



SOME REACTIONS OF CARBOXYLIC
ACIDS AND DERIVATIVES WITH
FREE RADICALS

A THESIS
PRESENTED FOR THE DEGREE OF
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IN THE
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by

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1964

STATEMENT

This thesis contains no material that has previously been submitted for a degree in any University, except where due reference has been made in the text.


J.E. Goodrich

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CHAPTER 1

GENERAL INTRODUCTION

In a molecular system containing a certain functional group, the facility with which a reactant attacks a specific atom is dependent upon a number of factors. The most significant of these are the nature of the attacking species and the substrate, with special emphasis on the type of functional group present. These factors in turn give rise to other important considerations such as the effect of the functional group on the other atoms in the molecule. This may be purely steric or may be electronic in nature, the latter operating through part of the framework of the molecule or through space. Furthermore, the selectivity of reaction will be controlled by the relative ease of formation and breakdown of any intermediate or transition state through which the reaction may operate.

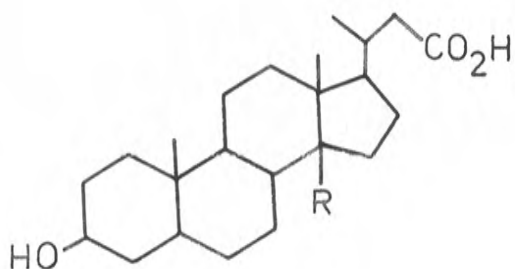
In dealing with the selective introduction of a hydroxyl group - or a radical such as halogen which can give rise to a hydroxyl group after reaction - into a long chain aliphatic acid or derivative, the following general observations can be made. The effect of the functional group will be to promote selective attack by polar reagents in the α -position. Radical attack (e.g. by $\text{Cl}\cdot$) on such a system will not be at all selective due to the second

factor previously mentioned - the energy required for radical attack in this case is approximately the same for any hydrogen-bearing carbon atom in the chain. From the above considerations, it is evident that a first sight none of these reactions appears to be satisfactory for carrying out a selective process at a position more than one carbon atom removed from the functional group, with the eventual formation of a hydroxy acid or lactone.

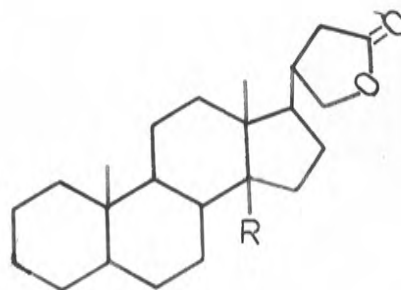
For the investigation of a selective reaction which will be of use in the preparation of the abovementioned compounds, two types of reaction appear to be promising. They are firstly, the selective hydroxylation of tertiary carbon atoms by means of oxy-salts of certain elements, and secondly, the isomerization of radicals by intramolecular hydrogen transfer, where the new radical is capable of reacting with a species such as a halogen radical. The significance of these reactions will become apparent in the following chapters.

There are many reasons why it is highly desirable to selectively attack a saturated position in an aliphatic chain containing a carboxylic acid or derived group to yield a specific hydroxy-acid or lactone. The fields of terpenes and steroids alone provide excellent examples of the utility of such a reaction from the point of view of both synthetic and degradative studies. Thus satisfactory application of such a reaction in the side chain of a norcholanic acid derivative (I) could lead to a general method for the

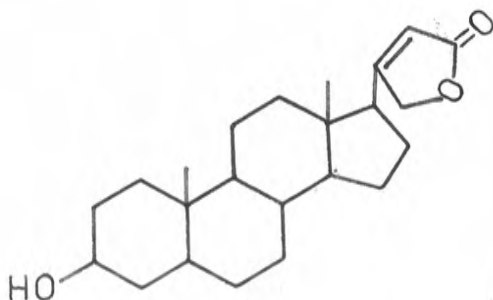
synthesis of the butenolide skeleton (II), the importance of which is reflected in the pharmacological activity of digitoxigenin (III) and digitoxin.



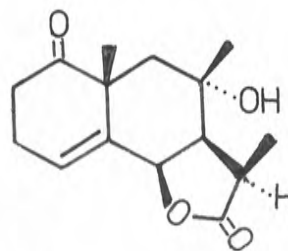
(I)



(II)



(III)

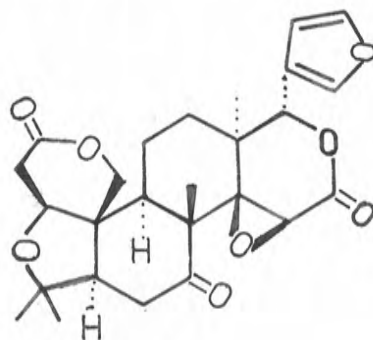


(IV)

The degradation in a single step of the acyclic portion of a fully hydrogenated steroid side chain acid or any steroid e.g. cholesterol, which is capable of being converted into such an acid, is of significance. As yet, no method has been developed for achieving this whilst leaving the steroid nucleus intact. Selective hydroxylation of the side chain at a carbon atom near the nucleus followed by dehydration and oxidation would give two fragments which would

immediately indicate the nature of both nucleus and side chain—a method invaluable in the determination of the structures of new steroids, biogenetic pathways etc. Application of selective hydroxylation to various positions in the steroid nucleus itself, would enable the chemist to carry out in the laboratory, reactions which have hitherto been achieved only with enzymes.

In the terpene series, one has to look no further than the santonins and bitter principles to realize the significance of a selective hydroxylation reaction. Thus the structures of lumisantonin and ψ -santonin (IV) have been elucidated but the molecules themselves have not been synthesized. The knowledge of the structure of certain bitter principles e.g. those obtained from citrus seed oils, has reached varying stages. Thus although limonin (V) has not been synthesized, its structure including the stereochemistry is known, whereas the structures of the closely related substances nomulin and obacunone are known but their stereochemistry is uncertain. The application of selective



(V)

hydroxylation to the acyclic acids from which these compounds are derived, could lead both a correct structural assignation and synthesis.

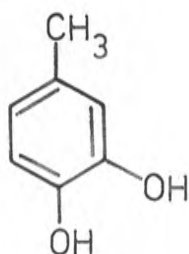
CHAPTER 2

REVIEW OF THE OXIDATION REACTIONS OF
PEROXYDISULPHATES PERMANGANATES AND MANGANATES

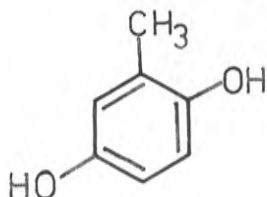
The salts of several oxy-acids incorporating the higher valence states of both sulphur and manganese, show remarkable oxidation properties towards a wide variety of organic and inorganic substrates. In particular, oxidation-reduction systems involving peroxydisulphates, permanganates and to a lesser extent, manganates, have received considerable attention.

The scope of the peroxydisulphate ion oxidation, while smaller than that of reactions involving manganese oxy-salts, is nevertheless sufficiently wide to be of great significance in organic chemistry. It was only five years after the preparation of peroxydisulphuric acid¹ that Elbs² discovered that the action of its salts on monohydric phenols in alkaline solution gave rise to dihydric phenols in the oxidation reaction that now bears his name. It was found that para-hydroxylation was preferred to ortho, unless the former reaction was prevented by the presence of a substituent. Later workers have extended the reaction to aromatic amines,^{3,4} and coumarins,⁵ and have put forward a modified mechanism to explain the anomalous results in the former case.⁶ The reaction of p-cresol is of interest because it demonstrates the versatility of the peroxydisulphate ion.⁷ Oxidation

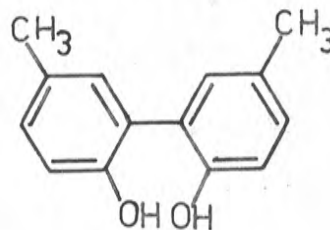
in alkaline solution results in the formation of the normal Elbs product, 3,4-dihydroxytoluene (VI), whereas in acid, the reaction brings about the formation of the rearranged product, 2,5-dihydroxytoluene (VII). In neutral solution 2,2'-dihydroxy-5,5' dimethylbiphenyl (VIII) is produced.⁸



(VI)



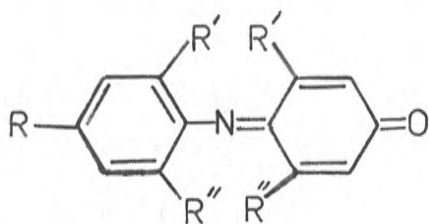
(VII)



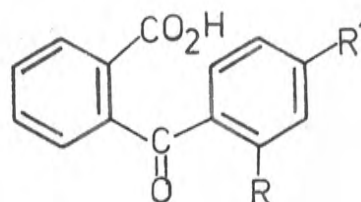
(VIII)

The latter reaction is not general for the action of peroxydisulphates on toluene derivatives as the usual products are bibenzyls,^{9,10} aromatic aldehydes and acids. In addition, both phenylacetic acid^{11,12} and diphenylacetic acid¹¹ have been reported to undergo benzyl hydrogen elimination, followed by dimerization and decarboxylation to give bibenzyl and 1,1,2,2-tetraphenylethane respectively.

The extent of oxidation of compounds containing a nitrogen atom attached to an aromatic ring, is dependent on the nature of the substituent as a whole. Thus nitroaromatic compounds such as picric acid undergo degradation to hydrogen cyanide.¹³ p-Substituted anilines give rise to quinones of Schiff's bases (IX), the stability of which depends on the nature of R, R' and R".^{14,15}



(IX)



(X)

One of the most extensively studied reactions of the peroxydisulphate ion is its effect on various carboxylic acids. Those with one or no C-H bonds such as formic and oxalic acid undergo oxidation to carbon dioxide in accordance with the stoichiometric equations:



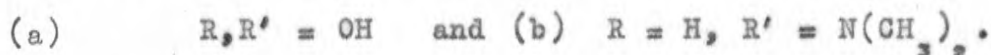
but in fact the reaction is considerably more complex¹⁶ and there is still some doubt as to the exact nature of the oxidations since they are catalysed by certain metallic ions!^{17, 18}

The first study of the oxidation of the lower fatty acids was carried out by Gordon¹⁹ who reported that the action of potassium peroxydisulphate on acetic acid at elevated temperatures gave rise to methane, ethane, unsaturated hydrocarbons and carbon dioxide. This work was extended to a number of aliphatic acids by Fichter and Lapin,²⁰ and the products included saturated and unsaturated hydrocarbons as well as alcohols and esters derived from the acid oxidized. The nature of the products was dependent on the acid used,

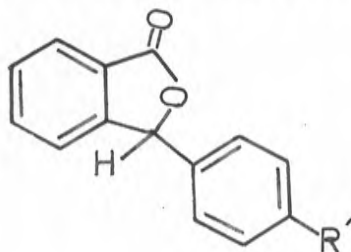
although saturated hydrocarbons were detected in all oxidations. The results were comparable with those of Hofer and Moest²¹ who obtained alcohols from the electrolysis of the salts of the lower fatty acids in the presence of inorganic sulphates. Since previous workers had shown that peroxydisulphates were formed by electrolysis of sulphates, it was considered that the products of oxidation and electrolysis resulted essentially from the same reaction. It was subsequently shown, however, that the reaction could proceed in the absence of sulphates. Thus Fichter and Zumbrunn²² demonstrated that the electrolysis of potassium hexanoate in alkaline solution produced a mixture of n-decane, pentanol, pent-1-ene, pentyl hexanoate and an ether-soluble peroxide. These workers explained the path of the reactions by initial decomposition of the peroxide, followed by elimination of carbon dioxide from the intermediates. The mechanism, although incorrect since it was largely empirical, provided the basis of explanation of peroxydisulphate ion reactions by later workers. Furthermore, subsequent results by Fichter and Suenderhauf,²³ who isolated dimeric acids from oxidation of lower fatty acids, could not be explained by the mechanism, although the similarity between these results and the "dimerizations" of Moritz and Wolffenstein⁹ was recognized.

More recently, Russell and Thomson²⁴ have shown that benzoic acid on treatment with alkaline potassium

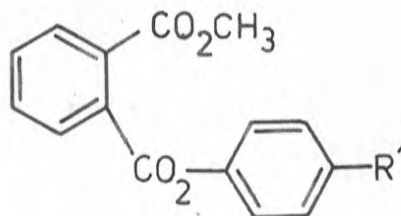
peroxydisulphate gave rise to phenol, biphenyl and biphenyl-4-carboxylic acid. Repetition of the reaction in pyridine resulted in the formation of 2-pyridone, 2,2'-bipyridyl and the three isomeric phenylpyridines in low yields. o-Benzoylbenzoic acids which are theoretically capable of fluorenone formation on decarboxylation followed by intramolecular cyclization, produced the expected products in yields varying from 2-30%, although no reaction of this type was observed with the acid (X) where



The arylations of pyridine find an analogy in electrolytic experiments previously studied. Bunyan and Hey²⁵ were able to isolate 2-pyridone and the three phenylpyridines in the Kolbe electrolysis of benzoic acid in alkaline pyridine after earlier experiments by Fichter and Stenzl²⁶ had indicated the presence of these compounds. On the other hand, similar reaction of a number of p-substituted benzoylbenzoic acids (X, $R = H$)²⁷ yielded substituted 3-phenyl phthalides (XI) and phthalic acid monoesters (XII)



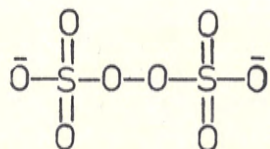
(XI)



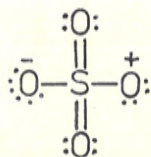
(XII)

rather than fluorenones and only in two cases was direct intramolecular cyclization observed.

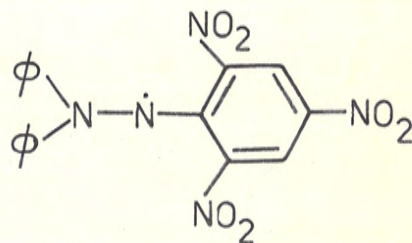
The mechanism of decomposition of solutions of peroxydisulphates at varying pH, both in the presence and absence of oxidizable substrates, has been clarified only since the widespread acceptance of the free radical as a chemical entity. Following the work of Caro²⁸ and Palme,²⁹ three types of peroxydisulphate ion decompositions have been observed. They all involve the breaking of a bond connecting one of the central oxygen atoms of the peroxydisulphate ion (XIII) itself.



(XIII)



(XIV)



(XV)

These may be written stoichiometrically as follows:—

(a) in basic and neutral medium,



(b) in dilute acid medium, both (a) and



(c) in strong acid,



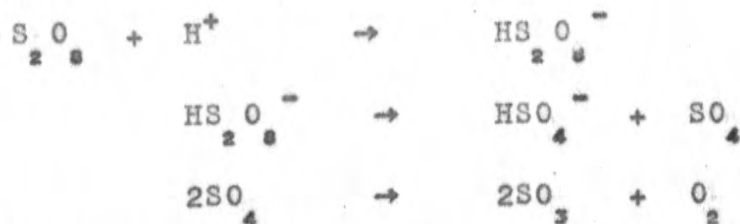
Kolthoff and Miller³⁰ by studying the kinetics of the

decomposition of potassium peroxydisulphate in water enriched with ^{18}O , derived the following mechanism:

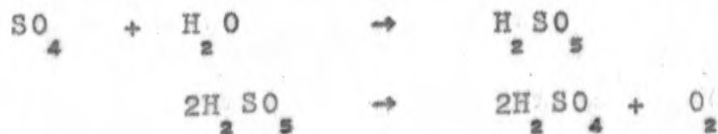
(a) hydrogen ion independent.



(b) hydrogen ion catalysed



(c) if acid of concentration $> 2\text{M}$. is used,



There is considerable disagreement as to the exact nature of path (a) postulated by Kolthoff and Miller. Cotman and Bartlett³¹ consider that a chain mechanism may be operating with

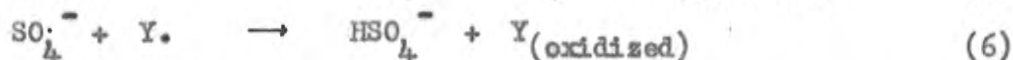
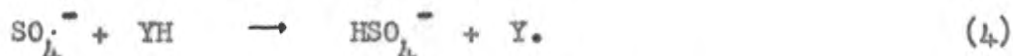
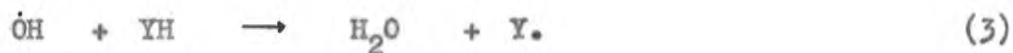
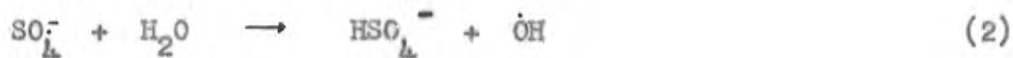


as propagating step. On the other hand Fronaeus and Ostman³² find that the kinetics of decomposition are consistent with a mechanism which involves direct attack by water on the peroxydisulphate ion thus:



Path (b) seems to be open to question from the aspect of postulation of sulphur tetroxide as an intermediate. This entity, if present, will not react with the free radical trap diphenylpicrylhydrazyl (XV),³³ and hence must have the unusual dipolar structure (XIV). Sulphur tetroxide, however, has been postulated as an intermediate in peroxydisulphate ion decompositions in the presence of substrates^{34,35} and although these views have been criticized³⁶ the possibility of the presence of this species cannot be eliminated. Path (c) is thought to be more complex than the original mechanism of Kolthoff and Miller indicates, since hydrogen peroxide is also an intermediate in the decomposition.³⁷

The kinetic studies which have been carried out on reactions between peroxydisulphate ions and organic substrates include those involving amines^{38,39}, amino-alcohols^{40,41} toluenes⁴² alcohols^{31,34-36}, thiols and sulfoxides,⁴³ as well as peroxydisulphate ion induced polymerizations of unsaturated compounds in the presence of thiols.⁴⁴ The results of the above, together with the qualitative results observed in the decomposition of aromatic amines, phenols and carboxylic acids, indicate that while the mechanistic elucidation of such reactions is not complete, certain steps may be regarded as extremely likely to occur. Considering an oxidizable organic substrate YH, the following steps may be written with certainty:



If YH is capable of ready ionization into H^+ and Y^- , the following may also occur:



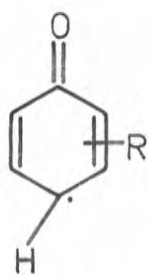
where $Y.$ can break down into a new radical $Y.'$ with elimination of a molecule A.



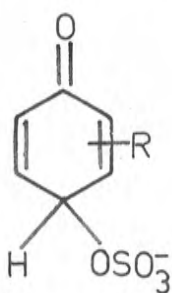
where ArH is an aromatic molecule present in the reaction medium.

The decomposition equation (1) is essential in all peroxydisulphate oxidations. The reactions of lower alcohols

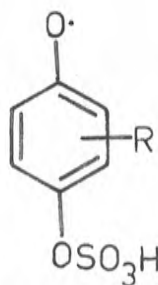
and thiols to give the respective aldehydes, ketones and their thio-analogues (Y_{oxidized}), most certainly involve steps (1-6). It is considered that the Elbs persulphate oxidation takes place via steps (1), (8) and (9). This may be most readily pictured by assuming that the phenoxide ion is oxidized to the phenoxy radical. The p-quinonoid resonance form of the radical (XVI) is attacked by a sulphate anion radical to give the sulphate ester (XVII) which is subsequently oxidized to (XVIII) and hydrolysed to the dihydric phenol (XIX). The alternative mechanism postulated by Baker and Brown⁴⁵ which involves the analagous ionic reaction, seems less likely.



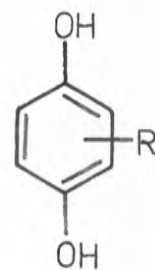
(XVI)



(XVII)



(XVIII)

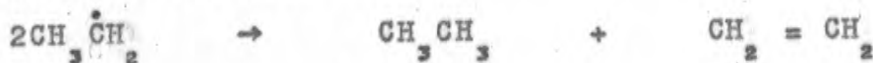


(XIX)

The formation of bibenzyls from toluene derivatives occurs by equations (1) and/or (2), (3) and/or (4) followed by dimerization (equation (10)), the stability of the benzyl radical providing the driving force for the first step in the reaction.

The reactions of carboxylic acids are mainly explained by equations (1), (7) and (10 - 14). The sulphate anion radical is considered by Russell and Thomson²⁴ to remove an electron from the carboxylate anion with the formation of

an acyloxy or aryloxy radical (equation 7) in a manner analagous to the Kolbe electrolysis of sodium salts of carboxylic acids. The abovementioned radicals may lose carbon dioxide to give an alkyl or aryl radical (equation 11, $A = CO_2$) which may dimerize to an alkane²² or biaryl (equation 12), combine with an acyloxy radical to yield an ester (equation 13), or react with a hydroxy radical to form an alcohol (equation 14). The above steps, however, do not indicate how either alkenes or dimeric dicarboxylic acids are formed. It is considered that they arise from hydrogen abstraction reactions. Considering the oxidation of propionic acid, steps (1-4, 11) result in the formation of ethyl radicals which may undergo hydrogen abstraction by disproportionation:-



This results in ethylene observed as a product.²⁰

Furthermore, hydrogen abstraction from the α -carbon atom of propionic acid by a hydroxy radical or sulphate anion radical would yield the species $\overset{\cdot}{\text{C}}\text{H}_2\text{CH}_2\text{CO}_2\text{H}$ which on dimerization would give the dicarboxylic acids obtained by Fichter and Suenderhauf.²³

The phenylation reactions observed by Russell and Thomson²⁴ can be explained by equations (1), (7), (11), (12) and (15). Thus the sulphate ion radical abstracts an electron from the benzoate ion to give the benzoyloxy radical which decomposes to the phenyl radical with the elimination of

carbon dioxide (equation 11, $A = CO_2$). Indiscriminate phenylation of pyridine then occurs as shown in equation (15). In the absence of such a substrate, phenyl radical dimerization results (equation 12). The presence of biphenyl-4-carboxylic acid can only be attributed to an attack of a phenyl radical on benzoic acid itself.

Since the presence of radicals as attacking species in peroxydisulphate reactions has been established, it was considered that, in a further study of the reaction, it would be of interest to introduce a site to compete for such radicals, with the carboxylate ion and the α -carbon atom of carboxylic acids. It is known that radicals attack tertiary hydrogen atoms at a much greater rate than primary or secondary atoms present in acids previously studied. Depending on which reaction predominates, hydroxy-acids (or lactones) or dicarboxylic acids (XL, $n = 0, 2$) or esters and alcohols derived from the acid (pg. 16), or tetrasubstituted succinic acids (XL, $n = 0$) should be obtained from the acid (XXXIX, $n = 0, 2$). Accordingly, a study was made of the behaviour of a number of branched chain aliphatic and alkylaromatic carboxylic acids in the presence of both alkaline and dilute acid potassium peroxydisulphate solution in order to determine the nature of the products formed.

By analogy with the removal of the equivalent of an electron from a carboxylate ion by a sulphate ion radical, it was considered that the reaction

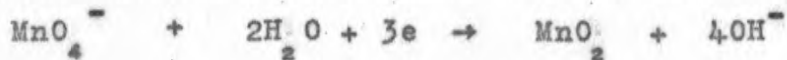
The entity (XXVI) is an hypoiodite and if formed would react with a primary amide in a manner analagous to t-butyl hypochlorite. At the elevated temperature used in the reaction, homolysis of the N-I bond would occur with formation of a γ -iodo-amide (XXV) by an intramolecular hydrogen transfer involving the species (XXI) and (XXII). Thus assuming both mechanisms (a) and (b) are operating at comparable rates, the yield of γ -lactone on hydrolysis of the reaction mixture should be higher when the peroxydisulphate oxidation is carried out in the presence of iodine. Accordingly, 4-methylpentanamide was oxidized under the above conditions to determine the course of the reaction.

Oxidations involving the permanganate ion appear at first sight to be more complex than those of the peroxydisulphate ion. The mode of reaction of the former is pH dependent, and the elucidation of oxidation mechanisms is further complicated by the possible presence of ions derived from every valence state of manganese from +2 to +6. The overall electron transfer reactions may be summarized as follows:

1 electron transfer. (alkaline solution)



3 electron transfer. (alkaline or neutral solution)

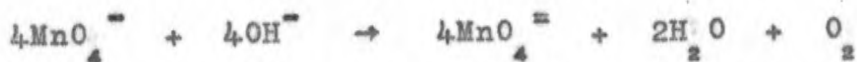


5 electron transfer. (acid solution).

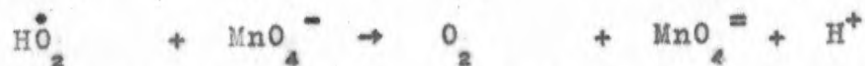
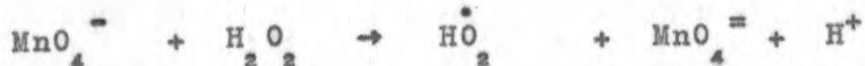


Thus the pH and the nature of the oxidizable substrate will determine which of the electron transfers will occur. A detailed account of all the known reactions of the permanganate ion is unnecessary, but a brief outline of the scope of the reaction is given in table 2.1 (pg. 20 a). The conditions referred to are those used in the reactions indicated in the references and are not necessarily the only conditions under which such reactions proceed.

The stoichiometric equation for the initial decomposition of potassium permanganate in alkaline solution is



Duke⁸⁹ in attempting to explain the mechanism by which oxygen was liberated, had to take into consideration the fact that indirect electron exchange had been observed between permanganate ions⁹⁰. The following was postulated.

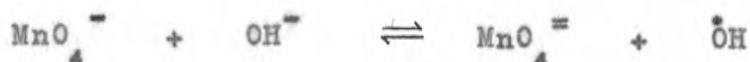


The first step has been criticized on the grounds that a three-bodied collision is unlikely to occur in the reverse direction. The modified step

Table 2.1 Action of Potassium Permanganate on Organic Substrates

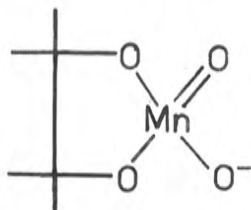
Substrates	Conditions*	Products	References
Saturated hydrocarbons	n.	alcohols; straight chain acids, hydroxy-acids	47,48
Alkylaromatic hydrocarbons	a. or al.	aldehydes, ketones, aliphatic and aromatic acids	49-53
Alkenes	a. or al.	cis-glycols; acyloins	54,55
Styrenes	al.	aromatic aldehydes, arylacetaldehydes	56
Stilbenes	a.	aromatic aldehydes; phenanthrenes	57,58
Primary alcohols	a.	mono- and dicarboxylic acids	52(a,c),59
Secondary alcohols	al.	ketones	60
1,2-Glycols	al.	mono- and dicarboxylic acids of lower mol. wt.	61
Aliphatic aldehydes	a. or al.	aliphatic acids	62
Aromatic aldehydes	a.	aromatic acids	63,64
Sugars	a.,al. or n.	formaldehyde; hydroxy-acids e.g. citric, tartaric	65,66
Formic, oxalic acid	a. or al.	carbon dioxide	67-71
Straight chain carboxylic acids	a.,al. or n.	straight chain acids of lower mol.wt., dicarboxylic acids	72-75
Branched chain " "	al.	hydroxy-acids, ketones	76
Alkene " "	al.	diolic acids	77
Aromatic " "	a.	carbon dioxide	78,79
Sulphinic acids	n.	sulphonic acids	57
Hydroxamic acids	al.	nitrogen, nitrous oxide	80
Phenols	a. or al.	dihydroxydiphenyls: carbon dioxide	81-85
Aromatic amines	a. or al.	ring fission products	86
Trimethylammonium bases	a. or al.	trimethylamine	87
8-Hydroxyquinolines	al.	pyridine-2,3-dicarboxylic acids	88

* a. - acid al. - alkaline n. - neutral

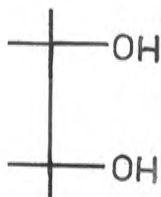


is feasible despite the interaction of like charges because the manganese atom in the permanganate ion has a vacant d-orbital and hence is electrophilic in character. The postulation of anhydroxy radical did not concur with the work of Drummond and Waters⁹¹ who found that molecules such as ethers which were readily oxidized by hydroxy radicals⁹² did not undergo attack by alkaline permanganate. On the other hand acetone, and malonic and fumaric acids are readily attacked by alkaline permanganate but not by hydroxy radicals generated from other sources. The latter observation, however, could be explained by the difference in pH of the respective media. In spite of this refutation, the existence of the hydroxy radical or its conjugate base, the oxygen anion radical, was given added support by the observations of Symons and co-workers.⁹³⁻⁹⁵

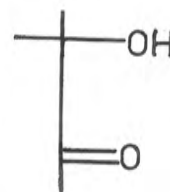
The fact that a purely radical mechanism involving one-electron transfer does not operate in all alkaline permanganate ion decompositions, is borne out by the reactions of olefines in dilute alkaline solution to give cis-diols and acyloins. This has been explained on the basis of a two-electron transfer from substrate to permanganate ion and the decomposition of the resultant cyclic ester (XXVII) into a 1,2-glycol (XXVIII) or an acyloin (XXIX)⁹⁶



(XXVII)



(XXVIII)



(XXIX)

The two main types of permanganate ion decomposition in alkaline solution have been adequately summarized by Cullis and Ladbury⁶¹:

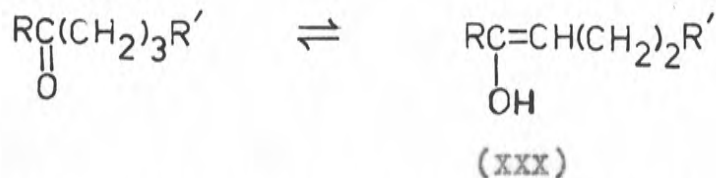
- (a) At high alkaline concentrations ($>3N$), hydroxyl ions are attacked in preference to the substrate by permanganate ions, resulting in the production of an hydroxy or derived radical which attacks the substrate.
- (b) At low alkaline concentrations, the two-electron transfer is preferred, followed by disproportionation of the resulting ion of lower valence state with a permanganate ion to give manganate ions.

The above observations agree with the work of Symons⁶⁷ who found that when acrylonitrile was treated with alkaline potassium permanganate, polymerisation accompanied oxidation only when the concentration of alkali was $3N$ or greater.

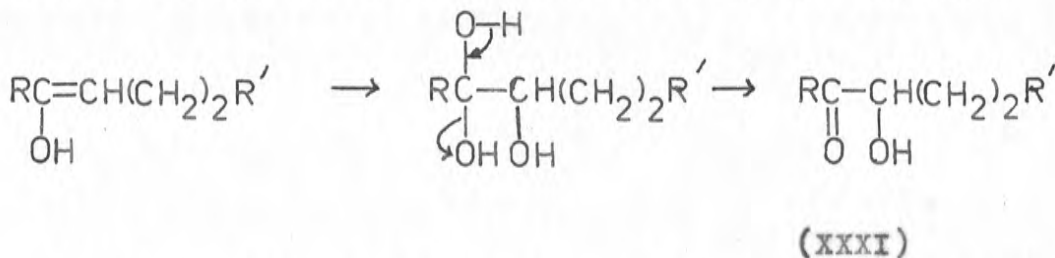
The effect of ions incorporating the other valence states of manganese has not been found to be significant in

alkaline permanganate oxidations. Thus Mn^{+++} formed would be immediately oxidized to the permanganate ion whereas the tetravalent Mn^{4+} ion can only exist in strong acid.⁹⁸

The mechanism of the oxidation of aliphatic aldehydes and ketones is of considerable importance because these molecules are considered to be intermediates in the degradation of aliphatic chains, whether they be attached to aromatic nuclei or hydroxy, formyl or carboxy groups. Drummond and Waters⁹¹ have shown that the oxidation of aldehydes and ketones proceeds extremely rapidly in alkali with considerable degradation. This can be explained on the basis of an enolization.



The entity (XXX) would be attacked in a manner similar to olefines with the formation of fragmentation products. For this to occur, it is considered that in the sequence



oxidation must be followed by rapid enolization of the acyloin (XXXI) because α -dicarbonyl systems are stable towards alkaline permanganate, as shown by the resistance to

oxidation of pyruvic acid and butan-2,3-dione. It is significant that formaldehyde and chloral hydrate which cannot form enols, are not readily oxidized in this way.⁹¹

The action of the permanganate ion on carboxylic acids has received wide attention. Both oxalic and formic acids undergo decomposition to carbon dioxide. The mechanism of the former reaction, which proceeds only in acid solution, has been adequately reviewed by Cullis and Ladbury.⁷¹ The oxidation of formic acid proceeds according to the stoichiometric equation



Wiberg and Stewart⁶⁹ consider that the reaction proceeds through a two-electron transfer



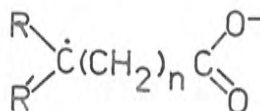
followed by disproportionation of the hypomanganate (MnO_4^{\equiv}) ion.

The straight chain fatty acids undergo degradation in the presence of neutral potassium permanganate to yield both mono- and dicarboxylic acids of lower molecular weight⁷²⁻⁷⁵ Hexanoic acid produced propionic, butyric and pentanoic acids as well as oxalic and succinic acids. Heptanoic acid gave propionic and pentanoic acids and the dicarboxylic acids succinic, glutaric and adipic. Some of the results obtained, e.g. the detection of oleic acid in the oxidation of heptanoic acid, seem open to doubt, but no criticism of this has appeared in the literature. The results indicate that

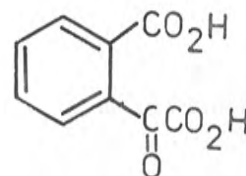
the carbon atom α - to the carboxy group, and the terminal methyl group are first attacked with the formation of hydroxy - acids. The acids arising from terminal carbon atom attack are further oxidized to aldehyde- and keto-acids which are then degraded through their enolic forms (pg. 23) to lower molecular weight acids. Alternatively, proton elimination from the carbon atom adjacent to the atom of initial attack would give rise to oxidizable unsaturated acids. The fact that both of these mechanisms were operating was confirmed by the ^{14}C studies of Daudel.⁹⁹

Aromatic acids such as benzoic⁷⁸ and phthalic⁷⁹ acid have been oxidized by acid potassium permanganate with degradation to carbon dioxide. A study of the reaction indicates that it proceeds through cis-1,2-diol formation by a two-electron transfer to the permanganate ion.

The action of alkaline potassium permanganate on branched chain carboxylic acids gives good yields of α - and γ - hydroxy acids from α - and γ - branched chain acids, but no analagous compounds from β - branched chain acids.⁷⁶ The products in all cases were explained by assuming the formation of an hydroxy radical or an oxygen anion radical which abstracts 3 hydrogen from the appropriate carbon atom to give the species (XXXII, $n = 0, 1, 2$). This undergoes addition with another hydroxy radical to give the appropriate hydroxy-acid. In the oxidation of β - branched chain acids, the formation of the product is immediately followed by



(XXXII)



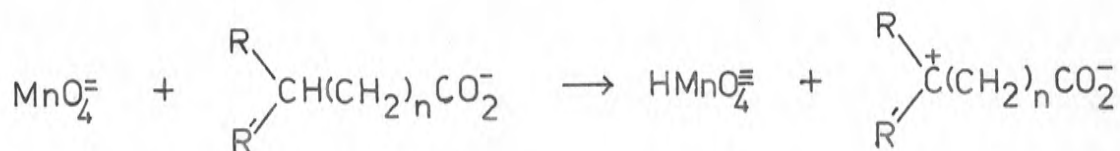
(XXXIII)

dehydration to the acrylic acid and subsequent degradation to a ketone. On the basis of such a mechanism, a carboxylic acid with an asymmetric tertiary carbon atom should give racemic products and this has been observed.^{76b}

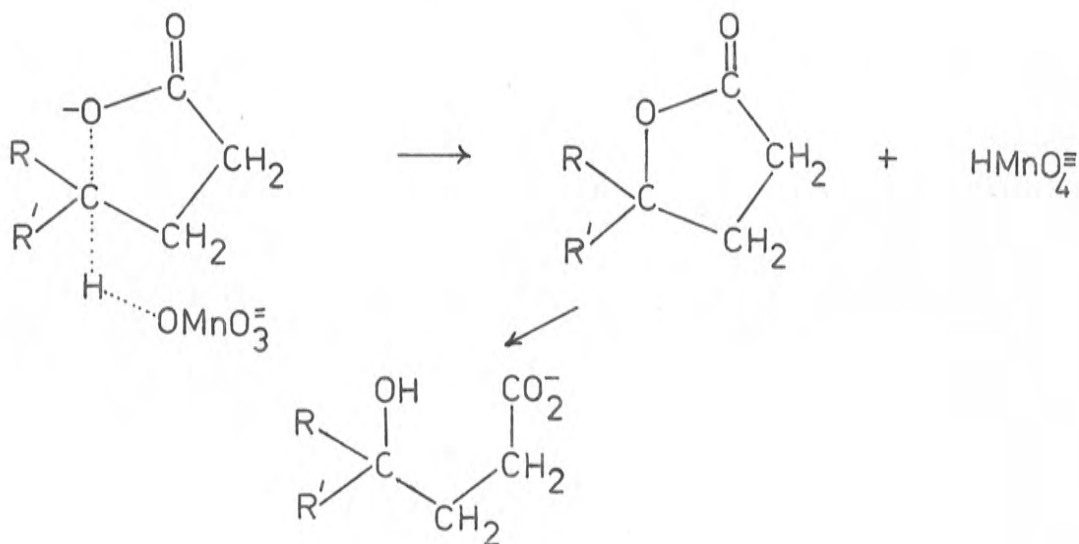
The scope of oxidations involving the manganate ion is more limited than those involving the permanganate ion. This is due firstly to the lower oxidation power of the manganate ion and secondly to its extreme instability in any medium other than alkali. Tcherniak¹⁰⁰ was the first to make use of the reagent in degrading naphthalene to phthalonic acid (XXXIII). It was not, however, until Rusakova and Tursin¹⁰¹ found that the action of the manganate ion on a sorbose derivative produced the same degradation product that had been obtained with permanganate ions, that the significance of the former as an oxidizing species was realized. This particular aspect of manganate ion oxidation has now been developed to such an extent that sugars such as dulcitol and sorbitol can be quantitatively determined.¹⁰² Kahane and Simenauer¹⁰³ have studied the

permanganate oxidation of quaternary amines such as choline and betaine and have concluded that the manganate ion is the active agent in the reaction.

In conjunction with the work on permanganate ion oxidations of branched chain acids (pg. 25), Kenyon and Symons studied their behaviour with dilute alkaline manganate⁷⁶. No α - or β - hydroxy-acids were obtained but γ - hydroxy-acids were formed in yields of the order of 70 - 80%. Optically active acids whose asymmetry was located at the γ - tertiary carbon atom produced optically active lactones.^{76b} The results were explained on the basis of an attack by the manganate ion on the tertiary carbon atom:



In the reaction of α - or β - branched chain acids this reaction would be followed by a proton elimination from the appropriate adjacent carbon atom giving an acrylic acid which would break down as previously described. With γ - branched chain acids, however, hydride ion removal would occur simultaneously with internal nucleophilic attack by the carboxylate ion to produce the γ -lactone, which would hydrolyse under the alkaline conditions. The scheme is outlined below.



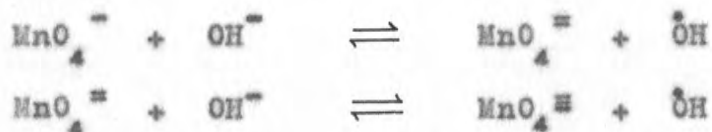
The above mechanism satisfactorily explains the observed retention of optical activity.

In connection with the formation of acrylic acids it is interesting to note that Rigby,¹⁰⁴ using alkaline manganate under milder conditions than those of Kenyon and Symons, was able to hydroxylate acrylic acids such as crotonic or cinnamic acids to give the cis-diols threo - α -, β -dihydroxybutyric acid and threo - β -phenylglyceric acid respectively, in yields below 50%. No mention was made of the detection of acetaldehyde or benzaldehyde or their corresponding acids which would be expected under the conditions of Kenyon and Symons.

In one of a series of publications investigating the relative importance of ions involving the various valence

states of manganese in oxidations, Pode and Waters¹⁰⁵ studied the effect of manganate ions in both N- and 1 ON-alkaline solution. From their qualitative observations on a wide range of oxidization substrates they were able to make the following generalizations:

- (a) The action of manganate ions was no more specific than that of permanganate ions.
- (b) Oxidation of phenols, certain alcohols and carbonyl compounds proceeded via one-electron transfers, whereas with alkenes, the reaction operated through a single stage two-electron transfer. These workers visualised the latter reaction occurring via a cyclic transition state in a manner analagous to permanganate ion oxidations of such compounds.
- (c) The results from the reaction of long chain carboxylic acids concurred with those of Kenyon and Symons in that neither primary nor secondary carbon atoms were hydroxylated by manganate ions.
- (d) The resistance of ethers to oxidation in strongly alkaline manganate solution is similar to their behaviour in dilute alkaline permanganate. Pode and Waters claimed that this was due to the fact that the equilibria

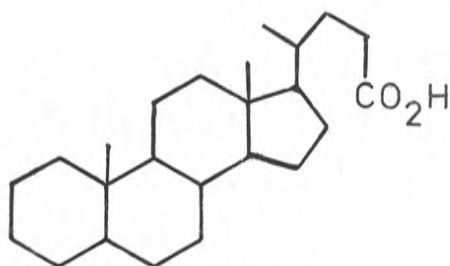


must lie to the left i.e. there is a low concentration

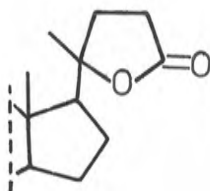
of $\dot{O}H$ radicals present.

The chief inference to be drawn from the results of both Kenyon and Symons, and Pede and Waters is that in all manganate ion oxidations in the absence of permanganate ion, there is no evidence for initial attack on the substrate by any species other than the manganate ion itself.

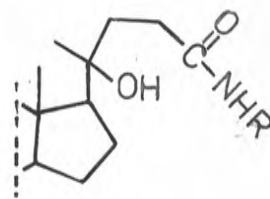
From the brief summary of the reactions involving the manganate and permanganate ions, only the selective hydroxylation of branched chain carboxylic acids appears to have any value from a synthetic point of view. Applying such a reaction to a steroid side chain acid, the main prerequisite for a satisfactory result would be the absence of other oxidizable groups in the steroid nucleus. Accordingly, the oxidation of cholanic acid (XXXIV) was carried out in both alkaline permanganate and manganate in the hope of preparing and subsequently degrading the expected 20-hydroxy-acid lactone (XXXV)



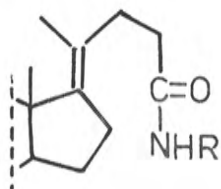
(XXXIV)



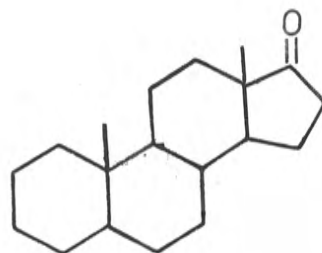
(XXXV)



(XXXVI)

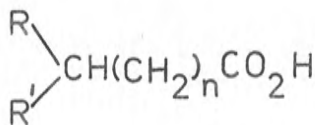


(XXXVII)

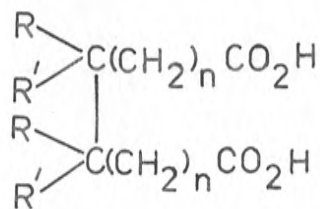


(XXXVIII)

by opening the newly-formed ring with formation of an hydroxy-amide (XXXVI). Dehydration of (XXXVI) would give the unsaturated amide (XXXVII) which on oxidation would result in the formation of androstan-17-one (XXXVIII)- a compound which has been prepared from cholanic acid by a series of carbon unit degradations. In addition, it was decided to repeat the selective oxidation on branched chain aliphatic acids not used by Kenyon and Symons, to determine firstly, whether comparable yields of hydroxy-acids could be obtained, and secondly, in the permanganate oxidations, to observe whether any products arising from radical dimerization such as dicarboxylic acids of the type (XL, $n=0,2$) could be detected.

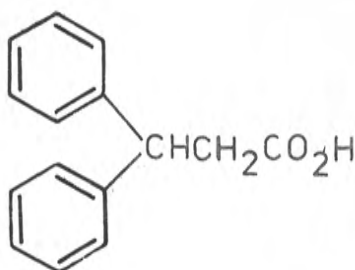


(XXXIX)



(XL)

In the oxidation of β -branched chain acids, Kenyon and Symons claimed the formation of ketones due to degradation of acrylic acids, but gave no experimental evidence to confirm this. 3,3-Diphenylpropionic acid (XLI) was therefore



(XLI)

prepared and oxidized with the purpose of determining the extent of this type of reaction by the isolation of benzophenone. The above acid was chosen because it affords maximum opportunity for acrylic acid formation since the dehydration of the hydroxy-acid is aided by the stabilization of the product by conjugation with the phenyl groups.

The oxidations of the branched chain alkylaromatic acids p- and p-isopropyl benzoic acids were carried out to determine whether the ability of an α - branched chain acid to undergo selective oxidation could be transmitted through an aromatic ring. The extent of dehydration of the expected hydroxy acids was also to be investigated. As there appeared to be some controversy connected with the properties of o-isopropylbenzoic acid, it was

decided to synthesize this compound by a new route in order to clarify the problem.

RESULTS AND DISCUSSION

(a) Branched Chain Acids.

Whenever the required acid could not be obtained directly, its preparation is discussed below.

(1) 3,3-Diphenylpropionic acid.

It was decided to prepare this acid from diphenylacetyl chloride by the Arndt-Eistert method. Difficulty was experienced in hydrolysing the intermediate diazoketone without formation of tarry by-products. When the temperature of decomposition was lowered, a product of much higher purity resulted, but since the best yield obtained was 11%, it was found more satisfactory to prepare the acid from cinnamic acid and benzene by the method of Vorlander et al.¹⁰⁶

(2) Cholanic acid.

This was prepared by reduction of 3,7,12-triketocholanic acid under various conditions. The Huang-Minlon modification of the Wolff-Kishner method¹⁰⁷ gave low yields but modification of the conditions considerably improved the efficiency of the reaction. This method was found to be sensitive towards slight changes in conditions so that in some runs low yields of impure cholanic acid resulted. This material gave a blood-red Liebermann-Burchard test¹⁰⁸ characteristic of 3-hydroxy-steroids. The presence of the secondary alcoholic impurity is not surprising since such compounds

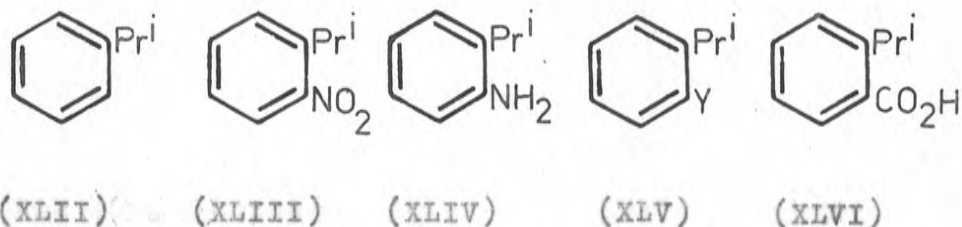
are known by-products in Huang-Minlon reductions. They arise from hydrolysis of the hydrazone followed by the reduction of the resultant ketone by the sodium alkoxide. Dutcher and Wintersteiner¹⁰⁹ obtained mainly cholestan-3-ol by the analagous reaction of cholestanone. Since the sterically favourable hydrazone of the 3-keto group of 3,7,12-triketocholanic acid would preferentially hydrolyse, it is considered that a similar reaction is occurring in this case with formation of traces of lithocholic acid. Esterification of the contaminated acid followed by both chromatography and distillation in vacuo failed to remove the impurity, but the product was shown by analysis to be methyl cholanate, indicating that the hydroxy-acid was present in trace amounts. The inconsistent results obtained from the keto-acid reduction, however, resulted in the Clemmenson reduction of Elderfield and co-workers¹¹⁰ being carried out. In one run cholanic acid was prepared in comparable yields with those of the above workers, but in most runs semi-solid gums were obtained. In one such reaction the product was esterified and the crude methyl ester chromatographed on alumina to give in addition to gums, methyl 7,12-diketocholanate. The corresponding acid has been prepared by the Clemmenson reduction of 3,7,12-triketocholanic acid,¹¹¹ so its presence in the above reaction is not suprising.

Eventually a Clemmenson method was developed using an acetic acid-hydrochloric acid solvent in such a ratio that cholanic acid was precipitated as soon as it was formed. This method resulted in yields in excess of any achieved by previous workers. Reduction of the by-products of the reaction by the same method gave low yields of cholanic acid, indicating that the reduction was proceeding by two competitive paths, only one of which was giving the required product. This was not investigated further.

(3) o-Isopropylbenzoic acid.

This acid has been known since 1888, but in view of the conflicting physical properties, e.g. m.p. and solubility, which have been ascribed to it, new methods of synthesis were investigated in order that its authenticity might be established before oxidation. Three main possible sources were investigated.

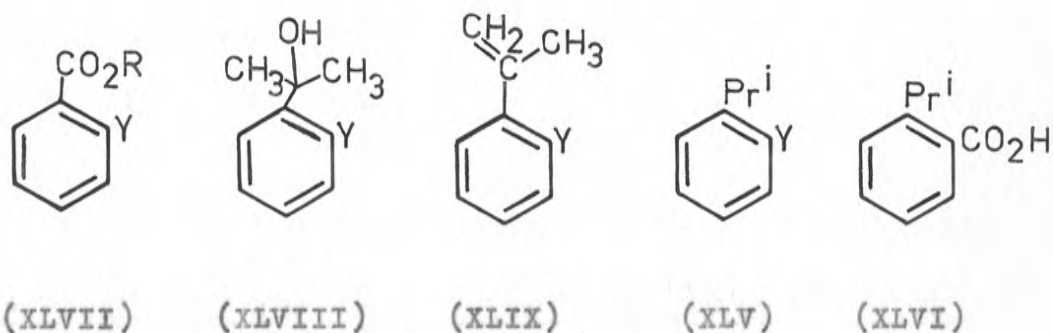
Scheme I. The following series of reactions was visualized:



Nitration of isopropylbenzene (XLII) by the method of Hansch and Helmkamp^{1,2} gave a mixture of the three isomers from which o-nitro isopropylbenzene (XLIII) was

separated. Reduction of (XLIII) to *o*-isopropylaniline (XLIV) proceeded smoothly in the presence of Raney nickel. Conversion of (XLIV) to *o*-bromoisopropylbenzene (XLV, Y=Br.) could not be achieved satisfactorily using Sandmeyer conditions, the required product being obtained in trace yields. This is attributed to the steric effect of the isopropyl group, since the competitive reaction resulting in *o*-isopropylphenol formation is preferred. Accordingly, this route was abandoned.

Scheme II. This involved the reaction sequence:



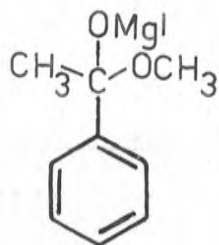
The route was advantageous in being unambiguous.

o-Chlorobenzoic acid (XLVII, R = H Y = Cl) was esterified (XLVII, R = CH₃, Y = Cl) and the production treatment with methylmagnesium iodide gave 1-(*o*-chlorophenyl)-1-methyl-ethanol (XLVIII, Y = Cl) in good yield. An unsuccessful attempt was made to convert this into the styrene derivative (XLIX, Y = Cl) by the method of Bergmann and Weizmann.¹¹³ Attempted reduction of the tertiary alcohol with zinc dust under acid conditions to give *o*-chloroisopropylbenzene (XLV, Y = Cl), resulted in the formation of *o*-chloro- α -methylstyrene (XLIX, Y = Cl.).

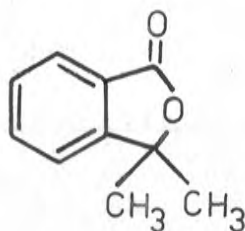
Evidently the added stability of the double bond due to conjugation was sufficient to prevent its reduction. The styrene was treated with magnesium in ether and the reaction mixture subjected to carbon dioxide in order to obtain o-isopropenylbenzoic acid (XLIX, Y = CO₂H), but only traces of acidic material were observed. Repetition of the reaction in tetrahydrofuran as solvent - a method developed by Ramsden and co-workers¹¹⁴ resulted in a low yield of crystalline acidic material. The m.p. was not in agreement with that of o-isopropenylbenzoic acid prepared from 3,3-dimethylphthalide (LII) and potassium cyanide by Kothe.¹¹⁵ Repetition of the latter reaction failed to yield any acidic products despite variation of conditions. Reaction of 3,3-dimethyl phthalide with aqueous ethanolic alkali by the method of Berti et al.,¹¹⁶ produced o-isopropenylbenzoic acid in good yield and this product was found to be identical with that obtained from o-chloro- α -methylstyrene. Reduction of the styrene acid was achieved quantitatively in alkaline solution with Raney nickel. The m.p. of the product was in agreement with that of o-isopropylbenzoic acid obtained by Elsner and co-workers,¹¹⁷ and Harvey,¹¹⁸ but not with those of Crawford and Stewart,¹¹⁹ and van Zanten and Nauta.¹²⁰ All workers who obtained m.p.s. differing from that obtained in the present study, prepared

o-isopropylbenzoic acid by a series of reactions, the first step of which involved the nitration of isopropylbenzene. It is tentatively suggested that an efficient separation of isomers was not achieved, so that the acid finally obtained was a mixture of isomers of isopropylbenzoic acid. It must be mentioned that Sterling and Bogert¹² tested the purity of o-nitro-isopropylbenzene prepared using the nitration method, by oxidation to o-nitrobenzoic acid. Since these workers, however, gave no details of the identification of this acid, it is impossible to determine whether small amounts of the other isomeric acids were present.

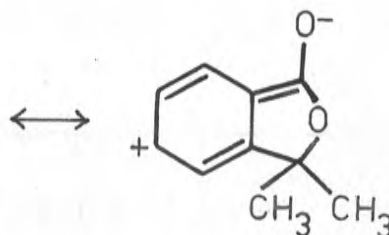
The steps (XLVII - XLVI Pg. 37) were carried out on the analagous bromo-acid (XLVII, R = H, Y = Br) in order to improve the yield of o-isopropylbenzoic acid in the final step, since both steric and electronic considerations would predict an easier carboxylation reaction. Initially, difficulty was experienced in the step (XLVII, R = CH₃, - XLVIII) in that the second mole of methylmagnesium iodide instead of exclusively attacking the hemi-ketal complex (LI) in the expected



(LI)



(LII)



(LIII)

manner, caused reductive removal of bromine with the formation of significant quantities of acetophenone (identified as its 2,4-dinitrophenylhydrazone).

This side reaction was prevented by the use of milder reaction conditions. In the light of the above experience it was doubted whether 1-(o-bromophenyl)-1-methylethanol (XLVIII, Y = Br) would escape bromine removal in the attempted zinc and acid reduction but in fact good yields of o-bromo- α -methylstyrene (XLIX, Y = Br), and subsequently o-isopropenylbenzoic acid, were obtained.

Scheme III was concerned with the ring opening of 3,3-dimethylphthalide (LII) followed by reduction of the resultant hydroxy-acid. Such a reaction would be favoured in alkaline medium and accordingly reductions were carried out under Bouveault - Blanc conditions. Since such reactions were unsuccessful, attempts were made to carry out reductions which had proved successful with terpene lactones e.g. geigerin.¹²² Reagents included activated zinc dust and acetic acid, amalgamated zinc and hydrochloric acid, and chromous chloride, and in all cases complete recovery of (LII) resulted. The lack of reactivity of this compound is indicative of the enhanced stability that the fused phenyl group imparts to the ring, and is due to the participation of canonical forms such as (LIII). The cyclization of the compound even at relatively high pH can be explained on similar

grounds. 3,3-Dimethyl phthalide is a cyclic benzyl ester and it was considered that a hydrogenolysis reaction could be effected. Accordingly an alkaline solution of the phthalide was treated with nickel - aluminium alloy and o-isopropylbenzoic acid having the same physical properties as the acid resulting from scheme II, was obtained. The best yields resulted when several hours hydrogenolysis was employed.

(b) Summary of Results of Oxidations.

The yields of hydroxy acids (or lactones) from the various oxidations are summarized in Table 2.2

Table 2.2

Acid Oxidized	% Yield of hydroxy acid from method*			
	a	b	c	d
2-methylpropionic	14	5	40	-
diphenylacetic	-	0	-	-
3,3-diphenylpropionic	-	0	-	-
4-methylpentanoic	trace	1	11	13
<u>o</u> -isopropylbenzoic	41	44	2	61
<u>p</u> -isopropylbenzoic	12	44	0	0
cholanic	0	0	0	0

The results do not agree with those of Kenyon and Symons, since poor yields of hydroxy-acids (or lactones) were obtained with both dilute alkaline potassium manganate

*Footnote: a,b,c,d, refer to the oxidation methods described on page 79-84.

and concentrated alkaline potassium permanganate. Improved yields were generally obtained when acid or alkaline potassium peroxydisulphate was the oxidant. In all oxidations involving the manganate and permanganate ions, considerable quantities of starting material were recovered. Since this did not occur in the oxidations of Kenyon and Symons, it is assumed that the slightly different conditions used in the present study were responsible for the startling difference in results. The above authors prepared dilute alkaline potassium manganate solution by heating the appropriate quantities of potassium permanganate and potassium hydroxide in water at 80-90° for 30 minutes, followed by partial neutralization of the cooled green solution with dilute sulphuric acid. On repetition of this reaction it was found that even after several hours heating, only partial colour change had occurred and the reaction required as long as 12 hours for completion, although traces of ferric ion added did increase the rate of colour change. During the partial neutralization of this solution, despite all precautions, oxidation to the permanganate ion invariably occurred. The problem was finally resolved by the introduction of small quantities of sulphur dioxide to the hot dilute potassium permanganate solution before use. Kenyon and Symons prepared concentrated alkaline potassium

permanganate solution by a method which could not be reproduced since the high concentration of potassium ions already present in the alkaline solution would permit only partial solubility of the potassium permanganate. This difficulty was almost overcome by addition of a solution of potassium permanganate in dilute alkali to a solution of the substrate in concentrated alkaline solution.

It was observed that the rates of reaction of acids containing a sterically hindered tertiary carbon atom were much smaller than those claimed by Kenyon and Symons for acids of similar structure. The alkaline manganate oxidation of o-isopropylbenzoic acid, for example, required 12 hours for complete formation of manganese dioxide.

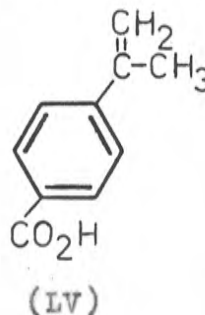
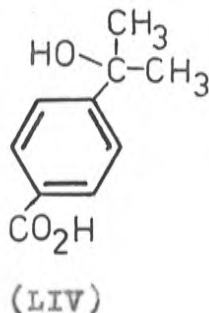
(c) Oxidations Involving Alkaline Manganate

As observed by Kenyon and Symons, γ -lactones were obtained from the oxidation of γ -branched chain acids. The yields, however, were considerably lower. In contrast to the above authors, poor yields of α -hydroxy-acids were observed. It is significant to note that in the preparation of alkaline potassium manganate, Kenyon and Symons considered that the formation of a permanent green colour indicated the exclusive presence of the manganate ion. No spectral evidence was put forward at the time to show the absence of permanganate ion, although the results obtained with optically active branched chain acids,^{6b} and subsequent

spectral work by Symons⁹³ and den Boef et al.¹²³ indicates that their assumption was correct. In experiments connected with the present work, it was found that addition of solid potassium permanganate did not alter the green colour of potassium manganate solutions, indicating that colour alone is not a criterion for postulating the exclusive presence of the manganate ion. Thus it is probable that the solution of manganate used in the present oxidations contained an appreciable quantity of permanganate ion. Furthermore, during the oxidation of some of the acids, development of a purple colour was observed, indicating that the permanganate ion was also playing a part in a rather complex oxidation.

The results of Kenyon and Symons indicated that no α -hydroxy acids were obtained from manganate oxidations because of their subsequent degradation to ketones and carbon dioxide. Actually, scission of the $\alpha\beta$ double bond of the intermediate acrylic acid would give rise to the oxalate ion as well as ketone. The former would not be further oxidized in alkaline solution and the corresponding acid might be isolated from the acidified reaction mixture by continuous ether extraction. This technique was adopted but no oxalic acid was detected. This result is not conclusive, but the fact that no benzene-dicarboxylic acids were observed to any extent in the manganate ion oxidation of o- and p-isopropylbenzoic acid, indicates that in the

present series of oxidations, the dehydration reaction was not occurring to any extent. The dehydration of p-(1-hydroxy-1-methylethyl) benzoic acid (LIV) would be



facilitated due to the stabilization of the unsaturated acid (LV) by resonance. It might be argued that the isopropenylbenzoic acids (XLIX, $Y = CO_2H$) and (LV) would be stable towards further attack by manganate ion but tests on similar compounds indicate that decolourization of manganate occurs under even milder conditions. Furthermore, the unsaturated acids have not been detected by paper chromatography and it has been shown that their R_f values differ from those of the corresponding saturated acids, by a sufficient amount to enable their characterization. The absence of unsaturated acids is in accord with the results of Rigby¹⁰⁴ who showed that cinnamic acid reacted with manganate ions across the double bond at 0° . The observation that phthalic acid was not detected in the oxidation of o-isopropylbenzoic acid, might be attributed to the formation of 3,3-dimethylphthalide which is insoluble in dilute alkali and would thus be removed from the sphere

of reaction so quickly that 1,2-dehydration of the hydroxy-acid would not occur. Since, however, no phthalic acid was observed in oxidations in an alkaline solution of such a concentration that potassium o-(1-hydroxy-1-methylethyl)benzoate would be present in appreciable amounts, it is concluded that no o-isopropenylbenzoic acid was being formed.

In agreement with Kenyon and Symons, no dimeric dicarboxylic acids were detected in the manganate ion oxidations. In the reaction of γ -branched chain acids, the internal nucleophilic attack of the carboxylate ion on the tertiary carbon atom prevents any other reaction at this position. If an analagous initial reaction for α -branched chain acids is assumed, i.e.



then the absence of dimeric acids is explained. Since the presence of the permanganate ion has also been demonstrated in this reaction, it is possible that the tertiary radical (LX) formed in such oxidations would dimerize.

(d) Oxidations Involving Alkaline Permanganate

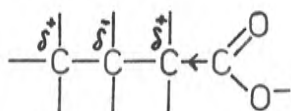
The yields of hydroxy-acids and lactones from

permanganate oxidations are lower than those obtained by Kenyon and Symons. Low molecular weight products were found to be water-soluble but their isolation by continuous ether extraction did not result in significant increase in yields. In the oxidation of higher molecular weight acids e.g. diphenylacetic acid, it was observed that the sodium salt was not readily soluble in the medium used but the significance of this is uncertain.

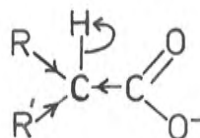
The reaction of 3,3-diphenylpropionic acid with alkaline permanganate produced trace yields of benzophenone. 3,3-Diphenyl-3-hydroxypropionic acid and 3,3-diphenylacrylic acid were not detected in the product which consisted mainly of starting material. This result indicates that β -branched chain acids are unaffected, rather than extensively degraded as previously suggested.

The results of Kenyon and Symons from the reaction of the permanganate ion on optically active α -branched chain acids, indicate beyond doubt that the mechanism cannot involve either a tertiary carbonium ion or carbanion at the position of hydroxylation. Their discussion of the mechanism, however, gives the impression that the carboxylate ion is more significant in promoting the reaction than the groups attached to the tertiary carbon atom and consequently they do not adequately explain how the presence of electron releasing groups attached to the tertiary atom causes exclusive reaction at that atom, whereas electron withdrawing

groups (as in diphenylacetic acid) appear to inhibit the reaction as observed in the present study. It has been suggested that an alternative polarity effect, indicated in (LVI), is induced by the carboxylate ion,



(LVI)

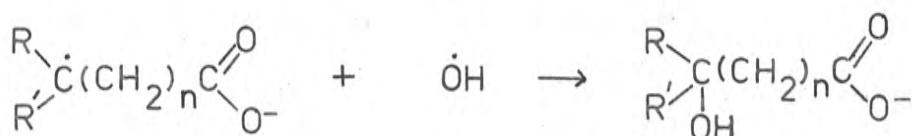


(LVII)

but this would imply that hydroxylation by radical attack as postulated by Kenyon and Symons would preferably occur at the α - and γ -positions. This is because the hydrogen atoms attached to these positions have a higher electron density associated with them. The fact that no α -hydroxyacids were obtained from γ -branched chain acid oxidations indicates that the effect of the carboxylate ion is small compared with that of the substituent groups at the tertiary carbon atom. The results can most satisfactorily be explained by assuming that the permanganate ion generates hydroxy radicals which attack the tertiary hydrogen atom in the manner described by Kenyon and Symons. It is considered that the oxygen anion radical also suggested as an attacking species by the above authors, does not effect reaction since the charge repulsion as depicted in (LVII) would inhibit the attack of this radical which must be nucleophilic in character. A similar initial reaction occurs with γ -branched chain acids except that the

carboxylate ion will have a smaller effect on the release of the tertiary hydrogen atom. This is borne out by the fact that the yields of 4-hydroxy-4-methylpentanoic acid lactone were lower than those of 2-hydroxy-2-methylpropionic acid.

The next step in the mechanism involves the hydroxylation of the tertiary radical formed.

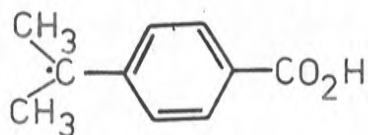


The absence of dicarboxylic acids of the type (XL) is surprising. In other reactions involving tertiary radicals as intermediates, dimerization products have been observed. Thus the reaction of such radicals derived from branched chain acids by the action of abstraction agents such as diacetyl peroxide,¹²⁴ results in the formation of dicarboxylic acids. It must be remembered, however, that in the present experiments, the carboxylate ion rather than the free acid is the substrate. Furthermore, hydroxy radicals are absent in the former type of reaction. This indicates that if a carboxylate tertiary radical is able to undergo radical hydroxylation or dimerization, the former must be preferred. In an endeavour to clarify the problem an α - and a γ -branched chain acid were separately subjected to hydroxy radical attack with hydrogen peroxide in alkaline solution.

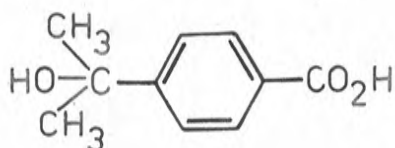
No reaction occurred.

Summarizing, it may be said that in permanganate ion oxidations, hydroxy-acids (or lactones) are formed as a result of hydroxy radical attack on the tertiary carbon atom, but the function of the carboxylate ion in promoting the reaction is uncertain.

The fact that both o- and p-isopropylbenzoic acid undergo hydroxylation in both alkaline manganate and permanganate solution, indicates that the effect of the carboxylate ion can be transmitted through an aromatic ring. The reaction of the latter acid indicates that this effect does not operate through space since interaction of carboxylate ion and tertiary hydrogen atom is prevented by the planarity of the molecule. The relatively high yield of p-(1-hydroxy-1-methylethyl) benzoic acid (LIX) from p-isopropylbenzoic acid in the permanganate oxidation, may be attributed to the stabilization of the intermediate benzyl radical (LVIII) by resonance. The analagous



(LVIII)



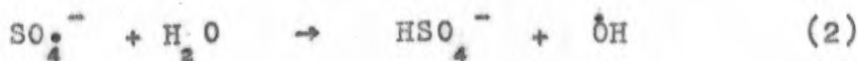
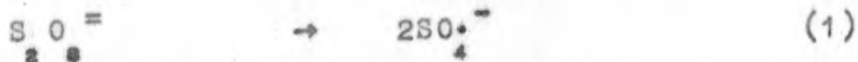
(LIX)

carbonium ion which must be formed as an intermediate in the manganate ion oxidation of the acid, although stabilized by resonance will be of higher energy due to charge separation effects. This could explain the lower yield of

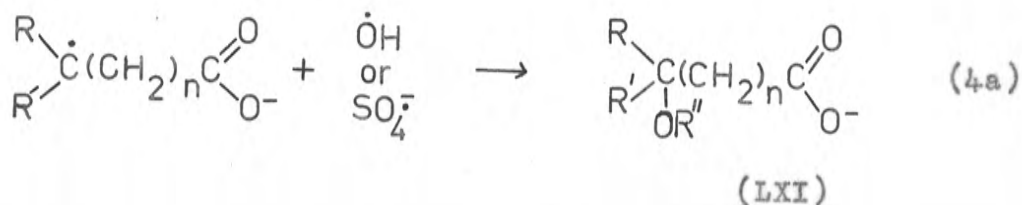
hydroxy-acid in the latter case. In the oxidation of o-isopropylbenzoic acid where incipient carbonium ion formation is followed by internal nucleophilic attack by the carboxylate ion, the yields of lactone from oxidations (a) and (b) are similar.

(e) Reactions Involving Potassium Peroxydisulphate.

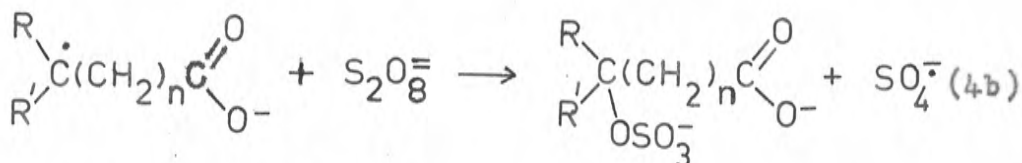
Oxidation by both acid and alkaline potassium peroxydisulphate appears to take place by the same mechanism since similar yields of 4-hydrox-4-methylpentanoic acid are obtained. This supports the results of Kolthoff and Miller.⁴⁴ The relative yields of hydroxy-acids indicate that the peroxydisulphate ion is a more efficient hydroxylating agent than either the manganate or permanganate ion. Furthermore, the presence of a substrate increases the rate of peroxydisulphate ion decomposition. These results imply that the reaction may be proceeding by a chain process in addition to the normal tertiary hydroxylation reaction. The mechanisms may be summarized as follows.



then



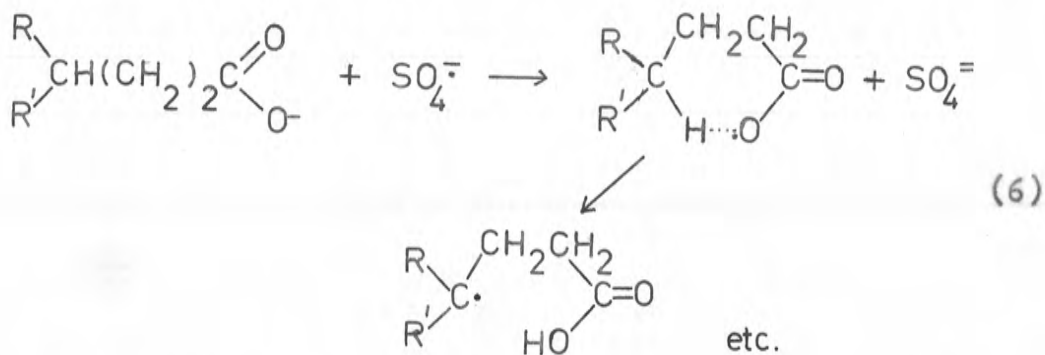
or



the chain propagating step.



An alternative mechanism could explain the oxidation of γ -branched chain acids



The postulation of an attack by a sulphate ion radical as well as an hydroxy radical in (3) and (4a) is explained by the fact that step (2) may not occur since less energy would be required to break a tertiary C-H bond than an O-H bond of water. The chief objection to this mechanism is that the formation of the hydroxy-acid (or lactone) will

depend on the ease of hydrolysis of the half-ester (LXI, R" = SO₃⁻). In neutral solutions this species would be relatively stable but in reactions carried out under such conditions, no ester of this type has been observed. An alternative method of generation of hydroxy radicals involves an electron transfer from a hydroxyl ion to a sulphate ion radical thus:

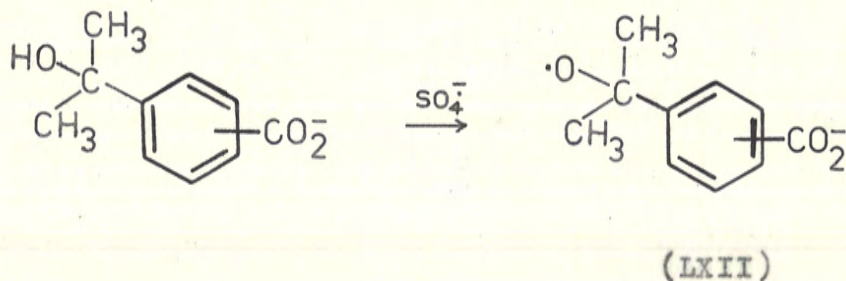


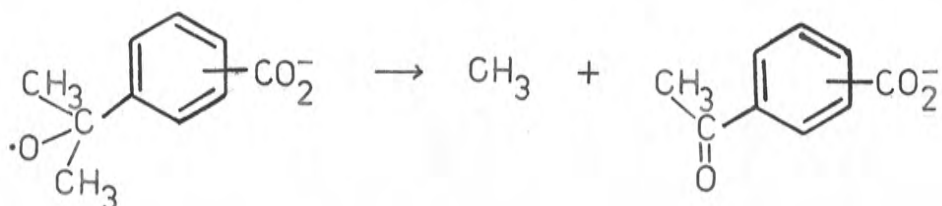
By analogy with observations on permanganate oxidations, the above step would occur only at relatively high concentrations of hydroxyl ions. Hence in oxidations involving alkaline peroxydisulphate, the hydroxy radical is the hydrogen abstracting agent, whereas in acid solution the sulphate anion radical may be the species involved.

Occurring simultaneously with the above hydroxylation mechanism is a chain reaction, the propagating step of which is (4b). The main objection in this case lies in the interaction of two similarly charged species. Since, however, the site of reaction is relatively remote from the location of the charges, this repulsion will be minimized, leaving steric interaction as the main factor in the inhibition of the reaction.

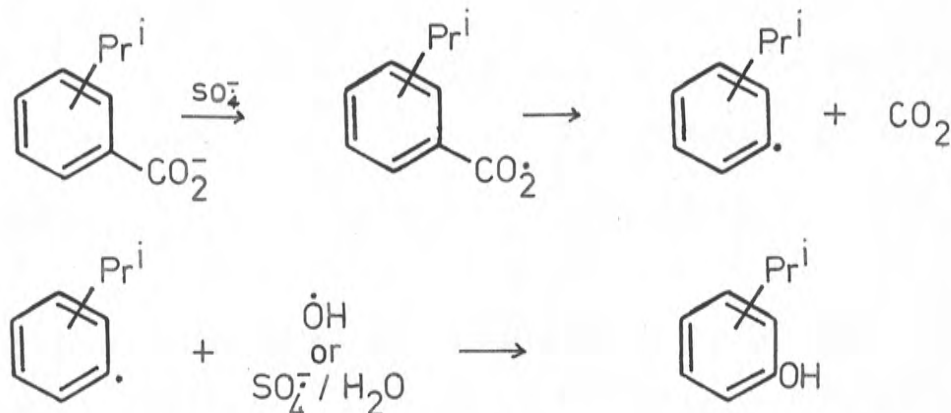
The reaction of peroxydisulphate ions with the isomeric o- and p-isopropylbenzoic acids exhibited features not shown in oxidations (a) and (b) in that acetylbenzoic acids and traces of phenols were formed. No hydroxy acid

was obtained in the oxidations of p-isopropylbenzoic acid. In the alkaline oxidation of o-isopropylbenzoic acid, traces of 3,3-dimethylphthalide were observed, the main product being a gum from which o-acetylbenzoic acid was isolated and phenols were detected. With acid peroxydisulphate, the main product was 3,3-dimethylphthalide and the gum containing o-acetylbenzoic acid and phenols was the minor constituent. The above results indicate that the initial reaction involves abstraction of hydrogen from the tertiary carbon atom followed by hydroxylation of the radical either directly or via the hydrolysis of the sulphate ester as previously described. In the acid oxidation of o-isopropylbenzoic acid, cyclization to the phthalide occurs and the hydroxy group is no longer available for radical attack. In acid solution p-(1-hydroxy-1-methylethyl) benzoic acid, and in alkaline solution both hydroxy acids undergo hydrogen abstraction from the hydroxy group to form the cumyloxy radical (LXIII). The following mechanism is put forward to explain the products:





also



The fact that the hydroxy-acid is the intermediate in the degradation of the alkylaromatic acids, is supported by the fact that 3,3-dimethylphthalide in the presence of alkaline peroxydisulphate ions, gave o-acetylbenzoic acid and traces of phenols. The path indicated for the decomposition of the substituted cumyloxy radical (LXII) is supported by the results of Kharasch and co-workers¹²⁵ who decomposed cumyl hydroperoxide in the presence of acetic acid to give acetophenone and phenol among other products, and postulated the formation of the ketone by a mechanism analogous to the above. The first step in the mechanism of phenol formation is similar to that postulated by Russell and Thomson.²⁴ The appropriate isopropylphenyl radical arises and subsequently reacts

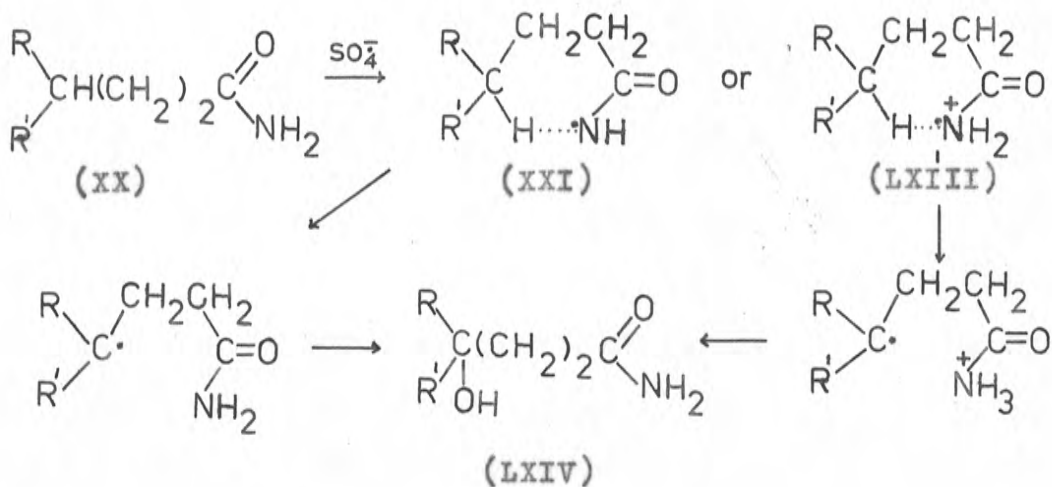
with an hydroxyl radical or a sulphate anion radical.

The absence of dicarboxylic acids among the products of oxidation is surprising in view of previous results^{2,3} but is consistent with the results of permanganate oxidation where the same tertiary radical is the intermediate.

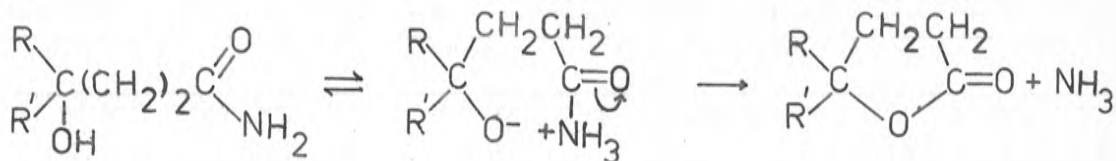
The fact that peroxydisulphate ions can take part in an electron exchange with the carboxylate ion to give the corresponding radical, suggests a possible alternative mechanism for oxidation of γ -branched chain carboxylic acids (equation 6). In order to determine whether an analogous reaction could occur with a primary amide with the formation of the species (XXI) by abstraction of hydrogen radical, or the radical (LXIII) by removal of an electron from the nitrogen atom of the amide, the unsubstituted amide 4-methylpentanamide (XX, $R, R' = CH_3$) was treated with neutral potassium peroxydisulphate solution, and a small yield of 4-hydroxy-4-methylpentanoic acid lactone was produced. Since bisulphate ions are formed in the decomposition of peroxydisulphate ions the former species was possibly catalysing the hydrolysis of the amide to the carboxylic acid which was undergoing hydroxylation as previously described. This was confirmed when reaction of the above amide with potassium bisulphate solution gave a small yield of 4-methylpentanoic acid. The amide was found to be unaffected when heated

in solutions of pH 5.5-7, so the oxidation was carried out in this pH range throughout the reaction. The lactone was again formed, indicating that the amide was hydroxylated via one or both of the following mechanisms.

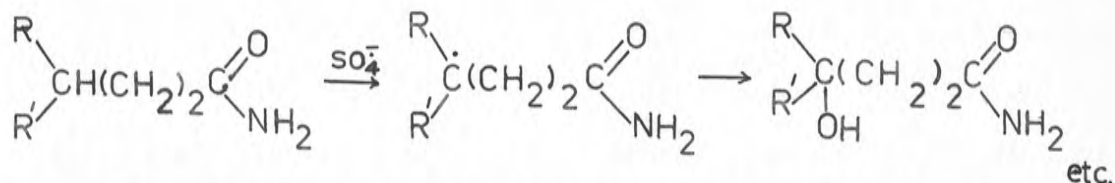
(a)



then

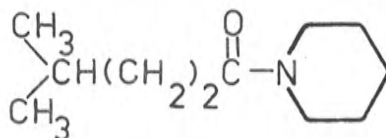


(b)



Thus the intermediate was the γ -hydroxy-amide (LXIV) no matter which mechanism was operating. To obtain more information concerning mechanisms (a) and (b), N-(4-methylpentanoyl) piperidine (LXV) - a tertiary amide

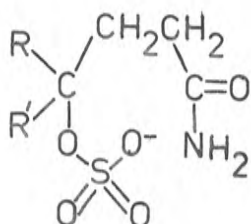
stable in the pH range 5.5-7 - was treated with the



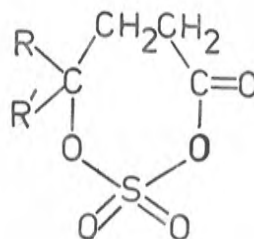
(LXV)

peroxydisulphate ion in this range. The lactone (XXIII, R,R' = CH₃, Y = O) was formed and since (LXV) is incapable of forming the amide radical (XXI) as shown in mechanism (a) it follows that the part of the mechanism involving this species as intermediate cannot be operating. The above result does not, however, preclude the operation of this mechanism through the radical cation (LXIII) since hydrogen transfer is possible in this case. The low yields of lactone, coupled with the fact that similar yields were obtained from the neutral peroxydisulphate oxidation of the methyl ester of 4-methylpentanoic acid where the analogous electron removal would be extremely unlikely, indicate that this part of mechanism (a) is not operating. Thus the oxidation of γ -branched chain amides proceeds through hydrogen abstraction from the tertiary carbon atom followed by hydroxylation of that atom as shown in mechanism (b). Internal nucleophilic attack by the hydroxyl group then occurs with the expulsion of the $-\overset{+}{\text{N}}\text{H}_3$ group as the corresponding base. The possibility of the sulphate half-ester (LXVI) taking part in the mechanism has not been overlooked, but on

steric grounds it would appear that the sulphate anion would initiate nucleophilic attack with the formation of (LXVII). This compound has not been detected in the



(LXVI)



(LXVII)

oxidation. The formation of lactone from tertiary amide indicates that the imino-lactone (XXIII, Y =NH) is not an intermediate in the oxidation. This agrees with the results of studies on the hydrolysis of 4-hydroxybutyramide in neutral solution.¹²⁶

The above results indicate that a hydrogen radical cannot be abstracted from an amide -NH₂ group in preference to a tertiary carbon atom. A similar conclusion has been reached by Cadogan¹²⁷ from hydrogen abstraction reactions involving alkoxy radicals. Since the energy of the N-H bond is lower than that of O-H bond, it follows that hydrogen abstraction by peroxydisulphate ions from the carboxy group of unionized carboxylic acids is unlikely and the rearrangement mechanism (6) will occur only if it involves the carboxylate ion. Since at low pH the concentration of this species is small it is considered that the mechanism as a whole is unlikely for acids and

impossible for amides as they have a much lower acid strength.

The effect of adding iodine to the acid catalysed hydroxylation of 4-methylpentanamide did not result in a significant increase in yield of lactone. This indicated that the peroxydisulphate ion was not involved in an oxidation with iodine since the yields of lactone would have been lower. On the other hand it seemed unlikely that the N-iodoamide (XXIV) was formed since thermal homolysis would have resulted in an increased yield of lactone. In view of the observed thermal stability of N-chloroamides (pg.134), hydrolysis rather than homolysis might occur in this case although the energy of the N-I bond would be lower than that of the N-Cl bond by analogy with the hypohalites.

The most disappointing aspect of all the oxidations was their inability to be adapted to the hydroxylation of cholanic acid. No trace of lactone was produced from any oxidation. A study of a model of the steroid acid indicates that the steric effect of neighbouring groups, although greater than that encountered in the lower molecular weight branched chain acids, would not be sufficient to prevent reaction. The only reason that can be given for the lack of activity of this acid is the extreme insolubility of the potassium salt in the alkaline media used. It is concluded that any technique developed

for extensive side chain degradation of cholanic acid cannot involve the hydroxyl radical as attacking species.

EXPERIMENTAL

(a) General

Infrared spectra were determined with a Perkin-Elmer Infracord Model 137. Melting points were determined in capillaries and are uncorrected. Analyses were performed by the Australian Microanalytical Service, Melbourne.

(b) Purification of Materials

All solvents and liquid reagents were redistilled and where necessary, dried or further purified by standard procedures. Liquid acids to be oxidized were purified by careful fractionation.

(c) Analytical Methods

(i) Paper chromatography Monocarboxylic acids were detected on Whatman No.1 paper using the system 1.5N-aqueous ammonia - butanol (1:1) for descending chromatography. Spots were visualized by spraying with bromocresol purple solution. Dicarboxylic acids and keto-acids were detected using the system toluene-butanol - 50% aqueous acetic acid (10:1:5) and visualizing the spots with bromocresol green. In all cases the acids were identified by comparison of their R_f values with those of authentic samples run concurrently.

(ii) Adsorption chromatography. - Where necessary, esters were separated on columns of alumina

(Spence type U.G.1), activated by the method of Beckwith,¹²⁸ and partially deactivated by shaking with distilled water (10% W/W).

(d) Synthesis of Starting Materials

3,3-Diphenylpropionic acid

(i) Diphenylacetyl chloride. - Diphenylacetic acid (10 g.) was treated with thionyl chloride (20 ml.) at room temperature (2 hr.) then warmed on a water-bath at 80° (2 hr.). The excess of thionyl chloride was subsequently removed by distillation in vacuo, and the residual pale yellow solid was recrystallized from anhydrous petroleum ether as thick colourless plates (9 g., 83%) m.p 53-55° (lit.¹²⁹ 56 - 57°).

(ii) Diphenyldiazoacetone - Etheral diazomethane was prepared from N-methyl-N-nitrosourea (11 g.) and dried (4.5 hr.) over potassium hydroxide pellets. To this well stirred solution, diphenylacetyl chloride (6.0 g.) in anhydrous ether (20 ml.) was added at such a rate that the temperature was maintained below 10°. The solution was set aside at room temperature overnight and the ether cautiously removed on a warm water-bath to give the pale yellow diazoketone. A sample recrystallized from hexane had m.p 64-66°.

(iii) Decomposition of the diazoketone - The diazoketone was dissolved in dioxan (30 ml.) and the solution was added dropwise with stirring to a suspension of silver oxide (1.5 g.)

in aqueous sodium carbonate (2.5 g. in 50 ml.) to which had been added sodium thiosulphate (1.5 g.). The mixture was maintained at 40° (1 hr.), then cooled and acidified with concentrated nitric acid. The precipitated material was extracted with chloroform. This in turn was extracted with saturated sodium bicarbonate solution from which 3,3-diphenylpropionic acid was obtained by acidification. The solid was collected by filtration, and after it had been dried over concentrated sulphuric acid, was crystallized from benzene as fine colourless cubes (1.2 g. 11%) m.p. 156°. The product was identical with that prepared by the method of Vorländer et al.¹⁰⁶

Cholanic acid - This compound was prepared from

3,7,12-triketocholanic acid by the following procedures:

(a) A modification of the method of Huang-Minlon¹⁰⁷ was employed. 3,7,12-Triketocholanic acid (5 g.), hydrazine sulphate (9.75 g.), potassium hydroxide (17.5 g.) and diethylene glycol (87.5 ml.) were heated under reflux (0.5 hr.). The condenser was removed and the water formed during the reaction was allowed to evaporate until the temperature of the reaction mixture reached 200°. The mixture was further heated under reflux for an hour, then cooled to room temperature and poured into an excess of 6N-sulphuric acid. The acid suspension was shaken thoroughly with ether and the organic layer dried

(magnesium sulphate). The residual brown semi-solid mass (4.2 g.) was crystallized several times from acetone to yield cholanic acid (2.2 g., 49%) as colourless plates m.p. 162-163° (lit. 164°). The product gave an almost colourless Liebermann-Burchard test. The above yield was the optimum in several runs. Most reactions resulted in a very low yield of material which gave a red Liebermann-Burchard test. In one such case a sample of the product was esterified at 0° with diazomethane. The methyl ester formed which gave a red Liebermann-Burchard test was recrystallized from methanol to m.p. 87-88.5°, and hence appeared to be mainly methyl cholanoate. (Found: C, 79.8; H, 11.05; O, 8.65. Calc. for $C_{25}H_{42}O_2$: C, 80.0; H, 11.3; O, 8.55%).

(b) A modification of the method of Elderfield and co-workers¹¹⁰ was employed. 3,7,12-Triketocholanic acid (30 g.) was dissolved in glacial acetic acid (330 ml.), and concentrated hydrochloric acid (250 ml.) and amalgamated zinc powder (300 g.) were added. The mixture was heated under reflux while dry hydrogen chloride was bubbled through the reaction mixture. After 10 hr. reflux, a further quantity of zinc powder (100 g.) was added, and reflux in the presence of hydrogen chloride continued for a further 20 hr. The mixture was then cooled and the waxy solid formed was removed and dissolved in chloroform. The residual amalgam was

warmed with chloroform and the organic extracts combined and dried (magnesium sulphate). Removal of the solvent gave a gum which on two crystallizations from acetone gave cholanic acid (10.4g, 39%) m.p 162-164°. In several runs this reduction gave rise to non-crystallizable oils. In one such case the oil (7 g.) was treated at 0° with diazomethane. The crude material produced was chromatographed on alumina (700 g.) deactivated with 15%w/w of water. Elution with ether gave a quantity of gum which was shown by infrared spectroscopy to be a mixture of keto-esters and was not further identified. A later fraction yielded a colourless solid (0.6 g.) which crystallized from methanol as colourless needles (0.35 g.) m.p. 138-140° identified as methyl 7,12-diketocholanate. (Found: C, 74.6; H, 9.4; Calc. for $C_{23}H_{38}O_4$: C, 74.6; H, 9.5%).

(c) 3,7,12-Triketocholanic acid (10 g.) was dissolved in hot glacial acetic acid (140 ml.) and poured on to freshly prepared zinc amalgam (100 g.). To the mixture was added concentrated hydrochloric acid at such a rate that gentle reflux was maintained. Dry hydrogen chloride was slowly passed into the reaction mixture (5 hr.). During this time a colourless oil was formed on the surface of the refluxing suspension, and occasional shaking ensured thorough mixing of the reactants. The mixture was then cooled and the product

worked up as in (b). The solid was crystallized twice from glacial acetic acid and finally from acetone. The yield of colourless needles m.p. 162-163° was 3.6g. The mother liquors from the crystallizations were removed by distillation in vacuo and the resultant oil (6.5g.) re-reduced. Cholanic acid (0.6g.) was obtained giving an overall yield of 47%.

p-Isopropylbenzoic acid - This acid was prepared by a modification of the method of Newman and Easterbrook¹³⁰ from isopropylbenzene (150g.), aluminium chloride (150g.) and chloroacetyl chloride (150g.) in dry carbon disulphide. The reaction mixture was set aside overnight and then cautiously poured on to a mixture of crushed ice and hydrochloric acid. The resultant red oil was extracted with ether (500 ml.), the organic layer was dried (calcium chloride) and the ether removed by distillation. Dry pyridine (80 ml.) was added to the reaction mixture which was set aside at room temperature (15 min.) and then cautiously warmed on a water-bath whereupon an exothermic reaction took place and the mixture solidified. The brown crystals were dissolved in an excess of sodium hydroxide solution (10% w/v) and the brown solution continuously extracted with ether for 50 hr., then shaken with decolourizing charcoal (10g.) with heating and filtered hot. The cooled solution was acidified with concentrated hydrochloric acid and the precipitated acid

collected by filtration and dried (24 hr.) at 45°. The crude p-isopropylbenzoic acid was recrystallized twice from hexane using decolourizing charcoal. The yield of long colourless needles m.p. 116° (lit 116-117°) was 96 g. (47%).

o-Isopropylbenzoic acid

Scheme I (pg 36).

(i) Nitration of isopropylbenzene - Isopropylbenzene (468g.) was nitrated by the method of Hansch and Helmkamp^{1,2}. The crude product was fractionated in vacuo using a column 2m x 6 cm. (diameter) packed with glass helices. The following fractions were collected:

- | | | |
|-------|-----------------|-------|
| (i) | 110-112°/15 mm. | 42g. |
| (ii) | 116-123°/15 mm. | 132g. |
| (iii) | 124-138°/15 mm. | 76g. |
| (iv) | 142-143°/16 mm. | 230g. |

The first fraction was identified as unchanged isopropylbenzene by comparison of the infrared spectrum with that of an authentic sample. The second fraction was re-fractionated in vacuo using a column 0.5m x 2 cm (diameter). The following were collected:

- | | | |
|------|-----------------|------|
| (i) | 122-125°/15 mm. | 14g. |
| (ii) | 125-126°/15 mm. | 90g. |

The second fraction corresponded to pure o-nitroisopropylbenzene (14%) found (by gas-liquid chromatography) to be free from the other isomers. The

remaining fractions from the first distillation were purified by re-fractionation to yield m-nitroisopropylbenzene (37g. 6%) and p-nitroisopropylbenzene (263g. 41%) respectively.

(ii) o-Isopropylaniline - o-Nitroisopropylbenzene

(50g.) in ethanol (200 ml.) was hydrogenated over Raney nickel (5g.) at a pressure of 200 atmospheres. After 3 hr. when the hydrogenation was complete, the catalyst was removed by filtration and the solvent was distilled under reduced pressure in a stream of nitrogen. The residual red liquid was distilled in vacuo under nitrogen, and the fraction boiling at 104-105°/14 mm. was collected to yield o-isopropylaniline (36g. 80%) as a colourless liquid. A benzoyl derivative was prepared as colourless needles (from ethanol) m.p. 144-145°.

(iii) Attempted formation of o-bromoisopropylbenzene -

A solution of cuprous bromide was prepared from sodium bromide (6.16g.), cupric sulphate (2.52g.) and copper turnings (0.8g.), and dilute sulphuric acid. The solution was cooled to 0° and treated dropwise with constant stirring with a solution of the diazonium sulphate of o-isopropylaniline prepared from the amine (5.25g.), aqueous sulphuric acid (100 ml., 11%_{v/v}) and sodium nitrite (2.4g.). At the end of the addition, the mixture was heated at 30° (1 hr.) and then at 100° (1 hr.). The tarry suspension was cooled and poured with stirring into a mixture

of sodium hydroxide (20g.) in water (50 ml.). The reaction mixture was steam-distilled, the distillate extracted with ether and the latter washed with aqueous sodium hydroxide and dried (magnesium sulphate). Removal of the solvent gave a red oil (1.1g.) which was distilled in vacuo, yielding a colourless oil (0.6g.) b.p. 98-100°/24mm. which on gravimetric analysis was found to contain 12.7% bromine; o-bromoisopropylbenzene requires 40% bromine. Repetition of the Sandmeyer reaction at 100° did not improve the result.

Scheme II (pg. 37).

(i) Methyl o-halobenzoates - Methyl o-chlorobenzoate was prepared from o-chlorobenzoic acid, methanol and sulphuric acid as a colourless liquid b.p. 126-127°/21mm. in a yield of 70%. Similarly, methyl o-bromobenzoate was obtained from the corresponding acid as a colourless liquid b.p. 144-145°/29mm. in a yield of 74%.

(ii) 1-(o-Halophenyl)-1-methyl ethanols - 1-(o-Chlorophenyl)-1-methylethanol was prepared in 65% yield as a colourless liquid b.p. 126-127°/30mm. (lit.¹³¹ 108-111°/12mm.) by the method of Bradsher and Smith¹³¹. 1-(o-Bromophenyl)-1-methylethanol was similarly prepared as a colourless liquid b.p. 130-132°/19mm. in a yield of 78%.

(iii) o-Halo- α -methylstyrenes - A mixture of 1-(o-chlorophenyl)-1-methylethanol (34g.), glacial acetic acid (200 ml.) and concentrated sulphuric acid (1.2 ml.) was heated to boiling and powdered zinc (50g.) was added in small portions with stirring. The mixture was heated under reflux (4 hr.), cooled, and cautiously basified with sodium hydroxide (300g.) in water (1 l.). The alkaline suspension was steam-distilled (3 hr.). Crude o-chloro- α -methylstyrene was removed from the distillate by extraction with benzene. The extract was dried (magnesium sulphate) and subsequently carefully fractionated using an efficient column. The fraction b.p. 182-184° was collected. o-Chloro- α -methylstyrene (23g. 76%) was obtained as a colourless liquid. (Found: C, 70.9; H, 6.0. C₉H₉Cl requires C, 70.8; H, 5.9%). Similarly, o-bromo- α -methylstyrene was prepared in 79% yield as a colourless liquid b.p. 87-89°/19 mm.

(iv) o-Isopropenylbenzoic acid - o-Chloro- α -methylstyrene (5.3g,) distilled over lithium aluminium hydride) was added dropwise to a suspension of iodine-activated magnesium (0.8g.) in anhydrous tetrahydrofuran (10 ml.). Ethyl iodide (0.2 ml.) was added and the mixture heated under gentle reflux until a faint precipitate was observed (3.5 hr.). The yellow solution was poured on to powdered dry ice with vigorous stirring. Thorough

mixing of the reagents was continued for 45 min after which dilute hydrochloric acid was added and the acid suspension extracted with ether. The organic layer was shaken with sodium hydroxide solution (100 ml., 5% w/v) and the alkaline solution acidified with concentrated hydrochloric acid. The oily precipitate was shaken with ether and the latter extracted with sodium bicarbonate solution (40 ml.). Careful acidification with a mixture of concentrated hydrochloric acid and ice gave a precipitate which was removed by filtration and dried. The colourless solid was recrystallized from petroleum ether b.p. 40-60° to give o-isopropenylbenzoic acid (1.9g. 23%) m.p. 73-74° (lit¹¹⁶ 69-70°). (Found: C, 74.3; H, 6.2; O, 19.8; mol. wt. 159. Calc. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.2; O, 19.7 mol. wt. 162).

(v) o-Isopropylbenzoic acid - o-Isopropenylbenzoic acid (0.2g.) in sodium hydroxide solution (0.2 ml., 10% w/v) was hydrogenated by means of nickel-aluminium alloy. The catalyst was removed and the solution acidified and the precipitate collected by filtration and dried. The colourless solid was sublimed in vacuo to give o-isopropylbenzoic acid (0.2g. 100%) m.p. 59-60°.

Scheme III (pg. 40)

(i) 3,3-Dimethylphthalide - This compound was prepared from phthalic anhydride and methylmagnesium iodide in 79%

yield by the method of Bauer.¹³² The product was purified by passing the crude material through a column of alumina with ether elution. The product crystallized as thick colourless plates m.p. 68-69° (lit. 67-68°).

(iia) Attempted reduction of 3,3-dimethylphthalide - The compound was treated with the following reagents: (a) chromous chloride in aqueous ethanol at room temperature and 100°, (b) zinc and glacial acetic acid in the presence and absence of copper, (c) sodium and ethanol or anyl alcohol under reflux.

Only in (c) were acid products isolated and these were formed in insufficient quantities for purification. In all cases 3,3-dimethylphthalide was recovered in almost quantitative yield.

(iib) Hydrogenolysis of 3,3-dimethylphthalide - The compound (13g.) was heated under reflux with a solution of potassium hydroxide (80g.) in water (400 ml.) until a clear solution was obtained (ca. 1 hr.). This was cooled to 0° and portions of Raney nickel alloy (22g.) were added with vigorous stirring at such a rate that a minimum amount of frothing occurred. The reaction mixture was allowed to stand at room temperature for 1 hr., then diluted with water (800 ml.) and heated under reflux to complete hydrogenolysis. The mixture was cooled in ice and carefully acidified with concentrated hydrochloric acid until all the aluminium hydroxide formed had dissolved.

The oily suspension was extracted with ether (300 ml.) and the ethereal solution was washed with water and extracted with sodium bicarbonate solution (150 ml.). Acidification of the alkaline solution by dropwise addition into a mixture of concentrated hydrochloric acid and ice gave a precipitate which was collected by filtration. The product was dried in vacuo at room temperature and sublimed under reduced pressure. The ethereal solution from the initial extraction was dried (magnesium sulphate) and the solvent distilled to recover unchanged 3,3-dimethylphthalide.

The table below illustrates the yields of o-isopropylbenzoic acid and recovery of 3,3-dimethylphthalide using various hydrogenolysis times.

Table 2.3

Results of hydrogenolysis to o-isopropylbenzoic acid

Total hydro- genolysis time	%Yield of <u>o</u> -isopropyl- benzoic acid	%Recovery of 3,3-dimethyl- phthalide
5 hr.	35	57
7 hr.	43	42
12 hr.	68	31

The recovered 3,3-dimethylphthalide was recycled in order to produce more acid which was purified by sublimation at 20 mm. pressure. o-Isopropylbenzoic acid (10.6g., 81%) was obtained as colourless needles m.p. 61-62°. (Found : C, 73.35; H, 7.4; O, 19.5. C₁₀H₁₂O₂ requires C, 73.15; H, 7.4; O, 19.5%). The p-phenylphenacyl ester

crystallized from ethanol as colourless plates m.p. 111° .
(Found: C, 80.35; H, 6.15. $C_{24}H_{22}O_3$ requires C, 80.4;
H, 6.2%).

4-Methylpentanamide - 4-Methylpentanoyl chloride was prepared from the corresponding acid and thionyl chloride by the method of Giesler and Rupe.¹³³ The product had b.p. $137-140^{\circ}$ (lit. $129-130^{\circ}$). The acid chloride (25g.) was added dropwise with shaking to an excess of aqueous ammonia (sp. gr. 0.88) at 0° . The product was collected by filtration and recrystallized from water as colourless needles m.p. $117-118^{\circ}$ (lit.¹³⁴ 121°) in a yield of 23.2g. (73%).

N-(4-Methylpentanoyl) piperidine - 4-Methylpentanoyl chloride (4.2g.) was added dropwise to piperidine (3g.) with shaking and cooling. The orange suspension was poured into cold water, the resultant oil extracted with ether and the organic layer washed successively with very dilute hydrochloric acid, water and sodium bicarbonate solution. The ethereal layer was dried (magnesium sulphate) and the solvent subsequently removed by distillation. The residual liquid was fractionated under reduced pressure and the fraction b.p. $152-153^{\circ}/18$ mm. was collected. N-(4-Methylpentanoyl) piperidine (3.8g., 69%) was obtained as a colourless liquid.

Methyl 4-methylpentanoate - This compound was prepared in 60% yield from the corresponding acid by heating the latter

under reflux for several hours in an excess of methanol with a trace of concentrated sulphuric acid. The product was a colourless liquid b.p. 142° (lit.¹³⁵ $139-141^{\circ}/750$ mm.).

(e) Synthesis of Reference Compounds

2-Hydroxy-2-methylpropionic acid. - This compound was prepared by a modification of the method of Fittig and Thomsen¹³⁶ 2-Bromo-2-methylpropionic acid (25g.) was heated in water (200 ml.) at 80° with continuous stirring until a homogeneous solution had formed (36 hr.). This was cooled and then continuously extracted with ether (24 hr.). The ether solution was dried (magnesium sulphate) and the solvent removed by distillation. The residual semi-solid mass was distilled under reduced pressure. The fraction b.p. $118-120^{\circ}/24$ mm. was collected and recrystallized from benzene as colourless needles m.p. 77° (lit.¹³⁷ 79°) in a yield of 13g. (83%).

3,3-Diphenyl-3-hydroxypropionic acid - Benzophenone (9.1g.) dissolved in benzene (10 ml.) was added dropwise with stirring to a gently refluxing solution of an organo-zinc complex prepared from ethyl bromo-acetate (8.5g.) and zinc wool (3.5g.) in anhydrous benzene (30 ml.). Reflux was continued for 2 hr., then the reaction mixture was cooled and poured into dilute hydrochloric acid (100 ml.). The organic layer was dried (magnesium sulphate) and the solvent removed to give a red oil (3.3g.). This was heated under reflux (4 hr.) with potassium hydroxide (4g.) in ethanol (20 ml.)

and water (20 ml.). The ethanol was removed by distillation, water (20 ml.) was added and the alkaline solution acidified. The precipitate which formed was dissolved in ethyl acetate and the latter extracted with sodium carbonate solution. Acidification of the aqueous layer gave crude 3,3-diphenyl-3-hydroxypropionic acid (1.2g., 10%) which crystallized from ether as colourless plates m.p. 205-206° (lit.¹³⁸ 212°).

4-Hydroxy-4-methylpentanoic acid lactone - This compound was prepared from ethyl laevulinate and methylmagnesium iodide by the method of Porter¹³⁹ as a colourless liquid b.p. 204-206° (lit. 205-210°).

p-(1-Bromo-1-methylethyl) benzoic acid - p-Isopropylbenzoic acid (4.1g.) was dissolved in carbon tetrachloride (30 ml.) and a portion (2 ml.) of a solution of bromine (4.1g) in carbon tetrachloride (20 ml.) was added at room temperature with stirring. The mixture was irradiated with a 150-watt tungsten lamp. After an induction period (2 min.) decolourization of the solution took place and the remainder of the bromine solution was then added dropwise at such a rate that decolourization took place before the addition of the next drop. Towards the end of the reaction a precipitate formed. The reaction mixture was set aside (1.5 hr.) at room temperature and the precipitate collected by filtration. p-(1-Bromo-1-methylethyl) benzoic acid (5.2g. 85%) crystallized from benzene-hexane as colourless

plates m.p. 131-132° (dec.). (Found: O, 13.00.

$C_{10}H_{11}BrO_2$ requires O, 13.15%).

(ii) Hydrolysis - The above compound (1g.) was warmed with water (50 ml.) until it had dissolved and then heated at 80° for an additional 15 min. The solution was cooled, extracted with ether and the ethereal layer was dried (magnesium sulphate). The solvent was removed at room temperature to give p-(1-hydroxy-1-methylethyl) benzoic acid (0.4g., 54%) which crystallized from benzene as colourless needles m.p. 155-156° (main melt) (lit¹³⁷ 155-156°). (Found: C, 66.7; H, 6.9; O, 26.4 Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.7; O, 26.6%).

2,3-Dimethyl-2,3-di-(p-carboxyphenyl) butane -

p-Isopropylbenzoic acid (16.4g.) was dissolved in warm chlorobenzene (75 ml.) and di-*t*-butyl peroxide (7.5g.) was added with shaking. The mixture was heated under reflux in a stream of nitrogen for 24 hr., during which time a precipitate formed. The mixture was cooled in ice and the solid collected by filtration. The chlorobenzene solution was extracted with an excess of aqueous sodium hydroxide. The alkaline solution was extracted with ether and acidified. The resultant precipitate recrystallized from hexane to yield p-isopropylbenzoic acid m.p. 116° (12.1g.). The original precipitate was recrystallized from dimethylformamide to give 2,3-dimethyl-2,3-di-(p-carboxyphenyl) butane (2.6g. 16%)

as thick colourless plates m.p. 313-315° (evacuated tube)
(lit.¹⁴⁰ 275-280° dec.) (Found: C, 73.2; H, 6.85;
O, 19.6. Calc. for C₂₀H₂₂O₄: C, 73.6; H, 6.8; O, 19.6%).

o-Acetylbenzoic acid - This compound was prepared from
phthalic anhydride and malonic acid by the method of Yale.¹⁴¹
The product crystallized from benzene as colourless needles
m.p. 114° (lit. 114-115°).

(f) Oxidation of Branched Chain Carboxylic Acids

General Methods

In the oxidations ANALAR potassium permanganate,
potassium peroxydisulphate and potassium hydroxide were
used.

(a) With potassium manganate in dilute alkaline solution.

Potassium manganate solution was prepared by heating
potassium permanganate (6.3g., 0.04 mole) and potassium
hydroxide (6.4g.) in water (250 ml.) on a steam-bath (30 min.).
The solution was cooled and sulphur dioxide was carefully
bubbled below the surface until a permanent green colour was
attained. The carboxylic acid (0.02 mole) was added and
the solution maintained at 90-95° until all the manganate
had been converted into manganese dioxide. The alkaline
solution was cooled in ice and treated with sulphur dioxide
until almost all the manganese dioxide had dissolved. The
reaction mixture was shaken several times with ether, the
organic extract dried (magnesium sulphate) and the solvent
removed by distillation. When the products were ether-

insoluble solids it was found more convenient to remove all solid material by filtering the acid suspension and extracting the dried residue with benzene in a Soxhlet extractor to obtain the products. When γ -hydroxy-acids were formed, the reaction mixture was warmed (3 hr.) on a water-bath in the presence of dilute sulphuric acid (10% w/v). The cooled solution was extracted with ether and the organic layer was shaken with several portions of saturated aqueous sodium bicarbonate. The latter was acidified with concentrated hydrochloric acid and extracted with ether. Both ethereal extracts were dried (magnesium sulphate) and the products obtained on removal of the solvents.

(b) With potassium permanganate in concentrated alkaline solution.

The acid (0.02 mole) in a solution of potassium hydroxide (55g.) in water (100 ml.) was shaken with a solution prepared from potassium permanganate (6.3g., 0.04 mole), potassium hydroxide (5g.) and water (100 ml.). The latter was added dropwise at $40^{\circ} \pm 2^{\circ}$. The reaction mixture was poured on to undissolved potassium permanganate remaining from the latter solution and maintained at 40° with shaking until a permanent green colour had been attained. The solution was cooled in ice and worked up as in (a).

(c) With potassium peroxydisulphate in alkaline solution

The acid (0.05 mole) was dissolved in a solution of potassium hydroxide (40g.) in water (380 ml.) and heated to 90°. Potassium peroxydisulphate (34g., 0.0125 mole) was added in small quantities with vigorous stirring. After 2 hr. the reaction was complete as shown by the fact that a sample of the reaction mixture did not liberate iodine from a solution of potassium iodide in dilute sulphuric acid. The reaction mixture was cooled, acidified with concentrated hydrochloric acid to pH2 and extracted several times with ether. The products were isolated by carrying out the procedure described in (a).

(d) With potassium peroxydisulphate in acid solution

The acid (0.04 mole) was suspended in a solution of potassium peroxydisulphate (34g., 0.0125 mole) in water (250 ml.) to which dilute sulphuric acid had been added until the pH was 2. The mixture was vigorously stirred (5 hr.) at 90°. The solution was cooled, extracted with ether and worked up in the usual way to obtain the products.

The yields of hydroxy-acids (or lactones) from oxidations (a - d) are summarized in table 2.2 (page 41)

(g) Specific Oxidations

2-Methylpropionic acid - This compound was oxidized by methods (a) (b) and (c). The products were isolated by careful fractionation of the acid mixture under reduced

pressure to remove unchanged 2-methylpropionic acid followed by repeated recrystallization of the residue from benzene until a colourless material was obtained. This resulted in 2-hydroxy-2-methylpropionic acid m.p. and mixed m.p. 75°. 2-Methylpropionic acid was recovered in yields of 52%, 61%, and 43% respectively. The residual acid solution after the insoluble organic acids had been removed was continuously extracted with ether (24 hr.). The ethereal solution was dried (magnesium sulphate) and the solvent distilled to give a trace of residue which on paper chromatography indicated the presence of hydroxy-acid, but not dicarboxylic acids.

Diphenylacetic acid - Oxidation (b) was carried out.

A sample of the crude product was chromatographed on paper but as the R_f values of diphenylacetic acid and benzilic acid were similar, no satisfactory estimate of the extent of hydroxylation could be obtained. A spot test with concentrated sulphuric acid failed to give the red colour characteristic of benzilic acid. A portion of the product (1g.) was suspended in ether at 0° and shaken with ethereal diazomethane until complete solubility had been achieved. The solvent was removed to give a colourless solid which on recrystallization from aqueous methanol gave methyl diphenylacetate (1.0g) m.p. 61-62° (lit. 57-58°). The infrared spectrum

of the product showed an absence of absorption in the range $3150-3600\text{cm}^{-1}$ indicating that no benzoic acid had been formed in the oxidation.

3,3-Diphenylpropionic acid - Oxidation (b) was carried out. The alkaline solution at the completion of the oxidation was thoroughly shaken with ether and the organic layer dried (magnesium sulphate) and distilled to yield a semi-solid oil (0.19g.) with an infrared spectral maximum at 1690cm^{-1} characteristic of an aromatic ketone.

A 2,4-dinitrophenyl hydrazone was prepared from an ethanolic solution of the oil. The product was recrystallized from acetic acid as orange needles m.p. 242° which was not depressed on admixture of an authentic sample of benzophenone 2,4-dinitrophenylhydrazone. The acid component of the oxidation product was isolated in the usual way and shown to consist mainly of 3,3-diphenylpropionic acid.

4-Methylpentanoic acid. - In all cases the lactonic fraction was isolated as described. The crude product was distilled and the fraction b.p. $102-103^{\circ}/17\text{mm.}$ was collected. The infrared spectrum was found to be identical with that of an authentic sample of 4-hydroxy-4-methylpentanoic acid lactone. (Found: C, 63.1; H, 8.9. Calc. for $\text{C}_6\text{H}_{10}\text{O}_2$: C, 63.1; H, 8.85%). The recovery of 4-methylpentanoic acid was 78%, 72%, 76% and 67% respectively. The detection of dicarboxylic acids

was attempted by the method described under 2-methylpropionic acid. From oxidation (c) a dicarboxylic acid was detected by paper chromatography, but it could not be identified.

Modification of the oxidation of 4-methylpentanoic acid

with alkaline potassium permanganate - The oxidation was repeated using twice the quantity of alkaline potassium permanganate and doubling the time of the addition of the reagent. When the products were worked up, the neutral fraction yielded a yellow oil (0.03g, 0.7%) which was shown to be 4-hydroxy-4-methylpentanoic acid lactone.

Attempted oxidation of 4-methylpentanoic acid with alkaline

hydrogen peroxide. - 4-Methylpentanoic acid (2.3g.) was dissolved in sodium carbonate solution (30 ml. 20% w/v) and hydrogen peroxide solution (33 ml., 30%) was added. The mixture was allowed to stand in sunlight until the evolution of oxygen had ceased. The reaction mixture was worked up in the usual way to give 4-methylpentanoic acid (2.2g.). No trace of lactonic material was observed.

p-Isopropylbenzoic acid

- From oxidation (a) and (b) the crude acid mixture was extracted with hot hexane from which unreacted p-isopropylbenzoic acid m.p. 114-117° was recovered after several recrystallizations. The residue was extracted with hot benzene from which p-(1-hydroxy-1-methylethyl) benzoic acid m.p. 152-154° was obtained. The residue from this extraction contained traces of hydroxy-acid together with a small amount of higher melting substance which was not

identified although paper chromatography showed that it was not terephthalic acid. No traces of dimeric dicarboxylic acids were detected. The recoveries of *p*-isopropylbenzoic acid were 46% and 34% respectively.

From oxidation (c) an organic gum was obtained from which *p*-isopropylbenzoic acid was extracted. A portion of the residue (1.0g.) which contained no hydroxy-acid and gave a brown colour with ferric chloride was dissolved in ether and treated with an excess of ethereal diazomethane at 0°. The ether was filtered to remove traces of insoluble material and removed by distillation to give an orange gum (1.0g.) which was chromatographed on alumina. Elution with benzene yielded a colourless solid which was crystallized from a mixture of low-boiling petroleum ethers. This gave methyl *p*-acetylbenzoate (0.3g., 30%) m.p. 91-94° (lit.¹³⁷ 92°) (Found: C, 67.35; H, 5.8; O, 26.6. Calc. for C₁₀H₁₀O₃: C, 67.4; H, 5.65; O, 26.9%). From oxidation (a) no hydroxy-acid was isolated and traces of phenols were observed and *p*-acetylbenzoic acid was isolated as the methyl ester in 35% yield.

o-Isopropylbenzoic acid - The acidic and lactonic products from oxidations (a) and (b) were separated as described. The neutral material was shown to be 3,3-dimethylphthalide m.p. 68-69° (from petroleum ether). The m.p. was not depressed on admixture of an authentic specimen. The

acidic fraction was shown to consist mainly of o-isopropylbenzoic acid. Sublimation in vacuo gave the acid m.p. 61-62° in recovery of 11% and 34% respectively. From oxidation (b) the presence of phthalic acid was detected by means of a phthalein test.

From oxidation (c) involving o-isopropylbenzoic acid (3.2g.), a neutral oil (0.23g.) was obtained from which 3,3-dimethylphthalide (0.05g., 2%) was obtained. The acid material was triturated with hot hexane and distillation of the latter followed by sublimation of the residue gave o-isopropylbenzoic acid (0.05g.). The residue was shown by comparative paper chromatography to contain o-acetylbenzoic acid. Sublimation in vacuo of a portion of this (0.2g.) followed by recrystallization of the sublimate from benzene gave o-acetylbenzoic acid (0.03g., 14%) m.p. and mixed m.p. 112-114°.

From oxidation (a) using o-isopropylbenzoic acid (1.1g.), 3,3-dimethylphthalide (0.67g., 61%) m.p. 67-68° and starting material (0.1g.) were obtained. The residual oil (0.19g.) was sublimed to give o-acetylbenzoic acid (0.1g, 9%) m.p. 112-114° .

Reaction of 3,3-dimethylphthalide with alkaline potassium peroxydisulphate. - 3,3-Dimethylphthalide (1.0g.) was subjected to oxidation (c). The neutral fraction contained a trace of starting material. The residual acidic oil gave no test for phthalic acid. o-Acetylbenzoic acid

(0.4g.) was isolated in the usual way.

In all oxidations involving o-isopropylbenzoic acid phenols, were detected by ferric chloride tests.

Cholanic acid - This compound was oxidized by methods (a - d). In all cases quantitative recovery of starting material resulted. The compound was identified by m.p., mixed m.p. and infrared spectrum.

4-Methylpentanamide - The amide (0.6g.) was dissolved in hot water (10 ml.) and potassium peroxydisulphate (3.4g.) was added in portions at 90° with stirring. The solution was heated (2 hr.) after which time the pH was less than 2. The solution was cooled and then extracted with ethyl acetate. The latter was extracted with sodium bicarbonate solution. Acidification of the alkaline extract gave 4-methylpentanoic acid (0.1g.) identified by comparative paper chromatography. The ethyl acetate was dried (magnesium sulphate) and the solvent removed to give an oil (0.4g.) the infrared spectrum of which showed maxima at 1755cm^{-1} and 1680cm^{-1} indicating a mixture of γ -lactone and primary amide. The mixture was hydrolysed with aqueous sodium hydroxide (1 ml., 10% w/v). Acidification followed by continuous extraction of the solution with ether (24 hr.) gave an oil (0.22g.) which on distillation in vacuo afforded 4-hydroxy-4-methylpentanoic acid lactone (0.12g.) identified by its characteristic infrared spectrum.

Reaction of 4-methylpentanamide with potassium bisulphate. -

4-Methylpentanamide (0.6g.) was treated with a solution of potassium bisulphate (3.4g.) in water (20 ml.) under the conditions described in the previous experiment. The products identified were 4-methylpentanoic acid (0.15g.) and 4-methylpentanamide (0.35g.).

Reaction of 4-methylpentanamide with potassium peroxy-
disulphate at pH 5.5-7 -

The amide (0.6g.) was dissolved in water (20 ml.) and potassium peroxydisulphate (3.4g.) added. The mixture was heated to 90° and saturated sodium carbonate solution was immediately added at such a rate that the pH of the reaction mixture was maintained between 5.5 and 7, a check being made by spot tests on BDH narrow range indicator papers. After 3 hr., the solution was cooled and worked up in the usual way. The neutral product (0.02g.) was identified as 4-hydroxy-4-methylpentanoic acid lactone. No acidic material was obtained.

Reaction of N-(4-methylpentanoyl)-piperidine under the above
conditions. -

The amide (0.9g.) was suspended in water (20 ml.) at 90° with stirring, and treated with potassium peroxydisulphate solution at pH 5.5-7 as previously described. The product (0.4g.) was shown by infrared spectroscopy to contain tertiary amide and γ -lactone. No 4-methylpentanoic acid was detected.

Repetition of the previous experiment using methyl 4-methylpentanoate. - Methyl 4-methylpentanoate was oxidized as described. The products identified were unchanged ester and 4-hydroxy-4-methylpentanoic acid lactone.

Behaviour of 4-methylpentanoic acid derivatives in the pH range 5.5-7. - 4-Methylpentanamide, N-(4-methylpentanoyl) piperidine and methyl 4-methylpentanoate were in turn heated at 90° in pure water. In all cases no hydrolysis had occurred after 5 hr., as indicated by the absence of the corresponding acid.

In the last two cases the starting material was recovered quantitatively. The above experiments were repeated in a buffered solution pH 5.5 prepared from aqueous solutions of potassium dihydrogen phosphate ($\frac{N}{15}$, 18 ml.) and disodium hydrogen phosphate ($\frac{N}{15}$, 2 ml.). No hydrolysis was observed under these conditions.

Effect of iodine on the reaction of 4-methylpentanamide with potassium peroxydisulphate. - The experiment (pg. 87) was carried out in duplicate on the amide (1.4g.) except that in the second case iodine (1 equivalent) was added. The acidified solutions containing the products were continuously extracted with ether (24 hr.) and the organic layer shaken in turn with sodium bicarbonate solution, sodium metabisulphite solution and a small quantity of water. The ether solution was dried (magnesium sulphate)

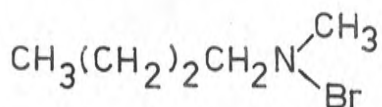
and removal of the solvent gave 4-hydroxy-4-methylpentanoic acid lactone (0.30g.) and (0.36g.) respectively.

CHAPTER 3.

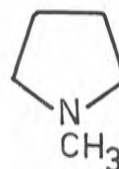
INTRAMOLECULAR HYDROGEN TRANSFER REACTIONS

Although it has been known for a considerable time that the free radical $R(\text{CH}_2)_4Y^\cdot$ ($Y = \text{CH}_2, \text{NH}, \text{O}, \text{etc.}$) is capable of intramolecular hydrogen abstraction with the formation of an isomeric radical, interest in the reaction has only developed since the realization of the significance of its specificity. The application of this type of reaction has been to date, limited to the fields of smaller acyclic and alicyclic compounds and steroids. It will become obvious from the following examples, however, that such a reaction may be applied successfully to any radical which has a spatially favourable hydrogen atom attached to an aliphatic chain.

In one of the first recorded intramolecular hydrogen abstraction reactions, Löffler and Freytag¹⁴³ formed N-methylpyrrolidine (LXIX) by heating N-bromo-N-methylbutylamine (LXVIII) with concentrated sulphuric acid. Coleman and Goheen¹⁴⁴ improved the yields of the reaction by



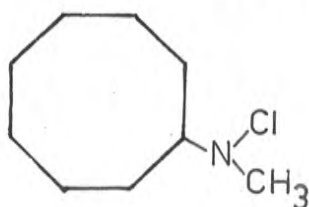
(LXVIII)



(LXIX)

modifying the conditions and extended its scope to N-chloroamines.

The reaction was put on a sound theoretical basis by Wawzonek and Thelen¹⁴⁵ who subjected the N-Chlorocyclo-octylamine (LXX) under acid conditions to ultraviolet radiation and also hydrogen peroxide, to determine whether N-methylgranatanine (LXXI) or 9N-methyl-aza-bicyclo [4,2,1] nonane (LXXII) would be preferably



(LXX)

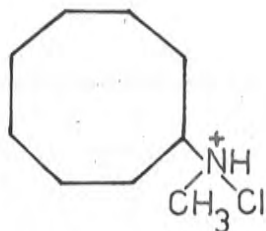


(LXXI)

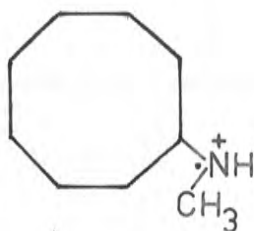


(LXXII)

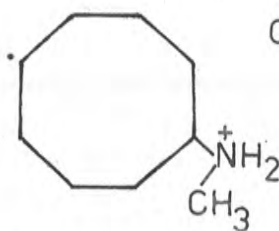
formed. In fact the former compound was formed exclusively, although in poor yield, and the reaction was considered to proceed by one of two paths. The initial step in both cases is the protonation of the base to give the ion (LXXIII) which in the presence of ultraviolet



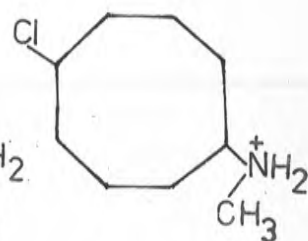
(LXXIII)



(LXXIV)



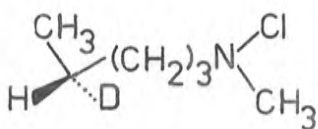
(LXXV)



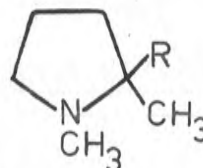
(LXXVI)

light or the radical reagent, results in the formation of the radical (LXXIV). This may undergo intramolecular hydrogen abstraction to yield (LXXV), which initiates a chain process by abstraction of a chlorine atom from the

ion (LXXIII) to give (LXXVI) which on treatment with base yields N-methylgranatanine. On the basis of the structure of the cyclo-octane ring, it was considered that the 4-position allows more facile hydrogen abstraction than the 3-position. As an alternative mechanism it was thought that the radical ion (LXXIV) might undergo direct cyclization with the elimination of a hydrogen radical. The intramolecular nature of this reaction was confirmed by Corey and Hertler¹⁴⁶ who found that the decomposition of the optically active deuterated amine (-)-N-chloro-N-methyl amyamine-4-d (LXXVII) gave rise to the inactive pyrrolidine (LXXVIII, R = H or D) with a preponderance (7:2) of the non-deuterated form. The reaction was

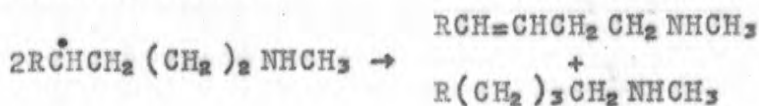


(LXXVII)

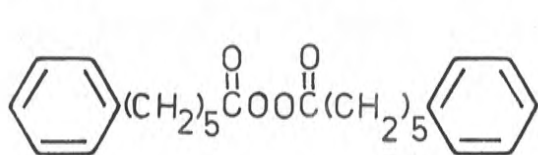


(LXXVIII)

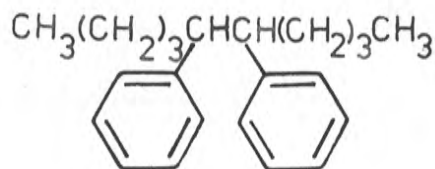
found to be catalysed by ferrous ions and inhibited by oxygen. The authors were uncertain as to whether the protonated form (LXXIII) or the corresponding free base was responsible for the propagation step, and also which of the two species was involved in the disproportionation termination step.



Rearrangement products formed from alkyl radicals under pyrolytic conditions may often be explained by intramolecular hydrogen abstraction mechanisms. Thus Grob and Kammüller¹⁴⁷ obtained 5,6-diphenyldecane (LXXX) from di-(ϵ -phenylhexanoyl) peroxide (LXXIX) and explained its formation on the basis of the decomposition of the

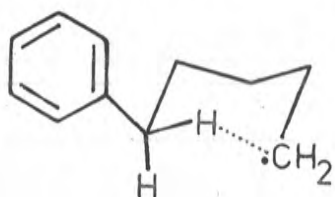


(LXXIX)

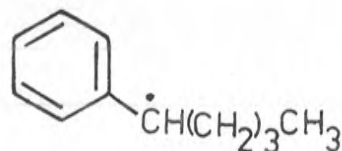


(LXXX)

peroxide to give 5-phenylpentyl radicals, which by assuming the chair conformation (LXXXI) could undergo hydrogen abstraction from the reactive benzylic position to give the radical (LXXXII) and hence the dimer (LXXX).



(LXXXI)

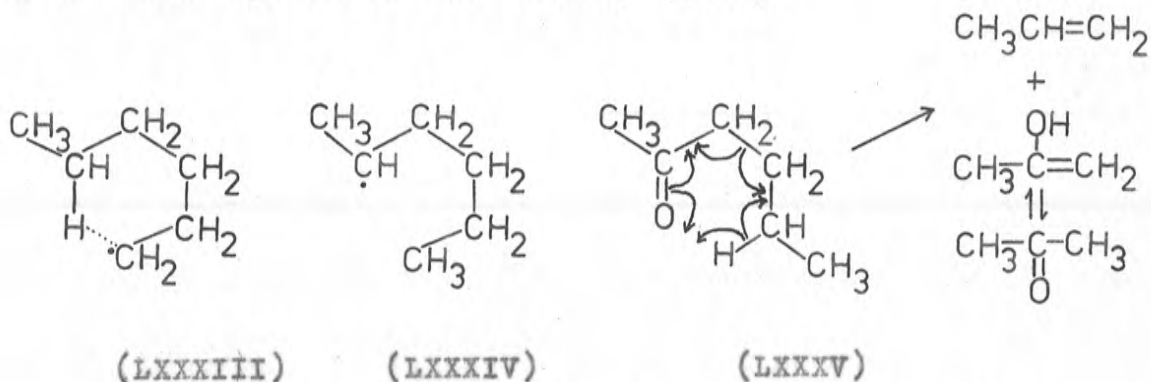


(LXXXII)

Rice and Kossiakoff¹⁴⁸ in order to explain the yields of products formed in the chain decomposition of hexane, heptane and octane, considered radical isomerization via intramolecular hydrogen abstraction to be an important factor, e.g. with hexane, the 1-hexyl radical (LXXXIII) isomerizes to the 2-hexyl radical (LXXXIV). Roedel¹⁴⁹ found that in the polymerization of ethylene at various temperatures, studies of the flow rate and the tensile

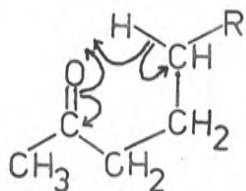
strength of the product indicated that chain branching was occurring by an intramolecular hydrogen abstraction process, resulting in a new propagating species.

The most widely investigated source of intramolecular hydrogen abstraction reactions is the alkoxy radical derived from the homolysis of hydroperoxides and peroxides and various organic or inorganic esters of long chain aliphatic alcohols, or the incipient alkoxy radical observed in the photolysis of ketones. In connection with the latter aspect, Davis and Noyes¹⁵⁰ isolated acetone and propene from the photolysis of hexan-2-one (LXXXV). Since no chain effect was observed, the authors considered that hydrogen abstraction from a spatially favourable carbon atom was being effected by the oxy-radical formed on π bond rupture of the carbonyl group:

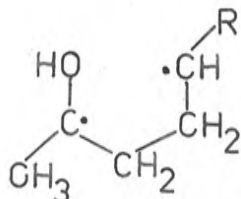


The only criticism of the mechanism was that the yields of decomposition products did not vary with the temperature of photolysis. In an extension of this work¹⁵¹ it was observed that aliphatic methyl ketones possessing a γ -hydrogen atom e.g. (LXXXVI) gave rise to

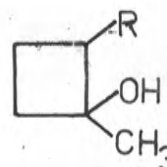
acetone, olefine and a cyclobutanol (LXXXVIII), the latter being formed via the diradical (LXXXVII). This type of



(LXXXVI)



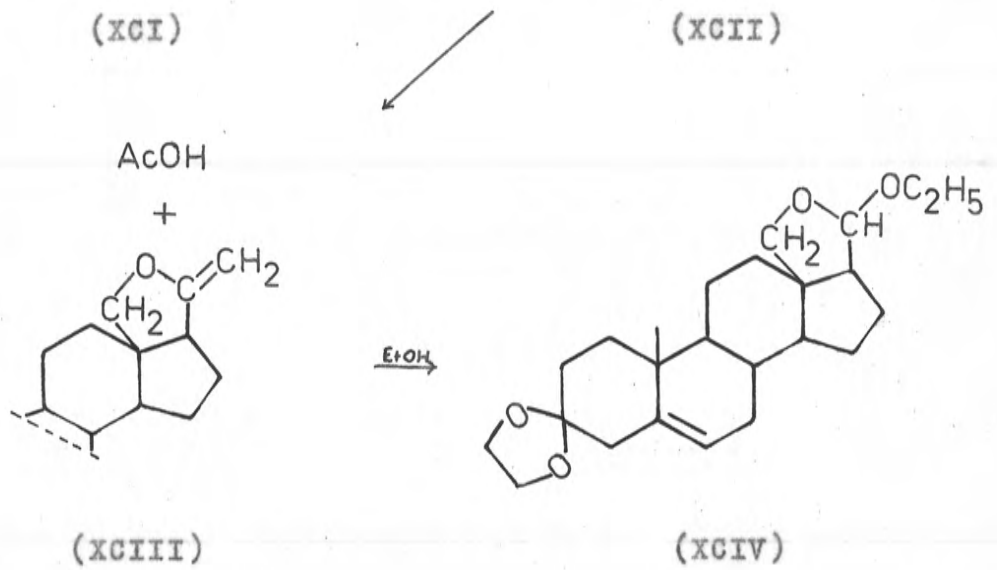
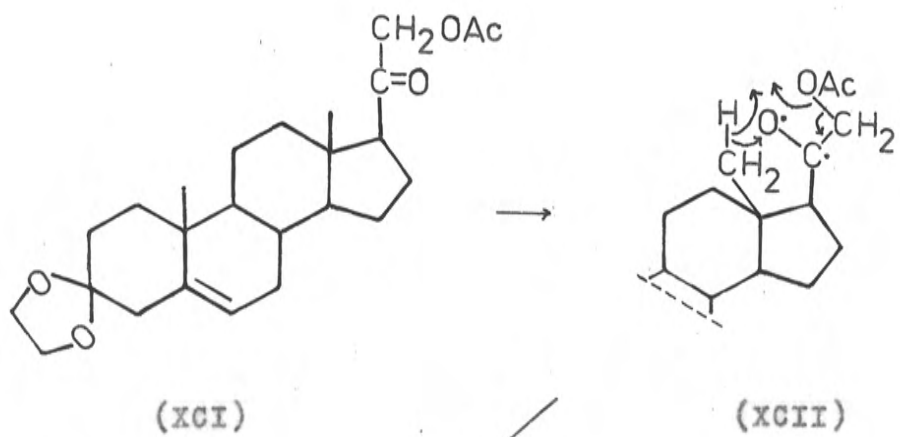
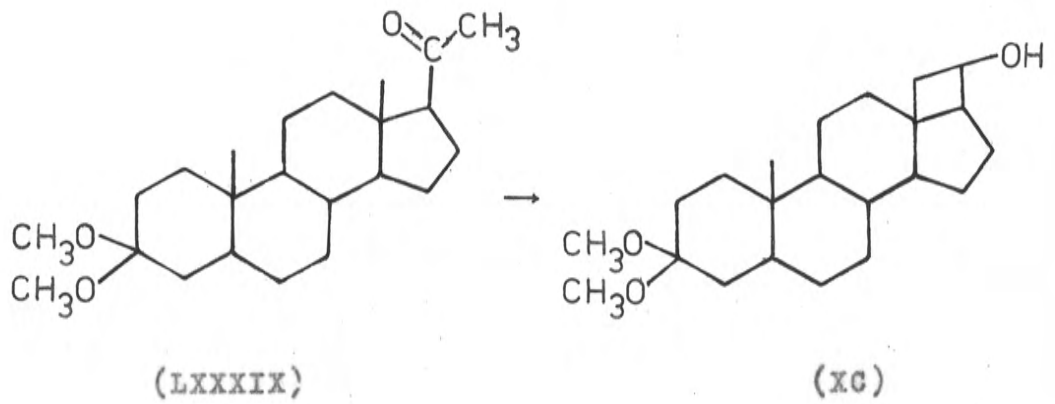
(LXXXVII)



(LXXXVIII)

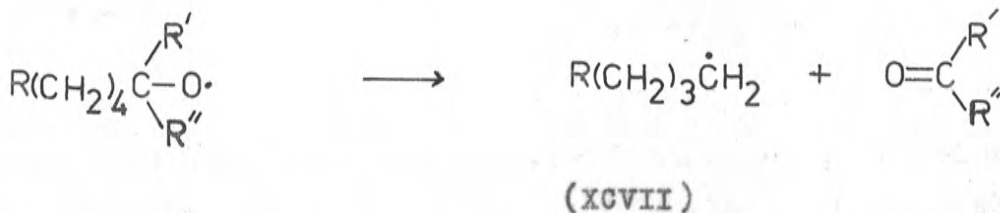
reaction has been applied successfully to the steroid series¹⁵² with the formation of 18,20-cyclo-steroids from 20-pregnanones. Thus 3,3-di-methoxypregnan-20-one (LXXXIX) on irradiation gave 3,3-dimethoxy-18,20-cyclo-pregnan-20-ol (XC) as well as ring-rupture products.¹⁵³ In the photolyses of 21-acetoxypregnen-20-ones, hemi-acetals were formed in a reaction unique in that intramolecular hydrogen abstraction proceeded simultaneously with the removal of the functional group initiating the abstraction.¹⁵⁴ Thus 3,3-ethylenedioxy-20-oxo-21-acetoxy- Δ^5 -pregnene (XCI) on photolysis in ethanol produced 3,3-ethylene dioxy-18,20-oxido-20-ethoxy- Δ^5 -pregnene (XCIV) via intermediates (XCII) and (XCIII).

In the presence of traces of salts of transition elements in their higher oxidation states e.g. Cu^{++} , hydroperoxides^{155, 156} (XCV, Y = H), peroxides (XCV, Y = $\text{R}(\text{CH}_2)_4\text{CR}'\text{R}''$) and peresters of long chain alcohols, decompose with the formation of alkoxy radicals (XCVI).

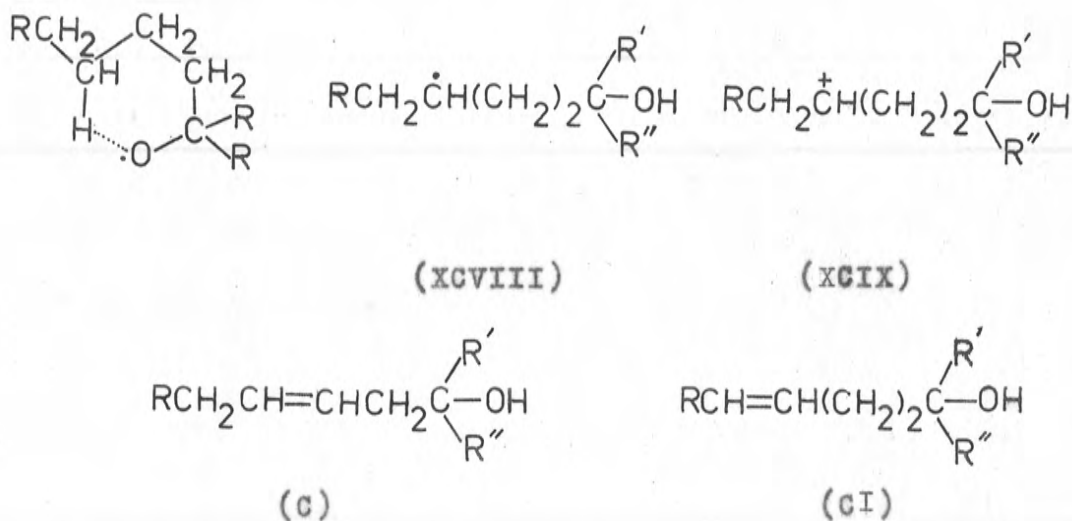




These may undergo decomposition in two competitive ways to give either alkyl radicals (XCVII), and carbonyl compounds:

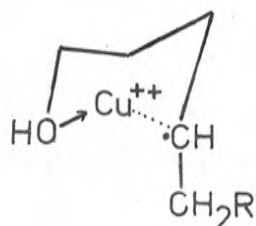


or the hydrogen-abstracted hydroxyalkyl radical (XCVIII). This is readily oxidized by the cupric ion to the

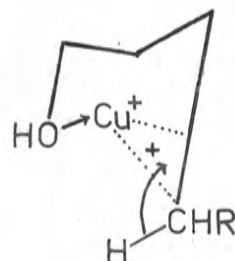


carbonium ion, and simultaneous removal of a proton from a carbon atom adjacent to that bearing the charge, results

in the formation of the isomeric alkene alcohols (C) and (Cl). The alkyl radical (XCVII) is likewise oxidized to an alkene-1. In photolyses involving 2-methyl-2-hexyloxy radicals (XCVI, $R = H$, $R, R' = CH_3$) Kochi¹⁵⁶ obtained both isomeric 2-methyl-2-hydroxyhexenes, but Acott and Beckwith¹⁵⁵ obtained only the isomer (Cl) from the reaction of a series of peracetates (XCV, $Y = CH_3-C=O$) and hydroperoxides under similar conditions. The latter workers postulated a "chair" type of cyclic transition state (CII→CIII) involving complexed cupric ion to account for the exclusive formation of (Cl).



(CII)



(CIII)

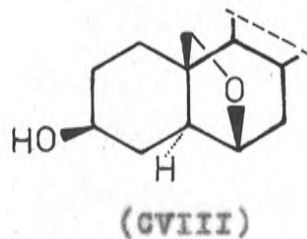
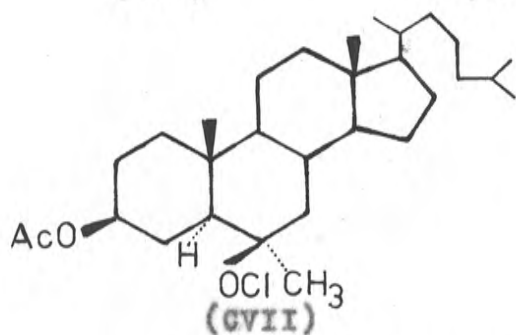
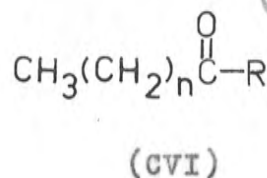
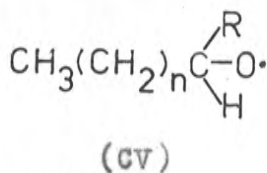
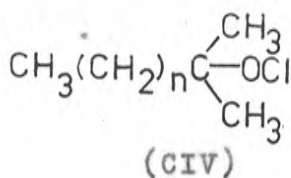
The decompositions of long chain and steroid hypochlorites have provided further examples of intramolecular hydrogen abstraction, and they exhibit certain characteristics which are unique. Padwa and Walling¹⁵⁷ in a series of thermal decompositions of hypochlorites of the type (CIV), showed that when $n = 0$ or 1 the main products were acetone and the alkyl chloride $CH_3(CH_2)_nCl$.

formed via the same mechanism as that observed in the decomposition of peroxides etc. (pg. 97). When $n \geq 2$, the β -carbon scission was accompanied by a 1,5-hydrogen shift resulting in the formation of a δ -chloroalcohol. These workers failed to obtain a product of this type from the photolyses of suitable primary or secondary alcohols. The radical (CV) tended to undergo α -hydrogen abstraction rather than intramolecular hydrogen abstraction and the carbonyl compound (CVI) was the result. Jenner¹⁵⁸ using modified conditions was, however, able to isolate 4-chlorobutan-1-ol from the decomposition of butyl hypochlorite. Only traces of butyraldehyde - the main product observed by Padwa and Walling - were detected but good yields of butyl butyrate were obtained, doubtless arising from the butyraldehyde or a derived radical.

The effect of the solvent on the intramolecular hydrogen abstraction reaction appeared to be variable. Greene and co-workers¹⁵⁹ found that the yield of 5-chloro-2-methyl hexan-2-ol from the photolysis of the hypochlorite of 2-methyl hexan-2-ol (CIV, $n = 3$) increased when trichloro-fluoromethane was replaced as solvent by the hydrogen donor cyclohexene. This change did not, however, markedly lower the yields of β -fragmentation products. On the other hand Walling and Padwa¹⁶⁰ observed very little difference in the yields of δ -chloro-alcohol with variation in solvent. The latter workers

investigated the products of photolyses of a number of tertiary hypochlorites in order to determine whether 1,5-hydrogen transfer occurred to the exclusion of other types of intramolecular hydrogen abstraction. Previous work had never revealed any products which could be attributed to a cyclic transition state containing other than six annular atoms. The photolyses of the hypochlorites of 2-methyl heptan-2-ol (CIV, $n = 4$) and 2-methyl octan-2-ol (CIV, $n = 5$) where formation of a seven-membered transition state would result in the abstraction of a secondary hydrogen atom, ϵ -chloroalcohols were indeed observed. The ratio of ϵ - to δ -chloro-alcohols was shown to be 1:15. Activation of the ϵ -position by the presence of a substituent phenyl group, resulted in the ratio being raised to 1:9. Thus the activity of ϵ -*s*-benzyl hydrogen atoms towards intramolecular radical attack is $5/3$ that of ϵ -aliphatic hydrogen atoms which agrees with the relative activities of these atoms towards attack by other radical species.

The decomposition of hypochlorites by homolysis followed by intramolecular hydrogen shift has been extended to the steroid series by Barton and Akhtar¹⁶¹. 3β -Acetoxy- 6α -methyl cholestan- 6β -yl hypochlorite (CVII) on photolysis followed by hydrolysis produced 6α -methyl- $6,19$ -oxido-cholestan- 3β -ol (CVIII) in fair yield.



Intramolecular hydrogen abstraction by alkoxy radicals formed in the decomposition of organic hypoiodites has been investigated exclusively in connection with steroids. The general method involves the treatment of the appropriate alcohol with iodine and lead tetra-acetate and photolysing the hypoiodite formed in situ. The products obtained are either cyclic ethers or hemi-acetals depending on the steric arrangement of the reactive centres in the iodohydrin intermediate. The results are shown in the following table. A refers to the position of the hydroxyl group and B to the carbon atom or atoms attacked.

Table 3.1

Photolysis of Steroid Hypoiodites

A	B	Product	Reference
6 β	19 β	6 β ,19 β -exo-steroid	205
20	18	20-ketone-18,20-hemi-ketal	206
11 β	18 β ,19 β	11 β ,18 β or 11 β ,19 β exo-steroid	207, 208
2 β	19 β	19-aldehyde-2 β ,19 β -hemi-acetal	209

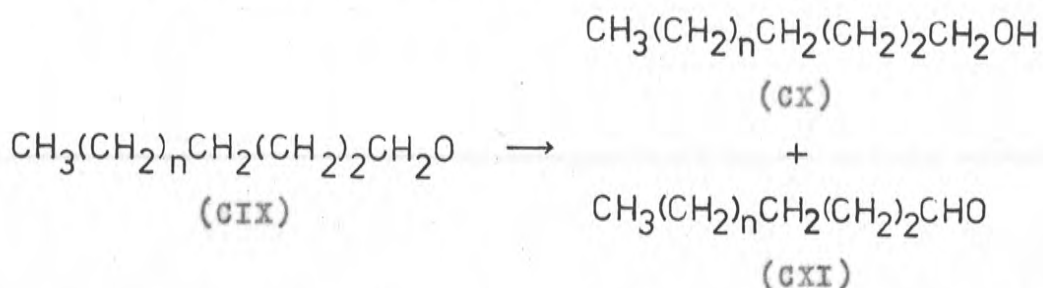
Table 3.1 (Con'd)

Photolysis of Steroid Hypoiodites

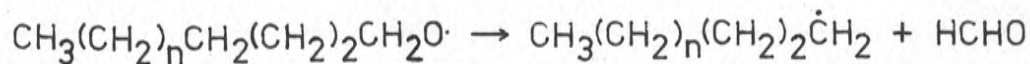
A	B	Product	Reference
4 β	19 β	19-aldehyde-4 β ,19 β -hemi-acetal	209
6	19*	6 β ,19 β oxo-steroid; 19-aldehyde 6 α , 19-hemi-acetal	205

Although the conception of organic nitrites undergoing homolyses followed by intramolecular hydrogen abstraction was first conceived by Barton,¹⁶² its application to long chain aliphatic nitrite esters in solution was initially investigated by Kabasakalian and co-workers.¹⁶³ They observed three main reactions resulting from the alkoxy radicals (CIX) formed.

- (a) a disproportionation into the alcohol (CX) and the corresponding aldehyde (CXI)

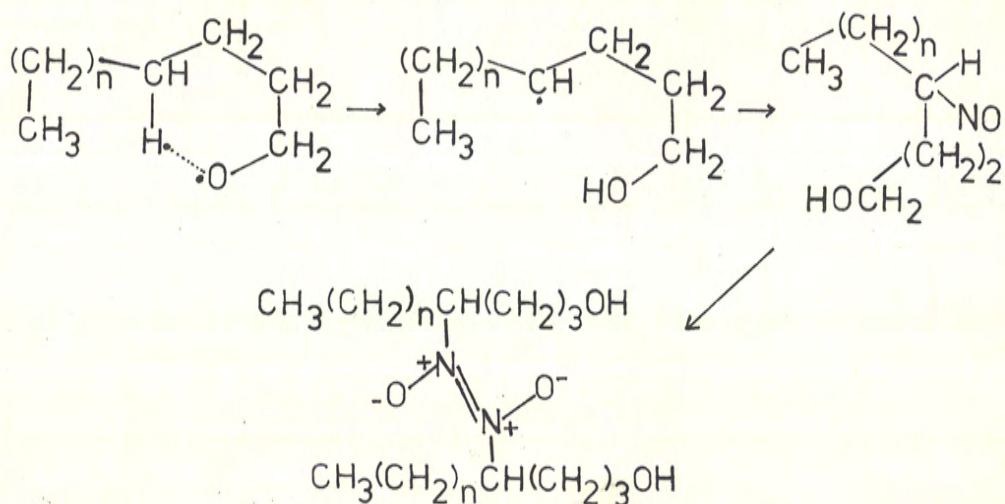


- (b) scission of the $\alpha\beta$ -bond with the formation of alkyl radicals and carbonyl compounds, observed in other alkoxy radical photolyses - the radical decomposition reaction:



*11-acetyl group present.

(c) hydrogen abstraction from a spatially favourable carbon atom - the Barton reaction - followed by re-combination of the new radical with nitric oxide and subsequent dimerization of the nitroso-compound formed.

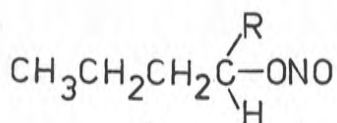


Reaction (c) is in sharp contrast to the photolyses of alkyl nitrites in the vapour phase where reactions (a) and (b) predominate.¹⁶⁴

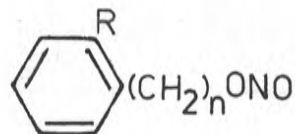
In the photolyses of long chain nitrites of primary alcohols reaction (c) predominated over reaction (a) and the contribution of (b) was negligible. The yield of nitroso-alcohol dimer from butyl nitrite, however, dropped sharply and reaction (a) predominated. These results were explained by the fact that it requires less energy to abstract a hydrogen radical from a secondary carbon atom than from a primary carbon atom. Similar effects were observed with the nitrites of secondary alcohols except that reaction (b)

rather than (a) was of major importance after the intramolecular hydrogen abstraction reaction. In the photolysis of the nitrite (CXII, R = CH₃, C₂H₅), low yields of nitroso-alcohol dimer were again observed and reaction (b) predominated with the formation of acetaldehyde, nitrosopropane dimer from (CXII, R = CH₃), and products of the fission of either of the two αβ carbon-carbon bonds from (CXII, R = C₂H₅). In general it can be said that in the photolyses of secondary alkyl nitrites, intramolecular hydrogen abstraction occurs predominantly over, but not to the exclusion of, the radical decomposition mechanism. The photolyses of tertiary alkyl nitrites resulted in a much more selective reaction. Thus when the Barton reaction required the abstraction of a secondary hydrogen atom, this mechanism operated exclusively, whereas radical decomposition was preferred to primary hydrogen radical abstraction.

In order to determine whether a six-membered transition state was a prerequisite for the Barton reaction, Kabasakalian and co-workers¹⁶³ photolysed a series of phenylalkyl nitrites (CXIII, R = H, n = 0-5; R = CH₃, n=0)



(CXII)



(CXIII)

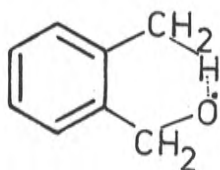
The results are summarized as follows.

Table 3.2

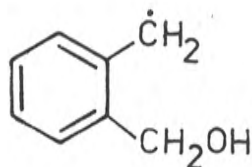
Photolysis of Phenylalkyl Nitrites

R	n	Result
H	1,3	no dimer
H	2	<i>o</i> -nitrosotoluene dimer
H	4,5	<i>4</i> -nitroso-alkan-1-ol dimer
CH ₃	1	<i>o</i> -(nitrosomethyl)benzyl alcohol

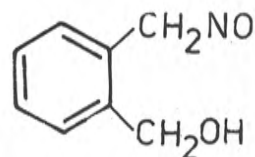
The fact that dimers of δ -Nitroso-alcohols were formed exclusively when the aliphatic chain was sufficiently long to permit 1,6-hydrogen shift, indicated that the six-membered transition state alone occurred. The evidence for this is further strengthened by the fact that no 5-nitroso-5-phenyl pentan-1-ol dimer was observed in the photolysis of 5-phenylpentyl nitrite (CXIII, R = H, n=5) although hydrogen atoms are preferentially removed from benzylic carbon atoms in intermolecular abstraction reactions. The yields of nitroso-alcohol dimer from both 4-phenylbutyl nitrite and 5-phenylpentyl nitrite were identical indicating that the benzyl group seems to play no part in determining the extent of hydrogen radical abstraction. This is in contrast to the hydrogen rearrangements in hypochlorites (pg. 100). The six-membered transition state accounts for the formation of (*o*-nitroso-methyl)benzyl alcohol from *o*-methyl benzyl nitrite (CXIII, R = CH₃, n=1) if the steps (CXIV - CXVI) are postulated. The nitroso-compound obtained from



(CXIV)



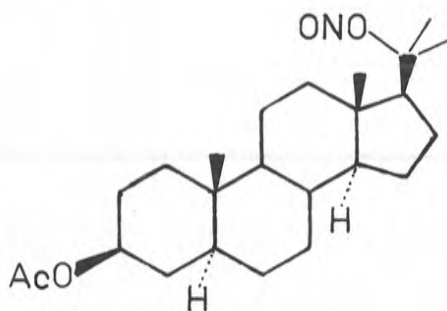
(CXV)



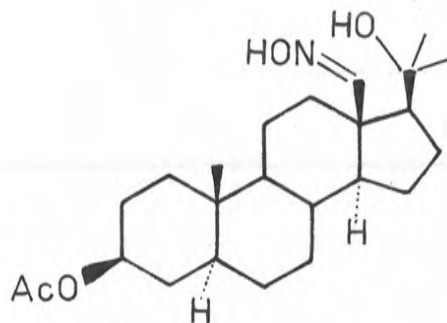
(CXVI)

2-phenylethyl nitrite (CXIII, R = CH₃, n=2) has been accounted for by the radical decomposition mechanism.

In the steroid series, Barton and co-workers¹⁶⁵ have observed reactions analagous to those achieved with alkyl nitrites, but due to steric considerations, oximes are often obtained instead of nitroso-alcohol dimers. Thus 3 β -acetoxy-5 α -pregnan-20 β -nitrite (CXVII) on photolysis yielded 18-oximino-5 α -pregnan-3 β , 20 β -diol-3-acetate (CXVIII)



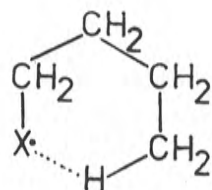
(CXVII)



(CXVIII)

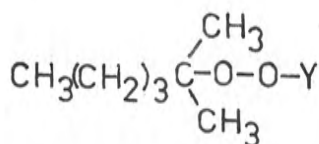
The fact that 1,5-intramolecular abstraction of hydrogen is preferred to 1,6-transfer, and both occur to the exclusion of other types of transfer, has been given considerable thought. Thus Corey and Hertler¹⁴⁶ and

Walling and Padwa¹⁶⁰ consider that the quasi six-membered transition state (CXIX) is the smallest in which the

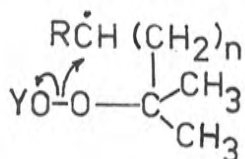


relative C,H and X atoms can approximate to linearity in order to achieve the maximum orbital overlap required for facile bond formation. In support of this statement, Corey and Hertler point out that where linear 1,5-hydrogen transfer cannot occur as in N-chloro-N-methyl-cyclohexylamine, the Hofmann-Löffler-Freytag reaction is both slow and inefficient. The fact that this linear requirement is not met, as well as the considerable steric interaction and angle strain involved in such a transformation, prevents, 1,3- and 1,4-hydrogen shifts. The 1,5- and higher order shifts can theoretically involve an angle of approximately 180° , but hydrogen abstraction of an order of 1,7 or higher is considered to be precluded by entropy factors. The 1,5 hydrogen transfer is preferred to the 1,6 shift because the former can involve a cyclohexane-like chair conformation which minimizes angle strain and interaction of non-bonded atoms with little loss of linearity across the point of hydrogen transfer.

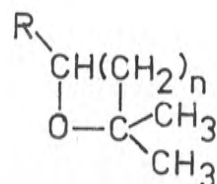
The above theoretical considerations appear to be sound but recent papers have thrown a doubt on their rigidity, since possible examples of 3- and 4-membered cyclic transition states have been observed. de la Mare and Rust¹⁶⁶ detected 3- and 4-membered cyclic ethers (CXXII, n=0, R=n-C₃H₇; n=1, R=C₂H₅) from the decomposition of di-(2-methyl-2-hexyl) peroxide (CXX, Y=2-methyl-2-hexyl) and explained their formation through the intermediate (CXXI, n=0, R=n-C₃H₇; n=1, R=C₂H₅) where a three or four-membered cyclic



(CXX)

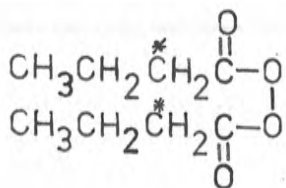


(CXXI)

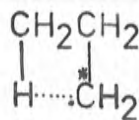


(CXXII)

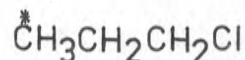
transition state is involved. More recently Reutkov and Shatkina¹⁶⁷ thermally decomposed dibutyryl [2-¹⁴C] peroxide (CXXIII) in carbon tetrachloride and obtained [3-¹⁴C] propyl



(CXXIII)



(CXXIV)



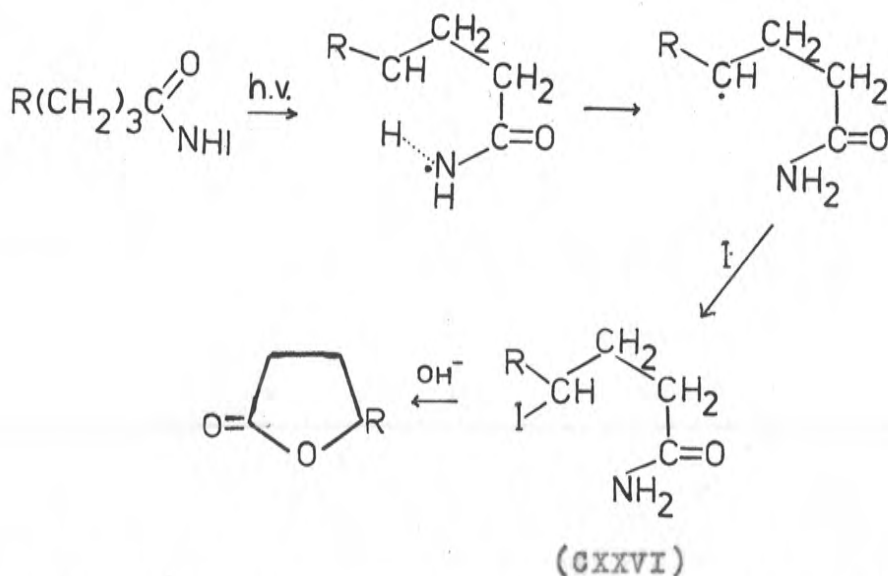
(CXXV)

chloride (CXXV) indicating that a 4-membered transition state (CXXIV) was taking part in the reaction.

The intramolecular abstraction of hydrogen from an α-carbon atom of an alkoxy radical generated under similar

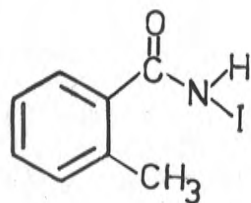
conditions, depends on the source of that radical. Thus Walling and Padwa¹⁶⁰ observed the formation of products arising from a seven-membered transition state when a hypochlorite was the substrate whereas Kabasakalian¹⁶³ searched in vain for a product arising from such a transition state in a nitrite photolysis.

In an investigation into new methods of preparing lactones in satisfactory yields, Barton and Beckwith¹⁶⁸ studied the photolyses of N-iodoamides of acids possessing a γ -methylene group. The following hydrogen transfer mechanism was envisaged.

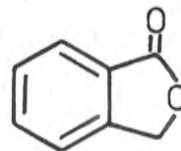


In no case could the intermediate γ -iodoamide (CXXVI) be isolated, but on hydrolysis, γ -lactones were isolated in fair yield. The only other identifiable products were the primary amide and the corresponding acid indicating that no competitive fragmentation reaction was occurring. It is of interest to note that in the photolysis of

N-iodo-o-toluamide (CXXVII) despite the fact that spatial conditions appear ideal for intramolecular hydrogen abstraction, poor yields^s of phthalide (CXXVIII) were obtained



(CXXVII)

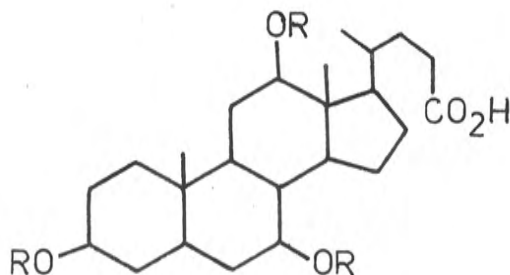


(CXXVIII)

Examination of the products of the photolyses of N-iodoamides containing a secondary δ -carbon atom indicated the presence of small amounts of δ -lactone, arising, no doubt, from 1,6-hydrogen transfers analagous to those described (pg. 109)

As a continuation of the above work it was decided to prepare and irradiate several N-chloroamides derived from long chain aliphatic and alkylaromatic unsubstituted amides in order to determine whether better yields of lactones could be obtained. Furthermore, since few γ -chloroamides are known,^{169, 170} attempts were to be made in the more favourable cases to isolate the intermediate, in order to determine whether the photolytic reaction could be developed into a preparative method for such compounds. Should satisfactory yields of lactones be obtained from the above photolyses, the ultimate aim of the investigation was to prepare and photolyse the N-chloroamides of branched chain steroid acids such as derivatives of cholanic acid (XXXIV). The lactone could then be degraded to androstan-17-one

(XXXVIII) as outlined in chapter 2 (page 31.). The steroid degradation problem was also approached by investigation into the photolyses of the amides of the abovementioned steroid acids in the presence of lead tetra-acetate and iodine. If the yields of lactones from the N-iodoamides of cholanic acid and 3,7,12-triketocholanic acid were satisfactory, the reaction was to be extended to the amides of more labile acids such as 3,7,12-triacetylcholic acid (CXXIX, R = CH₃C=O).



(CXXIX)

Since the above acid had been previously synthesized by a lengthy procedure,¹⁷¹ it was decided to investigate its preparation by a more convenient route e.g. by direct acetylation of cholic acid (CXXIX, R = H).

RESULTS AND DISCUSSION

(a) Preparation of Starting Materials.

Cholanamide - This compound was prepared satisfactorily by reaction of oxalyl chloride with cholanic acid in benzene solution, followed by treatment of the crude acid chloride with aqueous ammonia. The m.p. of the product was different from that reported by Borsche¹⁷² but agreed with that reported by Osaki.¹⁷³

3,7,12-Triketocholanic acid chloride and amide. - Farbenind¹⁷⁴ described the formation of colourless 3,7,12-triketocholanic acid chloride, m.p. 208-209° by the action of thionyl chloride on the acid in boiling benzene. Repetition of this work resulted in the formation of a tarry product which on treatment with ammonia gave an intractable brown solid of indefinite m.p.. This material was shown by its infrared spectrum to contain the expected amide. Repetition of the reaction in benzene, ether and tetrahydrofuran at 0° did not improve the quality of the product. The problem was overcome by the use of oxalyl chloride in benzene. The colourless product had m.p. 53-54° and afforded a colourless amide m.p. 278-280°.

Triacetylcholic acid. - The synthesis of this compound has been previously reported¹⁷¹ but the four-step process resulted in a non-crystalline product.

Scheme I, involved the following compounds: cholic acid (CXXIX, R=H); methyl cholate (unsolvated);

methyl 3,7-diacetylcholate; 3,7-diacetylcholic acid, 3,7,12-triacetylcholic acid. Unsolvated methyl cholate was acetylated by the method of Fieser and Rajagopalan.¹⁷⁵ An attempt to hydrolyse selectively the methyl ester with methanolic potassium hydroxide yielded an ester (infrared maximum at 1730 cm.⁻¹) which on quantitative saponification and analysis gave results indicating that one of the acetyl groups had been preferentially removed giving a solvated monoacetate of methyl cholate. Accordingly the scheme was abandoned.

Scheme II, consisted of the direct acetylation of cholic acid under various conditions. It was found that treatment of this compound with acetic anhydride in pyridine for periods greater than 15 hours at room temperature produced a non-crystallizable gum. This was esterified and partial saponification of the ester by the method of Elderfield et al.¹⁷⁴ gave 7,12-diacetylcholic acid. Quantitative saponification of the original material indicated that it was a mixture of di- and 3,7,12-triacetyl-cholic acids. It must be concluded that acetylation of cholic acid had produced the desired triacetyl-acid, but that in the process involving removal of anhydrides, partial hydrolysis at the 3-position had occurred simultaneously. The mixture of acetyl-cholic acids was acetylated by the method of Reichstein and Fuchs.¹⁷⁶ A colourless oil was obtained which on esterification gave a crystalline methyl ester with an m.p. a little below that

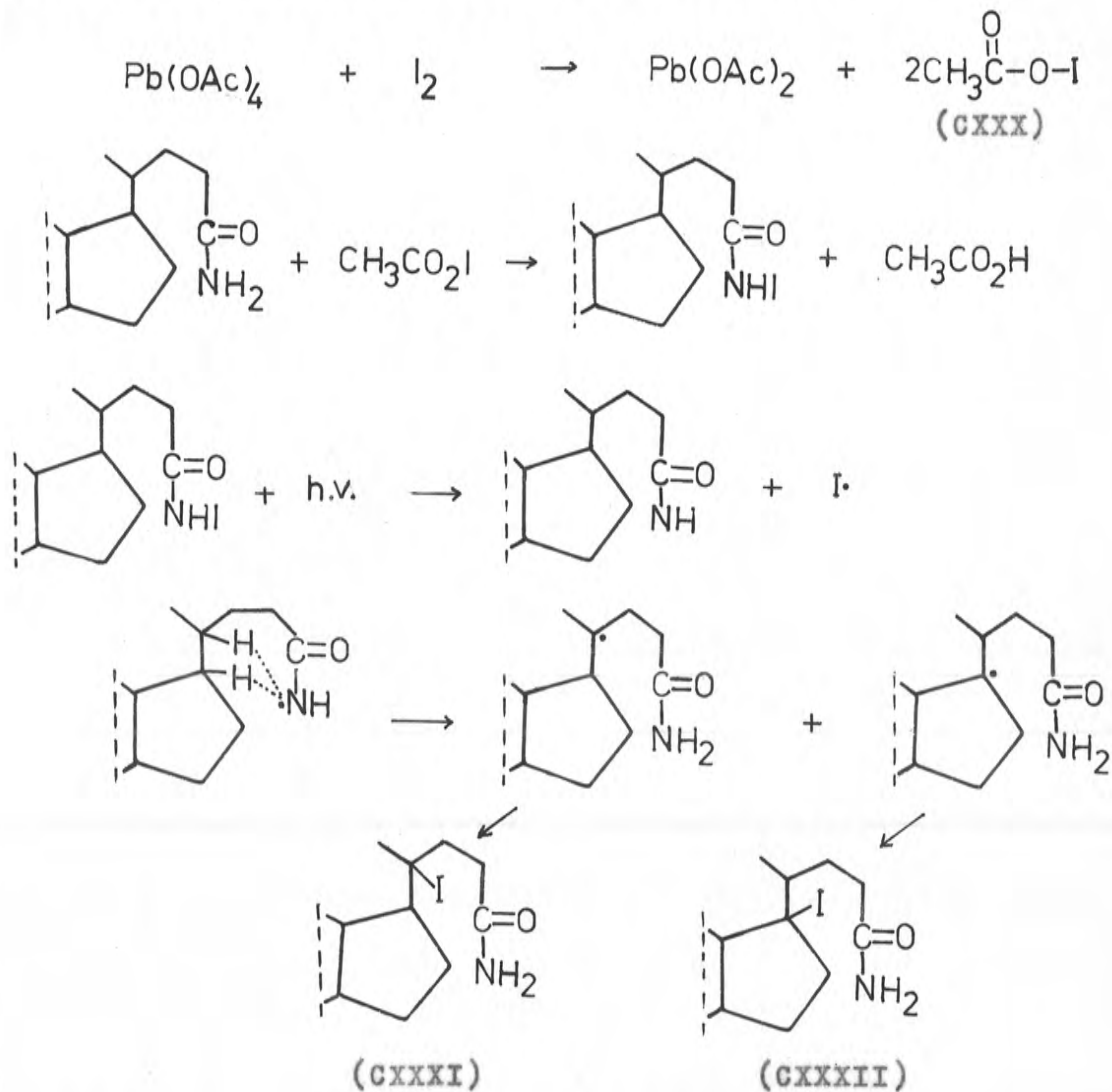
given in the literature for methyl 3,7,12-triacetylcholate. The m.p., however, was not depressed when the product was mixed with a sample of the authentic compound.

Photolyses of amides in the presence of lead tetra-acetate and iodine.

Cholanamide and 3,7,12-triketocholanamide were photolysed as described (pg. 145). In all cases the colour of the iodine disappeared only to be regenerated during the reaction. The N-iodo-amides and carbon-substituted iodo-amides, presumed to be intermediates in the reaction, were not isolated but the crude product was hydrolysed in aqueous ethanolic alkali and the lactone obtained after the removal of neutral and acidic products. Isolation of the lactonic material proved difficult since the complete hydrolysis of unreacted amide could not be brought about even under vigorous alkaline conditions. This was particularly troublesome in the cholanamide photolysis, due to the insolubility of all compounds involved, under the normal conditions of separation. On the other hand the extreme water-solubility of the products of 3,7,12-triketocholanamide reaction gave such a low recovery of lactonic material that purification was impracticable. The isolation procedure was further complicated by the fact that both epimers of γ - and δ -lactones are possible products in the reaction and it is considered that the presence of these four compounds prevented the satisfactory crystallization of the lactonic

fraction from the reaction of cholananamide.

The fact that both γ - and δ -lactones were formed after hydrolysis is in agreement with the results of Barton and Beckwith¹⁶⁸ and implies that an intramolecular hydrogen abstraction reaction is occurring as follows:



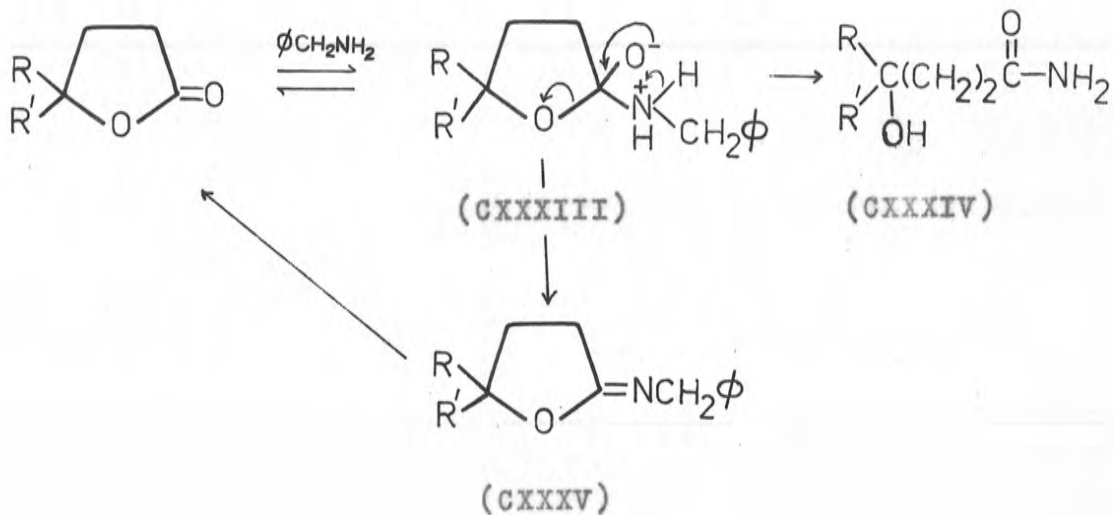
In view of the oxidizing properties of lead tetra-acetate, the formation of acetyl hypoiodite (CXXX) seems reasonable and the action of this compound in N-iodinating the amide

would be analagous to that of t-butyl hypochlorite observed in the present work. This type of hypiodite, furthermore, has been postulated by Barton and Serebryakov¹⁷⁷ in the lead tetra-acetate-iodine decarboxylation of acids. The reappearance of iodine in the photolyses is surprising. Barton and Serebryakov observed the same effect in the decarboxylation reaction but gave no explanation of its cause. It is probable, however, that a side reaction involving the oxidation of the intermediates (CXXXI) and (CXXXII) is involved.

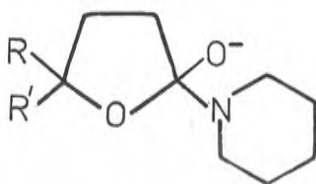
Attempted degradation of the lactone mixture from cholananamide photolysis

The lactone mixture derived from cholanic acid afforded the best possibilities for degradation to an androstan-17-one since it was formed from the photolysis in good yields, and the absence of other reactive functional groups in the molecule would result in the absence of unwanted side effects. Accordingly the lactone was oxidized in acid solution with a mixture of potassium permanganate and potassium metaperiodate. Both infrared spectrum and spot tests for 17-keto-steroids carried out on the product indicated that little or no reaction had occurred. This proved that under these conditions the lactone was sufficiently stable to inhibit ring opening and hence the reactions analagous to (XXXV) - (XXXVIII) were incapable of occurring.

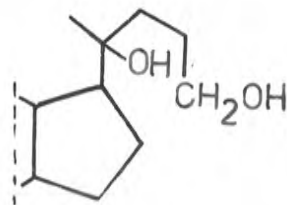
From the previous result it was recognized that for any oxidation procedure to be effective the ring must be opened prior to the oxidation process being carried out. Accordingly, the lactone was treated with benzylamine in order that the γ -hydroxy-amide (XXXVI, $R = C_6H_5CH_2$) could be oxidized. It was observed, however, that amide formation only partially occurred even after several hours vigorous treatment. In order to determine the nature of the effect of the substituents at the 20-position of the steroid on the ease of hydroxy-amide formation, butyrolactone (XXIII, $R, R' = H, Y = O$) and 4-hydroxy-4-methyloctanoic acid lactone (XXIII, $R = CH_3, R' = n-C_4H_9, Y = O$) were treated with benzylamine under similar conditions. The unsubstituted lactone gave excellent yields of the hydroxy-amide (CXXXIV, $R, R' = H$) on warming the reactants at 100° for 2 hours whereas the 4,4-disubstituted lactone reacted partially even under more vigorous conditions. The results



appeared to be explained by the inductive effects of the alkyl groups R and R' in inhibiting the fission of the 1-carbon-oxygen bond of the charge-separated form of the hydroxy-amine (CXXXIII). This intermediate may therefore either revert to the lactone since the first step is reversible, or may undergo dehydration to the imino-lactone (CXXXV) which is hydrolysed to the lactone. In order to prevent the possibility of the latter reaction occurring, the steroid lactone was treated with piperidine. The intermediate in this case (CXXXVI) cannot undergo imino-lactone formation. In practice it was found that complete ring opening could not be achieved. Repetition of the



(CXXXVI)



(CXXXVII)

reaction with the aliphatic lactones (XXIII, R,R' = H; R = H, R' = n - C₄H₉, Y = O) resulted in complete ring opening in the first instance but only partial reaction in the second. This implies that either the electronic effects of the substituents result in the direct formation of the lactone by the reverse step of the initial reaction or that the steric effects of the substituents are sufficiently great to inhibit this reaction. The latter consideration is borne out by a study of models of the

lactones which indicates that the normal motion of the larger groups such as n-butyl or the steroid nucleus attached to the γ -carbon atom, will hinder the attack of the relatively large benzylamine or piperidine molecule on the carbonyl group of the lactone. It was demonstrated however, that the smaller but less basic hydrazine molecule was able to open the ring of 4-hydroxy-4-methyloctanoic acid lactone quantitatively, and this reagent should prove useful in subsequent degradations of the lactone derived from the photolysis of cholanamide.

Lithium aluminium hydride has been successfully used in reducing to diols, steroid lactones of similar structure to that under discussion.^{17*} Accordingly the lactone (XXXV) was treated in this manner to give a low yield of crystalline diol of presumed partial structure (CXXXVII) on chromatography. Several small scale oxidations were carried out on the crude product to determine whether androstan-17-one could be formed by oxidative fission. Spot tests and infrared spectral studies failed to indicate the presence of this compound and in the majority of reactions crude γ -lactonic material was recovered. This indicated that probably due to steric effects, the primary hydroxy group was oxidized to the exclusion of the tertiary hydroxy group, with the formation of hydroxy-acid. The relative rate of oxidation is in agreement with the work of Franke and Kohn^{17*} who

who obtained 4-hydroxy-4-methylpentanoic acid lactone from 2-methylpentan-2,5-diol under similar conditions.

The results of the attempted ring opening and degradation of the steroid-20-hydroxy-24-carboxylic acid lactone may be considered unsatisfactory and it will require the development of the use of reagents such as hydrazine before this problem is overcome.

Preparation and photolysis of N-Chloro-amides.

The N-chloro-amides were satisfactorily prepared by the action of t-butyl hypochlorite on solutions of primary amides in the presence of a trace of bromine. As was observed by Barton and Beckwith,¹²² no reaction occurred unless the latter was present. The function of this catalyst is uncertain but since the colour of bromine disappears only to be regenerated later, t-butyl hypobromite may be an active intermediate in the reaction.

The N-chloro-amides were found to be thermally stable since the lower members could be distilled, and the higher members sublimed in vacuo without decomposition. They slowly liberated chlorine when exposed to air for long periods.

The photolysis of the N-chloro-amides was extremely rapid in all cases, taking 30-45 minutes to complete, compared with 2-5 hours with N-iodo-amides. This fact, coupled with the observation that use of solvents of varying polarity did not appear to alter the rate of reaction, and

the nature and yield of the products, suggests that a radical chain mechanism is involved. During the photolyses in fractionated benzene, chloroform and carbon tetrachloride both chlorine and hydrogen chloride were evolved but when ANALAR toluene-free benzene was used, the production of these gases appeared to be lower although the reaction rate did not decrease. The crude product which often weighed more than the N-chloro-amide initially used, was hydrolysed with aqueous ethanolic potassium hydroxide and the product separated into neutral, acidic and lactonic fractions. Since the yields of lactones were of primary interest, the results are set out in the following table.

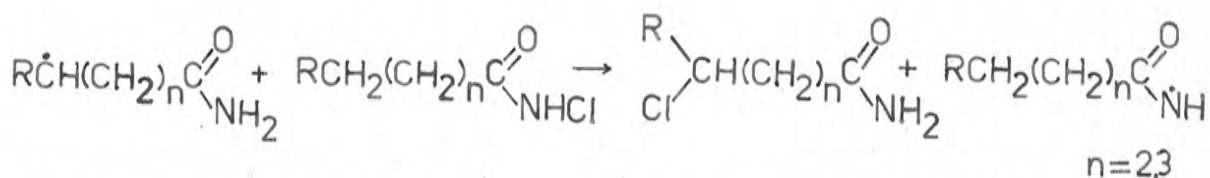
Table 3.3

N-Chloroamide	Type of Lactone	% Combined Yield
butyr-	γ	36
hexan-	γ, δ	20
cyclohexane carbox-	δ	trace
myrist-	γ, δ	36
benz-	-	-
o-tolu-	γ	31
4-phenylbutyr-	γ	32

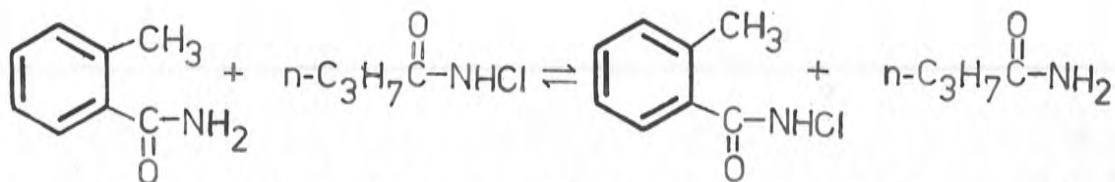
The fact that γ - and where possible δ -lactones are formed in hydrolyses of the products of photolyses indicates that nitrogen-chlorine bond fission is occurring followed

by an intramolecular hydrogen abstraction reaction involving both 6- and 7-membered transition states analogous to those described (pg. 109, 110). This results in the formation of 4- and 5-chloro-amides which are subsequently hydrolysed.

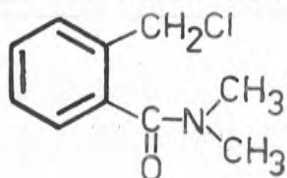
It was at first considered that in addition to the overall halogen transfer reaction, a chain process analogous to that observed by Wawzonek and Thelen¹⁴⁵ for the reaction of N-chloro-amines was occurring with



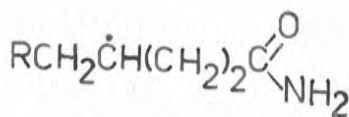
as the propagating step. This implies that the chlorine atom is not free during the photolysis. A mixture of N-chlorobutyramide and N,N-dimethyl-o-toluamide was photolysed, the latter being used in preference to o-toluamide itself to prevent a possible equilibrium of the type



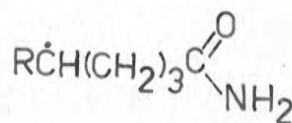
Phthalide was isolated from the hydrolysis of the reaction mixture indicating that chlorine radicals must have attacked the benzyl hydrogen atoms of the tertiary amide to give o-chloromethyl-N,N-dimethyl benzamide (CXXXVIII)



(CXXXVIII)



(CXXXIX)

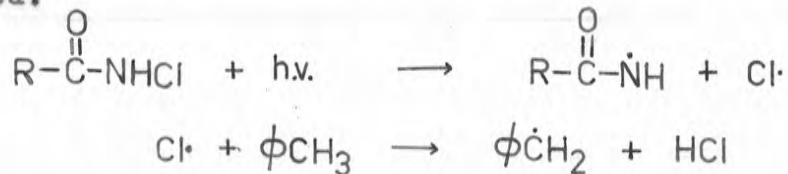


(CXL)

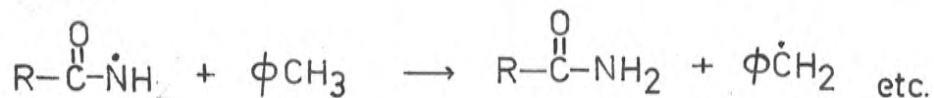
The presence of the intermediates (CXXXIX) and (CXL) in the photolysis is demonstrated by the fact that the chlorine atom migrates exclusively to the γ - and where possible the δ -carbon atom. Examination of the acidic products of the photolyses indicates the absence of α -, β - or other hydroxyacids which could have arisen from random chlorine radical substitution reactions.

It is significant that poor yields of lactones are obtained in the photolyses. In addition, there is production of relatively large quantities of what appear to be the primary amides derived from the N-chloro-amides being photolysed. These facts coupled with the observation that chlorine and hydrogen chloride are evolved during the irradiation indicates that an unwanted side reaction is occurring. In this connection a solution of N-chloro-o-toluamide was treated with anhydrous hydrogen chloride. Chlorine was evolved and a quantitative yield of o-toluamide was obtained. This implied that hydrogen chloride was causing the formation of primary amides in the photolyses.

Initially, the cause of hydrogen chloride production was considered to be the solvent used in the irradiations. Benzene, for example, might contain small quantities of toluene not removed by fractionation. The following was visualized:

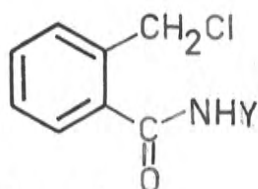


also possibly

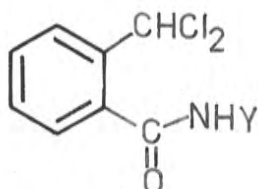


From the yields of lactone generally obtained using benzene as photolysis solvent it was calculated that the presence of 1.5 by weight of toluene would be sufficient to convert N-Chloro-amide to primary amide and this would be outside the limit of the toluene impurity in the benzene employed. Furthermore, use of ANALAR toluene - free benzene did not result in improved yields of lactones. The results from the photolysis of N-chloro-o-toluamide are significant in this connection. Intermolecular hydrogen abstraction would be effected from this compound in preference to toluene since it is present in higher concentrations. This results in the following conclusions.

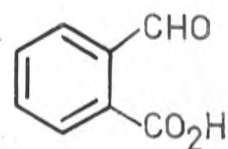
- (a) If no more than one hydrogen atom is abstracted per molecule of N-chloro-o-toluamide, the resultant increase in the number of derived benzyl radicals should result in increased yields of o-chloromethyl benzamide and subsequently phthalide. Comparison of these yields with those of lactones from other photolyses indicates that this is not so.
- (b) If more than one hydrogen radical is abstracted per molecule of N-chloro-amide i.e., the species (CXLI; X=H, Cl) and (CXLII, Y=H, Cl) can undergo further hydrogen removal, the yields of phthalide will



(CXLI)



(CXLII)



(CXLIII)

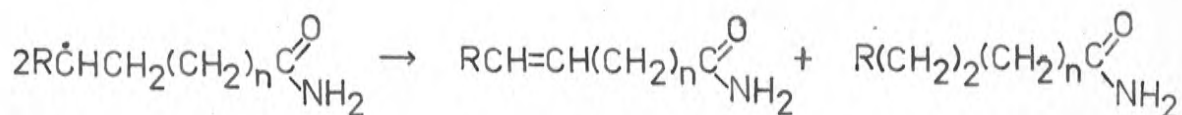
be lower but the formation of phthalaldehydic acid (CXLIII) and phthalic acid should be observed.

In fact these acids were not detected although Barton and Beckwith¹⁶⁸ obtained small quantities of the latter in similar photolyses. From these observations, therefore, it must be concluded that toluene is not the cause of hydrogen chloride formation in photolyses carried out in benzene.

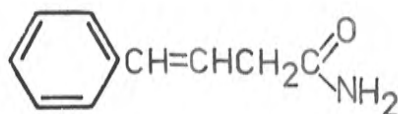
It seemed improbable that hydrogen abstraction from benzene itself was occurring since the energy required for such a process would be too high, but the hypothesis was nevertheless tested. N-Chlorobenzamide was photolysed and the residual liquid from the reaction was carefully fractionated. No trace of chlorobenzene was observed in the volatile components and biphenyl was detected only in trace yields in the residue. Benzene was irradiated under similar conditions but only a trace of biphenyl was observed after purification and ultraviolet spectral examination of the residue after unchanged benzene had been removed. The likelihood of hydrogen abstraction from chloroform and

impurities present in carbon tetrachloride, when these solvents were used in photolyses, is also extremely small. Hexachloroethane, the expected product of such a reaction, was detected only in one instance and then in small yield.

From the irradiation of N-chloromyristamide, both the crude product and the acidic component of the subsequent hydrolysate exhibited marked activity towards potassium permanganate. Accordingly, a sample of the photolysis product was oxidized by the method of Lemieux and von Rudloff¹⁸⁰ to determine whether unsaturation was present. This resulted in the formation of a monocarboxylic acid containing eight, nine or ten carbon atoms. Repetition of the oxidation on the acid fraction of the hydrolysis, produced succinic and glutaric acids in addition to the above. This implies the formation of an olefinic bond across the 3,4- and 4,5-carbon atoms of myristamide during photolysis. Hence subsequent to the intramolecular hydrogen abstraction process at the 4- or 5-carbon atoms, a disproportionation reaction of the type



where $R = n-C_8H_{17}, n=2$ or $R = n-C_8H_{17}, n=3$ must be occurring. This process should occur readily in the photolysis of N-chloro-4-phenylbutyramide since the unsaturated compound (CXLIV) would be resonance stabilized. It was established



(CXLIV)

that such a reaction did indeed occur, but the nature of the products could not be determined by the von Rudloff oxidation technique since 4-phenylbutyramide itself is susceptible to oxidation, giving rise to the same products as those expected from the unsaturated compound.

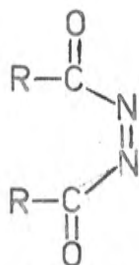
The preceding results partially account for the formation of hydrogen chloride and hence the recovery of primary amide in the reaction mixture. The following observations, however, indicate that this side reaction is not the only contributing factor.

- (a) The infrared spectra of the crude reaction mixtures from the photolyses of N-chloromyristamide and N-chloro-4-phenylbutyramide indicate that the unsaturated compound is present in small amounts compared with the saturated amide.
- (b) Olefinic compounds were not observed in the photolyses of other N-chloro-amides studied, when such products were theoretically possible.
- (c) N-Chloro-o-toluamide which is incapable of undergoing olefin formation gives rise to a good recovery of o-toluamide.

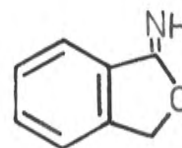
It is essential to hydrolyse the photolyses products in alkaline medium to prevent olefinic acid formation which would occur under acid hydrolysis conditions. The former method is, however, extremely inefficient and the possibility of incomplete hydrolysis of the γ - and δ -chloro-amides has not been overlooked. The controlling factor in such a reaction will be the formation of the hydroxy-amide which must occur readily under these conditions as shown by the absence of halogen in the product of hydrolysis. Bruice and Marquardt¹²⁶ have shown that the ratio of the rate constants in the alkaline hydrolyses of γ -hydroxy-amides and unsubstituted amides respectively, is of the order of 15:1. It follows, therefore, that the percentage of the hydroxy-amide present after the hydrolyses under discussion would be negligible. It has been shown, furthermore, that authentic o-chloromethyl benzamide hydrolyses completely under the conditions used and also that on hydrolysis of the products of photolysis of N-chloro-o-toluamide, the neutral material consists of o-toluamide in a high state of purity.

From previous observations it follows that the primary amides are regenerated from N-chloro-amides by means of hydrogen chloride of unknown origin. In an attempt to trap the intermediate responsible, a photolysis was carried out on N-chloro-o-toluamide and infrared spectral observations were made on the reaction mixture at intervals. The main

features noticed were a gradual development of an N-H stretching frequency at 3400cm.^{-1} and a slight increase of absorption in the region $1500-1750\text{cm.}^{-1}$ with a broadening of the carbonyl stretching frequency around 1660cm.^{-1} . A gradual increase in absorption in the region $700-740\text{cm.}^{-1}$ due to the development of a carbon-chlorine stretching frequency was also noticed. The reaction mixture was allowed to stand for 24 hours and a subsequent spectrum of a sample indicated that a new absorption maximum was emerging at 1750cm.^{-1} , probably due to γ -lactone formation. Except for the fact that N-chloro-amide was being converted to a carbon substituted amide, the studies revealed very little about the nature of the reaction. The absence of characteristic absorption frequencies, indicated that certain reactions whereby hydrogen chloride might be generated, were not occurring. Isocyanates, for example, which might be formed by a Hofmann rearrangement, initiated by the photolytic elimination of hydrogen chloride from the nitrogen atom, were not present since no absorption was observed at 2300cm.^{-1} . Nitriles which could theoretically arise from dehydration of the amides, were eliminated as possible products by virtue of absence of absorption at 2400cm.^{-1} . An extremely unlikely product from intermolecular elimination of hydrogen chloride would be a diacyl or diaroyle di-imide (CXLV) but this can be discounted since



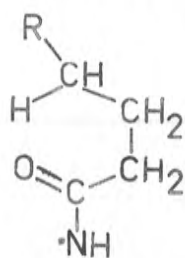
(CXLV)



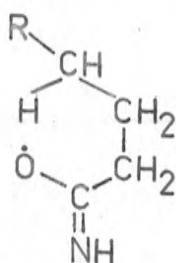
(CXLVI)

the species absorbs in the region 1730-1780cm.⁻¹ ¹⁸¹ and photolyses of such compounds give rise to entirely different products.¹⁸² The possibility of lactam formation has also been considered but since the characteristic absorption frequency lies in the range 1700-1730cm.⁻¹ and hydrolysis produces water-soluble amino-acids, the theory was discarded.

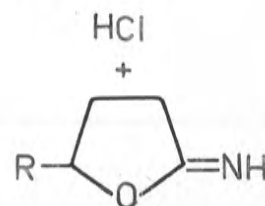
Amide radical isomerization followed by cyclization as depicted in (CXLVII) - (CXLIX) could give rise to an imino-lactone which considering the amide under discussion would be the 1-imino phthalan derivative (CXLVI).



(CXLVII)



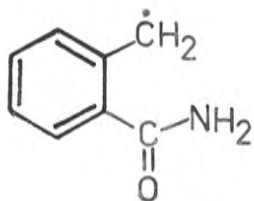
(CXLVIII)



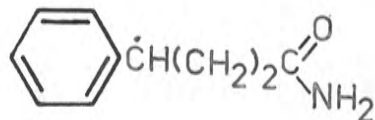
(CXLIX)

This compound is unknown but it is conceivable that it could arise under photolytic conditions giving an equivalent of hydrogen chloride, and forming a γ -lactone on hydrolysis. Furthermore, infrared spectral study of a steroid imino-lactone ¹⁶² indicates that characteristic C=N stretching

occurs at 1670cm.^{-1} and even allowing for a small shift to longer wavelength due to phenyl conjugation, the frequency still occurs in the region where activity was observed in the present study. The initial isomerization to give the radical (CXLVIII) is possible since the position of the halogen atom in N-chloro-amides has not been established and the imine hypochlorite structure may be significant.



(CL)



(CLI)

Although there is no stronger evidence for the imino-lactone intermediate, no facts have been observed to contradict its existence. It must be pointed out, however, that even if imino-lactone formation were exclusively occurring, lactones should be formed in 50% yield whereas the figure even in the most ideal cases is considerably lower than this, indicating that a more complex reaction is involved in the photolysis.

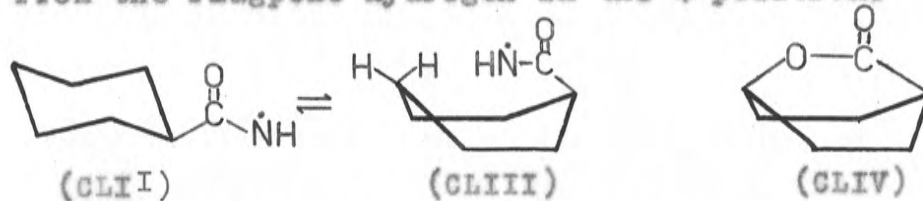
In an endeavour to improve the yields of lactone, a photolysis of N-chloro-o-toluamide was carried out using an excess of t-butyl hypochlorite in order to convert the primary amide as soon as it was formed in the photolysis, to N-chloro-amide. This resulted in a 20% improvement in the yield of phthalide. This implies that the

N-chloro-amide was being re-formed but also that the t-butyl hypochlorite was being removed from the medium by a competing reaction. Since Walling and Jacknow¹⁸³ have shown that this compound undergoes decomposition under similar conditions with the formation of acetone, chlorinated t-butyl alcohols etc., the inefficiency of the reaction is explained.

It is significant to note that the yields of lactone from the photolyses of N-chloro-o-toluamide and N-chloro-4-phenylbutyramide, where the intermediate radicals (CL) and (CLI) would be stabilized by resonance, are not greater than those obtained from N-chlorobutyramide and N-chloromyristamide where such stabilization cannot occur. A similar effect was observed by Townley and Kabasakalian¹⁶³ in the photolyses of phenylalkyl nitrites (pg. 105). Walling and Padwa,¹⁶⁰ however showed that the presence of a benzylic carbon atom did improve the yields of ϵ -chloro-alcohols in the irradiation of hypochlorites (pg. 100). This problem cannot be resolved since the conditions of photolysis in the present work are similar to those used by the latter workers. A study of models of the intermediate radicals (CL) and (CLI) indicates that the nitrogen, hydrogen and carbon atoms in the transition state would be linear as required by Corey and Hertler.¹⁴⁶ The anomalous results suggest that the side reaction occurring in the photolysis is independent of the nature

of the C-H bonds in the substrate.

Results of the photolyses serve to confirm the linearity requirement of atoms directly concerned in the hydrogen transfer. This is borne out in the reaction of cyclohexane N-chloro carboxamide. Studies of both theoretical conformations of the molecule indicate that intramolecular hydrogen abstraction can only take place in the boat form of the intermediate (CLIII) and then only from the flagpole hydrogen in the 4-position.

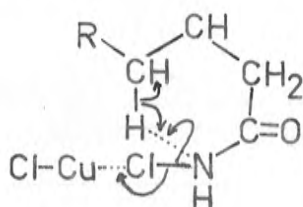


The conformation change (CLII \rightleftharpoons CLIII) would require considerable energy in view of the steric interactions involved. In fact the irradiation of cyclohexane N-chloro carboxamide yields traces of lactonic material (infrared maximum 1780cm.^{-1}) which is considered to contain cis 4-hydroxy-cyclohexane carboxylic acid lactone (CLIV). The carbonyl stretching frequency of the authentic compound is 1785cm.^{-1} 184

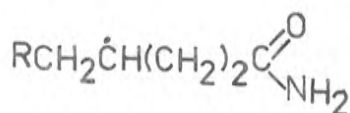
In view of the fact that no general method is available for the preparation of γ -chloro-amides, attempts were made to isolate these intermediates in the photolyses of N-chlorohexanamide and N-chloro-p-toluamide. In the former case, separation was found to be impossible because of the structural similarity of the required compound and the unsubstituted primary amide. From the photolysis

of the latter a sample of o-chloromethyl benzamide contaminated with small quantities of o-toluamide was obtained. The compound was not stable due to the lability of the halogen attached to the benzyl group.

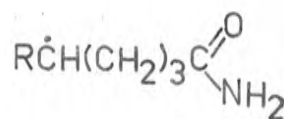
The N-chloro-amides, although photolytically reactive, were found to be thermally stable. Samples were heated under reflux in boiling carbon tetrachloride for 48 hours without any decomposition occurring. In the presence of cuprous chloride, however, reaction took place with the formation of γ - and where possible δ -lactones on hydrolysis. It is considered that the cuprous salt effects the homolytic breakdown of the N-Cl bond by forming an activated complex (CLV). The transition state then breaks



(CLV)



(CXXXIX)



(CXL)

down, with simultaneous intramolecular hydrogen abstraction to give the radical (CXXXIX) and cupric chloride, and subsequently the γ -chloro-amide by chlorination via the cupric halide. An analagous series of reactions may be postulated for the formation of δ -chloro-amide. Although the reaction was not further investigated, the low yields of lactones after hydrolysis were probably due to the formation of unsaturated amides by disproportionation

of the radical (pg. 126) or by oxidation of that species by the cupric salt present to give the carbonium ion followed by proton elimination as observed by Kochi.¹⁵⁶

Summarizing, it may be said that N-chloro-amides undergo intramolecular hydrogen abstraction on photolysis, by a mechanism which is essentially the same as that postulated for the photolytic decomposition of N-iodo-amides. The yields are generally poor and until an improvement in the efficiency of the reaction can be effected, its application to steroid side chain amides in the hope of subsequently bringing about side-chain degradation, would be unsatisfactory.

EXPERIMENTAL

(a) General

In addition to the techniques described on page 62, ultraviolet spectra were determined on an Optica CF4 Spectrophotometer.

(b) Analytical Methods

In addition to the techniques described on page 62, the following were also used:

(i) Adsorption chromatography - In the attempted separation of amide mixtures samples of Woelm alumina partially deactivated with water were used: in addition to the above, "Mallinckrodt" 100 mesh A.R. silica gel was employed in the separation of the products of steroid reactions.

(ii) Thin film chromatography - The number of components in the products of photolyses and steroid reactions was determined by chromatography on alumina films. Spots were visualized by spraying the dried plates with a dilute alkaline solution of potassium permanganate.

(iii) Oxidation - In the determination of unsaturated amides and acids the method of Lemieux and von Rudloff¹⁸⁰ was employed. The acid fragments were detected by comparative paper chromatography as previously described.

(c) Preparation of Reagents

Lead tetra - acetate - This compound was prepared by the method of Mendel.¹⁸⁵ The product was stored

moistened with ANALAR acetic acid and before use was dried overnight in vacuo over phosphorus pentoxide and potassium hydroxide.

t-Butyl hypochlorite - The method of Bell and Teeter¹⁸⁶ was employed. The rate of chlorine addition was lower than that employed by the above workers in order to minimize loss of product by entrainment. The hypochlorite was stored at 0° in a stoppered vessel surrounded by aluminium foil.

(d) Purification of Solvents and Reagents

ANALAR chloroform and carbon tetrachloride were dried by allowing them to stand (2 hr). over concentrated sulphuric acid with occasional shaking. The upper layer was decanted and passed through a column of Spence alumina partially dried at 100°. Benzene was fractionated and dried over sodium. Thionyl chloride was distilled over anhydrous quinoline and subsequently over boiled linseed oil.

(e) Preparation of Starting Materials

Acid chlorides - Unless otherwise stated, the acid was dissolved in twice its volume of thionyl chloride and set aside at room temperature until the effervescence had modified. The reaction mixture was heated under reflux (2 hr) then the excess of thionyl chloride was removed by distillation. The acid chloride was obtained by fractionation of the residue. The following were prepared:

hexanoyl chloride - A colourless liquid b.p. 148-152°

(lit.¹⁸⁷ 151-153°), from hexanoic acid in 75% yield;
cyclohexane carboxylic acid chloride - a colourless liquid b.p. 187-190° (lit.¹⁸⁸ 184°), from cyclohexane carboxylic acid in 76% yield;

tetradecanoyl (myristoyl) chloride - a colourless liquid b.p. 190°/28mm. (lit.¹⁸⁹ 179-180°/22mm.), from myristic acid in 85% yield;

o-tolucyl chloride - a colourless liquid b.p. 125-127°/31mm (lit.¹⁹⁰ 110-111°/29mm.), from o-toluic acid in 93% yield;

4-phenylbutyryl chloride - a colourless liquid b.p. 150-156°/27mm. (lit.¹⁹¹ 140-142°/12mm.), from 4-phenylbutyric acid in 69% yield.

Cholanic acid chloride - Cholanic acid (3.0g.) was dissolved with gentle warming in anhydrous benzene (12 ml.) Oxalyl chloride (3.0 ml.) was added and the mixture was allowed to stand at room temperature (1 hr.) and then heated at 85° (1 hr.). The benzene and excess of oxalyl chloride were removed by distillation under reduced pressure in a stream of nitrogen. The acid chloride crystallized as an almost colourless mass with a characteristic absorption maximum in the infrared at 1780cm⁻¹. The product was not purified but converted directly to cholanamide.

3,7,12-Triketocholanic acid chloride - The previous method was employed on 3,7,12-triketocholanic acid. The product crystallized from hexane as colourless plates

m.p. 53-54° (lit.¹⁷⁴ 208-209°) in 88% yield.

Amides - Unless otherwise stated, the freshly distilled acid chloride was added with shaking to a mixture of an excess of aqueous ammonia (sp. gr. 0.88) and ice. The aliphatic amides which precipitated were extracted with two 200 ml. portions of ether and the organic extract dried (magnesium sulphate). The ether was removed by distillation to yield the amide which was purified by recrystallization from a suitable solvent. The precipitated aromatic amides were removed by filtration and recrystallized from a suitable solvent. The following were prepared:

hexanamide - colourless plates (from hexane) m.p. 98-99° (lit.¹⁹² 98°) in 80% yield.

cyclohexane carboxamide - colourless plates (from water) m.p. 183° (lit.¹⁸⁸ 184°) in 87% yield;

myristamide - colourless plates (from water) m.p. 101.5 - 102° (lit.¹⁹³ 100°) in 96% yield;

o-toluamide - colourless needles (from benzene) m.p. 140-141° (lit.¹⁹⁴ 140°) in 87% yield;

4-phenylbutyramide - fine colourless plates (from water) m.p. 83° (lit.¹⁹⁵ 84.5°) in 80% yield.

Butyramide - Due to its extreme solubility in water, the amide could be prepared in a yield of only 25% using the previously described method. Accordingly, butyryl chloride (20g.) was dissolved in anhydrous benzene (50 ml.) and dry

ammonia was passed over the shaken solution until no more heat appeared to be evolved. The process took approximately 1 hr. The solvent was removed by distillation in vacuo and the resultant solid was continuously extracted with ether (10 hr.) Removal of the ether gave crude butyramide (10g. 61%) which crystallized as colourless plates m.p. 114° (lit.¹⁹⁰ 115.5 - 116°) from benzene-hexane.

N,N-Dimethyl o-toluidamide - o-Toluidoyl chloride (10g.) was added dropwise to an ice-cold solution of dimethylamine in water (100 ml., 25-30%) with shaking. The colourless solution was extracted with two 150 ml. portions of chloroform and the organic extract dried (magnesium sulphate). The solvent was removed by distillation, and the residue distilled in vacuo. The fraction b.p. 160-162°/29mm. (lit.¹⁹⁷ 147°/18mm.) was collected to give the amide as a colourless liquid (7.6g. 84%).

Cholanamide - Crude cholanic acid chloride (1.0g.) was dissolved in anhydrous benzene (10 ml.) and added dropwise with continuous shaking to aqueous ammonia (20 ml., sp. gr. 0.88) at 0°. The gummy solid was collected by filtration, washed with water and dried. Cholanamide (0.85g., 93%) crystallized from methanol as colourless needles m.p. 189-190° (lit. 70°, ¹⁷² 189¹⁷³). (Found; C, 80.0; H, 11.35. Calc. for C₂₄H₄₁NO: C, 80.15; H, 11.5%)

3,7,12-Triketocholanamide. 3,7,12-Triketocholanic acid

chloride (1g.) was treated using the method described for cholananamide. 3,7,12-Triketocholananamide (0.8g., 94%) was obtained as fine colourless needles m.p. 278-280° (Found: C, 71.75; H, 8.65. $C_{24}H_{32}NO_4$ requires C, 71.8 H, 8.8%).

N-Chloro-amides - In each case the amide (0.01 mole) was dissolved or suspended in purified chloroform. Bromine (2 drops) was added followed by t-butyl hypochlorite (0.014 mole). Immediate decolourization of the reaction mixture occurred. The suspension was shaken until it had completely dissolved. This process generally took about 10 min. and if residual solid was present after this time more bromine was added and the shaking continued. The solution was set aside at room temperature (30 min.) at the end of which time regeneration of colour had occurred. The chloroform and t-butyl alcohol were removed by distillation in vacuo and the resultant oil cooled in dry ice to induce solidification where possible. Liquid N-chloro-amides were used directly, solid N-chloro-amides were recrystallized from a suitable solvent. The following were prepared:

N-chlorobutyramide - A pale yellow liquid distillable at 0.15mm. pressure without decomposition, in 92% yield;

N-chloro-hexanamide - an almost colourless oil which solidified at 0° and had m.p. 10-16°. The yield was quantitative;

N-chloromyristamide - colourless plates (from hexane)
m.p. 62-63° in 69% yield. (Found: C, 63.9; H, 10.75.
 $C_{14}H_{25}ClNO$ requires C, 64.2; H, 10.8%);

Cyclohexane N-chlorocarboxamide - colourless needles,
(from benzene) m.p. 131-132° in 91% yield. (Found:
C, 52.1; H, 7.4 $C_7H_{12}ClNO$ requires C, 52.1; H 7.5%);

N-chlorobenzamide - colourless cubes (from benzene)
m.p. 116-117° (lit.¹⁹⁸ 117°) in 80% yield. (Found: C,
54.15; H, 3.95. Calc. for C_7H_6ClNO : C, 54.05;
H, 3.90%);

N-chloro-o-toluidamide - colourless plates (from benzene)
m.p. 88-89° in 73% yield. (Found: C, 56.7; H, 4.85.
 C_8H_9ClNO requires C, 56.65; H, 4.75%);

N-chloro-4-phenylbutyramide - thick colourless needles
(from benzene) m.p. 104-105° in 58% yield (Found: C, 61.05;
H, 6.05; N, 6.95; O, 8.45. $C_{10}H_{12}ClNO$ requires C, 60.75;
H, 6.1; N, 7.1; O, 8.1%).

3,7,12-Triacetylcholic acid

Scheme I (pg. 112)

(i) Methyl cholate (unsolvated). - The method of Fieser
and Rajagopalan¹⁷⁵ was employed. The ester was prepared in
84% yield and had m.p. 156-157° (lit. 156-157°).

(ii) Methyl 3,7-diacetylcholate - This compound was
prepared in 60% yield from methyl cholate by the method of
Fieser and Rajagopalan.¹⁷⁵ The product had m.p. 185°
(lit. 187 - 188°).

(iii) Attempted formation of 3,7-diacetylcholic acid - Methyl 3,7-diacetylcholate (1.0g.) was dissolved in 0.45 N-methanolic potassium hydroxide and gently warmed on a water-bath. The reaction mixture was cooled and the precipitated solid was collected by filtration. Weighed samples of this material were heated under reflux (4 hr.) with a calculated excess of standardized methanolic potassium hydroxide. The residual alkali was determined by titration of the cooled solution with standardized sulphuric acid solution. The results indicated that 2 equivalents of potassium hydroxide solution had been consumed showing that 1 acetoxy group was present in the unknown. The solid was recrystallized several times from methanol to give colourless needles of methyl acetylcholate methanolate (0.7g., 76%) m.p. 112-114°. (Found : C, 68.1; H, 9.55; O, 22.6. $C_{27}H_{44}O_6$ CH_3OH requires C, 67.7; H, 9.75; O, 22.55%).

Scheme II (pg. 113)

(i) Acetylation of cholic acid - A mixture of cholic acid (25g.), acetic anhydride (250 ml.) and pyridine (25 ml.) was allowed to stand at room temperature for 20 hr. At the end of this time the solution was heated under reflux (4 hr.). After the mixture was cooled, water (50 ml.) was cautiously added and the resultant solution heated under reflux (1 hr.), cooled and then poured into an excess of ice and water. The following was carried out at an

external temperature of 0°-: the solid was triturated with water, the latter decanted and the process was repeated until a filterable mixture was obtained. The product (30g.) could not be stored above 0° without becoming gummy. A weighed sample of the product was quantitatively hydrolysed as previously described. The results indicated that the material was a mixture of diacetyl- and 3,7,12-triacetyl-cholic acid. Another sample of the product (1.0g.) was esterified with diazomethane at 0°. The solvent was removed to give a colourless oil (1.0g.) which was hydrolysed by the method of Kapitel and Wieland.¹⁹⁹ The product crystallized from ethyl acetate - ether as colourless cubes of 7,12-diacetylcholic acid m.p. 204.5-205.5°. (Found: C, 67.95; H, 8.75. Calc. for $C_{28}H_{44}O_7$: C, 68.25; H, 9.00%).

(ii) Acetylation - The mixture of acetylcholic acids (1.5g.) was treated with acetic anhydride (18 ml.) and pyridine (22 ml.) by the method of Reichstein and Fuchs.¹⁷⁶ The oily solid formed (1.1g.) was esterified with ethereal diazomethane at 0°. The resultant oil was dissolved in a minimum quantity of boiling methanol and water was added dropwise until the solution was saturated. The solution was cooled overnight at 0°. The solid which crystallized was collected and recrystallized from methanol-water to give methyl 3,7,12-triacetylcholate m.p. 80-83°. The m.p. was

not depressed on admixture of a sample of methyl 3,7,12-triacetylcholate prepared from 7,12-diacetylcholic acid by the method of Elderfield et al.¹⁷

(f) General Photolysis Conditions

N-Iodo-amides - The amide (0.005 mole) was dissolved in the appropriate solvent (50 ml.) in a three-necked Pyrex flask fitted with a nitrogen inlet and sealed Hershberg stirrer. Dry resublimed iodine (2.5g., 0.01 mole) and lead tetra-acetate (2.1g., 0.005 mole) were added and a stream of oxygen-free dry nitrogen was passed through the stirred suspension. The mixture was irradiated by means of a Philips 125 watt mercury-quartz lamp positioned directly underneath the flask immersed in a Pyrex glass bath in which cold water was circulating. At the end of 2 hr. the solution had become red and a further portion of lead tetra-acetate (2.1g.) was added whereupon the purple colour of iodine was regenerated. The process was repeated at the end of 4 hr. At the conclusion of the reaction (6 hr.) the mixture was worked up as subsequently described.

N-Chloro-amides - Unless otherwise described, the N-chloro-amide (0.01 mole) was dissolved (with warming if necessary) in a suitable solvent (50 ml.) in a quartz flask fitted with a calcium chloride drying tube. The flask was irradiated and the temperature of reaction maintained below 45° by means of external air cooling from which the lamp

was shielded. The extent of the reaction was observed by treating samples of the reaction mixture with a solution of potassium iodide in dilute acetic acid. The absence of liberated iodine indicated that the photolysis was complete and in most cases this occurred after 30-45 minutes irradiation. The reaction mixture was cooled and the solvent removed under reduced pressure. The product was worked up as subsequently described.

(g) Particular Photolyses

Reaction of cholanamide with lead tetra-acetate and iodine -

The amide (1.8g.) was photolysed in chloroform using the conditions for N-iodo-amides. At the conclusion of the reaction, the suspension was poured into sodium metabisulphite solution (200 ml., 10% w/v) and thoroughly shaken whereupon precipitation of lead iodide occurred. The solid was removed by filtration, washed thoroughly with chloroform and the combined extracts washed with water and dried (magnesium sulphate). Removal of the solvent by distillation gave a dark brown oil (2.2g.). The infrared spectrum (chloroform) showed maxima at 1750, 1720 and 1680 cm^{-1} .

Hydrolysis of the reaction mixture - The oil (2.2g.) was heated under reflux (4 hr.) with a solution of potassium hydroxide (2.5 g.) in water (5 ml.) and ethanol (45 ml.). During this time both ammonia and iodine were liberated. Ethanol (20 ml.) was removed by distillation

and water (45 ml.) was added. Distillation in vacuo was continued until the bulk of the ethanol had been removed. Dilute sulphuric acid was added dropwise until the pH of the solution was below 2; the mixture was then heated (2 hr.) on a water-bath, cooled and extracted with ether (50 ml.). The ethereal solution was extracted with sodium bicarbonate solution (50 ml., 10% w/v) and hexane (50 ml.) added to achieve separation. The organic layer was dried (magnesium sulphate) and the solvent removed by distillation to give a pale brown oil (1.92g.). The infrared spectrum of the product (chloroform) indicated maxima at 1705, 1720 cm^{-1} (shoulder) and a smaller maximum at 1680 cm^{-1} . Attempted chromatography of this oil (0.8g.) on Woelm alumina deactivated with 5% aqueous acetic acid (4 ml. per 100g.) using chloroform as eluant failed to separate the oil into crystalline constituents. Extraction of the alumina in sections with hydrochloric acid followed by infrared spectral studies of the recovered oils showed the presence of γ -lactone and carboxylic acid (combined recovery 0.4g.).

Reaction of 3,7,12-triketocholanamide with lead tetra-

acetate and iodine. - The amide (2.0g.) was suspended in glacial acetic acid and photolysed under the conditions described for cholanamide. The volatile components of the reaction mixture were removed by distillation in vacuo. The residual solid was shaken with ethyl acetate (50 ml.)

and the residue from this extraction was continuously extracted with acetone until the latter had become colourless (4 hr.). The acetone was removed by distillation and the residue was dissolved in a minimum volume of cold ethyl acetate. The combined ethyl acetate extracts were shaken with a saturated solution of sodium metabisulphite (50 ml.). The organic layer was dried (magnesium sulphate) and the solvent removed by distillation. Finally, the residue was heated on a water-bath in vacuo to remove traces of volatile materials. The residue (2.07g.) was a black gum. The infrared spectrum (chloroform) showed maxima at 1755, 1720 and 1700cm^{-1} with a shoulder at 1680cm^{-1} .

Hydrolysis of the reaction mixture. - The crude oil from the photolysis was heated under reflux (4 hr.) with potassium hydroxide (2.5g.) in water (25 ml.). The mixture was cooled and extracted with ethyl acetate (two 25 ml. portions). The alkaline solution was cooled to 0° and cautiously acidified with dilute sulphuric acid to pH below 2. The acid solution was warmed on a water-bath (1 hr.) cooled, and extracted with ethyl acetate. The organic layer was shaken with saturated sodium bicarbonate solution and dried (magnesium sulphate). The solvent was removed by distillation to give a crude brown oil which on treatment with petroleum ether gave a pale brown

solid (0.1g.). The infrared absorption spectrum showed maxima at 1755cm^{-1} and 1700cm^{-1} . The sodium bicarbonate solution was continuously extracted with ether (24 hr.) to yield a small quantity of non-crystallizable oil, the infrared spectrum of which indicated the presence of γ -lactone.

N-Chlorobutyramide. - The amide (1.2g.) was photolysed in benzene. The oily product (1.0g) was hydrolysed by heating under reflux with potassium hydroxide (1.5g.) in ethanol (7.5 ml.) and water (7.5 ml.). The ethanol was removed by distillation and water (7.5 ml.) was added. The alkaline solution was extracted with ether to remove neutral material and acidified with concentrated hydrochloric acid. The acid solution was continuously extracted with ether (24 hr.) and the organic layer dried (magnesium sulphate). Removal of the solvent and distillation of the residue in vacuo gave butyrolactone (0.31g., 36%) b.p. $78-80^{\circ}/19\text{mm}$. The lactone (0.25g.) was heated with benzylamine (0.5 ml.) in a sealed tube at 100° (2 hr.). The product was washed with petroleum ether b.p. $40-60^{\circ}$ and recrystallized from benzene as fine colourless crystals of N-benzyl-4-hydroxybutyramide (0.48g., 91%) m.p. 56° (lit.²⁰⁰ $70-72^{\circ}$).

N-Chlorohexanamide - (a) The amide (2.5g.) was photolysed as described and the residual brown semi-solid (3.0g.) was crystallized from benzene until the m.p. remained constant at $74-75^{\circ}$. The solid (1.6g) was hydrolysed with potassium

hydroxide (2.0g.), ethanol (15 ml.) and water (5 ml.) and worked up in the usual way. The lactonic fraction yielded a mixture of 4- and 5-hydroxyhexanoic acid lactone. The infrared spectrum showed maxima at 1755cm.^{-1} (γ -lactone) and 1720cm.^{-1} (δ -lactone) with the former predominating. The acid fraction gave an oil (0.31g.) shown by paper chromatography to contain hexanoic acid.

(b) The photolysis was repeated, the entire product (3.1g.) hydrolysed in the usual manner and the products isolated as described above. This yielded a mixture of 4- and 5-hydroxyhexanoic acid lactone (0.4g., 20%).

The acid fraction (0.37g.) was unreactive towards alkaline potassium permanganate solution and the only identifiable product was hexanoic acid. The neutral fraction consisted mainly of unchanged hexanamide (infrared maximum at 1670cm.^{-1}).

(c) The photolysis was repeated and a sample of the product was chromatographed on a thin film of alumina using ethyl acetate as developer. Two spots of similar R_f were observed; that with the smaller R_f value corresponded to hexanamide. Accordingly, a portion of the reaction product (1.5g.) was chromatographed on a Woelm alumina (100g., activity IV) using benzene as eluant. Initial fractions gave crude 4-hydroxyhexanoic acid lactone (0.42g.). A portion of this (0.1g.) on treatment with

benzylamine as described (pg.¹⁴⁹) produced an N-benzyl-hydroxy-amide (0.1g.) m.p. 151-153° (from benzene).

Benzene - ether as eluant produced a colourless solid m.p. 79-80°. Hydrolysis of this material gave a trace of lactone. Elution of the column with more polar solvents failed to yield any more lactonic material.

Cyclohexane N-chlorocarboxamide. - The amide (1.2g.) was photolysed in benzene as described. The product (1.3g.) was hydrolysed with potassium hydroxide (1.5g.) in ethanol (7.5 ml.) and water (7.5 ml.) and worked up in the usual way. The neutral material (0.5g.) was a brown oil which contained cyclohexane carboxamide but was not further examined. The acid fraction (0.1g.) contained cyclohexane carboxylic acid. The lactonic fraction consisted of a trace of oily material, the infrared spectrum of which indicated a maximum at 1780cm^{-1} (strained δ -lactone).

N-Chloromyristamide. - (a) The amide (1.5g.) was photolysed as described using chloroform as solvent. The product was a red-brown oil (1.5g.) which was crystallized repeatedly from benzene-hexane to yield colourless needles (1.1g.) m.p. 81-83° shown by gravimetric analysis to contain 7.26% chlorine (pure monochloro-myristamide contains 13.54% chlorine).

(b) The photolysis was repeated and a sample of the product was treated with potassium permanganate in aqueous sodium carbonate. Complete reaction was effected after

30 minutes. Accordingly, a sample of the reaction mixture was oxidized as described (pg. 136). The product contained a C₈, C₉ or C₁₀ monocarboxylic acid. The remainder of the photolysis product was hydrolysed with potassium hydroxide (2.0g.) in ethanol (15ml.) and water (5 ml.) and worked up in the usual way to give a mixture of 4- and 5-hydroxymyristic acid lactone (0.4g., 36%). The acid fraction was submitted to the von Rudloff oxidation procedure. The product contained a C₈, C₉ or C₁₀ monocarboxylic acid and succinic and glutaric acids.

(c) The photolysis was repeated using

(i) N-Chloromyristamide prepared in situ in chloroform and,

(ii) pure N-chloromyristamide in carbon tetrachloride.

In the former case the lactone mixture was formed in 48% and in the latter, 35%.

N-Chlorobenzamide - The amide (1.1g.) was photolysed in warm benzene as described. The reaction took several hours to complete and during this time precipitation occurred. The solid was collected by filtration to give benzamide (0.66g.) identified by infrared spectrum, m.p. and mixed m.p. The benzene solution was fractionated in order to check the presence of chlorobenzene, but the entire volatile components of the mixture had b.p. 80.5°. An infrared spectrum of the halogen-free residue indicated maxima at 2300cm.⁻¹ (isocyanate), 1790, 1750, 1710, 1670,

1650 cm^{-1} (amide), 1600 and 1570 cm^{-1} . The residue was chromatographed on alumina and eluted with hexane.

Removal of the eluant gave a trace of biphenyl.

N-Chloro-o-toluanide. - The amide (1.7g.) was photolysed in benzene as described. During the reaction a precipitate was formed. Collection of this material by filtration gave 1.4g. of colourless lachrymatory material m.p. 108-170°. Repeated recrystallizations from benzene raised the m.p. to 170-180°. The infrared spectrum of the product showed maxima at 3400 cm^{-1} , 3240 cm^{-1} and 1680 cm^{-1} (chloroform) and 730 cm^{-1} (nujol). The entire solid was hydrolysed with potassium hydroxide (1.5g.) in ethanol (10 ml.) and water (5 ml.). The neutral fraction (0.84g.) on recrystallization from benzene yielded o-toluanide m.p. 142°. The acid fraction (0.24g.) m.p. 105-200° was shown by paper chromatography to contain o-toluic acid but a phthalein test failed to reveal the presence of phthalic acid. The lactone fraction on recrystallization from water gave phthalide (0.42g., 31%) m.p. 70°. An infrared spectrum of the material indicated a maximum at 1745 cm^{-1} . The m.p. of the product was not depressed on admixture of an authentic specimen.

(b) The process was repeated in the presence of 1.5 equivalent excess of t-butyl hypochlorite. Bromine was added at the rate of 1 drop every 5 minutes during the irradiation. The lactonic oil formed was chromatographed

on alumina and on elution with hexane phthalide (0.35g., 51%) m.p. 69-70° was obtained.

N-Chloro-4-phenylbutyramide. - The amide (1.97g.) was photolysed in benzene as described. A brown oil (2.1g.) was obtained which decolourized alkaline potassium permanganate at a much greater rate than did 4-phenylbutyramide. The product was hydrolysed with a mixture of potassium hydroxide, (2.5g.) ethanol (15 ml.) and water (10 ml.) and worked up in the usual way. The acid fraction (0.7g.) contained 4-phenylbutyric acid and traces of unsaturated acid, the latter shown by absorption at 1630cm^{-1} and 1320cm^{-1} in the infrared. The neutral fraction (0.6g.) was shown by infrared spectroscopy to contain mainly 4-phenylbutyramide. The lactonic fraction on distillation in vacuo gave 4-phenylbutyrolactone (0.51g., 32%) b.p. 134-135°/0.3mm. (lit.²⁰¹ 130-130.3°/0.1mm.) (Found: C, 73.95; H, 6.4; O, 19.9. Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_2$ C, 74.05; H, 6.2; O, 19.7%). A sample of the lactone (0.4g.) was heated at 100° under nitrogen in a sealed tube (3 hr.) with benzylamine (0.5 ml.) to give N-benzyl-4-hydroxyphenylbutyramide (0.5g., 76%) m.p. 92-93° (lit.²⁰² 93-94°).

(h) Miscellaneous Reactions

Photolysis of a mixture of N,N-dimethyl-o-toluamide and N-chlorobutyramide. - N,N-Dimethyl-o-toluamide (3.4g.) and N-chlorobutyramide (2.4g.) were dissolved in benzene

(50 ml.), photolysed and worked up in the usual way.

Butyrolactone was removed from the lactonic fraction by distillation in vacuo and the residue was chromatographed on alumina to give phthalide (0.35g., 14%) m.p. 70°.

Reaction of N-chloro-o-toluamide with cuprous ions. -

N-Chloro-o-toluamide (0.85g.) was suspended in carbon tetrachloride (2.5 ml.) and anhydrous cuprous chloride (0.02g.) was added. The suspension was heated under reflux (24 hr.) in a stream of nitrogen. At the end of this time no trace of N-chloro-amide was present. The solid material was removed by filtration and the solvent was distilled. The residual material was hydrolysed and worked up in the usual way. The lactone fraction on recrystallization from water gave phthalide (0.21g., 31%) m.p. 69°. Repetition of the reaction in the absence of cuprous chloride for 72 hr. gave a product which contained N-chloro-amide. Hydrolysis of the material gave no phthalide.

Repetition of the previous reaction using N-chloromyristamide. -

N-Chloromyristamide (0.3g.) was treated with cuprous chloride in carbon tetrachloride (10 ml.) as previously described. The product was worked up in the usual way to give 0.08g. of a mixture of 4- and 5-hydroxy-myristic acid lactone.

Reaction of N-chloro-o-toluamide with hydrogen chloride. -

The amide (1g.) was dissolved in benzene and anhydrous hydrogen chloride was bubbled through the solution.

Within a few minutes precipitation commenced and after 15 minutes, a spot test indicated that no N-chloro-amide was present. The solid was collected by filtration and recrystallized from benzene to yield o-toluamide (0.8g., 100%) m.p. 142°.

o-Chloromethyl benzonitrile. - o-Toluonitrile was chlorinated by the method of Gabriel and Otto.²⁰³ After completion of the reaction, the resultant oil was distilled in vacuo and the fraction b.p. 148-153°/32mm. was collected. The crude brown nitrile was redistilled and the fraction b.p. 152°/34mm. was collected as a colourless liquid which subsequently solidified. A sample after rapid recrystallization from anhydrous ethanol had m.p. 55-57° (lit. 60-61.5°).

o-Chloromethyl benzamide - o-Chloromethyl benzonitrile hydrolysed by the method of Gabriel.¹⁶⁹ The crude amide was quickly triturated with sodium bicarbonate solution to remove traces of o-chloromethyl benzoic acid, and subsequently dried over concentrated sulphuric acid (24 hr.) to give a colourless solid (3.9g., 87%). A sample after rapid crystallization from anhydrous ethanol had m.p. 180-183° (lit. 190°).

Hydrolysis of o-chloromethyl benzamide - o-Chloromethyl benzamide (1.0g.) was hydrolysed using the conditions described for the hydrolysis of the photolysis products of N-chloro-o-toluamide. The yield of phthalide m.p. 69° was 0.6g. (80%).

4-Hydroxy-4-methyloctanoic acid lactone - This compound was prepared in 47% yield from ethyl laevulinate by the method of Cason et al.²⁰⁴. The product had b.p. 82-83°/0.4 mm. (lit. 76-79°/0.3mm.)

Reaction of butyrolactone with benzylamide. - Butyrolactone (8.6g., 7.6 ml.) and benzylamine (15 ml.) were heated at 100° (2 hr.). At the end of this time an infrared spectrum of a sample showed no absorption due to γ -lactone, indicating complete reaction. The product was triturated with petroleum ether b.p. 40-60° until complete solidification had occurred, and the product was collected by filtration. On recrystallization from benzene, N-benzyl-4-hydroxybutyramide (13.6g., 56%) was obtained as colourless plates m.p. 69-70° (lit. 70-72°).

Reaction of butyrolactone with piperidine - Butyrolactone (4.3g.) was dissolved in piperidine (8.0 ml.) and heated at 100° (6 hr.). An infrared spectrum of a sample (film) showed maxima at 1750cm⁻¹ (small) and 1680cm⁻¹ indicating that reaction was almost complete. The oily product was cooled and repeatedly washed with petroleum ether b.p. 40-60° to remove the excess of piperidine. The residue was cooled in dry ice to induce crystallization. The product was set aside overnight at 0° and triturated at this temperature with a mixture of ice-cold benzene-petroleum ether (2:3) to remove traces of unchanged butyrolactone. N-(4-Hydroxybutyryl) piperidine (6.6g., 85%) was obtained

as an almost colourless crystals which liquified at room temperature.

Reaction of 4-hydroxy-4-methyloctanoic acid lactone with benzylamine. - The lactone (0.8g., 0.8 ml.) was heated with benzylamine (1.5 ml.) for 12 hours at 100° in an atmosphere of nitrogen. The infrared spectrum of a sample of the reaction mixture showed maxima at 1755cm⁻¹ and 1680cm⁻¹ with the intensity of the former predominating, indicating only partial formation of hydroxy-amide. Repetition of the reaction in a sealed tube at 140° for 2 hr. did not result in complete reaction.

Reaction of 4-hydroxy-4-methyloctanoic acid lactone with piperidine. - The lactone (0.8g.) was heated with piperidine (1 ml.) at 100° for 20 hr. The infrared spectrum of a sample (film) showed maxima at 1755cm⁻¹ and 1645cm⁻¹ with the intensity of the former predominating, indicating that the expected hydroxy-amide was being formed in low yields.

Reaction of 4-hydroxy-4-methyloctanoic acid lactone with hydrazine. - The lactone (0.1g.) was heated at 100° (2 hr.) with hydrazine (0.2 ml., 100%). An infrared spectrum of a sample (film) indicated a maximum at 1640cm⁻¹ with absence of absorption at 1750cm⁻¹ indicating complete ring opening with formation of 4-hydroxy-4-methyloctanoic acid hydrazide.

Photolysis of benzene. - Benzene (50 ml.) was photolysed

under the conditions used in the irradiations of N-chloro-amides. The colourless liquid was carefully fractionated to remove unchanged benzene. The brown semi-solid residue (0.1g.) was chromatographed on alumina. Elution with hexane produced a trace quantity of biphenyl identified by its ultra-violet spectrum.

(1) Reactions of the Mixture of 17- and 20-Hydroxycholelanic Acid Lactone

Attempted oxidation of the lactone mixture - The oily lactonic mixture (0.1g.) from the photolysis of cholanamide was dissolved in glacial acetic acid (4 ml.) and concentrated sulphuric acid (1 drop) was added. Potassium permanganate (0.2g.) and potassium metaperiodate (0.22g.) were added and the mixture was heated on a water-bath at 85° (2 hr.) At the end of this time, decolourization of the solution was almost complete. The reaction mixture was cautiously neutralized to pH 7 with sodium carbonate solution, subsequently extracted with chloroform and the organic layer dried (magnesium sulphate). Removal of the solvent afforded a yellow oil (0.87g.) the infrared spectrum of which (nujol) showed a maximum at 1755cm^{-1} (γ -lactone) with a slight inflexion at 1700cm^{-1} . The oil was tested for the presence of androstan-17-one by treatment with ethanolic potassium hydroxide and m-dinitrobenzene. A slight red colouration was produced indicating the possible presence of the required ketone in trace yields.

Repetition of the oxidation under more vigorous conditions did not improve the result.

Treatment of the lactone mixture with benzylamine - The lactonic oil (0.6g.) was heated for several hours on a steam-bath with benzylamine (1.5 ml.) under a stream of carbon dioxide-free nitrogen. An infrared spectrum carried out on a sample of the reaction mixture indicated maxima at 3600cm^{-1} , 1755cm^{-1} (γ -lactone) and 1680cm^{-1} (amide). The reaction mixture was poured into an excess of cold dilute acetic acid and the resultant tarry solid was triturated thoroughly with water and dried to constant weight (0.6g.). Attempted crystallization of the product from various solvents gave gums which were shown by infrared spectroscopy to contain a mixture of γ -lactone and hydroxyamide.

Reduction of the lactone mixture - The lactonic oil (1.9g.) was dissolved in anhydrous ether (25 ml.) and lithium aluminium hydride (1.0g.) was added in portions. The reaction mixture was heated under reflux (4 hr.). At the end of this period the ethereal suspension was cooled and poured into water (50 ml.). The mixture was carefully acidified with concentrated hydrochloric acid and the resultant suspension extracted with chloroform. The organic solution was dried (magnesium sulphate) and the solvent removed by distillation to yield a pale brown oil (1.1g.). The infrared spectrum of the product indicated

an absence of lactone. A sample of the crude product was chromatographed on a film of alumina using benzene as developer. The presence of at least four compounds was indicated. A portion of the oil (0.3g.) was chromatographed on a column of Woelm alumina (5g., activity IV). Elution with hexane and hexane-benzene gave non crystallizable yellow oils which were not further identified. Benzene-ether was used as eluant and a gum was obtained which on trituration with petroleum ether gave a colourless solid m.p. 112-154° (0.03g.). Repeated recrystallization from benzene-hexane gave suspected cholane-20,24-diol m.p. 172° .

Oxidation of crude cholane-20,24-diol. - Portions (0.02g.) of the crude diol were oxidized using the conditions listed below:

- (a) Potassium permanganate in 20% sodium hydroxide solution (15 min.).
- (b) potassium permanganate in glacial acetic acid in the presence of a trace of concentrated sulphuric acid (20 min.).
- (c) chromic oxide in acetic acid and concentrated sulphuric acid (1 hr.).

Infrared spectral studies of the products showed that the diol had undergone little or no reaction under the conditions of (a). In (b) and (c) maxima at 1755cm^{-1} and 1720cm^{-1} indicated that a mixture of 17- and 20-hydroxy-acid

lactones had been formed. In all cases spot tests for 17-keto-steroids failed to reveal the presence of androstan-17-one.

SUMMARY

Two methods of selective substitution in an aliphatic chain have been investigated. In the first case, oxidations of α - and γ - branched chain carboxylic acids with permanganate and manganate ions in alkaline solution and peroxydisulphate ions in acid and alkaline solution result in low yields of acids hydroxylated at the position of branching. β -Branched chain acids produce low yields of ketones. The nature of products is explained by postulation of reaction of a hydroxy-radical in oxidations involving manganese oxy-salts, and a radical chain mechanism involving an hydroxy radical or sulphate radical anion in peroxydisulphate reactions. The oxidation of amides and esters by the latter reagent proceeds by a mechanism, the initial step of which is analagous to that of the oxidation of the acids themselves.

The irradiation of N-chloro-amides results in homolysis of the nitrogen-chlorine bond followed by an intramolecular hydrogen abstraction involving a 6- or 7-membered transition state to give an isomeric radical and finally, a γ - or δ -chloro-amide. Side reactions occur, resulting in the evolution of hydrogen chloride which converts N-chloro-amide to primary amide.

Neither type of reaction has been successfully adapted to the selective substitution and subsequent partial degradation of steroid molecules.

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