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The Stereochemistry Of The Ring Opening Reactions Of Acyloxonium Ions And Epoxides

Alan Dennis Allbutt

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Department of Chemistry

Submitted in partial fulfillment

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ABSTRACT

Several 2,3-acyloxonium (1,3-dioxolenium ions) fused to rigid six-membered rings have been prepared and their ring opening reactions with a number of reagents studied.

It has been established that, in general, reaction with chloride ion, bromide ion and carboxylate anion yields almost entirely trans diaxial products and that the diaxial opening rule, which had previously been applied to three-membered rings fused to six-membered rings (6-3 fusion) may formally be extended to include 6-5 ring fusions. One case is reported in which axial opening is inhibited and diequatorial opening is favoured over diaxial opening.

The hydrolytic cleavage of the acyloxonium ions has been found to be highly stereospecific, yielding cis-hydroxyesters in which the ester group is in the axial position. The hydrolysis of orthoesters fused to rigid six-membered rings and the Woodward-Prevost reaction with Δ^2-octalin also give cis-hydroxyesters in which the ester group is in the axial position.

It has also been found, with both of the epoxides derivable from cholest-2-ene and with trans-decalin-2:3 epoxide, that ring opening with hydrogen bromide is not exclusively diaxial but that small amounts of the diequatorial bromohydrins are formed.

Possible reasons for the stereospecificity of these ring opening reactions are proposed.

The reductive elimination of 1,2-dibromides and halohydrin sulphonate esters with sodium borohydride and related compounds has been investigated and the results are reported in an appendix.

ACKNOWLEDGEMENTS

The author would like to express his sincere appreciation to Professor J. F. King for his invaluable advice, guidance and encouragement during the course of this work.

The contribution of the other members of the Faculty and of fellow graduate students is also gratefully recognized.

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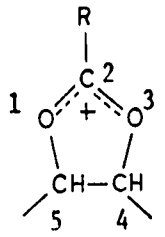
PART I

GENERAL INTRODUCTION

Reactions in which acyloxonium ions, such as the acetoxonium ion I, are believed to occur have been the subject of many studies during the past 25 years. Initially such ions were postulated to account for the stereochemical and kinetic results found with certain solvolytic reactions where the possibility of participation by a neighbouring acyl group occurred, and a large amount of data was obtained as evidence for the intermediacy of these ions. More recently it has been found that acyloxonium ions form quite stable salts with anions such as perchlorate, tetrafluoroborate and hexafluoroantimonate and can be isolated as crystalline solids. The study of the reactions of these salts fully confirms the previous work on the properties of acyloxonium ions. An extensive review of work in this field up to 1963 may be found in the Ph.D. thesis of C.B. Anderson. (1).



I

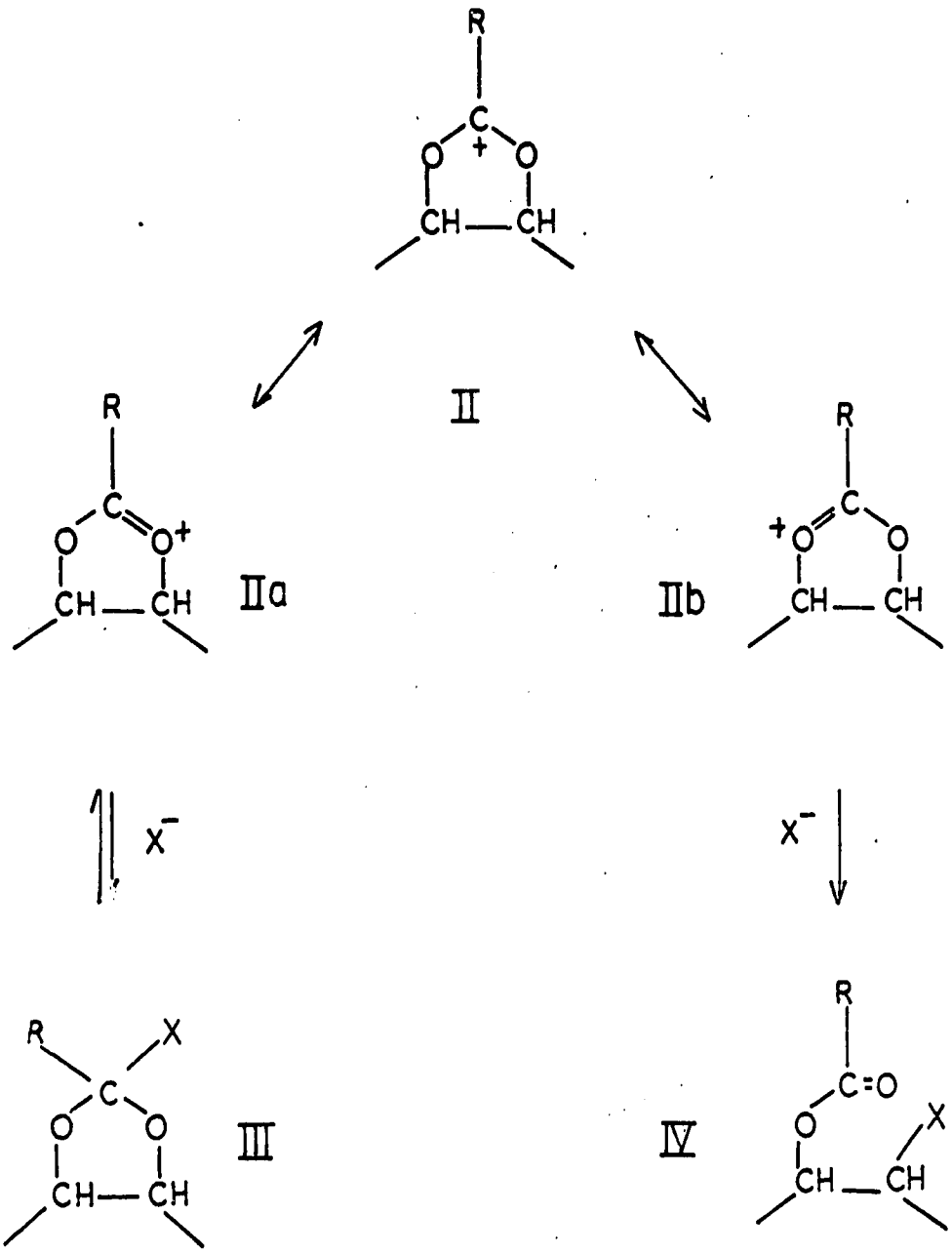
Two methods of naming ions such as I have been used:

a) as a derivative of the acyl group, i.e. "acetoxonium" or more generally "acyloxonium".

b) as a derivative of 1,3-dioxolane, i.e. "dioxolenium".

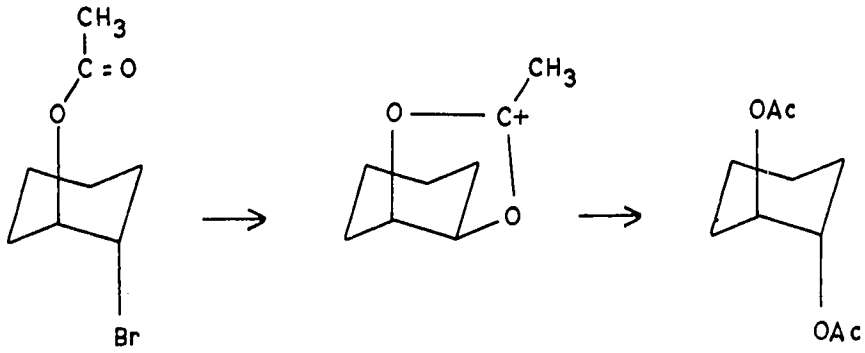
The former method is preferred here since it can be applied quite generally. The term "dioxolenium" is perfectly satisfactory when carbons 4 and 5 are part of a carbon chain or of a single ring, but when they are part of a multiple ring system, such as a steroid, the problems of nomenclature become quite awkward.

Acyloxonium ions may be considered to be members of a class of compounds known as ambident cations (2,3). Thus they can react with nucleophiles at two positions; (a) at carbon 2, (b) at either carbon 4 or 5. The ions can be written as resonance structures, i.e. II, involving two major canonical forms, IIa and IIb. A nucleophile X^-, can add at the position of lowest electron density, that is to say at carbon 2. If the energy released on formation of the new bond is large III will be the kinetically controlled product. However, if an equilibrium between III and II occurs then the reaction will lead to IV. Since the transformation of II to IV results in release of the resonance energy of the ester as well as the energy of charge neutralization, IV must be the thermodynamically stable product (3). The chemistry of these ions show both types of behaviour. Since the major portion of this thesis is concerned with some of the reactions of these ions it was

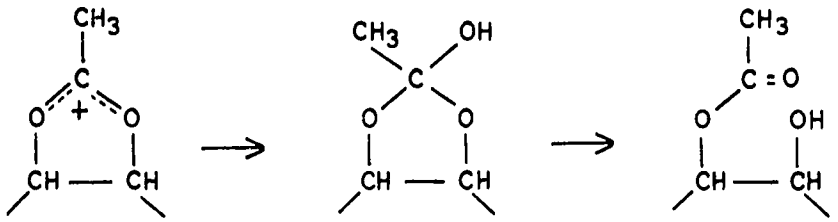

R
C
+
O
O
CH
CH
II
R
C
O
O+
CH
CH
IIa
IIb
X⁻
X⁻
R
X
C
O
O
CH
CH
III
R
C=O
O
X
CH
CH
IV

thought that a brief review of previous work on this subject would be desirable.

The acetoxonium ion I was first proposed by Winstein (4). It was found that reaction of silver acetate in dry acetic acid with erythro-and threo-2-acetoxybromobutane, trans-1-acetoxy-2-bromocyclohexane, meso and dl-2,3-dibromobutane and trans-1,2-dibromocyclohexane proceeded with predominant retention of configuration to give the corresponding diacetates. Also optically active 2,3-dibromobutane and trans-1-acetoxy-2-bromocyclohexane gave rise to completely inactive diacetates. Winstein interpreted these results by proposing the formation of an intermediate acetoxonium ion. The loss of optical activity was said to result from formation of the acetoxonium ion which is symmetrical and hence internally compensated (2).

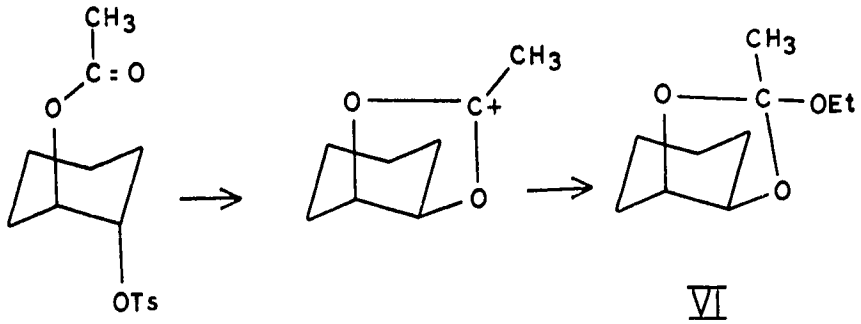


Continuing this work Winstein and Buckles found that small amounts of water in the acetic acid used in the above reactions gave rise to a different result, namely that the products were mainly cis mono-acetates (5). To account for this result it was suggested that the intermediate acetoxonium ion reacted with water to give an orthoester intermediate (V) which then tautomerized to give the corresponding cis-monoacetate.



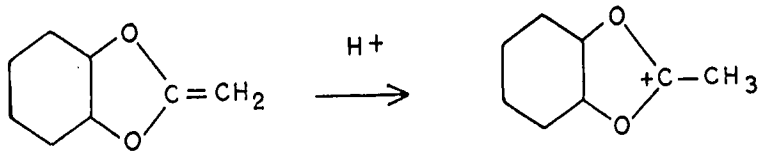
V

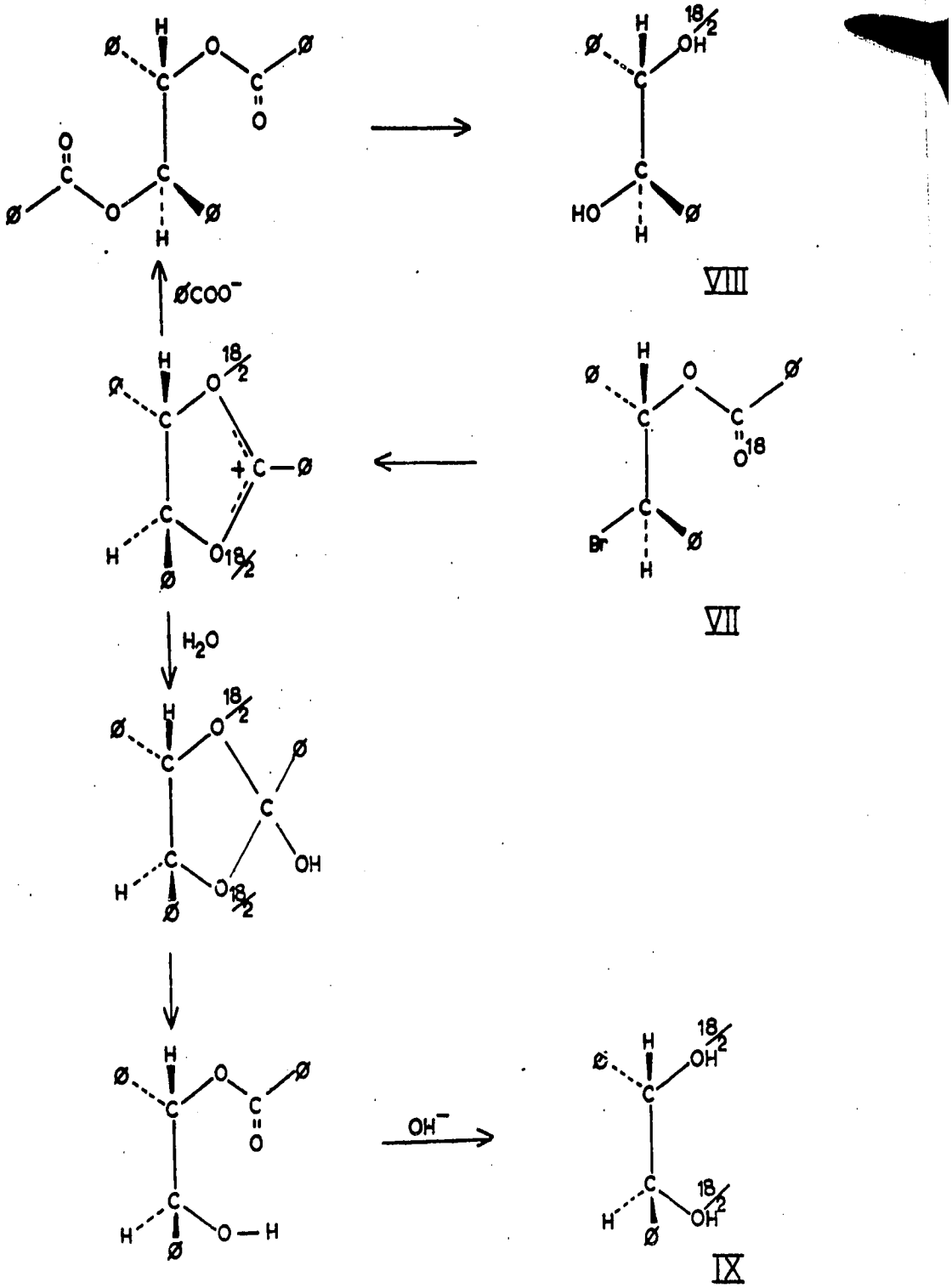
Further evidence for the existence of the acetoxonium ion was obtained from the solvolysis of trans-2-acetoxycyclohexyl p-toluenesulphonate in dry ethanol in the presence of potassium acetate (6). The cis ethyl orthoacetate (VI) was isolated in good yield and its formation was suggested to arise by attack at carbon 2.



VI

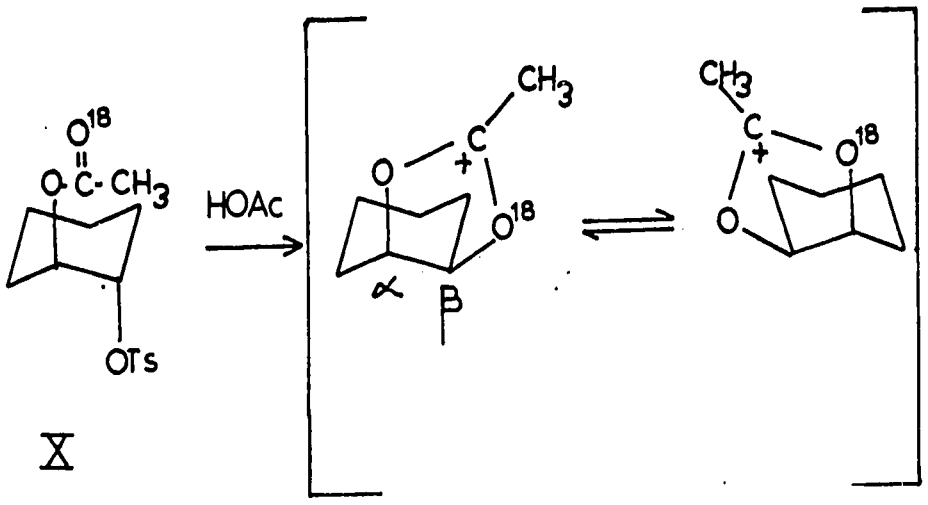
Winstein and co-workers have studied the acetolysis of trans-2-acetoxycyclohexyl p-toluenesulphonate in acetic acid with and with out potassium acetate and found the results to be fully consistent with the formation of an intermediate acetoxonium ion (7). This research group also examined the reactions of the ketene acetal of cyclohexanediol, 2-methylene-cis-4,5-tetramethylene-1,3-dioxolane as a method of generating the corresponding acetoxonium ion (8). The products from treatment of this compound with acetic acid and with p-toluenesulphonic acid in acetic acid were also in agreement with the formation of an acetoxonium ion.



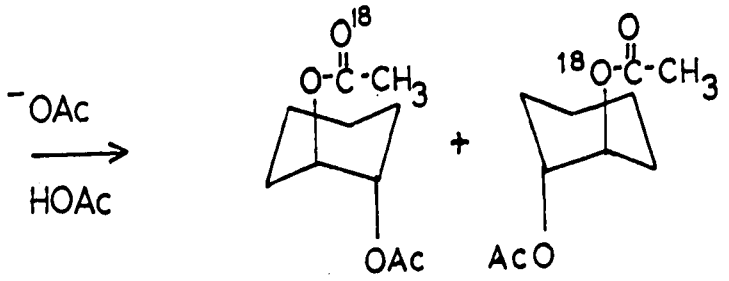

ØCOO⁻
H₂O
OH⁻
VIII
VII
IX

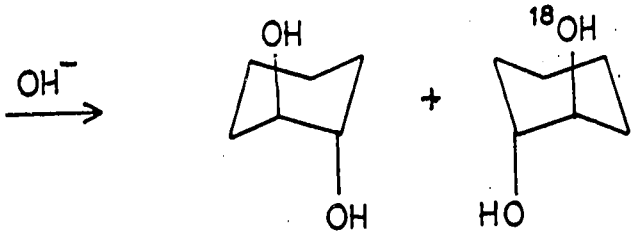
Experiments involving the use of oxygen-18 labelled esters have been used in confirming the existence of acyloxonium ions. Thus Wiberg and Saegebarth (9) reacted erythro-1-benzoxy-2-bromo-1,2-diphenylethylene-carbonyl-O-18 (VII) with silver benzoate under the conditions of the "dry" Prevost reaction. Hydrolysis of the product gave meso-hydrobenzoin (VIII) having one half of the ^{18}O of the bromobenzoate. When the reaction was carried out under the conditions of the "wet" Prevost reaction the product was threo-2-benzoxy-1,2-diphenylethanol, saponification of which gave dl-hydrobenzoin (IX) having the same ^{18}O content as the bromobenzoate. These results are in accord with a mechanism involving formation of an intermediate "benzoxonium" ion.

A more recent study has been reported by Gash and Yuen, who prepared 1-O-acetyl-2-O-p-toluenesulphonyl-trans-1,2-cyclohexanediol-carbonyl-^{18}O (X) and subjected this compound to acetolysis with acetate ion in acetic acid (10). A mixture of trans diacetates was obtained, ^{18}O analysis of which showed that acetolysis occurred with almost complete (99%) retention of ^{18}O. Thus there was no loss by way of acetyl exchange. Alkaline hydrolysis of the diacetate mixture gave trans-1,2-cyclohexanediol which was found to contain 46% of the original ^{18}O. The authors suggested that the acetoxonium ion intermediate was highly symmetrical and that backside attack occurred with equal ease at either the α or β carbon atoms; thus for a perfectly


O18
O-C-CH3
OTs
HOAc
CH3
C+
O
O18
α
β
CH3
C+
O18
O

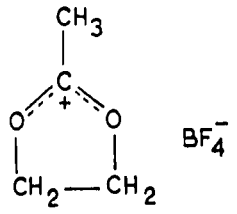
X


−OAc
HOAc
O18
O-C-CH3
OAc
+
O
18O-C-CH3
AcO


OH−
OH
OH
+
18OH
HO

symmetrical* acetoxonium ion intermediate a 50% incorporation of O-18 would be expected in the final product.

In 1955 Meerwein reported the synthesis of the ethylene acetoxonium ion (XI), 2-methyl-1,3-dioxolenium tetrafluoroborate (11).

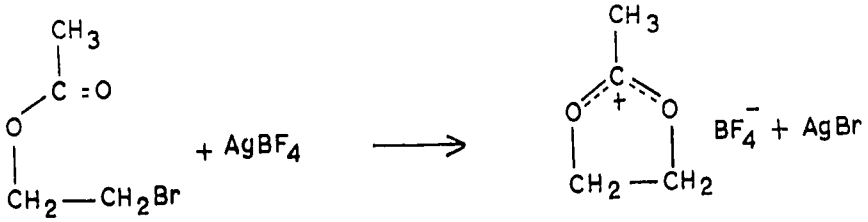


XI

* Several authors (1,10) have used the term "symmetrical" in reference to the cyclohexane acetoxonium ion and have pictured this ion in planar drawings. If, however, the ion is drawn as above it is obviously not symmetrical but is a mixture of d-and l-conformational isomers. The statement of Gash and Yuen that attack can occur with equal ease at the α or β carbons, based on planar drawings, suggests that equatorial ring opening is as favourable as axial ring opening. If the ion is considered as a dl-mixture, as depicted, then their result is explicable in terms of axial opening. Of course if the cyclohexane ring flips into the boat conformation then a symmetrical ion may be obtained.

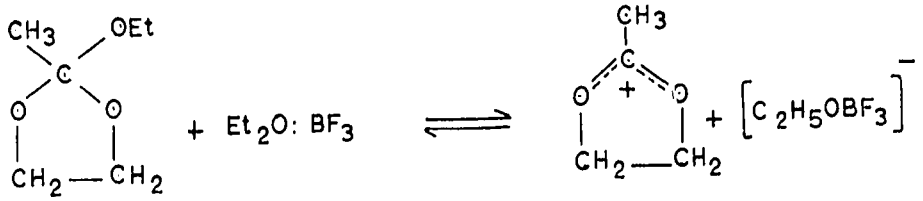
The preparation and properties of this and other acyloxonium ions were reported in a series of papers between 1955 and 1960. (11, 12, 13, 14). The preparative procedures employed may be classified into two types.

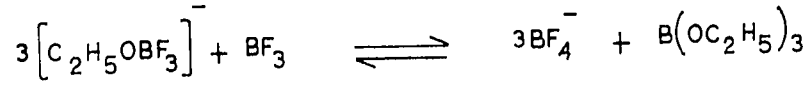
1) Treatment of 1,2-haloesters with silver salts.



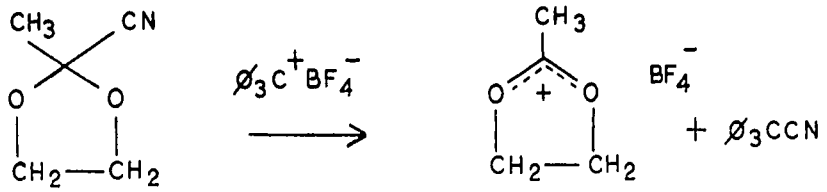
2) Removal of some group from a 1,3-dioxolane ring system.

a) Removal of an alkoxide group from an orthoester.

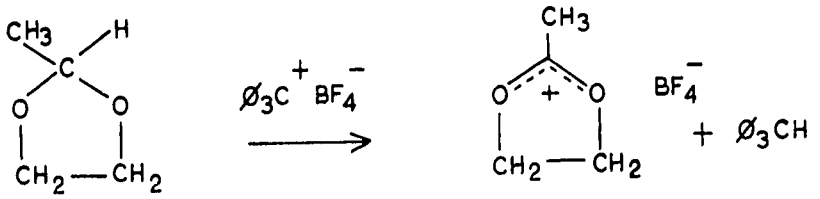




b) Removal of a cyanide group.

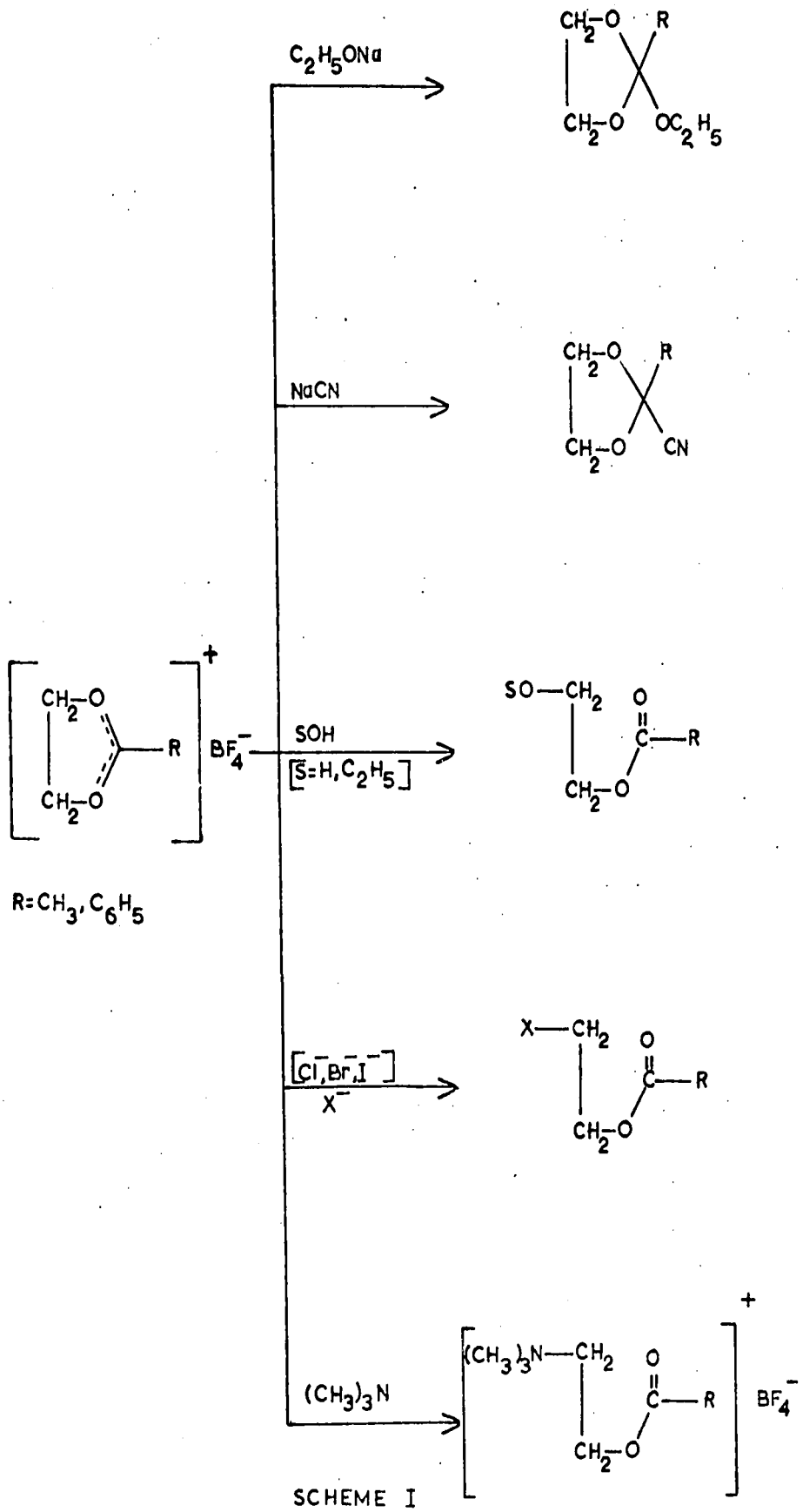


c) Abstraction of a hydride ion.



Some of the reactions of 2-methyl-1,3-dioxolenium tetrafluoroborate found by Meerwein are summarized in scheme I.

In 1963 Winstein and Anderson reported the preparation of the corresponding cis-cyclohexene acetoxonium salt, 2-methyl-cis-4,5-tetramethylene-1,3-dioxolenium tetrafluoroborate (XII) (15).

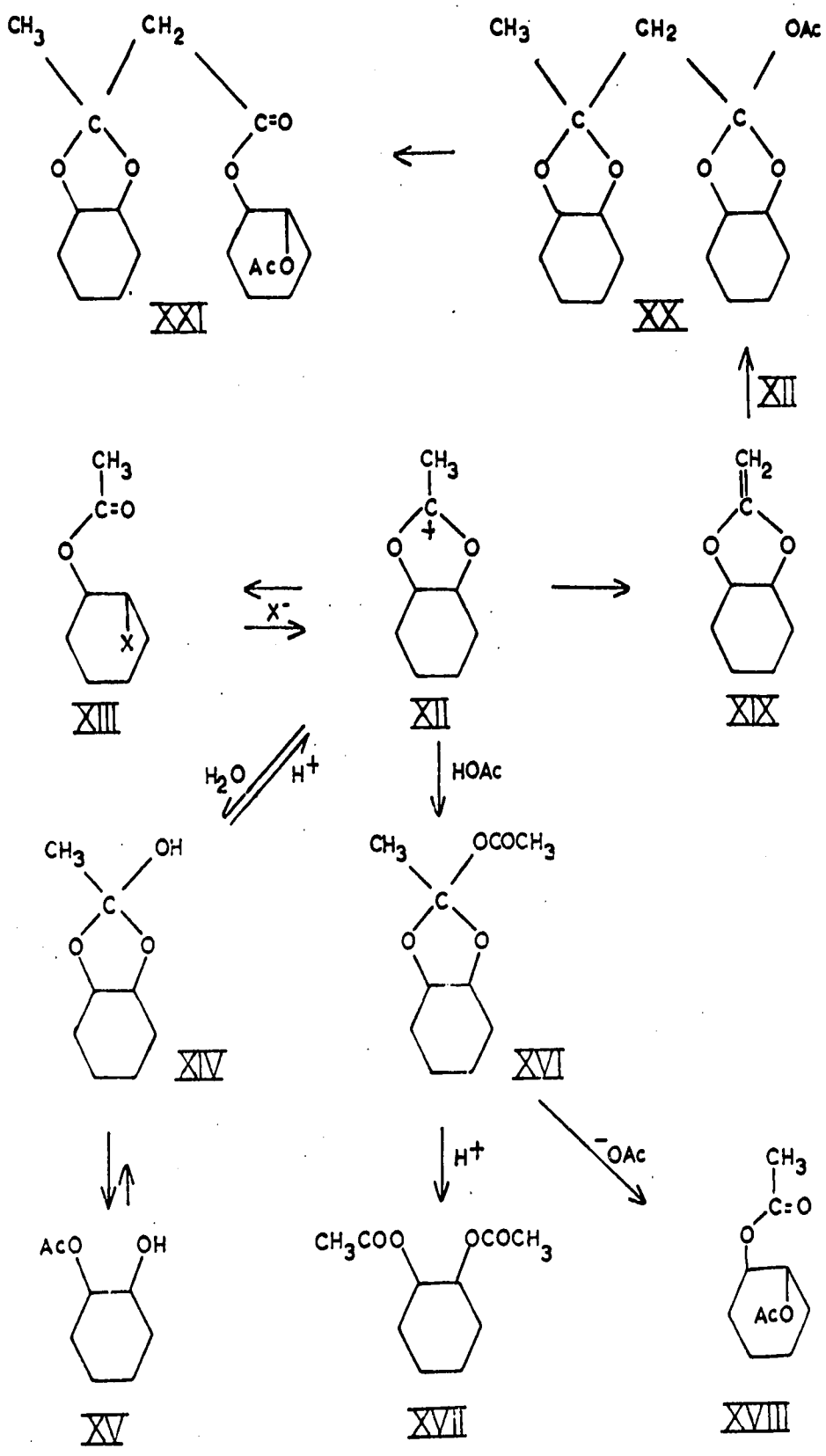


SCHEME I

The properties of this compound were fully consistent with the results obtained previously. In moist acetic acid 2-acetoxycyclohexanol (XV) was formed quantitatively and was shown to be >99.5% cis, no trans hydroxyester being detected at all. In anhydrous acetic acid containing potassium acetate a 50% yield of diacetate was found to be 94% trans and 6% cis. The remainder of the product (∿50%) was a dimeric product the cis-1,2-cyclohexanediol ketal of trans-2-aceto-acetoxycyclohexyl acetate (XXI), and it was suggested that this arose from the addition of the ion to the ketene acetal (XIX). Treatment of the salt in anhydrous acetic acid with p-toluenesulphonic acid gave up to 65% of the trans-2-acetoxycyclohexyl p-toluenesulphonate. Reaction with Cl^- and Br^- gave the corresponding trans haloacetates in yields of 80 to 90%.

Winstein and Anderson also reported an n.m.r. study of the reactions of XII. In anhydrous acetic acid the only proton signals corresponded to the dioxolenium ion. Addition of water caused immediate disappearance of the dioxolenium proton signals and the appearance of a spectrum corresponding to the cis-2-acetoxycyclohexanol. Treatment of the dioxolenium salt with potassium acetate produced a spectrum corresponding to formation of the orthodiacetate, dimeric orthodiacetate XX, the dimeric product XXI and the trans diacetate XVIII.

Relatively rapid exchange of the dioxolenium 2-methyl protons for deuterium was noticed when the dioxolenium salt was dissolved in deuterioacetic acid and presumably occurs via the ketene acetal XIX.

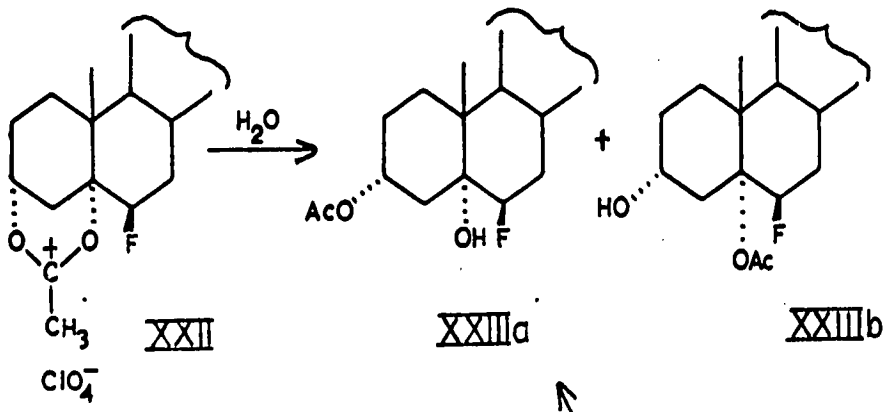

CH3
CH2
C=O
AcO
XXI
CH3
CH2
OAc
XX
XII
CH3
C=O
X
XIII
X-
CH3
XII
CH2
XIX
H2O
H+
HOAc
CH3
OH
XIV
CH3
OCOCH3
XVI
AcO
OH
XV
H+
-OAc
CH3COO
OCOCH3
XVII
CH3
C=O
AcO
XVIII

This fairly rapid loss of proton would account for the formation of the dimeric product XXI.

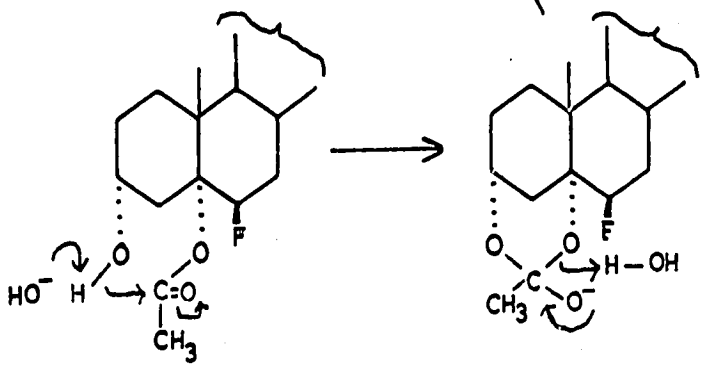
Another example of an acetoxonium ion has recently been reported (16,17). Treatment of 3β-acetoxy-6β-fluorocholestan-5α-ol with acetic anhydride:perchloric acid was found to give 3α:5α-acetonium-6β-fluorocholestane perchlorate (XXII). Hydrolysis of this salt using aqueous sodium bicarbonate in boiling dioxan gave a mixture of 3α-hydroxy-5α-acetate XXIIIb and 5α-hydroxy-3α-acetate XXIIIa. It was found that the relative amounts of these two hydroxyacetates was dependent on the reaction time. After two minutes the proportion of XXIIIa to XXIIIb was found to be 1:9, while after two hours the ratio was 6:4. When pure XXIIIb was treated under the same hydrolytic conditions it was converted virtually quantitatively into the other hydroxyacetate XXIIIa. The authors suggested that this acetate transfer occurred via an orthoester intermediate such as XXV.

In a later communication the same research group has reported preparation of more "acetonium" ions of this kind by treatment of the 5α-acetoxy-3α-hydroxy compound with sulphuric acid:acetic anhydride followed by addition of perchloric acid to give XXVI a,b,c. (18). Hydrolysis with sodium bicarbonate in aqueous acetone at 20° gave the corresponding 3α-hydroxy-5α-acetoxy compound only. (XXVII).

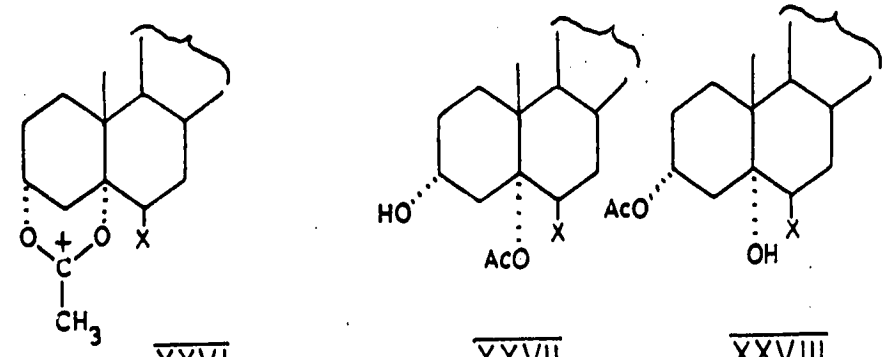
A surprising result was found on treatment of the 3α:5α- acetonium ion with anhydrous acetic acid and sodium acetate. In contrast to the previous work of Winstein where the acetoxonium ion gave under



XXII XXIIIa XXIIIb



XXIV XXV

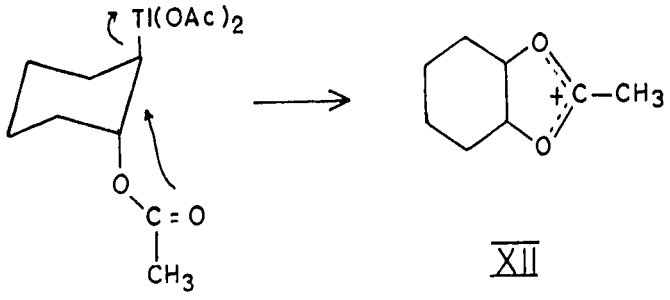


XXVI XXVII XXVIII

a) X = βCl, H
b) X = βOAc, H
c) X = O

these conditions a trans diacetate, the corresponding 3α-acetoxy-5α-hydroxy derivative was obtained. The authors suggest that this compound arises merely by isomerization of the 3α-hydroxy-5α-acetoxy derivative. However, this is a little difficult to visualize since it raises the question of where the 3α-hydroxy-5α-acetoxy compound came from in the first place.

Anderson and Winstein have studied the oxidation of cyclohexene with thallic acetate and found among the products the cis and trans diacetates of cyclohexane (50 to 55% of the total product) (19). In dry solvent the diacetate mixture was mainly trans (up to 88% trans) and in moist solvent the mixture was mainly cis (up to 81% cis). The authors consider this large reversal from trans to cis effected by water to be a criterion for the occurrence of the acetoxonium ion XII as an intermediate in the oxidation reaction.

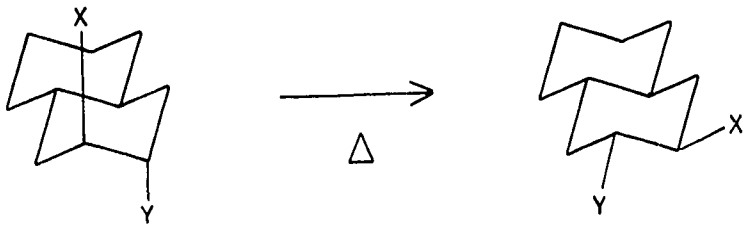


XII

Participation of a neighbouring acyl group has also been observed in many reactions of carbohydrates. A review of work in this field up to 1963 has been given by Anderson (1).

The hydrolysis of orthoesters and both the "wet" and "dry" Prevost reactions are considered to involve the formation of acyloxonium ions. Some previous work on these reactions will be considered later in this thesis.

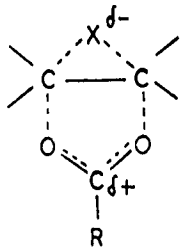
Another reaction which may be considered, formally, to involve the intermediacy of an acyloxonium ion is the diaxial to diequatorial rearrangement of halohydrin carboxylate esters. The diaxial to diequatorial rearrangement may be illustrated in the general case by the following equation.



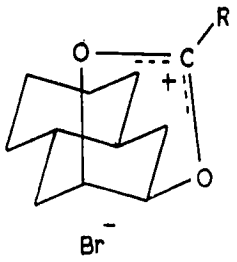
The rearrangement has been shown to proceed with dibromides, halohydrin carboxylic esters and bromohydrin sulphonate esters (20).

The rearrangement has been investigated for the case where X = Br, and Y = RCOO-, and it was concluded by the authors that the intermediate or transition state was of the type (XXIX). This transition state is polarized so that the halogen bears a negative

charge and the ester carries a positive charge (21).

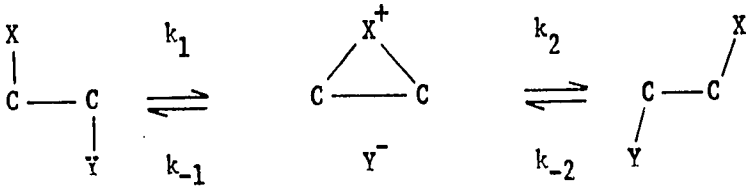


XXIX



XXX

The mechanism of the rearrangement, at least in polar solvents, has been formulated in terms of the following equation, in which XXXIa represents a diaxial compound and XXXIc represents the diequatorial isomer.

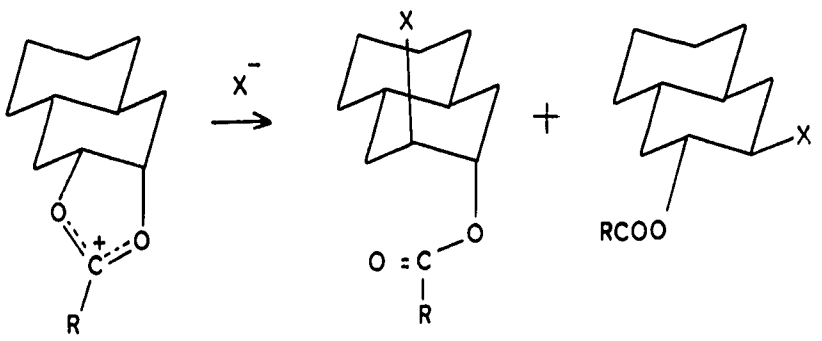


XXXIa XXXIb XXXIc

It has been suggested that in the case of a diaxial bromoanisate (X = Br, Y = p-$CH_3OC_6H_4COO$-) the transition state XXIX might be polarized to such an extent that an ion-pair would be formed, i.e. to give an acyloxonium bromide XXX. If this were the case, then the rate of the diaxial to diequatorial rearrangement would be dependent, to some extent, on the diaxial to diequatorial ring opening ratio of

the acyloxonium ion, i.e. on the ratio of k_{-1}/k_2. It was further suggested, from a consideration of the various factors involved in the ring opening reaction, that the diaxial opening rule, which at that time was restricted almost entirely to the opening of three-membered rings, might not apply since the "onium" ion, in this case was part of a five-membered ring (20).

The diaxial to diequatorial rearrangement has been under study for some time in this laboratory and in connection with these studies it was considered of interest to know the diaxial to diequatorial ring opening ratio of acyloxonium ions such as XXX. Previous work ' on the ring opening of acyloxonium ions fused to a six-membered ring with nucleophiles such as halide or carboxylate anion was confined, at the time the work presented in this thesis was initiated, to those cases where the ring was cyclohexane. With this ring the products are conformationally mobile and although it had been shown that the products were trans, no information could be derived concerning the ratio of diaxial to diequatorial opening. It was therefore decided to undertake a study of the ring opening reactions of acyloxonium ions fused to a rigid six-membered ring with halide ion and to determine the ratio of diaxial to diequatorial products.



The results of this study together with a brief investigation of the ring opening of some epoxides fused to rigid six-membered rings are reported in Part II of this thesis.

Besides the nucleophilic ring opening reaction leading to trans products, acyloxonium ions can open by an alternate route, namely by hydrolytic cleavage, to give cis-hydroxyesters. The results of a study on the stereochemistry of the hydrolysis of acyloxonium salts, and of some related reactions in which acyloxonium ions are thought to occur as intermediates, are given in Part III of this thesis.

PART II

THE BIMOLECULAR RING OPENING OF ACYLOXONIUM IONS AND EPOXIDES

A. The Diaxial to Diequatorial Ring Opening Ratio of Acyloxonium Ions.

1. The preparation of acyloxonium hexafluoroantimonates.

The most suitable system on which to carry out a study of the conformational preferences of a reaction seemed to be that of a steroid, to be more specific, on derivatives of cholest-2-ene. The molecule is rigid and also a lot of work has been carried out on the stereochemistry of derivatives such as halohydrins and haloesters etc., which would render the task of assigning structures to the products far easier than with some less extensively studied system. However the cholestane system does have one disadvantage in that approach of an attacking species from above to the C-2 position, i.e. from the β side, would be interfered with by the C-19 methyl group. Consequently acyloxonium salts were also prepared from suitably substituted trans-decalin derivatives. In this system, again one has a rigid ring system, but there are no bulky alkyl substituents present to interfere with an attacking species.

In choosing the type of acyloxonium ion to be used in this study the work of Winstein was considered. Winstein had found that the ace-

toxonium ion of cyclohexane was quite readily transformed into a ketene acetal, by proton loss, which then could undergo various other reactions (see Introduction). In order to avoid this type of reaction phenyl substituted acyloxonium salts were prepared. The phenyl group would be expected to enhance the stability of the salts, and would also give acyloxonium ions which would correspond quite closely to the intermediate proposed in the diaxial to diequatorial rearrangement of diaxial halobenzoates. At the time this work was initiated acyloxonium salts of this type were not known.

Several methods of preparing the acyloxonium salts were available (see Introduction). The most useful method for the purposes of this study seemed to be that by treatment of a diaxial haloester with a suitable silver salt. This has the advantage that the product from diaxial opening with halide, using the same halide ion, would yield starting material, thus reducing the amount of synthetic work. The steroidal acyloxonium salts (XXXV, XXXVIIIa and b) were prepared from the corresponding diaxial bromoesters. Apart from 3α-bromo-5α-cholestan-2β-yl benzoate, the bromoesters were all known compounds. In each case the bromoesters were treated with an equivalent amount of silver hexafluoroantimonate in nitromethane overnight at 50°. After filtration, to remove precipitated silver bromide, and evaporation of the nitromethane, the acyloxonium salts were easily crystallized from methylene chloride by addition of ether.

The trans-decalin haloesters were not known compounds but were readily synthesized from Δ^2-trans-octalin by conventional methods.[1.] Their structures followed from the mode of synthesis and from spectral data. The decalin bromoesters were more soluble in nitromethane than the steroidal compounds. Addition of silver hexafluoroantimonate resulted in an immediate reaction with the precipitation of silver bromide. The acyloxonium salts XXXIIa and XXXIIb were isolated in the same manner as the steroidal acyloxonium salts.

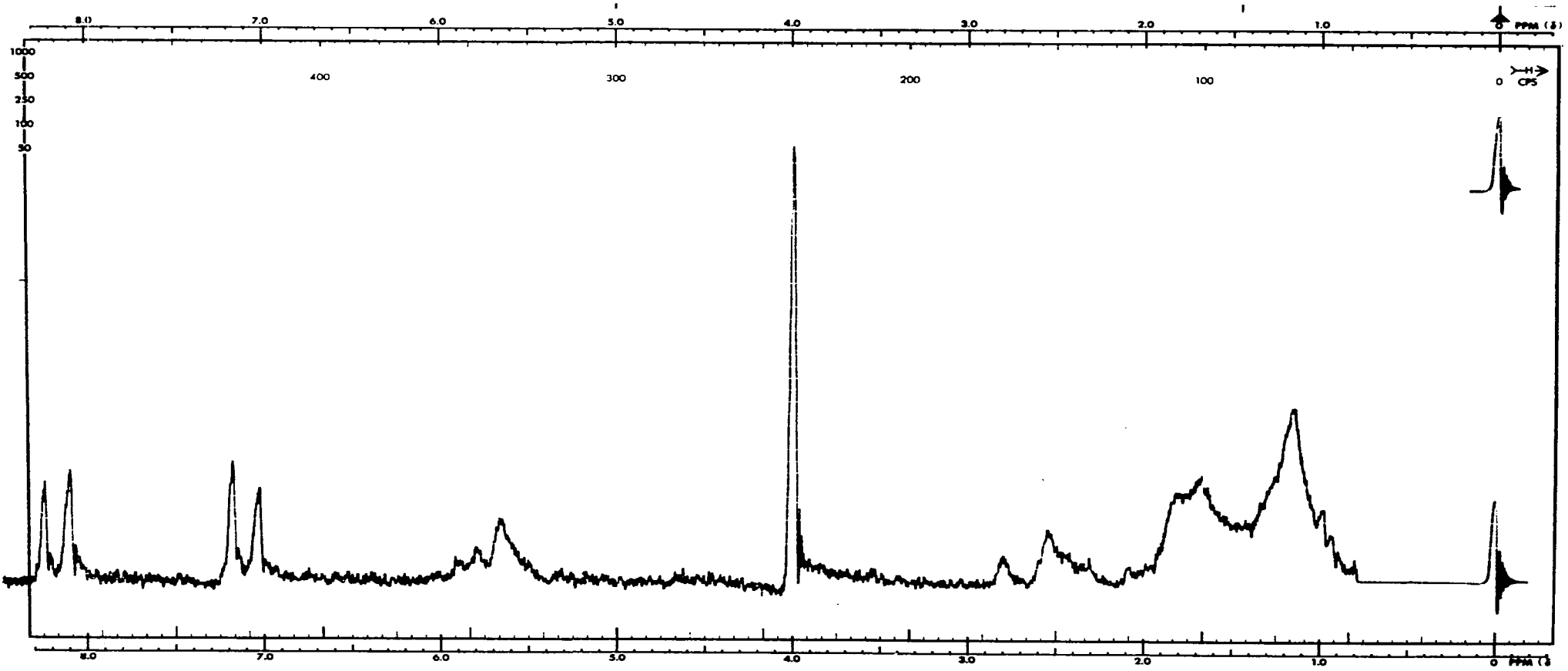
All of the acyloxonium salts were readily crystallized from methylene chloride by addition of ether to give white crystalline salts with satisfactory analyses.[2.] Since it has been reported (1) that cyclohexane acetoxonium tetrafluoroborate was extremely hygroscopic, all procedures involving the preparation and handling of the acyloxonium salts were carried out inside a dry box. All the salts were quite stable and some samples, stored under dry conditions, were unchanged after two years. These acyloxonium salts were so stable

*
1. In the naming of the derivatives of trans-decalin the nomenclature of Henbest, Smith and Thomas has been used. (22).

*
2. Except for 5α-cholestan-2β:3β-benzoyloxonium hexafluoroantimonate XXXVIIIb which, despite several attempts, did not give a good analysis. Its structure seems fairly certain however, based upon its spectral properties, hydrolysis and upon its reaction with bromide ion.

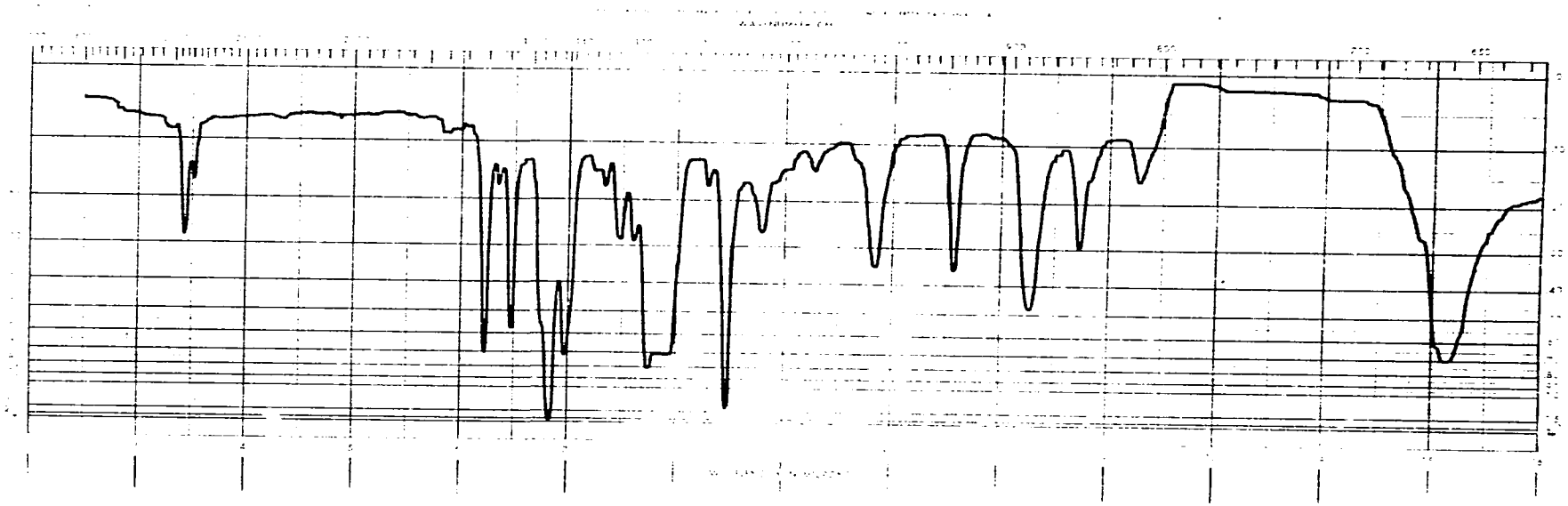
that one of them, the decalin benzoyloxonium salt XXXIIb survived exposure to air (accidently!) overnight without any ill effects.

The structures of the salts were based upon the following evidence; (a) acid hydrolysis yielded the cis-hydroxyesters which upon saponification gave the corresponding cis-diols; (b) their infrared spectra showed no carbonyl absorption but did show a strong band at $\sim$ 660 cm^{-1} indicating the presence of the SbF_6^- ion (23); (c) their n.m.r. spectra. In the spectra of the anisoxonium salts the quartets due to the phenyl groups, which were treated as simple AB systems, were shifted downfield by $\sim$ 0.25 p.p.m. compared to the corresponding bromoester absorption. Similar shifts of the phenyl hydrogen absorption were noted in the cases of the benzoyloxonium salts. The hydrogens situated at the ring junction, i.e. at C-2 and C-3, also showed quite large shifts. In the n.m.r. spectra of the diaxial bromoesters the protons on the carbons bearing bromine appear at $\sim$ 4.5 p.p.m. and the protons on the carbons bearing the ester group appear at $\sim$ 5.4 p.p.m. Both protons in the starting materials are equatorial and show up as relatively narrow bands. In the formation of the acyloxonium ring, inversion occurs at the carbon bearing bromine with the result that the hydrogen at that position becomes axial. As will be mentioned later in this thesis, axial protons on cyclohexane rings couple strongly with neighbouring axial protons and less strongly with neighbouring equatorial protons, and in many cases appear as broad bands. An equatorial hydrogen, on the other hand, couples less strongly with neighbouring protons and



N.m.r. spectrum of 9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate (CD_2Cl_2)

Fig. 1



Infrared spectrum of 9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate (CH_2Cl_2)

Fig. 2

appears as a narrow band. Both types of bands have been found to have characteristic widths at half band height (24). The axial and equatorial protons at the ring junction of the acyloxonium ions appeared as complex multiplets at around 5.79 p.p.m. These multiplets seem to have some structure in that they could be regarded as a superimposition of two bands, a broad band due to the axial proton and a narrow band due to the equatorial proton (Fig. 1).

2. The reaction of acyloxonium salts with halide ion.

The preparation of several acyloxonium salts having been achieved and their structures established, the study of the reactions of these salts with halide ion was undertaken. The reactions were carried out in the following manner. A known amount of the acyloxonium salt was treated with a 10 molar excess of the particular tetraethylammonium halide in methylene chloride at room temperature for periods of 30 minutes to 1 hour. The crude products were analysed by one of a number of methods, mentioned below, and the results are listed in Table I.

With the decalin anisoxonium hexafluoroantimonate the products were most easily analysed by quantitative thin layer chromatography. In this method the intensity of the spots produced by the charring of mixtures of the diaxial and diequatorial halo-anisates were compared with the intensity of the spots found with the product. Although an accurate evaluation of the quantities of each product could not

TABLE I

The Reaction of Acyloxonium Salts with Halide Ion.

Acyloxonium Salt	Halide	Solvent	Haloester* Diaxial	Haloester* Diequatorial	Ratio of diaxial to diequatorial haloester	Method of Analysis	Percentage yield of total haloester
5α-Cholestan-2β: 3β-p-anisoxonium hexafluoroantimonate (XXXVIIIa).	Br^-	CH_2Cl_2	98	2	49:1	1,2	83
5α-Cholestan-2α: 3α-p-anisoxonium hexafluoroantimonate (XXXV).	Br^-	CH_2Cl_2	32	68	0.47:1	1,2	94
"	Br^-	CH_3CN	32	68	0.47:1	1,2	78
"	Br^-	CH_3NO_2	40	60	0.66:1	1,2	90
5α-Cholestan-2β: 3β-benzoyloxonium hexafluoroantimonate (XXXVIIIb).	Br^-	CH_2Cl_2	72	-	-	3	-
9β:10α-Decalin-2β: 3β-p-anisoxonium hexafluoroantimonate (XXXIIa).	Br^-	CH_2Cl_2	95	5	19:1	4	99
"	Cl^-	CH_2Cl_2	94	6	15.7:1	4	92

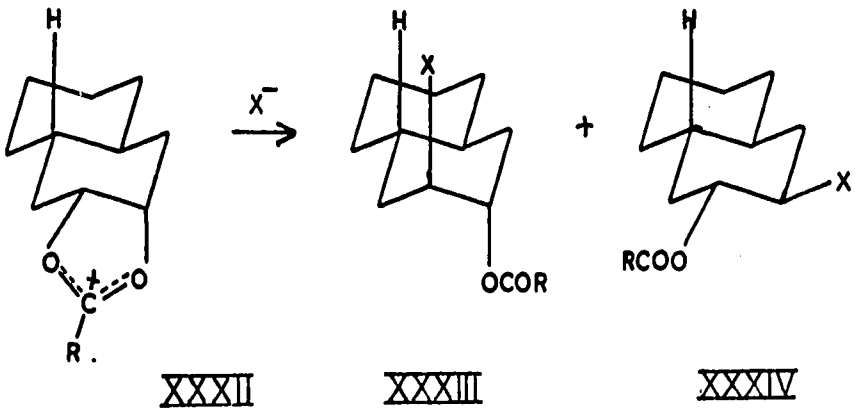
* Percentage of total haloester.

1. - as determined from infrared spectra; 2, - as determined from optical rotation measurements; 3, - isolated yield; 4, - as determined by quantitative thin layer chromatography.

be obtained, certain limits could be put on the amount of the diequatorial isomers and the results are probably accurate to ± 2%. This method of analysis did not prove to be suitable in the case of the steroid bromoanisates, since it was found to be quite difficult to separate the diaxial and diequatorial compounds by thin layer chromatography.

One method of analysis that was used was to determine the optical rotation of the product mixture and then, using the known rotations of the pure diaxial and diequatorial bromoanisates, to calculate the composition of the mixture. Thus the product from treatment of 5α-cholestan-2β:3β-p-anisoxonium hexafluoroantimonate (XXXVIIIa) with tetraethylammonium bromide in methylene chloride had a rotation of + 34°. For 3α-bromo-5α-cholestan-2β-yl p-anisate (XXXIXa, X = Br), the rotation was found to be + 35.5°, and for the diequatorial compound, 2α-bromo-5α-cholestan-3β-yl p-anisate (XLa, X = Br), the rotation has been reported as - 44° (25). Thus the rotation of the product mixture corresponds to ∿ 98% diaxial and ∿ 2% diequatorial bromoanisate. Similarly the rotation of the product obtained from the reaction of the 5α-cholestan-2α:3α-p-anisoxonium salt XXXV with bromide ion was found to be 0°. Here the rotation of the product mixture corresponds to a mixture of 30% diaxial and 70% diequatorial bromoanisates.

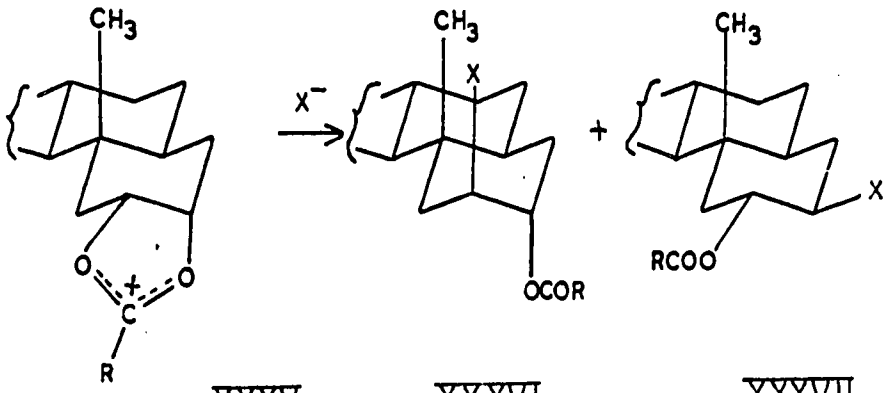
An alternative method of analysis for the steroid bromoanisate mixtures was by infrared spectroscopy. Above 800 cm^{-1} the spectra



XXXII XXXIII XXXIV

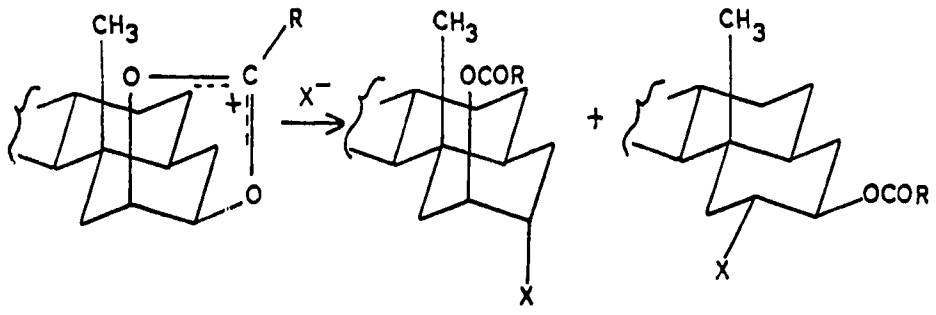
a)R=$CH_3OC_6H_4$—

b)R=C_6H_5—



XXXV XXXVI XXXVII

R=$CH_3OC_6H_4$—



XXXVIII XXXIX XL

a)R=$CH_3OC_6H_4$—

b)R=C_6H_5—

of the diaxial and diequatorial bromoanisates, in both cases, were very similar. However, in the region 800 cm^{-1} to 600 cm^{-1} significant differences were observed. The diaxial bromoester XXXVI (X = Br) had a band at 695 cm^{-1} (m) while the diequatorial bromoanisate XXXVII (X = Br) showed absorption at 695 cm^{-1} (w) and 714 cm^{-1} (m). By comparison of the peak heights of these bands in standard mixtures of XXXVI (X = Br) and XXXVII (X = Br), with the same bands in the product obtained by treatment of XXXV with bromide ion, an estimate of the ratio of diaxial to diequatorial bromoanisates in the product was obtained. A similar procedure was used to analyse the product from treatment of XXXVIIIa with bromide ion. In this case the diequatorial bromoanisate XLa (X = Br) had a band at 716 cm^{-1}, which did not appear in the spectrum of the diaxial ester XXXIXa (X = Br), and which was used for comparison purposes. The figures obtained by this method were, within experimental error, the same as those found from the rotation measurements.

3. The reaction of acyloxonium salts with carboxylate anion

Treatment of an olefin with a mixture of iodine and the silver salt of a carboxylic acid, in a suitable solvent such as benzene, under anhydrous conditions, yields a trans-diol diester. This reaction is known as the Prevost reaction and has been used to prepare trans-1,2-glycols (26). The generally accepted mechanism of this reaction is discussed on page 84; the trans-diester is thought to arise from the

attack of a carboxylate anion upon an acyloxonium ion. Winstein found that solvolysis of trans-2-bromocyclohexyl acetate and trans-1,2-dibromocyclohexane in acetic acid gave the corresponding trans-diacetates and also suggested that these diesters arose from attack by a carboxylate anion upon an acyloxonium ion. These and some other examples of this type of reaction have been mentioned earlier (see Introduction). As was noted before, none of these reactions were carried out upon a conformationally rigid system and thus no estimate of the ratio of diaxial to diequatorial ring opening was possible.

More recently, Meakins and colleagues have reported on a study of the Prevost reaction with cholest-2-ene, using silver benzoate in benzene (27). At room temperature a low yield (30%) of a mixture of trans-dibenzoates was obtained, consisting of 2β:3α-dibenzoyloxy-and 2α:3β-dibenzoyloxy-5α-cholestane in the ratio of 9:1. When the reaction was carried out under reflux (∿80°) the ratio of diaxial to diequatorial dibenzoates was found to be 2:1. These results suggested that the diaxial to diequatorial ring opening ratio of acyloxonium ions with carboxylate might differ somewhat from that found with halide ion, in that the ring opening seemed to be less stereospecific than was found with halide ion. However, since the above reaction was carried out under conditions quite different from those used in the studies of the ring opening of acyloxonium ions with halide, the results were not strictly comparable. It was therefore decided to undertake a study of the reaction of some carboxylic acid salts with

acyloxonium ions in methylene chloride, i.e. under conditions more similar to those used in the halide ring opening reactions.

In order to have a system comparable to that of Meakins' 9β:10α-decalin-2β:3β-benzoyloxonium hexafluoroantimonate XXXIIb was prepared and its reaction with benzoate anion studied. It was first attempted to carry out this reaction by treating a solution of the benzoyloxonium salt in methylene chloride with lithium benzoate. However the lithium salt did not appear to be very soluble in methylene chloride and the only product isolated was the hydroxybenzoate from hydrolysis of the salt during work up. A similar result was obtained when dry absolute ethanol was used as a solvent. It was thought that a substituted ammonium salt of the carboxylic acid might prove to be more soluble in methylene chloride. However tetraethylammonium benzoate is quite hygroscopic and has been prepared only as a hydrate (28). This hydrate would be of little use for the purposes of the reaction under consideration here since hydrolysis products would be obtained. A solution containing equimolar quantities of N,N-diisopropylethylamine and benzoic acid in methylene chloride was therefore prepared. This solution was assumed to contain the corresponding ammonium salt. Treatment of the decalin benzoyloxonium salt with a solution of the substituted ammonium benzoate for 24 hours at room temperature gave a 72% yield of trans-dibenzoates. The diaxial and diequatorial dibenzoates were readily separable by thin layer chromatography and the product mixture was found to consist of 87% diaxial(XXXIIIb, X = C_6H_5COO-) and 13% diequa-

torial(XXXIVb, X = C_6H_5COO-) dibenzoates. Both the diaxial and diequatorial dibenzoates were identified by a comparison of their properties with those of the dibenzoates prepared by esterification of the corresponding diaxial and diequatorial diols.

The addition of a carboxylate anion containing an electron withdrawing group, such as trifluoroacetate, to an acyloxonium ion was then considered. Lithium trifluoroacetate was not very soluble in methylene chloride and it was anticipated that the tetra-alkylammonium salts would be difficult to prepare in an anhydrous state. Consequently a similar procedure to that above was used, i.e. a solution containing equimolar quantities of N,N-diisopropylethylamine and trifluoroacetic acid was prepared and was reacted with the decalin anisoxonium salt. A 64% yield of the diaxial diester, 9β:10α-decalin-2β-yl trifluoroacetate-3α-yl p-anisate (XXXIIIa, X = CF_3COO-) was obtained. This compound had a satisfactory analysis, infrared and n.m.r. spectra. A slight trace of a second material was visible upon thin layer chromatography of the crude product, and was thought to be the diequatorial diester. However, attempts to isolate this second compound failed. Both of these products decomposed somewhat upon thin layer chromatography, leaving smears from the origin. The major product from this decomposition had the same R_f value as 3β-hydroxy-9β:10α-decalin-2β-yl p-anisate (LXXXIVa) and it would appear that the diester was ionizing to give the anisoxonium ion which then hydrolysed. Thus no estimate of the amount of diequatorial opening was possible, al-

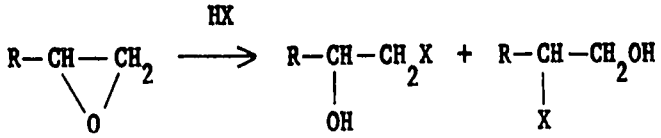
though to judge from thin layer chromatography evidence, the amount was small.

B. The Ring Opening Reactions of Epoxides

1. Introduction.

a. The mechanism of ring opening

Most of the reactions of epoxides in solution involve the opening of the ring and addition of a molecule of reagent . Cleavage can occur under acidic, neutral and basic conditions. If the epoxide is unsymmetrical then two products are possible.

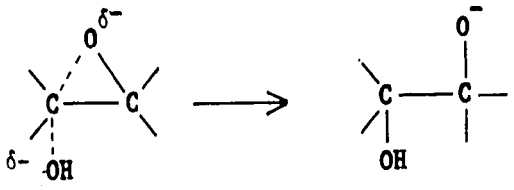


Addition to the least substituted carbon has been designated "normal" while addition to the most substituted carbon has been designated "abnormal" (29).

The orientation of the ring opening is influenced by both steric and electronic effects. Under basic or neutral conditions, attack usually occurs at the least substituted carbon to give the normal product. However substitution of the epoxide with polar groups or with groups capable of interacting by conjugation may enhance the formation of the abnormal product. With acid-catalysed cleavage, addition still tends to give the normal product, but substitution of

the epoxide with polar groups and especially with groups capable of stabilizing an incipient positive charge can lead to the abnormal product being produced. In many cases it is apparent that there is a balance between the electronic and steric effects controlling the ratio of normal to abnormal addition. A discussion of the various factors involved in the orientation of epoxide opening may be found in the review article by Parker and Isaacs (29).

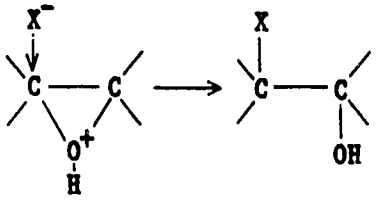
Base-catalysed cleavage is generally considered to occur by an S_N2 type of mechanism. The reaction between benzylamine and various phenyl substituted styrene oxides has been shown to be bimolecular (30). Also the reactions of both ethylene and propylene epoxides with sodium hydroxide have been found to have negative volumes of activation, indicative of an S_N2 reaction (30).



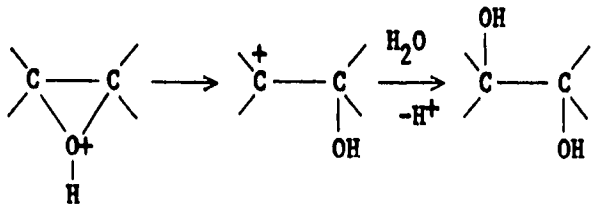
In acid-catalysed cleavage, the conjugate acid of the epoxide is involved in the reaction. Thus the ring opening of ethylene oxide with hydrogen chloride and with hydrogen bromide have been found to exhibit a third order rate law.

$$\text{rate} = k_3 \text{ (epoxide) } (H^+) \ (X^-).$$

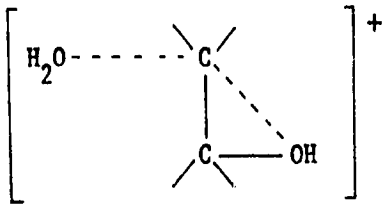
This result is consistent with attack of the protonated epoxide by halide ion (31).



A study of the hydration of several epoxides with aqueous perchloric acid has been carried out by Long and colleagues. In each case it was found that log k was proportional to H_0, the Hammett acidity function. This result was interpreted as indicating that the ring opening was unimolecular and that the hydration occurred via an A1 mechanism (29).



This conclusion was disputed by Parker and Isaacs on several accounts. An A1 mechanism did not explain the stereochemical results observed upon ring opening, namely that inversion is almost always observed. If the reaction occurred through an A1 mechanism then a mixture of products would have been expected. It was suggested that the reaction probably occurred through an A2 type of mechanism in which bond breaking was more important than bond making in the rate determining step, this mechanism being termed a "borderline S_N2".



This idea was supported by Whalley, who found negative volumes of activation for the acid-catalysed hydrolyses of ethylene, propylene and isobutylene epoxides, consistent with an A2 mechanism (32), and seems to be generally accepted at the present time (33).

b. The stereochemistry of ring opening.

A bimolecular mechanism is also indicated by the stereochemical results found with the ring opening of epoxides. Treatment of trans-2,3-epoxybutane with ammonia yields only erythro-3-amino-2-butanol. Similarly, the acid catalysed hydration of cyclohexene oxide gives only trans-cyclohexane-1,2-diol none of the cis isomer being detected. Both of these reactions result in inversion of the carbon attacked and this appears to be a general rule for all ring opening reactions of epoxides whether under basic, neutral or acidic conditions.

A few epoxides open up with retention of configuration under acidic conditions. These cases involve epoxides substituted with a phenyl or acyl group and it has been suggested that the retention observed is a result of double inversion, the epoxide first being opened up by neighbouring group participation, followed by attack

of reagent and displacement of the neighbouring group. There are also a few cases of epoxides which give rise to products derived from both retention and inversion of configuration, these are thought to arise from both the S_N2 reaction and by double inversion occurring together (29).

c. The diaxial opening rule.

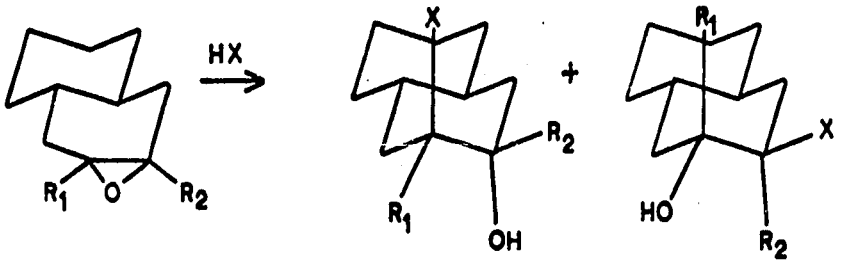
When an epoxide is fused to a six membered ring, ring opening with inversion leads to trans products exclusively. The generalization known as the diaxial opening rule was proposed by Furst and Plattner and was based upon the observed preference of steroid epoxides to react with both acidic and basic reagents to give not only trans but also diaxial products (34). Thus treatment of 5α-cholestan-2α3α and 2β:3β-epoxides with either hydrogen chloride or hydrogen bromide yields the corresponding diaxial halohydrins as the only isolated products (35). An extensive list of the reactions of steroid epoxides which give diaxial products has been compiled by Hanack (36).

The diaxial opening rule also appears to apply to electrophilic addition to carbon-carbon double bonds. Bromination of 5α-cholest-2-ene has been shown to give 88% of the diaxial and only 12% of the diequatorial dibromides. The reaction is presumed to occur via a three-membered bromonium ring species which then opens mainly diaxially when attacked by bromide ion. Addition of chlorine and of hypobromous and hypochlorous acids also occurs with predominant formation of the

diaxial products (36). It has been shown that aziridines such as 2β:3β-imino-5α-cholestane open to give diaxial products also (37). Very recently it has been shown that the diaxial opening rule is also applicable to the ring opening of episulphonium ions. Treatment of 5α-cholestan-2α:3α-phenyl episulphonium hexafluoroantimonate with chloride ion yields the diaxial chlorosulphide (38).

Henbest and co-workers have studied the acid-catalysed hydration of trans-decalin-2:3-epoxide XLIa and found a 90% yield of the diaxial diol XLIIa, no cis-diol or trans-diequatorial diol XLIIIa being detected. Hydration of the dimethyl substituted epoxide XLIb gave a mixture of the trans diaxial diol XLIIb and the trans diequatorial diol XLIIIb in 71% and 23% yields respectively, and again no cis-diol was found (22).

A few examples of epoxides which open to give diequatorial products are known. For example the 2β:3β-epoxide of lanostane (and of lanost-8-ene) gives the equatorial 3β-alcohol on reduction with lithium aluminum hydride. Treatment with hydrogen bromide yields the diequatorial bromohydrin. These reactions have been rationalized by assuming that ring A is in a half boat conformation. Diaxial ring opening then leads to a diaxial boat which by ring inversion then gives the observed diequatorial products (36).

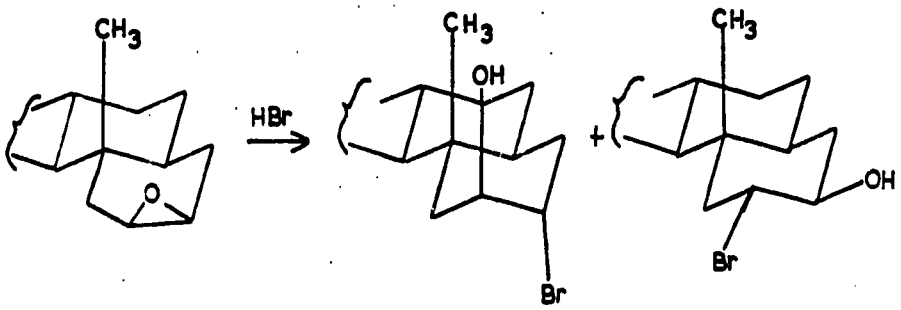


XLI XLII XLIII

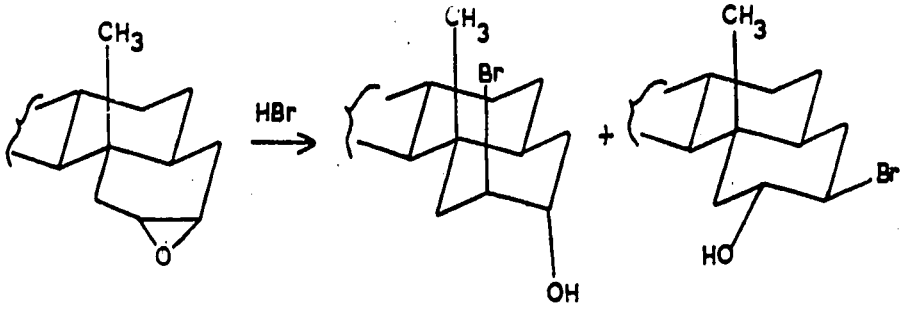
a) $R_1 = R_2 = H$, X=OH

b) $R_1 = R_2 = CH_3$, X=OH

c) $R_1 = R_2 = H$, X=Br



XLIV XLV XLVI



XLVII XLVIII XLIX

2. The reaction of epoxides with hydrobromic acid.

A brief examination of the literature on the diaxial opening of epoxides shows that apart from one or two cases (cf. Henbest) very little quantitative work has been carried out on this subject. Although many cases have been reported of epoxide opening where the formation of the diaxial compound is the major product, few attempts have been made to determine the amount, if any, of the diequatorial products. For this reason, and also to have a system with which to compare the ring opening ratios found with the acyloxonium ions, it was decided to investigate the products of the ring opening of suitable epoxides with hydrogen bromide, with the purpose of determining the amount of diequatorial products produced. The following reactions were carried out by treating a solution of the particular epoxide in methylene chloride with aqueous 48% hydrobromic acid. One problem with work of this nature is the detection of very small amounts of secondary products. Thin layer chromatography appeared to offer a possible solution. It was anticipated that the diequatorial bromohydrins would be eluted at different rates from the diaxial bromohydrins and that an estimate of the amount of diequatorial product might be obtained by quantitative thin layer chromatography.

Unfortunately this did not prove to be the case with the bromohydrins derived from 2,3-epoxy-9β:10α-decalin XLIc. Both the diaxial XLIIc and diequatorial XLIIIc bromohydrins were found to run at almost

the same rate upon silica gel. The product from treatment of the epoxide with hydrobromic acid appeared as a single spot on silica gel plates with the same R_f value as both of the bromohydrins. The only indication of the presence of the diequatorial bromohydrin was found by developing the thin layer plates with iodine vapour. The diequatorial bromohydrin showed up by this method, but the diaxial isomer did not. With the product from the hydrobromination of the epoxide a slight trace of material which absorbed iodine, and had the same R_f value as the diequatorial bromohydrin, was observed. Thin layer chromatography using alumina was more successful, separation of the two bromohydrins being achieved, with the diequatorial compound moving slower than the diaxial. However, due to the poor development of the spots, upon charring, no estimate of the amount of the diequatorial bromohydrin could be made, although it was certainly quite small.

Thin layer chromatography proved to be more useful with products derived from 5α-cholestan-2α:3α- and 2β:3β-epoxides, XLVII and XLIV. In both cases the diaxial and diequatorial bromohydrins could be separated on silica gel. In the products obtained from treatment of each epoxide with hydrobromic acid, a small amount of material corresponding in R_f value to the diequatorial bromohydrins was detected in each case. For the 2β:3β-epoxide XLIV the amount of diequatorial bromohydrin was estimated at $\sim$ 3% and with the 2α:3α-epoxide the amount was estimated at $\sim$ 5% of the total product. An unexpected

result found with the bromohydrins derived from the α-epoxide was that the equatorial isomer ran faster on chromatography than the axial isomer.

C. Discussion of Results

1. Epoxide opening.

It has been shown, with both of the epoxides derivable from cholest-2-ene and with trans-decalin-2:3 epoxide, that ring opening with hydrogen bromide is not exclusively diaxial but that small amounts of diequatorial bromohydrins are formed.

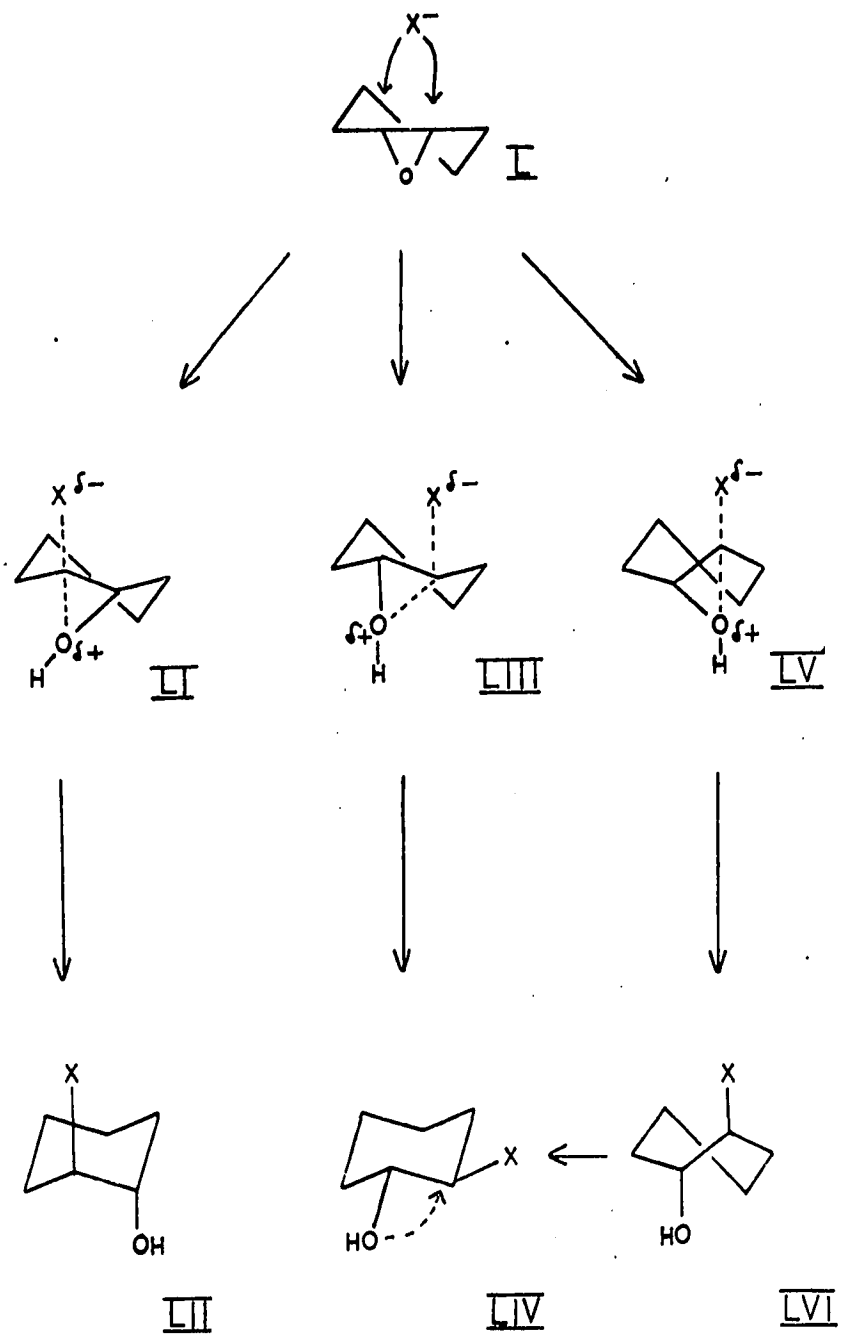
The preference of epoxides to open to give diaxial products has been rationalized in the following manner (39). As was mentioned above, the ring opening reactions of epoxides are generally considered to occur by a S_N2 type of mechanism, and result in the inversion of the carbon which is attacked. For such a mechanism a linear, co-planar arrangement of incoming and leaving groups is desirable. The conformation of the cyclohexane ring of the epoxides may be considered to be similar to that of cyclohexene, i.e. L (Ref. 36, p. 149). If the chair conformation of the cyclohexane ring is partly re-established in the transition state leading to diaxial opening then the partial bonds (dotted lines) can be nearly linear and co-planar, allowing more efficient overlap of orbitals (LI) and fulfilling the requirements of the S_N2 mechanism.

This is not true for the transition state leading to diequatorial opening and resulting in the formation of the diequatorial chair product directly (LIII). In this case the partial bonds are not linear or

co-planar. If one considers that as the reaction proceeds the transition state begins to assume the form of the products, i.e. that the partial bonds have some equatorial character, then it is evident from LIII that not only is the transition state non-linear and non-planar but that considerable lengthening and distortion of the angles of the partial bonds must occur. The degree of distortion more readily can be visualized if one considers the transition state required for the reverse reaction, i.e. formation of an epoxide from a diequatorial chair bromohydrin (LIV). As indicated by the arrow in LIV a large amount of twisting and bond lengthening must occur before a suitable alignment of reactive centres is achieved.

A linear co-planar transition state can be achieved however, if the cyclohexane ring inverts to form a boat conformation. In this case the transition state (LV) leads to the formation of a diaxially substituted twist boat (LVI) which can then give the diequatorial chair product by ring inversion.

By this route the difference between the free energies of activation for the formation of the diaxial and diequatorial isomers is controlled by the free energy difference between a partly formed diaxial chair and a partly formed diaxial twist boat. It seems probable that all of the diequatorial product observed in the ring opening reactions of the epoxides with hydrogen bromide arises by way of the boat conformation since the route via a chair conformation seems very unlikely.


X⁻
O
I
X δ−
O δ+
H
II
III
IV
V
OH
HO
VI

Presumably the reverse reaction, formation of an epoxide from an equatorial halohydrin, would also occur via a boat type of transition state.

In the case of the cholestan-2α:3α-epoxide the presence of the C-19 methyl group at the ring juncture does not affect the ring opening reaction to any great extent, the ratio of axial to equatorial opening being very little different from that of the 2β:3β-epoxide. The cyclohexane ring is considerably flattened by fusion to the oxiran ring and it would appear that any interactions, which could arise in the transition state between the methyl group and the attacking reagent are not sufficient to alter the course of the reaction.

2. Acyloxonium ring opening.

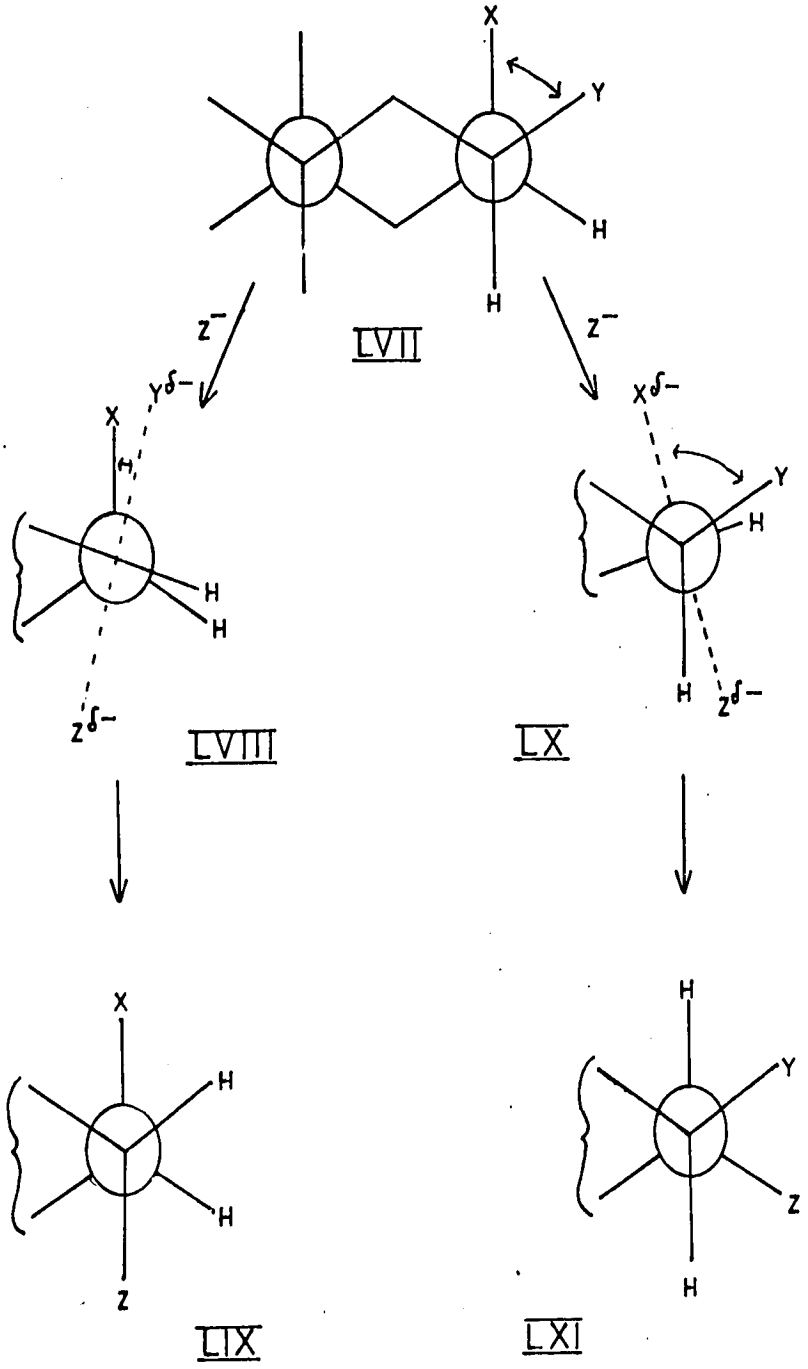
The previously mentioned results (Part II A) show that the normal mode of ring opening of acyloxonium ions, fused to cyclohexane rings, with halide ions and with carboxylate anion is trans and diaxial (however, see page54), and that the diaxial opening rule, which had previously been applied to three-membered rings fused to six-membered rings (6-3 fusion) may be extended to include 6-5 fusion.

In contrast to the arguments used in the case of epoxide opening, substitution to give the diequatorial chair products directly would not involve a large amount of bond lengthening, because of the size of the acyloxonium ring and would involve less movement of the group being displaced, i.e. in the transition state for diequatorial opening (LXIII) the incipient ester group has more equatorial character than is the

case with epoxides. Other reasons for the predominance of axial over equatorial opening must therefore be suggested.

The ring opening reaction presumably occurs by a bimolecular substitution mechanism. This supposition is supported by the stereochemistry of the reaction in which the products are invariably trans and which results in the inversion of the carbon attacked. The preference for diaxial over diequatorial opening can be rationalized as a consequence of the steric requirement of such a mechanism, in that the incoming and leaving groups must be linear and co-planar.

First the general case of the bimolecular substitution of a cis-1,2-disubstituted cyclohexane ring (LVII) which is in the chair conformation will be considered. For the substitution of the equatorial group Y, leading to the diaxial product (LIX), a linear co-planar arrangement of the incoming and leaving groups would result in a transition state LVIII, in which the dihedral angle between the leaving group (Y) and the other cis substituent (X) is decreased. Substitution of the axial group X however, to give the diequatorial product LXI, would result in a transition state LX in which there is an increase in the dihedral angle between the leaving group (X) and the cis substituent Y. When X and Y form part of a ring, it follows that in the transition state leading to diaxial products, i.e. LVIII, the ring would be flattened, while in the transition state leading to diequatorial products, i.e. LX, the ring would be twisted. It is suggested here that these changes in the dihedral angle between the adjacent groups of a cis-1,2-disubstituted

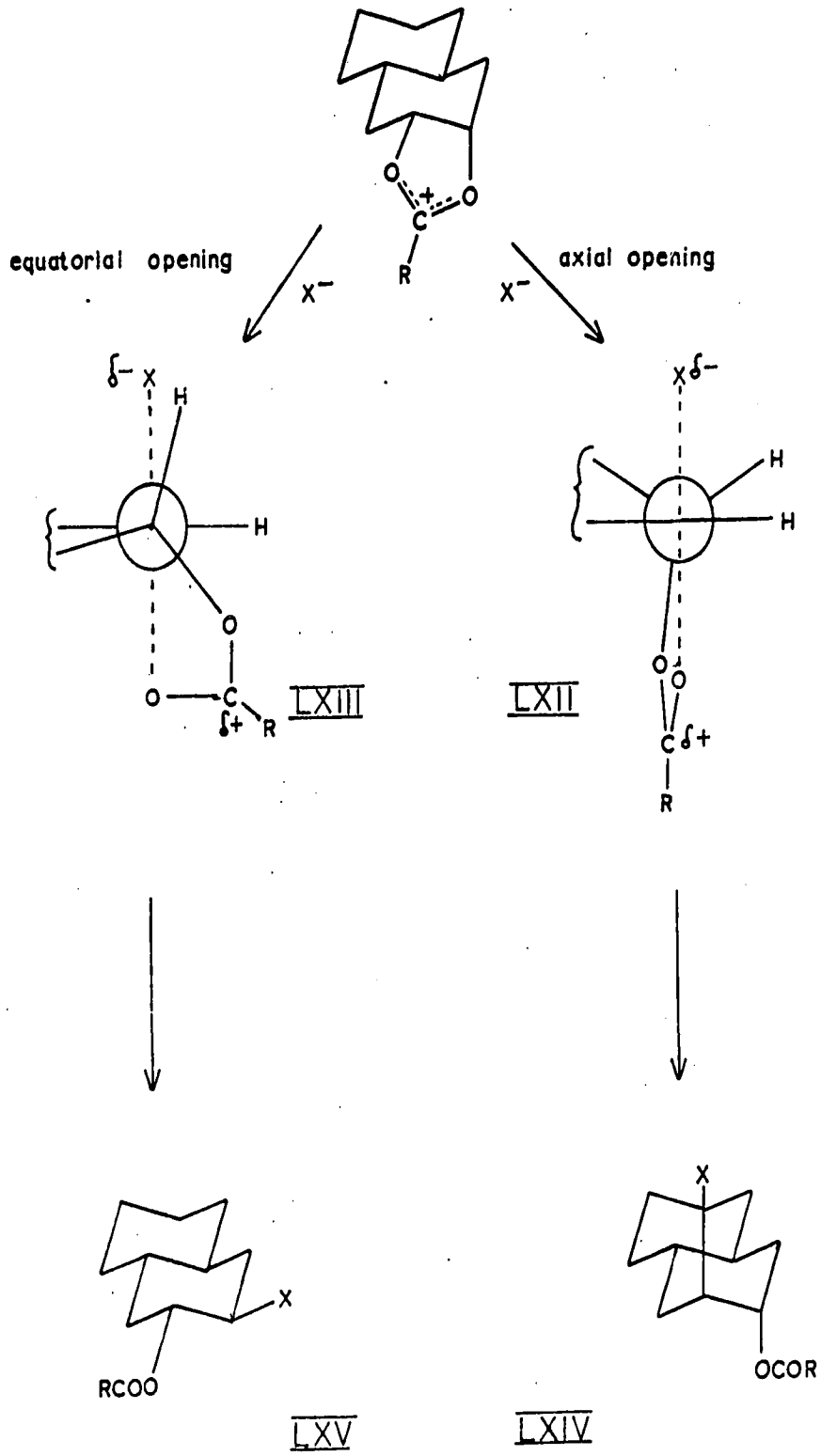

X
Y
H
H
LVII
Z⁻
Yδ−
X
H
H
H
Zδ−
LVIII
Z⁻
Xδ−
Y
H
H
Zδ−
LX
X
H
H
Z
LIX
H
Y
Z
H
LXI

cyclohexane ring, when either group is undergoing substitution, and the concomitant flattening or twisting which occurs when both substituents are part of the same ring, result in the diaxial opening of the acyloxonium rings predominating over diequatorial opening.

Acyloxonium ions are stabilized by resonance involving the two oxygens and maximum charge delocalization would be achieved with the acyloxonium ring being planar. From the above discussion it follows that in the transition state (LXII), leading to diaxial products (LXIV), the acyloxonium ring can become or remain planar (at the present time it is not known whether the acyloxonium ring when fused to a rigid six-membered ring is planar or slightly twisted), while in the transition state (LXIII), which would give the diequatorial products (LXV) directly, the ring is considerably twisted with consequent loss of resonance stabilization.

A transition state (LXVI) in which there is a linear co-planar arrangement of incoming and leaving groups, and in which the acyloxonium ring is planar, can be achieved if the cyclohexane ring assumes a twist (or boat) conformation. In this case the initial product is a diaxially substituted boat (LXVII), which by ring inversion yields the diequatorial products (LXVIII).

Thus the axial to equatorial opening ratio is dependent upon the free energy difference between a partly formed diaxial chair and either a partly formed diequatorial chair or diaxial boat. At the present time no distinction can be made between the latter possibilities since


equatorial opening
axial opening
X⁻
X⁻
δ−
X
H
H
O
O
C
δ+
R
LXIII
LXII
RCOO
X
OCOR
LXV
LXIV

it is not known if the degree of deformation of the oxonium ring in LXIII would be prohibitive to direct diequatorial opening.

The generalization that diaxial opening is the normal mode for acyloxonium ions fused to six-membered rings applies for those cases where no perturbing factors are present. However, in the case of the cholestan-2α:3α-_p_-anisoxonium ion, diaxial opening is strongly inhibited by the proximity of the C-19 methyl group to the site of attack at C-2, and equatorial opening is favoured over axial opening by a ratio of ∿ 2:1. This result is in contrast with the opening of the analogous epoxide in which the presence of the methyl group makes little difference to the ring opening ratio. Since the cyclohexane ring of the acyloxonium ion would not flatten as much as the corresponding epoxide, approach of reagent to C-2 must be hindered to a greater extent. Presumably in the formation of the diaxial product a strong 1,3-interaction between the methyl group and the attacking species would arise and this results in the transition state LXIX being destabilized with respect to either LXIII or LXVI leading to the equatorial products.

With benzoate anion the opening of the acyloxonium ring is slightly less stereospecific than with halide ion. A similar result was obtained by Meakins (27) who suggested that the reason for the formation of more diequatorial product was due to the increased size of the attacking group. However both the results of Meakins', and the results reported here with benzoate anion, were obtained using different counter-cations than were used in the halide ring opening reactions. Although in the case of the

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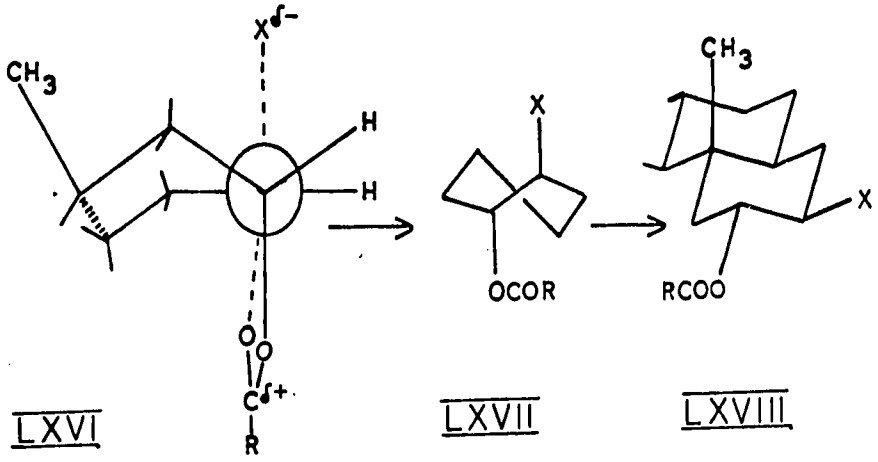
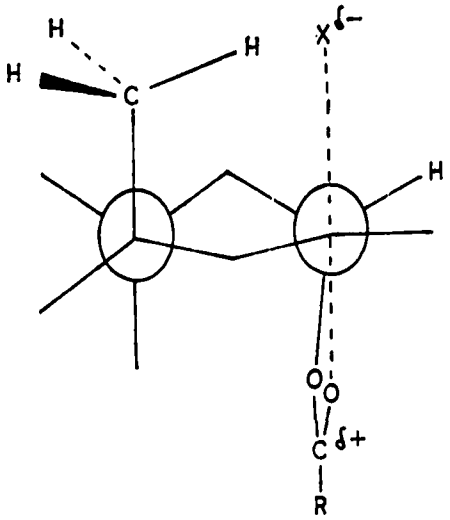


LXVI LXVII LXVIII



LXIX

benzoate anion the cation differs only slightly from that used with halide anion the results may still not be strictly comparable. Also, since the nature of the transition state leading to equatorial opening is uncertain, detailed discussion on this point is unwarranted.

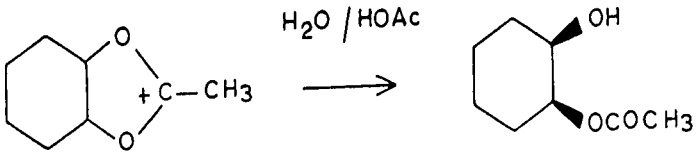
PART III

THE HYDROLYTIC CLEAVAGE OF ACYLOXONIUM IONS

A. The Hydrolysis of Acyloxonium Salts.

1. Introduction.

Winstein and Buckles, in their original work on the reaction of silver acetate in acetic acid with trans-1,2-dibromocyclohexane and trans-1-acetoxy-2-bromocyclohexane, found that in the presence of water, cis-monoacetates were the major products (5). Similarly treatment of 2-methyl-cis-4,5-tetramethylene-1,3-dioxolenium tetrafluoroborate with moist acetic acid gave 2-acetoxycyclohexanol which was 99.5% cis, no trans-hydroxyester being detected (15). In none of these hydrolytic cleavages of acyloxonium ions could any stereochemistry be assigned to the products other than that the hydroxyesters were cis.



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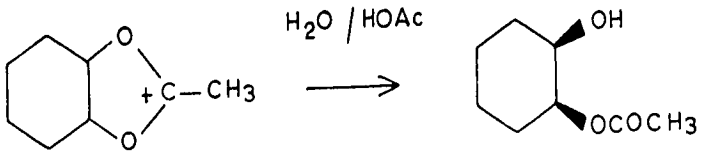
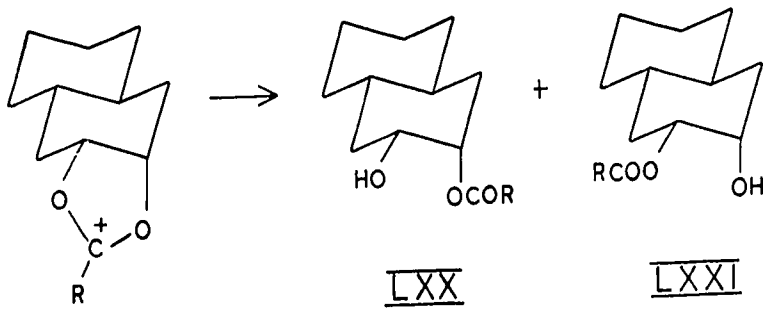


The hydrolysis of acyloxonium ions fused to rigid six-membered rings could in principle, yield two cis-hydroxyesters, one in which the ester group is axial and one in which the ester group is equatorial. LXX and LXXI.



LXX LXXI

It was anticipated, in the absence of any reasons to suspect otherwise, that hydrolysis of such salts would yield mixtures of both hydroxyesters in comparable amounts. However, as will be related below, it was found that hydrolysis of acyloxonium salts, such as the steroid and decalin anisoxonium hexafluoroantimonates, was highly stereospecific and yielded one cis-hydroxyester almost entirely.

2. Hydrolysis of acyloxonium salts.

As part of the proof of their structure the steroid cis-anisoxonium salts XXXV and XXXVIII were hydrolysed to the corresponding hydroxyesters, which were then saponified to give the cis-diols. The initial hydrolyses were carried out by treating a solution of the acyloxonium salt in methylene chloride with dilute aqueous acetic acid. The products, obtained in almost quantitative yield, in both cases had infrared spectra

showing the expected bands for alcohol and ester groups. On examination of either of the products by thin layer chromatography however, a rather surprising result was observed, namely that in each case the material consisted of almost entirely one compound. A small amount of a second compound was visible, running ahead of the main product, but was present in only trace amounts.

The first observations concerning the structure of these hydroxy-anisates were made from the results of the thin layer chromatography experiments, i.e. that the second material, present in trace amounts and presumed to be the alternate isomer, ran faster than the major product. It has been found in many cases, although not exclusively, that a compound with an equatorial alcohol group will be eluted more slowly than the same compound with an axial alcohol group. Thus the early indications were that the hydrolysis product, in each case, had an equatorial hydroxyl group and thus would correspond to LXXII and LXXIII respectively. That this expectation was correct was shown by the following experiments.

Oxidation of either of the hydrolysis products obtained from XXXV and XXXVIII gave in each case the corresponding keto-anisates, which were then reduced with zinc and acetic acid. 5α-Cholestan-2-one (LXXVI) was the only cholestanone obtained from the hydrolysis product of XXXV, and 5α-cholestan-3-one (LXXVII) was the only cholestanone obtained from the hydrolysis product of XXXVIII. From these results it follows that in each case the hydrolysis product corresponds to the

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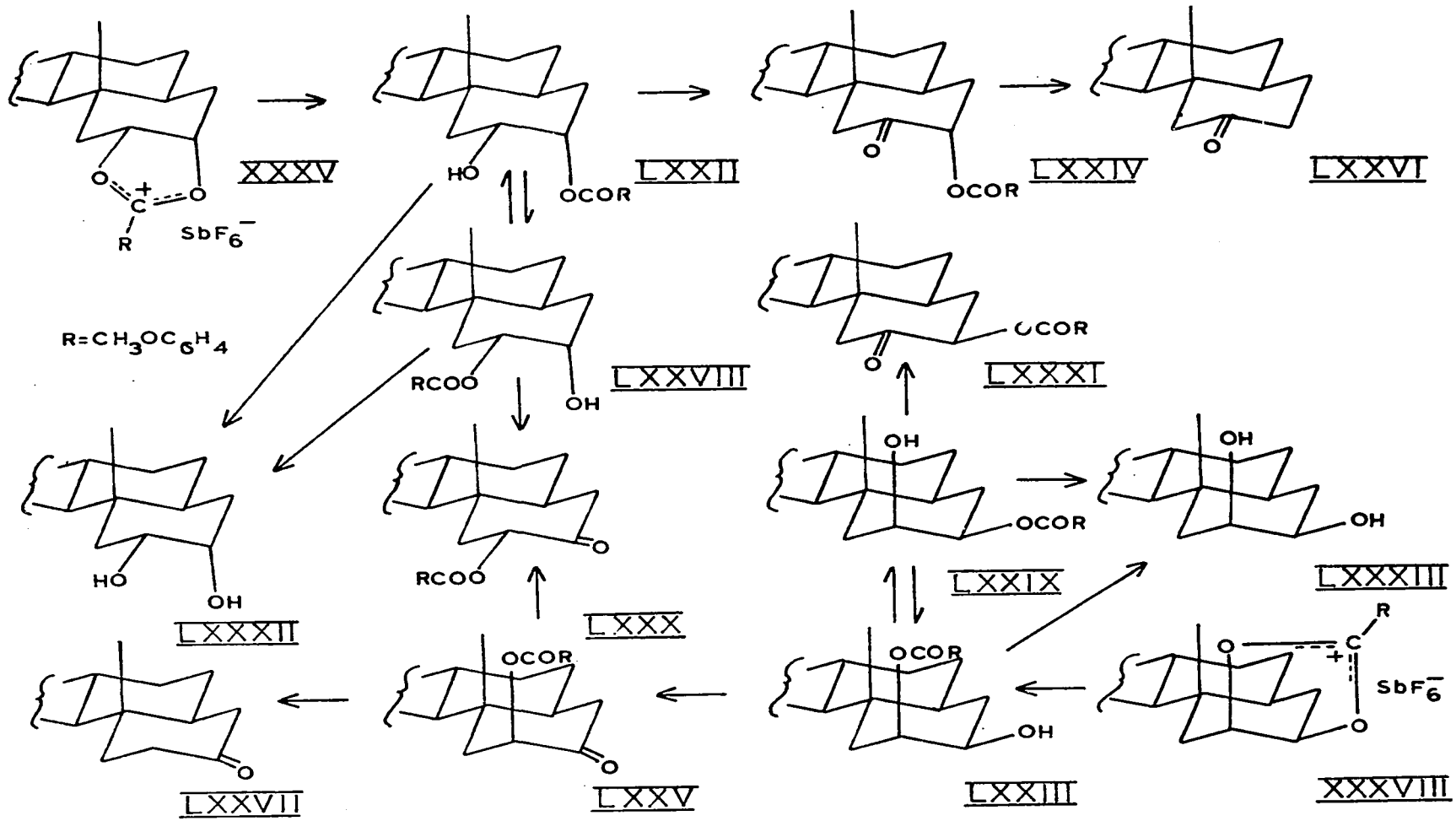
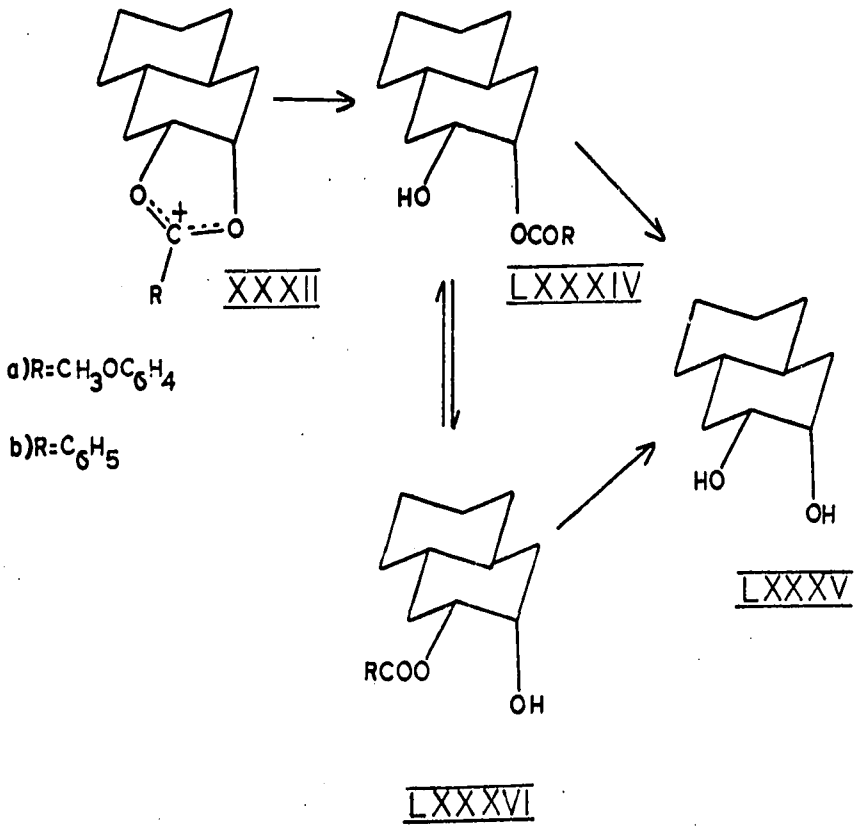

XXXV
LXXII
LXXIV
LXXVI
R=CH3OC6H4
LXXVIII
LXXXI
LXXXII
LXXX
LXXIX
LXXXIII
LXXVII
LXXV
LXXIII
XXXVIII

equatorial alcohol-axial ester, LXXII and LXXIII.

The n.m.r. spectra of these two hydroxyanisates were in excellent agreement with the above conclusions. Hassner and Heathcock, from a study of the n.m.r. spectra of steroids with axial and equatorial substituents have formulated the following rule, "the half-width (W 1/2) of the bands due to equatorial protons is 5-10 c.p.s., while that for axial protons is 15-30 c.p.s." (24). Thus LXXII had an n.m.r. spectrum with a broad band at 3.87 p.p.m. (W 1/2 20 c.p.s.) attributable to the axial proton at C-2 and a narrow band at 5.29 p.p.m. (W 1/2 6 c.p.s.) corresponding to the equatorial proton at C-3. Similarly LXXIII had bands at 3.87 p.p.m. (W 1/2 22 c.p.s., axial C-3 proton) and 5.29 p.p.m. (W 1/2 8 c.p.s., equatorial C-2 proton).

The decalin acyloxonium salts XXXIIa and b behaved in the same manner upon hydrolysis and gave an almost quantitative yield of the cis-hydroxyesters LXXXIVa and b. The structures of these two compounds were established in a similar manner to that above, i.e. by their n.m.r. spectra which had a similar pattern with respect to the C-2 and C-3 protons as found with the steroid hydroxyanisates (see Appendix II) and also by saponification of each to the decalin cis-diol (LXXXV). Also as noted before, a small amount of a second material running ahead of the major product, was observed upon thin layer chromatography. In each case, with both the steroid and decalin hydroxyesters, this trace of a second product was found to have the same R_f value as the corresponding axial alcohol-equatorial ester, i.e. - LXXVIII, LXXIX and LXXXVIa, b.

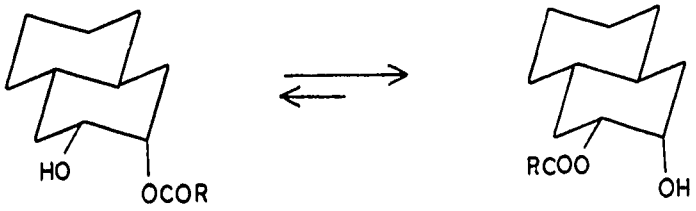

O
C
O
R
XXXII
HO
OCOR
LXXXIV
a)R=CH3OC6H4
b)R=C6H5
HO
OH
LXXXV
RCOO
OH
LXXXVI

Quantitative thin layer chromatography showed that, if this second material is the axial alcohol-equatorial ester, then in the case of the steroid and decalin hydroxyanisates it is present in an amount estimated at less than 0.5% of product.

Base-catalysed hydrolysis of the acyloxonium salts yielded the same result as found for the acid-catalysed hydrolyses. Treatment of a methylene chloride solution of the decalin anisoxonium salt with aqueous 5% potassium hydroxide solution resulted in complete hydrolysis of the acyloxonium salt and gave an almost quantitative yield of 2β-hydroxy-9β:10α-decalin-3β-yl p-anisate (LXXXIVa).

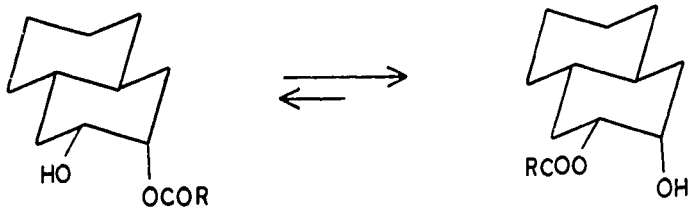
3. The acid-catalysed rearrangement of the equatorial alcohol-axial anisates.

It has been shown in the preceeding section that the hydrolysis of cis-acyloxonium ions fused to rigid six-membered rings yields cis-hydroxyesters in which the ester groups are axial. These products would appear to be derived from kinetic rather than thermodynamic control since, of the two possible cis-hydroxyesters which could be formed, the one with the ester group equatorial would be expected to be the more stable. Thus if an equilibrium was set up between the two hydroxyesters it would be anticipated that the axial alcohol-equatorial ester would be favoured over the equatorial alcohol-axial ester.



That this expectation was correct was demonstrated by the results of the following experiments. When each of the hydroxyanisates LXXII, LXXIII and LXXXIVa was refluxed in benzene with a small amount of D-10-camphorsulphonic acid a mixture was obtained consisting of the starting material plus the corresponding rearranged hydroxyanisate i.e. LXXVIII, LXXIX and LXXXVIa. These mixtures were readily separable by thin layer chromatography and in almost every case more of the axial alcohol-equatorial ester than the equatorial alcohol-axial ester was found.

Similarly, treatment of the hydroxyanisates LXXVIII, LXXIX and LXXXVIa as above gave mixtures of the two possible hydroxyanisates in which the axial alcohol-equatorial ester predominated. The structures of the rearranged hydroxyesters were established by evidence similar to that used for the corresponding equatorial alcohol-axial esters. Each gave a satisfactory analysis and had infrared spectra



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Similarly, treatment of the hydroxyanisates LXXVIII, LXXIX and LXXXVIa as above gave mixtures of the two possible hydroxyanisates in which the axial alcohol-equatorial ester predominated. The structures of the rearranged hydroxyesters were established by evidence similar to that used for the corresponding equatorial alcohol-axial esters. Each gave a satisfactory analysis and had infrared spectra

showing the expected bands for alcohol and ester groups. Alkaline hydrolysis gave, in each case, the corresponding cis-diol. Their n.m.r. spectra were also consistent with their assigned structures, the axial hydrogen on the carbon bearing the ester group appearing as a broad band or multiplet at ∿ 4.9 p.p.m., while the equatorial hydrogen on the carbon bearing the alcohol group appeared as a narrow band at ∿ 4.1 p.p.m.

It may be noted that, in these acid-catalysed rearrangements, the results obtained represent only an apparent equilibrium. In each rearrangement it was found that the D-10-camphorsulphonic acid was involved in a reaction with the hydroxyanisate. Upon thin layer chromatography of the product mixtures traces of a third compound, running ahead of the hydroxyanisates, were observed. Also not all of the starting material could be accounted for by the mixture obtained after rearrangement. The relative amounts of the two possible hydroxyanisates obtained in any one of the rearrangements depended somewhat on the quantity of D-10-camphorsulphonic acid used. Thus 3β-hydroxy-5α-cholestan-2β-yl p-anisate (LXXIII), which would have been expected to rearrange quite readily due to the 1,3 interaction between the ester and C-19 methyl group, under the conditions used, gave a mixture in which the starting material predominated.

In one case, that of the rearrangement of 3β-hydroxy-9β:10α-decalin-2β-yl p-anisate, this third material represented approximately one third of the total product, and was investigated briefly. The infrared

spectrum had absorption at 1745 cm^{-1} and 1710 cm^{-1}. Attempts to crystallize this material failed and it was found later by thin layer chromatography, eluting with a less polar solvent, that it consisted of at least three compounds. These compounds were not investigated further.

4. Oxidation of the steroid hydroxyanisates.

The structure of the hydroxyanisates obtained by hydrolysis of the steroid anisoxonium salts was based on a) their n.m.r. spectra, b) hydrolysis to cis-diol, and c) their oxidation and subsequent reduction to cholestan-2-one and cholestan-3-one respectively. It was considered that a rearrangement might conceivably have occurred during the oxidative step and consequently it was decided to isolate and characterize the keto-anisates derived from both the primary hydrolysis products (LXXII and LXXIII) and from the rearranged hydroxyanisates LXXVIII and LXXIX.

Initially it was anticipated that an oxidizing agent involving a strong acid might result in epimerizing the axial ester groups in LXXII and LXXIII. An account has recently been published on the use of a mixture of dimethyl sulphoxide and acetic anhydride as an oxidizing agent for alcohol groups and this mixture was claimed to have some advantages for the oxidation of sterically hindered hydroxyl groups and also for the oxidation of sensitive compounds (40). Treatment of 3β-hydroxy-5α-cholestan-2β-yl p-anisate (LXXIII) and 2β-hydroxy-5α-cholestan-3β-yl p-anisate (LXXIX) with this reagent gave high yields of the keto-

anisates LXXV and LXXXI as the only products. However, oxidation of 2α-hydroxy-5α-cholestan-3α-yl p-anisate (LXXII) with dimethyl sulphoxide and acetic anhydride gave quite a different result. The crude product had an infrared spectrum in accord with that of the expected keto-anisate, showing no hydroxyl absorption and having a band at 1710 cm^{-1}. Attempts to crystallize this material failed, and on examination by thin layer chromatography it was shown to consist of two compounds running quite close together. These two materials were separated by thin layer chromatography, the faster moving material being designated as Fraction A and the slower moving compound as Fraction B.

Fraction B had a correct elemental analysis and infrared spectrum expected for the keto-ester and its n.m.r. spectrum was also in agreement with that expected for 5α-cholestan-2-one-3α-yl p-anisate (LXXIV).

Fraction A comprised about one third of the total product from the oxidation of LXXII with dimethyl sulphoxide and acetic anhydride. The infrared spectrum was quite similar to that of 5α-cholestan-2-one-3α-yl p-anisate and it was first concluded that this material was the product of epimerization of the ester group, i.e. 5α-cholestan-2-one-3β-yl p-anisate (LXXXI). However, Fraction A did not have the same infrared spectrum, m.p. or rotation as LXXXI, and furthermore its analysis did not agree with that expected from an anisoxycholestanone. The n.m.r. spectrum was quite different from that of any of the other keto-esters and showed, besides the presence of the p-methoxyphenyl group, two bands at 4.66 p.p.m. (W 1/2 11 c.p.s.) and 5.50 p.p.m.

(W 1/2 θ c.p.s.). No other bands were found in the n.m.r. spectrum apart from the saturated hydrocarbon absorption between 0.5 and 1.5 p.p.m. The two bands at 4.66 and 5.50 could be assigned to two equatorial protons, which would mean that the compound is substituted diaxially. A Beilstein test proved negative, showing the absence of halogen. A sodium fusion test for sulphur was also negative. This oxidation is anomalous since of the four hydroxyanisates this was the only one in which a large amount of secondary product was obtained. Evidently some steric factor could be operating in this case. It has been reported recently that methylthiomethoxy derivatives (CH_3-S-CH_2-O-) are formed upon oxidation of certain alcohols (41). A' derivative of this type could be ruled out by the failure to detect sulphur and by the n.m.r. spectrum which showed no absorption corresponding to the CH_3-S- or -S-CH_2-O- groups. The acetoxymethyl ether derivative (CH_3CO-CH_2-O-) of cholesterol has also been isolated from the oxidation of the alcohol with dimethyl sulphoxide and acetic anhydride (42) but a compound of this type would not fit the empirical formula or the n.m.r. spectrum of Fraction A. At the present time no structure for this compound can be put forward.

Since the isolation of two compounds from the oxidation of LXXII for a time confused the structural assignments, the oxidations of the four hydroxyanisates were repeated using sodium dichromate and sulphuric acid in acetone (Jones reagent). This procedure gave the keto-anisates in quite high yields. Some epimerization was noted during

the oxidation of LXXII, a small amount (10%) of LXXXI being isolated in addition to the major product LXXIV. Upon oxidation of LXXIX a second product, amounting to 30%, was isolated as well as the expected oxidation product LXXVII. This second material was an oil and could not be induced to crystallize. It may be noted that 5α-cholestan-3-one-2β-yl p-anisate (LXXV) had a rather wide melting point range, of ∿ 8°. Despite purification by thin layer chromatography and crystallization several times a sharp melting point could not be obtained.

The four keto-anisates had satisfactory analyses, and their infrared, n.m.r. and optical rotatory dispersion spectra were in good agreement with their assigned structures. The rotatory dispersion spectra of the keto-anisates LXXIV, LXXV, LXXX and LXXXI were in accordance with simple application of the octant rule (43), in all cases positive Cotton effects being observed (fig. 4). With both of the ketones with axial ester groups, the amplitudes of the curves were considerably larger than those from the ketones with equatorial ester groups. Due to the strong ultraviolet absorption of the esters, a value for the amplitude of the axial keto-anisates could not be obtained, however it was estimated that for the 3α and 2β-anisates LXXIV and LXXV the amplitudes were greater than 217 and 149 respectively. The corresponding values for the 2α and 3β-anisates LXXX and LXXXI were 23 and 47. These results differ from those found by Johnson and Williamson (44), who report that the amplitudes were greater

ORD. SPECTRA of the CHOLESTANE KETO-ANISATES (CH_2Cl_2)

1. 5α-Cholestan-2-one-3α-yl p-anisate
2. 5α-Cholestan-3-one-2β-yl p-anisate
3. 5α-Cholestan-2-one-3β-yl p-anisate
4. 5α-Cholestan-3-one-2α-yl p-anisate

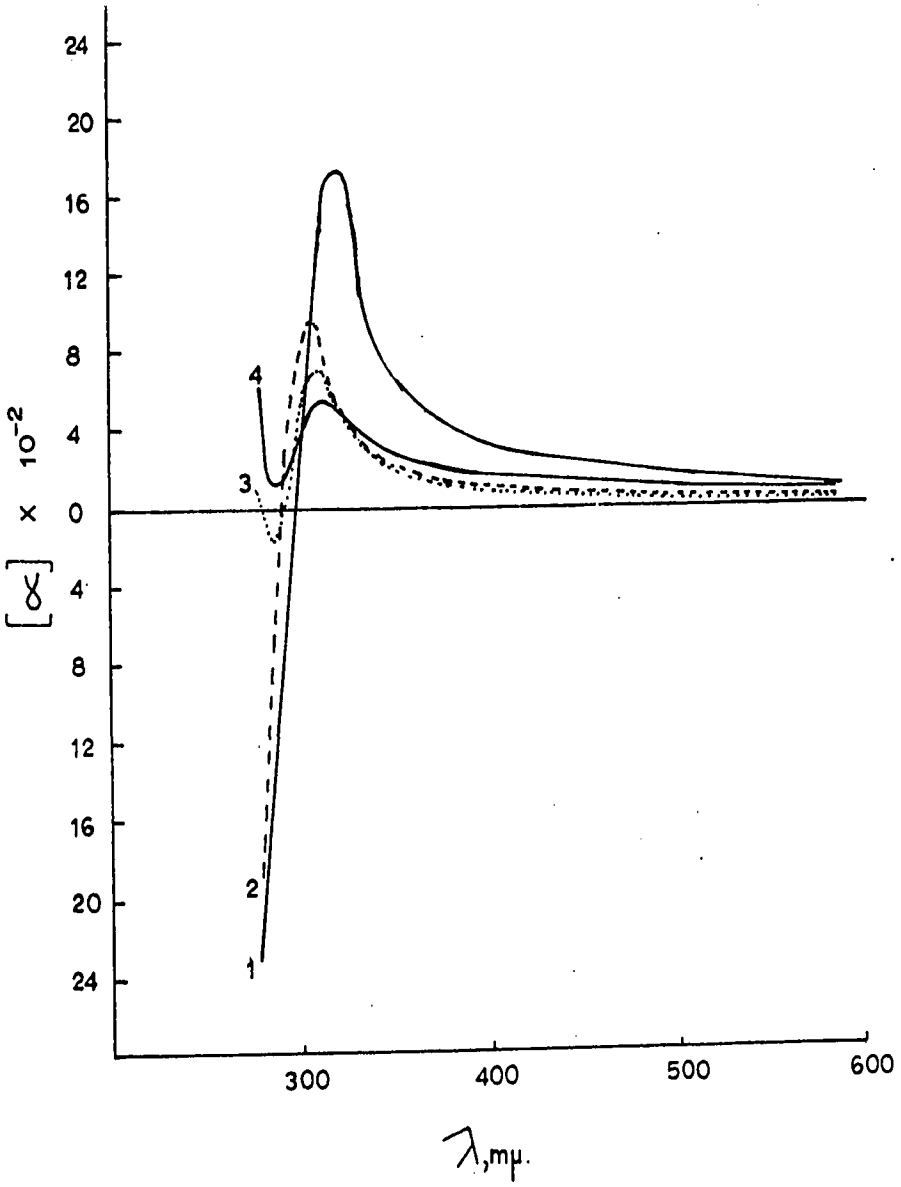


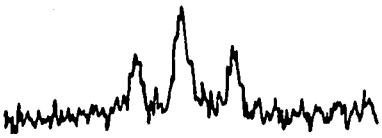
Fig.3

for the equatorial keto-acetates (i.e. LXXX and LXXXI, R=CH_3) than for the axial keto-acetates (LXXIV and LXXV, R=CH_3). The spectra of the keto-anisates were determined in methylene chloride while those of the keto-acetates were run in methanol, and these spectra may not be strictly comparable. However, the spectra were similar with regard to the shifts of the first extrema on going from an equatorial to an axial substituent. With the ketones epimeric at C-3, the first extremum of the axial keto-anisate was 10 mμ at longer wavelength than the first extremum of the equatorial keto-anisate. This effect has been observed in a series of 11-keto-12-acetates of bile acids and sapogenins (45) and also with the 3-acetoxy-5α-cholestan-2-ones (44). However, with the cholestan-3-one-2α and 2β p-anisates, the first extremum of the 2β-anisate was shifted by 5 mμ to shorter wavelength compared to the first extremum of the 2α-anisate. A similar shift was found also by Johnson and Williamson who noted that the first extremum of 2β-acetoxy-5α-cholestan-3-one was shifted 15 mμ to shorter wavelength compared to that of the 2α-acetate.

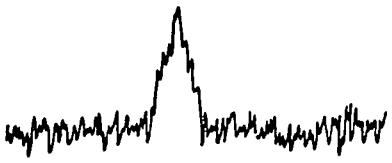
The n.m.r. spectra of all four keto-anisates were also quite similar to those recorded for the corresponding keto-acetates (44). Thus with 5α-cholestan-3-one-2α-yl p-anisate (LXXX) the axial proton at C-2 appeared as a quartet, as was found with the 2α-acetoxycholestanone. The spectra of the cholestan-2-one-3α and 3β-p-anisates LXXIV and LXXXI showed a similar pattern to those of the corresponding acetates, the C-3 proton appearing in the 3α-anisate (LXXIV) as a

N.M.R. SPECTRA of the CHOLESTANE KETO-ANISATES ($CDCl_3$)

5α-CHOLESTAN-3-ONE-
2α-YL P-ANISATE (LXXX)



5α-CHOLESTAN-3-ONE-
2β-YL P-ANISATE (LXXV)



5α-CHOLESTAN-2-ONE-
3α-YL P-ANISATE (LXXIV)

5α-CHOLESTAN-2-ONE-
3β-YL P-ANISATE (LXXXI)

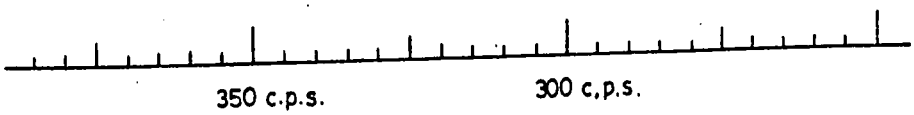


Fig. 4

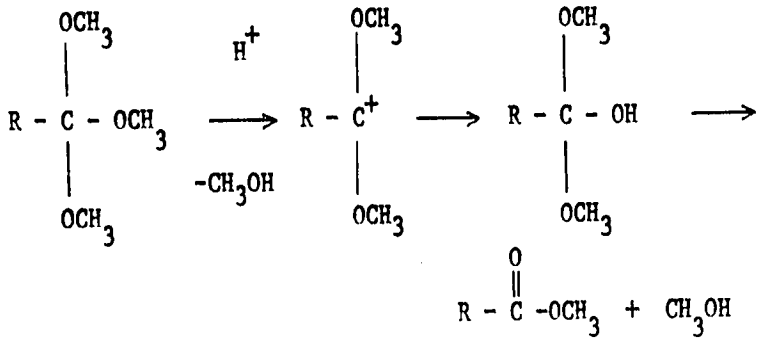
narrow band, and as a broad, poorly resolved multiplet in the 3β-anisate LXXXI. The C-2 equatorial proton of cholestan-3-one-2β-yl p-anisate (LXXV) however, appeared as a poorly resolved triplet, in contrast to the 2β-acetoxyketone in which the proton showed up as a quartet. Johnson and Williamson, from the shift of the first extremum in the rotatory dispersion spectra and from the quartet observed in the n.m.r. of the C-2 hydrogen concluded that the cyclohexanone ring, in the case of the 2β-acetoxyketone (LXXV, R = CH_3), was deformed by the 1,3 interaction between the 2β-ester group and the C-19 methyl group of the steroid, and could be more properly represented as in a twist conformation. Effects of a similar nature are also observed here with the 2β-anisate LXXV.

The inter-relationship of two of these keto-anisates was shown by the epimerization of LXXV to LXXX. Refluxing a solution of the 2β-keto-anisate LXXV in benzene together with a small amount of D-10-camphorsulphonic acid gave the 2α-keto anisate (LXXX).

B. The Acid-Catalysed Hydrolysis of Orthoesters.

1. Introduction

The acid-catalysed hydrolyses of orthoesters are currently believed to involve the formation of an intermediate carbonium ion such as LXXXVII (46, 47).



LXXXVII

In 1943 Winstein and Buckles studied the reactions of cyclohexene ethyl orthoacetate (VI) (6). Hydrolysis in wet ethanol and in wet acetic acid gave 95% cis-2-acetoxycyclohexanol and 5% cis 1,2-cyclohexanediol. Acetolysis with acetic anhydride with or without potassium acetate gave the trans-diacetate and treatment with p-toluenesulphonic acid gave the trans-2-acetoxycyclohexyl tosylate. Reaction with hydrogen chloride or lithium chloride gave trans-2-acetoxycyclohexyl chloride. All of these results are most readily explained by the formation of the acetoxonium ion XII.

VI XII

Recently a study of the rate of hydrolysis of methyl orthobenzoate by n.m.r. spectroscopy has been reported (46). The authors found first order rate constants for the disappearance of methoxy protons, appearance of methyl protons of methanol and appearance of methoxy protons of product and concluded that these results require the rate determining step of the hydrolysis to be carbonium ion formation.

If the hydrolysis of orthoesters such as LXXXVIII, fused to a rigid six-membered ring, proceeds via an intermediate dialkoxycarbonium ion then the same stereoselectivity that was found with the hydrolysis of the acyloxonium salts should be observed. Consequently, the preparation of some orthoesters of trans-decalin-2β:3β-diol and a study of their hydrolyses was undertaken.

2. The preparation of orthoesters.

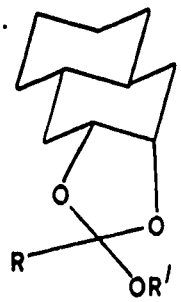
The decalin orthoesters LXXXVIII a,b,c, were synthesized by a modified version of the method used by Buckles and Winstein in their preparation of the cyclohexene ethyl orthoacetate (VI). This procedure involves reaction of the diol and ethyl orthoester together with a small amount of acid catalyst, and removal of the ethanol produced in the reaction by distillation. Unfortunately this procedure, which had given good yields in the case of the cyclohexene ethyl orthoester, did not work very well with the decalin compounds. Even after prolonged heating

a)R=H — $R'=-CH_2CH_3$

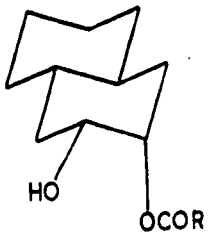
b)R=CH_3 — $R'=-CH_2CH_3$

c)R=CH_3CH_2 — $R'=-CH_2CH_3$

d)R=C_6H_5 — $R'=-CH_3$



LXXXVIII

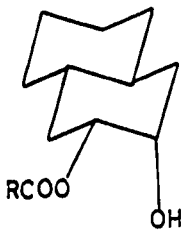


LXXXIX

a)R= H —

b)R=CH_3 —

c)R=CH_3CH_2 —



XC

at high temperature only about 50% of the expected yield of alcohol distilled over and the oily residue remaining was practically undistillable. When the reaction was carried out in a solution of benzene however quite reasonable yields of decalin ethyl orthoformate LXXXVIIIa (65%), orthoacetate LXXXVIIIb (41%), and orthopropionate LXXXVIIIc (82%) were obtained. These compounds proved to be oils and gave satisfactory analyses. Their infrared spectra showed no hydroxyl bands and had strong absorption between 1000 cm^{-1} and 1200 cm^{-1}.

In all of these orthoesters there exists the possibility of isomerization about the ortho-carbon. In the n.m.r. spectrum of the decalin orthoformate the formyl proton appeared as two separate peaks at 5.73 and 5.80 p.p.m. in a ratio of 2:7. Both the methylene quartet at 3.60 p.p.m. and the methyl triplet at 1.22 p.p.m. also appeared to be superimposed upon other peaks, indicating that a mixture was present. Similar effects were noted in the spectra of the orthoacetate and the orthopropionate, in both cases the multiplicity of peaks appears to indicate that mixtures were formed.

An attempt was also made to prepare the decalin methyl orthobenzoate (LXXXVIIId) from trans-decalin-cis-2,3-diol and methyl orthobenzoate. Using the same procedure as used for the other orthoesters no orthobenzoate was obtained. After the solvent benzene had been distilled off the thick oily residue remaining could not be distilled.

Under high vacuum and at high temperatures the only material that distilled over was a small amount of methyl orthobenzoate. Prolonged heating resulted in a solid material condensing on the inside of the still head, this proved to be the trans-decalin-cis-2:3-diol. The infrared spectrum of the oily residue showed only slight hydroxyl absorption, and also had small peak at 1710 cm^{-1}. The carbonyl absorption seemed to indicate the presence of some hydrolysis product. An attempt was made to purify this material by column chromatography on basic alumina, but the material eluted with petroleum ether (35-60) still showed carbonyl absorption in the infrared spectrum.

3. The acid-catalysed hydrolysis of orthoesters.

The hydrolyses of the orthoesters were carried out by treatment of a methanol solution with aqueous acetic acid. With the orthoacetate and orthopropionate an almost quantitative yield of hydroxyester was obtained. The products from the hydrolysis of these two compounds were identified as the corresponding equatorial alcohol-axial esters by similar evidence to that used in the case of the products from the hydrolysis of the acyloxonium salts. Thus both products had infrared spectra showing absorption for hydroxyl and carbonyl groups, and both gave correct analyses. The n.m.r. spectra, in both cases were almost identical to those of the hydroxyanisates with respect to the hydrogens at C-2 and C-3. The hydroxyacetate showed a broad band at 3.77 p.p.m.

(W 1/2 20 c.p.s.) and a narrow band at 5.17 p.p.m. (W 1/2 8 c.p.s.) while the hydroxypropionate had a similar pattern with a broad band at 3.70 p.p.m. (W 1/2 30 c.p.s.) and a narrow band at 5.13 p.p.m. (W 1/2 7 c.p.s.).

Thin layer chromatography of these products also gave results similar to those obtained previously and showed in each case only a trace of a second material apart from the main product.

Hydrolysis of the decalin orthoformate was first attempted by treating a methanol solution with a small amount of aqueous hydrochloric acid (50%). The major product from this reaction appeared to be 9β:10α-decalin-2β:3β-diol, i.e. complete hydrolysis had occurred. When the hydrolysis was carried out in a similar manner to that of the orthoacetate and orthopropionate an almost quantitative yield of hydroxyester was obtained. The crude product was an oil, and had an infrared spectrum with the expected peaks for hydroxyl and carbonyl groups. However on examination of this material by thin layer chromatography it was observed that the product appeared to be a mixture of two compounds, running quite close together and present in almost equal amounts. There was also a continuous smear between the two spots. An attempt was made to separate these two compounds by thin layer chromatography, but the two fractions obtained from the thin layer plates had infrared spectra identical to one another and to the original crude hydrolysis product. Also, when each fraction was again subjected to thin layer chromatography the same two spots were found as had been

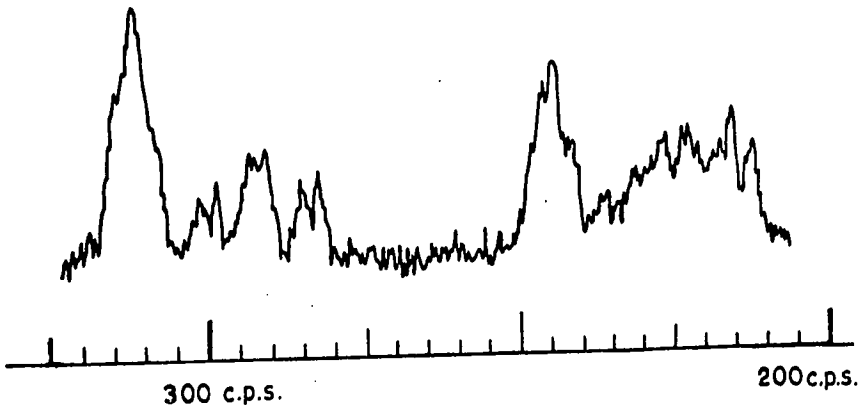
observed with the hydrolysis product. Attempts were made to separate the two materials by thin layer chromatography on alumina but the material showed only smears, with no separation.

A portion of the hydrolysis product, dissolved in pentane, gave a white crystalline solid. This compound was shown to be 3β-hydroxy-9β:10α-decalin-2β-yl formate (LXXXIXa) by the following evidence: a) the material had the correct elemental analysis, b) the n.m.r. spectrum showed the now familiar pattern for the protons at C-2 and C-3 of the decalin ring, c) the infrared spectrum showed peaks corresponding to hydroxyl and carbonyl groups.

The infrared spectrum of this hydroxyformate was of interest since it was noticed that it differed from the infrared spectrum of the crude hydrolysis product in the region 900 cm^{-1} to 1100 cm^{-1}. In the spectrum of the hydrolysis product there were two extra peaks at 980 cm^{-1} and 960 cm^{-1}, and the peak at 1130 cm^{-1} was of greater intensity than in the spectrum of the pure hydroxyformate.

From the attempted separation of the original crude hydrolysis product it appeared that the material isomerized upon silica gel. This idea was confirmed by the following experiment. A small amount of 3β-hydroxy-9β:10α-decalin-2β-yl formate was chromatographed upon the silica gel plates, and the product recovered; the infrared spectrum of this material was identical to that of the original hydrolysis product, i.e. it contained the two extra peaks at 980 cm^{-1} and 960 cm^{-1}.

N.M.R. SPECTRUM of crude product from hydrolysis of 9β:10α - DECALIN - 2β:3β - ETHYL ORTHOFORMATE ($CDCl_3$)



N.M.R. SPECTRUM of 3β - HYDROXY - 9β:10α - DECALIN - 2β - YL FORMATE LXXXIX a ($CDCl_3$)

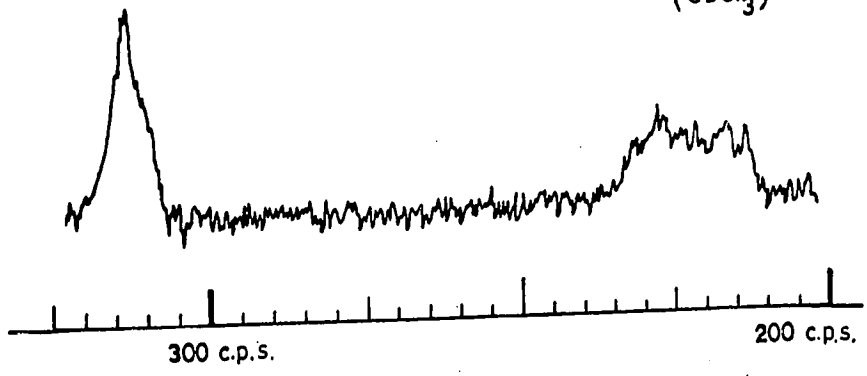


Fig. 5

The hydroxyformate (LXXXIXa) was recovered unchanged when subjected to the hydrolysis conditions thus showing that isomerization does not occur at that step.

The hydrolysis of the decalin orthoformate was repeated and the n.m.r. spectrum of the product showed clearly that a mixture of the two possible hydroxyformates, LXXXIXa and XCa, was obtained. Thus two bands at 3.70 p.p.m. and 5.22 p.p.m. were identical to those of the equatorial alcohol-axial formate LXXXIXa; and the two bands at 4.07 p.p.m. and 4.87 p.p.m. can be assigned to the equatorial formate-axial alcohol compound XCa (see fig. 5).

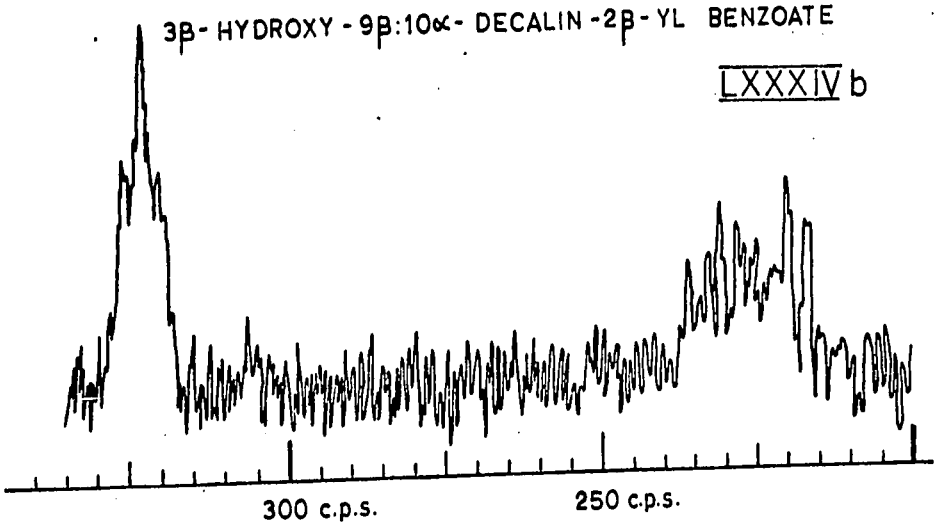
Some attempts were made to isolate XCa by fractional crystallization but no material could be isolated. Thus it would appear that in the case of the decalin ethyl orthoformate a mixture of both possible hydroxyformates was obtained; from the n.m.r. spectra of the mixture slightly more of the equatorial alcohol-axial formate (LXXXIXa) being formed.

Although the attempts to prepare the decalin methyl orthobenzoate (LXXXVIIId) had failed it was felt that the residue remaining after the solvent benzene had been removed probably contained a high proportion of the orthobenzoate, especially since the infrared spectrum of this material showed little hydroxyl absorption. The preparation was repeated and the oily residue was hydrolysed in a similar manner to that of the other orthoesters. The product was shown by thin layer

N.M.R. SPECTRA of the TRANS DECALIN CIS HYDROXY-BENZOATES ($CDCl_3$)

3β-HYDROXY-9β:10α-DECALIN-2β-YL BENZOATE

LXXXIV b



2β-HYDROXY-9β:10α-DECALIN-3β-YL BENZOATE

LXXXVI b

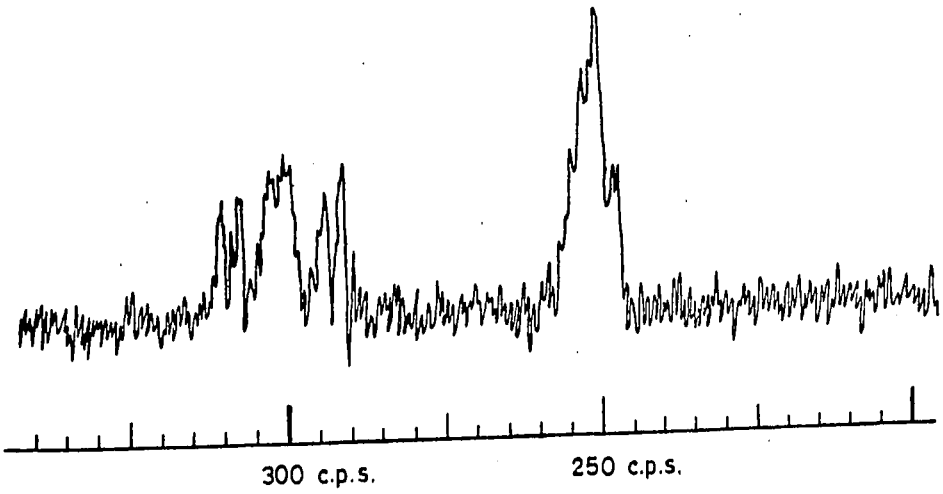


Fig. 6

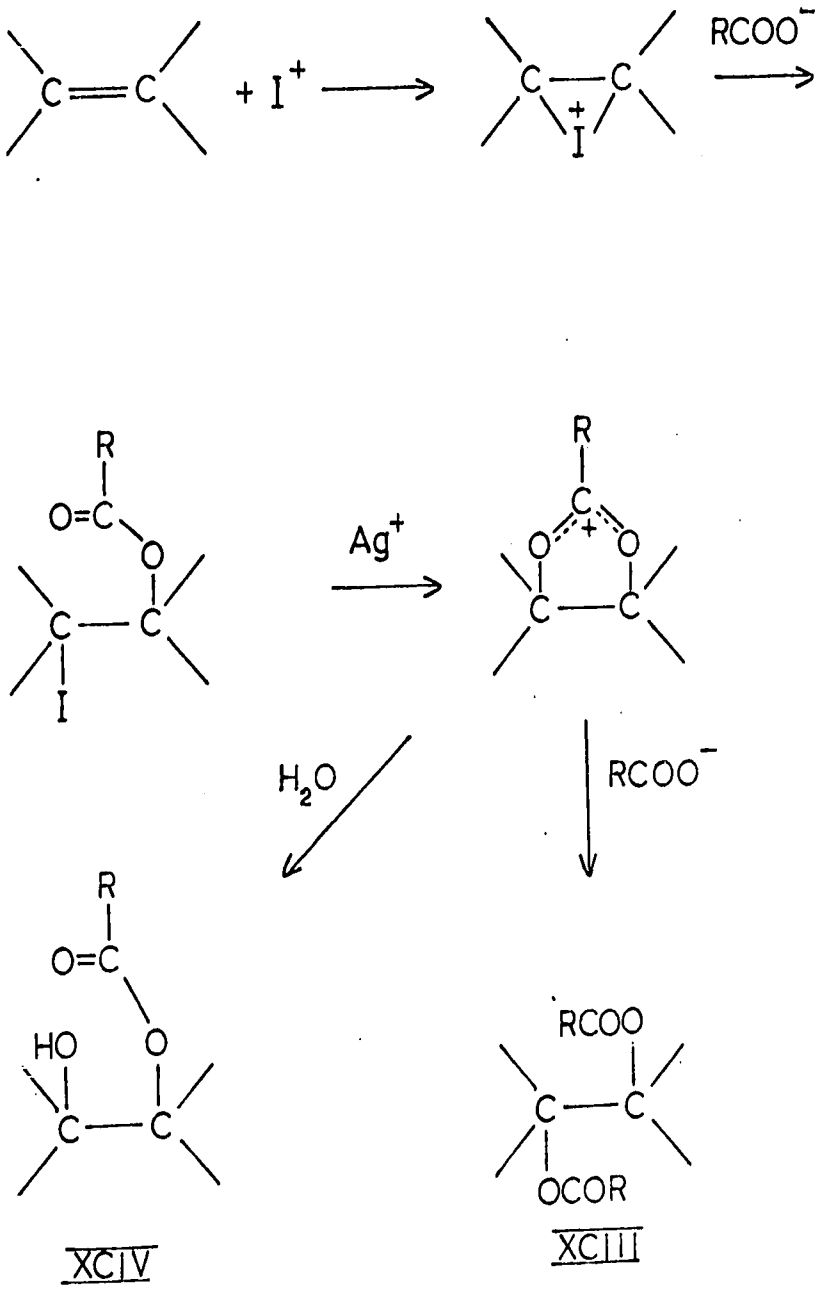
chromatography to consist of a mixture of hydroxyester and unreacted diol. These two materials were separated by column chromatography and a 72% yield of 3β-hydroxy-9β:10α-decalin-2β-yl benzoate (LXXXIVb) was obtained. Also 18% of unreacted diol was recovered. The structure of the hydroxybenzoate follows from its elemental analysis, infrared and n.m.r. spectra (fig. 6). The yield of the hydroxybenzoate based upon reacted starting material was 91%.

In order to show that this hydroxybenzoate resulted from the hydrolysis of an intermediate acyloxonium ion, the decalin-2β:3β-diol was esterified directly with one equivalent of benzoyl chloride. The equatorial ester, 2β-hydroxy-9β:10α-decalin-3β-yl benzoate, LXXXVIb, was obtained in 93% yield, based on reacted glycol. That the products obtained from the hydrolysis of the orthoesters, LXXXVIIIb,c, and d were those of kinetic control was demonstrated by the rearrangement of each of the hydroxyesters, LXXXIXb,c, and LXXXIVb to the corresponding axial alcohol-equatorial esters XCb, c and LXXXVIb, by treatment with D-10-camphorsulphonic acid in benzene. In each case the apparent equilibrium favoured the compounds with an equatorial ester group.

C. The Prevost Reaction

1. Introduction

The Prevost reaction involves the reaction of an olefin with halogen and the silver salts of carboxylic acids. In a molar ratio of 1:1, iodine and a silver carboxylate react to form an acyl hypoiodite



SCHEME II

(XCI), but with a molar ratio of 1:2 a "Simonini complex" is formed. The structure of this complex is unknown, but is usually formulated as XCII (26).

$$RCOOAg + I_2 \longrightarrow \underset{XCI}{RCOOI} + AgBr. \xrightarrow{RCOOAg}$$

RCOOI. RCOOAg XCII

Both the hypoiodite and the "Simonini comples" serve as sources of electrophilic iodine. Under anhydrous conditions the subsequent reaction with olefin leads to a diester (XCIII), whereas in the presence of water a hydroxyester (XCIV) is obtained (Woodward's method (48)).

The mechanism of this reaction has been studied in some detail and is summarized in scheme II (27). Addition of positive iodine to the olefin followed by attack of carboxylate anion results in the formation of an iodoester. Reaction of this iodoester with silver ion leads to the intermediate acyloxonium ion which can then form the products as depicted.

1. The "wet" Prevost reaction with Δ^2-Octalin.

Since the Woodward modification is merely the hydrolysis of an acyloxonium ion then this reaction should, when carried out under suitable conditions, show the same stereospecificity as was found in the hydrolysis of the acyloxonium salts and of the orthoesters. That

this expectation was justified was shown by the reaction of iodine and silver acetate in moist acetic acid with Δ^2-9β:10α-octalin. Column chromatography of the crude product gave a 79% yield of 3β-hydroxy-9β:10α-decalin-2β-yl acetate (LXXXIXb).

D. Discussion of Results.

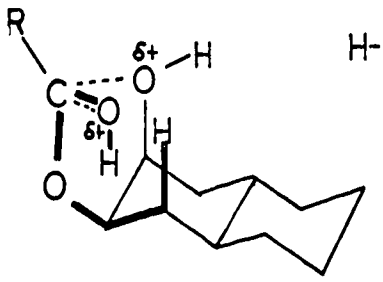
The results reported in the above sections on the hydrolysis of acyloxonium salts, orthoesters fused to rigid six-membered rings and of the wet Prevost reaction result in formation of the kinetically controlled product and yield almost exclusively hydroxyesters with the ester group in the axial position. There are two factors which may be involved in the hydrolysis reaction and which would account for the observed stereospecificity. It may be noted that, except in the case of the orthoformate, the stereospecificity is of high order. Even in the supposedly stereospecific diaxial ring opening of the cholestane-2,3-epoxides (α and β), significant amounts of the equatorial bromohydrins were found. In the case of the hydrolysis of the anisoxonium salts, quantitative thin layer chromatography shows that there is certainly less than 0.5% of the product with an equatorial ester group.

One factor which may be considered to account for the observed stereospecificity is a possible difference in basicity between the two ring oxygens. A difference in basicity between axial and equatorial amines has been observed, with the equatorial amino group being more

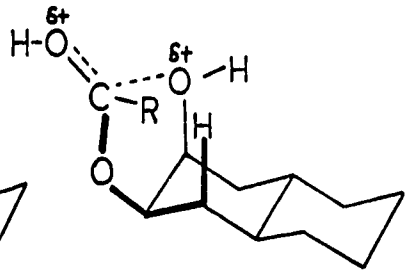
basic (49). By analogy it might be expected that the equatorial oxygen of the dioxolane ring would be slightly more basic than the axial oxygen. A similar explanation has been put forward to account for the observed stereospecificity found with the hydrolysis of 3α:5α-acetonium-6β-substituted chloestane salts (50). Hydrolysis of these compounds yields the 3α-hydroxy-5α-acetate exclusively and it was suggested that this stereospecificity was due to preferential protonation of the 3α-oxygen. In this series of compounds, an electron withdrawing substituent is present at the 6β position and the author felt that this would cause a reduction of electron density at the 5α-oxygen, thus favouring the 3α-oxygen with respect to protonation. In the series of compounds studied here, no such inductive effects are present.

If protonation of the oxygens of the hydroxydioxolane ring were the deciding factor and all other effects remained the same, then a faster rate of formation of the axial ester would always be expected. However this does not seem to be the case since with the decalin orthoformate an almost equal amount of both possible hydroxyformates is produced.

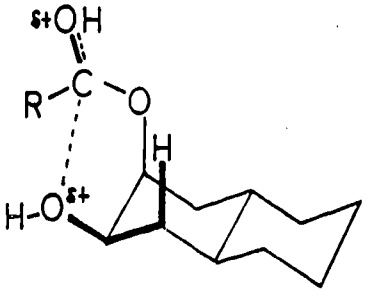
The second factor could be the energy of the replusive non-bonding interactions which arise in the opening of the ring to form the equatorial ester. If one considers the transition state leading to ring opening with formation of the equatorial ester



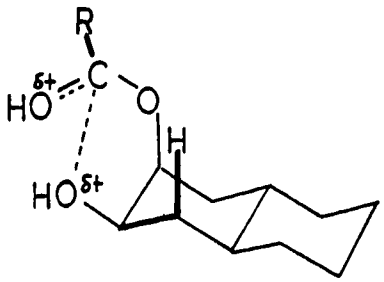
XCV



XCVI



XCVII



XCVIII

(i.e. XCV or XCVI) it may be seen that a strong non-bonding interaction could arise between either the incipient carbonyl oxygen (XCV) or the R group (XCVI) and the nearest cis-axial hydrogen. However, in the transition state leading to the axial ester, these interactions would be greatly reduced, especially since the bond between the partially formed carbonyl group and equatorial oxygen is lengthening, with the result that the partially formed ester group is moving away from the cis-axial hydrogen (XCVII and XCVIII).

That this steric interaction plays an important part in determining the stereochemistry of the products is well supported by the results found with the hydrolysis of the decalin ethyl orthoformate. Here R is H, and it would be expected that in the transition state (XCVI) the non-bonding interactions would be reduced, due to the smaller size of hydrogen, and thus a greater proportion of equatorial ester would be expected. This is exactly what is found to occur.

PART IV

EXPERIMENTAL

Unless otherwise stated, the following are implied:petroleum ether refers to the fraction of b.p. 30°-60°, rotations and infrared spectra were determined in chloroform solution. Melting points, which were determined on a Kofler hot stage, and boiling points are uncorrected. The infrared spectra were determined on either a Beckman IR-5 or IR-10 instrument, the peak positions are quoted in wave numbers. The n.m.r. spectra were determined in deuteriochloroform, unless otherwise stated, on a Varian A-60 spectrometer; the chemical shifts are reported in p.p.m. downfield from the tetramethylsilane signal. Optical rotary dispersion and ultraviolet spectra were determined on a Jasco model O.R.D./U.V.5. spectrophotometer. Thin layer chromatography (abbreviated to T.L.C.) was carried out using Camag silica gel D.F.5 or where appropriate Merck aluminium oxide G. The refractive indices were determined with a thermostatically controlled Bausch and Lomb refractometer. Microanalyses were performed by Dr. A. Bernhardt, Microanalytisches Laboratorium, Mülheim (Ruhr), Germany and A.B. Gygli, Toronto, Organic extracts were dried with anhydrous magnesium sulphate.

Preparation of Acyloxonium Hexafluoroantimonates

The general procedure used was similar to that used by C.B. Anderson (I). A known amount of diaxial bromo-ester in nitromethane was treated with an equimolar quantity of silver hexafluoroantimonate (Alfa Inorganics Inc. Beverly, Mass. U.S.A.). After standing overnight at room temperature the reaction mixture was filtered and the filtrate evaporated under reduced pressure at room temperature. The residue was dissolved in a minimum quantity of methylene chloride and crystallization effected by the addition of anhydrous ether. The product was collected by filtration and dried under high vacuum. All of the above steps were carried out in a dry box containing phosphorous pentoxide and filled with nitrogen; in all the experiments involving these acyloxonium salts all weighings and transfers were carried out in a dry box.

The preparation of the steroidal acyloxonium salts differed in one respect from the preparation of the decalin salts. Due to the low solubility of the steroid bromoesters it was found necessary to heat the reaction mixture at 50°.

5α-Cholestan-2α:3α-p-anisoxonium hexafluoroantimonate (XXXV)

2β-Bromo-5α-cholestan-3α-yl-p-anisate (1.0g) was treated overnight with silver hexafluoroantimonate (0.57g) in nitromethane (10ml) at 50°. The product was isolated as described above. Crystallization from methylene chloride:ether gave 5α-cholestan-2α:3α-p-anisoxonium hexafluoroantimonate (0.7g), m.p. 196°-198° (sealed capillary tube), $[\alpha]_D$ + 21°

(CH_2Cl_2), $\nu_{max}^{CH_2Cl_2}$ 658. Calculated for $C_{35}H_{53}O_3SbF_6$: C, 55.40; H, 7.0. Found: C, 55.42; H, 7.0. The n.m.r. spectrum showed signals at 0.83 (singlet), 4.0 (singlet), a broad multiplet centred at 5.77 and a quartet centred at 7.75 (J_{AB} 9 c.p.s., $\delta_B-\delta_A$ = 66 c.p.s.). These peaks were assigned to the C-19 methyl group,* the phenylmethoxy group, the C-2 and C-3 hydrogens (axial and equatorial) and to the phenyl hydrogens respectively.

5α-Cholestan-2β:3β-p-anisoxonium hexafluoroantimonate (XXXVIIIa)

3α-Bromo-5α-cholestan-2β-yl p-anisate (1.82g) was treated with silver hexafluoroantimonate (1.07g) in nitromethane (10ml) as described above. Crystallization from methylene chloride:ether gave 5α-cholestan-2β:3β-p-anisoxonium hexafluoroantimonate (1.31g), m.p. 188°-189° (sealed capillary tube), $[\alpha]_D$ - 74° (CH_2Cl_2), $\nu_{max}^{CH_2Cl_2}$ 660. Calculated for $C_{35}H_{53}O_3SbF_6$: C, 55.40; H, 7.0. Found: C, 54.95; H, 6.87. The n.m.r. spectrum showed peaks at 0.87 (singlet) and 4.03 (singlet), a broad unresolved multiplet centred at 5.82 and a quartet at 7.75 (J_{AB} 9 c.p.s. $\delta_B-\delta_A$ = 66 c.p.s.). These bands were assigned to the C-19 methyl group, the phenylmethoxy group, the C-2 and C-3 hydrogens (equatorial and axial) and to the phenyl hydrogens respectively.

* The assignment of the C-19 methyl peak position followed from the observation that it was only methyl peak whose position changed in the various ring A derivatives. The other methyl peaks appeared at 38, 48 and 54 c.p.s. downfield from the tetramethylsilane signal, and since these peaks did not change with the ring A substituents, they are not recorded.

5α-Cholestan-2β:3β-benzoyloxonium hexafluoroantimonate. (XXXVIIIb)

A solution of 3α-bromo-5α-cholestan-2β-yl benzoate (1.07g) in nitromethane (15ml) was treated with silver hexafluoroantimonate (0.57g) for 12 hours at 50°. The product was isolated as described above. Crystallization from methylene chloride:ether gave 5α-cholestan-2β:3β-benzoyloxonium hexafluoroantimonate (0.85g), m.p. 140°-141°, $[\alpha]_D$ -28° (CH_2Cl_2). $\nu_{max}^{CH_2Cl_2}$ 660. Calculated for $C_{34}H_{51}O_2SbF_6$: C, 56.12; H, 7.07. Found: C, 55.45; H, 6.68.

9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate. (XXXIIa)

2β-Bromo-9β:10α-decalin-3β-yl p-anisate (1.93g) was treated with silver hexafluoroantimonate (1.8g) in nitromethane (18ml) as above. Crystallization from methylene chloride:ether gave 9β:10α-decalin-2β:3β-p-anisoxonium hexafluoroantimonate (2.15g), m.p. 178°-179° (sealed capillary tube), $\nu_{max}^{CH_2Cl_2}$ 655. Calculated for $C_{18}H_{23}O_3SbF_6$: C, 41.32; H, 4.43. Found: C, 40.92; H, 4.61. The n.m.r. spectrum (CD_2Cl_2) had a peak at 4.02 (singlet), an unresolved multiplet at 5.78 and a quartet at 7.75 (J_{AB} 9 c.p.s., $\delta_B-\delta_A$ = 66 c.p.s.). These bands were assigned to the phenylmethoxy group, the C-2 and C-3 hydrogens (equatorial and axial) and the phenyl hydrogens respectively.

9β:10α-Decalin-2β:3β-benzoyloxonium hexafluoroantimonate (XXXIIb)

2β-Bromo-9β:10α-decalin-3α-yl benzoate (1.0g) was treated with silver hexafluoroantimonate (1.0g) in nitromethane (10ml), as described above. Crystallization from methylene chloride:ether gave 9β:10α-decalin-

2β:3β-benzoyloxonium hexafluoroantimonate (1.24g), m.p. 142°-144° (sealed capillary tube). Calculated for $C_{17}H_{21}O_2SbF_6$: C, 41.41; H, 4.30. Found: C, 41.49; H, 4.32. $\nu_{max}^{CH_2Cl_2}$ 655. The n.m.r. (CD_2Cl_2) had an unresolved multiplet centred at 5.89 and a complex multiplet centred at 8.08. These signals were assigned to the C-2 and C-3 hydrogens (equatorial and axial) and the phenyl hydrogens respectively.

Reaction of Acyloxonium Salts with Halide Ion

Reaction of 5α-Cholestan-2α:3α-p-anisoxonium hexafluoroantimonate with bromide ion in methylene chloride.

A solution of the salt (250 mg) in methylene chloride (10ml) was treated with tetraethylammonium bromide (670 mg). After standing for 1 hour at room temperature the reaction mixture was diluted with ether and washed several times with water, dried and the solvent removed under reduced pressure. The product (197 mg), $[\alpha]_D$ 0°, was shown by T.L.C. (benzene) to consist of two compounds corresponding to the diaxial (R_f 0.53) and the diequatorial (R_f 0.56) bromoanisates. The infrared spectrum showed also that a mixture had been obtained.

Analysis of products by infrared spectroscopy

The following spectra were determined on a Beckman IR-5A spectometer equipped with cesium bromide optics and using potassium bromide cells. The diaxial bromoester, 2β-bromo-5α-cholestan-3α-yl p-anisate had absorption at 695 (m) while the diequatorial bromoester, 3β-bromo-5α-cholestan-2α-yl p-anisate had absorption at 695 (w) and

714 (m). The product from the reaction above was dissolved in CS_2 to give a suitable concentration and the infrared spectrum taken between 800 and 600 cm^{-1}. Mixtures of the diaxial and diequatorial bromoanisates were prepared and dissolved in CS_2 to give the same concentration as that of the product, and their infrared spectra in the same region were determined. From a comparison of the peak heights at 714 and 695 it was concluded that the product contained approximately 68% diequatorial and 32% diaxial bromoanisate.

Reaction of 5α-Cholestan-2β:3β-p-anisoxonium hexafluoroantimonate with bromide ion in methylene chloride.

A solution of the salt (154 mg) in methylene chloride (10ml) was treated with tetraethylammonium bromide (500 mg) for 30 minutes as described above. T.L.C. (C_6H_6) showed the product to be almost entirely diaxial bromoanisate with a small amount of material at the origin (most likely hydrolysis product). The product was purified by T.L.C. (C_6H_6), being detected by ultraviolet light. The product (101 mg), $[\alpha]_D$ + 34°, had an infrared spectrum almost identical with that of 3α-bromo-5α-cholestan-2β-yl p-anisate. Crystallization from methylene chloride: pentane gave 3α-bromo-5α-cholestan-2β-yl p-anisate identified by m.p., mixed m.p. and infrared spectrum.

Analysis of reaction product.

(a) T.L.C. The two bromoesters could not be separated very easily by T.L.C. In most solvent compositions used for T.L.C. the product showed

only one spot. However, multiple elution in benzene (7x) showed the product to consist of two materials corresponding to the diaxial and diequatorial bromoanisates, with only a trace of the diequatorial compound being present.

(b) Infrared In a second experiment the anisoxonium salt (297 mg) gave, on treatment with tetraethylammonium bromide in methylene chloride, 229 mg of product, which was dissolved in CS_2 to give a suitable concentration. The infrared spectra were determined on a Beckman IR-5A spectrometer equipped with cesium bromide optics and using potassium bromide cells. In the infrared spectrum of the diequatorial bromoanisate, 2α-bromo-5α-cholestan-3β-yl p-anisate, there was a peak at 716 cm^{-1} (w) which did not appear in the spectrum of the diaxial bromoester, 3α-bromo-5α-cholestan-2β-yl p-anisate. Mixtures of the diaxial and diequatorial bromoanisates were prepared and dissolved in CS_2 to give same concentration as that of the product. From the intensity of the peak at 716 cm^{-1} in the infrared spectra of the mixtures of diaxial and diequatorial bromoanisates and in the spectrum of the product, it was estimated that there was less than 3% of the diequatorial bromoanisate present in the reaction product.

Reaction of 5α-Cholestan-2α:3α-p-anisoxonium hexafluoroantimonate with bromide ion in acetonitrile.

The anisoxonium salt (225 mg) was treated with tetraethylammonium bromide (630 mg) in acetonitrile (10ml) for 1 hour as described above. The product, $[\alpha]_D$ 0°, had an infrared spectrum (CS_2), in the region

800 to 600 cm^{-1} which corresponded to the same product composition as obtained above i.e. 68% diequatorial and 32% diaxial bromoanisates.

Reaction of 5α-Cholestan-2α:3α-p-anisoxonium hexafluoroantimonate with bromide ion in nitromethane.

The salt (0.23g) was treated with tetraethylammonium bromide (0.59g) in nitromethane (10ml) for 23 hours at room temperature as previously described, and gave 164 mg of bromoanisate mixture $[\alpha]_D$ + 5°. The infrared spectrum (CS_2) corresponded to a product composition of 60% diequatorial and 40% diaxial bromoanisate.

Reaction of 9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate with bromide ion in methylene chloride.

A solution of salt (0.26g) in methylene chloride (10ml) was treated with tetraethylammonium bromide (1.05g) for 1 hour at room temperature as described above. The product (0.18g) had an infrared spectrum almost identical with that of 2β-bromo-9β:10α-decalin-3α-yl p-anisate. T.L.C. [benzene:cyclohexane (1:1)], after two elutions, showed two compounds corresponding to the diaxial (R_f 0.44) and diequatorial (R_f 0.35) bromoanisates, with only a trace of the diequatorial bromoester being present. Crystallization from petroleum ether gave 2β-bromo-9β:10α-decalin-3α-yl p-anisate, identified by m.p., mixed m.p. and infrared spectrum.

Analysis of reaction product by T.L.C.

The crude product from above was dissolved in chloroform (0.7ml). Mixtures of the diaxial and diequatorial bromoanisates were prepared and dissolved in chloroform to give the same concentration as that of the product. A standard number of drops of each solution were applied to T.L.C. plates which were then eluted twice with benzene:cyclohexane (1:1). The plates were sprayed with 30% sulphuric acid and charred, and the intensities of the spots compared. By this method it was estimated that the amount of diequatorial bromoanisate was approximately 5%.

Reaction of 9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate with chloride ion in methylene chloride.

A solution of the salt (95 mg) in methylene chloride (10ml) was treated with tetraethylammonium chloride (350 mg) for 30 minutes at room temperature. T.L.C. [benzene:cyclohexane (1:1)] after two elutions, showed the product (54 mg) to consist of almost entirely diaxial chloroanisate together with a small amount of the diequatorial compound. Crystallization from methylene chloride:methanol gave 2β-chloro-9β:10α-decalin-3α-yl p-anisate (38 mg) identified by m.p., mixed m.p. and infrared spectrum.

Analysis of reaction product by T.L.C.

The crude product (54 mg) from the above reaction was dissolved in chloroform (0.5ml). Mixtures of the diaxial and diequatorial chloroanisates were prepared and also dissolved in chloroform to give the same

Analysis of reaction product by T.L.C.

The crude product from above was dissolved in chloroform (0.7ml). Mixtures of the diaxial and diequatorial bromoanisates were prepared and dissolved in chloroform to give the same concentration as that of the product. A standard number of drops of each solution were applied to T.L.C. plates which were then eluted twice with benzene:cyclohexane (1:1). The plates were sprayed with 30% sulphuric acid and charred, and the intensities of the spots compared. By this method it was estimated that the amount of diequatorial bromoanisate was approximately 5%.

Reaction of 9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate with chloride ion in methylene chloride.

A solution of the salt (95 mg) in methylene chloride (10ml) was treated with tetraethylammonium chloride (350 mg) for 30 minutes at room temperature. T.L.C. [benzene:cyclohexane (1:1)] after two elutions, showed the product (54 mg) to consist of almost entirely diaxial chloroanisate together with a small amount of the diequatorial compound. Crystallization from methylene chloride:methanol gave 2β-chloro-9β:10α-decalin-3α-yl p-anisate (38 mg) identified by m.p., mixed m.p. and infrared spectrum.

Analysis of reaction product by T.L.C.

The crude product (54 mg) from the above reaction was dissolved in chloroform (0.5ml). Mixtures of the diaxial and diequatorial chloroanisates were prepared and also dissolved in chloroform to give the same

concentration as that of the product. A standard number of drops of each solution (from the same dropping pipette) were applied to T.L.C. plates, which were then eluted with benzene:cyclohexane (1:1) four times. The plates were charred and the intensities of the spots compared. By this method it was estimated that the amount of diequatorial chloroanisate was about 6% of the product.

Reaction of 5α-Cholestan-2β:3β-benzoyloxonium hexafluoroantimonate with bromide ion in methylene chloride.

A solution of the benzoyloxonium salt (250 mg) in methylene chloride (15ml) was treated with tetraethylammonium bromide (1.0 g) for 1 hour at room temperature. The product (182 mg) showed one spot upon thin layer chromatography [benzene] and had an infrared spectrum almost identical with that of the diaxial bromobenzoate. Crystallization from ether:methanol gave 3α-bromo-5α-cholestan-2β-yl benzoate (140 mg), m.p. 115°-116°, mixed m.p. with authentic sample 114°-115°, $[\alpha]_D$ + 51°. The infrared spectrum was identical with that of an authentic sample.

Reaction of Epoxides with Hydrobromic Acid.

i) 2:3-Epoxy-9β:10α-decalin

A solution of the epoxide (198 mg) in methylene chloride (20ml) was shaken with 48% aqueous hydrobromic acid (5ml) for 5 minutes. The methylene chloride solution was washed with dilute solutions of sodium bisulphite and sodium bicarbonate, water, dried and then evaporated. The residue (279 mg)

was dried under high vacuum.

On silica gel thin layer chromatography [benzene:ether (1:1)] it was found that the diaxial and diequatorial bromohydrins had the same R_f value. If the T.L.C. plate was developed with iodine vapour, the diequatorial bromohydrin showed up, but the diaxial did not develop. With the product from the reaction a small amount of the diequatorial material was detected using this method. On alumina thin layer chromatography [ether:methanol (98:2)], separation of the bromohydrins was achieved, with the diequatorial compound moving slower than the diaxial material. In the product from the epoxide opening reaction a small amount of the diequatorial bromohydrin was again detected, but owing to the poor development, on charring, no estimate of the amount of this compound could be made.

5α-Cholestan-2α:3α-epoxide.

(ii) The epoxide (99 mg) in methylene chloride (30ml) was treated with aqueous hydrobromic acid as described above (i). T.L.C. [benzene:ether (9:1)] showed the product (115 mg) to consist of a mixture of the corresponding diaxial and diequatorial bromohydrins (R_f 0.38 and 0.55) with only a small amount of the diequatorial material being present.

5α-Cholestan-2β:3β-epoxide

(iii) The epoxide (104 mg) in methylene chloride was treated as above (i). The residue (122 mg) was shown by T.L.C. [benzene:ether (9:1)] to be

a mixture of the two possible bromohydrins, again only a small amount of the diequatorial compound being detected. In this case the diequatorial bromohydrin (2α-bromo-5α-cholestan-3β-ol) ran slower (R_f 0.39) than the diaxial bromohydrin (R_f 0.49).

Analysis of Product Mixtures

The analyses of the products from (ii) and (iii) were carried out by quantitative thin layer chromatography in a similar manner to that described for the analysis of the decalin bromoanisate mixtures. For 5α-cholestan-2α:3α-epoxide the product mixture was estimated to consist of 95% of diaxial and 5% diequatorial bromohydrins. For 5α-cholestan-2β:3β-epoxide the product was estimated to contain 97% diaxial and 3% diequatorial bromohydrins.

Reaction of Acyloxonium Hexafluoroantimonates with Carboxylate Anions.

Reaction of 9β:10α-Decalin-2β:3β-benzoyloxonium hexafluoroantimonate with benzoic acid and N,N-diisopropylethylamine.

N,N-diisopropylethylamine (131 mg) (Fluka AG. Buchs SG. Switzerland) was dissolved in methylene chloride (2.5ml) and added to a solution of benzoic acid (128 mg) in methylene chloride (2.5ml). To the resulting mixture was added the decalin benzoyloxonium salt (100 mg) and the solution was stood at room temperature for 24 hours. The reaction was washed several times with water, dried and the solvent evaporated. T.L.C. (benzene) showed two spots corresponding in R_f values

to the diaxial and diequatorial dibenzoates with only a small amount of the diequatorial compound being present. These two materials were separated by T.L.C. eluting with benzene and gave 9β:10α-decalin-2α:3β-diol dibenzoate (7 mg), crystallized from ether:methanol and identified by m.p., mixed m.p. with authentic sample and infrared spectrum; and 9β:10α-decalin-2β:3α-diol dibenzoate (48 mg), crystallized from ether:methanol and identified by m.p., mixed m.p. with authentic sample, and infrared spectrum.

Reaction of 9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate with N,N-diisopropylethylamine and trifluoroacetic acid.

N,N-diisopropylethylamine (125 mg) in methylene chloride (2.5ml) was added to a solution of trifluoroacetic acid (113 mg) in methylene chloride (2.5ml). To the resulting solution the decalin anisoxonium salt (100 mg) was added and the reaction was stood at room temperature for 36 hours. The solution was washed several times with water, dried and the solvent evaporated. T.L.C. (benzene) showed the product (49 mg) to consist of almost entirely one compound together with a trace of a second compound, both being visible under ultraviolet light. Crystallization from pentane gave 9β:10α-decalin-2β-yl p-anisate-3α-yl trifluoroacetate, m.p. 66°-68°. Calculated for $C_{20}H_{23}O_5F_3$: C, 59.99; H, 5.79. Found: C, 59.81; H, 5.87. ν_{max} 1780, 1710. The n.m.r. spectrum showed peaks at 3.83, 5.25 (2H, multiplet, W 1/2 5 c.p.s.) and 7.43 (quartet, J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 63 c.p.s.). These absorptions

were assigned to the phenylmethoxyl group, C-2 and C-3 hydrogens (both diequatorial) and the phenyl ring hydrogens respectively.

Acid catalysed hydrolysis of Acyloxonium Hexafluoroantimonates

General Procedure:

A solution of the acyloxonium salt in methylene chloride (10ml) was shaken with aqueous acetic acid (10ml, 10%) for several minutes. The reaction mixture was then washed with dilute sodium bicarbonate solution, water, dried and the solvent evaporated under reduced pressure.

5α-Cholestan-2β:3β-p-anisoxonium hexafluoroantimonate.

A solution of the salt (250 mg) in methylene chloride was treated as above. T.L.C. [ether:benzene (1:1)] showed the product (180 mg) to consist of almost entirely one compound (R_f 0.64) together with a trace of a second compound (R_f 0.85), both spots being visible under ultraviolet light as well as on charring. Crystallization from acetone:petroleum ether gave 3β-hydroxy-5α-cholestan-2β-yl p-anisate, m.p. 132°-133°, $[\alpha]_D$ - 22°, ν_{max} 3570, 1700. Calculated for $C_{35}H_{54}O_4$: C, 78.01; H, 10.10. Found: C, 77.73; H, 9.95. The n.m.r. spectrum had bands at 0.98 (singlet), 2.48 (singlet; OH), 3.78 (singlet), a broad band at 3.87 (W 1/2 22 c.p.s.), a narrow band at 5.29 (W 1/2 8 c.p.s.) and 7.38 (quartet, J_{AB} 9 c.p.s. $\delta_B-\delta_A$ = 65 c.p.s.). These bands were assigned to the C-19 methyl group, the hydroxyl group, the phenylmethoxyl group, C-3 hydrogen (axial), C-2 hydrogen (equatorial) and the phenyl ring hydrogens respectively.

5α-Cholestan-2α,3α-p-anisoxonium hexafluoroantimonate.

A solution of the salt (370 mg) in methylene chloride was treated as described above. T.L.C. [ether:benzene (1:1)] showed the product (255 mg) to consist of almost entirely one compound (R_f 0.54) together with a trace of a second compound (R_f 0.64), both being visible under ultraviolet light as well as upon charring. Crystallization from acetone: water gave 2α-hydroxy-5α-cholestan-3α-yl p-anisate, m.p. 146°-148°, $[\alpha]_D$ + 45°, ν_{max} 3580, 1700. Calculated for $C_{35}H_{54}O_4$: C, 78.01; H, 10.10. Found: C, 77.68; H, 10.08. The n.m.r. spectrum contained signals at 0.82 (singlet), 2.47 (singlet, OH), 3.80 (singlet), a broad band at 3.87 (W 1/2 20 c.p.s.), a narrow band at 5.29 (W 1/2 6 c.p.s.) and a quartet at 7.41 (J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 65 c.p.s.). These signals were assigned to the C-19 methyl group, the hydroxyl group, the phenylmethoxy group, the C-2 hydrogen (axial), the C-3 hydrogen (equatorial) and to the phenyl hydrogens respectively.

5α-Cholestan-2β:3β-benzoyloxonium hexafluoroantimonate.

A solution of salt (180 mg) in methylene chloride (10ml) when treated with aqueous acetic acid as described above gave 143 mg of product, ν_{max} 3570, 1715. This material was not characterized but was saponified directly by dissolving in methanol (25ml) and ether (10ml) and treatment with potassium hydroxide (1.0g) overnight. The reaction was poured into water and extracted with ether; the ether extracts were washed several times with water, dried and evaporated. Crystallization

of the product (78 mg) from chloroform:methanol gave 5α-cholestan-2β:3β-diol, m.p. 178°-179°, $[\alpha]_D$ + 44°. Reported m.p. 174°-177°, $[\alpha]_D$ + 43°. The m.p. was undepressed upon mixture with an authentic sample of the diol.

9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate.

A solution of the salt (500 mg) in methylene chloride was treated with aqueous acetic acid as outlined above. T.L.C. [ether:benzene (1:1)] showed the product (286 mg) to consist of almost entirely one compound (R_f 0.32) together with a trace of a second compound (R_f 0.50). Crystallization from ether:petroleum ether gave 3β-hydroxy-9β:10α-decalin-2β-yl p-anisate, m.p. 92°-94°, ν_{max} 3580, 1700. Calculated for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.90; H, 7.87. The n.m.r. spectrum showed bands at 2.88 (singlet, OH), 3.71 (broad band, W 1/2 21 c.p.s.) 3.77 [singlet), 5.30 (narrow band, W 1/2 7 c.p.s.), and 7.39 (quartet, J_{AB} 9 c.p.s., $\delta_B-\delta_A$ = 65 c.p.s.). These bands were assigned to the C-3 hydroxyl group, the C-3 hydrogen (axial), the phenylmethoxy group, the C-2 hydrogen (equatorial) and to the phenyl hydrogens respectively.

9β:10α-Decalin-2β:3β-benzoyloxonium hexafluoroantimonate.

A solution of the benzoyloxonium salt (100 mg) in methylene chloride (10ml) was treated with aqueous acetic acid as described above. T.L.C. [benzene:ether (1:1)] showed the product (52 mg) to be almost entirely one compound. Crystallization from ether:pentane

gave 3β-hydroxy-9β:10α-decalin-2β-yl benzoate, m.p. 105°-107°. Calculated for $C_{17}H_{22}O_3$: C, 74.40; H, 8.09. Found: C, 74.34; H, 7.83. ν_{max} 3600, 1705. The n.m.r. spectrum had signals at 2.40 (singlet, OH), 3.78 (broad band, W 1/2 21 c.p.s.), 5.37 (narrow band, W 1/2 7 c.p.s.), 7.42 and 8.05 (both multiplets). These signals were assigned to the C-3 hydroxyl group, the C-3 hydrogen (axial), the C-2 hydrogen (equatorial), and the phenyl hydrogens respectively.

Reaction of 9β:10α-Decalin-2β:3β-p-anisoxonium hexafluoroantimonate with base.

Potassium hydroxide.

A solution of the decalin anisoxonium salt (200 mg) in methylene chloride (10ml) was shaken with aqueous potassium hydroxide solution (10ml; 5%) for 2 minutes. The methylene chloride was washed several times with water, dried and evaporated under reduced pressure. T.L.C. [benzene:ether (1:1)] showed the product to consist of one compound with the same R_f value as 2β-hydroxy-9β:10α-decalin-3β-yl p-anisate. Crystallization from ether:petroleum ether gave 2β-hydroxy-9β:10α-decalin-3β-yl p-anisate (112 mg) identified by m.p., mixed m.p. with authentic sample and infrared spectrum.

Hydrolysis of Anisoxonium Hexafluoroantimonates and analysis of the products by T.L.C.

A known amount of the particular anisoxonium salt in methylene chloride was treated with aqueous acetic acid as described previously.

The product was dissolved in chloroform to give a suitable concentration. Standard mixtures of the two possible hydrolysis products were prepared, i.e. of the equatorial alcohol, axial anisate and axial alcohol, equatorial anisate compounds, and were dissolved in chloroform to give the same concentration as that of the hydrolysis product. A standard number of drops of each solution (from the same dropping pipette) were applied to T.L.C. plates and which were eluted with ether:benzene (1:1). The plates were sprayed with 30% sulphuric acid and charred, and the intensities of the resulting spots were compared.

For the 5α-cholestan-2α:3α-p-anisoxonium, 5α-cholestan-2β:3β-p-anisoxonium and 9β:10α-decalin-2β:3β-p-anisoxonium salts the amount of axial alcohol-equatorial ester was estimated at less than 0.5% of the product.

Alkaline hydrolyses of Hydroxyanisates.

General Procedure.

A solution of the hydroxyanisate (50-100 mgm) and potassium hydroxide (200-300 mgm) in methanol (5ml) and ether (1ml) was stood overnight at room temperature. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed several times with water, dried and evaporated under reduced pressure.

2α-Hydroxy-5α-cholestan-3α-yl p-anisate.

Product crystallized from chloroform:acetone, m.p. 222°-224° $[\alpha]_D$ + 31°. Reported for 5α-cholestan-2α:3α-diol (51) m.p. 212°-214°

$[\alpha]_D$ + 32°. Mixed m.p. with 5α-cholestan-2α:3α-diol, 223°-225°.

3α-Hydroxy-5α-cholestan-2α-yl p-anisate.

Product crystallized from chloroform:acetone, m.p. 225°-226° $[\alpha]_D$ + 29°. Reported for 5α-cholestan-2α:3α-diol (51), 212°-214°, $[\alpha]_D$ + 32°. Mixed m.p. with authentic sample, 224°-226°.

2β-Hydroxy-9β:10α-decalin-3β-yl p-anisate.

Product crystallized from benzene:petroleum ether, m.p. 140°-141°, mixed m.p. with authentic sample, 139°-140°. Reported for 9β:10α-decalin-2β:3β-diol m.p. 140°-141° (22).

3β-Hydroxy-9β:10α-decalin-2β-yl p-anisate.

Product crystallized from benzene:petroleum ether, m.p. 141°-142°, mixed m.p. with authentic sample, 141°-142°.

2β-Hydroxy-5α-cholestan-3β-yl p-anisate.

Product crystallized from ether:petroleum ether, m.p. 174°-176° $[\alpha]_D$ + 40°, mixed m.p. with authentic sample, 177°-179°.

3β-Hydroxy-5α-cholestan-2β-yl p-anisate.

Product crystallized from ether:methanol, m.p. 174°-176° $[\alpha]_D$ +42°. Mixed m.p. with authentic sample, 175°-177°.

Oxidation of the Steroid Hydroxyanisates.

A) Using dimethyl sulphoxide and acetic anhydride

(i) 3β-Hydroxy-5α-cholestan-2β-yl p-anisate.

A solution of the hydroxyanisate (147 mg) in dimethyl sulphoxide (2ml) and acetic anhydride (2ml) was stood at room temperature for 36 hours. The reaction mixture was diluted with ether and washed with dilute sodium bicarbonate solution, several times with water, dried, and the ether evaporated. Crystallization from ether:pentane gave 5α-cholestan-3-one-2β-yl p-anisate (124 mg), m.p. 68°-74°, $[\alpha]_D$ +51°, ν_{max} 1705. Calculated for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 77.96; H, 9.92. The n.m.r. spectrum had bands at 0.95 (singlet), 3.81 (singlet), 5.52 (triplet, J 7.75 c.p.s.) and 7.44 (quartet J_{AB} 9 c.p.s. $\delta_B - \delta_A$ = 67 c.p.s.). These bands were assigned to the C-19 methyl, the phenylmethoxy group, the C-2 hydrogen (equatorial) and to the phenyl hydrogens respectively. Optical rotatory dispersion in methylene chloride (C, 0.04): $[\alpha]_{650}$ + 25°, $[\alpha]_{589}$ + 50°, $[\alpha]_{307}$ + 950°, $[\alpha]_{290}$ 0°, $[\alpha]_{280}$ - 1825°; amplitude > 149. Ultraviolet in methylene chloride, λ_{max} 257, log ε 4.35.

(ii) 2α-Hydroxy-5α-cholestan-3α-yl p-anisate.

The hydroxyanisate (304 mg) was treated with dimethyl sulphoxide (3ml) and acetic anhydride (3ml) as described in (i) above. Attempted crystallization of the product from several solvent mixtures failed.

T.L.C. [ether:benzene (1:1)] of the product showed one spot; however, elution twice with ether:benzene (5:95) showed two compounds to be present. These two materials were designated Fraction A (R_f 0.53) and Fraction B (R_f 0.49), and were separated by T.L.C., eluting the plates three times with ether:benzene (5:95). The two materials were readily detected under ultraviolet light.

Fraction B (192 mg) on crystallization from ether:petroleum ether gave 5α-cholestan-2-one-3α-yl p-anisate, m.p. 86°-88°, $[\alpha]_D$ + 88°, ν_{max} 1720. Calculated for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 78.55; H, 9.96. The n.m.r. spectrum showed bands at 0.80 (singlet), 3.83 (singlet), 5.05 (narrow band, W 1/2 5 c.p.s.) and 7.44 (quartet, J_{AB} 9 c.p.s., $\delta_B-\delta_A$ = 63 c.p.s.). These bands were assigned to the C-19 methyl group, the phenylmethoxy group, the C-3 hydrogen (equatorial) and to the phenyl hydrogens respectively. Optical rotatory dispersion in methylene chloride (C, 0.039): $[\alpha]_{650}$ + 100°, $[\alpha]_{589}$ + 100°, $[\alpha]_{320}$ + 1715, $[\alpha]_{298}$ 0°, $[\alpha]_{280}$ - 2330; amplitude > 217.

Fraction A (85 mg) was crystallized from ether:petroleum ether, m.p. 108°-110°, $[\alpha]_D$ + 65°. Calculated for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 74.36; H, 9.93. ν_{max} 1700. The n.m.r. spectrum showed bands at 0.90 (singlet), 3.83 (singlet, OCH_3), 4.66 (narrow band, W 1/2 11 c.p.s.) 5.50 (narrow band, W 1/2 8 c.p.s.) and 7.43 (quartet, J_{AB} 9 c.p.s. $\delta_B-\delta_A$ = 65 c.p.s.). A Belstein test with copper wire showed that no halogen was present. A Lassaigne sodium fusion test for sulphur with sodium nitroprusside was negative.

(iii) 2β-Hydroxy-5α-cholestan-3β-yl p-anisate.

The hydroxyanisate (134 mg) was treated with dimethyl sulphoxide (2ml) and acetic anhydride (2ml) for 72 hours, and the product was isolated as described in (i) above. This oxidation appeared to be slower than the previous ones (i) and (ii), since T.L.C. [ether:benzene (1:9)] showed that besides the keto-anisate (R_f 0.66) a small amount of starting material was present. The keto-anisate was purified by T.L.C. [ether:benzene (1:9)] and the product (77 mg) was crystallized from chloroform:petroleum ether, giving 5α-cholestan-2-one-3β-yl p-anisate, m.p. 178°-179°, $[\alpha]_D$ +45°, ν_{max} 1725, 1705. Calculated for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 78.52; H, 9.53. The n.m.r. spectrum had bands at 0.82 (singlet) 3.80 (singlet), 5.42 (broad diffuse band), and 7.43 (quartet J_{AB} 9 c.p.s., $\delta_B-\delta_A$ = 68 c.p.s.). These signals were assigned to the C-19 methyl group, the phenylmethoxy group, the C-3 hydrogen (axial) and to the phenyl hydrogens respectively. Optical rotatory dispersion in methylene chloride (C, 0.04): $[\alpha]_{650}$ + 37°, $[\alpha]_{589}$ + 44°, $[\alpha]_{310}$ + 700°, $[\alpha]_{292}$ 0°, $[\alpha]_{285}$ - 175°, $[\alpha]_{280}$ 0°, amplitude 47.

B) Using the Jones procedure.

The oxidizing agent used in these experiments consisted of a solution of sodium dichromate (13g) and concentrated sulphuric acid (8.7ml) in water (30ml). To a stirred solution of the hydroxyanisate (150 mg - 250 mg) in acetone (10 - 25ml), at room temperature, was added a few drops of the above oxidizing agent (usually 0.3ml) so

that the solution was a red-orange colour. After 3 minutes a dilute aqueous solution of sodium metabisulphite ($Na_2S_2O_5$) was added to the reaction mixture until a blue-green colour was obtained. After dilution with water, the reaction mixture was extracted with ether. The ether extracts were washed with dilute sodium bicarbonate solution, water, dried and the ether evaporated under reduced pressure.

2α-Hydroxy-5α-cholestan-3α-yl p-anisate.

The hydroxyanisate (214 mg) in acetone (10ml) gave on oxidation as described above 195 mg of crude product. T.L.C. [ether:benzene(5.95)] showed very little starting material present and that the product consisted of almost entirely one compound (R_f 0.48) with a small amount of a second product running slightly ahead of the main spot. This faster running material was designated as Fraction A and the main product as Fraction B. T.L.C. separation [ether:benzene (5:95)] of these two materials gave for Fraction A, 15 mg, and for Fraction B, 150 mg.

Fraction A was crystallized from methylene chloride:petroleum ether and identified by m.p., mixed m.p. with authentic sample and infrared spectrum as 5α-cholestan-2-one-3β-yl p-anisate.

Fraction B was crystallized from methylene chloride:petroleum ether and identified by m.p., mixed m.p. with authentic sample and infrared spectrum as 5α-cholestan-2-one-3α-yl p-anisate.

3α-Hydroxy-5α-cholestan-2α-yl p-anisate.

The hydroxyanisate (180 mg) in acetone (15ml) was oxidized as described previously. The crude product (176 mg) had no OH peaks in the infrared spectrum. Crystallization from pentane gave 5α-cholestan-3-one-2α-yl p-anisate, m.p. 148°-150°. $[\alpha]_D$ + 105°. Calculated for $C_{35}H_{52}O_4$: C, 78.30; H, 9.77. Found: C, 77.97; H, 9.68. ν_{max} 1725, 1705. The n.m.r. spectrum had a band at 1.17 (singlet), 3.78 (singlet), 5.50 (quartet, J_{ae} 6.5 c.p.s., J_{aa} 12.5 c.p.s.), and 7.43 (quartet, J_{AB} 9 c.p.s., $\delta_B-\delta_A$ = 66 c.p.s.). These bands were assigned to the C-19 methyl group, the phenylmethoxy group, C-2 hydrogen (axial) and the phenyl group respectively. Optical rotatory dispersion in methylene chloride (C, 0.04): $[\alpha]_{650}$ + 50°, $[\alpha]_{589}$ + 100°, $[\alpha]_{312}$ + 550°, $[\alpha]_{288}$ + 125°, $[\alpha]_{280}$ + 625°. Amplitude 23.

3β-Hydroxy-5α-cholestan-2β-yl p-anisate.

The hydroxyanisate (215 mg) in acetone (15ml) was oxidized as described above. T.L.C. [ether:benzene (5.95)] showed the crude product to consist mainly of one compound (R_f 0.52) together with a small amount of starting material. Purification by T.L.C. [ether:benzene (5.95)] gave 5α-cholestan-3-one-2β-yl p-anisate (139 mg), crystallized from ether: pentane, m.p. 65°-75°. The infrared spectrum was identical to the product obtained by oxidation of 3β-hydroxy-5α-cholestan-2β-yl p-anisate with dimethyl sulfoxide and acetic anhydride.

2β-Hydroxy-5α-cholestan-3β-yl p-anisate.

The hydroxyanisate (233 mg) in acetone (25ml) was treated with the oxidizing solution as described above. T.L.C. [ether:benzene (1:9)] showed two compounds to be present, a second material (Fraction B) running slightly slower than the major product (Fraction A). These two materials were separated by T.L.C. [ether:benzene (1:9)].

Fraction A (130 mg) gave 5α-cholestan-2-one-3β-yl p-anisate, m.p. 180°-181°, mixed m.p. (with product from dimethyl sulphoxide:acetic anhydride oxidation) 177°-179°. The infrared spectrum was also identical to that of the product from the oxidation of this hydroxyanisate with dimethyl sulphoxide and acetic anhydride.

Fraction B (60 mg, oil), had an infrared spectrum with bands at 1740 and 1700. No material could be crystallized from this oil, which was not investigated further.

Epimerization of 5α-Cholestan-3-one-2β-yl p-anisate to 5α-Cholestan-3-one-2α-yl p-anisate.

A solution of 5α-cholestan-3-one-2β-yl p-anisate (35 mg) and D-10-camphorsulphonic acid (5 mg) in benzene (5ml) was refluxed overnight. The reaction mixture, after dilution with ether, was washed with dilute sodium bicarbonate solution and water, dried and the solvent removed by evaporation under reduced pressure. The crude product had an infrared spectrum very similar to that of 5α-cholestan-3-one-2α-yl p-anisate. The product was purified by T.L.C. [ether:benzene (1:9)];

two crystallization from ether:pentane gave 5α-cholestan-3-one-2α-yl p-anisate, m.p. 146°-148°; mixed m.p. (with authentic sample) 146°-148°. The infrared spectrum was identical with that of 5α-cholestan-2-one-2α-yl p-anisate.

Reductive elimination of 5α-Cholestan-3-one-2β-yl p-anisate.

To a solution of the keto-anisate (69 mg) in ether (4ml) and acetic acid (1.5ml) was added zinc dust (1.0g), and the mixture was refluxed for four hours. More ether was added to the mixture, which was then filtered (through Supercell). The filtrate was washed with dilute sodium carbonate solution, water, dried and the ether evaporated under reduced pressure. T.L.C. [ether:benzene (1:9)] showed the product to consist of one compound which had the same R_f value as 5α-cholestan-3-one (R_f 0.56) and differed from 5α-cholestan-2-one (R_f 0.66) and from the keto-anisate (R_f 0.61). Crystallization from ether:methanol yielded 5α-cholestan-3-one, (30 mg), m.p. 128°-129°. Mixed m.p. with authentic sample of 5α-cholestan-3-one, 127°-129°; mixed m.p. with authentic sample of 5α-cholestan-2-one, 103°-118°.

Reductive elimination of 5α-Cholestan-2-one-3α-yl p-anisate.

2α-Hydroxy-5α-cholestan-3α-yl p-anisate (150 mg) was oxidized with dimethyl sulphoxide (2ml) and acetic anhydride (2ml), as described above. The crude keto-anisate (123 mg) was dissolved in acetic acid, zinc dust (2.5g) was added, and the mixture was refluxed for 3 hours. The product was isolated as described for the 5α-cholestan-3-one-2β-yl

p-anisate reduction. T.L.C. [ether:benzene (5.95)] showed the product to consist of several compounds. The major reaction product had the same R_f value (0.45) as 5α-cholestan-2-one, which differed from that of 5α-cholestan-3-one (R_f 0.37). The other products of the reaction most probably arose from degradation of "Fraction A". T.L.C. [ether: benzene (5.95)] separation of the reaction product yielded cholestan-2-one (42 mg), crystallized from ether:methanol, m.p. 128°-130°. Mixed m.p. with 5α-cholestan-2-one, 129°-131°; mixed m.p. with 5α-cholestan-3-one, 103°-123°.

Preparation of Orthoesters.

9β:10α-Decalin-2β:3β-ethyl orthoformate.

A solution of 9β:10α-decalin-2β:3β-diol (2.02g), triethyl orthoformate (Eastman Practical grade) (1.75g) together with a few crystals of D-10-camphorsulphonic acid in benzene (10ml) was refluxed for 15 min. The benzene and alcohol produced by the reaction were distilled off at atmospheric pressure, a few crystals of calcium carbonate were added, and the residue was finally distilled under vacuum. The product (1.75g) distilled at 108°-109° (0.5mm), n_D^{25} 1.4755. Calculated for $C_{13}H_{22}O_3$: C, 69.05; H, 9.82. Found: C, 68.97; H, 9.65. The n.m.r. showed signals at 1.22 (triplet, J 7 c.p.s.), 3.60 (quartet, j 7 c.p.s.), 4.17 (broad band), 4.25 (narrow band, W 1/2 7 c.p.s.) 5.73 (singlet) and 5.80 (singlet). The last two peaks were in a ratio of 2.7. These signals were assigned to the methyl and methylene of

the ethoxy group, the C-3 and C-2 hydrogens of the decalin ring, and the formyl hydrogens respectively.

9β:10α-Decalin-2β:3β-ethyl orthopropionate.

A solution of 9β:10α-decalin-2β:3β-diol (2.0g), triethyl orthopropionate (Eastman practical grade) (2.17g) and a few crystals of D-10-camphorsulphonic acid in benzene (10ml) was refluxed for 30 minutes. The benzene and alcohol were distilled off slowly at atmospheric pressure and, after the addition of a few crystals of sodium carbonate, the residue was distilled under vacuum. The product (1.23g) distilled over at 112° (0.6mm), n_D^{25} 1.4735. Calculated for $C_{15}H_{26}O_3$: C, 70.84; H, 10.30. Found: C, 70.76; H, 10.37. The n.m.r. spectrum showed a complex multiplet in the region 0.8 to 1.3 and poorly resolved quartet centred at 3.52 (J 7 c.p.s.), a broad band centred at approximately 4.17 (W 1/2 12 c.p.s.) and a narrow band at 4.38 (W 1/2 7 c.p.s.). These bands were assigned to the two methyl groups, the two methylene groups, and the C-3 and C-2 hydrogens of the decalin ring respectively.

9β:10α-Decalin-2β:3β-ethyl orthoacetate.

This compound was prepared as described above from 9β:10α-decalin-2β:3β-diol (1.53g) and triethyl orthoacetate (Eastman practical grade) (1.62g). The product (1.77g) distilled at 106°-108° (0.6mm), n_D^{25} 1.4717. Calculated for $C_{14}H_{24}O_3$: C, 69.97; H, 10.07. Found: C, 70.21; H, 10.12. This compound had n.m.r. bands at 1.18 (triplet, J 7 c.p.s.), 1.62 (singlet), 3.57 (quartet, J 7 c.p.s.), 4.17 (broad band) and 4.38 (narrow

band, W 1/2 7 c.p.s.). These bands were assigned to the methyl of the ethoxy group, the acetate methyl, the methylene of the ethoxy group and the C-3 and C-2 hydrogens of the decalin ring respectively.

9β:10α-Decalin-2β:3β-methyl orthobenzoate.

A solution of 9β:10α-decalin-2β:3β-diol (1.37g), trimethyl orthobenzoate (1.56g) and a few crystals of D-10-camphorsulphonic acid in benzene (10ml) was refluxed for 30 minutes. The benzene was distilled off at atmospheric pressure, a few crystals of sodium bicarbonate were added, and the residual oil was subjected to vacuum distillation. At 145° (oil-bath temperature) and 0.5 mm pressure no distillate was observed. Some material crystallized out in the still head, this was found to be 9β:10α-decalin-2β:3β-diol, presumably subliming. In a second attempt, 9β:10α-decalin-2β:3β-diol (2.33g) and trimethyl orthobenzoate (2.48g) were reacted as described above. After the benzene had been distilled off, a small amount of sodium bicarbonate was added. The oily residue was then dissolved in pentane and a white precipitate (diol?) was observed. After filtration, the solvent was removed under reduced pressure. The infrared spectrum of the oily residue showed small absorption at 3570 cm^{-1} and 1710 cm^{-1}. Attempted distillation of a portion of this material gave only trimethyl orthobenzoate. Filtration of another portion of this material through a column of alumina [3.5g Woelm Grade I, Basic], eluting with petroleum ether, gave only mixtures of the decalin methyl orthobenzoate plus 3β-hydroxy-9β:10α-

decalin-2β-yl benzoate i.e. the hydrolysis product, as inferred from the infrared spectra of various fractions.

3β-Hydroxy-9β:10α-decalin-2β-yl benzoate.

A solution of 9β:10α-decalin-2β:3β-diol (500 mg) and trimethyl orthobenzoate (567 mg) together with a small amount of D-10-camphorsulphonic acid in benzene (5ml) was refluxed for 30 minutes. The benzene was distilled off at atmospheric pressure. A solution of the residue in methanol (20ml) and ether (5ml) was treated with aqueous acetic acid (5ml, 20%) for 15 minutes, after which the reaction mixture was extracted with ether, and the ether solution was washed with dilute sodium bicarbonate solution, water, dried and the solvent removed under reduced pressure. T.L.C. [ether:benzene (1:1)] showed the product (799 mg) to consist mainly of the hydroxybenzoate together with some decalin diol. These two materials were separated by column chromatography (B.D.H. silica gel, 32g) the hydroxybenzoate (597 mg) eluted with ether:benzene (1:9) and the diol (93 mg) eluted with ether. The hydroxybenzoate was identified as 3β-hydroxy-9β:10α-decalin-2β-yl benzoate by m.p. mixed m.p. with authentic sample, and infrared spectrum.

2β-Hydroxy-9β:10α-decalin-3β-yl benzoate.

9β:10α-Decalin-2β:3β-diol (250 mg) in pyridine (5ml) was treated with benzoyl chloride (209 mg) overnight as described previously. T.L.C. [ether:benzene (1:1)] showed the crude product (310 mg) to consist of a mixture of the hydroxybenzoate and unreacted diol. T.L.C.

separation [ether:benzene (1:1)] gave 275 mg of the hydroxybenzoate, crystallized from ether:pentane, m.p. 102°-104°, mixed m.p. (with authentic sample) 101°-103°. 9β:10α-Decalin-2β:3β-diol (66 mgm) was also recovered from the T.L.C. plates, identified by m.p. and mixed m.p.

Hydrolysis of Orthoesters.

9β:10α-Decalin-2β:3β-ethyl orthoformate.

1) The orthoformate (150 mg) in methanol (5ml) was treated with a few drops of aqueous hydrochloric acid (50%). The reaction solution was stood at room temperature for 10 minutes, diluted with water and extracted with ether. The ether extract was washed with dilute sodium bicarbonate solution and water, dried, and the ether removed under reduced pressure. T.L.C. [ether:benzene (1:9)] showed the product to be mainly 9β:10α-decalin-2β:3β-diol.

2) The orthoformate (829 mg) in methanol (10ml) was treated with aqueous acetic acid (5ml, 10%) for 10 minutes at room temperature. The reaction was diluted with water and extracted with ether, and the ether extract was washed with dilute sodium bicarbonate solution and water, dried and the solvent removed under reduced pressure. T.L.C. [ether:benzene (1:1)] showed the product (700 mg) to consist of two compounds in roughly equal proportions. The infrared spectrum had bands at approximately 3580, 1720 1165 (m), 1145 (m), 1130 (m),

1000 (w), 980 (m), 970 (w), 960 (m), and 938 (w).

It was attempted to separate these two materials by T.L.C. One half of the hydrolysis product was applied to T.L.C. plates (silica gel) which were then eluted with ether:benzene (1:1). The material was detected on the T.L.C. plates with iodine vapour and showed up as a broad band. This band was divided in half and each half was removed from the plates and extracted with ether.

The infrared spectrum of each fraction were identical to each other and to that of the original hydrolysis product. Upon T.L.C. [ether:benzene (1:1)] each fraction showed two spots, the same as was found in the original material. Thin layer chromatography upon alumina, eluting with ether, of this material showed only smears from the origin.

The remaining half of the original hydrolysis product was crystallized from pentane and gave 3β-hydroxy-9β:10α-decalin-2β-yl formate (237 mg), m.p. 70°-72°, calculated for $C_{11}H_{18}O_3$: C, 66.65; H, 9.13. Found: C, 66.27; H, 9.14. ν_{max} 3580, 1720, 1165 (m), 1145 (m), 1130 (w), 1000 (w), 970 (w), 938 (w). The n.m.r. spectrum had bands at 2.45 (singlet, OH), 3.70 (broad multiplet, W 1/2 21 c.p.s.), 5.22 (narrow multiplet, W 1/2 6 c.p.s.) and 8.15 (singlet), These bands were assigned to the C-3 hydroxyl group, the C-3 and C-2 hydrogens and to the formyl hydrogen respectively.

3) The orthformate (501 mg) was hydrolysed as above. The product (433 mg) had an infrared spectrum identical to that obtained previously.

The n.m.r. spectrum included the following signals: 3.13 (singlet, OH), 3.70 (broad band, W 1/2 22 c.p.s.), 4.07 (narrow band, W 1/2 7 c.p.s.), 4.87 (broad multiplet), 5.20 (narrow band, W 1/2 7 c.p.s.), 8.08 and 8.17 (both singlets). The signals at 3.70, 5.20 and 8.17 were assigned to the C-3 (axial) and C-2 (equatorial) hydrogens and to the formyl proton respectively of 3β-hydroxy-9β:10α-decalin-2β-yl formate. The signals at 4.07, 4.87 and 8.08 were assigned to the C-2 (equatorial) and C-3 (axial) hydrogens and to the formyl proton respectively of 2β-hydroxy-9β:10α-decalin-3β-yl formate.

Stability of 3β-Hydroxy-9β:10α-decalin-2β-yl formate to hydrolysis conditions.

The hydroxyformate (49 mg) in methanol (10ml) was treated with aqueous acetic acid as described previously. The residue had an infrared spectrum identical with that of the starting material.

Stability of 3β-Hydroxy-9β:10α-decalin-2β-yl formate to thin layer chromatography upon silica gel.

The hydroxyformate was eluted upon silica gel. The product was recovered by extraction of the silica gel and was found to have an infrared spectrum identical to that of the hydrolysis product, and contained the two extra peaks at 980 and 960 cm^{-1}.

9β:10α-Decalin-2β:3β-ethyl orthopropionate.

The orthopropionate (267 mg) in methanol (10ml) was treated with aqueous acetic acid (5ml; 10%) for 15 minutes as described above.

T.L.C. [ether:benzene (1:1)] showed that the product (235 mg) consisted of almost entirely one compound (R_f 0.44) with only a slight trace of a second material (R_f 0.53). Crystallization from petroleum ether gave 3β-hydroxy-9β:10α-decalin-2β-yl propionate, m.p. 45°-48°. ν_{max} 3580, 1720. Calculated for $C_{13}H_{22}O_3$: C, 68.98; H, 9.81. Found: C, 69.08; H, 9.81. N.m.r. spectrum: 1.15 (triplet, J 7 c.p.s.), 2.38 (quartet, J 7 c.p.s.), 2.57 (singlet, OH), 3.77 (broad band, W 1/2 20 c.p.s.), and 5.17 (narrow band, W 1/2 8 c.p.s.). These bands were assigned to the methyl and methlene of the propyl group, the C-3 hydroxyl and to the C-3 (equatorial) and C-2 (axial) hydrogens respectively.

The second material in the hydrolysis product had the same R_f value as 2β-hydroxy-9β:10α-decalin-3β-yl propionate.

9β:10α-Decalin-2β:3β-ethyl orthoacetate.

The orthoacetate (214 mg) in methanol (5ml) and ether (1ml) was treated with a few drops of aqueous acetic acid (50%) as described previously. T.L.C. [ether:benzene (1:1)] showed the product (188 mg) consisted of almost entirely one compound (R_f 0.39) together with a slight trace of a second material (R_f 0.45). Crystallization from ether:pentane gave 3β-hydroxy-9β:10α-decalin-2β-yl acetate, m.p. 73°-75°, ν_{max} 3570, 1720. Calculated for $C_{12}H_{20}O_3$: C, 67.89; H, 9.51. Found: C, 68.23; H, 9.45. The n.m.r. spectrum showed absorption at 2.10 (singlet), 2.67 (singlet, OH), 3.70 (broad band, W 1/2 21 c.p.s.)

and 5.13 (narrow band, W 1/2 7 c.p.s.). These signals were assigned to the acetate methyl group, the C-3 hydroxyl group and to the C-3 (axial) and C-2 (equatorial) hydrogens respectively.

Acid catalysed rearrangements of the Hydroxyesters.

General Procedure.

A solution of the hydroxyester and D-10-camphorsulphonic acid in benzene was refluxed overnight. The products of the reaction were separated by T.L.C. eluting with benzene, the compounds being detected under ultraviolet light. In all cases, the compounds with an equatorial alcohol group ran slower than the compounds with an axial alcohol group, and were thus easily separated.

2α-Hydroxy-5α-cholestan-3α-yl p-anisate.

A solution of the hydroxyester (142 mg) and D-10-camphorsulphonic acid (14 mg) in benzene (15 ml) was treated as described above and gave starting material (48 mg) and 3α-hydroxy-5α-cholestan-2α-yl p-anisate (48 mg), crystallized from chloroform:methanol, m.p. 186°-188°, $[\alpha]_D$ + 61°, ν_{max} 3590, 1700. Calculated for $C_{35}H_{54}O_4$: C, 78.01; H, 10.10. Found: C, 78.08; H, 9.86. The n.m.r. spectrum showed signals at 0.90 (singlet), 2.25 (singlet, OH), 3.78 (singlet), 4.13 (narrow band, W 1/2 6 c.p.s.), 5.13 (broad band, W 1/2 21 c.p.s.), and 7.38 (quartet, J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 65 c.p.s.). These signals were assigned to the C-19 methyl group, the hydroxyl group, the phenylmethoxy group, the C-3 (equatorial), and C-2 (axial) hydrogens and to the phenyl hydrogens respectively.

In two other rearrangements the following results were obtained: (i) the hydroxyanisate (372 mg) gave starting material (93 mg) and 3α-hydroxy-5α-cholestan-2α-yl p-anisate (147 mg); (ii) from the hydroxyanisate (456 mg) was obtained starting material (155 mg) and the rearranged hydroxyanisate (222 mg).

3β-Hydroxy-5α-cholestan-2β-yl p-anisate.

The hydroxyester (416 mg) and D-10-camphorsulphonic acid (17 mg) in benzene (5ml) gave starting material (211 mg) and 2β-hydroxy-5α-cholestan-3β-yl p-anisate (168 mg), crystallized from chloroform:cyclohexane, m.p. 210°-212°, $[\alpha]_D$ + 27°. ν_{max} 3560, 1700. Calculated for $C_{35}H_{54}O_4$: C, 78.01; H, 10.10. Found: C, 78.10; H, 10.37. The n.m.r. spectrum had bands at 1.07 (singlet), 1.87 (singlet, OH), 3.75 (singlet), 4.18 (narrow band, W 1/2 6 c.p.s.), 4.95 (broad band, W 1/2 21 c.p.s.), and 7.38 (quartet, J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 65 c.p.s.). These bands were assigned to the C-19 methyl group, the C-2 hydroxyl group, the phenylmethoxy group, the C-2 hydrogen (equatorial), the C-3 hydrogen (axial) and the phenyl hydrogens respectively.

3α-Hydroxy-5α-cholestan-2α-yl p-anisate.

The hydroxyanisate (63 mg) plus D-10-camphorsulphonic acid (3 mg), in benzene (3ml) gave starting material (46 mg) and 2α-hydroxy-5α-cholestan-3α-yl p-anisate (13 mg), both compounds being identified by T.L.C. R_f values and infrared spectra.

2β-Hydroxy-9β:10α-decalin-3β-yl p-anisate.

From the hydroxyester (59 mg) plus D-10-camphorsulphonic acid (7 mg) in benzene (3ml) was obtained starting material (43 mg) and 2α-hydroxy-9β:10α-decalin-3β-yl p-anisate (15 mg), both compounds being identified by T.L.C. R_f values and infrared spectra.

3β-Hydroxy-9β:10α-decalin-2β-yl p-anisate.

The hydroxyanisate (404 mg) plus D-10-camphorsulphonic acid (67 mg) in benzene (5ml) gave starting material (130 mg) and 2β-hydroxy-9β:10α-decalin-3β-yl p-anisate (170 mg), crystallized from ether:petroleum ether, m.p. 96°-98°, ν_{max} 3600, 1700. Calculated for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.71; H, 7.80. The n.m.r. spectrum had signals at 2.62 (singlet, OH), 3.75 (singlet), 4.13 (narrow band, W 1/2 6 c.p.s.), 4.95 (broad multiplet) and 7.38 (quartet, J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 67 c.p.s.). These signals were assigned to the phenylmethoxy group, the C-2 (equatorial) and C-3 (axial) hydrogens and to the phenyl hydrogens respectively.

In addition to the above two materials, a third fraction (139 mg) was isolated from the T.L.C. plates, which ran faster than either of the hydroxyanisates. The infrared spectrum had absorption at 1745 and 1710. Thin layer chromatography, eluting with benzene, showed this material to consist of at least three compounds, and this material was not investigated further.

2β-Hydroxy-5α-cholestan-3β-yl p-anisate.

From this hydroxyester (57 mg) plus D-10-camphorsulphonic acid (3 mg) in benzene (2ml) was obtained starting material (40 mg) and 3β-hydroxy-5α-cholestan-2β-yl p-anisate (15 mg), both identified by T.L.C. R_f values and infrared spectra.

3β-Hydroxy-9β:10α-decalin-2β-yl acetate

From the hydroxyacetate (641 mg) and D-10-camphorsulphonic acid (50 mg) in benzene (10ml) was obtained starting material (225 mg) and 2β-hydroxy-9β:10α-decalin-3β-yl acetate (236 mg), crystallized from ether:pentane, m.p. 81°-83°, ν_{max} 3500, 1720. Calculated for $C_{12}H_{20}O_3$: C, 67.89; H, 9.51. Found: C, 67.89; H, 9.40. N.m.r. spectrum; 2.07 (singlet), 2.38 (OH), 4.08 (narrow band, W 1/2 7 c.p.s.) and 4.78 (broad multiplet). These bands were assigned to the acetate methyl group, the hydroxyl group, the C-2 hydrogen (equatorial) and the C-3 hydrogen (axial).

3β-Hydroxy-9β:10α-decalin-2β-yl benzoate.

The hydroxybenzoate (820 mg) and D-10-camphorsulphonic acid (40 mg) in benzene (10ml) gave starting material (345 mg) and 2β-hydroxy-9β:10α-decalin-2β-yl benzoate (433 mg), crystallized from ether:pentane, m.p. 102°-103°. Calculated for $C_{17}H_{22}O_3$: C, 74.40; H, 8.09. Found: C, 74.53; H, 8.19. ν_{max} 3580, 1700. The n.m.r. showed signals at 2.23 (OH), 4.18 (narrow band, W 1/2 5 c.p.s.) 5.03 (broad multiplet) and phenyl absorption centred at 7.47 and 8.03 (multiplets). These signals

were assigned to the C-2 hydroxy group, the C-2 hydrogen (equatorial) and to the C-3 hydrogen (axial) respectively.

3β-Hydroxy-9β:10α-decalin-2β-yl propionate.

The hydroxypropionate (400 mg) and D-10-camphorsulphonic acid (22 mg) in benzene (4ml) gave starting material (159 mg) and 2β-hydroxy-9β:10α-decalin-3β-yl propionate (213 mg), crystallized from ether:pentane, m.p. 59°-61°. Calculated for $C_{13}H_{22}O_3$: C, 68.98; H, 9.81. Found: C, 69.18; H, 9.74. ν_{max} 3590, 1730. The n.m.r. showed bands at 1.13 (triplet, J 7 c.p.s.), 2.18 (singlet, OH), 2.35 (quartet, J 7 c.p.s.), 4.05 (narrow band, W 1/2 = 6 c.p.s.), and 4.80 (broad multiplet). These bands were assigned to the methyl group, the C-2 hydroxyl group, the methylene group, the C-2 hydrogen (equatorial) and the C-3 hydrogen (axial) respectively.

The Woodward Prevost reaction on Δ^2-9β:10α-Octalin.

To a solution of Δ^2-9β:10α-octalin (2.0g) in glacial acetic acid (300ml) was added silver acetate (6.2g). The mixture was stirred vigorously and powdered iodine (3.3g) was added slowly over 30 minutes. After a further 30 minutes, when no iodine was visible, the mixture was treated with aqueous acetic acid (4ml, 80%) and then stirred overnight. A solution of sodium chloride (6.4g) in water (20ml) was added and the stirring stopped. After a few minutes the mixture was filtered and the filtrate evaporated. The residue was dissolved in ether and washed with dilute sodium bicarbonate solution, dilute sodium bisulphite solution,

water, dried and the ether removed by evaporation. T.L.C. [benzene: ether (1:1)] showed the product (2.96g) to be nearly all one compound, with the same R_f value as 3β-hydroxy-9β:10α-decalin-2β-yl acetate. Column chromatography using silica gel and eluting with ether:benzene gave 3β-hydroxy-9β:10α-decalin-2β-yl acetate (2.46g), crystallized from methylene chloride:petroleum ether and identified by m.p., mixed m.p. with authentic sample and infrared spectrum.

5α-Cholest-2-ene.

This compound was prepared from 2α-bromo-5α-cholestan-3-one (52) as described by R.G. Pews. (25).

2α:3α-Epoxy-5α-cholestane.

Prepared from cholest-2-ene and perbenzoic acid as described by Furst and Plattner (53) with the exception that benzene rather than chloroform was used as a solvent; m.p. 100°-104°; reported m.p. 103°-105°.

2β:3β-Epoxy-5α-cholestane.

Prepared from 2α-bromo-5α-cholestan-3β-ol as described by Alt and Barton (35); m.p. 87°-90°; reported m.p. 89°-91°.

Δ^2-9β:10α-Octalin.

This compound was prepared by the method of Johnson et. al. (54). b.p. 46° (5 mm), n_D^{25} 1.4776; reported b.p. 59° (8 mm), n_D^{25} 1.4796.

2:3-Epoxy-9β:10α-decalin.

This compound was prepared by the method of Johnson et. al. (54). b.p. 78°-80° (5 mm), n_D^{25} 1.4835; reported b.p. 105° (21 mm), n_D^{25} 1.4835.

Preparation of Halohydrins.

3α-Bromo-5α-cholestan-2β-ol.

This compound was prepared from 2β:3β-epoxycholestane as previously described by Alt and Barton (35); m.p. 135°-137° reported m.p. 133°-135°.

2β-Bromo-5α-cholestan-3α-ol.

This compound was prepared from 2α,3α-epoxycholestane as described by Alt and Barton (35); m.p. 118°-120°; reported m.p. 115°-118°.

2β-Bromo-9β:10α-decalin-3α-ol.

Prepared by treatment of 2:3-epoxy-9β:10α-decalin with aqueous hydrobromic acid (48%). The product was crystallized from petroleum ether, m.p. 77°-78°. Calculated for $C_{10}H_{17}O$ Br: C, 51.50; H, 7.35; Br, 34.27. Found: C, 51.61; H, 7.32; Br, 34.44. ν_{max} 3600. The n.m.r. spectrum showed signals at 2.08 (singlet) and 4.23 (multiplet). These bands were assigned to the hydroxyl group and to the two protons at C-2 and C-3 of the decalin ring.

2α-Bromo-5α-cholestan-3β-ol.

Prepared by reduction of 2α-bromo-5α-cholestan-3-one with sodium borohydride as previously described (55). The product was eluted from

alumina (Woelm, grade III, neutral), with benzene:cyclohexane (1:3), and crystallized from ether:methanol, m.p. 111°-113°, reported m.p. 111°-112°. The infrared spectrum was identical to that of an authentic sample.

2α-Bromo-9β:10α-decalin-3β-ol.

A solution of 2α-bromo-9β:10α-decalin-3β-yl p-anisate (180 mg) plus 35% perchloric acid (2ml) in dioxan (10ml) was refluxed for 96 hours. The reaction was diluted with water and extracted with ether; the ether extracts being then washed with dilute sodium bicarbonate solution and water, dried and evaporated. T.L.C. [benzene:ether (9:1)] showed the product to consist of two compounds (R_f 0.63 and 0.38). The faster running material had the same R_f value as the starting material and was visible under ultraviolet light. The second compound was not visible under ultraviolet light. These two materials were separated by T.L.C., the plates being developed with iodine vapour. The slower moving band gave 70 mg of 2α-bromo-9β:10α-decalin-3β-ol crystallized from ether:pentane, m.p. 86°-87°. ν_{max} 3480. Calculated for $C_{10}H_{17}OBr$: C, 51.50; H, 7.35; Br, 34.27. Found: C, 51.56; H, 6.93; Br, 34.40. The n.m.r. had a band at 2.57 (singlet, OH), and a broad multiplet centred at 3.75 (C-2 and C-3 hydrogens, equatorial).

2β-Chloro-9β:10α-decalin-3α-ol.

Prepared by treating a solution of 2:3-epoxy-9β:10α-decalin in methylene chloride (20ml) with hydrogen chloride gas for 5 minutes.

The reaction solution was washed with dilute sodium bicarbonate solution, water, dried and the solvent evaporated under reduced pressure. The product was crystallized from ether:pentane, m.p. 72°-73°. Calculated for $C_{10}H_{17}ClO$: C, 63.63; H, 9.08; Cl, 18.79. Found: C, 63.68; H, 8.98; Cl, 18.75. ν_{max} 3600. The n.m.r. spectrum had bands at 2.18 (singlet, O-H) and 4.08 (2H, W 1/2 11 c.p.s., axial hydrogens).

Preparation of Halohydrin Benzoate Esters.

About 1 to 2 equivalents of the benzoyl chloride were added to a solution of the alcohol in 5 to 10 times its weight in pyridine. After standing at room temperature overnight, the reaction mixture was poured into ether and washed with dilute hyrochloric acid solution, dilute sodium bicarbonate solution and water, dried and the solvent evaporated. Column chromatography (silica gel) eluting with benzene gave the pure haloesters.

3α-Bromo-5α-cholestan-2β-yl benzoate.

Crystallized from ether:methanol, m.p. 114°-115°, $[\alpha]_D$ + 50°. Calculated for $C_{34}H_{51}O_2Br$: C, 71.43; H, 8.99. Found: C, 71.15; H, 9.04. ν_{max} 1715. The n.m.r. spectrum had absorption at 4.53 (multiplet), 5.48 (multiplet), 7.57 and 8.07 (both multiplets). These bands were assigned to the C-3 hydrogen (equatorial), the C-2 hydrogen (equatorial) and to the phenyl hydrogens respectively.

3α-Bromo-5α-cholestan-2β-yl p-anisate.

Crystallized from ether:methanol, m.p. 117°-120°, $[\alpha]_D$ +35.5°. Reported m.p. 115°-118°, $[\alpha]_D$ + 36° ($CHCl_3$). (25) The n.m.r. spectrum showed signals at 1.07 (singlet), 3.88 (singlet), 4.50 (narrow band, W 1/2 8 c.p.s.), 5.43 (narrow band, W 1/2 8 c.p.s.), and 7.49 (quartet, J_{AB} 9 c.p.s., $\delta_B-\delta_A$ = 63 c.p.s.). These signals were assigned to the C-19 methyl group, the phenylmethoxy group, the C-3 hydrogen (equatorial), the C-2 hydrogen (axial) and to the phenyl hydrogens respectively.

2β-Bromo-5α-cholestan-3α-yl p-anisate.

Crystallized from ether:methanol, m.p. 107°-109°, $[\alpha]_D$ + 82°. Reported m.p. 136°-138°, $[\alpha]_D$ + 83° (21). Comparison of the infrared spectrum and T.L.C. R_f value showed the compound to be identical with an authentic sample. Mixed m.p. with authentic sample, 134°-136°. The n.m.r. spectrum showed absorption at 1.17 (singlet), 3.87 (singlet), 4.45 (narrow multiplet, W 1/2 7 c.p.s.), 5.40 (narrow multiplet, W 1/2 7 c.p.s.) and 7.49 (quartet, J_{AB} 9 c.p.s., $\delta_B-\delta_A$ = 61 c.p.s.). These bands were assigned to the C-19 methyl group, the phenylmethoxy group, the C-2 hydrogen (equatorial) the C-3 hydrogen (equatorial) and to the phenyl hydrogens respectively.

2α-Bromo-5α-cholestan-3β-yl p-anisate.

Crystallized from ether:methanol, m.p. 173°-175°; reported m.p. 174°-176°. (25). The n.m.r. spectrum showed signals at 0.90 (singlet) 3.88 (singlet), 4.37 and 5.13 (both broad diffuse bands) and 7.50

(quartet, J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 66 c.p.s.). These signals were assigned to the C-19 methyl group, the phenylmethoxy group, the C-2 and C-3 hydrogens (both equatorial) and to the phenyl hydrogens respectively.

2β-Bromo-9β:10α-decalin-3α-yl p-anisate.

Crystallized from petroleum ether, m.p. 61°-63°. Calculated for $C_{18}H_{23}O_3Br$: C, 58.86; H, 6.31; Br, 21.49. Found: C, 58.99; H, 6.46; Br, 21.60. ν_{max} 1705. The n.m.r. spectrum had signals at 3.78 (singlet), 4.50 (narrow band, W 1/2 6 c.p.s.), 5.38 (narrow multiplet), and 7.48 (quartet, J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 62 c.p.s.). These bands were assigned to the phenylmethoxy group, the C-2 and C-3 hydrogens (both axial) and to the phenyl hydrogens respectively.

2β-Chloro-9β:10α-decalin-3α-yl p-anisate.

Crystallized from methylene chloride:methanol, m.p. 57°-59°. Calculated for $C_{18}H_{23}O_3Cl$: C, 66.95; H, 7.18; Cl, 10.98. Found: C, 66.73; H, 7.03; Cl, 11.04. ν_{max} 1705. The n.m.r. spectrum showed absorption at 3.85 (singlet), 4.35 (narrow band, W 1/2 8 c.p.s.) 5.28 (narrow band, W 1/2 7 c.p.s.) and 7.48 (quartet, J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 63 c.p.s.). These bands were assigned to the phenylmethoxy group, the C-2 and C-3 hydrogens (both axial) and to the phenyl hydrogens respectively.

2β-Bromo-9β:10α-decalin-3α-yl benzoate.

Crystallized from methylene chloride:petroleum ether, m.p.

110°-111°. Calculated for $C_{17}H_{21}BrO_2$: C, 60.53; H, 6.28; Br, 23.69. Found: C, 60.57; H, 6.28; Br, 24.01. ν_{max} 1710. The n.m.r. spectrum had signals at 4.47 (narrow band, W 1/2 7 c.p.s.), 5.37 (narrow multiplet), 7.43 (multiplet) and 8.0 (multiplet). These signals were assigned to the C-2 and C-3 hydrogens (both equatorial) and the phenyl hydrogens respectively.

Rearrangement of 2β-Chloro-9β:10α-decalin-3α-yl p-anisate to 2α-Chloro-9β:10α-decalin-3β-yl p-anisate.

The diaxial chloroanisate (500 mg) in a test tube, flushed with nitrogen and stoppered by a plug of cotton wool, was heated at 140° for 96 hours. T.L.C. [benzene:cyclohexane (1:1)] of the product (a dark brown oil) showed two spots running very close together. These two materials were separated by T.L.C., eluting with benzene:cyclohexane (1:1) five times; under ultraviolet light the materials showed up as a wide spread band on the T.L.C. plates. This band was cut in half and each half extracted, the upper half gave 390 mg which was almost entirely diaxial chloroanisate, and the lower half (108 mg) gave the diequatorial chloroanisate, crystallized from methylene chloride:methanol, m.p. 106°-107°. ν_{max} 1705. Calculated for $C_{18}H_{23}O_3Cl$: C, 66.95; H, 7.18; Cl, 10.98. Found: C, 66.74; H, 7.02; Cl, 10.98. The n.m.r. had absorption at 3.80 (singlet) 4.0 (broad multiplet), 5.0 (broad band) and 7.42 (quartet, J 9 c.p.s., $\delta_B-\delta_A$ = 66 c.p.s.). These signals were assigned to the phenylmethoxy group, the C-2 hydrogen (equatorial), the C-3 hydrogen (equatorial) and the phenyl hydrogens respectively.

3β-Bromo-5α-cholestan-2α-yl p-anisate.

This compound was prepared by the diaxial to diequatorial rearrangement of 2β-bromo-5α-cholestan-3α-yl p-anisate by heating at 135° for 3 hours under nitrogen. Crystallized from acetone:methanol, m.p. 112°-115°, $[\alpha]_D$ - 35°. Reported m.p. 114°-115°, $[\alpha]_D$ - 37° (21).

2α-Bromo-9β:10α-decalin-3β-yl p-anisate.

This compound was prepared from 2β-bromo-9β:10α-decalin-3α-yl p-anisate (0.4g) by heating at 130° for 18 hours under nitrogen. T.L.C., eluting four times with benzene:cyclohexane (1:1), showed two spots, very close together, with R_f values of 0.63 and 0.54 respectively, the faster moving material corresponding to the diaxial bromoanisate. The pyrolysis product was separated by T.L.C., eluting with benzene:cyclohexane (1:1) four times. Under ultraviolet light a broad band was observed on the T.L.C. plates, with no apparent separation. The lower half of this band was removed from the T.L.C. plates and extracted with chloroform (+ 1% methanol). After filtration, evaporation of the extract yielded 2α-bromo-9β:10α-decalin-3β-yl p-anisate, crystallized from ether:petroleum ether, m.p. 122°-124°. Calculated for $C_{18}H_{23}O_3Br$: C, 58.86; H, 6.31; Br, 21.49. Found: C, 58.76; H, 6.20; Br, 21.72. ν_{max} 1730. The n.m.r. spectrum had bands at 3.80 (singlet), 4.0 (multiplet), 5.08 (broad band) and 7.42 (quartet J_{AB} 9 c.p.s., $\delta_B - \delta_A$ = 66 c.p.s.). These bands were assigned to the phenylmethoxy group, the C-2 and C-3 hydrogens (both axial) and to the phenyl hydrogens respectively.

9β:10α-Decalin-2α:3β-dibenzoate.

Prepared by treatment of 9β:10α-decalin-2α:3β-diol with a twofold excess of benzoyl chloride in pyridine. The product was purified by T.L.C. (C_6H_6) and the dibenzoate was crystallized from ether:methanol, m.p. 113°-115°. ν_{max} 1710. Calculated for $C_{24}H_{26}O_4$: C, 76.14; H, 6.92. Found: C, 76.24; H, 6.70. The n.m.r. had bands at 5.30 (broad band), 7.33 and 7.70 (both complex multiplets). These bands were assigned to the C-2 and C-3 hydrogens and to the phenyl hydrogens.

9β:10α-Decalin-2β:3α-dibenzoate.

Prepared by treatment of 9β:10α-decalin diol with a two fold excess of benzoyl chloride in pyridine as previously described. The crude product was purified by T.L.C. [ether:benzene (5:95)] and crystallized from methylene chloride:petroleum ether, m.p. 148°-150°. Calculated for $C_{24}H_{26}O_4$: C, 76.14; H, 6.92. Found: C, 75.80; H, 6.62. ν_{max} 1710. The n.m.r. spectrum had bands at 5.35 (multiplet, W 1/2 4 c.p.s.), 7.42 and 8.02 (multiplets). These signals were assigned to the C-2 and C-3 hydrogens (both equatorial) and to the phenyl hydrogens.

Preparation of Diols.

9β:10α-Decalin-2β:3β-diol.

This compound was prepared from Δ^2-9β:10α-octalin and osmium tetroxide by the method of Henbest, Smith and Thomas (22), m.p. 140°-141°,

reported m.p. 140°-141°.

5α-Cholestan-2α:3α-diol.

This compound was prepared from cholest-2-ene and osmium tetroxide as described by Henbest and Smith (51), m.p. 214°-217°; reported m.p. 212°-214°.

5α-Cholestan-2β:3β-diol.

This compound was prepared from cholest-2-ene by the method of Henbest and Smith (51), with the exception that the reaction mixture was heated for 3 1/2 hours at 80° and also that the product, after alkaline hydrolysis, was purified by T.L.C. [ether:benzene (1:1)], the product being detected by iodine vapour, m.p. 177°-180°, $[\alpha]_D$ + 37°, reported m.p. 174°-177°, $[\alpha]_D$ + 43°.

9β:10α-Decalin-2α:3β-diol.

Prepared by the method of Ali and Owens (56). 9β:10α-Decalin-2β:3β-diol (500 mg) was added to a solution of sodium (0.7g) in commercial absolute alcohol (20ml) in a thick walled glass tube. After flushing out with air the tube was sealed and heated at 160° for 36 hours. The reaction mixture was taken up in ether and washed with aqueous hydrochloric acid (10%), dilute sodium bicarbonate solution and water: after drying the solvent was removed under reduced pressure. T.L.C. [methanol:ether (2:98)] showed the product to consist of two materials in almost equal amounts the faster moving material corresponding

to starting material. The two materials were separated by T.L.C. [methanol:ether (2:98)], being detected on the T.L.C. plates by iodine vapour. The diequatorial diol, i.e. the slower moving of the two materials on the T.L.C. plates, was extracted from the silica gel and crystallized from benzene, m.p. 166°-168°. Reported m.p. 168°.

9β:10α-Decalin-2β:3α-diol.

Prepared by hydration of 2:3-epoxy-9β:10α-decalin with aqueous sulphuric acid as described by Henbest et. al.(22), crystallized from benzene:petroleum ether, m.p. 161°-162°, reported m.p. 163°-164°.

Trimethyl Orthobenzoate.

Prepared from benzotrichloride and sodium methoxide by the method of McElvain and Venerable. (57), b.p. 55°-56° (1.0 mm), n_D^{25} 1.4974. Reported b.p. 114°-115° (25 mm), n_D^{25} 1.4858.

5α-Cholestan-3-one.

Prepared by oxidation of 5α-cholestan-3β-ol as previously described (52).

5α-Cholestan-2-one.

Sample kindly provided by Professor E.W. Warnhoff.

3β-Bromo-5α-Cholestan-2α-ol.

Sample provided by Dr. R.G. Pews.

Tetraethylammonium bromide and chloride.

Eastman Organic Chemicals material were, in both cases, recrystallized from methylene chloride:petroleum ether and dried under high vacuum prior to use.

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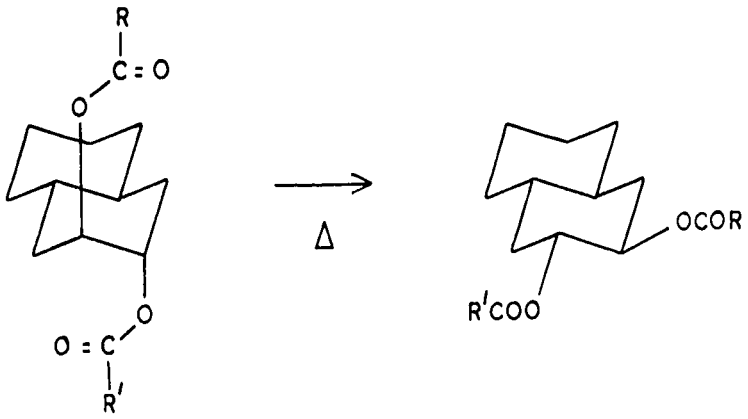
APPENDIX I

Attempted diaxial to diequatorial rearrangement of 9β:10α-decalin-2β-yl-trifluoroacetate-3α-yl p-anisate.

Some attempts have been made to see if diaxial dicarboxylic esters such as I will undergo the diaxial to diequatorial rearrangement to give the corresponding diequatorial diester II (1).



To date, no example of this rearrangement with diesters has been discovered, though its possibility has been suggested (2). It was considered that the trans-decalin trifluoroacetate p-anisate diaxial diester (I, R = $CH_3O.C_6H_4$-; R' = CF_3-) might very well undergo this type of rearrangement since it contains ester groups substituted with both electron withdrawing and electron donating groups. Also to judge from the results found upon thin layer chromatography of this diester

on silica gel, i.e. that hydrolysis via an anisoxonium ion seems to occur (see page 36), the trifluoroacetate would appear to act as a leaving group.

After refluxing for 36 hours in dioxan the diester however, as evidenced by thin layer chromatography and the infrared spectrum, was unchanged. After refluxing for a week in dioxan, no evidence of any rearranged diester was obtained although thin layer chromatography indicated that some decomposition had occurred.

There are several factors which may be responsible for the failure of the diester to undergo rearrangement. It may be that an insufficiently high temperature was used or that the solvent did not have a high enough ionizing power. However the most probable reason is simply that, under the conditions used, the trifluoroacetate group does not act as a good leaving group. The ability of a group to ionize, partially or fully, appears to be a necessary requirement for the diaxial-diequatorial rearrangement to occur, since in all the cases reported of this rearrangement, one of the groups involved is generally regarded as being a good leaving group.

Experimental

A solution of the diester (21 mg) in dioxan (1 ml) was refluxed for 36 hours. The solvent was removed by evaporation and the product examined by T.L.C., eluting with benzene. Apart from the starting material no trace of any other material was visible under ultraviolet

light. The infrared spectrum was identical to the starting material. The experiment was repeated, using the same conditions as above except that the solution was refluxed for one week. Again examination of the product by T.L.C. failed to show any signs of rearranged diester.

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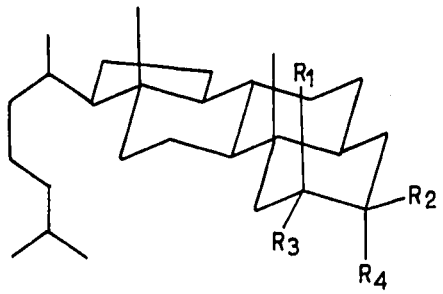
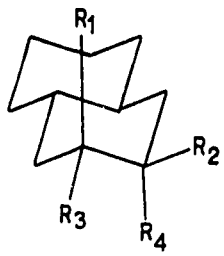
APPENDIX II

Summary of n.m.r. data

The chemical shifts are reported in p.p.m. downfield from the tetramethylsilane signal. Peak widths at half peak height (W 1/2) are reported in c.p.s.; C-19 methyl resonances are reported in c.p.s. downfield from tetramethylsilane.



	H_E p.p.m.	W 1/2 c.p.s	H_A p.p.m.	W 1/2 c.p.s.	C-19 Methyl (c.p.s.)
R_1 = p$CH_3OC_6H_4COO$-, R_2 = OH, R_3 = R_4 = H.	5.29	8	3.87	22	59
R_1 = OH, R_2 = p$CH_3OC_6H_4COO$-, R_3 = R_4 = H.	4.18	6	4.95	21	64
R_1 = R_2 = H, R_3 = OH, R_4 = p$CH_3OC_6H_4COO$-.	5.29	6	3.87	20	49
R_1 = R_2 = H, R_3 = p$CH_3OC_6H_4COO$-, R_4 = OH.	4.13	6	5.13	21	54



	H_E	W 1/2	H_A	W 1/2
	p.p.m.	c.p.s.	p.p.m.	c.p.s.
$R_1 = R_2 = H, R_3 = OH, R_4 = \underline{p}CH_3OC_6H_4COO-$.	5.30	7	3.71	21
$R_1 = R_2 = H, R_3 = \underline{p}CH_3OC_6H_4COO-, R_4 = OH$.	4.13	6	4.95	-
$R_1 = R_2 = H, R_3 = OH, R_4 = C_6H_5COO-$.	5.37	7	3.78	21
$R_1 = R_2 = H, R_3 = C_6H_5COO-, R_4 = OH$.	4.18	5	5.03	-
$R_1 = R_2 = H, R_3 = OH, R_4 = HCOO-$.	5.22	6	3.70	21
$R_1 = R_2 = H, R_3 = OH, R_4 = CH_3COO-$.	5.13	7	3.70	21
$R_1 = R_2 = H, R_3 = CH_3COO-, R_4 = OH$.	4.08	7	4.78	-
$R_1 = R_2 = H, R_3 = OH, R_4 = CH_3CH_2COO-$.	5.17	8	3.77	20
$R_1 = R_2 = H, R_3 = CH_3CH_2COO-, R_4 = OH$.	4.05	6	4.80	-

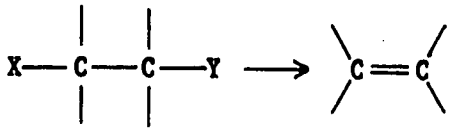
2) trans-Haloesters	R (p.p.m.)	W 1/2 (c.p.s.)
a) Steroid compounds		
R_1 = Br, R_4 = $CH_3OC_6H_4COO$-, R_2 = R_3 = H	R_3 4.45 R_2 5.40	7 7
R_1 = $CH_3OC_6H_4COO$-, R_4 = Br, R_2 = R_3 = H	R_2 4.45 R_3 5.40	7 7
R_1 = R_4 = H, R_3 = Br, = $CH_3OC_6H_4COO$-.	R_1 4.37 R_4 5.13	- -
b) Decalin compounds		
R_1 = Br, R_4 = $CH_3OC_6H_4COO$-, R_2 = R_3 = H.	R_3 4.50 R_2 5.38	6 -
R_1 = R_4 = H; R_2 = $CH_3OC_6H_4COO$-, R_3 = Br.	R_1 4.00 R_4 5.08	- -
R_1 = Cl, R_4 = $CH_3OC_6H_4COO$-, R_2 = R_3 = H	R_3 4.35 R_2 5.28	8 7
R_1 = R_4 = H; R_2 = $CH_3OC_6H_4COO$-, R_3 = Cl	R_1 4.00 R_4 5.00	- -
R_1 = Br, R_4 = C_6H_5COO-, R_2 = R_3 = H.	R_3 4.47 R_2 5.37	7 -

APPENDIX III

The reductive elimination reaction with complex metal hydrides.

I Introduction

The elimination reaction leading to the formation of a carbon-carbon double bond may be expressed by the following equation.



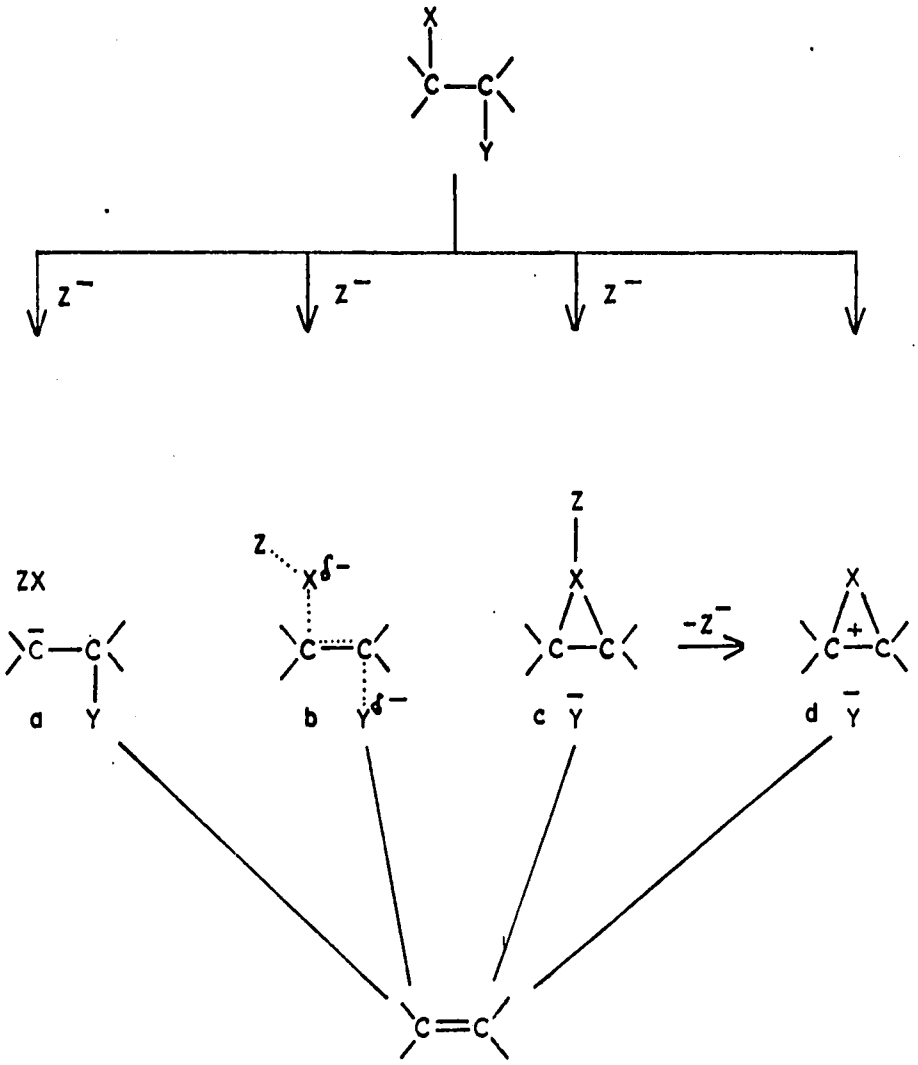
Reactions of this type can be classified into three general types: oxidative (i.e. dehydrogenation), reductive (X,Y = halogen) and metathetical (X = H, Y = halogen) (1).

Most of the studies made on the reductive elimination reaction have been undertaken using an alkali metal iodide as the reducing agent. Recently a study of the reductive elimination of 1,2-dihalides and halohydrin-toluenesulphonates has been reported (1,2). The major part of this work was concerned with the use of lithium aluminum hydride to effect the reaction. It was found, in general that trans-diaxial dibromides and bromohydrin p-toluenesulphonates were reduced to the olefin in high yields. It was also found that although the trans-diaxial orientation of the groups (X and Y) was most favourable for the elimination reaction, in some cases a cis elimination could occur.

Thus reduction of dl-stilbene dibromide at-10° gave 95% trans-stilbene (formally the product of cis-elimination). Also cis-1,2-dibromocyclohexane was found to give cyclohexene and it was concluded that this reaction occurred via a "true" cis-elimination process.

The reductive elimination reaction has been discussed in terms of four possible mechanisms (2), as outlined in scheme I. Any mechanistic proposal must account for the normal formation of the olefin via a trans-elimination process, although in special cases, cis-elimination may be preferred. It has been suggested by DuPuy (3) that co-planar transition states, whether cis or trans, are preferrable to non-co-planar ones as far as concerted elimination reactions are concerned. Mechanism (a), analogous to the E_1cb metathetical elimination was excluded since it did not explain the apparent stereospecificity of the reduction with lithium aluminum hydride. It has been suggested that the transition state (b) would appear to be more probable than either (c) or (d) since it could account for all of the observed eliminations (both cis and trans), however the evidence was not regarded as conclusive.

Pews also briefly investigated the use of other complex metal hydrides as reagents for the reductive elimination reaction. Using 2β:3α-dibromo-5α-cholestane as substrate the following results were obtained. Unreacted starting material was the principal constituent of the product recovered after treatment under the following conditions; (a) sodium borohydride in methanol at room temperature, (b) sodium



Scheme 1

trimethoxyborohydride in diglyme (diethylene glycol dimethyl ether) at room temperature, (c) lithium tri-tert-butoxyaluminohydride in refluxing tetrahydrofuran, (d) lithium borohydride in ether or tetrahydrofuran under reflux, (e) diborane in diglyme at room temperature. With sodium borohydride in triglyme (triethylene glycol dimethyl ether) at 136°, lithium tri-tert-butoxyaluminohydride in triglyme at 136° and sodium-borohydride and aluminum chloride in diglyme at 100° neither starting material nor cholest-2-ene were isolated. However sodium trimethoxy-borohydride in diglyme at 136° was found to give cholest-2-ene in 88% yield.

The kinetics of the reduction of 2β:3α-dibromo-5α-cholestane and 2α3β-dibromo-5α-cholestane with sodium trimethoxyborohydride in dioxan were investigated and it was found that the diaxial dibromide was reduced about 35 times faster than the diequatorial dibromide, again suggesting that a trans-elimination process was operating here.

In the study of the reductive elimination reaction with lithium aluminum hydride it had been found that the diaxial dibromide 2β:3α-dibromo-5α-cholestane, was reduced at about the same rate as both of the corresponding diaxial bromohydrin p-toluenesulphonates, 2β-bromo-5α-cholestan-3α-yl p-toluenesulphonate and 3α-bromo-5α-cholestan-2β-yl p-toluenesulphonate. This observation, it was noted, differed from the results found with sodium iodide. Cristol and co-workers have found that trans-2-bromocyclohexyltosylate was reduced about 20 times faster than trans-1,2-dibromocyclohexane (4). With sodium trimethoxyborohydride

in dioxan, Pews found that 2β:3α-dibromo-5α-cholestane was reduced approximately 20 times faster than 2β-bromo-5α-cholestan-3α-yl p-toluenesulphonate, and it was suggested that "since a single mechanism cannot readily accommodate such an inversion of relative rates, it seems likely that the reductive elimination reaction may proceed through more than one mechanistic path".

The work presented here is part of an attempt to extend and to clarify the features of the reductive elimination reaction of 1,2-dibromides and halohydrin sulphonate esters using complex metal hydrides such as sodium trimethoxyborohydride.

Unfortunately, the elimination reaction of 1,2-dibromides with sodium borohydride and trimethoxyborohydride did not turn out to be as general as in the case of lithium aluminum hydride. In many cases although an apparent reaction occurred between the dibromide and the hydride reagent, as evidenced by loss of starting material, no olefin was found in the products. Since the main purpose of this investigation was to study an elimination reaction, no real attempt was made to identify the products in those cases where starting material was consumed and no olefinic products were obtained. Since an elimination reaction occurred with only a few dibromides it did not seem worthwhile to carry out an intensive study of these rather few special cases.

In summary it may be said that the "list of reactions in which neither starting material or olefin was found" (Ref. 2, page 51) has been extended!

II. Reaction of 1,2-dibromides with sodium borohydride

Table I summarizes a number of experiments designed to show the range of compounds reducible with sodium borohydride.

It was found that meso-stilbene dibromide was rapidly reduced to trans-stilbene in high yield. Thus when sodium borohydride was added to a solution of the dibromide in diglyme at room temperature, an immediate reaction occurred, with the evolution of gas. trans-Stilbene was the only product isolated after 15 minutes. That an elimination reaction occurs with meso-stilbene dibromide was not very surprising since the number of reagents which will effect this reaction are quite numerous, Pews has listed fourteen (2). In fact diglyme itself causes some elimination. meso-Stilbene dibromide is not very soluble in cold diglyme and has to be heated for some time in order to obtain a solution. From this solution a small amount of trans-stilbene was obtained, amounting to 11.5%.

dl-Stilbene dibromide also reacted quite readily with sodium borohydride at room temperature, although at a slower rate than meso-stilbene dibromide. As found with lithium aluminum hydride (2) a mixture of cis and trans-stilbenes was obtained with trans-stilbene predominating. With 2β:3α-dibromo-5α-cholestane very little elimination was observed, most of the product being unchanged starting material.

That the reaction between sodium borohydride and some dibromides can be quite complicated was demonstrated by the reaction of 5α:6β-dibromocholestane with hydride reagent. Thin layer chromatography of

TABLE I

Reaction of sodium borohydride with 1,2-dihalides

Substrate	Product	Yield %	Reaction Conditions		
			Solvent	Temp.	Time
meso-Stilbene dibromide	trans-Stilbene	95	Diglyme	R.T.	15 min.
dl-Stilbene dibromide	cis-Stilbene (25%) trans-Stilbene (75%)	39	Diglyme	R.T.	30 min.
2β:3α-Dibromo-5α-cholestane	Cholest-2-ene	10%	Diglyme	85°	11 hours.
5α 6β-Dibromocholestane	Cholest-5-ene	0	Diglyme	R.T.	15 hours.
trans-1,2-Dibromocyclohexane	Cyclohexene	0	Diglyme	110°	12 hours.
Ethylene dibromide	Ethylene	0	Diglyme	60°	1.5 hours.

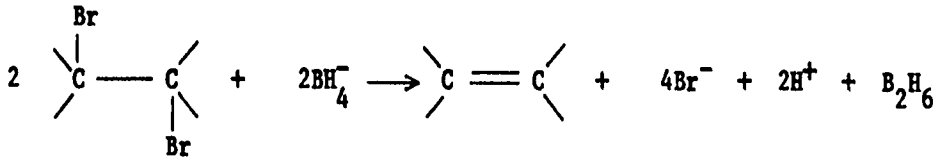
the product showed at least eight materials to be present, none of which corresponded to either the starting material or cholest-5-ene.

The rate of reaction of sodium borohydride with trans-1,2-dibromocyclohexane, ethylene dibromide and octane-1,2-dibromide in diglyme was determined by potentiometric titration of the bromide ion formed during the reaction (2). A 20 fold excess of hydride was used in each case and the results were treated in a pseudo first order manner. All three compounds were found to react quite readily, the ethylene dibromide being the fastest and the dibromocyclohexane being the slowest. However these reactions do not correspond to an elimination. Ethylene dibromide when treated with hydride for a period equivalent to three half lives gave no ethylene detectable as ethylene dibromide. The stoichiometry of this reaction was found by following the rate of the reaction by both bromide ion analysis and by determining the amount of borohydride consumed. It was found that approximately twice as much borohydride was used up as bromide ion formed.

In the reaction of octane-1,2-dibromide with lithium aluminum hydride it has been noted that the substitution reaction product predominated over the elimination product (5). With ethylene dibromide, in which both bromine atoms are primary, the substitution reaction, to give ethane or bromoethane, could presumably occur quite readily; however no attempts were made to detect either of these possible products.

Similarly with the dibromocyclohexane, no cyclohexene was found upon treatment with sodium borohydride in diglyme, despite the fact that some 60% of the starting material had been consumed no cyclohexane was detected either.

One possibility which might account for the loss of starting material is outlined in the following equation.



This equation also corresponds with stoichiometry of the reaction mentioned above. An elimination reaction might occur with the concomitant formation of diborane. Brown and co-workers have shown that, in ethereal solvents, diborane reacts rapidly with olefins to give the corresponding alkylboranes (6). Consequently the product from treatment of the dibromocyclohexane with borohydride might possibly

be a cyclohexylborane. Alkylboranes are quite readily oxidized by alkaline hydrogen peroxide to give alcohols. To test this idea trans-1,2-dibromocyclohexane was reacted with sodium borohydride in diglyme at 110° for 60 hours. The resulting solution was treated with alkaline hydrogen peroxide as described by Brown. Only 3.4% of cyclohexanol was detected, by vapour phase chromatography, along with 11% of cyclohexyl bromide, and 62.5% of the starting material. Thus the formation of an alkylborane does not seem to play an important part in this reaction. The small amount of cyclohexanol could have arisen by a substitution reaction on the monobromide. If this were the case then approximately 15% of cyclohexyl bromide would appear to have been formed.

III. Reaction of 1,2-Dibromides with sodium trimethoxyborohydride

Sodium trimethoxyborohydride was originally prepared by Brown, Schlesinger et al (7). As a reducing agent toward many organic compounds it appeared to be stronger than sodium borohydride. Pews (2) had already shown that sodium trimethoxyborohydride would do the reductive elimination reaction on 2β:3α-dibromo-5α-cholestane, giving cholest-2-ene in 88% yield and it was thought that this compound might prove to be another general reagent for such elimination reactions. As can be seen from Table II, sodium trimethoxyborohydride did react with a wider range of dibromides, to give olefin, than sodium borohydride. However it soon became apparent that, as had been found with sodium borohydride, in many cases while little or no olefinic product was obtained a considerable amount

of starting material had been consumed.

Both meso and dl-stilbene dibromide were reduced readily by sodium trimethoxyborohydride, apparently at a slightly slower rate, to judge by the yields, than with sodium borohydride. In both cases trans-stilbene was the only product isolated. The product from the reduction of dl-stilbene dibromide with trimethoxyborohydride showed no trace of cis-stilbene, as judged by the absence of absorption at 925 cm^{-1} in the infrared spectrum.

A general trend can be seen from the results listed in Table II. Apart from the stilbene dibromides, the highest yields of olefin were obtained from the most highly substituted dibromides. In the cases where the substitution is the same, i.e. the cholestane dibromide, dibromocyclohexane and the butane dibromides, the highest yields of olefin were obtained from the most hindered dibromide. Conversely, the less hindered or less substituted the dibromide, the more susceptible it appeared to be to other (?) reactions.

The observation of Pews that bromohydrin tosylates were reduced at a slower rate than dibromides with trimethoxyborohydride has been confirmed in the case of the cyclohexyl compounds; the dibromocyclohexane giving about 5 times as much cyclohexene as the bromotosylate when both were allowed to react under the same conditions. The 2,3-dibromobutanes gave low yields of the 2-butenes. meso-2,3-Dibromobutane in tetrahydrofuran gave a mixture of butenes, 90% of which was trans. In dioxan a somewhat higher yield of 2-butene was obtained which was

TABLE II

Reaction of sodium trimethoxyborohydride with 1,2-dihalides and halohydrin p-toluenesulphonate.

Substrate	Product	Yield %	Reaction Conditions		
			Solvent	Temp.	Time
meso-Stilbene dibromide	trans-Stilbene	72	Diglyme	R.T.	15 mins.
dl-Stilbene dibromide	trans-Stilbene	70	Diglyme	R.T.	1 hour.
2β:3α-Dibromo-5α-cholestane	Cholest-2-ene	81	Diglyme	100°	2.75 hours.
5α:6β-Dibromo-cholestan-3β-ol	Cholest-5-ene-3β-ol	80	Diglyme	25°	24 hours.
5α-6β-Dibromocholestane	Cholest-5-ene	80	Diglyme	25°	24 hours.
trans-1,2-Dibromocyclohexane	Cyclohexene	79	Diglyme	100°	24 hours.
trans-1,2-Dibromocyclohexane	Cyclohexene	56	Tetrahydrofuran	75°	24 hours.
trans-1,2-Dibromocyclohexane	Cyclohexene	30	Dioxan	Reflux	24 hours.
trans-2-Bromocyclohexyl-tosylate	Cyclohexene	10	Tetrahydrofuran	75°	24 hours.
meso-2,3-Dibromobutane	trans-2-Butene (90%) cis-2-Butene (10%)	11.6	Tetrahydrofuran	100°	24 hours.
meso-2,3-Dibromobutane	trans-2-Butene	21	Dioxan	Reflux	10.5 hours.
dl-2,3-Dibromobutane	cis-2-Butene (58%) trans-2-Butene (42%)	5	Tetrahydrofuran	100°	24 hours.
dl-2,3-Dibromobutane	cis-2-Butene (56%) trans-2-Butene (44%)	8	Dioxan	Reflux	10.5 hours

Substrate	Product	Yield %	Reaction Conditions		
			Solvent	Temp.	Time
2:3-Dibromo-2-methylbutane	2-Methylbutene-2	23	Diglyme	90°	24 hours.
Octane-1:2-dibromide	1-Octene	Trace	Dioxan	Reflux	48 hours.
Ethylene dibromide	Ethylene	0	Dioxan	Reflux	47 hours.

all trans, only a very slight trace of cis-2-butene being detected. The reaction of dl-2,3-dibromobutane with sodium trimethoxyborohydride was much less stereospecific in both tetrahydrofuran and in dioxan cis and trans-2-butene being detected in a ratio of 3:2. Since the yields in both cases, were so low, to put forward any mechanistic proposals to account for this lack of stereospecificity would be unjustifiable.

The reaction of the dibromobutanes presents a good example of some of the complexities involved in the study of these reactions. In dioxan, the yields of 2-butene were higher in both cases than in tetrahydrofuran; moreover a large amount of starting material was detected and with both meso and dl-dibromobutanes from 70 to 80% of the material could be accounted for either as 2-butene or unreacted starting material. This may be contrasted with the results obtained in tetrahydrofuran. Not only were the yields of 2-butenes lower, but very little starting material was detected and in the case the dl-dibromide approximately 90-95% of the starting material could not be accounted for. Neither 1-butene or n-butane was detected in any of the reaction products.

A similar solvent effect may be noted in the reaction of trans-1,2-dibromocyclohexane with sodium trimethoxyborohydride. In this case the yield of cyclohexene was highest when the solvent was diglyme, and lowest when dioxan was used.

Some attempts were made at studying the kinetics of the reaction between trans-1,2-dibromocyclohexane and sodium trimethoxyborohydride. Even

though a large excess (20x) of hydride reagent was used, the results did not conform to any simple rate expression. A plot of log (100-%R) v. time gave a curve, with the rate decreasing with time. The most noticeable feature of such plots was that initially a quite fast reaction occurred, to 10-20%R, after which the rate slowed appreciably. It was also found that the reactivity of different preparations of sodium trimethoxyborohydride differed quite widely. Despite many attempts the hydride could not be prepared in greater than 90% purity.

When this study was first initiated it was thought that sodium trimethoxyborohydride, in solution, was a stable compound. However, when the material was dissolved in either tetrahydrofuran or diglyme it was observed that a white precipitate rapidly formed. This was first attributed to solvent impurities reacting with the hydride and rigorous precautions were taken in purifying the solvents. Even with very pure solvents formation of a precipitate still occurred. A rather belated literature survey was conducted and it was found that Brown had observed the same phenomena some years earlier (8). A study of the dissolution of sodium trimethoxyborohydride in both diglyme and tetrahydrofuran had led Brown and co-workers to conclude that in solution in either of these two solvents the hydride disproportionated according to the following equation.

$$4NaBH(OCH_3)_3 \rightarrow NaBH_4 + 3NaB(OCH_3)_4.$$

In diglyme sodium borohydride was soluble but the sodium tetramethoxyborohydride was insoluble and precipitated out. In tetrahydro-

furan, however, sodium tetramethoxyborohydride was soluble, but sodium borohydride was insoluble. It was also found that whereas in diglyme the tetramethoxyborohydride precipitated out almost completely, in tetrahydrofuran the sodium borohydride did not precipitate completely. Apparently sodium borohydride has a certain solubility in solutions of sodium tetramethoxyborohydride in diglyme.

Thus in one solvent (tetrahydrofuran) used to study the reductive elimination reaction, one has the situation in which a large amount of the available hydride is removed from solution by precipitation, and in the other case, that of diglyme, most of the alkoxyborate is removed.

However, from the results obtained with the dibromides the disproportionation reaction does not seem as simple as first proposed by Brown. In many of the reactions reported here, various dibromides, which undergo an elimination reaction with solutions of sodium trimethoxyborohydride, either do not react or do not give any simple elimination products with sodium borohydride. Also the initial fast rate of reaction of the hydride with trans-1,2-dibromocyclohexane seemed to indicate that, at least initially, a stronger reducing agent than sodium borohydride was present. In fact the rate of reaction of dibromocyclohexane with sodium trimethoxyborohydride was several times faster than that of the dibromide with sodium borohydride alone.

The results obtained from the reaction of the dibromobutanes with trimethoxyborohydride are now, if not completely explicable, then a little less obscure since it is apparent that in the different

solvents used quite different reducing species might be present. In dioxan the sodium trimethoxyborohydride did not appear to have any great solubility under the conditions used.* Sodium borohydride is quoted as being generally insoluble in ethers (9), and as to exactly what species of hydride ion is present, in solution, in dioxan it is not possible to say.

IV. Reaction of 1,2-dibromide with sodium borohydride:sodium tetramethoxyborohydride.

Since the dissolution of sodium trimethoxyborohydride apparently gives, in certain solvents, a mixture of sodium borohydride and sodium tetramethoxyborohydride, it was thought to be of interest to see if, starting with such a mixture, the same results were obtained upon reaction with dibromides as were found using the trimethoxyborohydride. Some of the results obtained are listed in Table III. Using a 3:1 mixture of tetramethoxyborohydride to borohydride in diglyme essentially the same results were obtained as found with sodium trimethoxyborohydride. Also, as noted previously, no elimination product could be detected from the reaction of octane-1,2-dibromide with hydride mixture, and no starting material was found in the product either. It was attempted to detect a possible alkylborane derivative by oxidation of the product with alkaline hydrogen peroxide. Some 1-octanol (11.5%)

* Solubility of sodium trimethoxyborohydride in dioxan has been given, in g/100g of solvent, as 1.6 (25°) and 4.5 (75°). (7).

TABLE III

Reaction of a mixture of sodium borohydride and sodium tetramethoxyborohydride with dibromides.

Substrate	Product	Yield %	Reaction Conditions		
			Solvent	Temp.	Time
2β:3α-Dibromo-5α-cholestane	Cholest-2-ene	73	Diglyme	100°	2 hours.
trans-1,2-Dibromo-cyclohexane	Cyclohexene	71	Diglyme	100°	24 hours
trans-1,2-Dibromocyclohexane	Cyclohexene	55	Diglyme	110°	2 hours.
2,3-Dimethyl-2,3-dibromo-butane.	Tetramethyl-ethylene	60	Diglyme	110°	20 mins.
Octane-1,2-dibromide	1-Octane	0	Diglyme	110°	30 mins.

was detected - but no dibromide or 1-octene was found.

Although the formation of an alkylborane is not disproved by this result, if it is formed it does not appear to be the major product. As was noted in the case of the reductions with sodium trimethoxyborohydride, the more substituted dibromides gave higher yields of olefin, i.e. 2, 3-dimethyl-2,3-dibromobutane gave quite a good yield of olefin.

Some kinetic studies were carried out with the mixture of borohydride and tetramethoxyborohydride. Using a large excess of hydride mixture again the results did not conform to a "pseudo" first order rate expression. With trans-1,2-dibromocyclohexane, using a plot of log (100-%R) v. time, a curve was obtained.

In contrast to the result obtained with sodium trimethoxyborohydride, the reaction was slow initially but the rate increased continually. When the results were plotted simply as %R v. time then a straight line was obtained. This result corresponds to a "pseudo" zero order reaction, i.e. the rate does not depend on the concentration of the substrate. It must again be noted that the overall rate of reaction varied somewhat depending on the origin of the hydride mixture. With each batch of tetramethoxyborohydride or borohydride the results were reasonably consistent, but use of a different sample of either sometimes gave quite different results.

It would seem from these results that the mixture of borohydride and tetramethoxyborohydride must give rise to some other hydride species which is the effective reagent for the elimination reaction, and that

the rate of reaction is dependent on the concentration and rate of formation of this species. This would also explain the slowing down of the rate observed with trimethoxyborohydride, since initially it may be supposed there would be a high concentration of reducing agent present and that after a short time the amount of this species would be reduced, either by the disproportionation or by reaction with dibromide, and that the rate of reaction would then become independent of substrate.

It must also be pointed out that the rate of reaction of trimethoxyborohydride and of the tetramethoxyborohydride: borohydride mixture did not bear any simple relationship to one another. The rate of reaction of the hydride mixture with the dibromocyclohexane was considerably faster than that of the trimethoxyborohydride.

If the rate of the reaction between the dibromides and the hydride mixture, as determined by potentiometric titration of the bromide ion formed, are to be meaningful, they must be related directly to the yields of elimination products. This was determined in one case, that of trans-1,2-dibromocyclohexane. At 110° a yield of 72% of cyclohexene would have been expected from the results of the rate study at this temperature after 2 hours. From a product isolation experiment a 55% yield of cyclohexene was detected after 2 hours at 110°, equivalent to 76.5% of that expected.

At 110°, a plot of log (100-%R) v. time more nearly approximates to a straight time, i.e. the reaction obeys a "pseudo" first order rate

expression. This could possibly mean that as the temperature increases the rate of reaction is becoming more substrate dependent, due to an increasing concentration of the reducing agent. However, raising the temperature of the reaction also causes the reaction to increase to such a rate that it becomes difficult to measure with the techniques employed here.

The rate of reaction of the hydride-alkoxyhydride mixture with trans-2-bromocyclohexyl p-toluenesulphonate was also determined at 110°, and was found to be approximately 12 times slower than the corresponding reaction with dibromocyclohexane. Since no product isolation experiment was carried out on this reaction in diglyme not much significance can be attached to this result (although a low yield of cyclohexene was isolated from the reaction of the bromotosylate with trimethoxyborohydride in tetrahydrofuran).

The effect on the rate of the reaction of dibromides with sodium borohydride to give bromide ion, upon adding tetramethoxyborohydride, was demonstrated by the results found with octane-1,2-dibromide. At 100° the rate of reaction of the dibromide with the hydride mixture was approximately 12 times that of the reaction with sodium borohydride alone.

CONCLUSION

With regard to the mechanism of the reductive elimination reaction using metal hydrides, the results obtained in this study serve more to confuse rather than to clarify. Since in only a few cases were high yields of elimination products obtained, no general conclusions concerning the mechanism of the elimination reaction can be drawn.

Concerning the nature of the reducing agent it has been shown that both sodium trimethoxyborohydride and the sodium borohydride-sodium tetramethoxyborohydride mixture give rise, in diglyme and tetrahydrofuran, to some reactive species capable of doing the reductive elimination reaction, and thus the disproportionation reaction may be, to a slight extent, reversible. Three possible alkoxyborohydrides which could be formed are $BH(OCH_3)_3$, $BH_2(OCH_3)_2$ and $BH_3(OCH_3)$. Any, or all, of these hydrides may be the reducing agent responsible for the elimination reaction.

EXPERIMENTAL

Purification of Solvents

Tetrahydrofuran

Fisher certified reagent grade was refluxed for several hours with lithium aluminum hydride, then distilled.

Dioxan

Fisher certified Reagent grade was purified by the method outlined by Vogel (10).

Benzene

B.D.H. "Analar" benzene was refluxed over calcium hydride and then distilled.

Diglyme

Commercial diglyme (diethylene glycol dimethyl ether supplied under the trade name Ansul Ether 141 by the Ansul Chemical Company) was distilled initially from sodium and then from lithium aluminum hydride under reduced pressure.

Inorganic preparations

Sodium borohydride

Commercial sodium borohydride analysed at between 84-88% by the method previously reported (11). A more pure material could be obtained by crystallization from diglyme by the method of Brown and co-workers. (12). This material analysed at 99%.

Sodium trimethoxyborohydride

Prepared from sodium hydride and trimethylborate as previously described (7), and purified by the method of Pews (2); the product analysed at 85-90% purity.

Sodium tetramethoxyborohydride

Prepared from trimethylborate (Anderson Chemical Co.) and sodium methoxide by the method of Brown and Mead (13).

Preparation of 1,2-dibromides and halohydrin p-toluenesulphonate

meso-Stilbene dibromide

Prepared from trans-stilbene as described by Fieser (14) and crystallized from toluene; m.p. 237°; reported m.p. 237° (14).

dl-Stilbene dibromide

Prepared from cis-stilbene as previously described (14); m.p. 113°-114°; reported m.p. 113°-114° (14).

meso-2:3-Dibromobutane

Sample kindly provided by Dr.R.G. Pews, b.p. 72°-73° (51 mm), n_D^{20} 1.5120; reported b.p. 72.7°-72.9° (50 mm), n_D^{20} 1.5116 (15).

dl-2:3-Dibromobutane

Prepared from cis-2-butene [Matheson Inc. C.P. Grade] by the method previously described (2); b.p. 85° (60 mm), n_D^{25} 1.5144; reported b.p. 75.6°-75.8° (50 mm), n_D^{20} 1.5147 (15).

trans-1:2-Dibromocyclohexane

Sample provided by Dr. R.G. Pews, n_D^{25} 1.5507; reported n_D^{25} 1.5507 (16).

2β:3α-Dibromo-5α-cholestane

Prepared from cholest-2-ene as described previously (17); m.p. 122°-123°, $[\alpha]_D$ + 74°; reported m.p. 123°-124°, $[\alpha]_D$ +76° (17).

5α:6β-Dibromocholestan-3β-ol

Prepared by the method of Fieser (14) and crystallized from ether: petroleum ether, m.p. 114°-115°, $[\alpha]_D$ - 43° reported m.p. 112°-114°, $[\alpha]_D$ - 44° (18).

trans-2-Bromocyclohexanol

Prepared from cyclohexene and N-bromosuccinimide by the method of Winstein and Buckles (19); b.p. 51° (1.5 mm), n_D^{25} 1.5182; reported b.p. 86.6°-88.4° (10 mm), n_D^{25} 1.5184.

trans-2-Bromocyclohexyl tosylate

Prepared from trans-2-bromocyclohexanol and p-toluenesulphonyl chloride by the general procedure of Winstein, Grunwald and Ingraham (20); m.p. 44°-46°; reported m.p. 44°-45° (4).

Cholest-5-ene

Prepared from cholesteryl chloride by reduction with sodium in liquid ammonia as described previously (21); product crystallized from ether:acetone, m.p. 92°-93°, $[\alpha]_D$ - 57° reported m.p. 92°-93°, $[\alpha]_D$ - 53° (21).

5α:6β-Dibromocholestane

Prepared from cholest-5-ene by the method of Grob and Winstein (22). The product was crystallized from ether:methanol, m.p. 94°-95°, $[\alpha]_D$ - 36°; reported m.p. 109.5°, $[\alpha]_D$ - 40°. Grob and Winstein also reported a dimorphic form of the dibromide, m.p. 95°-96°.

2:3-Dibromo-2-methylbutane

Prepared from 2-methylbut-2-ene [Phillips Petroleum Co. 99 mole % minimum] by the same method used for the bromination of 1-octene. The product distilled at 48°-50° (15 mm), n_D^{25} 1.5100; reported b.p. 63° (19 mm), n_D^{20} 1.5090 (23).

2:3-Dibromo-2:3-dimethylbutane.

This compound was prepared from tetramethylethylene (Columbia Organic Chemicals Inc.) by the same method as used for the bromination of oct-1-ene. The product was crystallized from ether:petroleum ether, m.p. 175°-176° (sealed capillary tube); reported m.p. 177°-177.5° (24).

Octane-1:2-dibromide

A solution of oct-1-ene (15.9g) in carbon tetrachloride (100 ml) was maintained at -10° to -20° while a solution of bromine (22.5g) in carbon tetrachloride (150 ml) was added over a period of 2 hours. The resulting solution was washed with dilute sodium bisulphite solution, dilute potassium hydroxide solution and water; after drying the solvent was removed and the residue distilled under reduced pressure. Octane-1:2-dibromide distilled at 48°-50° (2 mm), n_D^{25} 1.4950. Reported b.p. 118.5° (15 mm) n_D^{20} 1.4970 (25).

cis-Stilbene

A sample of cis-stilbene was prepared by the pyrolysis of cis-1:2-diphenylethylene sulphone (provided by Dr. A. Durst).

Possible isomerization of cis-Stilbene

cis-Stilbene (25 mg) was heated with sodium trimethoxyborohydride (250 mg) in tetrahydrofuran (5 ml) under reflux. The product was shown by T.L.C. (petroleum ether) to be almost entirely cis-stilbene.

Ethylene dibromide

British Drug Houses laboratory reagent grade material was distilled at atmospheric pressure, the fraction boiling at 130°-131° being collected.

Reaction of Dibromides with Hydride Reagents

I. Sodium borohydride

meso-Stilbene dibromide

meso-Stilbene dibromide (68 mg) was added to diglyme (10 ml) and the mixture was heated at 80° until all of the dibromide had dissolved. The solution was cooled to room temperature and sodium borohydride (76 mg) was added. An immediate evolution of gas was observed. After standing for 15 minutes at room temperature, the reaction was poured into acidified water and extracted with ether. The ether extracts were washed with dilute sodium bicarbonate solution, water, dried and the solvent removed under reduced pressure. The crude product (34 mg) was shown by infrared and T.L.C. [benzene:petroleum ether (1:1)] to be trans-stilbene. Crystallization from ether:methanol gave trans-stilbene, m.p. 123°-124°, mixed m.p. with authentic sample 123°-124°.

dl-Stilbene dibromide

To a solution of the dibromide (68 mg) in diglyme (10 ml) was added sodium borohydride (76 mg). A slow evolution of gas was observed. The reaction was stood at room temperature for 30 minutes, then the product was isolated in a similar manner to that for the meso-stilbene dibromide. T.L.C. [benzene:cyclohexane (1.9)] showed two spots corresponding in R_f to trans-stilbene and to dl-stilbene dibromide. The infrared spectrum also showed that a mixture of stilbenes had been obtained with peaks at 960 cm^{-1} and 925 cm^{-1}. The mixture was separated

by T.L.C. [benzene:cyclohexane (1:9)] and gave a mixture of cis and trans-stilbenes (14 mg) and dl-stilbene dibromide (32 mg). In the mixture of stilbenes trans-stilbene predominated and from the intensity of the peaks at 962 cm^{-1} (trans) and 925 cm^{-1} (cis) it was estimated that the mixture consisted of 75% trans-stilbene and 25% cis-stilbene.

Stability of meso-Stilbene dibromide in diglyme

meso-Stilbene dibromide (70 mg) was heated at 80° in diglyme until the dibromide had dissolved (30 minutes). The solution was cooled and stood at room temperature for 2 hours. The reaction mixture was poured into water and the product isolated by extraction with ether. T.L.C. [benzene:petroleum ether (1:1)] showed the product (63 mg) to consist of mainly meso-stilbene dibromide but a small amount of trans-stilbene was detectable. The mixture was separated by T.L.C. [benzene:petroleum ether (1:1)] and trans-stilbene (4 mg) was isolated and identified by its infrared spectrum and m.p.

Stability of dl-Stilbene dibromide in diglyme

The dibromide (69 mg) was dissolved in diglyme (10 ml) and the solution stood at room temperature for 3 hours. The product was isolated as described above. The infrared spectrum was almost identical with that of dl-stilbene dibromide. Upon T.L.C. [benzene:petroleum ether (1:9)] no stilbene was detectable.

2β:3α-Dibromo-5α-cholestane

A solution of the dibromide (58 mg) and sodium borohydride (38 mg) in diglyme (10 ml) was heated at 85° for 11 hours. The reaction mixture was poured into water and extracted with ether; the ether extracts were washed with water, dried, and the solvent evaporated. T.L.C. [petroleum ether] showed that the product (52 mg) consisted of mainly the starting material, together with some 2α:3β-dibromo-5α-cholestane and a slight trace of cholest-2-ene. From the intensity of the spot corresponding to cholest-2-ene it was estimated that there was less than 10% of this elimination product present.

5α:6β-Dibromocholestane

To a solution of the dibromide (108 mg) in diglyme (10 ml) was added sodium borohydride (77 mg) and the reaction was stood at room temperature for 15 hours. The reaction solution was poured into acidified water and extracted with ether; the ether extracts were washed with dilute sodium bicarbonate solution, water, dried, and the ether evaporated. T.L.C. [benzene:cyclohexane (5.95)] showed the following: (1) no cholest-5-ene or starting material was detected, (2) several spots ran almost with the solvent front, (3) at least four or five spots were visible near the origin. These materials were not investigated further.

trans-1,2-Dibromocyclohexane

a) A solution of the dibromide (0.966g) and sodium borohydride

(0.76g) in diglyme (25 ml) was heated at 100° for 24 hours under reflux. Benzene (10 ml) was added to the reaction mixture which was distilled at 100° (oil bath temperature) in a stream of nitrogen. The distillate was made up to 25 ml. in a graduated flask with benzene and analysed by v.p.c. using 20% carbowax 20M. column (6' x 1/4") at an oven temperature of 80°. No trace of cyclohexene or cyclohexane was found.

b) The dibromide (246 mg) and sodium borohydride (750 mg) in diglyme (50 ml) were heated at 110° for 12 hours in a sealed tube. After cooling, the tube was opened and carbon tetrachloride was added to the reaction mixture, which was then poured into water and extracted with more carbon tetrachloride. The extracts were washed with water, dried and made up to 50 ml in a graduated flask, and analysed by v.p.c. using the same conditions as described above. Also as described above, no cyclohexene was found. With a column temperature of 150°, some dibromocyclohexane was detected. By comparison of the peak area of the product solution to the peak areas found with standard solution of dibromocyclohexane in carbon tetrachloride it was estimated that 41% of the starting material remained.

c) Attempted oxidation of alkylborane intermediate.

A solution of trans-1,2-dibromocyclohexane (24g) and sodium borohydride (20g) in diglyme (500 ml) was heated at 110° for 60 hours under reflux. To the hot reaction mixture was added 100 ml of water,

to hydrolyse the sodium borohydride, followed by 50 ml of 3N sodium hydroxide solution. The solution was cooled to 80° and 50 ml of 30% hydrogen peroxide was added slowly. Finally the reaction mixture was cooled to room temperature and extracted with carbon tetrachloride (200 ml); the extracts were washed with water and dried. The carbon tetrachloride solution so obtained was distilled (steam-bath); and both the distillate and the residue were made up to 250 ml in a graduated flask. Both distillate and residue solutions were analysed by v.p.c. using a 20% carbowax 20M. column. With both solutions only a trace of cyclohexene and no cyclohexane was detected at a column temperature at 65°. In the residue solution dibromocyclohexane was detected (at 160°), and it was estimated, by comparison with standard solutions, that 62.5% of the starting material was unchanged. Some dibromocyclohexane was detected, equivalent to 11% of the starting material and small amount of cyclohexanol, corresponding to 3.4% of the starting material was also found. Analysis for these two compounds was carried out with a column temperature of 120°.

Ethylene dibromide

A solution of the dibromide (0.49g) and sodium borohydride (1.5g) in diglyme (125 ml) was heated at 60° for 1 1/2 hours. During this time nitrogen was bubbled through the reaction mixture and passed, via a cold trap immersed in acetone/dry ice, into a solution of bromine (0.5g) in carbon tetrachloride (75 ml). The carbon tetrachloride solution was washed with dilute sodium bisulphite solution, dilute sodium

bicarbonate solution, water, dried and made up to 50 ml in a graduated flask. This solution was analysed by v.p.c., using a 20% carbowax 20M.column at 114°; no ethylene dibromide was detected.

Rate Measurements

The method of bromide analysis was essentially the same as that used by Pews (2). The reaction mixture was poured into dilute aqueous acetic acid (5%) and benzene (10 ml) was added to extract the organic material. The amount of bromide ion was then determined by potentiometric titration with silver nitrate solution (0.01N) using an Electronic Instruments Ltd. (Surrey, England) pH meter, Model 23A, and the following electrode system: a silver electrode immersed in the bromide ion solution and a calomel electrode immersed in a saturated ammonium nitrate solution which was connected to the bromide ion solution by an ammonium nitrate bridge.

General Procedure

Sodium borohydride (76 mg, 2.0m.mole) was weighed into thick wall pyrex tubes. To each tube was added 5 ml of a solution containing 0.1m.mole of the dibromide in diglyme. The weighing of the borohydride and addition of dibromide solution were carried out inside a dry box. The tubes were stoppered, removed from the dry box and quickly sealed. The tubes were then suspended in a constant temperature bath. The reaction was stopped by cooling the tube in ice and the contents were titrated as described above.

Reaction of sodium borohydride with 1,2-dibromides

Solvent - Diglyme

Ethylene dibromide — **Temp.** 100° ± 1°

Titre for 100% of Br^- = 20.0 ml of 0.01N silver nitrate solution.

Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
5	3.2	16.0	1.9243
10	5.8	29.0	1.8513
16	8.8	44.0	1.7482
20	10.4	52.0	1.6812
30	13.8	69.0	1.4914
40	15.2	76.0	1.3802

Solvent - Diglyme

trans-1,2-Dibromocyclohexane — **Temp.** 60° ± 1°

Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
10	1.9	9.5	1.9566
30	2.1	10.5	1.9518
60	3.0	15.0	1.9294
120	4.2	21.0	1.8976
180	5.2	26.0	1.8692
240	6.9	34.5	1.8162
345	9.0	45.0	1.7404

Octane-1,2-dibromide — Solvent - Diglyme

Temp. 100° ± 1°

a)

Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
5	3.5	17.5	1.9165
10	3.7	18.5	1.9112
15	4.5	22.5	1.8893
30	5.3	26.5	1.8663
60	6.9	34.5	1.8162
120	9.7	48.5	1.7118
240	12.5	62.5	1.5740
360	15.5	77.5	1.3522

b) Solvent - Diglyme

Temp. 100° ± 1°

Concentration of dibromide 0.1m.mole

Concentration of sodium borohydride 0.5m.mole

Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
7	3.3	16.5	1.9217
15	4.3	21.5	1.8949
30	5.7	28.5	1.8543
60	8.1	40.5	1.7745
120	9.1	45.5	1.7364
180	10.0	50.0	1.6990

Determination of the stoichiometry of the reaction between Ethylene dibromide and sodium borohydride at 60° ± 1°.

The rate studies were carried out in an identical manner to that described above; except that 0.5m.mole of the dibromide was reacted with 0.5m.mole of sodium borohydride . In this experiment, two tubes were removed from the constant temperature bath at each time interval. The contents of one tube were titrated for bromide ion as described above. The contents of the second tube were titrated for active hydrogen using a standard solution of iodine in benzene (2, 11). In this case a 5 ml aliquot of the iodine in benzene solution (0.718N) was added to the tube; after standing for 10 min the mixture was poured into water and titrated with 0.1N sodium thiosulphate. The results are listed on the following page.

Results of stoichiometry experiment.	Temperature 60° ± 1°
Concentration of bromide ion	0.5m.mole
Concentration of silver nitrate solution	0.01N
Concentration of sodium borohydride	0.5m.mole

1) Analysis for bromide ion

Titre for 100% of bromide ion = 20.0 ml of 0.01N silver nitrate solution.

Time (min)	Titre (ml)	% of Br^-
15	1.0	10
30	1.7	17
60	2.6	26
90	2.7	27
120	3.3	33
189	3.7	37

2) Analysis for sodium borohydride

5.0 ml I_2 in benzene solution = 35.9 ml 0.1N $Na_2S_2O_3$.

5.0 ml I_2 in benzene solution + 2.0m.mole sodium borohydride ≡ back titration of 17.1 ml of 0.1N $Na_2S_2O_3$.

∴ 2.0m.mole of sodium borohydride = 18.8 ml of 0.1N $Na_2S_2O_3$.

∴ % $NaBH_4$ remaining in reaction mixture =

$$\frac{\text{ml 0.1N } Na_2S_2O_3 \text{ consumed} \times 100}{18.8}$$

Time	Back Titre (x) (ml 0.1N $Na_2S_2O_3$)	35.9-x (ml 0.1N I_2) solution consumed	%$NaBH_4$ remaining	%$NaBH_4$ consumed
15	21.9	14.0	75.5	24.5
30	23.2	12.7	67.5	32.5
60	25.7	10.2	54.3	45.7
90	27.0	8.9	47.3	52.7
120	27.9	8.0	42.5	57.5
180	29.4	6.5	34.5	65.5
189	31.9	4.0	21.3	78.7

II. Sodium trimethoxyborohydride

meso-Stilbene dibromide

meso-Stilbene dibromide (70 mg) was dissolved in diglyme (10 ml) by heating at 80° for 30 minutes. The solution was cooled and sodium trimethoxyborohydride (260 mg) was added. An immediate evolution of gas was observed, and the reaction was stood at room temperature for

15 minutes. The reaction mixture was poured into acidified water and extracted with ether; the ether extracts were washed with dilute sodium bicarbonate solution and water, dried and the solvent evaporated. T.L.C. [benzene:petroleum ether (1.9)] showed the presence of trans-stilbene and starting material. The infrared spectrum also showed the presence of trans-stilbene as evidenced by the peak at 962 cm^{-1}. trans-Stilbene (26 mg) was isolated by T.L.C., crystallized from ether:methanol, m.p. 122°-124°, mixed m.p. with authentic sample 123°-124°.

dl-Stilbene dibromide

To a solution of the dibromide (68 mg) in diglyme (10 ml) was added sodium trimethoxyborohydride (260 mg). The reaction was stood at room temperature for 1 hour. The product was isolated as described above for meso-stilbene dibromide. T.L.C. [benzene:cyclohexane (1:9)] showed that the product (46 mg) consisted of a mixture of trans-stilbene and starting material. The infrared spectrum had a large peak at 960 cm^{-1}; there was no evidence of any peak at 925 cm^{-1} which would have indicated the presence of cis-stilbene. trans-Stilbene (25 mg) was isolated by T.L.C., crystallized from ether:methanol, m.p. 122°-124°, mixed m.p. with authentic sample 123°-124°.

2β:3α-Dibromo-5α-cholestane

a) The dibromide (57 mg) was heated with sodium trimethoxyborohydride (50 mg) in diglyme (5 ml) at 100° in a sealed tube for 2 3/4 hours. The product (40 mg) was isolated as described above. T.L.C. (petroleum

ether) showed the product to consist mainly of cholest-2-ene together with small amounts of starting material and of the corresponding di-equatorial dibromide. Column chromatography (alumina, Woelm grade I, neutral), eluting with petroleum ether, gave cholest-2-ene (32 mg) crystallized from ether:methanol, m.p. 72°.

b) A solution of the dibromide (53 mg) and the hydride (130 mg) in diglyme (10 ml) was stood at room temperature for 24 hours. T.L.C. [petroleum ether] showed the product (44 mg) to consist mainly of unchanged starting material. Crystallization from ether:methanol gave 2β:3α-dibromo-5α-cholestane (40 mg) identified by m.p. and mixed m.p.

5α:6β-Dibromocholestan-3β-ol

A solution of the dibromide (53 mg) and sodium trimethoxyborohydride (130 mg) in diglyme (10 ml) was stood at room temperature for 24 hours. The product was isolated as described above and was identified as cholest-5-ene-3β-ol (30 mg), crystallized from ether-methanol, m.p. 146°, mixed m.p. with authentic sample 142°-144°. T.L.C. [ether: petroleum ether (1:1)] R_f value identical to that of cholesterol.

5α:6β-Dibromocholestane

A solution of the dibromide (50 mg) in diglyme (10 ml) was treated with sodium trimethoxyborohydride (130 mg) and the reaction was stood at room temperature for 24 hours. The product was shown by T.L.C. [petroleum ether] to be almost entirely cholest-5-ene; crystallized

ether) showed the product to consist mainly of cholest-2-ene together with small amounts of starting material and of the corresponding di-equatorial dibromide. Column chromatography (alumina, Woelm grade I, neutral), eluting with petroleum ether, gave cholest-2-ene (32 mg) crystallized from ether:methanol, m.p. 72°.

b) A solution of the dibromide (53 mg) and the hydride (130 mg) in diglyme (10 ml) was stood at room temperature for 24 hours. T.L.C. [petroleum ether] showed the product (44 mg) to consist mainly of unchanged starting material. Crystallization from ether:methanol gave 2β:3α-dibromo-5α-cholestane (40 mg) identified by m.p. and mixed m.p.

5α:6β-Dibromocholestan-3β-ol

A solution of the dibromide (53 mg) and sodium trimethoxyborohydride (130 mg) in diglyme (10 ml) was stood at room temperature for 24 hours. The product was isolated as described above and was identified as cholest-5-ene-3β-ol (30 mg), crystallized from ether-methanol, m.p. 146°, mixed m.p. with authentic sample 142°-144°. T.L.C. [ether: petroleum ether (1:1)] R_f value identical to that of cholesterol.

5α:6β-Dibromocholestane

A solution of the dibromide (50 mg) in diglyme (10 ml) was treated with sodium trimethoxyborohydride (130 mg) and the reaction was stood at room temperature for 24 hours. The product was shown by T.L.C. [petroleum ether] to be almost entirely cholest-5-ene; crystallized

from ether:acetone (31 mg), m.p. 91°-93°, $[\alpha]_D$ - 52°, mixed m.p. with authentic sample 89°-91°.

trans-1:2-Dibromocyclohexane.

(i) A solution of the dibromide (0.97 g) and the hydride (2.6g) in diglyme (25 ml) was heated at 100°C for 24 hours. Benzene (10 ml) was added to the reaction solution which was then distilled in a stream of nitrogen at 100°, to distill off the volatile components. The resulting distillate was made up to 25 ml in a graduated flask and analysed by vapour phase chromatography. Comparison of the peak area of cyclohexene in the product solution to the peak areas of standard solutions of cyclohexene in benzene gave a yield of 79% of cyclohexene.

(ii) A solution of the dibromide (0.97 g) and sodium trimethoxyborohydride (2.6g) in tetrahydrofuran (25 ml) was heated at 75° for 24 hours. The reaction mixture was distilled at 80° and the distillate was analysed by vapour phase chromatography as in (i) above, a 56% yield of cyclohexene being detected.

(iii) A solution of the dibromide (1.94 g) and sodium trimethoxyborohydride (5.2g) in dioxan (100 ml) was refluxed for 24 hours. The reaction mixture was poured into water and extracted with ether; the ether extracts were washed thoroughly with water, dried and made up to 50 ml in a graduated flask. This solution was analysed by vapour phase chromatography. A 27% yield of cyclohexene was detected, and analysis for

starting material showed that 70% of the trans-1,2-dibromocyclohexane remained.

trans-1-Bromocyclohexane-2-toluenesulphonate.

A solution of the bromotosylate (1.31 g) and sodium trimethoxyborohydride (2.6 g) in tetrahydrofuran (25 ml) was heated in a sealed tube at 75° for 24 hours. More tetrahydrofuran was added and the reaction solution was distilled at 80°. The distillate was made up to 50 ml in a graduated flask and analysed by vapour phase chromatography, as outlined in the previous experiment. A yield of 10.5% of cyclohexene was detected. The material remaining after distillation was dissolved in ether, washed several times with water, dried and the ether evaporated. The residue (1.053 g) had an infrared spectrum very similar to that of the starting material.

meso-2:3-Dibromobutane.

a) The dibromide (5.52 g) and sodium trimethoxyborohydride (6.4 g) in tetrahydrofuran (30 ml) were heated in a sealed tube at 100° for 24 hours. The tube was cooled in an acetone:dry ice bath and opened; the contents were rapidly transferred to two-necked 100 ml flask which was also cooled in acetone:dry ice. The flask was attached via a reflux condenser to a trap cooled in acetone:dry ice; the flask was then allowed to warm to room temperature and nitrogen was bubbled through the reaction mixture for 3-4 hours. The condensate in the trap was dissolved in cold ether (cooled in acetone:dry ice) and made up to 50 ml in a graduated flask.

A standard solution of trans-2-butene (Matheson C.P. grade) in ether was prepared as follows: approximately 8 ml of ether in a 10 ml graduated flask was weighed and then cooled in acetone:dry ice. Trans-2-Butene was bubbled through the ether for several minutes after which the graduated flask was removed from the cold bath, allowed to warm to room temperature and reweighed, and made up to the mark. In a similar fashion a standard solution of cis-2-butene in ether was prepared. The product solution was analysed by vapour phase chromatography, using a propylene carbonate column (12' x 1/8") at 50°. From a comparison of the peak areas of the product solution with the peak areas of standard solutions of cis and trans-2-butene a yield of 10.5% of trans-2-butene was found. A small amount of cis-2-butene was also detected, in a yield of 1.1%.

The remaining reaction solution was taken up in ether, washed several times with water and dried. Evaporation of the solvent gave approximately 1.0 g of an oil, the infrared spectrum of which showed it to be mainly meso-butane dibromide.

b) A second experiment was carried out in an exactly similar manner to that above, using the following quantities of materials; meso-butane dibromide (4.34 g) plus sodium trimethoxyborohydride (26.0 g) in diglyme (30 ml). Analysis of the material found in the cold trap gave a yield of 9.2% trans-2-butene and 1.4% cis-2-butene, almost exactly the same as that found above.

The residue from the distillation was dissolved in water, which

was extracted with ether and the ether extracts were further washed with water, dried and made up to 50 ml in a graduated flask. Analysis by v.p.c. using a 20% carbowax 20M column at 120° showed no trace of the starting material.

c) A solution of meso-butane dibromide (2.18 g) and sodium trimethoxyborohydride (13.0 g) in dioxan (150 ml) was refluxed for 10 1/2 hours. During this time nitrogen was bubbled through the reaction and passed, via a reflux condenser, through an acetone:dry ice trap and a liquid nitrogen trap. The condensate was dissolved in ether and analysed as described above. A yield of 21.4% of trans-2-butene was detected. Only a trace of cis-2-butene was evident, in a quantity too small to measure. The mixture remaining from the distillation was poured into water and extracted with ether; the ether extracts were washed with water, dried, and made up to 250 ml in a graduated flask. Analysis of this residue solution by v.p.c., on a 20% carbowax 20M column at 120°, showed the presence of meso-butane dibromide, to the extent of 60% of the starting material.

dl-2:3-Dibromobutane

1) The dibromide (5.53 g) and sodium trimethoxyborohydride (6.4 g) in tetrahydrofuran (30 ml) were heated in a sealed tube at 100° for 24 hours. The reaction mixture was treated in an analogous fashion to that for the meso-butane dibromide above. A small amount of 2-butenes were detected (4.7%), which analysed at 58% cis-2-butene and 42% trans-2-butene. The residue from distillation was treated

as described above. Analysis showed that slightly more than 2% of dl-butane dibromide was present.

2) A solution of the dibromide (2.18 g) and sodium trimethoxyborohydride (13.0 g) in dioxan (150 ml) was refluxed for 10 1/2 hours. During this time nitrogen was bubbled through the reaction mixture and passed, via a reflux condenser, through first a acetone:dry ice trap and then through a liquid nitrogen trap. The condensates found in the traps were dissolved in cold ether and analysed as described above. The yield of 2-butenes found was 8.3%, which consisted of 56% of cis-2-butene and 44% of trans-2-butene. The residue was treated as described above; analysis by v.p.c. showed that 65% of the starting material remained unchanged.

In these experiments no 1-butene or n-butane was detected by vapour phase chromatography.

Octane-1:2-dibromide

1) A solution of the dibromide (1.34 g) and sodium trimethoxyborohydride (13.0 g) in dioxan (150 ml) was refluxed for 48 hours. The reaction was poured into water and extracted with ether, which was dried and made up to 250 ml in a graduated flask. The product was analysed by vapour phase chromatography: very little oct-1-ene was detected; also practically no octane-1:2-dibromide was detected.

2) The dibromide (544 mg) and sodium trimethoxyborohydride (2.6 g)

in diglyme (100 ml) were heated at 60° for 3 hours. The reaction mixture was poured into water and extracted with ether, which was made up to a known volume and analysed by vapour phase chromatography. No oct-1-ene and very little octane-1,2-dibromide was detected.

Ethylene dibromide

A solution of ethylene dibromide (1.88 g) and sodium trimethoxyborohydride (13.0 g) in dioxan (150 ml) was refluxed for 47 hours. The reflux condenser was connected through a dry ice:acetone trap to a gas bubbler immersed in a solution of bromine in carbon tetrachloride. After 47 hours nitrogen was passed through the reaction mixture and into the bromine solution for 1 hour. The carbon tetrachloride was washed with dilute sodium bisulphite solution, water, dried, and made up to 250 ml in a graduated flask. No ethylene dibromide was detected by v.p.c. The reaction solution was extracted with ether; approximately 15% of the starting material was detected by v.p.c.

2:3-Dibromo-2-methylbutane.

A solution of the dibromide (924 mg) and sodium trimethoxyborohydride (2.6 g) in diglyme (100 ml) was heated at 90° for 24 hours. Benzene (40 ml) was added to the reaction mixture, which was then washed thoroughly with water. The benzene solution was dried and made up to 50 ml. Analysis by v.p.c. gave a yield of 22.5% of 2-methylbut-2-ene. The amount of dibromide remaining could not be estimated since diglyme had the same R_f value.

Rate Measurements

The rate measurement of the reaction of sodium trimethoxyborohydride with trans-1,2-dibromocyclohexane was carried in the same way as described previously for the reaction between sodium borohydride and dibromides. Sodium trimethoxyborohydride was weighed into thick wall Pyrex tubes and 5 ml of a solution of the dibromide in diglyme was added; this procedure was carried out inside a dry box. The tubes were sealed and heated at 110° in a constant temperature bath. The bromide ion was titrated potentiometrically as described previously, with 0.01N silver nitrate solution.

The example given here is typical of many rate studies on this system.

Reaction of sodium trimethoxyborohydride with trans-1,2-dibromocyclohexane

Solvent: Diglyme

Temp.: 110° ± 1°

Titre for 100% of Br^- = 20.0 ml of 0.01N silver nitrate solution

Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
3	1.5	7.5	1.9661
6	2.2	11.0	1.9494
7 1/2	2.8	14.0	1.9345
9	3.6	18.0	1.9138
15	4.4	22.0	1.8921
30	5.6	28.0	1.8757
60	9.5	47.5	1.7202
90	11.9	59.5	1.6075
120	13.8	69.0	1.4914
180	15.2	76.0	1.3802

III Sodium borohydride:sodium tetramethoxyborohydride.

2β:3α-Dibromo-5α-cholestane

The dibromide (52 mg) was heated for 2 hours, at 100°, in a sealed tube with a mixture of sodium borohydride (10 mg) and sodium tetramethoxyborohydride (40 mg) in diglyme (5 ml). T.L.C. [petroleum ether] showed the product (35 mg) to be mainly cholest-2-ene together with traces of starting material and 2α:3β-dibromo-5α-cholestane. Column chromatography (alumina, Woelm, grade I, neutral) eluting with petroleum ether gave cholest-2-ene (27 mg) crystallized from ether:methanol, m.p. 71°-73°.

trans-1:2-Dibromocyclohexane.

1) The dibromide (0.97 g) was heated at 100° for 24 hours with a mixture of sodium borohydride (0.19 g) and sodium tetramethoxyborohydride (2.37 g) in diglyme (25 ml). Benzene (10 ml) was added to the reaction which was distilled in a stream of nitrogen at 100°. The distillate was made up to 25 ml and analysed by v.p.c., a 71% yield of cyclohexene was found.

2) The dibromide (245 mg) plus sodium tetramethoxyborohydride (2.4 g) and sodium borohydride (190 mg) in diglyme (50 ml) were heated for 2 hours at 110° in a sealed tube. The reaction mixture was poured into water and extracted with carbon tetrachloride; the extracts were washed several times with water, dried and made up to 50 ml in a graduated flask. By vapour phase chromatography a 55% yield of cyclohexene was detected, and 34% of the starting material was found.

Octane-1:2-dibromide

1) A solution of the dibromide (282 mg), sodium borohydride (200 mg) and sodium tetramethoxyborohydride (2.4 g) in diglyme (50 ml) was heated at 110° for 30 minutes in a sealed tube. The reaction mixture was extracted with benzene (40 ml); the benzene was washed with water, dried and made up to 50 ml. No oct-1-ene or octane-1,2-dibromide could be detected by v.p.c.

2) Attempted oxidation of an alkylborane.

The dibromide (2.24 g) together with sodium borohydride (0.4 g) and sodium tetramethoxyborohydride (4.8 g) in diglyme (100 ml) was heated at 110°, in a sealed tube, for 2 1/2 hours. The contents of the tube were transferred to a round bottomed flask equipped with a reflux condenser and dropping funnel. Water (20 ml) was added to destroy the sodium borohydride. When reaction ceased, 50 ml of 3N sodium hydroxide solution was added, followed by 25 ml of 30% hydrogen peroxide. The reaction mixture was stirred for 1 hour at room temperature, and then sodium hydroxide pellets were added. Addition of ether resulted in the separation of two layers; the ether layer was removed, washed with water, dried and made up to 100 ml in a graduated flask. This solution was analysed by v.p.c., 1-octanol to the extent of 11.5% was detected, but no dibromide or oct-1-ene was found.

2:3-Dimethyl-2:3-dibromobutane.

The dibromide (479 mg) together with sodium borohydride (200 mg)

and sodium tetramethoxyborohydride (2.4 g) in diglyme (50 ml) was heated in a sealed tube at 110° for 20 minutes. The sealed tube was cooled in ice, opened, and the reaction extracted with carbon tetrachloride. After washing and drying the carbon tetrachloride solution was made up to 50 ml and analysed by v.p.c., a 60% yield of 2:3-dimethylbut-2-ene was detected.

Rate Studies of the reaction of sodium borohydride:sodium tetramethoxyborohydride with dibromides.

The rate studies were carried out in a similar manner to that previously described. Sodium tetramethoxyborohydride (240 mg, 1.5m.mole) was weighed into thick wall Pyrex tubes, and a solution of sodium borohydride (19 mg, 0.5m.mole) plus dibromide (0.1m.mole) in diglyme (5 ml) was added. The tubes were sealed and heated in a constant temperature bath. The rate of the reaction was followed by potentiometric titration of the bromide ion formed during the reaction as previously described.

Reaction of sodium borohydride:sodium tetramethoxyborohydride with 1,2-dibromides.

trans-1,2-Dibromocyclohexane Solvent - Diglyme

Temp. 110° ± 1°

Titre for 100% of Br^- = 20.0 ml 0.01N silver nitrate solution

a)	Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
	15	1.6	8.0	1.9638
	30	3.6	18.0	1.9138
	60	8.6	43.0	1.7559
	90	12.0	60.0	1.6021
	120	14.5	72.5	1.4393
	150	15.6	78.0	1.3424

b) Solvent - Diglyme Temp. 100° ± 1°

Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
7 1/2	0.4	2.0	1.9912
15	1.9	9.5	1.9566
22 1/2	3.0	15.0	1.9294
30	4.0	20.0	1.9031
60	8.6	43.0	1.7559
90	13.9	69.5	1.4834
120	18.0	90.0	1.0000

Octane-1,2-dibromide Solvent - Diglyme

Temp. 100° ± 1°

a)

Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
5	3.5	17.5	1.9165
10	6.9	34.5	1.8162
15	10.0	50.0	1.6990
20	11.2	56.0	1.6435
25	12.5	62.5	1.5740
30	13.3	66.5	1.5250
40	14.4	72.0	1.4472
50	15.5	77.5	1.3522

b) Solvent - Diglyme Temp. 110° ± 1°

Time (min)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
2 1/2	3.1	15.5	1.9269
5	5.4	27.0	1.8633
7 1/2	7.6	38.0	1.7924
10	10.2	51.0	1.6902
12 1/2	10.5	52.5	1.6767
15	12.4	62.0	1.5798
20	14.6	73.0	1.4314
25	14.8	74.0	1.4150
30	17.0	85.0	1.1761

trans-2-Bromocyclohexyl-p-toluenesulphonate

Solvent - Diglyme

Temp. 100° ± 1°

Time (hr)	Titre (ml)	% of Br^-	Log (100-% of Br^-)
2	2.3	11.5	1.9469
4	3.8	20.0	1.9031
6	4.6	23.0	1.8865
8.1	5.15	25.75	1.8707
10	6.8	34.0	1.8195
12	7.0	35.0	1.8129
16	8.0	40.0	1.7782

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