INTRAMOLECULAR REARRANGEMENTS OF AMIDES AND PEROXIDES

A THESIS

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DOCTOR OF PHILOSOPHY

in

THE UNIVERSITY OF ADELAIDE

by

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Department of Organic Chemistry

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CONTENTS.

PUBLICATIONS

Some of the work in this thesis has been published in the following papers:

1. Reactions of Alkoxy Radicals IV. Intramolecular Hydrogen-atom Transfer in the presence of Cupric Ion: A Novel Directive Effect.
   Aust.J.Chem., 1964, 17, 1342.

2. Reaction of Lead Tetra-acetate with Primary Amides. Formation of Acylamines.
   Chem. Communications, 1965, 151.

3. Reaction of Lead Tetra-acetate with Primary Amides. Formation of Alkyl Carbamates.
   Tetrahedron Letters, 1965, 4039.

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SUMMARY

Developments in the intramolecular hydrogen abstraction reactions of free radicals are reviewed.

Tertiary alkoxy radicals formed by redox decomposition of alkyl hydroperoxides and peracetates at ambient temperature and free of photolytic activation are shown to undergo intramolecular hydrogen abstraction. A temperature effect is proposed as the reason for the difference in modes of reactions of alkoxy radicals generated by photolysis and by pyrolysis.

The redox decomposition of 2-methyl-2-hexyl hydroperoxide with ferrous ion in the presence of cupric chloride and carbon tetrachloride affords 5-chloro-2-methylhexan-2-ol *via* an intramolecular hydrogen abstraction reaction. A low yield of 2,5-dimethylhexan-2,5-diol is similarly obtained from the reaction between 2,5-dimethyl-2-hexyl hydroperoxide and aqueous acidic ferrous sulphate solution.

The decomposition of 2-methyl-2-hexyl hydroperoxide, 2,5-dimethyl-2-hexyl hydroperoxide, and 2-methyl-2-heptyl hydroperoxide with ferrous ion in the presence of cupric ion and aqueous acetic acid produces the corresponding δ- and γ-olefinic alcohols, again *via* a 1,5-hydrogen transfer process. Similar results are obtained from the redox decomposition of the corresponding peracetates. However, the δ-olefinic alcohol, formed *via* cupric ion oxidation of the intermediate δ-hydroxyalkyl radical, is obtained as the major reaction product. These results are rationalised in terms of an internal directive effect due to the

presence of the hydroxyl group.

2-Methyl-5-hexen-2-ol copper (I) chloride complex is formed by heating 2-methyl-5-hexen-2-ol and cuprous chloride but no analogous complex forms between 2-methyl-4-hexen-2-ol and cuprous chloride. The relevance of this result to the preferred formation of the δ-olefinic alcohols from the hydroperoxide decompositions is discussed.

Photolysis of N-chloro-amides affords the appropriate γ-chloro-amides via an intramolecular hydrogen-atom rearrangement of the intermediate primary amido radicals. Such γ-chloro-amides are isolated as crystalline mixtures with the corresponding saturated amides. However, successful separation of a mixture of butyramide and γ-chlorobutyramide, obtained from the photolysis of N-chlorobutyramide, is described.

A similar rearrangement occurs on photolysis of suitably constituted alkyl N-chlorocarbamates in which the α-methylene group of the amide is replaced by an oxygen atom.

Photolysis of N-alkyl-N-chloro-acetamides yields products attributable to an intramolecular hydrogen abstraction reaction. 1,5-Hydrogen transfer by the acetamido radical in both possible resonance contributors is achieved. However, in the examples in which intramolecular hydrogen abstraction by both canonical forms is conceivable, abstraction by the nitrogen radical occurs to the exclusion of the alternative possibility.

The reaction of lead tetra-acetate with primary alkyl amides in benzene solution affords the appropriate N-alkylacetamides as the major products together with N,N'-dialkylureas as a by-product. The scope of

the reaction is extended to include simple aliphatic and steroidal amides as well as olefinic amides. In the last example, the lead tetra-acetate reacts with the amide group in preference to the olefinic bond.

The reaction occurs in the presence of methanol, in which case the appropriate methyl N-alkylcarbamate is obtained. A fine balance between the reactivity of the lead tetra-acetate toward the primary amide group and the methanol is observed. Isocyanates are intermediates in the reaction mechanism. The formation of such isocyanates is suggested to proceed via a polar mechanism rather than a nitrene intermediate. A mechanism is also proposed for the conversion of isocyanates into the isolated reaction products.

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STATEMENT.

The work described in this thesis incorporates no material previously submitted for a degree in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person except where due reference is made in the text.

Brenton Acott.

December, 1966.

ACKNOWLEDGEMENTS

I would like to express my appreciation of the invaluable assistance and encouragement given to me by my supervisor, Professor A.L.J. Beckwith, who initiated the project. My thanks are also due to the other members of the Department of Organic Chemistry for their enlightening suggestions and helpful advice. I wish to record my appreciation to Dr. T. McL. Spotswood and Mr. C.I. Tanzer for the helpful discussions during the interpretation of nuclear magnetic resonance spectra.

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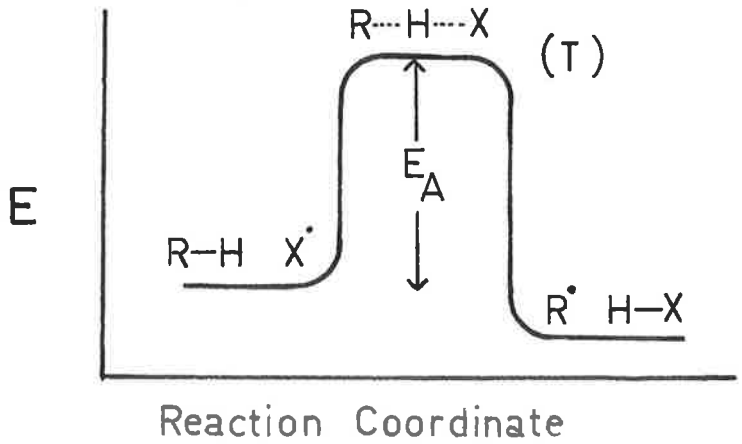
I. INTRODUCTION

1. General.

The abstraction of a hydrogen atom from a neutral molecule by a free radical is one of the most common of all radical propogation steps known. In general, the controlling factor influencing atom transfer reactions is the activation energy, E_A, necessary to elevate the attacking radical and the neutral molecule to the higher energy transition state, T, as is depicted by the energy diagram below.

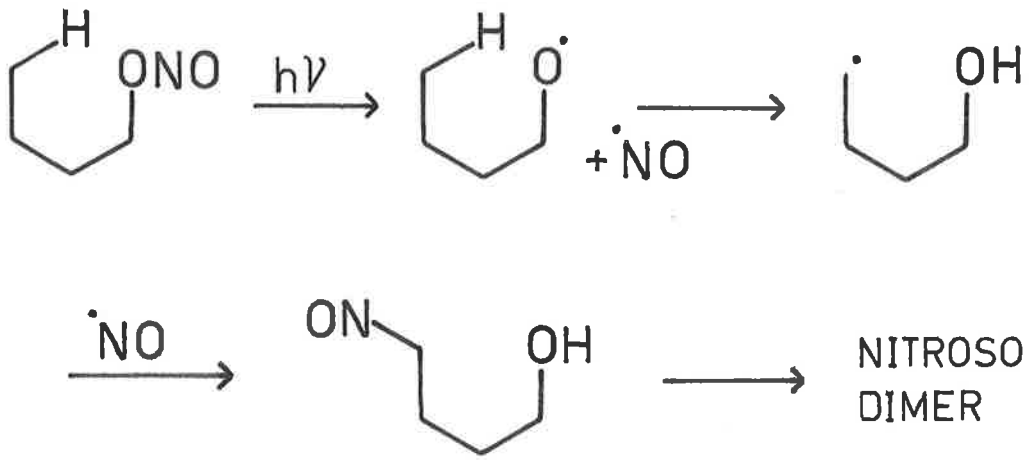


Szwarc[1a] explains that in the transition state of such an atom transfer process, the bond to be ruptured is only stretched and the formation of a new bond between the radical, X, and the transferred atom, H, provides the driving force of the process. He suggests this is why the activation energy of the reaction is substantially lower than the R-H bond dissociation energy. Hirschfelder[1b] has derived an approximate expression relating the activation energy to the bond dissociation energy (B.D.E.) of the bond being broken. For exothermic reactions,

$E_A \simeq$ 5.5% of the B.D.E. of the bond being broken.

Gray and Williams[2] have shown that the bond dissociation energies of the methylene C-H bonds in alkyl chains $R(CH_2)_nR'$ are approximately the same. Relating these two approximations, it follows that the activation energy required for the abstraction of any hydrogen atom along the chain $R(CH_2)_nR'$ is approximately constant. Random hydrogen abstraction by an attacking radical could thus be expected and for intermolecular radical attack this is actually observed.[3]

However, Barton[4] found that random hydrogen transfer does not occur in intramolecular radical reactions. Barton and coworkers[4b] photolysed various alkyl nitrites and found that the ensuing alkoxy radicals transfer specifically the δ-hydrogen atoms. The proposed mechanism[5] for this reaction, subsequently designated[5] as the Barton reaction, involves a six-membered cyclic intermediate which is illustrated in Scheme 1.

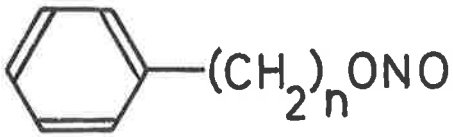


Scheme 1.

The reaction was initially developed with steroid compounds[4] as it proved to be an excellent method for functionalising carbon atoms δ- to an appro-

priate oxy-radical. Since Barton's original work, numerous examples have appeared in which nitrite ester photolysis has been used in steroid synthesis.[6,7]

To acquire a more detailed understanding of the mechanism, Kabasakalian and coworkers[8a] photolysed various aralkyl nitrites (I, n = 1-5).



I.

Their results are summarised in the following Table I.

Photolysis of Phenylalkyl nitrites

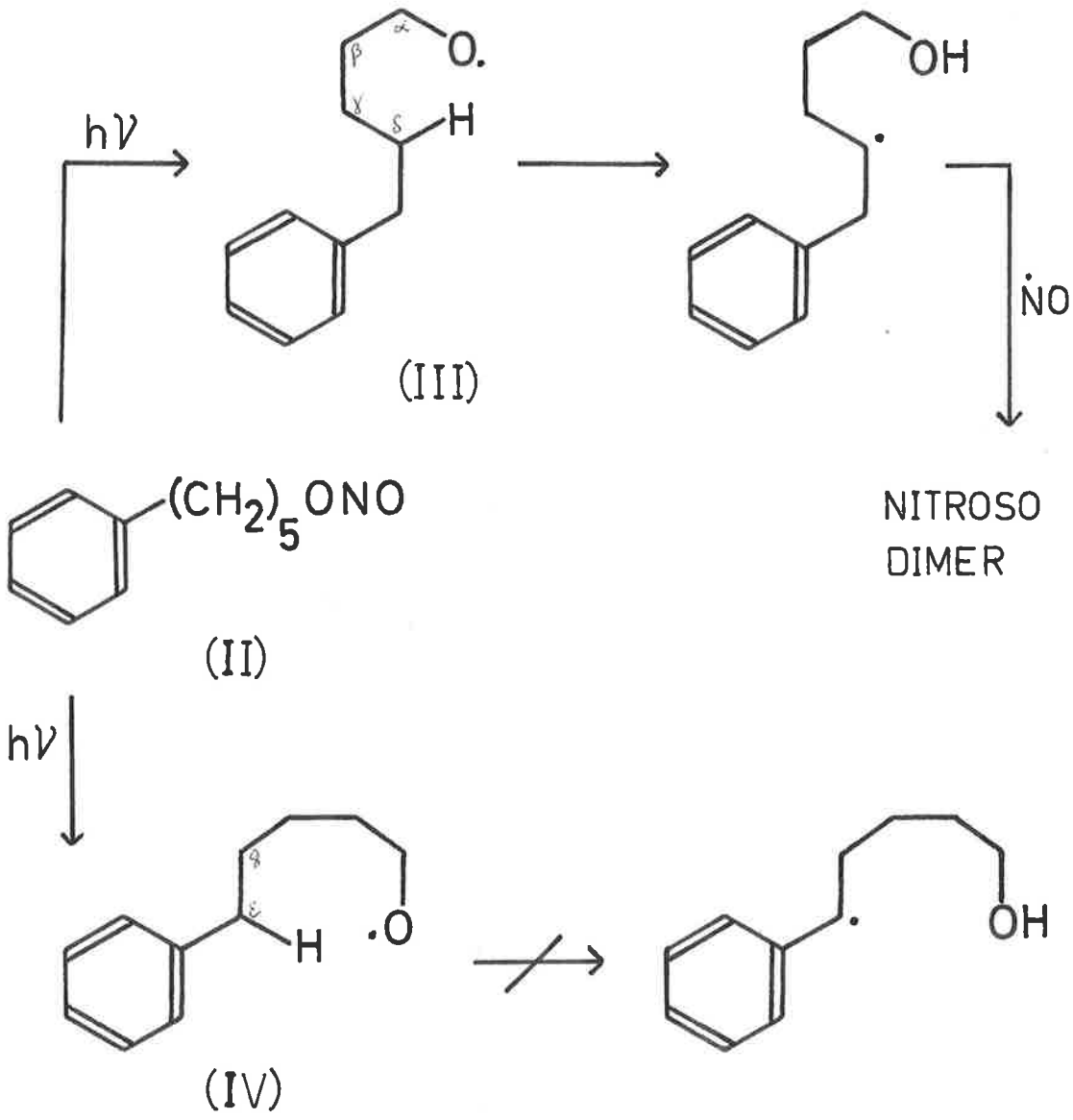
(I)

n	Products.
1	No nitroso dimer.
2	ω-nitrosotoluene dimer.
3	No nitroso dimer.
4	4-nitroso-4-phenylbutan-1-ol dimer.
5	4-nitroso-5-phenylpentan-1-ol dimer.

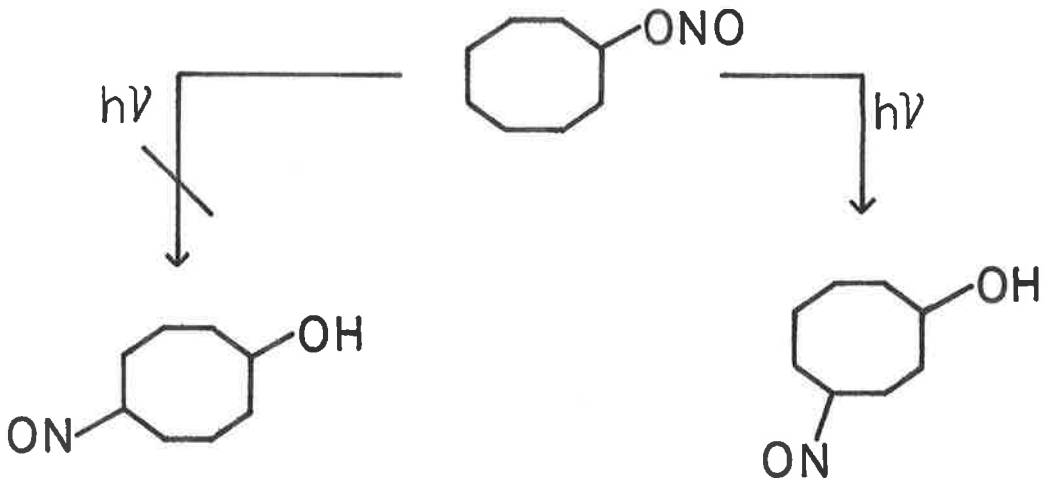
Table I.

Kabasakalian[8] found that regardless of the nature of the hydrogen atoms available, the hydrogen ε- to the oxy-radical is the only atom re-

moved. The most important evidence to support this conclusion is the formation of 4-nitroso-5-phenylpentan-1-ol dimer from the photolysis of 5-phenyl-1-pentyl nitrite (II). In spite of the presence of easily abstractable benzylic hydrogen atoms which could be transferred by way of a seven-membered intermediate (IV), exclusive 1,5-hydrogen transfer via a six-membered cyclic system (III) occurs.

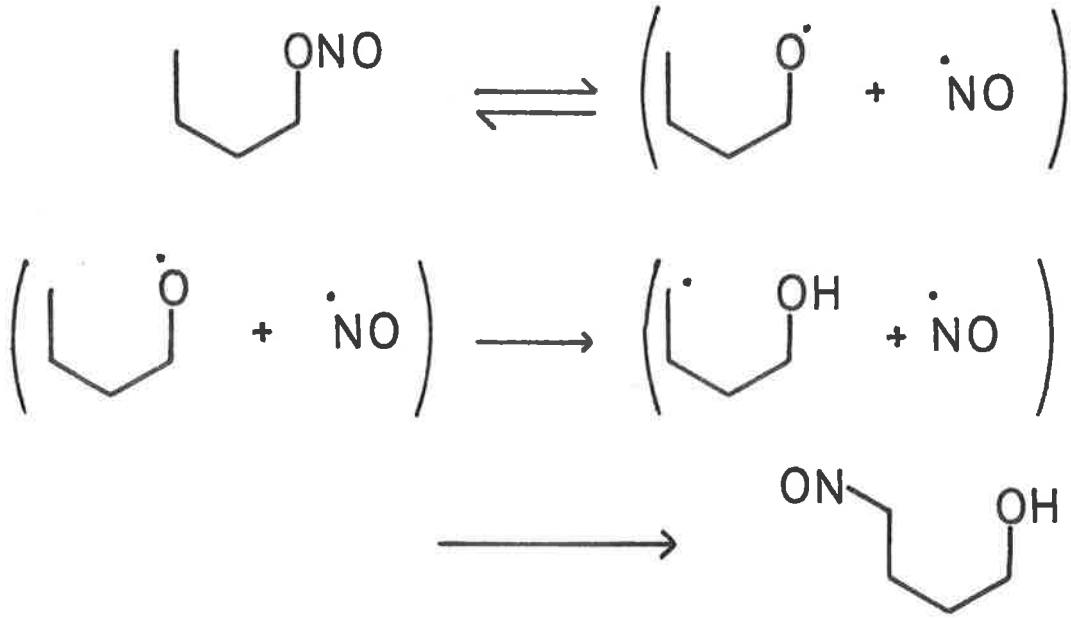


Further work by Kabasakalian and Townley[9] showed that cycloheptyl and cyclo-octyl nitrites undergo the Barton reaction the same as their straight chain counterparts with specific 1,5-hydrogen transfer. These workers concluded that such transannular free radical rearrangements do not seem to be influenced by the ring size or 'proximity effects' found by Cope[10] and Prelog[11] for transannular rearrangements involving hydride shifts.



Kabasakalian and Townley[12] added further to the understanding of the reaction mechanism by determining the quantum yield in the photolysis of octyl nitrite. A value of 0.76 was obtained which indicates that a 'nonchain' radical reaction is involved.

Barton[4b] originally conceived that the complete reaction takes place in a protecting solvent 'cage' in which the carbon radical, derived from intramolecular hydrogen abstraction, couples with the same nitric oxide group set free by the initial photolysis. This mechanism is illustrated in Scheme 2.

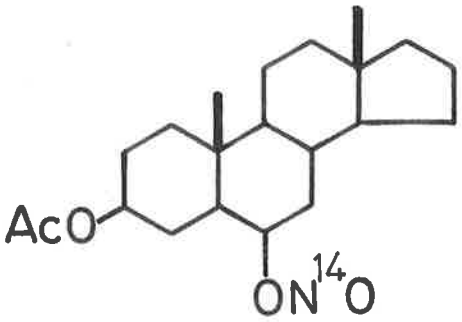


Scheme 2.

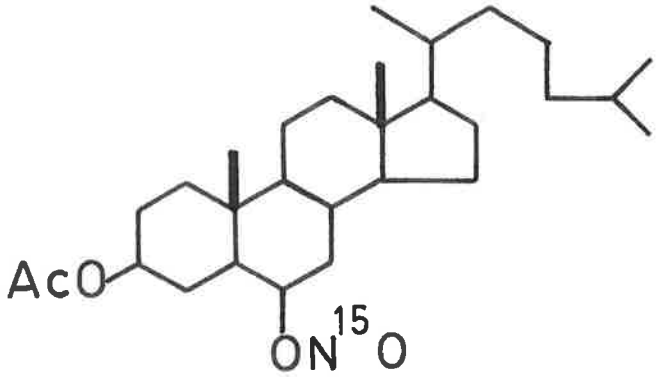
His assumption[4b] was based on the fact that solvents such as toluene and 5% cumene in benzene have no effect on the yield of nitroso dimer.

However, recent work by Akhtar and Pechet[13] has contradicted Barton's[4b] earlier deduction. These workers photolysed a mixture of the N^{14} steroid nitrite (V) from the androstane series and the N^{15} labelled steroid nitrite (VI) from the cholestane series. The ratios of $N^{15}:N^{14}$ in the androstane and cholestane products were 1:1.32 and 1:1.25 respectively showing that scattering of nitric oxide occurs during the reaction and thus indicating that a 'noncage' mechanism is involved.

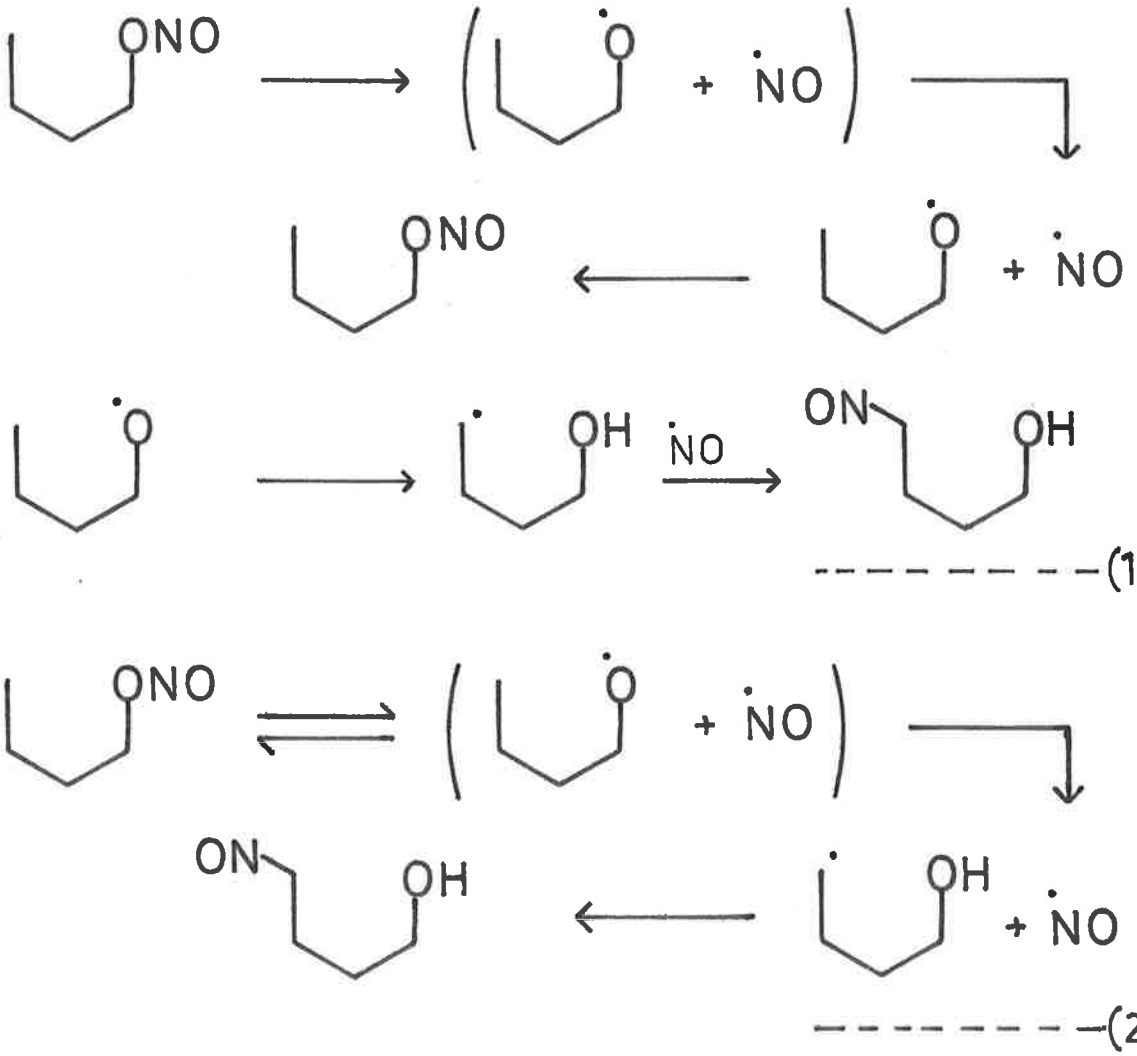
Akhtar and Pechet[13] believed both mechanisms (1) and (2) agreed with their experimental results.



(V)



(VI)

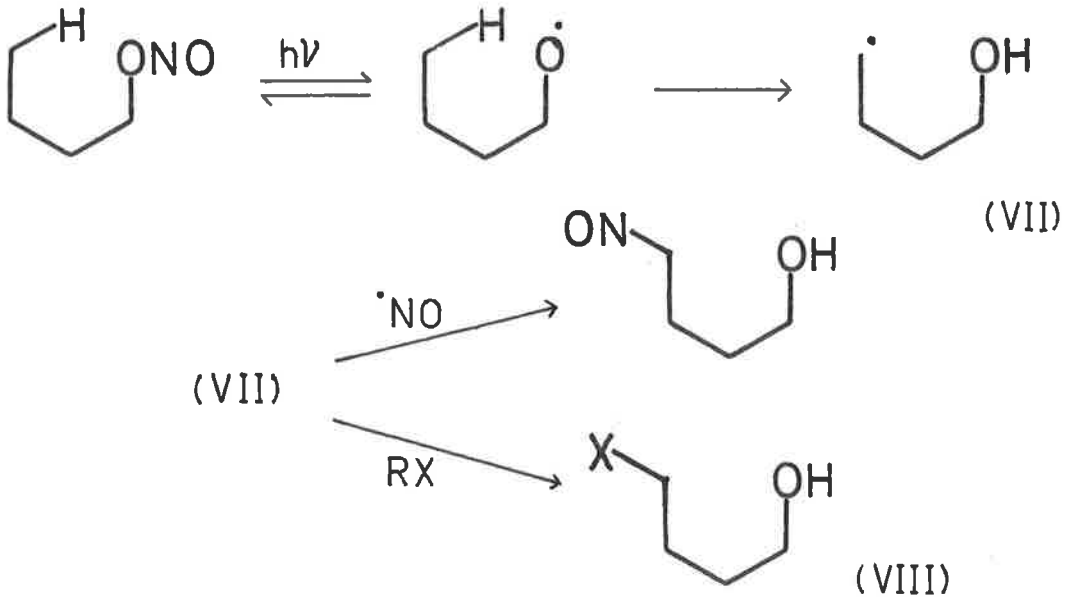


Mechanism (1) involves a completely 'noncage' process in which both the reversible homolysis of the nitrite ester and the irreversible rearrangement occurs outside of a solvent 'cage'.

Mechanism (2) involves generate recombination of alkoxy radical and nitric oxide within a 'cage' but an irreversible 'noncage' rearrangement of the alkoxy radical followed by coupling of the so-formed carbon radical with an NO group.

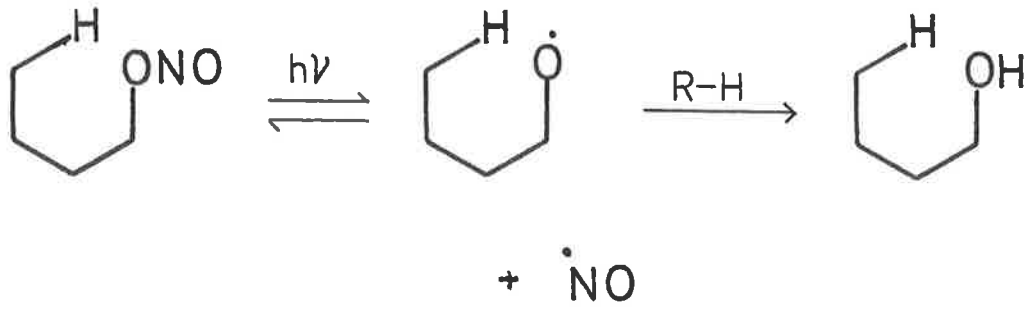
They[13] distinguished between these two mechanisms by photolysing the same mixture of appropriate N^{14} and N^{15} labelled steroids, (V) and (VI), but allowed the photolysis to go to only partial completion. The recovered unchanged nitrite of the cholestane series (VI) was rephotolysed to completion and the ratio of $N^{15}:N^{14}$ in the product was found to be 1.00:0.00. This finding is only compatible with the generate recombination of the alkoxy radical and nitric oxide during the reversible homolytic step from which Akhtar and Pechet[13] concluded that the Barton reaction proceeds via mechanism (2).

As an extension of the previous work, Akhtar and coworkers[14] considered that addition of an alternative radical source to the irradiated nitrite ester might lead to competition for the resulting alkyl radical between the nitric oxide and the alternative radical (Scheme 3). Introduction of iodine and bromotrichloromethane does lead to radical exchange reactions from which the corresponding δ-iodo- and δ-bromohydrins (VIII, X = I and Br respectively) were isolated.[14] Incorporation of a 36% atom excess of deuterium onto the δ-carbon atom (VIII, X = D) from the nitrite



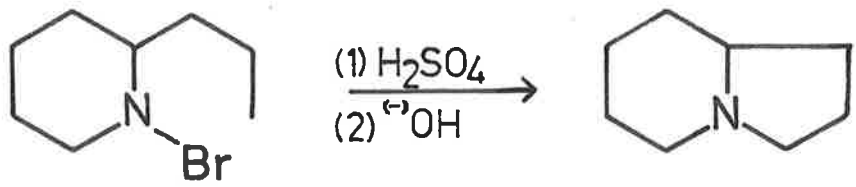
Scheme 3.

photolysis in the presence of 2 mole-equivalents of deuterated thiophenol (PhSD) was observed and this led Akhtar[14a] to conclude that it is substantially the carbon radical that is quenched (Scheme 3, X = D) and not the alkoxy radical as had been previously suggested by Sneen and Matheny[15] (Scheme 4).



Scheme 4.

1,5-Hydrogen transfer is not confined to alkyl nitrite photolysis. In fact the first example of intramolecular hydrogen transfer to be reported[16] involves the formation of octahydroindolizine (X) by heating a sulphuric acid solution of N-bromo-2-propylpiperidine (IX) (Scheme 5). This is a specific example of the Hofmann-Loeffler reaction.[17]



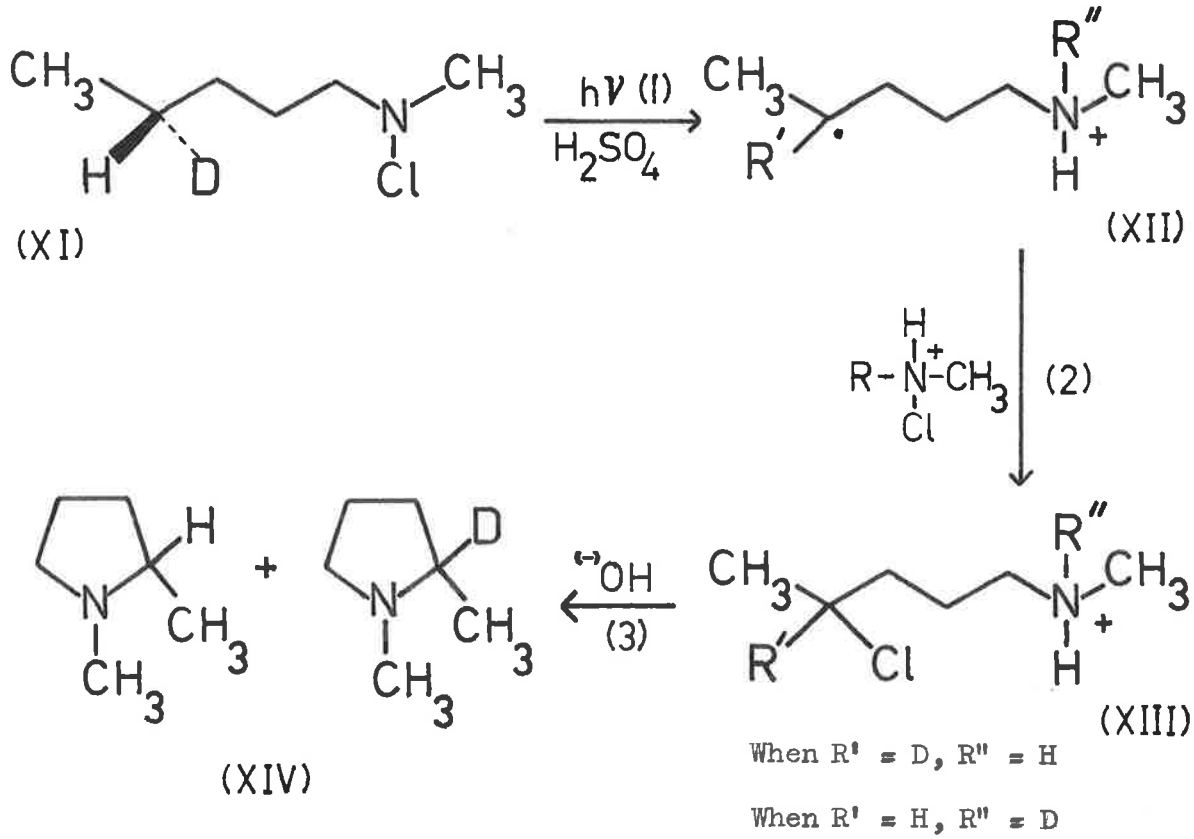
(IX) (X)

Scheme 5.

Originally Hofmann[16] discovered the reaction and later Loeffler and Freytag[18] applied it as a general synthesis of pyrrolidines. These workers observed that invariably five-membered rings are formed when simple secondary N-halo-amines are heated in acid and they[18] attributed this to the "proximity of the nitrogen to the δ-carbon atom". However no actual mechanism was proposed.

Wawzonek and Thelen[19] concluded that the reaction involves a radical chain mechanism since they deduced that it is not only initiated by heat, as Hofmann[16] had discovered, but also by hydrogen peroxide and ultraviolet light in the presence of chlorine. This deduction was further substantiated by Corey and Hertler[20] who followed, more thoroughly than the previous workers,[19] the influence of such radical initiating species as ultraviolet light alone and ferrous ion.

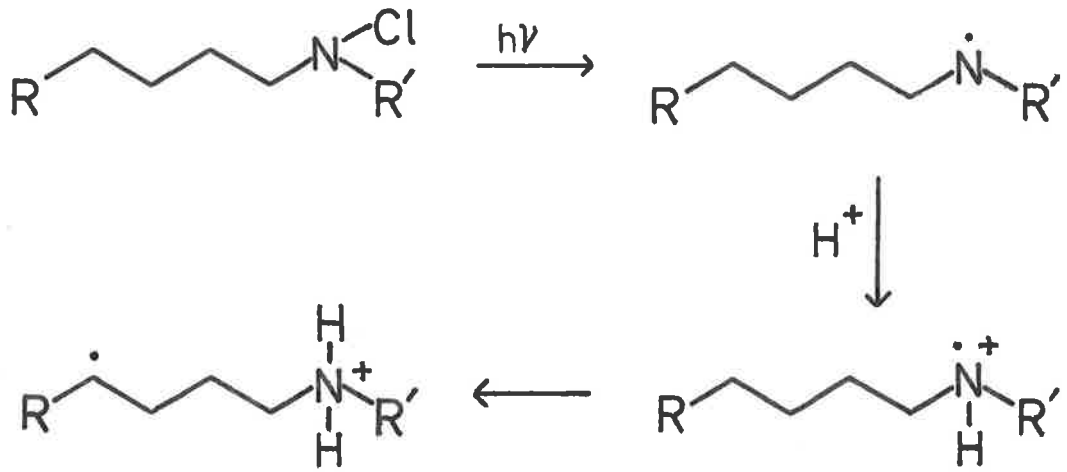
Corey[20] assumed a δ-carbon radical (XII) is involved in the mechanism since he isolated the optically inactive 1,2-dimethylpyrrolidine (XIV) from the photolysis in acid solution of the optically active N-chloro-derivative of methylamylamine (XI). He assumed that the δ-chloro-amine intermediate (XIII) is formed via abstraction of chlorine by the carbon radical (XII) in a chain process (step (2), Scheme 6) and cyclises to 1,2-dimethylpyrrolidine (XIV) during basification. The formation of the δ-chloro-amine intermediate has been verified by Wawzonek and Culbertson[21] who isolated 4-chlorodibutylamine hydrochloride from the Hofmann-Loeffler reaction on N-chlorodibutylamine.



Scheme 6.

The most significant difference between the Hofmann-Loeffler reaction and the Barton reaction is the catalytic effect of strong protonating acid on the former. This is of special significance since mechanisms proposed for both reactions[5,19] are essentially free radical in nature.

Corey and Hertler[20] suggested that a strong protonating acid is not necessary for the initiation step to occur but is essential for the propagation step in which the abstracting species is actually the aminium radical, $R\overset{\cdot}{\underset{H}{\overset{+}{N}}}R'$. These workers suggested that the initial radical forming process involves the photolysis of the unprotonated N-chloro-amine to form the amino-radical, $R\overset{\cdot}{N}R'$, which is immediately protonated to the aminium radical. Photolytic decomposition of the conjugate acid, $R-\underset{Cl}{\overset{H^+}{N}}-R'$, was discounted as such compounds are known[22] to show relatively short wavelength absorption in the ultraviolet compared with the unprotonated base.



The suggestion by Corey[20] that the aminium radical is essential for the propogation step was further substantiated by the discovery of Wawzonek and Nordstrom[23] who found that intramolecular hydrogen transfer

does not occur during the photolysis of N-chlorodibutylamine (XV) in carbon tetrachloride. The only product isolated was dibutylamine hydrochloride (XVII) (Scheme 7). Wawzonek[23] suggested that disproportionation (step (2)) of the amino radical (XVI) occurs before intramolecular hydrogen abstraction can take place whereas protonation of the amino radical in the Hofmann-Loeffler reaction, as proposed by Corey,[20] prevents disproportionation due to the electrostatic repulsion of the aminium radicals.

$$(C_4H_9)_2N\,Cl \xrightarrow{h\nu} (C_4H_9)_2N^{\bullet} + Cl^{\bullet} \qquad \text{.....(1)}$$

(XV) (XVI)

$$2(C_4H_9)_2N^{\bullet} \longrightarrow (C_4H_9)_2NH + C_4H_9N{=}CHCH_2C_2H_5 \qquad \text{.....(2)}$$

(XVI)

$$Cl^{\bullet} + C_4H_9N{=}CHCH_2C_2H_5 \longrightarrow HCl + C_4H_9N{=}C\dot{H}CHC_2H_5 \qquad \text{.....(3)}$$

$$C_4H_9N{=}C\dot{H}CHC_2H_5 + (C_4H_9)_2NCl \longrightarrow C_4H_9N{=}CHCH(Cl)C_2H_5 + (C_4H_9)_2N^{\bullet} \qquad \text{....(4)}$$

$$(C_4H_9)_2NH + HCl \longrightarrow (C_4H_9)_2NH{\cdot}HCl \qquad \text{.....(5)}$$

(XVII)

Scheme 7.

Corey and Hertler[24] photolysed N-chlorodibutylamine in acetic acid, a nonprotonating solvent, and isolated only dibutylamine hydrochloride. This result is completely analogous to the work of Wawzonek and Nordstrom[23] as the free amino radical formed by photolysis is not

protonated and therefore disproportionates.

Another theory has been presented by Neale and Walsh[25] concerning the initiation step of the photolytic Hofmann-Loeffler reaction. These workers extensively studied the Hofmann-Loeffler reaction on N-chloro-dibutylamine in which they varied (1) the acidity, (2) the degree of purity of the N-chloro-amine, (3) the wavelength and intensity of the applied ultraviolet radiation, and (4) the rate at which the reaction mixture was swept with nitrogen. From the results obtained, they concluded that the initiation step does not involve any unprotonated N-chloro-amine as had been postulated by Corey and Hertler.[20] Instead they[25] suggested that a 'Hofmann elimination-type' decomposition of the N-chlorodibutylamine conjugate acid to N-dichlorobutylamine and the dibutylamine conjugate acid occurs; the rate at which this takes place decreases with increased acidity but at low pH a catalytic quantity of the dichloro-amine is nevertheless formed (Scheme 8).

$$Bu_2N^+HCl + H_2O \longrightarrow BuNHCl + H_3O^+ + (C_4 \text{ fragment})$$

$$BuNHCl + H^+ \rightleftharpoons BuNH_2^+Cl$$

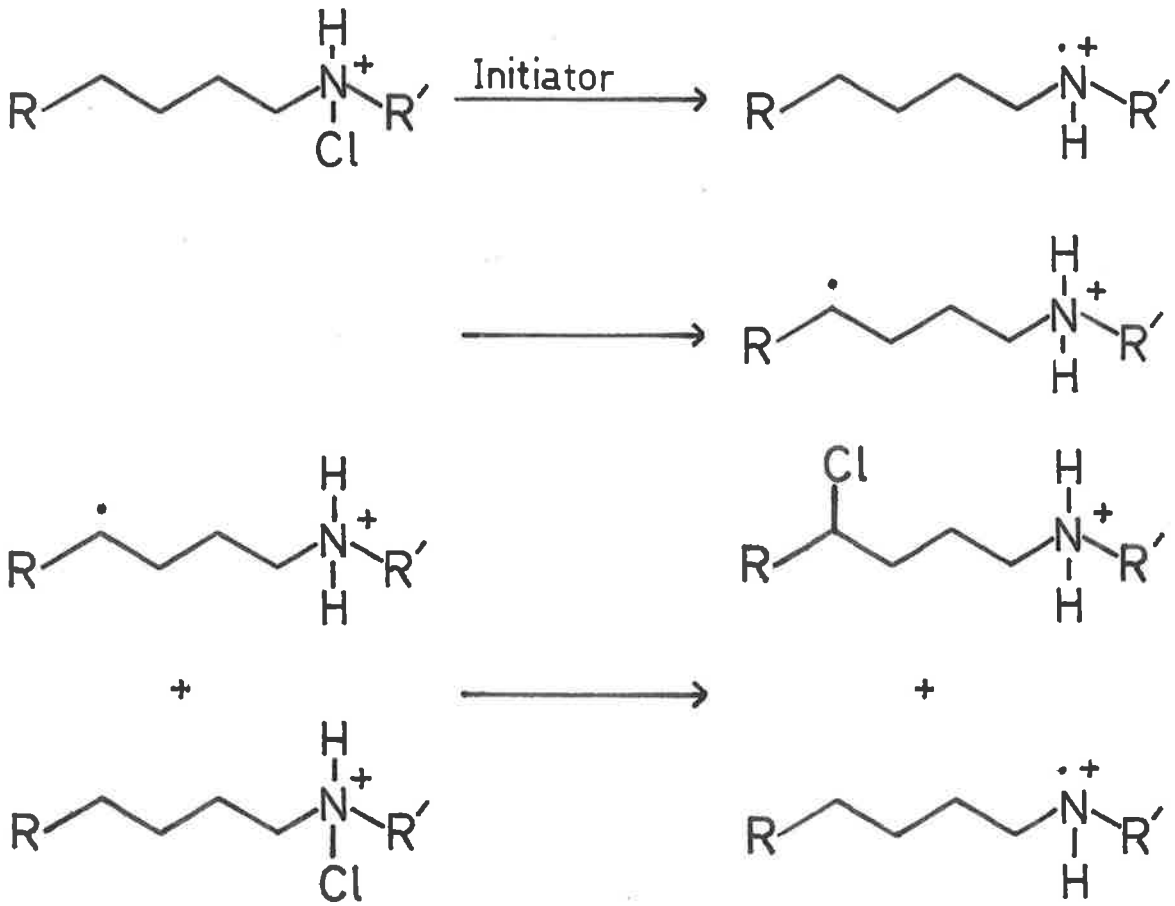
$$BuNHCl + Bu_2NH^+Cl \longrightarrow BuNCl_2 + Bu_2NH_2^+$$

Scheme 8.

Photolysis of the reaction mixture achieves decomposition of only the N-dichlorobutylamine which gives rise to free radical species which in

turn catalyse a radical chain decomposition of the protonated N-chloro-dibutylamine. Neale and Walsh[25] agree with previous workers[20] that the propogation step involves the aminium radical.

From the results obtained by these various groups of workers, it appears that the Hofmann-Loeffler reaction, whether catalysed photochemically,[19,20,25] reductively,[20,26] or by heat,[16] proceeds via the same general mechanism (Scheme 9) in which the initiation step involves the formation



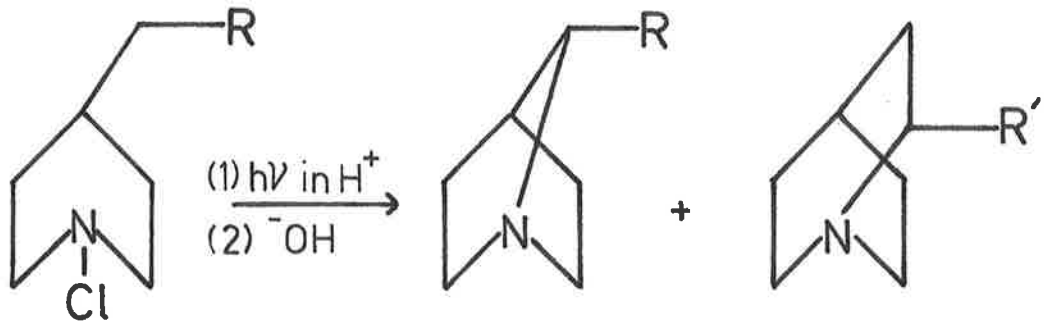
Scheme 9.

of the all important aminium radical which, in turn, undergoes intra-

molecular hydrogen abstraction to form the carbon free radical. The chain mechanism is continued by intermolecular halogen transfer from the N-chloro-amine conjugate acid to the alkyl radical.

Although it has been established that the Barton reaction involves specific 1,5-hydrogen transfer,[8] this is not the case with the Hofmann-Loeffler reaction. Preferred 1,5-hydrogen transfer occurs in most examples which have been considered.[27] However, products arising from 1,6-hydrogen transfer have been isolated in quite significant quantities,[19,28-30] usually along with the 1,5-transfer product.

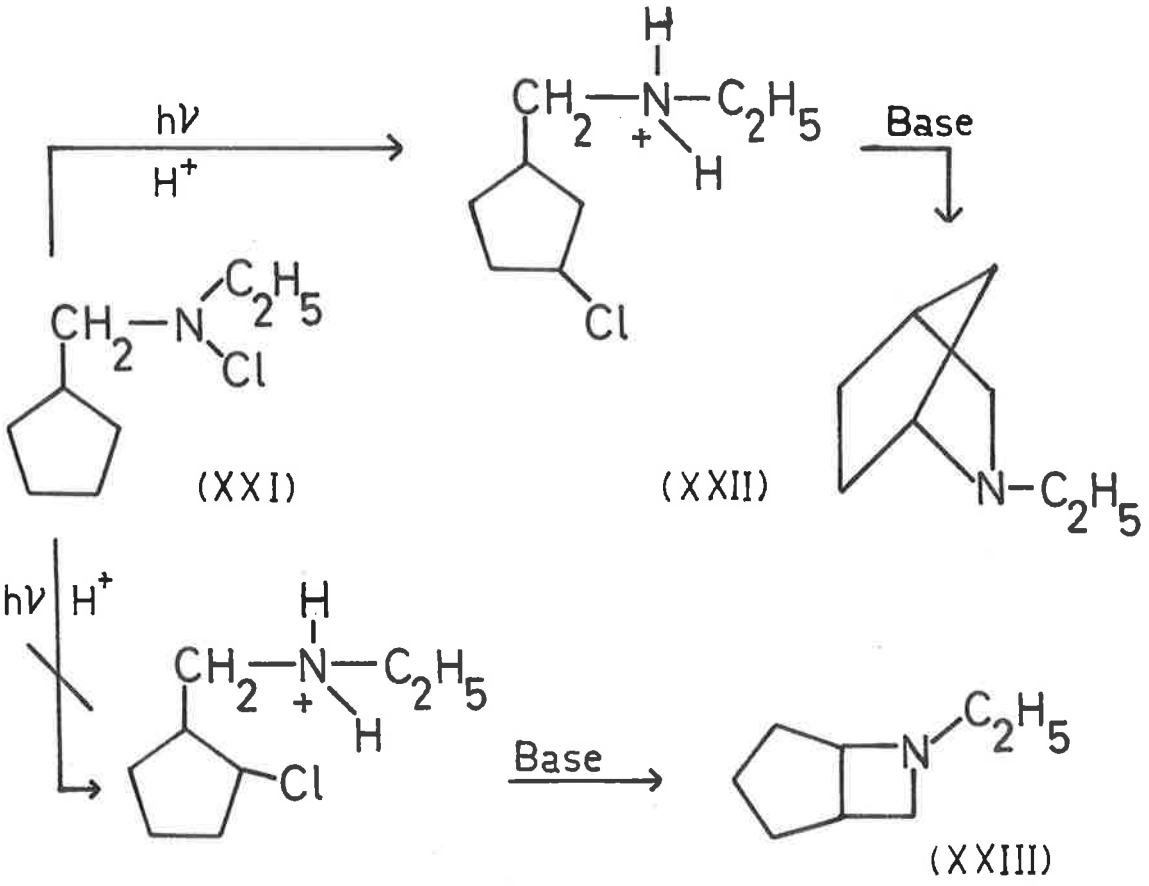
Wawzonek and Wilkinson[28] performed the Hofmann-Loeffler reaction on N-chloro-4-ethylpiperidine (XVIII, R = CH_3) and, contrary to the results of previous workers,[29,31] found that both 7-methyl-1-azabicyclo-[2.2.1] heptane (XIX, R = CH_3) and quinuclidine (XX, R' = H) are formed; the former through a 1,5-hydrogen transfer mechanism and the latter via a 1,6-atom transfer process.



(XVIII) (XIX) (XX)

Specific 1,6-hydrogen transfer was achieved by these workers[28] in the photolysis of N-chloro-4-propylpiperidine (XVIII, R = C_2H_5) in acid.

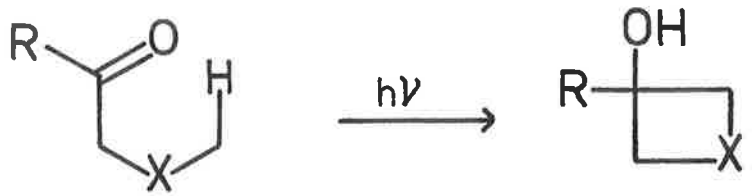
2-Methylquinuclidine (XX, R' = CH_3) was obtained but 7-ethyl-1-azabicyclo-[2.2.1]heptane (XIX, R = C_2H_5) could not be detected. Similarly 1,6-hydrogen transfer is achieved during the photolysis of N-chloro-N-methyl-cyclo-octylamine under acid conditions.[19]



Attempts have been made to achieve 1,4-hydrogen transfer. Loeffler[32] tried to cyclise N-chloro-N-methyl-2-butylamine under the Hofmann-Loeffler reaction conditions but failed to obtain any 4-membered ring tertiary amine. A more recent attempt by Gassman and Heckert[33] to force preferential γ-hydrogen abstraction over δ-hydrogen abstraction also failed as only the 1,5-hydrogen transfer product was isolated. These

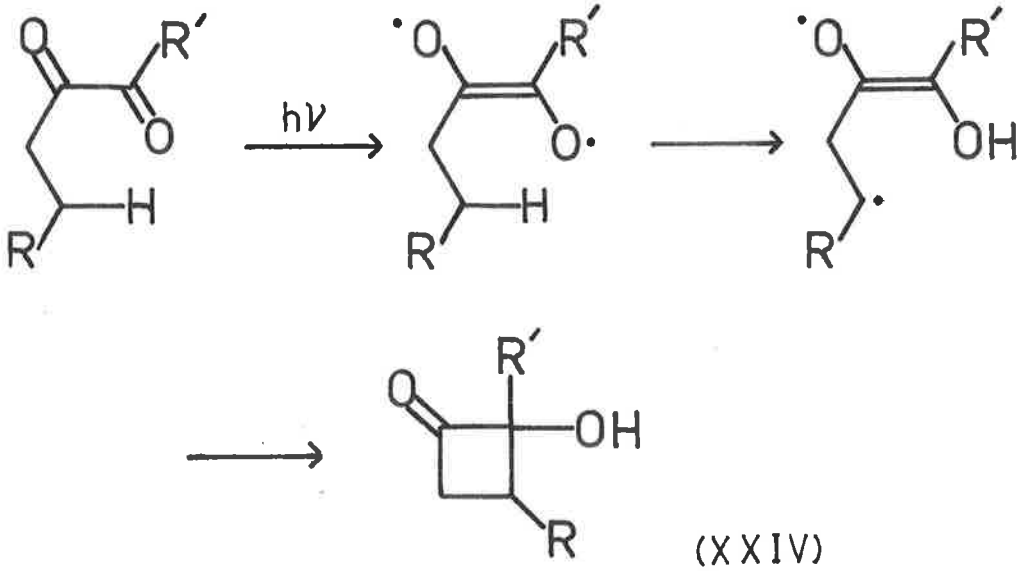
workers photolysed N-chloro-N-ethylaminomethylcyclopentane (XXI) in acid and expected to isolate N-ethyl-6-azabicyclo[3.2.0]heptane (XXIII) after treatment of the reaction product with base. Their predictions were based on the greater ring strain incorporated into the cyclopentane ring during 1,5-hydrogen transfer compared with the 1,4-atom shift. However, only N-ethyl-2-azabicyclo[2.2.1]heptane (XXII) is formed.

Numerous examples in which intramolecular hydrogen abstraction occurs during the photolysis of aliphatic ketones have been reported. Most of these involve the formation of cyclobutanol compounds[34] (Scheme 10, X = CH_2) and application of this particular reaction has been used in cyclosteroid synthesis.[35] A cognate reaction in which α-alkoxyketones afford 3-oxetanols (Scheme 10, X = O) has also been reported by Yates[36] and LaCount[37] and their coworkers.



Scheme 10.

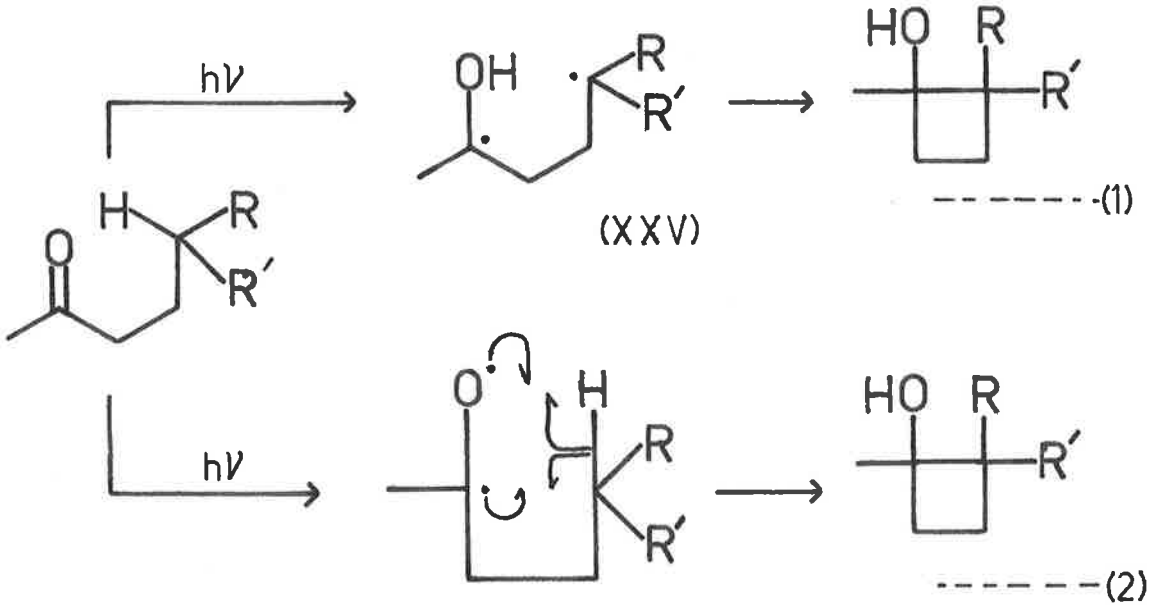
Similarly Urry and coworkers[38] have found that 1,2-diketones undergo γ-hydrogen transfer to form the corresponding 2-hydroxycyclobutanone (XXIV) as is illustrated in Scheme 11.



(XXIV)

Scheme 11.

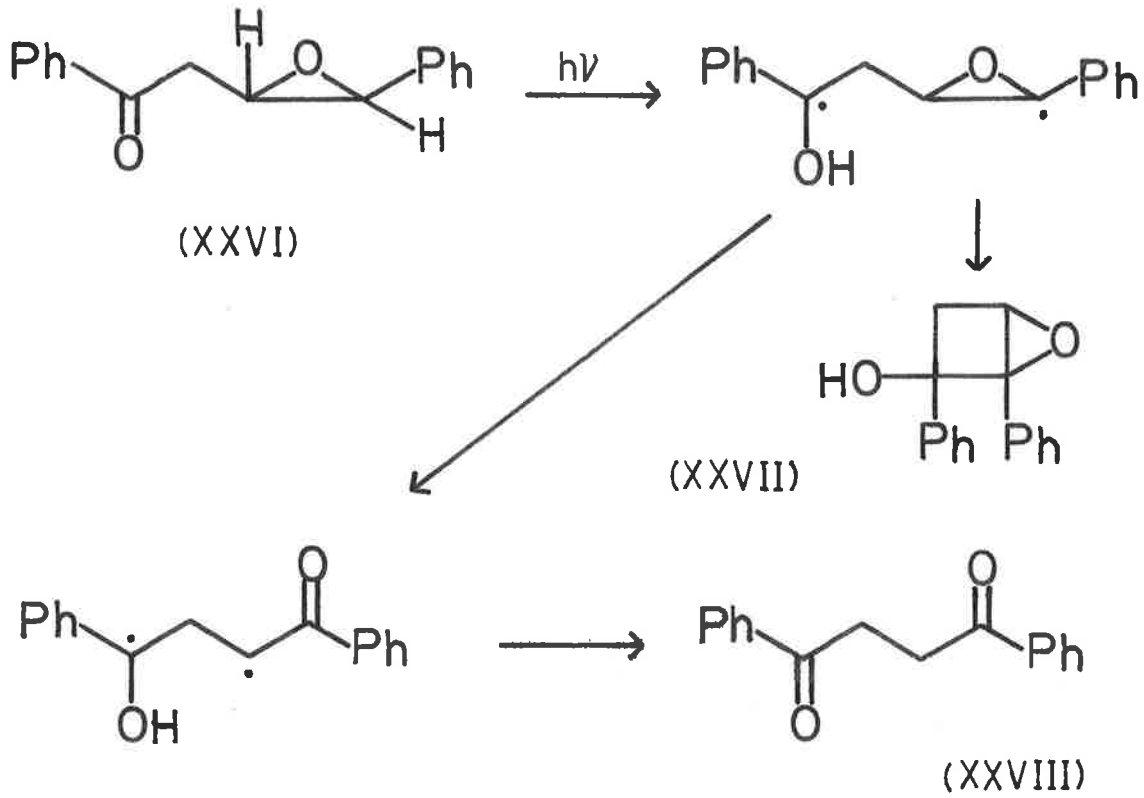
Two mechanisms have been proposed for the cyclobutanol formation; one by Yang and Yang[39] invokes a stepwise process in which a diradical (XXV) acts as an intermediate (equation (1), Scheme 12) while the other by Shulte-Elte and Ohloff[40] involves a concerted pathway (equation (2), Scheme 12).



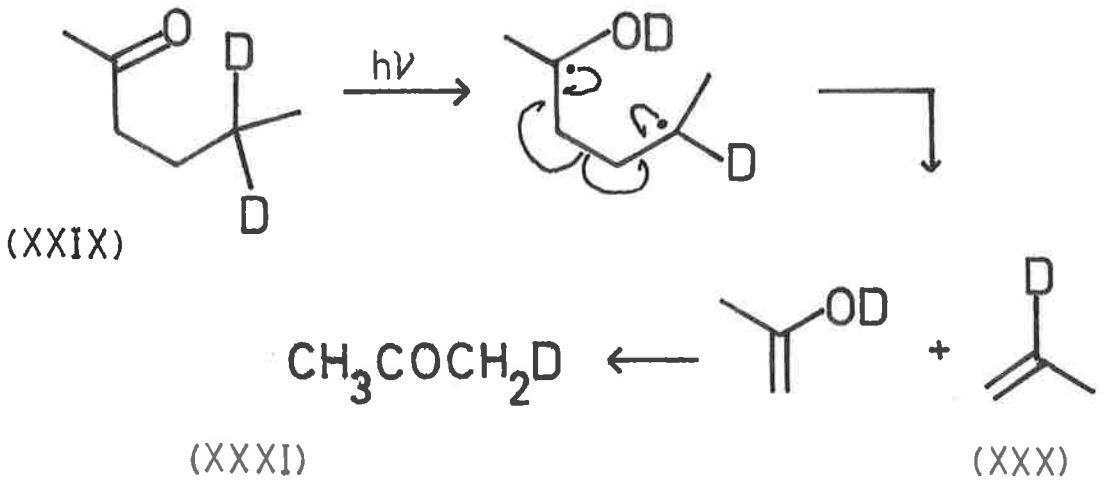
Scheme 12.

The latter workers prefer the concerted mechanism since they isolated optically active terpinen-4-ol and only one of the possible stereo-isomers of the cyclobutanol product from the photolysis of optically active 2,6-dimethyloct-7-en-3-one. They state that only a four-centred process, as is inferred by their concerted mechanism, can account for the retention of optical activity. However, Schaffner and coworkers[41] photolysed an optically active ketone and obtained a cyclobutanol with partial retention of configuration. These workers suggest that the results are compatible with the production of a short-lived intermediate diradical whose rates of racemisation and of cyclisation are of the same order of magnitude. Padwa[42] believes that the formation of dibenzoylethane (XXVIII) along with (XXVII) during the photolysis of trans-1,4-diphenyl-3,4-epoxybutan-1-one (XXVI) adds strong support for the stepwise process (Scheme 13).

Products arising from the fragmentation of the intermediate diradical, assuming a stepwise mechanism is involved, have been isolated by various groups of workers.[43] Srinivasan[44] photolysed 5,5-dideutero-2-hexanone (XXIX) and isolated monodeuteropropane (XXX) and monodeuteroacetone (XXXI). This is in accord with the products expected from a 1,5-hydrogen transfer mechanism. McMillan and coworkers[45] have recently observed by infrared spectroscopy the enol form of the ketone that is obtained transiently.

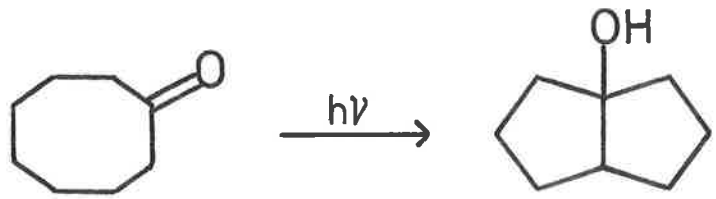


Scheme 13.



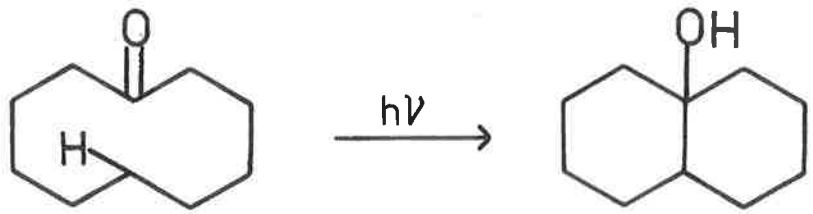
γ-Hydrogen abstraction by the incipient alkoxy radical has been inferred in each of the preceeding examples. However, as was the

case with the Hofmann-Loeffler reaction,[19,28-30] 1,6-hydrogen transfer has also been detected. Barnard and Yang[46] photolysed cyclo-octanone (XXXII) and obtained 1-hydroxybicyclo[3.3.0]octane (XXXIII).



(XXXII) (XXXIII)

These workers[46] observed an even greater divergence from the normal 1,5-hydrogen transfer rule when they photolysed cyclodecanone (XXXIV) and obtained high yields of the cis- and trans- 9-decalol (XXXV), presumably formed through a 1,7-hydrogen transfer process.

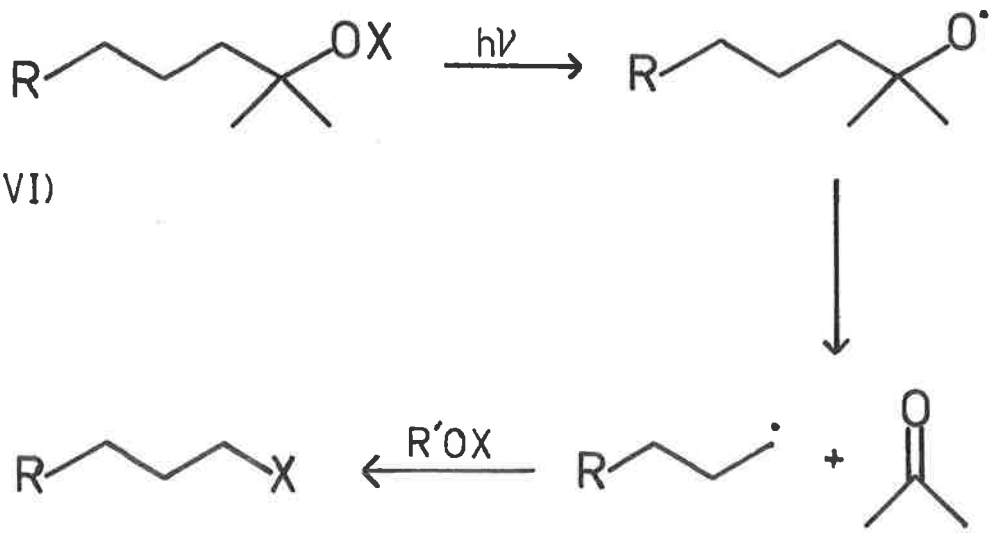


(XXXIV) (XXXV)

The explanation used to account for this deviation apparently lies in the proximity of such hydrogen atoms to the reactive carbonyl group.[47,48] It is significant that only 1,5- and not 1,6- or 1,7-hydrogen transfer occurs during the photolysis of the straight chain ketone, 2-octanone.[43g]

Alkoxy radicals generated by photolysis of alkyl hypochlorites[6k,49] undergo intramolecular hydrogen abstraction in a similar manner to those formed in the Barton reaction. Various groups of workers have photolysed long-chain tertiary hypochlorites and obtained the δ-chlorohydrins.[50] The reaction has been successfully applied to functionalise the 18- and 19-methyl groups in the steroid series.[6k,51]

Since both the Barton reaction and hypochlorite photolysis afford alkoxy radicals,[12,49] a close similarity between the two reaction mechanisms could be expected. It is true that both[12,49] give rise to the corresponding δ-substituted alcohols and that the side reaction products are analogous. Namely, fragmentation of the tertiary alkoxy radicals (Scheme 14) afford a ketone and alkyl radicals which in turn form the nitroso-alkane[12] (XXXVII, X = NO) and alkyl chloride[49] (XXXVII, X = Cl) respectively. Such fragmentation reactions of alkoxy radicals are well known.[5,12]



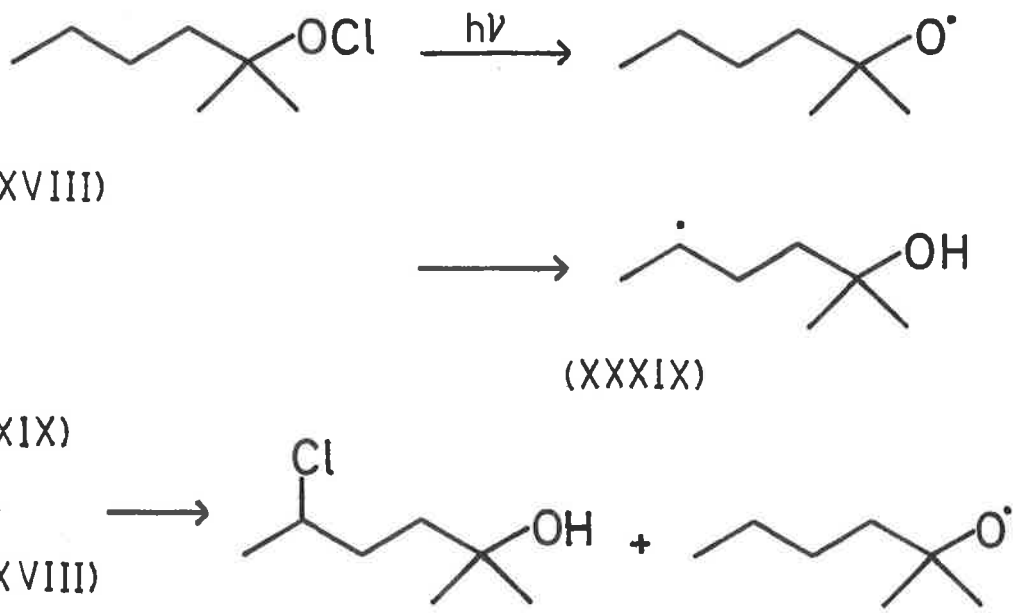
(XXXVI)

(XXXVII)

Scheme 14.

However two major differences are apparent.

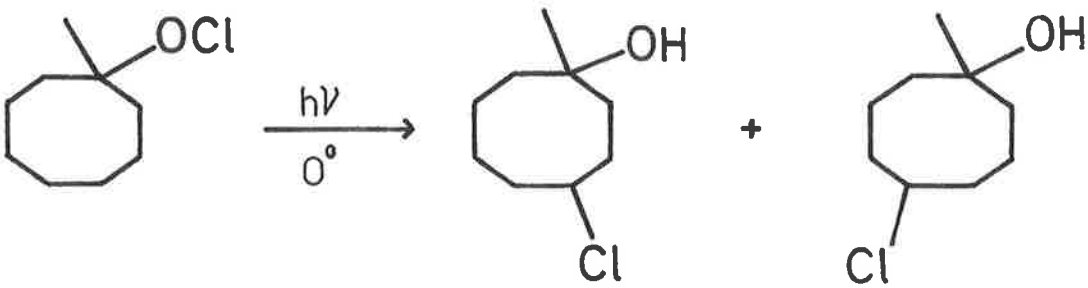
It has been previously mentioned that the Barton reaction seems to be a 'nonchain' radical process[12] in which 'noncage' coupling of alkyl radical and nitric oxide occurs.[13] However, Greene[49] and Walling[52] and their coworkers have both obtained evidence which indicates that the photolysis of alkyl hypochlorites initiates long-chain radical reactions in which intermolecular halogen abstraction by the intermediate alkyl radical occurs. The mechanism proposed by Walling and Padwa[52] is illustrated in Scheme 15.



Scheme 15.

Although specific 1,5-hydrogen transfer occurs in the Barton reaction, 1,5- along with 1,6- atom transfer takes place during hypochlorite photolysis.[52] Various groups of workers[52,53] have observed this irregularity which is also characteristic of the Hofmann-Loeffler reaction[19,28-30]

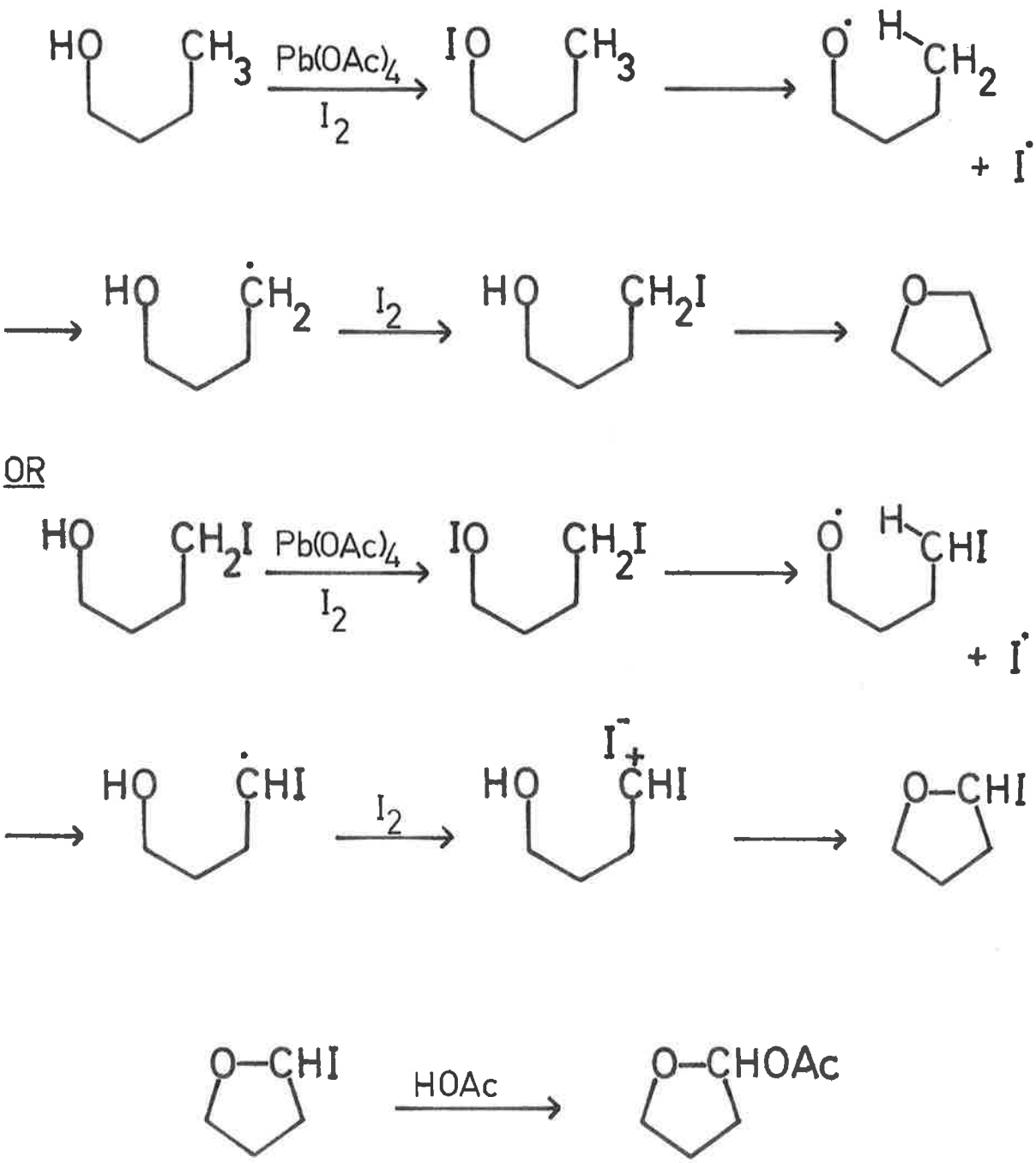
and ketone photolysis.[46] However, the most significant example has been described by Cope and coworkers[53] who photolysed 1-methylcyclo-octyl hypochlorite (XL) and isolated both the 4- and 5- chlorohydrins, (XLI) and (XLII) respectively.



(XL) (XLI) (XLII)

A "proximity effect" is again proposed[53] to account for the ε-chlorohydrin formation. Cope[48] suggests that when the cyclo-octane ring is in the favoured skewed-crown conformation, the oxy-radical can approach a hydrogen at C-5 easily but cannot come close to one at C-4. Specific hydrogen transfer from C-4 occurs when the ring is in a less favoured conformation. This postulate seems to be supported by examination of Dreiding models. However, a discrepancy appears to exist between this work and that of Kabasakalian and Townley[9] who isolated only the 4-nitrosohydrin from the photolysis of cyclo-octyl nitrite.

A hypohalite reaction with wider applicability than the hypochlorite reaction was developed by Heusler and coworkers[54] and has since been extensively used in the steroid systems.[6k, 7, 55] Alkyl hypo-iodites

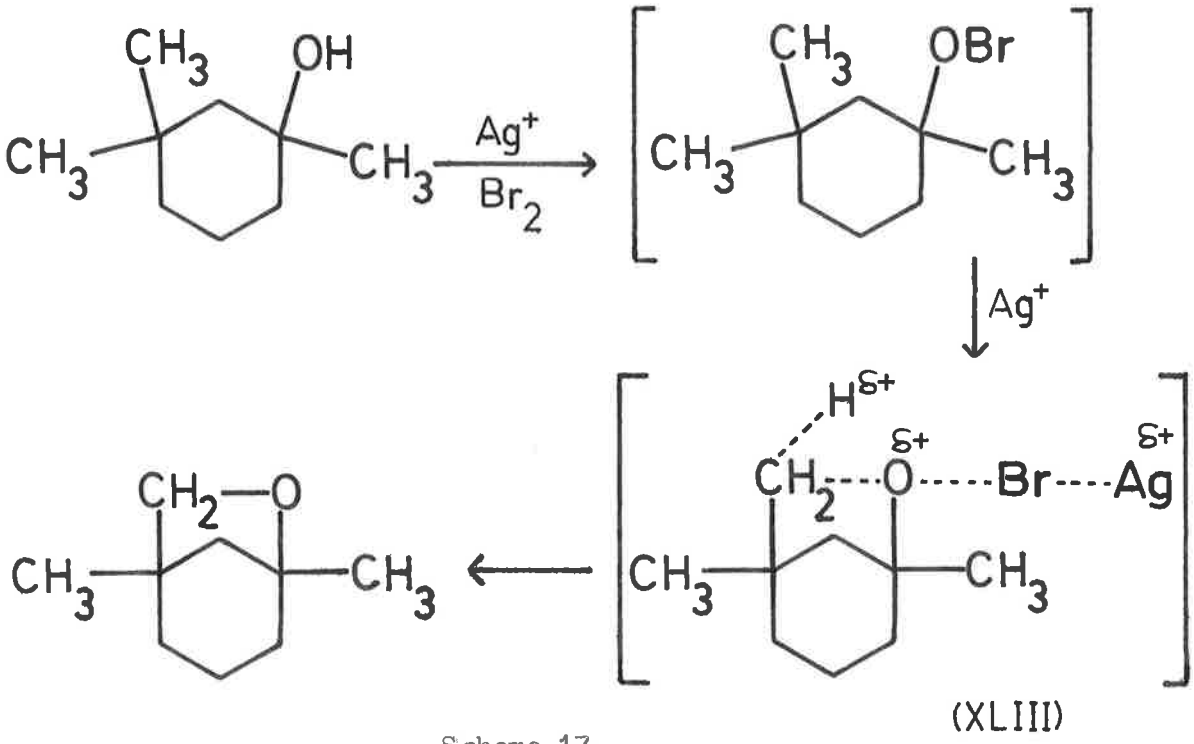

HO
CH3
Pb(OAc)4
I2
IO
CH3
O·
H
CH2
+ I·
HO
·CH2
I2
HO
CH2I
O
OR
HO
CH2I
Pb(OAc)4
I2
IO
CH2I
O·
H
CHI
+ I·
HO
·CHI
I2
I⁻
HO
+CHI
O–CHI
O–CHI
HOAc
O–CHOAc

Scheme 16.

are prepared *in situ* by the reaction of mercuric salts, silver salts, or preferably lead tetra-acetate with iodine and the alcohol.[56] Photolysis or thermal decomposition affords the alkoxy radical which undergoes 1,5-hydrogen abstraction analogous to the hypochlorite reaction and forms the δ-carbon radical which couples with iodine to form the iodohydrin. A review by Heusler and Kalvoda[56] illustrates the pathways by which the δ-iodohydrin may react depending on the substitution of the δ-carbon atom. It is unique for this particular type of reaction that disubstitution of the C-4 atom may be achieved. This is illustrated in Scheme 16 but is described in much greater detail by Heusler and Kalvoda.[56]

Hypobromites formed *in situ* from the alcohol with silver oxide and bromine likewise rearrange to tetrahydrofuran derivatives through a free radical intramolecular hydrogen abstraction reaction. Sneen and Matheny[15,57] originally suggested that such reactions of hypobromites with silver salts are not free radical in nature but rather take place through a concerted three-centred cyclisation mechanism (Scheme 17) in which, they suggest, a complex polar intermediate (XLIII) is involved.

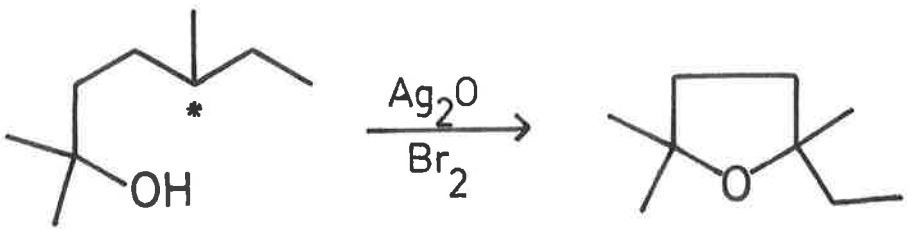
However, Smolinsky and Feuer[58] isolated optically inactive 2-ethyl-2,5,5-trimethyltetrahydrofuran (XLV) from the reaction of (+)-(S)-2,5-dimethylhexan-2-ol (XLIV) with silver oxide and bromine from which they concluded that a stepwise intramolecular hydrogen abstraction reaction by the intermediate alkoxy radical takes place. This mechanism seems to be the more likely as it is analogous to the previously mentioned hypochlorite and hypo-iodite reactions. It is further supported by Akhtar and coworkers[59]



(XLIII)

Scheme 17.

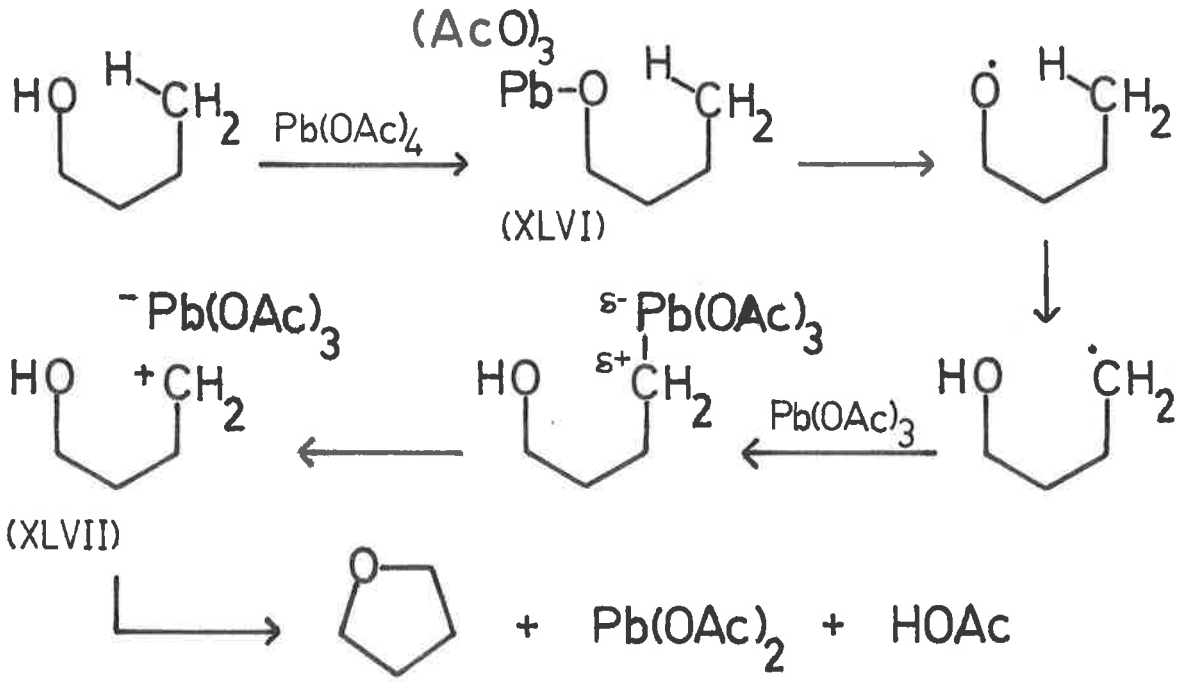
who found that decomposition products, characteristic of the intermediacy of alkoxy radicals, are formed from the reaction of a series of cyclic tertiary alcohols with silver oxide and bromine.



(XLIV) (XLV)

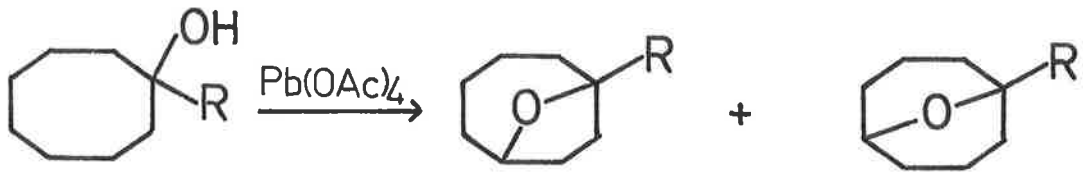
Oxidation of alcohols with lead tetra-acetate alone to the tetrahydrofuran derivatives has been achieved with a great deal of success[7,60] and the scope of the reaction has been extended mainly through the work

of Mihailovic[61] and workers.[62] Although the intramolecular functionalisation of the δ-carbon atom has been found to occur through a free radical process, the resulting C-4 atom has been shown to possess carbonium ion character.[61b,63] The mechanism[63] which has been accepted involves initial formation of a lead alkoxide (XLVI) which is homolysed to the alkoxy radical and lead triacetate. 1,5-Hydrogen transfer to the alkoxy radical affords the δ-carbon radical which is oxidised by the lead triacetate to a carbonium ion (XLVII).



Various groups of workers[61,62] have identified both tetrahydropyran and tetrahydrofuran products resulting from 1,6- and 1,5- hydrogen transfer respectively. However, the yield of the six-membered cyclic ether is low compared with that of the tetrahydrofuran product. Nevertheless, products arising from ε-hydrogen abstraction in the lead tetra-

acetate oxidation of cyclo-octanol (XLVIII, R = H) would be expected to form a major product contribution if the "proximity effect", proposed by Cope[48] for medium size rings, operates. However, Moriarty and Walsh[64] failed to detect any such products. The only compound resulting from transannular hydrogen transfer is 1,4-epoxycyclo-octane (XLIX, R = H) which forms <u>via</u> a 1,5-hydrogen shift. This result is in agreement with that of Kabasakalian and Townley[9] who showed that only 4-nitrosocyclo-octanol is produced in the photolysis of cyclo-octyl nitrite.



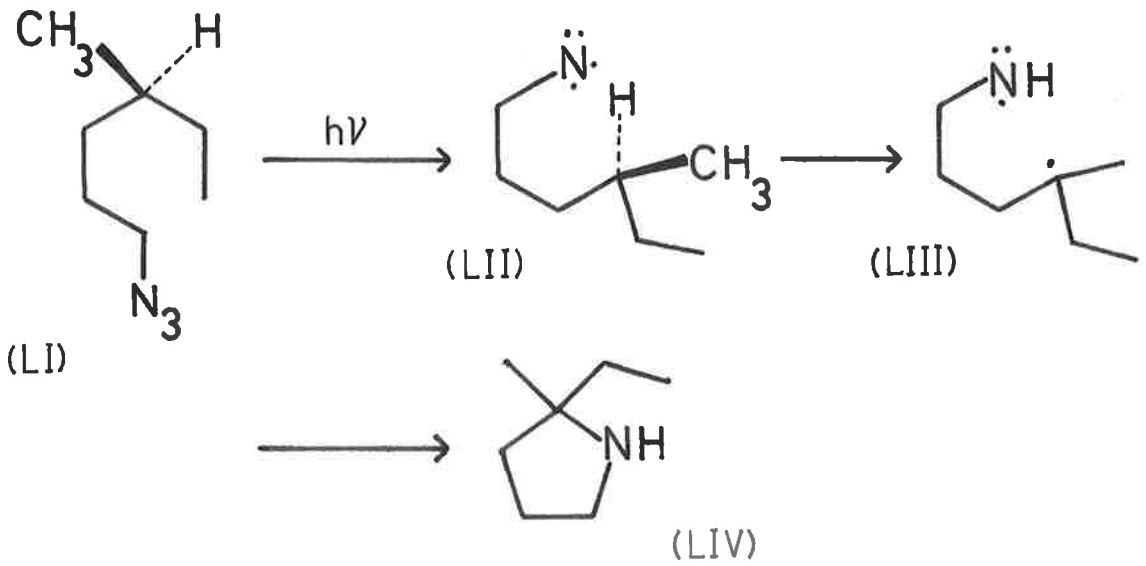
(XLVIII) (XLIX) (L)

Cope and co-workers[65] found that the reaction of lead tetra-acetate with 1-methylcyclo-octanol (XLVIII, R = CH_3) afforded both 1,4- (XLIX, R = CH_3) and 1,5-epoxy-1-methylcyclo-octane (L, R = CH_3) through 1,5- and 1,6- hydrogen transfer respectively. This result is in agreement with Cope's[53] previous observation that photolysis of 1-methylcyclo-octyl hypochlorite affords a mixture of the 1,4- and 1,5- chlorohydrins. Apparently a 'proximity effect' influencing 1,6-hydrogen transfer operates with the 1-methylcyclo-octyloxy radical but not with the unsubstituted cyclo-octyloxy radical[9,64] in which only 1,5-hydrogen transfer occurs.

Two groups of workers[66,67] have found that the decomposition of

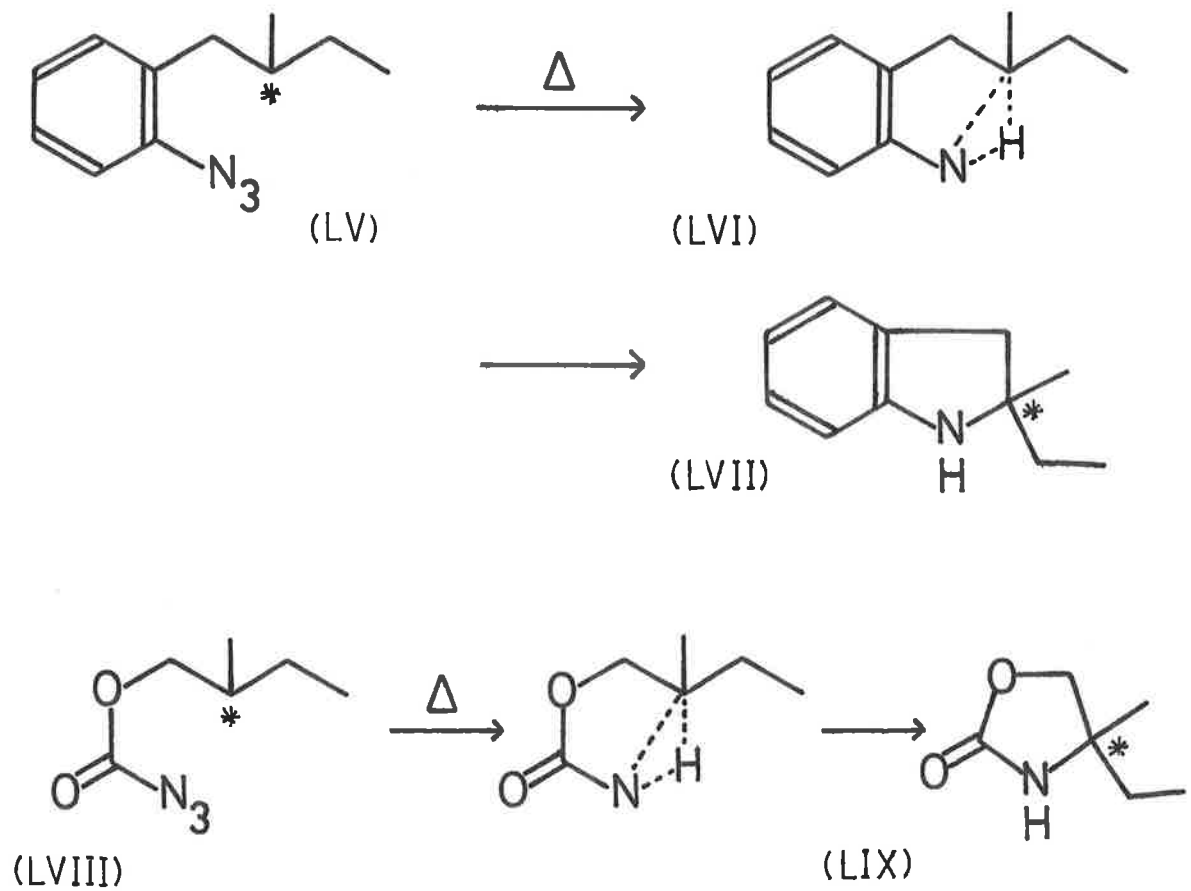
alkyl azides give rise to five-membered ring pyrrolidine compounds. It is generally agreed[66-69] that an alkyl nitrene participates in the reaction scheme. However, conflicting results have led these two groups to disagree as to the actual reaction mechanism.

Barton and Morgan[66] photolysed the optically active alkyl azide (LI) and isolated optically inactive 2-ethyl-2-methylpyrrolidine (LIV). They suggested that the nitrene intermediate (LII) achieves 1,5-hydrogen transfer to form a diradical (LIII) which has time to isomerise before radical coupling occurs and gives the racemic pyrrolidine product (LIV).



However, Smolinsky and coworkers[67] have found the results of the previous workers non-reproducible and furthermore have shown that the pyrolysis of optically active 1-azido-2-(2-methylbutyl)benzene (LV) and 2-methylbutyl azidoformate (LVIII) in the vapour phase affords optically active 2-ethyl-2-methylindoline (LVII) and 4-ethyl-4-methyloxazol-2-one

(LIX) respectively. Smolinsky concedes that a mechanism involving a di-radical intermediate which couples to form the pyrrolidine product before isomerisation to the racemic compound can occur, adequately satisfies his results. There is an analogy between such a mechanism and the scheme of Schaffner[41] for cyclobutanol formation from the ketone photolysis (refer to page 20). However, Smolinsky[67] prefers a nitrene insertion mechanism incorporating a three-membered intermediate (LVI) to account for the retention of optical activity (Scheme 18). Yamada and coworkers[69] have



Scheme 18.

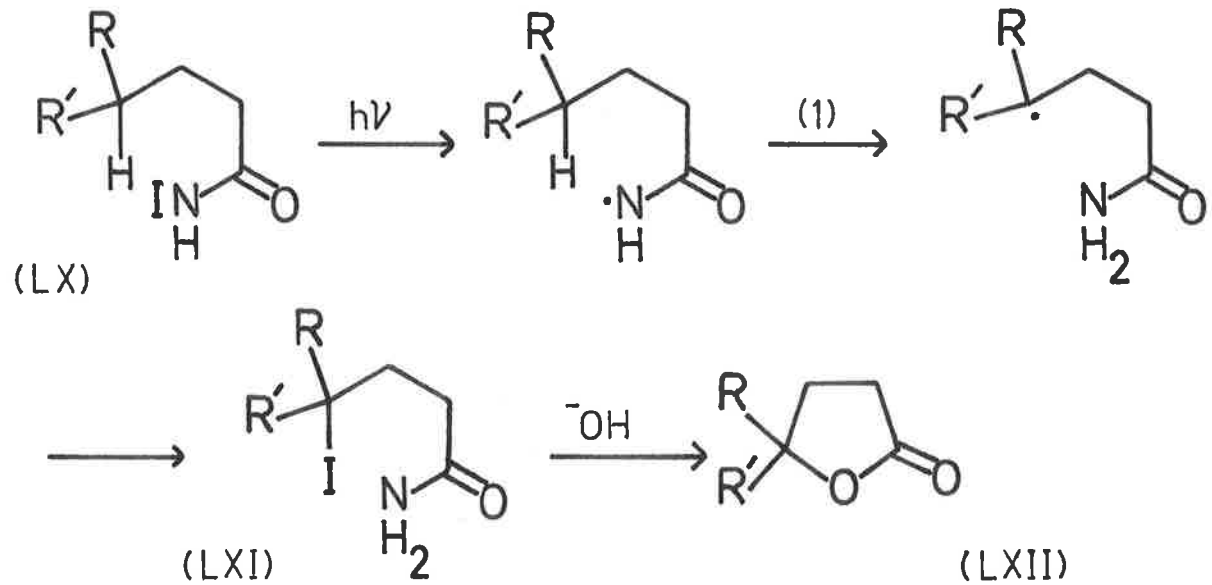
obtained similar results by pyrolysis of optically active 2-methylbutyl

azidoformate (LVIII) in solution and similarly propose an insertion mechanism.

Abramovitch and Davis[70] suggest that the nitrene intermediates produced under different conditions are conceivably in different electronic states; namely, the singlet state from the thermal decomposition and the triplet state from the photochemical decomposition. This suggestion gains added support from the work of Saunders and Caress[71] who have confronted a similar discrepancy between the reactions of thermally and photochemically derived aralkylnitrenes. These workers showed that the ratio of 1,2-phenyl/methyl group migration varies considerably depending on the mode of azide decomposition. In order to explain this discrepancy, Saunders[71] suggested that pyrolysis affords singlet nitrene which undergoes rearrangement in such an electronic state whereas photolysis affords a high energy singlet azide which passes to triplet nitrene by either of two pathways; singlet azide ⟶ triplet azide ⟶ triplet nitrene, or singlet azide ⟶ singlet nitrene ⟶ triplet nitrene. Since the rearrangement can involve either singlet or triplet nitrene, then the quantitative difference in products depends on the difference in modes of azide decomposition, pyrolytic or photolytic. As a simple rationale to the conflicting results of Barton[66] and Smolinsky,[67] it therefore seems possible that photolysis of alkyl azides afford triplet nitrenes which give rise to optically inactive products *via* the mechanism of Barton and Morgan[66] whereas pyrolysis of the corresponding azides either in the vapour phase[67] or solution[67,69] afford singlet nitrenes which react *via* the mechanism proposed by Smolinsky[67] to give rise to the optically active pyrrolidines.

The whole situation concerning the work of Barton and Morgan[66] has become confused following a report by Barton and Starratt[6m] that they cannot reproduce the original results. Moriarty and Rahman[72] have confronted a similar problem. These workers originally achieved photochemical cyclisation of n-octyl azide to 2-butylpyrrolidine by an analogous method to that used by Barton and Morgan but have since been unable to repeat this work.

In an investigation into new methods of preparing γ-lactones, Barton and Beckwith[73a] photolysed N-iodo-amides (LX) possessing a γ-methylene group. They envisaged an intramolecular hydrogen transfer process of the type illustrated in Scheme 19.



Scheme 19.

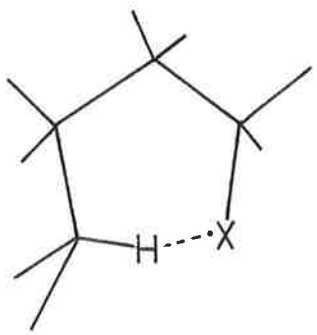
γ-Lactones (LXII) were obtained and results of carefully conducted experiments[73] indicated that γ-iodo-amides (LXI) do occur as

intermediates in the reaction mechanism although such compounds (LXI) were never isolated. In order to prove that the γ-iodo-amide (LXI) is formed *via* an intramolecular radical reaction (step (1), Scheme 19) the photolysis of optically active N-iodo-4-methylhexanamide (LX, R = Me, R' = Et) was carried out. Hydrolysis of the reaction product afforded racemic 4-methyl-4-hexanolactone (LXII, R = Me, R' = Et) from which it follows that a radical hydrogen abstraction process (step (1), Scheme 19) actually participates.

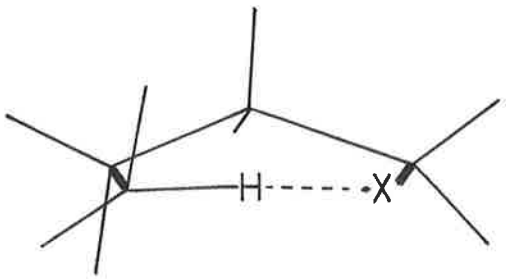
As was predicted,[73] γ-lactones form the major intramolecular hydrogen transfer product. However, δ-lactones resulting from 1,6-hydrogen transfer were also detected; a result which conforms with most other intramolecular hydrogen abstraction reactions.

Mori and Matsui[74] have recently applied this reaction to the synthesis of lactonic diterpenoid compounds. Beckwith and Goodrich[75] have achieved similar results from the photolysis of N-chloro-amides. Petterson and Wambsgans[76] have extended the scope of N-halo-amide photolysis by applying such a reaction to various N-chloroimides from which the corresponding 4-chloro-imides were obtained. A further extension of the N-halo-amide photolysis has been reported by Neale and coworkers[77] who have photolysed various N-bromo-amides, N-bromo-N-alkylamides, and N-chloro-N-alkylamides and have similarly obtained the corresponding 4-halo-amides. Further results of significance concerning intramolecular hydrogen abstraction by amido radicals have been obtained by Gilpin[78] who detected mass peaks of compounds resulting from intramolecular hydrogen transfer reactions during the mass spectral analysis of various aliphatic amides.

A general consideration of all intramolecular hydrogen abstraction reactions in straight chain, terpenoid, and steroidal compounds indicates that 1,5-hydrogen transfer is preferred to 1,6-hydrogen shift and both occur to the exclusion of all other types of intramolecular transfer processes. Corey and Hertler[20] consider that a prerequisite for hydrogen abstraction is that the three atoms participating in the hydrogen transfer process must be collinear or at an angle as close to 180° as possible. The smallest cyclic system to fulfil such a requirement is the quasi six-membered transition state which is represented diagramatically from above the plane of the ring as (LXIII) and in the plane as (LXIV).



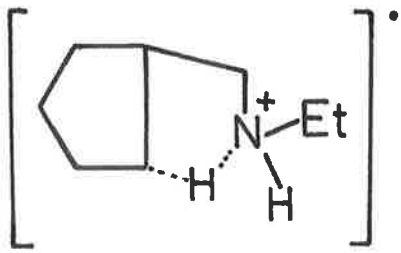
(LXIII)



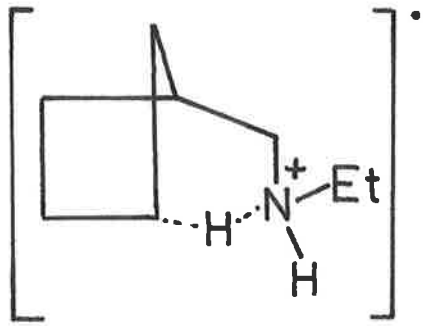
(LXIV)

Hydrogen transfer through a five- and lower-membered cyclic intermediate is excluded[80] due to the inability of such systems to fulfil the above requirement. As mentioned previously, Gassman and Heckert[33] attempted to force 1,4-hydrogen transfer by carrying out the Hofmann-Loeffler reaction on N-chloro-N-ethylaminomethylcyclopentane but failed to isolate any product from γ-hydrogen transfer. These workers deduced

that the proximity of the γ-hydrogen to the aminium radical can remain at about 1.8Å° whereas the closest the δ-hydrogen atom can come to the aminium radical in the preferred conformation of the cyclopentane ring is about 2.2Å° which is considerably greater than the optimum interatomic distance for hydrogen abstraction. In order to shorten this latter interatomic distance to much less than 2.2Å°, Gassman predicted a large amount of strain must be incorporated into the system which would result in out-of-plane folding of the cyclopentane ring. On this basis it was expected that γ-hydrogen abstraction would occur much more readily than δ-hydrogen abstraction. However, balanced against this effect of ring strain is the preference for a linear transfer of hydrogen from carbon to nitrogen. These workers estimated the C...H....N angles in the γ- and δ-hydrogen transfer intermediates (LXV) and (LXVI) to be about 120° and 145° respectively. Since only δ-hydrogen atoms are abstracted, Gassman and Heckert concluded that "linearity of hydrogen transfer is far more important than the inhibition of hydrogen transfer due to the effect of internal strain".



(LXV)



(LXVI)

Corey and Hertler[20] indicate that the energy difference between the 1,5- and 1,6- hydrogen transfer processes is approximately 1.3Kcal/mole.

This difference does not appear to be too significant. In fact, Walling and Padwa[52] have shown that the relative yields of 1,5- and 1,6-hydrogen transfer products do not vary with reaction temperature during the hypochlorite photolysis. This infers that the activation energy for intramolecular hydrogen transfer by both processes is relatively unimportant. Corey[20,80] suggests that the participation of a quasi six-membered ring is more favourable than a seven-membered intermediate due to the higher probability of the system existing in such a conformation compared with the 1,6-transfer intermediate. Nevertheless, partial importance of the energy difference between the 1,5- and 1,6- intermediates seems definite because of the fact that yields of 1,6-transfer products are not greatly increased when the possibility of 1,5-hydrogen transfer is eliminated.[79] Beckwith[75] suggests that preference for the quasi six-membered intermediate is partly due to the nonbonded interactions between adjacent hydrogen atoms. Examination of Dreiding models shows that the adjacent atoms are in a "skewed" conformation in the quasi six-membered intermediate but are partially eclipsed in the corresponding seven-membered system. Reference to the influence of non-bonded interactions has also been made by Corey and Hertler.[20] Mihailovic[80] suggests that products arising from 1,7- and higher-order hydrogen shifts are not formed probably due to the unfavourable free energy change associated with the formation of the corresponding eight and higher-membered cyclic transition states.

From the suggestions made by these various workers, it appears

that approximate collinearity of the C...H...X atoms is a prerequisite for radical hydrogen transfer and provided such a requirement is fulfilled, the order of hydrogen shift then depends on the lowest energy and highest probability of the appropriate cyclic transition states. Although 1,5-hydrogen transfer is preferred in most systems, it would be expected that 1,6- or 1,7-hydrogen transfer could occur in preference to 1,5-hydrogen shift in a system in which collinearity of the C...H...X atoms cannot be achieved in the six-membered but can be achieved in higher order transition states. Such cases do exist. Wawzonek and Wilkinson[28] (refer to page 16) have found that preference for C-5 (1,6-) over C-4(1,5-) hydrogen transfer occurs in the Hofmann-Loeffler reaction on N-chloro-4-propyl-piperidine. Examination of Dreiding models for the 4-alkylpiperidines shows that the C...H...$^{\circ}N^{+}$ angle for the hydrogen transfer is 180° for the seven-membered ring transition state involving C-5 abstraction and 128° for the analogous six-membered ring involving C-4 abstraction.

As mentioned previously, a deviation from the normal 1,5-transfer rule also occurs in the photolysis of 1-methylcyclo-octyl hypochlorite,[53] cyclo-octanone,[46] and N-chloro-N-methylcyclo-octylamine in acid,[19] and the lead tetra-acetate oxidation of 1-methylcyclo-octanol.[65] Cope[48] explains that the proximity of the C-5 hydrogen atom, when the cyclo-octane ring is in the favoured skewed-crown conformation, leads to the 1,6-transfer products. C-4 Hydrogen transfer is assumed to occur when the ring is in a less favoured conformation. Such an effect conforms with a deviation in which approximate C...H...X collinearity can be achieved in both the 1,5- and 1,6-hydrogen transfer intermediates but a higher proba-

bility of the occurrence of a seven-membered cyclic intermediate leads to higher yields of 1,6-transfer products. A similar rationalisation may be used to account for the formation of the 1,7-hydrogen transfer product, 9-decalol, from the photolysis of cyclodecanone[46] (refer to page 22).

Although Cope[48] has adequately explained how the "proximity effect" should enhance 1,6-hydrogen transfer in the 1-methylcyclo-octyl system, there has been no explanation why a similar effect does not operate in the simple cyclo-octyl system (refer page 25). Examination of Dreiding models indicates that approximate collinearity of the C...H...O atoms is possible for both the 1,5- and 1,6- hydrogen transfer intermediates in both the cyclo-octyloxy and 1-methylcyclo-octyloxy radicals. It seems likely therefore that the discrepancy between the products of the two systems lies in the energy or probability factors influencing participation of the various cyclic transition states. Because only the 1,5-hydrogen transfer product is obtained from the cyclo-octyl compounds,[9,64,65] it appears that the energy difference between the six- and seven- membered transition states is large enough to counteract the higher probability of the cyclo-octane ring existing in the skewed-crown conformation; the conformational isomer which, Cope[48] suggests, enhances 1,6-hydrogen transfer.

However, in the case of the 1-methylcyclo-octyloxy radical,[53,65] it would appear that the 1-methyl substituent introduces some steric repulsion which enhances the participation of the seven-membered transition state. Examination of Dreiding models indicates that a nonbonding interaction between the 1,2-methyl-hydrogen groups could inhibit conformational

interconversion to a small degree; enough to hold the molecule in the skewed-crown conformation long enough to enable 1,6-hydrogen transfer to occur and therefore counteract to a large extent the energetically preferred 1,5- hydrogen transfer.

It seems a greater understanding of the preferred conformations of the substituted cyclo-octane ring system is necessary before this discrepancy between the cyclo-octyloxy radical and the 1-methylcyclo-octyloxy radical reactions can be completely understood. Anet and St. Jacques[81] have recently studied the nuclear magnetic resonance spectra of various substituted cyclo-octane systems and have interpreted their results in terms of preferred conformations of the cyclo-octane ring in such compounds. Perhaps the desired results required for the rationalisation of the above problem will be soon forthcoming.

2. Aims of the Investigation.

Barton[4b] found that alkyl nitrite photolysis affords the corresponding δ-nitrosohydrin via an intramolecular hydrogen abstraction reaction whereas pyrolysis of the same nitrite ester gives rise only to fragmentation products. To explain the different pathways by which the analogous alkoxy radicals react under these two different sets of conditions, Barton[4b] suggested that a 'hot' or 'activated' alkoxy radical is necessary for intramolecular hydrogen abstraction to be achieved. However, such a conclusion did not seem to be completely justified. Since the photolyses had been carried out at ambient temperatures whereas the pyrolyses naturally occurred at high temperatures, it seemed possible that a temperature effect may have caused the difference in reaction products. A study of the reactions of 'unactivated' alkoxy radicals derived at ambient temperatures by redox reactions of alkyl hydroperoxides and peracetates with metal ions was therefore undertaken.

Although Beckwith and Goodrich[75] had achieved intramolecular hydrogen transfer during the photolysis of primary N-chloro-amides, the actual γ-chloro-amides had not been isolated; γ-lactone formation had been used to show that 1,5-hydrogen transfer had occurred. It was therefore decided to repeat this work with the aim of isolating the actual γ-chloro-amides. Furthermore, extension of the scope of intramolecular nitrogen radical reactions was visualised through the photolysis of various alkyl-N-chlorocarbamates and N-alkyl-N-chloro-acetamides.

The reactions of lead tetra-acetate with alcohols in the presence

and absence of iodine[7] had both been shown to produce intramolecular hydrogen abstraction products *via* an intermediate alkoxy radical. The reaction of lead tetra-acetate with primary amides in the presence of iodine[73] had also been found to afford intramolecular hydrogen transfer products by way of the amido radical. Since the reaction between lead tetra-acetate and primary amides alone had not been studied, it seemed important that such a project should be undertaken.

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II. RESULTS AND DISCUSSION

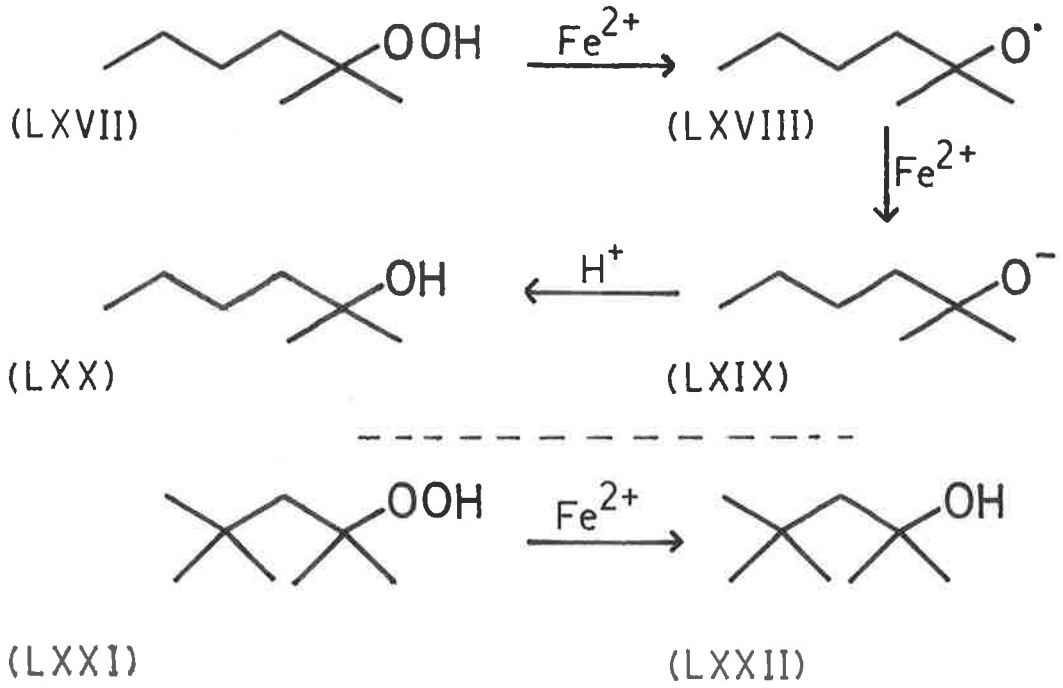
1. Decomposition of Alkyl Hydroperoxides and Peracetates.

The reductive decomposition of alkyl hydroperoxides is a well-known method[15,82-94] for the formation of alkoxy radicals at ambient temperature and free of photolytic activation. Fission of the O-O bond in an alkyl hydroperoxide by a metal ion is often represented by a one-electron transfer process[15,82-94] from the metal ion to the peroxide (refer to analogous electron transfer processes involving alkyl radicals, page 46) although a reverse ligand transfer mechanism (also refer to later discussion, page 47) may also operate. The reaction may be induced by a number of metal ions[88] including those of copper, cobalt, chromium, and manganese but the most effective appears to be ferrous ion which reacts rapidly with a variety of hydroperoxides in dilute acid without heating. The reaction may be represented as follows:

$$ROOH + M^{n+} \longrightarrow RO^{\bullet} + {}^{(-)}OH + M^{(n+1)+}$$

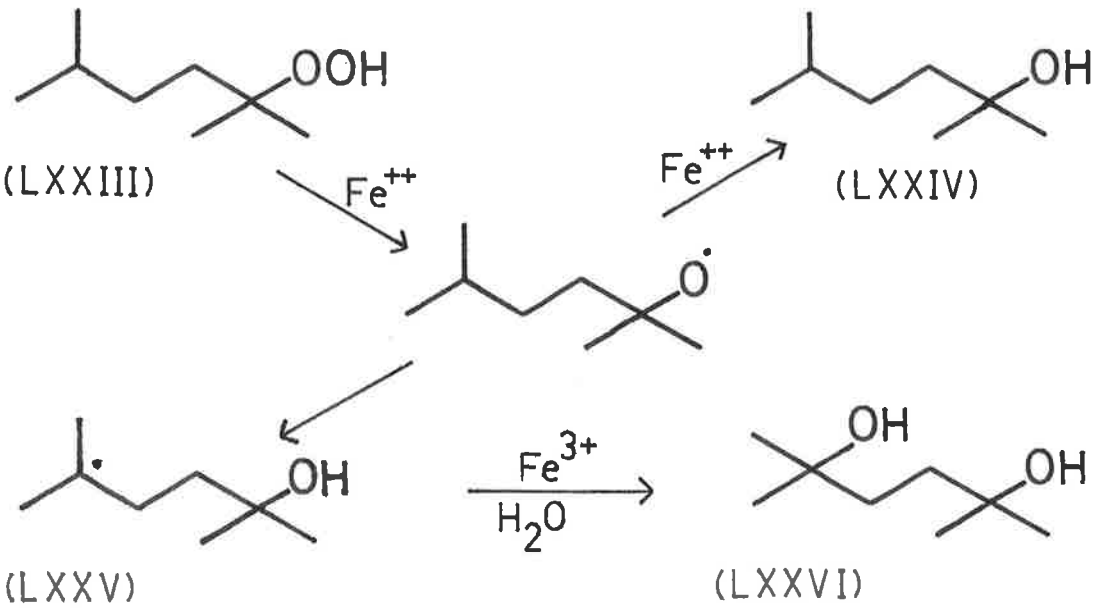
The types of products obtained from such reactions give ample evidence for the intermediate formation of alkoxy radicals.[88-89] Davies[89] has summarised the types of reactions which alkoxy radicals, derived under redox conditions, may undergo and one possible pathway involves further reduction to the alkoxide ion.[88,98] Such a reaction was found to predominate in the simple redox decomposition of 2-methyl-2-hexyl hydroperoxide (LXVII). The 2-methyl-2-hexyloxy radical (LXVIII), generated by addition of ferrous sulphate to the hydroperoxide (LXVII) in dilute sulphuric acid at ambient temperature, affords 2-methylhexan-2-ol (LXX). Apparently the radical (LXVIII) in the presence of excess ferrous ion

undergoes further reduction to the alkoxide ion (LXIX) much faster than intramolecular hydrogen abstraction since the same radical (LXVIII) when formed photolytically at 0° from 2-methyl-2-hexyl hypochlorite has been shown previously[49] to undergo intramolecular hydrogen-atom transfer to the extent of approximately 75%. Treatment of 2,4,4-trimethyl-2-pentyl hydroperoxide (LXXI) with acidified aqueous ferrous sulphate similarly afforded 2,4,4-trimethylpentan-2-ol (LXXII) along with another by-product, acetone. Formation of the latter compound may be ascribed to the fragmentation of the intermediate alkoxy radical; a well-known alkoxy radical reaction.[2,88,95-97]

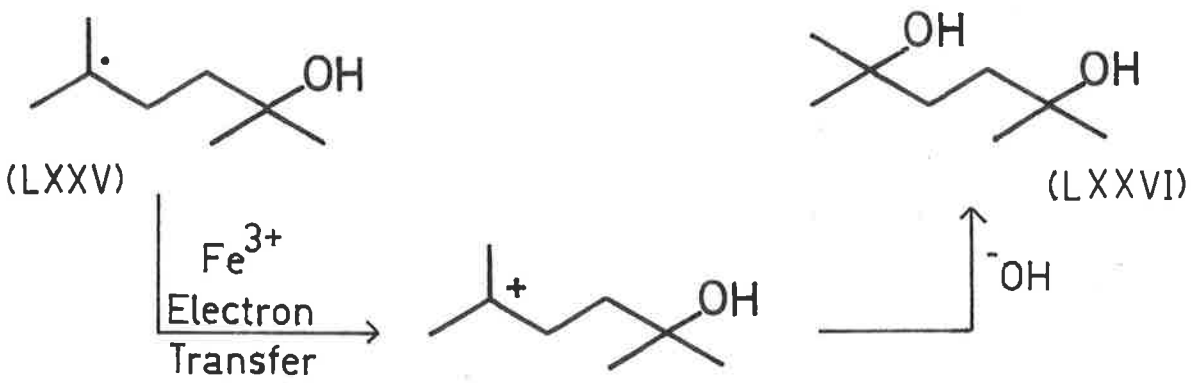


A low yield of 2,5-dimethylhexan-2,5-diol (LXXVI) together with a high yield of the saturated alcohol (LXXIV) was obtained from the ferrous sulphate decomposition of 2,5-dimethyl-2-hexyl hydroperoxide (LXXIII). This reaction provides the first indication that an alkoxy

radical formed by a redox reaction undergoes intramolecular hydrogen-atom transfer. Conversion of the rearranged radical (LXXV) into the alcohol (LXXVI) by interaction with aqueous ferric ion accords with previous studies of the oxidation of saturated alkyl radicals.[98]



In this regard, De La Mare and coworkers[98] found that alkyl radicals undergo dimerisation in non-hydrogen-donating solvents and low ferric ion concentration but are oxidised to the corresponding alcohols when the ferric ion concentration is increased. The process by which the oxidation occurs is described as an electron transfer mechanism[99,100] in which the metal ion accepts the free electron of the alkyl radical to form a free carbonium ion (or a species possessing high carbonium ion character) which is subsequently solvolysed to the alcohol. Such a mechanism seems to operate in the formation of 2,5-dimethylhexan-2,5-diol (LXXVI).



Scheme 20.

This type of electron transfer process is distinct from ligand transfer[100-102] in which the ligand associated with the metal ion is transferred via an intermediate represented as (LXXVII)[101,102] or (LXXVIII)[100] to the alkyl radical.

$$R^{\bullet} + Fe^{3+}Cl_3 \longrightarrow \left[R\cdots\cdots Cl\cdots\cdots Fe^{2+}Cl_2\right] \longrightarrow RCl + FeCl_2$$

(LXXVII)

$$R^{\bullet} + M^{n+}X_n \longrightarrow \left[R^{\bullet}\ X\text{—}MX_{n-1} \longleftrightarrow R\text{—}X\quad MX_{n-1}\right] \longrightarrow RX + M^{(n-1)+}X_{n-1}$$

(LXXVIII)

The principle factor determining whether or not an alkyl radical is oxidised to the substituted product by way of electron transfer or ligand transfer is the type of ligand available. De La Mare and coworkers[98] have found that ligands such as sulphate and perchlorate favour electron transfer whereas chloride, bromide, and thiocyanate enhance ligand transfer. In the absence of suitable bridging ligands, oxidation may occur by the

electron transfer mechanism as takes place in the ferrous sulphate induced decomposition of 2,5-dimethyl-2-hexyl hydroperoxide (LXXIII). However, in the presence of suitable ligands, oxidation of the available alkyl radicals via ligand transfer occurs almost quantitatively.

Kochi[103] suggests that ligand transfer and electron transfer processes represent extreme situations in redox reactions. He suggests that the majority of intermediate free radical, ligand, and metal salt reactions cannot be separated distinctly into these classifications but rather the transition state for redox reactions should be represented as a resonance hybrid (LXXIX) between ligand transfer and electron transfer contributions. The importance of each depends on the nature of the free radical, ligand, and metal ion present.

$$R^{\circ} + Cu^{++}X \longrightarrow \left[R{-}X \;\; Cu^{+} \longleftrightarrow R^{\circ} \;\; X{-}Cu^{++} \longleftrightarrow R^{+} \;\; X{-}Cu^{+} \right]$$

ligand transfer — electron transfer

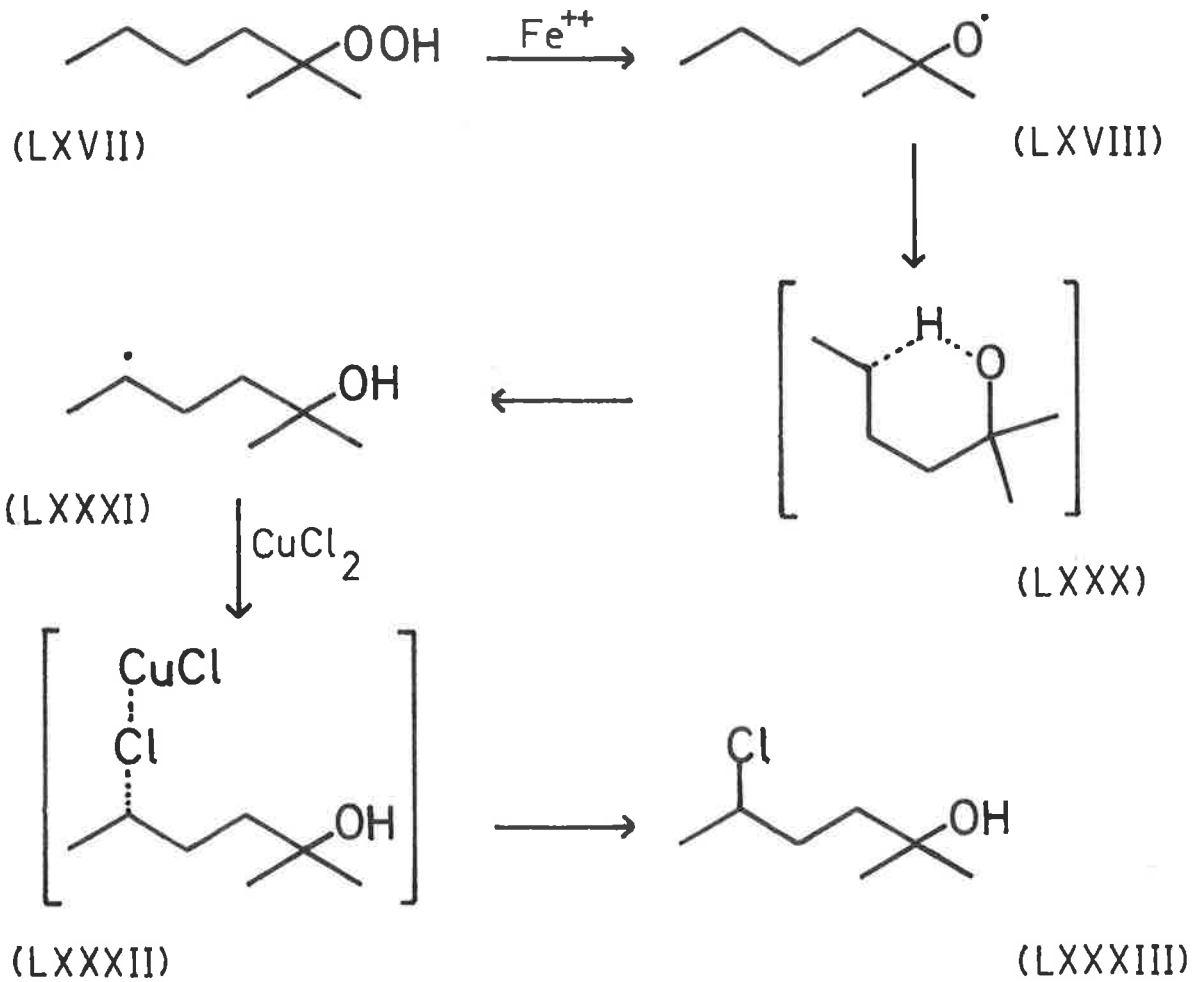
(LXXIX)

$$\longrightarrow \text{products} + Cu^{+}$$

Applying such a convention, the oxidation (Scheme 20) of the alkyl radical (LXXV) to 2,5-dimethylhexan-2,5-diol (LXXVI) must then be assumed to proceed through a transition state involving a major contribution from the electron transfer structure.

However, the formation of 5-chloro-2-methylhexan-2-ol (LXXXIII) from the ferrous ion induced decomposition of 2-methyl-2-hexyl hydroperoxide (LXVII) in the presence of cupric chloride/carbon tetrachloride seems to

proceed through a transition state in which the major contribution is from the ligand transfer structure. Compounds such as the solvolysis and olefinic products, expected to be formed from an intermediate carbonium ion, if an electron transfer process operates, could not be detected. It is suggested that the 5-chloro-2-methylhexan-2-ol (LXXXIII) results from a series of steps illustrated in Scheme 21. The alkoxy radical (LXVIII)

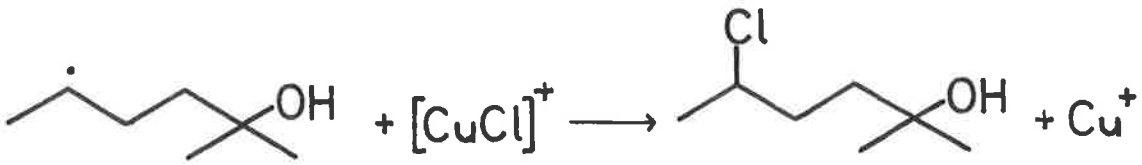


Scheme 21.

formed from a one-electron transfer reaction between ferrous ion and the

hydroperoxide (LXVII) rearranges via a 1,5-hydrogen transfer process (LXXX) to form the alkyl radical (LXXXI) which is oxidised by the cupric chloride via the ligand transfer intermediate (LXXXII) (or a hybrid mechanism involving a major ligand transfer contribution) to the δ-chlorohydrin (LXXXIII).

In order to achieve maximum conversion of the alkyl radical (LXXXI) to the δ-chlorohydrin (LXXXIII), carbon tetrachloride was used as solvent along with a catalytic quantity of cupric chloride. Reactions illustrated in Scheme 22 are thought to have been involved in the incorporation of the chlorine onto the alkyl radical (LXXXI).



(LXXXI) (LXXXIII) .....(1)

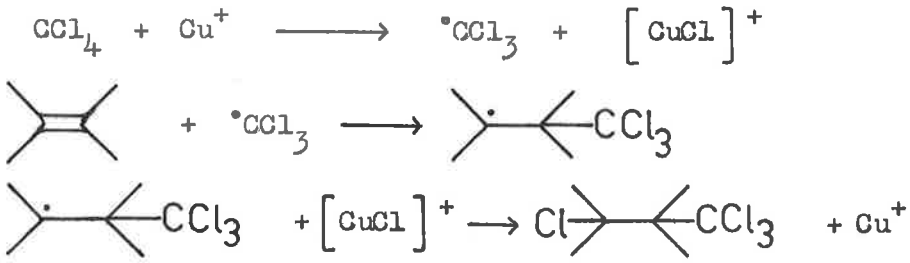
$Cu^{+} + CCl_4 \longrightarrow Cu^{++}Cl^{-} + {}^{\bullet}CCl_3$ .....(2)

$2\ {}^{\bullet}CCl_3 \longrightarrow Cl_3C\text{-}CCl_3$ .....(3)

Scheme 22.

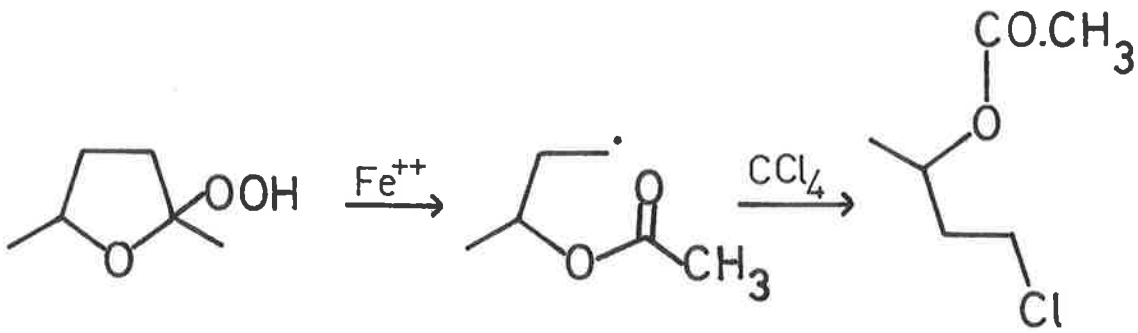
Step (1) involves the normal ligand transfer oxidation of an alkyl radical to the alkyl chloride whereas step (2) involves a reverse ligand transfer process in which the ligand is transferred from the organic moiety to the metal ion. Asscher and Vofsi[104] have suggested similar steps in the mechanism for the addition of carbon tetrachloride to an olefine in the

presence of catalytic quantities of ferrous and cuprous salts (Scheme 23).



Scheme 23.

Digman and Anderson[92] suggest that 4-chloro-2-butyl acetate (LXXXVI), formed during the ferrous ion decomposition of 2,5-dimethyl-tetrahydrofuran hydroperoxide (LXXXIV) in carbon tetrachloride, results from intermolecular chlorine abstraction by the alkyl radical (LXXXV) from the carbon tetrachloride. An analogous process could be proposed for the formation of 5-chloro-2-methylhexan-2-ol (LXXXIII).



(LXXXIV) (LXXXV) (LXXXVI)

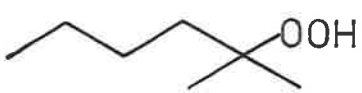
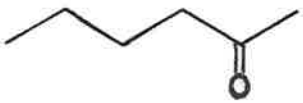
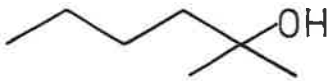
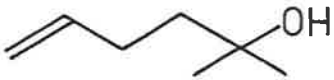
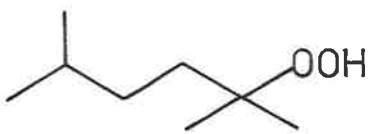
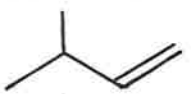
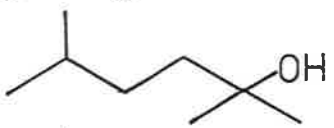
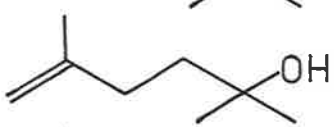
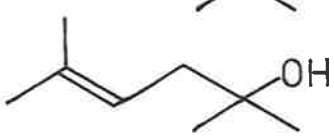
However, Asscher and Vofsi[104,105] have studied extensively the influence of ferrous and cuprous ions on the reactions of carbon tetrachloride and

chloroform and have shown that the presence of metal ions greatly enhances the rate of addition of carbon tetrachloride and chloroform to olefines compared with the analogous reactions in the absence of metal ions. These results suggest that the redox ligand transfer mechanism is the actual process participating in the formation of the δ-chlorohydrin (LXXXIII).

A study of the decomposition at ambient temperature of suitably constituted alkyl hydroperoxides in aqueous acetic acid containing both ferrous and cupric ion provides the most compelling evidence in support of the contention that alkoxy radicals generated in a redox reaction can undergo intramolecular hydrogen transfer. The results of the experiments with 2-methyl-2-hexyl hydroperoxide (LXVII), 2,5-dimethyl-2-hexyl hydroperoxide (LXXIII), and 2-methyl-2-heptyl hydroperoxide (LXXXVII) are summarised in Table II.

The reactions were carried out by slow addition of the hydroperoxide to a stirred and cooled solution of ferrous sulphate and cupric acetate in aqueous acetic acid. The products were identified by a combination of chemical (microhydrogenation, ozonolysis, and chemical derivatives) and physical (nuclear magnetic resonance and infrared spectroscopy, and gas chromatography) methods, which are described in detail in the Experimental section. Where necessary, authentic compounds were synthesised by unequivocal routes.

In a second series of experiments, the acetate esters of the hydroperoxides listed in Table II were decomposed by boiling under reflux a benzene solution of the appropriate peracetate in the presence of a cata-

Hydroperoxide	Products	% Yield
 (LXVII)	Acetone	39
		39
		8
		7·6
		40
		4*
 (LXXIII)	Acetone	23
		23
		6·7
		>44+ } 49
		< 5+ }

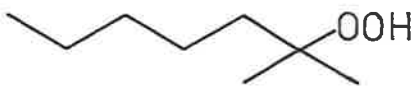
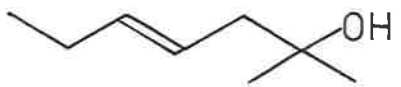
Hydroperoxide	Products	% Yield
 (LXXXVII)	Acetone	48
		48
		7·3
		31*
		4*

Table II. Products obtained from the decomposition, catalysed by Fe^{2+}/Cu^{2+}, of tertiary alkyl hydroperoxides.

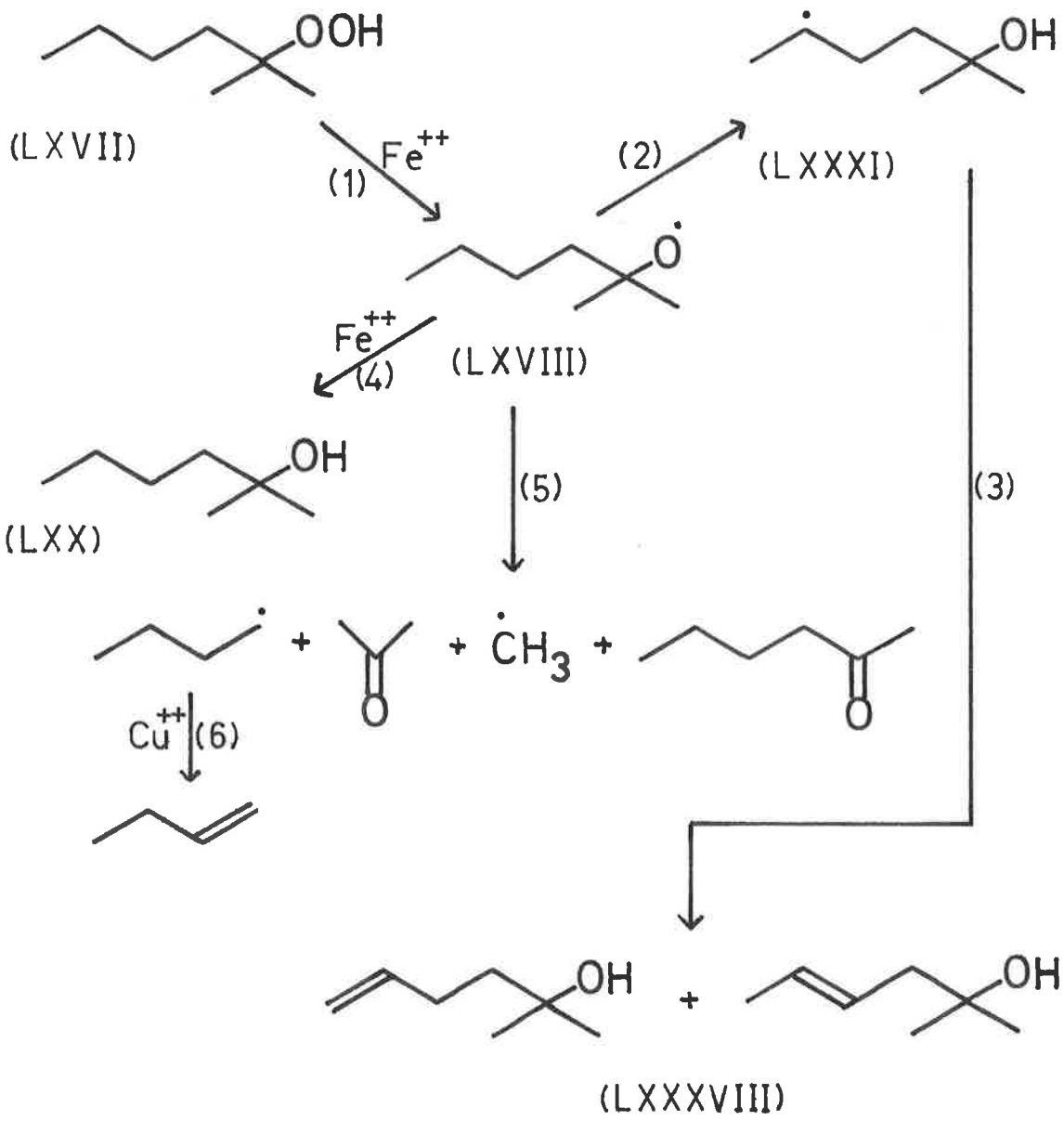
* No separate estimate of cis and trans isomers was made.

† Compounds not resolved by gas chromatography.

lytic quantity of cuprous bromide. Such a process has been used previously[87,106] for the catalytic decomposition of peracetates and peroxides. In each case, the combined alcohol yield was slightly lower than the yields of products from the corresponding hydroperoxide decomposition. However, spectral analysis showed that such products were identical with the corresponding hydroperoxide products. The mechanism by which such compounds are formed is considered to follow the same path as occurs during the redox decomposition of the appropriate alkyl hydroperoxides.

The respective products from the decomposition of the three hydroperoxides listed in Table II undoubtedly arise in each series from analogous reaction mechanisms. The various pathways leading to these products may best be illustrated by considering a specific example, 2-methyl-2-hexyl hydroperoxide (LXVII). Such pathways are set out in Scheme 24.

2-Methylhexan-2-ol (LXX) undoubtedly arises from ferrous ion reduction, step (4), of the alkoxy radical (LXVIII) by the same process mentioned previously (refer to page 44). However, in this case such a reaction occurs to only a minor extent, probably due to the lower ferrous ion concentration compared with the previous examples, enabling the alkoxy radical to undergo intramolecular hydrogen abstraction, step (2), to a far greater extent. The other by-products, 1-butene, acetone, and 2-hexanone, resulting from fragmentation, step (5), of the intermediate alkoxy radical (LXVIII) are obtained as major constituents due to the ease with which such alkoxy radical fragmentation reactions occur.[95] (The relative ease of fragmentation and intramolecular hydrogen abstraction

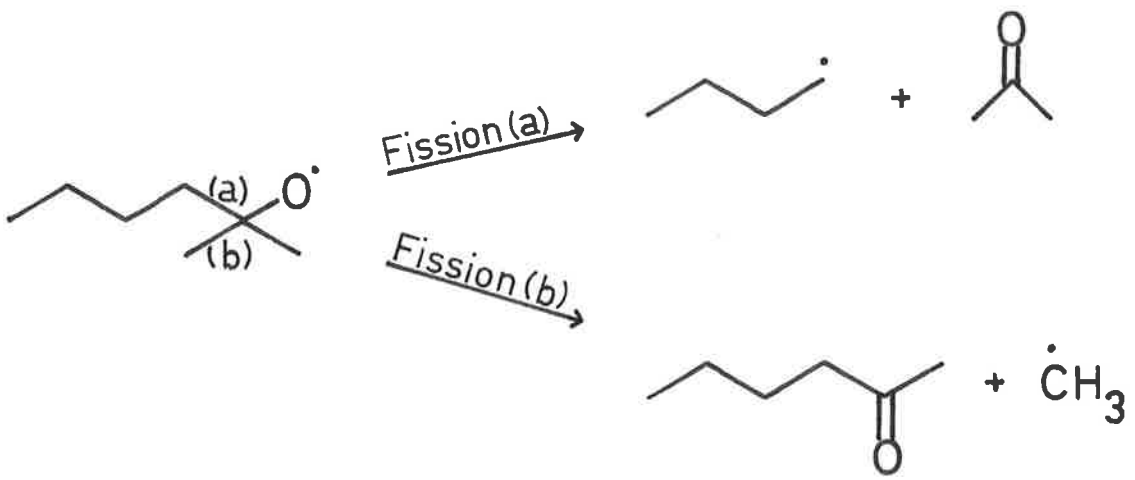


Scheme 24.

reactions will be discussed later; refer to page 60).

It is significant that acetone (and 1-butene formed as a result of the same fragmentation process) is produced in much higher yield than

is 2-hexanone, the alternative fragmentation product. Various groups of workers[49,96,97,107] have studied the fragmentation of tertiary alkoxy radicals and have similarly found that fragmentation occurs via a pathway that produces the most stable alkyl radical. In this particular case (Scheme 25) bond (a) breaks in preference to bond (b) due to the greater stability of the butyl radical as compared with the methyl radical.



Scheme 25.

The olefinic products listed in Table II undoubtedly arise by cupric ion oxidation of the appropriate alkyl radicals. In particular, the olefinic alcohols (LXXXVIII) result from the oxidation of the alkyl radicals (LXXXI)(Scheme 24). Comparison of the relative yields of such 1,5-hydrogen transfer products from the decomposition of 2,5-dimethyl-2-hexyl hydroperoxide, 2-methyl-2-hexyl hydroperoxide (Table II) and 2,4,4-trimethyl-2-pentyl hydroperoxide indicates that intramolecular abstraction of a tertiary hydrogen atom occurs with greater facility than that of a secondary hydrogen atom and both occur much more readily than primary

hydrogen atom abstraction. Similar results have been obtained by Walling and Padwa[52] who carried out a more quantitative estimation of the relative yields of primary, secondary, and tertiary intramolecular hydrogen abstraction products from alkyl hypochlorite photolyses. These workers found that the relative ease of intramolecular hydrogen abstraction is in the ratio, primary:secondary:tertiary, 1:9:47; approximately the same ratio as had been obtained[108] for radical reactions involving intermolecular hydrogen abstraction. It therefore appears that free radicals undergoing intramolecular reactions possess the same relative reactivity toward primary, secondary, and tertiary hydrogen atoms as their counterparts undergoing intermolecular reactions regardless of the fact that radicals undergoing the former type reactions are far more restricted regarding the possible positions of attack.

A further consideration of the products from the decomposition of the hydroperoxides (Table II) indicates that 40-50% of tertiary alkoxy radicals generated at ambient temperature by reductive processes undergo intramolecular hydrogen transfer. Such a result fulfils the original aim of the investigation in that it shows that it is unnecessary to invoke the concept of 'activated' alkoxy radicals[4b] to account for the results of nitrite photolysis. However, since this work was begun other workers[49,82] published results which showed that alkoxy radicals derived at ambient temperature and free of photolytic activation may undergo intramolecular hydrogen abstraction. These results therefore only confirm the observations of these other workers.

It seems likely that any free radical, capable of inducing hydrogen abstraction, can undergo intramolecular hydrogen transfer provided the conditions for such 1,5-atom transfer reactions are favourable (reference is made to specifically 1,5-transfer but the same applies to 1,6-transfer as well). These conditions are that the spatial requirements for intramolecular hydrogen abstraction are fulfilled (refer to page 39) and that side reactions capable of proceeding faster than the 1,5-hydrogen transfer reaction do not interfere(disproportionation of the amino radicals[23] produced in the absence of protonating acid (refer to page 13) and the further reduction of alkoxy radicals to alkoxide ions (refer to page 44) may be cited as previously encountered examples of this latter condition).

The fact that alkoxy radicals are capable of inducing hydrogen abstraction and that they can fulfil the spatial requirements for 1,5-hydrogen transfer is undisputed (refer to the Barton reaction, page 2 , and hypohalite photolysis, page 23). Since the suggestion of Barton[4b] that 'activation' of the alkoxy radical is a prerequisite for intramolecular hydrogen-atom abstraction has now been discounted, it appears that the only reason for the failure of pyrolytically formed alkoxy radicals to undergo intramolecular hydrogen abstraction is the interference of a faster side reaction.

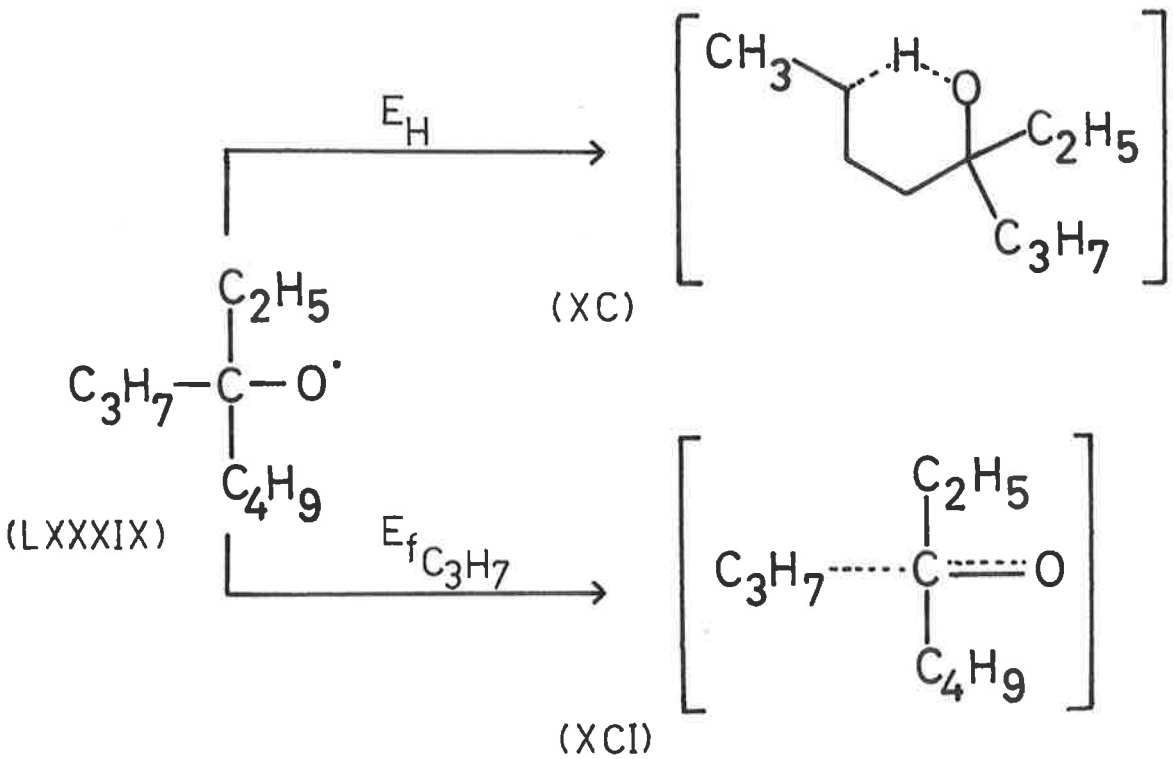
A possible reason for an interfering side-reaction occurring with pyrolytically-formed alkoxy radical reactions but not with photolytically-formed alkoxy radical reactions is that the mode of reaction depends

on the temperature at which such alkoxy radicals are generated. Alkoxy radicals formed at high temperatures by pyrolysis, as carried out by Barton,[4b] undergo mainly fragmentation but do not achieve intramolecular hydrogen abstraction. However, alkoxy radicals formed at the other end of the temperature scale by photolysis at $< 20^{\circ}$ [4b,8b,49] and by redox reactions at approximately 25° (refer to Table II) rearrange by intramolecular hydrogen transfer to the extent of approximately 49% and 45% respectively, together with lower yields of fragmentation products. From a consideration of the results of reactions carried out in the intermediate temperature range (Table III), it is further apparent that with increasing temperature, alkoxy radicals show decreasing ability to achieve intramolecular hydrogen-atom transfer.

Abstracting Radical	Source	Temp. °C	Intramol. Hydr.Abstr. Products,%	Reference
2-Methyl-2-hexyloxy	Hypochlorite hν	0	75	49
"	Nitrite hν	<20	49	8b
"	Hydroperoxide/redox	~25	44	*
"	Peracetate/redox	86	22	82
"	Hydroperoxide/redox	115	18	82
"	Peroxide/redox	121	10	82
Steroidal alkoxy	Nitrite hν	<20	35	4b
" "	Nitrite Δ	160	0	4b

Table III. Yields of Intramolecular Hydrogen Transfer products from alkoxy radicals generated at varying temperatures. * Results of alkoxy radical reactions in this investigation, previously summarised in Table II.

An explanation for this temperature effect on intramolecular hydrogen transfer and fragmentation reactions of alkoxy radicals could possibly lie in the relative activation energies of the two processes. Bacha and Kochi[96] have calculated the difference in activation energies of intramolecular hydrogen abstraction (E_H) and fragmentation (E_f) of alkoxy radicals and have shown that the activation energy for fragmentation is greater than that for intramolecular hydrogen transfer. For the alkoxy radical (LXXXIX), these workers estimate $E_{f\ C_3H_7} - E_H$ to be approximately 4.1 Kcal/mole.

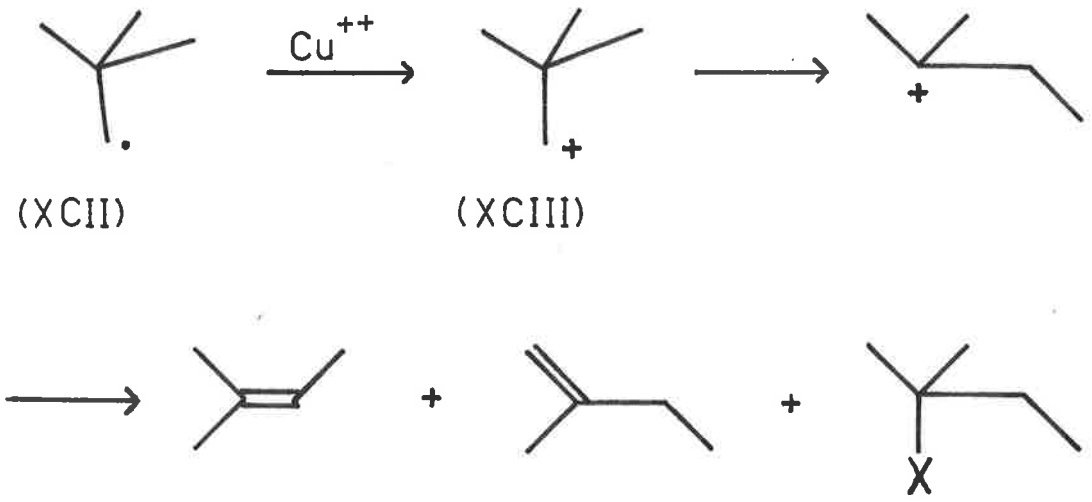


It seems likely that at low temperatures in which sufficient energy is not available to excite the alkoxy radical to the higher energy

transition state, intramolecular hydrogen abstraction should predominate. However, with increased temperature the activation energy factor becomes less important as the energy necessary to excite the alkoxy radical to the higher energy transition state for fragmentation becomes more readily available. Under such conditions (it is assumed that such is the case in the pyrolysis of alkyl nitrites) the pathway by which the alkoxy radical reacts is then determined by probability factors. Since fragmentation is a monomolecular bond-fission process whereas intramolecular hydrogen abstraction is an internal atom-transfer reaction requiring that approximate collinearity of the C...H...X atoms in the quasi six-membered ring is achieved (refer to page 39), it seems feasible that at high temperatures, fragmentation of alkoxy radicals should occur much faster than, and to the exclusion of, intramolecular hydrogen transfer. A similar temperature effect on the relative yields of fragmentation and intramolecular hydrogen abstraction products has been observed by Walling and Padwa.[50a]

In the examples discussed previously, oxidation of the intermediate alkyl radicals to the substituted products has been attributed to a hybrid mechanism involving a large contribution of either electron transfer or ligand transfer processes. However, the oxidation of alkyl radicals to olefinic products has not been introduced. Such a consideration seems important in order to explain the formation of both the alkenes and the olefinic alcohols during the reductive decomposition of 2-methyl-2-hexyl hydroperoxide, 2-methyl-2-heptyl hydroperoxide, and 2,5-dimethyl-2-hexyl hydroperoxide (Table II).

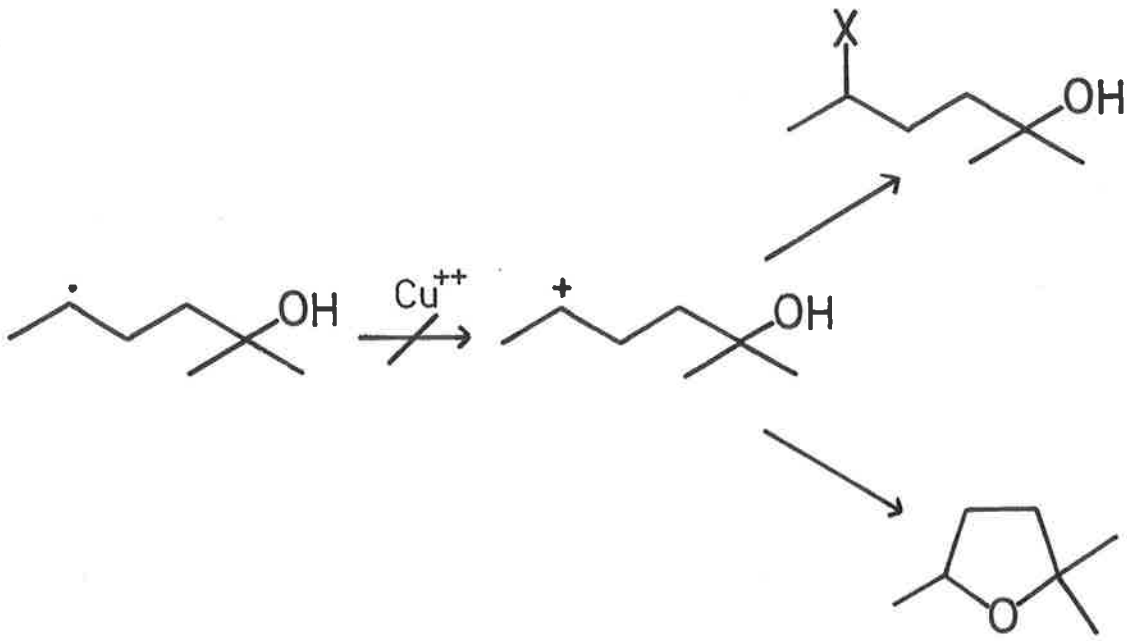
Kochi and coworkers[82,109] have carried out a most comprehensive investigation into the oxidation of alkyl radicals by cupric salts. These workers[82] found that, when the cupric ion is in the complexed form such as the bis(bipyridyl)cupric ion complex, electron transfer occurs forming a free carbonium ion which either eliminates a proton to form the corresponding olefin or undergoes solvolysis. A similar process takes place when an alkyl radical such as the neopentyl radical (XCII) containing no hydrogen atom on the β-carbon atom is oxidised by simple cupric salts.[82] The formation of a carbonium ion intermediate (XCIII) is demonstrated by the isolation of products arising from 1,2-alkyl shifts (Scheme 26).



Scheme 26.

However, it seems unlikely that such a mechanism incorporating the formation of a free carbonium ion is involved in the production of the olefinic products (Table II) from the decomposition of the hydroperoxides

(LXVII), (LXXIII), and (LXXXVII) since solvolysis products and tetrahydrofuran derivatives (Scheme 27) would be expected to result to some extent but such compounds could not be detected.



Scheme 27.

Kochi[82] has found that cupric ion oxidation of alkyl radicals containing a β-hydrogen atom proceeds more rapidly than the previously mentioned electron transfer oxidation and affords olefins rather than solvolysis or carbonium ion rearrangement products. According to Kochi[82] such redox reactions proceed by a simultaneous electron transfer from the alkyl radical to the copper moiety and expulsion of a proton from the β-carbon atom. It seems likely that such a mechanism is involved in the oxidation of the alkyl radical (LXXXI) to the olefinic products (step (3), Scheme 24) as well as in the formation of 1-butene from the intermediate

butyl radicals (step (6), Scheme 24). In fact Kochi[82] carried out a similar decomposition of 2-methyl-2-hexyl hydroperoxide (LXVII) and likewise identified the olefinic alcohols (LXXXVIII) although in much lower yield. He used this concerted radical oxidation - β-proton elimination mechanism to account for such products.

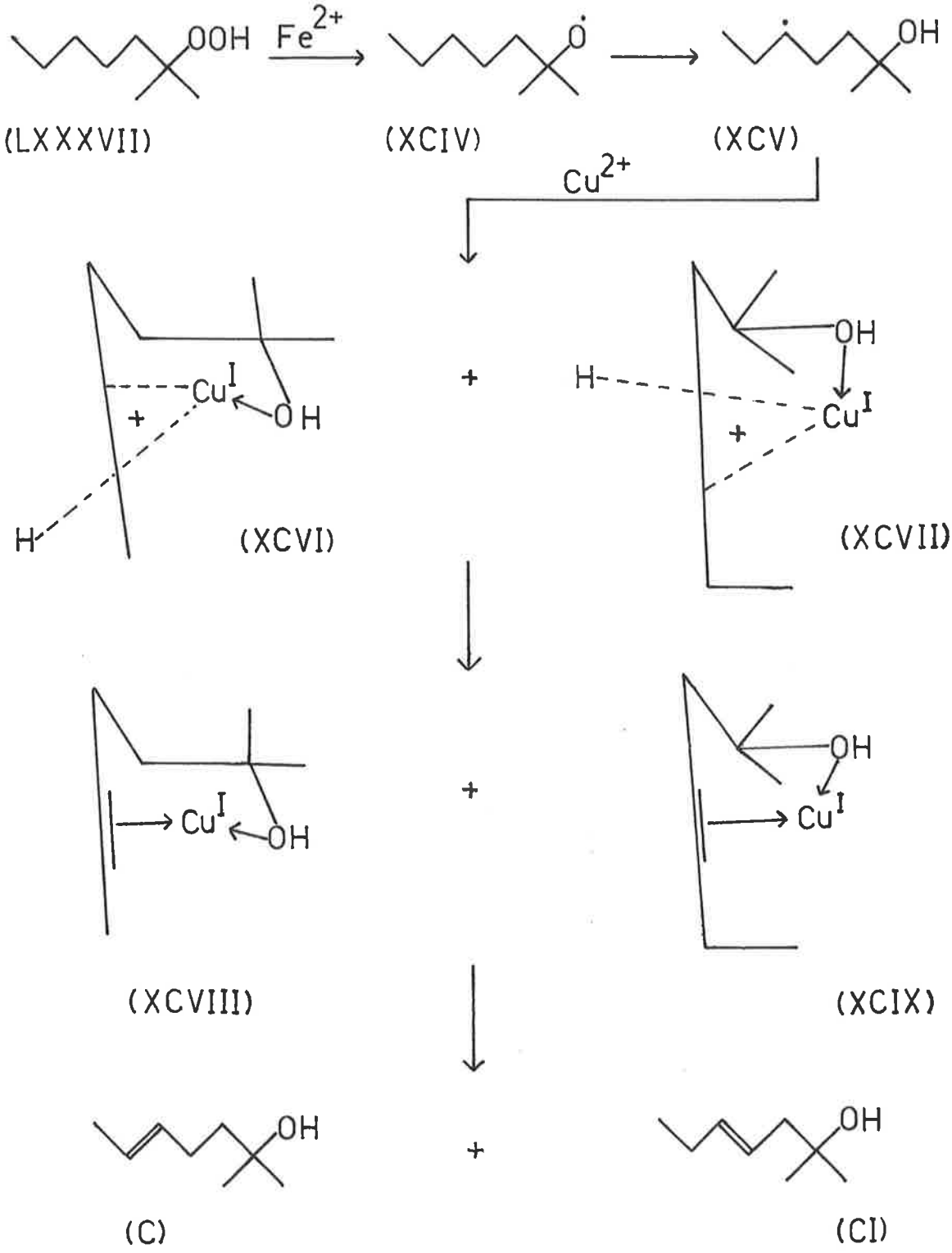
The preferred formation of 2-methyl-5-hexen-2-ol, 2-methyl-5-hepten-2-ol, and 2,5-dimethyl-5-hexen-2-ol over the other possible olefinic isomers, 2-methyl-4-hexen-2-ol, 2-methyl-4-hepten-2-ol, and 2,5-dimethyl-4-hexen-2-ol respectively, is illustrated in Table II and requires further consideration. In each case the olefinic bond δ- to the hydroxyl group is preferred to the double bond in the γ-position. The most significant example of the three considered is the oxidation of the 2-hydroxy-2-methyl-5-heptyl radical (XCV) from which the two products, (C) and (CI), obtained, each contain a disubstituted olefinic bond subjected to very similar electronic substituent effects. Simple oxidation of such a radical (XCV) would be expected normally to afford approximately equal quantities of the isomers (C) and (CI). Since such an isomer distribution is not obtained, it seems definite that some directive effect operates to enforce preferred formation of the δ-olefinic alcohol (C). The only major difference between the molecular environments of the two olefinic bonds is the position of each with respect to the hydroxyl group. It therefore seems logical to conclude that the hydroxyl group exerts a directive effect on the formation of the olefinic bond. The possibility that the γ-olefinic alcohol is formed in comparable yield with the δ-olefinic alcohol but isomerises to the latter after formation was discounted following the unsuccessful

attempt to isomerise 2-methyl-4-hexen-2-ol to 2-methyl-5-hexen-2-ol under the reaction conditions.

This directive effect of the hydroxyl group is rationalised in terms of a cyclic transition state which incorporates the OH group, the cupric ion, the carbon radical being oxidised, and the β-hydrogen to be eliminated. The overall course of the reaction of 2-methyl-2-heptyl hydroperoxide (LXXXVII) with Fe^{2+}/Cu^{2+}, depicting the cyclic transition states (XCVI) and (XCVII), is illustrated in Scheme 28.

In both oxidation procedures leading to the products (C) and (CI), it is inferred that the lone pair electrons on the hydroxyl group become complexed with the cupric ion and it is this complexed cupric ion which intramolecularly oxidises the δ-alkyl radical by the procedure described previously in which simultaneous elimination of a proton from the carbon atom β- to the alkyl radical occurs. In order that the oxidation process goes through the transition states (XCVI) and (XCVII), it is inferred that the complexed cupric ion delocalises one of its positive charges over the atoms involved in the oxidation process and thus becomes a cuprous ion partially bound to the two carbon atoms involved in the respective double bond formation. At the point when oxidation is complete and the β-proton has been eliminated, complexes of the structure (XCVIII) and (XCIX) could be expected to exist. However, under the reaction conditions such complexes readily break down to the products (C) and (CI).

In order to explain the directive effect of such a mechanism,


OOH
Fe^{2+}
O·
OH
(LXXXVII)
(XCIV)
(XCV)
Cu^{2+}
Cu^{I}
OH
H
(XCVI)
+
OH
H
Cu^{I}
(XCVII)
Cu^{I}
OH
(XCVIII)
+
OH
Cu^{I}
(XCIX)
OH
(C)
+
OH
(CI)

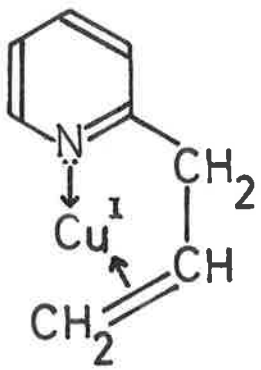
Scheme 28.

the transition states (XCVI) and (XCVII) must be compared. The cuprous ion is complexed to the 5- and 6- carbon atoms in the transition state (XCVII) whereas it is complexed to the 6- and 7- atoms in (XCVI). In (XCVII), the cyclic system appears to be more crowded and strained than the alternative intermediate (XCVI) and this is borne out by construction of models of the two systems. It is suggested that, because of this less strain involved in forming the transition state (XCVI) compared with the alternative possibility (XCVII), oxidation of the δ-alkyl radical occurs much more readily through this intermediate (XCVI) so that the δ-olefinic alcohol (C) is formed as the major oxidation product.

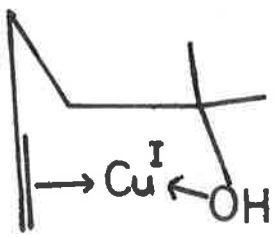
It has been mentioned previously that complexes (XCVIII) and (XCIX) may be intermediate products in the formation of the olefinic alcohols (C) and (CI), provided the mechanism inferred by Scheme 28 operates. Furthermore, complex (XCVIII) may be expected to predominate over (XCIX) if the ring strain suggested to favour the formation of the transition state (XCVI) is also involved. Although stability constants of cuprous chloride, olefinic alcohol complexes in solution had been studied,[110] complexes of the type suggested above had not been obtained. Nevertheless, attempts were made to form cuprous complexes analogous to (XCVIII) and (XCIX) with both 2-methyl-5-hexen-2-ol and 2-methyl-4-hexen-2-ol in order to find whether or not such compounds do exist and, if so, whether or not cuprous ion prefers to complex with the δ- or γ- olefinic alcohol.

In this regard, solubility studies proved very encouraging. It was found that cuprous chloride dissolves in a carbon tetrachloride solution of 2-methyl-5-hexen-2-ol but does not dissolve in an analogous

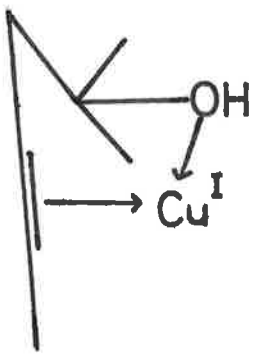
solution of the olefinic isomer, 2-methyl-4-hexen-2-ol. This seems to suggest that a complex is in fact formed in solution with the former alcohol but not with the latter. Quantitative solubility studies were attempted but these proved to be unsuccessful, possibly due to the very low solubility or stability of such complexes in the solvents used. However, more conclusive evidence was obtained from the reaction of cuprous chloride with the pure olefinic alcohols. Cuprous chloride readily dissolves in 2-methyl-5-hexen-2-ol to afford a colourless crystalline complex whereas the cuprous chloride does not appear to dissolve at all in 2-methyl-4-hexen-2-ol.



(CII)

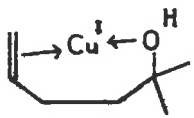
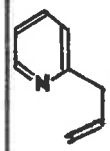
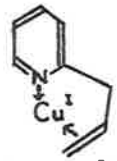


(CIII)



(CIV)

Although accurate analysis figures could not be obtained for the 2-methyl-5-hexen-2-ol copper (I) chloride complex (proposed structure (CIII)), comparison of the physical data obtained with the relevant physical data for 2-allylpyridinecopper (I) chloride (CII)[111] seems to indicate (Table IV) that the compound isolated is a 1:1 2-methyl-5-hexen-2-ol/cuprous chloride complex in which both the olefinic linkage and the

Property	 a b	 a b	 a b	 a b
ν_{as} (= CH_2)	3070 m	3010 w	3080 m	3050 w
ν (-CH = CH_2)	1645 m	1553 w	1640 m	1553 m
ν (O - H)	3360 s	3305 s	-	-
Colour	-	Colourless solid - turns light green on standing in air		Colourless solid- turns pale green on standing in air
M.Pt.	-	89-90°(dec.)	-	113-125°(dec.)
Solubility	-	Very weakly soluble in organic solvents with partial decomp.	-	Very low solubility in benzene with partial decomposition.

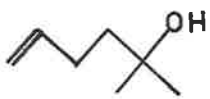
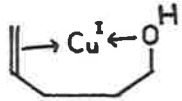
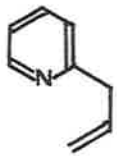
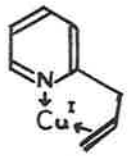
Property	 a b	 a b	 a b	 a b
Mode of Formation	-	Olefinic alcohol and cuprous chloride heated to form brown solution from which complex crystallised.	-	2-Allylpyridine and cuprous chloride refluxed in ethanol to form amber solution from which complex crystallised.

Table IV. ν-stretching vibration in the infrared; as, assymetric; a, Wave Numbers in cm^{-1}; b, Intensities: S, strong; m, medium; w, weak.

hydroxyl group are co-ordinated to the cuprous ion. The fact that 2-methyl-5-hexen-2-ol forms a complex with cuprous chloride but 2-methyl-4-hexen-2-ol does not, seems most significant. In both compounds, olefinic and alcoholic functions are present so that a linear complex in which the cuprous ion is bound to the alcoholic group in one molecule and the double bond in another could be expected for both. However, the fact that 2-methyl-4-hexen-2-ol does not form a complex at all indicates that such a linear arrangement is not present in the 2-methyl-5-hexen-2-ol copper (I) chloride complex.

Yingst and Douglas[111] attributed the shifts in absorption frequencies in the regions 3010 cm^{-1} and 1553 cm^{-1}, when going from 2-allylpyridine to 2-allylpyridinecopper (I) chloride (CII), to the co-ordination of the olefinic bond to the metal atom. In such a complex the metal-bonded olefine group has the nature of a perturbed carbon-carbon double bond. Similar effects probably cause similar frequency shifts in the formation of the 2-methyl-5-hexen-2-olcopper (I) chloride complex (CIII) from 2-methyl-5-hexen-2-ol. The shift in absorption frequency of 55 cm^{-1} for the O-H stretching vibration is possibly due to the electron withdrawing effect of the cuprous ion which induces electron withdrawal from the adjacent O-H bond, thus weakening that bond and shifting the O-H absorption to lower wave numbers.

Although accurate analysis figures and further physical measurements must be obtained for the cuprous chloride/2-methyl-5-hexen-2-ol

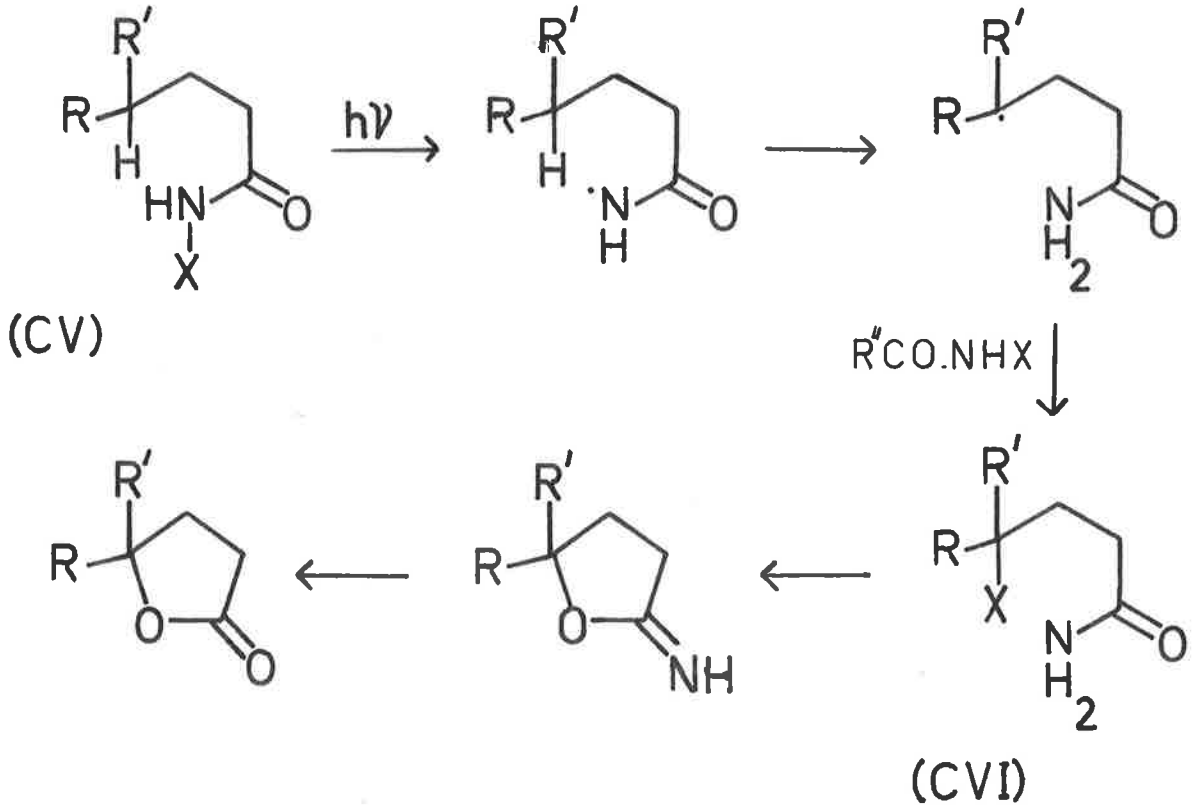
complex isolated, it appears from the above comparison with 2-allylpyridinecopper (I) chloride that the structure may be represented as (CIII), 2-methyl-5-hexen-2-olcopper (I) chloride. Assuming this structure to be correct, then (CIII) appears to be the first of its type to be isolated in which the cuprous ion is co-ordinated to both an olefinic bond and hydroxyl group. The fact that such a complex can form adds further support for the contention that the complex (XCVIII) participates (Scheme 28) in the formation of (C). It also follows that cuprous ions complex with δ-olefinic alcohols but do not form analogous complexes (CIV) with the corresponding γ-olefinic alcohols. The interpretation of this result in terms of the preferred formation of δ-olefinic alcohols from the decomposition of alkyl hydroperoxides (Table II) requires consideration.

As mentioned previously, (Scheme 28 and page 67), the relative ease of formation of the olefinic alcohols (C) and (CI) depends on the ease of formation of the respective transition states (XCVI) and (XCVII). The fact that the cuprous complex (CIII) forms but (CIV) does not, seems to suggest that the former complex is much less strained compared with the latter. Taking an analogy between the complexes, (CIII) and (CIV), and the transition states, (XCVI) and (XCVII), it follows that the transition state (XCVI) should be much less strained compared with the alternative (XCVII). Thus the isolation of complex (CIII) and the failure to detect any analogous complex (CIV) adds support for the contention that preferred formation of δ- over γ-olefinic alcohols during the redox decomposition of alkyl hydroperoxides (Table II) is due to the preferred formation of the intermediate transition state (XCVI).

2. Photolysis of N-Chloro-amides.

(a) Reactions of Primary Amido Radicals.

It has been shown[73,75] (see page 34) that photolysis of N-halo-amides produces the corresponding γ-halo-amides via an intramolecular hydrogen transfer process. However, the γ-halo-amides produced[73,75] were not isolated but were directly converted to the appropriate lactones by hydrolysis of the crude reaction products. In particular, Beckwith and Goodrich[75] photolysed various N-chloro-amides and estimated the yields of intramolecular hydrogen abstraction products by estimating the amount of γ-lactone produced upon hydrolysis. The mechanism proposed by these workers to account for the products is illustrated by Scheme 29.



Scheme 29.

In the present work, such reactions were repeated with the particular intention of isolating the intermediate γ-chloro-amides (CVI, X = Cl). N-Chlorobutyramide (CV, R = R' = H, X = Cl), N-chloropentanamide (CV, R = CH_3, R' = H, X = Cl), and N-chloro-4-methylpentanamide (CV, R = R' = CH_3, X = Cl) were each photolysed in a dichloromethane solution for approximately 3 hours and the purified crystalline reaction products were identified by a combination of chemical (hydrolysis) and physical (infrared spectroscopy and thin-film and gas-phase chromatography) methods which are described in detail in the Experimental section. The purified reaction product was found to be a mixture of saturated amide (CV, X = H) and γ-chloro-amide (CVI, X = Cl), following the formation of the appropriate aliphatic acid and γ-lactone during hydrolysis. The yields of the saturated amides and γ-chloro-amides in the mixtures were estimated from the proportion of the appropriate aliphatic acids and γ-lactones, determined by gas-phase chromatography of the hydrolysis products. The results of these experiments are listed in Table V.

N-Chloro-amide	Yield of γ-Chloro-amide
N-Chlorobutyramide CV, R=R'=H, X=Cl	34%
N-Chloropentanamide CV, R=CH_3, R'=H, X=Cl	35%
N-Chloro-4-methylpentanamide. CV, R=R'=CH_3, X=Cl	51%

Table V.

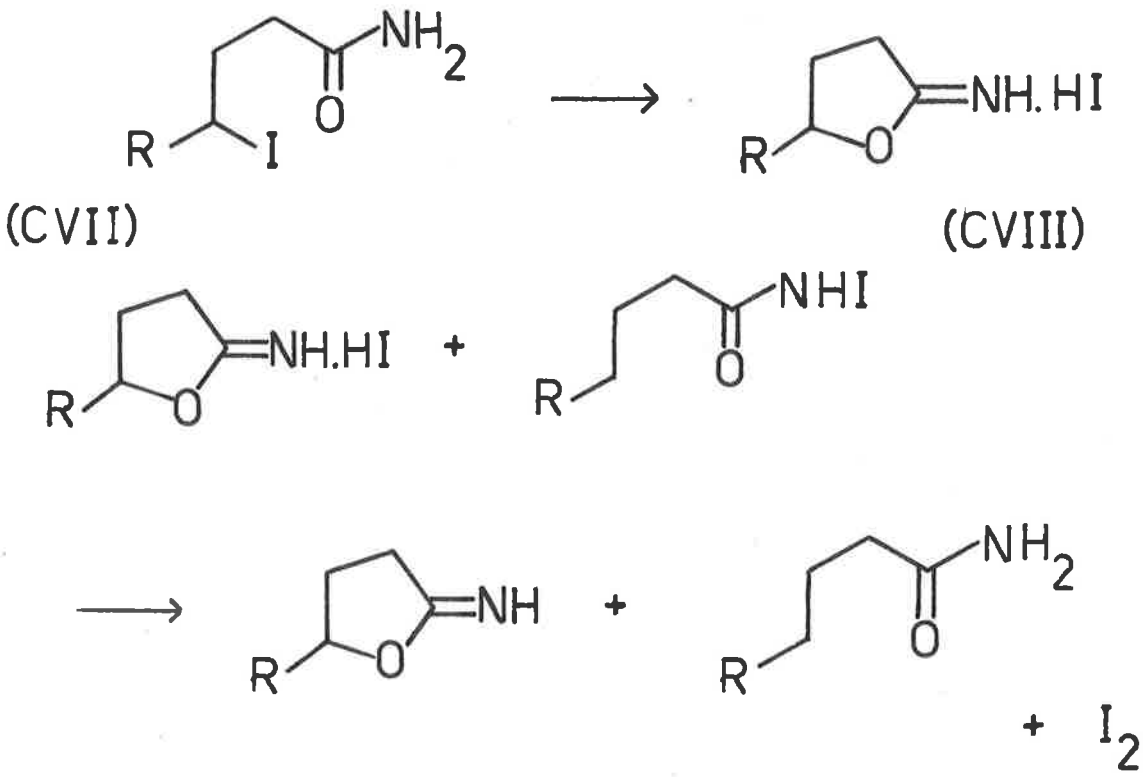
Attempts were made to separate the mixture of butyramide and 4-chlorobutyramide obtained from the photolysis of N-chlorobutyramide. The successful method involved thin-layer chromatography of an extended film of the mixture, precipitated onto the adsorbent out of methylene chloride solution, using upward elution with tetrahydrofuran. The separate bands, visualised by standing the dried plate in an iodine tank, were separately removed and the respective amides extracted from the adsorbent with chloroform. Evaporation of the solvent afforded the separate amides as crystalline solids which were shown by physical techniques to be pure butyramide and γ-chlorobutyramide respectively. Such a technique for the isolation of γ-chlorobutyramide has obvious limitations. Not only is it unsatisfactory as a method for accurate estimation of the yields of the products, but it is also inefficient since only small quantities of compound can be separated on each 'run'. Nevertheless, it overcame the problem confronting the work since it enabled the pure γ-chlorobutyramide to be isolated. Although attempts were not made to separate the amide mixtures from the photolysis of N-chloropentanamide and N-chloro-4-methylpentanamide, it is anticipated that similar success would be achieved in these examples.

The fact that γ-chloro-amides can be isolated from the photolysis of the appropriate N-chloro-amides is conclusive proof that such compounds are actually formed during N-chloro-amide photolyses and it thus gives added support for the validity of the mechanism (Scheme 29) proposed by Beckwith and Goodrich.[75] Two other groups of workers[76,77] have photolysed analogous N-chloro-amides and have essentially been unsuccessful in their attempts to isolate products from 1,5-hydrogen transfer. Petterson and Wambsgans[76]

who had been successful in isolating intramolecular hydrogen abstraction products from the photolysis of N-chloro-imides (refer to page 35) found that photolysis of N-chloro-amides (CV, X = Cl) in general failed to afford γ-chloro-amides (CVI, X = Cl) although photolysis of N-chloro-4-phenyl-butyramide (CV, R = Ph, R' = H, X = Cl) was found to afford the γ-chloro-amide (CVI, R = Ph, R' = H, X = Cl) in 19% yield. They[76] attributed the latter product to a mechanism involving intermolecular abstraction of the benzylic hydrogen atoms. Neale and coworkers[77] photolysed N-chloropentan-amide and also found that such an N-chloro-amide compound is quite unreactive; no intramolecular hydrogen abstraction products could be isolated. Contrary to the findings of these two groups of workers, [76,77] this present work supports the results of Beckwith and Goodrich[75] in that it shows that N-chloro-amides do in fact afford intramolecular hydrogen abstraction products in good yield. The fact that the γ-chloro-amides are formed as the only identifiable chlorination products (although Beckwith and Goodrich[75] had detected δ-chloro-amides in low yield and attributed such to 1,6-hydrogen transfer) seems sufficient proof that intra- and not intermolecular hydrogen abstraction occurs. It is suggested that the γ-chloro-amide (CVI, R = Ph, R' = H, X = Cl) obtained by Petterson and Wambsgans[76] likewise arises from an intramolecular hydrogen abstraction process.

The disconcerting feature of the photolysis of N-chloro-amides is the fact that the saturated amides (CV, X = H) are formed as co-products with the γ-chloro-amides (CVI, X = Cl). Such a problem is not confined to this work. In the original photolyses of N-iodo-amides carried out by

Barton and Beckwith,[73] the yield of γ-iodo-amide was restricted to a maximum of 50% due to the side reaction represented by Scheme 30.

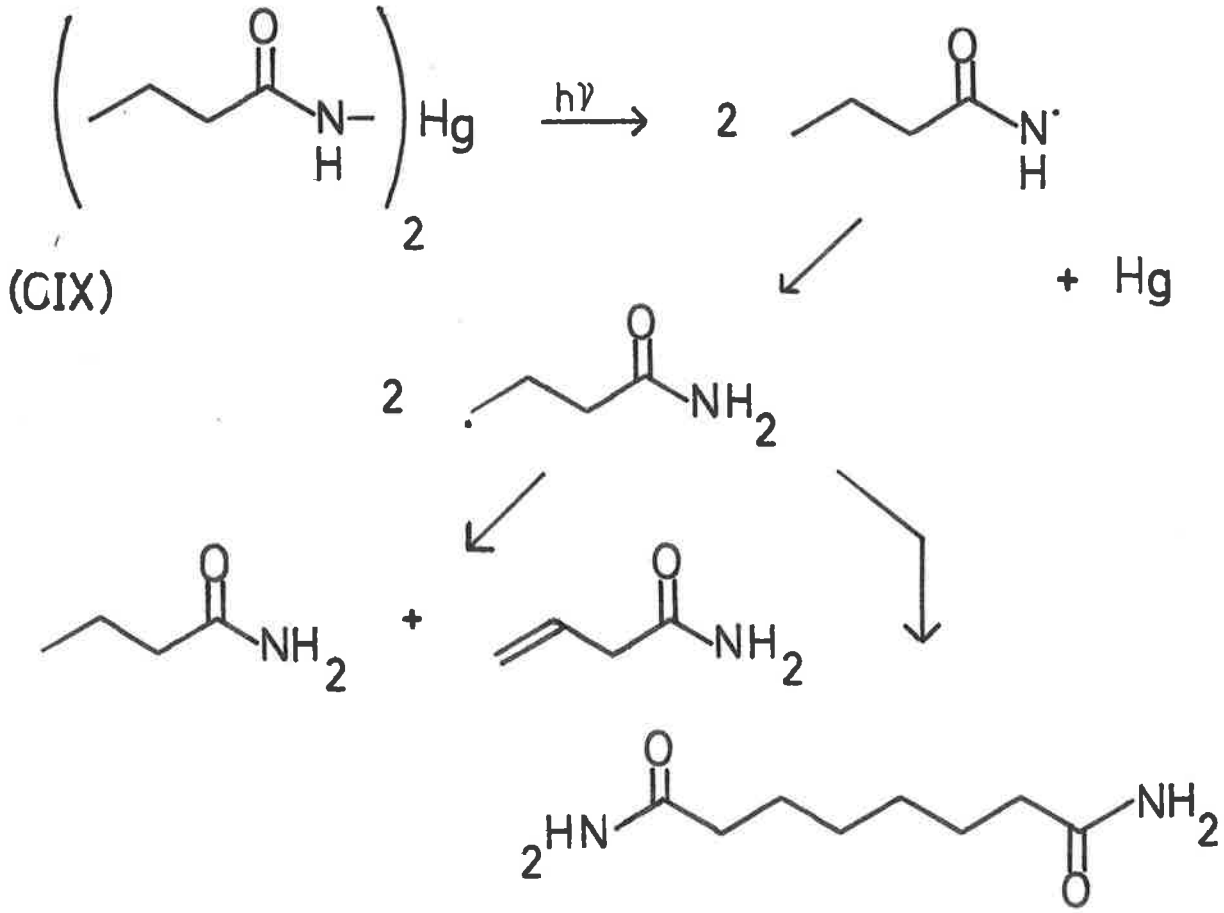


Scheme 30.

Barton and Beckwith[73b] attributed this reaction to the instability of the intermediate γ-iodo-amide (CVII) which readily cyclises during the reaction period to liberate hydrogen iodide which in turn reacts with the starting N-iodo-amide thus rendering the latter compound inactive (Scheme 30). It seems significant that the γ-iodo-amides could not be isolated. However, the fact that the appropriate γ-chloro-amides can be easily isolated and require vigorous hydrolytic conditions to achieve cyclisation seems to

eliminate the probability that such a side reaction is the cause of the saturated amide formation in this particular case. Beckwith and Goodrich[75] who were confronted by a similar problem carried out various experiments in an attempt to elucidate the mechanism of the formation of saturated amide. However, no completely satisfactory explanation became obvious.

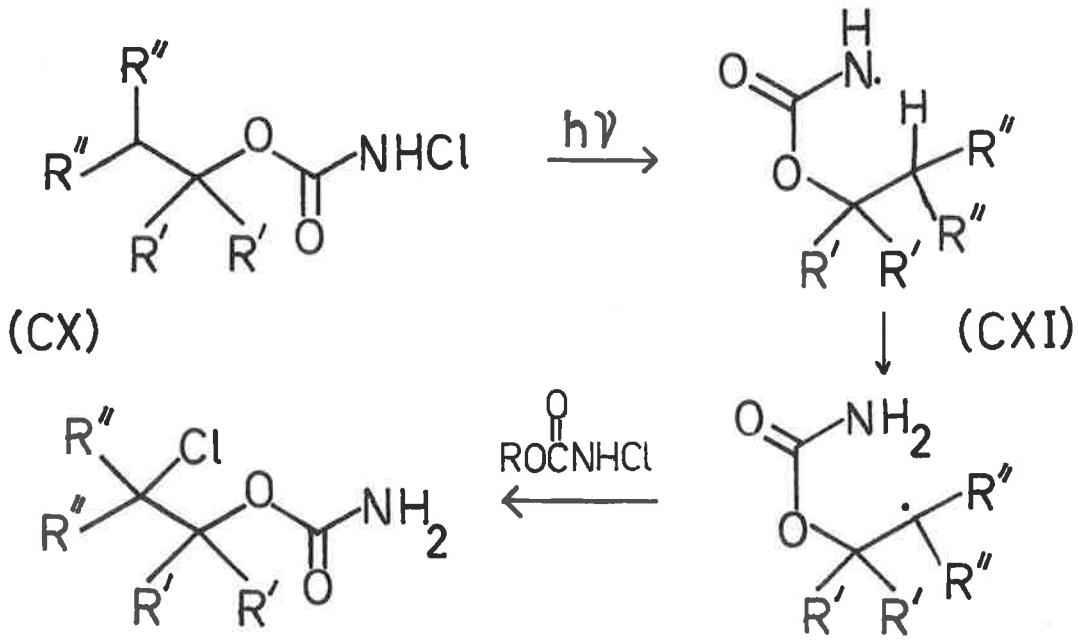
Attempts to generate amido radicals by the photolysis of the diamidomercury compound (CIX) also failed to produce the expected results. The pathway envisaged is illustrated by Scheme 31. It was thought that the reaction of amido radicals in the absence of active chlorine might help to elucidate the problem confronting the N-chloro-amide photolysis.



Scheme 31.

However, all attempts to achieve N-Hg homolysis failed - starting compound (CIX), contaminated by a small amount of butyric acid (presumably formed *via* hydrolysis), was recovered.

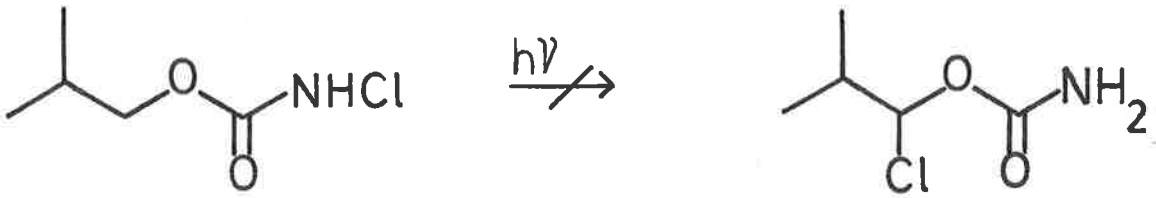
Extension of the *N*-chloro-amide photolysis reaction to alkyl *N*-chlorocarbamates was successfully achieved when 2-chloro-2-methylpropyl carbamate (CXII, R' = H, R" = CH_3) and 2-chloro-1,1-dimethylethyl carbamate (CXII, R' = CH_3, R" = H) were each obtained as reaction products in yields of 26% and 18% respectively from the photolysis of *iso*-butyl *N*-chlorocarbamate (CX, R' = H, R" = CH_3) and *t*-butyl *N*-chlorocarbamate (CX, R' = CH_3, R" = H). The mechanism proposed is analogous to that suggested for the *N*-chloro-amide reaction.



(CXII)

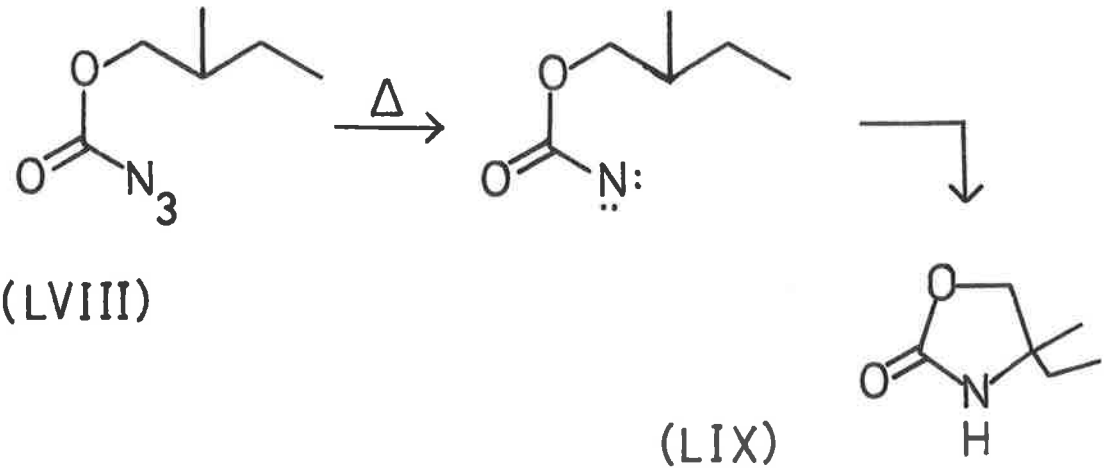
It is unlikely that such chlorination products (CXII) result from an intermolecular chlorination mechanism since the hydrogen atoms most readily

abstracted by such a process would be those on the carbon atom α- to the oxygen atom.[100b, 112] It is significant that (CXIII) was not obtained from the photolysis of iso-butyl N-chlorocarbamate.



(CXIII)

The fact that the intermediate amido radical (CXI) is capable of undergoing intramolecular hydrogen abstraction had been implied by the previous work of Smolinsky,[67a] and Yamada[69] and their coworkers who showed that pyrolysis of the azide (LVIII) affords the cyclic product (LIX) (refer to page 32).



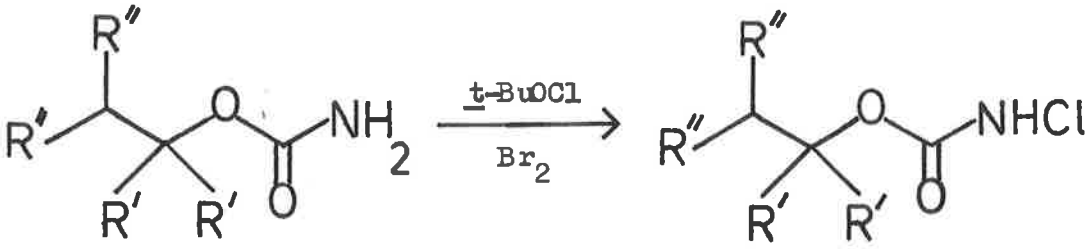
(LVIII)

(LIX)

Obviously substitution of an oxygen atom for a methylene group in the alkyl chain does not alter the fact that the six-membered cyclic intermediate (CXI) has the lowest energy and most probable arrangement of atoms in which the N...H...C atoms are approximately collinear. Such an effect has also

been noted in the photolysis of ketones,[36,37] the reaction of lead tetra-acetate with alcohols[61d] (refer to pages 18 and 29), and the Hofmann-Loeffler reaction.[27a]

The alkyl N-chlorocarbamates (CX) were prepared by a method analogous to that developed by Beckwith and Goodrich[75] for the formation of N-chloro-amides. The carbamate (CXIV) was dissolved in methylene chloride to which was added a drop of bromine and a mole of t-butyl hypochlorite. However, one difference between the two systems was evident - chlorination of the alkyl carbamate required a much longer time (approx. 15 hrs) than that needed for the chlorination of primary amides (approx. 1 hr). Although no unequivocal evidence is available about the basicity of alkyl carbamates, it seems possible that the difference in rates of chlorination may be due to the greater availability of the amide nitrogen lone-pair electrons compared with the carbamate lone-pair.



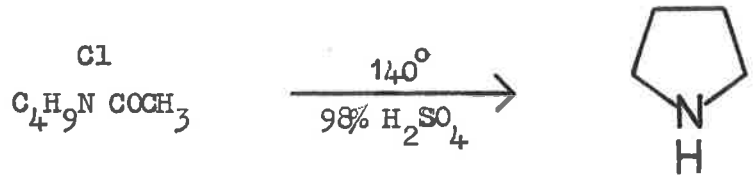
(CXIV) (CX)

The crystalline compound obtained by purification of the crude reaction product was identified by infrared and nuclear magnetic resonance (n.m.r.) spectroscopy as a mixture of the saturated starting carbamate (CXIV) and the 2-chloro-alkyl carbamate (CXII). It would seem probable

that the starting carbamates (CXIV) are formed as by-products in a similar way to the saturated amides from the photolysis of the appropriate N-chloro-amides. However, the pathway by which such by-products are formed is similarly unknown.

(b) Reactions of N-Alkylacetamido Radicals.

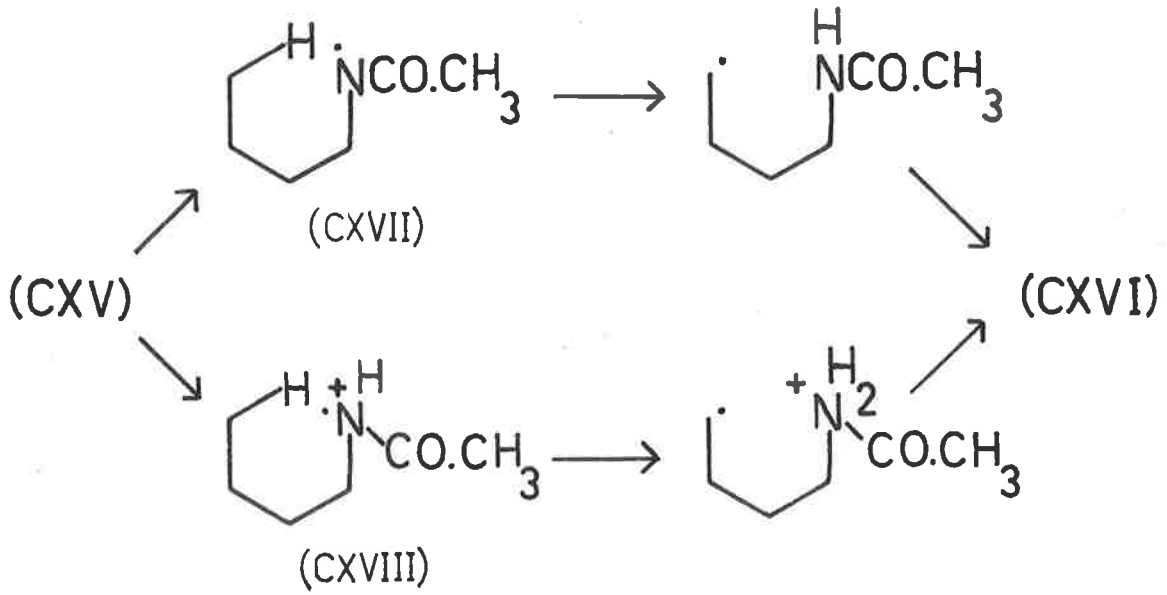
During an investigation into the Hofmann-Loeffler reaction on N-chloro-amines, Coleman and coworkers[113] heated N-butyl-N-chloro-acetamide (CXV) in concentrated sulphuric acid to 140° and obtained pyrrolidine (CXVI) in 50% yield.



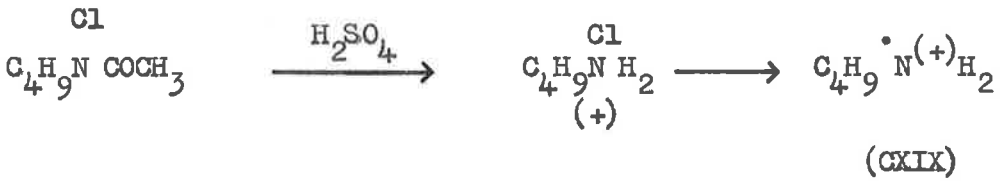
(CXV) (CXVI)

Although it seems certain that an intramolecular hydrogen abstraction process participates in the formation of (CXVI), the actual species inducing such hydrogen transfer is not so obvious. It is possible that either the amido radical (CXVII) or the amidinium radical (CXVIII) could participate (Scheme 32). However, the fact that pyrrolidine (CXVI) is obtained as the reaction product shows that hydrolysis occurs at some stage during the reaction so that it is highly probable that neither of the species (CXVII) or (CXVIII) participate in the hydrogen transfer but rather the aminium radical (CXIX) is involved (refer to page 12). If this is so, then the reaction is simply another example of the normal Hofmann-Loeffler reaction

of N-chloro-amines.[17]



Scheme 32.

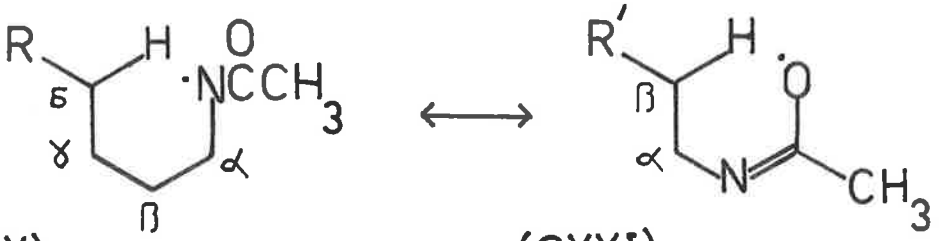


(CXIX)

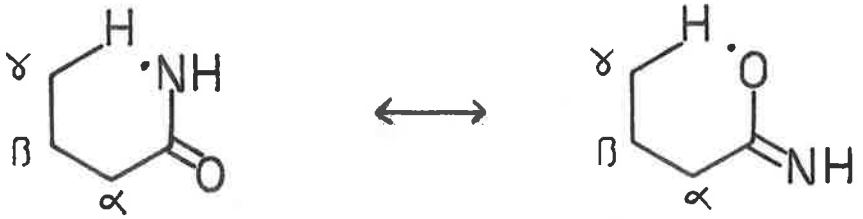
Because of the ambiguity surrounding the mechanism of such a reaction,[113] it seemed necessary that the photolysis of N-alkyl-N-chloro-acetamides should be carried out in a non-hydrolysing solvent so that it could be determined unambiguously whether or not the N-alkylacetamido radical can undergo intramolecular hydrogen abstraction.

Furthermore, such a study seemed important as a means of determining whether or not the resonance structure (CXXI), as compared with the alternative structure (CXX), can induce 1,5-hydrogen transfer. Although Beckwith

and Goodrich[75] suggested that it is the amido radical (CXXII) which abstracts the γ-hydrogen atom during the photolysis of N-chloro-amides (refer to page 73), these workers did not discount the possibility that the structure (CXXIII) may be involved.



(CXX) (CXXI)



(CXXII) (CXXIII)

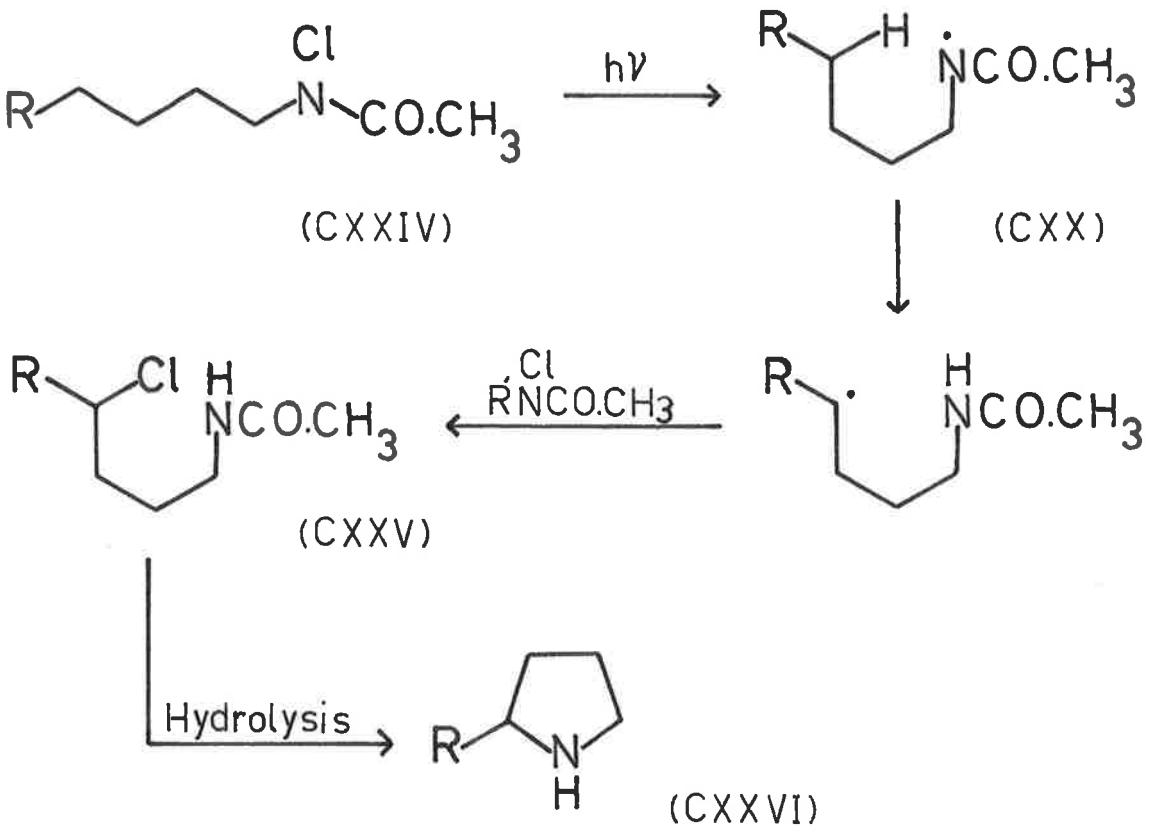
In the case of the primary amido radicals, it is impossible to distinguish between the two species (CXXII) and (CXXIII) since the same product results from both processes. However, with the N-alkyl-N-chloro-acetamide photolyses, the position of hydrogen abstraction differs so that the nature of the products should indicate which intermediate participates in the hydrogen transfer process. It is significant that models of the two species (CXX) and (CXXI) indicate that both intermediates are sterically capable of undergoing 1,5-hydrogen transfer.

The compounds photolysed were N-butyl-N-chloro-acetamide, N-(iso-butyl)-N-chloro-acetamide, and N-chloro-N-hexylacetamide which were prepared

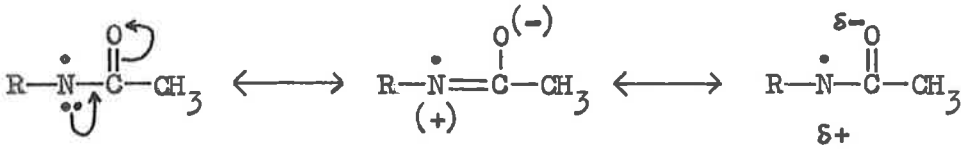
by reaction between the appropriate acetamide and t-butyl hypochlorite under similar conditions to those used for the preparation of N-chloro-amides and alkyl N-chlorocarbamates. The photolyses were carried out in methylene chloride, also in a similar manner to the N-chloro-amide photolyses and the yields and nature of the reaction products were determined by physical (infrared and n.m.r. spectroscopy and gas-phase chromatography) and chemical (hydrolysis) methods which are described in detail in the Experimental section.

From the photolysis of N-butyl-N-chloro-acetamide (CXXIV, R = H) and N-chloro-N-hexylacetamide (CXXIV, R = Et), the corresponding 4-chloro-acetamides (CXXV, R = H) and (CXXV, R = Et) were obtained in 31% and 27% yields respectively. That such 4-chloro-acetamides were formed was confirmed by the fact that the corresponding pyrrolidine compounds (CXXVI, R = H) and (CXXVI, R = Et) were detected from the hydrolysis of the reaction products. The mechanism proposed for the formation of N-(4-chlorobutyl)-acetamide (CXXV, R = H) and N-(4-chlorohexyl)acetamide (CXXV, R = Et) is illustrated in Scheme 33.

These results indicate that acetamido radicals (CXX) can undergo 1,5-hydrogen transfer and that such radicals do not require protonation of the nitrogen atom, as is necessary for the corresponding amino radicals[20,23] (refer to page 12), to achieve intramolecular hydrogen abstraction. The reason for protonation not being necessary in such acetamido radical reactions could be due to the same effect which causes amides to be less basic than amines; that is, the participation of the resonance structures depicted below. As has been mentioned previously, the failure of non-protonated amino radicals to achieve 1,5-hydrogen transfer is attributed



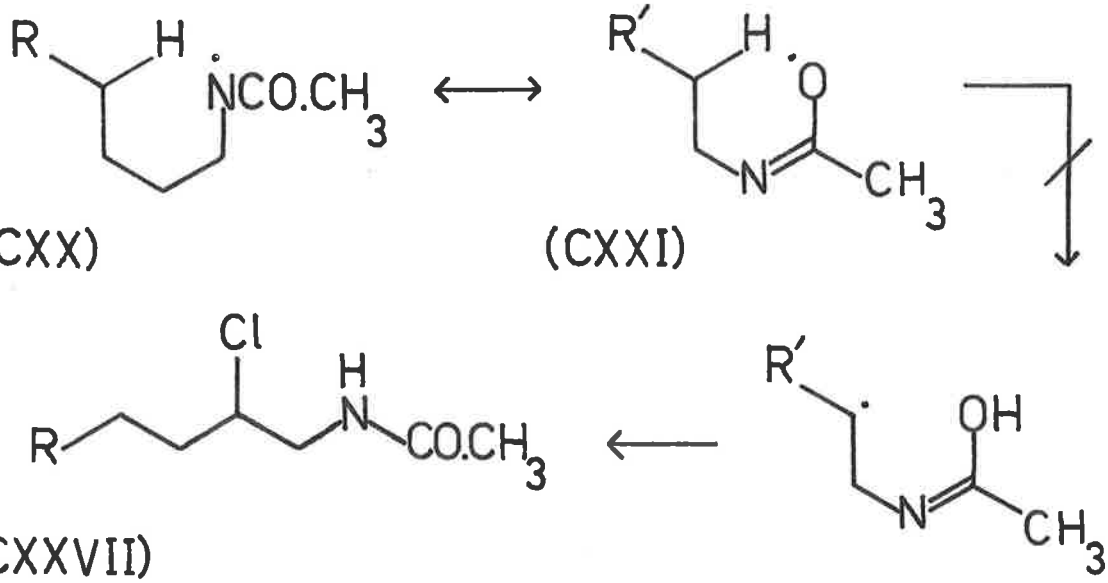
Scheme 33.



to faster disproportionation[20,23] (refer to page 13). However, in the case of the acetamido radical, it seems probable that the δ+ charge on the nitrogen atom would be sufficient to prevent disproportionation of such acetamido radicals taking place.

From the photolysis of N-chloro-N-hexylacetamide and N-butyl-N-chloro-acetamide, it was also found that the corresponding 2-chloro-acetamides (CXXVII, R = Et) and (CXXVII, R = H) were not formed. It is

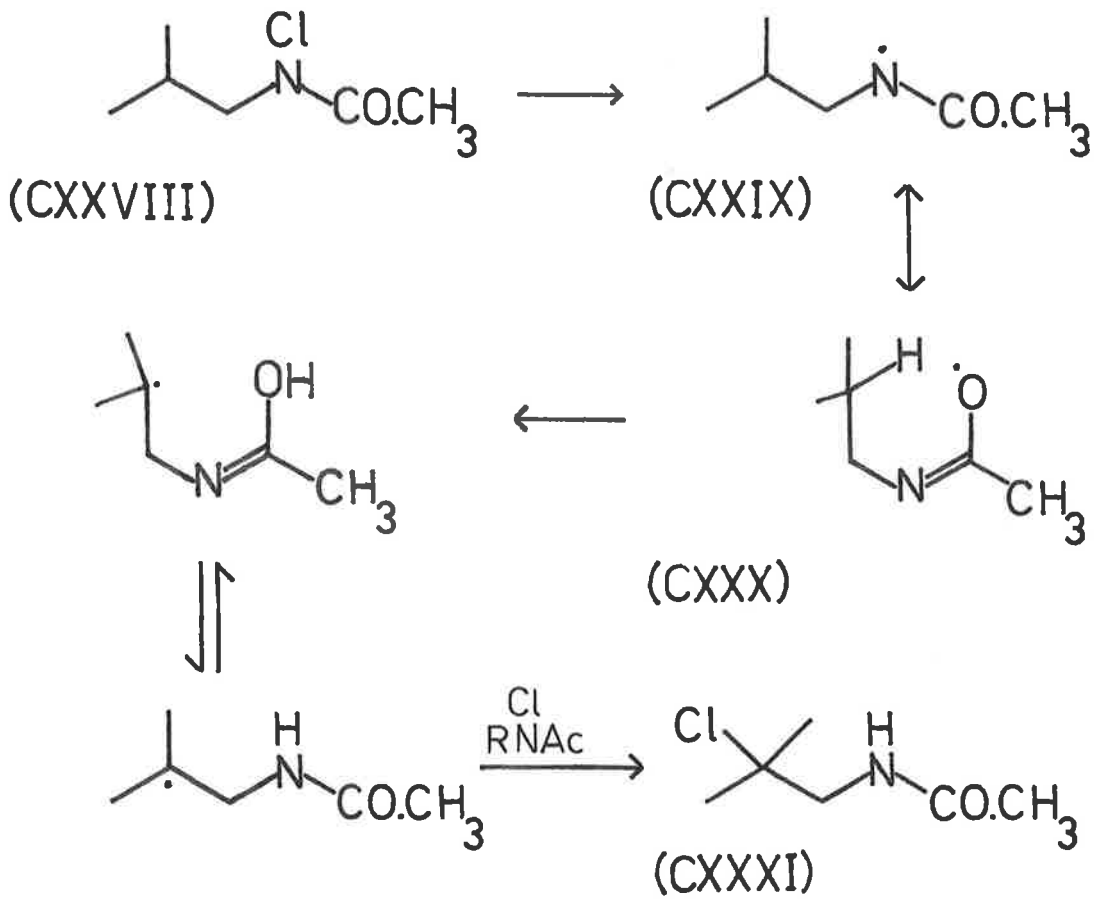
thus apparent that the acetamido radical (CXX) undergoes intramolecular hydrogen abstraction with greater facility than the alternative resonance structure (CXXI). However, the most significant result concerning the



(CXX) (CXXI) (CXXVII)

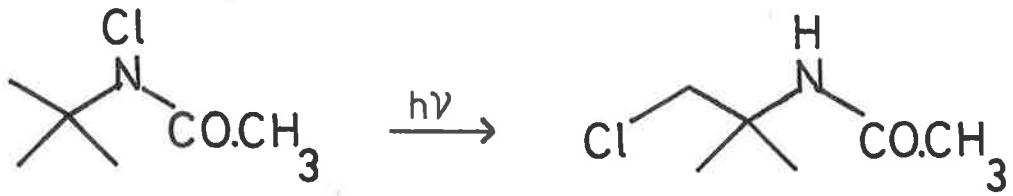
actual participation of the acetamido radical in the resonance form (CXXI) was obtained from the photolysis of N-(iso-butyl)-N-chloroacetamide (CXXVIII). In such a system it is not possible for the nitrogen radical (CXXIX) to undergo intramolecular hydrogen abstraction since the alkyl chain is of insufficient length. Nevertheless, the possibility of 1,5-hydrogen transfer involving the radical (CXXX) does exist and in fact the 2-chloro-acetamide (CXXXI) was obtained in 36% yield. The mechanism suggested to operate in the formation of (CXXXI) involves intramolecular hydrogen abstraction by such an intermediate (CXXX) and is illustrated by Scheme 34.

Neale and coworkers[77] have photolysed N-(t-butyl)-N-chloro-acetamide (CXXXII) and isolated the 2-chloro-acetamide (CXXXIII). These workers[77] suggested that such a product is formed via an intermolecular



Scheme 34.

hydrogen abstraction process. However, such an intermolecular mechanism



(CXXXII) (CXXXIII)

cannot be involved in the formation of (CXXXI) since the hydrogen atom α-to the nitrogen atom would be abstracted with much greater facility[112]

than the tertiary hydrogen atom which is actually removed. Because of the close similarity between the products (CXXXI) and (CXXXIII) from the photolysis of the respective N-chloro-acetamides (CXXVIII) and (CXXXII), it is suggested that (CXXXIII) is actually formed by an intramolecular hydrogen abstraction process analogous to that illustrated in Scheme 34 rather than the intermolecular mechanism suggested by Neale and coworkers.[77]

In each of the examples considered, a high yield of the saturated acetamide compound was recovered together with the appropriate chloro-acetamide. Because of the participation of side reactions depicted[77] in Scheme 35, the formation of such a by-product can be partially accounted for.

$$R\,CH_2\overset{Cl}{N}\,COCH_3 \longrightarrow R\,CH = N\text{-}COCH_3 + HCl$$

$$R\,CH_2\overset{Cl}{N}\,COCH_3 + HCl \longrightarrow R\,CH_2\overset{H}{N}\,COCH_3 + Cl_2$$

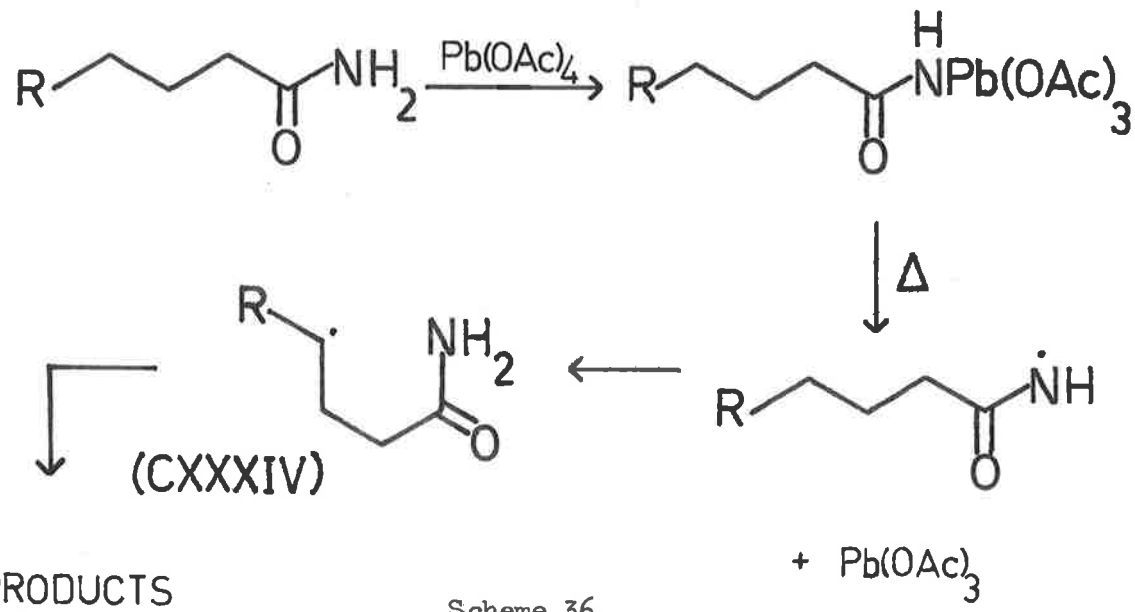
$$R\,CH = N - COCH_3 \longrightarrow \text{polymeric material.}$$

Scheme 35.

Polymeric resins were obtained in each case. However, such side reactions cannot account for all the saturated acetamide compound formed. It is probable that undefined side reactions analogous to those operating in the previously mentioned primary N-chloro-amide and alkyl N-chlorocarbamate photolyses also occur in these reactions.

3. Reactions of Lead Tetra-acetate with Primary Amides.

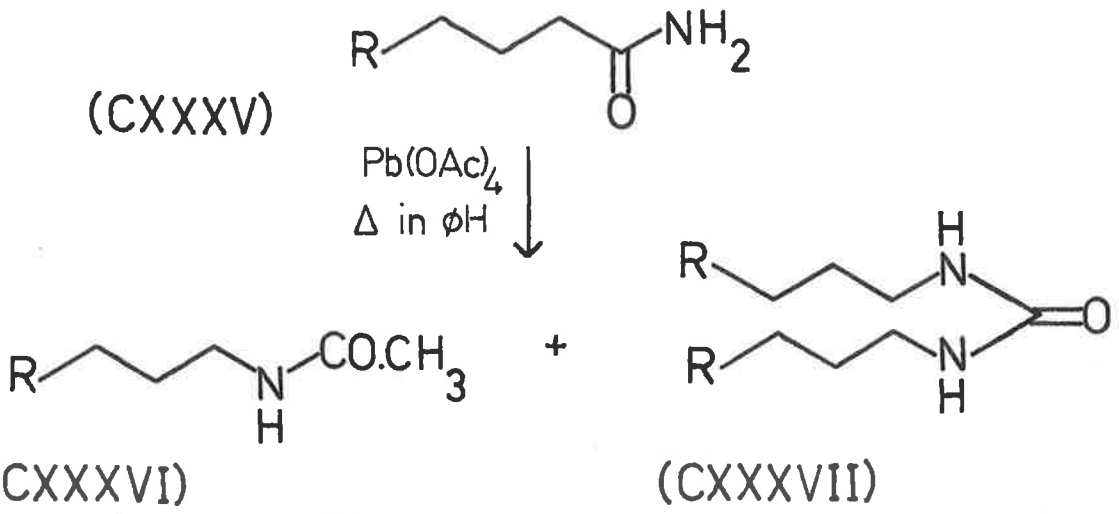
Since analogous pathways are involved in the reactions of alcohols[56] and primary amides[73] with lead tetra-acetate and iodine, it was expected that a close agreement would further exist between the pathways of the reactions of such alcohols[63] and primary amides with lead tetra-acetate alone (refer to page 29). It was predicted that products resulting from the participation of a reaction mechanism represented by Scheme 36 would be obtained. However, when the amides (CXXXV) were treated with lead



Scheme 36.

tetra-acetate in benzene, mixtures of the appropriate N-acetylamine (CXXXVI) and dialkylurea (CXXXVII) were obtained. A particular example involves the formation of N-butylacetamide (CXXXVI, R = CH_3) and N,N'-dibutylurea (CXXXVII, R = CH_3) from the reaction of pentanamide (CXXXV,

R = CH_3) with lead tetra-acetate in benzene. The reaction conditions simply involved heating a benzene solution of the amide and lead tetra-acetate (present in molar ratios) under reflux until such time that all the lead (IV) had been converted to lead (II).



Baumgarten and Staklis[114] also carried out reactions of primary amides with lead tetra-acetate under slightly different conditions and obtained products resulting from a similar reaction mechanism. The products (CXXXVI and CXXXVII) appear to arise from a polar rearrangement process. However, derivatives of an intermediate free radical (CXXXIV) could not be detected. Because of the unexpected nature of such a reaction of primary amides with lead tetra-acetate, an investigation into the scope and mechanism was carried out.

(a) Scope:

The reaction of lead tetra-acetate with primary amides was first applied to simple saturated aliphatic amides and, as has been mentioned

previously, occurs very smoothly to afford the corresponding acetylamine and dialkylurea. Such a reaction has been successfully extended to include more complex saturated amides; the yields of the corresponding products are shown in Table VI. The most diverse examples considered were the reactions of the simple straight chain compound, pentanamide, and the complex steroid compound, cholanamide. In both cases, good yields of the rearrangement products were obtained. Consideration of Table VI indicates that approximately 70% yield of rearrangement products was obtained in the range of compounds studied. However, the relatively low yields of N-butylacetamide (45%) and N-pentylacetamide (40%) are probably due to the method of isolation of such products compared with the other examples. Such compounds are liquids and their yields were thus estimated from the amount of distilled product whereas N-cyclohexylacetamide and the higher homologues are solids so that their yields were estimated with greater accuracy. In regard to the determination of the yields of such higher homologue rearrangement products, the crude reaction product was carefully triturated with acetone - the acetamide compound readily dissolved whereas the urea compound was insoluble. Beside these two types of reaction products, no other by-products appeared to have been formed.

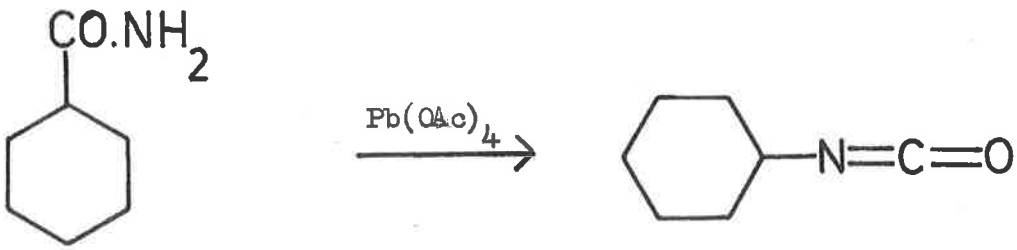
The initial reaction of lead tetra-acetate with cyclohexanecarboxamide (XCLI) afforded a product which showed strong absorption at 2268 cm^{-1} in the infrared, indicating[115] the presenceof cyclohexyl

Amide (CXXXVIII)	Solvent	Yields %	
R		Acylamine (CXXXIX)	Urea (XCL)
Butyl	Benzene	45	5
Pentyl	"	40	5
Cyclohexyl	Benzene-Acetic acid	65	8
Heptadecyl	"	61	9
24-Nor-5β-cholanyl	"	81	-

Table VI.

$$\underset{\text{(CXXXVIII)}}{R\,CONH_2} + Pb(OAc)_4 \longrightarrow \underset{\text{(CXXXIX)}}{R\,NH.COCH_3} + \underset{\text{(XCL)}}{R\,NH.CO.NH\,R}$$

isocyanate (XCLII). It was deduced from this that isocyanates are involved as intermediates in such reactions of lead tetra-acetate with primary amides and in this particular example, incomplete conversion of the isocyanate into the acetamide product had occurred.



(XCLI) (XCLII)

Obviously such incomplete conversion of isocyanate lowers the yield of the required acetamide compound. In an attempt to effect complete conversion of isocyanate to acetamide as well as eliminate the formation of dialkylurea as a by-product, it was decided to carry out the reactions of lead tetra-acetate with primary amides in acetic acid/benzene as solvent. This was partially successful in that complete conversion of the isocyanate was achieved. However, the presence of acetic acid did not seem to suppress the formation of dialkylurea. Nevertheless, it was a step in the right direction as Beckwith and Hassanali[116] have since carried out various reactions in acetic acid alone as solvent and under such conditions have been successful in completely suppressing the formation of dialkylurea. Furthermore, these workers have carried out such reactions in propionic acid as solvent and have obtained the appropriate propionylamine. From such a reaction with cyclohexanecarboxamide, N-propionylcyclohexylamine was obtained in 69% yield. It would thus appear likely that the reaction of lead tetra-acetate with primary amides in any aliphatic acid, $R'CO_2H$, as solvent would produce products as depicted in Scheme 37.

$$R\,CO.NH_2 + Pb(OAc)_4 \xrightarrow[\text{as solvent}]{R'CO_2H} R\,\overset{H}{\underset{|}{N}}\,\overset{O}{\overset{\|}{C}}\,R'$$

Scheme 37.

For the reaction of lead tetra-acetate with primary amides in benzene as solvent, it has been previously mentioned that the reaction

conditions involved heating the solution under reflux until complete conversion of lead (IV) to lead (II) had occurred. Such conditions were similarly applied to the above reactions in both acetic acid/benzene and acetic acid alone as reaction media. Furthermore, it may be noted that such conditions were applied in all reactions of lead tetra-acetate in this work including those to be discussed in due course.

The fact that rearrangement products are obtained in good yield from the reactions in both benzene and acetic acid as solvents seems to contradict the finding of Baumgarten and Staklis[114] that "simple aliphatic amides did not react appreciably with lead tetra-acetate in acetic acid and reacted only sluggishly in nonpolar solvents such as benzene". It would appear from a consideration of their successful reaction conditions that these workers[114] possibly allowed the reactants to stand at room temperature or slightly above for several days but did not venture to heat the solution under reflux; a necessity for the reaction to be successful. Further discordance with the work of Baumgarten and Staklis[114] is also apparent concerning the reaction of lead tetra-acetate with phenylacetamide.[116] These workers[114] found that their "reaction conditions were sufficiently vigorous to preclude the use of amides with functional groups capable of reacting with lead tetra-acetate under milder conditions, e.g; methylene groups (phenylacetamide)". However, Beckwith and Hassanali[116] heated an acetic acid solution of lead tetra-acetate and phenylacetamide under reflux and found that N-benzylacetamide is formed in a 67% yield without any detectable quantities of products arising from acetoxylation of the active benzylic hydrogen atoms.

It is therefore obvious that under these conditions, lead tetra-acetate reacts preferably with the amide group rather than the active methylene group. Apparently the reaction conditions developed in this work and applied by Beckwith and Hassanali are sufficiently mild to enable specific reaction of lead tetra-acetate with amide to occur whereas those of Baumgarten and Staklis[114] produce less specific results.

An attempt to extend the reaction of lead tetra-acetate in benzene solution to aromatic amides failed when no acetanilide could be obtained from the reaction with benzamide. Instead a deep-red oily tar, from which starting amide could be isolated, was obtained. A similar red oily tar was obtained when phenyl*iso*cyanate and acetanilide were separately heated under reflux with lead tetra-acetate in benzene solution. It seems probable that the lead tetra-acetate reacts further with phenyl*iso*cyanate or acetanilide as they are formed during the reaction, thus preventing the isolation of acetanilide and causing unchanged benzamide to remain. However, it is significant that Beckwith and Hassanali[117] have been successful in isolating an appropriate rearrangement product from the reaction of lead tetra-acetate with benzamide under modified reaction conditions (to be discussed later, page 101).

The scope of the reaction of lead tetra-acetate and primary amides was further extended by carrying out such reactions in the presence of methanol. The product resulting was the corresponding methyl carbamate (XCLIV) which is presumably formed *via* addition of methanol to the N = C bond of the intermediate *iso*cyanate (XCLIII).

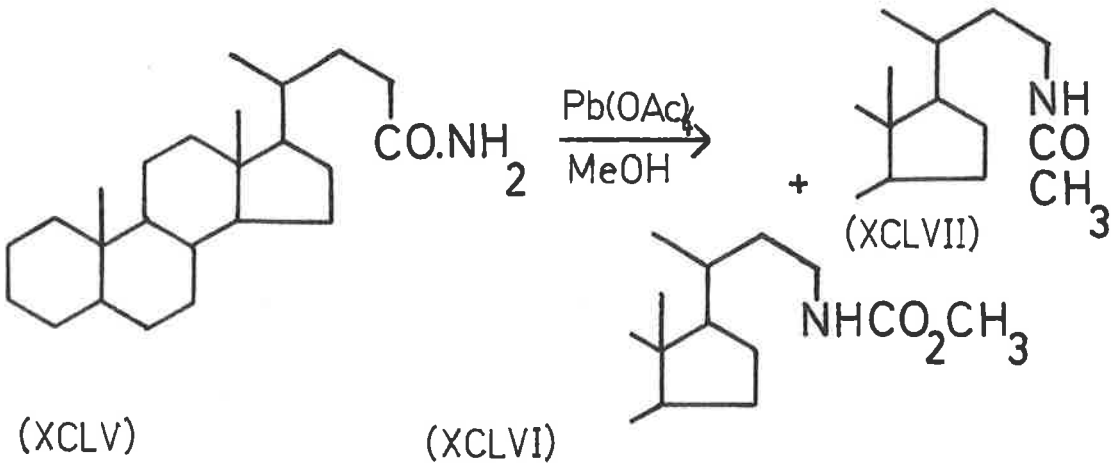
$$R\,CO.NH_2 \xrightarrow{Pb(OAc)_4} R{-}N{=}C{=}O \xrightarrow{MeOH} R\,N(H)\,CO_2Me$$

(XCLIII) (XCLIV)

The original amide considered was 5β-cholanamide (XCLV) which contained one mole of methanol of crystallisation. Methyl N-(24-nor-5β-cholanyl)carbamate (XCLVI) was obtained in 58% yield along with N-acetyl-24-nor-5β-cholanylamine (XCLVII) in 29%. These two products were separated by chromatography on a silica gel column with chloroform as eluant. The carbamate (XCLVI) came off the column first as colourless crystals and was identified by physical (n.m.r. and infrared spectroscopy and analysis) and chemical (hydrolysis) methods and comparison with the authentic compound. The acetamide (XCLVII) was the second fraction off the column as a yellow glass; trituration of such a product with methanol afforded a colourless solid which was purified and identified by physical (n.m.r. and infrared spectroscopy and melting point) and chemical (hydrolysis) methods.

Apparently the mole of methanol of crystallisation present was sufficient to convert most of the intermediate norcholanyl isocyanate into the carbamate (XCLVI). When the same reaction was repeated in a 3 : 1 mixture of benzene and methanol as solvent, complete conversion of the isocyanate into carbamate was achieved since only methyl N-(24-nor-5β-cholanyl)carbamate (XCLVI) was obtained in 86% yield. However, when the reaction of cholanamide and lead tetra-acetate was carried out in pure methanol as solvent, only a very low yield of the methyl carbamate (XCLVI) was obtained although the lead tetra-acetate was rapidly used up. Mainly

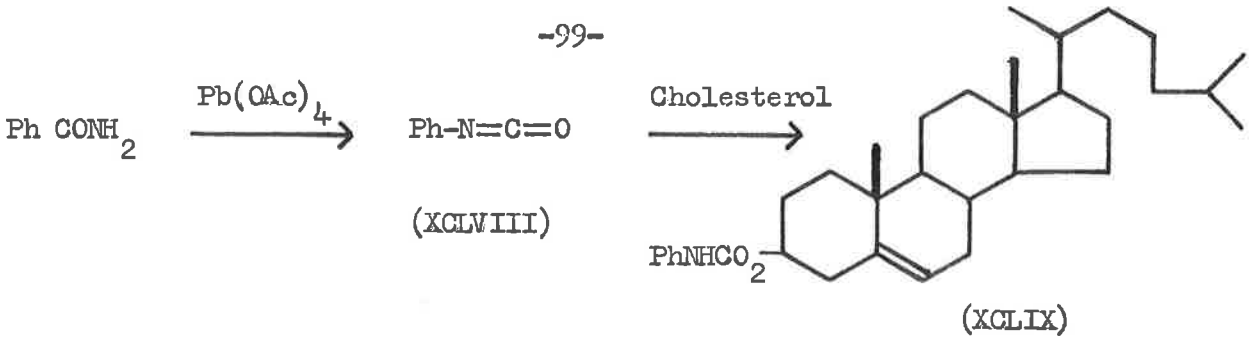
starting cholanamide was recovered. Apparently lead tetra-acetate



(XCLV) (XCLVI)

undergoes a reaction with primary amides in preference to methanol when a benzene-methanol solvent is used. However, when only methanol is used as solvent, the lead tetra-acetate is probably quenched by the methanol causing it to oxidise the alcohol before it can react with the amide.

Beckwith and Hassanali[117] have further delineated the scope of this reaction by carrying out the reaction of various primary amides with lead tetra-acetate in the presence of ethanol, t-butyl alcohol, and cholesterol and with the latter two alcohols in the presence of pyridine. The reaction[117] involving benzamide in the presence of cholesterol is particularly significant since it illustrates the versatility of such a reaction of primary amides with lead tetra-acetate in the presence of alcohols. Regardless of the fact that cholesterol is an alcohol consisting of a large complex alkyl group, such an alcohol nevertheless adds to the intermediate phenyl isocyanate (XCLVIII) to afford a fair yield (34%) of cholesteryl N-phenylcarbamate (XCLIX).



Scheme 38.

Comparison of this work involving the reaction of lead tetra-acetate and primary amides in alcohols with that of Baumgarten and Staklis[114] shows that discordance again exists between the two sets of results. Although Baumgarten and Staklis[114] obtained similar results to those of Beckwith and Hassanali[117] when they carried out the reaction in t-butyl alcohol, they found that "methyl and ethyl alcohols could not be substituted for t-butyl alcohol for these alcohols reacted more rapidly with the reagent than did the amides". It is with these reactions in methyl and ethyl alcohol that the difference arises. It is true that the previously mentioned reaction of lead tetra-acetate with cholanamide in pure methanol as solvent was unsuccessful due to the faster oxidation of the methanol than cholanamide. Such is in accord with the results of Baumgarten and Staklis.[114] However, Beckwith and Hassanali[117] have been able to successfully carry out reactions of various less complex amides with lead tetra-acetate in methanol and ethanol so that discordance between the two sets of results does nevertheless exist.

It seems probable that the difference lies in the actual reaction conditions. In the original work with methanol (refer to page 96) as

well as in that extended by Beckwith and Hassanali,[117] the lead tetra-acetate and amide were heated under reflux in the presence of the appropriate alcohol (with or without benzene as solvent) for approximately 4 hours, whereas Baumgarten and Staklis[114] added triethylamine dropwise to the solution of amide and lead tetra-acetate in the alcohol at 50-60°. Their reaction apparently occurred very rapidly under such conditions to afford the isocyanate which was allowed to react with the alcohol over a period of a few days to form the appropriate carbamate. As the colour of the intermediate amide - lead tetra-acetate complex takes much longer to disappear under the reflux conditions compared with the method of Baumgarten and Staklis[114] using triethylamine, it would appear that the latter conditions are much more vigorous. It seems probable that this vigour of such conditions causes the lead tetra-acetate to react indiscriminately with the result that the scope of the procedure of Baumgarten and Staklis is greatly restricted.

Furthermore it is possible that a fine balance exists between the reactivity of the lead tetra-acetate towards the amide and the alcohol so that slight variations not only in the vigour of the reaction conditions but also in the reactivity of the amide or alcohol present may cause the lead tetra-acetate to react specifically with one or the other of amide or alcohol. Thus cholanamide does not undergo a reaction to any great extent with lead tetra-acetate in pure methanol (refer to page 97) whereas simple aliphatic amides, which are probably more reactive toward lead tetra-acetate due to their lower complexity, react[117] appreciably in pure methanol to afford the appropriate methyl carbamate (refer to page 99).

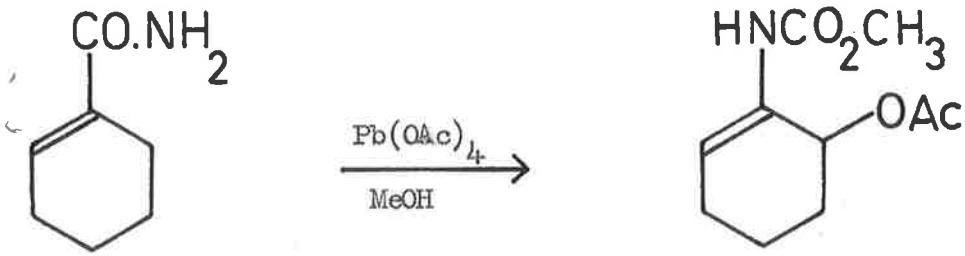
The reaction of lead tetra-acetate with benzamide in the presence of cholesterol[117] (Scheme 38) has further significance since it shows that primary aromatic amides do, in fact, undergo a rearrangement analogous to aliphatic amides (refer to page 96). Baumgarten and Staklis[114] have similarly been successful in forming a carbamate from benzamide with lead tetra-acetate in the presence of t-butyl alcohol. Beckwith and Hassanali[116] have further extended such a reaction to the substituted aromatic amide, p-nitrobenzamide, and to the pyridine amide, nicotinamide.

Since the isocyanate (XCLVIII) is presumably formed in the presence of both acetic acid and cholesterol, it would seem likely that such an intermediate is not the compound with which the lead tetra-acetate further reacts when the reaction is carried out in the presence of acetic acid (refer to page 96). It is probable therefore that under such conditions, lead tetra-acetate reacts further with the acetanilide. However, this seems characteristic of only anilide compounds since attempts to bring about a reaction between lead tetra-acetate and N-alkylacetamides proved unsuccessful. Moriarty and coworkers[118] have likewise failed to effect a reaction between lead tetra-acetate and an N-alkylacetamide.

The scope of the reaction of lead tetra-acetate with primary amides was further extended following the formation of N-dec-9-enylacetamide (53%) and N,N'-didec-9-enylurea (3%) from the reaction with dec-9-enylcarboxamide in benzene-acetic acid solution. This indicates that lead tetra-acetate reacts preferably with the amido group rather than the

isolated double bond so that products from the amide rearrangement are obtained but compounds resulting from the acetoxylation of olefinic bonds could not be detected. Beckwith and Hassanali[117] have confirmed this result by carrying out the reaction on 3β-acetoxyandrost-5-ene-17β-carboxamide in the presence of methanol from which they obtained methyl N-(3β-acetoxyandrost-5-ene-17β-yl)carbamate in 51% yield.

However, limitations to the scope of the reaction with olefinic carboxamides are evident from the work of Beckwith and coworkers[116,119] on cyclohex-1-enecarboxamide (CL) and cinnamamide in which the double bond is α,β- to the carboxamide group. Beckwith and Vickery[119] found that the reaction of cyclohex-1-enecarboxamide (CL) with lead tetra-acetate in methanol-benzene affords the acetoxylated rearrangement product (CLI) together with unchanged starting amide. It seems likely that the α,β-double bond undergoes further reaction with the lead tetra-acetate rather than allow complete reaction of the amido group with the reagent.



(CL) (CLI)

Baumgarten and Staklis[114] have not been able to apply the reaction to any olefinic carboxamides. However this limitation is again probably due to the greater vigour of their reaction conditions.

From a consideration of the overall scope so far developed for the reaction of lead tetra-acetate with primary amides under the conditions of refluxing solvent and from a comparison of such a scope with that of the analogous reaction developed by Baumgarten and Staklis,[114] it appears that the conditions developed in this work are, in general, much more versatile. Such conditions seem to be of sufficient vigour to effect a reaction between the lead tetra-acetate and primary carboxamide but mild enough, in most cases, to enable specific reaction with such amide groups in the presence of other reactive functional groups. The optimum conditions for the formation of acylamine appear to require that the reaction between the amide and lead tetra-acetate be carried out in the appropriate acid as the refluxing solvent whereas the best conditions for the formation of alkyl carbamates require that the reaction be carried out in refluxing benzene as solvent in the presence of sufficient alcohol to ensure that complete conversion of the intermediate isocyanate to carbamate occurs.

(b) Mechanism.

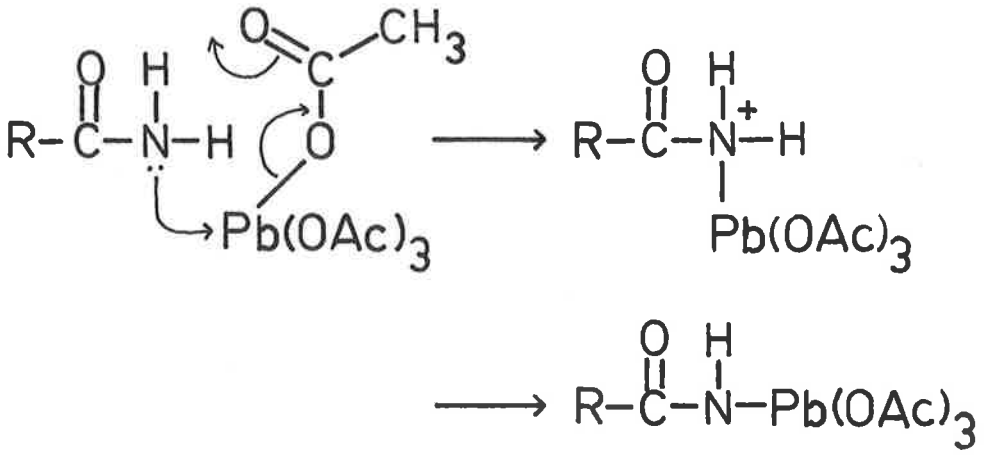
The most important intermediate detected in the reaction of lead tetra-acetate with primary amides is the appropriate isocyanate (XCLIII).

$$\underset{\text{(CXXXVIII)}}{R\,CO.NH_2} + Pb(OAc)_4 \longrightarrow \underset{\text{(XCLIII)}}{R{-}N{=}C{=}O} \longrightarrow \text{Products.}$$

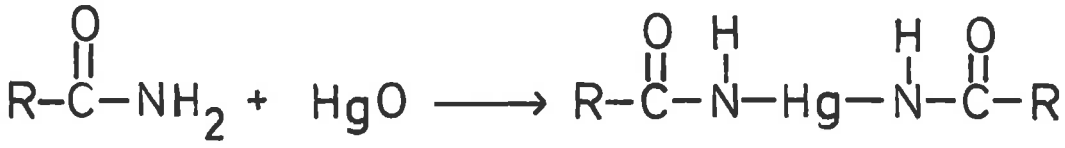
It has been mentioned previously that cyclohexyl isocyanate (XCLIII, R = C_6H_{11}), was present in the crude product from the incomplete reaction of

cyclohexanecarboxamide (CXXXVIII, R = C_6H_{11}) with lead tetra-acetate (refer to page 92). Beckwith and Hassanali[116] have since found that styryl isocyanate participates in the reaction of cinnamamide with lead tetra-acetate. However, the most conclusive evidence has been obtained by Baumgarten and Staklis[114] who actually isolated and positively identified t-butyl isocyanate (XCLIII, R = t - Bu) from the reaction of lead tetra-acetate with pivalamide (CXXXVIII, R = t - Bu).

The mechanism for the formation of such isocyanate intermediates is not known with any certainty. It seems probable that an organometallic complex, represented by the structure (CLII) is formed from the initial reaction between the primary amide and lead tetra-acetate. Such reactions with compounds R-X-H possessing a hetero-atom, X, seem to be usual for lead tetra-acetate[61,120] although neither the resulting complexes of general structure R-X-Pb(OAc)$_3$ nor those (CLII) specific for the amide system have been isolated. It seems significant that mercury (II) which is isoelectronic with lead (IV) forms stable complexes (CLIII) with primary amides.[121] It also seems significant that the benzene solution of lead tetra-acetate becomes coloured upon addition of the amide. The colour appears to vary, depending on the alkyl group, R. Large alkyl groups such as steroidal groups produce a deep brown-red solution whereas amides of small alkyl chain length such as pentanamide produce pale yellow solutions. Further investigation into such colour variation has not been undertaken. Nevertheless, such colours are attributed tentatively to the intermediate complexes (CLII).

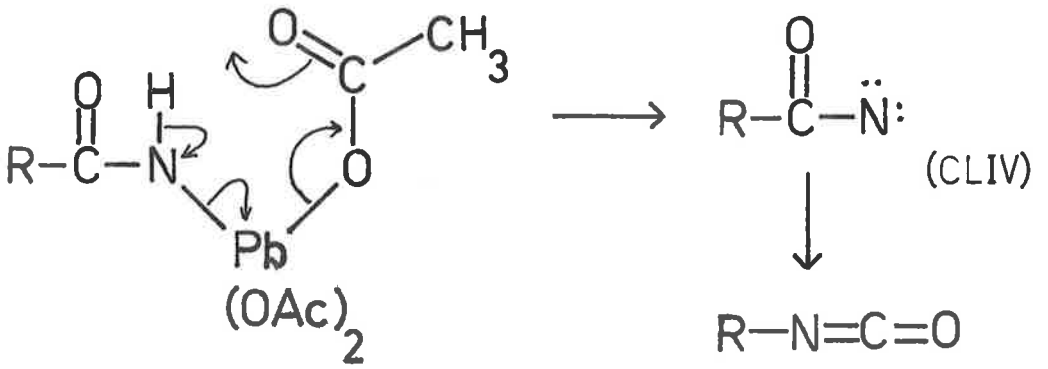


(CLII)



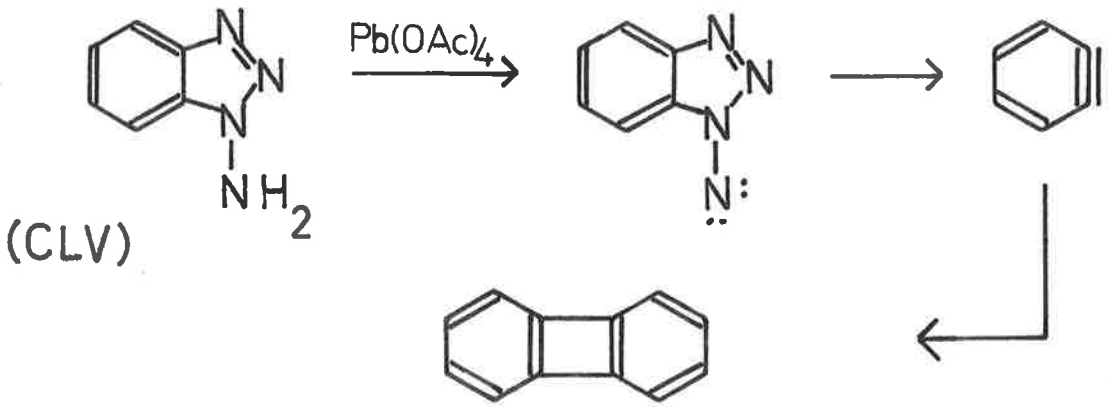
(CLIII)

Although it seems probable that complexes (CLII) are formed as intermediates, there is conjecture concerning the mechanism by which such complexes (CLII) are converted into the corresponding isocyanates (XCLIII). Baumgarten and Staklis[114] have suggested that an acyl nitrene (CLIV) is formed and such an intermediate is converted to the isocyanate in a similar way to the nitrene rearrangement of the Hofmann[122] reaction. However, Baumgarten and Staklis[114] did not offer any proof for the intermediacy of such nitrenes but simply drew this conclusion from an analogy with previous work[123] on the reaction of lead tetra-acetate with various amino compounds. In such reactions,[123] nitrene intermediates have also been suggested.



Scheme 39.

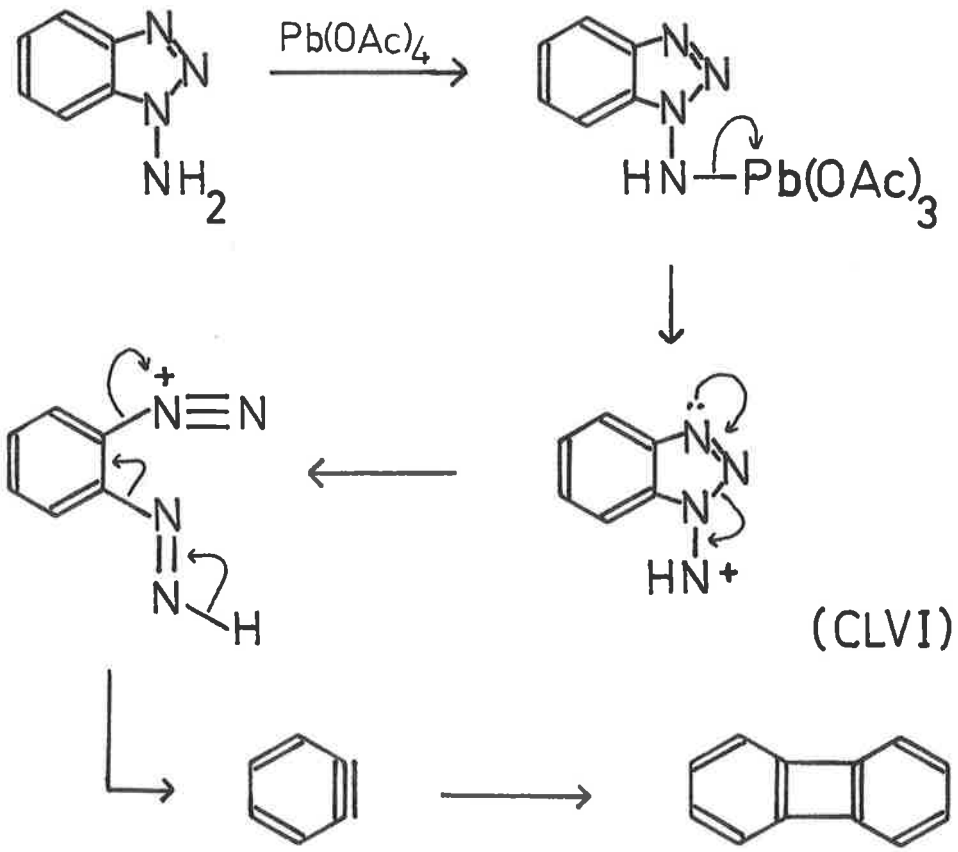
A particular example[123(b)] with which these workers[114] drew the analogy involves the reaction between 1-aminobenzotriazole (CLV) and lead tetra-acetate. The mechanism proposed is illustrated in Scheme 40.



Scheme 40.

However, taking into account the facts known about the reactions of lead tetra-acetate with both 1- and 2-aminobenzotriazole[123b,125] as well as other amino[120(b-d), 123a,126] and organic[124] compounds (there does not appear to be unequivocal proof for the intermediacy of nitrenes in these

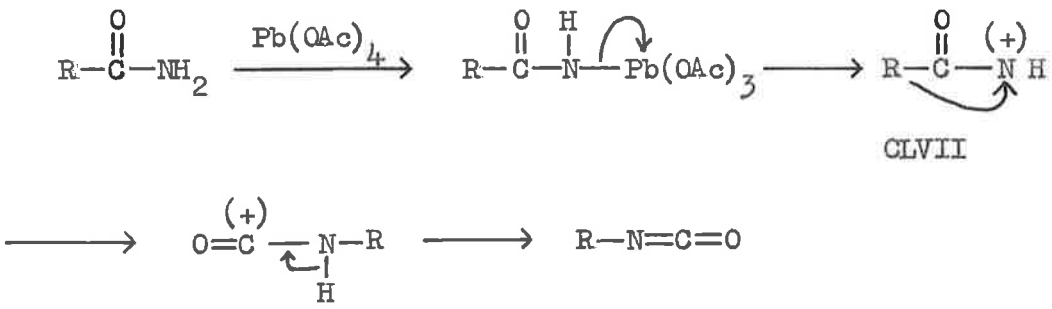
reactions), it is proposed that the mechanism represented by Scheme 41 (or one involving an analogous concerted process in which simultaneous elimination of $Pb(OAc)_3$ and rearrangement occurs) seems equally as feasible as that illustrated by Scheme 40.



Scheme 41.

Similarly a polar rearrangement mechanism involving an intermediate nitrenium ion (CLVII) (analogous to (CLVI) in Scheme 41) is suggested as an alternative to the nitrene process (Scheme 39) for the reaction of lead tetra-acetate with primary amides. Such a mechanism is illustrated by

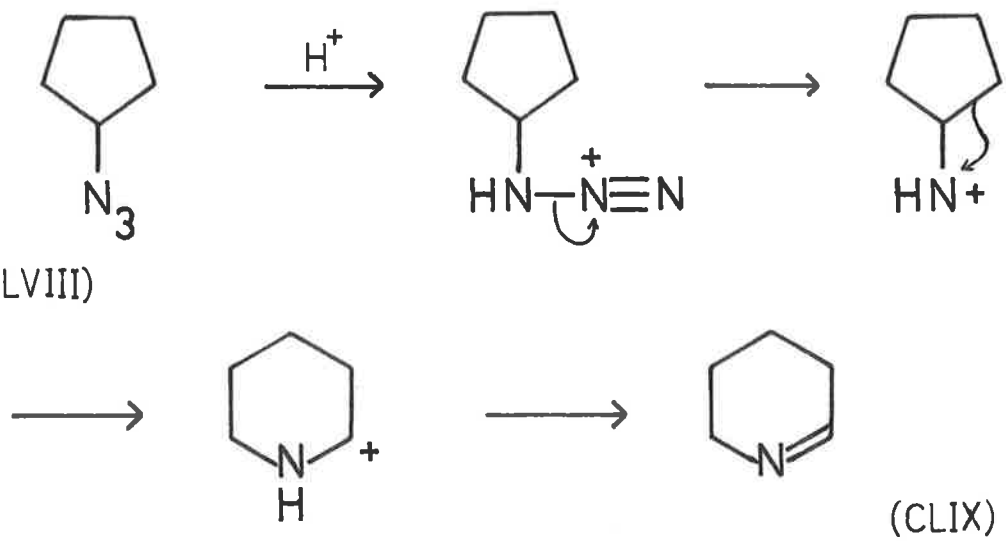
Scheme 42.



Scheme 42.

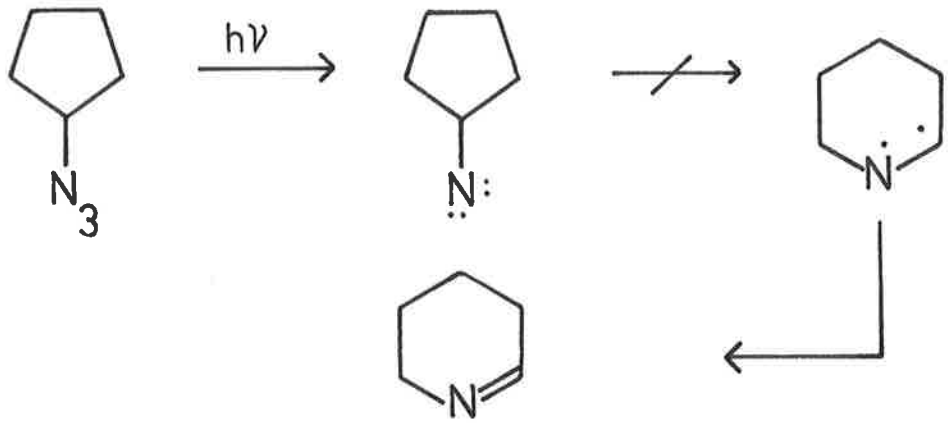
Again a scheme depicting a more concerted process than is represented by Scheme 42 may be involved. In such a process, simultaneous alkyl group (R) rearrangement and $Pb(OAc)_3$ elimination would occur so that (CLVII) would not act as a free intermediate. However, the difference between the two processes would seem to be minor.

It seems significant that nitrenium ion rearrangements have been found to participate in various other reaction processes.[127,128] One such example[127] is illustrated in Scheme 43.



Scheme 43.

It may be noted that without contrary evidence, it could be suggested that a nitrene is involved as an intermediate in this particular reaction (Scheme 44). However, the fact that the ring expanded product (CLIX) is only obtained when the azide (CLVIII) is treated with a strong protonating acid[127a] and not by photolysis[127b] seems strong evidence for the participation of the nitrenium ion intermediate.

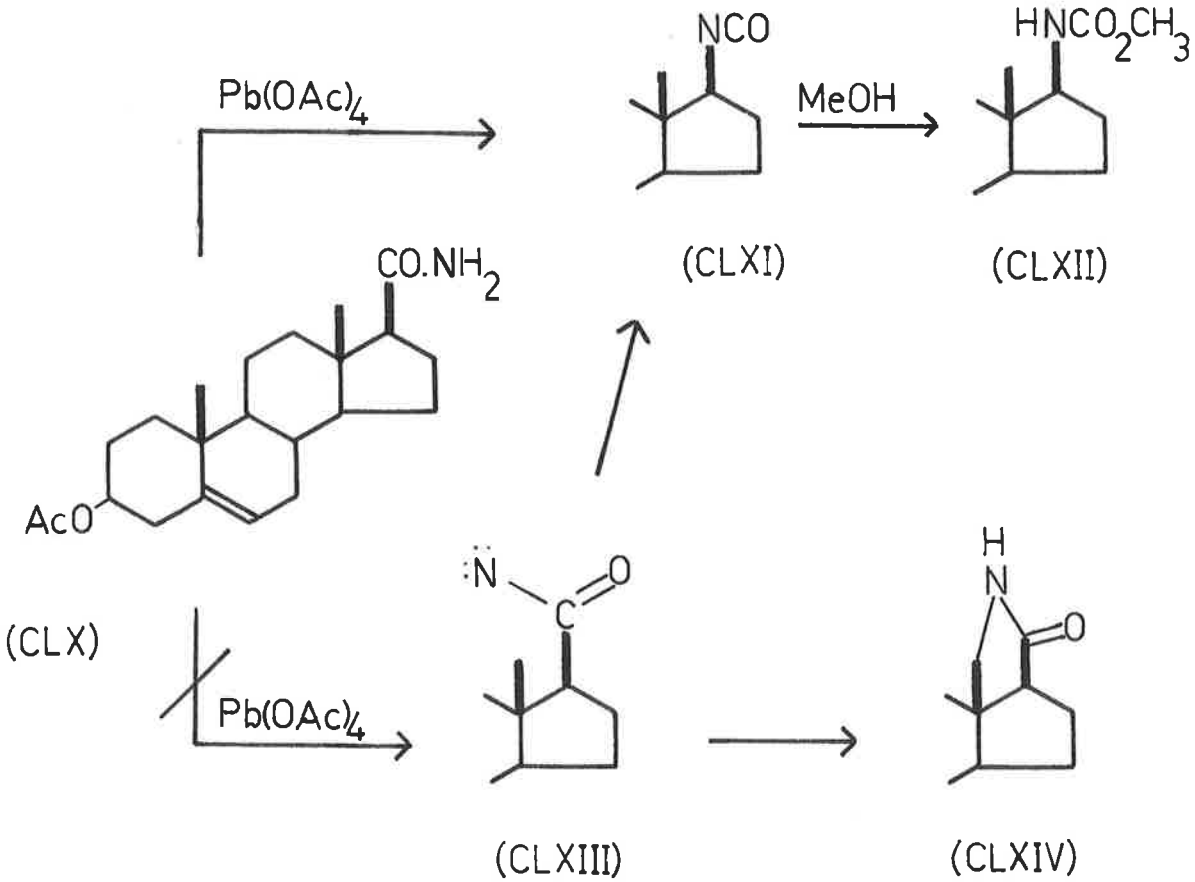


Scheme 44.

It has been mentioned previously that Baumgarten and Staklis[114] based their opinion that a nitrene is involved in the reaction of lead tetra-acetate with primary amides on a comparison with the analogous reactions with primary amines. Comparison of the reaction of primary amides and lead tetra-acetate with the pyrolysis of acyl azides (Curtius reaction[129]) seems to further support this conclusion of Baumgarten and Staklis.[114] Both reactions afford isocyanate intermediates; the latter reaction giving rise to such a compound via a nitrene intermediate formed by the elimination of nitrogen.

However, such an analogy again has no firm experimental basis. In fact, Beckwith and coworkers[117] have obtained results which indicate that a nitrene intermediate is not actually involved in the reaction of lead tetra-acetate and primary amides.

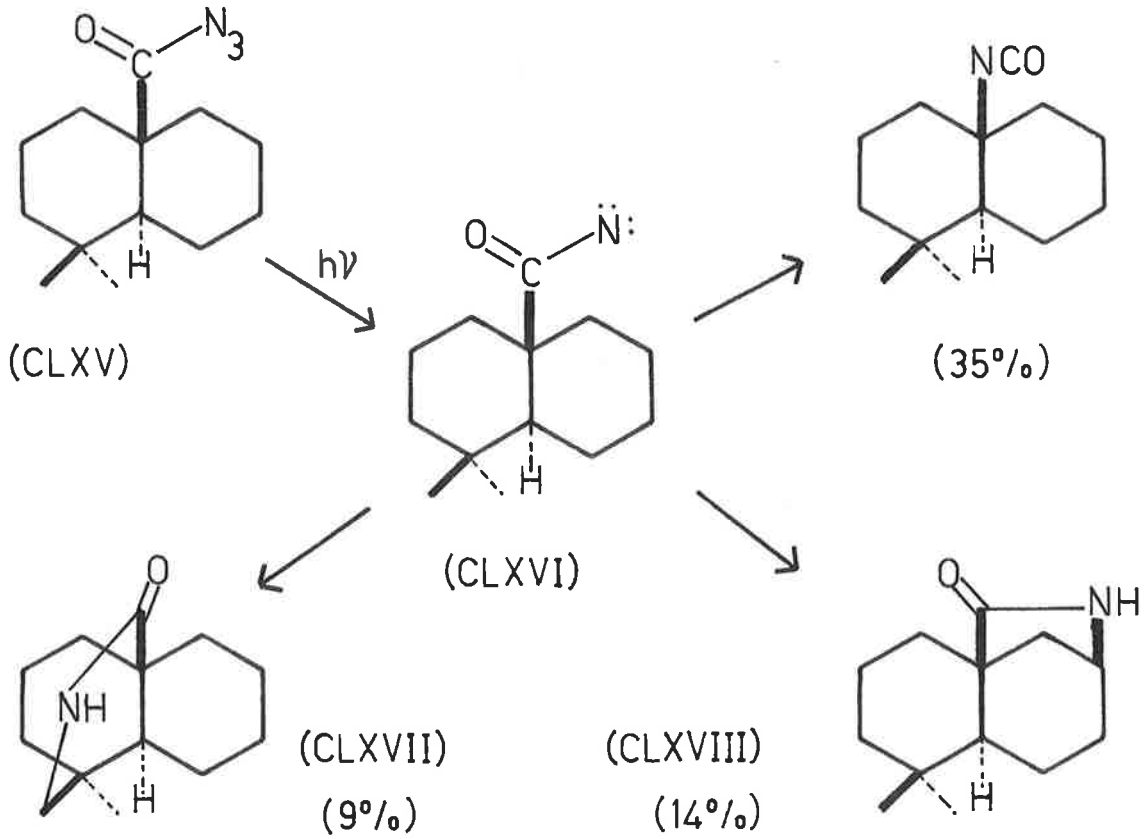
The most convincing evidence has been obtained by Beckwith and Hassanali[117] who heated lead tetra-acetate and 3β-acetoxyandrost-5-en-17β-carboxamide (CLX) in the presence of methanol and obtained a 51% yield of the methyl carbamate (CLXII) (refer to page 102) but did not detect any pyrrolidone compound (CLXIV).



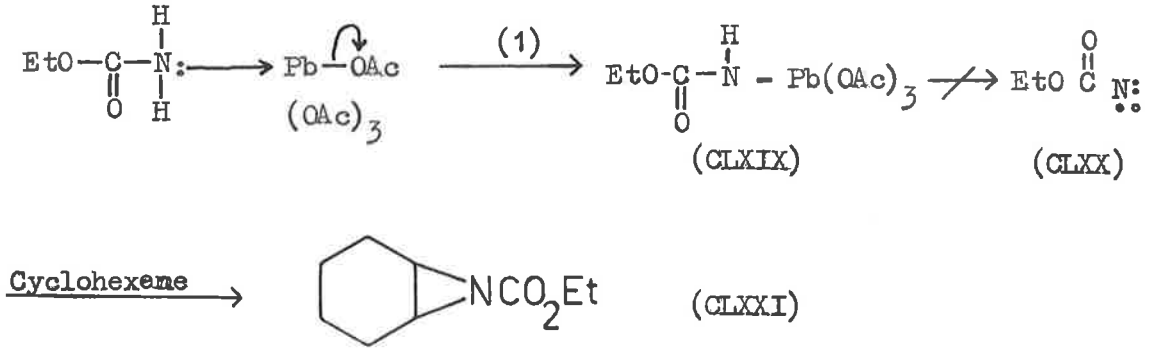
If the nitrene (CLXIII) had been involved in the formation of the isocyanate (CLXI), then a significant yield of the pyrrolidone compound (CLXIV), whether formed by intramolecular hydrogen abstraction or carbon-hydrogen insertion by the nitrene (CLXIII) (refer to page 31), would have been expected, especially since the appropriate carbon-hydrogen bond and the nitrene are held in the necessary close proximity by the rigidity of the steroid molecule.

It is pertinent to consider the photolysis of the acyl azide (CLXV).[130] The nitrene (CLXVI) is not held in as close proximity to the appropriate hydrogen atoms as the nitrene (CLXIII) would be to the β-methyl hydrogen atoms if such a nitrene (CLXIII) were formed. Nevertheless, significant yields of the cyclic lactams (CLXVII) and (CLXVIII) are formed[130] from the nitrene (CLXVI). Since the cyclic amide (CLXIV) is not obtained, it is concluded that such acyl nitrenes do not participate in the reactions of lead tetra-acetate with primary amides.

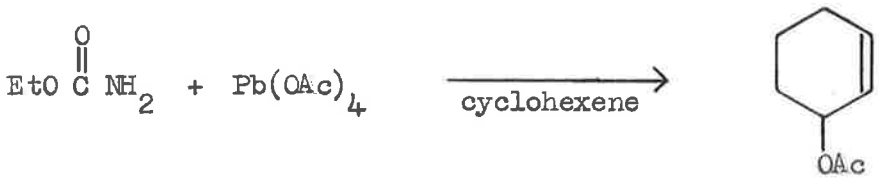
Less conclusive evidence to support this conclusion has been obtained by Beckwith and Redmond.[117] These workers have found that treatment of ethyl carbamate with lead tetra-acetate in cyclohexene does not afford the aziridine (CLXXI), known to be formed by addition of carbethoxynitrene (CLXX) to cyclohexene, but gives solely 3-cyclohexenyl acetate (CLXXII, Scheme 46) together with unchanged ethyl carbamate. These workers anticipated that, if the acyl nitrene (CLIV) is formed from the reaction of lead tetra-acetate with primary amides by the scheme proposed by Baumgarten and Staklis (Scheme 39), then lead tetra-acetate and ethyl



carbamate would likewise afford the nitrene (CLXX) which would add across the double bond (Scheme 45). Since no aziridine (CLXXI) is formed, Beckwith and Redmond[117] concluded that acyl nitrenes are not involved in the reactions of lead tetra-acetate with primary amides.



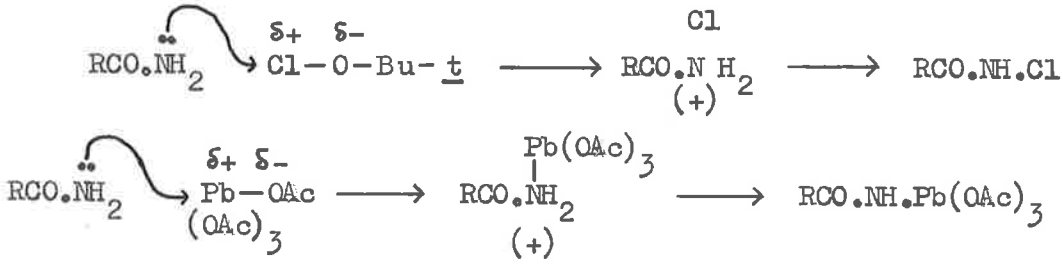
Scheme 45.



(CLXXII)

Scheme 46.

However, this latter conclusion does not seem to be completely justified. The fact that primary amides undergo a reaction with lead tetra-acetate does not necessarily mean that ethyl carbamate should do likewise. A comparison of the respective reactions of lead tetra-acetate and t-butyl hypochlorite with primary amides, N-alkylacetamides, and alkyl carbamates seems significant. It has been mentioned previously that alkyl carbamates are much more lethargic toward t-butyl hypochlorite than the primary amides (refer to page 81). Furthermore, it has been found that N-alkylacetamides show a similar order of reactivity to the alkyl carbamates although the latter compounds seem to be slightly more reactive. N-Alkylacetamides have been shown not to react with lead tetra-acetate (refer to page 101). Thus, assuming that similar schemes are involved in the formation of RCO.NH.Cl and $RCO.NH.Pb(OAc)_3$, it could be reasoned that alkyl carbamates may show similar reactivity towards lead tetra-acetate as do the N-alkylacetamides, from which it follows that an intermediate capable of undergoing rearrangement would probably not be formed during the reaction of lead tetra-acetate and ethyl carbamate.

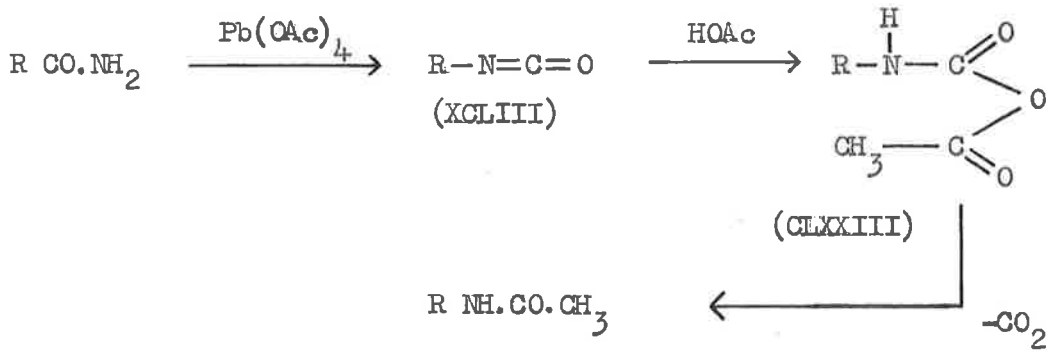


Nevertheless, Beckwith and Redmond are of the opinion that the increased rate of oxidation of ethanol with lead tetra-acetate in the presence of ethyl carbamate compared with the same reaction in the absence of ethyl carbamate indicates that the initial complex (CLXIX) is formed and it is this complex which causes the increased rate of alcohol oxidation. However, further studies on the influence of ethyl carbamate on the rate of oxidation of alcohols by lead tetra-acetate seems necessary before any conclusions may be drawn from these results.

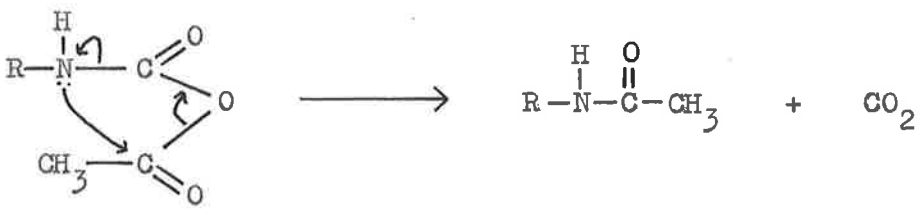
From the work carried out so far concerning the reaction mechanism, it appears that the reaction between lead tetra-acetate and primary amides does not proceed *via* a nitrene intermediate but occurs *via* some other intramolecular rearrangement process, one possibility of which has been suggested previously (Scheme 42). The fact that an intermolecular rearrangement, involving the formation of free carbonium ion, cannot be involved has been shown by Beckwith and Vickery[119] who have found that the reaction between lead tetra-acetate and an optically active amide proceeds with retention of configuration at the shifting carbon atom.

The conversion of the *isocyanate* intermediate into the corresponding acetylamine and dialkylurea in the reactions carried out in benzene solution is assumed to proceed *via* an anhydride intermediate (CLXXIII) which is

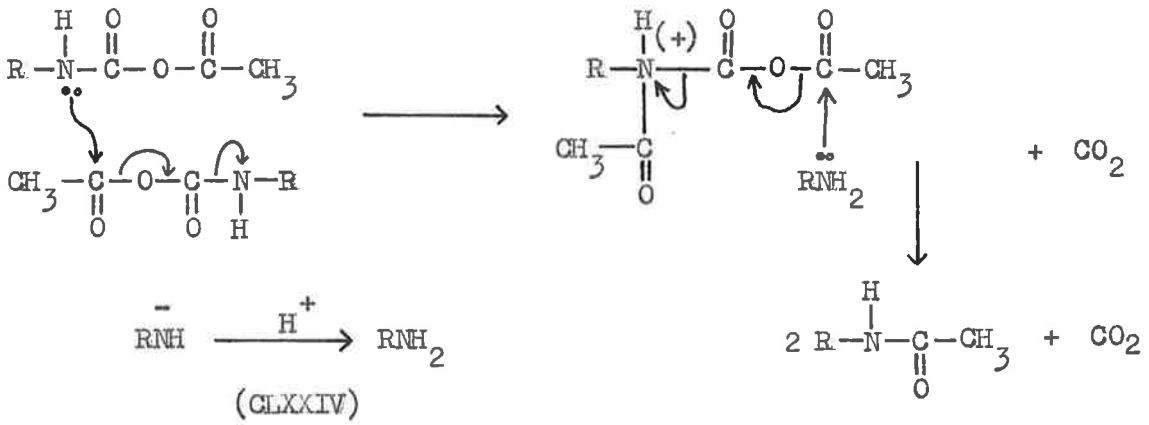
presumably formed by addition of acetic acid across the N=C bond of the isocyanate (XCLIII). Such a compound (CLXXIII) has been previously depicted as an intermediate in the Curtius reaction carried out in acetic acid.[132]



The conversion of such mixed anhydrides (CLXXIII) to the acetamides (CXXXIX) could proceed by an intra- or intermolecular decarboxylation reaction (Schemes 47 and 48 respectively).

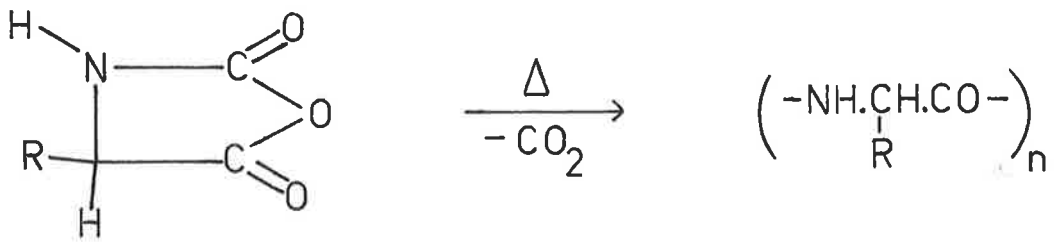


Scheme 47.



Scheme 48.

Mixed anhydrides with the cyclic structure (CLXXV), analogous to the proposed intermediates (CLXXIII), are well-known compounds[131] and have been found, in fact, to undergo decarboxylation on heating to afford polypeptides (CLXXVI).[131a]

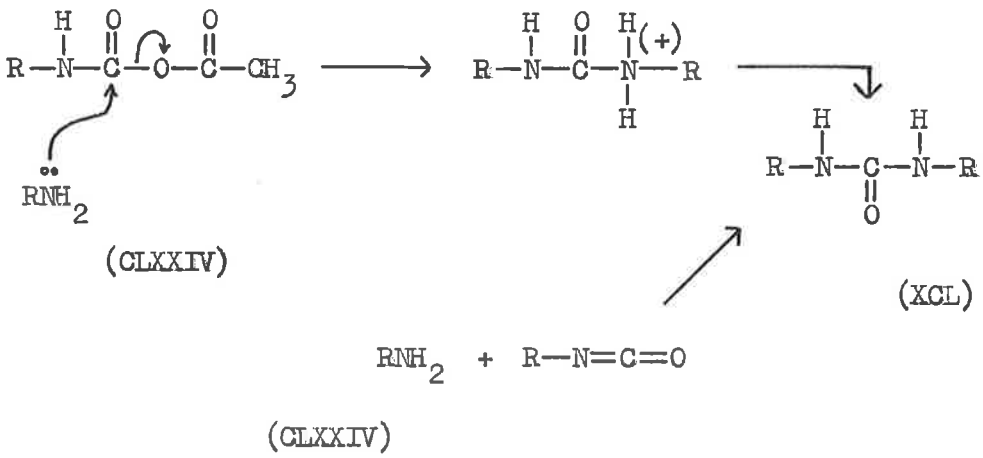


(CLXXV) (CLXXVI)

However, the fact that such polypeptides (CLXXVI) are formed seems to indicate that elimination of carbon dioxide in such a system (CLXXV) occurs via an intermolecular process. By analogy with such a system, it is suggested that decarboxylation of (CLXXIII) occurs via a similar

intermolecular process (Scheme 48). Consideration of the effect of acetic acid on the nature of the products from the reaction of lead tetra-acetate with primary amides further indicates that an intermolecular decarboxylation mechanism (Scheme 48) operates.

When the reaction is carried out in pure benzene as solvent, it is conceivable that the amine (CLXXIV) could undergo a side-reaction as is illustrated in Scheme 49 to afford the corresponding urea.[132]



Scheme 49.

As has been mentioned previously, such urea compounds (XCL) are in fact obtained when benzene and benzene/acetic acid are used as solvents (refer to page 94). Furthermore, Baumgarten and Staklis[114] have accentuated such a reaction by adding primary amine to their reaction medium and have thus obtained high yields of the appropriate urea. However, it is further conceivable that such a side reaction would be suppressed when the reaction of lead tetra-acetate and primary amide is carried out in pure acetic acid as solvent since the amine (CLXXIV) would then be expected to afford the

acetamide (CXXXIX) from further reaction with the solvent (Scheme 50) rather than react with the isocyanate or anhydride intermediates.

$$RNH_2 + CH_3CO_2H \longrightarrow RNH.COCH_3$$

(CXXXIX)

Scheme 50.

Again such an effect is actually observed; increased yields of acetamide and suppressed yields of urea are obtained when the reactions of lead tetra-acetate and primary amides are carried out in pure acetic acid as solvent.[116]

An alternative mechanism analogous to that suggested for the formation of urea compounds in the Curtius reaction[132] may also be proposed to account for the formation of the alkyl urea compounds in the reactions of lead tetra-acetate and primary amides. However, the above mechanism is preferred since the alternative scheme[132] does not seem to account for the effect of acetic acid on the reaction products as well as that proposed above.

A general consideration of the mechanism of the reaction of lead tetra-acetate with primary amides thus indicates that an amide-tetravalent lead complex is initially formed and such a complex is converted to the isocyanate intermediate via an intramolecular rearrangement process (not involving the participation of an acyl nitrene). Such an isocyanate is converted to the corresponding N-alkylacetamide, N,N'-dialkylurea, or N-alkylcarbamate depending on the solvent conditions; the former two products resulting from the decarboxylation of an anhydride intermediate.

III. EXPERIMENTAL

1. General.

Analyses. - Micro-analyses were carried out by the Australian Micro-analytical Service, Melbourne, under the direction of Dr. K.W. Zimmermann.

Infrared absorption spectra. - Spectra were measured on a Perkin-Elmer 237 Grating Infrared Spectrophotometer.

Gas-phase chromatography. - Chromatographs were carried out on a Perkin-Elmer 800 Gas Chromatograph, using both sensing and reference columns.

Nuclear magnetic resonance. - Spectra were recorded at 60 mc/sec. with tetramethylsilane as standard on a Varian D.P.60 spectrometer with super-stabilizer and electronic integrator. The spectra were calibrated by a "side-band" technique using a Muirhead-Wigan (Type D 890A) decade oscillator.

Melting Points. - These were determined in capillaries on a "hot-stage" apparatus.

Photolyses. - All photolyses were carried out with a Hanovia 125W HPK mercury quartz burner, externally irradiating the reaction solution contained in a quartz flask.

Redox Decompositions, Photolyses, and Lead Tetra-acetate Reactions. - All were carried out under a dry, oxygen-free nitrogen atmosphere.

Nitrogen. - Dry, oxygen-free nitrogen for reactions was obtained by passing the commercial gas through four Drechsel bottles in the following order: two containing a solution of vanadyl sulphate (5 gm) in 2N H_2SO_4 (150 ml) over zinc amalgam (5 gm), one containing conc. H_2SO_4, and one containing KOH pellets.

Solvents. - All solvents were dried (using the appropriate methods) and distilled.

2. Decomposition of Alkyl Hydroperoxides and Peracetates.

(a) Starting Materials.

Tertiary Alcohols -

Each alcohol was prepared by the method of Church et.al.[133] in which an ethereal acetone solution was slowly added to an ether solution of the appropriate alkylmagnesium iodide.

2-Methylhexan-2-ol was obtained as a colourless liquid, b.p. 139-142° (lit.[133] 141-143°/730 mm).

2-Methylheptan-2-ol distilled as a colourless liquid, b.p. 156-158° (lit.[133] 155-156°).

2,5-Dimethylhexan-2-ol was obtained as a colourless liquid, b.p. 155-157° (lit.[134] 152-154°).

Alkyl Hydroperoxides -

2,4,4-Trimethyl-2-pentyl hydroperoxide, b.p. 46-48°/0.7 mm (lit.[135] 44-45°/0.9 mm) was prepared from di-isobutylene, 30% hydrogen peroxide, and 70% sulphuric acid by the method described by Hoffman.[136]

2-Methyl-2-hexyl hydroperoxide, 2,5-dimethyl-2-hexyl hydroperoxide, and 2-methyl-2-heptyl hydroperoxide were each prepared by the following general method - a modification of the method of Hoffman.[136]

A solution of 96% sulphuric acid (267 gm) and crushed ice (103 gm) was cooled to 0° and to this solution was added the appropriate tertiary alcohol (0.7 mole) at such a rate that the temperature remained below 5°. This solution was added slowly with rapid stirring to 30% hydrogen peroxide (267 gm) at 0°. After the addition the mixture was vigorously stirred at room temperature for 24 hours and the upper layer was then separated, washed with an aqueous suspension of magnesium carbonate, and dried ($MgSO_4$). The alkyl hydroperoxide was isolated by fractional distillation under reduced pressure through a 12" helix-packed column.

2-Methyl-2-hexyl hydroperoxide distilled as a colourless liquid, b.p. 40-42°/1.0 mm, n_D^{22} 1.4260 (lit.[137] b.p. 57-59°/2.0 mm, n_D^{26} 1.4237).

2,5-Dimethyl-2-hexyl hydroperoxide was obtained as a colourless liquid, b.p. 48-49°/0.9 mm, n_D^{22} 1.4280.

2-Methyl-2-heptyl hydroperoxide distilled as a colourless liquid, b.p. 52°/0.7 mm, n_D^{22} 1.4290.

The percentage purity of the alkyl hydroperoxides was determined by iodometric analysis by the method of Tobolsky and Mesrobian[138] with slight modifications: the alkyl hydroperoxide (approx. 0.1 gm) was weighed accurately into an Erlenmeyer flask filled with nitrogen, and t-butyl alcohol (20 ml) was added. Excess iodine-free aqueous potassium iodide solution and acetic acid (1 ml) was added and the flask stoppered and warmed on a water-bath for 10 minutes. The liberated iodine was titrated

with a standard solution of sodium thiosulphate (0.1 N).

Alkyl Peracetates -

To a solution of the hydroperoxide (0.1 mole) in pyridine (30 ml) and ether (50 ml) cooled in an ice-bath was added acetyl chloride (14 gm) very slowly with stirring. After the addition the mixture was stirred at room temperature for 3 hours and then poured onto ice. The upper ethereal layer was separated, washed with dilute hydrochloric acid, aqueous $NaHCO_3$ solution, and dried ($MgSO_4$). Fractional distillation under reduced pressure afforded the alkyl peracetate.

2-Methyl-2-hexyl peracetate was obtained as a colourless liquid, b.p. 56-57°/1.5 mm, n_D^{22} 1.4230 (lit.[137] 81-83°/2mm, n_D^{26} 1.4208) (Found: C, 62.2; H, 10.3; O, 27.4%. Calc. for $C_9H_{18}O_3$: C, 62.0; H, 10.4; O, 27.6%).

2,5-Dimethyl-2-hexyl peracetate distilled as a colourless liquid, b.p. 64°/0.8 mm, n_D^{22} 1.4250 (Found: C, 63.3; H, 10.9; O, 25.7%. $C_{10}H_{20}O_3$ requires C, 63.8; H, 10.7; O, 25.5%).

2-Methyl-2-heptyl peracetate distilled as a colourless liquid, b.p. 57°/0.6 mm, n_D^{22} 1.4260 (Found: C, 64.0; H, 10.6%. $C_{10}H_{20}O_3$ requires C, 63.8; H, 10.7%).

2,4,4-Trimethyl-2-pentyl peracetate distilled as a colourless liquid, b.p. 70°/2.2 mm. Satisfactory elemental analyses for this compound were not obtained.

Each of the above peracetates showed characteristic absorption bands in the infrared, $\nu_{max.}$ (film) at 1780 cm^{-1} (C=O).

(b) Decomposition of Alkyl Hydroperoxides.

(1) Ferrous-Ion Induced Decomposition of Alkyl Hydroperoxides. General Method.

$FeSO_4 \cdot 7H_2O$ (21 gm) in 2N H_2SO_4 (70 ml) was added dropwise with stirring to the alkyl hydroperoxide (10 gm) and 2N H_2SO_4 (30 ml) at 20°. The resultant mixture was stirred for 5 hr and was then extracted with ether. The ethereal solution was washed (aqueous $NaHCO_3$) and dried ($MgSO_4$). Removal of the ether under reduced pressure afforded a residual oil which was identified by the procedure described below for each particular hydroperoxide.

2-Methyl-2-hexyl hydroperoxide.

Distillation of the crude product afforded 2-methylhexan-2-ol (0.76 gm), b.p. 56-58°/17 mm (lit.[139] 58-60°/20 mm) which formed a 3,5-dinitrobenzoate derivative by treatment of the alcohol with 3,5-dinitrobenzoic acid and toluene-p-sulphonyl chloride in pyridine.[140] 2-Methyl-2-hexyl 3,5-dinitrobenzoate crystallised from light petroleum (b.p. 40-60°) in plates, m.p. 62-63°. Comparison with the authentic compound by m.p. and m.m.p. confirmed the identity. A small amount of unsaturated impurity, detected by infrared spectroscopy, was obtained in a less pure sample (4.8 gm) of 2-methylhexan-2-ol.

2,4,4-Trimethyl-2-pentyl hydroperoxide.

A sample of the reaction mixture before extraction with ether afforded acetone 2,4-dinitrophenylhydrazone, m.p. 126-127° (lit.[141] 128°) when treated with Brady's reagent. When the higher boiling liquid was chromatographed on alumina, the only identifiable product was 2,4,4-trimethylpentan-2-ol which formed a 3,5-dinitrobenzoate derivative by treatment with 3,5-dinitrobenzoic acid and toluene-p-sulphonyl chloride in pyridine.[140] 2,4,4-Trimethyl-2-pentyl 3,5-dinitrobenzoate crystallised from light petroleum (b.p. 40-60°) in plates, m.p. 88-89° (identical with the same compound obtained from a different reaction, refer to page 131).

2,5-Dimethyl-2-hexyl hydroperoxide.

Distillation of the crude product afforded 2,5-dimethylhexan-2-ol, b.p. 66-67°/17 mm, containing a small amount of unsaturated impurity detected by infrared spectroscopy. Trituration of the brown tarry residue with light petroleum (b.p. 40-60°) gave 2,5-dimethylhexan-2,5-diol (0.09 gm, 0.9%) which crystallised from light petroleum (b.p. 40-60°) as needles, m.p. 88-89° (lit.[142] m.p. 88.5-89.5°) (Found: C, 66.0; H, 12.3; O, 22.1%. Calc. for $C_8H_{18}O_2$: C, 65.7; H, 12.4; O, 21.9%), $\nu_{max.}$ (nujol) at 3300 cm^{-1} (O-H stretching vibration). The nuclear magnetic resonance (n.m.r.) spectrum showed singlets at τ 8.84 (gem-dimethyl groups), τ 8.49 (methylene protons), and τ 6.47 (hydroxyl protons) which integrated in the ratio 6 : 2 : 1. No splitting of the methylene protons was observed as the compound is symmetrical about the bond linking these two carbon atoms.

(2) Decomposition of 2-Methyl-2-hexyl hydroperoxide in the Presence of Cupric Ion, Ferrous Ion, and Carbon Tetrachloride.

$FeSO_4.7H_2O$ (21.6 gm) and $CuCl_2.4H_2O$ (0.5 gm) were dissolved in 2N hydrochloric acid (60 ml). A portion (10 ml) of this solution was stirred at 5° while the remainder and the hydroperoxide (10.8 gm) in carbon tetrachloride (50 gm) were simultaneously added dropwise at equal rates. The mixture was stirred for a further 3 hr after which the two phases were separated and the aqueous solution extracted with ether. The combined ether and carbon tetrachloride solutions were washed (aqueous $NaHCO_3$) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a liquid residue which was distilled and afforded 5-chloro-2-methylhexan-2-ol (3.2 gm, 26%), b.p. 90-92°/17 mm (lit.[143] 78-79°/10 mm), shown by infrared spectroscopy and gas-phase chromatography to be identical with an authentic sample. 5-Chloro-2-methyl-2-hexyl 3,5-dinitrobenzoate, formed by treatment of the alcohol with 3,5-dinitrobenzoic acid and toluene-p-sulphonyl chloride in pyridine,[140] crystallised from light petroleum (b.p. 40-60°) in plates, m.p. 68-69° (Found: C, 49.3; H, 5.0; Cl, 10.7; N, 7.7%. $C_{14}H_{17}ClN_2O_6$ requires C, 48.8; H, 5.0; Cl, 10.3; N, 8.1%).

(3) Decomposition of Alkyl Hydroperoxides in the Presence of Ferrous Ion, Cupric Ion, and Acetic Acid.

General Methods.

Two general methods were used. The first was designed to provide information concerning the nature of the reaction products. The second

allows accurate estimation of the yields of such products.

(i) A sample of wet ferrous hydroxide was prepared by the addition of a boiling 20% NaOH solution to a hot $FeSO_4$ solution followed by filtration of the gelatinous product through a sintered glass funnel - filtration being enhanced by 'celite' filter-aid. A sample of this wet ferrous hydroxide (approx. 8 gm) along with cupric acetate (13 gm), acetic acid (100 ml), and water (20 ml) was stirred under nitrogen at 25° while the hydroperoxide (10 gm) was added dropwise. After the addition, the mixture was stirred for 1 hr. Water was added to dissolve the inorganic salts and solid Na_2CO_3 added to neutralise excess acetic acid. The resultant solution was extracted with ether and the ethereal solution washed with water and dried ($MgSO_4$). Removal of the ether under reduced pressure gave a residual oil which was distilled <u>in vacuo</u> and the product collected was examined by infrared and n.m.r. spectroscopy. An aliquot sample of the product was hydrogenated on a microscale in ethanol over 5% palladium on carbon.

(ii) A mixture of cupric acetate (0.30 gm), ferrous sulphate (0.2 gm), acetic acid (1.0 ml), and water (0.5 ml) was placed in one arm of a U-tube immersed in dry ice/ethanol. When the mixture had completely solidified, further acetic acid (0.5 ml) was added to achieve complete separation of reactants. When the acetic acid layer had frozen, the hydroperoxide (0.25 gm) in acetic acid (0.5 ml) was added and was also allowed to freeze. The U-tube was then evacuated (approx. 5 mm) and sealed. When the tube was gradually warmed the contents melted and the reaction

commenced. The reaction mixture was allowed to stand at approx. 25° with occasional shaking for 1 hr. With the decomposition complete, the empty arm of the U-tube was placed in the dry ice/ethanol and the reaction tube heated in a boiling water-bath until distillation of all volatile constituents from the reaction mixture was complete. The U-tube was then opened and the distillate analysed by vapour-phase chromatography. Only in one reaction (that using 2-methyl-2-hexyl hydroperoxide) was authentic specimens of all products available. However, in the other cases the information obtained from method (i) allowed unambiguous identification of each fraction and the yields of products could thus be accurately estimated.

2-Methyl-2-hexyl hydroperoxide.

The main fraction, b.p. 56-57°/17 mm, obtained by method (i) was shown by microhydrogenation to contain 83% olefinic alcohol and 17% saturated alcohol. The presence of a major constituent containing a terminal methylene group was indicated by a strong absorption at 912 cm^{-1} in the infrared spectrum[144] (compare with authentic 2-methyl-4-hexen-2-ol and 2-methyl-5-hexen-2-ol) and by the presence of a strong resonance signal at τ5.26 in the n.m.r. spectrum.[145] The complete n.m.r. spectrum in $CDCl_3$/CCl_4 solution showed resonance at τ8.88 (singlet) gem-dimethyl protons, τ8.76 (triplet) non-allylic methylene protons, τ7.97 (multiplet) allylic methylene protons, τ6.53 (singlet) hydroxyl proton, τ5.26 (multiplet) terminal olefinic protons, and τ4.52 (weak broad multiplet) non-terminal olefinic proton. Absorption in the infrared at approx. 970 cm^{-1} and resonance in the n.m.r. spectrum at τ8.30 (allylic methyl protons) attri-

butable to an internal ethylenic bond was not detected (refer to authentic compounds). Recrystallisation from light petroleum (b.p. 40-60°) of the crude product formed by treatment of the alcohol with 3,5-dinitrobenzoic acid and toluene-p-sulphonyl chloride in pyridine[140] afforded 2-methyl-5-hexen-2-yl 3,5-dinitrobenzoate as plates, m.p. 54-55° (Found: C, 54.7; H, 5.5; N, 9.1%. $C_{14}H_{16}N_2O_6$ requires C, 54.5; H, 5.2; N, 9.1%). The n.m.r. spectrum of the 3,5-dinitrobenzoate in $CDCl_3/CCl_4$ solution showed resonance at τ 8.35 (singlet integrating for 6 protons) gem-dimethyl protons shifted downfield compared to the alcohol (compare τ 8.88) due to the influence of the aromatic ring, τ 7.92 (a split peak integrating for 4 protons) both allylic and non-allylic methylene protons forming overlapping peak - the latter protons shifted downfield from τ 8.76 due to the influence of the aromatic ring, τ 5.00 (multiplet integrating for 2 protons) terminal olefinic protons, τ 4.10 (weak broad peak integrating for 1 proton) vinylic proton, and τ 0.90 (multiplet) aromatic protons integrating for 3 protons. The olefinic protons showed an identical absorption pattern to the terminal olefinic protons in authentic 2-methyl-5-hexen-2-ol.

The distillate obtained by method (ii) was shown by vapour-phase chromatography on a 15% UCON (polypropylene glycol ester) column (12 ft) to consist of the respective reaction products in the yields listed in Table II (refer to page 53).

2,5-Dimethyl-2-hexyl hydroperoxide.

Microhydrogenation of the distillate from method (i) decomposition indicated the main fraction, b.p. 64-66°/15mm, contained 12% saturated

alcohol and 88% olefinic alcohol. The distillate showed strong absorption at 910 cm^{-1} in the infrared spectrum[144] and strong resonance signals at τ 8.28 and τ 5.34 in the ratio 2 : 1 in the n.m.r. spectrum indicating the major constituent was terminal olefinic alcohol with a low proportion of internal olefinic isomer. The presence of an internal olefinic bond could not be detected by infrared spectroscopy. The complete n.m.r. spectrum in $CDCl_3/CCl_4$ solution showed resonance at τ 8.85 (singlet) gem-dimethyl protons β- to the alcohol group, τ 8.67 (multiplet) non-allylic methylene protons, τ 8.28 (singlet) allylic methyl protons, τ 7.89 (multiplet) allylic methylene protons, τ 7.47 (broad singlet) hydroxyl proton, and τ 5.34 (singlet with slight splitting, possibly due to long range coupling with allylic methylene protons) terminal olefinic methylene protons. Vapour-phase chromatography of the distillate from method (ii) failed to separate completely 2,5-dimethyl-5-hexen-2-ol and 2,5-dimethyl-4-hexen-2-ol. However, it allowed the total yield of unsaturated alcohols to be determined and the yields of the respective products listed in Table II (p.53) could thus be estimated from information obtained by analysing the spectroscopic data of the distillate from method (i).

2-Methyl-2-heptyl hydroperoxide.

The main fraction, b.p. 94-96°/63 mm, obtained from method (i) was shown by microhydrogenation to contain 87% unsaturated alcohol and 13% 2-methylheptan-2-ol. The distillate had a strong absorption band at 968 cm^{-1} in the infrared spectrum.[146] That 2-methyl-5-hepten-2-ol was the major

constituent of the mixture was indicated by a strong resonance signal at τ8.37 in the n.m.r. spectrum, characteristic of allylic methyl protons[147] compared with allylic methylene protons[148] which absorb at τ7.96. Integration indicated the allylic methyl, allylic methylene protons were present in the approximate ratio 3 : 2 as is required for 2-methyl-5-hepten-2-ol to be the major constituent. The complete n.m.r. spectrum of the product in $CDCl_3/CCl_4$ solution showed resonance signals at τ8.85 (singlet) gem-dimethyl protons, τ8.64 (multiplet) non-allylic methylene protons, τ8.37 (multiplet; doublet further split due to long range coupling) allylic methyl protons, τ7.96 (broad multiplet) allylic methylene protons, τ7.50 (broad singlet) hydroxyl proton, and τ4.62 (symmetrical sextet) olefinic protons.

An aliquot of the distillate was ozonised in acetic acid and the resulting ozonides were decomposed reductively with zinc dust.[149] Steam distillation of the reduced product afforded principally acetaldehyde together with a trace of propionaldehyde, both of which were identified by thin-layer chromatography of the 2,4-dinitrophenylhydrazones on aluminium oxide G using cyclohexane-ethyl acetate (10 : 1) as eluant.

Vapour-phase chromatography on 15% UCON (12 ft) column of the distillate from method (ii) showed the products to have been produced in the respective yields listed in Table II (p.53).

2,4,4-Trimethyl-2-pentyl hydroperoxide.

Only method (i) was employed. The distillate, b.p. 50-52°/15 mm,

consisted of principally 2,4,4-trimethylpentan-2-ol, the 3,5-dinitrobenzoate[140] of which crystallised from light petroleum (b.p. 40-60°) as colourless plates, m.p. 88-89° (Found: C, 55.8; H, 6.3; N, 8.4%. Calc. for $C_{15}H_{20}N_2O_6$: C, 55.6; H, 6.2; N, 8.6%).

(4) Cuprous - Ion Catalysed Decomposition of Alkyl Peracetates in Benzene.

2-Methyl-2-hexyl peracetate.

A mixture of 2-methyl-2-hexyl peracetate (10 gm), cuprous bromide (0.1 gm), and benzene (100 ml) was boiled under reflux with stirring for 24 hr. The cooled solution was washed (aqueous $NaHCO_3$) and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure and the residue fractionally distilled. The fraction, b.p. 54°/16 mm, was spectroscopically indistinguishable from the decomposition product of 2-methyl-2-hexyl hydroperoxide. An accurate estimate of the yield was not obtained. However, comparison of the yields of isolated alcohols with the corresponding yields from method (i) decomposition of 2-methyl-2-hexyl hydroperoxide indicated the actual yields of the alcohols, both saturated and unsaturated, were below those from the hydroperoxide decomposition.

When 2,5-dimethyl-2-hexyl peracetate, 2-methyl-2-heptyl peracetate, and 2,4,4-trimethyl-2-pentyl peracetate were each similarly treated with cuprous bromide in benzene, similar results to those obtained from 2-methyl-2-hexyl peracetate were observed.

(5) Attempted Isomerisation of 2-Methyl-4-hexen-2-ol to 2-Methyl-5-hexen-2-ol in Aqueous Acetic Acid with Ferrous Hydroxide and Cupric Acetate.

A mixture of ferrous hydroxide (approx. 0.4 gm), cupric acetate (0.5 gm), acetic acid (15 ml), water (4 ml), and 2-methyl-4-hexen-2-ol (0.2 gm) was stirred at 20° for 1 hr. Excess acetic acid was neutralised with aqueous sodium carbonate and the resultant solution was extracted with ether. The ethereal layer was washed with aqueous sodium bicarbonate, water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a residual liquid which was examined by vapour-phase chromatography, infrared, and n.m.r. spectroscopy. No isomerisation of the 2-methyl-4-hexen-2-ol to 2-methyl-5-hexen-2-ol could be detected.

(6) Attempted Determination of Stability Constants of Complexes of Cuprous Chloride with 2-Methyl-5-hexen-2-ol, and 2-Methyl-4-hexen-2-ol.

The appropriate alcohol (approx. 0.5 gm) was accurately weighed into a flask and dissolved in aqueous acetic acid (1 : 5 vol.) (75 ml) to which was added excess (approx. 0.3 gm) cuprous chloride. The flask was flushed with nitrogen, stoppered, and vigorously shaken at 30°C (thermostat) for 24 hr. An aliquot (50 ml) sample was transferred into a nitrogen filled flask (taking care that undissolved cuprous chloride was not removed), diluted with water (50 ml), and titrated with potassium iodate solution by the method described by Vogel.[150] However, the presence of dissolved

cuprous ion could not be detected in either 2-methyl-5-hexen-2-ol or 2-methyl-4-hexen-2-ol solution.

(7) Formation of a Complex between 2-Methyl-5-hexen-2-ol and Cuprous Chloride.

(i) 2-Methyl-5-hexen-2-ol (1.0 gm) and cuprous chloride (0.1 gm) were heated on a boiling water-bath (5 min). The 2-methyl-5-hexen-2-ol immediately became a brown solution. Carbon tetrachloride (0.5 ml) was added and excess cuprous chloride was carefully filtered off (under suction) and the filtrate cooled in ice. A complex of 2-methyl-5-hexen-2-ol and cuprous chloride precipitated out and recrystallised from 2-methyl-5-hexen-2-ol/carbon tetrachloride solution as colourless fibres, m.p. 89-90° (decomposition to a liquid and inorganic solid) (Found: C, 41.8; H, 7.6; Cl, 13.6%. $C_7H_{14}ClCuO$ requires C, 39.4; H, 6.6; Cl, 16.7%). The presence of copper in such a product was shown by pyrolysis (leaves an inorganic ash) and by warming the compound in water and adding aqueous ammonia solution (a blue solution resulted). Attempts to recrystallise the compound from various organic solvents were generally unsuccessful due to its insolubility - the only result from such attempts was partial decomposition affording a more impure product. Absorption bands in the infrared spectrum, characteristic of the O-H and C=C bonds in 2-methyl-5-hexen-2-ol, were found to be shifted to lower wave numbers in the cuprous chloride complex; the strong O-H absorption at 3360 cm^{-1} shifted to 3305 cm^{-1}, the medium olefinic C-H

absorption at 3070 cm^{-1} shifted to a weak band at 3010 cm^{-1}, and the medium C=C band at 1645 cm^{-1} shifted to a very weak band at 1553 cm^{-1}. A small amount of uncomplexed 2-methyl-5-hexen-2-ol remained as impurity in the complex (identified by normal O-H, $C{=}C\overset{H}{\diagup}$, and C=C bands in the infrared). Such an impurity would account for the high C,H, and low Cl analysis figures and its presence is probably due to the fact that all the excess 2-methyl-5-hexen-2-ol (used as solvent for recrystallisation) was not removed by drying <u>in vacuo</u> in the presence of P_2O_5.

(ii) The filtered carbon tetrachloride solution of the above preparation was tested for the presence of dissolved copper complex by shaking with an aqueous ammonia solution - a blue aqueous solution was obtained which indicated the presence of a carbon tetrachloride soluble cuprous chloride/2-methyl-5-hexen-2-ol complex.

(8) <u>Attempted Formation of a Complex between 2-Methyl-4-hexen-2-ol and Cuprous Chloride</u>.

(i) Any attempt to isolate a solid complex analogous to that formed in the previous section failed - warming of the alcohol with cuprous chloride failed to even decolourise the 2-methyl-4-hexen-2-ol compared with the previous example in which similar treatment caused the 2-methyl-5-hexen-2-ol to become a brown solution.

(ii) 2-Methyl-4-hexen-2-ol and cuprous chloride were heated on a boiling water-bath, carbon tetrachloride was added, and the solution was filtered.

By testing the filtrate with aqueous ammonia for the presence of copper, the formation of a dissolved cuprous chloride/2-methyl-4-hexen-2-ol complex was discounted due to the absence of any blue colouration.

(9) Reference Compounds.

2-Methyl-5-hexen-2-ol.

4-Pentenoic acid was obtained by the 'malonic ester synthesis' in which allyl bromide was added to sodium diethyl malonate as is described by Vogel.[151] Hydrolysis and decarboxylation of the resulting ester afforded the 4-pentenoic acid.

Esterification of the 4-pentenoic acid with ethereal diazomethane solution afforded methyl 4-pentenoate which was treated in the usual way with methylmagnesium iodide and gave 2-methyl-5-hexen-2-ol, b.p. 58-59°/17 mm (lit.[152] b.p. 57°/16 mm), $\nu_{max.}$ (film) at 912 cm^{-1} (terminal $>C=CH_2$). The n.m.r. spectrum was identical both in position and nature of the resonance bands to the spectrum of the compound obtained from the method (i) decomposition of 2-methyl-2-hexyl hydroperoxide with ferrous and cupric ions in acetic acid (refer to page 127).

2-Methyl-4-hexen-2-ol.

3-Pentenoic acid was prepared by the reaction of propionaldehyde with malonic acid in triethanolamine.[153] The methyl ester, obtained from treatment of the acid with ethereal diazomethane solution, was treated with ethereal methylmagnesium iodide and gave 2-methyl-4-hexen-2-ol, b.p.

52°/19 mm (lit.[154] b.p. 142-143°), ν_{max} (film) at 970 cm^{-1} (1,2-disubstituted C=C). The n.m.r. spectrum in $CDCl_3/CCl_4$ solution showed resonance at τ 8.83 (singlet) gem-dimethyl protons, τ 8.30 (split doublet) allylic methyl protons, τ 7.93 (multiplet) allylic methylene protons, τ 6.67 (broad singlet) hydroxyl proton, and τ 4.55 (multiplet) olefinic protons.

Hexan-2-one.

Oxidation of hexan-2-ol with chromic acid gave hexan-2-one, b.p. 126° (lit.[141] 128°).

5-Chloro-2-methylhexan-2-ol.

2-Methyl-2-hexyl hypochlorite, which was prepared by adding 2-methylhexan-2-ol in carbon tetrachloride to an aqueous solution of sodium hypochlorite, was added slowly to a refluxing solution of dibenzoyl peroxide (10 mgm) in cyclohexene and the resulting mixture was boiled under reflux for 30 minutes. By following this method of Greene et al.,[143] 5-chloro-2-methylhexan-2-ol was obtained as a colourless liquid, b.p. 79°/10 mm (lit.[143] 78-79°/10 mm).

3. Photolysis of N-Chloro-amides.

(a) Starting Materials.

t-Butyl Hypochlorite.

Chlorine gas was bubbled through a sodium hydroxide solution of t-butyl alcohol maintained at $< 5^{\circ}C$, according to the method of Bell and Teeter.[155] The hypochlorite was not distilled but was stored at 0° over anhydrous $CaCl_2$ in a stoppered vessel surrounded by aluminium foil.

Acid Chlorides.

Butyroyl chloride, Pentanoyl chloride, and 4-Methylpentanoyl chloride were each prepared by heating the appropriate acid (0.1 mole) and thionyl chloride (0.15 mole) under reflux for 2 hr. Removal of excess thionyl chloride by distillation under reduced pressure afforded the crude acid chloride which was converted directly into the appropriate amide.

Primary Aliphatic Amides.

All amides in this section were prepared by the reaction between dry ammonia and the appropriate acid chloride in dry benzene. The solid obtained by removal of the solvent under reduced pressure was continuously extracted with chloroform. Evaporation of the solvent afforded the crude amide which was recrystallised from hexane.

Butyramide was obtained as colourless plates, m.p. 113-114° (lit.[156] 115°).

Pentanamide crystallised as colourless plates, m.p. 104-106° (lit.[156] 105.8°).

4-Methylpentanamide formed as colourless plates, m.p. 118-119° (lit.[157] 120°).

N-Alkylacetamides.

The primary amine (0.1 mole) was slowly added to acetic anhydride (0.15 mole) and the resulting solution was heated under reflux for 2 hr. Excess acetic acid was neutralised with aqueous sodium carbonate solution and the organic layer separated and dried ($MgSO_4$). Distillation under reduced pressure afforded the N-alkylacetamide.

N-Hexylacetamide was obtained as a colourless liquid, b.p. 108°/2 mm (lit.[158] 120-126°/3.2 mm).

N-Butylacetamide distilled as a colourless liquid, b.p. 89°/2.5 mm (lit.[159] 132-139°/18 mm).

N-(2-Methylpropyl)acetamide was obtained as a colourless liquid, b.p. 96°/3.0 mm.

The above acetamides showed characteristic absorption in the infrared, ν_{max} (film) at 1650 cm^{-1} (C=O) and bands at 3281 cm^{-1} and 3072 cm^{-1} (N-H).

N-Chloro-amides.

The method of Beckwith and Goodrich[75] was used in which the amide (0.1 mole) was dissolved in chloroform (100 ml) after which bromine (0.2 ml) and t-butyl hypochlorite (0.14 mole) were added. The reaction mixture

immediately decolourised and was allowed to stand at room temperature until the bromine colour reappeared.* Removal of the chloroform and t-butyl alcohol by distillation in vacuo afforded the N-chloro-amide as a viscous oil which was used without further purification. The purity of the N-chloro-amide was determined by the modified method of Tobolsky and Mesrobian.[138] [The modified procedure was the same as that used for the estimation of the purity of the alkyl hydroperoxides (refer to page 121)].

* With the primary alkyl amides, the time required for complete conversion to N-chloro-amide was approximately 1 hour. For complete conversion of N-alkylacetamides to the corresponding N-chloro-acetamides, approximately 24 hours were necessary.

N-Chlorobutyramide, N-chloropentanamide, and N-chloro-4-methylpentanamide were obtained as colourless viscous liquids with a purity of $>$ 94%.

Each of the above N-chloro-amides showed characteristic absorption in the infrared; ν_{max} (film) at 1701 cm^{-1} (C=O) and a weaker band at 3400 cm^{-1} (N-H). [cf. For primary amides, absorption in the infrared occurred at ν_{max} (CH_2Cl_2) 1678 cm^{-1} (C=O) and weaker bands at 3410 cm^{-1} and 3530 cm^{-1} (NH_2)].

N-Chloro-N-hexylacetamide, N-butyl-N-chloro-acetamide, and N-chloro-N-(2-methylpropyl)acetamide were obtained as pale yellow viscous liquids with a purity of $>$ 95%.

Each of these N-chloro-acetamides showed absorption in the infrared, ν_{max} (film) at 1680 cm^{-1} (C=O). [cf. For the N-alkylacetamides, ν_{max}

(film) at 1650 cm^{-1} (C=O)].

Alkyl carbamates.

Both iso-butyl carbamate and t-butyl carbamate were prepared by the method of Loev[160] in which trifluoracetic acid (21 ml) was slowly added to a slowly stirred suspension of sodium cyanate (17.5 gm) in the appropriate alcohol (10 gm) and benzene (20 ml).

iso-Butyl carbamate crystallised from hexane as colourless prisms, m.p. 63-65° (lit.[161] 65-66°).

t-Butyl carbamate was obtained from hexane as colourless prisms, m.p. 107-108° (lit.[162] 108-108.5°).

Alkyl N-chlorocarbamates.

The alkyl N-chlorocarbamates were prepared by an analogous method to that used to obtain the N-chloro-amides (refer to page 138) with the slight modification in the time required for the complete conversion of the alkyl carbamate to the alkyl N-chlorocarbamate (15 hr). Removal of the chloroform and t-butyl alcohol afforded the alkyl N-chlorocarbamate as a viscous liquid which was used without further purification.

The purity of the alkyl N-chlorocarbamate was determined by the same modified method of Tobolsky and Mesrobian[138] as was used for the estimation of the purity of the alkyl hydroperoxides and N-chloro-amides (refer to page 121).

iso-Butyl-N-chlorocarbamate and t-butyl N-chlorocarbamate were obtained as colourless viscous liquids with a purity of 95%.

Both alkyl N-chlorocarbamates showed characteristic absorption bands in the infrared, ν_{max} (CH_2Cl_2) at 1754 cm^{-1} (C=O) and a weaker band at 3383 cm^{-1} (N-H). [cf. For the primary alkyl carbamates, ν_{max} (CH_2Cl_2) at 1726 cm^{-1} (C=O) and weaker absorption at 3428 cm^{-1} and 3540 cm^{-1} (NH_2)].

Dibutyramidomercury.

The method of Lutsenko and Tyuleneva[163] was used in which a benzene solution of butyramide and mercuric oxide was boiled under reflux. Dibutyramidomercury was obtained as colourless needles, m.p. 150-152° (lit.[163] 152-153°) by recrystallisation from ethanol, ν_{max} (nujol) at 1580 cm^{-1} (C=O) and 3240 cm^{-1} (N-H).

(b) Photolysis of Primary N-Chloro-amides.

(i) N-Chlorobutyramide.

The N-chloro-amide (2.85 gm) in dichloromethane (50 ml) was irradiated at 20° with a high pressure mercury discharge lamp until a sample of the solution failed to liberate iodine when added to an aqueous acetic acid solution of potassium iodide. Approximately 3 hr of irradiation was necessary. The solvent was removed under reduced pressure leaving an oily solid (2.7 gm) which was shown by infrared spectroscopy to consist of mainly primary amide. The crude product (2.7 gm) was divided into two equal parts and worked up by two different procedures.

(1) Trituration of the crude product (1.35 gm) with ether afforded a colourless solid (0.9 gm) which was found to be a mixture of butyramide and 4-chlorobutyramide. Infrared spectroscopy showed ν_{max} (CH_2Cl_2) at 1679 cm^{-1} (C=O) and weaker bands at 3411 cm^{-1} and 3530 cm^{-1} (NH_2) indicating the presence of primary amide. The presence of chlorine was indicated by analysis. A sample of the mixture (0.4 gm) was hydrolysed in a boiling solution of KOH (1.0 gm) in ethanol (5 ml) and water (5 ml) for 3 hr. After most of the ethanol had been removed by distillation the solution was acidified with dilute hydrochloric acid and continuously extracted with ether for 24 hr. The ether was removed and the residue was analysed by vapour-phase chromatography (v.p.c.) which showed the presence of butyric acid and γ-butyrolactone in the ratio 1.2 : 1. The ratio of butyramide and 4-chlorobutyramide in the mixture was thus assumed to be 1.2 : 1. The overall yield of 4-chlorobutyramide from the photolysis was thus estimated as 34%.

Separation of the butyramide and 4-chlorobutyramide was achieved by thin-layer chromatography on Kieselgel HF254 with tetrahydrofuran as liquid phase. To obtain satisfactory quantities of the separated amides, an extended thin-film of amide mixture was deposited out of chloroform solution onto a wide plate. Following elution with tetrahydrofuran, the solvent was allowed to evaporate and the separate amide bands were visualised by standing the plate in an iodine tank. The separate amide bands were scraped off and extracted from the adsorbant with chloroform. Removal of the solvent and recrystallisation from benzene afforded colourless crystals of butyramide, m.p. 112-114° (lit.[156] 115°), and 4-chlorobutyramide

m.p. 99-100° (lit.[164] 99-100°). Complete separation was verified by comparison of the products with the authentic compounds (v.p.c. using a 6 ft. silicon column at 200°, m.p. and m.m.p.). However, this method did not lend itself to accurate estimation of the amide yields.

(2) Hydrolysis of the crude oily solid (1.35 gm) by the same method used to hydrolyse the amide mixture in (1) above was used. Analysis of the resulting residue by v.p.c. indicated that the total yield of butyramide and 4-chlorobutyramide was 40% and 38% respectively indicating that only a very low amount of cyclisation of 4-chlorobutyramide occurs during the reaction.

(ii) N-Chloropentanamide.

A solution of the N- chloro-amide (3.08 gm) in dichloromethane (50 ml) was irradiated at 20° as in the previous photolysis until no active chlorine could be detected (2½ hr). The oily solid (2.9 gm) obtained as the crude reaction product was repeatedly triturated with ether and afforded a colourless solid (2.1 gm) which crystallised from benzene as colourless plates. Infrared spectroscopy, ν_{max} (CH_2Cl_2) at 1680 cm^{-1} (C=O) and weaker bands at 3410 cm^{-1} and 3530 cm^{-1} (NH_2), and analysis indicated the solid was a mixture of pentanamide and 4-chloropentanamide. The amide mixture was hydrolysed by boiling an aqueous-ethanolic potassium hydroxide solution under reflux as in the previous experiment. Gas chromatography of the residual oil indicated the presence of pentanoic acid and γ-valerolactone

in the ratio 1.3:1 indicating that the amide mixture consisted of pentanamide and 4-chloropentanamide in the ratio 1.3:1. The yield of 4-chloropentanamide was thus estimated at 35%.

(iii) N-Chloro-4-methylpentanamide.

The N-chloro-amide (2.1 gm) in dichloromethane (50 ml) was irradiated by the method described previously and thus afforded the crude reaction product as an oily solid (1.95 gm). Trituration with ether gave a colourless solid (1.7 gm) which was shown by infrared spectroscopy and analysis to be a mixture of 4-methylpentanamide and 4-chloro-4-methylpentanamide. Hydrolysis of the mixture by the method described previously afforded a residue which was shown by v.p.c. to be a mixture of 4-methylpentanoic acid and 4,4-dimethyl-γ-butyrolactone in the ratio of 1:1.3. The yield of 4-chloro-4-methylpentanamide was thus estimated as 51%.

(c) Photolysis of Dibutyramidomercury.

A solution of the dibutyramidomercury (2.5 gm) in t-butyl alcohol (50 ml) was irradiated at 40° with a high pressure mercury discharge lamp for 24 hr. A small quantity of mercury was formed. However, removal of the solvent under reduced pressure afforded unchanged starting material contaminated with a trace of butyric acid.

The above experiment was repeated by photolysis in sunlight for 1 week. However, similar results were again obtained.

(d) Photolysis of Alkyl N-chlorocarbamates.

(i) t-Butyl N-chlorocarbamate.

The N-chlorocarbamate (2.4 gm) in benzene (50 ml) was irradiated at 30° with a high pressure mercury discharge lamp until a sample of the solution failed to liberate iodine when added to an aqueous acetic acid solution of potassium iodide (12 hr). By removing the solvent under reduced pressure, the reaction solution afforded an orange oily solid (2.5 gm) which recrystallised from hexane as a colourless solid (1.45 gm). Infrared spectroscopy showed absorption at 1726 cm^{-1} (C=O) and 3427 cm^{-1}, 3540 cm^{-1} (NH_2) characteristic of alkyl carbamates (refer to page 141). Analysis indicated the presence of chlorine from which it was deduced that the product was a mixture of t-butyl carbamate and 2-chloro-1,1-dimethylethyl carbamate. Nuclear magnetic resonance (n.m.r.) spectroscopy verified this assumption and indicated the respective compounds were present in the ratio of 3:1. The n.m.r. showed resonance at τ 8.57 (singlet) methyl protons of t-butyl carbamate, τ 8.49 (singlet) methyl protons of the 2-chloro-carbamate (the shift[165] being due to the influence of the chlorine on the γ-carbon atom), τ 6.21 (singlet) methylene protons of the chloromethyl group[166] in the 2-chloro-carbamate, and τ 5.11 (broad peak) amide protons. Comparison with analogous examples[165,166] verified the position of resonance for the protons in the 2-chloro-carbamate. From the amount of carbamate mixture obtained (1.45 gm) and from the proportion of 2-chloro-carbamate in the mixture (estimated from integration of n.m.r. spectrum), the yield of 2-chloro-1,1-dimethylethyl carbamate was estimated at 18%. Separation of

the mixture into the two components was not attempted although it is anticipated that a method analogous to that used for the isolation of 4-chlorobutyramide (refer to page 142) would be successful.

(ii) iso-Butyl N-chlorocarbamate.

The N-chlorocarbamate (2.0 gm) in benzene (50 ml) was photolysed and worked up by the same procedure described in the previous experiment. The crude oily solid (2.1 gm) crystallised from hexane as a colourless solid (1.45 gm) which was shown by infrared spectroscopy and analysis to consist of primary alkyl carbamate and chlorine. N.m.r. spectroscopy indicated that the solid was a mixture of iso-butyl carbamate and 2-chloro-2-methylpropyl carbamate in the ratio 2.3:1. The n.m.r. spectrum of the solid in $CCl_4/CDCl_3$ solution showed resonance characteristic of iso-butyl carbamate at τ 9.07 (doublet with coupling constant 6.5 c/s) methyl protons coupled with adjacent methyne proton, τ 8.13 (multiplet with coupling constant 6.5 c/s) methyne proton coupled with adjacent methyl and methylene protons, and τ 6.19 (doublet with coupling constant 6.5 c/s) methylene protons adjacent to oxygen atom and coupled with adjacent methyne proton, in the ratio 6:1:2. Resonance peaks characteristic of 2-chloro-2-methylpropyl carbamate appeared at τ 8.43 (singlet) methyl protons shifted downfield by the influence of the chlorine on the β-carbon atom, and τ 5.86 (singlet) methylene protons adjacent to the oxygen atom and shifted further downfield by the influence of the chlorine atom on the β-carbon atom. Such peaks integrated in the ratio 6:2. Resonance at τ 4.69 (broad peak) characteristic of amide protons in both iso-butyl carbamate and 2-chloro-2-

methylpropyl carbamate was also present. The positions of resonance for the protons in 2-chloro-2-methylpropyl carbamate are supported by analogous examples.[165] An estimate from the amount of solid (1.45 gm) and the proportion of 2-chloro-carbamate in the mixture indicated that 2-chloro-2-methylpropyl carbamate was formed in 26% yield.

(e) Photolysis of N-Alkyl-N-chloro-acetamides.

(i) N-Butyl-N-chloro-acetamide.

The N-chloro-amide (5.2 gm) in dichloromethane (75 ml) was photolysed by the same method described in the previous experiments until no active chlorine could be detected (8 hours). Evaporation of the solvent afforded a crude liquid which was distilled under reduced pressure and thus gave a colourless viscous liquid (4.3 gm) which boiled over the range 100-135°/0.6 mm. A black tarry residue remained in the distillation flask. Infrared spectroscopy, ν_{max} (film) at 1649 cm^{-1} (C=O) and bands at 3280 cm^{-1} and 3072 cm^{-1} (N-H), and analysis indicated that N-butylacetamide and chlorine were present in the distilled reaction product. N.m.r. spectroscopy indicated that the product was a mixture of N-butylacetamide and N-(4-chlorobutyl)acetamide in the ratio 2.2:1. The n.m.r. spectrum showed resonance at τ 8.08 (singlet) acetyl methyl protons of both components, τ 6.83 (broad peak) methylene protons adjacent to the amide nitrogen atom in both components, τ 6.03 (a multiplet partially overlapping with the previous broad peak) methylene protons of the chloromethyl group in N-(4-chlorobutyl)acetamide, τ 1.8 (broad peak which disappears when the spectrum is run with deuterium exchange) amide proton of both components, and a mass

of peaks at approximately τ8.45 (methylene protons in both components). From the estimated proportion of chloro-acetamide in the mixture and the amount of mixture obtained, the yield of N-(4-chlorobutyl)acetamide was found to be approximately 31%. The presence of N-(4-chlorobutyl)acetamide in the distilled reaction product was verified by alkaline hydrolysis - gas chromatography of the distilled hydrolysis product indicated the presence of pyrrolidine.

N-Chloro-N-hexylacetamide.

The N-chloro-amide (5.6 gm) in dichloromethane (75 ml) was photolysed by the same procedure as has been described previously until no active chlorine could be detected (9 hours). Distillation of the crude reaction product *in vacuo* afforded a colourless viscous liquid (5.2 gm) which boiled over the range 130-160°/0.6 mm. Infrared spectroscopy and analysis indicated the presence of N-hexylacetamide and chlorine. The n.m.r. spectrum of the distilled reaction product in $CCl_4/CDCl_3$ solution showed resonance at τ8.6 (mass of peaks over a range, attributed to unsubstituted methyl and methylene protons), τ8.07 (singlet) acetyl methyl protons, τ6.82 (broad peak) methylene protons adjacent to the amide nitrogen atom, τ6.00 (multiplet) methyne proton[167] attached to the carbon atom α- to the chlorine in N-(4-chlorohexyl)acetamide, and τ2.5 (broad peak) amide proton. The n.m.r. spectrum indicated that the reaction product was a mixture of N-hexylacetamide and N-(4-chlorohexyl)acetamide in the ratio 3:1 from which the yield of N-(4-chlorohexyl)acetamide was estimated to be approximately 27%.

Gas-phase chromatography of the distilled product obtained from the alkaline hydrolysis of the purified reaction product showed the presence of 2-ethylpyrrolidine.

N-(iso-Butyl)-N-chloro-acetamide.

Irradiation of the N-chloro-amide (4.1 gm) in dichloromethane (50 ml) for 7 hours by the same method described previously and distillation of the crude reaction product afforded a colourless viscous liquid (3.4 gm) which boiled over the range 95-130°/0.6 mm. A dark tarry residue remained in the distillation flask. Infrared spectroscopy and analysis indicated the presence of N-(iso-butyl)acetamide and chlorine. The n.m.r. spectrum showed resonance absorption attributed to N-(iso-butyl)acetamide at τ 9.07 (doublet with the coupling constant 6 c/s) methyl protons coupled with the adjacent methyne proton, τ 8.4 (multiplet) methyne proton coupled with adjacent methyl and methylene protons, τ 7.95 (singlet) acetyl methyl proton, τ 6.87 (broad peak which collapses to a doublet with the coupling constant 6 c/s when the spectrum is carried out with deuterium exchange) methylene protons adjacent to the amide nitrogen atom, and τ 1.67 (broad peak which disappears when the spectrum is run with deuterium exchange) amide proton. Resonance attributed to N-(2-chloro-2-methylpropyl)acetamide occurred at τ 8.42 (singlet) methyl protons shifted downfield from the normal methyl frequency (τ 9.07) by the influence of the chlorine atom on the β-carbon atom,[165] and τ 6.48 (broad peak which collapses to a singlet when the spectrum is run with deuterium exchange) methylene protons adjacent to the amide nitrogen

atom and shifted downfield from τ 6.87 by the influence of the chlorine atom on the β-carbon atom. Resonance due to the acetyl methyl protons and the amide proton occurred at τ 7.95 and 1.67 respectively - as for the N-(iso-butyl)acetamide. Integration of the spectrum indicated that the two amides were present in the ratio 5:3 respectively from which the yield of N-(2-chloro-2-methylpropyl)acetamide was estimated to be 36%.

(f) Reference Compounds.

4-Chlorobutyramide was obtained via 4-chlorobutyroyl chloride which was prepared by heating γ-butyrolactone and thionyl chloride under reflux according to the method of Reppe.[168] Conversion of the crude acid chloride to the amide was achieved by passing dry ammonia through a benzene solution of the acid chloride (refer to page 137). 4-Chlorobutyramide recrystallised from benzene as colourless needles, m.p. 99-100° (lit.[164] 99-100°).

4. Reaction of Lead Tetra-acetate with Primary Amides.

(a) Starting Materials.

Lead Tetra-acetate was kept over potassium hydroxide pellets and phosphorous pentoxide in a vacuum desiccator.

Acid Chlorides.

Pentanoyl chloride, hexanoyl chloride, cyclohexanecarboxylic acid chloride, stearoyl chloride, and dec-9-enylcarboxylic acid chloride were each prepared by the method described previously (refer to page 137).

Cholanic acid chloride.

Oxalyl chloride (6 ml) was added to a dry benzene (25 ml) solution of cholanic acid (5 gm) and the solution was allowed to stand at room temperature for 1 hour after which it was heated under reflux (1 hr). The benzene and excess oxalyl chloride were removed under reduced pressure and the crude acid chloride converted directly into 5β-cholanamide.

Primary Aliphatic Amides.

Pentanamide and hexanamide were both prepared by the method described previously (refer to page 137).

Cyclohexanecarboxamide, stearamide, and dec-9-enylcarboxamide were prepared by the dropwise addition of the appropriate acid chloride to an aqueous ammonia solution (sp.gr. 0.88) with cooling (0°) and vigorous shaking. The precipitated amide was filtered, washed with water, dried, and recrystallised.

Cholanamide was prepared by an analogous method to that described previously with the modification that the cholanic acid chloride was dissolved in benzene before addition to the aqueous ammonia. Cholanamide crystallised from methanol as colourless needles, m.p. 188-189° (lit.[169] 189°).

Pentanamide crystallised from hexane as colourless plates, m.p. 104-106° (lit.[156] 105.8°).

Hexanamide was obtained by recrystallisation from hexane as colourless plates, m.p. 97-98° (lit.[156] 101°).

Cyclohexanecarboxamide crystallised from water as colourless plates, m.p. 182-183° (lit.[170] 184°).

Stearamide crystallised from benzene as colourless plates, m.p. 107-108° (lit.[171] 108.5-109°).

Dec-9-enylcarboxamide crystallised from water as colourless plates, m.p. 86-87° (lit.[172] 87°).

(b) Reactions involving Lead Tetra-acetate.

Reaction of Pentanamide with Lead Tetra-acetate.

Lead tetra-acetate (22.5 gm) was added to pentanamide (5 gm) in benzene (100 ml) and the resulting solution immediately turned light yellow. The solution was stirred and boiled under reflux at 80° until (3 hr) a sample of the reaction mixture failed to give a brown precipitate of lead dioxide upon addition of water. At this point the yellow reaction mixture

had changed to a clear colourless solution. After allowing to cool, the solution was washed with aqueous 10% $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent by distillation under reduced pressure afforded a yellow oil (4.5 gm) which was fractionally distilled and gave N-butylacetamide (2.6 gm, 45%), b.p. 86°/1.8 mm (lit.[159] 132-139°/18 mm). The N-butylacetamide was positively identified by comparison of the n.m.r. and infrared spectra of the product with those of the authentically prepared compound. The infrared spectrum showed ν_{max} (film) at 1649 cm^{-1} (C=O) as well as N-H bands at 3280 cm^{-1} (strong) and 3072 cm^{-1} (medium) (compare with authentic compound, page138). The n.m.r. spectrum in $CDCl_3/CCl_4$ solution showed resonance at τ 9.06 (triplet) three methyl protons coupled with adjacent methylene protons, τ 8.57 (multiplet) four methylene protons, τ 8.04 (singlet) three acetyl methyl protons, τ 6.82 (broad multiplet) two methylene protons adjacent to the amide nitrogen atom, and τ 3.26 (broad peak) one amide proton.

Trituration of the brown residue (1.1 gm) with petroleum ether (b.p. 40-60°) gave no solid residue. Chromatography of the brown residue on silica gel (10 gm) with benzene as eluant gave a yellow viscous oil which was triturated with petroleum ether (b.p. 40-60°) and afforded N,N'-dibutylurea (0.2 gm, 5%) as a colourless amorphous solid which recrystallised from acetone as a colourless powder, m.p. 66-68° (lit.[173] 70.5-71°). The infrared spectrum showed a single N-H stretching absorption at 3319 cm^{-1} and ν_{max} (nujol) at 1621 cm^{-1} (C=O) (compare with N,N'-dipentylurea, refer to page 154).

Reaction of Hexanamide with Lead Tetra-acetate.

The yellow solution of hexanamide (5 gm) and lead tetra-acetate (19.5 gm) in benzene (100 ml) was stirred and heated under reflux until the colour had disappeared and all lead (IV) had been converted to lead (II) (4 hr). The procedure for working up the reaction product was the same as was used in the previous experiment. Fractional distillation of the crude oil (4.4 gm) afforded N-pentylacetamide (2.25 gm, 40%), b.p. 114°/3.0 mm (lit.[174] 110-112°/2.0 mm) which showed absorption in the infrared due to N-H stretching vibrations at 3281 cm^{-1} (strong) and 3072 cm^{-1} (medium) and ν_{max} (film) at 1650 cm^{-1} (C=O), characteristic of N-alkyl-acetamide compounds (refer to page 138). The n.m.r. spectrum in $CDCl_3$/CCl_4 solution showed resonance at τ9.1 (triplet) three methyl protons, τ8.66 (multiplet) six methylene protons, τ8.10 (singlet) three acetyl methyl protons, τ6.89 (broad multiplet) two methylene protons adjacent to the amide nitrogen atom, and τ2.24 (broad peak) one amide proton.

The brown residue was treated in a similar manner to the previous experiment and yielded N,N'-dipentylurea (0.2 gm, 5%) which crystallised from acetone as a colourless powder, m.p. 86-87° (lit.[173] 92.8°) (Found: C, 65.5; H, 12.0; N, 14.4; O, 8.0%. Calc. for $C_{11}H_{24}N_2O$: C, 65.95; H, 12.1; N, 14.0; O, 8.0%), ν_{max} (nujol) at 1622 cm^{-1} (C=O) and 3319 cm^{-1} (N-H) in the infrared. The n.m.r. spectrum in $CDCl_3/CCl_4$ solution showed absorption at τ9.1 (triplet) six methyl protons, τ8.67 (multiplet) twelve methylene protons, τ6.88 (broad multiplet) four methylene protons adjacent to the amide nitrogen atoms and τ4.12 (broad peak) two amide-type protons.

Reaction of Cyclohexanecarboxamide with Lead Tetra-acetate.

(i) Lead tetra-acetate (11.5 gm) was added to a benzene (200 ml) solution of cyclohexanecarboxamide (3.0 gm) and the resultant deep yellow solution stirred and boiled under reflux until all lead tetra-acetate had reacted (12 hr). Aqueous sodium bicarbonate solution was added and the resulting two-phase solution filtered. The benzene layer was separated, washed with $NaHCO_3$ solution, water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded an oily solid (2.1 gm) which showed a strong absorption at 2268 cm^{-1} in the infrared, characteristic of aliphatic isocyanates.[115] Attempts to isolate the actual isocyanate were unsuccessful.

(ii) Lead tetra-acetate (8.0 gm) was added to a solution of cyclohexanecarboxamide (1.95 gm) in benzene (150 ml) and the resulting deep yellow solution stirred and boiled under reflux for 12 hours. Acetic acid (25 ml) was then added and the solution heated under reflux for a further 5 hours. Excess acetic acid was neutralised with saturated sodium carbonate solution after which the benzene layer was separated and the aqueous layer extracted with benzene. The combined benzene solutions were dried ($MgSO_4$) and the solvent was removed *in vacuo* leaving a colourless solid (1.9 gm) which did not show any absorption at 2268 cm^{-1} in the infrared. The powdered solid was repeatedly triturated with cold acetone leaving *N,N'*-dicyclohexylurea as a colourless solid (0.14 gm, 8%) which crystallised from acetone as a colourless powder, m.p. 230-231° (lit.[175] 229-230°) (Found: C, 70.3; H, 11.0; N, 11.9%. Calc. for $C_{13}H_{24}N_2O$:

C, 69.6; H, 10.8; N, 12.5%), ν_{max} (nujol) at 1625 cm^{-1} (C=O) and 3311 cm^{-1} (N-H).

Evaporation of the acetone solution from the trituration gave crude N-cyclohexylacetamide which crystallised from hexane as colourless needles (1.4 gm, 65%), m.p. 102-104° (lit.[159] 105-106°), ν_{max} (nujol) at 1640 cm^{-1} (C=O) and N-H absorption at 3278 cm^{-1} (strong), and 3072 cm^{-1} (medium).

Reaction of Stearamide with Lead Tetra-acetate.

Lead tetra-acetate (9.5 gm) was added to a solution of stearamide (5.0 gm) in benzene (200 ml) and the resulting reddish-brown solution was stirred and boiled under reflux for 24 hours. Acetic acid (30 ml) was added and the solution heated under reflux for a further 18 hours. The colourless solution was worked up by the same procedure as was described in the previous experiment. The crude reaction product (5.0 gm) was ground to a powder and repeatedly triturated with cold acetone, leaving N,N'-diheptadecylurea which crystallised from methanol as a colourless amorphous solid (0.5 gm, 9%), m.p. 108-109° (Found: C, 78.0; H, 13.5; N, 5.4%. $C_{35}H_{72}N_2O$ requires C, 78.3; H, 13.5; N, 5.2%), ν_{max} (nujol) at 1623 cm^{-1} (C=O) and 3315 cm^{-1} (N-H).

Evaporation of the acetone solution afforded crude N-heptadecylacetamide which recrystallised from hexane as colourless needles (3.1 gm, 61%), m.p. 69-70° (lit.[176] 62°) (Found: C, 76.7; H, 13.2; N, 4.7%. Calc. for $C_{19}H_{39}NO$: C, 76.7; H, 13.2; N, 4.7%), ν_{max} (nujol) at 1638 cm^{-1} (C=O) and N-H absorption at 3261 cm^{-1} (strong) and 3079 cm^{-1} (medium) in the infrared. The n.m.r. spectrum in $CDCl_3/CCl_4$ solution showed resonance at

τ 9.13 (triplet) three methyl protons, τ 8.73 (broad multiplet) thirty methylene protons, τ 8.06 (singlet) three acetyl methyl protons, τ 6.84 (broad multiplet) two methylene protons adjacent to the amide nitrogen atom, and τ 2.91 (broad peak) one amide proton.

Reaction of Benzamide with Lead Tetra-acetate.

Benzamide (6.0 gm) and lead tetra-acetate (22 gm) were dissolved in benzene (125 ml) and the resulting deep orange solution was boiled under reflux. At the end of 2 hours, the colour of the solution had turned dark red. Aqueous $NaHCO_3$ was added and it was noted that no lead dioxide was precipitated. The $NaHCO_3$ - washed benzene layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. A red tarry product was obtained and this was chromatographed on silica gel using benzene as eluant. Unreacted benzamide was thus obtained while the polar red tar remained on the column. However, no acetanilide could be detected.

Reaction of Acetanilide with Lead Tetra-acetate.

Lead tetra-acetate (2.0 gm) was added to a solution of acetanilide (0.5 gm) in benzene (10 ml). The resultant yellow solution rapidly turned deep red when heated under reflux. Addition of water did not afford a brown precipitate indicating that all lead (IV) had been converted to lead (II).

Reaction of Phenyl isocyanate with Lead Tetra-acetate.

Lead tetra-acetate (2 gm) was added to a solution of phenyl iso-

cyanate (0.5 gm) in benzene (10 ml). The solution rapidly turned reddish-brown in colour when boiled under reflux but failed to afford a precipitate of lead dioxide upon addition of water, thus indicating that all lead (IV) had been converted to lead (II).

Attempted Reaction between Lead Tetra-acetate and N-Butylacetamide.

N-Butylacetamide (1.0 gm) and lead tetra-acetate (2 gm) were dissolved in benzene (10 ml) and the resulting solution was heated under reflux for 4 hours. Addition of water afforded a dense brown precipitate of lead dioxide which was removed by suction filtration (aided by celite 'filter-aid'). The benzene solution was washed with sodium carbonate solution, water, and dried ($MgSO_4$). Removal of the solvent afforded unchanged N-butylacetamide, b.p. 88°/1.0 mm, ν_{max} (film) 1649 cm^{-1} (C=O) and N-H absorption at 3280 cm^{-1} and 3072 cm^{-1} in the infrared.

Reaction of Dec-9-enylcarboxamide with Lead Tetra-acetate.

(i) A solution of dec-9-enylcarboxamide (3.0 gm) and lead tetra-acetate (8.0 gm) in benzene (150 ml) was heated under reflux for 20 hours. Acetic acid (30 ml) was added and the solution was boiled for a further 3 hours. The reaction solution was worked up by the method described previously (see page 155). The crude reaction product (3.1 gm) was obtained as an oil which afforded N-dec-9-enylacetamide (1.35 gm, 42%) as a colourless liquid, b.p. 146°/0.9 mm, ν_{max} (film) at 1650 cm^{-1} (C=O) and N-H absorption at 3285 cm^{-1} and 3075 cm^{-1} in the infrared. The presence of a

band at 912 cm^{-1} in the infrared spectrum confirmed the presence of a terminal double bond. Hydrogenation of the distilled product over 5% palladium on carbon in ethanol solution confirmed that the N-dec-9-enylacetamide contained more than 94% unsaturation. Distillation of the hydrogenated product afforded N-decylacetamide as a colourless liquid, b.p. 127°/0.2 mm, ν_{max} (film) at 1650 cm^{-1} (C=O) and N-H absorption at 3285 cm^{-1} and 3075 cm^{-1} in the infrared. No N,N'-didec-9-enylurea could be isolated from the tarry residue.

(ii) The previous experiment was repeated with the modification that the crude reaction product was immediately hydrogenated over 5% palladium on carbon in ethanol solution. Distillation of the hydrogenated product afforded N-decylacetamide (53%), b.p. 166°/4.0 mm. Trituration of the residue with acetone afforded N,N'-didecylurea (3%) which crystallised from acetone as a colourless amorphous solid, m.p. 94-96°, ν_{max} (nujol) at 1625 cm^{-1} (C=O) and 3318 cm^{-1} (N-H).

Reaction of Cholanamide containing one mole of Methanol of crystallisation with Lead Tetra-acetate.

5β-Cholanamide (1.25 gm) which had been recrystallised from methanol and contained one mole of methanol of crystallisation was heated under reflux with lead tetra-acetate (2.0 gm) in benzene (150 ml) for 3 hours. The solution changed from a deep red colour to pale yellow. Acetic acid (25 ml) was added and the resulting solution was heated under reflux for a further 15 hours, after which the cooled benzene solution was washed with

aqueous sodium carbonate solution and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a yellow glassy solid (1.3 gm) which was chromatographed on silica gel (20 gm) using chloroform as eluant.

The first compound to come off the column was methyl N-(24-nor-5β-cholanyl)carbamate as a colourless crystalline solid (0.79 gm, 58%) which crystallised from chloroform-methanol as colourless rosettes, m.p. 185.5-187° (Found: C, 77.0; H, 10.95; N, 3.5%. $C_{25}H_{43}NO_2$ requires C, 77.1; H, 11.1; N, 3.6%), ν_{max} (nujol) at 1720 cm^{-1} (C=O) and 3300 cm^{-1} (N-H), $\alpha_D^{26.5}$ = + 20.5 ($CHCl_3$). The n.m.r. spectrum measured in deuterochloroform solution showed resonance at τ 9.36 and 9.09 (singlets) two sets of methyl protons, τ 8.73 (broad multiplet) thirty-one aliphatic and alicyclic protons, τ 6.83 (broad multiplet) two methylene protons adjacent to the nitrogen atom, τ 6.33 (singlet) three methoxyl protons, and τ 5.43 (broad band) one amide-type proton.

Comparison of m.p., m.m.p., and spectral data of methyl N-(24-nor-5β-cholanyl)carbamate prepared authentically with the reaction product confirmed the identity.

Hydrolysis of methyl N-(24-nor-5β-cholanyl)carbamate (0.4 gm), obtained as the reaction product, in 70% sulphuric acid at 150° for 4 hours afforded a colourless gelatinous solid which was isolated by filtration through a sintered glass funnel. The gelatinous product was heated under reflux with a saturated sodium carbonate solution (4 hours). The filtered and dried product afforded 24-nor-5β-cholanylamine as a colourless amorphous powder, m.p. 95-96° (lit.[177] 95°) upon sublimation.

The second fraction to be eluted from the column was a yellow glassy solid (0.50 gm) which was triturated with methanol and thus afforded N-acetyl-24-nor-5β-cholanylamine (0.43 gm, 33%) as a colourless solid which crystallised from methanol as colourless rosettes, m.p. 175-176° (lit.[177] 177°), ν_{max} (nujol) at 1638 cm^{-1} (C=O) and N-H absorption at 3270 cm^{-1} and 3070 cm^{-1} in the infrared, characteristic of N-alkylacetamides. The n.m.r. spectrum in $CDCl_3$ solution showed resonance at τ 9.37 and 9.10 (singlets) two sets of methyl protons, τ 8.75 (broad multiplet) thirty-one aliphatic and alicyclic protons, τ 8.05 (singlet) three acetyl methyl protons, τ 6.73 (broad multiplet) two methylene protons adjacent to the nitrogen atom, and τ 4.45 (broad band) one amide proton.

Hydrolysis of N-acetyl-24-nor-5β-cholanylamine by an analogous method to that used for the hydrolysis of methyl N-(24-nor-5β-cholanyl)-carbamate likewise afforded 24-nor-5β-cholanylamine.

Reaction of Cholanamide (free of Methanol) with Lead Tetra-acetate.

5β-Cholanamide (0.7 gm), which had been recrystallised from toluene free from methanol, and lead tetra-acetate (1.2 gm) were heated under reflux in a benzene (100 ml) solution for 1 hr. Acetic acid (10 ml) was added and the resulting solution was boiled under reflux for a further 12 hours. The reaction solution was worked up by the method described in the previous experiment. The crude reaction product, obtained as a yellow glassy solid, was triturated with methanol and thus gave N-acetyl-24-nor-5β-cholanylamine

(0.59 gm, 81%) as a colourless solid which crystallised from methanol as colourless rosettes, m.p. 175-176° (lit.[177] 177°), ν_{max} (nujol) at 1639 cm^{-1} (C=O) and N-H bands at 3270 cm^{-1} and 3072 cm^{-1} in the infrared characteristic of N-alkylacetamides.

Reaction of Cholanamide with Lead Tetra-acetate in Methanol.

(i) 5β-Cholanamide (1.0 gm) and lead tetra-acetate (1.6 gm) were dissolved in dry methanol (50 ml) and the resultant solution was heated under reflux for 3 hours. The lead tetra-acetate was rapidly used up. Ethyl acetate (100 ml) and aqueous sodium bicarbonate solution were added to the reaction solution and the two layers separated. The lower aqueous layer was further extracted with ethyl acetate and the combined organic layers then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded crude reaction product which was shown by infrared spectroscopy to consist of mainly unchanged cholanamide together with a very low yield of methyl N-(24-nor-5β-cholanyl)carbamate, identified by the presence of a weak absorption at 1720 cm^{-1} in the infrared.

(ii) A solution of cholanamide (0.6 gm) and lead tetra-acetate (2.0 gm) in benzene (30 ml) and methanol (10 ml) was heated under reflux for 10 hours. During this time, the initial deep red colour of the reaction solution turned colourless. Ethyl acetate was added and the resulting solution was washed with dilute Na_2CO_3 solution and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a yellow solid which was chromatographed on silica gel (10 gm) with chloroform as eluant. Methyl

N-(24-nor-5β-cholanyl)carbamate (0.56 gm, 86%) was the only compound to come off the column. Recrystallisation from chloroform-methanol afforded methyl N-(24-nor-5β-cholanyl)carbamate as colourless rosettes, m.p. 185-186°, ν_{max} (nujol) at 1720 cm^{-1} (C=O) and 3300 cm^{-1} (N-H), identical to the previously identified compound.

Reference Compounds.

Methyl N-(24-nor-5β-cholanyl)carbamate was obtained by the method of Vanghelovici[177] via the Curtius reaction on cholanic acid azide in dry methanol. Methyl N-(24-nor-5β-cholanyl)carbamate crystallised from chloroform-methanol as colourless rosettes, m.p. 185-186°, ν_{max} (nujol) at 1720 cm^{-1} (C=O) and 3300 cm^{-1} (N-H).

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REACTIONS OF ALKOXY RADICALS

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By B. Acott and A. L. J. Beckwith

Acott, B. & Beckwith, A. L. J. (1964). Reactions of alkoxy radicals. IV. Intramolecular hydrogen-atom transfer in the presence of cupric ion: a novel directive effect. *Australian Journal of Chemistry, 17*(12), 1342-1353.

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