A THESIS

entitled

THE ADDITION OF HALOGEN ACIDS TO OLEFINS

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in

THE UNIVERSITY OF GLASGOW

by

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INTRODUCTION

The heavy isotope of hydrogen, deuterium, has found many uses in organic and biological chemistry since its discovery in 1932.[1]

Compounds containing deuterium differ from the corresponding hydrogen compounds in their physical properties. These differences are slight , but well defined. As extensive use is made in this thesis of deuterium chloride and bromide a comparison of the physical properties of these compounds and the hydrogen halides is given below.

Compound	m.p. °A	b.p.°A	latent heat evapn. cal./mol.	critical temp.
HCl	162.2	188.1	4081	51.0
DCl	158.2	191.6	4151	50.3
HBr	186.2	206.3	4257	89.9
DBr	185.7	206.3	4258	88.8

There exist several standard methods for the introduction of deuterium into organic compounds, and these are listed under the headings below.

1. Interaction between carbides and deuterium.
2. Catalytic deuterisations.
3. Addition of deuterium, e.g. as deuterium halide, to suitable molecules.
4. Grignard reactions.
5. Exchange reactions, e.g. enolisation of ketones in the presence of deuterium oxide.
6. Reductions with specific reagents, e.g. lithium aluminium deuteride.

Deuterium differs from most other isotopic elements in several ways. It is easily stored and handled in the form of deuterium oxide, being non-radioactive. Its presence is easily ascertained, e.g. by the infrared -C-D and -O-D adsorptions. It is freely commercially available at a reasonable price. There exist the simple methods listed above for the introduction of deuterium into organic molecules. Finally, it can be accurately estimated quantitatively by a variety of methods.

The work in this thesis is conveniently divided into four sections.

Section I

In this section deuterium is used to establish the proper assignment of some bands in the infrared spectra of steroidal halides. The validity of a claim by Corey[2,3] that a distinction is possible between axial and equatorial deuterium in steroidal molecules from their infrared spectra has also been examined.

Section II

This section deals with a form of exchange reaction between the hydrogens of a carbonium ion formed by protonation of a double bond and deuterium ions present. Incidentally to this a study has been made of the formation of exocyclic olefins by pyrolysis of tertiary acetates. The 5,6, and 7 membered ring olefins have been studied, and this branch of the work makes use of the comparatively new chemical tool of gas liquid chromatography.

Section III

Here an exchange reaction analogous to that dealt with in section II is studied, involving carbonium ions formed from cyclopropane rings.

Section IV

This section is devoted to an investigation of the stereochemistry of the free radical addition of hydrogen and deuterium bromide to cholest-2-ene, cholest-5-ene, and to 3-methylcholest-2-ene.

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SECTION I

HISTORICAL

Within the last decade conformational analysis has emerged as an intrinsic part of organic chemistry, and a large number of papers illustrating the significance of the preferred conformations of various organic compounds have appeared. The physical and chemical properties of a molecule are directly related to its preferred conformation, the most important example of such a relationship with physical properties being the occurrence of specific absorptions associated with a particular conformation in the ultraviolet or infrared spectra of the molecules.

It is generally acknowledged that the principles of conformational analysis are best illustrated by reference to molecules such as steroids or triterpenoids which are composed of a series of fused cyclohexane rings, and where the stereochemical configurations render a choice of preferred conformation unambiguous.

The effect of α-halogen substitution on the carbonyl frequency of cyclohexanones in both the infrared and ultraviolet regions of the spectrum is

indicated in Table I. In the infrared α-halogeno-ketones exhibit a displacement of maxima if the substituent is equatorial, but none if it is axial,[4,5,6,7] whereas in the ultraviolet region the converse is the case.[8,9] There are differences in the ultra-violet region between axially and equatorially substituted α-hydroxy ketones (or their acetates) although infrared examination fails to distinguish between the two.[8,10]

Table I

α-Substituent	shift in carbonyl frequency			
	infrared (cm^{-1})		ultraviolet (mμ)	
	equatorial	axial	equatorial	axial
Cl	+20	+5	-7	+20
Br	+20	0	-5	+28
OH	-	-	-12	+17
OAc	-	-	-5	+10

Even more direct is the correlation between a substituent, its own conformation, and the position of the carbon-substituent stretching frequency in the infrared. This is illustrated in Table II.[11-18]

Table II

Bond	range of frequency in which bond occurs (cm^{-1})			
	equatorial		axial	
C-D	2155-2162	2171-2177	2114-2138	2139-2164
C-O (ofC-OH)	1037-1044		996-1036	
C-O (ofC-OAc)	[1013-1022]	⟸⟹	[1025-1031]	
C-O (ofC-OMe)	1100-1104		1086-1090	

The general rule has been proposed that equatorially substituted cyclohexanes absorb at higher frequencies than do axially substituted derivatives.[16] This can be explained qualitatively in that the stretching of an equatorial substituent causes appreciable expansions and contractions of the cyclohexane ring whereas the stretching motion of an axial substituent is largely normal to the plain of the ring, and will have a smaller effect.[16,18] It follows that the restoring force should be less for the axial than that for the corresponding equatorial motion and should induce a lower vibration frequency.

In 1956 Barton, Page, and Shoppee[17] extended these observations to include the carbon-halogen

stretching frequencies in halogenosteroids. For the equatorial carbon-chlorine stretching frequency they quoted 13 examples with absorption in the range 736-856 cm^{-1} , and 21 cases of axial substituents absorbing within the range 646-730 cm^{-1} were given. For the equatorial carbon-bromine frequency the range quoted, with 16 examples, was 682-833 cm^{-1}; and for the axial carbon-bromine frequency 542-692 cm^{-1}, with 13 examples. The region of these absorptions is free from interference from other functional groups.

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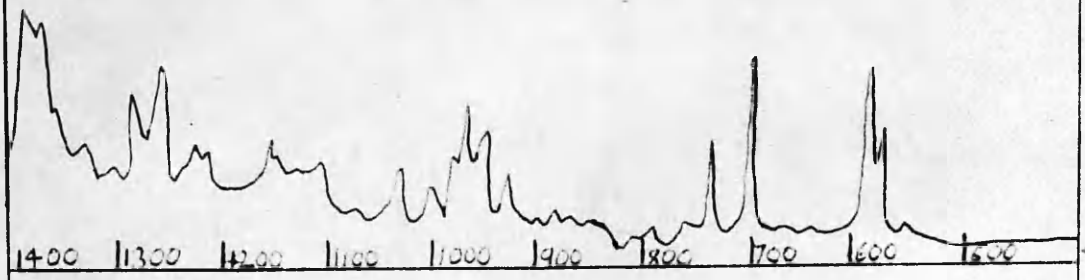
DISCUSSION

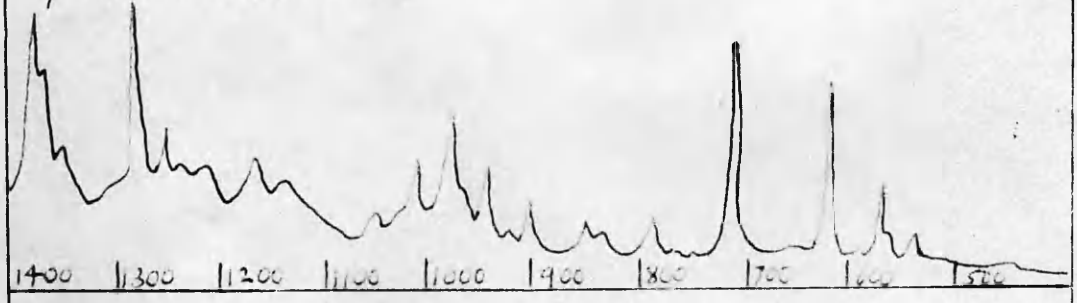
The spectra of the halogeno steroids examined by Barton et. al.[17], either in the solid state or in solution, were usually found to contain not one but several strong bands in the 800 - 400 $cm.^{-1}$ region of the spectrum, and some selection had to be made for the assignment of their "carbon - halogen stretching frequency". A few examples from the 1956 paper illustrate this. (See diagram I.) In general the strongest band present in the region was chosen. Although simple alkyl halides and halogenocyclohexanes often exhibit internal rotation[19] and therefore yield differing infrared and Raman spectra in the solid and liquid states, this effect is not observed in steroids. That is to say, the existence of gauche and trans forms of the molecule cannot be used to explain the multiplicity of bands observed. However, with many simple halogeno - hydrocarbons it has been found that the high frequency band was associated with the trans form. With ethylene chloroiodide, $CH_2Cl.CH_2I$, for example, studied by

DIAGRAM T

3α-CHLOROCHOLESTANE



3β-CHLOROCOPROSTANE



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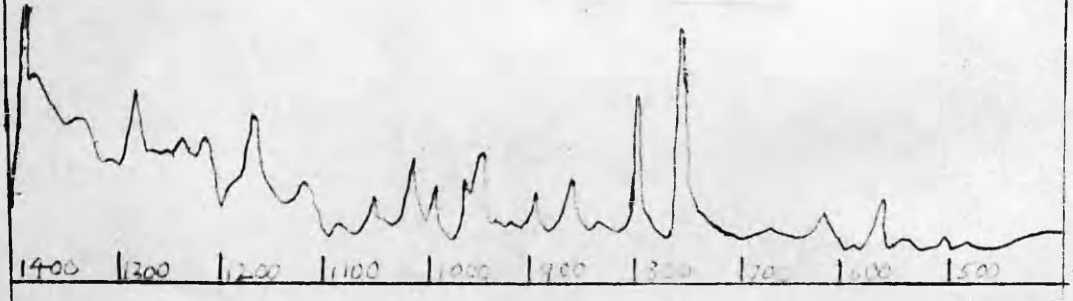
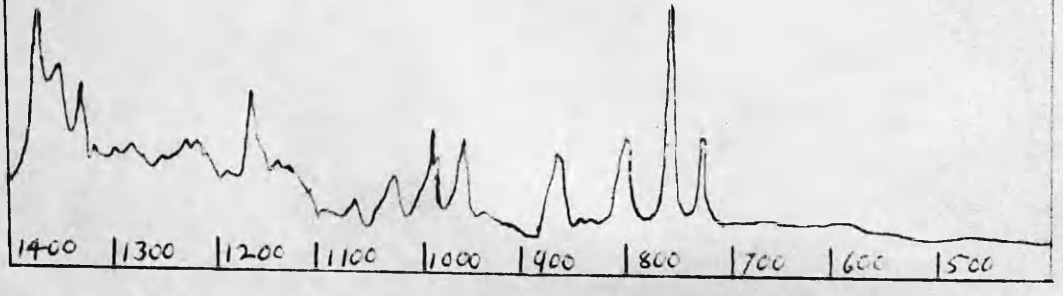
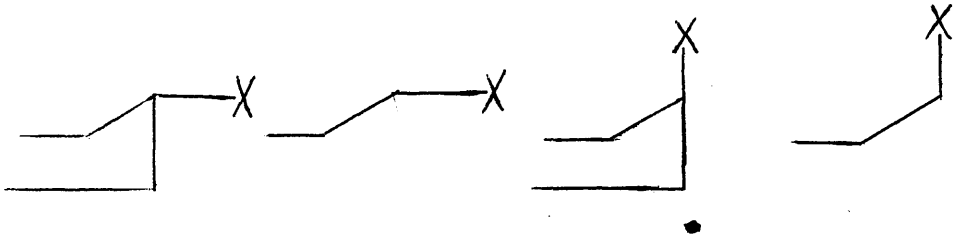


3β-CHLOROCHOLESTANE



Raman spectroscopy, the two halogen atoms have frequencies well separated from one another, and can be assumed to be relatively independent. In the liquid state the C-Cl stretching frequencies for this molecule occur at 707 cm.$^{-1}$ and 660 cm.$^{-1}$; but in the solid state only the band at 707 cm.$^{-1}$ persists, and by comparison with other more fully assigned spectra of related molecules this has been shown to be associated with the <u>trans</u> isomer. Sheppard[20] has pointed out the analogy between the <u>gauche</u> and <u>trans</u> forms in simple monohalogeno-hydrocarbons and the axial and equatorial forms in the halogenosteroids. The analogy is illustrated diagramatically below.



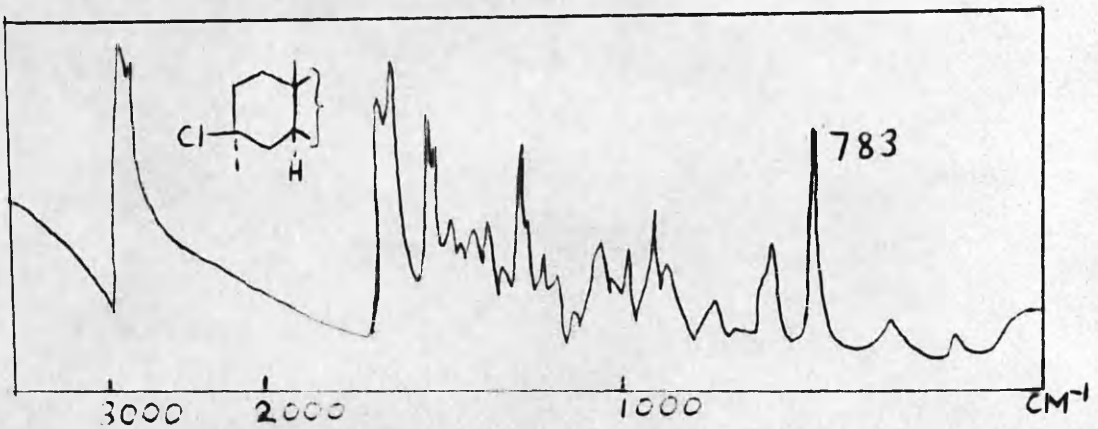
equatorial trans axial gauche

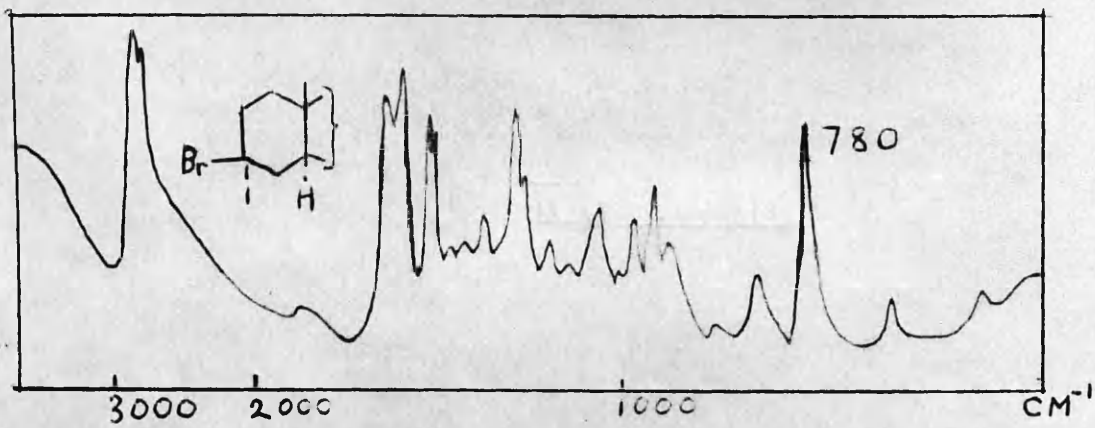
In general, the C-X stretching frequency for equatorial or trans halogen substituents is greater than that for axial or gauche substituents. Further, in the steroidal halogen compounds examined by Barton et. al., it was found that axial halogen atoms gave rise to a greater multiplicity of bands than equatorial halogen substituents. Sheppard has suggested that the additional band - or bands - arose from a modified $-CH_2$ rocking mode, and that, for reasons of symmetry, such a modified mode cannot occur with equatorial halogen substituents. There is once more an analogy here in that the C-X stretching frequency of n-propyl halides can interact with suitable $-CH_2$ rocking vibrations with the gauche, but not with the trans form.

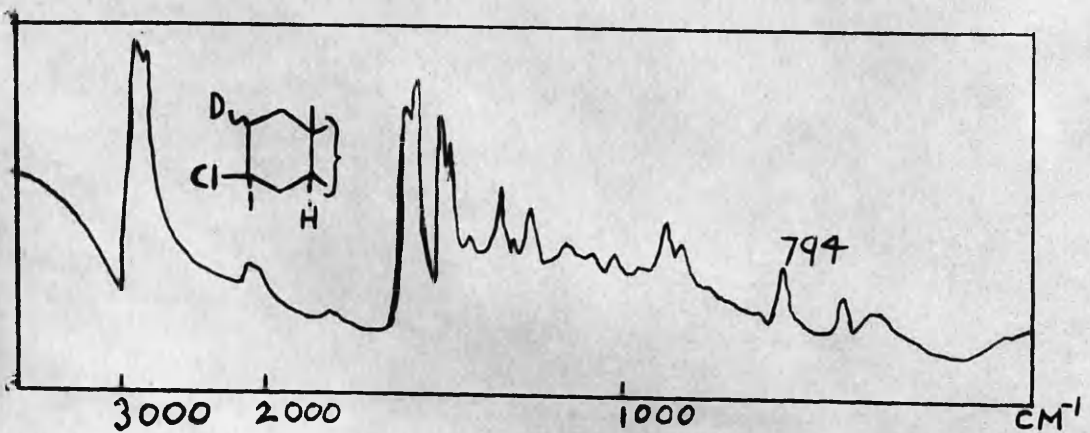
The range quoted for the carbon-chlorine frequency by Barton, Page, and Shoppee agrees well with the values reported for monohalogenocyclohexanes[19], but the values for the carbon-bromine linkages are somewhat higher than those quoted by Bellamy[21] for simpler compounds.

The infrared spectra of 1-chloro-1-methylcyclo-

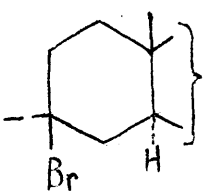
DIAGRAM II


Cl
H
783
3000
2000
1000
CM⁻¹

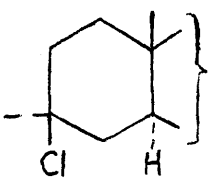

Br
H
780
3000
2000
1000
CM⁻¹


D
Cl
H
794
3000
2000
1000
CM⁻¹

hexane and 1-bromo-1-methylcyclohexane are surprisingly alike over the region 3600 cm.$^{-1}$ to about 700 cm.$^{-1}$, and when 3β-bromo-3α-methylcholestane (I) was prepared in connection with some studies of the addition of halogen acids to double bonds, a striking similarity, approaching an identity, was observed with the spectrum of 3β-chloro-3α-methylcholestane over this same region, (See diagram II.) although there were differences below 700 cm.$^{-1}$. In particular, the



I



II

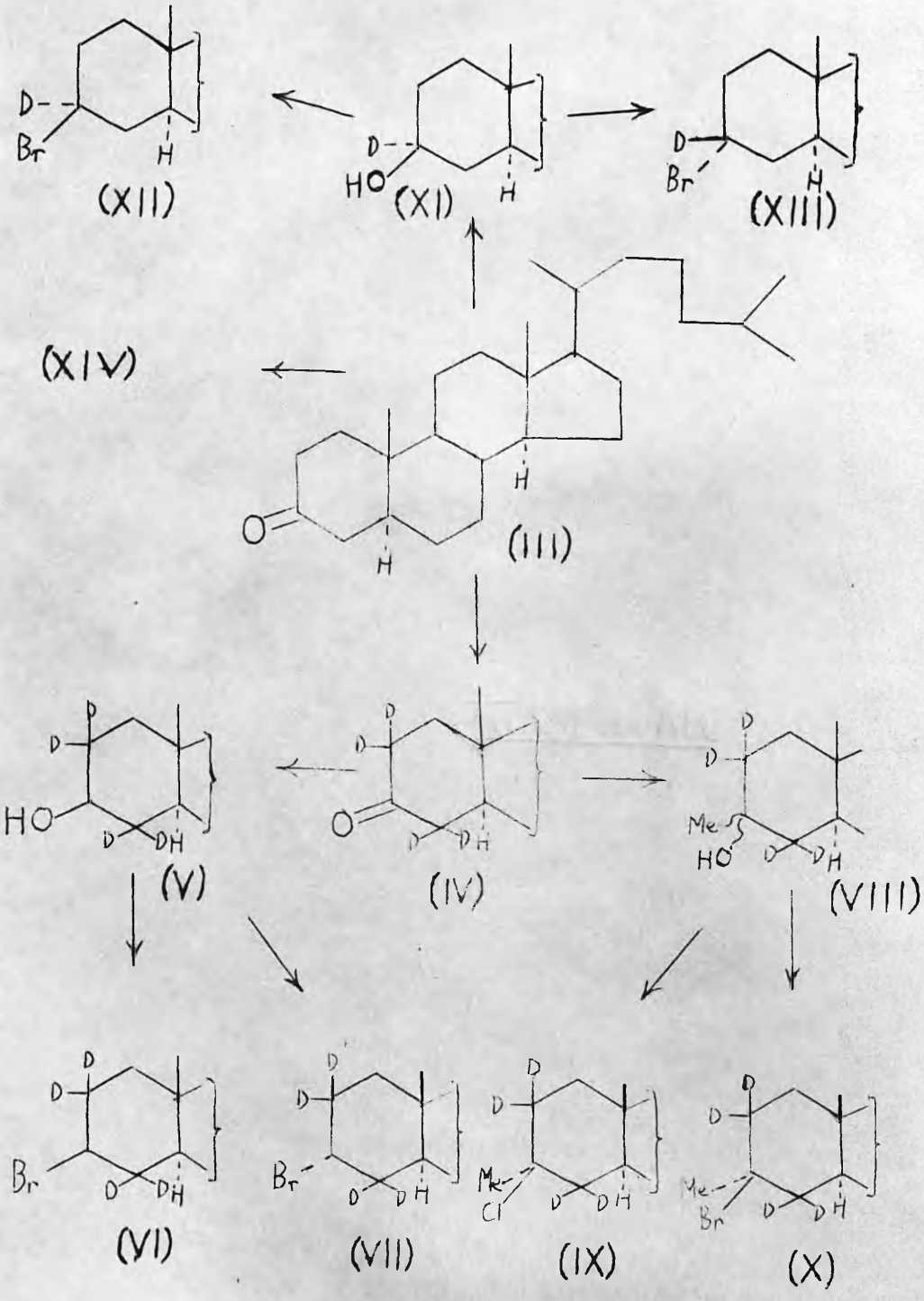
only strong bands present in the spectra above 700 cm.$^{-1}$ not present in the spectrum of 3β-methylcholestane, i.e. the hydrocarbon portion of the molecules, were those at 1168 cm.$^{-1}$ and 782 cm.$^{-1}$ For equatorial halogens in the 3 position in steroids Barton et. al. quote the ranges 708 -704 cm.$^{-1}$ and 782 -749 cm.$^{-1}$ respectively for the bromine and chlorine linkages.

The 3-bromosteroid 3β-bromo-3α-methylcholestane is thus absorbing well outwith the range assigned to such compounds, and indeed at a higher frequency than shown by any bromosteroid of the 29 examples in the original paper. (Range of equatorial carbon-bromine absorption 754-704 cm.$^{-1}$.) If this is discounted and the assumption made that in 3β-bromo-3α-methylcholestane the carbon-bromine frequency is higher than any previously found it is still unlikely that both the carbon-bromine and carbon-chlorine stretching frequencies in the analogous compounds (I) and (II) should be at identical positions. Bellamy[22] has shown that, at least in the case of the methyl halides, the frequency of the carbon-halogen stretching vibration is a function of the electronegativity of the halogen atom.

The immediate alternatives to accepting the bands at 1168 cm.$^{-1}$ and 782 cm.$^{-1}$ in the compounds discussed as being those of a carbon-halogen substituent itself is that they are:-

a) Carbon-hydrogen deformations of hydrogens situated on adjacent carbon atoms to the halogen

DIAGRAM III


(XII)
(XI)
(XIII)
(XIV)
(III)
(V)
(IV)
(VIII)
(VI)
(VII)
(IX)
(X)

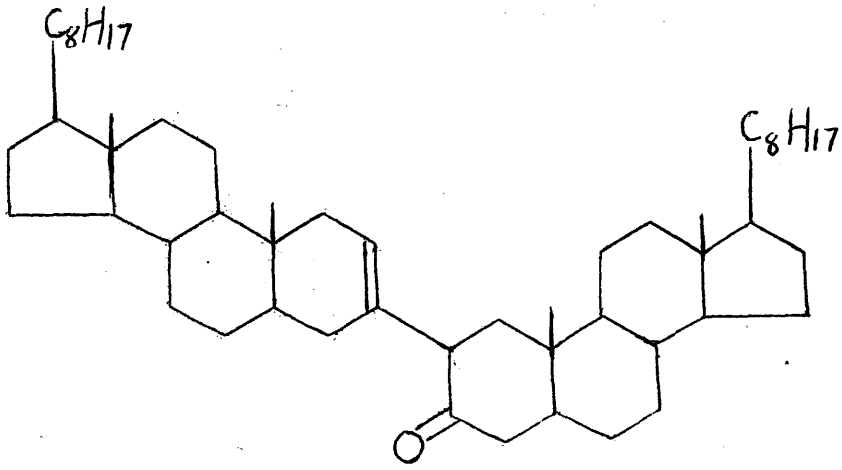
substituent, and which have been polarised by it. or b) Some form of coupled vibration involving hydrogen atoms in the position adjacent to the halogen substituent.

To test these hypotheses it was decided to synthesise some deuterohalogenosteroids. (See diagram III.)

First synthesised was a deuterated form of 3β-bromo-3α-methylcholestane (X) in which all the α-hydrogens with respect to the halogen atom had been replaced by deuterium (excepting those in the 3α-methyl group.) In this compound the bands at 1168 $cm.^{-1}$ and 782 $cm.^{-1}$ were no longer present. When the corresponding deuterochloride (IX) was prepared the same effect was observed. With 2,2:4,4-tetradeutero-3α-bromocholestane (VII) and the corresponding 3β-bromide (VI) the band at 690 $cm.^{-1}$ in the former and at 706 $cm.^{-1}$ in the latter associated with undeuterated material was greatly reduced in intensity, virtually disappearing. Below 700 $cm.^{-1}$, i.e. in the KBr region, the introduction of even

a single atom of deuterium, e.g. in the 3-deutero-3-bromocholestanes (XII and XIII), produced quite drastic changes in the spectra, the carbon - bromine bands again being affected.

The preparation of 2,2:4,4-tetradeuterocholestan-3-one (IV) from cholestanone (III) was carried out by enolisation in the presence of deuterium oxide. This method is more readily applicable to the scale of work involved in this thesis than that in the literature[23], and has the advantage that the preparation of methanol-d is avoided. The material obtained was deuterated to the same extent as that in the literature (3.6 atoms of deuterium per molecule) and had an identical infrared spectrum in carbon tetrachloride.[24] When an attempt was made to carry out the enolisation under slightly modified conditions, which involved heating with sodium in dioxane moistened with deuterium oxide, the product was not deuterocholestanone, but the condensation product (XIV). The structure follows from the mode of formation, a positive tetranitromethane test for unsaturation, carbonyl absorption in the infrared at

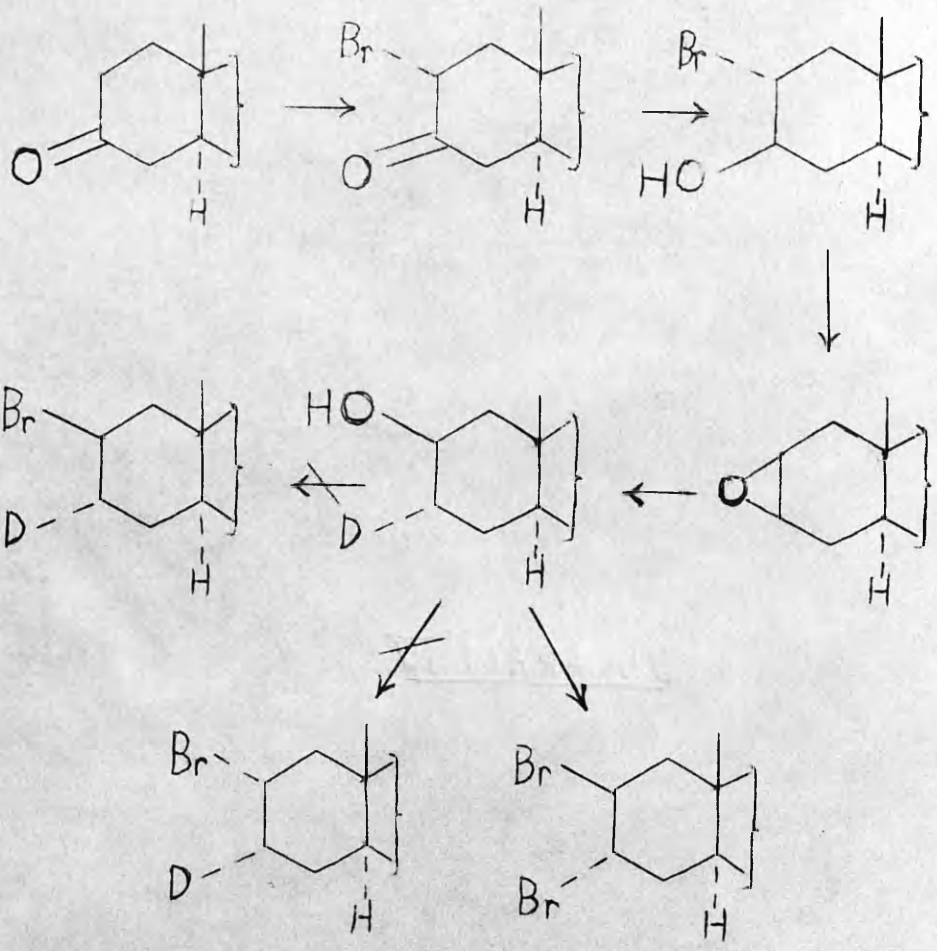


(XIV)

1704 cm^{-1}, carbon and hydrogen analysis, and the correlation between the physical constants and those of material obtained by Corey and Young.[25] (This experiment was carried out in conjunction with Dr. R.B.Pinero.)

In connection with other work deuterium chloride was added to 3-methylcholest-2-ene and cholest-5-ene. Some exchange of hydrogen and deuterium occurs in both of these reactions, but the deuterium content of the resultant chlorides does not exceed 1.7 atoms of deuterium per molecule. (See section II.) In these deuterohalides it was again found that the

DIAGRAM IV


O
H
Br
O
H
Br
HO
H
O
H
HO
D
H
Br
D
H
Br
D
H
Br
Br
H

bands ascribed by Barton, Page, and Shoppee to the carbon-halogen stretching vibration had vanished. (See diagram II.) This suggested that one, or at most two, hydrogens in a specific conformation α to the halogen atom produced the bands observed. As a consequence the synthesis of conformationally specifically monodeuterated halogenosteroids became of interest. An attempt towards this end was made as indicated. (See diagram IV). This broke down at the final stage. When cholestan-2β-ol was treated with phosphorous pentabromide the product was not the expected 2α-bromocholestane, but 2β:3α-dibromocholestane, i.e. the diaxial dibromide. It appears that the reaction proceeds by facile elimination of the elements of water from the axial alcohol - perhaps catalysed by free hydrogen bromide in the reaction mixture - followed by addition of bromine to the double bond. The 2α (equatorial) bromide is unlikely to be an intermediate in the reaction. Diaxial addition to double bonds in steroid molecules is common, and Barton[26] has suggested that such a mode of addition is general for all electrophilic

reagents in which the initial portion of the addendum is not H^+. In order to confirm that cholest-2-ene was an intermediate in the reaction it was treated with phosphorous pentabromide under the reaction conditions and found to give a good yield of 2β:3α-dibromocholestane. This reaction of axial alcohols to give the diaxial dihalogen compound has been previously noted[27] and appears to be general.

In view of this difficulty further work along these lines was abandoned.

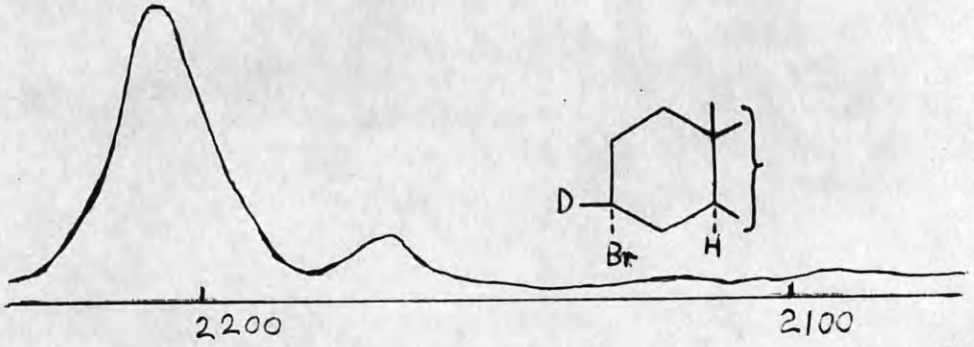
Barton[28], in a footnote, and later Page[29], pointed out that although the bands put forward in the 1956 paper may not be true carbon-halogen stretching vibrations, and that this observation was of fundamental interest, it did not effect the intrinsic value of the empirical correlation of the bands for the assignment of conformation in halogeno-steroids. To a large extent this is true, but in view of the anomalous spectrum of 3β-bromo-3α-methyl-cholestane it appears that such conformational assignments, although helpful, must be tentative and should be used with care. This will be particularly

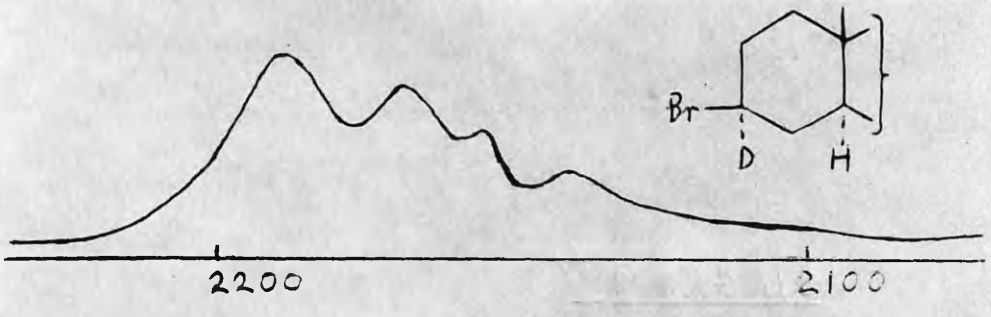
true of new halogenosteroids in which the halogen atom is tertiary in nature, or in which the positions α to the halogen atom are highly substituted.

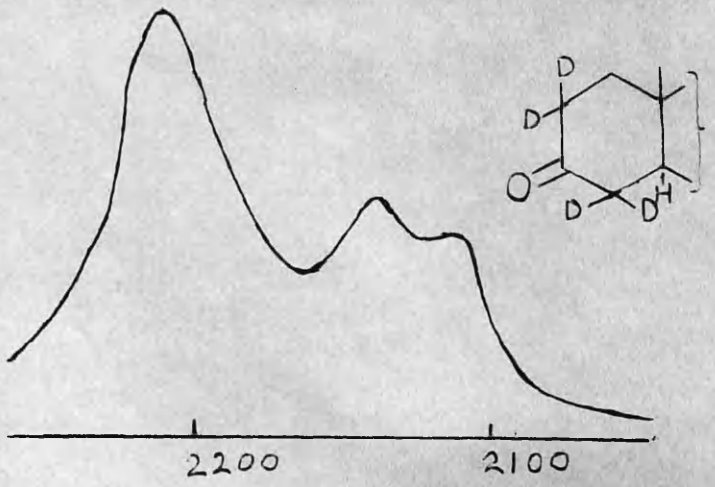
The deuterated halogenosteroids and intermediates used in the preceding work were also examined over the range 2300 cm.$^{-1}$ to 2000 cm.$^{-1}$ in the infrared using high resolution apparatus. It is within this range that the carbon-deuterium stretching absorption occurs. In general, with monodeuterated steroids, the results were in accord with those assignments proposed by Corey et. al.[2,3]

3α-Deuterocholestan-3β-ol had absorption peaks at 2146 cm.$^{-1}$, 2124 cm.$^{-1}$, and 2100 cm.$^{-1}$, in good agreement with Corey's values of 2143 cm^{-1}, 2117 cm.$^{-1}$, and 2090 cm.$^{-1}$ as only the highest frequency peak is sufficiently sharp to allow accurate measurement. 3β-Bromo-3α-deuterocholestane had two bands (2207 cm.$^{-1}$) and 2170 cm.$^{-1}$) the higher frequency band being the more intense, whereas 3α-bromo-3β-deuterocholestane showed four bands (2190 cm.$^{-1}$, 2170 cm.$^{-1}$, 2156 cm.$^{-1}$ and 2140 cm.$^{-1}$) The highest frequency band was again

DIAGRAM V


D
Br
H
2200
2100


Br
D
H
2200
2100

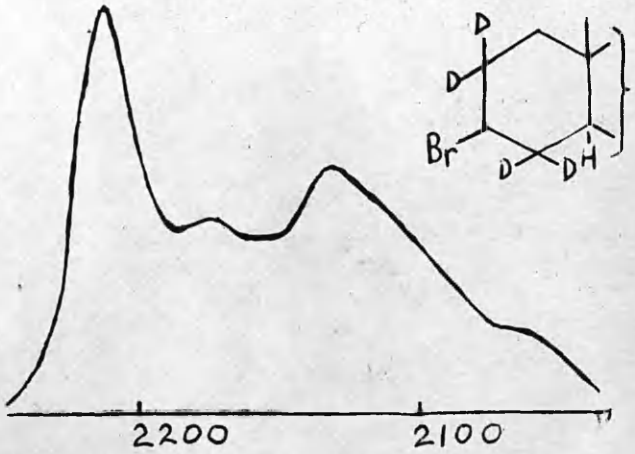

D
D
O
D
D
H
2200
2100

the most intense, but in this case the intensity differencies were much smaller. (See diagram V). The spectra suggest that possibly a greater multiplicity of bands is more commonly associated with an axial deuterium substituent than with an equatorial deuterium atom. The presence of the halogen atom appears to raise the frequency at which these characteristic deuterium absorptions occur.

The spectra of 2,2:4,4:-tetradeuterocholestan-3-one, 2,2;4,4-tetradeutero-3α-bromocholestane, 2,2:4,4-tetradeutero-3β-bromocholestane, 2,2:4,4-tetradeutero-3β-bromo-3α-methylcholestane, and 2,2:4,4-tetradeutero-3β-chloro-3α-methylcholestane all conform to a general pattern in which three major bands occur, and in which the highest frequency absorption is the most intense. (See diagram VI). This band again occurs at a relatively high frequency, in tetradeuterocholestanone appearing at 2216 cm.$^{-1}$

Callow[30] has observed and exchange reaction between deuterium acetate and tigogenin acetate (XV) in which two atoms of deuterium are incorporated into the tigogenin molecule. On reasonable evidence these atoms are assumed to reside on the C23 carbon atom,

DIAGRAM VI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D
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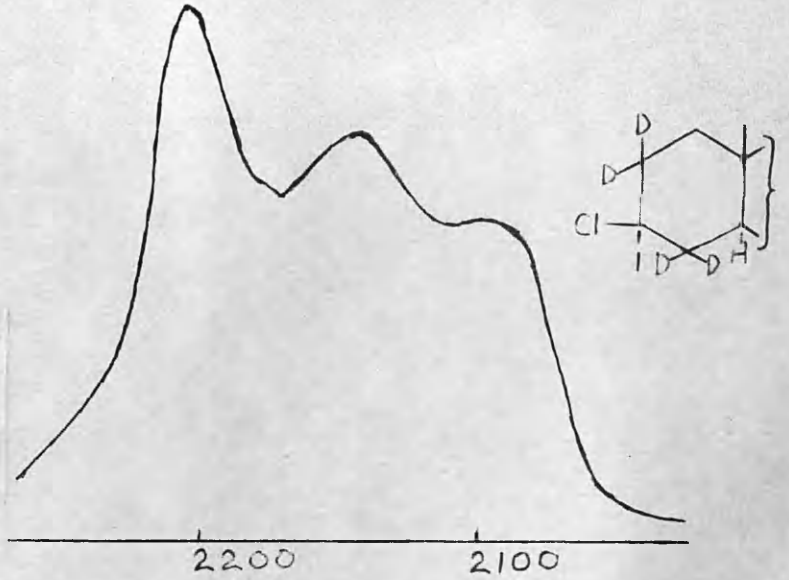
D
D
H
2200
2100


D
D
Cl
D
D
H
2200
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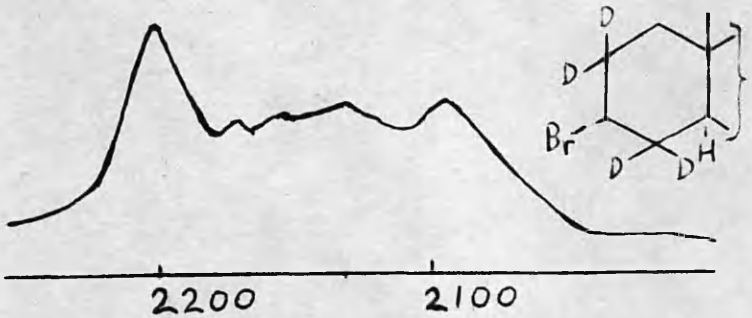
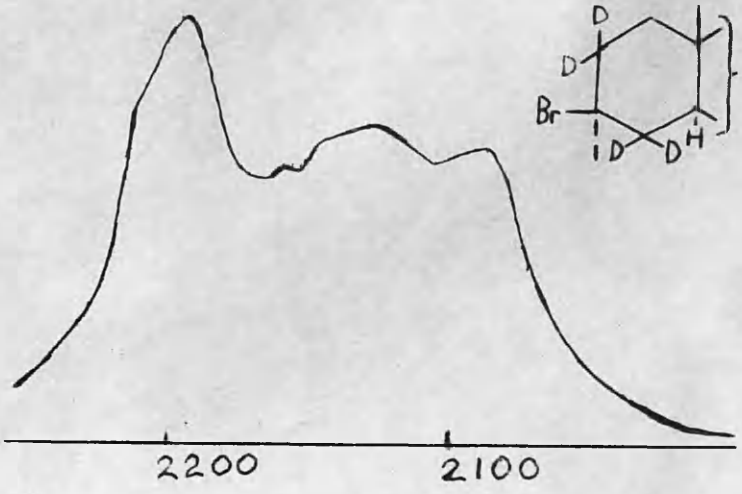
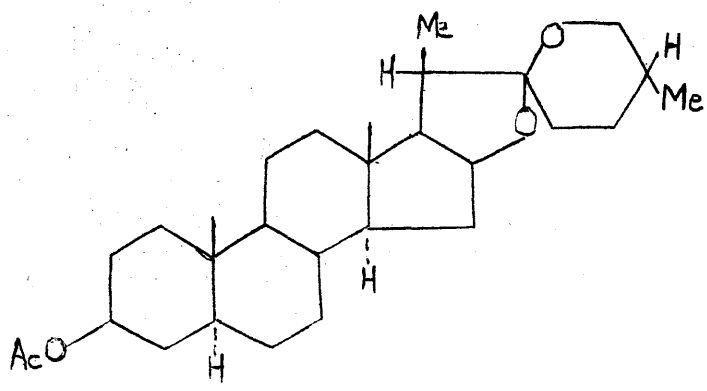

D
D
Br
D
D
H
2200
2100


D
D
Br
D
D
H
2200
2100



XV

and the infrared spectrum shows bands at 2210 cm^{-1}, 2146 $cm.^{-1}$, 2216 $cm.^{-1}$ Corey et. al.[2,3] have recorded bands at 2187 $cm.^{-1}$, 2155 $cm.^{-1}$, and 2104 $cm.^{-1}$ in the spectrum of 3:3-dideuterocholestane and at 2220 $cm.^{-1}$ and 2131 $cm.^{-1}$ in the spectrum of 6:6-dideutero-3β-acetoxycholestan-7-one. The same workers found four bands in the spectrum of 1:1-dideutero-4-phenyl-cyclohexane, at 2201 $cm.^{-1}$, 2189 $cm.^{-1}$, 2160 $cm.^{-1}$, and 2106 $cm.^{-1}$. The additional band observed in this case may well be attributable to the non-steroidal nature of the molecule.

These observations, in conjunction with our own results, strongly suggest that the triple absorption is characteristic of the gem-dideutero group, although the suggestion has been made that the weaker central

absorption may be attributed to incomplete deuteration of some positions giving rise to the normal mono-deutero absorption.[3] This would appear to be unlikely, as in several of the tetradeuterocholestane spectra examined in the present work the central band was more intense than the low frequency band. (See diagram VI). Disregarding the central band the separation of more than 80 $cm.^{-1}$ between the high frequency and low frequency bands is quite characteristic.

--ooOoo--

SECTION II

HISTORICAL

The work presented in this section of the thesis on exchanges occurring during the addition of deuterium halides to olefinic linkages is closely related to exchange reactions involving the hydrogens of aromatic rings and protons, the exchange reactions of saturated hydrocarbons with dideuterium sulphate, and some hydration studies of olefins. A brief review of each of these topics and of some other relevant material follows.

Exchange reactions involving aromatic rings.

Ingold, Raisin, and Wilson[31] reported the exchange between the hydrogens of benzene and 90% sulphuric acid. Horuti and Polanyi[32], commenting on the exchange, suggested that it was a special case of a general principle. They postulated that, as it had been shown that a definite equilibrium is established between them whenever an ethylenic compound and water are present in appreciable quantities,[33] the alcohol so formed would be in turn be dehydrated

by any dehydrating agents present. This reverse reaction could explain exchange with olefins allowing for the approximate chemical equivalence of hydrogen and deuterium. The process may be depicted as:

$$-CH{=}CH- \; + \; D_2O \rightarrow -\underset{OD}{CH}-\underset{D}{CH}- \rightarrow \begin{cases} -CH{=}CH- + D_2O \\ -CH{=}CD- + HOD \end{cases}$$

The argument was extended to include the transitory addition of hydrogen halides to an ethylenic linkage. In the presence of a catalyst by which the splitting off of the hydrogen halide with concomitant formation of a double bond was effected they suggested that there would be three manifestations of the process.

a) Hydrogen replacement.

b) Cis-trans inversion.

c) Wandering of the double bond.

Finally the argument was extended to include the aromatic case of benzene.

Ingold et. al.[34], in reply, accepted that such a mechanism could possibly apply to simple

ethylenic structures, but suggested that it did not operate when the compounds involved were aromatic in nature. They proposed, instead, an extension of Ingold's view of substitution by electrophilic reagents, and suggested that the ordinary orientation laws should be obeyed. They eliminated the remote possibility that exchange proceeded by sulphonation followed by desulphonation.[35] In the main, Ingold's proposals have been supported by the results of later workers.

Recent work has shown that the rate of hydrogen-deuterium exchange with benzene in acidic media follows Hammett's acidity function Ho over a wide range of pH values. It was concluded, accepting the Zucker-Hammett hypothesis,[36] that the first species of carbonium ion formed is not one in which a deuterium and a hydrogen occupy equivalent positions, as exchange is many times slower than the rate of protonation. It was suggested that the first formed "outer complex" ion gives rise to the rate determining step as it rearranges to the "inner complex" ion.[37]

The "outer complex" ion, it is reasonable to suppose, is analogous to the non-classical carbonium ions or π-complexes postulated by Taft[38] during his work on olefin hydrations.

Other aromatic exchange reactions involving heterogeneous catalysts[39], e.g. aluminium chloride, are well known, but are not relevant to this discussion.

Exchange reactions involving saturated hydrocarbons.

Following earlier and less detailed work[40,41] two papers from a group of workers in the Shell Development Company, published in 1951[42] and 1952,[43] gave details of the exchange reactions between the hydrogens of saturated hydrocarbons and deuterium under strongly acid conditions. They used n-butane-1d, n-butane-2d, isobutane-1d, and isobutane-2d, circulating them through sulphuric acid under various conditions and analysing the products (gaseous) mass spectrometrically. It was found that with n-butane no exchange occurred, and in no case was skeletal isomerisation found. With isobutane,

however, exchange reactions did occur. The "primary" hydrogens, i.e., those adjacent to the tertiary carbon atom, exchanged with the protons of the sulphuric acid used, and the "tertiary" hydrogen atoms of the isobutane molecules underwent intermolecular exchange. To account for this they postulated an ionic chain mechanism, in which the chain carrying step was a transfer of a tertiary hydrogen (with its electron pair) from an isobutane molecule to an ion. The chains, it was suggested, were initiated by oxidation of isobutane by sulphuric acid to form ions (and sulphur dioxide) and the chains terminated by reaction of ions to form non-reactive, non-volatile products. It was also suggested that while a particular ion exists its primary hydrogen atoms exchange very rapidly with acid protons derived from the medium, thereby giving the regenerated hydrocarbon a new set of primary hydrogen atoms. The chain carrying step is, in effect, a hydride shift between the carbonium ion and the dissolved isobutane molecules. The second paper extends this work, and among other conclusions

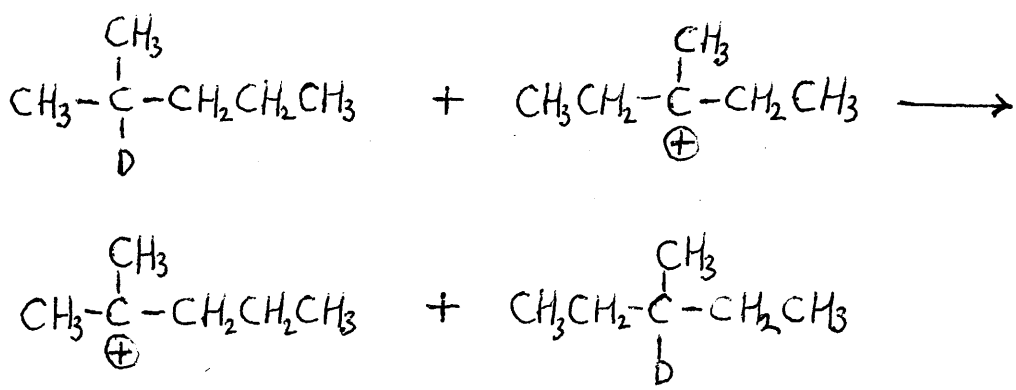
were the following:-

a) Only alkanes and cycloalkanes with a tertiary carbon atom undergo exchange.

b) The maximum number of hydrogen atoms exchanged in any one molecule is one less than the total.

c) The minimum number of hydrogen atoms exchanged in any one molecule is equal to the number of hydrogen atoms adjacent to the tertiary carbon atom.

Some studies were also made of accompanying isomerisations, and the hydride shift postulated in the earlier paper was established by the reaction of 2-methylpentane-2d with sulphuric acid. The sole product was 3-methylpentane-3d, without loss of deuterium to the acid.



Thus, the chain propagation reaction consisted

exclusively of transfer of a tertiary hydrogen atom with its bonding electrons to the tertiary carbon atom of a tertiary carbonium ion. It was also suggested that exchange of a greater number of hydrogens than those adjacent to the tertiary carbon centre was caused by methyl group migrations producing a new tertiary centre.

Hydration studies with olefins.

A study of the mechanism of the hydration of olefins using deuterated solvent was undertaken by Purlee and Taft[38] with, as substrates, 2-methylbut-2-ene and 1-methylcyclopentene.

Previous work[44] had suggested that the hydration of olefins involves a reversible proton transfer from hydronium ion to the olefin preceding the rate determining step. Work by Levy, Taft, and Hammett[45], however, showed, using 2-methylbut-2-ene and 2-methylbut-1-ene, that olefin removed from the hydration reaction after 50% of the original olefin present had reacted contained no isomers of the starting olefins. This precludes the formation

of a classical carbonium ion in the preliminary proton transfer. If an ion of this type was formed then the same ion (XVII) would be produced from both olefins, and would be one which is known to give an equilibrium mixture of 89% of 2-methylbut-2-ene (XVI) and 11% of 2-methylbut-1-ene (XVIII) at 25°C. By carrying out the hydration of 2-methylbut-2-ene in deuterated water containing nitric acid Purlee and Taft confirmed this earlier work. The elimination of the proton over the elimination of the deuteron is favoured both statistically and kinetically, and it was found that the olefin removed at the completion of half-life of the reaction contained no detectable deuterium. The conditions used were such that the hydration was virtually irreversible. This work leads to two alternative conclusions:-

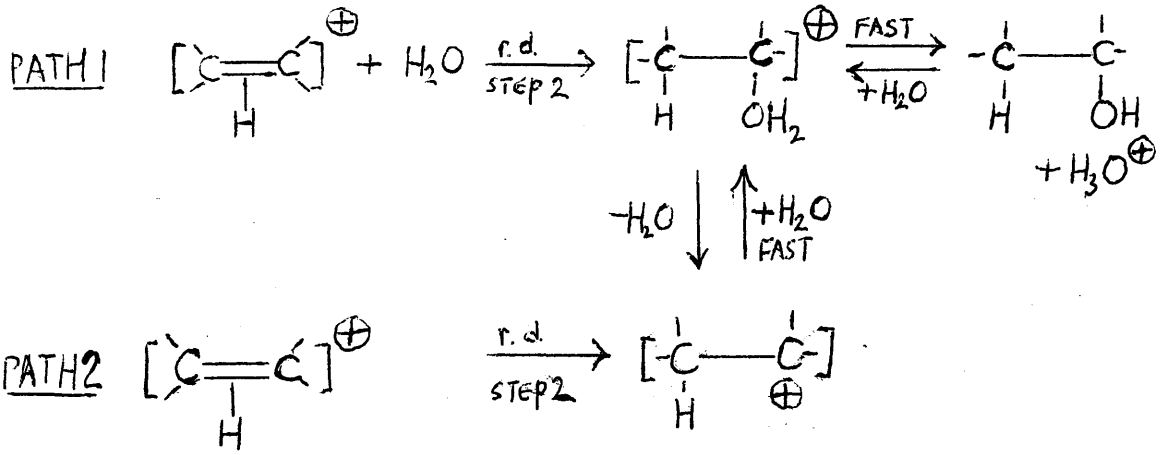
either 1) The reaction involves a rate-determining process with a large Bronsted α, so that the only detectable catalyst is hydronium ion.

or 2) A non-classical type of carbonium ion is formed in which all the α-hydrogen atoms

are not equivalent.

The authors concluded that their results upheld the view that there existed a preliminary reversible proton transfer from the hydronium ion to the olefin, and since the classical carbonium ion structure was not acceptable they postulated the formation of a complex, planar about the carbon-carbon double bond, and with the proton embedded in the orbital perpendicular to this plane. This proton is obviously not equivalent to the hydrogens bonded by sp^2 or sp^3 orbitals in the olefin.

The mechanisms suggested in the paper are as shown below.



The evidence in the paper itself is insufficient to distinguish between the two possible paths, but some evidence exists favouring the second route. Dostrovsky and Klein[46] found that the acid catalysed O^{18} exchange between tert.-butyl alcohol and water is about twenty fold greater than the rate of formation of isobutylene, but at the same time these authors propose that this exchange reaction involves a rate determining formation of the carbonium ion from the protonated alcohol. If this is so then the formation of the olefin from the tert.-butyl alcohol must involve step 2 of path 2 as a subsequent rate determining step, - the formation of the π-complex.

Other relevant exchange reactions.

Cannell and Taft[47] have considered the reaction of isobutylamine with nitrous acid. They have shown that there is no detectable exchange of hydrogen in the hydrogen migration to give the tert.-butyl alcohol when the reaction is carried out in deuterium oxide, illustrating that the tert.-butyl cation intermediate does not undergo direct hydrogen-

deuterium exchange. The products of the reaction were:-

tert.-butyl alcohol

sec.-butyl alcohol

iso-butyl alcohol

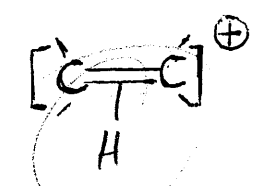
but-1-ene

cis and trans but-2-ene

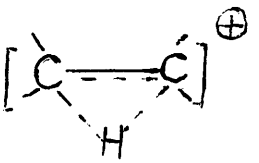
iso-butylene.

The alcohols constituted about 70% of the total products, tert.-butyl alcohol predominating (60-70% of alcohols produced.) In deuterated water the quantity of deuterium present in the tert.-butyl alcohol produced was too small to be detected, and the results are claimed to show that at no stage in the migration does the moving hydrogen pass through a state corresponding to the π-complex invoked in Taft's discussions on hydration. Such a complex eliminates the added proton much more readily than it reacts to produce tert.-butyl alcohol, contrary to the products obtained from the reaction involving isobutylamine. To explain these differences a second type of non-classical carbonium ion

was postulated - a bridged protonium ion, obtained either as a transition state or as an intermediate in intramolecular hydrogen transfers, as distinct from the π-complex supposedly occurring as an intermediate preceeding the rate determining step in the hydration of aliphatic olefins with a tertiary carbon centre. i.e.



π-complex

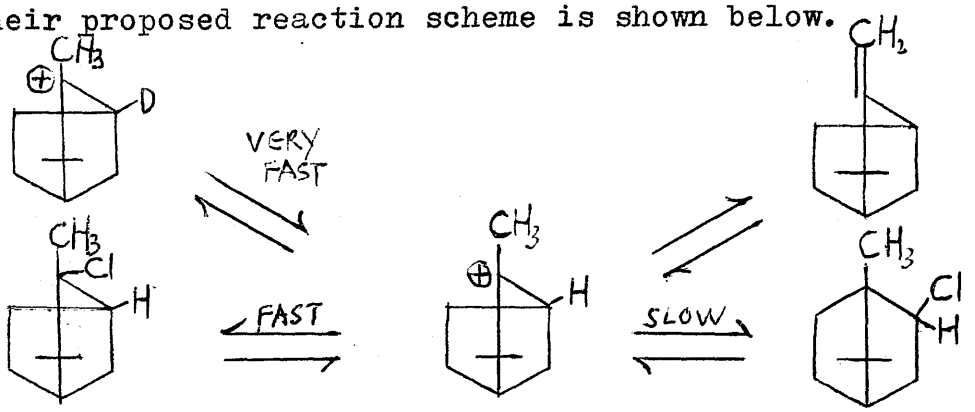


bridged protonium ion.

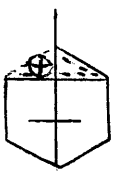
Roberts and Yancey[48] had suggested that nitrous acid reactions with ethylamine did not give a bridged ethylene protonium ion, and work by Roberts and Halmann[49] had suggested that the corresponding rearrangement of 1-propylamine-1-C^{14} to 1-propanol leading to 8.5% rearrangement showed that the reaction of amines and nitrous acid provides as "free" a carbonium ion - in aqueous solution - as any known

reaction. Some evidence is also available to suggest that "relatively free" isobutyl, sec.-butyl, and tert.-butyl cations are formed in the reaction between isobutylamine and nitrous acid.[50] It was concluded that the exchanges noted by Otvos et.al.[42,43] were not, infact, caused by a separate carbonium ion exchange process, but must be the result of rapid olefin-π-complex-carbonium ion interconversions.

Much earlier, Nevel, de Salas, and Wilson[51] had observed that the hydrogen exchange between camphene hydrochloride and $D^{36}Cl$ could not be explained by postulating simple loss of a proton, and had suggested that exchange occurred through the cation formed on ionisation of camphene hydrochloride. Their proposed reaction scheme is shown below.



They found that exchange of chloride ion was very much more rapid than isomerisation to isobornyl chloride, and postulated independent chloride ionisation. Simple loss of a proton following this would amount to fission and must be discounted. They then suggested that the explanation lay in a rapid bimolecular interchange of hydrogen between the organic cation and hydrogen chloride. In addition to this comment another of the features of this paper was the tentative proposal that the carbonium ion, or one of the carbonium ions, formed in the reaction had the non-classical structure(XIX).



XIX

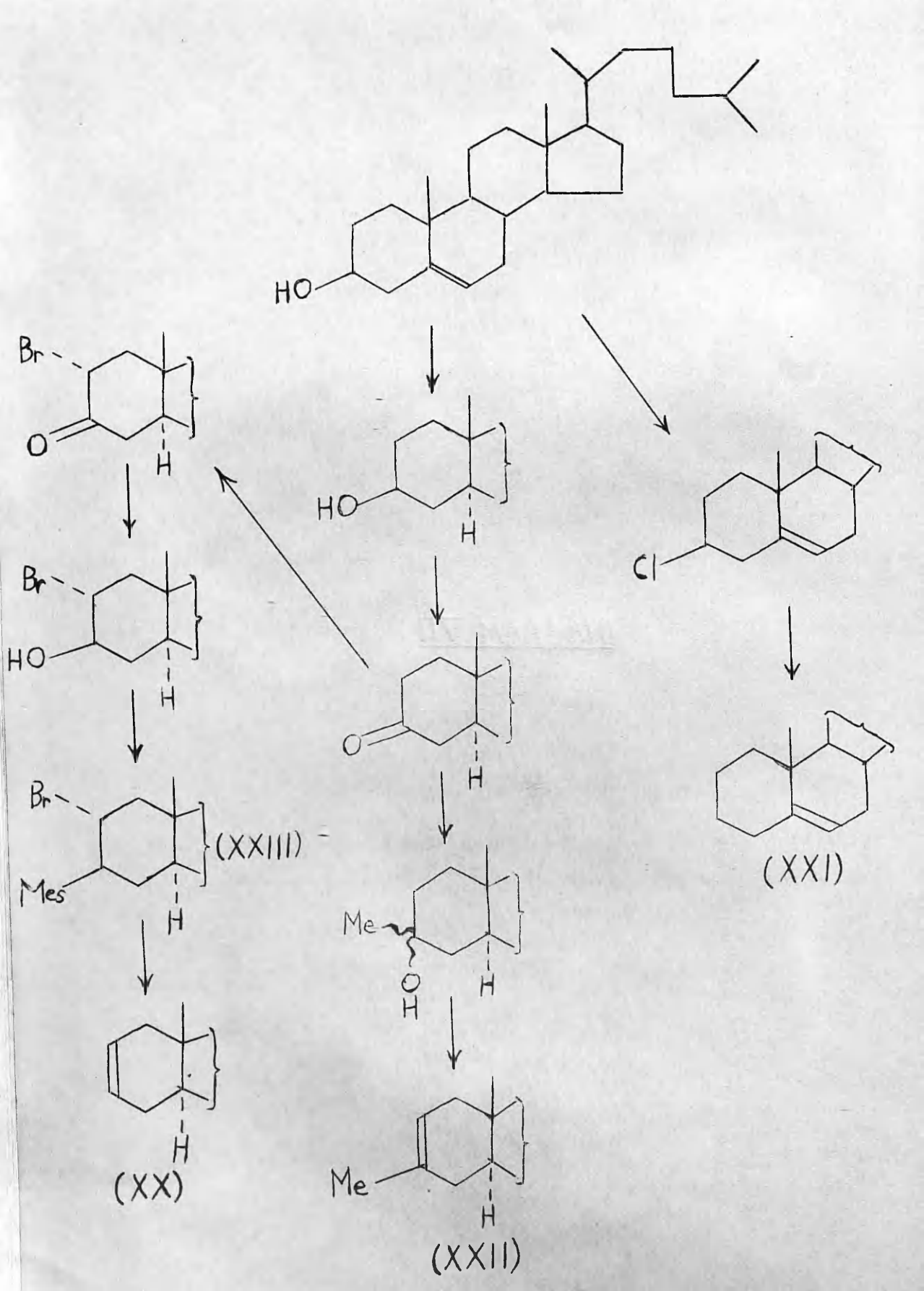
In 1956 Russian workers[52] studied the hydrogen-deuterium exchange reaction between 1-methylcyclohexan-1-ol and deuterium enriched phosphoric acid (H_3PO_4). Considerable exchange occurred. It was shown, in addition, that under the same conditions

1-methylcyclohexene failed to exchange to any marked extent, and did not hydrate. These observations ruled out the olefin as a possible intermediate in the alcohol exchange reaction, and it was concluded that exchange occurred through some form of carbonium ion. The exchange figures forthe alcohol ranged up to 88% of the total hydrogen content. Figures including up to nearly 60% exchange (i.e. 8 hydrogens) can be accounted for on the basis of the hydrogens adjacent to the tertiary centre being involved, but values of exchange greater than this must presumably arise from methyl group migrations producing new tertiary centres. Otvos et. al.[43], working with methylcyclohexane and deuterosulphuric acid found species containing up to 13 deuterium atoms present, and concluded that migrations of the methyl group around the cyclohexane ring did occur.

The historical aspects of the preparation of certain olefins used in the work in this thesis will be dealt with under the following section heading.

--ooOoo--

DIAGRAM VII


HO
Br
O
H
HO
H
Cl
Br
HO
H
O
H
Br
Mes
H
(XXIII)
Me
OH
H
(XXI)
(XX)
Me
H
(XXII)

DISCUSSION

The discussion of this section of the work is most conviently divided into subsections.

Synthesis of Olefins

a) Steroidal olefins

The steroidal olefins used in this section of the thesis, cholest-2-ene (XX), cholest-5-ene (XXI), and 3-methylcholest-2-ene (XXII), were prepared by standard routes (See diagram VII). During the hydrogenation of cholesterol in ethyl acetate containing a little perchloric acid it was found that some transesterification was occurring, giving rise to cholestanyl acetate. The introduction of a hydrolysis step effected a 15-20% improvement in the yield of cholestanol. During the preparation of cholest-2-ene it was found that - in these preparations - the introduction of the strongly electron attracting mesyl grouping to form (XXIII) led to an improvement in yield.

b) Non-steroidal olefins

For the work on exchange reactions involving deuterium in the present section pure samples of both exocyclic olefins, such as methylenecyclohexane, and the corresponding endocyclic olefins, such as 1-methylcyclohexene, were required. The principal literature method available for the preparation of the endo isomers was dehydration of the tertiary methyl alcohols by distillation from iodine.[53] It has been shown that 1-methylcyclohexene prepared by this method gives 93% of the expected ketone, but no detectable formaldehyde on ozonolysis. The physical constants of the material produced by different groups showed consistent agreement. This was not so with regard to the exocyclic isomers. Methylenecyclohexane, for example, had been assigned boiling points ranging from 101° to 109°.

The principal methods available for the preparation of these exocyclic olefins are:-

a) The Wittig reaction[54]

b) The pyrolysis of N-oxides[55]

c) From NN-dimethylcycloalkyl methylamine methiodides by Hofmann degradation[56]

d) The pyrolysis of cycloalkylcarbinol acetates[57]

e) The pyrolysis of tertiary methyl alcohol acetates[58]

f) The pyrolysis of unsaturated cycloalkyl carboxylic acids.[59]

The Wittig reaction seems to be well authenticated, and has actually been used to prepare methylenecyclohexane. Using triphenylmethylphosphonium bromide in the preparation of methylenecyclopentane, however, would lead to a mixture of the desired product and benzene arising from the break-down of the phosphonium complex. These two substances have very similar boiling points and separation would probably not be easy.

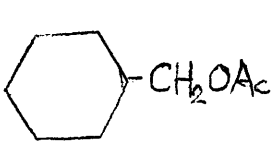
The preparation of the exocyclic olefins from N-oxides in the cases of the 5, 6, and 7 membered rings has been fully investigated by Cope et. al.[55] They made use of the revealing separations afforded by gas-liquid chromatography. The use of this comparatively new analytical instrument is of significance in this field, as much of the difficulty

encountered by earlier workers undoubtedly lay in the lack of a rapid and accurate method of separating or distinguishing between the endo-and exo-cyclic isomers, the boiling points of which are never more than a few degrees apart; although infrared analysis has, of course, been available for some time.

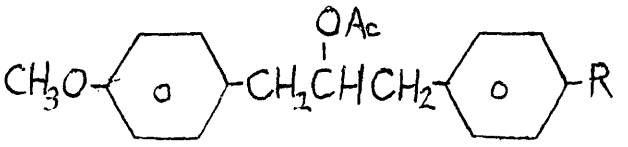
The Hofmann degradation, as applied to the preparation of exocyclic olefins has also recently been examined[56], and it seemed desirable that a reinvestigation of the acetate pyrolyses should be carried out as, despite claims that pure exocyclic olefins were obtained, later work had cast doubts as to the purity and homogeneity of the products. If the original claims were correct the route provided a convienent and direct method of preparing the required olefins. If the claims were unfounded then the reinvestigation of the pyrolyses of the acetates was of chemical importance.

Bailey[58], in a series of papers on the pyrolysis of acetates, claimed that pyrolysis of the acetate of 1-methylcyclohexanol yielded methylenecyclohexane, identified by its infrared spectrum, identical with

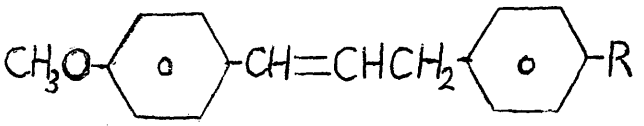
methylenecyclohexane prepared by pyrolysis of cyclohexylcarbinol acetate (XXIV).[57] DePuy and Leary[60],



XXIV

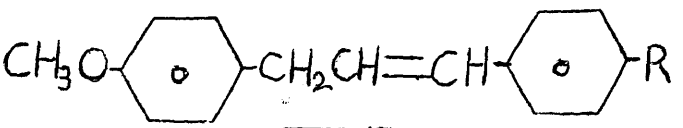


however, conducted some elegantly designed experiments, and found that on pyrolysis of some acetates of 1:3-diphenyl-2-propanols (XXV) the possible olefins were produced in proportions in which the olefin which predominated on equilibration of the two possible olefins again predominated. This is not what would have been expected from loss of the most acidic hydrogen (i.e. XXVI is produced in preference to XXVII). Bailey's work, contrary



XXVI

R = H or Cl



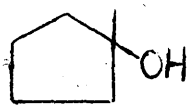
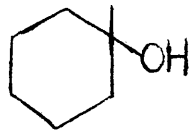
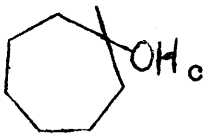
XXVII

to this, involves the loss of the most acidic hydrogen.

Trynham and Pascual[61] used the pyrolysis of tertiary acetates according to Bailey to prepare 5, 6, and 7 membered exocyclic olefins. In the case of methylenecyclohexane they were dissatisfied with the physical constants of the material obtained and investigated its purity. On forming the diol by treatment with peroxyformic acid they obtained a claimed 52% yield of material melting at 76-77°. The literature melting point for the diol from the exocyclic olefin is 77°, and from the endocyclic isomer 84°. On heating the diol obtained with concentrated hydrobromic acid they obtained an 81% yield of material boiling at 49.5°/10 mm., and from this the known 2:4-dinitrophenylhydrazone of cyclohexancarboxaldehyde[62] was obtained in unspecified yield. Trynham and Pascual then considered that they had pure methylenecyclohexane, but confessed their inability to explain the difference in boiling points between their own material and literature values for material obtained by alternative modes of preparation.

The endocyclic olefins, prepared from the appropriate tertiary methyl alcohol by dehydration effected by distillation from a little iodine, proved to be virtually pure. (See Table III).

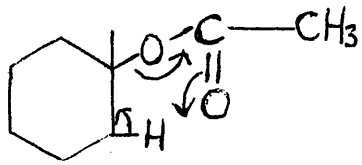
Table III

Material Dehydrated.	Olefins (%total olefin) Endo	Exo	Methods of Analysis	Detected Impurities
	96.7	3.3	g.l.c. i.r.	ether (from work up)
	98.6	1.4	g.l.c. i.r.	-
	major component	minor component	i.r.	trace of cycloheptanone

The pyrolysis of the acetates of the same tertiary alcohols was next investigated. Although the reaction is not thermodynamically controlled, and free rotation of the methyl group could conceivably give rise to a particularly favourable conformation for a cis elimination[63] to take place,

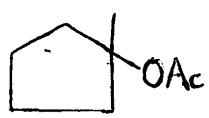
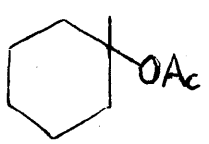
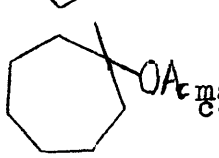
it seemed open to question that the reaction should be completely specific. The work of DePuy and Leary[60] aggravated these doubts, and the work of Trynham and Pascual[61] was unconvincing. The reported " Small differences in position and relative intensities of the infrared absorption bands...." is hardly an adequate description of the differences to be expected in the spectra of the endo and exo isomers in the series investigated. The formation of a glycol melting about 76° is easily explained as being a mixture of the exo and endo glycols, the higher melting glycol from the endocyclic olefin predominating. (This is in accord with the relative proportions of the olefins prepared by tertiary acetate pyrolysis in this thesis.) The subsequent stage in the degradation yielded a liquid, and no yield was quoted for the final 2:4-dinitrophenylhydrazone formation. In the present work pyrolyses of the tertiary methyl alcohol acetates of the 5,6, and 7 membered rings were carried out according to Bailey, and in all three cases the major product was the endocyclic olefin. (See Table IV). The

probable mechanism of the cis elimination is shown below. There was some carbonisation in the pyrolysis



tube. That this slight carbonisation had not led

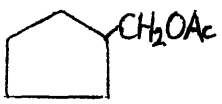
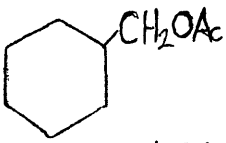
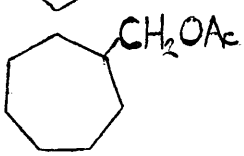
Table IV

Material Pyrolysed	Olefins (%total olefin) Endo	Exo	Methods of Analysis	Detected Impurities
	86.0	14.0	g.l.c. i.r.	ether (from work up)
	81.9	18.1	g.l.c. i.r.	-
	major component	minor component	i.r.	trace of starting acetate, acid

to rearrangement in the 5 and 6 membered ring cases was illustrated by pyrolysis of the acetates of the cycloalkylcarbinols in the same apparatus at a slightly higher temperature. With a similar

degree of carbonisation in the tube substantially pure methylenecyclopentane, and methylenecyclohexane contaminated by some compound absorbing at 675 $cm.^{-1}$ and 728 $cm.^{-1}$ in the infrared, and therefore probably aromatic in nature, were obtained. With the seven membered ring a complete breakdown resulted and six peaks were obtained in the gas-liquid chromatographic analysis carried out. The results are summarised in Table V.

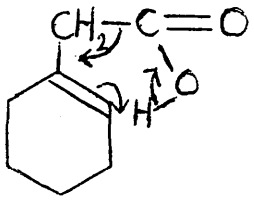
Table V

Material Pyrolysed	Olefins (%total olefin) Endo	Exo	Methods of Analysis	Detected Impurities
	1.0	99	g.l.c. i.r.	ether (from work up)
	6.5	93.5	g.l.c. i.r.	aromatic hydrocarbon
	-	-	g.l.c. i.r.	complex mixture of at least 6 components

When the unsaturated cycloalkyl carboxylic acids were pyrolysed virtually pure exocyclic olefins were produced, contaminated only by traces of acid./

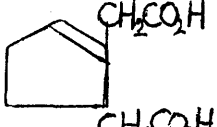
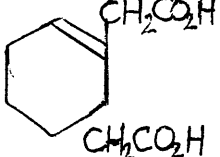
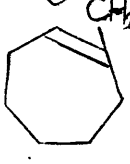
See Table VI.

(See Table VI). The probable mechanism of such a decarboxylation is shown below. Although con-



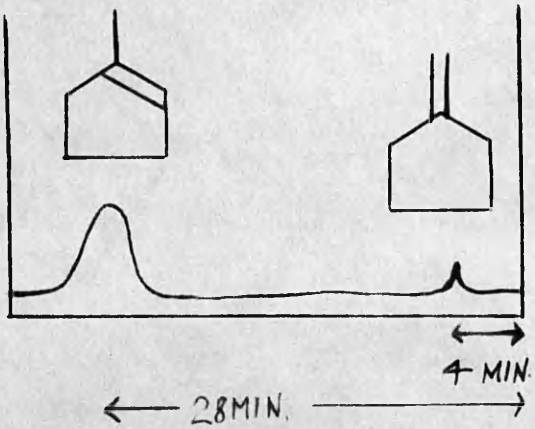
sidered here to be pure cycloalkene acids, for convienence of discussion, it is known that in each case a marked percentage of cycloalkylidene acid is present.[64] The overall yields, although an improvement on those in the literature, remained poor.

Table VI

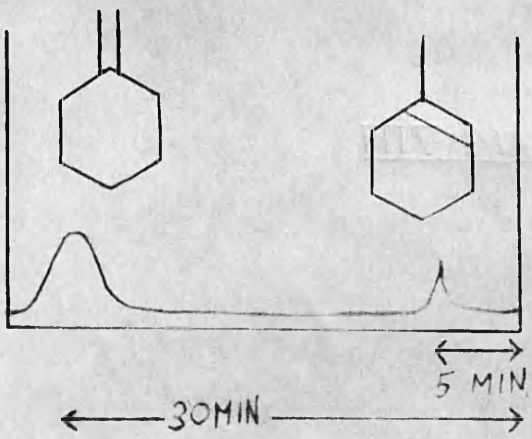
Material Pyrolysed	Olefins (%total olefin) Endo	Exo	Methods of Analysis	Detected Impurities
	1.0	99	g.l.c. i.r.	trace of acid
	6.8	93.2	g.l.c. i.r.	trace of acid
	minor component	major component	i.r.	trace of acid

Although it is well known that benzilic[65] and other suitably unsaturated alcohols[66] may be de-

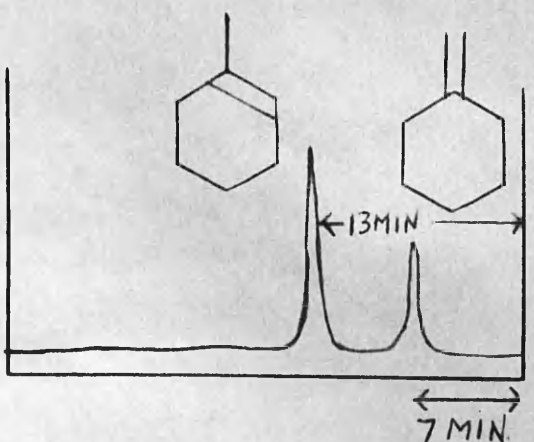
DIAGRAM VIII



COLUMN - $AgNO_3$/GLYCOL
(ROOM TEMP.)



COLUMN - $AgNO_3$/GLYCOL
(55°)



COLUMN - SILICONE 301
(72°)

hydrated under alkaline conditions, it was thought most improbable that the cycloalkylcarbinols could be so dehydrated, and an attempt at such a dehydration failed.

Details of the gas-liquid chromatography techniques used are given in the appropriate experimental section. The columns and conditions used did not effect a spearation of the seven membered ring isomers. It was found that 1-methylcyclopentene could be separated from methylene cyclopentane using a column of glycol saturated with silver nitrate on celite, although such a separation was not obtained on a silicone 301/celite column. 1-Methylcyclohexene and methylene cyclohexane could be separated on either column. A point of interest was the complete inversion of retention times of these later isomers with respect to boiling points, to the behaviour on the silicone column, and to the analogous five membered ring compounds, occurring on the silver nitrate column. (See diagram VIII). In the work of Cope and his associates[55] use was made of a silver nitrate/glycol column,

but, although, naturally, other columns were available to them, no mention was made of this reversal. As the only major difference in the proportions of olefins produced occurred in the case of the six-membered ring oxides (See table VII.) the possibility that the peaks on the gas-liquid chromatography charts had been misassigned arises. As, however,

Table VII.

Olefins obtained from amine oxides and trimethylammonium hydroxides. (Cope et. al.)

Ring size	Olefins (%total olefin)	
Amine Oxides	Exo	Endo
5	2.5	97.5
6	97.2	2.8
7	15.2	84.8
Trimethylammonium Hydroxides		
5	91.0	9
6	98.6	1.4
7	78.2	21.8

the Hofmann degradation products were simultaneously

examined this does not appear likely.

A paper by Siegel and Dunkel[67] on the pyrolysis of 1:2-, 1:3-, and 1:4-dimethylcyclohexanyl acetates apparently supports the results obtained by Bailey and King[58], but no detailed report was available.

Simultaneously with the writing of this thesis and the submission of a preliminary report[56] on the acetate pyrolyses two papers have appeared supporting the work in this thesis and correcting the work of Bailey.

Royals[68] found that pyrolysis of secondary acetates, e.g. 2-heptyl acetate, gave both possible alkenes as well as cis and trans isomers, and concluded that the experimental observations and published generalisations of Bailey and his associates on this topic were in grave error.

Even more closely related to the present work are the recently (1959) published observations of Benkeser and Hazdra[69] on the pyrolysis of the xanthate esters of 1-alkylcyclohexanols and alkylcyclohexylcarbinols. In every instance isomers containing double bonds exo to a six membered ring were dis-

favoured. In an attempt to obtain a reference sample of methylenecyclohexane the pyrolysis of 1-methylcyclohexyl acetate was carried out. Several runs at varying temperatures (250-500°) were made, but in each case only about 20% of the olefin produced was the exocyclic isomer, in good agreement with the results inthis thesis.

The present experiments and those above conclusively show the work of Bailey and his associates to be in error, and lend support to Barton's[63] original suggestions on the cis nature of the elimination in pyrolysis reactions.

The Additions of Deuterohalides to Olefins

In the course of a study of the addition of hydrogen chloride to the double bond in 3-methyl-cholest-2-ene and in cholest-5-ene, Barton and Campos-Neves[70], hoping to make use of the infrared distinction between axial and equatorial deuterium[2,3] used deuterium chloride. The infrared spectrum of the 3β-chloro-3α-methylcholestane produced had absorption at 2158 cm.$^{-1}$ and 2174 cm.$^{-1}$, characteristic of equatorial deuterium; and the 5α-chlorocholestane produced showed absorption at 2158 cm.$^{-1}$ and 2167 cm.$^{-1}$, again characteristic of equatorial deuterium. Thus, in the first case, the addition appeared to be trans and diequatorial, and in the second cis equatorial:axial. On re-examination of the infrared spectra of these deuterated halogeno compounds it appeared that the distinction between axial and equatorial deuterium was not clear cut, and that, infact, the spectra could be best explained on the basis of there being more than one deuterium atom

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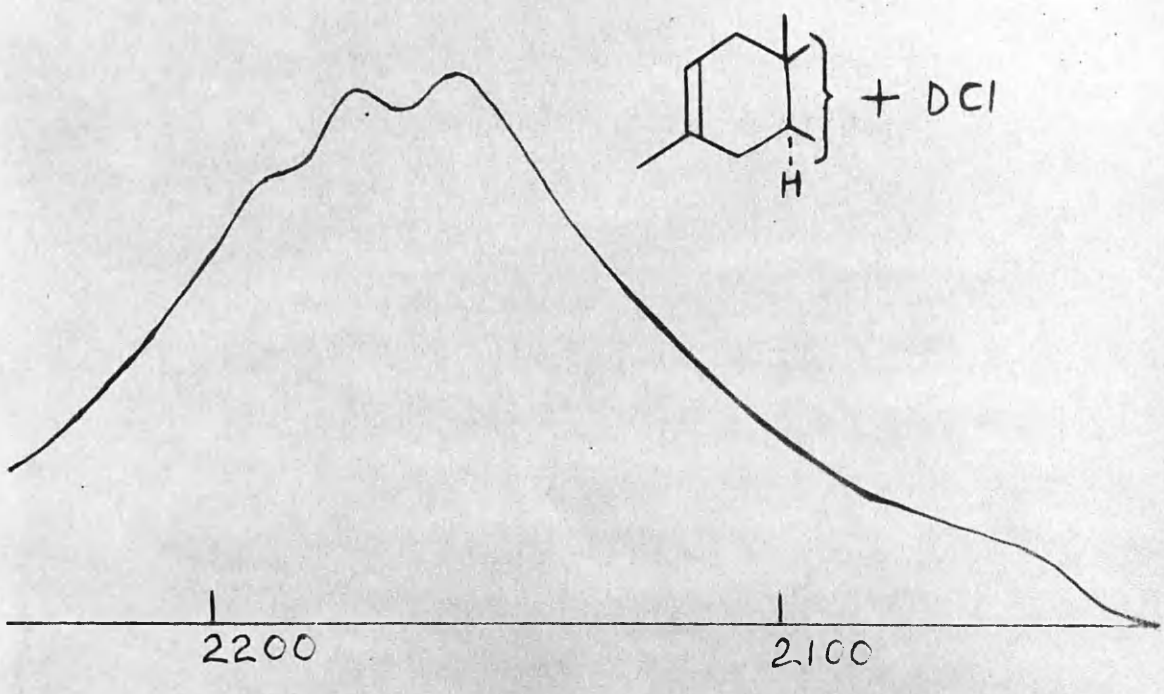
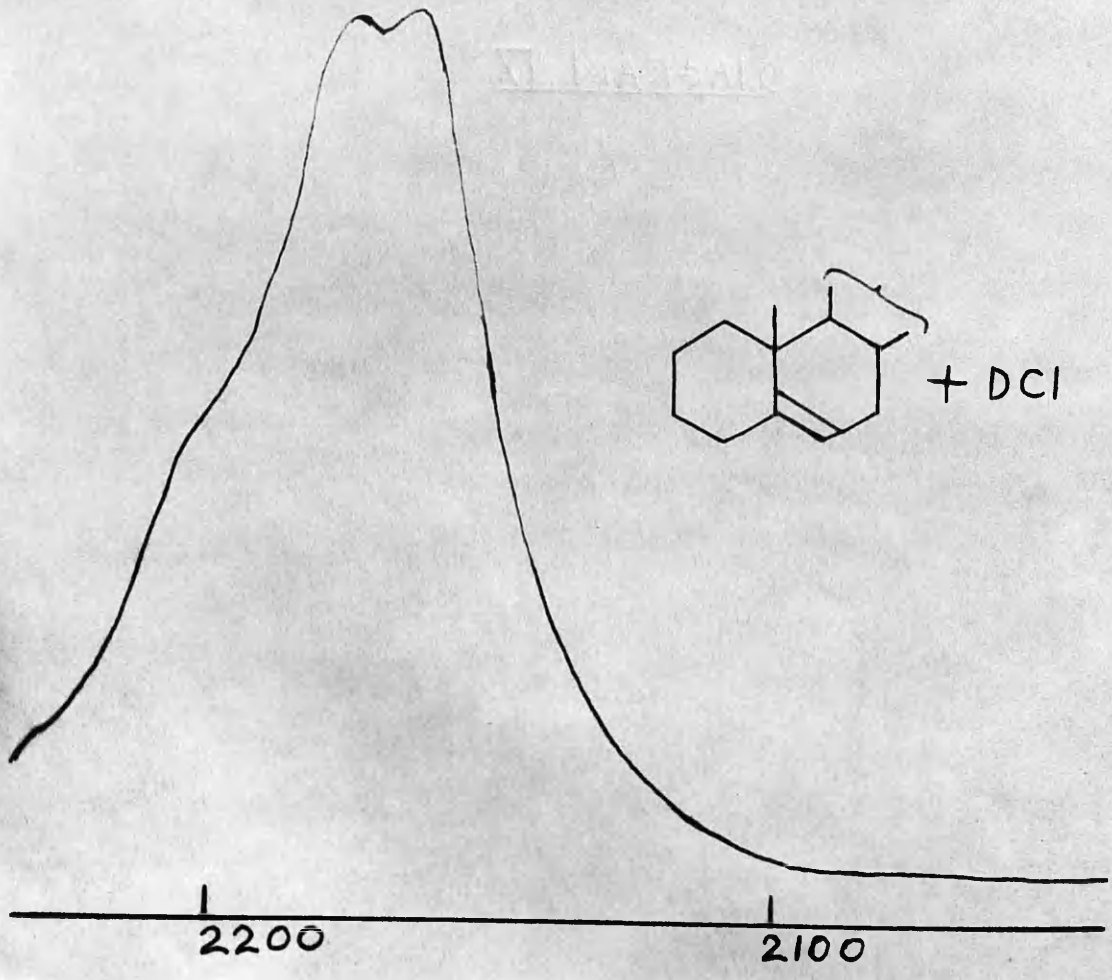
The preliminary experiments and conclusions discussed above are, in part, the work of Dr. A.da S. Campos-Neves, working under Professor D.H.R.Barton.

DIAGRAM IX


+ DCl
H
2200
2100


+ DCl
2200
2100

in the molecules examined. (See diagram IX).

On repeating the additions of deuterium chloride to 3-methylcholest-2-ene and cholest-5-ene, the deuterium content being directly determined as described in the appropriate experimental section, the results confirmed that during the course of the additions 1.5 atoms of deuterium were incorporated into the final products. Results have since been obtained explaining satisfactorily where the initial indirect deuterium analyses were erroneous. (See section III).

As a prelude to the above work, an examination of the addition of hydrogen chloride to 3-methyl-cholest-2-ene in various solvents was carried out. Of the solvents studied dioxane proved most satisfactory, for the following reasons:-

a) The product separated in a pure state, in crystalline form, and in good yield, directly from the reaction mixture.

b) Dioxane could be used as a solvent for deuterium chloride additions without hydrogen-deuterium exchange with the solvent molecules interfering.

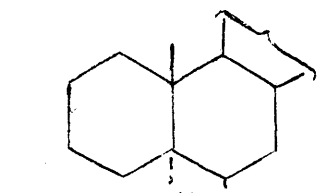
c) Using dioxane as solvent allows the reaction to proceed at such a rate that its progress may be easily followed in the polarimeter.

In addition to the experiments in which dioxane was used as solvent, a few runs were carried out with deuterium chloride in n-hexane at -70°. The 3β-chloro-3α-methylcholestane produced had the same deuterium content and infrared spectrum as the material obtained from the experiments in dioxane.

The question of the stage of the addition at which the excess deuterium atoms entered the molecules immediately arises. This problem was tackled as follows:-

a) The starting materials were isolated after the approximate half-life of the reactions, and examined for deuterium content. It was found that when 3-methylcholest-2-ene was treated with deuterium chloride, the reaction being followed in the polarimeter, ($[\alpha]_D$ 3-methylcholest-2-ene $+74^{\circ}$; $[\alpha]_D$ 3β-chloro-3α-methylcholestane $+32^{\circ}$), and stopped at the half-way stage, then the starting material recovered on working up the reaction mixture contained no deuterium. In an identical experiment with cholest-5-ene

difficulty was found in separating the initial olefin from the chloride produced in the reaction, and to overcome this the reaction mixture was treated with osmium tetroxide, forming the 5α:6α-cholestane diol (XXIVa.) This was easily separated from the



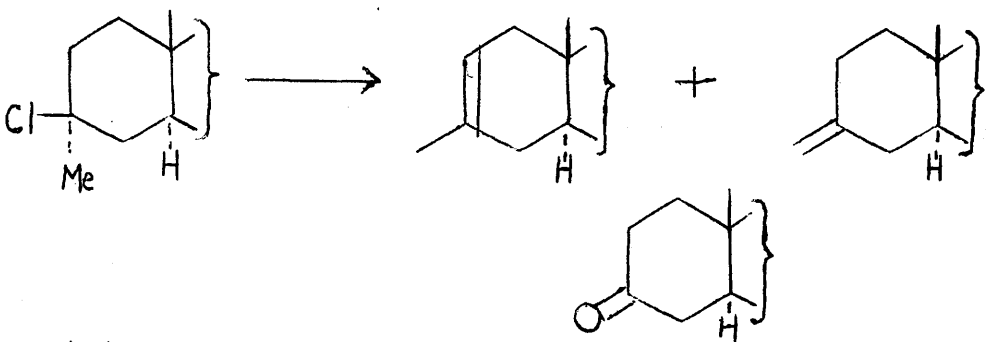
XXIVa

5α-chlorocholestane present. Hydroxylations with osmium tetroxide are known to be molecular in nature, and it is most improbable that treatment with this reagent could have caused any change in the deuterium content of the olefin. The diol isolated contained no deuterium. These results show that exchange does not occur directly through the initial olefins.

b) The final products of the reactions were examined. No deuterium was incorporated when the chlorides (hydrogen chloride addition) were treated under the appropriate conditions with deuterium chloride. Thus, exchange does not occur through the chlorides.

In order to throw some light on the position of

the extra deuterium atoms, deuterated 3β-chloro-3α-methylcholestane, obtained by addition of deuterium chloride to 3-methylcholest-2-ene, was degraded to cholestan-3-one as shown below, the product being isolated by fractional crystallisation. This material



contained 1.5 atoms of deuterium, which would indicate that little or no deuterium enters the methyl group. Further work along this route could reasonably consist of an acid-catalysed benzylidene condensation with the cholestanone obtained. This is known to occur preferentially in the 2 position, and by deuterium analysis of the product the quantity of deuterium, if any, in the 4 position could be determined.

Vigorous attempts to add hydrogen chloride to cholest-2-ene (XX), with a view to studying the nature and behaviour of a carbonium ion lacking a

tertiary carbon centre failed. Surprisingly, cyclohexene itself added hydrogen or deuterium chloride with comparative ease. Mass spectrometric analysis of the product of deuterium chloride addition revealed that there had been no exchange of excess deuterium into the molecule, and that the initial olefin recovered after partial reaction contained no deuterium. (See table VIII). The nature and results

Table VIII

Material treated with deuterium chloride	Deuterium content
Cyclohexene (recovered after partial reaction)	-
Chlorocyclohexane (put through addition reaction conditions)	-
Products of reaction	
a) 1.6% chlorocyclohexane	-
b) 98.4% chlorocyclohexane	1 D atom/mol.

of attempts to add hydrogen chloride to cholest-2-ene are shown in table IX.

/over.

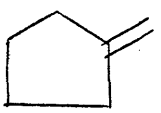
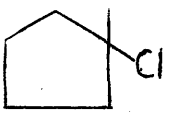
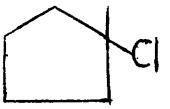
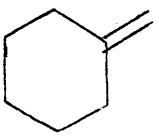
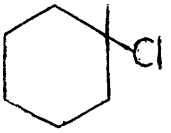
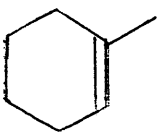
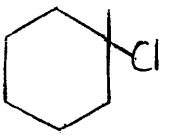
Table IX

Wt. cholest-2-ene used (mgs.)	conditions	reaction time	cholest-2-ene recovered mgs.	%
119.0	dioxane(15ml.) saturated with HCl at room temp.	1hr.5min.	94.0	79
104.2	ether(15ml.) saturated with HCl at room temp.	1hr.	95.3	92
210.5	acetic acid (15ml.)saturated with HCl at room temp.	1hr.	195.3	93
113.7	cyclohexane (15ml.)saturated with HCl at room temp.	1hr.	101.6	90
135.2	n-hexane(15ml.) saturated with HCl at -70°.	1hr.30min.	111.3	83
101.1	ether(5ml.) shaken with conc. aqueous HCl at room temp.	72hr.	91.2	90
113.0	carbon tetrachloride(5ml.) shaken with conc. aqueous HCl at room temp.	30days	99.5	88

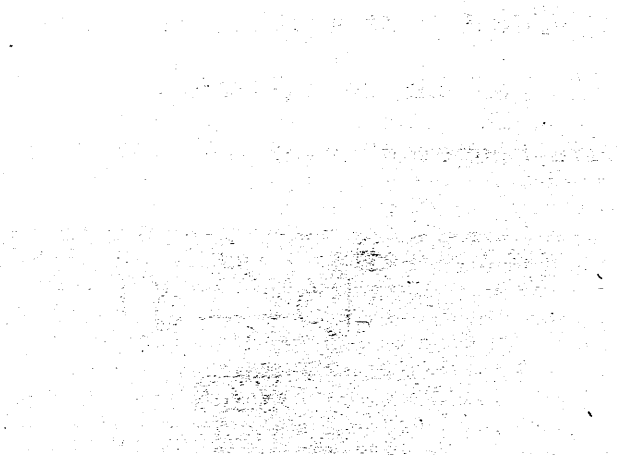
When an attempt was made to carry out the addition using the more reactive hydrogen bromide as the addendum free radical addition resulted. (See section IV).

In order to confirm, extend, and generalise the results obtained, additions of deuterium chloride to methylenecyclopentane, 1-methylcyclopentene, methylenecyclohexane, and 1-methylcyclohexene were carried out. The products were analysed in the mass spectrometer by Dr. R.I.Reed of this department. The results are shown in table X. In neither case

Table X

Olefin	Product	Composition of product %undeuterated	%one D atom	%two D atoms
		2	92	6
		3	90	7
		2	91	7
		1	91	8

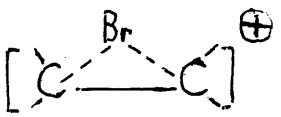
did the final chloride undergo exchange under the reaction conditions, and in no case did the reaction first involve isomerisation of either of the 5 or 6 membered ring olefins to its isomer. The examinations for isomerisation were carried out using infrared spectrometry. The olefins when examined after more than 50% reaction completion contained no detectable deuterium (mass spectrographic analysis.) The percentages of exchange encountered although small are quite significant.



The Nature of the Exchange Reactions

A carbonium ion is commonly defined as a singly positively charged organic ion for which conventional formulae involving only tetravalent carbon atoms cannot be written. Generally, the existence of carbonium ions can only be inferred from a study of reaction mechanisms and products, unless the ions involved are unusually stable when physical methods normally used in the study of electrolytes, e.g., conductivity and cryoscopic measurements, can be applied.

In 1937 Roberts and Kimball[71] sought to explain the *trans* addition of bromine to a double bond by postulating the formation of the non-classical carbonium ion (XXVa). In this "bridged" structure



XXVa

free rotation about the carbon-carbon single bond nominally present in the classical carbonium ion where the charge is localised on one carbon atom

is prevented. For steric reasons the consummating bromine anion would be expected to add on the side away from the bromine bridge. These observations, marking the origin of the non-classical carbonium ion concept, have been confirmed and extended by later workers[51] to compounds containing solely carbon and hydrogen.

The results presented in this section of the thesis can only be accounted for on the basis of an exchange reaction occurring through the carbonium ions intermediate in the reactions. Taft et.al.[38] found sufficient evidence to indicate that an initial and rapidly established equilibrium existed between protons and the olefinic double bond in the substrates used in his hydration studies, and it seems probable that a similar equilibrium is set up in the additions under discussion. Considerable additional evidence, largely circumstantial, suggests that olefin-proton π-complexes are common, and they have been described as "well authenticated".[72] Hydrogen chloride can be dissolved in olefins without isomerisation of their more labile double bonds, and the formation

of solid complexes between acids and olefins at low temperatures[74] argues for the existence of some form ofcomplex in the liquid phase. There exist, too, the analogies of the silver complexes with olefins and the bromonium ion. (The preference in this thesis is to write such ions as π-bonded structures rather than in a definitely bonded form.) The evidence that π-complexes are formed with aromatic structures is extensive, and an extension to the simple olefinic bond is not difficult to conceive.

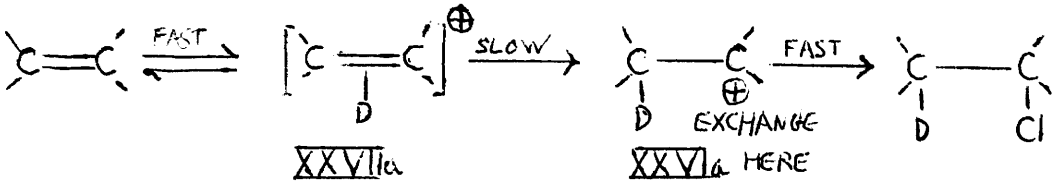
If it is allowed that there is a rapidly established equilibrium set up between the olefinic bonds and deuterium ions, then such an initially formed ion cannot have a classical carbonium ion structure, for this would result in:-

a) Isomerisation of the double bonds in the isomeric olefins examined (no isomerisation was encountered).

b) The introduction of deuterium into olefins isolated after partial reaction (no deuterium was found in the olefins.)

It is postulated that the initially formed

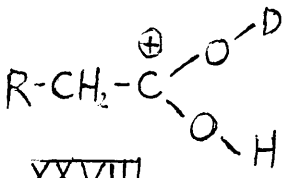
complex is identical to the non-classical -bonded ions of the Taft hydration studies. The rate determining step in the reaction is postulated as being the formation of the classical ion (XXVI) from the $\widetilde{\pi}$-bonded complex (XXVII). The exchange of



XXVIIa XXVIa HERE

excess deuterium into the molecule occurs at this classical ion stage, and must be extremely rapid. The final consummating chloride ion addition must be rapid, as the preceeding step is effectively non-reversible, otherwise deuterium would have been found in the olefins isolated after partial reaction. This gives the overall picture as represented above. Upon the addition of the chloride ion exchange ceases. This picture is analogous to that given by Taft et. al.[38] for the acid catalysed hydration of the butenes, and there are at least superficial similarities to the exchange reaction reported during the isomerisation of camphene hydrochloride to isobornyl hydrochloride.[51]

In addition, Russian workers[75-80] have duplicated the work of Otvos et. al.[42,43] on the exchange of saturated hydrocarbons with deuterium sulphate, and reached identical conclusions, i.e. that exchange occurred through a carbonium ion, and only hydrogens α to a carbonium ion centre exchanged. Further, the Russians have studied exchange reactions with organic acids and aldehydes and deuterium sulphate. Only α hydrogens in these substances exchanged, presumably because of the proximity of the positive charge in such structures as (XXVIII). When no α hydrogen atoms were present no exchange was ob-



XXVIII

served. (e.g. in α-bromoacids.) This work seems to demand a separate carbonium ion exchange process.

The exact mechanism of these exchange reactions is far from clear. It appears to be well established, however, that hydrogens adjacent to a positive centre are labile and likely to exchange with deuterium ions present in the reaction mixture. The picture

of the addition reaction given above is in accord with the existing stereochemical evidence. Barton[81] has suggested, with many authenticated examples to support his claim, that all electrophilic additions to olefinic bonds in steroids are diaxial in nature, with the exception of the cases where the initial addendum is H^+. He has pointed out that the stereospecificity of such additions is adequately explained by the formation of a bridged ion or π-complex, and that the exception of the halogen acids may be rationalised if the first formed π-complex rearranges to a classical carbonium ion before completion of the reaction. This proposal is in full accord with the results in this thesis.

The absence of any exchange reaction on the addition of deuterium chloride to cyclohexene requires further explanation. Secondary carbonium ions, i.e., those formed from double bonds lacking a potential tertiary centre, might generally be regarded as extremely short lived, unstable entities, and it is possible that the short life-time of the ion would allow no time for an exchange reaction to occur. If an initial rapidly established equilibrium

with protons is again assumed, however, the assumption of the non-classical carbonium ion is still required. The absence of exchange could then be accounted for in any of the following ways:-

a) A classical carbonium ion is never formed, the reaction proceeding directly through the non-classical ion.

b) After an initial formation of a non-classical ion the life-time of the next formed classical ion is too short to permit any exchange reaction.

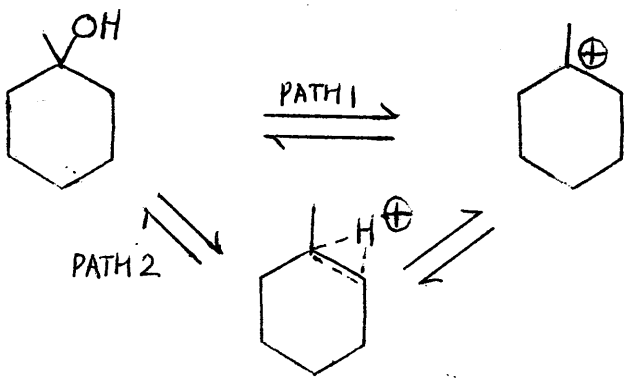
c) The entire reaction is molecular in nature. This cannot be entirely discounted, particularly where the conditions are unfavourable to both ionic and free radical addition, as here, where the unsubstituted double bond in the cyclohexane ring does not favour the formation of a (classical) ionic intermediate , and where the polar nature of the reaction medium and the addendum used make a free radical addition most improbable. The reverse process is known.[82]

Without doubt, the reaction scheme postulated for acid catalysed hydrations by Taft, with its

definitely related reaction rates was never intended to be applied generally to all other reactions involving carbonium ion intermediates. At the same time, it seems reasonable that it could apply to closely analogous cases such as those encountered in the work presented in this section.

The work of Cannell and Taft[47] on the nitrous acid reaction with isobutylamine appeared to justify the conclusion that the tert.-butyl cation did not undergo direct hydrogen-deuterium exchange, and it was therefore concluded that the exchanges encountered by Otvos et. al.[42,43] were best accounted for on the basis of a high rate of olefin-π-complex-carbonium ion interconversions, and that no independent carbonium ion exchange process existed. The present work does not provide support for this view. Failure to detect deuterium in any of the olefins examined after partial reaction, using several independent analytical methods, proves conclusively that there can be no rapid π-complex-carbonium ion interconversions, the rearrangement being almost irreversible because of the speed of the suceeding step. Further support for the ideas accepted in this thesis arises

from the experiments conducted by Setkina and Kursanov[52] with 1-methylcyclohexanol and deuterophosphoric acid. Here a consummating step in the reaction does not take place, and the classical carbonium ion will have many residencies in the solvent, and many opportunities to equilibrate with any deuterium ions present. Extensive exchange was indeed found, and the Russian workers concluded that this exchange occurred through some form of carbonium iom. The exact nature of this intermediate ion is an interesting point. It was shown that under the reaction conditions hydration of 1-methylcyclohexene occurred to a very limited extent, and that comparatively little deuterium was incorporated into the olefin. This result, in the present view, seems to imply that the reaction conditions were such that the classical carbonium ion was never formed from the initial π-complex. The reaction scheme with the tertiary alcohol may then be represented as either following path 1 or 2 as shown below, an initial protonation of the alcohol probably being a preliminary to either route. The π-complex



XXIX

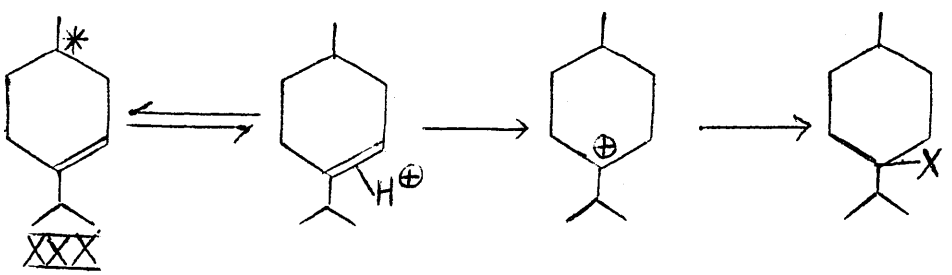
cannot be a reaction intermediate. Cannel and Taft[47] have already found it necessary to postulate the existence of at least two distinct types of non-classical carbonium ion (see historical part) in order to explain the results obtained with the iso-butylamine/nitrous acid reaction, and the structure (XXIX) above represents a bridged protonium ion as distinct from a π-complex.

It has already been pointed out by Winstein[83] that several pairs of reactions are known where the carbonium ion intermediates formed by addition of HX and ionisation of RX cannot be equivalent. The work of Cannel and Taft provides but a further example of this phenomenon.

In contrast to the Russian experiments with 1-methylcyclohexanol, Skull, Oakwood, and Rank[84] treated tert.-butyl alcohol-d9 with concentrated hydrochloric acid at room temperature and detected

no measurable hydrogen-deuterium exchange. This reaction, however, was only one step along a synthetic pathway. The experiment was not conducted with the object of investigating any possible exchange reaction, and if we make the assumption that the formation of the tert.-butyl chloride causes a cessation of exchange - as is reasonable on the basis of our own results - failure to detect the exchange of 0.5 molecules of deuterium in the highly deuterated molecule examined would not be surprising.

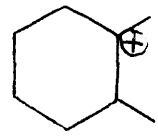
Very recently the non-classical carbonium ion concept of Taft has been extended to mixed and non-aqueous solvents. By showing that the rate of racemisation of optically active 3-p-menthene (XXX)



was equal to the rate of addition to the double bond in highly acidic aqueous/alcoholic solutions, a reaction sequence in which a classical carbonium ion was formed in a preliminary proton equilibrium

step was excluded. A reaction scheme analogous to that postulated in this thesis and to that proposed by Taft was suggested as shown above.

In 1954 Hammond and Nevitt[86] studied the addition of hydrogen bromide to 1:2-dimethylcyclohexene, 2:3-dimethylcyclohexene, and 2-methylmethylenecyclohexane in acetic acid. If a classical carbonium ion intermediate is formed the same classical ion (XXXI) should be formed from each of these molecules.



XXXI

It was found, however, that the additions were stereospecifically trans in nature, and furthermore, different proportions of cis addition product were formed, depending upon the nature of the initial olefin. It was concluded that the results were best explained by assuming that a direct attack by a bromide ion upon an initially formed π-complex took place. Kwart and Weisfeld[85] have suggested that this is not the case, and that interaction between the positive charge in the classical carbonium and acetic acid solvent molecules allows the ion

to retain its configurational identity during the course of the addition - i.e. a classical carbonium ion which reacts stereospecifically. Numerous examples of similar phenomena have been documented.[87] It is, however, beyond question that the substrate structure, solvent, and addendum will all effect the ease of formation of an ion, the nature of the ion formed, and any rearrangement of one particular ion into another before completion of a reaction.

Despite evidence of its essential carbonium ion nature, the reaction of nitrous acid with amines cannot be claimed to be a well defined carbonium ion process. In the light of the present work and the various Russian papers, but contrary to the views of Cannel and Taft, it appears that a separate and distinct exchange does occur through the classical carbonium ion intermediates of various reactions, and this original explanation of the results obtained by Otvos et. al.[42,43] is probably correct.

There exists ample evidence that non-classical carbonium ions of various types participate to some extent in a large number of reactions (e.g., the

work of Taft[38,47] dealt with previously, work on camphane derivatives[88], and the work of Cram[89] on phenyl bridged ions.) The structure and stability of the various types of carbonium ion are not yet completely understood, but mesomerism would be expected to be one of the main factors in such extra stability as may be conferred upon a non-classical ion.

Recently, Long and Paul[90] concluded that it was not easy to completely exclude the possibility that olefin hydration reactions involved a slow proton transfer as the rate determining step. This appears to be contrary to the bulk of the available evidence, but must be borne in mind. Accepting this view, the concept of a carbonium ion exchange process is still required, but the necessity for the non-classical structures is eliminated.

It has already been suggested that it is unlikely that all the notions of carbonium ion chemistry now in vogue will stand the test of time[91], and that it may even be that the abundance of non-classical phenomena in the chemical literature indicates a serious weakness in modern underlying structural

concepts.

The monodeuterated chlorocyclohexane obtained on addition of deuterium chloride to cyclohexene is currently being examined in this department[92], inthe hope that information regarding the nature of the addition e.g., cis or trans stereospecificity, can be obtained from deuterium and halogen absorption bands present in the spectrum when the material is frozen. (See section I.) In the work carried out for this thesis the spectrum of the deutero-chlorocyclohexane was taken as a liquid film (0.05 m.m. film). In the carbon-deuterium stretching region the major band occurred at 2182 cm.$^{-1}$, with a weaker band at 2143 cm.$^{-1}$ There were several shoulders and minor peaks, the main shoulder occurring at 2170 cm.$^{-1}$

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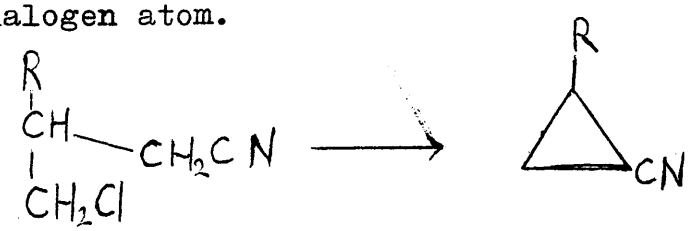
SECTION III

HISTORICAL

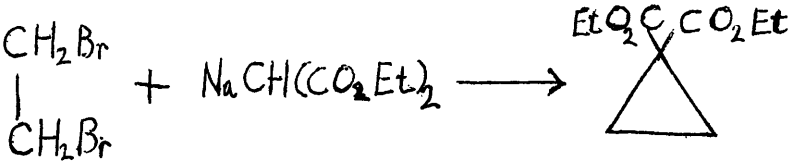
The cyclopropane ring is of comparatively rare occurrence in natural products, but some examples are well known, e.g., the pyrethins[93], certain long chain acids[94], and some triterpenoids such as phyllanthol[95] or cycloartenol[96].

There are several synthetic routes to cyclopropanes, and five of those of the most practical value may be summarised briefly as follows:-

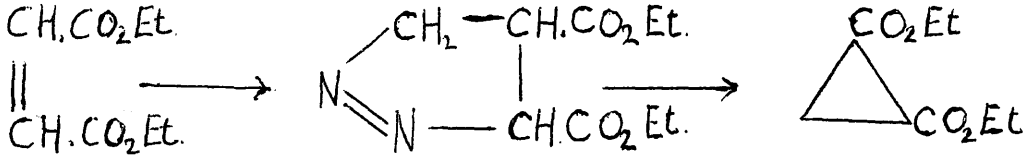
a) Intramolecular dehydrohalogenation. This reaction proceeds most satisfactorily when the initial halide possesses an active methylene group β to the halogen atom.



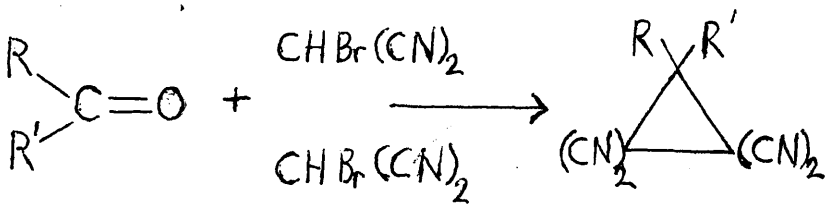
b) A variation of the above scheme involving a condensation with sodiomalonic ester and a vic. dihalide.



c) Pyrazolines may be converted into cyclopropane derivatives by elimination of nitrogen, diazomethane being commonly used to form the initial pyrazoline from an olefinic linkage.

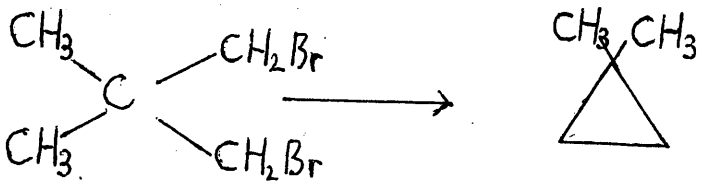


d) Cyclopropane tetranitriles can be prepared from a suitable carbonyl compound with bromomalononnitrile and potassium iodide.



e) An elimination of halogen from 1:3-dibromides using, generally, zinc. This method using zinc powder in molten acetamide is the one preferred in the present work.

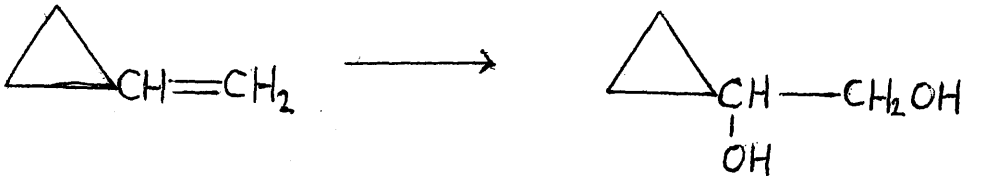
/over.



In this reaction primary bromides give better yields than primary - secondary dibromides, and especially mild conditions are required to prevent reactions involving a tertiary bromine atom giving olefinic compounds.

It has long been known that cyclopropane rings possess many of the properties most commonly associated with the olefinic linkage, e.g., they can be hydrogenated to give propanes, and react with bromine or iodine to give 1:3-dihalogenopropanes. With the halogen acids propyl halides are obtained. With substituted cyclopropanes the Markownikov rule is obeyed, i.e., the ring always opens between the carbon atoms holding the largest and the smallest number of alkyl groups. The yellow coloration given in the tetranitromethane test for carbon-carbon double bonds is also given by cyclopropyl compounds.

The main chemical points of difference between the two classes of compounds are that ozone does not readily attack the cyclopropane ring, and cold dilute potassium permanganate solution will react more readily with the olefinic double bond than with a cyclopropane ring. The following example is most striking.[97]



The similarity between the olefins and cyclopropanes extends to their physical properties (see discussion) and is so close that several elegant studies have been designed to prove the very existence of the cyclopropane ring. Perhaps the most elegant and conclusive is the independent fission of a 1:2:3-unsymmetrically substituted cyclopropane at each of its three sides carried out by Kohler and Conant.[98]

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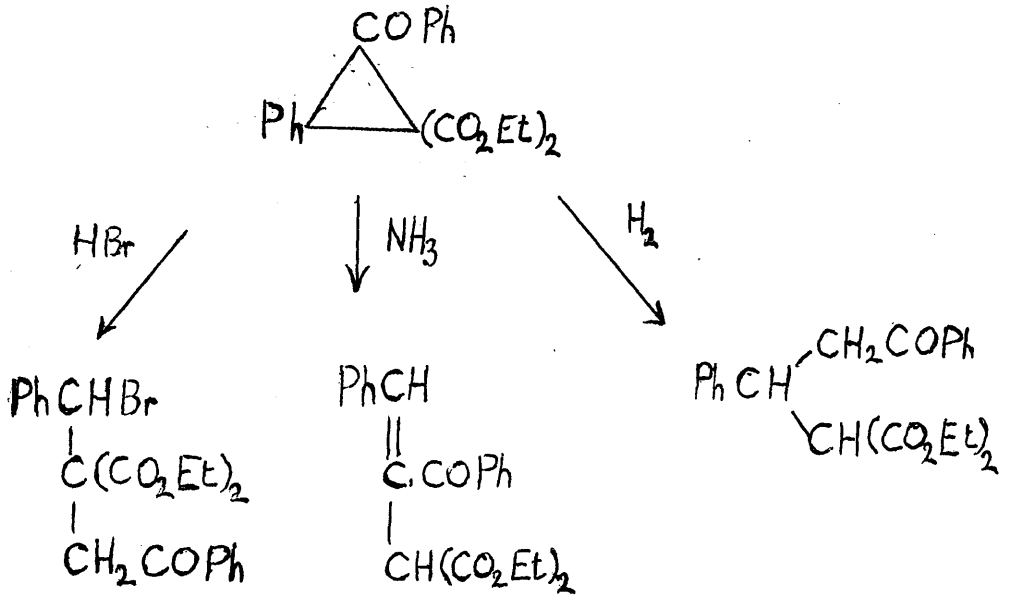

Absorption spectra can be used to help distinguish cyclopropyl compounds from olefinic materials, and it has been demonstrated that the cyclopropane ring can conjugate with unsaturated groupings in the same manner as the ethylenic linkage with analogous effects.[99]

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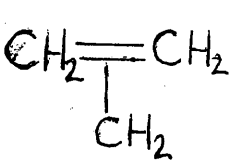
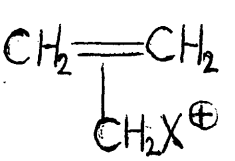
DISCUSSION

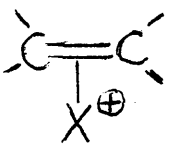
The structure of the cyclopropane ring has been the subject of considerable physical study. It has been shown by Rogers and Roberts[100] that the electrons associated with the carbon-carbon bonds in the three-membered ring are more weakly bound than the normal single bond electrons, and consequently exhibit the characteristics of the more mobile π electrons. Other physical data confirm this view.[101,102] In 1947 Walsh[103] proposed that the structure of cyclopropane was, infact, that of a π-complex of the type (XXXII). This suggestion has been subject to much criticism[104-106], and seems to be unacceptable. The geometrical form of the three-membered ring has been shown to be a symmetrical, planar ring, in the form of an equilateral triangle.[107,108]



XXXII



XXXIII



XXXIV

Dewar[109] has proposed that, regardless of the finer details of the cyclopropane structure, enough is known concerning its general nature to suggest that it would combine readily with cationoid reagents to give complexes of type (XXXIII). If the subsequent reactions of (XXXIII) and the analogous complex formed from an olefinic linkage (XXXIV) are similar - as seems most probable - then the orientation of additions to substituted ethylenes and to cyclopropanes should be similar. Thus the π-complex formed by attack of the cationic addendum on the most negative carbon atom of the three membered ring is followed by the addition of the anion to the most positive carbon atom - i.e. Markownikoff's rule should be obeyed. This is in accordance with the observed facts.

The close similarity between cyclopropanes and olefins suggested that an exchange reaction analogous to that observed in Section II might take place when the three membered ring is opened with deuterium halides. It seemed probable that some form of initial complex would be formed in which the adding proton was not equivalent to the

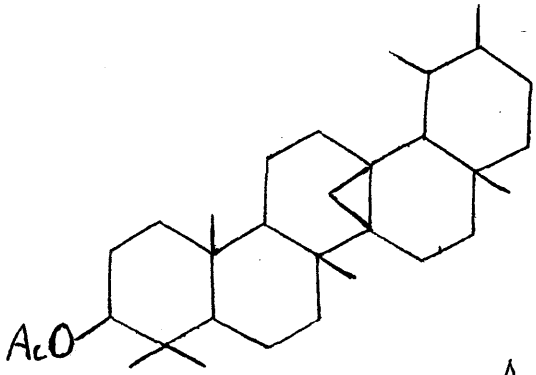
hydrogen atoms of the substrate. If we assume - as again seems likely - that there is a rapidly established equilibrium between protons and the cyclopropane ring analogous to that with the double bond we have two very similar situations. In one case we have "two carbon unsaturation" and in the other "three carbon unsaturation".

A search of the literature was rewarding. Barton and de Mayo, in the course of a study of phyllanthyl acetate (XXXV), in which they established the presence of a cyclopropane ring, showed the location of the ring by opening it with deuterium chloride[110]. The α-amyrin acetate (XXXVI) produced contained more than one atom of deuterium per molecule. To account for this they suggested that the extra deuterium atom was exchanged into the molecules either,

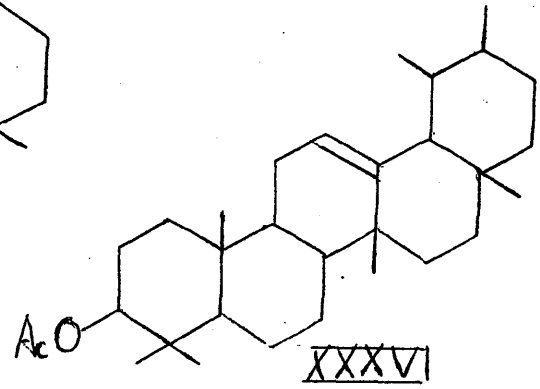
a) Through deuteration of the acetate residue through the ester enol.

or,

b) Through vinylogous hydrogens at the 612 position in the initially formed α-amyrin acetate being replaced by deuterium.



XXXV



XXXVI

That exchange did not occur by route a) was established by the original workers, who carried out an alkaline hydrolysis of the deuterated α-amyrin acetate obtained, followed by reacetylation, and recovered α-amyrin acetate with an unchanged deuterium content. The exchange was ascribed to route b). The present work shows that this also is not the case. When α-amyrin acetate was treated under the appropriate reaction conditions with deuterium chloride no deuterium was emplaced in the molecule. The exchange observed by Barton and de Mayo[110] was also confirmed. When phyllanthyl acetate was treated with deuterium chloride under the conditions described by those workers, the α-amyrin acetate produced contained 1.4 atoms of deuterium per molecule.

Bearing in mind the results obtained in the preceeding section, these observations suggested

that the cyclopropane ring was emulating its relative the olefinic double bond in that carbonium ions formed by protonation-or deuteration - underwent hydrogen exchange. A study of the opening of some lower molecular weight cyclopropanes with deuterium halides was therefore undertaken. Cyclopropane, methylcyclopropane, and 1:1-dimethylcyclopropane were used. All underwent exchange, and the products were analysed mass spectrometrically, again by Dr. R.I.Reed. The results are given in table XI.

Table XI

Substrate	Product	% Composition			
		undeuterated	1Datom	2Datom	3Datom
cyclopropane	n-propyl bromide	1.0	68.2	21.0	10.7
methylcyclo-propane	2-chloro-butane	3.0	87.4	9.6	1.0
1:1-dimethyl-cyclopropane	tert.-amyl-chloride	1.0	92.9	6.6	1.0

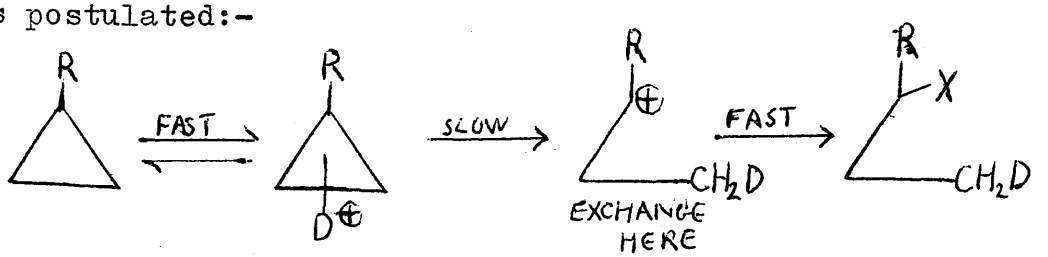
When cyclopropane was treated with deuterium chloride there was no reaction under the conditions used after three hours, and the recovered cyclopropane

contained no deuterium. Recourse was made to the more reactive deuterium bromide. The opening of the ring proceeded readily, the ionic nature of the reaction being illustrated by the following observations:-

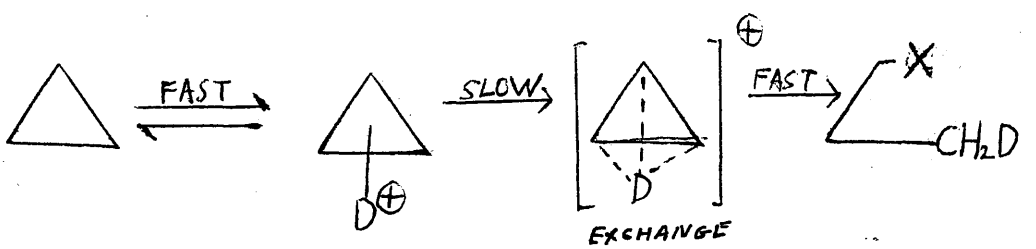
a) With hydrogen bromide the product was n-propyl bromide and not isopropyl bromide. (See the work of Karasch et. al.[111]).

b) The reaction was not inhibited by the presence of either diphenylamine or hydroquinone.

When methylcyclopropane and 1:1-dimethylcyclopropane were isolated after treatment for 35 minutes with deuterium chloride under the reaction conditions, they were found to contain no detectable deuterium. In no case did the halogeno product of the reaction undergo exchange under the reaction conditions. To accomodate these observations the following reaction scheme, analogous to that used in Section II to cover the additions of deuterium halides to olefins, is postulated:-



The varying degrees of exchange noted in these reactions is quite remarkable. The figures for cyclopropane itself are not directly comparable with the others, as deuterium bromide, and not deuterium chloride, was used in the ring opening in this case. However, a preliminary inspection of the results might lead one to suspect that the opening of cyclopropane itself followed a different path from the opening of the substituted cyclopropanes examined. It is conceivable that a classical carbonium ion intermediate is never formed in the case of the cyclopropane ring, but that the reaction proceeds through an "outer complex" followed by an "inner complex" in which the proton adding and the hydrogens of the ring are equivalent. (c.f. Deuterium exchange with acids and aromatic rings -Section II.) This could be represented as below.



In the original work on the addition of deuterohalides to steroidal olefins[112] (See section II.) the method of deuterium analysis used entailed the use of some deuterated organic standard, and α-amyrin acetate produced by treatment of phyllanthyl acetate with deuterium chloride was chosen, it being assumed that this contained one deuterium atom per molecule. The deuterium analyses obtained by these workers using this standard were correspondingly low in value.

The results obtained in this section constitute an extension of the work in Section II.

For the future, much information concerning the nature of the reaction intermediates in organic ionic reactions may be gained using isotopic tracers, in particular deuterium; and the next decade will undoubtedly produce many interesting discoveries which will enhance our knowledge of this most fundamental aspect of modern organic chemistry.

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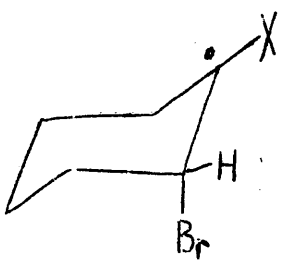
SECTION IV

HISTORICAL

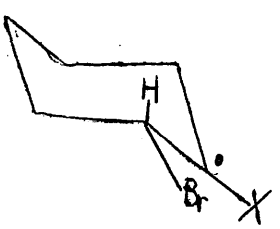
Recently, a considerable quantity of work has been carried out on the stereochemical nature of radical additions to olefins. The literature contains examples of both stereospecific and non-stereospecific additions.

The leader of a school which has found and studied a series of stereospecific additions is Goering. His work, with collaborators, on the free radical addition of hydrogen bromide to 1-substituted cyclohexenes[113] marks the beginning of a sequence of papers all suporting a stereospecific mode of addition in radical reactions. In this paper a three membered ring intermediate was postulated to explain the results obtained, i.e., a non-classical type of radical analogous to the bromonium ion which occurs in the course of ionic addition of bromine to an olefinic double bond. In a subsequent paper[114], perhaps in view of work by Steinmetz and Noyes[115] on the facile bromine catalysed isomerisation of cis and trans-dibromoethylene, Goering and his co-workers chose to explain the stereospecific

addition of hydrogen bromide to 1-halocyclohexenes in terms of a dipole-dipole interaction. It was suggested that this caused the more stable conformation of the first formed radical to be that in which the entering bromine atom was axially orientated and the halogen in the original substrate equatorially situated. As an alternative it was suggested that the radical(XXXVII) was first formed and that the reaction with the hydrogen atom occurred more rapidly than inversion to (XXXVIII) -i.e., the products



XXXVII



XXXVIII

of the reaction were kinetically controlled. Goering and his co-workers have therefore, in two papers, suggested all three forms of product control possible: steric control, thermodynamic control, and kinetic control.

Khan[116] has shown that nitrogen dioxide effectively isomerises some aliphatic double bonds, and has

postulated the reversible formation of an olefin-radical π-complex, giving it the property of free rotation. His results can, however, be readily explained by assuming that the initial radical addition is reversible. It has already been shown that the initial radical addition of thiols and of hydrogen bromide to olefins is reversible and non-rate determining.[117]

In a third paper Goering et. al.[118] studied the addition of thioacids to 1-chlorocyclohexene. The results appear to exclude the possibility of a three membered ring intermediate; for it was observed that stereospecificity in these additions was considerably less than for hydrogen bromide additions, whereas it would seem that as the sulphur atom has more electrons and orbitals available it should form a π-complex more readily than the bromine atom. In this publication the previously suggested kinetic control is favoured. Although the equatorial position for bulky substituents is the more stable with the cyclohexane ring in the chair conformation Goering suggests that the radical has a short life-

time and that the second consummating radical adds before the initially emplaced (axial) group has time to reach the equatorial position by ring inversion. Further evidence was put forward in favour of kinetic control in more recent work from the Goering school on the free radical addition of hydrogen bromide to trans-2-bromobutene.[119] The product was almost exclusively dl-2:3-dibromobutane (trans addition), while, correspondingly, cis-2-bromobutene gave meso-2:3-dibromobutane. The conditions used, however, are favourable to a rapid transfer step, and in this case the possibility that an olefin-acid π-complex is of importance has not been eliminated. (In his work on the addition of hydrogen bromide to 1-bromocyclohexene Goering put forward evidence to show that such complex formation was of no consequence as regards the stereochemistry of the reaction.)

Non-stereospecific additions have been reported in work on the addition of dinitrogen tetroxide to acetylenes[120] and Skell and Woodworth[121], studying the light catalysed addition of bromotrichloromethane to cis and trans-but-2-ene, found that the same

diastereomeric mixture of the 1:1-adduct was obtained from both olefins. The conditions used were such that no cis-trans isomerisation took place. This points to the intermediate radical having time to reach equilibrium among its possible configurations. More recent publications from this school[122] reported that addition of benzene sulphonyl chloride to cis and trans-but-2-ene gave a mixture of isomers, and that in radical co-polymerisation of cis and trans-but-2-ene with sulphur dioxide the same polymer was obtained from both monomers.

Brand and Stevens[123] pointed out that additions to trisubstituted cyclic olefins appear to be stereospecific or nearly so, trans addition predominating; while with disubstituted cyclic olefins a mixture of cis and trans isomers is obtained. Results in accord with this were obtained by Brand and Stevens in their own work on the addition of dinitrogen tetroxide to cyclohexene and 1-methylcyclohexene. (See table XII).

Very recently, Galbraith and Eglinton[124] have studied the addition of dinitrogen tetroxide to a

series of unsaturated fatty acids, and have found that with these long-chain disubstituted olefins the additions are non-stereospecific.

Table XII

Olefin	Adduct	%trans-Addition
1-methylcyclohexene	HBr	100
1-methylcyclohexene	MeCOSH	85
1-bromocyclohexene	HBr	99.5
1-chlorocyclohexene	HBr	99.7
1-chlorocyclohexene	H_2S	86-93
1-methylcyclopentene	MeCOSH	70
cyclohexene	N_2O_4	58
cyclohexene	NO_2Cl	62
1-methylcyclohexene	N_2O_4	100
cyclopentene	N_2O_4	84

The work of Kharasch et. al.[125] on the radical addition of hydrogen bromide to 3-bromocyclohexene to yield exclusively 1:3-dibromocyclohexene can be explained on the basis of the steric advantage existing in an initial trans addition of the bromine atom of the addendum with respect to the bromine in the substrate - regardless of whether this substituent was initially pseudoequatorial or pseudoaxial.[123] (This can be clearly seen from scale

models). This determines the stereochemistry of the product, regardless of the nature of the final hydrogen atom addition.

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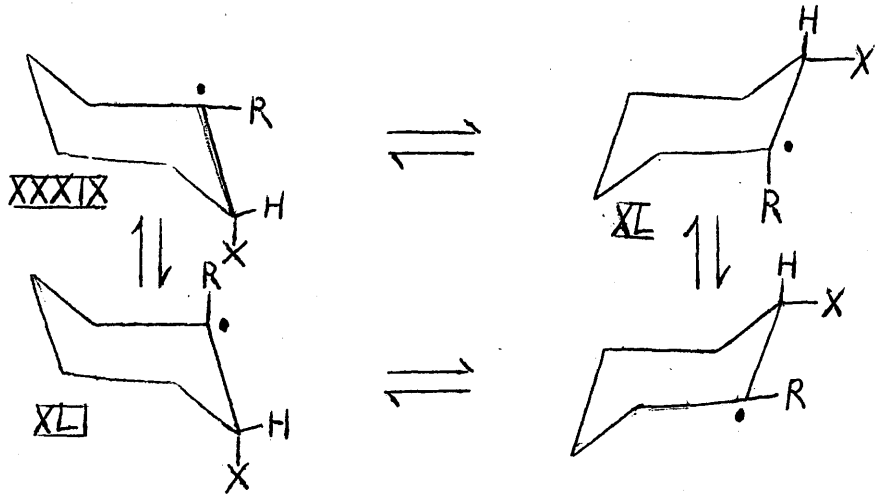
DISCUSSION

Based on the evidence briefly reviewed in the preceding section Goering has postulated that in cyclohexene systems the initial attack of a radical on the double bond is axial. The stereochemistry of such an attack was discussed in more detail by Brand and Stevens[123], who concluded that in additions to cyclohexene systems the available evidence suggested that the intermediate free radical had a pyramidal configuration, the chair-chair interconversions being slow compared to the second step of the addition reaction. Further, on this basis, and on the assumption of an initial axial attack - this giving the maximum overlap of the $\widetilde{\pi}$-electron cloud - it seemed probable that as the entering group approaches the odd electron is thrust out of the opposite axial position to form the radical XXXIX), which can either undergo ring inversion to the radical(XL) or radical centre inversion to (XLI). Assuming that ring inversion was slow compared to the second step of the radical process, Brand and Stevens concluded that the stereochemistry of the addition

would depend on the relative abundances of the forms (XXXIX) and (XLI). It is necessary, in addition, to assume that the rate of ring inversion is of the same order for R=Me,Br, etc., or R=H, and



that the rapid radical centre inversion is of the same order, regardless of the nature of the group R. The 1:3-diaxial non-bonded interactions in (XLI) in the case of the odd electron or R=H will be negligible, and there will be little difference in the stability of the two forms, and hence little stereospecificity of addition. The case of R=Me, or Cl, Br, etc. is entirely different. Here, where the group R is large, when it is in the axial position there will be a most considerable 1:3 non-bonded

interaction in (XLI), and this will tend to destabalise this form of the radical in favour of (XXXIX), where R is in the equatorial position and subject to less steric compression. Hence the degree of stereospecific trans addition in such a case will be high. To explain varying percentages of trans addition observed using the same substrate but different addenda it is necessary only to postulate varying rates of addition allowing a greater or a shorter lifetime in which ring inversion may occur.

It seemed desirable, in order to clarify the position, to carry out experiments with conformationally rigid olefin systems. An attempt was made in this direction by Brand and Stevens[123] who added dinitrogen tetroxide to 3-methylcholest-2-ene, and although some products were isolated they could not be conformationally characterised. The free radical addition of hydrogen bromide to steroid systems has been studied by various Japanese workers, who used as substrates cholest-5-ene[126], and 3-halogenocholest-5-enes.[127] No experiments capable of determining the conformation of the added atoms were performed,

but in each case a single product, quite distinct from the ionic addition product, was isolated.

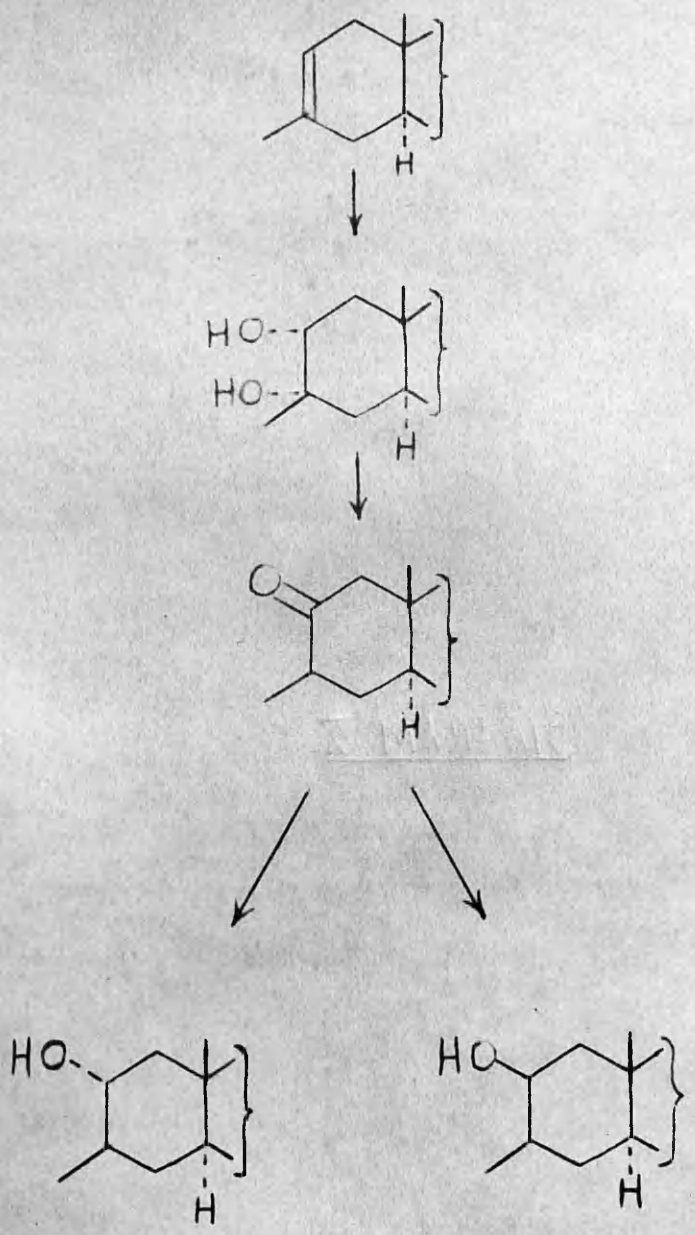
The present work was carried out using the steroidal olefins cholest-2-ene, cholest-5-ene, and 3-methylcholest-2-ene, the addendum again being hydrogen bromide.

In cholest-2-ene we have a disubstituted double bond, but one in which ring inversion cannot take place as a consequence of the rigidity of the steroid nucleus. When cholest-2-ene was treated with hydrogen bromide the sole isolated product was 3α-bromocholestane. This is the thermodynamically less stable axial bromide, and indicates that the initial attack of the bromine radical is on the underside of the steroid molecule. This direction of attack holds a considerable steric advantage for the radical approach because of the C10 methyl group at the steroid AB ring junction. The free radical nature of the addition was demonstrated by the inhibition of the reaction by diphenylamine. The reaction otherwise proceeded readily, without added catalyst, on passing dry hydrogen bromide into a hexane solution of the

steroid. If radical centre inversion is of importance in determining the stereochemistry of the addition with cholest-2-ene we should still get non-stereospecific addition. The formation of a single bromide does not necessarily imply that the addition was stereospecific in nature. Although the bromine radical attack was exclusively from the α-side of the steroid molecule, the consummating hydrogen atoms may be distributed approximately equally between the 2α and 2β positions. It was hoped that by using deuterium bromide as the addendum this possibility could be investigated, and these experiments are discussed later.

The addition of hydrogen bromide to 3-methylcholest-2-ene in a radical fashion was now of immediate interest. On the basis of the theories discussed and the results obtained with cholest-2-ene a diaxial trans addition might be expected. Numerous attempts to add hydrogen bromide to 3-methylcholest-2-ene in a free radical fashion failed. The reasons for this are not apparent, but it is known that the electron donation effect of the methyl group should

DIAGRAM X

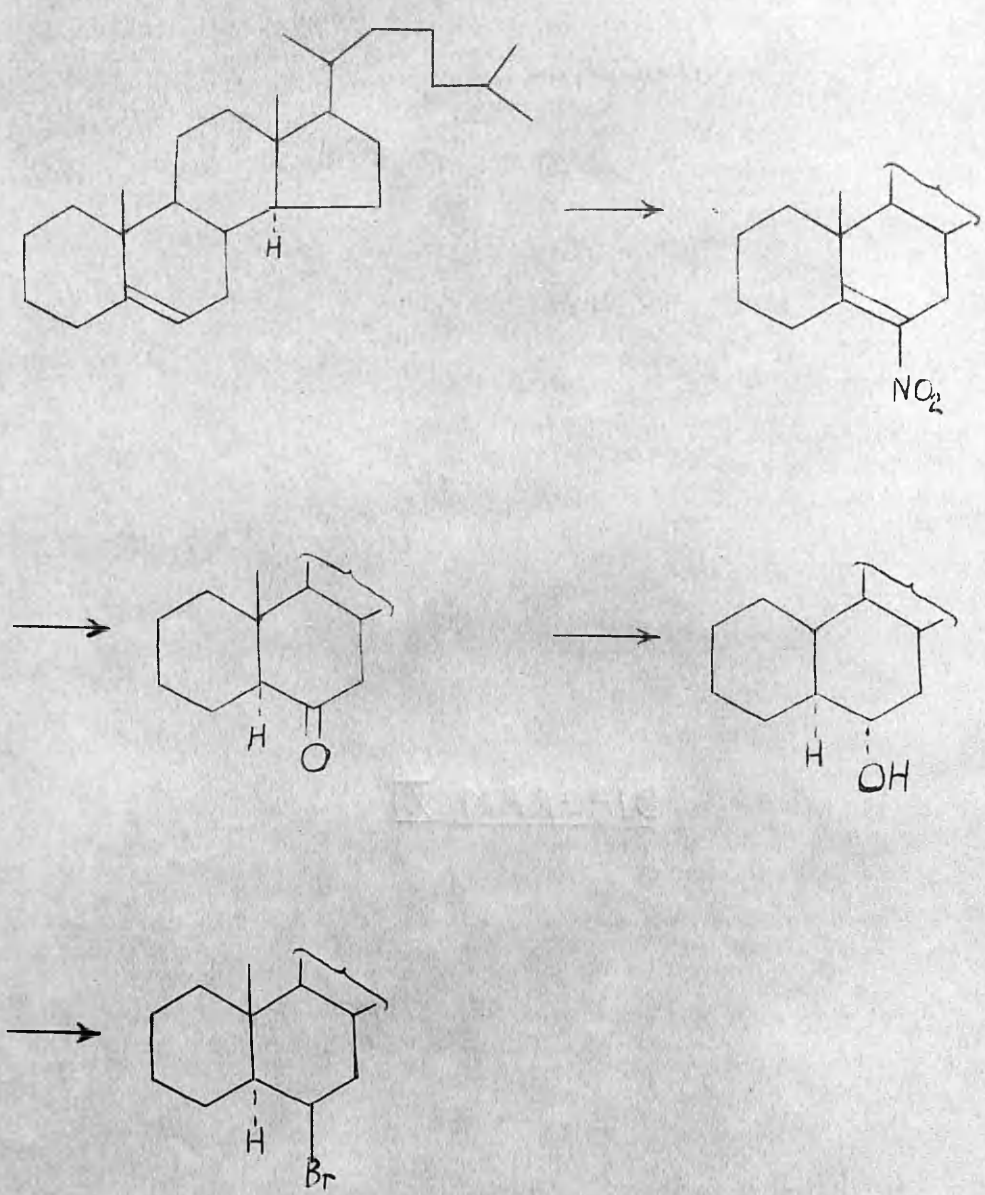

H
HO
HO
H
O
H
HO
H
HO
H

facilitate the competing ionic addition to give 3β-bromo-3α-methylcholestane. In the course of the attempts what appeared to be an impure dibromide was isolated. The material was obtained as colourless needles, m.p. 105-109°, and gave a positive Beilstein test for halogen and a negative tetranitomethane test for unsaturation. In 3-methylcholest-2-ene the approach of a bromine radical to the 2β (axial) position is severely hindered, but 2β:3α-dibromo-3β-methylcholestane is known and this steric hinderance alone does not appear to be sufficient to preclude the formation of a 2β-bromide.

In anticipation of a successful addition to 3-methylcholest-2-ene, 3β-methylcholestan-2α-ol and 3β-methylcholestan-2β-ol were synthesised (See diagram X). It had been hoped that the product of addition, if a single compound, could have been subjected to an Sn2 solvolysis[128] to yield the alcohol of opposite conformation, and so have been identified. Alternatively, 2α-bromo-3β-methylcholestane and 2β-bromo-3β-methylcholestane could have been synthesised from 3β-methylcholestan-2α-ol.

The addition of hydrogen bromide to cholest-5-ene in a free radical manner yielded a single uniform compound, m.p.86-87° $[\alpha]_D$ -2.7° ($CHCl_3$). The infrared spectrum of the product was consistent with an axially orientated bromine atom, and the rotation was not in disagreement with this. However, neither of these observations is conclusive. (See SectionI). The bromide was reduced to cholestane using lithium in liquid ammonia, illustrating the conformation adopted by the added hydrogen atom, as the bromide - which gave the expected analytical figures - had been shown to be secondary in nature. The method used is a general one for the estimation of tertiary bromides is the presence of secondary bromides, and depends upon the preferential solvolysis of the tertiary bromide, and back titration of the hydrogen bromide released. Analogous methods exist in the literature[129], but the solvent mixtures quoted are not suitable for steroids, and the reactions often involve heating in sealed tubes, which is inconvenient. An attempt to chemically determine the conformation of the bromine atom by Sn2 acetolysis followed

DIAGRAM XI


H
NO2
H
O
H
OH
H
Br

by hydrolysis to the known alcohol of opposite conformation from the initial bromide failed. The original olefin was the sole isolated product. An attempt to synthesize the bromide obtained from the addition reaction was therefore made by the route shown. (See diagram XI.) While this work was in progress a note appeared in which attention was drawn to the formation of 6α-bromocholestane on treatment of cholestan-6α-ol with either phosphorous tribromide or thionyl bromide,[130] i.e., no inversion occurred when phosphorous tribromide was used as the brominating agent. The attempted synthesis was therefore abandoned , as the physical constants of the bromide obtained by Shoppee and Howden, in which the bromine atom is claimed to be equatorial, and of the bromide from the addition reaction leave no doubt that the bromine atom in the latter is axial. (See table XIII.) Therefore, the free radical addition of hydrogen bromide to cholest-5-ene proceeds in a stereospecific trans diaxial fashion. Here, however, non-diaxial addition after an initial

Table XIII

	Addition product (6β-bromocholestane)	6α-bromocholestane (Shoppee and Howden)
Melting point	86-87°	141-142°
Rotation	-2.7°	+50°
Infrared (bands at)	533 cm^{-1} & 584 cm^{-1}	710 cm^{-1} (no absorption at 690 cm^{-1})

axial bromine atom attack would require the formation of a cis AB ring junction in the steroid.

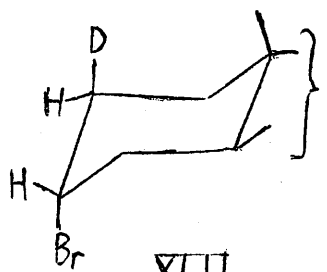
The initial axial attack of the bromine atom is not without interest. Apparently the hindrance on the β side of the steroid molecule is overcome by the preference shown by the entering group to approach the orbitals of the double bond projecting in the vertical(axial)plane directly and not at right angles. (Maximum π-bond overlap.)

On addition of deuterium bromide, rather than hydrogen bromide, to cholest-2-ene, the possible products (if no exchange reaction occurs) are

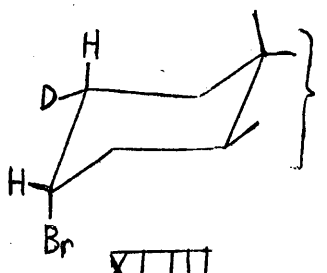
(XLII) and (XLIII). If only (XLII) is produced - or (XLIII), although this seems unlikely - this would suggest that radical centre inversion is of little importance in determining the stereochemistry of the reaction. It was hoped that a tentative distinction between (XLII) and (XLIII) or a mixture of both resulting from non-stereospecific addition could be made from the infrared spectrum of the product. Unfortunately, the initial experiment with deuterium bromide yielded a product containing little or no deuterium, and circumstances did not permit an early repetition of the reaction. The experiment will be repeated in the near future.[131] The cause of the low deuterium content is not known as yet, and may have been due simply to a fault in the experimental technique.

The results in this section confirm that the initial attack of the bromine radical in the course of free radical additions of hydrogen bromide to cyclohexene systems is axial; and provided at least one more well authenticated case of a stereospecific addition to an olefinic double bond which is tri-

substituted.



XLII



XLIII

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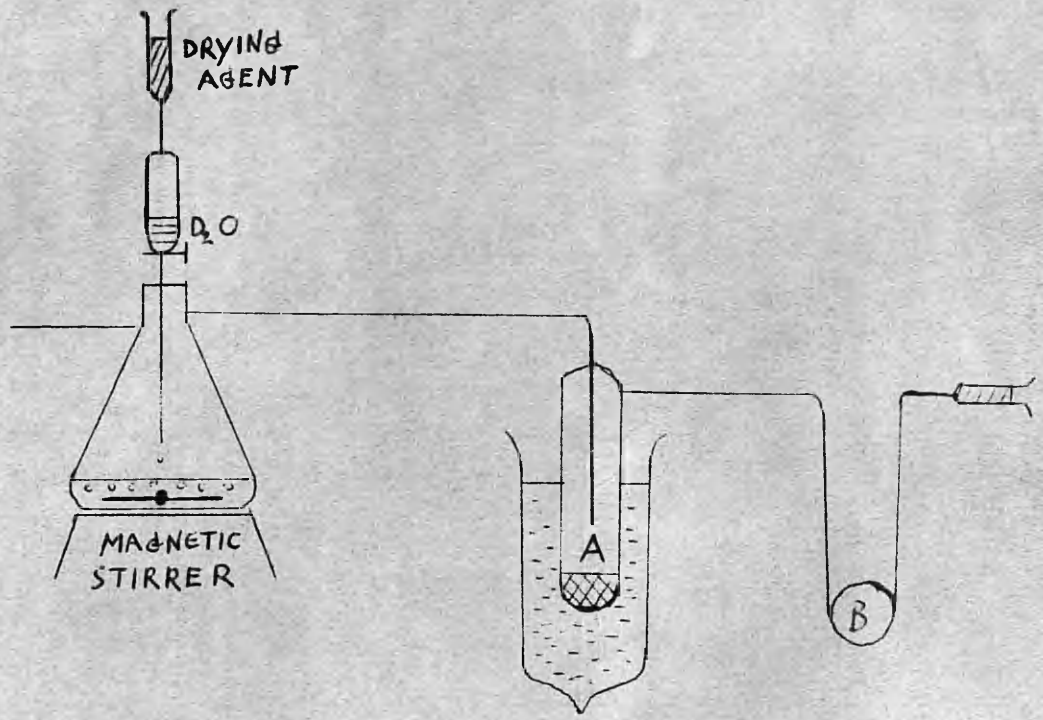
EXPERIMENTAL

DIAGRAM XII


DRYING AGENT
D_2O
MAGNETIC STIRRER
A
B

GENERAL EXPERIMENTAL

Melting points are uncorrected. Optical rotations were taken in a one decimetre tube in chloroform solution using the sodium D line. Infrared spectra were taken on the Perkin-Elmer model 13, or occasionally the "Infracord". The high resolution spectra (Section I) were taken on the Unicam S.P.100. Deuterium oxide used was "Norsk Hydro" 99.9%. "Pet. ether" refers to the 40-60° fraction of petroleum ether unless otherwise stated.

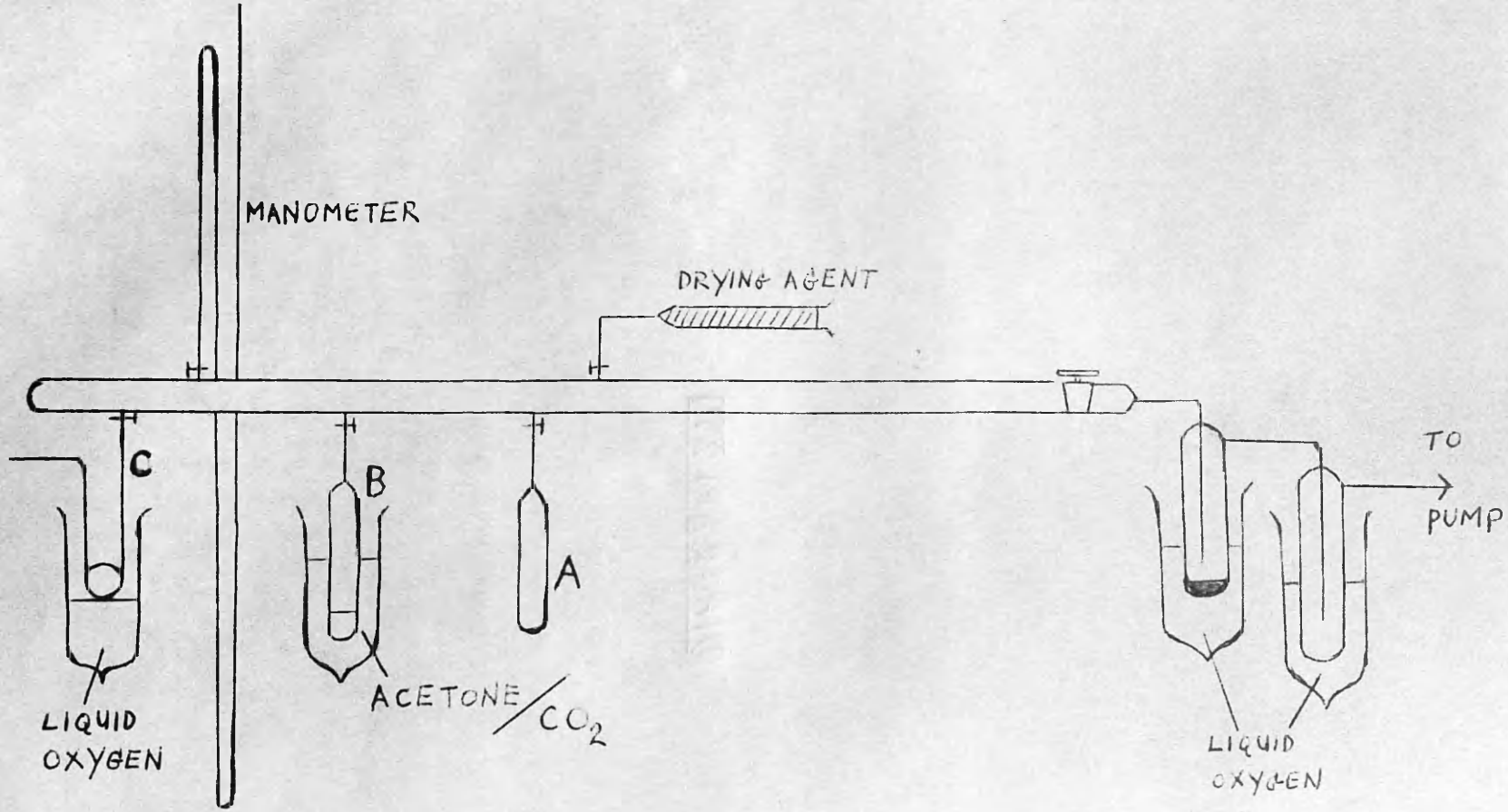
Apparatus and Techniques

a) The preparation of deuterium bromide and chloride.

The deuterium halides were prepared by dropping deuterium oxide onto phosphorous tribromide or chloride in the apparatus shown. (See diagram XII.) The deuterium halide produced was first collected in A, and redistilled into B, liquid oxygen being used to cool the traps.

b) Vacuum line.

DIAGRAM XIII


MANOMETER
DRYING AGENT
C
B
A
TO
PUMP
LIQUID
OXYGEN
ACETONE / CO_2
LIQUID
OXYGEN

A standard three limb vacuum line was used to handle experiments involving organic reactants. (See diagram XIII.) The reactant (e.g., cyclopropane) was distilled in vacuuo from A into B, the latter being immersed in an acetone/solid carbon dioxide bath. The trap containing the deuterium halide (C) was allowed to warm until the apparatus was filled to a pressure of one atmosphere with the deuterium halide, and by adjustment of the liquid oxygen level cooling (C) this pressure was maintained until the reaction was completed.

c) Deuterium analyses.

Analyses of volatile deuterium containing compounds were kindly carried out by Dr. R.I. Reed, of this department, using a mass spectrograph. The procedure was as follows:-

The spectrum of an undeuterated sample of the material to be examined was taken, low electron accelerating energies being used to minimise break-down of the molecule under examination and avoid production of ionic fragments. The spectrum of

the deuterated material was then taken, and the number of deuterium atoms present in the molecule calculated from the intensity of the molecular ion peaks.

The sample pressure at the bottom of the ionisation tube was about 3×10^{-5} mm. of mercury, and the temperature in the head was below 160°. The ionisation potential used was about 0.3-0.4 e.v. above the molecular ionisation potential, and was normally in the region 11-14 e.v. Impurities present (e.g. solvent) do not effect such analyses, provided that their molecular weight is different from that of the sample, and the impurities do not fragment under the conditions used. In the present work there was little danger of interference from this source as the molecular weights of the samples were usually greater than that of any solvent with which they were in contact. The results were calculated from a set of simultaneous equations based on the molecular peak heights. The presence of chlorine and bromine isotopes involves only a slight complication of the spectra and calculations.

Non-volatile deuterated compounds were analysed

by combustion in the apparatus shown, (See diagram XIV) followed by quantitative infrared analysis of the water produced.

Generally, analyses for deuterium can be classed under two headings.

1) Determination of the deuterium present in the actual compound by physical measurments (e.g., infrared procedures.)

2) Determination of the deuterium content of water produced on combustion of the compound examined.

1) The difficulties encountered by previous workers using this method have already been touched upon; and it might be expected that in the infrared a carbon-deuterium band would vary in intensity and wavelength with environment, as a carbon-hydrogen band does, more especially when in the vicinity of polar groups. Any such effect could well be enhanced when the deuterium substituent is in a suitable conformation for maximum dipolar interaction. A variation of this technique would be to take infared analysis measurements on strong non-coincident

bands in the spectra of the hydrogen compound and the deuterated substance, where such differencies occur in regions of the spectrum other than the recognised carbon-deuterium frequencies at ca. 2200 $cm.^{-1}$ At present, however, it would seem that a greater certainty as to the significance of the results obtained can be achieved using combustion techniques.

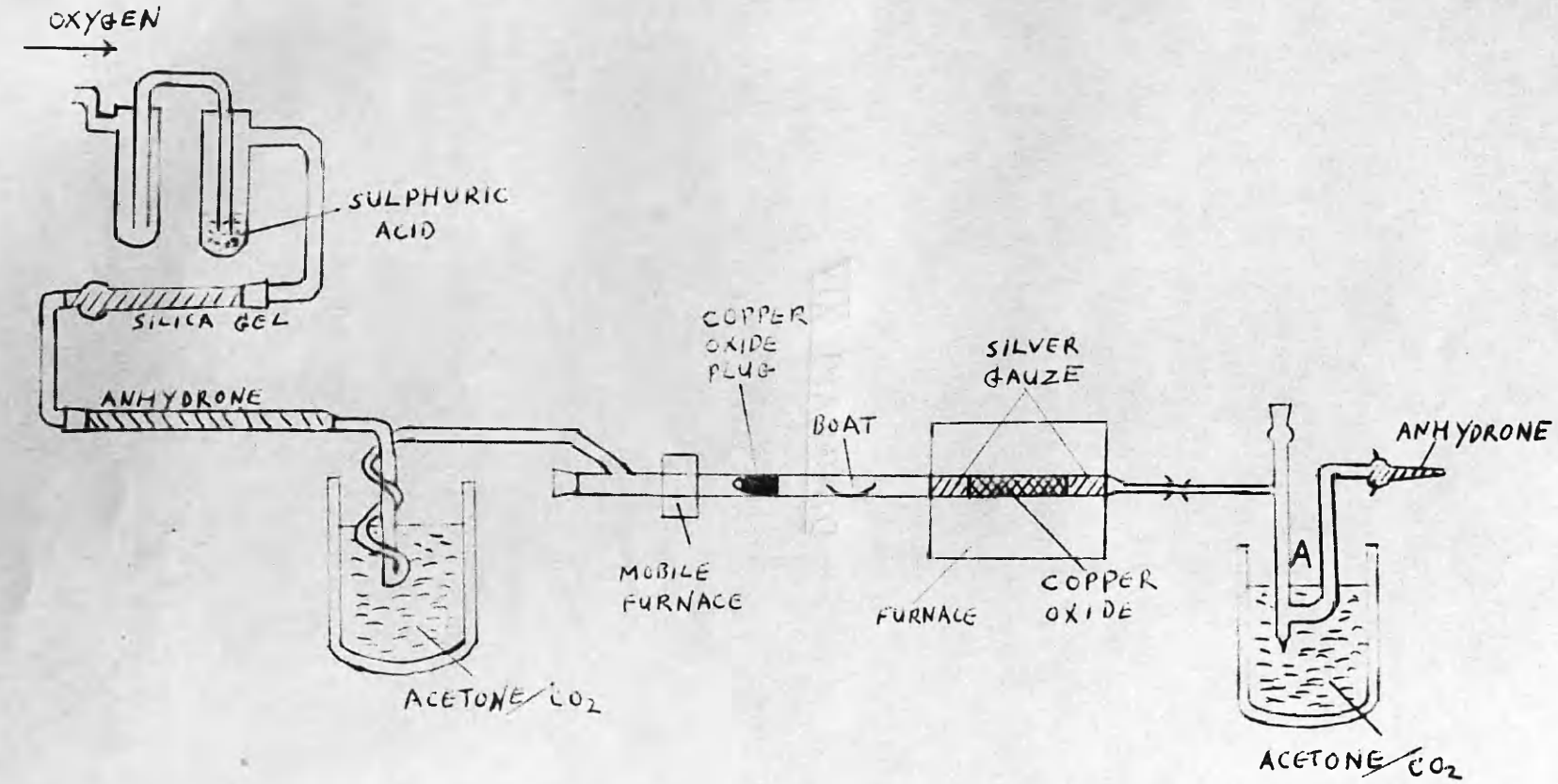
2) Here, after the initial combustion, various physical techniques exist for the examination of the water produced, e.g., determinations of water density, thermal conductivity, nuclear magnetic resonance spectra, refractive indices, and infrared spectra. In the present work the infrared method was used, as it offered considerable savings in time and trouble, and avoided possible contamination with atmospheric moisture during the elaborate distillation and purification techniques required by other methods. The sample was combusted in a conventional combustion train and the water produced collected and stored in a sealed ampoule. The sample size was chosen so as to afford approximately 20 mg.

of water, this being compared with a known standard in a ratio recording infrared spectrometer, and the deuterium content estimated from a calibration curve of optical density at 2490 cm.$^{-1}$ against the weight percentage of deuterium oxide. The range used was 0.5-2.0% deuterium oxide (with an upper limit at about 6% - at this level complications arise from the presence of D_2O in addition to DOH and H_2O.) The samples were diluted to the required range before combustion with suitable undeuterated material. The combustion train was based on that described by Keston, Rittenberg, and Schoenheimer,[132] and that of Thompson.[133] The infrared procedure is an adaptation of that described by Gaunt and Callow.[134]

Combustion.

The apparatus is shown in diagram XIV. A stream of oxygen (from a Dewar flask containing liquid oxygen) was dried by passage through a sulphuric acid bubbler, drying tubes of silica gel and Drierite, and a spiral trap immersed in acetone/solid carbon dioxide. The combustion tube of quartz (5/8 " diameter and 20" long) was packed with copper oxide (M.A.R.) held in place by plugs

DIAGRAM XIV


OXYGEN
SULPHURIC ACID
SILICA GEL
ANHYDRONE
COPPER OXIDE PLUG
BOAT
SILVER GAUZE
ANHYDRONE
MOBILE FURNACE
FURNACE
COPPER OXIDE
A
ACETONE/CO2
ACETONE/CO2

of silver gauze to remove any halogeno products of combustion. The tube was heated constantly at 750° by an electrical furnace, and a mobile electrical furnace was arranged to slowly raise the sample boat to red heat. The procedure was as follows:-

a) The apparatus was run without sample, and the set up was considered satisfactory if there was no trace of moisture in trap A after half-an-hour.

b) The copper oxide plug and the boat were removed, heated to red heat, and cooled in a desiccator. The dry sample was weighed out into the silica boat, and the boat and plug reinserted in the apparatus.

c) The mobile oven was set in motion so that the sample was slowly combusted and the boat raised to red heat.

d) The ice in A was allowed to melt and the trap removed from the combustion line, rapidly attached to a pumping system, an ampoule inserted open end down, and the trap restoppered.

e) The system which now included A was partially evacuated, and dry air then admitted, forcing the

water sample up into the ampoule, which was removed and sealed.

Infrared estimation.

The cells used were prepared by Dr. J.C.D. Brand of this department, and were made by cementing a quartz microscope slide to each side of lead spacers of 0.08 mm. thickness. The cement was picene, and gentle even heating ensured an even seal. The exact thickness of the cell was determined by weighing it empty and then full of water. Suitable metal holders for the cells were also made. The actual procedure used in the estimations was as follows:-

a) A series of eight standards (0.0-6.0% D_2O) was prepared.

b) Calibration curves of optical density against the concentration of deuterium oxide were plotted, first with ordinary water as reference standard, and then with deuterium oxide concentrations of about 2% and 4% as reference standards.

c) The cells filled rapidly when the tip was broken from the sample ampoule, and the open end held against the cell end. It was important to

ensure that there were no small air bubbles or particles in the beam of either cell, and no grit on the outer surfaces when making the actual measurements.

d) Optical density measurements were made at the peak of the HOD fundamental at 2490 $cm.^{-1}$ in the usual manner, the zero transmission and 100% transmission being set immediately before use. The samples were grouped according to the expected percentage of deuterium oxide and run in rapid succession against the required standard. Measurements had to be made rapidly to minimise exchange of the water sample while in the cell.

e) The cells were emptied from the opposite end to which the water was admitted by suction. The suction was continued for about 20 seconds after all visible traces of moisture had been removed.

The equation for the conversion of weight percentage deuterium oxide to atom percentage is as given below:-

/ over

$$\text{Atom \% i.e.,} \quad \frac{D}{D + H} = \frac{100}{1 + \frac{10}{9}\left(\frac{100-x}{x}\right)}$$

where x is weight % D_2O.

d) Gas-liquid chromatography.

The apparatus used was the Griffin and George Mk.II. Using six foot long columns the packings used were:-

a) Silicone 301 on celite

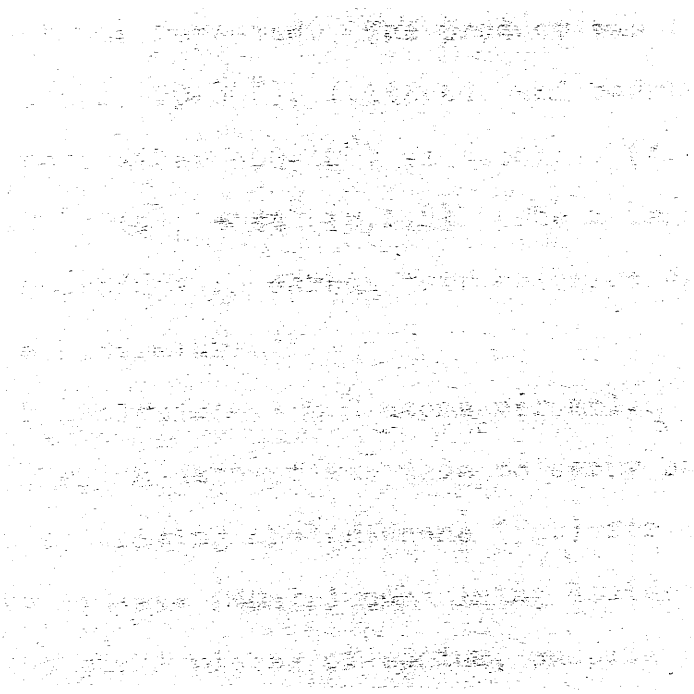
b) Reoplex on celite

c) Silver nitrate/glycol on celite.

The silver nitrate/glycol column was made up as follows:-

Redistilled glycol was shaken mechanically with finely divided silver nitrate crystals until no more would dissolve (ca. 10g. in 100ml.) The solution was then mixed with the correctly graded celite, one third of the total weight of the column consisting of the solution. The column was packed to the desired density (0.43 g./ml.) by gentle tapping, the volume of the column having been previously measured by weighing the volume of water required to fill the column.

In general the column temperature used was about 20^{o} below the mean boiling point of the materials thought to be present, or, with the silver nitrate/ glycol column, room temperature or near it.



SECTION I

2,2:4,4-Tetradeuterocholestan-3-one - Cholestanone (5.5g.) was dissolved in dry dioxane (30ml.) and deuterium oxide (5ml.) and a little dry sodium ethoxide (freshly prepared by dissolving a little sodium in dry (Borroughs) alcohol and pumping to dryness) added. The reaction mixture was refluxed for 15 minutes, then pumped to dryness. The whole process was repeated. The product was taken up in pet. ether (60-80°), filtered, and recrystallised from pet. ether (60-80°) as needles, (4.4g.), m.p. 128-129°, $[\alpha]_D$ + 44° (c,1.8). The infrared spectrum of the product in carbon tetrachloride agreed with that in the literature.[23]

D analysis:- 3.6 D atoms per mol.

When an attempt was made to carry out the deuteration by heating cholestanone (5g.) for 15 minutes in dry dioxane (40ml.) containing deuterium oxide (4ml.) and two small pieces of sodium, pumping to dryness, and repeating the process, a product was obtained (3.5g.) which recrystallised from benzene/ethanol

as needles, m.p. 207°, $[\alpha]_D$ + 41° (c,1.3). This compound gave a positive tetranitromethane test for unsaturation, and showed ketonic absorption at 1704 $cm.^{-1}$ in the infrared. In conjunction with the carbon and hydrogen analysis these facts indicated that the product had structure (XIV). Found:- C, 85.6; H, 12.2 $C_{54}H_{90}O$ requires:- C, 85.8; H, 12.0%. The physical constants were also in agreement with those recorded by Corey and Young[25], who had previously prepared the compound.

2,2:4,4-Tetradeuterocholestan-3β-ol - 2,2:4,4-Tetradeuterocholestanone (1.7g.) was treated with excess of lithium aluminium hydride in anhydrous ether (150ml.), the reaction mixture being refluxed for four hours. The reaction was worked up in the usual manner with ethyl acetate, water, and dilute mineral acid. After washing free of acid, drying, and pumping down, the organic layer yielded 2,2:4,4-tetradeuterocholestan-3β-ol (1.1g.) as needles from ethyl acetate/methanol, m.p. 138-140°, $[\alpha]_D$ + 23° (c,2.0).

D analysis:- 3.6 D atoms per mol.

2,2:4,4-Tetradeutero-3α-bromocholestane (cf. Shoppee et. al.[135]) - 2,2:4,4-Tetradeuterocholestanol (1.1g.) was dissolved in refluxing benzene (50ml.) and phosphorous tribromide (2ml.) added dropwise over one hour. After a further half-an-hour the solvent was removed under reduced pressure and the residue poured into water. Extraction with ether afforded a product which was chromatographed through alumina in pet. ether. The fractions of melting point 70-80° were rechromatographed, and the early fractions from this chromatograph, after several recrystallisations from ethyl acetate/methanol, yielded 2,2;4,4-tetradeutero-3α-bromocholestane (9mg.) as needles, m.p. 102-103°. In the infrared spectrum of this compound the band at 690 cm^{-1} associated with undeuterated 3α-bromocholestane was not present.

D analysis:- 3.1 D atoms per mol.

2,2:4,4-Tetradeutero-3β-bromocholestane (cf. Shoppee et.al.[135]) - 2,2:4,4-Tetradeuterocholestanol (300mg.) was treated with thionyl bromide (1.0ml.)

and left to stand at room temperature over night. The reaction mixture was poured into 2% sodium hydroxide and this extracted with ether to give a product which was chromatographed over alumina in n-hexane. The earlier fractions were recrystallised from acetone as needles (50mg.), m.p. 113-114°. In the infrared spectrum of this compound the band at 706 cm^{-1} associated with undeuterated 3β-bromocholestane was not present.

D analysis:- 3.3 D atoms per mol.

2,2:4,4-Tetradeutero-3-methylcholestan-3-ol (cf. Barton et.al.[136]) - 2,2:4,4-Tetradeuterocholestanone (2.0g.) in ether (25ml.) which had been dried by distillation from lithium aluminium hydride was added with stirring to methyl magnesium iodide [prepared from magnesium (0.5g.) and redistilled methyl iodide (1.0ml.) in carefully dried ether (18ml.)] over 15 minutes. The solution was refluxed for 30 minutes and then water and just sufficient acid to dissolve the solids present added. The ether layer was removed, washed free of acid, and

dried over sodium sulphate. Removal of the ether gave a mixture of the deuterated 3α-methylcholestan-3β-ol and 3β-methylcholestan-3α-ol, which recrystallised from methanol as needles (1.8g.).

D analysis:- 3.2 D atoms per. mol.

2,2:4,4-Tetradeutero-3β-bromo-3α-methylcholestane (cf. Barton et.al.[136]) - Deuterated 3-methylcholestan-3-ol (700mg.) was treated for five days at room temperature with a dry dioxane solution of deuterium bromide (50ml.). The product (600mg.) crystallised out in pure condition during the course of the reaction, and had m.p. 138-139°, $[\alpha]_D$ + 35° (c,1.1).

D analysis:- 3.5 D atoms per mol.

2,2:4,4-Tetradeutero-3β-chloro-3α-methylcholestane (cf. Barton et.al.[136]) - Deuterated 3-methylcholestan-3-ol (500mg.) was treated for five days at room temperature with a dry dioxane solution of deuterium chloride (50ml.). The product (410mg.) crystallised out in pure condition during the course

of the reaction and had m.p. 154-156°, $[\alpha]_D$ + 33° (c,1.0).

D analysis:- 3.6 D atoms per mol.

3α-Deuterocholestan-3β-ol - This was prepared by reduction of cholestanone (2.0g.) with lithium aluminium deuteride (0.5g.) in ether (300ml.). The product (1.6g.) had m.p. 140-142°, $[\alpha]_D$ +21° (c,1.5).

D analysis:- 0.8 D atoms per mol.

3β-Bromo-3α-deuterocholestane - This was prepared from the appropriate deuterated cholestanol according to the directions of Shoppee et. al.[135] for the preparation of the undeuterated material, and had m.p. 113-114°.

3α-Bromo-3β-deuterocholestane - This was prepared from the appropriate deuterated cholestanol according to the directions of Shoppee et. al.[135] for the preparation of the undeuterated material, and had m.p. 102-103°.

2β:3β-Epoxycholestane - This was prepared from 2α-bromocholestan-3-one (20g.) by reduction with excess sodium borohydride and then treatment with isopropanolic potassium hydroxide (24g. in 600ml.) at 55° for 1.5 hours according to the method of Barton and Alt[137], with the following modification. The isomeric alcohols produced in the initial reduction of the bromoketone were not separated, but the product from the subsequent base treatment was treated with sodium borohydride (to reduce cholestanone formed from the unwanted bromoalcohol to cholestanol) and the impurities then removed by chromatography in pet. ether over alumina. On evaporative recrystallisation from ether/methanol the epoxide was obtained in the form of large needles (2.2g.), m.p. 89-91°, $[\alpha]_D$ + 57° (c,1.5).

Cholestan-2β-ol - 2β:3β-Epoxycholestane (1.2g.) in dry ether (100ml.) was treated with lithium aluminium hydride (300mg.) in dry ether (50ml.) and left overnight at room temperature. On working up

in the usual way with ethyl acetate, water, and dilute mineral acid, the organic layer yielded cholestan-2β-ol (850mg.) crystallising from chloroform/methanol as rosettes of needles (reported in the literature[73] as plates, m.p. 152-154°) m.p. 151-154° $[\alpha]_D$ + 34° (c,0.9).

Cholestan-2β:3α-dibromide from cholestan-2β-ol - Cholestan-2β-ol (500mg.) was ground in a mortar with a slight excess of phosphorous pentabromide for 15 minutes, and then the reaction mixture treated with water at 40° for 40 minutes. Ether extraction and chromatography in pet. ether over alumina afforded cholestan-2β:3α-dibromide as plates (301mg.) m.p. and mixed m.p. with an authentic sample of the dibromide 124-125°, $[\alpha]_D$ + 77° (c,0.9). Found: C, 61.3 ; H,8.9 $C_{27}H_{46}Br_2$ requires C, 61.1 ; H, 8.7.

Cholestan-2β:3α-dibromide from cholest-2-ene - The experiment above was repeated using cholest-2-ene (100mg.) in place of cholestan-2β-ol. Working up as before gave cholestan-2β:3α-dibromide (80mg.) as plates, m.p. and mixed m.p. with an authentic

sample of the diaxial dibromide, $[\alpha]_D$ + 77°.

Cholestan-2β:3α-dibromide - Authentic cholestan-2β:3α-dibromide was prepared from cholest-2-ene according to Barton and Alt[137] by the addition of bromine in carbon tetrachloride, and had m.p. 124-125° $[\alpha]_D$ + 76° (c,2.1).

SECTION II

Cholestanol - Cholesterol (20g.) was hydrogenated over platinum oxide (600ml.) activated with perchloric acid (5 drops) in ethyl acetate (800ml.), the solvent washed free of acid with dilute sodium carbonate solution, and then removed on the pump. The reaction product was hydrolysed for two hours with 5% ethanolic potassium hydroxide (200ml.). Cholestanol was deposited on cooling this solution, and was recrystallised from ethyl acetate/methanol as needles (17g.), m.p. 141-142°, $[\alpha]_D$ + 23° (c,2.3). The reduction product before hydrolysis was shown to contain cholestanyl acetate. (Bands in the infrared at 1735 $cm.^{-1}$ and 1236 $cm.^{-1}$). Chromatography of a portion over alumina in pet. ether yielded cholestanyl acetate, m.p. 103-106° (undepressed on admixture with authentic cholestanyl acetate), $[\alpha]_D$ + 12° (c,2.5). When pure cholestanol was left overnight in ethyl acetate containing a few drops of perchloric acid , the solution washed to remove the acid, and the solvent removed, the infrared spectrum indicated

that the resulting solid was largely cholestanyl acetate.

3-Methylcholest-2-ene - Cholestanol (10g.) was oxidised using chromic acid according to the directions of Bruce[138], to yield cholestanone (8.1g.), m.p. 128-129°, $[\alpha]_D$ + 44° (c,1.7) and this was converted to 3-methylcholest-2-ene by formation of the mixture of isomeric methylcholestanols, and dehydration according to Barton et. al.[136]. The olefin crystallised from ethyl acetate/methanol as needles (7.9g.), m.p. 83-84°, $[\alpha]_D$ + 75° (c,2.6).

Cholest-2-ene - 2α-Bromocholestan-3-one was prepared from cholestanone (9.6g.) by the method of Butenandt and Wolff[139], and reduced to 2α-bromocholestan-3-ol with sodium borohydride in absolute ethanol according to the directions of Fieser and Huang.[140] The solid obtained on working up the reaction was dissolved in the minimum of dry pyridine and mesyl chloride (3.7ml.) in dry pyridine (10ml.) added. After standing overnight the pyridine was

removed under reduced pressure. The red product was dissoved in the minimum of glacial acetic acid and zinc dust (8.0g.) added portion-wise over one hour to the refluxing solution. Filtration, removal of the acetic acid, and filtration in pet. ether through alumina gave cholest-2-ene (2.0g.) as needles, m.p. 74-75°, $[\alpha]_D$ + 66° (c,1.9). In the present work the introduction of the mesylation step gave a superior yield to the original literature process.[137]

Cholest-5-ene - This was prepared from cholesterol by treatment with thionyl chloride followed by reduction with sodium in n-propanol according to the directions of Mauthner[141], and crystallised in large prisms, m.p.91-92°, $[\alpha]_D$ + 55°.

Additions of Hydrogen Chloride to 3-Methylcholest-2-ene - With the object of determining which solvent would be most suitable for use in experiments with hydrogen and deuterium chloride, a series of reactions between hydrogen chloride and 3-methylcholest-2-ene in various solvents was carried

Table XIV

Solvent	temp.	product	m.p.	$[\alpha]_D$	wt. used (mg.)	wt. recovered (mg.)
acetone	room temp.	3β-chloro-3α-methyl-cholestane	153-156°	+32°	92	99
acetic acid	"	"	153-156°	+33°	153	132
chloroform	"	"	154-156°	+33°	51	56
dioxane	"	"	152-155°	+33°	125	144
ether	"	"	152-155°	+33°	146	152
toluene	-70°	"	152-155°	+35°	82	86
n-hexane	-70°	"	151-155°	+34°	157	157
n-hexane	-20°	3-methyl-cholest-2-ene	82-84°	+74°	109	98
cyclohexane	room temp.	"	82-84°	+74°	149	130
carbon tetrachloride	"	"	82-83°	+73°	99	96
toluene	"	mixture	94-112°	+68°	96	99
cyclohexane +H_2O						

/over

Table XIV (contd.)

Solvent	temp.	product	m.p.	$[\alpha]_D$	wt. used (mg.)	wt. recovered (mg.)
cyclohexane $+H_2O$	room temp.	3-methyl-cholest-2-ene	82-83°	+74	152	129
alcohol	"	mixture	below 140°	+38	90	76

The product precipitated from the reaction solution.

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out. The results obtained and the conditions used are shown in Table XIV. The reactions were left overnight or until the product precipitated - whichever was the shorter time. The working up, where necessary, consisted of removal of the solvent and hydrogen chloride under reduced pressure and recrystallisation of the product from ethyl acetate/methanol. As a result of these experiments dioxane was chosen as the solvent to be used.

Addition of Deuterium Chloride to 3-Methylcholest-2-ene - 3-Methylcholest-2-ene (1.0g.) was dissolved in dry dioxane saturated with deuterium chloride (100ml.) and left overnight at room temperature. On cooling in the refrigerator needles of pure deuterated 3β-chloro-3α-methylcholestane (0.6g.) were obtained, m.p. 154-156°, $[\alpha]_D$ +33° (c,1.8).

D analysis:- 1.5 D atoms per mol.

Non-exchange of 3β-Chloro-3α-methylcholestane with Deuterium Chloride - 3β-Chloro-3α-methylcholestane (101mg.), prepared by hydrogen chloride treatment of 3-methylcholest-2-ene, was dissolved in a saturated solution of deuterium chloride in dry dioxane (17ml.) and left at room temperature for five days. On cooling in the refrigerator the chloride reprecipitated (79mg.) m.p. 154-156°, and analysis showed that it contained no deuterium.

Non-introduction of Deuterium into 3-Methylcholest-2-ene - 3-Methylcholest-2-ene (256mg.) was dissolved in a saturated solution of deuterium

chloride in dioxane (25ml.) and the progress of the resultant reaction followed to the half-way stage by taking rotation readings. The reaction was then "killed" by pouring the reaction mixture, with stirring, into dry pyridine (200ml.) at -38°. The reaction mixture was allowed to warm to room temperature and the solvents removed under reduced pressure without further heating. The product was chromatographed in pet. ether over silica. A fraction of unchanged starting material was recovered from the crystalline material (168mg.) eluted from the column, and had m.p. 81-83°, $[\alpha]_D$ +75° (c,1.6). The material contained no deuterium and its infrared spectrum was identical with that of authentic undeuterated 3-methylcholest-2-ene.

Degradation of Deuterated 3β-Chloro-3α-methylcholestane - Deuterated 3β-chloro-3α-methylcholestane (481mg.) was dissolved in dry collidine (12ml.) and the solution refluxed for three hours. The collidine was removed under reduced pressure and the product

dissolved in dry dioxane (5ml.) and treated with osmium tetroxide (622mg.) in dry dioxane (5ml.) for three days at room temperature. Hydrogen sulphide was passed into the solution and the black precipitate formed filtered off.[142] The colourless solution was pumped to dryness, and the resultant mixture of diols dissolved in dry benzene (30ml.) and lead tetra-acetate (455mg.) in dry benzene (30ml.) added to this. After ten minutes the brown precipitate was filtered off, the benzene solution shaken with solid sodium carbonate, filtered, and pumped to dryness. The white solid obtained was fractionally crystallised from ethyl acetate/methanol several times, and from pet. ether (60-80°) to yield cholestanone (33mg.), m.p. 124-127°, undepressed on admixture with an authentic sample of cholestanone.

D analysis:- 1.7 D atoms per mol.

Addition of Deuterium Chloride to Cholest-5-ene - Cholest-5-ene (361mg.) was dissolved in dioxane saturated with deuterium chloride (50ml.) and left at room temperature for five days. The solvent and excess of deuterium chloride were then pumped

off to yield, after several recrystallisations from ethyl acetate/methanol, 5α-chlorocholestane (126mg.), m.p. 94-96°, $[\alpha]_D$ +5° (c,1.7).

D analysis:- 1.5 D atoms per mol.

Non-exchange of 5α-Chlorocholestane with Deuterium Chloride - 5α-Chlorocholestane (150mg.) was dissolved in dry dioxane saturated with deuterium chloride. After five days standing at room temperature, removal of the solvent and excess deuterium chloride on the pump gave unchanged 5α-chlorocholestane (121mg.) containing no deuterium. The infrared spectrum of the recovered material was identical with that of authentic undeuterated 5α-chlorocholestane.

Non-introduction of Deuterium into Cholest-5-ene - The same procedure was used as for the corresponding experiment with 3-methylcholest-2-ene, with cholest-5-ene (327mg.) in dry dioxane saturated with deuterium chloride (25ml.). However, as difficulty was found in isolating unchanged cholest-5-ene

from the reaction, the whole reaction product was dissolved in dry dioxane (7ml.) and treated with osmium tetroxide (301mg.) dissolved in dry dioxane (5ml.). On working up after three days standing by passing in hydrogen sulphide and filtering, removing the solvent, and chromatographing in pet. ether over silica, cholestane-5α:6α-diol was obtained, m.p. 177-178°, needles from chloroform/pet. ether. This diol contained no deuterium.

Attempted Addition of Hydrogen Chloride to Cholest-2-ene - A series of attempts to add hydrogen chloride to cholest-2-ene was unsucessful. The working up consisted of removal of the solvent and hydrogen chloride under reduced pressure and recrystallisation of the product from ethyl acetate/ methanol. The conditions used and the results obtained have already been summarised in Table IX (Section II, Discussion.) Attempts to add the more reactive hydrogen bromide to cholest-2-ene resulted in free radical addition. (Section IV.)

Addition of Hydrogen Chloride to Cyclohexene - Cyclohexene (10g.) was shaken with concentrated aqueous hydrogen chloride (100ml.) for 24 hours, and the two phases left in contact for 60 hours. The organic layer was separated, washed with water, sodium carbonate solution, and water, and dried over sodium sulphate. The product distilled as a colourless liquid (9.3g.), b.p. 140-142°, n_D^{20} 1.4614, and was identified as chlorocyclohexane. Table XV indicates the nature and results of attempts to add hydrogen chloride to cyclohexane under other conditions.

Table XV

Solvent	time	temperature	products
none	1.5 hrs.	room temp.	black tar and unchanged starting material.
none	3 hrs.	-70°	unchanged starting material
n-hexane	1.5 hrs.	room temp.	black tar and unchanged starting material
n-hexane	3 hrs.	-70°	unchanged starting material.

Addition of Deuterium Chloride to Cyclohexene - Cyclohexene (1.0ml.) was shaken with a saturated solution of deuterium chloride in deuterium oxide (4ml.) in a small sealed flask for 72 hours. The organic layer was separated, treated with solid sodium carbonate, and filtered.

D analyses:- recovered cyclohexene -no deuterium.
chlorocyclohexene -1.6% no deuterium.
-98.4% one D atom.

Addition of Deuterium Chloride to 1-Methylcyclopentene, Methylenecyclopentane, 1-Methylcyclohexene, and Methylenecyclohexene - The olefin (1ml.) was shaken with a solution of deuterium chloride in deuterium oxide (2ml.) for five minutes. The two layers were separated, the organic layer washed with dilute sodium carbonate solution, dried, and analysed. The results of the deuterium analyses have already been given in Table X (Section II, Discussion.) The infrared spectra of the reaction mixtures showed that there had been no isomerisation of the initial olefins during the course of the

reaction.

Non-exchange of Methyl cyclopentyl and cyclohexyl Chlorides - 1-Chloro-1-methylcyclopentane and 1-chloro-1-methylcyclohexane were treated as in the preceding experiment, and the recovered chlorides examined by infrared analysis for deuterium. They contained no deuterium.

1-Methylcycloalkenes and Methylenecycloalkanes from 1-Methylcycloalcohols - A conventional Grignard reaction was carried out on the appropriate cycloalkanone (1 mole) to afford an ethereal solution of the tertiary alcohol. This was divided into two portions.

a) To one portion was added a few crystals of iodine, and the ether was slowly distilled off, followed by the olefin and water. The olefin was separated, dried over sodium sulphate, and redistilled. This yielded:-

1-Methylcyclopentene, b.p. 75-76°, n_D^{21} 1.4318. Even after careful distillation this was slightly

contaminated with ether. (i.r., g.l.c.) The product contained 3.3% of methylenecyclopentane. (i.r., g.l.c.)

1-Methylcyclohexene, b.p. 109-110°, n_D^{21} 1.4517. This material contained 1.4% of methylenecyclohexane. (i.r., g.l.c.)

1-Methylcycloheptene, b.p. 137-138°, n_D^{21} 1.4601. This material contained upwards of 10% of methylenecycloheptane. (i.r.)

b) The second portion was converted to the appropriate tertiary acetate by the method of Traynham and Pascual,[61] using acetyl chloride in pyridine. So prepared were:-

1-Methylcyclopentyl acetate, b.p. 156°, n_D^{21} 1.4322.

1-Methylcyclohexyl acetate, b.p. 178-180°, n_D^{21} 1.4382

1-Methylcycloheptyl acetate, b.p. 88-90°/20mm., n_D^{21} 1.4540

Pyrolysis of Acetates - The acetates prepared as above were pyrolysed in a 45cm. length of pyrex tubing of 9mm. internal diameter, 25cm. of the tubing being packed with 3mm. pyrex glass helices,

and heated to 450°. The acetates were added at a rate of approximately one drop per second in a slow stream of "white spot" nitrogen. The products of pyrolysis were condensed into a cold trap, taken up in ether, and washed free of acid. Drying over sodium sulphate and distillation yielded products with physical constants and compositions as detailed below:-

86% 1-Methylcyclopentene and 14% methylenecyclopentane. (g.l.c.) b.p. 75-76°, n_D^{21} 1.4315.

81.9% 1-Methylcyclohexene and 18.1% methylenecyclohexane (g.l.c.) b.p. 107-110°, n_D^{21} 1.4508.

Major component 1-Methylcycloheptene and minor component methylenecycloheptane (i.r.), b.p. 138-140°, n_D^{21} 1.4575.

These pyrolysis products had infrared spectra in accord with the percentage compositions determined by gas-liquid chromatography.

Cycloalkylcarbinols - The cycloalkylcarbinols were prepared from a suitable alkyl halide (cyclic) via the corresponding Grignard reagent by reaction

with gaseous formaldehyde according to Gilman and Catlin[143]

Cyclopentyl bromide (149g.) gave cyclopentylcarbinol (57g.), b.p. 162-164°, n_D^{21} 1.4584.

Cyclohexyl chloride (118.5g.) gave cyclohexylcarbinol (77g.), b.p. 90-93°/20mm., n_D^{20} 1.4652.

Cycloheptyl bromide (48g.) gave cycloheptylcarbinol (16g.), b.p. 110°/25mm., n_D^{20} 1.4678.

The cycloheptyl bromide required was prepared by lithium aluminium hydride reduction of cycloheptanone (50g.) and saturation of the cycloheptanol (b.p. 186-187°, n_D^{20} 1.4758, 43g.) so obtained with gaseous hydrogen bromide. Working up according to the literature[144] gave cycloheptyl bromide (48g.), b.p. 80°/25mm.

Cycloalkylcarbinol Acetates - The acetates of the above carbinols were formed by heating the appropriate carbinol with a slight excess of acetic anhydride for 1.5 hours. Prepared thus were:-

Cyclopentylcarbinol acetate, b.p. 176-178°, n_D^{20} 1.4371.

Cyclohexylcarbinol acetate, b.p. 195-196°.

Cycloheptylcarbinol acetate, b.p. 226°, n_D^{21} 1.4500. Found: C, 70.7; H, 10.5. $C_{10}H_{18}O_2$ requires: C, 70.6, H, 10.6%.

Pyrolysis of Cycloalkylcarbinol Acetates - The cycloalkylcarbinol acetates were pyrolysed exactly as described for the pyrolysis of the tertiary acetates, but the temperature of the column was raised to 560°. Even at 500° it was found that no reasonable quantity of acetic acid was split out. Thus obtained were:-

Methylenecyclopentane, b.p. 75-76°, n_D^{21} 1.4300. This material contained less than 1% of 1-methylcyclopentene.(i.r., g.l.c.)

Methylenecyclohexane, b.p. 101-102°, n_D^{21} 1.4511. This material contained 6.5% of 1-methylcyclohexene. (i.r., g.l.c.)

"Methylenecycloheptane", fraction boiling 137-138° collected. The material produced appeared to be a mixture of at least seven components. (i.r., g.l.c.)

During the pyrolyses there was a similar degree

of carbonisation (slight) in the pyrolysis tube as was encountered in the pyrolyses of the tertiary acetates.

Cycloalkene Carboxylic Acids - These acids were prepared by condensing diethylmalonate (80g.) with the appropriate ketone (0.5 mole.) in acetic anhydride (50ml.) and zinc chloride (30g.) according to Kon and Speight.[64] The ether extract from the working up was fractionally distilled to yield, in the respective cases:-

Ethylcyclopentene malonate, b.p. 138-140°/15mm.

Ethylcyclohexene malonate, b.p. 156-166°/20mm.

Ethylcycloheptene malonate, b.p. 170-180°/20mm.

These esters were hydrolysed using an excess of slightly ethanolic potassium hydroxide (30%), refluxing for 1.5 hours. This afforded:-

Cyclopentene malonic acid, m.p. 169° (decomp.) as prisms from ethyl acetate/pet. ether. (8.5g.)

Cyclohexene malonic acid, m.p. 150° (decomp.) as prisms from ethyl acetate/pet. ether (9.0g.)

Cycloheptene malonic acid could not be induced to crystallise, and was not isolated in any state

of purity.

Pyrolyses of Malonic Acids - The dibasic acids obtained as described in the preceding experiment on distillation under 10mm. pressure gave the monobasic acids, and the monobasic acids on distillation at atmospheric pressure gave:-

Methylenecyclopentane, b.p. 75-76°, n_D^{21} 1.4304. This product contained less than 1% of 1-methylcyclopentene. (i.r., g.l.c.)

Methylenecyclohexane, b.p. 101-102°, n_D^{21} 1.4516. This product contained 6.8% of 1-methylcyclohexene. (i.r., g.l.c.)

Methylenecycloheptane, b.p. 137-138°, n_D^{21} 1.4573. This product contained only a small percentage of 1-methylcycloheptene. (i.r.)

Cycloheptene acetic acid was also prepared according to Wallach[145], cycloheptanone (28.5g.) being condensed with ethylbromoacetate (42.5g.) using zinc shavings (16g.) in dry benzene (125ml.). This gave the hydroxyester (15g.), b.p. 138°/30mm.

Hydrolysis and dehydration by refluxing with dilute sulphuric acid for three hours gave the unsaturated acid on steam distillation, b.p. 142-146°/15mm. (7.0g.), and this on distillation at atmospheric pressure gave methylenecycloheptane, b.p. 138°, n_D^{21} 1.4569. This product contained only a small percentage of 1-methylcycloheptene.

Attempted Dehydration of Cyclohexylcarbinol - Cyclohexylcarbinol (10g.) was added dropwise to molten potassium hydroxide (50g.) at 30mm. pressure, and refluxed for two hours. Distillation afforded unchanged cyclohexylcarbinol (9g.).

Section III

Cyclopropane - Cyclopropane was obtained from the British Oxygen Gas Co., Ltd., and was anæsthetically pure. It was redistilled in vacuo before use.

Methylcyclopropane - This was prepared from butane-1:3-dibromide (itself prepared from butane-1:3-diol[146] in 92% yield). Ring closure was effected by the method of Haas and McBee,[147] the method of Gustavson[148] having proved unsatisfactory in the present work. The gas generated was dried over potassium hydroxide and phosphorous pentoxide, collected in a cold trap, and stored at -15°. The methylcyclopropane produced boiled at $+5^{\circ}$ and was redistilled in vacuuo before use.

1:1-Dimethylcyclopropane - 2:2-Dimethyl-1:3-propanediol (100g.) was treated with phosphorous tribromide, which was added to the diol at such a rate as to maintain the temperature of the reaction

mixture above 70° and below 80°, this temperature range being initially attained by heating in a metal bath.[149] The product (82g.) appeared to be largely bromo-alcohol (i.r.), but was ring closed according to the directions of Haas and McBee[147] 1:1-Dimethyl-cyclopropane (12ml.), b.p. 20° was distilled from the reaction mixture and dried over potassium hydroxide and phosphorous pentoxide. It was redistilled in vacuo before use.

Treatment of Cyclopropane with Deuterium Chloride - Cyclopropane was held in a trap at -70° and treated with one atmosphere of deuterium chloride for four hours. No reaction occurred, and the infrared spectrum of the recovered cyclopropane, after bubbling through dilute potassium hydroxide solution and drying, showed that it contained no deuterium.

Opening of Cyclopropane with Hydrogen Bromide - a) Cyclopropane was treated as above with one atmosphere of hydrogen bromide for two hours at -70°. The trap was allowed to warm and excess of hydrogen

bromide boiled off. The liquid in the trap was treated with a little solid sodium carbonate and sodium sulphate. The infrared spectrum of the product was identical with that of authentic n-propyl bromide, but different from that of iso-propyl bromide.

b) When the experiment was repeated with diphenylamine (21mg.) in the trap the results were as before.

c) When the experiment was repeated with hydroquinone (15mg.) in the trap the results were as before.

Opening of Cyclopropane with Deuterium Bromide - Section a) of the above experiment was repeated using deuterium bromide. The product was analysed for deuterium content. The results are given below.

Undeuterated material - 1.0%

1 D atom - 68.2%

2 D atoms - 21.0%

3 D atoms - 10.7%.

Opening of Methylcyclopropane with Hydrogen

Chloride - Methylcyclopropane was treated with one atmosphere of hydrogen chloride for 1.5 hours at -70° and worked up as in the preceding experiments. The infrared spectrum of the product was identical with that of authentic 2-chlorobutane.

Opening of Methylcyclopropane with Deuterium Chloride - The above experiment was repeated using deuterium chloride, and the product analysed for deuterium content. The results are given below.

Undeuterated material - 3.0%

1 D atom - 87.4%

2 D atoms - 9.6%

3 D atoms - 1.0%.

Opening of 1:1-Dimethylcyclopropane with Hydrogen Chloride - 1:1-Dimethylcyclopropane was treated with one atmosphere of hydrogen chloride for 1.5 hours at -70° and worked up as above. The product had an infrared spectrum identical to that of tert.-amyl chloride.

Opening of 1:1-Dimethylcyclopropane with Deuterium Chloride - The above experiment was repeated using deuterium chloride and the product analysed for deuterium content. The results are given below.

Undeuterated material - 1.0%

1 D atom - 92.9%

2 D atoms - 6.6%

3 D atoms - 1.0%

Non-exchange of Products - Under the reaction conditions appropriate to each n-propyl bromide, 2-chlorobutane, and tert.-amyl chloride failed to incorporate any deuterium.

Non-exchange of Starting Materials - Cyclopropane, methylcyclopropane, and 1:1-dimethylcyclopropane, isolated after 35 minutes treatment at -70° with one atmosphere of the appropriate deuterium halide, contained no detectable deuterium.

Opening of Phyllanthyl Acetate with Deuterium Chloride - Phyllanthyl acetate was treated with

deuterium chloride in chloroform according to the directions of Barton and de Mayo[110], and the product isolated and analysed for deuterium. The α-amyrin acetate so obtained contained 1.5 D atoms per mol.

Non-exchange of α-Amyrin Acetate - When α-amyrin acetate (80mg.) was treated under the reaction conditions above with deuterium chloride in chloroform the recovered material (61mg.) was found to contain no deuterium.

SECTION IV

The preparations of cholest-2-ene, cholest-5-ene, and 3-methylcholest-2-ene are described in Section II.

3α-Bromocholestane - Cholestanol (4.0g.) in benzene (100ml.) was treated with phosphorous tribromide (2ml.) according to the directions of Shoppee et. al.[135] After purification by treatment with perphthalic acid recrystallisation from acetone gave needles m.p. 104-105°, $[\alpha]_D$ + 28° (c,1.6).

3β-Bromocholestane - This material was also prepared according to the directions of Shoppee et. al.[135] Cholesterol (10g.) in benzene (50ml.) being treated with phosphorous tribromide (3.5ml.), and the product (5.7g.) catalytically reduced over platinum oxide (698mg.). Recrystallisation from acetone yielded 3β-bromocholestane (4.3g.) as plates, m.p. 113.5-114.5°, $[\alpha]_D$ + 29° (c,2.0).

The Free Radical Addition of Hydrogen Bromide

to Cholest-2-ene - Cholest-2-ene (234mg.) was dissolved in cyclohexane (15ml.) and dry hydrogen bromide gas passed through the solution at room temperature for 45 minutes. Solid sodium carbonate was then added, the solution filtered, and the cyclohexane removed under reduced pressure to yield a white solid (217mg.). Chromatography over alumina and recrystallisation from ethyl acetate/methanol yielded 3α-bromocholestane as needles, m.p. 101-103° (undepressed on admixture with an authentic sample of 3α-bromocholestane, but depressed to 83-88° on admixture with 3β-bromocholestane.), $[\alpha]_D$ + 28° (c,1.2). The infrared spectra of 3α-bromocholestane and the product of the reaction were identical.

Inhibition - The experiment above was repeated using cholest-2-ene (332mg.) in cyclohexane (20ml.) containing diphenylamine (31mg.) as a free radical inhibitor. When hydrogen bromide gas was passed into the solution there was an immediate precipitate of diphenylamine hydrobromide. On working up as before unchanged cholest-2-ene (306mg.), m.p. and

mixed m.p. 71-73°, $[\alpha]_D$ + 65° (c,2.0) was obtained.

The Free Radical Addition of Hydrogen Bromide to Cholest-5-ene - Cholest-5-ene (571mg.) was dissolved in n-hexane (spectroscopic, 200ml.) and dry hydrogen bromide gas passed through the solution for two hours at room temperature. Solid sodium carbonate was added to the solution, which was then filtered and pumped to dryness. The product was taken up in pet. ether and filtered through silica. Recrystallisation from acetone afforded a product m.p. 86-87°, $[\alpha]_D$ -2.7° (c,1.9) as needles. The material gave a negative tetranitromethane test for unsaturation and a positive Beilstein test for halogen. Found: C, 72.2; H, 10.0; Br, 17.6%. $C_{27}H_{47}Br$ requires: C, 72.0; H, 10.4 ; Br, 17.7%.

Method of Estimating the Percentage of Tertiary Bromide Present in a Mixture of Secondary and Tertiary Bromides - The method is dependent upon the selective solvolysis of the tertiary bromide present. The solvent and solvolysing agent was dioxane (12ml.)

containing water (1.2ml.). The hydrogen bromide produced after two hours gentle refluxing was titrated with $\frac{n}{10}$ sodium hydroxide. A blank titration was always run alongside the actual estimation and any positive titration found in the blank subtracted from the estimation titration. To test and develop the method mixtures of sec.-butyl bromide with tert.-butyl bromide, and of 3β-bromocholestane with 3β-bromo-3α-methylcholestane were used. The results are shown in table XVI.

Solvolytic Estimation of the Product of Free Radical Addition of Hydrogen Bromide to Cholest-5-ene - The bromide (30.8mg.) was solvolysed as described above. Titre - 0.17ml. of $\frac{n}{10}$ sodium hydroxide. This corresponds to amaximum value of .001377g. of hydrogen bromide, and the material examined therefore contained a secondary carbon-bromine linkage.

Reduction of Bromide from Cholest-5-ene - The bromide (200mg.) was dissolved in sodium dried ether

Table XVI

Tert.-butyl bromide + sec.-butyl bromide

Total wt. mgs.	Wt. 3^{ry} bromide (mgs.)	Titre $\frac{n}{10}$ NaOH	Found wt. 3^{ry} bromide (mgs.)	Error mgs.	Error %total	% 3^{ry} bromide
140.0	74.7	5.92	72.6	2.1	1.5	2.8
135.4	83.2	6.05	83.0	0.2	0.2	0.2
127.8	28.8	2.02	27.6	1.2	0.9	4.2
123.6	81.8	5.60	76.6	5.2	4.2	6.3

3β-Bromo-3α-methylcholestane + 3β-bromocholestane

Total wt. mgs	Wt. 3^{ry} bromide (mgs.)	Titre $\frac{n}{10}$ NaOH	Found wt. 3^{ry} bromide (mgs.)	Error mgs.	Error %total	% 3^{ry} bromide
139.4	55.4	1.30	60.4	5.0	3.6	9.0
76.5	26.3	0.60	27.7	1.4	1.8	5.3
121.4	71.6	1.49	69.5	2.1	1.7	2.9
90.9	32.7	0.73	33.9	1.2	1.3	3.6

(30ml.) and added slowly to a solution of lithium (150mg.) in liquid ammonia (60ml.) with stirring. Crystallisation of the product (negative Beilstein and tetranitromethane tests) from ether/methanol gave cholestane (22mg.) m.p. and mixed m.p. 78-80°, $[\alpha]_D$ + 24° (c,0.9).

Cholestan-6-one[150] Cholest-5-ene in glacial acetic acid was treated with fuming nitric acid to yield 6-nitrocholest-5-ene, and this nitro compound was reduced with zinc in acetic acid to yield cholestan-6-one in 40% yield.

Cholestan-6α-ol[151] Cholestan-6-one (500mg.) was reduced with sodium in n-amyl alcohol to afford cholestan-6α-ol (350mg.), m.p. 129-130°

2α:3α-Dihydroxy-3β-methylcholestane - 3-Methylcholest-2-ene (517mg.) was dissolved in dry dioxane (5ml.) and osmium tetroxide (540mg.) in dry dioxane (5ml.) added to this and the reaction flask left for 48 hours tightly stoppered. Hydrogen sulphide was then passed into the solution and the black precipitate filtered off. The clear solution obtained was evaporated to dryness to yield a white solid (502mg.), which was recrystallised from acetone as fine needles (307mg.), m.p, 187-187.5°, $[\alpha]_D$ + 26° (c,1.0). Found: C, 80.6; H, 11.8. $C_{28}H_{50}O_2$ requires C, 80.4; H, 12.0%.

3β-Methylcholestan-2-one - 2α:3α-Dihydroxy-3β-methylcholestane (1.0g.) was dissolved in chloroform (20ml.) and dry hydrogen bromide gas passed through the solution at room temperature for half-an-hour. The chloroform was removed under reduced pressure and the product recrystallised from acetone as needles (590mg.), m.p. 149-149.5°, $[\alpha]_D$ + 52° (c,1.8). Found: C, 83.6; H, 11.9. $C_{28}H_{48}O$ requires C, 83.9; H, 12.1%.

3β-Methylcholestan-2β-ol - 3β-Methylcholestan-2-one (190mg.) was reduced by refluxing for four hours with excess lithium aluminium hydride in sodium dried ether (20ml.). The excess reagent was destroyed with ethyl acetate, water, and 2N hydrochloric acid, the organic layer separated, the aqueous layer extracted with ether and the combined organic layers washed free of acid. The solvents were removed under reduced pressure and the product recrystallised from ethyl acetate/methanol as fine needles (150mg.), m.p.119-121°, $[\alpha]_D$ + 32° (c,0.8). Found: C, 83.8; H, 12.5. $C_{28}H_{50}O$ requires: C, 83.5; H, 12.5%.

The infrared spectrum in nujol showed an -OH peak but no carbonyl absorption. The infrared spectrum in carbon tetrachloride had a peak at 992cm.$^{-1}$, characteristic of an axial hydroxyl grouping.

3β-Methylcholestan-2α-ol - 3β-Methylcholestan-2-one (75mg.) was dissolved in dioxane (30ml.) containing dry alcohol (3ml.) and refluxed with vigorous stirring for 2.5 hours while sodium was added in portions to the solution. Some of the solvent was removed under reduced pressure after all the excess of sodium had been destroyed with ethanol. The residue was poured into water and extracted with ether. The product was filtered through alumina to yield fine needles (45mg.) on recrystallisation from aqueous acetone, m.p. 114-114.5°, $[\alpha]_D$ + 18° (c,1.0). Found: C, 83.3; H, 12.2. $C_{28}H_{50}O$ requires: C, 83.5; H, 12.5%. The infrared spectrum in nujol showed an -OH peak but no carbonyl absorption. The infrared spectrum in carbon tetrachloride had a peak at 1038cm.$^{-1}$, characteristic of an equatorial hydroxyl grouping.

Attempted Additions of Hydrogen Bromide to 3-Methylcholest-2-ene in a Free Radical Manner -

a) 3-Methylcholest-2-ene (526mg.) was dissolved in cyclohexane (150ml.) and benzoyl peroxide (23ml.) added to the solution. The reaction vessel was irradiated with an ultraviolet lamp (the heat from which caused the solution to reflux) and dry hydrogen bromide passed through the solution for one hour. The solution was cooled, neutralised with solid sodium carbonate, filtered, and pumped to dryness. Chromatography through silica in pet. ether yielded only unchanged 3-methylcholest-2-ene (200mg.), m.p. and mixed m.p. 82-84°. A black tar was deposited in the reaction vessel during the course of the reaction.

b) 3-Methylcholest-2-ene (150mg.) and benzoyl peroxide (27mg.) were dissolved in pet. ether (50ml.) and dry hydrogen bromide gas passed through the solution at room temperature for two hours. The solution was neutralised with solid sodium carbonate, filtered, and pumped to dryness. The solid obtained was unchanged 3-methylcholest-2-ene, recrystallised

from ethyl acetate/methanol as needles, (121mg.), m.p. and mixed m.p. 82-84°.

c) Dry hydrogen bromide gas was passed through a solution of 3-methylcholest-2-ene (199mg.) and ascaridol (5drops) in cyclohexane at room temperature for 1.25 hours. The reaction vessel was stoppered and shaken overnight. A black tar was deposited in the reaction vessel. The solution was neutralised with solid sodium carbonate, filtered, pumped to dryness, and chromatographed through alumina using pet. ether as elutant. Unchanged 3-methylcholest-2-ene (110mg.), m.p. and mixed m.p. 82-84° was obtained, together with a little 3β-bromo-3α-methylcholestane (10mg.), m.p. and mixed m.p. 138-139°, $[\alpha]_D$ + 35° (c,0.6).

d) 3-Methylcholest-2-ene (300mg.) was dissolved in n-hexane (100ml.) and maintained at -20° for one hour while hydrogen bromide gas was bubbled through the solution with a stream of dry air. At the beginning of the reaction and every fifteen minutes during the course of the reaction three drops of a solution of tert.-butyl peroxide were added to the reaction mixture. The solution was allowed to

warm to room temperature, neutralised with solid sodium carbonate, filtered, and pumped to dryness. Recrystallisation from ethyl acetate/methanol gave fine needles (300mg.), m.p. 105-108° (Positive Beilstein and negative tetranitro methane test.). Found: C, 64.4, 64.9; H, 9.8, 9.2; Br, 26.4%. $C_{28}H_{49}Br$ requires; C, 72.3; H, 10.6; Br, 17.2%. $C_{28}H_{48}Br_2$ requires: C, 61.8; H, 8.9; Br, 29.4%.

Numerous attempts were made to carry out the addition (free radical) of hydrogen bromide to 3-methylcholest-2-ene, and those above are representative examples.

3β-Bromo-3α-methylcholestane - 3β-Bromo-3α-methylcholestane was prepared from 3-methylcholest-2-ene in 60% yield according to the directions of Barton et. al.[136]

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APPENDIX

After the section of the work in which it was shown that the results of Bailey et. al. on the pyrolysis of acetates was in error had been completed, and a preliminary note submitted and accepted for publication[1] , papers by DePuy[2] and his associates, and by Bailey and Hale[3,4] appeared covering much the same ground. Bailey's papers, in effect, constitute a retraction of virtually the whole of his earlier work on acetate pyrolyses, in agreement with the findings in this thesis.

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