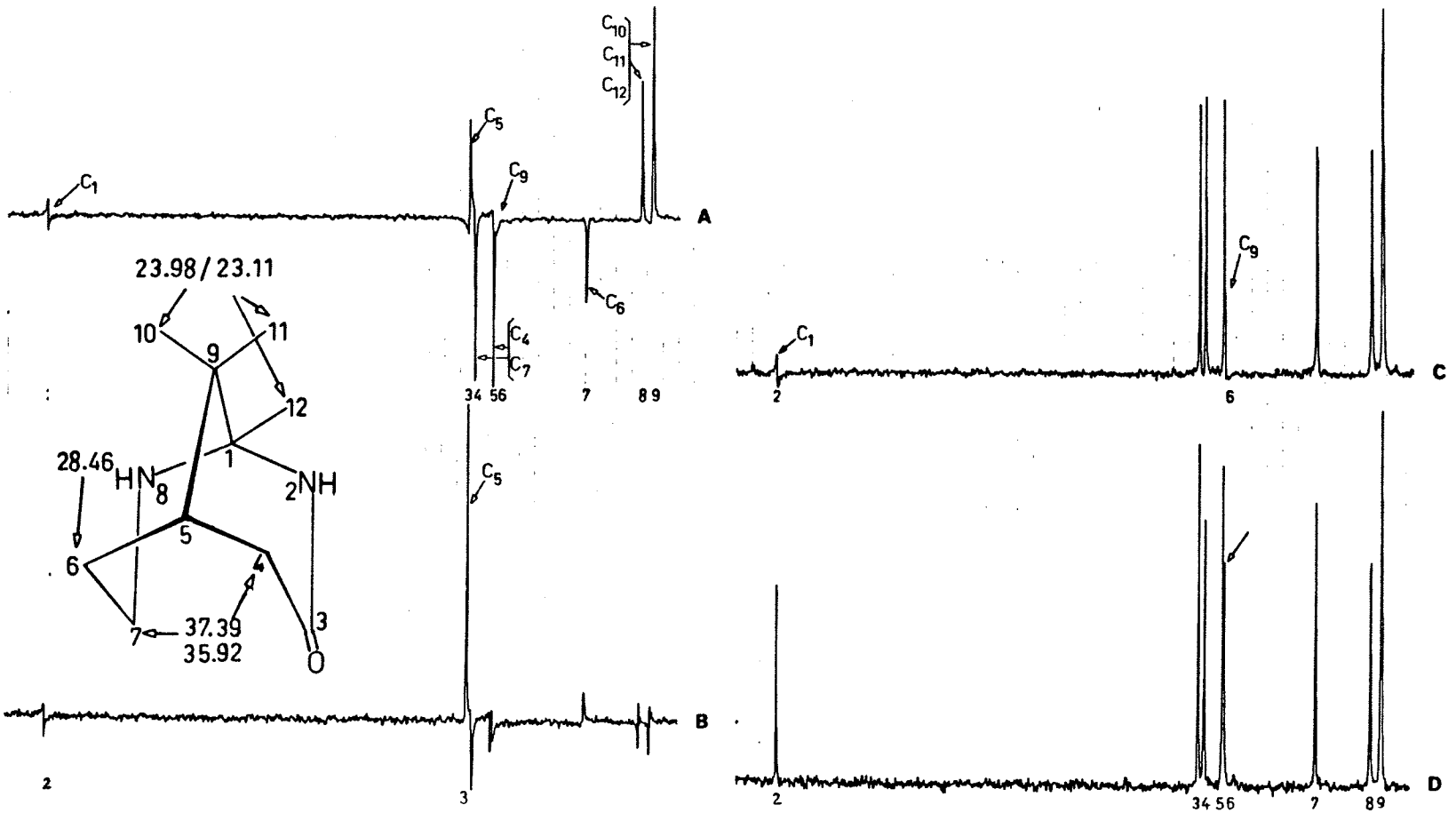
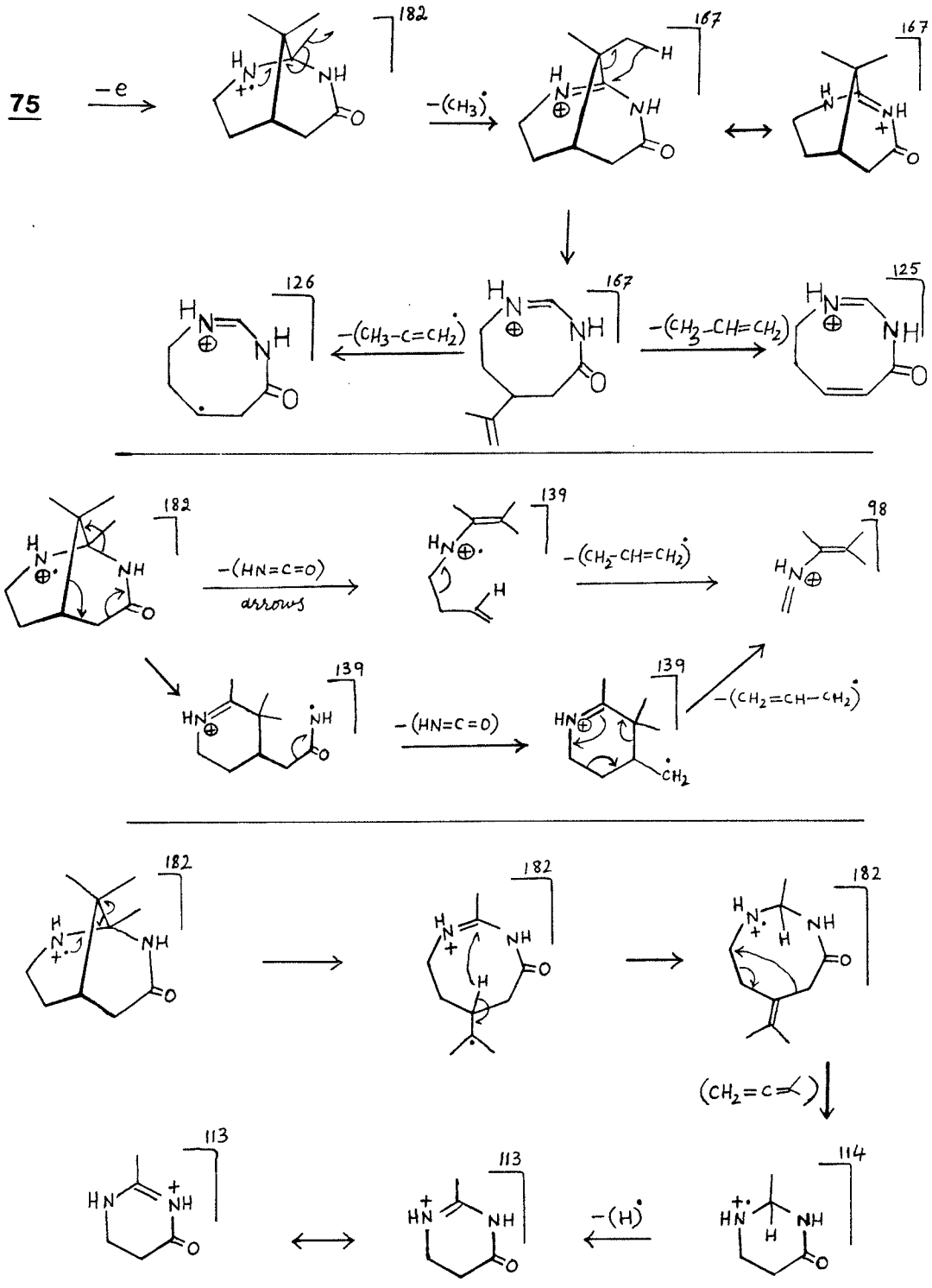


FIGURE 7. Carbon-13 nmr spectra of aminolactam 75 ; A-C are INEPT spectra, A: CH_3 and CH are up and CH_2 are down, B: CH are up ↑, C: all carbons except C_q are up ↑, D: broad band ^1H-decouled spectrum.



SCHEME 7. The tentative mass-spectral fragmentation mechanisms of aminolactam 75 .

identification of the products of the addition reactions of 75. These products will be discussed in the next section.

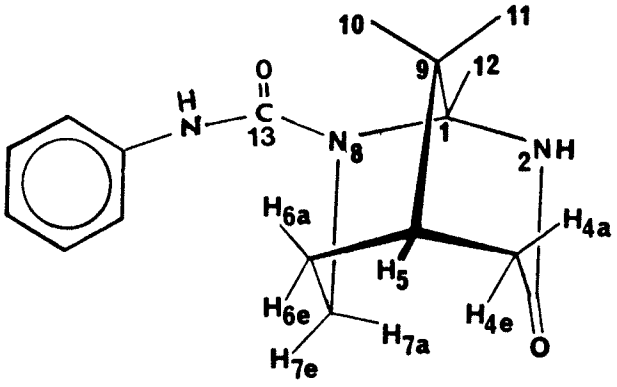
E. PRODUCTS OF ADDITION REACTIONS OF AMINOLACTAM

(1) N_8-(Phenylcarbamoyl)aminolactam 77:

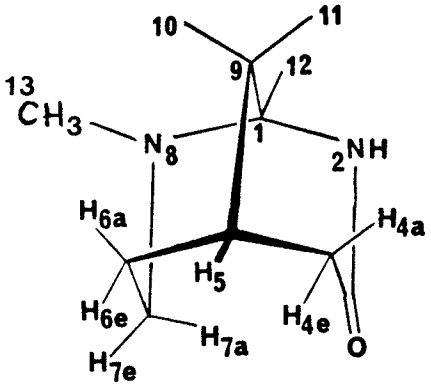
This very polar product was crystallized from ethyl acetate-methanol (3:1, v:v) solution to give colorless shiny crystals; mp 163-165°C. The infrared spectrum showed absorptions for N-H stretch. The proton nuclear magnetic resonance (90 MHz) spectrum in DMSO-d_6 showed the N_{14}-H at δ 8.18 (1H, broad singlet), aromatic protons at δ 7.46 - 6.80 (5Hs, m) and the N_2-H at δ 6.10(1H, m). The N_8-H proton, which absorbs at δ 1.60 in the aminolactam 75, was not observed in the spectrum of the addition product 77. The carbon-13 nuclear magnetic resonance (regular broad-band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are shown in Table 11 below.

TABLE-11. THE CARBON-13 NMR DATA OF N_8-(PHENYLCARBAMOYL)-AMINOLACTAM 77

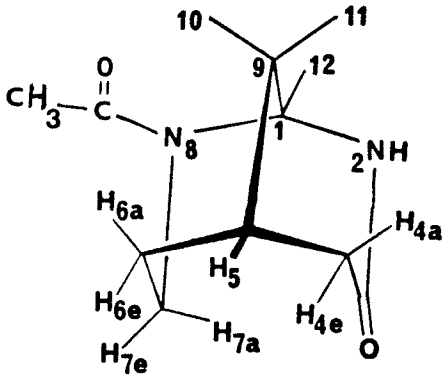
Chemical Shifts (ppm)	171.1	155.2	88.6	39.3	37.2	34.5	32.6	30.1	20.9	17.1	17.1
^{1}H-decoupled INEPT	-	-	-	C_q	CH_2	CH_2	CH	CH_2	CH_3	CH_3	CH_3
^{13}C-Assignments	3	13	1	9	7	4	5	6	10, 11 and 12		


10
11
9
12
O
H
N
C
13
N8
1
2NH
H6a
H4a
H5
H6e
H4e
H7a
H7e
O

77


10
11
9
12
13
CH3
N8
1
2NH
H6a
H4a
H5
H6e
H4e
H7a
H7e
O

78


10
11
9
12
O
CH3
C
N8
1
2NH
H6a
H4a
H5
H6e
H4e
H7a
H7e
O

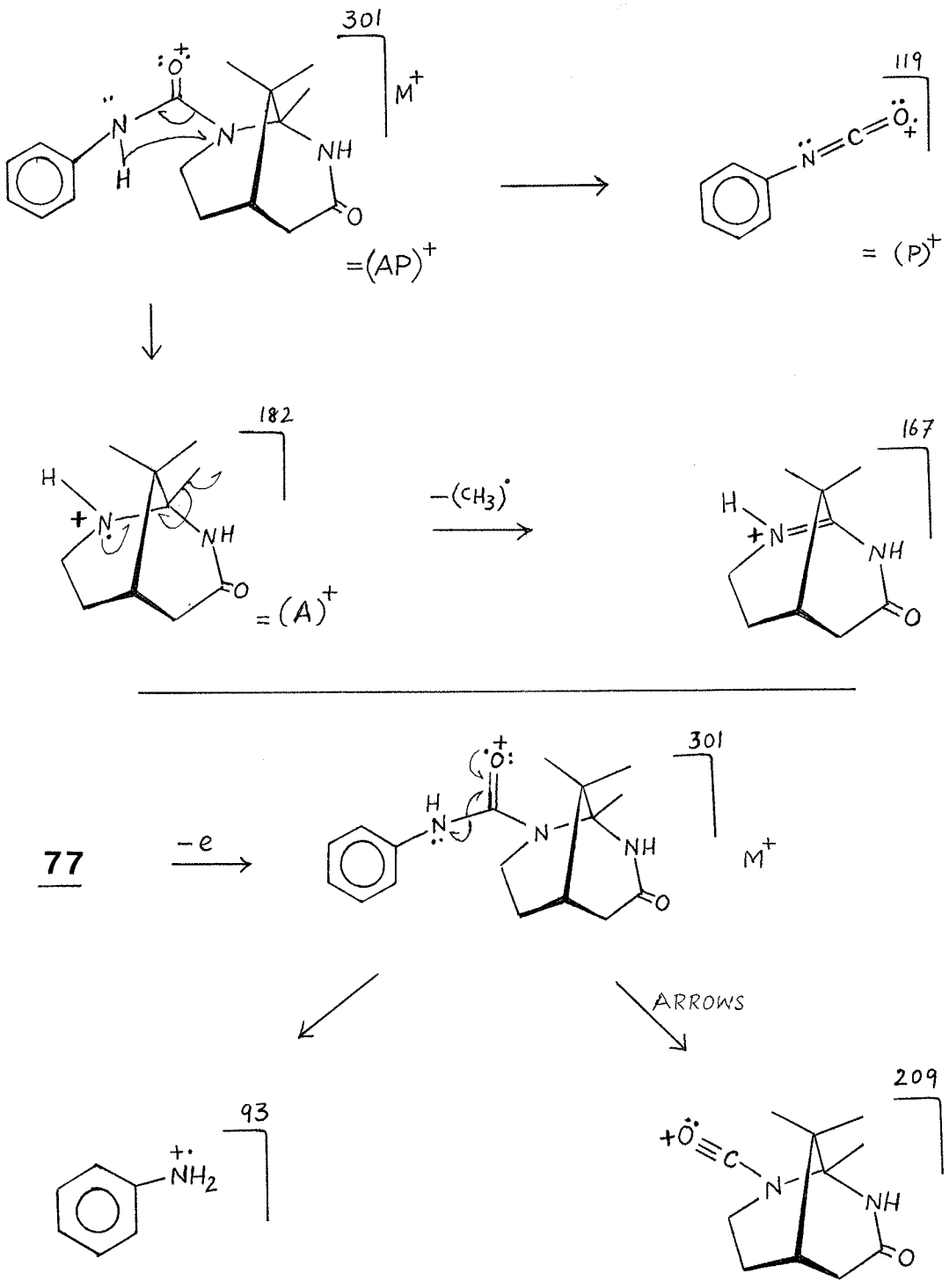
79

The aromatic carbons C-1', C-ortho, C-meta and C-para (not shown in Table 11), absorb at 140.53, 117.62, 128.54 and 120.89 ppm, respectively.

In the mass spectrum of the adduct 77, abbreviated as AP (A for the aminolactam portion and P for the phenylcarbamoyl portion), the molecular ion peak $(AP)^+$ was only 3%. However, the appearance of the base peak $(P)^+$ at m/z 119 and the $(A)^+$ peak at m/z 182 (33%) suggest that electron impact caused the $(AP)^+$ peak (the molecular ion peak) to "split" into the original aminolactam (A) and the phenyl isocyanate (P). The tentative mass spectral fragmentation mechanisms are presented in Scheme 8.

(2) N_8-Methylaminolactam 78:

As discussed earlier, compound 78 was prepared by methylation of 75 with Magic Methyl® (89-98% yield) or with methyl iodide (67% yield). The infrared spectrum showed absorptions for amidic N-H stretch and amidic C=O stretch. Compared to the proton nuclear magnetic resonance (90 MHz) spectrum of the aminolactam 75, the chemical shifts of H_{7a} and H_{7e} are now observed upfield between H_{4a} and H_{4e} in the N_8-methyl amino lactam 78; also the N_8-H absorption disappeared and instead a singlet at δ 2.16 (3Hs) for N_8-CH_3 is observed. The carbon-13 nuclear magnetic resonance (regular broad-band ^{1}H-decoupled) data and assignments are given in Table 12 below.



SCHEME 8. The tentative mass-spectral fragmentation mechanisms of N_8-(phenylcarbamoyl)aminolactam 77 .

TABLE 12. THE CARBON-13 NMR DATA OF N_8-METHYLAMINOLACTAM 78

Chemical Shifts (ppm)	174.1	75.1	47.2	37.9	37.8	36.8	35.9	28.4	24.9	23.1	20.5
^{13}C-Assignments	3	1	13	7	5	4 and 9		6	10, 11 and 12		

Since the ^{1}H-decoupled INEPT technique was not used in this case, the carbon-13 assignments were made using the aminolactam 75 as a comparison.

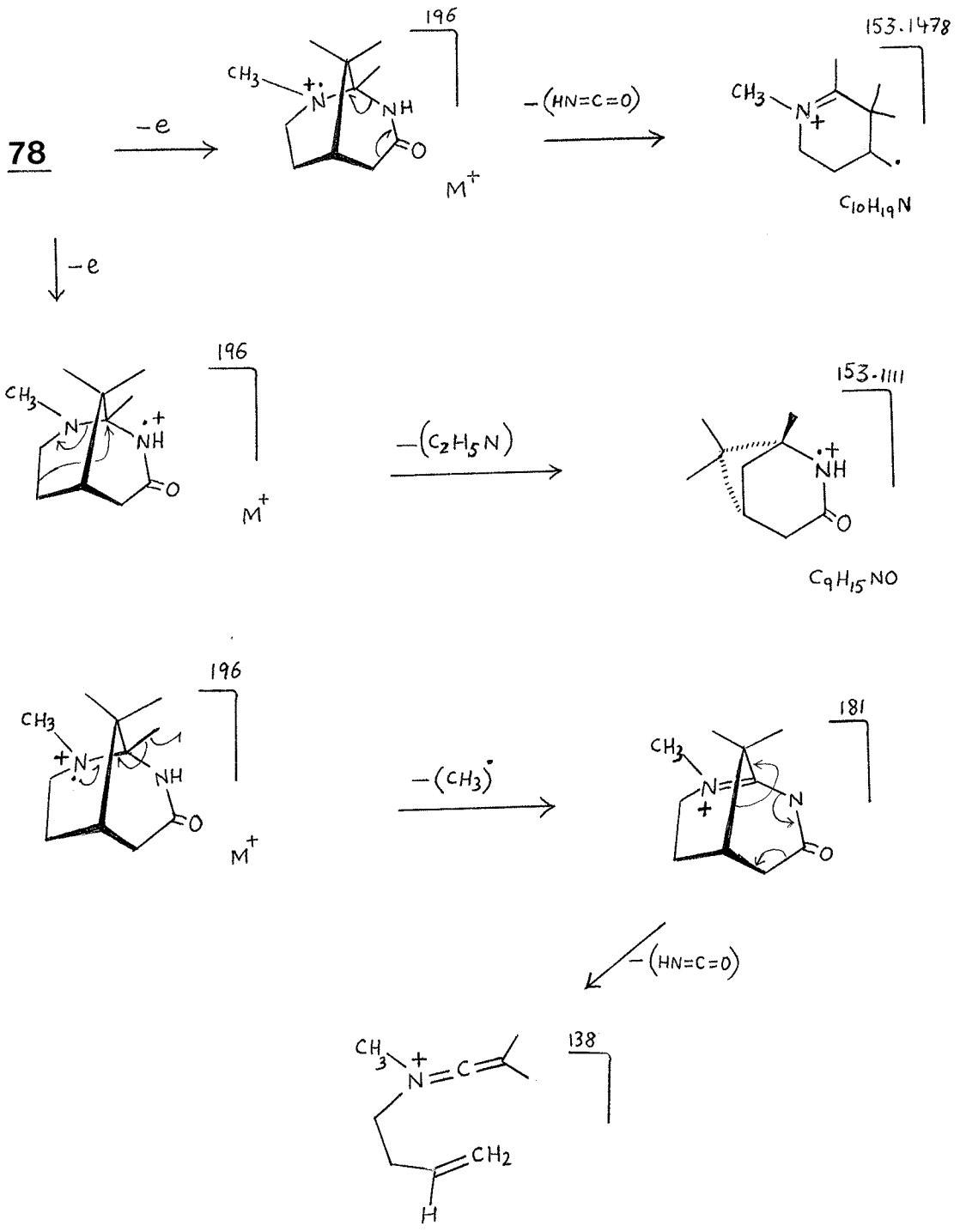
The high resolution mass spectrum of 78 showed the molecular ion peak at m/z 196.1578 (100%) for $C_{11}H_{20}N_2O$. The exact mass calculated for $C_{11}H_{20}N_2O$ is 196.1576. The most abundant peaks with the % intensity and their elemental composition from the high resolution mass spectrum of 78 are given in Table 13 below.

TABLE 13. THE HIGH RESOLUTION MASS SPECTRAL DATA OF N_8-METHYLAMINO-LACTAM 78.

MEAS MASS[a]	% INT[a]	ELEMENTS[a]				FRAGMENTS
		C	H	N	O	
196.1578	100	11	20	2	1	$[M^+]$
181.1340	17.05	10	17	2	1	$(M^+)-(CH_3)$
153.1478	20.27	10	19	1	0	$(M^+)-(43),[(M^+)-(HN=C=O)]$
153.111	11.89	9	15	1	1	$(M^+)-(43),[(M^+)-(CH_3-N=CH_2)]$
138.1280	28.15	9	16	1	0	$(181)-(43),[(181)-(HN=C=O)]$
127.0874	36.95	6	11	2	1	$(M^+)-(69),[(M^+)-((CH_3)_2C-CH=CH_2]$
124.1127	21.91	8	14	1	0	$(138)-(14),[(138)-(CH_2)^{\cdot\cdot}]$
115.0872	30.58	5	11	2	1	-
112.1120	51.79	7	14	1	0	-
110.0607	34.54	6	8	1	1	-
82.0774	36.60	6	10	0	0	-

a = These values were obtained from the computer print out.

The tentative mass spectral fragmentation mechanisms are presented in Scheme 9.



SCHEME 9. The tentative mass-spectral fragmentation mechanisms of N_8-methylaminolactam 78 .

(3) N_8-Acetylaminolactam 79:

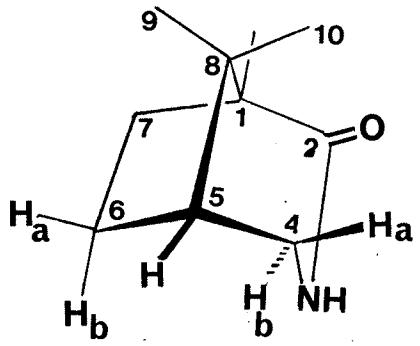
As discussed earlier, compound 79 was prepared in low yield by the action of acetyl chloride with the aminolactam 75. Only mass spectral analysis could be carried out which indicated a molecular ion peak at m/z 224. A fragment ion peak at m/z 181 indicated the loss of an acetyl radical from the molecular ion. Preparation of this compound on a larger scale and its further characterization was considered unnecessary.

F. OTHER MINOR PRODUCTS FROM THE SCHMIDT REACTION ON CAMPHOR

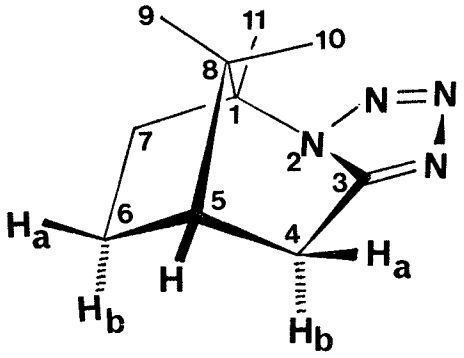
Other minor products, which were obtained in low yields and identified from the Schmidt reaction on camphor, are ∝-camphidone 71, camphortetrazole 83, and iminonitrile 84.

(1) ∝-Camphidone 71:

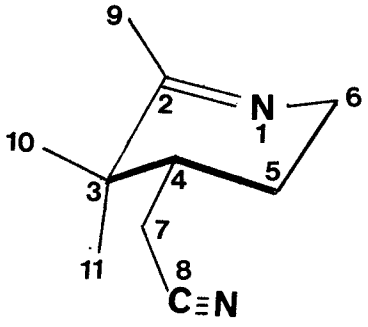
This compound was isolated from the diluted acidic reaction mixture in 5.3% yield after flash chromatography and crystallization: mp 242-244°C. Compound 71 has previously been reported in only 1% yield from the Schmidt reaction on camphor (55a). The infrared spectrum showed absorptions for N-H stretch and amidic C=0 stretch. The proton nuclear magnetic resonance (90 MHz) spectrum showed the amidic proton resonance at δ 5.90 (1H, m). The protons at H_{4a} and H_{4b} positions were coupled to the amidic proton (^{3}J = 1-2 Hz). This was confirmed by examination of an NH-decoupled proton nuclear magnetic resonance (90 MHz) spectrum where the coupling of H_{4a} and H_{4b} to the amidic proton disappeared. The carbon-13 nuclear magnetic resonance (regular broad-band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 14 below.


9
10
8
1
7
2
O
5
6
4
Ha
Ha
H
Hb
H
b
NH

71


9
11
10
8
1
N=N
7
N
2
N
3
5
6
4
Ha
Ha
H
Hb
Hb

83


9
2
N
6
1
10
5
3
4
7
11
8
C≡N

84

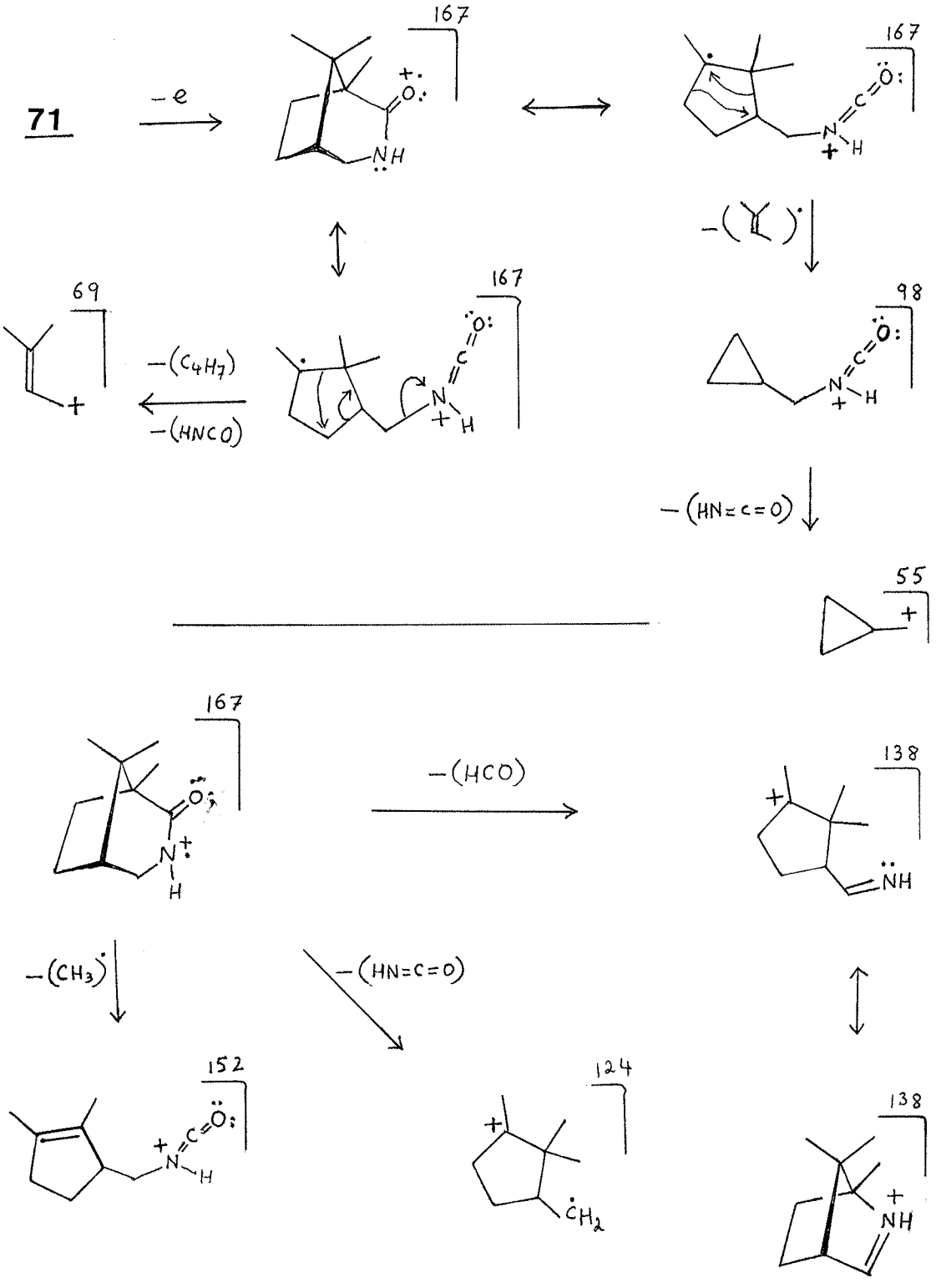
TABLE 14. THE CARBON-13 NMR DATA OF α-CAMPHIDONE 71.

Chemical Shifts (ppm)	178.9	52.3	47.2	43.7	42.3	37.9	27.8	23.1	19.3	13.4
^{1}H-decoupled INEPT	-	C_q	CH_2	CH	C_q	CH_2	CH_2	CH_3	CH_3	CH_3
^{13}C-Assignments	2	1	4	5	8	7	6	9 to 10		11

The mass spectrum of 71 showed the parent ion peak at m/z 167. The tentative mass spectral fragmentation mechanisms are shown in Scheme 10. The structure of this compound was assigned as 71, a methylene migrated product, rather than β-camphidone 73 which would have resulted from bridgehead migration. This conclusion was based upon the proton resonances at δ 3.44 (1H, H_{4a}) and δ 2.99 (1H, H_{4b}). As discussed above, these protons were also coupled to the adjacent amidic proton. The corresponding H_{4a} and H_{4b} (at alpha position to C=O group) in β-camphidone would be expected to absorb more upfield.

(2) Camphortetrazole 83:

This compound was isolated in only 1% yield. As discussed in the Introduction section, Schmidt (73) has reported the preparation of



SCHEME 10. The tentative mass-spectral fragmentation mechanisms of α-camphidone 71 .

camphortetrazole in 20% yield (mp 242-243°C) by the action of hydrazoic acid on camphor in the presence of conc. sulphuric acid and BENZENE. Schmidt did not report the concurrent formation of other products. He also did not elucidate the structure of camphortetrazole, i.e. whether the tetrazole involved a bridgehead migrated product or a methylene migrated product.

Compound 83 melts at 245-247°C in a sealed tube. The infrared spectrum showed absorption for C=N stretch of the tetrazole ring (49). The mass spectrum indicated the molecular ion peak at m/z 192. Loss of nitrogen (59) from the molecular ion yielded a fragment ion which was observed at m/z 164. Proton nuclear magnetic resonance (90 MHz) spectrum showed a double double doublet at δ 3.15 (1H, H_{4a})[$^{2}J(4a,4a)$ = -17 Hz, $^{3}J(4a,5)$ = 3.1 Hz, $^{4}J(4a,6a)$ = 1.5 Hz]; a double doublet at δ 2.95 (1H, H_{4b})[$^{2}J(4b,4a)$ = -17 Hz, $^{3}J(4b,5)$ = 2 Hz]; a singlet at δ 1.78 (3Hs, C-11 methyl) which is deshielded by the ring current effect of the tetrazole ring; and a singlet at δ 0.81 (3Hs) which is due to the C-10 methyl lying in the shielding cone of tetrazole ring. The structure 83, instead of a methylene migrated camphortetrazole structure, was assigned to this product based on the chemical shifts of H_{4a} and H_{4b} (see above) at C_4 alpha to C_3 of the tetrazole ring. The corresponding protons at C_4 alpha to N_3 of the tetrazole ring in a methylene migrated tetrazole 93 (see later, Scheme 13b) should absorb more downfield as observed in other tetrazoles (45,59). The carbon-13 nuclear magnetic resonance (regular broad-band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 15 below.

TABLE 15. THE CARBON-13 NMR DATA OF CAMPHORTETRAZOLE 83.

Chemical Shifts (ppm)	150.4	72.4	45.4	42.6	39.8	27.7	27.2	23.5	17.6	14.7
^{1}H-decoupled INEPT	-	C_q	C_q	CH	CH_2	CH_2	CH_2	CH_3	CH_3	CH_3
^{13}C-Assignments	3	1	8	5	4	7 and 6		9, 10 and 11		

The downfield absorption at 72.4 ppm of quaternary C_1, which is at the position alpha to N_2 of the tetrazole ring in 83, also supports the structure of a bridghead migrated tetrazole for this compound. The corresponding C_1 in a methylene migrated tetrazole should absorb at higher field. The same argument is true for C_4 in a reverse order in terms of its chemical shifts.

(3) Iminonitrile 84:

This compound [bp 65°C (0.1 mm Hg)] was isolated in 1% yield from the mother liquor from the crystallization of the aminolactam 75. The mass spectrum indicated the parent ion peak at m/z 164. The

fragment ion peaks (except those involving fragmentation of -CN group) were very similar to those of the iminoester 81 discussed earlier. The infrared spectrum showed absorptions for C≡N stretch and C=N stretch. The nuclear magnetic resonance (90 MHz) spectrum showed a double doublet at δ 1.88 (3Hs) assigned to the C-9 methyl coupled to H_{6a} and H_{6e}. All the couplings of protons in the iminonitrile 84 and the iminoester 81 were similar to each other in their 90 MHz proton nuclear magnetic resonance spectra. The only difference observed was in the chemical shifts of the protons of the side chain at the C_4 position. The carbon-13 nuclear magnetic resonance (regular broad-band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 16; and here also, except for the side chain at the C_4 position, the chemical shifts are similar to those of the iminoester 81.

TABLE 16. THE CARBON-13 NMR DATA OF IMINONITRILE 84.

Chemical Shifts (ppm)	172	119	48	39.3	38.6	25.5	23.8	22.4	20.7	18.6
^{1}H-decoupled INEPT	-	-	CH_2	CH	C_q	CH_3	CH_2	CH_3	CH_3	CH_2
^{13}C-Assignments	2	8	6	4	3	9	5	10 and 11		7

G. 3% METHANOLIC-HCL METHANOLYSIS OF N_8-METHYLAMINOLACTAM 78, AND CHARACTERIZATION OF THE PRODUCTS

Before the structure of the aminolactam 75 was confirmed by its proton nuclear magnetic resonance (400 MHz) spectrum, the following work was carried out towards the structural elucidation of the major product from the Schmidt reaction on camphor. It was envisaged that the N-methylated addition-products of the three possible candidates 74, 75 and 76 for the structure of the major product would yield different products from their 3% methanolic-HCl methanolysis.

The main product of 3% methanolic-HCl methanolysis (78) was the N-methylamidoketone 85 (85% yield) (see Scheme 11). From one trial a small amount of N,N-dimethylketoester 86 was also isolated. From another trial two other compounds were obtained and identified as the iminoester 81 (11%) and the amidoketone 87 (1%). Compound 86 and 87 could not be isolated during repeated trials. Fortunately, compound 87 was obtained in larger amounts as a result of a chance observation. Compound 87 appeared as a colorless crystalline solid in tubes containing nmr samples of iminoester 81 in $CDCl_3$ left at room temperature in the light for several months. Compound 87 could have been produced by the hydrolysis and recyclization of iminoester 81. The hydrolysis process probably occurred with atmospheric moisture and HCl which was produced by the decomposition of residual chloroform by light as follows:

$$CHCl_3 \xrightarrow[UV]{[O]} COCl_2 + HCl \qquad \text{eqn 35}$$

$$\underline{81} \xrightarrow[HCl]{H_2O} \underline{87}$$

Scheme 11 illustrates the production of the methanolysis products of 78.

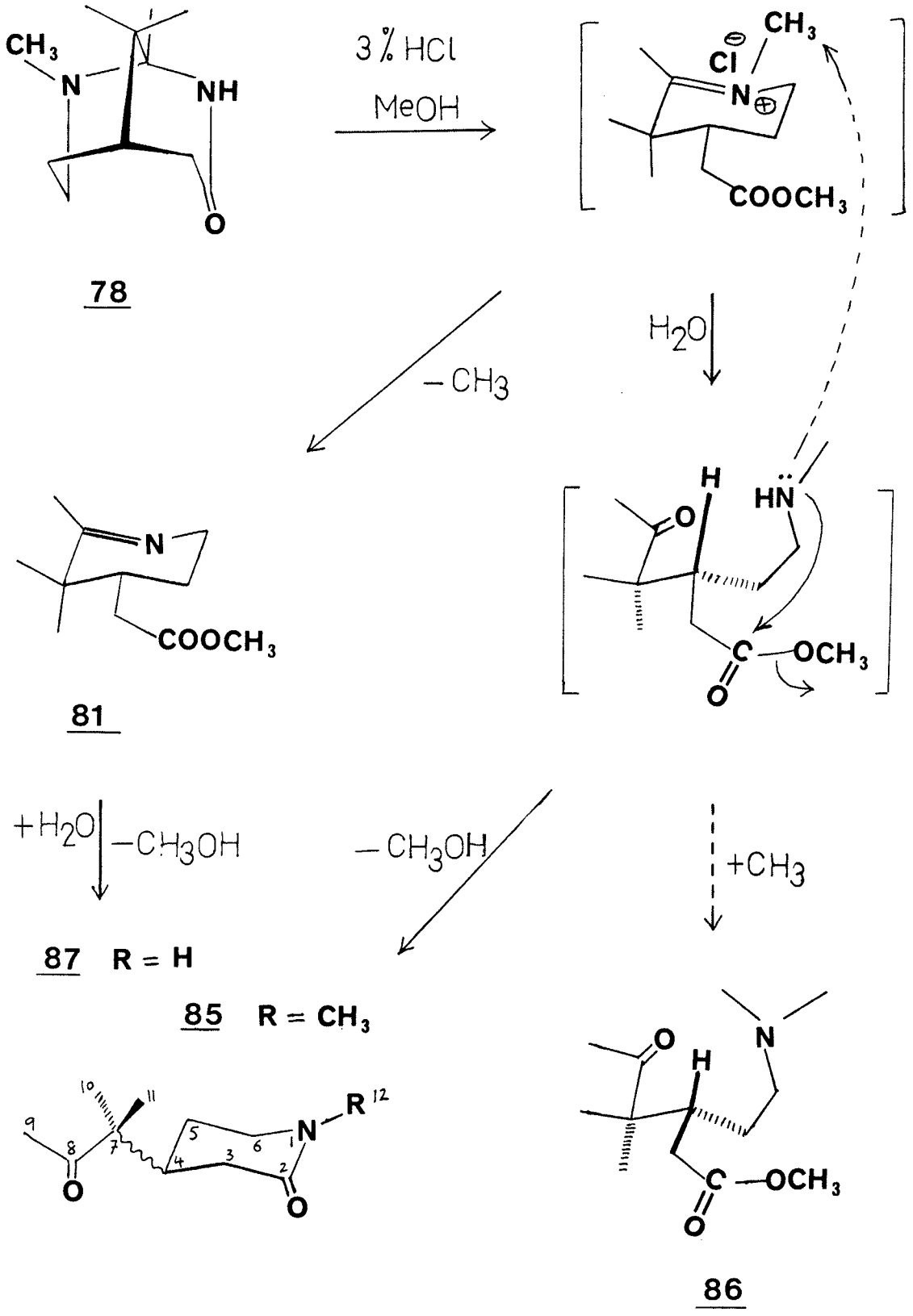
(1) N-Methylamidoketone 85:

This compound, bp 90°C (0.4 mm Hg), the major product of the 3% methanolic-HCl methanolysis of 78, was obtained in 83-85% yields from various trials. The infrared spectrum showed absorptions for saturated ketone and saturated amide groups. The proton nuclear magnetic resonance (90 MHz) spectrum showed, beside other peaks, a singlet at δ 2.92 (3Hs, N-CH_3), a singlet at δ 2.15(3Hs, O=C-CH_3), and two singlets at δ 1.11(3Hs) and δ 1.09(3Hs) [C-10 and C-11 methyls]. The carbon-13 nuclear magnetic resonance (regular broad-band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 17 below.

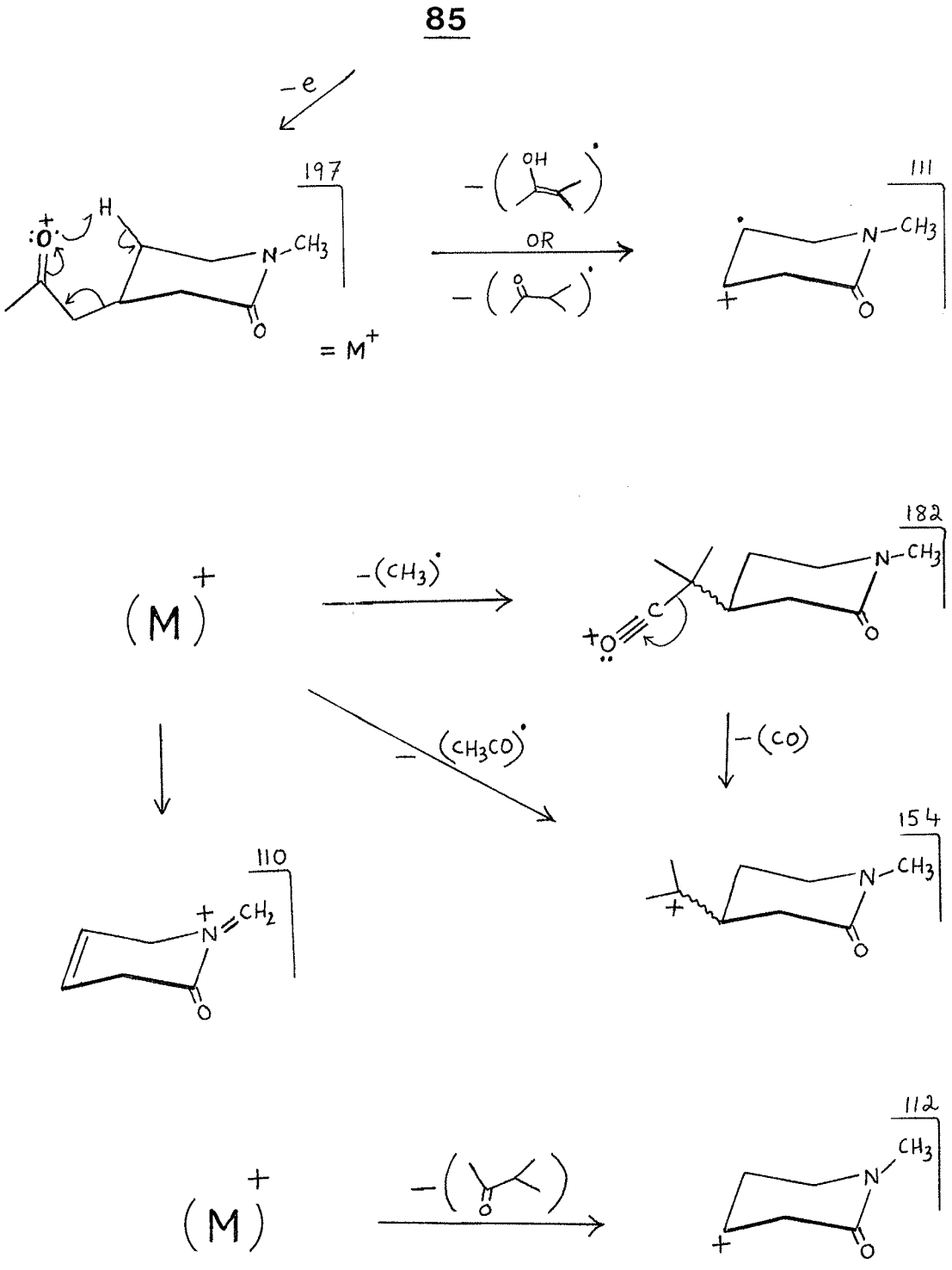
TABLE 17. THE CARBON-13 NMR DATA OF N-METHYLAMIDOKETONE 85.

Chemical Shifts (ppm)	212.4	169.2	49.3	49.1	38.9	34.1	33.4	25.4	24.5	21.1	20.0
^{1}H-decoupled INEPT	-	-	C_q	CH_2	CH	CH_3	CH_2	CH_3	CH_2	CH_3	CH_3
^{13}C-Assignments	8	2	7	6	4	12	3	9	5	10 and 11	

The high resolution mass spectrum showed the molecular ion peak at m/z 197.1416 for $C_{11}H_{19}NO$. Some of the tentative mass spectral fragmentation mechanisms are shown in Scheme 12. The abundant peaks with the % intensity and their elemental composition from the high resolution mass spectrum of 85 are given in Table 18.


CH3
N
NH
O
78
3% HCl
MeOH
Cl
CH3
N⊕
COOCH3
H2O
−CH3
N
COOCH3
81
H
O
HN
C
OCH3
O
+H2O
−CH3OH
−CH3OH
+CH3
87 R = H
85 R = CH3
R12
N
O
O
O
H
N
C
OCH3
O
86

SCHEME 11



SCHEME 12. The tentative mass-spectral fragmentation mechanisms of N-methylamidoketone 85 .

TABLE 18. THE HIGH RESOLUTION MASS SPECTRAL DATA OF N-METHYLAMIDO-KETONE 85.

MEAS MASS[a]	INT[a]	ELEMENTS[a]				FRAGMENTS
		C	H	N	O	
198.1448	10.8	11	20	1	2	$(M^+)+1$
197.1416	100	11	19	1	2	M^+
182.1180	9.5	10	16	1	2	$(M^+)-(CH_3)$
154.1235	66.6	9	16	1	1	$(M^+)-(CH_3CO)$ or $(182)-(CO)$
112.0763	31.6	6	10	1	1	$(M^+)-(CH_3-CO-C(CH_3)_2)$
111.0676	13.4	6	9	1	1	$(M^+)-(CH_3-CO-CH(CH_3)_2)$
110.0606	61.3	6	8	1	1	$(M^+)-[CH_3-CO-CH(CH_3)_2+H^\cdot]$
83.0864	39.7	6	11	0	0	$(154)^+-(CO+CH_2=N-CH_3)$
82.0786	13.4	6	10	0	0	$(83)^+-(H^\cdot)$
69.0707	44.5	5	9	0	0	-
55.0570	80.1	4	7	0	0	-

a = These values were obtained from the computer printout.

(2) N,N-Dimethylketoester 86:

This compound was isolated during only one trial (1% yield). The infrared spectrum showed absorptions for a saturated ester and a saturated ketone. The mass spectrum indicated the molecular ion peak to be at m/z 243. The proton nuclear magnetic resonance (60 MHz)

spectrum showed a singlet at δ 3.72 (3Hs, CO-O-CH_3), a singlet at δ 2.28 (3Hs, O=C-CH_3), a singlet at δ 2.20 [6Hs, $N(CH_3)_2$], and a singlet at δ1.10 [6Hs, O=C-$C(CH_3)_2$].

(3) Amidoketone 87:

Compound 87, isolated during the 3% methanolic-HCl methanolysis of 78, was identical to the solid obtained from the nuclear magnetic resonance samples of 81 left over several months in its tlc, mass and ^{1}H-nuclear magnetic resonance spectra (see Experimental). In comparison, the proton and carbon-13 nuclear magnetic resonance and infrared spectra of 87 and N-methylamidoketone 85, for the most part, were identical to each other. In addition, the infrared spectrum of 87 also showed absorptions for N-H stretch; and the ^{1}H-nuclear magnetic resonance spectrum showed a broad NH peak at δ 6.62. Also, the N-methyl peak, which was observed in the proton and carbon-13 nuclear magnetic resonance spectra of 85, was absent in these spectra of 87. The carbon-13 chemical shift of the secondary amidic-carbon was observed at 172.3 ppm as compared to 169.20 ppm observed for the tertiary amidic-carbon in 85. The carbon-13 nuclear magnetic resonance (regular broad-band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 19 below.

TABLE 19. THE CARBON-13 NMR DATA OF AMIDOKETONE 87.

Chemical Shifts (ppm)	212.6	172.3	49.6	41.6	38.8	33.1	25.6	24.2	21.4	20.2
^{1}H-decoupled INEPT	-	-	C_q	CH_2	CH	CH_2	CH3	CH_2	CH_3	CH_3
^{13}C-Assignments	8	2	7	6	4	3	9	5	10 and 11	

The high resolution mass spectrum of 87 indicated the molecular ion peak at m/z 183.1259 for $C_{10}H_{17}NO_2$. The mass spectral fragmentation mechanisms were considered to be essentially identical to those of 85. The abundant peaks, with their % intensities and their elemental composition from the high resolution mass spectrum of 87, are given below in Table 20.

TABLE 20. THE HIGH RESOLUTION MASS SPECTRAL DATA OF AMIDOKETONE 87.

MEAS MASS[a]	INT[a]	ELEMENTS[a]				FRAGMENTS
		C	H	N	O	
184.1297	4.2	10	18	1	2	$(M^+)+1$
183.1259	32.5	10	17	1	2	M^+
140.1077	88.5	8	14	1	1	$(M^+)-(43),[(M^+)-(CH_3-CO)]$
98.0977	24.2	6	12	1	0	$[(140)-(CH_2=C=O)]$
98.0607	45.7	5	8	1	1	$(M^+)-(43),[(M^+)-(CH_3CO-CH(CH_3)_2)]$
97.1013	23.2	7	13	0	0	$[(140)-(HN=C=O)]$
83.0857	13.5	6	11	0	0	-
82.0784	27.8	6	10	0	0	-
69.0707	26.6	5	9	0	0	-
55.0566	100	4	7	0	0	$[(140)-(CH_2-(CH_2)_2-CO-NH)]$

a = These values were obtained from the computer print out.

PART II MECHANISM OF THE SCHMIDT REACTION ON CAMPHOR

The work carried out towards the mechanism of the Schmidt on camphor will be discussed here in Part II. This discussion will proceed as follows:

(A) General discussion

(B) Discussion of routes to the formation of minor products

(C) Discussion of a route to the formation of the major product

A. GENERAL DISCUSSION

The structural elucidation of the new major product 75 and the minor products 71, 83 and 84 from the Schmidt reaction on camphor was followed by the second general step of an organic chemist, i.e., to investigate the route or mechanism of their formation.

The mechanism for the formation of minor products 71, 83 and 84 could be explained by the views currently available in the literature. However, the major product 75 is unexpected and its formation could not be visualized according to the existing two views of the mechanism of the Schmidt reaction on ketones that were reviewed in the Introduction Section. Therefore, a new route was suggested for the formation of the major product 75. The establishment of this route will be discussed in Section C in detail.

One of the important factors influencing the course of the Schmidt reaction on ketones is the nature of the medium where the reaction takes place. As mentioned in the Introduction Section the effects of solvents on the Schmidt reaction are poorly understood so far. Prager, et al. (50a) have shown that the Schmidt reaction may occur essentially either in the organic phase or in the sulphuric acid phase. Analysis of their experimental data and that of Fikes and Shechter (33,34) show that the site of the actual reaction, i.e., either the organic phase or the sulphuric acid phase, depends on the strength of the sulphuric acid and nature of the solvent. As mentioned earlier, Schmidt (73) had isolated only camphortetrazole in 20% yield from the reaction of hydrazoic acid on camphor in the

presence of conc. sulphuric acid and benzene. It is conjectured that the use of benzene as the organic phase (rather than chloroform as in our case) could be responsible for the results reported by Schmidt. Neverthless, other factors such as temperature, ratio of HN_3 etc. could also be responsible for the different results. A detailed study of the effect of different solvents, under otherwise identical conditions, could reveal some interesting results in future investigations. For this purpose it was considered important to know about the solvent effects at the site of the reaction.

As mentioned earlier, the reaction mixture (during the Schmidt reaction on camphor) consists of two layers, the top chloroform layer and the bottom viscous sulphuric acid layer. In order to know in which layer the reaction occurs, i.e., whether addition of hydrazoic acid to the carbonyl group takes place in the organic phase or in the conc. sulphuric acid phase, the relative solubilities of camphor in chloroform and in sulphuric acid were determined as follows. Camphor was stirred in a mixture of excess chloroform and excess sulphuric acid (98%). The two layers were separated and the amount of camphor was determined in the chloroform layer. The conc. sulphuric acid was then diluted with water and camphor was extracted with chloroform. The aqueous layer was then made basic with sodium hydroxide solution and further extrated. The results of this work are shown in Table 21 below:

TABLE 21. SOLUBILITY OF CAMPHOR IN CHLOROFORM AND CONC. SULPHURIC ACID.

Ratio[a] of Camphor:$CHCl_3$: H_2SO_4 (98%)	Stirring time[b] (h) at 45°C	Stirring time[b] (h) at Rt	%recovery from conc. acid layer ($CHCl_3$ layer)	%recovery from dil. acid layer	%recovery from basified aq. layer	%loss[c]
3.04g:60ml:10ml	0.3	20	8	86	-	6
" " "	0.7	3	6	88	-	6

a = These ratios are the same as the corresponding ratios during the Schmidt reaction. b = The stirring time was approximately that normally followed during the Schmidt reaction. c = Loss may be due to solubility of camphor in water or its sublimation on rotary evaporator.

These results indicate that most of the camphor stays in the sulphuric acid (98%) phase, probably in the protonated form, during the Schmidt reaction. The average value of the 'distribution ratio', n, for camphor in sulphuric acid and chloroform under these particular conditions is therefore:

$$n = \frac{(\text{camphor})_s}{(\text{camphor})_c} = \frac{87}{7} = 12.4 \qquad \text{eqn } 35$$

(The numbers 87 and 7, used in equation 35, are the average values from Table 21)

where $(camphor)_s$ = total amount of camphor in sulphuric acid (98%), and $(camphor)_c$ = total amount of camphor in chloroform. Bak and Prestgard (41) have determined the distribution constants n and f (eqn 36 and eqn 37) for hydrazoic acid (HN_3) in sulphuric acid and chloroform to be constant and f = n = 1 over the range 25-40% sulphuric acid. A sharp change in the distribution constant f was observed only in 78-85% sulphuric acid. In 85% sulphuric acid the value of f was found to be 20. This change was believed to be due to the protonation of hydrazoic acid.

$$n = \frac{[HN_3]_s}{[HN_3]_c} \qquad \text{eqn 36}$$

$$f = \frac{[HN_3]_s[H_2N_3^+]_s}{[HN_3]_c} \qquad \text{eqn 37}$$

The hydrazoic acid, therefore, stays in the sulphuric acid phase if it is distributed in a mixture of chloroform and sulphuric acid (78%).

It appears, therefore, that the Schmidt reaction on camphor takes place mostly in the sulphuric acid (98%) phase. However, there is also the possibility of this reaction taking place at the interface of the two phases if one of the reactants tends to stay in the chloroform layer.

In cases when temperature of the Schmidt reaction was controlled in an ice bath, about 10% unreacted camphor was recovered with chloroform from the reaction mixture containing 98% sulphuric acid. But when this reaction mixture, i.e., conc. sulphuric acid, was diluted about 51% unreacted camphor was recovered with chloroform. These results indicate that the reaction of hydrazoic acid with

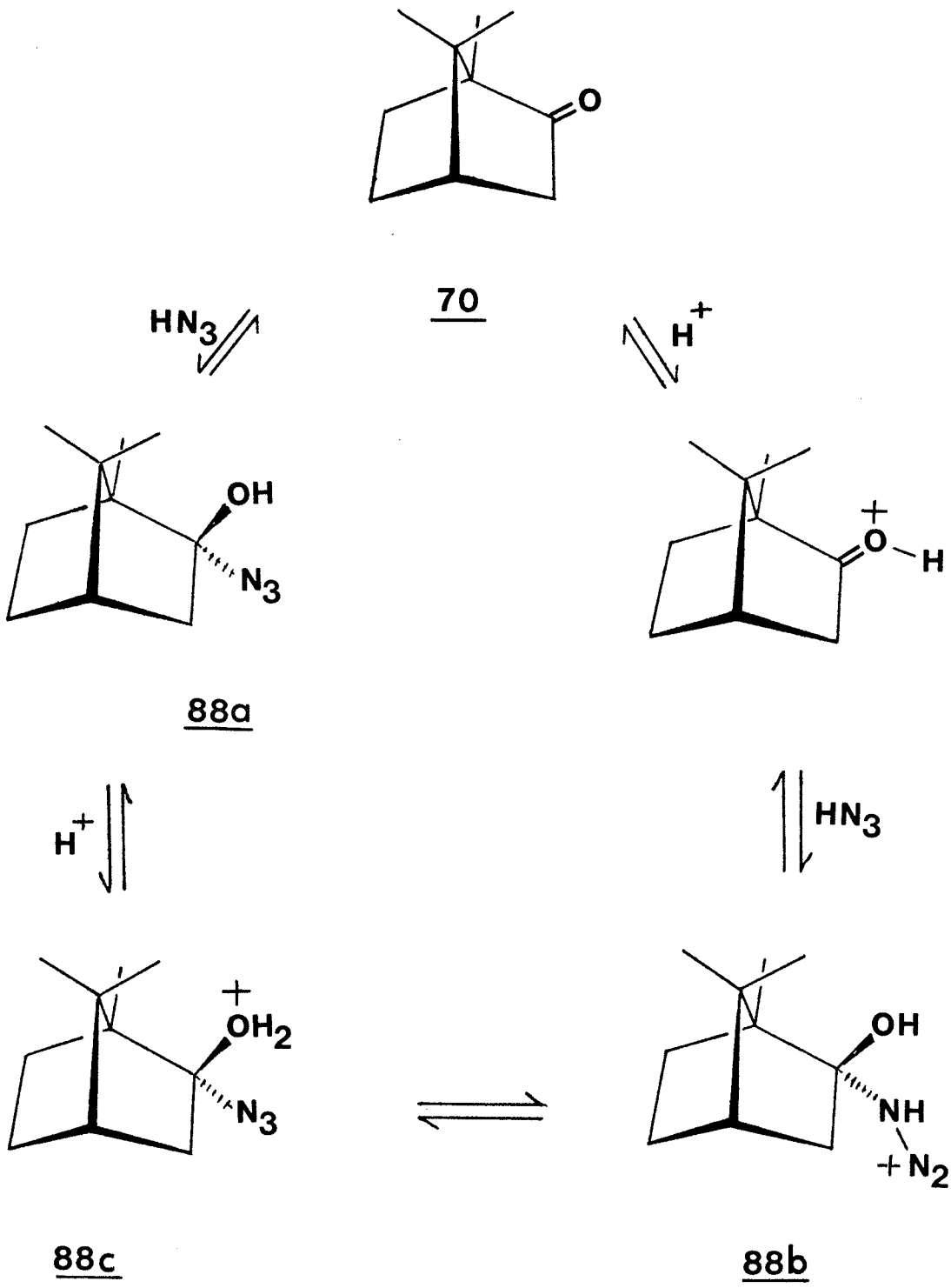
camphor in the presence of sulphuric acid is slower at lower temperatures.

Presumably higher temperatures are required for one or more of the following steps in order to drive the reaction in the forward direction: (a) Addition of hydrazoic acid to camphor (see Scheme 13a). (b) Direct rearrangement of the hydroazidohydrin 88a-c produced in step a. (c) Dehydration of 88c. (d) Fragmentation of 88b (see later). It is not possible at this stage to determine the rate determining step or the location of the primary equilibrium. Smith has suggested that the dehydration of hydroazidohydrins to the iminodiazonium ions is reversible (3). However, the direct rearrangement of hydroazidohydrin to one or both of the lactams (i.e., the bridgehead-carbon migrated lactam 73 or the methylene-carbon migrated lactam 71), and the fragmentation of the bicyclic ring system would be irreversible processes because both processes involve the concerted elimination of nitrogen.

The substantial recovery (86-88%) of camphor with chloroform from the diluted sulphuric acid layers suggests that camphor, at this dilution, is mostly unprotonated. This behavour also explains some of the results of Fikes and Shechter (see Introduction, Table 2) where large amounts of unreacted ketones were recovered when 50% sulphuric acid was employed during the Schmidt reaction on alkyl cyclopropyl ketones. Fikes and Shechter (34) did not explain this observation. However, they obtained 88 to 100% crude products when 83% sulphuric acid was used.

After characterization of the products 71, 75, 83 and 84 the simultaneous action of five mechanisms is suggested to explain the

formation of these products during the Schmidt reaction on camphor. The first step of the reaction is believed to be the addition of one mole of hydrazoic acid to camphor 70 which generates the intermediate hydroazidohydrin 88 (the general term hydroazidohydrin will be used hereafter for 88a-c) (Scheme 13a). Models show that the attack of hydrazoic acid on the carbon atom of the carbonyl group of camphor from the exo face is hindered by the syn-7-methyl. Such a nucleophilic attack at the carbon atom of a carbonyl group requires the attainment of 110° angle of Nu-C=O at the time of attack (79) which is favourable if the attack is from the endo face. On the other hand the attack of hydrazoic acid on the carbon atom of the carbonyl group of norcamphor 29 (53) and that of peracid during the Baeyer-Villiger oxidation of norcamphor (80) and fenchone (64) is believed to take place from the exo face because of the absence of the syn-7-methyl, and so the corresponding exo hydroazidohydrin and hydroxyperester are generated. Based on the relative percent yield of the aminolactam 75, it is inferred that most of the hydroazidohydrin 88 undergoes a cleavage process followed by addition of another mole of hydrazoic acid and cyclization to produce the aminolactam 75. (Experimental support for this suggestion will be presented in Section C). The formation of minor products 71, 83 and 84 from the hydroazidohydrin 88 stage or the next stage (i.e. iminodiazonium ion intermediate) will be discussed in Section B.

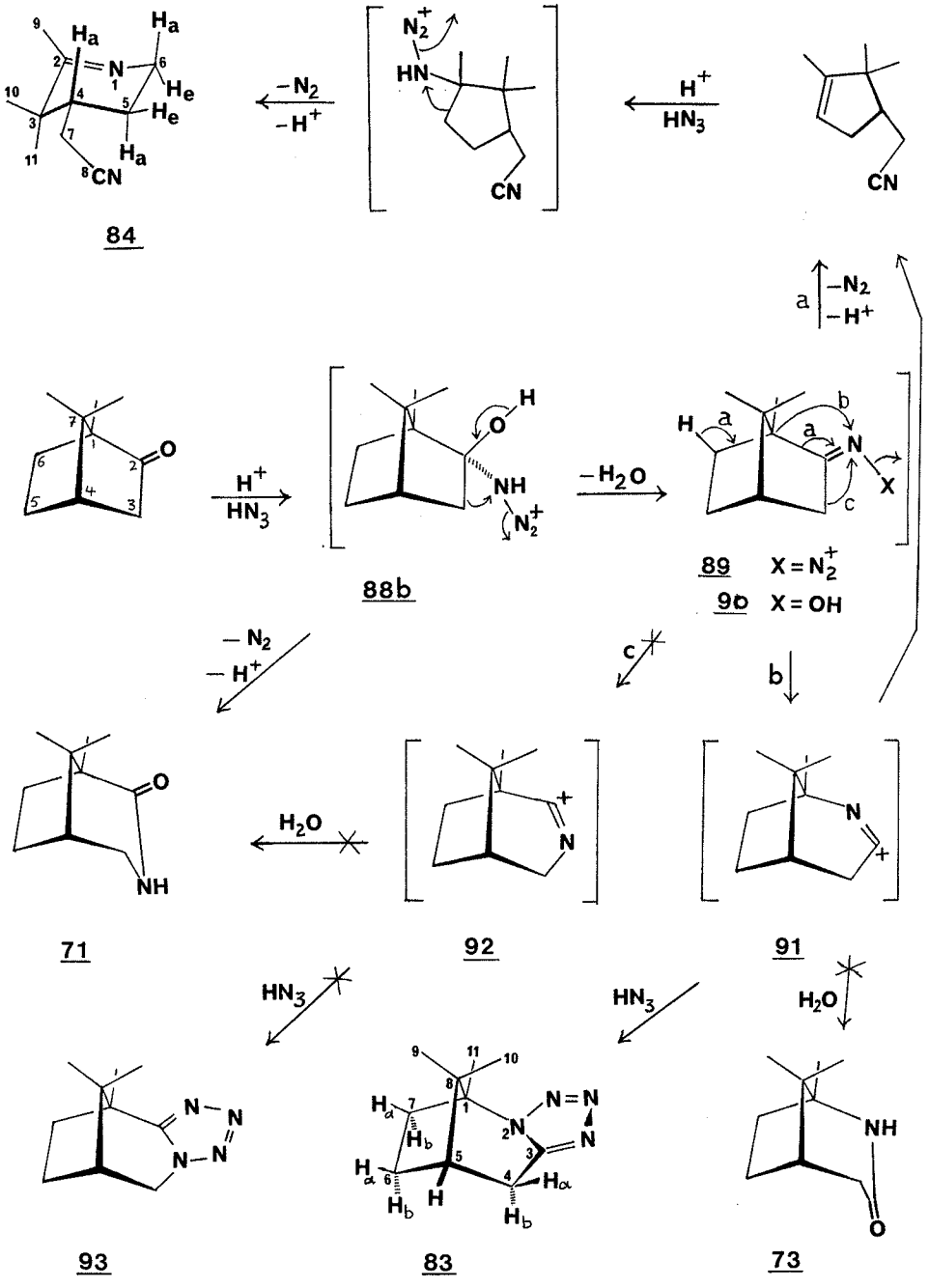


SCHEME 13a

B. ROUTE TO FORMATION OF MINOR PRODUCTS

As mentioned above, most of the hydroazidohydrin 88 undergoes a cleavage process. However, the isolation of compounds 83 and 84 indicates that some of 88 dehydrates thereby generating the iminodiazonium ion 89 (Scheme 13b) which is analogous to the protonated camphor oxime 90. The iminodiazonium ion 89 then rearranges in two ways to produce 83 and 84: (a) Cleavage between the bridgehead-carbon and the imine-carbon leading to α-campholenonitrile (Scheme 13b). [This type of cleavage has been observed for camphor oxime 90 (81), fenchone oxime (82) and the iminodiazonium ion 57 (58a). The α-campholenonitrile then adds one mole of hydrazoic acid to produce the iminonitrile 84 (α-campholenonitrile was not isolated during any of the trials)]. (b) Bridgehead-carbon migration to the nitrogen leading to the intermediate iminium ion 91 (Scheme 13b) which subsequently adds another mole equivalent of hydrazoic acid to yield the tetrazole 83 (45). [The iminium ion 91 can also lead to α-campholenonitrile. This type of cleavage between the bridgehead-carbon and the imine-carbon of the iminium ion has also been suggested for the iminium ion 42 formed by the Schmidt reaction on cis-8-methylhydrindan-1-one 38 (45) (vide supra)].

Roberts et al., (83) established the configuration of camphor oxime as having OH anti to the bridgehead-carbon. For the present argument it is probable that the iminodiazonium ion 89 and the camphor oxime 90 are isosteric (adopt the same configuration), since $-N_2^+$ is bulkier than OH. It is known (29) that iminodiazonium ion


84
$-N_2$
$-H^+$
H^+
HN_3
CN
a
b
c
H^+
HN_3
88b
$-H_2O$
89 X = N_2^+
90 X = OH
$-N_2$
$-H^+$
H_2O
71
92
91
HN_3
HN_3
H_2O
93
83
73

SCHEME 13b

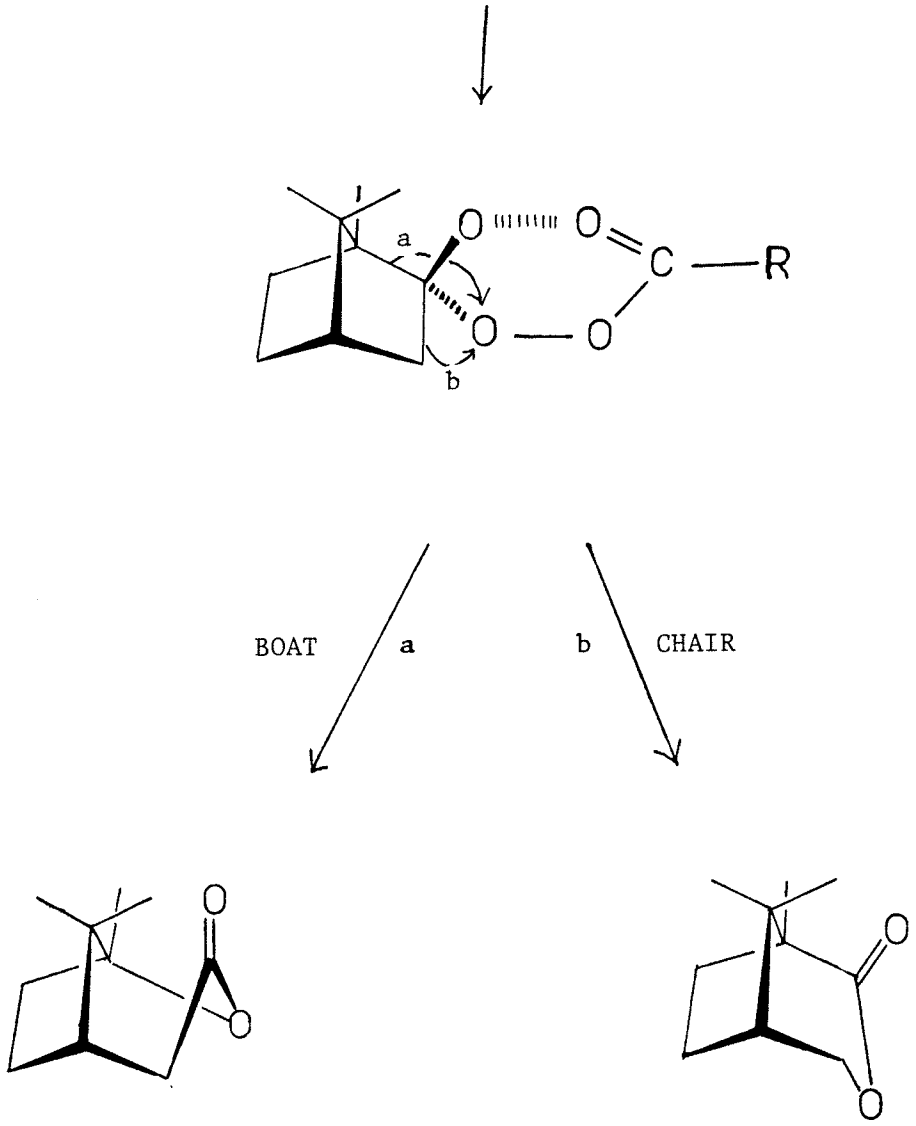
intermediates rearrange according to the rule of anti-migration which also operates in the Beckmann rearrangement. The anti-migration of the bridgehead-carbon to the nitrogen would result in the generation of iminium ion 91 which, in principle, should lead to the 2-azalactam 73 and the camphortetrazole 83. The isolation of 83 and the absence of 73 can be explained by the fact that excess hydrazoic acid present would react very rapidly with the iminium ion 91 yielding the tetrazole 83. It is much less likely that 91 would react with the small amount of water present to produce 73. [It is known (45) that tetrazoles cannot be produced under the Schmidt reaction conditions from the corresponding lactams. Therefore, 83 does not arise from 73]. The same argument can be applied to the iminium ion 92 (Scheme 13b) which would be produced if camphor iminodiazonium ion has the configuration with N_2^+ syn to the bridgehead-carbon. Since the camphortetrazole 93 was not isolated, as its formation would be expected if the iminium ion 92 had formed, the formation of 71 must proceed directly from rearrangement of the hydroazidohydrin 88b. Therefore, it is also suggested that some of the hydroazidohydrin 88b rearranges with methylene migration to nitrogen to produce α-camphidone 71.

Similar to the rearrangement of 88→71, the methylene migration during the rearrangement of other intermediate hydroazidohydrins and the intermediates formed by the attack, from the endo face, of peracids on camphor have been explained considering different factors. Murray, et al., (62), while determining the structure of steroidal D-ring lactones, have tried to identify the steric factors which operate concurrently with the electronic factors in the Baeyer-Villiger oxidation of camphor. They suggested that the

migration of the tertiary bridgehead-carbon involves a higher energy transition state of the boat form, (Scheme 14), while migration of the methylene-carbon involves a lower energy transition state of the chair form. On the same basis, DiMaio and Permutti (45) have suggested that the formation of lactam 37 (see Introduction) would be favoured by the chair transition state obtained during methylene migration. If the relative boat-chair conformational strain energies are a general factor during the rearrangement of intermediates produced in the Baeyer-Villiger reaction and the Schmidt reaction of bicyclo[2.2.1]heptanones, then the formation of α-camphidone 71 from 88b can be explained similarly. As indicated by the arrows in 88b (Scheme 13b), the migration of the methylene group would result in the formation of 71 via a transition state with an energetically favored chair conformation. The bridgehead-carbon migration of 88b to produce 73 (which was not isolated) would occur via a less favorable boat transition state. However, the relative boat-chair conformational strain energies may not be the only factor determining the methylene-carbon migration.

It is considered important to mention other cases which are germane to the subject. Cases have been found in which the migration occurs via transition states that are undoubtedly in the boat conformation. Sauers and Beisler (64) observed methylene migrated products from the Baeyer-Villiger oxidation of syn-7-chloronorcamphor and syn-7-bromonorcamphor. To explain their own results and similar results of earlier work (80,84) they considered forces which might work in opposition to both electronic and boat-form interactions in the transition states. The conformation of the leaving group should

CAMPHOR 70



SCHEME 14

not be an important factor since it can readily attain trans coplanarity with either of the possible migrating groups (85). Sauers and Beisler believed that the extra factor involved in these reactions is associated with the torsional strain caused by the eclipsed nonbonded interactions between the substituents on C_2 and the hydrogens on C_3. On the other hand, nonbonded interactons between substituents on C_2 and the bridgehead-carbon are much less severe since the dihedral angles involved are approximately 44° (H_1 with C_2 exo-substituent) and 79° (H_1 and C_2 endo-substituent). Thus, migration of the C_2-C_3 bond would proceed with considerable relief of eclipsing strain. Sauers and Beisler concluded that migration of the C_2-C_3 bond during the Baeyer-Villiger reactions of bridged bicyclic ketones will always be favored regardless of the substitution or orientation of the hydroxy-perester functions. Such a rationalization explains the observed migraton of the C_2-C_3 bond in fenchone under peracid oxidation conditions. In the case of fenchone, the electronic effects are essentially equal and the competition is between formation of the boat form and relief of torsional strain. The major product (approx. 60%) was the one predicted on the latter basis.

The same arguments could be applied to the case of hydroazidohydrin 88b where there would be torsional strain caused by the eclipsed nonbonded interactions between the substituents on C_2 and the hydrogens on C_3. Migration of the C_2-C_3 bond, yielding 71, would proceed with greater relief of eclipsing strain.

It appears that the two effects of: a) forces due to "the energetically favored chair conformation", and b) the greater relief of torsional strain caused by the eclipsed nonbonded interactions

between substituents on C_2 and C_3, probably operate concurrently in the same direction during the C_2-C_3 bond migration of the hydroazidohydrin 88b.

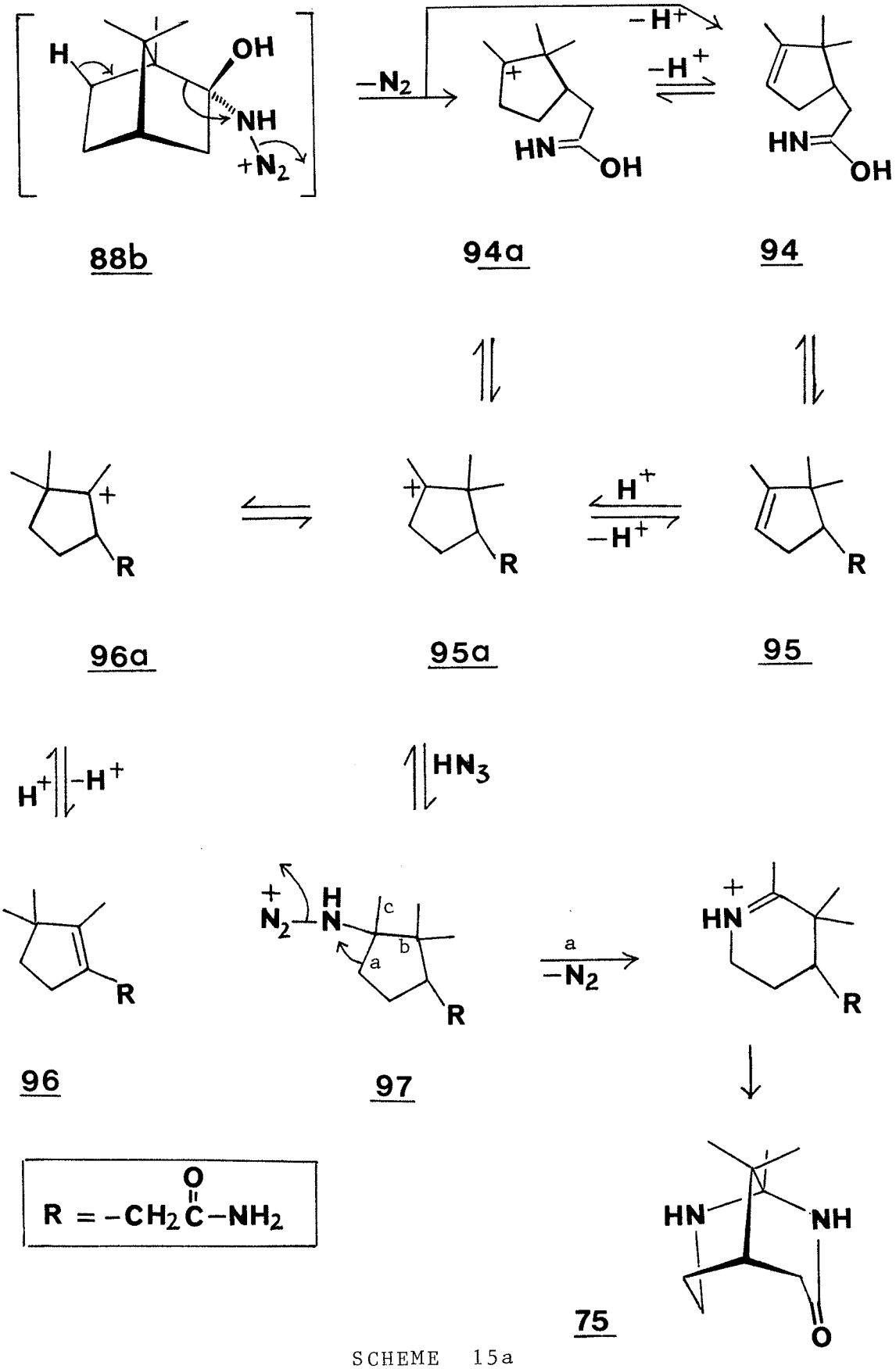
It would be unjustified to try to make any sweeping generalizations about the decisive forces responsible for the migration of either bridgehead-carbon or methylene-carbon during the Schmidt reaction (and also during the peracid oxidations) of bicyclic ketones. The rationalizations made above for the formation of α-camphidone 71 are based only on analogy with the other ring enlargement reactions mentioned above.

C. ROUTE TO FORMATION OF THE MAJOR PRODUCT

(1) General:

The two generally accepted views of the mechanism of the Schmidt reaction on ketones (Scheme 1), i.e., direct rearrangement of hydroazidohydrin or rearrangement of the iminodiazonium ion, can explain the insertion of only one nitrogen atom into a cyclic system. A literature survey reveals that no compound having two nitrogen atoms inserted into the cyclic system as a result of the Schmidt reaction have been reported so far. The formation of the major product 75, having two nitrogen atoms inserted into the bicyclic system of camphor, could not be explained by the existing two views of the Schmidt reaction. Therefore, as mentioned earlier, it is suggested that the hydroazidohydrin 88b undergoes a cleavage process (see arrows in Scheme 15a) resulting in the cleavage product intermediate 94. The intermediate 94 would, probably, exist mostly in its tautomeric form 95. The loss of nitrogen, and that of proton at position-6 from 88b may take place in a concerted manner. It is also possible that initially a bridgehead carbonium ion 94a is generated by the loss of nitrogen and breaking of C_1-C_2 bond. The carbonium ion 94a then immediately leads to the intermediate 94 by the loss of a proton from the alpha position.

The cleavage of hydroazidohydrin intermediate is not a common process during the Schmidt reaction. Krow (86) has quoted that the reaction of camphor oxime with (a) thionyl chloride, (b) sulphuric


H
OH
NH
+N2
−N2
−H+
−H+
HN
OH
HN
OH
88b
94a
94
R
R
R
96a
95a
95
H+
−H+
HN3
R
96
+N2
H
N
c
a
b
R
97
a
−N2
+
HN
R
R = −CH2C(=O)−NH2
HN
NH
O
75

SCHEME 15a

acid, (c) hydroiodic acid, (d) polyphosphoric acid, (e) benzenesulphonyl chloride/sodium hydroxide, (f) phosphorous pentaoxide, (g) by photolysis in methanol, or (h) by pyrolysis, affords no 2-azalactam 73 (but only products derived from initial bridghead cleavage such as nitriles). This behaviour of camphor oxime under the Beckmann rearrangement conditions constrasts sharply with the preference for bridgehead methine migration to 2-azalactam 33 [see Scheme 2 (Introduction)] reliably reported by several workers for the Beckmann rearrangement of norcamphor oxime. Some other bicyclo[2.2.1]heptanones, having bridgehead hydrogen, have been reported (6) to afford either the bridgehead methine migrated lactams or the methylene migrated lactams during the Beckmann rearrangement and the Schmidt reaction respectively. Although it would be difficult to find the exact reasons for the anomalous behaviour of camphor under the Schmidt reaction conditions that were employed in these studies and the Beckmann rearrangement, probably it is the electronic factors caused by the methyl at the bridgehead-carbon which favors the cleavage at the C_1-C_2 bond.

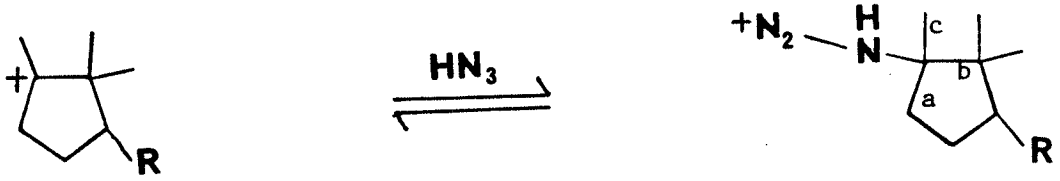
However, let us examine in detail some other rearrangements that could possibly occur if the intermediate 95 (α'-campholenamide) is produced. Intermediate 95 could be protonated at position-4 generating the carbonium ion species 95a. This latter ion could lead to the carbonium ion species 96a via a 1,2-methyl shift which, in turn, could generate the intermediate species 96 (β-campholenamide). Protonation of 96 could generate 96b (Scheme 15b). As shown in Schemes 15a and 15b, there would be rapid scrambling between the various intermediate species. In theory, each of the three carbonium

ion species 95a, 96a and 96b could add one mole of hydrazoic acid generating the intermediate protonated azides 97, 98 and 99 respectively. In the next step, the rearrangement of these protonated azides would occur via loss of nitrogen, migration of one of bonds a, b and c, followed by cyclization involving the amidic nitrogen (Scheme 15c). This rearrangement may take place either in a concerted manner or stepwise. The compounds 74 - 75 and 100a-f that could be formed through the possible routes, as discussed above, are shown in Schemes 15a-c.

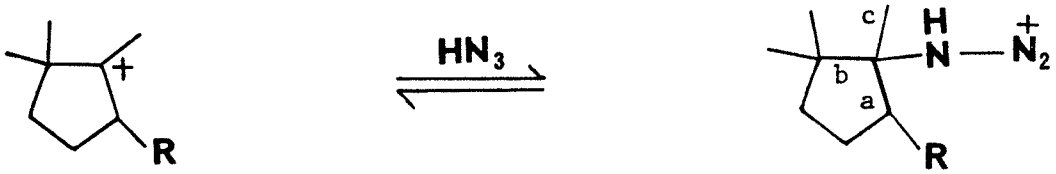
As mentioned earlier, the first task of this project was to assign the structure to the major products of the reaction. Compounds 100a-f were easily eliminated on the basis of infrared and proton nuclear magnetic resonance (60 MHz) spectra because these compounds either have 4- or 5-membered lactam rings or they have N-methyl groups. The work carried out for distinguishing between 74, 75 and 76 was discussed in detail in Part I.

The assignment of structure 75 to the major product of the Schmidt reaction on camphor confirms the involvement of the intermediates 95a and 97 (Scheme 15a). This does not eliminate the generation of intermediate species 95, 96 and 96a-b under the reaction conditions.

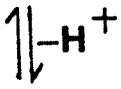
In order to confirm the involvement of intermediates 95, 95a, 96 and 96a-b, compounds 95 and 96 were first prepared, and were then separately subjected to the same Schmidt reaction conditions that were employed in the case of camphor. The results of this work will be discussed in the following sub-sections (2-6).

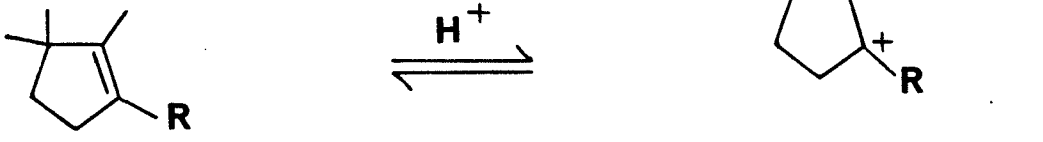


95a 97

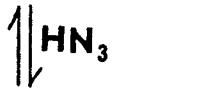


96a 98

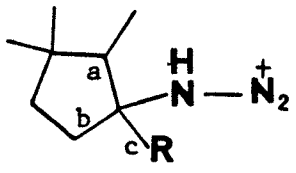




96 96b

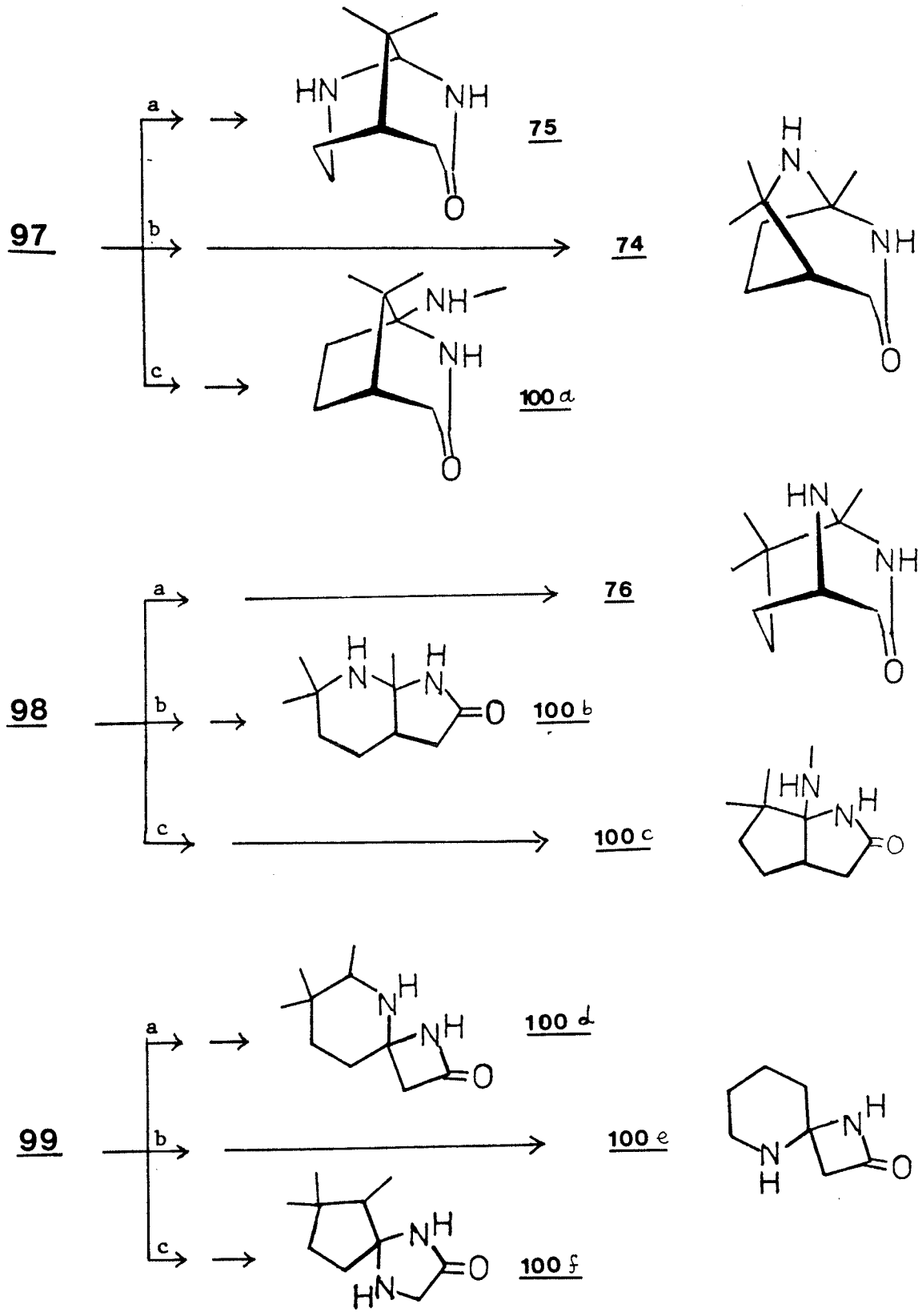


$R = -CH_2-CO-NH_2$



99

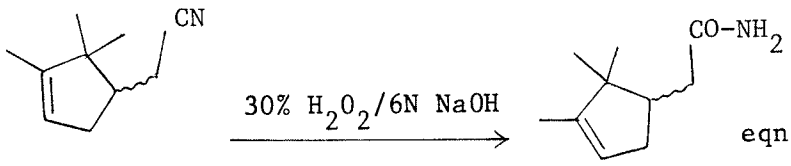
SCHEME 15b



SCHEME 15c

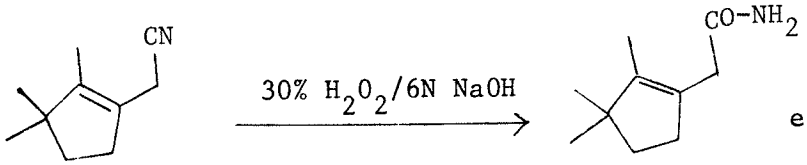
(2) Synthesis of α- and β-campholenamides and α- and β-campholenonitriles

(RS)-α- and β-campholenamides 95 and 96 were prepared, in moderate to high yields, by the oxidation of (RS)-α- and β-campholenonitriles 101 and 102 respectively using 30% hydrogen peroxide/6N sodium hydroxide reagent (87) (see Experimental):



eqn 38

101 95 (88%)



eqn 39

102 96 (47%)

β-campholenamide 96 was also prepared by the rearrangement of camphor oxime 103 using zinc chloride at 110°C (88). For this interesting reaction zinc chloride was freshly dried, as described in the Experimental section and then heated with dry camphor oxime in an

oil bath at exactly 110°C. During three trials, after exactly 10 minutes a vigorous reaction occurred with the evolution of white fumes and the solid mixture became liquid. β-Campholenamide was isolated in 20% yield. However, the major product of this reaction was β-campholenonitrile 102 (66% yield).

(1R)-(-)-α-campholenamide 104 was prepared in 69% yield by the reaction of (IR)-(+)-α-campholenonitrile 105 with 30% hydrogen peroxide/6N sodium hydroxide. After repeated crystallization the melting point of this product was 130-131°C compared to mp 109-112°C of racemic α-campholenamide. The specific rotation $[\alpha]_D^{22}$ was found to be -3.4°(c = 7.1 abs. ethanol); [the literature value is $[\alpha]_D$ = -4.1° in ethanol].

(IR)-(+)-α-campholenonitrile 105 was prepared in quantitative yield by the reaction of acetyl chloride with l-camphor oxime 103a; bp 56°C (0.8 mm Hg). The specific rotation $[\alpha]_D^{22}$ was found to be + 10.4°; [the literature value is $[\alpha]_D$ = + 7.5°].

(RS)-α-campholenonitrile 101 was prepared by the same procedure from dl-camphor oxime 103b; 96% yield; bp 74°C (0.9 mm Hg).

β-campholenonitrile 102 was prepared in good yield by the isomerization of α-campholenonitrile using conc. hydrochloric acid as a catalyst at 48°C. Compound 101 could not be isomerized to 102 when p-toluenesulphonic acid in toluene solution was used as a catalyst.

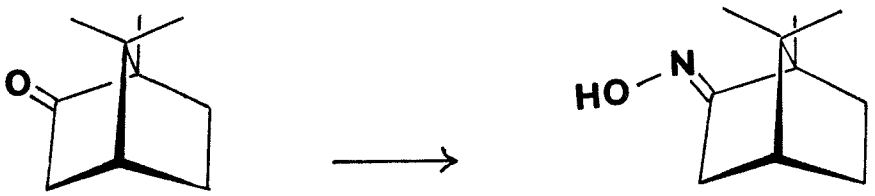
l-Camphor oxime 103a was prepared by heating an ethanol solution of d-camphor 106, hydroxylamine hydrochloride and pyridine; yields were 98-99%; mp 118-120°C; $[\alpha]_D^{26}$ = - 40.7° [C = 9.8, abs. ethanol]. The literature value is $[\alpha]_D^{25}$ = -42.5°[c = 10, abs. ethanol]. The

dl-camphor oxime 103b was prepared by the same procedure from dl-camphor (98-99% yields); mp. 118-120°C.

The detailed analyses of the above mentioned compounds 95, 96, 101, 102, 103a,b, 104, 105 are given in the Experimental Section. Scheme 16 shows the syntheses of these compounds.

(3) Preparation of aminolactam 75 from α- and β-campholenamides

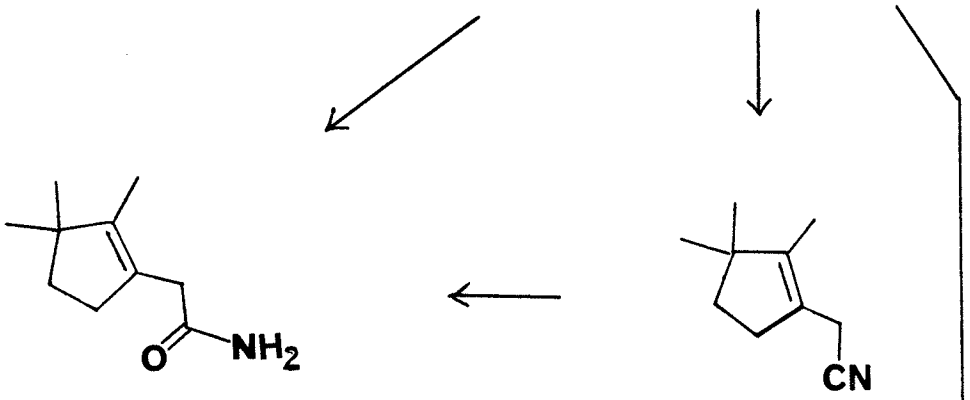
As shown in Schemes15a and 15b, α- and β-campholenamides 95 and 96 are believed to be transient intermediates during the formation of aminolactam 75 from camphor by the Schmidt reaction. If this mechanism is correct, it should be possible to prepare aminolactam 75 directly from 95 and 96 under the same reaction conditions as used for camphor. During one pair of trials when conc. sulphuric acid was added to a chloroform solution of either α- or β-campholenamide (0.006 mol) and sodium azide (0.013 mol), and worked up in usual way aminolactam 75 was obtained in 73% and 72% yields respectively. During another pair of trials under identical conditions of reaction and workup (see Experimental) aminolactam 75 was obtained in 66% yield from α-campholenamide and in 65% yield from β-campholenamide. The course of this reaction can be followed from Schemes 15a and 15b. The yields of aminolactam 75 from α- and β-campholenamides (95 and 96) are about twice as much as those from camphor under the identical conditions of the Schmidt reaction. Further, it should be noted that no other products were isolated from the Schmidt reaction on α- and β-campholenamides. If it is assumed



106 , d-Camphor

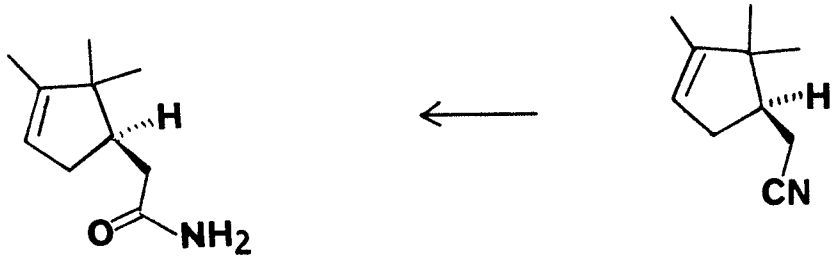
103a , l-Camphor oxime

103b , dl- " "



96

102



104 , (R)-Isomer

[**95** , When (RS)-]

105 , (R)-Isomer

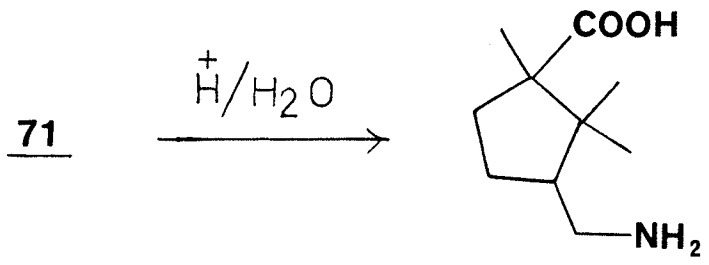
[**101** , When (RS)-]

SCHEME 16

that the best yield of aminolactam 75 from α- or β-campholenamides is 73%, then based on the best yield (42%) of 75 from camphor it can be roughly calculated that only 57% of hydroazidohydrin 88b converts into 95 (assuming there is 100% extraction of 75 from the reaction mixture (vida infra). These results indicate that approximately 40-45% of hydroazidohydrin 88b converts into (a) iminodiazonium ion (89, Scheme 13b) or, (b) 3-azalactam 71 via direct rearrangement. However, the total yield of the products 71, 83 and 84 (i.e., other than aminolactam 75) is 5.3% + 1% + 1% = 7.3%. The obvious question is to what does the rest of the hydroazidohydrin 88 lead?

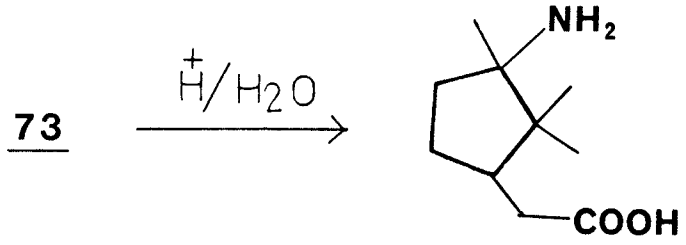
Although at present it can not be said with certainty, it is very likely that some amount of the 3-azalactam 71 may hydrolyse to the β-amino acid 107 (eqn 40). Although 2-azalactam 73 was not isolated at all, its formation either from hydroazidohydrin 88b or, more likely, from the iminodiazonium ion 89 is also possible. If 73 is formed it could hydrolyse to the β-amino acid 108 (eqn 41). β-Amino acids 107 and 108 would be highly soluble in both dilute aqueous acidic and basic mediums.

The preparation of the aminolactam 75 from campholenamides 95 and 96 confirms that the interconversions 95 $\rightleftharpoons$ 95a $\rightleftharpoons$ 96a $\rightleftharpoons$ 96 are reversible processes as shown in Schemes 15a and 15b.



107

eqn 40



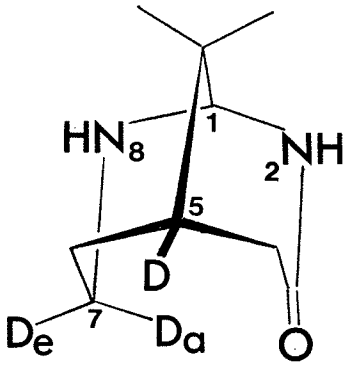
108

eqn 41

(4) Preparation of deuterated aminolactams in D_2SO_4 from α- and β-camphoelnamides and camphor:

It can be seen from Schemes 15a and 15b that if the interconversions of 95, 95a, 96a and 96 are indeed reversible processes then the Schmidt reaction in conc. sulphuric acid-d_2 should yield the aminolactam 109 (eqn 42) having deuterium incorporated at positions-5, 7a and 7e. In order to confirm this proposal the Schmidt reaction was carried out separately with α-campholenamide 95, β-campholenamide 96 and d-camphor in sulphuric acid-d_2 98% solution in D_2O, 99.5 + atoms % D. The deuterated aminolactams 109a-c were obtained from these reactions (eqn 42) in the same range of yield as that when conc. H_2SO_4 was employed with the same compounds. The melting point and infrared spectra of 109a-c were essentially the same as those of 75. The infrared spectra of 109a-c in addition showed absorptions for C-D_2 stretch at 2185 cm^{-1} and C-D stretch at 2060 cm^{-1}. The results from the proton nuclear magnetic resonance (400 MHz) spectra of 109a-c are summerized below (the chemical shifts for the peaks discussed below are the same as given in Table 8 for 75).

(a) The sharp multiplets for H_{7a}, H_{7e} and H_5, that were observed in the proton nuclear magnetic resonance (400 MHz) spectrum of undeuterated aminolactam 75, are absent in these spectra of 109a-c. Instead at the same positions there are lower integrating broad multiplets. The integration will be discussed later.



$2\ NaN_3$

$CHCl_3$

CONC. D_2SO_4

α – CAMPHOLENAMIDE ⟶ **109a**

β – CAMPHOLENAMIDE ⟶ // **109b**

d – CAMPHOR ⟶ // **109c**

EQUATION 42

(b) Three singlets are observed for the three methyls and are identical to those observed for 75. In addition, there are three multiplets at the same positions which are believed to be due to CH_2D and CHD_2 groups. The groups CH_2D and CHD_2 are formed more likely by the reversible processes shown in equation 43. However, the three multiplets due to CH_2D and CHD_2 in the spectrum of 109b are very weak. The three singlets due to the three CH_3 groups and the three multiplets due to three CH_2D and CHD_2 groups could not be integrated separately.

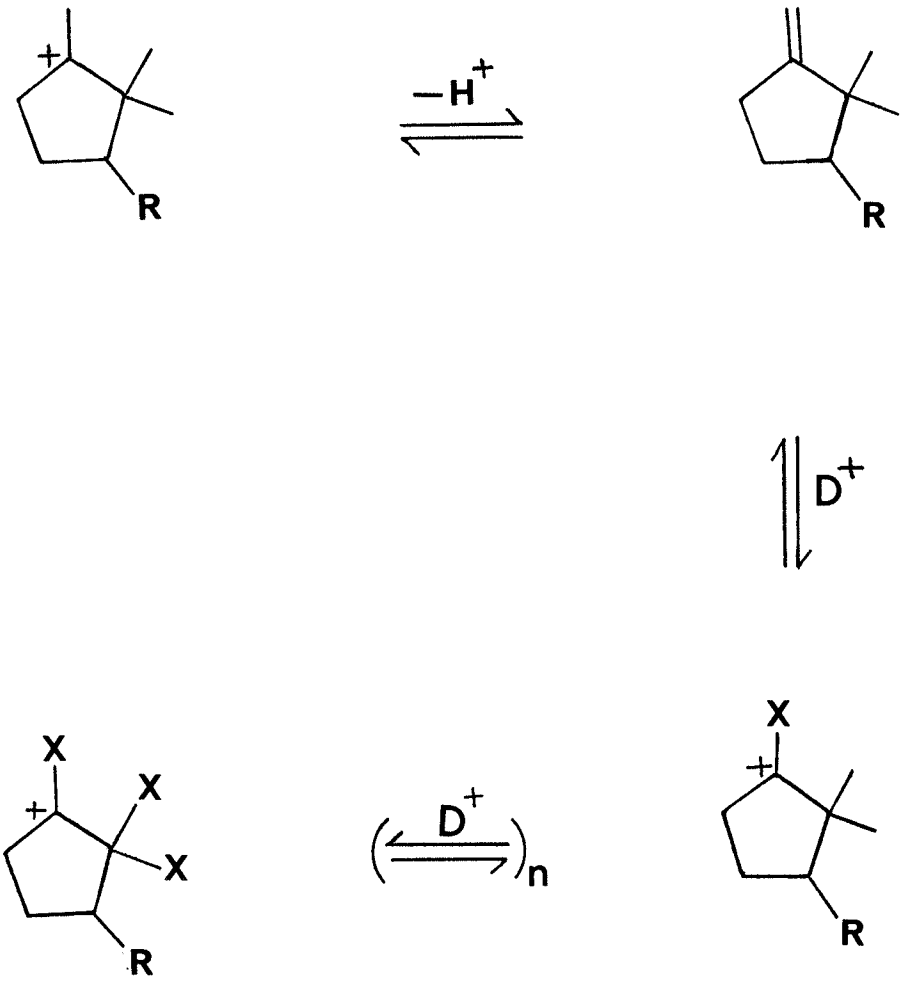
(c) The spectra of 109b and 109c show H_{6a} as double doublet [$^2J(6a,6e)$ = -13 Hz, $^4J(6a,4a)$ 1.5 Hz] and H_{4a} as double doublet [$^2J(4a,4e)$ = -18.5 Hz, $^4J(4a,6a)$ 1.5 Hz]. The spectrum of 109a shows H_{6a} as a broad doublet [$^2J(6a,6e)$ = -13 Hz] and H_{4a} as a broad doublet [$^2J(4a,4e)$ = -18.5 Hz]; the long range couplings between H_{6a} and H_{4a} could not be resolved.

(d) The H_{4e} protons are observed as doublet [$^2J(4e,4a)$ = -18.5 Hz] in all cases (109a-c).

(e) The H_{6e} proton is overlapped by N_8-H and by the methyls. The N_2-H and N_8-H protons are observed as broad peaks (identical to those in the 75).

(f) The overlapped deuterium decoupled-^1H spectra and proton decoupled-^2H spectra (see Figures 8,9,10) show ^2H-peaks at positions 7a, 7e and 5 for all compounds (109a-c) and at the positions of the three methyls for only 109a and 109c. In other words, these spectra do not show ^2H-peaks at positions 6a, 6e, 4a, 4e, N_8-H and N_2-H for all compounds (109a-c) and at positions of the three methyls for 109b.

$R = CH_2\text{-}CO\text{-}NH_2$, $X = CH_3$, CH_2D , CHD_2



EQUATION 43

The extent of deuterium incorporation at positions 7a, 7e, 5 and the three methyls of 109a-c is shown in Table 22 below.

TABLE 22. THE PERCENTAGE OF DEUTERIUM INCORPORATION AT POSITIONS-7a,7e,5 AND METHYLS OF THE DEUTERATED AMINOLACTAMS 109a-c

Compound	% at 7a		% at 7e		% at 5		% at methyls	
	^{1}H a	^{2}H b	^{1}H a	^{2}H b	^{1}H a	^{2}H b	^{1}H a	^{2}H b
109a	11.5	88.5	10	90	15	85	88.5	11.5
109b	35	65	24	76	25	75	100	0
109c	24	76	17	83	31	69	91	9

a = The percentage of ^{1}H was determined by averaging the measured integration of 3 ^{1}H-spectra (400 MHz) for each compound.

b = The percentage of ^{2}H was calculated by the difference of percentage of ^{1}H

The proton nuclear magnetic resonance (400 MHz) spectra of compounds 109a, 109b and 109c are given in Figures 8, 9 and 10 respectively; the chemical shifts are essentially the same as those given in Table 8 for undeuterated amino lactam 75 because all spectra were run in CD_2Cl_2.

The different percentages of deuterium incorporation given in Table 22 need to be discussed.

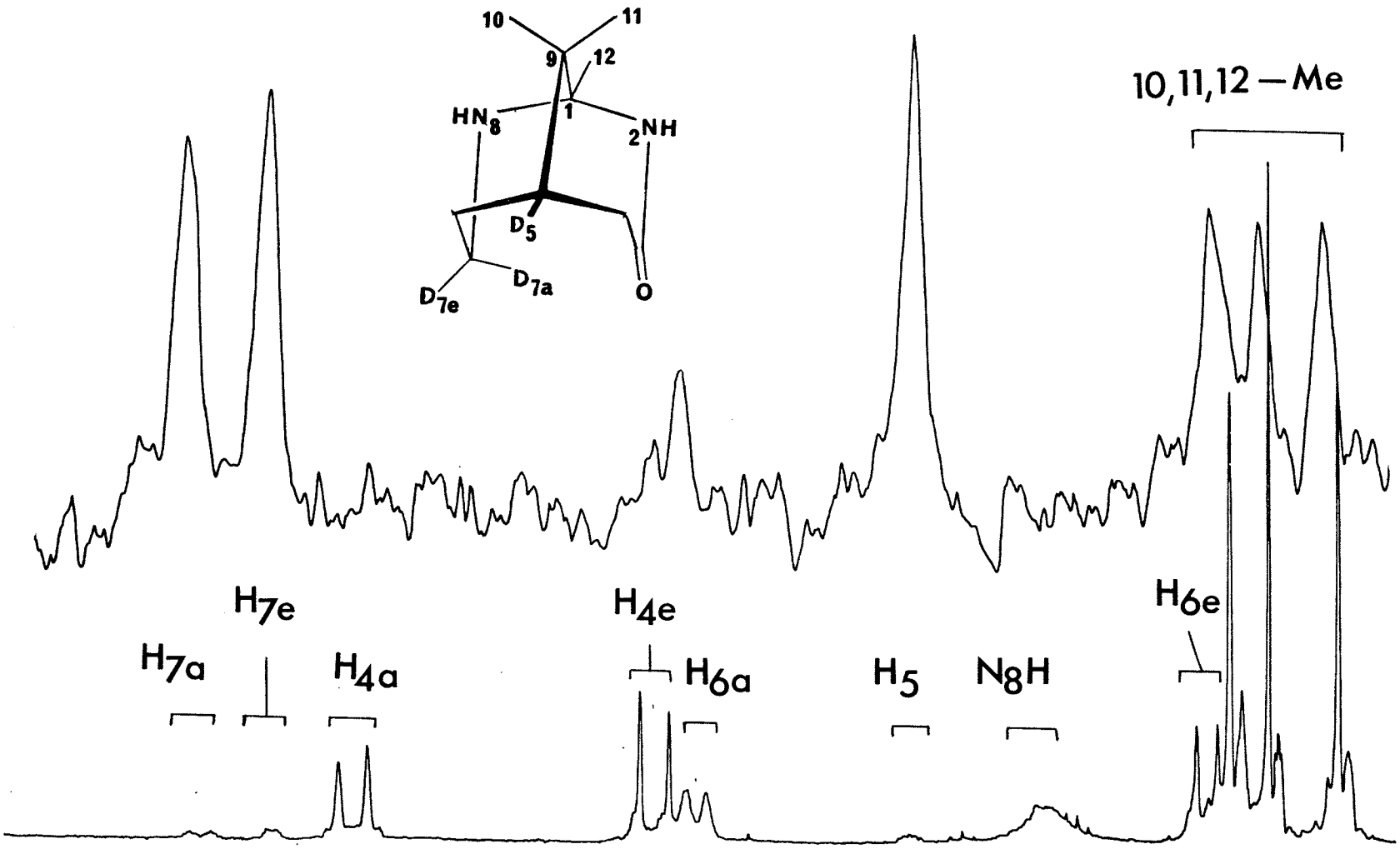


FIGURE 8. Top: $^{2}H\left[^{1}H\right]$-nmr spectrum, bottom: ^{1}H-nmr spectrum of deuterated aminolactam 109a .

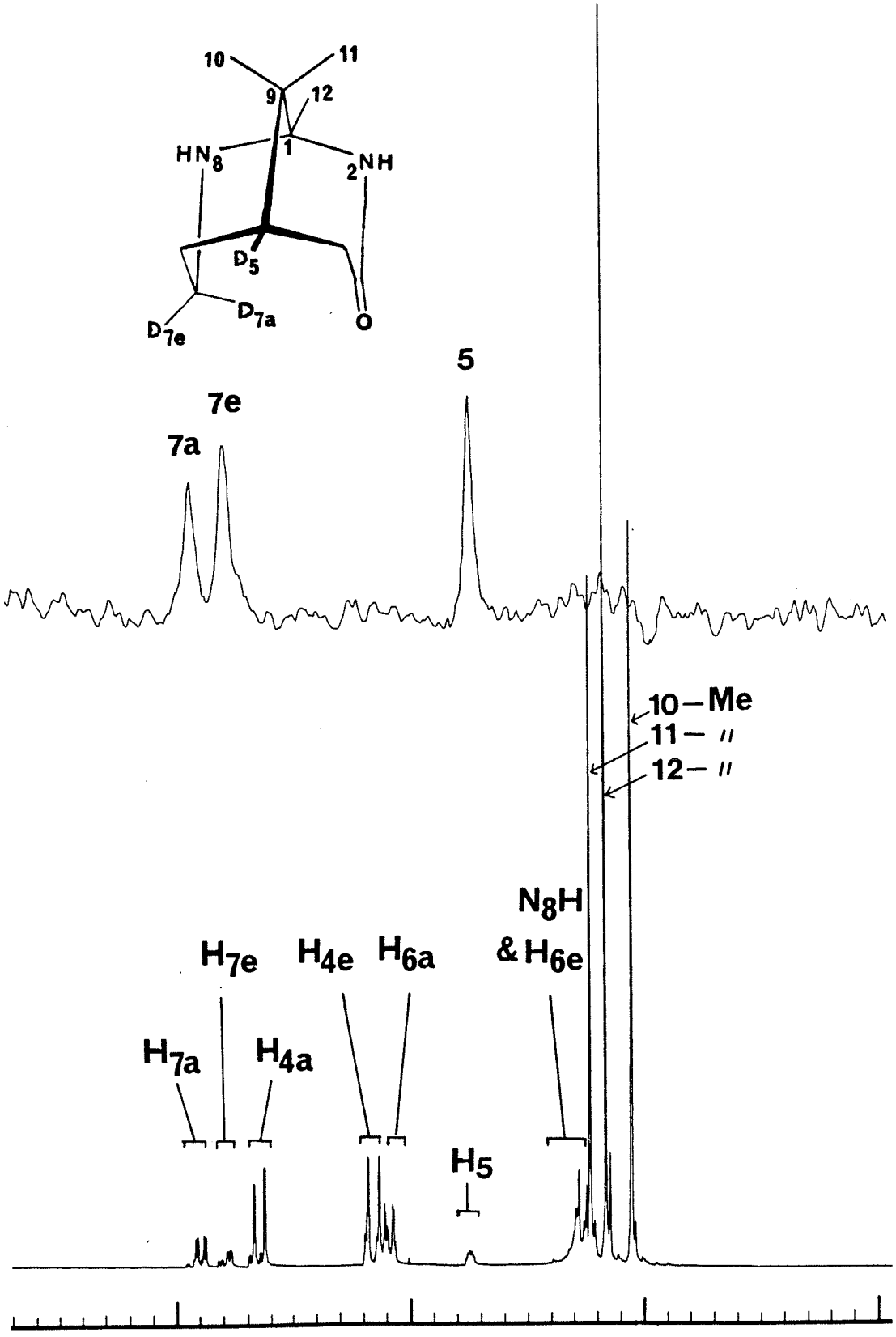


FIGURE 9. Top: $^{2}H[^{1}H]$-nmr spectrum, bottom: ^{1}H-nmr spectrum of deuterated aminolactam 109b .

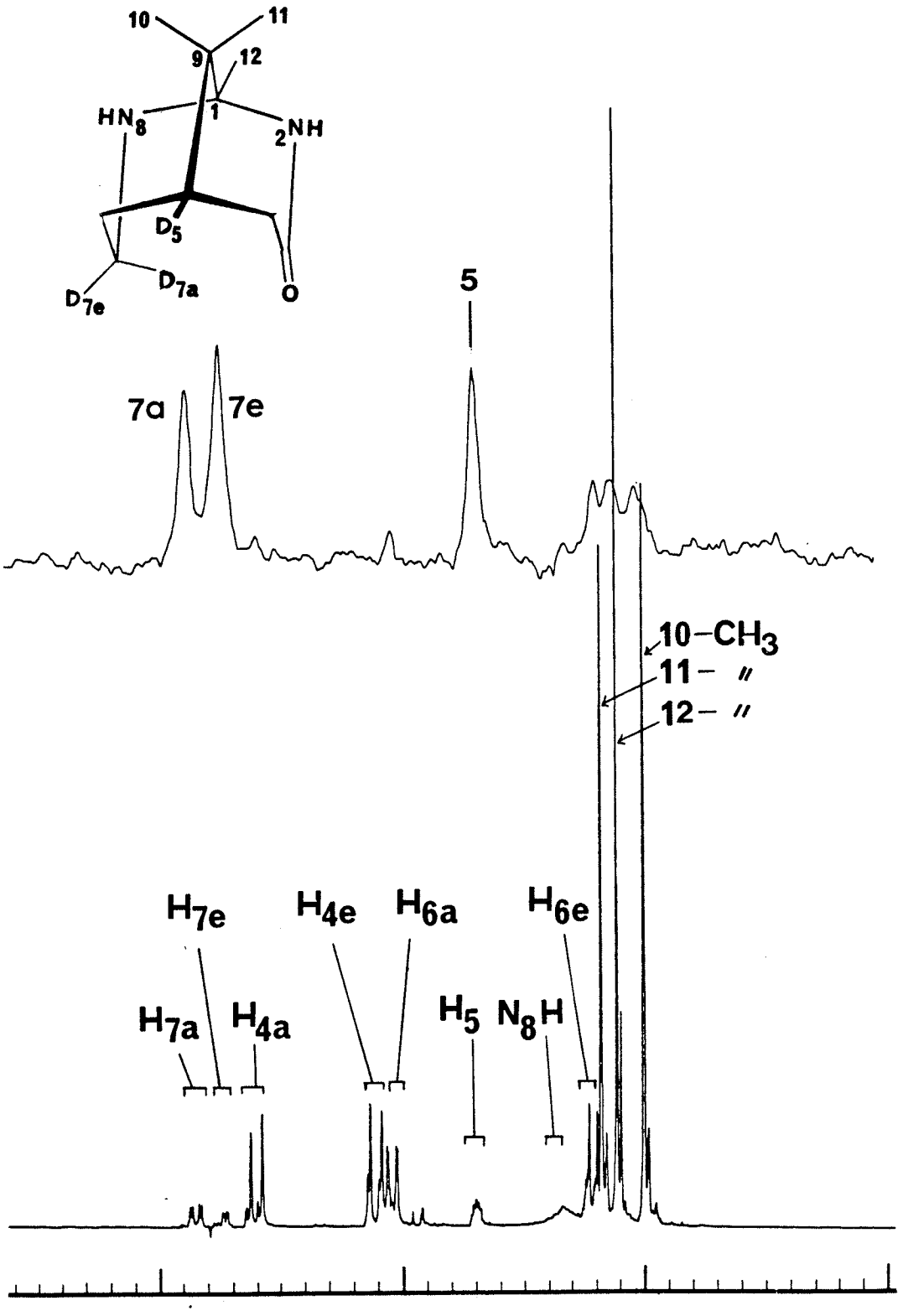


FIGURE 10. Top: $^{2}H[^{1}H]$-nmr spectrum, bottom: ^{1}H- nmr spectrum of deuterated aminolactam 109c .

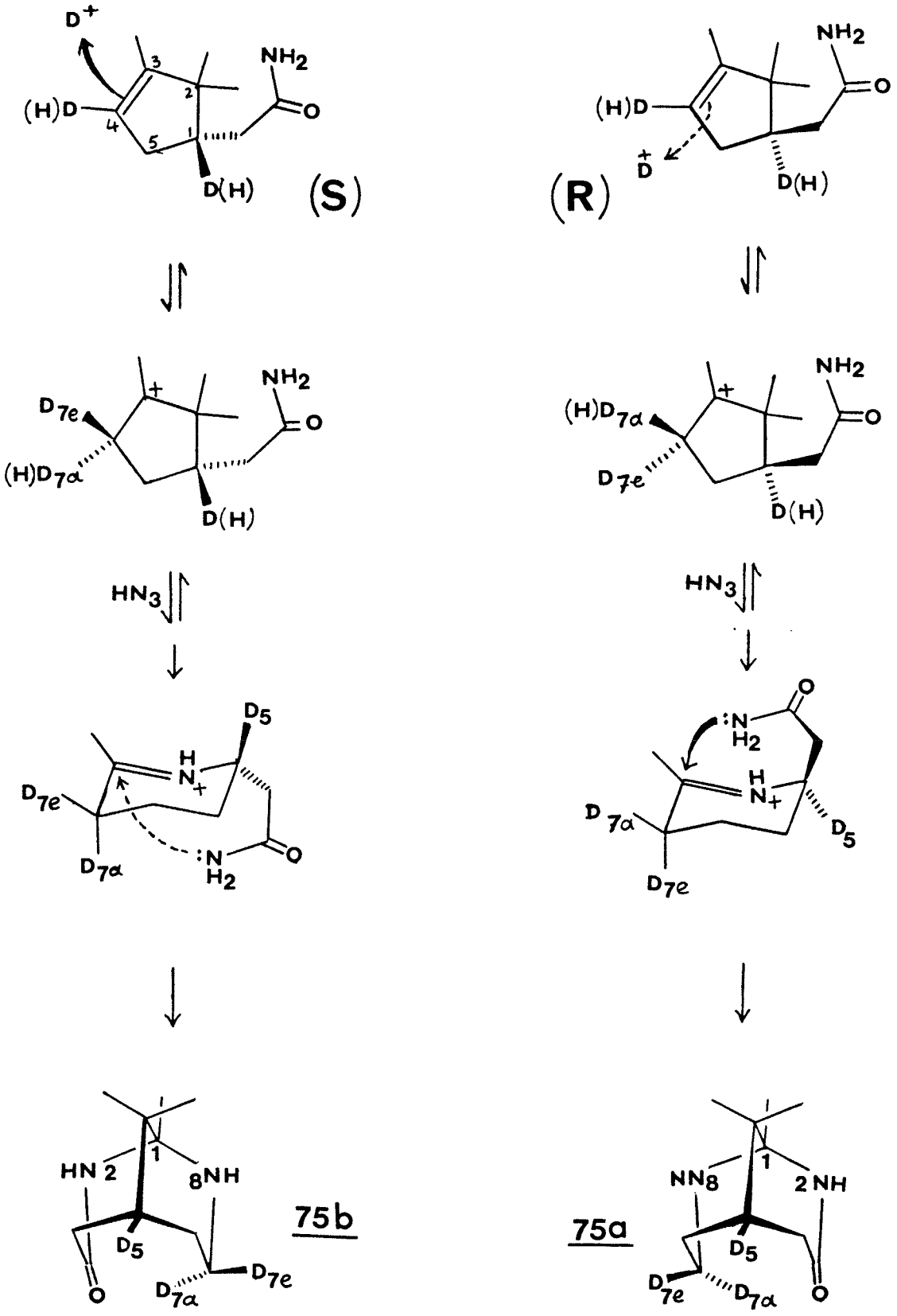
(a) The percentage of deuterium at positions-7e is more than that at the geminal position-7a of 109a-c. This is expected according to Scheme 17 wherein it can be seen that the electrophilic attack of deuterium on the double bond at position-4 of the ∝-campholenamide will take place more readily from the less hindered side, i.e., anti to the acetamido group; (position-4 of the ∝-campholenamide becomes position-7 in the aminolactam).

(b) In the aminolactams 109a and 109c the percentage of deuterium at position-5 is less than each of the percentage at positions-7a and 7e. This result would be expected according to Scheme 15a and Scheme 18 if the ratio of k_4/k_3 is larger than the ratio of k_5/k_6 and the value of k_4 is larger than that of k_3:

$$\underline{95} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \underline{95a} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \underline{96a} \underset{k_6}{\overset{k_5}{\rightleftharpoons}} \underline{96}$$

Scheme 18

c) According to Scheme 15a, the percentage of deuterium at position-5 in 109b should be more than that at each of the positions 7a and 7e. Table 22 shows that the percentage of deuterium at position-5 in 109b is more than that at position 7a, but approximately the same as that at position 7e. The approximately equal percentage of deuterium at positions 7e and 5 again suggests that the ratio of k_4/k_3 is larger than the ratio of k_5/k_6 and that the value of k_4 is larger than that of k_3. The validity of this



SCHEME 17

statement has been proved by the attack of HN_3 at the 95a carbonium ion which leads to the assigned aminolactam 75. So far, during repeated trials, no other aminolactam(s) were isolated which would arise by the attack of HN_3 at the 96a carbonium ion. The approximately equal percentage at positions 7e and 5 also suggest that k_1 and k_2 could be almost equal.

It should be noted that the above conclusions about the rate constants are made from the three compounds 109a-c which were each prepared only once. Identical results from several (2) samples of each compound would lay better grounds for any conclusion.

(d) The lack of incorporation of deuterium in the three methyls of 109b, an anaomalous result, cannot be explained at present.

The relatively higher percentage of deuterium at positions 7a, 7e and 5 in the aminolactam 109a, compared to the relatively lower percentage at the corresponding positions in 109b and 109c, is probably due to the following facts. The D_2SO_4 (98% solution in D_2O, 99.5% + atoms %D) used in the preparation of 109a was taken from a freshly opened bottle while D_2SO_4 used for the preparation of 109b and 109c was taken from the same bottle which had been repeatedly exposed to air over several months before, usage, and therefore, it could have absorbed moisture from the air.

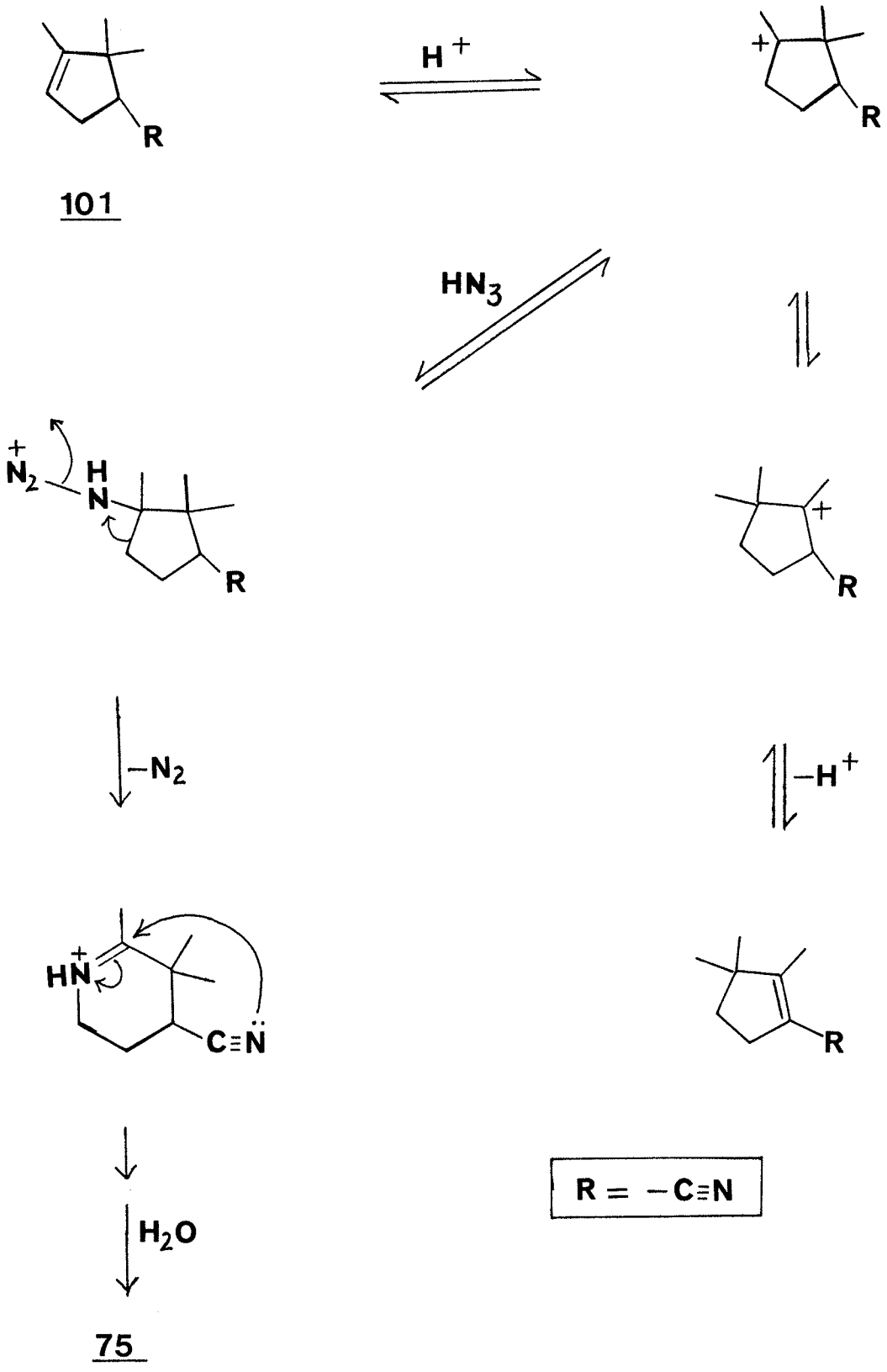
(5) Preparation of aminolactam 75 from α-campholenonitrile 101

Aminolactam 75 was prepared in 20% yield from α-campholenonitrile 101 under the same Schmidt reaction conditions as used for camphor

and the campholenamides. The lower yields of 75 in this case as compared to the 70% yields from α- and β-campholenamides and 42% yields from camphor suggest that α-campholenonitrile is not involved as a major intermediate in the conversion of camphor to aminolactam 75. It was already suggested (Part-IIB) that some of the iminodiazonium ion 89 or the iminium cation 91 (Scheme 13b) cleaves in order to yield α-campholenonitrile which subsequently adds another mole of HN_3 to produce the imino-nitrile 84 in 1% yield. These results do not exclude the possbility that a very small amount of aminolactam 75 is formed from camphor via α-campholenonitrile. However, as proved earlier, based on the yields of 75 from camphor, α-campholenonitrile, α- and β-campholenamides it can be safely concluded that the latter two are the major intermediates involved during the Schmidt reaction on camphor.

The route of formation of aminolactam 75 from 101 is shown in Scheme 19.

An oily compound (45 mg, 2%) was also isolated from the Schmidt reaction on α-campholenonitrile. The infrared spectrum of this compound showed absorptions for N-H stretch at 3330 cm^{-1}(m), C$\equiv$N stretch at 2200 cm^{-1}(s), C=N stretch at 1640 cm^{-1}(m). The mass spectrum showed the molecular ion peak at m/z 179 (66%). The proton nuclear magnetic resonance (60 MHz) spectrum showed, beside other peaks: a ddd at δ 3.80 - 3.53 (1H)[J values being 9.5 Hz, 5.5 Hz and 2 Hz] which is assigned to the proton H-C-N=C or the proton at the carbon alpha to an amine (H-C-N-C); sharp multiplets at δ 3.32 - 2.90 (3Hs) assigned to the proton H-C-N=C or H-C-N-C plus two protons



SCHEME 19

H_2C-C≡N; and three singlets at δ 1.30 (3Hs), δ 1.16(3Hs) and δ 1.00(3Hs). At present the structure 110 was tentatively assigned to this product. It may exist in form 110a or 110b. The formation of 110 probably follows the route as shown in Scheme 20.

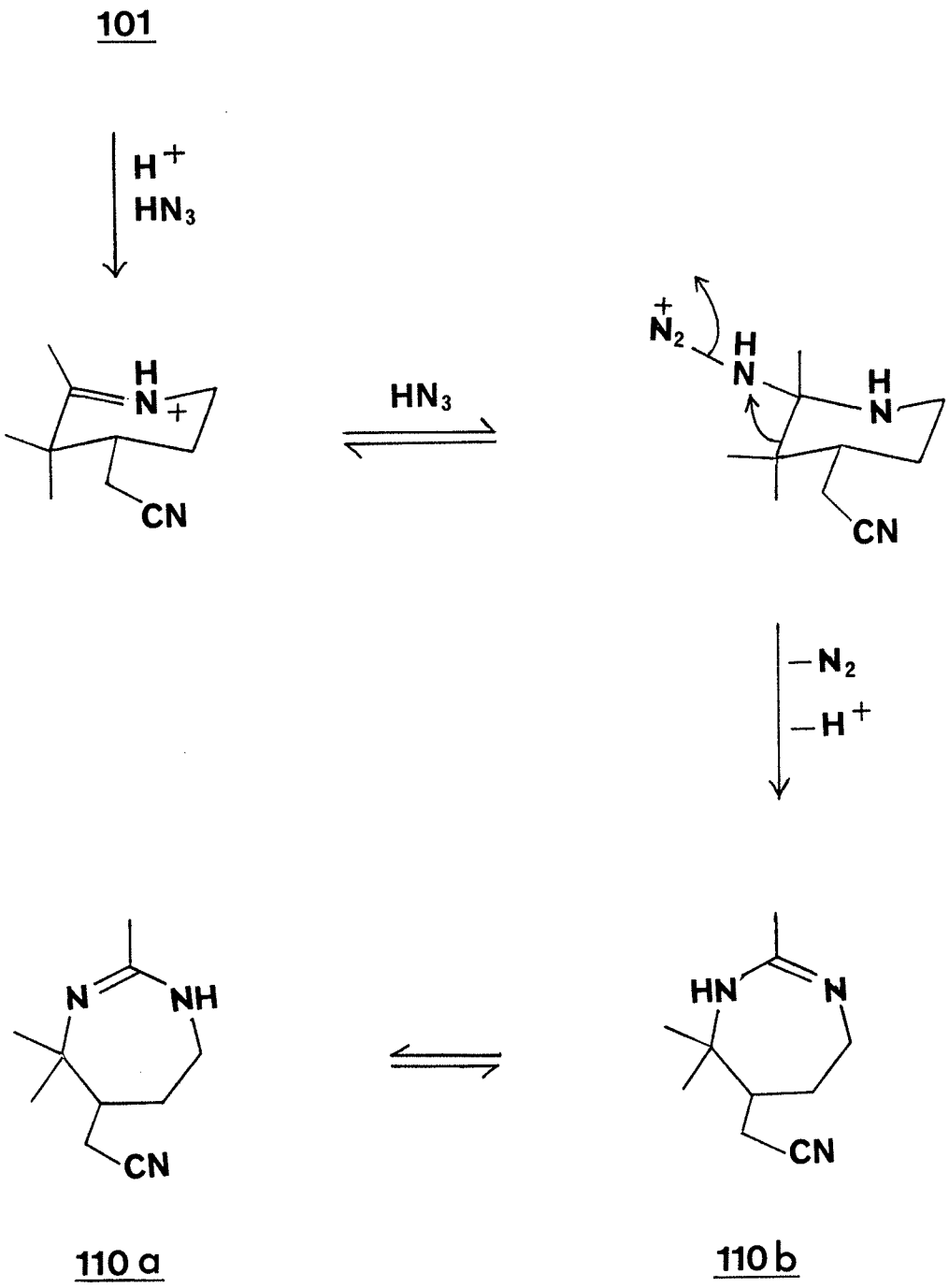
(6) Preparation of 75 from (R)-(-)α-campholenamide 104

It was envisaged that in the case of involvement of 96a and 96 as intermediates during the formation of aminolactam 75 (from camphor and from α-campholenamide) the final product 75 would be a racemic mixture if prepared from optically active α-campholenamide 104. For this purpose amino lactam 75 was prepared, in the usual way, from 104 having $[\alpha]_D^{22}$ = 3.4° (c = 7.1 abs. ethanol). The specific rotation $[\alpha]_D^{24}$ of the crystallized product was found to be -0.19 (c = 10, abs. ethanol). After another crystallization the product had mp 179.5 - 181°C and $[\alpha]_D^{20}$ = -0.17°.

The specific rotation -0.17° of the aminolactam is sufficiently close to zero to indicte that the product is optically inactive. This very low optical activity can be further explained as follows.

The product may be completely a racemic mixture possessing no optical activity and the observed value -0.17° is simply within the range of experimental error.

The value -0.17° may be a real property of this product, and if this is so, it may be due to two reasons: (a) one diastereomer 75a (see Scheme 17) may have been produced in slight excess as it can be



SCHEME 20

imagined from the relatively lower percentage of deuterium at position-5 compared to that at positions-7a and 7e of 109a (see Table 22). This comparatively lower percentage of deuterium at position-5 means that some of 95 and 95a do not equilibrate with 96a and 96 (see Schemes-15a, 15b and 18). (b) In theory it is possible that the product consists of only one enantiomer 75a (see Scheme 17) having a low value [-0.17°] of specific rotation. However, based on the observations regarding deuterium incorportion that were previously discussed, this last possibility is very unlikely. It seems most likely that the product is largely, but not totally, racemized.

(7) Reaction of aminolactam 75 with sulphuric acid-d_2

In order to confirm that deuterium incorporation in the deuterated aminolactams 109a-c, as discussed earlier, does not occur after the formation of the aminolactam but occurs at an earlier intermediate stage, a chloroform solution of 75 was stirred with conc. sulphuric acid-d_2 for 28.5 h at room temperature. After adjusting the pH of the acidic layer to 8, a colorless solid was recovered with chloroform in 21.4% yield. After further adjustment to pH 13-14 of this aqueous layer, an identical colorless solid was recovered with chloroform in 67.0% yield. These two colorless solids were identified as the starting amino lactam 75 (see Experimental). No evidence of deuterium incorporation was observed. From this experiment it was also noted that the amino lactam can be extracted in 21.4 + 67.0 = 88.4% yield from the reaction mixture. The 12% loss

of 75 could be considered as another factor, though not a major one, for the low yield of aminolactam from the Schmidt reaction on camphor.

8) Attempt to isomerize 104 to 96 in conc. sulphuric acid

In order to isomerize (1R)-α-campholenamide 104 to β-campholenamide 96, a chloroform solution of 104 was stirred vigorously with conc. sulphuric acid at room temperature for 24 h. After usual work-up a clear viscous liquid was obtained. This liquid, upon flash chromatography, did not yield the desired product 96. However, two other compounds were obtained and are discussed below (see Scheme 21).

Dihydro-β-campholenolactone 111:

The first set of fractions from the flash chromatography (see Experimental) yielded dihydro-β-campholenolactone 111 in 18.4% yield. This product was identified by mass, infrared, proton and carbon-13 nuclear magnetic resonance spectroscopy (see Experimental). The infrared spectrum showed a strong band at 1770 cm^{-1} for a 5-membered lactone. The mass spectrum indicated the molecular ion peak at m/z 168. The carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 23 below.

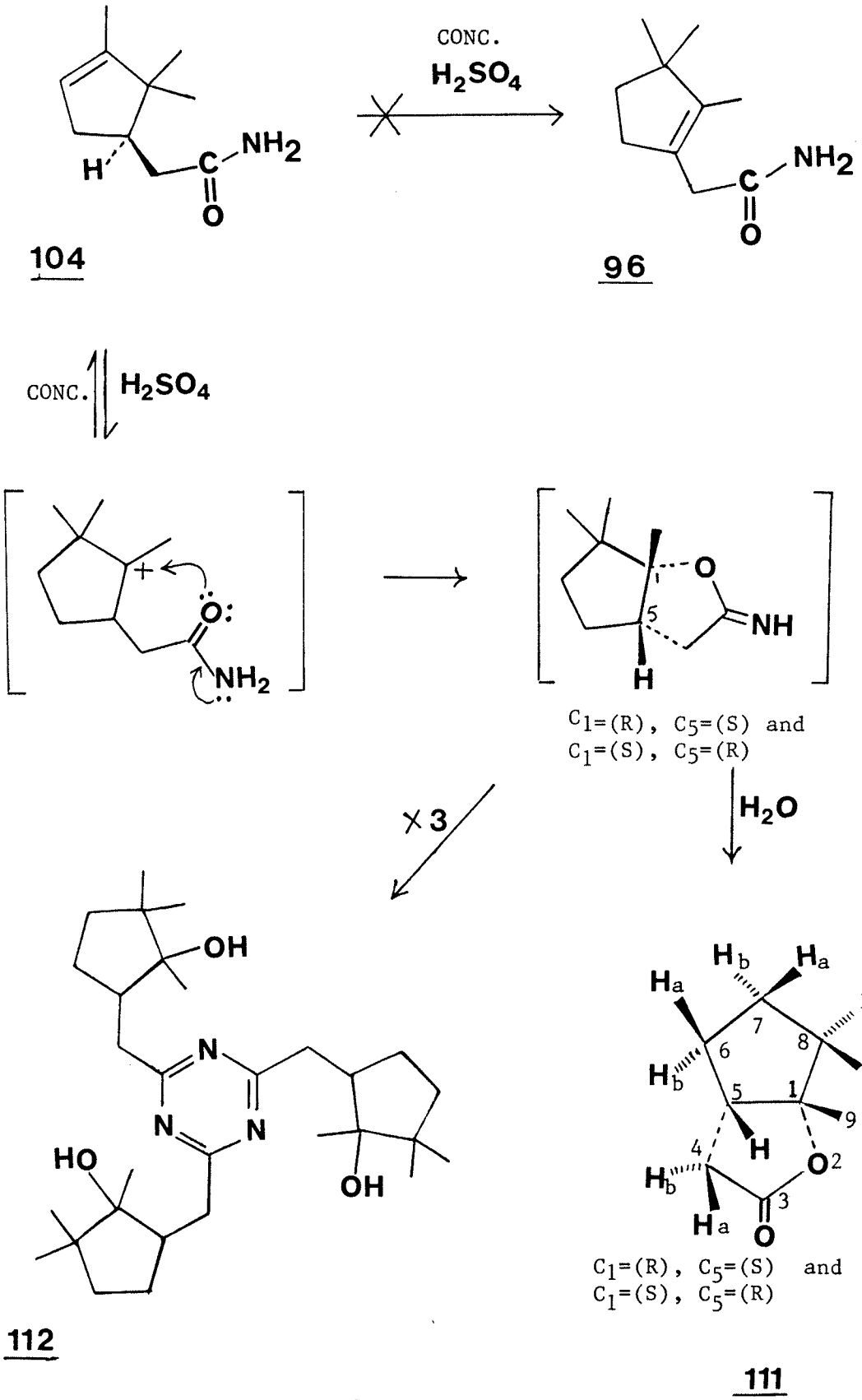
TABLE 23. THE CARBON-13 NMR DATA AND ASSIGNMENTS OF DIHYDRO-β-CAMPHOLENOLACTONE 11.

Chemical Shifts (ppm)	177.2	98.7	47.3	43.0	38.5	37.8	30.1	23.9	21.9	18.6
^1H-decoupled INEPT	-	-	C_q	CH	CH_2	CH_2	CH_2	CH_3	CH_3	CH_3
^{13}C-Assignments	3	1	8	5	4	7	6	10 and 11		9

Sauers (61) has reported that compound 111 can be obtained in 87% yield by the isomerization of β-campholide with dilute sulphuric acid in acetic acid. He suggested that this isomerization proceed via α-campholenic acid.

2,4,6-Tri(2'-hydroxy-2',3',3'-trimethylcyclopentylmethyl)-1,3,5-triazine 112:

Compound 112 (hereafter called the triazinetrimer) was isolated in 45% yield from the second set of chromatography fractions. The structure 112 was tentatively assigned to this product on the following basis. The mass spectrum indicated the molecular ion peak at m/z 501. The infrared spectrum showed a broad band (m) at 3500 cm^{-1} for OH stretch (probably hydrogen bonded OH group), and a strong band at 1540 cm^{-1} for C=N stretch of the triazine ring. The


CONC.
H2SO4
NH2
H
C
O
104
96
CONC.
H2SO4
O:
NH2
O
NH
1
5
H
C1=(R), C5=(S) and
C1=(S), C5=(R)
H2O
×3
OH
N
N
N
HO
OH
112
Hb
Ha
Ha
11
7
8
6
10
Hb
5
1
9
H
4
O2
Hb
3
Ha
O
C1=(R), C5=(S) and
C1=(S), C5=(R)
111

SCHEME 21

calculated elemental analyses for $C_{30}H_{51}N_3O_3$ are in excellent agreement with the observed elemental analyses (see Experimental). The carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 24 below.

TABLE 24. CARBON-13 NMR DATA AND ASSIGNMENTS OF TRIAZINETRIMER 112.

Chemical Shifts (ppm)	178.0	82.5	46.0	45.9	39.6	37.5	27.4	26.5	22.0	21.0
^{1}H-decoupled INEPT	-	-	CH	C_q	CH_2	CH_2	CH_2	CH_3	CH_3	CH_3
^{13}C-Assignments	1,3,5	2'	1'	3'	4'	6'	5'	7', 8' and 9'		

The results from the proton nuclear magnetic resonance (400 MHz) spectroscopy were interesting. Two different samples, each prepared in CD_2Cl_2 from the same recrystallized product produced two different spectra. These two spectra are shown in Figures 11 and 12.

In the spectrum shownin Figure 11, peaks No.1 (due to H6'a1) and No.4 (due to H6'b1) each integrate for 2/3 H and peaks No.2 (due to H6'a2) and No.5 (due to H6'b2) each integrate for 1/3 H. The coupling constants for peaks No.1 and No.2 are identical, and those for peaks No.4 and No.5 are identical. Peaks No.9, 10 and 11 (due to

three methyl groups) each show 2 peaklets with 2:1 ratio in terms of integration. The coupling constants for protons H6'a and H6'b, and the chemical shifts and assignments for all protons from the spectrum shown in Figure 11 are given in Table 25.

TABLE 25. ^{1}H-NMR (400 MHz) OF THE TRIAZINE TRIMER 112a. THE CHEMICAL SHIFTS ARE RELATIVE TO SOLVENT CD_2Cl_2 AT 5.32 PPM.

Protons[a]	Chemical Shifts[b] (ppm)	Coupling Constants
H6'a1	2.96	$^{2}J(6'a,6'b) = -17$ Hz, $^{3}J(6'a,1') =$ 8.5 Hz, and $^{5}J(6'a,5'a) = 0.8$ Hz
H6'a2	2.88	
H1'	2.56	
H6'b1	2.40	$^{2}J(6'b,6'a) = -17$ Hz and $^{3}J(6'b,1') = 0.9$ Hz
H6'b2	2.31	
H5'a	2.10	
H4'b	1.72	
H4'a	1.45	
H5'a	1.36	
C-7'Me	1.28	
	1.23	
C-8' Me	1.08	
	1.06	
C-9' Me	0.90	
	0.88	

a = The protons assignments were also made with the help of the assignments shown in Table 26 (see below).

b = The chemical shifts were measured at the middle of each peak.

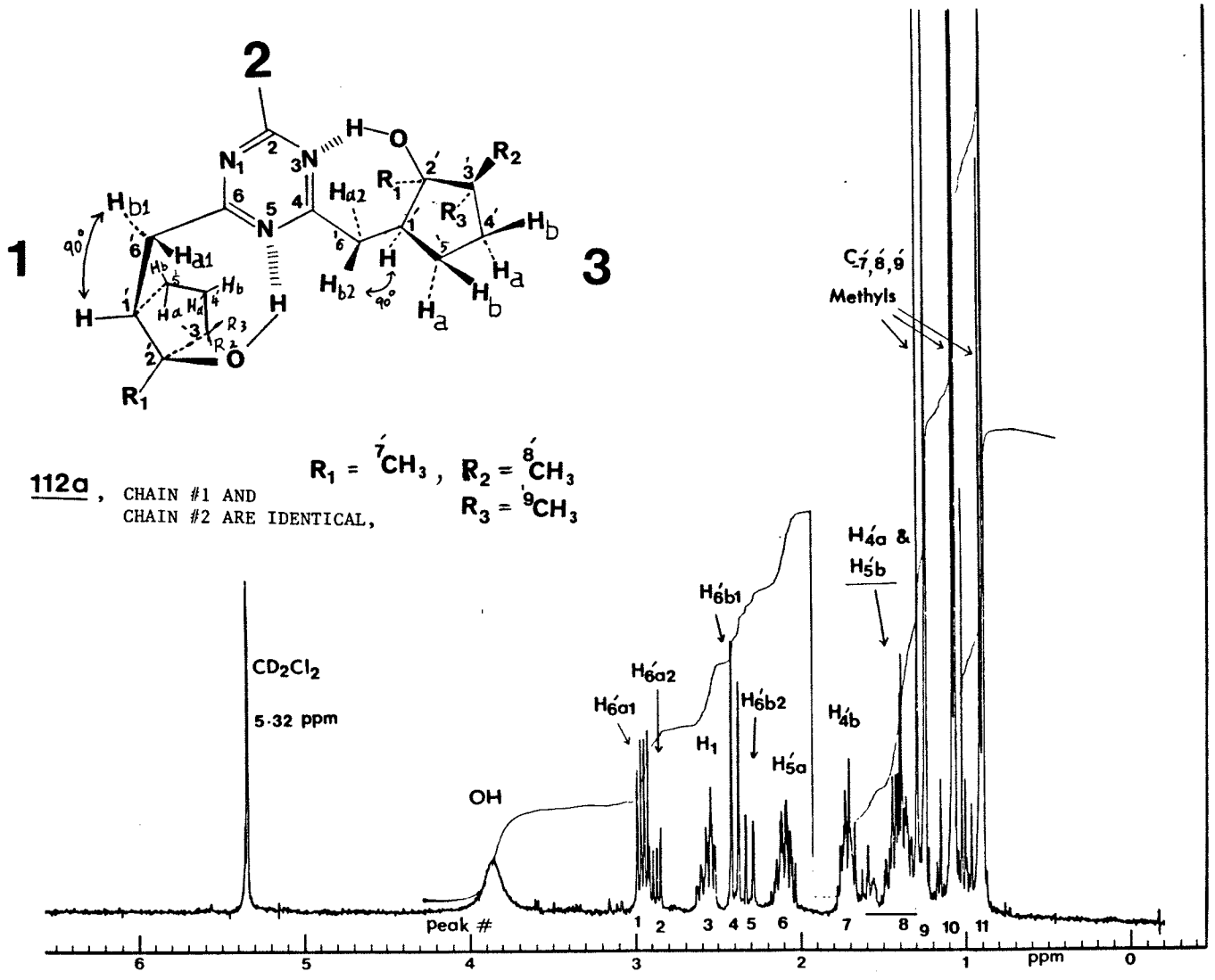


FIGURE 11. ^{1}H-nmr spectrum of the triazinetrimer 112a .

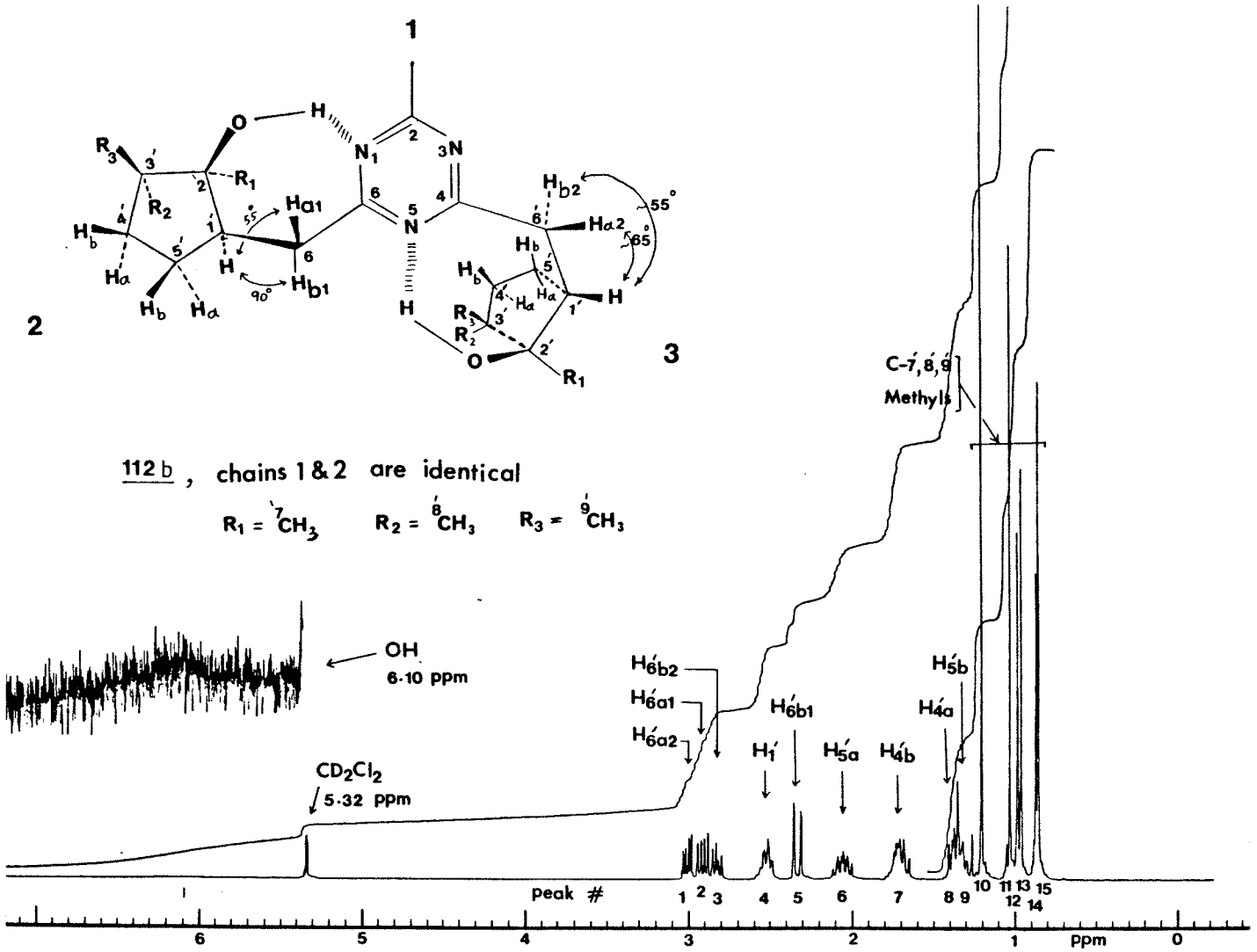


FIGURE 12. ^{1}H-nmr of the triazinetrimer 112b .

These results indicate that in the case shown in Figure 11, the configuration of the triazinetrimer was such that two of the side chains had identical spacial conformation while the third side chain had a different spacial conformation. However, the coupling constants indicate that the angles between H6'a - H1' and H6'b - H1', although different from each other, are each identical in all of the three side chains, i.e. the vicinal coupling $^{3}J(6'a,1) = 8.5$ Hz is the same in all of the three side chains, and the vicinal coupling $^{3}J(6'b,1') = 0.9$ Hz is the same in all of the three side chains. However, the different chemical shifts of peaks No.1 (H6'a1) and No.2 (H6'a2), and that of peaks No.4 (H6'b1) and No.5 (H6'b2) indicate that one side chain has a different conformation because the configuration of C-1' and C-2' carbons in this side chain is (S) and (R) respectively. While the configuration of C-1' and C-2' in the other two identical side chains is (R) and (S) respectively. These two different configurations at C-1' and C-2' carbons are responsible for the different conformations of the side chains. The attainment of identical conformation is also hindered by the bulkiness of the three side chains. It can be seen from the very small value of $^{3}J(6'b,1') = 0.9$, [peaks No.4 and 5] that the angle between H6'b-H1' is about 90° which indicates a rigid (cyclic) system. A tentative configuration of the triazinetrimer under the conditions which produced the spectrum shown in Figure 11 is given in structure 112a.

It can be seen from the spectrum shown in Figure 12 that peaks No.1 (due to H6'a2) and No.3 (due to H6'b2) each integrate for 1/3 H, while peaks No.2 (due to H6'a1) and No.5 (due to H6'b1) each integrate for 2/3 H. Similarly , peaks No.10, 11 and 15 each

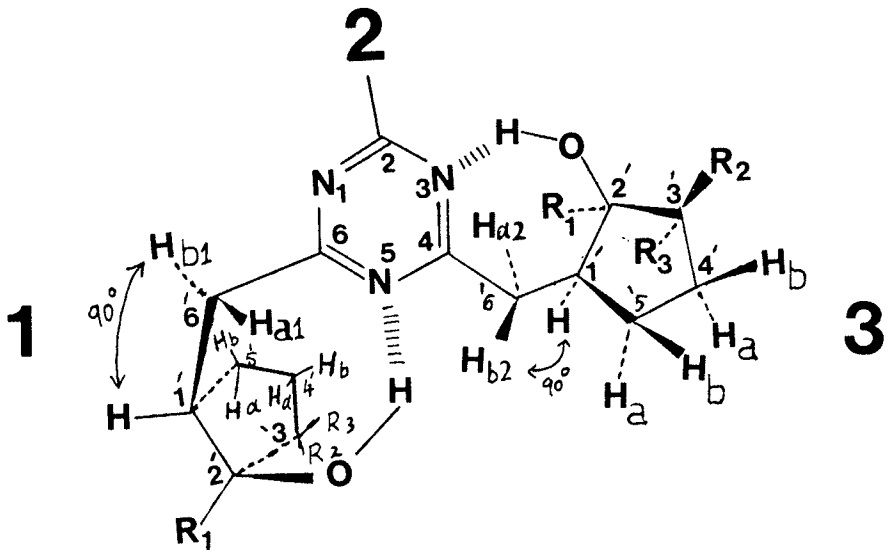
integrate for 2/3 CH_3, and peaks No.12, 13 and 14 each integrate for 1/3 CH_3. Peaks No. 10-15 were assigned to the three methyls. The coupling constants, chemical shifts and assignments from the spectrum shown in Figure 12 are given in Table 26.

TABLE 26. ^{1}H-NMR (400 MHz) DATA OF THE TRIAZINETRIMER 112b. THE CHEMICAL SHIFTS ARE RELATIVE TO SOLVENT CD_2Cl_2 AT 5.32 PPM. THE COUPLING CONSTANTS ARE GIVEN IN Hz.

	Hs	6'a2	6'a1	6'b2	1'	6'b1	5'a	4'b	4'a	5'b	7'	8'	9'
Hs	Chemical Shifts (ppm)	COUPLING CONSTANTS											
H6'a2	3.01	-		-13.8	6.2								
H6'a1	2.91		-		8.5	-17	0.9						
H6'b2	2.83	-13.8		-	8.3								
H1'	2.52	6.2	8.5	8.3	-	0.9	10.6	0.4	1	2.9			
H6'b1	2.33		-17		0.9	-	0.5	0.1					
H5'a	2.06		0.9		10.6	0.5	-	11.7	8.2	-13.7			
H4'b	1.71				0.4	0.1	11.7	-	-12.4	9.0			0.9
H4'a	1.40				1		8.2	12.4	-	1.2			
H5'b	1.32				2.9		-13.7	9	1.2	-			
C-7' Me	1.20 0.99												-
C-8' Me	1.04 0.97												0.5
C-9' Me	0.87 0.85							0.9				0.5	

These results indicate that two of the side chains of the triazinetrimer have identical spacial conformations; and the angles H6'a1 - H1' and H6'b1 - H1', although different from each other, are each identical in these two side chains. The third chain has a different spacial conformation. The angles H6'a2 - H1' and H6'b2 - H1' in this third side chains are slightly different from each other, and also each is different from the corresponding angles in the other two side chains. It can be seen from the very small value of $^{3}J(6'b1,1) = 0.9$ [peak No.5] that the angle H6'b1 - H1' is about 90° in the two identical side chains which indicates a rigid (cyclic) system. It can also be seen from Table 26 that the geminal coupling $^{2}J(6'a2, 6'b2) = -13.8$ Hz in one side chain is different from the corresponding geminal coupling in the other two identical side chains [$^{2}J(6'a1, 6'b1) = -17$ Hz]. This difference in the geminal coupling is probably due to the different conformation of the concerned protons with respect to the triazine ring [which has aromatic character] (89). A tentative configuration of the triazinetrimer under the conditions used for the spectrum shown in Figure 12 is expressed in structure 112b.

Although it can not be said with certainty, it is possible that the two different conformations 112a and 112b of the triazinetrimer are due to different concentrations of the two solutions used for obtaining the spectra. Some further work is in progress in our laboratories towards the confirmation of the structure of the triazinetrimer.

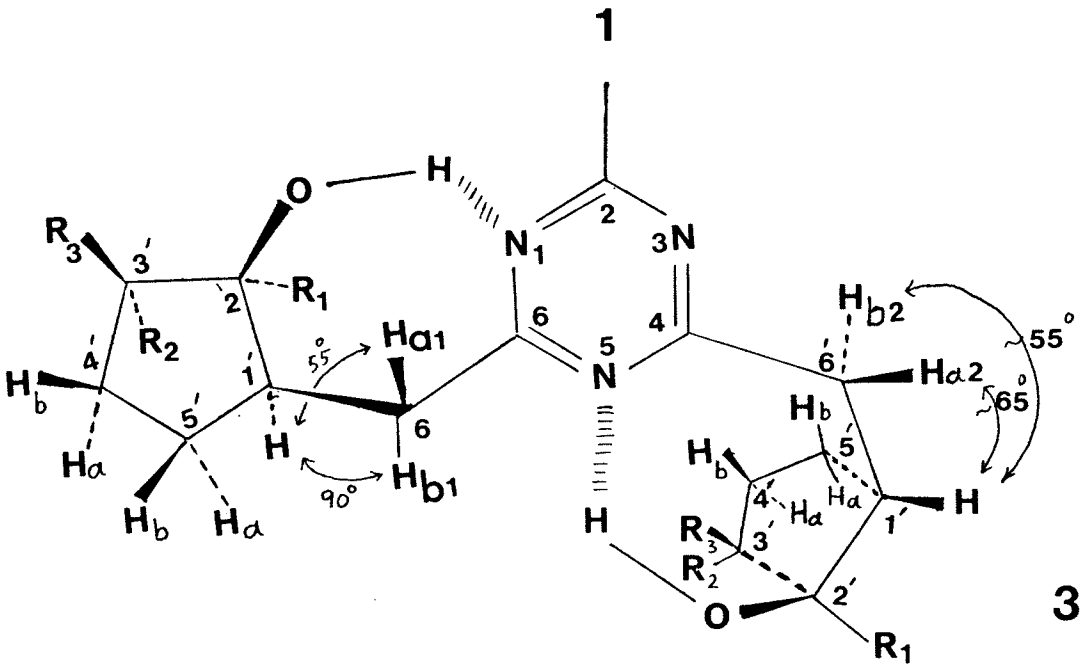


$R_1 = {}^{7}CH_3$, $R_2 = {}^{8}CH_3$

$R_3 = {}^{9}CH_3$

112a , CHAIN #1 AND CHAIN #2 ARE IDENTICAL,

THE ANGLES BETWEEN H'_{6a1} — H'_1 IN CHAINS 1 & 2 AND THE ANGLE BETWEEN H'_6a2 — H'_1 IN CHAIN 3 ARE APPROXIMATELY 55^{0} .



112 b , chains 1 & 2 are identical

$R_1 = {}^{7}CH_3$ $R_2 = {}^{8}CH_3$ $R_3 = {}^{9}CH_3$

CONCLUSION

CONCLUSION

The behaviour of camphor was studied under the modified Schmidt reaction conditions using excess hydrazoic acid. The major product 75 obtained in 42% yield from this reaction was not the normal Schmidt reaction product 3-azalactam 71 (or 2-azalactam 73) that one would generally expect. This major product was identified as 2,8-diaza-3-oxo-1,9,9-trimethylbicyclo[3.3.1]nonane 75 by carrying out the following studies: (a) Identification of the product iminester 81 which was obtained from the 3% methanolic-HCl methanolysis of 75. (b) Identification of the products 77 79 which were obtained from the addition reactions of 75. (c) Spectroscopic studies of the major product 75.

The 3% methanolic-HCl methanolysis 2,8-diaza-3-oxo-1,8,9,9-tetramethylbicyclo[3.3.1]nonane 78 was studied. Compounds 85 87 and 81 were isolated from this reaction and were characterized.

Three other minor products 71, 83 and 84 were also isolated from the Schmidt reaction on camphor and were characterized.

The formation of the product 75 from the Schmidt reaction on camphor could not be explained by either of the existing views regarding the Schmidt reaction on ketones, i.e., the direct rearrangement of the hydroazidohydrins, e.g., 88 or rearrangement of the iminodiazonium ions e.g., 89. Therefore a new route was proposed which adequately explains the mechanism of formation of 75. This route follows cleavage at the bridgehead-carbon (C_1-C_2 bond) generating the transient intermediate 94.

[The tautomeric form 95 (-campholenamide) of the intermediate 94 isomerizes to -campholenamide 96. Addition of another mole of hydrazoic acid to the protonated -campholenamide 95a, followed by recyclization leads to the major product 75. In order to support the view that the campholenamides 95 and 96 were produced during the formation of 75 from camphor, they were synthesized and subjected to the same Schmidt reaction conditions. From these reactions compound 75 was isolated in yields up to 73% which are about twice as much as those from camphor. Similarly, the possible intermediacy of campholenonitrile 101 during the formation of 75 was also tested by subjecting it to the same Schmidt reaction conditions. From this reaction compound 75 was isolated in only 20% yield. From these studies it was concluded that although a small portion of compound 75 may be produced via the intermediate 101 the major intermediates during the formation of 75 from camphor are campholenamides 95 and 96. The involvement of the intermediates 95 and 96 was further demonstrated by deuterium incorporation experiments.

This behaviour of camphor during the Schmidt reaction is different than many other bridged bicyclic ketones, e.g., norcamphor, which normally yield lactams. Nevertheless, similar cleavage at the bridgehead-carbon (C_1-C_2 bond) of the camphor oxime 90 has been observed during the Beckmann reaction (86). No doubt the electronic factors of the methyl at the bridgehead-carbon of camphor favor the observed cleavage.

Routes to the formation of the minor products 83 - 84 were suggested in the light of formation of analogous products during the Schmidt reaction on other bridged bicyclic ketones.

It was suggested that the minor product 71 arose by the direct rearrangement, in a synchronous manner, of the hydroazidohydrin 88b. The driving forces for this rearrangement were sought by analogies with the rearrangement of the intermediate (Scheme 14) during the Baeyer-Villiger oxidation of camphor (62) and with the rearrangement of the intermediate hydroazidohydrin 35 suggested for the Schmidt reaction on norcamphor (Scheme 2).

In conclusion, the sumultaneous action of five mechanisms was proposed as summarized in Schemes 13b and 15a. It was not possible to make sweeping generalizations regarding the forces, e.g., steric, electronic, solvent, catalytic, and temperature variables, which are responsible for the competition between the different routes. Hopefully, further empirical studies of the Schmidt reaction on other bicyclo[2.2.1]heptanones would provide the basis for making any generalization.

The interesting compound 2,4,6-tri(2'-hydroxy-2',3',3',-trimethylcyclopentylmethyl)-1,3,5-triazine 112 was isolated during the conversion of 95 to 96 and was characterized.

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined with a precalibrated Thermopan (Kofler-Hot Stage) melting point apparatus or with a CANLAB-Gallenkamp apparatus, if in a sealed tube, and were uncorrected. Infrared spectra were recorded on UNICAM SP 1000 IR spectrophotometer. Mass spectra were recorded on FINNIGAN 1015 mass spectrometer under electron-impact at 70 eV ionizing voltage, or on a high resolution A.E.I. Model MS 50 mass spectrometer. Proton magnetic resonance spectra were recorded on Bruker WH 90 (at 90 Hz) or on Bruker WH-400 (at 400 MHz) spectrometers, unless otherwise stated. Spectra were measured in deuterochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard, unless otherwise stated. Carbon-13 magnetic resonance spectra were recorded on a Bruker WH-90 (22.63 Hz) equipped with NIC 1180 computer, 293 A' pulse programmer, home built shifter and NTL FT software. Some carbon-13 magnetic resonance spectra were measured in $CDCl_3$ with $CDCl_3$ as an internal standard whose chemical shift was taken as being about 77.2 ppm relative to TMS.

Analytical thin layer chromatography (tlc) was performed on precoated sheets with silica gel 60 F_{254} (EM Reagents) of 0.2 mm thickness. Spots were detected under ultraviolet light or visuallized in an iodine chamber. Flash chromatography (90) was employed for all purification purposes. Silica gel Kieselgel 60 (230-400 mesh ASTM) was used in columns for flash chromatography. All solvent evaporations were carried out on rotary evaporators.

The three main reagents, used for the Schmidt reaction, were of the following grade:

Sulphuric acid - Reagent A.C.S. (Fisher); assay min. 95-max. 98

Sodium azide - Purified NaN_3 (Fisher)

Chloroform - certified A.C.S. (Fisher)

THE SCHMIDT REACTION ON CAMPHOR:

(1) 2,8-Diaza-3-oxo-1,9,9-trimethylbicyclo[3.3.1]nonane 75:

dl-Camphor (30.4 g, 0.2 mole) was dissolved in chloroform. Conc. sulphuric acid (100 ml) was added to this colorless solution which then turned yellow. To this rapidly stirred two-phase system, sodium azide (27 g, 0.41 mol) was added in small portions over a period of 3.25 h. During this addition the temperature of the reaction mixture remained mostly above 35°C and occasionally reached up to 50°C. Total stirring was continued for 3.5 h at the end of which the reaction mixture was placed in a freezer for 16 h. The upper chloroform layer was decanted from the bottom yellow viscous mass. The viscous mass was diluted with ice-water (600 g) and stirred for 5 minutes before extraction with chloroform (1 x 200 ml). This chloroform extract was reserved for later work-up (see below)**. The acidic aqueous layer was adjusted to pH 10 with 60% sodium hydroxide solution and then extracted with chloroform (3 x 150 ml). These combined chloroform extracts were dried with anhydrous sodium sulphate and the solvents were evaporated. This work-up left behind a semi-solid material (30 g, ^{1}H-nuclear magnetic resonance showed the

presence of some chloroform in it). The material was crystallized from boiling ethyl acetate ( )$^{+}$ to give 14.33 g (39.4%) of pure compound; mp 180-181°C (in a sealed tube). After repeated crystallization of this compound from ethyl acetate, followed by drying in a drying pistol for 4 h at 78°C (0.1 mm Hg), the mp was 181-183°C (in a sealed tube). This compound sublimes above 140°C.

ms (on FINNIGAN 1015), m/z: 182(38)[M^{+}], 167(10) [M-(CH_3)], 139(23) [M-(HN=C=O)], 114(46), 101(98), 98(77), 82(100).

ir (Nujol), cm^{-1}: 3310(m) and 3285(m) [NH stretch of amine], 3180(m) [NH stretch of amide], 1662(s) [C=O, amide band I], 1655-1640(s) [amide band II].

The carbon-13 and ^{1}H-nuclear magnetic resonance (400 MHz) data and assignments are given in Table 9 and Table 8 respectively.

The carbon-proton shift mapping is given in Figure 6.

Exact mass calcd. for $C_{10}H_{18}N_2O$: 182.1419; found (high resolution ms, 100%): 182.1420.

This compound, the major product from this reaction, was identified as the aminolactam 75.

$^{+}$The mother liquor saved from the above crystallization was concentrated and the solid product obtained was chromatographed on a silica gel column (10" x 1.5"). Sixty-four fractions (each 10 ml) were collected using chloroform-ethanol (20:1, v:v) as the eluting system. Based on the same R_f value in the above eluting system, fractions 15-21 and 30-62 were combined.

The solvents were evaporated from the fractions 30-62. A colorless solid (0.995 g, 2.73%) was obtained; mp 181-182°C (in a

sealed tube). This solid was identified as the aminolactam 75 by its infrared, proton nuclear magnetic resonance and mass spectra.

(2) 4-Cyanomethyl-2,3,3-trimethylcyclohexyl-1-imine 84: The combined fractions 15-21 from above (Section 1) were concentrated. A brown liquid (0.54 g) was obtained. This liquid was dissolved in chloroform (50 ml), stirred with a bit of activated charcoal, filtered and the solvents were evaporated off. The leftover liquid was further purified by rechromatography on a silica gel column (4" x 1") using chloroform as the eluant. The main component was a tlc pure liquid (0.315 g) which was distilled in a small cold finger distillation apparatus at 65°C (0.1 mm Hg).

ms, m/z: 164(18) [M^+], 149(2) [M - (CH_3)], 124(16) [M - (CH_2-CN)], 97(13) [$(CH_3)_2C$-C(CH_2)=N-CH_3]$^+$, 95(27) [M - (CH_3-C=N-CH_2-CH_2)], 83(100) [124 - (CH_3CN)], 68(47) [83 - (CH_3)], 55(76) [$(CH_3)_2C$=CH]$^+$. This mass spectral fragmentation pattern is identical to that of iminoester 81.

ir (thin film), cm^{-1}: 2240(m) [CN stretch of nitrile], 1651(s) [C=N stretch].

^{1}H-nmr (90 MHz) in $CDCl_3$, ppm: m centered at 3.54 (2Hs, H_{6a}, H_{6e}), dd at 2.44 (1H, H_7) [$^2J(7,7^*)$ = -16.5 Hz, $^3J(7,4a)$ = 4.0 Hz], dd at 2.08 (1H, H_{7^*}) [$^2J(7^*,7)$ = -16.5 Hz, $^3J(7^*,4a)$ = 9.5 Hz], dd at 1.88 (3Hs, C-9 methyl)[^5J(Me,6a) = 1.9 Hz, ^5J(Me,6e) = 1.6 Hz], m at 1.97 - 1.41 (3Hs, H_{4a}, H_{5a}, H_{5e}), two s at 1.13 (3Hs) and 0.97 (3Hs) [C-10 and C-11 methyls].

The carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 16.

(3) Camphortetrazole 83 and ∝-camphidone 71: The chloroform extract ( )** of the acidic aqueous layer (see Section 1) was washed with water, dried with anhydrous sodium sulphate and concentrated. A colorless solid (4.44 g) was obtained. Tlc in dichloromethane-methanol (100:2, v:v) showed two spots. The solid was chromatographed on a silica gel column (7.5" x 2") using dichloromethane-methanol (100:2, v:v) as the eluant. Based on the results, fractions 18-19 and 23-26 were combined separately:

(a) Camphortetrazole 83: The combined fractions 18 and 19 were concentrated to give a colorless shiny solid (0.349 g). Tlc showed one spot, R_f = 0.75 in dichloromethane-methanol (100:2, v:v). After repeated crystallization from hot ethyl acetate the product had mp 245 - 247°C (in a sealed tube).

ms, m/z: 192(8) [M^+], 164(5) [M - (N_2)], 163(10) [164 - (H)], 149(20) [164 - CH_3)], 124(15), 109(9), 108(25), 107(33), 97(79), 82(100).

ir (thin film), cm^{-1}: 1520(m) [C=N stretch of the tetrazole ring].

^{1}H-nmr (90 MHz) in $CDCl_3$, ppm: ddd at 3.15 (1H, H_{4a}) [$^{2}J(4a,4b)$ = -17 Hz, $^{3}J(4a,5)$ = 3.1 Hz, $^{4}J(4a,6a)$ = 1.5 Hz], dd at 2.95 (1H, H_{4b})[$^{2}J(4b,4a)$ = -17 Hz, $^{3}J(4b,5)$ = 2 Hz), sets of m at 2.42-1.92

(4Hs, H_5, H_{6a}, H_{7a}, H_{7b}), s at 1.78 (3Hs, C-11 methyl), m at 1.60 - 1.33 (1H, H_{6b}), s at 1.16 (3Hs, C-9 methyl), and s at 0.81 (3Hs, C-10 methyl).

The carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 15.

Anal. calcd. for $C_{10}H_{16}N_4$: C62.47, H8.39, N29.14; found: C62.35, H8.39, N29.12.

(b) ∝-Camphidone 71: The combined fractions 23-36 from the above chromatography were concentrated. A colorless solid (1.755 g, 5.3%) was obtained which was pure by tlc, R_f 0.44 in dichloromethane-methanol (100:2, v:v). After repeated crystallization the mp of this solid was 242-244 °C(in a sealed tube).

ms, m/z: 167(61) [M^+], 152(97) [M - (CH_3)], 139(6) [M - (CO)], 138(15) [M - (HCO)], 124(27) [M - (HN=C=O)], 98(94) [M - ((CH_3)$_2$C=CH-CH_2)], 69(100) [(CH_3)$_2$C=CH-CH_2]$^+$, 55(73) [98 - (HN=C=O)].

ir (Nujol), cm^{-1}: 3310(w), 3220(m) and 3090(w) [all due to N-H stretch], 1667(s) [C=O stretch].

^{1}H-nmr (90 MHz) in $CDCl_3$, ppm: broad m centered at 5.90 (1H, N-H), a dddd at 3.44 (1H, H_{4a}) [^{2}J(4a,4b) = -11.1 Hz, ^{3}J(4a,5) = 3.5 Hz, ^{3}J(4a, NH) = 1-2 Hz, ^{4}J(4a,6a) = 1.6 Hz], ddd at 2.99 (1H, H_{4b}) [^{2}J(4b,4a) = -11.1 Hz, ^{3}J(4b,5) = 2 Hz, ^{3}J(4b,NH) = 2.0 Hz], set of m at 2.22 - 1.42 (5Hs, H_5, H_{6a}, H_{6b}, H_{7a}, H_{7b}), three s at 1.10 (3Hs), 1.04 (3Hs) and 0.96 (3Hs)[C-9, C-10 and C-11 methyls].

NH-decoupled ^{1}H-nmr (90 MHz) in $CDCl_3$, ppm: ddd at 3.46 (1H,

H_{4a})[$^{2}J(4a,4b)$ = -11.1 Hz, $^{3}J(4a,5)$ = 3.5 Hz, $^{4}J(4a,6a)$ = 1.6 Hz], a dd at 3.01 (1H, H_{4b})[$^{2}J(4b,4a)$ = -11.1 Hz, $^{3}J(4b,5)$ = 2.0 Hz], NH absorption was not observed, and the rest of the spectrum is similar to the NH-coupled spectrum.

The carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 14.

3% METHANOLIC-HCl METHANOLYSIS OF AMINOLACTAM 75:

4-Methylcarbonylmethyl-2,3,3-trimethylcyclohexyl-1-imine 81: Acetyl chloride (12.0 g) was slowly added to methanol (240 ml) over a period of 0.5 h (78) followed by the addition of aminolactam 75 (2.0 g, 0.011 mol). The solution was heated under reflux for 3 days while the reaction was monitored by tlc. The solvents were evaporated and the remaining solid was dissolved in water (30 ml). The aqueous solution was made basic (pH 9-10) with dilute sodium bicarbonate solution and extracted with chloroform (3 x 30 ml). The combined chloroform extracts were dried with anhydrous sodium sulphate and the solvent was evaporated. A clear liquid (2.078 g) was obtained which was pure by tlc. After distillation at 85-90°C (0.4 mm Hg), 1.60 g (74%) of a colorless liquid was obtained; tlc: R_f 0.55 in chloroform-ethanol (10:1, v:v).

ms (on FINNIGAN 1015), m/z: 197(15) [M^+], 182(11) [M - (CH_3)], 166(12)[M - (OCH_3)], 128(47) [$(CH_3)_2C$-CH-CH_2-$COOCH_3$]$^+$, 124(47) [M-(CH_2-$COOCH_3$], 96(77), 69(100).

ir(thin film), cm^{-1}: 1745(s) [O=C-OCH_3], 1655(s) [C=N].

The data and assignments of proton nuclear magnetic resonance (400 MHz) and those of carbon-13 nuclear magnetic resonance (regular broad band ^1H-decoupled and ^1H-decoupled INEPT) are given in Tables 5 and 6 respectively.

Exact mass calcd for $C_{11}H_{19}NO_2$: 197.1416; found (high resolution ms, 64.8%), 197.1419.

PRODUCTS OF ADDITION REACTIONS OF AMINOLACTAM 75

(1) 2,8-Diaza-3-oxo-8-phenylcarbamoyl-1,9,9-trimethylbicyclo[3.3.1] nonane 77: A benzene (50 ml) solution of phenyl isocyanate (0.81 g) was added to a benzene (50 ml) solution of aminolactam 75 (1.09 g). Within two minutes a colorless solid started to appear. The mixture was stirred for an additional 16 h. The colorless solid produced in the solution was filtered , washed with fresh benzene (15 ml), and dried under suction (yield 1.78 g). This solid was found insoluble in cold: water, methanol, acetone, ethyl acetate, chloroform, dichloromethane, benzene, hexanes, and in boiling water or boiling ethyl acetate, but soluble in boiling methanol or ethanol. It was crystallized from boiling ethyl acetate-methanol (3:1, v:v) to given 1.072 g (60%) of compound 77. After repeated crystallizations, followed by drying for 10 h at 78°C (0.4 mm Hg), the mp of the colorless shiny crystals was 163 - 165°C. ms, m/z: 301(3) [M^+], 286(3) [M - (CH_3)], 209(5) [M - (Ph-NH)], 182(33) [M - (Ph-N=C=O)], 167(11) [182 - (CH_3)], 139(22) [182 -

(HN=C=O)], 119(100) $[Ph-N=C=O]^+$, 101(76), 98(54), 93(74) $[Ph-NH_2]^+$, 82(72).

ir(Nujol), cm^{-1}: 3330(m), 3200(m) and 3080(m) [all assigned to NH stretch], 1675(s) [C=O, urea], 1645(s) [C=O, amide], 1595(s) [C=C, aromatic].

^{1}H-nmr (90 MHz) in DMSO-d_6, ppm: broad s at 8.18 (1H, N_{14}-H), set of m at 7.46 - 6.80 (5Hs, aromatic), broad m at 6.10 (1H, N_2-H), m at 3.22-2.73 (3Hs, H_{7a}, H_{7e}, H_{4a}), sets of m at 2.40 - 1.50 (3Hs, H_{4e}, H_{6a}, H_5), m at 1.32 - 1.04 (1H, H_{6e}), three s at 1.23(3Hs), 0.92(3Hs) and 0.80(3Hs) [C-10, C-11 and C-12 methyls], the spectrum also showed a broad s at 8.38 (OH of methanol), s at 3.31 (H_2O from crystallization and DMSO), s at 3.12 (CH_3 of methanol), and m at 2.51 (DMSO-d_6 residual H), and OH and CH_3 peaks of methanol integrate for 0.85 mol of methanol.

Anal. calcd. for $C_{17}H_{23}N_3O_2$. 0.85 CH_3OH. 0.50 H_2O: C63.50, H8.18, N12.45; found: C63.84, H8.05, N12.31.

Carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 11; INEPT also shows a CH_3 peak at 48.26 ppm (the CH_3 of methanol).

(2) 2,8-Diaza-3-oxo-1,8,9,9-tetramethylbicyclo[3.3.1]nonane 78: (a) Aminolactam 75 (3.62 g) was dissolved in dichloromethane (50 ml). Magic Methyl® (97% methyl fluorosulphonate) (1.90g) was added to this solution over a period of 10 minutes. A colorless solid began forming immediately after the addition of methyl fluorosulphonate. The mixture was stirred at room temperature for 1.5 h while the

reaction was monitored by tlc. The dichloromethane was decanted from the solid which had formed. This colorless solid was washed with dichloromethane (5 ml), and then suspended in fresh dichloromethane (35 ml). A 1N aqueous sodium hydroxide solution (30 ml) was added to the organic solution and the mixture was stirred for 5 minutes while the colorless solid dissolved. After separation of the two layers, the aqueous layer was further extracted with chloroform (3 x 20 ml). The combined organic extracts were dried with anhydrous sodium sulphate and the solvents were evaporated off. A colorless solid (3.82 g, 98% crude) was obtained which was pure by tlc; R_f 0.5 in chloroform-ethanol (10:1, v:v). This solid (3.48 g) was recrystallized from ethyl acetate to given 2.73 g (70%) of compound 78; mp 150-151°C.

ms (on FINNIGAN 1015), m/z: 196(100) [M^+], 181(22) [M - (CH_3)], 153(44) [M - (HN=C=O)], 138(56) [181 - (HN=C=O)], 127(58), 124(50), 112(96), 110(89).

ir(Nujol), cm^{-1}: 3188(m) [NH stretch], 1672-1664(s) [C=O, amide band I overlapped by amide band II].

^{1}H-nmr (90 MHz), ppm: dd at 2.67(1H, H_{4a}) [$^2J(4a,4e)$ = -18 Hz, $^3J(4a,5)$ = 7 Hz], sets of m at 2.65-2.36 (2Hs, H_{7a}, H_{7e}), d at 2.22 (1H, H_{4e}) [$^2J(4e,4a)$, = -18 Hz] overlapped by a broad m at 2.32 - 1.94 (1H, H_{6a}), s at 2.16 (3Hs, N_8-CH_3), m at 1.72 (1H, H_5), m at 1.45 - 1.25 (1H, H_{6e}), s at 1.24 (6Hs) and s at 1.08 (3Hs) [C-10, C-11 and C-12 methyls].

Carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decouped) data and assignments are given in Table 12.

Exact mass calcd. for $C_{11}H_{20}N_2O$: 196.1576; found (high resolution ms, 100%): 196.1578.

Anal. calcd. for $C_{11}H_{20}N_2O$: C67.35, H10.20, N14.29; found: C66.78, H10.38, N14.13.

(b) A methanol solution of aminolactam 75 (3.0g, 0.0165 mol) and methyl iodide (7.5g, 0.0532 mol) was heated with stirring for 3 days at oil bath temperature of 55-62°C in a pressure bottle. The hot solution was then filtered under gravity, and the methanol was removed to leave a pale yellow solid. Recrystallization from methanol-pentane (1:1, v:v) gave a colorless hydroiodide salt (3.55g). The filtrate from this salt was made basic (pH 12) with dilute aqueous sodium hydroxide solution, and further diluted with water (30 ml). The organic layer was separated and the aqueous layer was further extracted with chloroform (2 x 30 ml). The combined organic layers were dried with anhydrous sodium sulphate and the solvents were evaporated to give a pale yellow solid (0.65 g, 20%). The hydroiodide salt from above was converted to the free base by dissolving it in water (100 ml) and adjusting to pH 10 with dilute sodium hydroxide solution. The free base was then obtained by extraction of this solution with chloroform (3 x 60 ml). After drying and evaporation to dryness, the combined chloroform extracts yielded a colorless solid (1.86 g, 58% crude). The two solids obtained after the above work-up were separately crystallized from ethyl acetate and were identified as N_8-methylaminolactam 78 by infrared, mass and proton nuclear magnetic resonance spectra.

(c) A 2-propanol (25 ml) solution of the aminolactam 75 (0.273 g) and methyl iodide (0.25 g) was stirred at room temperature for 16h. (This reaction was not be worked-up immediately but was left at room temperature for a week). 5% sodium hydroxide aqueous solution (20 ml) was added and this solution was extracted with chloroform (3 x 30 ml). After drying with anhydrous sodium sulphate and evaporation to dryness, the combined chloroform extracts gave a pale yellow solid (0.20 g). This solid was recrystallized from hot ethyl acetate to give a colorless solid (0.11 g, 37%) which was identified as 78 by tlc, mass and proton nuclear magnetic resonance spectra.

(3) 8-Acetyl-2,8-diaza-3-oxo-trimethylbicyclo[3.3.1]nonane 79: Aminolactam 75 (0.12 g) was dissolved in benzene (20 ml). A benzene (5 ml) solution of pyridine (0.25 g) was added to this solution followed by a slow addition of a benzene (5 ml) solution of acetyl chloride (0.12 g). This mixture was stirred at room temperature for 16 h while the reaction was monitored by tlc. This mixture was vigorously stirred with dilute hydrochloric acid and chloroform (25 ml) for 5 minutes. The organic layer was separated, dried and evaporated to dryness to give a colorless solid (50 mg, 40% crude). This solid was identified as N_8-acetylaminolactam 79 by mass and ^{1}H-nmr. Due to the low yield, further purification was not carried out.

3% METHANOLIC-HCl METHANOLYSIS OF N_8-METHYLAMINOLACTAM 78

Acetyl chloride (5 ml) was added dropwise to absolute methanol (100 ml) over a period of 0.5 h (78). N_8-Methylaminolactam 78 (1.97g, 0.01 mol) was dissolved in this 3% methanolic-HCl solution which was, then, heated under reflux. After 46 h a small portion (2 ml) of the reaction mixture was taken and worked up (as given below). Tlc of this portion indicated the completion of the reaction. Methanol was evaporated from the rest of the reaction mixture to give a solid which was dissolved in water (100 ml). This aqueous solution was made basic (pH 9) with dilute sodium bicarbonate solution and extracted first with dichloromethane (3 x 40 ml) and then with chloroform (3 x 30 ml). The combined organic extracts were back-washed with water (1 x 80 ml). The basic aqueous solution was saved.* The organic extracts were dried over anhydrous sodium sulphate and evaporated to dryness to give a brown oily material. Tlc of this product showed 3 spots. Purification of this crude product on silica gel preparative tlc, using ethyl acetate-ethanol (10:1, v:v), yielded three compounds (hereafter called A, B and C). Compound A, R_f 0.73, was identified as N-methylamidoketone 85 (22 mg, 1%). Compound B, R_f 0.57, was identified as amidoketone 87 (20 mg, 1%). Compound C, R_f 0.41, was identified as iminoester 81 (228 mg, 11%).

(1) N-Methylamidoketone 85: The basic aqueous solution* from above

was adjusted to pH 13-14 with 6N sodium hydroxide solution and extracted with chloroform (2 x 50 ml) and dichloromethane (2 x 50 ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to dryness. A clear liquid (1.66 g, 84%) was obtained which was pure by tlc and was identified as N-methylamidoketone 85 by ir, ^{1}H-nmr and ms spectra. This liquid was further purified by flash chromatography using dichloromethane-methanol (9:1, v:v) as the eluant. The clear liquid obtained in 50% yield based on 78 was distilled at 90°C (0.4 mm Hg).

ms (on FINNIGAN 1015), m/z: 197(35) [M^{+}], 154(90) [M - (CH_3-CO)], 112(95) [M - (CH_3CO-$C(CH_3)_2$)], 111(40) [M - (CH_3CO-$CH(CH_3)_2$)], 110(100) [M - (CH_3CO-$CH(CH_3)_2$ + $H^{\cdot}$)].

ir (thin film), cm^{-1}: 1710(s) [C=0, ketone], 1650(s) [C=0, amide].

^{1}H-nmr (90 MHz), ppm: m at 3.32 (2Hs, H_{6a}, H_{6e}), s at 2.92 (3Hs, CH_3-N), m centred at 2.20 (3Hs, H_{3a}, H_{3e}, H_4), s at 2.15 (3Hs, CH_3-C=0), m centred at 1.65 (2Hs, H_{5a}, H_{5e}), s at 1.11(3Hs) and 1.09(3Hs) [C-10 and C-11 methyls].

Carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 17.

Exact mass calcd. for $C_{11}H_{19}NO_2$: 197.1416; found (high resolution ms, 100%): 197.1416.

(2) N,N-Dimethylketoester 86: N_8-Methylaminolactam 78 (1.25 g) was subjected to 3% methanolic-HCl following the same procedure as given above. After usual work up a brown oil material (0.29 g) was obtained which was purified by flash chromatography using ether as

eluant. The compound which was eluted first was identified as N-methylamidoketone 85 (50 mg, 4%). The compound which eluted last was a clear liquid (30 mg, 2%) and was identified as 86 as follows:

ms, m/z: 243(7) [M^+], 212(24) [M - (OCH_3)], 200(19) [M - (CH_3CO)], 158(100) [M - (CH_3-CO-$C(CH_3)_2$)], 126(28) [$(CH_3)_2N$-CH_2-CH_2-CH=CH-CO^+], 58 (100).

ir(thin film), cm^{-1}: 2960-2940(s) [CH_2 and CH_3 stretch], 2810(m) and 2780(m) [CH stretch of N-CH_3], 1740(s) [COO-CH_3], 1710(s) [C=O, ketone].

^{1}H-nmr (60 MHz), ppm: s at 3.72 (3Hs, -COO-CH_3), s at 2.28 (3Hs, O=C-CH_3), s at 2.20 (6Hs, $N(CH_3)_2$), broad m at 2.60-1.80 (4Hs, N-CH_2- and COO-CH_2-), m at 1.70 - 1.12 (3Hs, -CH gama to -N and -CH_2 beta to -N), s at 1.10 (6Hs, $C(CH_3)_2$).

Due to low yield, no elemental analyses or carbon-13 nuclear magnetic resonance data could be obtained. This compound could not be isolated during other trials.

(3) Amidoketone 87: Four samples of iminoester 81 in $CDCl_3$ in nmr tubes were left exposed to light at room temperature. After a few months some colorless solid was observed in the nmr tubes which was crystallized from a mixture of benzene-hexanes (1:3, v:v), yield 60 mg; mp 116-118°C; R_f 0.57 in ethyl acetate-ethanol (10:1, v:v).

ms (on FINNIGAN 1015), m/z: 183(7) [M^+], 140(44) [M - (CO-CH_3)], 98(60) [140-(140-(CH_2=C=O)], 97(39) [140-(HN=C=O)] 82(25), 69(32), 55(100) [140-(CH_2-$(CH_2)_2$-CO-NH].

ir (thin film), cm^{-1}: 3428(s) and 3233(s) [NH stretch], 1707(m)

[C=O, ketone] and 1647-37(s) [C=O, amide].

^{1}H-nmr (90 MHz), ppm: broad m at 6.82 (1H, NH), m at 3.46-3.09 (2Hs, H_{6a}, H_{6e}), m at 2.42-2.02 (3Hs, H_{3a}, H_{3e}, H_4), s at 2.15 (3Hs, C-9 methyl), m at 1.87-1.26 (2Hs, H_{5a}, H_{5e}), two s at 1.11 (3Hs) and 1.09 (3Hs) [C-10 and C-11 methyls]. The coupling of H_{6a} and H_{6e} to the NH (for which no J values were measured) was indicated by the NH-decoupled ^{1}H-nmr (90 MHz) spectrum.

Exact mass calcd. for $C_{10}H_{17}NO_2$: 183.1259; found (high resolution ms, 32%): 183.1259.

Carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in Table 19.

PREPARATION OF 1-CAMPHOR OXIME 103a:

d-Camphor (60.0 g, 0.395 mol) was dissolved in ethanol (400 ml). Hydroxylamine hydrochloride (60.0 g, 0.863 mol) followed by pyridine (70 ml) was added to this solution and the mixture was heated under reflux for 1 h. The ethanol was evaporated and to the remaining semi-solid material water (250 ml) was added and the mixture was stirred for 5 min. A colorless crystalline solid appeared which was filtered off, washed with water (2 x 30 ml), and dried under suction for 16 h (65.37 g, 99%). A portion of this product was recrystallized from boiling petroleum ether; mp 118-120°C.

ir (thin film), cm^{-1}: 3295(s) [OH], 1683(s) [C=N].

ms, m/e: 167(100 [M^+], 152(33) [M - (CH_3)], 150(39) [M - (OH)], 124(82) [150 - (CN)].

^{1}H-nmr (90 MHz), ppm: broad m at 8.43 (1H, OH), ddd at 2.53 (1H, H_{3a}) [$^2J(3a,3b)$ = -18 Hz, $^3J(3a,4)$ = 4.5 Hz, $^4J(3a,5a)$ = 2.8 Hz], d at 2.07 (1H, H_{3b}) [$^2J(4b,3a)$ = -18 Hz], set of m at 1.97 - 1.14 (5Hs, H_4, H_{5a}, H_{5b}, H_{6a}, H_{6b}), three s at 1.02 (3Hs), 0.91 (3Hs), and 0.81 (3Hs) [C-8, C-9 and C-10 methyls].

$[\alpha]_D^{26}$ = -40.7° (c = 9.8 abs. ethanol).

The camphor oxime 103b prepared in 98.4% yield from dl-camphor was identical to the above oxime 103a by mp, ir, nmr and mass spectra.

PREPARATION OF dl-α-CAMPHOLENONITRILE 101

Acetyl chloride (112 ml, 1.57 mol) was added to ice-cooled racemic camphor oxime 103b (35.2 g, 0.211 mol) over a period of 30 min. The reaction mixture was then allowed to warm to room temperature. Some oxime remained undissolved, therefore, 40 ml of excess acetyl chloride was added to this mixture. This solution was poured over ice (150 g) and then extracted with benzene (3 x 100 ml). The benzene extracts were washed with 20% sodium carbonate solution, dried with sodium sulphate and the solvent was evaporated in vacuo. The liquid product remaining was distilled at 74°C (0.9 mm Hg) (25.3 g, 96%).

ms, m/z: 149(11) [M^+], 134(68) [M - (CH_3)], 109(15) [M - (CH_2CN)], 108(15) [109 - (H), or 134 - (CN)], 107(21) [108 - (H)], 94(34) [134 - (CH_2CN) or 109 - (CH_3)], 93(100) [94 - (H) or 108 - (CH_3)].

ir (thin film), cm^{-1}: 2235(m) [CN].

^{1}H-nmr (90 MHz), ppm: m at 5.24 (1H, vinyl proton), sets of m at 2.61-1.69 (5Hs, H_1, H_{5a}, H_{5b}, H_{6a}, H_{6b}), m at 1.61 (3Hs, C-10 methyl) two s at 1.07 (3Hs) and 0.86 (3Hs) [C-8 and C-9 methyls].

(1R)-α-Campholenonitrile 105 was prepared following the same procedure as discussed for the preparation of (101); bp 56°C (0.8 mm Hg), 94% yield: $[\alpha]_D^{22}$ = + 10.4° (c = 10, abs. ethanol). The ir, nmr and mass spectra were identical to those of racemic α-Campholenonitrile 101.

PREPARATION OF β- CAMPHOLENONITRILE 102:

A mixture of α-Campholenonitrile (101) (5.20 g, 0.0349 mol) and conc. hydrochloric acid (25 ml) was heated in an oil bath at 48°C for 3 h. Water (25 ml) was added to this mixture and was then left in an ice bath for one h. The mixture was further diluted with water (25 ml) and then extracted with benzene (3 x 40 ml). The combined benzene extracts were dried with anhydrous sodium sulphate and the solvents were evaporated off. A yellow liquid (3.31 g, 64%) was obtained; bp 45°C (0.05 mm Hg).

ms, m/z: 149(14) [M^+], 134(100) [M - (CH_3)], 109(9) [M - (CH_2CN)], 108(6) [109 - (H) or 134-(CN)], 107(17) [108 - (H)], 94(30) [134 - (CH_2CN) or 109 - (CH_3)], 93(86) [94 - (H) or 108 - (CH_3)].

ir (thin film), cm^{-1}: 2235(m) [CN].

^{1}H-nmr (90 MHz), ppm: sharp m at 3.08 (2Hs, H_{6a}, H_{6b}), m at 2.34 (2Hs, H_{5a}, H_{5b}), m at 1.70 (2Hs, H_{4a}, H_{4b}), sharp m at 1.54 (3Hs, C-8 methyl), s at 0.99 (6Hs, C-9 and C-10 methyls).

During another trial, the aqueous layer was extracted with benzene (3x) as above. The aqueous layer was saved. After one week an oily liquid floating on the aqueous layer was extracted with

benzene. Each set of benzene extracts separately yielded a brown oil. The tlc behaviour in benzene of both products was identical and each showed two spots. Therefore, both products were combined and purified by flash chromatography using benzene-ethanol (13:1, v:v). Only two fractions (each 10 ml) were collected after which the silica gel column accidently dried. Tlc of both fractions showed one identical spot. Evaporation of solvent to dryness from the combined fractions yielded a clear liquid (18%) which was identified as the lactone 111 by ir, nmr, and mass spectroscopy. Similar analysis for 111 are given later for a separate preparation. The dried silica gel column was thoroughly washed with acetone. Tlc of the material left after the evaporation of acetone showed 5 spots and was not further investigated.

PREPARATION OF β-CAMPHOLENAMIDE 96 (88)

Zinc chloride (41 g) was fused in a suction flask under house vacuum with a flame and allowed to solidify. After re-fusing and re-solidification the zinc chloride was crushed in a mortar and mixed quickly with dry camphor oxime 103b (70g, 0.419 mol). This mixture was heated with stirring in oil bath controlled at 110°C. After exactly 10 minutes a vigorous reaction occured with the evolution of white fumes and the solid mixture became liquid. This liquid was then cooled and diluted with water (150 ml). A thin layer of yellowish liquid separated from the water. Ether (150 ml) was added to this mixture and after gentle shaking the organic layer was

separated from the aqueous layer (the aqueous layer was saved)*. The ether layer was dried with anhydrous sodium sulphate and evaporated to dryness. A light brown colored liquid (27.0g, 66%) was obtained; tlc in benzene-methanol (13:1, v:v) showed one spot. This liquid was identified as β-Campholenonitrile 102.

The above aqueous layer* was extracted with ether (2 x 100ml). The ether extracts were combined and dried with anhydrous sodium sulphate and the solvent was evaporated off. A dark coloured liquid was obtained which was dissolved in chloroform and then extracted with large amounts of pentane. Evaporation of the pentane yielded β-campholenamide 96 as a colorless shiny solid which was crystallized from ethyl acetate, (9.34g, 20%); mp 103-105°C.

ms, m/z: 167(32) [M^+], 152(100) [M - (CH_3)], 135(28) 152 - (NH_3), 109(28) [M - (CH_2-CO-NH_2)], 108(14) [109 - (H) or 152 - ($O{=}C{=}NH_2^+$), 107(49) [108 - (H)], 94(5) [135 - (HCCO) or 109 - (CH_3)], 93(28) [108 - (CH_3) or 94 - (H)].

ir (nujol), cm^{-1}; 3420(m) and 3050(m) [NH stretch], 1661(s) [C=O stretch];.

^{1}H-nmr (90 MHz), ppm: 6.67 (1H, broad) and 6.00 (1H, broad) [NH_2], two s at 3.07 and 3.06 [2Hs, H_{6a}, H_{6b}], m at 2.28 (2Hs, H_{5a}, H_{5b}), m at 1.69 (2Hs, H_{4a}, H_{4b}), dd at 1.58 (3Hs, C-8 methyl) [$^5J(Me,H_{5a})$ 2 Hz, $^5J(Me, H_{5b})$ = 2 Hz], two s at 1.02 and 1.01 [6Hs, C-9 and C-10 methyls].

β - Campholenamide 96 was also prepared in 47% yield by 30% hydrogen peroxide/6N sodium hydroxide oxidation of β - campholenonitrile (102); (for the details of this oxidation, see below).

PREPARATION OF ∝- CAMPHOLENAMIDE 95 (87)

∝- Campholenonitrile 101 (8.00 g, 0.054 mol) was dissolved in a mixture of ethanol (40 ml) and 30% hydrogen peroxide (33 ml, 0.291 mol). Sodium hydroxide (6N) (4ml, 0.024 mol) was slowly added to this solution, and when the exothermic reaction (below 50°C) was over, the mixture was heated in an oil bath at 45-48°C for 16 h. The reaction was monitored by tlc. The mixture was adjusted to pH 6.8 with 5% sulphuric acid and allowed to stand for 2 hours at 0°C. The colorless shiny precipitate which appeared which was filtered, washed with hexanes and air dried under suction, (7.67 g, 88%); mp 109-112°C; ir, mass and ^{1}H-nmr spectra were identical to those of (1R)-∝-Campholenamide 104, (see next paragraph).

PREPARATION OF (1R)-∝-CAMPHOLENAMIDE 104

(1R)-∝-Campholenamide 104 was prepared by the 30% hydrogen peroxide/6N sodium hydroxide oxidation of (1R)-∝-Campholenonitrile 105 (as above) in 69% yield; mp 130-131°C.

ms, m/z: 167(22) [M^{+}], 152(16) [M - (CH_3)], 135(8) [152 - (NH_3)], 109(63) [M - (CH_2-CO-NH_2)], 108(92) [109 - (H) or 152 - (O=C=NH_2^{+})], 107(34) [108 - (H)], 94(10) [135 - (HCCO) or 109 - (CH_3)], 93(100) [108 - (CH_3) or 94 - (H)].

ir (nujol), cm^{-1}: 3395(m) and 3205(m) [NH stretch], 1667(s) [C=O, amide band I] and 1632(s) [amide band II].

^{1}H-nmr (90 MHz), ppm: broad m at 5.60 (2Hs, NH_2), m at 5.23 (1H,

vinyl H), sets of m at 2.57 - 1.78 (5Hs, H_1, H_{5a}, H_{5b}, H_{6a}, H_{6b}), m at 1.60 (3Hs, C-10 methyl), two s at 1.02 (3Hs) and 0.80 (3Hs) [C-8 and C-9 methyls].

$[\alpha]_D^{21}$ = - 3.4° (c = 7.1 abs. ethanol).

PREPARATION OF AMINOLACTAM 75 FROM α-AND β-CAMPHOLENAMIDES 95 AND 96

Sodium azide (0.85 g, 0.013 mol) was added to a chloroform (25 ml) solution of α-campholenamide (1.0g, 0.006 mol). To this rapidly stirring mixture, conc. sulphuric acid (4.0 ml) was added over a period of 20 min. The mixture was stirred at room temperature for 21 hours. Chloroform (30 ml) was added to the reaction mixture and then decanted from the lower viscous layer. Water (40 ml) and chloroform (40 ml) were added to the viscous mixture. After stirring for 5 minutes the two layers were separated. The aqueous layer was made basic (pH 9.5) with aqueous sodium hydroxide solution (20%) and then extracted with chloroform (4 x 30 ml). The chloroform layers were combined, dried with anhydrous sodium sulphate, and evaporated to dryness. A colorless solid was obtained (0.80 g, 73%), which was pure by tlc and nmr. This product was identified as the aminolactam 75 by its mass, ir, nmr and tlc.

β - Campholenamide 96, under the same conditions and on the same scale, yielded 0.78 g (72%) of the aminolactam 75.

During another pair of trials under identical condtiions, conc. sulphuric acid (4.1 ml) was added to the rapidly stirring mixtrue of the campholenamide (1.0g, 0.006 mol), chloroform (25 ml) and sodium

azide (0.90 g, 0.0138 mol) over a period of 30 minutes. Each of the reaction mixtures were stirred for 54 hours at room temperature. Identical workup (as above) yielded aminolactam 75 in 66% yield from α-campholenamide and in 65% yield from β-campholenamide.

PREPARATION OF AMINOLACTAM 75 FROM(1R)-α-CAMPHOLENAMIDE 104

Conc. sulphuric acid (10 ml) was added in one portion to a chloroform solution (80 ml) of optically active α-campholenamide (3.34 g, 0.02 mol) followed by the slow addition of sodium azide (2.60 g, 0.04 mol) over a period of 5 minutes. The mixture was stirred for 28 hours at room temperature. Following the work-up, as above, colorless crystals (2.18g, 60%) of the aminolactam 75 were obtained. The crystals were triturated with cold ethyl acetate (2 x 5 ml), and then recrystallized from ethyl acetate (1.52g, 42%); $[\alpha]_D^{24} = -0.185°$ (c = 10, abs. ethanol). A second recrystallization from ethyl acetate gave product of mp 179.5-181°C; $[\alpha]_D^{20} = -0.174$ (c = 11, abs. ethanol).

PREPARATION OF DEUTERATED AMINOLACTAM 109b FROM β-CAMPHOLENAMIDE 96

Sodium azide (0.43 g, 0.0066 mol) was added to a chloroform (25 ml) solution of β-campholenamide 96 (0.50 g, 0.003 mol). To this mixture conc. sulphuric acid-d_2(98% solution in D_2O, 99.5 + atoms %D) (2ml) was added with stirring over a period of 20 minutes. During

this addition the temperature reached 35°C. The gummy mixture was stirred for an additional 3.5 h at room temperature. Chloroform (30 ml) was added to the mixture, stirred for a minute and decanted from the gummy sulphuric acid layer. Upon evaporation of the chloroform a clear liquid (0.36 g) was obtained which was not identified. To the gummy acidic layer water (40 ml) and chloroform (40 ml) were added and after stirring for a minute, the chloroform layer was separated. The acidic aqueous layer was adjusted to pH 9.5 with sodium hydroxide (20%) solution and extracted with chloroform (4 x 30 ml). The combined chloroform extracts were dried with anhydrous sodium sulphate, and evaporated to dryness. The yellowish solid (0.32 g, 58%) obtained was triturated with ethyl acetate (5 ml). The remaining colorless solid (0.23 g, 42%) showed one spot in tlc, R_f 0.23, in chloroform-methanol (15:1, v:v). The crude product was recrystallized (2x) from ethyl acetate to give pure product; mp 179.5-181°C; the pure product was dried for 2 hours at 78°C (0.5 mm Hg).

ms(on FINNIGAN 1015) m/z: 187(4), 186(14), 185(30), 184(30), 183(14), 182(4) [these peaks accounts for M^+ peaks of the aminolactam incorporated with 5, 4, 3, 2, 1 and 0 deuterium(s) respectively], 171(3), 170(6), 169(6), 168(5), 167(4), 144(4), 143(8), 142(12), 141(16), 140(12), 139(7), 116(29), 115(34), 114(18), 102(50), 101(100); Exact mass calcd. for: $C_{10}H_{12}D_6N_2O$, $C_{10}H_{13}D_5N_2O$, $C_{10}H_{14}D_4N_2O$, $C_{10}H_{15}D_3N_2O$, $C_{10}H_{16}D_2N_2O$, $C_{10}H_{17}DN_2O$ and $C_{10}H_{18}N_2O$ were respectively: 188.1796, 187.1733, 186.1670, 185.1607, 184.1545, 183.1482, and 182.1419; found (on high resolution ms) were respectively; 188.1785(1), 187.1723(6), 186.1665(22), 185.1606(55),

184.1544(50), 183.1481(23), 182.1417(5).

The data from the ^{1}H-nmr (400 MHz) are given in the results and discussion section (see Part II, Section C4).

PREPARATION OF DEUTERATED AMINOLACTAM 109a FROM ∝-CAMPHOLENAMIDE 95

Conc. sulphuric acid-d_2 (98% solution in D_2O, 99.5 + atoms % D) (8 ml) was added to a chloroform (50 ml) solution of ∝-campholenamide 95 (1.67 g, 0.01 mol). Sodium azide (1.30 g, 0.02 mol) was added portionwise over a period of 10 minutes to this rapidly stirring mixture. During this addition the temperature reached 40°C. This two phase reaction mixture was stirred for 27.5 h at room temperature. The upper chloroform layer was decanted from the gummy sulphuric acid-d_2 layer. The sulphuric acid-d_2 layer was washed once more with chloroform (20 ml), diluted with water (20 ml), and then made basic (pH 9) with 20% sodium hydroxide solution. Extraction of the basified aqueous layer with chloroform (4 x 60 ml) gave combined chloroform extracts which were backwashed with fresh water (1 x 35 ml), dried over anhydrous sodium sulphate, and evaporated to dryness. A colorless solid (1.11 g, 61%) was obtained which was pure by tlc. After repeated recrystallization from ethyl acetate the crystals were dried for 4 h at 78°C (0.1 mm Hg); mp 180-181°C (in a sealed tube).

ir (nujol), cm^{-1}: 3310(m) and 3280(m) [H-N_8 stretch], 3180(m) [H-N_2 stretch], 2185 (w-m) [CD_2 stretch], 2060 (w-m) [CD stretch], 1660(s) [C=O, amide band I], and 1642(s) [amide band II].

ms (on FINNIGAN 1015) m/z: 191(2), 190(9), 198(19), 188(41),

187(64), 186(80), 185(64), 184(25), 183(4), and 182(0) [these peaks account for the M^+ peaks of the aminolactam containing with 9, 8, 7, 6, 5, 4, 3, 2, 1, and 0 deuterium(s) respectively], 174(1.5), 173(3), 172(6), 171(12), 170(12), 169(4), 168(3), 167(1.5) [these peaks are $M^+ - (CH_3)$], 147(2), 146(4), 145(8), 144(12), 143(17), 142(17), 141(14), 140(6), 105(4), 104(16), 103(50), 102(100), 101(98), 100(16), and 99(9).

Anal. Calcd. for $C_{10}H_{18}N_2O$: C64.82, H9.89, N15.12; found: C64.81, H9.73, N15.15.

Exact mass calcd. for: $C_{10}H_9D_9N_2O$, $C_{10}H_{10}D_8N_2O$, $C_{10}H_{11}D_7N_2O$, $C_{10}H_{12}D_6N_2O$, $C_{10},H_{13}D_5N_2O$, $C_{10}H_{14}D_4N_2O$, $C_{10}H_{15}D_3N_2O$, $C_{10}H_{16}D_2N_2O$, $C_{10}H_{17}D_1N_2O$, were respectively: 191.1984, 190.1921, 189.1858, 188.1796, 187.1733, 186.1670, 185.1607, 184.1545, 183.1482; found (on high resolution ms) were respectively: 191.1977(1), 190.1916(5), 189.1853(15), 188.1792(33), 187.1730(59), 186.1670(76), 185.1608(61), 184.1546(18), 183.1477(3).

The data from the ^{1}H-nmr (400 MHz) are given in the results and discussion section (see Part II, section C4).

PREPARATION OF DEUTERATED AMINO LACTAM 109c FROM d-CAMPHOR 106

Deuterated aminolactam 109c was prepared from d-camphor following the procedure as given previously except that this time sulphuric acid-d_2 (98% solution in D_2O, 99.5 + atoms %D) was added to the mixture of sodium azide, d-camphor and chloroform. After repeated

recrystallization of the crude product from ethyl acetate, the crystals were dried for 2 hours at 78°C (0.5 mm Hg); mp 180-181°C (in a sealed tube).

ms (on FINNIGAN 1015) m/z: 190(2.4), 189(4), 188(6.5), 187(11), 186(23), 185(30), 184(23), 183(15), 182(6), [these peaks account for the M^+ peaks of the aminolactam containing with 8, 7, 6, 5, 4, 3, 2, 1, and 0 deuterium(s) respectively], 171(4), 170(7), 169(6), 168(6), 167(7.5) [these peaks are $M^+-(CH_3)$], 145(5), 144(8), 143(10), 142(15), 141(16), 140(13), 139(8), 127(23), 126(33), 125(21), 117(19), 116(42), 115(42), 102(61), 101(100).

PREPARATION OF AMINOLACTAM 75 FROM ∝-CAMPHOLENONITRILE 101

Sodium azide (1.28 g, 0.02 mol) was added to a chloroform (38 ml) solution of the ∝-campholenonitrile (1.5 g, 0.01 mol) and the mixture was kept in an ice bath. Conc. sulphuric acid (6.0 ml) was added dropwise to this solution over a period of 30 minutes and the mixture was stirred vigorously for 24 h at room temperature. The chloroform layer was decanted and water (40 ml) and fresh chloroform (40 ml) were added to the bottom gummy layer. The mixture was stirred for a minute and the chloroform layer was separated. The acidic aqueous layer was adjusted to pH 9.5 with dilute aqueous sodium hydroxide solution, and extracted with chloroform (4 x 30 ml). The combined chloroform extracts were dried over anhydrous sodium sulphate and evaporated to dryness. A brown oily material was obtained which crystallized upon cooling (1.73 g, 94.5% recovery). This product

showed 4 spots on tlc in toluene-methanol (13:1, v:v). The crude product was purified by flash chromatography using toluene-methanol (13:1, v:v) as the solvent. Based on their R_f values fractions 6-10 and 23-38 were combined. Fractions 23-38 yielded a solid (20% yield based on the starting ∝-campholenonitrile) which was identified as the aminolactam 75 by nmr, ir, and mass spectroscopy.

Fractions 6-10 yielded 45 mg of an oily liquid.

^{1}H-nmr (60 MHz) in $CDCl_3$, ppm: ddd at 3.80-3.53(1H)[Js = 2 Hz, 5.5 Hz, and 9.5 Hz], sharp m at 3.32-2.90 (3Hs), broad m at 2.60-1.38(4Hs), three s at 1.30 (3Hs), 1.16 (3Hs) and 1.00 (3Hs).

ir (neat), cm^{-1}: 3330(m) [HN stretch], 2200(s) [C N], 1712(m), 1640(m).

ms, m/z: 179(66) [M^+], 164(35) [$M^+ - (CH_3)$], 138(43), 136(43), 125(80), 124(100), 123(70), 111(100), 110(100). The structure 110 was tentatively assigned to this compound.

REACTION OF THE AMINOLACTAM 75 WITH SULPHURIC ACID-D_2

Conc. sulphuric acid-d_2 (98% solution in D_2O, 99.5 + atoms %D) (8 ml) was added to a chloroform (50 ml) solution of aminolactam 75 (1.82g, 0.01 mol). The two phase reaction mixture was stirred for 28.5 h at room temperature. The reaction mixture remained clear. After addition of water (10 ml) to the reaction mixture, 20% sodium hydroxide solution (10 ml) was added to adjust the pH to 2-3. The chloroform layer was separated and the acidic aqueous layer was adjusted to pH 8 with 20% sodium hydroxide solution. The basified

aqueous layer was extracted with chloroform (4 x 60 ml). The combined chloroform extracts were washed with water (100 ml). The water washings were backwashed with fresh chloroform (50 ml). The combined chloroform extracts were dried over anhydrous sodium sulphate and evaporated to dryness. A colorless solid (0.39 g, 21% recovery) was obtained and was identified as the starting aminolactam by mass, ir and nmr spectra.

The above aqueous layer (pH 8) was adjusted to pH 13-14 with 20% sodium hydroxide solution and extracted with chloroform (4 x 50 ml). Following work-up as above the chloroform extracts yielded a colorless solid (1.22 g, 67% recovery). The above two products were identical by tlc and nmr. Therefore the two solids were combined and recrystallized from ethyl acetate; mp 181-183°C (in a sealed tube). ms, m/z: 183(7) [$M^+ + 1$], 182(47) [M^+], 167(10), 139(15), 114(37), 101(100), 98(44) (There was no evidence of deuterium incorporation). ir (nujol), cm^{-1}: 3310(m) and 3285(m) [HN_8 stretch], 3177(m) [HN_2 stretch], 1661(s) [C=0, amide band I], 1654-37(s) [amide band II].

The results of the ^{1}H-nmr were found identical to that of aminolactam 75 (undeuterated). No evidence of deuterium incorporation was observed.

ATTEMPT TO ISOMERIZE 104 TO 96 IN CONC. SULPHURIC ACID

(1R)-α-Campholenamide 104 was dissolved in chloroform (50 ml, Fisher certified A.C.S.). Conc. sulphuric acid was added to this solution, and the mixture was stirred at room temperature for 24 h.

The upper chloroform layer was decanted from the bottom sulphuric acid layer. Fresh chloroform (50 ml) was added to the acid layer and the mixture was stirred for 5 minutes. The chloroform layer was decanted again. The combined chloroform layers did not contain any material. The sulphuric acid layer was diluted with water (60 ml), and the pH was adjusted to 9 with 20% sodium hydroxide solution (46 ml). This basic aqueous layer was then extracted with chloroform (4 x 100 ml). The combined chloroform layers were dried with anhydrous sodium sulphate, and the chloroform was evaporated to dryness. A clear viscous liquid was obtained (3.20 g). Tlc in either benzene-methanol (9:1, v:v) or chloroform-ethanol (10:1, v:v) showed only one spot. Tlc in ethyl acetate showed three spots, the one with higher R_f value being visible only under UV light and the two with lower R_f values were visible only with iodine. Upon purification of this crude product by flash chromatography, using ethyl acetate as the solvent, only the two compounds of higher R_f value were collected in fractions 11-16 and 18-44 (each 20 ml) respectively. Characterization of these fractions is given below:

(1) Dihydro-β-Campholenolactone 111:

Evaporation of solvents from the combined fractions 11-16 yielded a clear liquid (0.805 g, 18%) which showed one spot in tlc in ethyl acetate and which solidifies below 22-25°C. It was distilled at 40°C (0.01 mm Hg) using a cold finger trap [literature (61) bp 78.5°C (0.52 mm Hg)].

ms, m/z: 168(12) [M^+], 153(6) [M - (CH_3)], 125(42) [153 - (CO)], 111(42) [153 - (CH_2=C=O)], 55(100) [$(CH_3)_2C=CH]^+$.

ir (thin film), cm^{-1}: 1770(s) [5-membered lactone].

^{1}H-nmr (90 MHz), : ddd at 2.88 (1H, H_{4a}) [^2J(4a, 4b) = -17.1 Hz, ^3J(4a,5) = 8.5 Hz, ^4J(4a,6a) = 1.3 Hz], a ddddd at 2.62 (1H, H_5 [^3J(5, 6a) = 9 Hz, ^3J(5, 4a) = 8.5 Hz, ^3J(5, 4b) = 2 Hz, ^3J(5,6b) = 2.5 Hz, ^4J(5, 7a) = 1-2 Hz], a dd at 2.33 (1H, H_{4b}) [^2J(4b, 4a) = -17.1 Hz, ^3J(4b, 5) 2 Hz], sets of multiplets at 2.37 - 1.20 (4Hs, H_{6a}, H_{6b}, H_{7a}, H_{7b}), three singlets at 1.30 (3Hs), 1.08(3Hs), and 0.91 (3Hs) [C-9, C-10 and C-11 methyls].

The carbon-13 nmr (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in the Results and Discussion Section.

(2) 2,4,6-Tri(2'-Hydroxy-2',3',3'-Trimethylcyclopentylmethyl)-1,3,5-Triazine, 112

The fractions from 18 to 44 (from above chromatography) each showed one spot of the same R_f value on tlc in ethyl acetate. At least every second fraction was checked by infrared and nmr spectroscopy, and they were found identical. Because fractions 18-25 did not shown any impurities they were combined separately from fractions 26-44. The solvents were evaporated from both sets of fractions. A colorless solid (1.118 g from fractions 18-25 and 0.753 g from fractions 26-44) was obtained. The solid obtained from fractions 18-25 was recrystallized (6x) from a very dilute solution

of hexanes; mp 143-146°C; R_f 0.6 [in EtOAc], 0.24 [in $CHCl_3$-MeOH (10:1, v:v)], 0.11 [in C_6H_6-MeOH (9:1, v:v)], on tlc the spot was visible under UV light but not with iodine.

Anal. calcd. for $C_{30}H_{51}N_3O_3$: C71.81, H10.25, N8.37; found: C71.75, H10.34, N8.38.

The samples were dried in a drying pistol at 78°C (0.1 mm Hg) for over 10 hours before sending for elemental analysis and ^{1}H-nmr (400 MHz) spectroscopic studies.

ir (thin film), cm^{-1}: broad band at 3500(m) [OH stretch], 1540(s) [C=N stretch of triazine].

ms (on FINNIGAN 1015), m/z: 501(9) [M^+], 458(81), 440(20), 422(55), 168(13), 123(61), 109(100).

The results from the ^{1}H-nmr (400 MHz) spectrum, and the carbon-13 nuclear magnetic resonance (regular broad band ^{1}H-decoupled and ^{1}H-decoupled INEPT) data and assignments are given in the Results and Discussion Section.

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