THE PHOTOCHEMISTRY OF α-TOSYLOXYKETONES

A Thesis

Submitted to the Faculty

of

Graduate Studies

The University of Manitoba

by

Hoi Kiong Lai

In Partial Fulfillment of the

Requirements for the Degree

of

Doctor of Philosophy

Department of Chemistry

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TO MY PARENTS, BROTHERS AND SISTERS

ACKNOWLEDGEMENTS

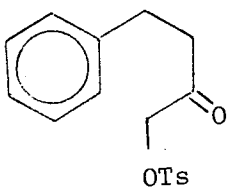
The author would like to thank Dr. J. L. Charlton for his guidance and patience in supervising this project.

Thanks also go to Dr. N. R. Hunter for his continued interest in this project, and to Drs. D. M. McKinnon, C. M. Wong and J. F. Templeton for their advice and criticism during the course of this work.

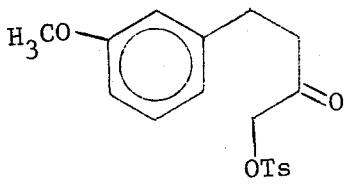
Graduate Fellowships provided by the University of Manitoba are also gratefully acknowledged.

ABSTRACT

Several α-tosyloxyketones have been chosen for model studies to determine the feasibility of photochemically induced polyene cyclizations. Accordingly the photochemistry of 1-tosyloxy-4-phenyl-2-butanone (I), 1-tosyloxy-4-(3-methoxy-phenyl)-2-butanone (II), 1-tosyloxy-3,7-dimethyl-6-octen-2-one (III), trans-1-tosyloxy-5-methyl-8-(3-methoxyphenyl)-5-octen-2-one (IV) and α-tosyloxyacetophenone (V) have been investigated.



(I)



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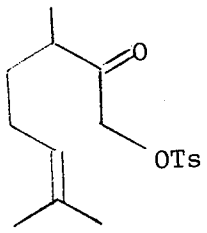

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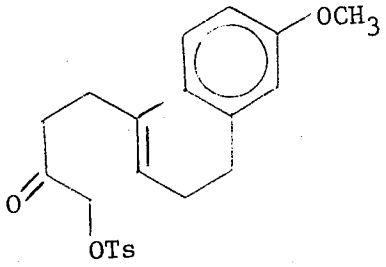

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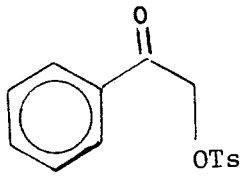

(V)

Radical and carbonium ion pathways are proposed to account for the photolysis products observed. A radical mechanism is proposed for photoreduction and photocyclization products, whereas a carbonium ion pathway is suggested for an observed Favörskii-type rearrangement. The photocyclization process is enhanced by the presence of an electron-rich aromatic nucleus bearing an electron-donating substituent. It is concluded that electron-transfer from the aromatic nucleus to the carbonyl function is responsible for the relatively high yields of cyclized products in compound (II). However, in a suitable substrate, radical cyclization is feasible even in the absence of an intramolecular interaction. This is demonstrated in the case of compound (III) where photocyclization, though of a lower yield, is observed.

The polyolefin, compound (IV), failed to give any detectable amount of the cyclization products. It is obvious that the influence of the methoxy-substituted benzene ring is too far removed to be effective in enhancing radical cyclization.

Compound (V) has been included in the photolysis studies in order to confirm the general occurrence of the Favörskii-type rearrangement in the photolysis of α-tosyloxyketones in ethanol. This reaction has not been reported for α-sulfonyloxyketones in the literature.

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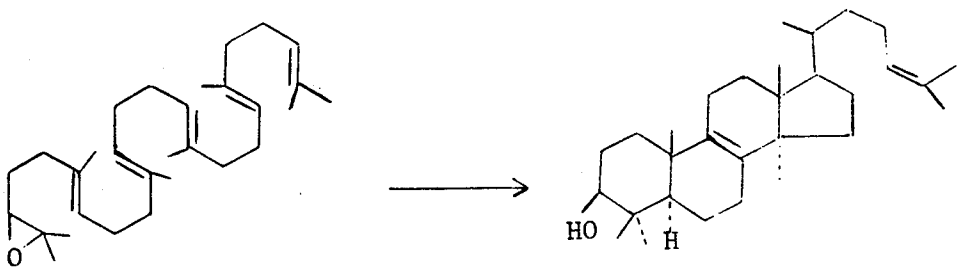
NON-ENZYMATIC BIOGENETIC-LIKE POLYENE CYCLIZATIONS

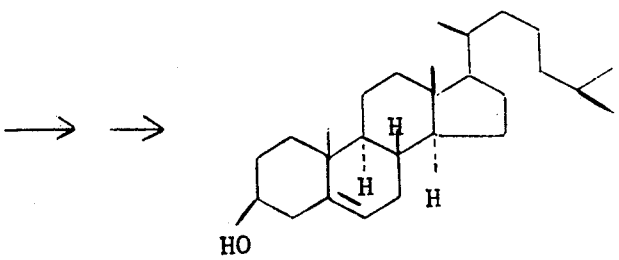
NON-ENZYMATIC BIOGENETIC-LIKE POLYENE CYCLIZATIONS

The cyclization of acyclic polyenes with concomitant re - arrangement of the polycyclic intermediates has long been conceded to be the key step in the biosynthesis of most classes of cyclic terpenoids [1]. Some of the most impressive examples of this type of biosynthesis involve the acyclic polyolefin squalene. Squalene oxide was first established as the intermediate in the cyclization reaction leading to lanosterol and eventually to cholesterol in 1966 [2]. Prior to these reports, speculation on the mechanism of squalene cyclization had led to a number of model studies [3 - 6] and even after the role of squalene oxide had been established, interest in both the mechanistic and synthetic aspects of polyene cyclizations did not diminish. Most attention has been focussed on the acid-catalyzed cationic cyclization [7 - 10], but studies on free radical polyene cyclizations have also been undertaken [11]. Before 1966 free radical intermediates were considered possible candidates in squalene cyclization [11].



Squalene oxide

Lanosterol



Cholesterol

The most impressive feature of the squalene cyclization is the fact that this polyolefin, which has no chiral centers, is converted into a single stereoisomer even though 128 different stereochemical forms are possible. It is this complete stereoselectivity that led to extensive studies by organic chemists on the possibility of effecting similar stereoselective cyclizations in the absence of enzymatic control.

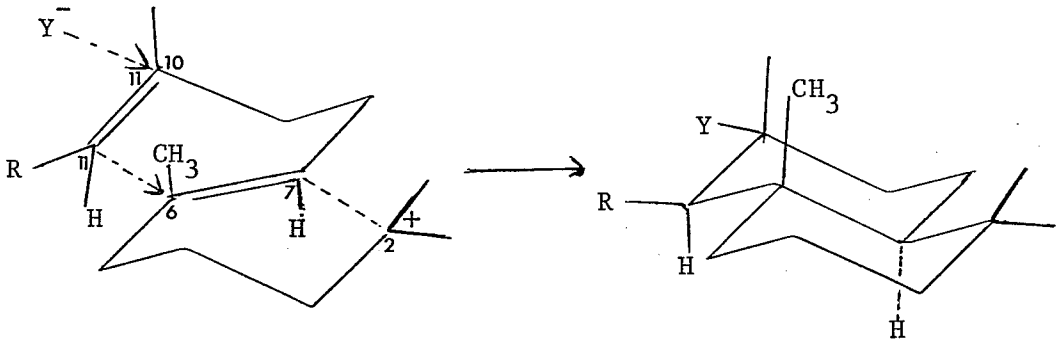
Mechanistically, there are two known types of non-enzymatic, biogenetic-like polyene cyclizations by which a tri- or tetracarbocyclic system is synthesized in a single-step reaction.

(A) Cationic Cyclizations

Extensive studies have now shown conclusively that stereoselective synthesis of polycyclic ring systems can be accomplished in good yield by non-enzymatic, cationic cyclization of suitable polyolefins [10, 12]. In their attempts to rationalize the high degree of stereoselectivity for these types of reactions, Stork [3] and Eschenmoser [4] have independently proposed that the stereochemistry of polycyclic compounds formed by biosynthetic cyclizations may be a consequence more of intrinsic stereoelectronic factors than of enzymatic conformational control.

The Stork-Eschenmoser hypothesis suggests a synchronous reaction in which all bonds involved in the formation of the polycyclic system are made and broken essentially simultaneously. Thus the electrophilic attack on the 6,7-olefinic bond [see figure below]

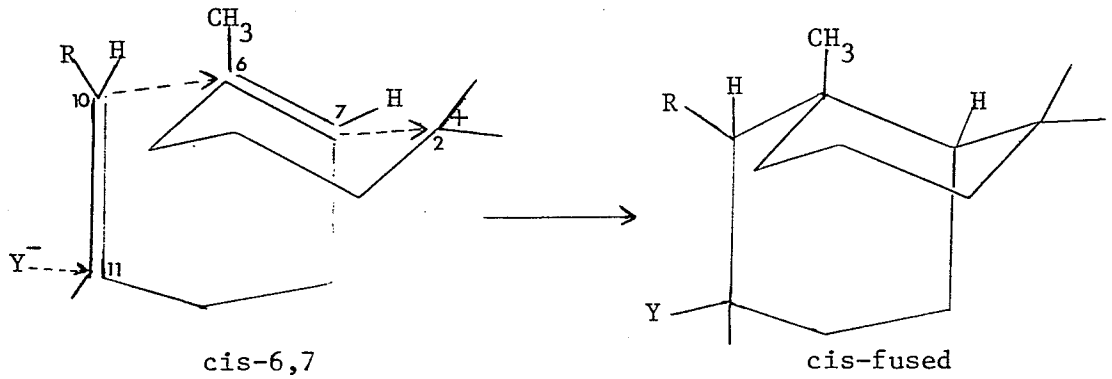
by the developing carbonium ion center at C_2 is accompanied by a nucleophilic attack by the 10,11-olefinic bond in such a way that the addition to the 6,7-olefinic bond is anti. If this olefinic bond is trans (structure 1) as in the case of squalene then the ring-fusion product will be trans and it follows that if the 6,7-olefinic bond is cis (structure 2), the ring-fusion will be cis. If the nucleophile Y^- is an olefinic bond in the side-chain R, as in the case of squalene, the cyclization process continues.



trans-6,7

1

trans-fused

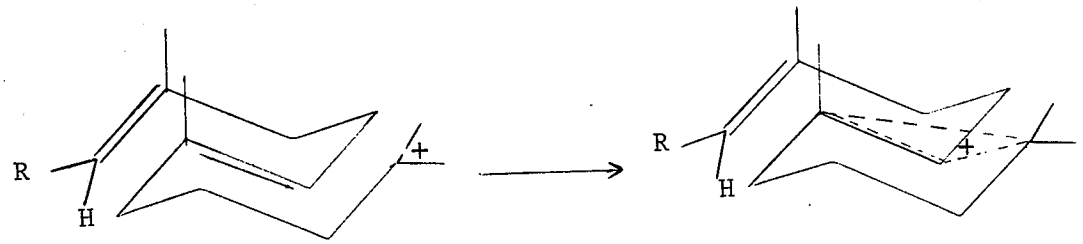


cis-6,7

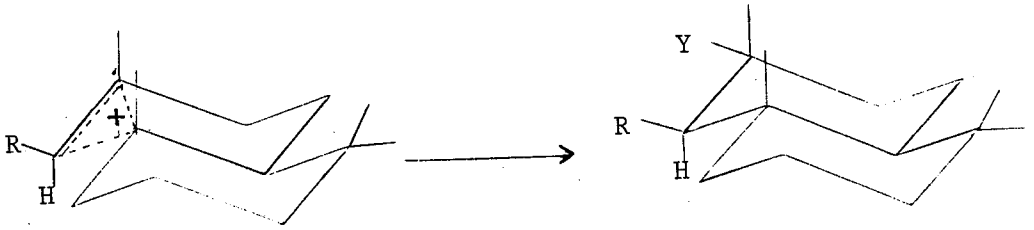
2

cis-fused

A slight variation of the Stork-Eschenmoser mechanism is preferred by Johnson in rationalizing the results of certain cyclizations of sulfonate esters [7, 13]. This mechanism involves the intermediate bridged-ions 3 and 4 . The stereochemical integrity is preserved by the necessity of "backside" opening of the bridged-ions.

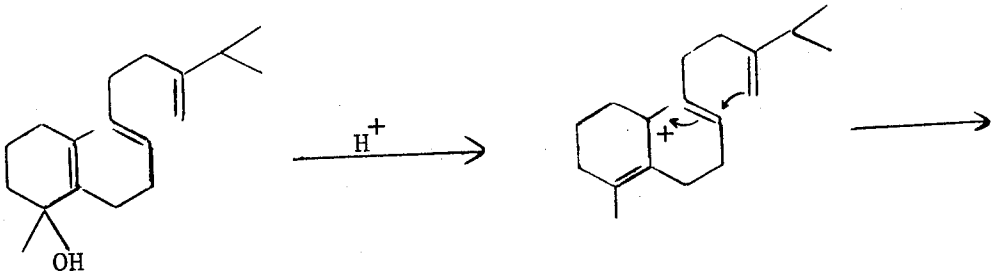


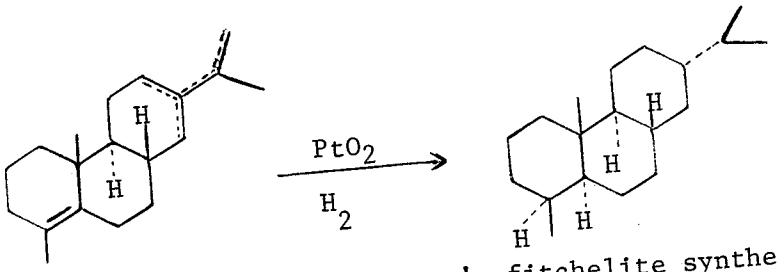
3



4

In a typical cationic cyclization reaction, a strong acid (e.g. formic acid, trifluoroacetic acid, stannous chloride) is used to induce the formation of a carbonium ion on a properly constructed substrate. The first non-enzymatic polyene cyclization to give a natural product was demonstrated in the synthesis of dl-fitchelite by Johnson and his co-workers [14]. This synthesis evolved from their long series of work on reactions of allylic alcohols.

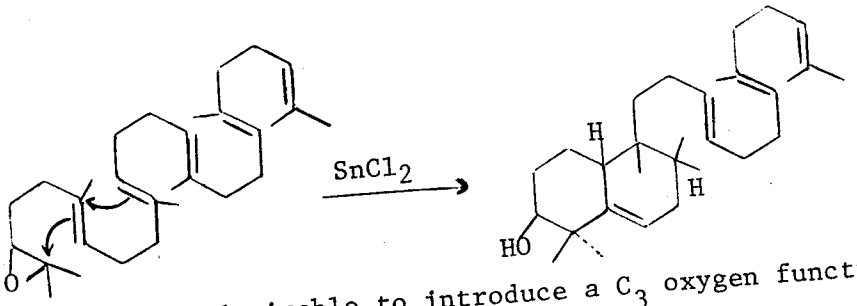




dℓ-fitchelite

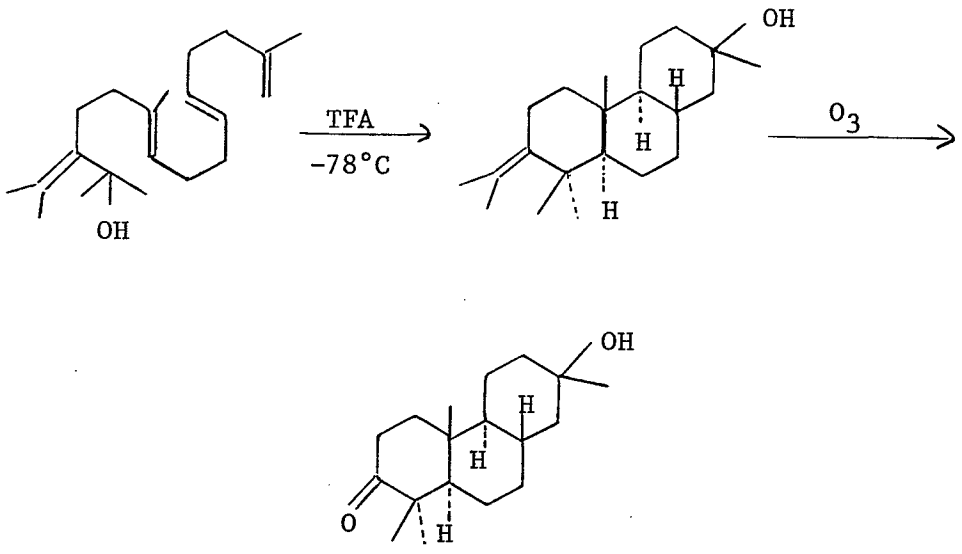
It is noted that in Johnson's fitchelite synthesis, and in the majority of his subsequent cyclization studies of other similar systems, the cyclization products obtained possess the "natural" configuration. That is, they have the trans, anti, trans, anti, trans configuration at the bridge-heads. It had also been established that in most cases there were no partially cyclized products and to this extent, the Stork-Eschenmoser-Johnson hypothesis has been validated.

The attempted acid-catalyzed cyclization of squalene oxide itself was reported by van Tamelen [12g] who found that the bicyclic alcohol 5 was the major product (20 - 25%) among a complex mixture of cyclization products (25 - 30%).

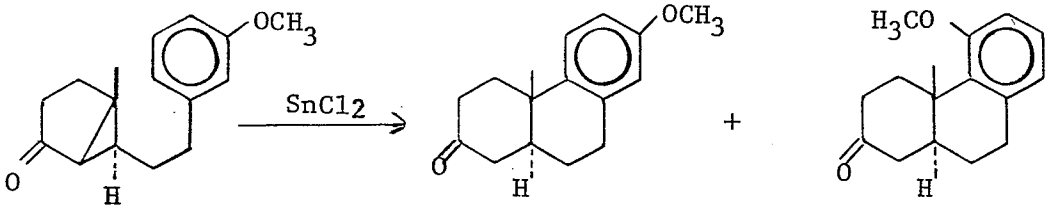


5

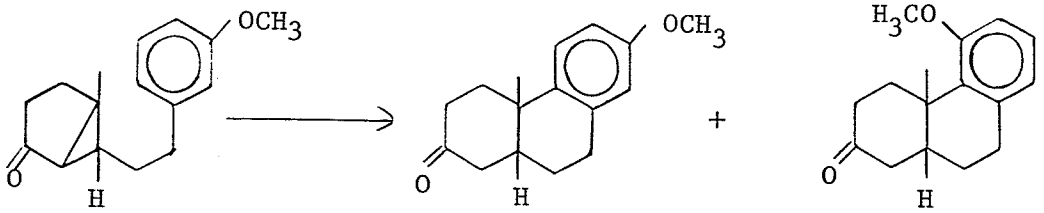
Since it is desirable to introduce a C_3 oxygen function (steroid numbering), which commonly occurs in natural terpenoids, Johnson and co-workers devised a way of achieving this by cyclization and ozonolysis of the allylic alcohol shown below [15].



Stork has provided one of the few reactions [16, 12e, 12h] in which the substrates contain a C_3 keto function prior to cyclization. In this case the stereoselectivity was pre-determined by the stereochemistry of the substrate 6.



trans-6



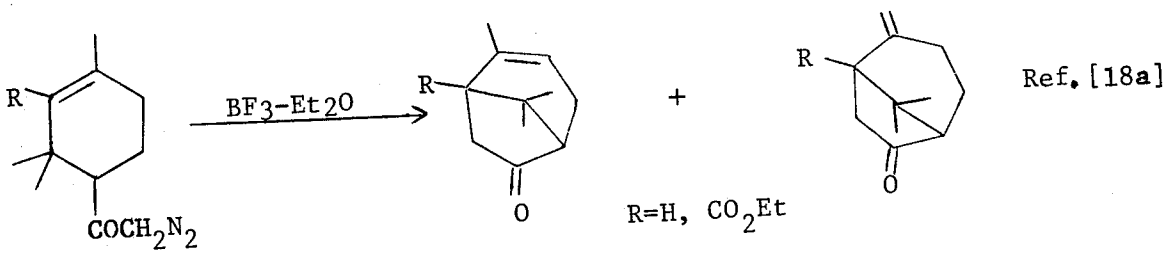
cis-6

As outstanding as the achievements in acid-catalyzed cationic cyclization have been, the mechanistic basis for the success of the Stork-Eschenmoser-Johnson hypothesis has been open to question. This

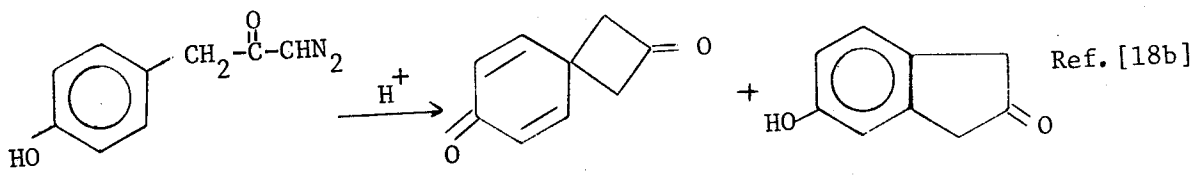
has been dealt with in an excellent review by Harding [17].

Perhaps much of the early difficulty that has been encountered lies in the fact that in acid-catalyzed cyclizations, the polyolefins are highly susceptible to a variety of other side reactions. Furthermore, the relatively strong acidic conditions generally employed to initiate the carbonium ion formation are also known to be conducive to such reactions as protonation, addition to, and isomerization of the olefinic bonds.

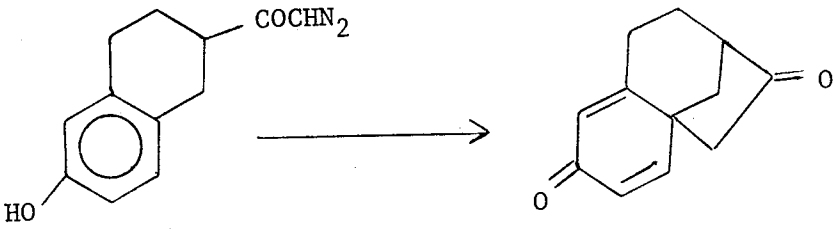
It is of interest to point out here that even though α - diazoketones have been known to generate α-carbonium ions in the acid -catalyzed intramolecular cyclizations of γδ- [18] and βγ-unsaturated diazoketones [19], these reactions are not selective and are even more vulnerable to the other side reactions discussed above. Therefore an acyclic polyolefin constructed on the basis of diazoketone functionality would serve little meaningful purpose for cyclization studies.



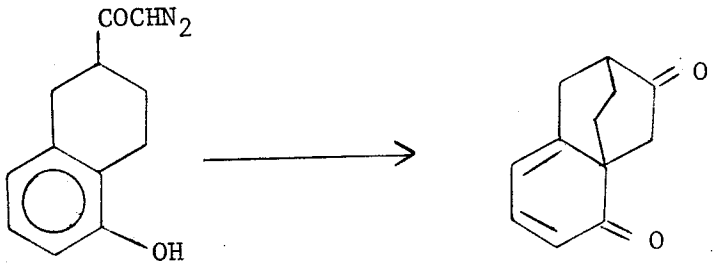
Ref. [18a]



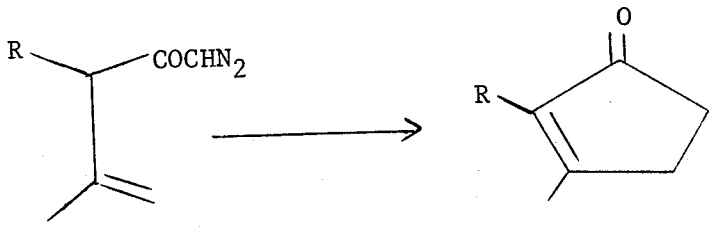
Ref. [18b]



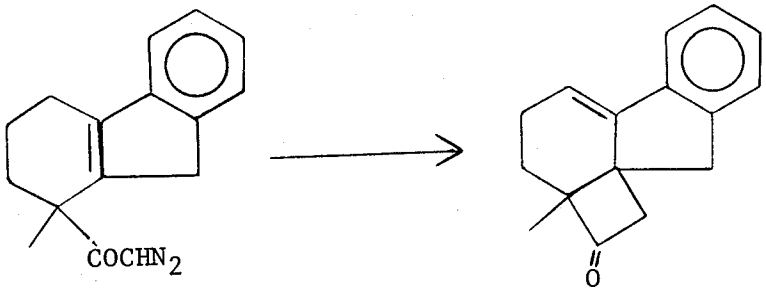
Ref. [18c]



Ref. [18d]



Ref. [19a]



Ref. [19b]

(B) Free Radical Cyclizations

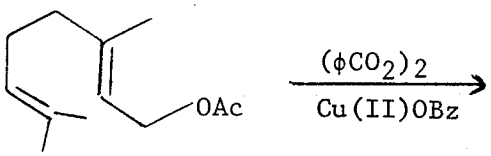
The concept that free radical intermediates might be involved in squalene biosynthesis was advanced by Breslow [11]. From the reaction of squalene with Fenton's reagent, Breslow observed that a radical process could initiate polyene cyclization. He concluded that the reaction was a stepwise process and the second double bond did not assist in the addition of the first (terminal double bond), even though the overall product was cyclized. The yields of totally cyclized products were poor and the reaction mixture was too complex to fully characterize.

Studies on the free radical oxidative cyclizations by Breslow [11b, 11c] on geranyl acetate and farnesyl acetate, and by Julia [20] on other related systems all led to similar mechanistic insights.

In a typical free radical cyclization reaction, an external radical source, commonly benzoyl peroxide, is decomposed thermally or photochemically so that the benzoyloxy radical adds in an anti-Markovnikov fashion to the most reactive double bond (e.g. the geminal dimethyl double bond in geranyl acetate) of the olefin. The reaction is usually conducted in the presence of cupric benzoate, which after the product radical has cyclized, terminates the reaction by oxidizing the radical with concerted hydrogen transfer.

These free radical oxidation cyclization reactions are complicated by the formation of acyclic and partially cyclized products

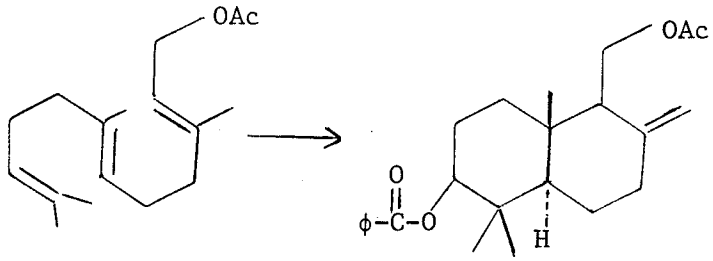
indicating that the formation of polycyclic material is stepwise. There is also evidence that oxidation of the intermediate radicals competes with the cyclization process [11].



Ref.[11b]

Geranyl acetate

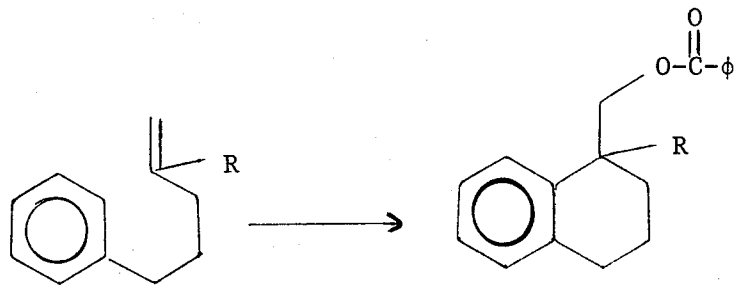
55-60% thermally
37% photochemically with peroxide
5-10% photochemically without peroxide



Ref.[11c]

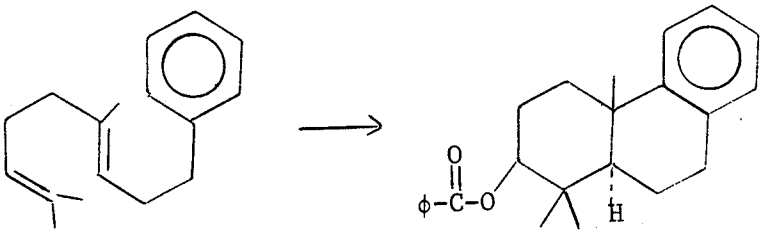
20-30% thermally
5-10% photochemically

Farnesyl acetate



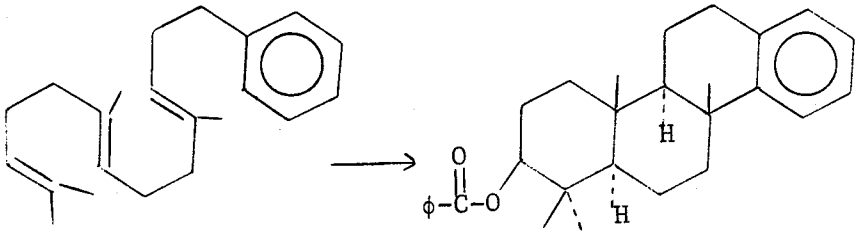
Ref.[20c]

22% if R = H
42% if R = CH_3



Ref. [20d]

≃ 20%



Ref. [20e]

12%

PART II

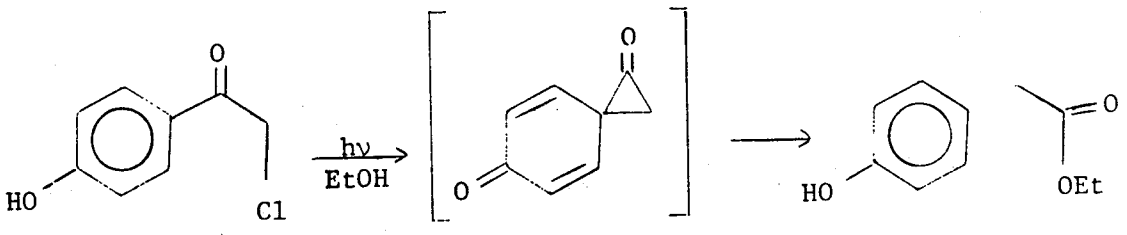
PHOTOCYCLIZATIONS OF α-SUBSTITUTED METHYL KETONES

Photocyclizations of α-Substituted Methyl Ketones

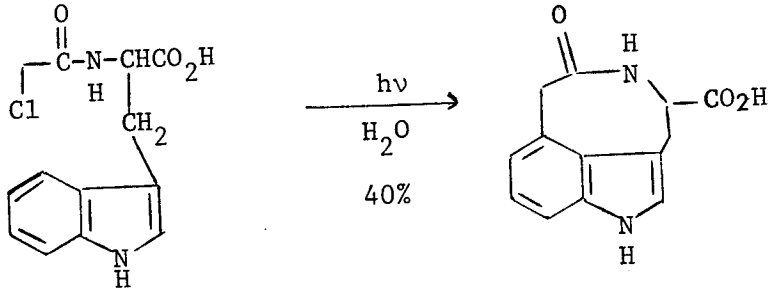
Because the cationic cyclizations discussed previously are complicated by side reactions caused by the acidic catalysts used, a less vigorous method for the preparation of the intermediate cation is required. The photolysis of α-substituted carbonyls might provide a route to cationic (or radical) species without the necessity of the catalyst. As well this method, when applied to polyene cyclization, leaves a C_3 carbonyl function.

(A) N-Chloroacetyl Derivatives

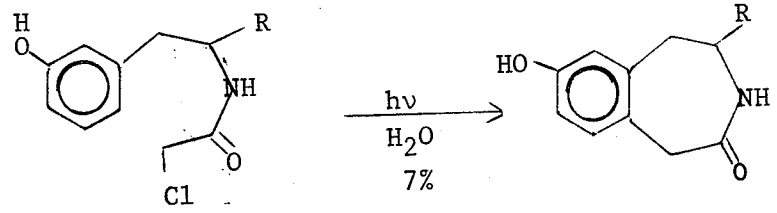
Although cyclization intermediate 8 had been proposed earlier [21a] in the photoconversion of substituted phenacyl chloride 7 to the rearranged ester 9, the first isolated photocyclization product of an α-substituted methyl ketone was reported in 1966 by Witkop et al. [22a]. Subsequently, a number of lactams were synthesized photochemically from the corresponding N-chloroacetyl derivatives [22].



7 8 9

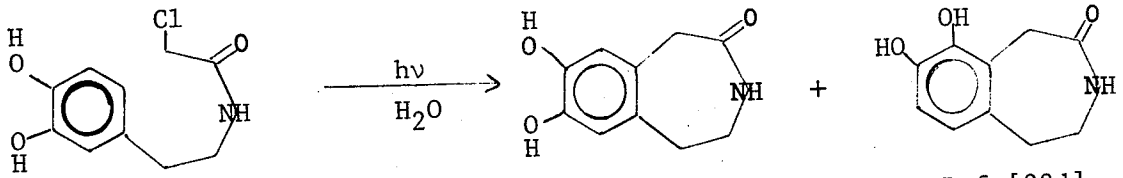


Ref. [22a]

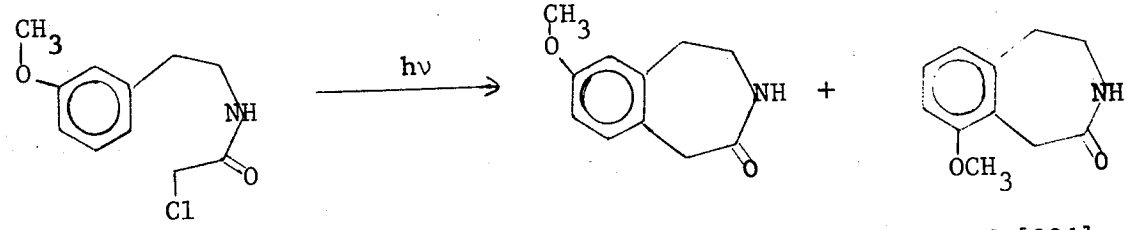


Ref. [22b]

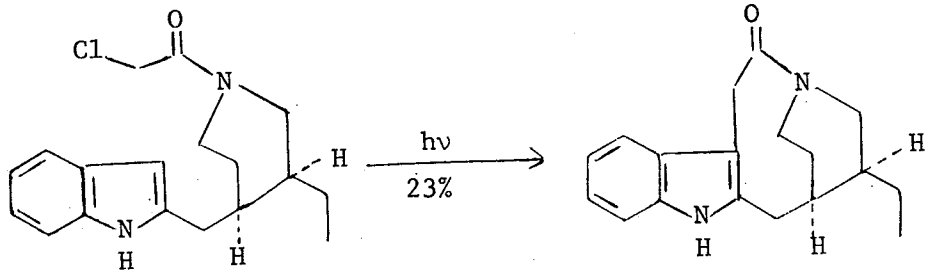
R=H, CO_2H



Ref. [22d]



Ref. [22d]

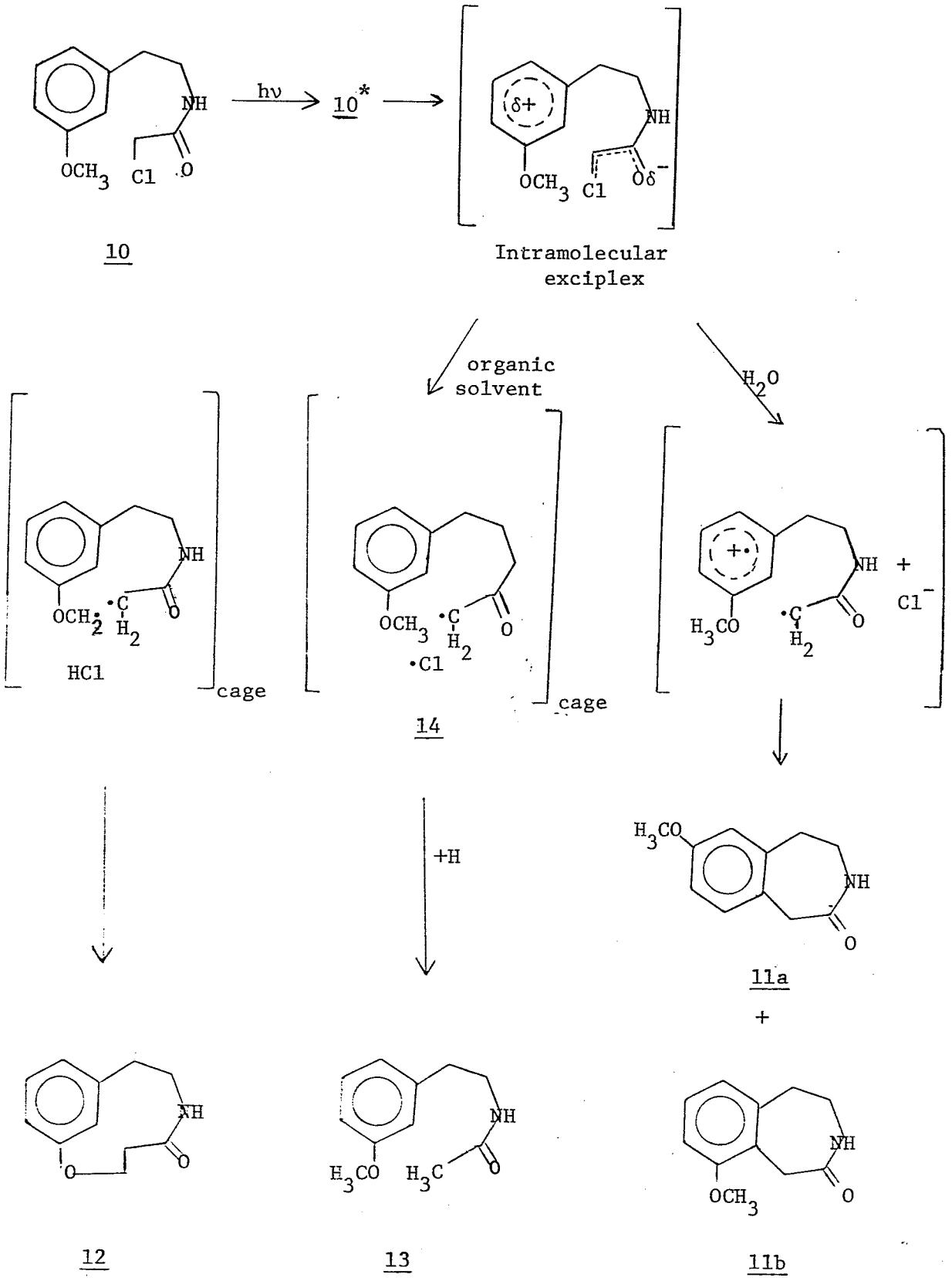


Ref. [22g]

It is noted that all cyclizations of the N-chloroacetyl derivatives were on aromatic nuclei with electron-donating substituents or the electron-rich indole nucleus. On the basis of studies of fluorescence quenching [22h], solvent effects [22c, 22i] and flash photolysis [22j], a dualistic mechanism based on an intramolecular exciplex had been proposed [22c, 22i, 22j] as illustrated by the example of N-chloroacetyl-3-methoxyphenethylamine 10. In water and protic solvents 11a and 11b were the main products; whereas in organic solvents, the formation of 11 decreased markedly and the lactam 12 and the N-acetyl compound 13 became the main products. Furthermore, the formation of 11 was dependent on the solvent polarity while that of 12 and 13 were not.

It was proposed that in aqueous solvent, intramolecular electron transfer from the excited state of the electron-rich aromatic nucleus to the chloroacetyl moiety via the loosely bound exciplex, led to the cleavage of C-Cl bond. The resulting methylene radical coupled readily with the aromatic radical cation to form the cyclized products.

An analogous mechanism was suggested to account for the formations of 12 and 13. In less polar solvents, decay of the exciplex led to homolytic cleavage of the C-Cl bond, resulting in radical intermediate 14 together with a chlorine radical in the solvent cage. Since the formation of 13 was strongly suppressed by oxygen, a good radical scavenger, while the presence or absence of oxygen did not alter the yield of 12, the two must have arisen from different pathways.


hν
10*
δ+
δ−
OCH3
Cl
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Intramolecular exciplex
organic solvent
H2O
HCl
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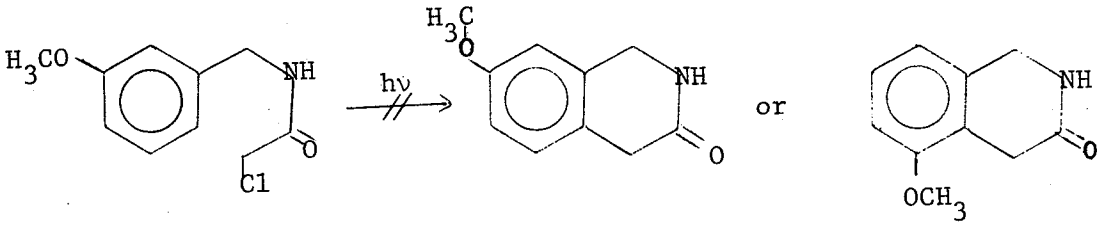
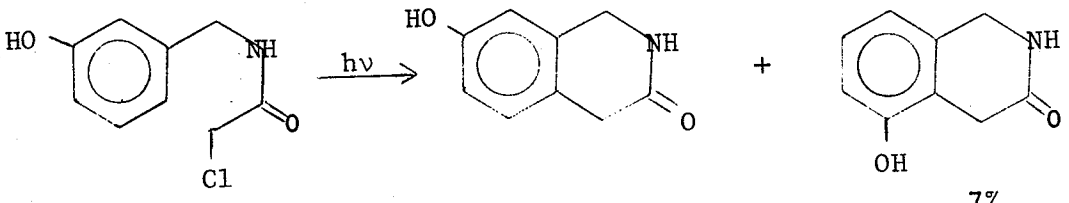
14
+•
Cl−
H3CO
+H
11a
+
12
13
11b

Accordingly, if the radical 14 escaped the solvent cage before the chlorine radical abstracted a hydrogen atom from the methoxy group, it would lead to the formation of compound 13 . On the other hand, abstraction of hydrogen by the chlorine radical in the solvent cage would lead eventually to the intramolecular recombination of the diradical giving rise to the lactam 12.

A case pertinent to the mechanism suggested above was found in the cyclization of N-chloroacetylbenzylamine 15 in contrast to its hydroxyl analog 16 [22f]. Thus the difference in reactivity between 15 and 16 was attributed to the ease of the electron ejection from the



15



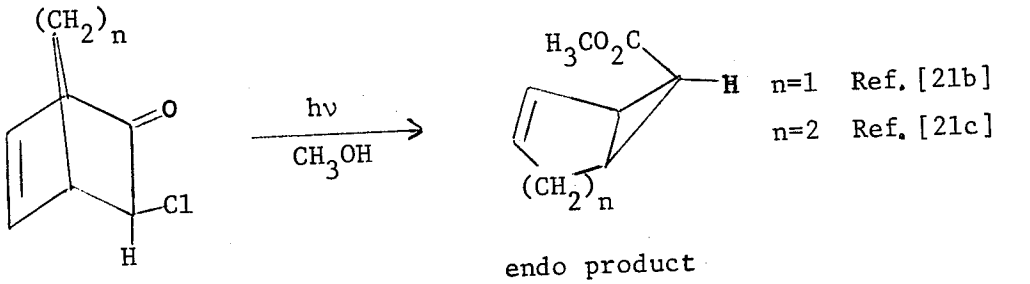
55% 7%

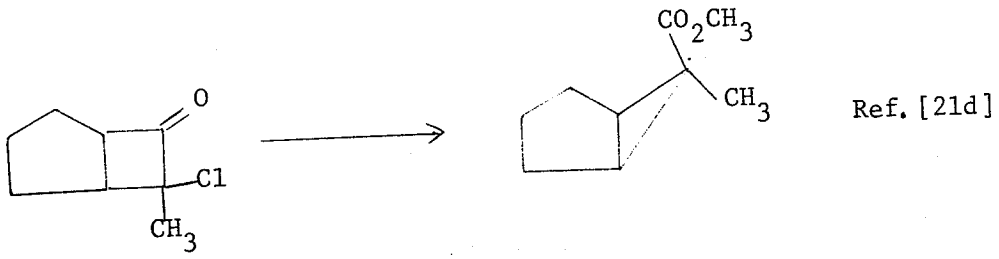
16

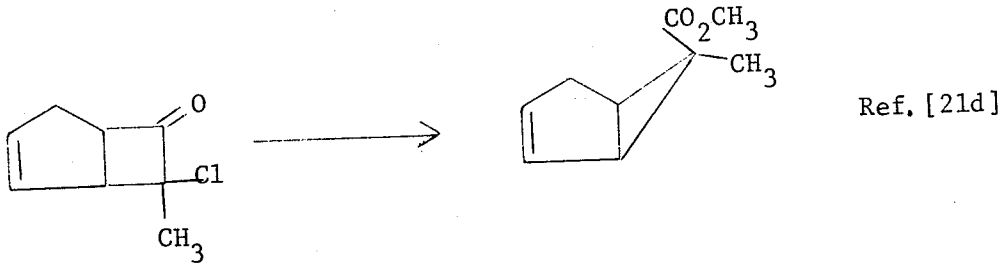
phenolic aromatic nucleus at the initial stage of photolysis and the reactivity of the resultant phenoxy radical cation. However, it is recalled that the homolog of 15, compound 10 did undergo cyclization.

(B) α-Chloro and α-Sulfonyloxy Ketones

Surprisingly, the Witkop photocyclization had not been extended to the synthesis of carbocyclic systems. α-Chloromethyl ketones, usually in the forms of rigid bicyclic systems, have been used photochemically for mechanistic studies [21]. A common feature in these

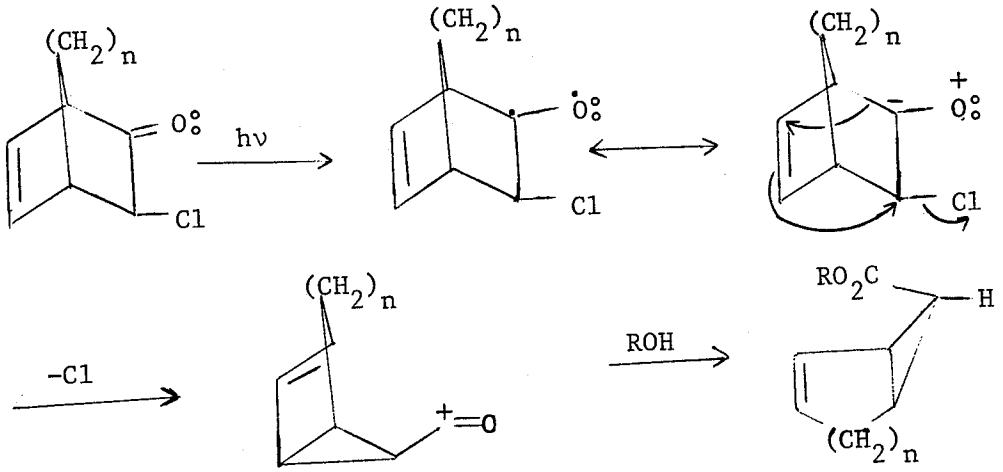






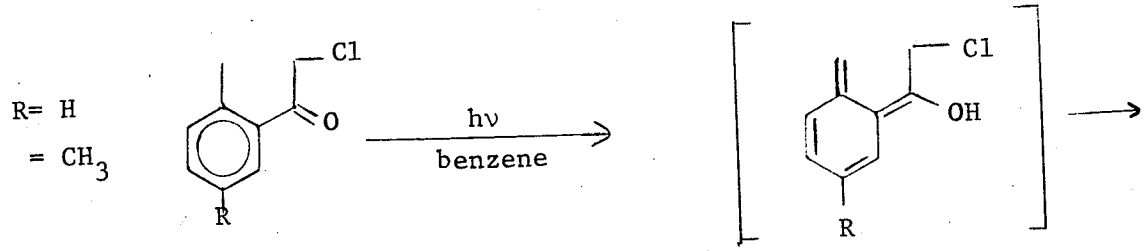
studies was the formation of the Favörskii-type ring contraction - solvolysis product.

A frequently suggested mechanism involves the photoionization of chloride followed by ring contraction to cyclopropyl acylium ion which is then trapped by the solvent to form the ester. A heterolytic cleavage of the C-Cl bond was also generally accepted [44a, 44b, 44d], although the possibility of formation of a tight radical

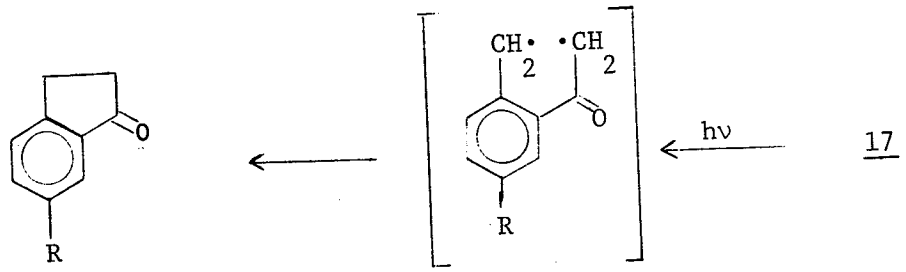


pair which disproportionated before solvent separation has not been ruled out [21c].

Recently [23], the chloromethyl ketone 17 was found to undergo photocyclization to give compound 18. It was suggested that the reaction involved the photo-enol intermediate 19a, a well-known reaction found in ortho-substituted ketones [24]. However, a coupling process via the radical intermediate 19b is also possible.



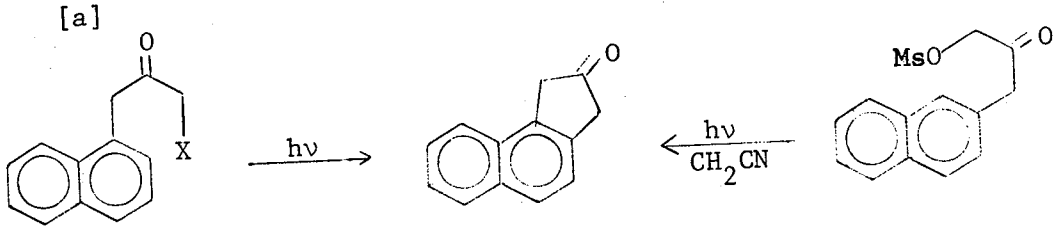
17 19a



18 19b 17

In 1968, Schaffner et al. [25] reported the formation of β-arylketones by intra- or intermolecular substitution of the corresponding α-sulfonyloxyketones on the aromatic nucleus. Among these [Equations a —— e] was the intramolecular cyclization of the 1- and 2-naphthyl mesyloxyketones 20 to the tricyclic ketone 22. However, with the corresponding chloronaphthyl ketone 21 no cyclization product was found. Again, as in the case of the Witkop cyclization, the electron-rich aromatic nucleus served as the substitution site. In

[a]



20a X=OMs
21 X=Cl

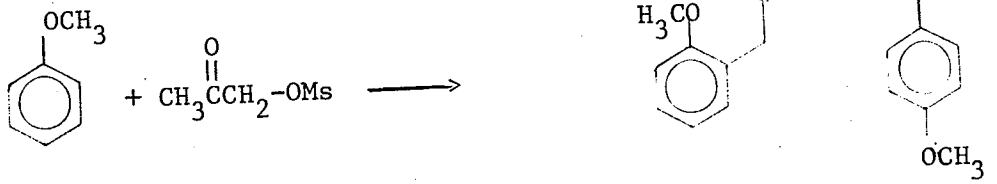
22 20b

[b]

R=H, CH_3

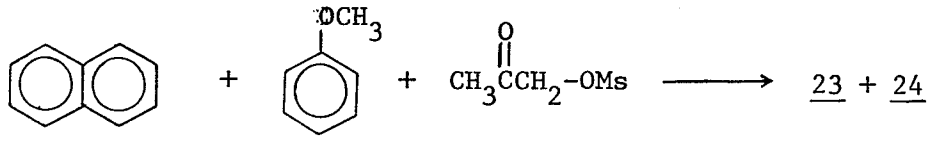
23a 23b

[c]

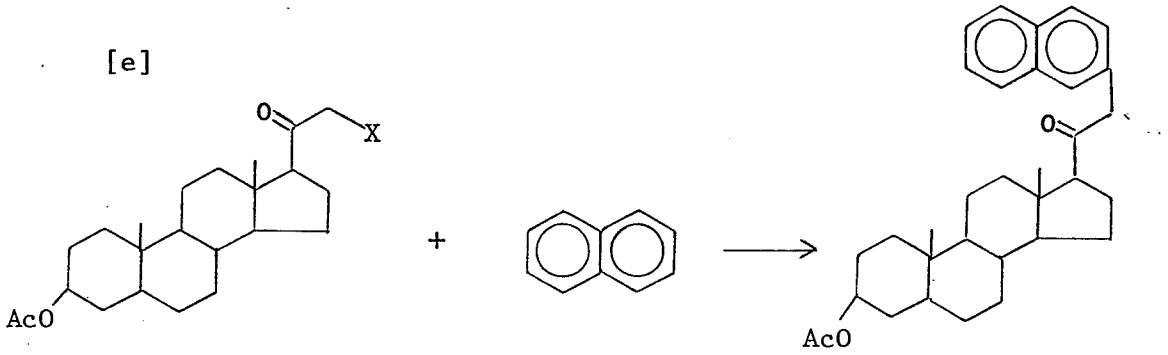


24a 24b

[d]



[e]

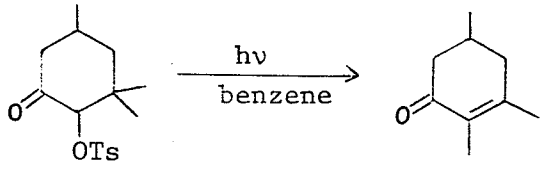


X = OMs

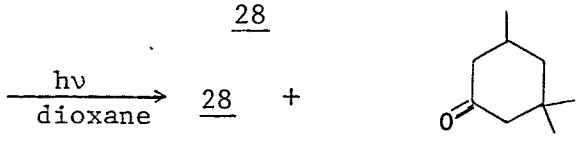
X = Cl

principle the substitution could either be a radical or an ionic process.

In their attempts to differentiate the radical and the ionic pathways, the authors [25b, 25c] also studied the photochemistry of



25 28



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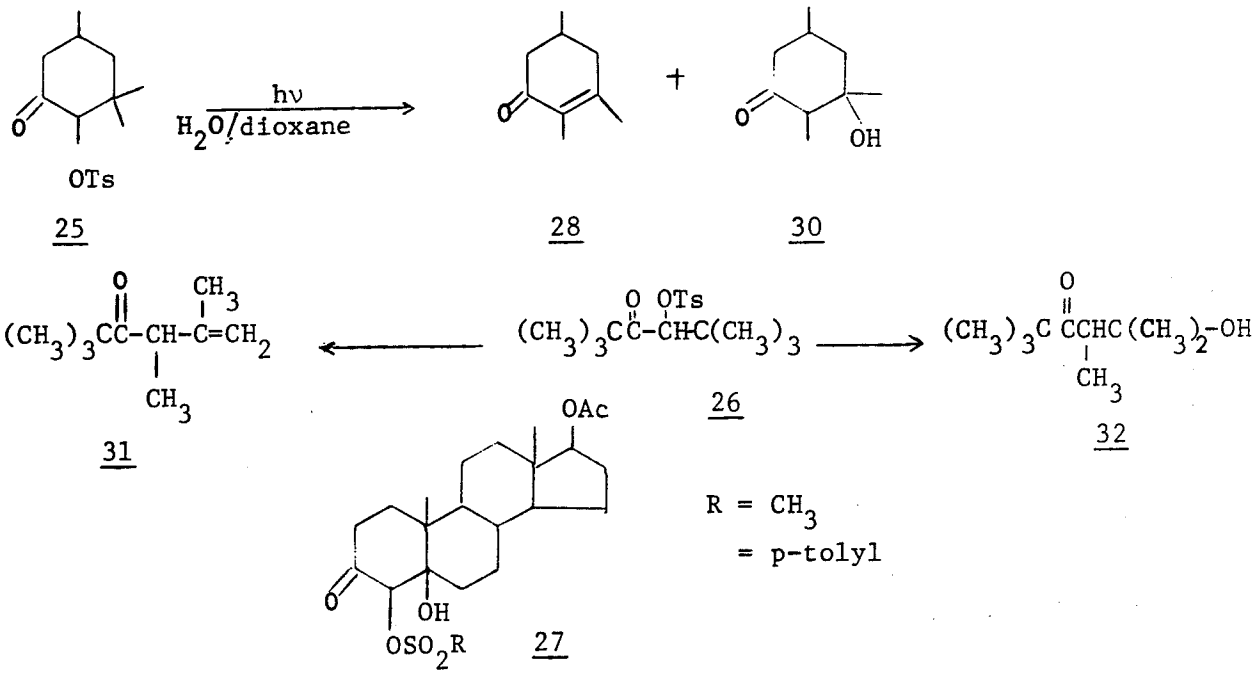
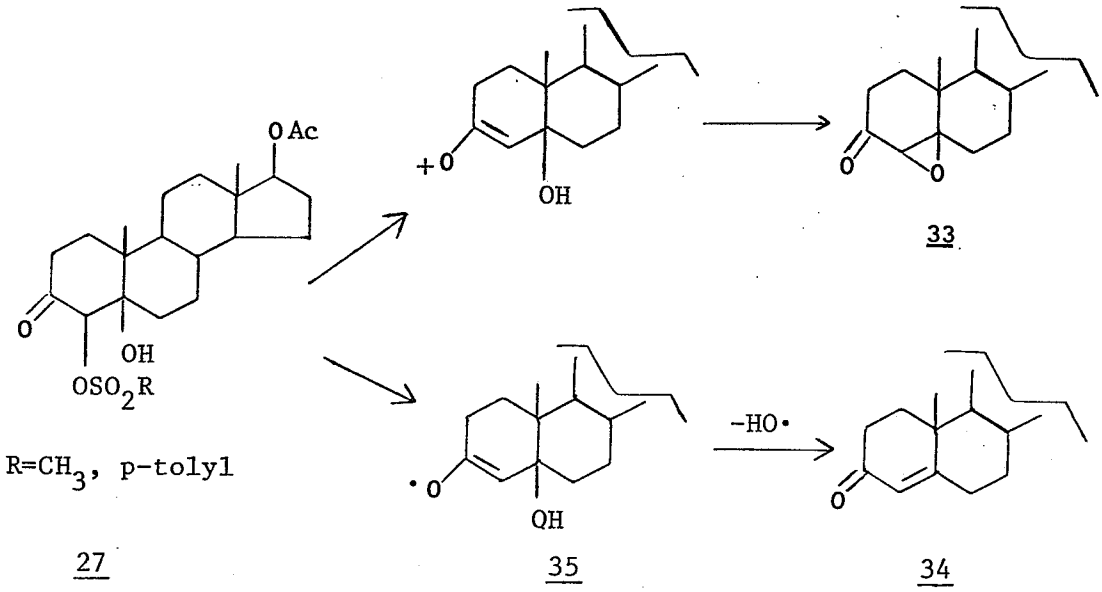


the monocyclic sulfonyloxyketone 25, the acyclic ketone 26 and the steroid 27. Irradiation of 25 in benzene gave the cyclohexenone 28, while in dioxane, irradiation gave a four to one mixture of 28 and the saturated ketone 29. When an aqueous dioxane solution of 25 was irradiated, the β-hydroxyketone 30 was formed in addition to 28.

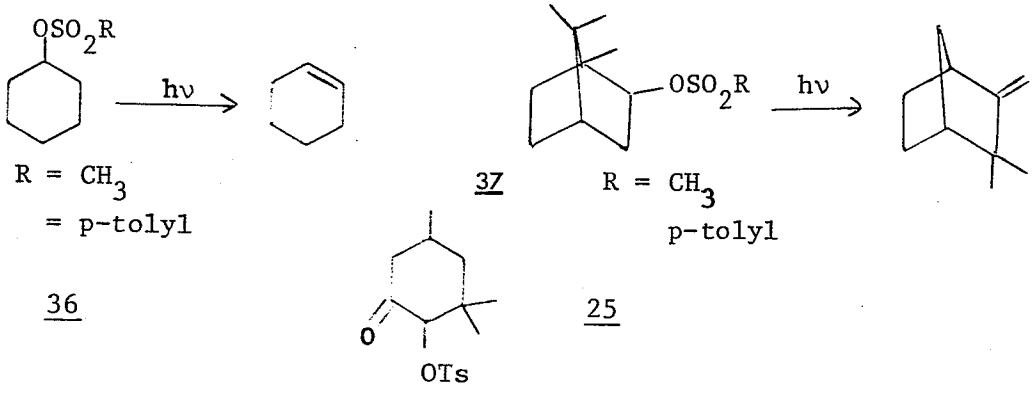
Similarly, the photoconversion of the acyclic compound 26 to the unsaturated ketone 31 was largely suppressed in aqueous dioxane and the hydroxyketone 32 was formed instead. These results seemed to suggest the involvement of cationic intermediates and hence pointed to a heterolytic cleavage of the C-O bond.

On the other hand, the steroid 27 gave two primary photoproducts which Schaffner suggested was indicative of two parallel modes of cleavage: a heterolytic cleavage of the C-O bond followed by epoxide ring closure and deprotonation of the cationic intermediate leading to the epoxyketone 33, and a homolytic cleavage, followed by elimina-

tion of an OH radical, leading to product 34. However, while compound 34 may be formed by a radical pathway, elimination of ·OH from the intermediate 35 as suggested by Schaffner seems unlikely and is not substantiated by literature precedent.

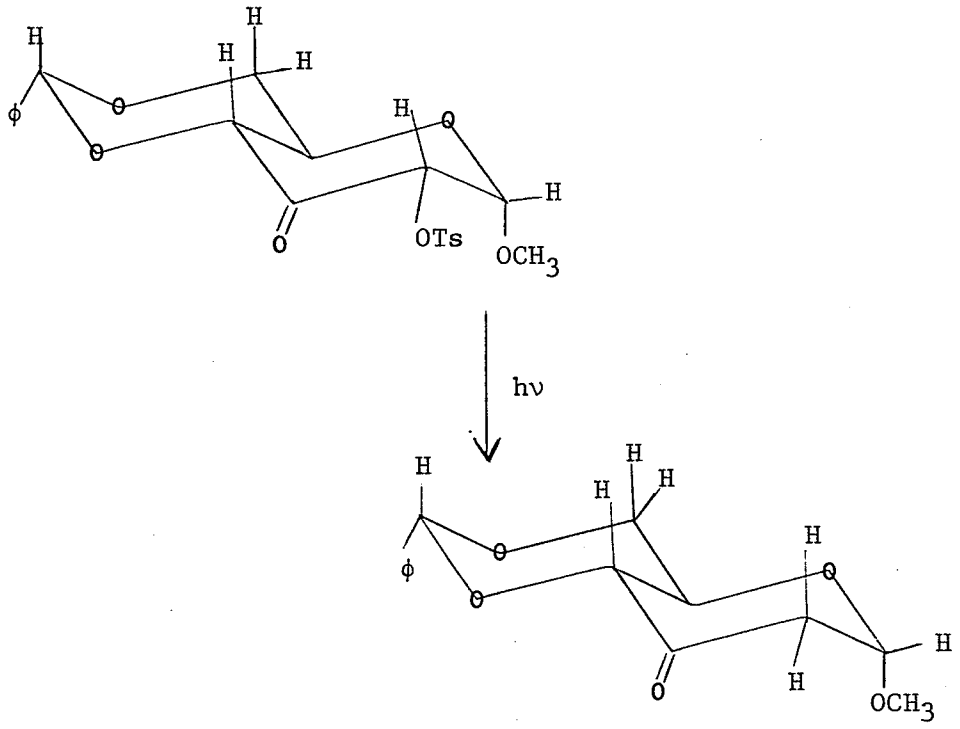


In other related studies, it was found that acetone sensitization of cyclohexyl sufonate 36 caused no chemical change, while the formation of cyclohexene was observed in benzene with 2537 Å irradiation. Similar results were obtained in the case of alkyl sulfonate 37. Comparative runs with 36, 37 and 25 indicated that elimination



of RSO_3H from the alkyl sufonates was less efficient than from the sulfonyloxyketones. These results pointed to the chemical participation of the excited carbonyl group in photolyses rather than a transfer of excitation energy from the carbonyl to the sulfonate moiety.

In connection with the photochemistry of α-sulfonyloxyketones it should be pointed out that the reductive cleavage of the C-O bond has been exploited in the synthesis of 38, a key intermediate in the syntheses of some rare sugars [26].



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OBJECT OF RESEARCH