STUDIES IN ARYNE CHEMISTRY

A Thesis

Submitted to

Loughborough University of Technology

by

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In Partial Fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

October 1969.

SUMMARY

The principal methods for the generation of arynes, and the Diels-Alder reactions of steroidal dienes are briefly reviewed.

Tetrafluorobenzyne (generated from pentafluorophenyl-lithium and pentafluorophenyl magnesium chloride) reacts with simple models for steroidal diene systems to give mainly 1,4-addition products.

Benzyne (generated from o-bromofluorobenzene and anthranilic acid), tetrachlorobenzyne (from tetra-chloroanthranilic acid) and tetrafluorobenzyne react with steroidal-5,7-dienes to give products of the ene-reaction. In addition, tetrafluorobenzyne forms a 5,8-adduct with a 5,7-diene and with a 5,7,9(11)-triene.

Cholesta-2,4-diene gives 1,4-adducts with benzyne and tetrafluorobenzyne which undergo retro-Diels-Alder reactions on pyrolysis. Steroidal-1(10),9(11)-dienes also give 1,11-adducts with benzyne and tetrachlorobenzyne.

The adducts of tetrafluorobenzyne with models for the oestrogen steroids, and with oestradiol dimethyl ether are reported. An unsuccessful attempt to synthesise an adduct from a steroidal styrene is described.

Finally the photoisomerisation of 5,6,7,8-tetrafluoro-1,4-dihydro-1,4-ethanonaphthalene is reported and a mechanism proposed.

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to Dr.H.Heaney and Dr.B.A.Marples for their guidance and enthusiasm throughout the course of this work. Their inspirations were a constant source of encouragement.

I would also like to thank my typist for her efficiency and patience in typing the manuscript.

I gratefully acknowledge the Science Research Council for a research studentship, and Imperial Smelting Corporation for generous supplies of fluorinated chemicals.

CONTENTS

INTRODUCTION

(1) Generation and Reactions of Arynes.

Although arynes have been postulated as intermediates since 1870,[1] it is only during the last sixteen years, following the decisive results of Roberts,[2] that they have been thought of as a worthwhile subject for study for the sake of their own potential chemistry. During this period many reviews have appeared.[3]

The existence of the parent aryne, variously referred to as benzyne, dehydrobenzene, ortho-phenylene or 1,3-cyclohexadien-5-yne, has been demonstrated. Its bond lengths have been calculated,[4] its half life measured by time-of-flight mass spectrometry[5] and by flash photolysis[6] and its ultra violet spectrum examined.[7] It is generally agreed that benzyne is a short lived, ($t_{\frac{1}{2}} \sim 10^{-4}$ sec) ground state singlet with its two extra electrons in a lower symmetrical orbital which slightly overlaps.[8] The molecule behaves as a strained olefin and the reactive site resembles another (partial) π -bond. Thus benzyne, which will undergo 1,2-cycloadditions, prefers to act as a dienophile and adds 1,4 in a Diels-Alder fashion when offered the opportunity. Both benzyne and tetrafluorobenzyne have now been stabilised as their nickel carbonyl complexes.[9]

Arynes and substituted arynes have been generated both in solution and in the gaseous phase in a number of different ways, all of which involve the elimination of simple, thermodynamically stable molecules from suitable ortho-disubstituted benzenes. The first method, which was the only one known during the development period of benzyne chemistry, was from

ortho-halogenophenyl anions (Scheme I).

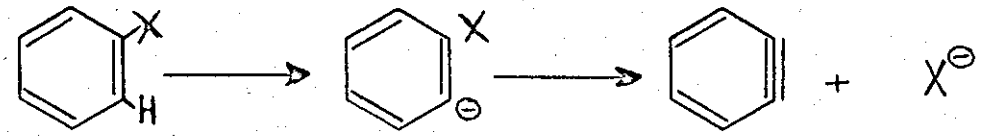
The most efficient methods are the decomposition of the ortho-mono-organometallic compounds derived from halogenobenzenes by the use of alkyl metal reagents [10-13] (Scheme II), or the treatment of aryl halides with a metal amide, either in an inert solvent[11-15] (e.g. ether, toluene) or in the presence of a free amine[16,17] (e.g. liquid ammonia, piperidine) (Scheme III).

Metal-halogen interconversion,[18] which may compete with the metallation of the aryl halide and so produce side reactions, can also be applied as a method for generating ortho-halogenophenyl anions.[19-21] For example, alkyl lithium compounds have been widely used with 1,2-dihalogenobenzenes for the production of benzyne (Scheme IV).

Unfortunately the choice of reaction partners is very limited using the above techniques since they all require the use of strong organometallic reagents. Wittig[22] provided the first means of getting round this problem by reacting 1,2-dihalogenobenzenes with magnesium or lithium amalgam (Scheme V). In this manner the Diels-Alder reactions of benzyne with various dienes,[23] amines,[24] sulphides,[25] and phosphorus derivatives[24] was demonstrated.

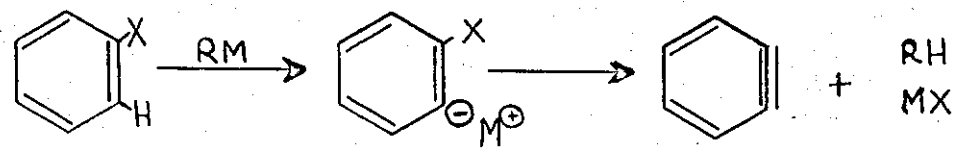
One of the simplest methods for generating arynes involves the diazotisation of anthranilic acid in aprotic media[26] (Scheme VI). The explosive intermediate, benzenediazonium-2-carboxylate is not always isolated. Friedman has isolated the hydrochloride salt and used it to generate benzyne.[27] The use of this method has meant that arynes can now be

Scheme I



X = F, Cl, Br.

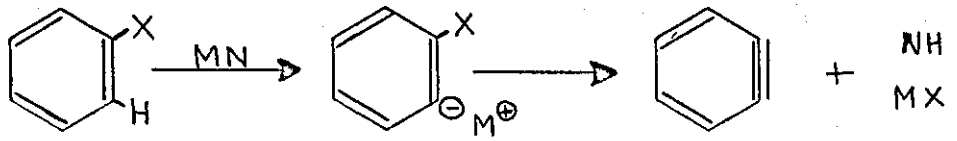
Scheme II



X = F, Cl, Br.
M = Li, Na.

R = Bu^n, Bu^t, Ph, Me.

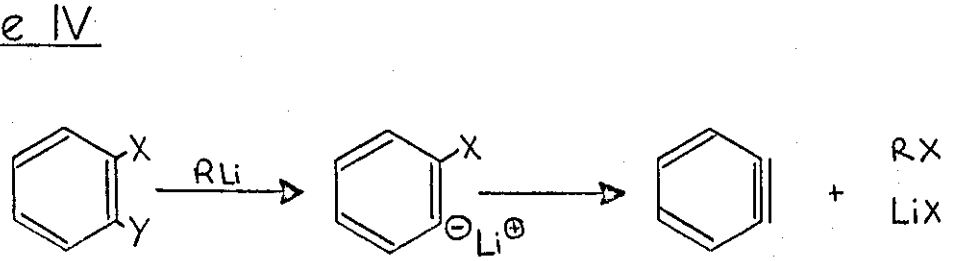
Scheme III



X = Cl, Br, I.
M = Li, Na, K.

N = NH_2, $N(Me)_2$, $N(Et)_2$, $NH{\cdot}NH_2$,  .

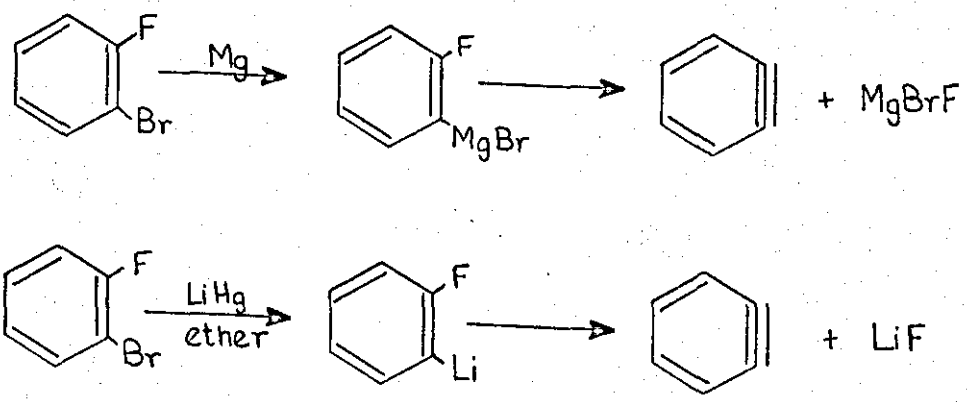
Scheme IV



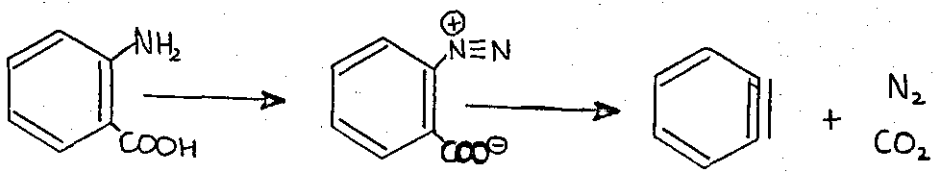
X = F, Cl, Br.
Y = Br.

R = Bu^n, Ph, Me.

Scheme V



Scheme VI



generated in the presence of molecules with reactive functional groups. For example in these laboratories, tetrachlorobenzyne has been made by this technique and reacted with a variety of unsaturated carbonyl compounds.[28] Benzenediazonium-2-carboxylate does not eliminate nitrogen and carbon dioxide simultaneously.[29]

Another important procedure for the production of benzyne is the decomposition of 1,2,3-benzothiadiazole-1,1-dioxide[30] in solution at 20°C (Scheme VII). The loss of nitrogen and sulphur dioxide is thought to be concerted in this case.

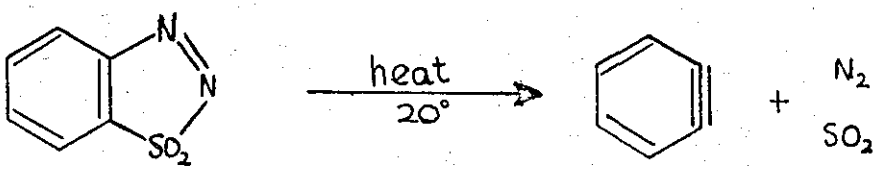
An oxidative method frequently used is the treatment of 1-aminobenzotriazole with lead tetraacetate or nickel peroxide.[31] The reaction is thought to proceed via a nitrene intermediate (Scheme VIII).

Other less important methods involve the flash photolysis of benzenediazonium-2-carboxylate and the photolytic decomposition of 1,2-diiodobenzene[32] and 2-iodophenylmercuric iodide.[33] The latter two radical reactions produce only small quantities of benzyne.

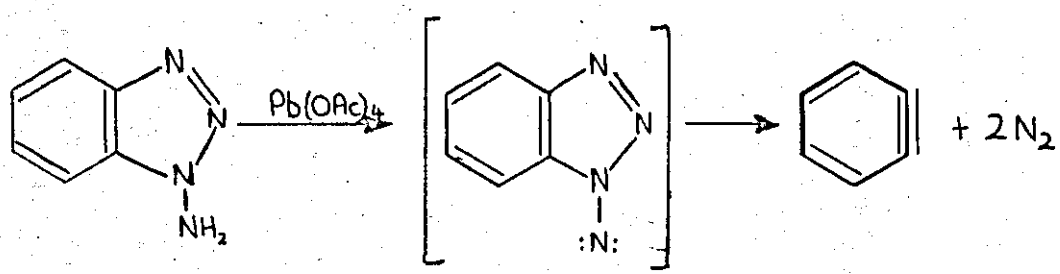
Finally a few pyrolytic methods exist for the generation of arynes, the most important of which is the thermal decomposition of diphenyliodonium-2-carboxylate[34] in diglyme at 160°C (Scheme IX).

For several years it was thought that the different methods of generation of the reactive intermediate resulted in "different" benzynes being produced (i.e. singlet or triplet benzyne). It has been shown conclusively by Huisgen[35]

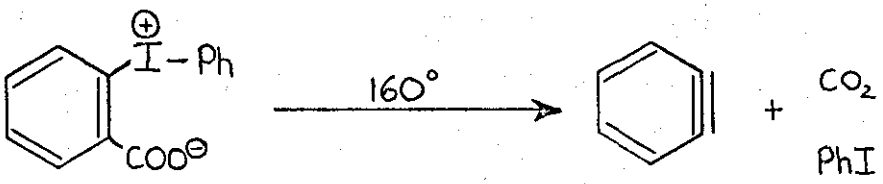
Scheme VII



Scheme VIII



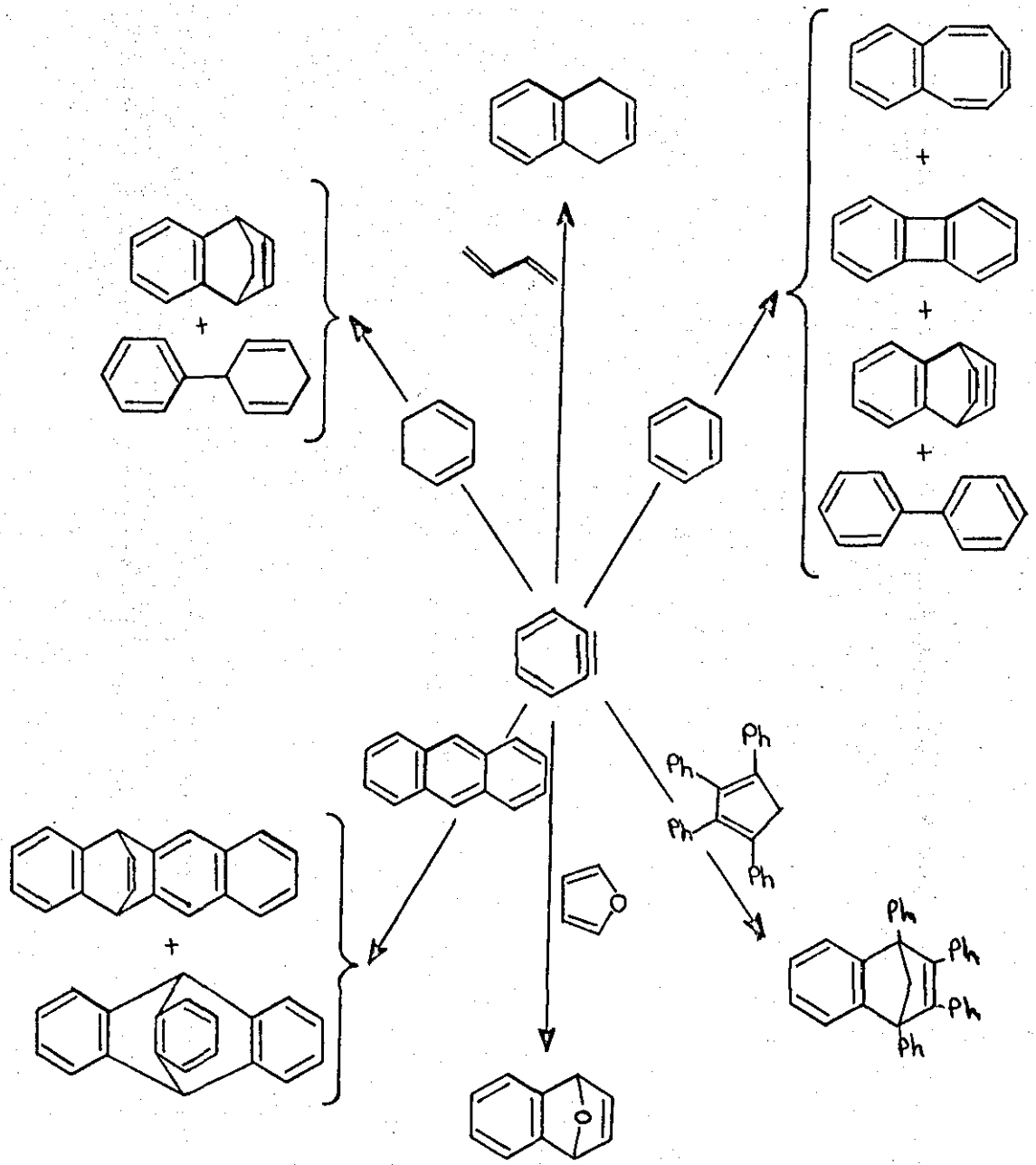
Scheme IX



and by Klanderman[36] that benzyne was the same when produced from a number of different precursors, provided there were no elements (e.g. iodine, silver) present which could modify the mode of reaction of the intermediate by use of their d-orbitals.[37]

The reactions of benzyne and substituted benzynes are well known.[3] It is an extremely electrophilic intermediate and adds by a concerted, one-step process to 1,3-dienes[38] and even to benzenes,[39] naphthalenes,[39] and anthracenes[40] in a Diels-Alder fashion. It will also add 1,2 to olefins but the reaction is not stereospecific and therefore two-step. Calculations suggest that there is no allowed concerted thermal pathway available.[41] It will also undergo insertion or ene reactions with suitable substrates. Some examples of its mode of reaction are shown in Scheme X.

Scheme X



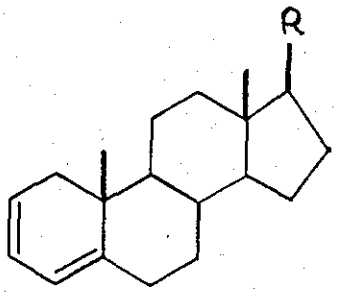
(2) Steroidal Diels-Alder Reactions.

The Diels-Alder reaction[42] has always attracted a considerable amount of attention and the field has been extensively reviewed during the past fifteen years.[43] It was recognised very early that the steric arrangement of substituents in the dienophile and in the diene was preserved in the one-to-one adduct, i.e. the diene addition was always "cis". This was formulated by Alder and Stein[44] as the cis principle. Woodward and Hoffmann have established the theoretical mechanistic principles of the reaction[45] in which orbital symmetry controls the stereochemical consequences in an easily discernable manner. Thus the universal cis addition can now be readily explained as a concerted 4+2 cycloaddition reaction between the two components.

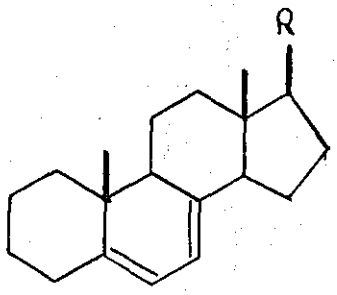
The total number of dienes that have been reacted with dienophiles is countless. The scope of this synthetic reaction is now so wide that this introduction will be limited to a discussion of the Diels-Alder reactions of some steroidal dienes and trienes. It is noteworthy that no reactions of arynes with steroidal dienes had been reported prior to the commencement of the work reported in this thesis.

There are a relatively small number of steroidal dienes which are suitable for a Diels-Alder reaction since there are only a limited number of places in which two double bonds can be put in a cisoid configuration (Scheme XI). Most of these dienes have homoannular double bonds except (XI,5) and (XI,6) which span 3 rings.

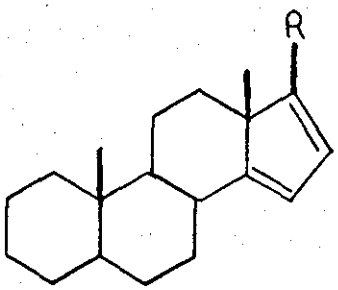
Scheme XI



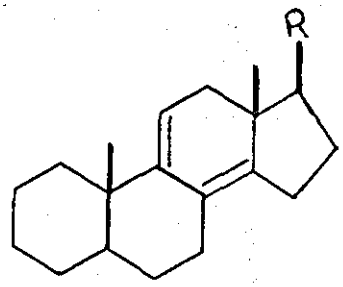
(XI,1)



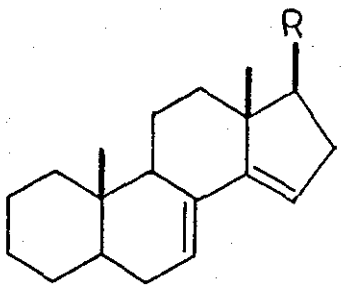
(XI,2)



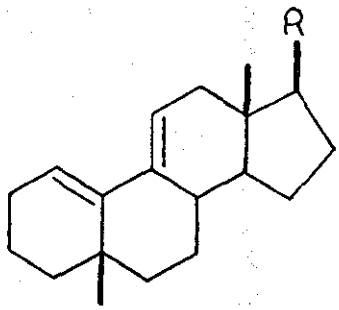
(XI,3)



(XI,4)



(XI,5)



(XI,6)

$R = C_8H_{17}$

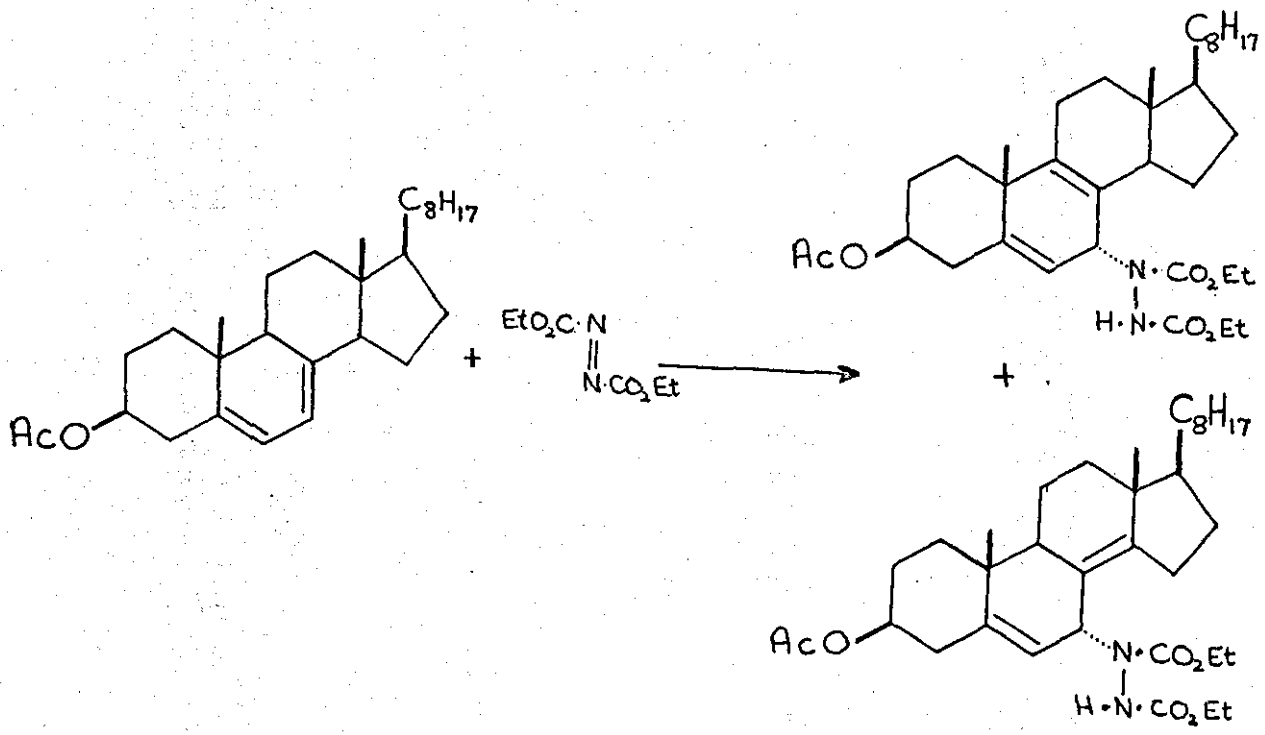
Before 1935, when ultra violet spectrophotometers were few in number, the establishment of the presence of cis-conjugated double bonds in a molecule, was frequently attempted by heating the compound with a dienophile and isolating a one-to-one adduct. Thus in the period of 1930 to 1938, there were several reports of adducts of maleic anhydride and steroidal dienes. These included cholesta-2,4-diene,[46] 7-dehydrocholesteryl acetate,[47] lumisteryl acetate,[48] and ergosterol.[49] The first adduct of this kind was obtained from 9(11)-dehydroergosteryl acetate by Windhaus[50] in 1930. Later reports, first by Windhaus and Luttringhaus[49] and then by Inhoffen[51] and by Hicks, Berg, and Wallis[52] showed that ergosterol itself could be made to react when forcing conditions were used. The reported products, although they were different in all three cases, were important in the determination of the structure of ergosterol.[53] Although no rigorous proof was presented and the structures of the adducts were unknown, it was assumed that they resulted from attack of maleic anhydride on the less hindered, rear face of the steroid to give the 5α, 8α, Δ^{6}-derivative. This was a reasonable assumption since the photooxidation of cholesta-2,4-diene in which oxygen functions as a dienophile and adds 1,4 was shown to give the 2α, 5α-peroxide[54] and only the 5α, 8α-peroxide has been isolated after the reaction of oxygen with ergosterol.[55] Maleic anhydride presumably has even greater steric requirements than oxygen and would

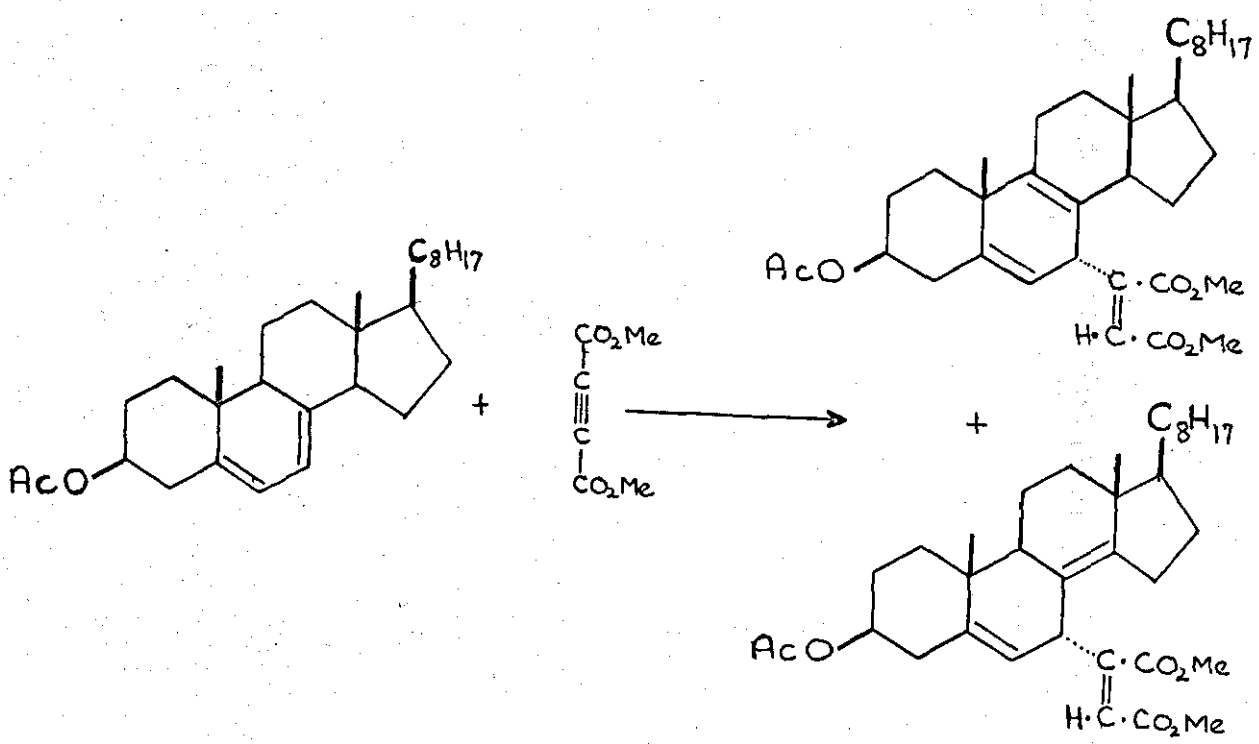
react exclusively with the α-face of the steroid. In many cases, the melting points of the same adducts varied and the yields, if they were reported, were very small. This is not surprising since 1,4-tetrasubstituted dienes are known to possess only a low reactivity towards 1,4-addition of compounds containing an activated double bond.

In 1960, Schubert and Böhme[56] studied the reaction of ergosterylbenzoate with maleic anhydride and obtained five one-to-one adducts, but four years later a reinvestigation by Jones and Thomas,[57] using n.m.r and thin layer chromatographic techniques, presented evidence which indicated that ergosteryl acetate gave four adducts which were the result of α- and β-attack on the steroid faces. This result turned out to be also incorrect and in a later publication[58] they revised their structures, indicating that only one 1,4-adduct was isolated which was a result of α-side attack on the steroid. The other three products were formed by an Alder 'ene' [59] reaction. This was addition at C-7 and abstraction of either the 9α- or the 14α-hydrogen to give 7α-succinic anhydride derivatives of 3β-acetoxyergosta-5,8,22-triene and 3β-acetoxyergosta-5,8(14),22-triene.

This ene-reaction had previously been observed by Huisman and his co-workers while attempting to obtain 1,4-adducts using esters of azodicarboxylic acid,[60,61] and dimethylacetylene dicarboxylate[62,63] with a variety of steroidal-5,7-dienes (Scheme XII). They found that they had only products of ene-reactions involving the 7,8-double bond and the allylic 9α- or 14α-hydrogens.

Scheme XII


C8H17
AcO
EtO2C·N
N·CO2Et
+
C8H17
AcO
N·CO2Et
H·N·CO2Et
+
C8H17
AcO
N·CO2Et
H·N·CO2Et

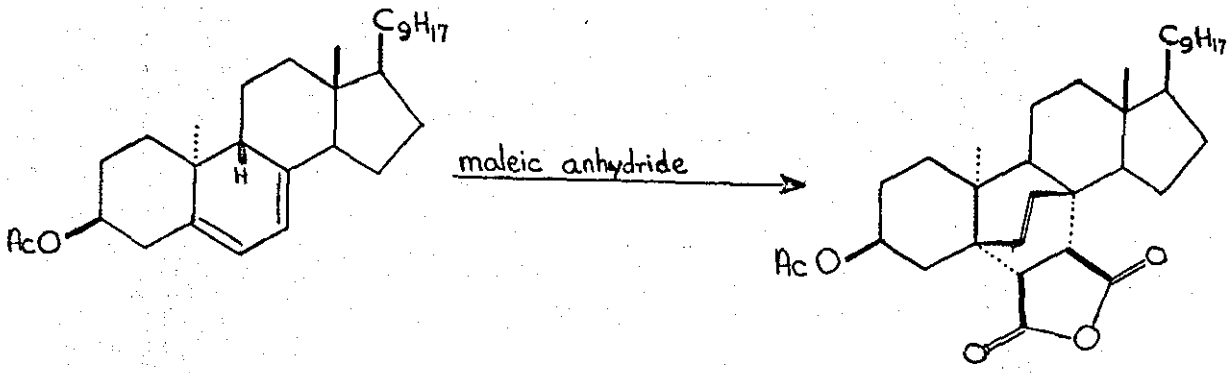

C8H17
AcO
+
CO2Me
C
C
C
CO2Me
C8H17
AcO
C·CO2Me
H·C·CO2Me
+
C8H17
AcO
C·CO2Me
H·C·CO2Me

It had been reported in 1933[64] that the introduction of an additional double bond in the 9,11- position in the ergosterol series, resulted in an increase in reactivity towards addition to the 5,7-diene system. This was found to be true in the cholesterol series also, when α-1,4-adducts of maleic anhydride, diethyl diazodicarboxylate and dimethyl acetylenedicarboxylate were readily obtained from cholesta-5,7,9(11)-triene.[65]

More recently, in order to determine the steric requirements for 1,4-cycloaddition, the reactions of steroidal 5,7-dienes with a number of dienophiles have been investigated. These include tetracyanoethylene,[66] acrylonitrile,[67] and α-acetoxy acrylonitrile.[67] In all these cases, whether the dienophile was symmetrical or unsymmetrical, the only products isolated were those of an ene-synthesis rather than the Diels-Alder adducts. These results are perhaps to be expected on consideration of the steric factors involved. The β-face of the steroid is almost completely blocked out by the C-18 Me and C-19 Me groups and on the α-face, although considerably less crowded, the α-hydrogens at C-3, C-4 and C-15 will interact with any approaching dienophile making an ene-reaction more likely.

It is of interest to note that maleic anhydride adds to the α-face of lumisteryl acetate to give a 1,4-adduct under forcing conditions[68] but no ene-products (Scheme XIII). The reverse stereochemistry of the C-19Me and C-9 hydrogen does not allow the dienophile to align itself correctly for a

Scheme XIII



concerted ene-reaction involving the double bond at C-7 and the C-14 α-hydrogen. At the same time the C-18Me does not allow addition at C-7 and the removal of the C-9 β-hydrogen.

The above reasoning does not apply to steroidal-14,16-dienes. These have been extensively studied by Solo and his co-workers.[69-72] The two double bonds in ring D are particularly reactive and readily form 1,4-Diels-Alder adducts with maleic anhydride,[69] acrolein,[69] methyl acrylate,[69] 4-phenyl-1,2,4-triazoline-3,5-dione,[69] ethylene,[70] and hexafluoro-2-butyne.[71] Irrespective of the dienophile used, only one addition product was isolated to which the 14β,17β-stereochemistry was assigned. In one case this was confirmed by X-ray analysis.[72] However in a recent reinvestigation by Popper and his co-workers,[73] both α- and β-adducts have been isolated although the former was present in very small quantities. Observations of models of this diene system make it clear that there is little steric interaction to an approaching dienophile on the β-face as compared to the α-face, in spite of the proximity of the C-18Me group.

Little work has been done on the preparation of adducts from the heteroannular diene systems (SchemeXI, 5 and 6), although a maleic anhydride adduct of 3β,6β-acetoxy-5β-methyl-19-norcholesta-1(10), 9(11) diene has been reported.[74]

SECTION 1

Reactions of Arynes with model compounds and with steroidal-5,7-dienes and trienes.

1. (a) Introduction

1. (b) Discussion

1. (c) Experimental

1. (a) Introduction.

The reactions of conjugated steroidal dienes in Diels-Alder and ene-reactions are well known. It has also been shown that carbenes and dihalocarbenes react with steroidal olefins and dienes.[75] For example on heating 3-benzylcholest-7-ene with phenyltrichloromethyl mercury a good yield of the expected α-gemdihalocyclopropyl adduct is obtained.[76] Reactions of this nature have been used to introduce new angular methyl groups into the steroid skeleton.[77] Surprisingly no reactions of arynes with similar systems have been reported, and three factors justified an investigation into this research area. These were:

(1) Only Maleic anhydride has ever been found to form a 5,8-adduct with steroidal-5,7-dienes and even then forcing conditions were used. It was hoped to prepare adducts from arynes using mild conditions.

(2) By varying the size of the aryne, i.e. using benzynes with large groups ortho to the active site, the stereochemical requirements of the 5,7-diene system could be determined. This might provide an answer to the question why do strong dienophiles exclusively form ene-derivatives instead of the expected 5,8-adducts.

(3) The adducts might possess some biological activity.

The arynes to be used in these reactions were benzyne, tetrafluoro- and tetrachloro-benzyne. The halogenoarynes were chosen because it was thought that they would have greater dienophilic properties than benzyne itself, and therefore give higher yields of adducts. Three reasons supported

this hypothesis. Primarily the halogeno-Grignard[78] and -lithium[79] reagents are known to be more stable than ortho-fluorophenyl-Grignard and -lithium reagents,[80] suggesting a higher activation energy for the formation of tetrahalogeno-benzynes. Secondly, it is known that dienes and aromatic hydrocarbons form charge-transfer complexes with fluorinated[81] and chlorinated[82] aromatic compounds. This could result in a high reactivity of halogenated benzynes (particularly towards aromatic compounds). Finally the inductive effects of the halogens would increase the electrophilicity of the aryne and so increase its reactivity. Experiments have now confirmed the higher reactivity of halogenated benzynes,[83,84] compared with benzyne, in reactions with 1,3-dienes and aromatic compounds.

In view of the high cost of steroidal starting materials, models of the appropriate parts of the steroid ring system were first synthesised and reacted with the arynes in order to find out the conditions and general trends of the reaction.

1. (b) Discussion

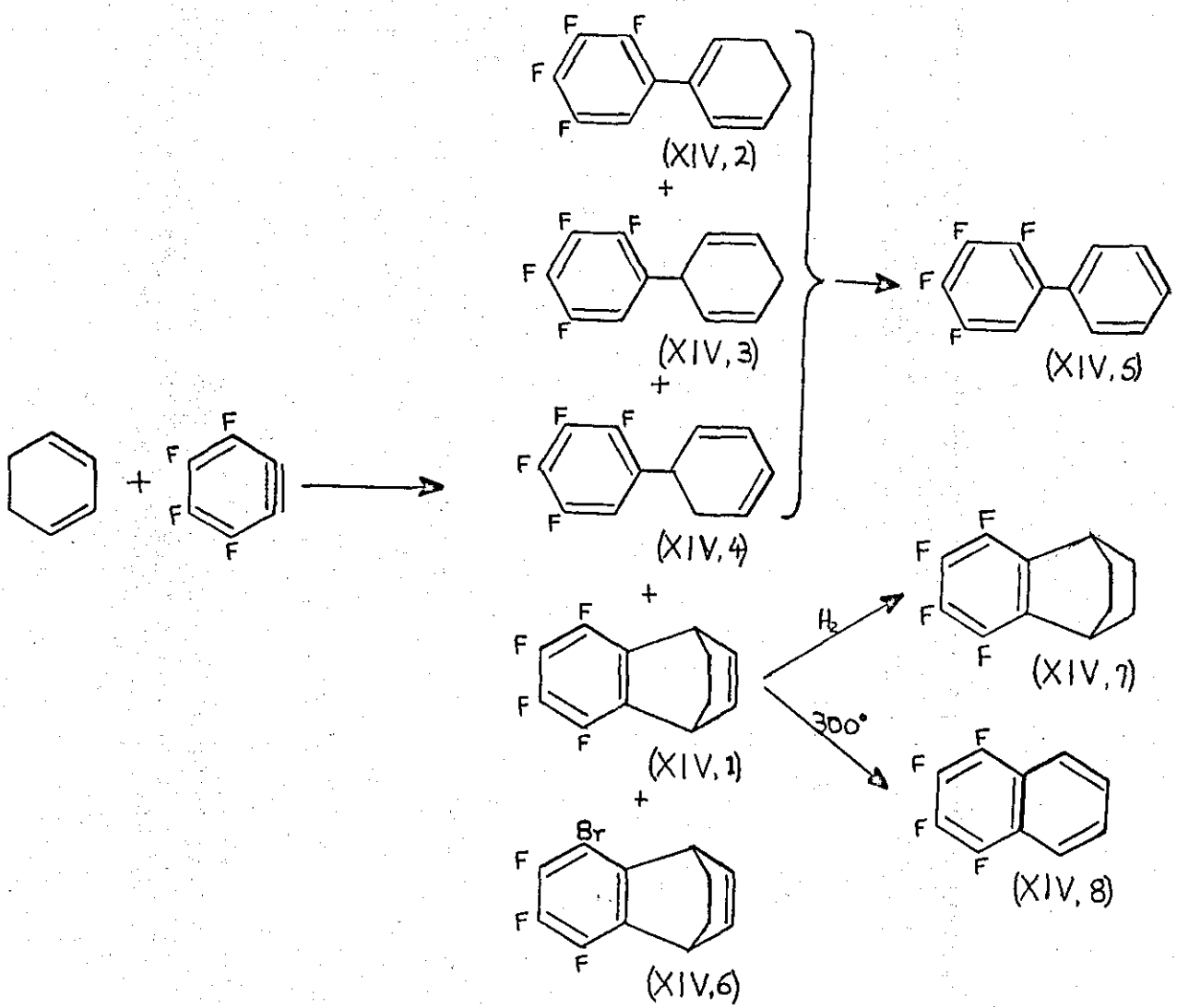
The first model system chosen was cyclohexa-1,3-diene which represents the 'B'-ring of 7-dehydrocholesterol or ergosterol or the 'A'-ring of cholesta-2,4-diene. Several attempts to prepare the model compound were made by dehydrating cyclohexane-1,2-diol using formic and ortho-phosphoric acid but without success. A modification of the known[85] preparation using N-bromosuccinimide and

cyclohexene followed by dehydrobromination was used.

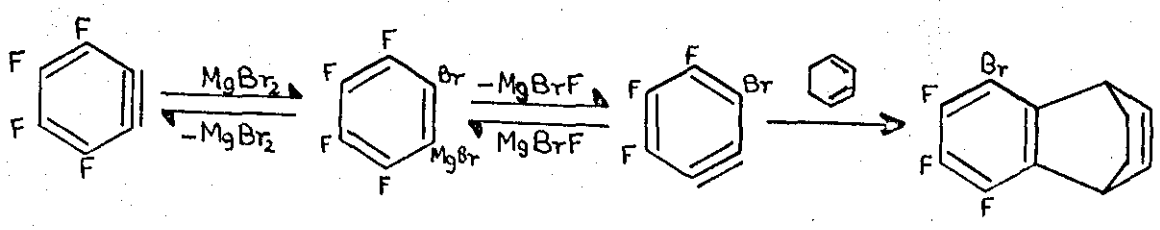
Tetrafluorobenzyne generated from pentafluorophenyl magnesium bromide and from pentafluorophenyl lithium reacted with cyclohexa-1,3-diene (Scheme XIV) to give a mixture (64% and 48% respectively) of three products. The major compound, the adduct (XIV,1)* (77%) was isolated in pure form by preparative gas-liquid chromatography and its structure assigned on the following evidence. Elemental analysis indicated a molecular formula $C_{12}H_8F_4$ and the ^1H n.m.r. spectrum showed absorptions at τ 3.3-3.7 (m, olefinic H), τ 5.4-5.9 (m,2 methine H), and τ 8.1-8.9 (m,4 methylene H). It absorbed one mole of hydrogen to give 5,6,7,8-tetrafluoro-1,4-ethanotetralin (XIV,7) and on pyrolysis at 300°C gave 1,2,3,4-tetrafluoronaphthalene, both compounds being identified by comparison with authentic samples.[83] A small quantity of an isomeric mixture of dihydro-1',2',3',4'-tetrafluorobiphenyls (XIV,2,3 and 4) was also isolated. These latter products, formed by the ene - reaction, partially dehydrogenated during chromatography to 2,3,4,5-tetrafluorobiphenyl (XIV,5), identified by comparison with an authentic sample prepared by an alternative route.[83] The third fraction (12%) which was isolated only from the Grignard method of generation of the aryne was identified as 5-bromo-6,7,8-trifluoro-1,4-ethenotetralin (XIV,6). This is thought to arise by the mechanism outlined in Scheme XV. Similar brominated products have been observed in many of the reactions of tetrafluorobenzyne with aromatic

* The photoisomerisation of this adduct is described in the Appendix.

Scheme XIV



Scheme XV

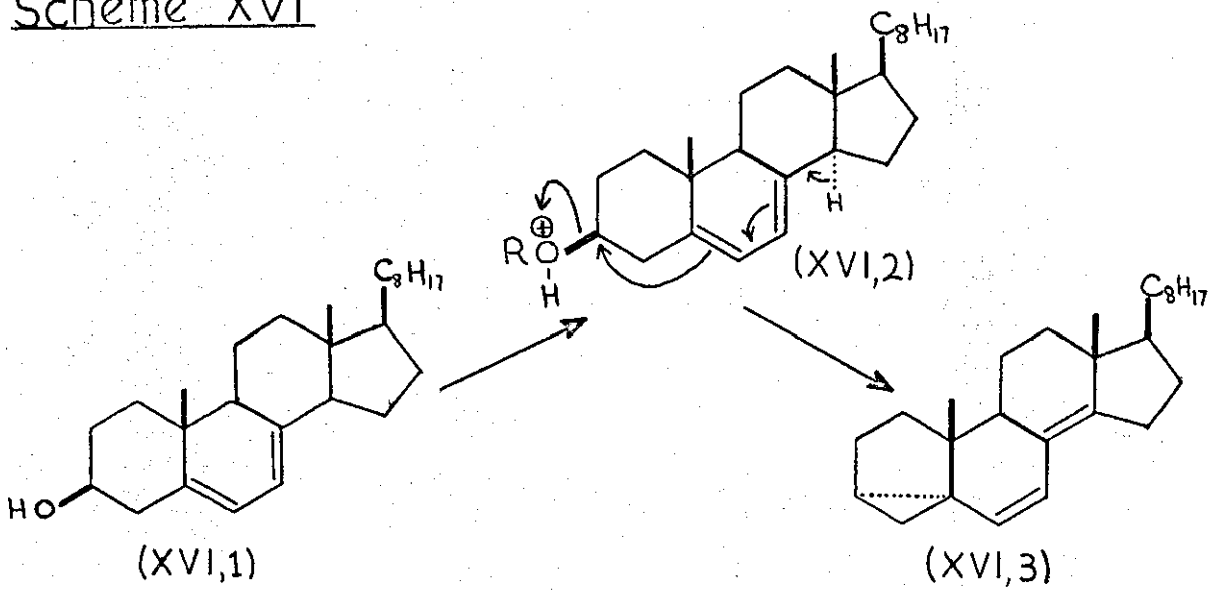


compounds.[83] The expected higher proportion of 1,4-adduct versus ene-product and the higher overall yield compared to the reaction of benzyne with cyclohexa-1,3-diene reported by other workers[86] was thus obtained.

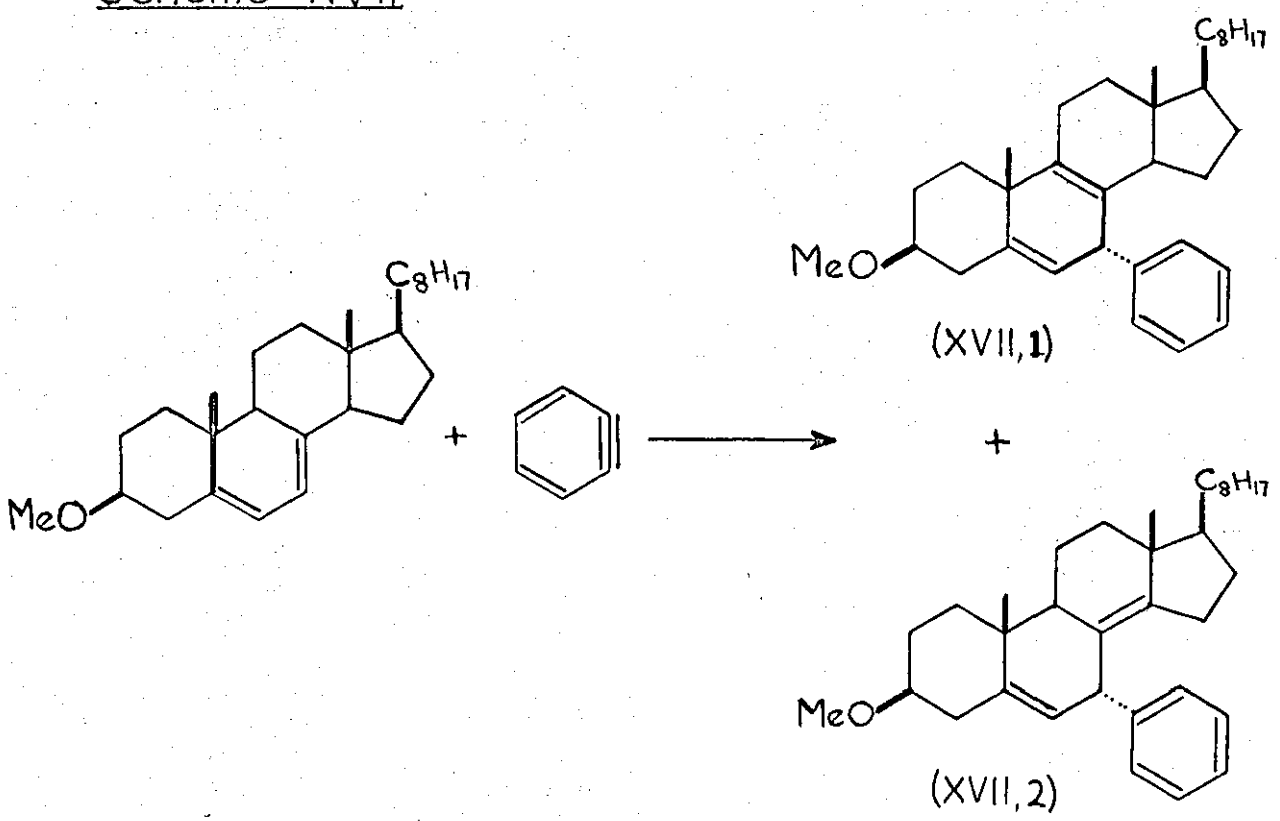
The first steroid chosen for reactions with arynes was 7-dehydrocholesteryl methyl ether. This was prepared in almost quantitative yield from 7-dehydrocholesterol using n-butyl lithium followed by methyl iodide in dimethyl sulphoxide. Attempted methylation with silver (II) oxide and methyl iodide[87] and with diazomethane in the presence or absence of borontrifluoride dietherate or fluoroboric acid[88] gave only poor yields, while the use of trimethylorthoformate and perchloric acid[89] gave largely the 3α,5α-cyclosteroid (XVI,3). This product is analogous to that obtained by solvolysis of ergosteryl tosylate,[90] and is probably formed by way of a mixed orthoester and a 3-homoallylic carbonium ion (Scheme XVI).[89]

Benzyne, generated from ortho-fluorophenylmagnesium bromide in tetrahydrofuran has been shown in these laboratories,[91,92] to react with 7-dehydrocholesteryl methyl ether (Scheme XVII) to give two dienes (XVII,1) (22%) and (XVII,2) (40%), both of which are formed by an 'ene - reaction involving addition at C-7 and abstraction of the allylic C-9 and C-14 α-hydrogens. The positions of the 8,9- and 8,14- double bonds followed from an examination of the ^{1}H n.m.r. spectra. These were analogous to the ene - products reported by other workers.[53,63,66,68] Compound (XVII,1) showed absorptions at

Scheme XVI



Scheme XVII



τ2.8-3.1 (m, 5 aromatic H), τ 4.7-4.9 (m, C-6 olefinic H), τ6.1-6.4 (m, Ph.CH), τ 6.8-7.4 (m, OCH), τ 6.82 (s, OMe) τ8.74 (s,C-19Me), τ 9.0-9.2 (d, side chain methyls), and τ9.30 (s, C-18Me). The 8,9-double bond shields the C-18Me but deshields the C-19Me group. Compound (XVII,2) showed absorptions at τ 2.8-3.0 (m, 5 aromatic H), τ 4.6-4.8 (m,C-6 olefinic H), τ 6.1-6.3 (m, Ph.CH) and τ 6.8-7.4 (m, O.CH). The signals due to the C-18Me, C-19Me, and side chain methyl groups appeared at the same chemical shift τ9.0-9.3. This is because the 8,14-double bond deshields the C-18Me but shields the C-19Me.

No 5,8-adduct was isolated from the reaction, its absence being explained in part by steric crowding in the transition state.

The reaction of tetrafluorobenzyne, generated from pentafluorophenyl lithium in light petroleum, with 7-dehydrocholesteryl methyl ether gave a complicated mixture (80% on steroid) of several products (Scheme XVIII). The Diels-Alder adduct (XVIII,1) (22%) and the ene-product (XVIII,2) (51%) were separated by t.l.c. on silica which had been impregnated with silver nitrate (10%).[93] Several attempts were made to separate a third fraction, containing at least one ene-product (observed by ^{1}H n.m.r. spectroscopy of the mixture) by t.l.c.. A number of different impregnated silica layers and a variety of elution solvents were tried but without success.

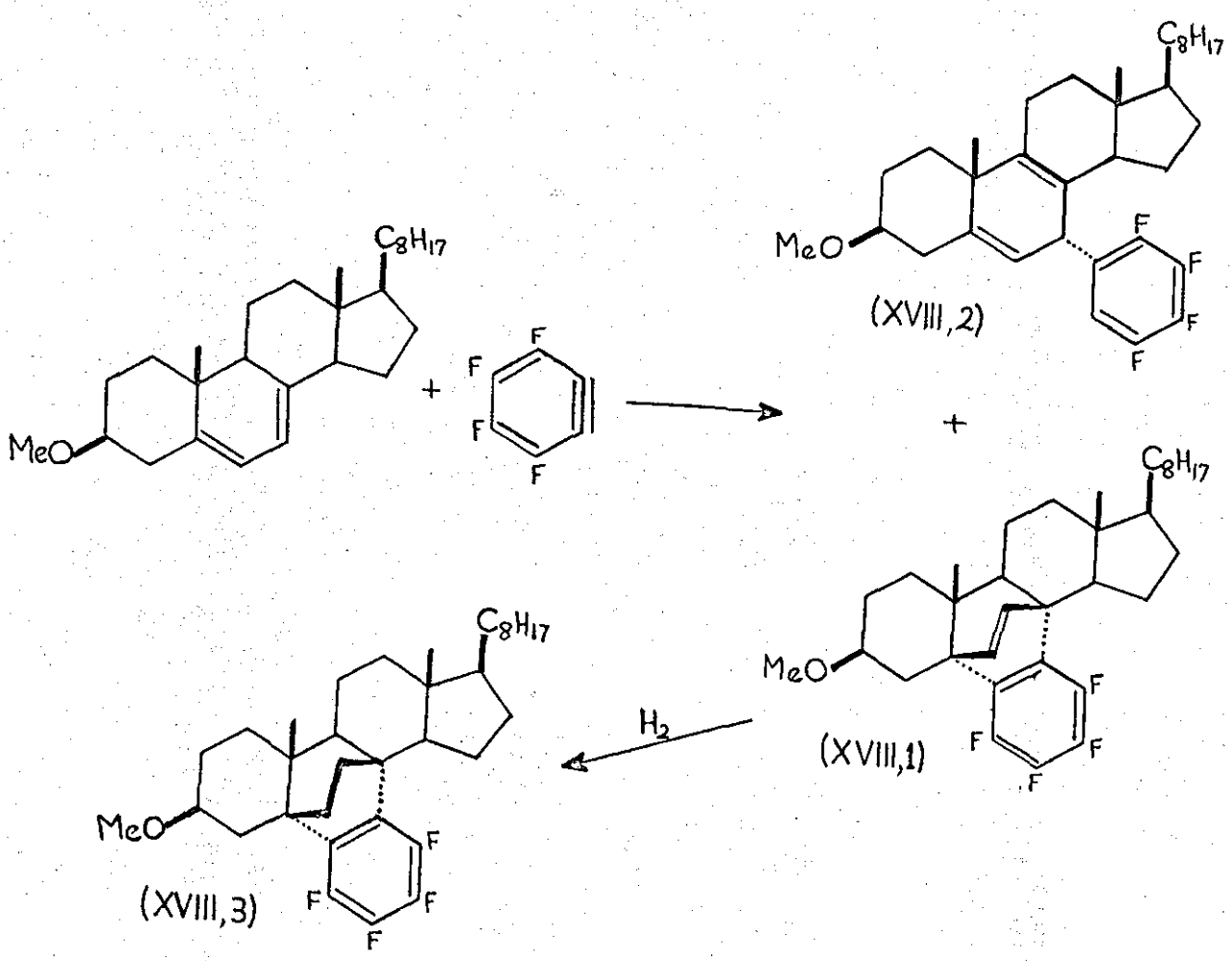
The ^{1}H n.m.r. spectrum of the Diels-Alder adduct (XVIII,1) showed absorptions at τ 3.7-3.9 (m,2 olefinic H),

τ 6.62 (s,OMe), τ 9.01 (s,C-19Me), τ 9.15 (d,side chain Me) and τ 9.16 (s,C-18Me). On hydrogenation of the double bond, the ^{1}H n.m.r. spectrum showed that the signals due to the C-18Me and the C-19Me groups had both moved downfield to τ 8.89 and τ 9.10 respectively. This shift is only compatible with a 5,8β-bridging double bond and hence the tetrafluorobenzyne must have attacked the steroid on its less sterically hindered α-face. Four multiplets were also observed in the ^{19}F n.m.r. spectrum of the adduct.

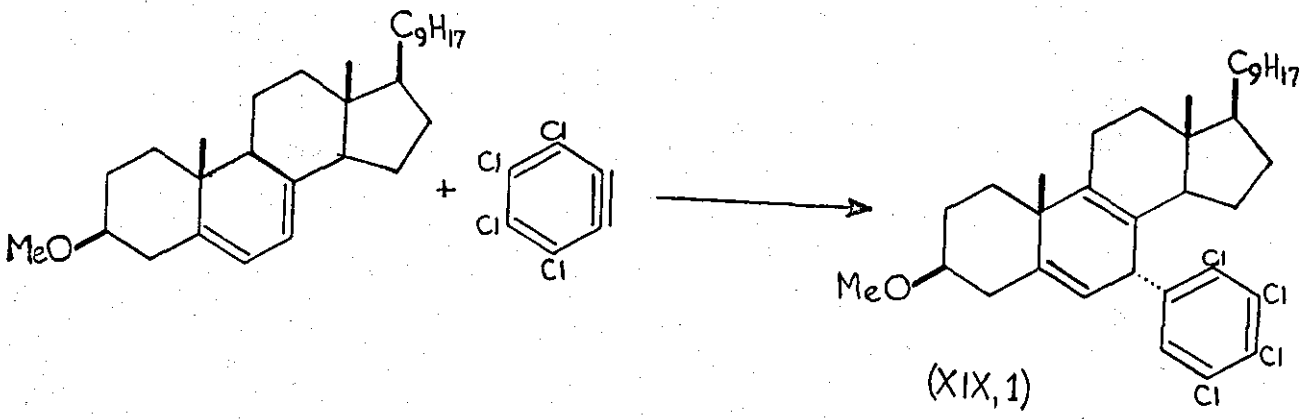
The ^{1}H n.m.r. spectrum of the ene-product (XVIII,2) was identical, except in the aromatic region, with the 5,8(9)-diene product obtained from the reaction of benzyne with the same steroid.[91] The 8,9-double bond again shields the C-18Me but deshields the C-19Me groups with the result that they appear at τ 9.30 (s,C-18Me) and τ 8.74 (C-19Me). Since the product was formed by the symmetry-allowed concerted[59b] addition at C-7 and removal of the 9α-hydrogen, the 7-tetrafluorophenyl group must have the α-configuration. Four multiplets were also observed in the ^{19}F n.m.r. spectrum.

Tetrachlorobenzyne, generated from tetrachloroanthranilic acid by aprotic diazotisation with 3-methylbutyl nitrite in methylene chloride,[82,83] reacted with the 5,7,22-triene ergosteryl acetate, prepared by acetylation of ergosterol, to give only one product (Scheme XIX). The compound (XIX,1) (24%) was isolated from the reaction mixture by t.l.c. Its ^{1}H n.m.r. spectrum showed a singlet at τ 2.92 (C_6Cl_4H) which

Scheme XVIII



Scheme XIX



indicated that it was an ene-product, and the chemical shifts of the C-19Me (τ 8.70) and C-18Me (τ 9.28) groups confirmed the presence of an 8,9 -double bond. Neither the ene - product derived from abstraction of the C-14 hydrogen, nor the Diels-Alder adduct were detected, although the reaction mixture and the de-acetylated reaction mixture were examined by t.l.c. on various impregnated silica layers.

The absence of the 8,14- ene-product is probably due to the interaction between the ortho-chlorine atoms on the tetrachlorobenzyne and the C-4 α-hydrogen. Similarly no Diels-Alder adduct is formed because of a large interaction of the same chlorine atoms with the C-3, C-4 and C-15 α-hydrogens.

In the three cases examined so far a pattern may be observed. Only very reactive arynes with small groups ortho to the active site (e.g. tetrafluorobenzyne) give 5,8α-adducts with a steroidal 5,7-diene. No β-adducts are formed. Thus there are two factors preventing the formation of an adduct; these are the electrophilicity of the aryne and the size (of the aryne).

Furthermore, when an ene-product is formed from a benzyne with large ortho-groups, the C-9 hydrogen is abstracted in preference to the C-14 hydrogen because the aryne cannot align itself for concerted removal of the C-14 hydrogen.

In the hope that more information could be obtained about the nature of these effects, it was decided to react the arynes with a 5,7,9(11)-triene. It had previously been reported that this olefinic system has a greater reactivity

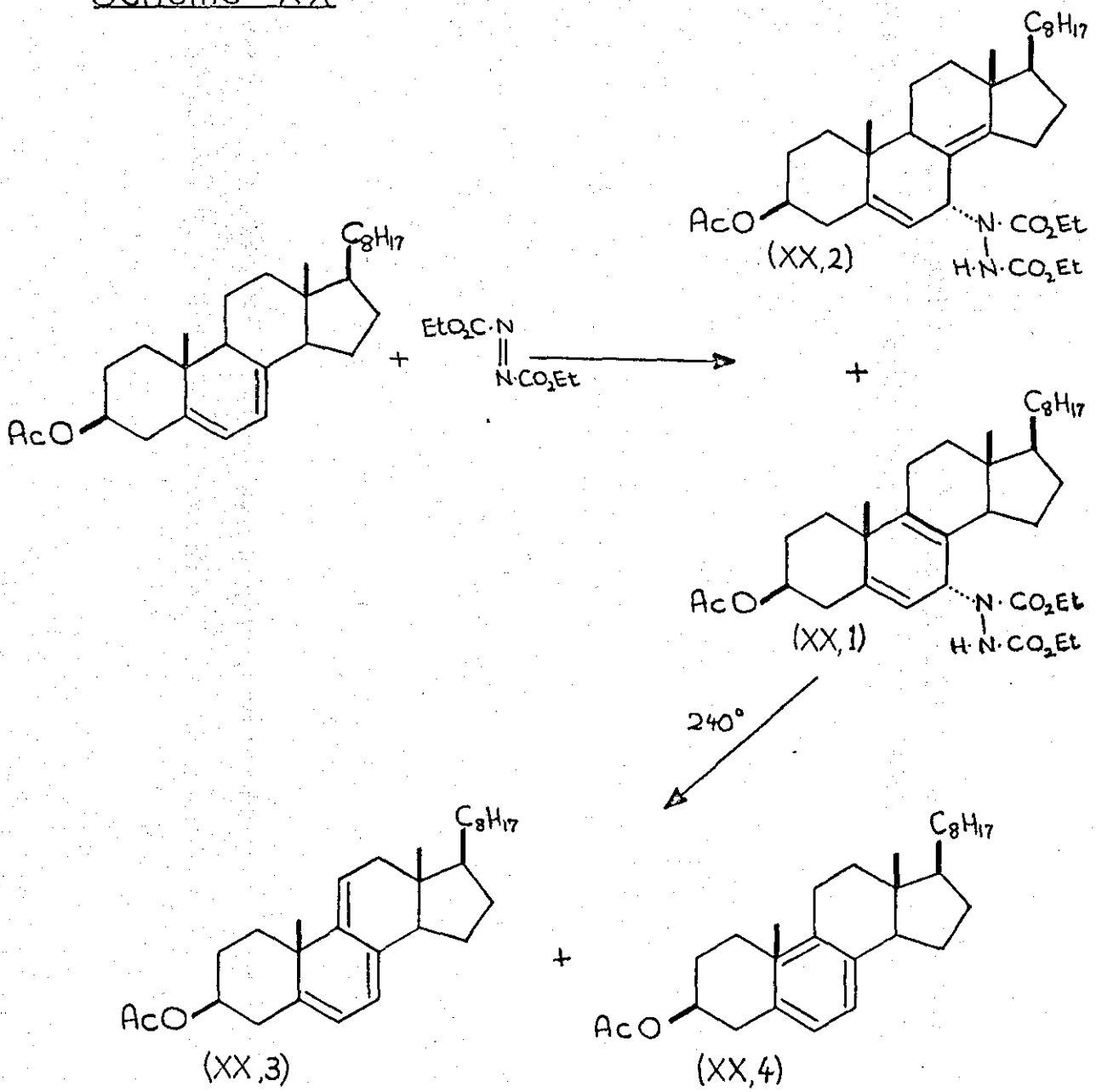
towards dienophiles than the corresponding 5,7-dienes.[64,65] For example 5,8-adducts of cholesta-5,7,9(11)-trienyl acetate with a variety of dienophiles have been reported by Huisman and his co-workers[65] as mentioned in the introduction.

Accordingly cholesta-5,7,9(11)-trienyl acetate (XX,3) was prepared (Scheme XX) in 15% yield overall by reacting 7-dehydrocholesteryl acetate with diethyl diazodicarboxylate and separating the 5,8(9)-diene product (XX,1).[60] Pyrolysis of the latter at 240° gave a mixture of an aromatic B-ring steroid (XX,4) and the required triene which was separated by t.l.c..

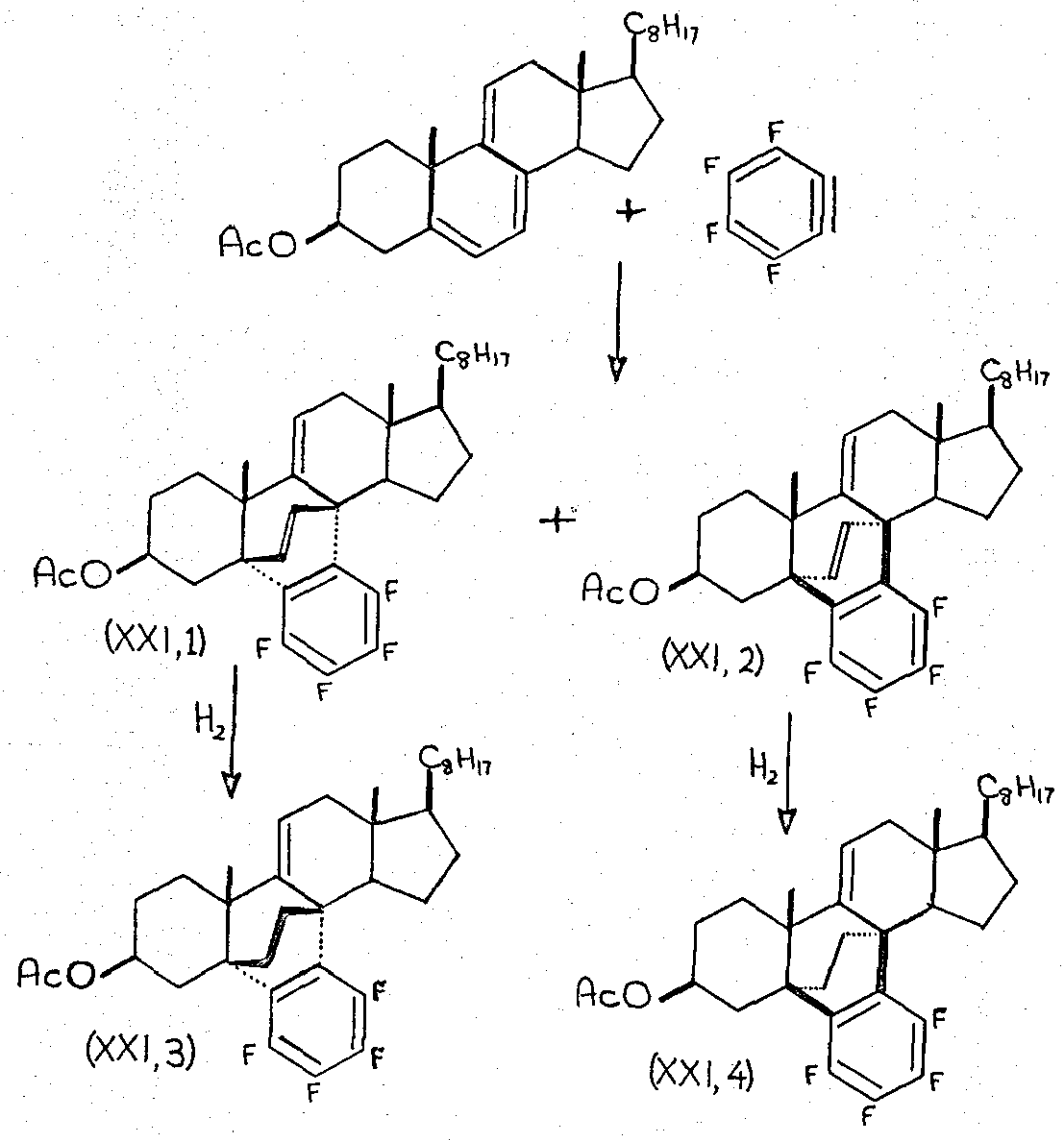
Tetrafluorobenzyne, generated from pentafluorophenyl lithium in light petroleum, reacted with the triene (Scheme XXI) to give, after re-acetylation and separation by t.l.c., two adducts, (XXI,1) (3%) and (XXI,2) (9%). The ^{1}H n.m.r. spectrum of (XXI,1) showed absorptions at τ 3.70 (q,CH=CH), τ 4.5-5.1 (m,=CH and AcO.CH), τ 6.8-7.3 (m, 4αH), τ 8.01 (s, AcO), τ 8.81 (s, C-19Me), τ 9.11 (d, side chain methyls), and τ 9.30 (s,C-18Me). On reduction only one mole of hydrogen was taken up and the ^{1}H n.m.r. of the reduced compound showed that both the C-19Me and C-18Me group signals had moved downfield to τ 8.70 and τ 9.18 respectively and the C-11 olefinic hydrogen remained. These chemical shifts are consistent with a β-bridging double bond indicating (XXI,1) was an α-adduct.

The ^{1}H n.m.r. spectrum of (XXI,2) showed absorptions at τ 3.71 (q, CH=CH), τ 4.5-4.8 (m, =CH and AcOCH),

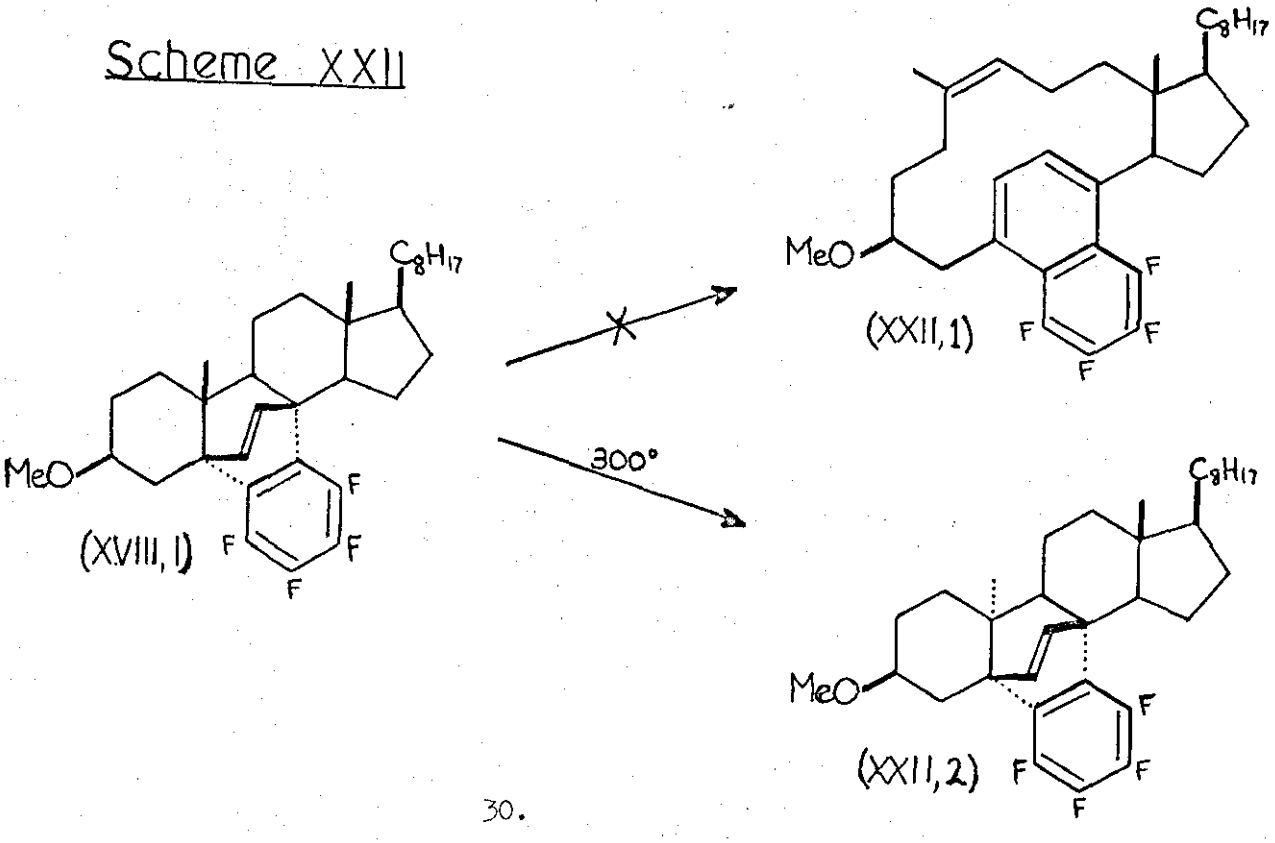
Scheme XX



Scheme XXI



Scheme XXII



τ 4.8-5.4 (m,AcOCH), τ 7.98 (s,AcO), τ 9.08 (s,C-18Me and C-19Me), and τ 9.12 (d, side chain). On reduction the adduct absorbed one mole of hydrogen and the ^{1}H n.m.r. spectrum of the reduced compound this time showed that both the C-19Me and C-18Me groups moved upfield to τ 9.08. This shift is consistent with an α-bridging double bond indicating that the tetrafluorobenzyne had reacted with the β-face of the steroid. The formation of a β-adduct across positions -5 and -8 has not previously been reported. It is apparent from observations of models of the steroid that the 9,11-double bond opens up the β-face of the 5,7-diene and there is much less interaction between the ortho-substituent on the aryne and the C-18Me group.

Attempts were made to reduce the 9,11 -double bond of the α-adduct (XXI,1) in order that its ^{1}H n.m.r. spectrum could be compared with that of the reduced tetrafluorobenzyne-7-dehydrocholesteryl methyl ether adduct (XVIII,3) which should be identical (apart from the acetate group). However the trisubstituted double bond could not be reduced at room temperature with platinum in the presence of either glacial acetic or perchloric acid.

The low yield of the adducts (12%) with the 5,7,9(11)-triene steroid as compared to the 5,7-diene (22%) may be due to a decrease in the reactivity of the triene system which is contrary to expectation. It is more likely to be due to the method of generation of the aryne since pentafluorophenyl lithium would react with the 3-acetate group at a lower

temperature than it would eliminate to form tetrafluorobenzyne. However this method of aryne generation had to be used because of the unavailability of tetrafluoroanthranilic acid, or any other suitable precursor.

When tetrachlorobenzyne was generated in the presence of cholesta-5,7,9(11)trienyl acetate, no 5,8-adduct or ene-product was isolated, in spite of a thorough search of the reaction mixture. The interaction between the C-4α-hydrogen and the ortho-chlorine atoms on the aryne must presumably prevent the formation of a 5,8(14),9(11)-triene product, in a similar fashion to that suggested in the reaction of tetrachlorobenzyne with ergosteryl acetate, and since there is no hydrogen atom at C-9, no ene-products can be formed. The fact that no 5,8-adduct either is formed implies a large interaction of the ortho-chlorine atoms in the adduct transition state although inspection of models suggests that the converse is true. Thus either other factors must be operating, or the steric interactions must be much larger than was originally envisaged.

In view of the fact that on pyrolysis the benzyne-cyclohexa-1,3-diene adduct underwent a retro-Diels-Alder with elimination of ethylene and formation of tetrafluoronaphthalene, it was of interest to examine the pyrolysis of the tetrafluorobenzyne-7-dehydrocholesteryl methyl ether adduct (XVIII,1). It was hoped that this might also undergo a retro-Diels-Alder reaction with expansion of the B-ring (Scheme XXII) to give the large macrocyclic molecule (XXII,1).

However the adduct was virtually unchanged after prolonged pyrolysis in vacuo at 250-300°C. (At higher temperatures the adduct rapidly carbonised). The only pure product isolated is formulated as the isomer (XXII,2) (14%). Its mass spectrum is very similar to that of the adduct (XVIII,1) and shows that they are isomeric (molecular weight 546) and very similar in structure. The ^{1}H n.m.r. spectrum shows an extremely high field C-19Me group at τ 9.56, and indicates that the 3-methine proton is in an equatorial conformation ($W\frac{1}{2}$ 8-9Hz). These data are consistent with a C-19Me group in the 10α-configuration, with the high field position due to the anisotropic shielding by the benzene ring.

The mechanism of the reaction leading to (XXII,2) is unknown but may involve homolysis of and reformation of the 9,10- bond.

1. (c) Experimental.

All reactions with organolithium and Grignard reagents were carried out under dry nitrogen in apparatus dried overnight at 120°. Solvents were redistilled and dried over sodium wire. Tetrahydrofuran was, in addition, freshly distilled from aluminium lithium hydride, and dimethyl sulphoxide was dried by stirring for 24 hours with calcium hydride and distilling onto activated molecular sieve (type 4A). Hydrolyses were effected with aqueous hydrochloric acid (4M) unless otherwise specified. Solutions of products were dried with anhydrous sodium sulphate and the solvents were removed in vacuo using a rotary evaporator. Light petroleum refers to that fraction having a boiling range of 60-80°. Column chromatography was carried out with deactivated (grade III) Camag or Woelm neutral alumina. Merck Kieselgel GF_{254} silica gel was used for analytical t.l.c. (0.25 mm. thickness). Plates were activated by drying for 2 hours at 120° and compounds were detected by spraying with chlorosulphonic acid (5%) in acetic acid followed by heating for 10 minutes at 200°. Compounds on silica impregnated with silver nitrate (10%) were detected by spraying with aqueous ammonium sulphate (20 g. in 100 ml. of water) containing sulphuric acid (4 ml.) followed by heating for 20 minutes at 200°. Preparative t.l.c. was carried out on 1m. plates with Merck Kieselgel PF_{254} (0.5 mm. thickness unless otherwise specified). Compounds were deposited in thin lines on warm plates as ether or chloroform solutions using a modified Desaga streaker.

Analytical gas chromatography was carried out using Pye 104 series gas chromatographs fitted with flame ionisation detectors. Preparative scale gas chromatography was carried out using Wikens Aerograph models 700 and 705 chromatographs, both fitted with flame ionisation detectors.

Infrared spectra were determined as potassium bromide discs for solids, as thin films in the case of liquids and as carbon tetrachloride or chloroform solutions for gums, with Perkin-Elmer 237 and 257 spectrophotometers. Ultraviolet spectra were determined for hexane solutions with a Unicam S.P. 800 spectrophotometer.

^{1}H n.m.r. (60 MHz) and ^{19}F n.m.r. (56.4 MHz) spectra were determined for carbon tetrachloride solutions unless otherwise specified, with a Perkin-Elmer R10 spectrometer.

Mass spectra were determined on A.E.I. M.S.9 and M.S.12 spectrometers.

Cyclohexa-1,3-diene. Cyclohexene (82 g.) and carbon tetrachloride (400 ml.) were warmed to 70° in a flask fitted with an efficient reflux condenser. N-bromosuccinimide (178 g.) was slowly added in small portions and the exothermic reaction controlled using an ice bath. The temperature of the reaction mixture had to be kept near 70° or the reaction stopped. After the addition was completed, the mixture was heated under reflux for 30 minutes, cooled, the succinimide filtered off, and the filtrate distilled through a 2 ft. Widmer column. The brown residue was

distilled at high vacuum, and 3-bromocyclohexene (113 g., (70%), b.p. 50-54° (10 mm)) was collected. Dehydrobromination was achieved by heating 3-bromocyclohexene (113 g.) and quinoline (260 g.) to its boiling point when cyclohexa-1,3-diene slowly distilled from the reaction flask. The crude distillate was washed with hydrochloric acid (2N, 100 ml.), water (100 ml.), dried, and redistilled through a short fractionating column to give cyclohexa-1,3-diene (48 g., b.p. 80-81°). Analysis by g.l.c. (3 ft., tricresyl phosphate (30%) on Chromasorb W at 100°) showed the product was 99% pure, (impurities were cyclohexene and benzene).

Tetrafluorobenzyne and cyclohexa-1,3-diene (Scheme XIV), (A) generated from pentafluorophenylmagnesium chloride. A suspension of magnesium turnings (4.86 g.) in a solution of chloropentafluorobenzene (20.2 g.) in ether (100 ml.) was maintained at 30° under nitrogen by cooling in an ice bath during the slow addition of 1,2-dibromoethane (18.7 g.). A solution of cyclohexa-1,3-diene (50 g.) in cyclohexane (200 ml.) was added and ether was removed from the mixture by distillation until the liquid temperature reached 78°. The mixture was heated under reflux for 6 hours and after cooling was hydrolysed. Extraction with ether gave a crude product which was filtered in light petroleum through a short column of alumina. The resultant pale yellow solid (17 g.) (74%) was shown by g.l.c. (5 ft., S.E.30 (10%) on

firebrick at 120°, programmed to 180° after 35 minutes at a rate of 48°/min.) to consist of the adduct (XIV,1) (77%), mixed dihydro-1',2',3',4'-tetrafluorobiphenyls (XIV,2,3, and 4) (11%) and brominated adduct (XIV,6) (12%). Preparative g.l.c. (5 ft., S.E.30 (30%) on firebrick at 200°) gave the adduct (XIV,1) m.p. 84-85° (from ethanol), $\nu_{max.}$ 720, 1040, 1630, and 3070 cm.$^{-1}$, ^{1}H n.m.r. see discussion, (Found: C, 63.1; H, 3.55; F, 33.5. $C_{12}H_8F_4$ requires C, 63.15; H, 3.55; F, 33.35%), and the mixed dihydro-1',2',3',4'-tetrafluorobiphenyls, a liquid, $\nu_{max.}$ 1040, 1630, and 3030 cm.$^{-1}$, $\lambda_{max.}$ 217 (ϵ 3,060), and 259 (ϵ 390) nm., ^{1}H n.m.r., τ 3.0-3.6 (m, aromatic H), 3.8-4.6 (m, olefinic H's), 5.9-6.2 (m, methine) 7.1-8.5 (m. methylenes). The latter compound dehydrogenated during chromatography to give some 1,2,3,4-tetrafluorobiphenyl m.p. 63-64° (sublimed), $\lambda_{max.}$ 242 (ϵ 14,000) nm., ^{1}H n.m.r. τ 2.62 (s,5H), 2.79-3.25 (m, 1H), identical to an authentic sample.[83]

5-Bromo-6,7,8-trifluoro-1,4-dihydro-1,4-ethanonaphthalene(XIV.6) (12%) pyrolysed in the injection port during chromatography to 1-Bromo-2,3,4-trifluoronaphthalene, m.p. 98-100°, (Found:, C, 45.9; H, 1.60; F, 22.0. $C_{10}H_4BrF_3$ requires C, 46.0; H, 1.55; F, 21.8%), identical to an authentic sample.[83]

(B) generated from pentafluorophenyl lithium. A solution of n-butyl lithium (19.5 ml. of a 2.5 M solution in hexane) was added to a stirred solution of the diene (40 g.) and

bromopentafluorobenzene (12.35 g., 1 equivalent) in light petroleum at -70° under nitrogen. After 2 hours the solution was allowed to slowly warm to room temperature and set aside overnight. The mixture was hydrolysed and extracted with ether. The solution was dried and the ether removed to give a mixture of compounds (11 g.) (48%). These were separated by preparative g.l.c. to give the products described in (A).

7-Dehydrocholesterol methyl ether (A) from silver oxide and methyl iodide. A suspension of freshly prepared dry silver oxide (15.0 g.) (made by mixing a hot solution of silver nitrate (23.8 g.) in water (200 ml.) with a solution of potassium hydroxide (5.6 g.) in water (200 ml.)) in methyl iodide (35 ml.) containing 7-dehydrocholesterol (5.0 g.) was heated under reflux in the dark for 12 hours after which further methyl iodide (10 ml.) and silver oxide (5.0 g.) were added. After a total reflux time of 48 hours, the silver oxide was filtered off and washed thoroughly with ether. Removal of the solvents gave 7-dehydrocholesteryl methyl ether (3.2 g.) m.p. 120-121° (from aqueous acetone) (lit.[95] m.p. 123-125°). The yield tended to vary from 60 to 95% depending on the batch of silver oxide used.

(B) from diazomethane and fluoroboric acid. A solution of diazomethane (15 ml. of 0.3M in methylene chloride) was added to a stirred solution of 7-dehydrocholesterol (0.5 g.) in methylene chloride (15 ml.) containing fluoroboric acid

(2.2 mole %). After 3 hours the mixture was diluted with more methylene chloride (50 ml.), filtered, washed with aqueous sodium bicarbonate solution followed by water, and dried. Removal of the solvent gave a pale yellow solid (0.514 g.) which was chromatographed on Florisil (15 g.). Elution with benzene:light petroleum (1:4) gave 7-dehydrocholesteryl methyl ether (50 mg.) (10%) followed by 7-dehydrocholesterol (100 mg.). The yield of methyl ether was not improved by the use of borontrifluoride diethyletherate instead of fluoroboric acid catalyst.

(C) from trimethylorthoformate and perchloric acid. A suspension of 7-dehydrocholesterol (3.0 g.) in trimethylorthoformate (20 ml.) and perchloric acid (60% aqueous solution, 0.35 ml.) was stirred at room temperature for 20 minutes and poured into cold saturated sodium bicarbonate solution. The mixture was extracted with ether and the product was chromatographed on alumina. Elution with benzene:light petroleum (1:9) gave 3α,5α-cyclocholesta--6,8(14)-diene (XVI,3) (1.85 g.) (60%) m.p. 48-49° (from ethanol), ^{1}H n.m.r. τ 4.43 (q. CH=CH, J_{AB} 9.7 Hz), 9.14 (d, side chain), 9.11 (s, C-19Me); 9.24 (s, C-18Me), and 9.4-9.7 (m, cyclopropane), $\lambda_{max.}$ 262 nm. (ε 24,400). (Found: C, 88.3 ; H, 11.6 . $C_{27}H_{42}$ requires C , 88.45; H, 11.55%). Elution with benzene:light petroleum (1:1) gave 7-dehydrocholesteryl methyl ether (1.2 g.).

(D) from n-butyl lithium and methyl iodide. n-Butyl lithium (6 ml. of a 2.5M solution in hexane) was slowly added to a stirred suspension of 7-dehydrocholesterol (5.0 g.) in dry dimethyl sulphoxide (50 ml.) cooled to near its freezing point under nitrogen. After 10 minutes, methyl iodide (5 ml.) was added and the resultant mixture poured into water. The precipitated methyl ether (5.0 g.) was isolated by filtration.

Reaction of benzyne with 7-dehydrocholesteryl methyl ether. A suspension of magnesium (0.9 g.) in a solution of 7-dehydrocholesteryl methyl ether (2.6 g.) in tetrahydrofuran (50 ml.) and dibromoethane (2 drops) was gently warmed and stirred. A solution of o-bromofluorobenzene (5.8 g.) in tetrahydrofuran was added dropwise at a sufficient rate to keep the solution boiling under reflux. After the addition was completed, the mixture was heated under reflux for 1 hour, and poured into an ammonium chloride/ice mixture. Extraction with ether gave a crude product which was chromatographed on alumina. Elution with benzene removed aromatic by-products and elution with ether:benzene (1:3) gave a mixture of compounds (1.8 g.). Preparative t.l.c. on silica impregnated with silver nitrate (10%) eluting (x3) with benzene:light petroleum (1:1) gave 3β-methoxy-7α-phenyl-cholesta-5,8(9)-diene (XVII,1) (675 mg.), m.p. 133-134 (from aqueous acetone) $\nu_{max.}$ 665, 702, 760, 1105, and 1602 cm.$^{-1}$, $\lambda_{max.}$ 219 nm., molecular weight (mass spectrum) 474, ^{1}H n.m.r. see discussion,

(Found: C, 85.7; H, 10.85. $C_{34}H_{50}O$ requires C, 86.0; H, 10.6%), and 3β-methoxy-7α-phenyl-cholesta-5,8(14)-diene (XVII,2) (1.1 g.), m.p. 102-104° (from aqueous acetone), $\nu_{max.}$ 667-702, 772, 1102, and 1602 cm.$^{-1}$, $\lambda_{max.}$ 217 nm., molecular weight (mass spectrum) 474, ^{1}H n.m.r. see discussion. (Found: C, 85.85; H, 10.5. $C_{34}H_{50}O$ requires C, 86.0; H, 10.6%).

Reaction of tetrafluorobenzyne with 7-dehydrocholesteryl methyl ether. n-Butyl lithium (5 ml. of a 2.5M solution in hexane) was added to a stirred solution of 7-dehydrocholesteryl methyl ether (2.55 g.) and bromopentafluorobenzene (3.16 g.) in light petroleum (200 ml.) cooled to -30° under nitrogen. After 30 minutes the mixture was allowed to warm to room temperature and was left overnight. Hydrolysis followed by ether extraction gave a crude product (4.7 g.) shown by g.l.c. (5 ft., QF1 (2%) on Chromosorb W at 240°) to be composed of the adduct (XVIII,1) (17%), ene-product (XVIII,2) (43%), an unidentified mixed fraction (19%) and starting material (21%). Preparative t.l.c. on silica impregnated with silver nitrate (10%) or urea (10%) eluting with benzene:light petroleum (3:7), gave 3β-methoxy-7α-2,3,4,5-tetrafluorophenyl-cholesta-5,8(9)-diene (XVIII,2), m.p. 119-120° (from ethanol), $\nu_{max.}$ 700, 1100, 1620, and 3040 cm.$^{-1}$, $\lambda_{max.}$ 217 and 263 (inflexion) nm., ^{1}H n.m.r. τ 3.1-3.7 (m, C_6F_4H), 4.75-4.9 (m,=CH), 5.7-5.9 (m, C_6F_4H.CH), 6.78 (s, OMe), 6.85-7.35 (m, OCH), 8.74 (s, C-19Me), 9.14 (d, side chain), and 9.30 (s, C-18Me), ^{19}F n.m.r. ϕ 139.8 (m, 1F), 157.0 (t, 1F), and 160.3 (m,2F).

(Found: C, 74.55; H, 8.45; F, 14.1. $C_{34}H_{46}F_4O$ requires C, 74.65; H, 8.5; F, 14.2%), and the adduct (XVIII,1) m.p. 172-175° (from ethanol), $\nu_{max.}$ 710, 765, 1095, 1630, and 3060 cm.$^{-1}$, $\lambda_{max.}$ 217 (ϵ 6,800), and 270 (ϵ 550) n.m., ^{1}H n.m.r. τ 3.78 (q, CH=CH, J_{AB}-8.6 Hz), 6.1-6.6 (m, OCH), 6.63(s,OMe), 6.8-7.3 (m, 4αH), 9.01 (s, C-19Me), 9.15 (d, side chain), and 9.16 (s, C-18Me), ^{19}F n.m.r. ϕ 144.4 (m, 1F), 146.6 (m, 1F), 160.1 (m, 1F), and 161.3 (m, 1F). (Found: C, 74.8; H, 8.45; F, 13.9. $C_{34}H_{46}F_4O$ requires C, 74.65; H, 8.5; F, 14.2%). Attempts were made without success to separate the mixture isolated by preparative t.l.c. using silica and alumina impregnated with mercuric chloride or caffeine. Solvents tried included mixtures of pyridine and N,N'-dimethylaniline with light petroleum, chloroform, benzene and diethyl ether.

Ergosteryl acetate. Ergosterol (5.0 g.) was warmed with acetic anhydride (5.0 ml.) in pyridine (50 ml.) then left for 12 hours. The resultant mixture was poured onto ice/water (250 g.), left for 3 hours, then filtered to give ergosteryl acetate (4.6 g., 92%) m.p. 180-181° (from ethanol), (Lit.[53] 181°).

Reaction of tetrachlorobenzyne with ergosteryl acetate. A solution of tetrachloroanthranilic acid (2.8 g.) in acetone (50 ml.) was added over 15 minutes to a stirred solution of ergosteryl acetate (4.4 g.) and 3-methylbutyl nitrite (3 ml.) in methylene chloride (100 ml.) which was heated under reflux.

After one hour octachloroacridone was removed by filtration and the solvent removed from the filtrate to give a pale yellow solid which was chromatographed on alumina. Elution with light petroleum gave a small fraction which was not investigated further, and elution with benzene:light petroleum (1:19) gave a white solid which crystallised from alcohol to give 3β-acetoxy-7α-2,3,4,5-tetrachlorophenyl-cholesta-5,8(9),22-triene(XIX,1)(1.35 g.) m.p. 202-204°, $\nu_{max.}$ 750, 1030, 1240, 1740, and 3050 cm.$^{-1}$, $\lambda_{max.}$ 217 n.m., ^{1}H n.m.r. τ 2.92 (s, C_6Cl_4H), 4.5-5.0 (m, 3=CH), 5.2-5.9 (m, AcOH and C_6Cl_4H.CH), 8.08 (s, OAc) 8.69 (s, C-19Me), and 9.0-9.4 (m, side chain and C-18Me). (Found: C, 66.6; H, 7.10; Cl, 21.8. $C_{35}H_{46}Cl_4O_2$ requires C, 66.3; H, 7.10; Cl, 21.8%). Ergosteryl acetate (1.04 g.) was recovered from the mother liquors.

3β-acetoxy-cholesta-5,7,9(11)-triene. Diethyl azodicarboxylate (4.8 g.) was added to a solution of 7-dehydrocholesteryl acetate (4.8 g.) in light petroleum (25 ml.) and the mixture heated under reflux until all the steroid starting material had reacted (analysed by t.l.c.), (ca. 8 hours). Removal of the solvent gave a yellow gum which was chromatographed on an alumina column. After the initial decomposition of excess diethylazodicarboxylate , elution with benzene:light petroleum (1:19) gave a yellow oil which slowly crystallised from acetone/water to give the ene-product (XX,1), (2.1 g.).

Compound (XX,1) (2.0 g.) was heated for 3 hours at 240° at 0.3 mm. of Hg. During the pyrolysis, 1,2-dicarbethoxyhydrazine condensed on the colder parts of the apparatus. The residual brown oil was chromatographed on an alumina column. Elution with light petroleum gave a yellow oil containing two compounds (XX,3) and (XX,4). Thin layer chromatography (eluting (x2) with benzene:light petroleum (1:1)) gave pure 3β-acetoxy-cholesta-5,7,9(11)-triene (XX,3) (300 mg., 15%), m.p. 97-98° (lit.[60] m.p. 96-98°), $\lambda_{max.}$ 310 (ϵ 10,100), 323 (ϵ 11,500), and 339 (ϵ 7,050) nm.

Reaction of tetrafluorobenzyne with 3β-acetoxy-cholesta-5,7,9(11)triene. n-Butyl lithium (3.9 ml. of 2.5M solution in hexane) was added to a stirred solution of bromopentafluorobenzene (2.47 g.) and 3β-acetoxy-cholesta-5,7,9(11)-triene (1.3 g.) at -60° in light petroleum (100 ml.). The solution was allowed to warm to room temperature and left for 16 hours. After removal of the solvent and acetylation with acetic anhydride in pyridine (1:10), the crude product (2.0 g.) was filtered through alumina in light petroleum. The resultant pale yellow oil (1.1 g.) gave, after preparative t.l.c. on silica impregnated with silver nitrate (10%), eluting (x3) with benzene:light petroleum (1:1), the α-adduct (XX1,1) (50 mg.) (3%), m.p. 109-110° (from ethanol), ^{1}H n.m.r. see discussion, molecular weight (mass spectrum) 572, and the β-adduct (XX1,2) (150 mg.) (9%), m.p. 164-165° (from ethanol) $\nu_{max.}$ 780, 1040, 1640, 1740, and 3060 cm.$^{-1}$, $\lambda_{max.}$ 220

(ϵ 9,500), and 268 (ϵ 500) mm., ^{1}H n.m.r. see discussion, molecular weight (mass spectrum) 572, (Found: C, 73.1; H, 7.65, $C_{35}H_{44}F_4O_2$ requires C, 73.4; H, 7.75%).

Hydrogenation of adducts. A solution of the adduct in ethyl acetate was stirred with 10% palladium on charcoal catalyst in an atmosphere of hydrogen until the gas uptake ceased. The solution was filtered and removal of the solvent gave the dihydro-compound.

Adduct (XIV,1) (100 mg.) gave the dihydrocompound (XIV,7) (100 mg.) m.p. 113-114° (from ethanol), (lit.[83] m.p. 113-115°).

Adduct (XVIII,1) (80 mg.) gave the dihydrocompound (XVIII,3) (80 mg.) m.p. 169-170° (from acetone), $\nu_{max.}$ 880, 1100, 2930 cm.$^{-1}$, ^{1}H n.m.r. τ 6.2-6.6 (m, OCH), 6.68 (s, OMe), 8.89 (s, C-19Me), 9.10 (s, C-18Me), and 9.12 (d, side chain), (Found: C, 74.2; H, 8.65; F, 13.7. $C_{34}H_{48}F_4O$ requires C, 74.4; H, 8.85; F, 13.6%).

Adduct (XXI,1) (10 mg.) gave the dihydro-compound (XXI,3) (10 mg.) a gum, ^{1}H n.m.r. τ 4.4-5.2 (m = CH and AcOCH), 8.02 (s, AcO), 8.70 (s, C-19Me), 9.12 (d, side chain), and 9.18 (s, C-18Me), molecular weight (mass spectrum) 574.

Adduct (XXI,2) (80 mg.) gave the dihydro-compound (XXI,4) (79 mg.) m.p. 162-162.5° (from ethanol) $\nu_{max.}$ 880, 1040, 1630, 1750, 2970 cm.$^{-1}$, ^{1}H n.m.r. τ 4.5-4.75 (m, =CH), 4.75-5.2 (m, AcOCH), 8.02 (s, AcO), 9.14 (s, C-18- and C-19Me), and 9.14 (d, side chain), molecular weight (mass spectrum) 574.

Pyrolysis of adducts. The adduct was heated in a nitrogen purged, evacuated Carius tube (ca. 500 ml. capacity) at the temperature and for the period of time specified.

Adduct (XIV,1) (100 mg.) after 12 hours at 300° gave 1,2,3,4-tetrafluoronaphthalene (88 mg.) m.p. 106-107° (from ethanol) (lit.[83] m.p. 110-111°).

Adduct (XVIII,1) (80 mg.) Gave, after 24 hours at 250°C, and after preparative t.l.c. on silica impregnated with silver nitrate (10%) (eluting (x2) with benzene:light petroleum (3:7)), the adduct (XXII,2) (8 mg.), a gum, ^{1}H n.m.r. τ3.40 (q, CH=CH, J_{AB}-7.9 Hz), 6.2-6.5 (m, OCH), 6.64 (s, MeO), 9.06 (s, C-18Me), 9.11 (d. side chain), and 9.62 (s, C-19Me), molecular weight (mass spectrum) 546, and starting material (67 mg.).

Section 2

Reactions of Arynes with model compounds and with the A-ring of various steroids.

2. (a) Introduction

2. (b) Discussion.

2. (c) Experimental.

2. (a) Introduction.

In view of the low yields of 5,8-adducts of arynes with steroidal-5,7-dienes, it was decided to react arynes with steroid systems in which there was less steric crowding. An inspection of models showed that there is considerably less steric interaction to an approaching dienophile in steroidal-2,4- and -1(10),9(11)-dienes, compared with 5,7-dienes, and it was therefore anticipated that arynes should react to give high yields of adducts with these dienes. The Diels-Alder reactions of these systems have been largely ignored in the past. Only maleic anhydride adducts, of unknown stereochemistry, of cholesta-2,4-diene[46] and 3β,6β-acetoxy-5β-methyl-19-norcholesta-1(10),9(11)-diene[74] have been briefly reported as part of the structural proof of the cisoid configuration of the olefins in these compounds.

It has been known for several years that benzyne can add to benzene[39] and its derivatives[3] to give Diels-Alder adducts, and it has been shown in these laboratories during the course of this work that halogenated arynes are better than benzyne itself in these reactions.[83,84] It was therefore decided to react tetrafluorobenzyne with aromatic A-ring steroids to obtain novel adducts with possible interesting physiological activity. In view of the extremely high cost of these steroids it was considered essential to prepare models of the aromatic parts of the ring system to determine the possible products and reaction conditions before carrying

out the reaction on the steroid itself. The models chosen were tetralin (1,2,3,4-tetrahydronaphthalene), 5,8-dimethyltetralin, and 6-methoxytetralin which represent the A and B rings of the oestrogen steroids.

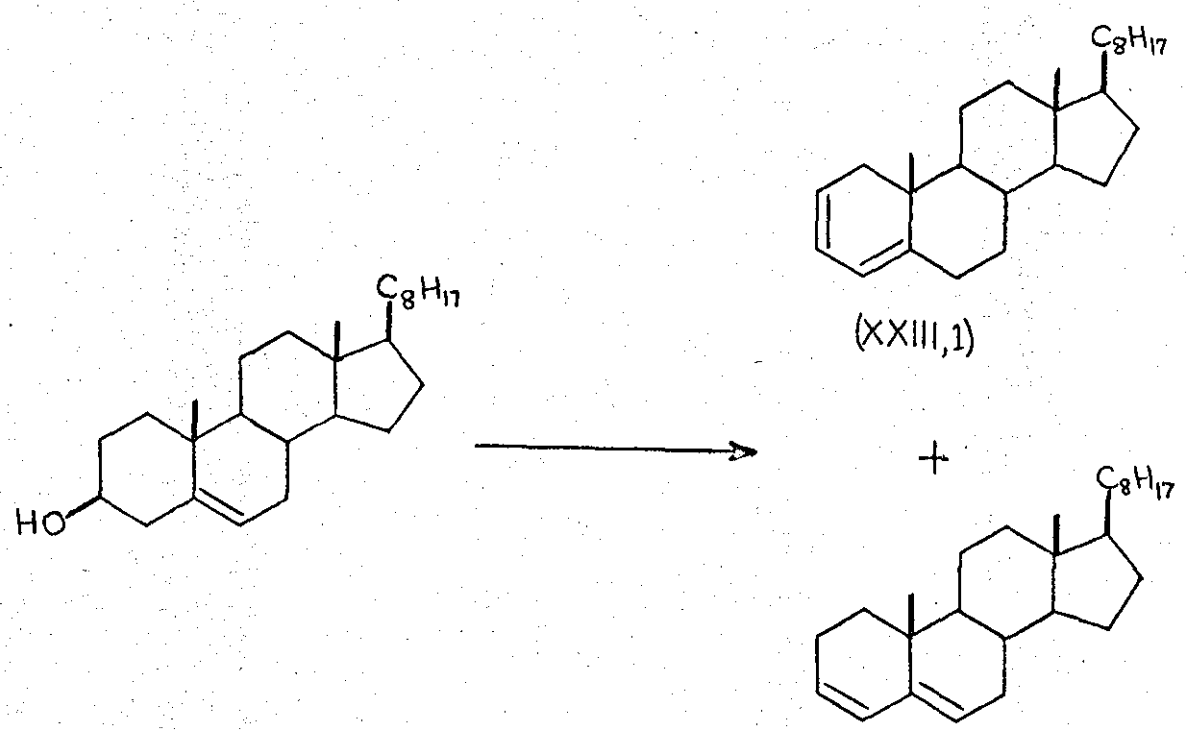
Benzyne[94] and tetrahalogenobenzynes[95] are also known to react readily with styrene, and substituted styrenes to give good yields of phenanthrenes and dihydrophenanthrenes, depending on the reaction conditions. It was decided to react tetrafluorobenzyne with 3,17β-dimethoxyoestra-1,3,5(10),9(11)-tetraene, since the adduct from this steroidal styrene should be similar to the adduct obtained from the 1(10),9(11)-diene system.

2. (b) Discussion.

Cholesta-2,4-diene (XXIII,1) was conveniently prepared in 50% yield by a modification of the method used by Bergman and his co-workers.[46] Cholesterol was dehydrated and isomerised by stirring with alumina in boiling p-cymene (Scheme (XXIII). The co-product, cholesta-3,5-diene (XXIII,2) was removed by preparative t.l.c. using silver nitrate-impregnated silica.

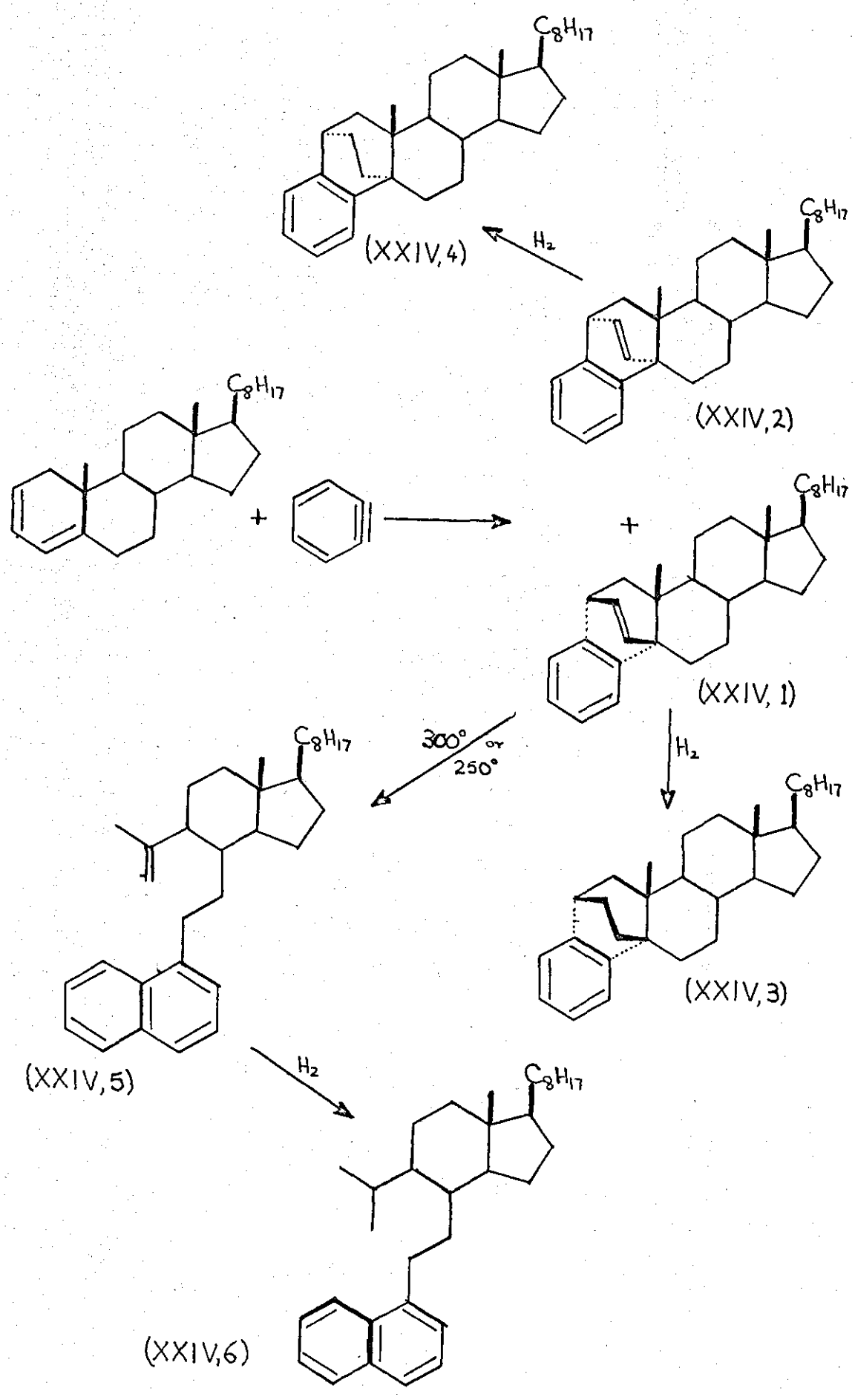
Benzyne, generated from o-fluorobromobenzene and magnesium, and by the aprotic diazotisation of anthranilic acid with 3-methylbutyl nitrite in methylene chloride, gave a mixture of 2,5-adducts in 4% and 8% yield respectively (Scheme XXIV). The lower yield in the case when benzyne was generated by the Grignard-reagent route is attributed to the high temperature (ca. 65°) required for benzyne formation, which probably partly isomerised

Scheme XXIII



(XXIII,1) + (XXIII,2)

Scheme XXIV



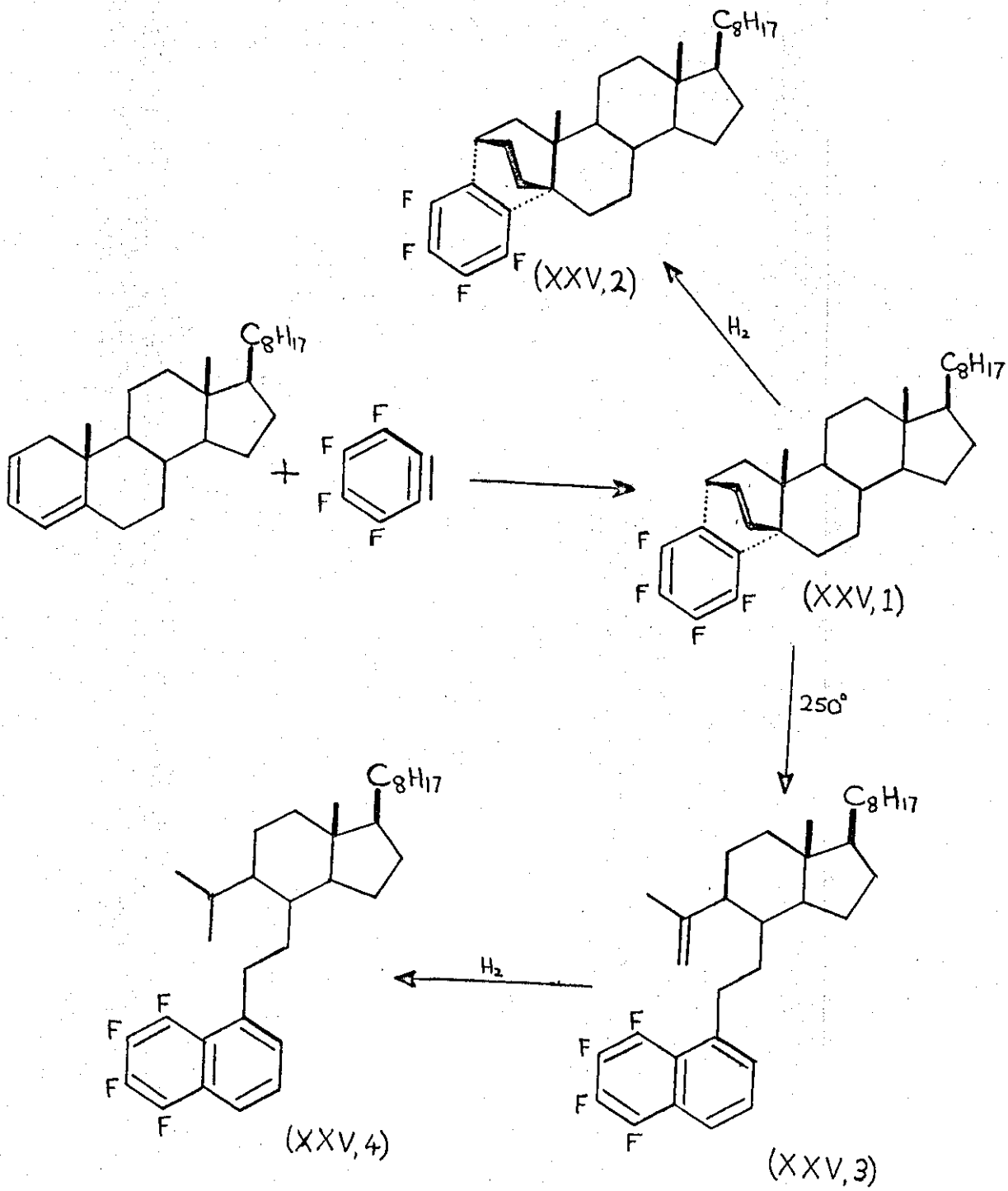
the cis-diene before it reacted with the aryne. After removal of the aromatic by-products from the crude product by steam distillation, and elution from alumina to remove polymeric material, preparative t.l.c. on silica followed by silver nitrate-impregnated silica gave the adducts (XXIV,1) and (XXIV,2) in the ratio 4 to 1. In the ^{1}H n.m.r. spectrum of compound (XXIV,1) the C-19 methyl showed as a singlet at τ 8.99. After reduction to the dihydrocompound (XXIV,3) the signal moved downfield to τ 8.85 due to the removal of the anisotropic shielding by the β-bridging double bond, thus proving that the benzyne had added to the α-face of the steroid. The ^{1}H n.m.r. spectrum of the β-adduct (XXIV,2) showed a singlet C-19 methyl signal at τ 9.62 which moved upfield to τ 9.69 on reduction. This high field position of the C-19 methyl signal in (XXIV,4) is due to the shielding by the benzene ring, an effect which has previously been observed in compound (XXII,2) isolated from the pyrolysis of the tetrafluorobenzyne-7-dehydrocholesteryl methyl ether adduct. An attempt was made to form a π-complex with the aromatic ring of the β-adduct (XXIV,2) with tetranitromethane,[96] thereby modifying its anistropic shielding effect and moving the C-19 methyl back downfield. However no such effects were observed in the ^{1}H n.m.r. spectrum; on addition of the complexing agent the C-19 methyl remained at τ 9.62.

A very small quantity of a third compound was isolated from the crude reaction mixture by preparative t.l.c. The ^{1}H n.m.r. spectrum indicated it was probably an insertion compound, but it decomposed before it could be identified.

Tetrafluorobenzyne, generated from pentafluorophenyl lithium, reacted with cholesta-2,4-diene to give the α-adduct (XXV,1) (15%) which was separated from the reaction mixture by preparative t.l.c. using silver nitrate impregnated silica. Hydrogenation of the adduct (XXV,1) gave the dihydrocompound (XXV,2) and the downfield shift of the C-19 methyl signal in the ^{1}H n.m.r. (τ 9.02 to 8.90) confirmed the α-stereochemistry of the tetrafluorophenyl group. Two unidentified compounds were also isolated from the reaction mixture. Their mass spectra showed they had very high molecular weights which indicated they were adducts in which tetrafluorobenzyne had added more than once to the steroid. No β-adduct was isolated as in the benzyne reaction.

Pyrolysis of the adducts (XXIV,1) and (XXV,1) at 250° gave the naphthalene derivatives (XXIV,5) and (XXV,3). At higher temperatures the retro-Diels-Alder reaction was accompanied by others and several products were detected by t.l.c. These were not investigated further. The ^{1}H n.m.r. spectrum of compound (XXIV,5) showed the presence of 7-aromatic protons (m, τ 1.8-2.8), 2 olefinic protons (broad s, τ 5.13) and a vinyl methyl group (broad s, τ 8.34)

Scheme XXV

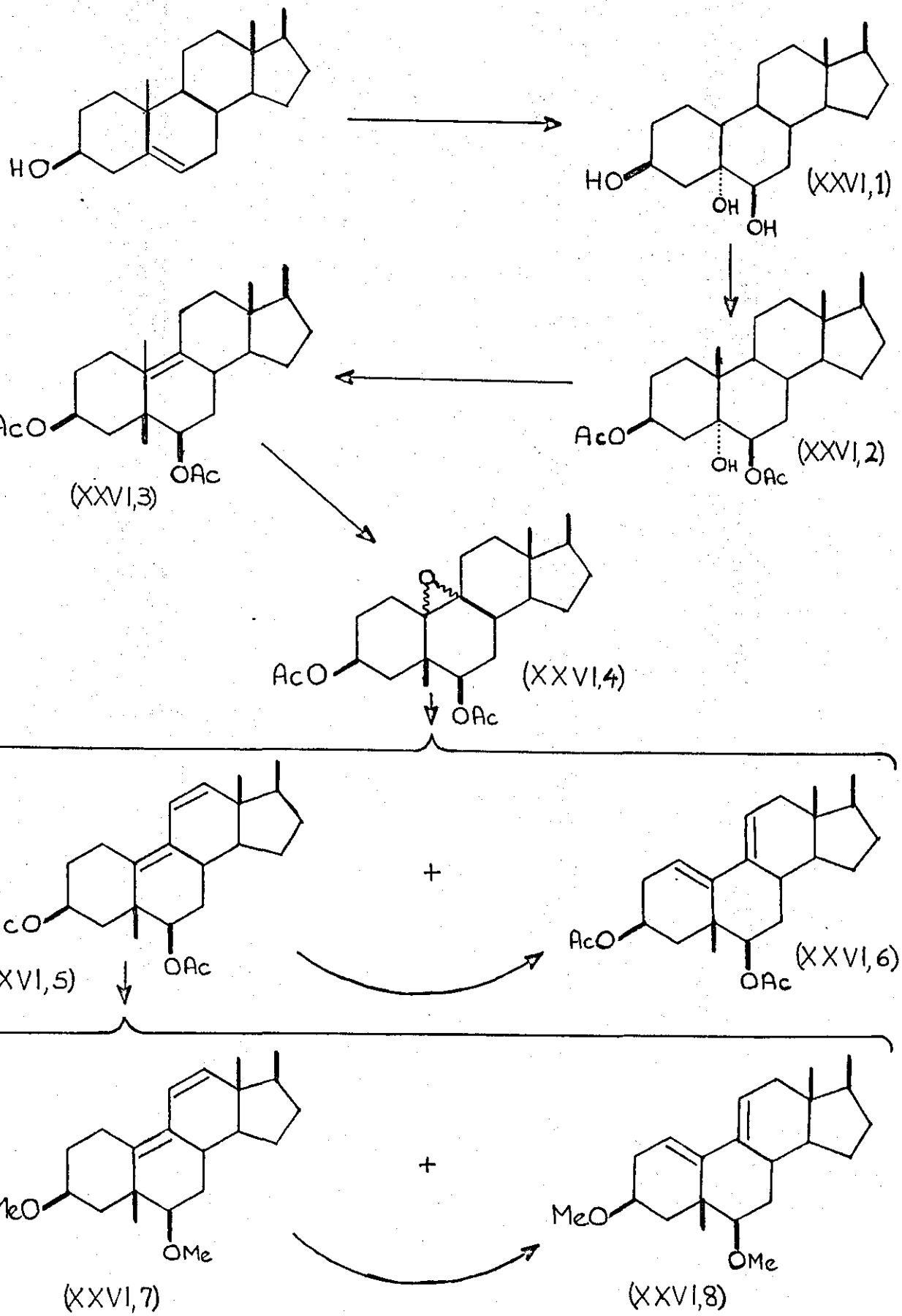

C8H17
F
F
F
F
(XXV,2)
H2
C8H17
F
F
F
+
C8H17
F
F
F
F
(XXV,1)
250°
C8H17
C8H17
H2
F
F
F
F
F
F
(XXV,4)
(XXV,3)

and it had a typical naphthalene u.v. spectrum. The compound (XXIV,5) was easily hydrogenated to the dihydro-compound (XXIV,6).

The ^{1}H n.m.r. spectrum of compound (XXV,3) was very similar to that of compound (XXIV,5) apart from the absorptions in the aromatic region. Irradiation of the vinyl methyl group in a double resonance experiment sharpened the olefinic proton signal ($W\frac{1}{2}$ 7 to 4 Hz.), and similarly irradiation of the latter signal sharpened the vinyl methyl group ($W\frac{1}{2}$ 4.5 to 2 Hz.). The sum of the coupling constants for spin-spin coupling between the olefinic protons and vinyl methyls is thus 2.5 to 3 Hz. The u.v. spectrum of compound (XXV,3) was similar to that of compound (XXIV,5), and on hydrogenation it gave the dihydrocompound (XXV,4).

3β,6β-Diacetoxy-5β-methyl-19-norcholesta-1(10),9(11)--diene (XXVI,6) was prepared in 10% overall yield by the method outlined by Petrow and his co-workers.[74,97] (Scheme XXVI). Cholesterol was epoxidised and the epoxide ring opened <u>in situ</u> to cholestane-3β,5α,6β-triol (XXVI,1). Acetylation gave 3β,6β-diacetoxycholestane-5α-ol(XXVI,2) which underwent the Westphalen rearrangement,[98] on treatment with sulphuric acid in acetic anhydride and acetic acid, to give 3β,6β-diacetoxy-5β-methyl-19-norcholesta-9(10)-ene (XXVI,3). Treatment of the latter compound with monoperphthalic acid gave a mixture of α- and β-epoxides

Scheme XXVI


HO
HO
OH
OH
(XXVI,1)
AcO
OAc
(XXVI,3)
AcO
OH
OAc
(XXVI,2)
AcO
OAc
(XXVI,4)
AcO
OAc
(XXVI,5)
+
AcO
OAc
(XXVI,6)
MeO
OMe
(XXVI,7)
+
MeO
OMe
(XXVI,8)

(XXVI,4), which ring opened and dehydrated in hydrochloric acid/ethanol solution to give a mixture of the required cis-1(10),9(11)-diene (XXVI,6), and the trans-diene; 3β,6β-diacetoxy-5β-methyl-19-norcholesta-9(10),11-diene (XXVI,5). The mixture was separated by preparative t.l.c. on silica impregnated with silver nitrate. Brief treatment (5 minutes) of the trans-diene (XXVI,5) with dry gaseous hydrogen chloride in chloroform at 0° partly isomerised the compound to the cis-1(10),9(11)-diene. By repeated isomerisations followed by separation of the products, a small quantity of pure cis-1(10),9(11)-diene was obtained. Prolonged treatment (20 minutes) of compound (XXVI,5) with gaseous hydrogen chloride in chloroform gave a complex mixture of deacetylated steroids which were not investigated further.

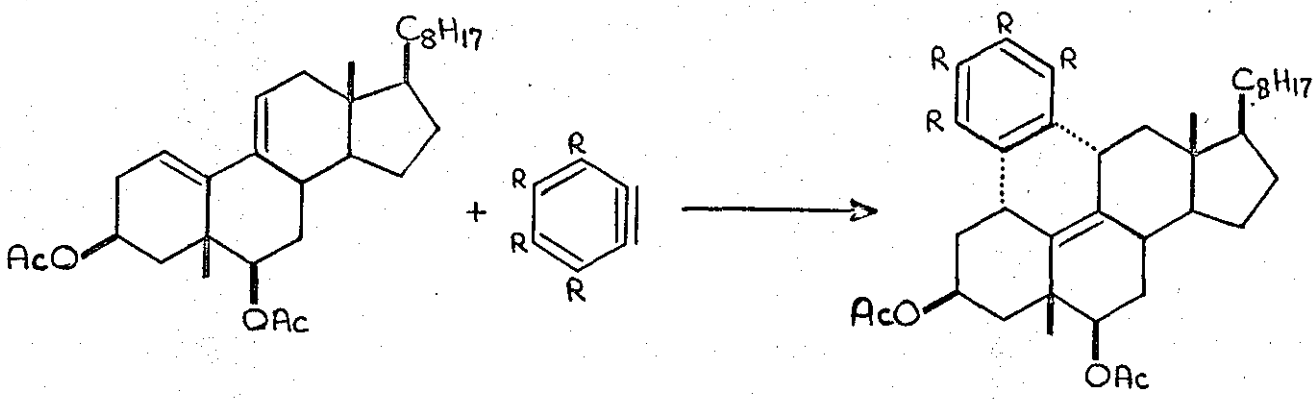
3β,6β-dimethoxy-5β-methyl-19-norcholesta-1(10),9(11)-diene (XXVI,8) was obtained directly from the 3β,6β-diacetate of the trans-9(10),11-diene by reacting it with an excess (5 equivalents) of n-butyl lithium and methyl iodide in dimethyl sulphoxide. It was separated from its co-product 3β,6β-dimethoxy-5β-methyl-19-norcholesta-9(10),11-diene (XXVI,7) by preparative t.l.c. A small quantity of mono-methylated-9(10),11-diene was also isolated which was converted into its dimethyl derivative by retreatment with n-butyl lithium and methyl iodide in dimethyl sulphoxide.

It is of interest to note that the trans-steroidal diene was partly isomerised to the cis-diene under the strongly basic conditions of the methylation procedure, probably involving removal of a proton at C-1.

Brief treatment of the trans-diene (XXVI,7) with dry gaseous hydrogen chloride in chloroform at 0° partially isomerised it to the cis-diene (XXVI,8), while prolonged treatment demethylated the steroid to give a complex mixture of products which were not investigated.

Benzyne, generated from benzenediazonium-2-carboxylate reacted with 3β,6β-diacetoxy-5β-methyl-19-norcholesta-1(10), 9(11)-diene in methylene chloride (Scheme XXVII) to give the adduct (XXVII,1) (20%) which was separated from the reaction mixture by preparative t.l.c.. The ^{1}H n.m.r. spectrum of the adduct showed absorptions at τ 2.98 (s, 4 aromatic H) τ 4.90-5.40 (m, 2AcO.CH), τ 6.10-6.90 (m, 2 C_6H_4CH), τ 7.95 and 8.00 (s, AcO), τ 8.78 (s, C-5Me), τ 9.03 (s, C-18Me) and τ 9.15 (d, side chain methyls). The 9,10-double bond strongly deshields the C-5 and C-18 methyl groups and masks any slight anisotropic effects which might be observed from an α- or β-benzene ring. However, the α-configuration of the benzene ring is deduced from the fact that the C-3α methine is moved slightly downfield from its position in the starting material (from τ 4.9-5.4 to τ 4.8-5.1). Inspection of models shows that this

Scheme XXVII



(XXVII, 1), R=H.

(XXVII,2), R=Cl.

deshielding can only be due to an α-configuration of the benzene ring in the adduct. Tetrachlorobenzyne, generated by the aprotic diazotisation of tetrachloroanthranilic acid, reacted with the steroidal-1(10),9(11)-diene to give the adduct (XXVII,2) (7%). The ^{1}H n.m.r. spectrum showed absorptions at τ 4.85-5.25 (m, 2AcO.CH), τ 5.80-6.50 (m, $2C_6Cl_4CH$), τ 7.97 (s,2AcO), τ 8.78 (s, C-5Me), τ 8.97 (s,C-18Me), and τ 9.14 (d, side chain methyls). The α-configuration of the tetrachlorobenzene ring was assigned to the adduct because of the similarity, apart from the aromatic region, of the ^{1}H n.m.r. spectrum to that of the benzyne adduct (XXVII,1).

In spite of the greater dienophilic properties of tetrachlorobenzyne compared with benzyne, the yield of adduct was smaller with the former aryne than that obtained with benzyne. Inspection of models suggests that this could be due to steric interaction between the o-chlorine atoms on the aryne and the C-2- and C-13-α hydrogen atoms of the steroid. No β-adduct was found in either reaction presumably because of the steric hindrance to an approaching aryne by the C-5 and C-18 methyl groups.

When 3β,6β-dimethoxy-5β-methyl-19-norcholesta-1(10),9(11)-diene was treated with pentafluorophenyl lithium in an attempt to obtain an adduct with tetrafluorobenzyne, a mixture of at least twelve compounds (observed by t.l.c.) was obtained. Attempts to separate the products by preparative t.l.c. failed

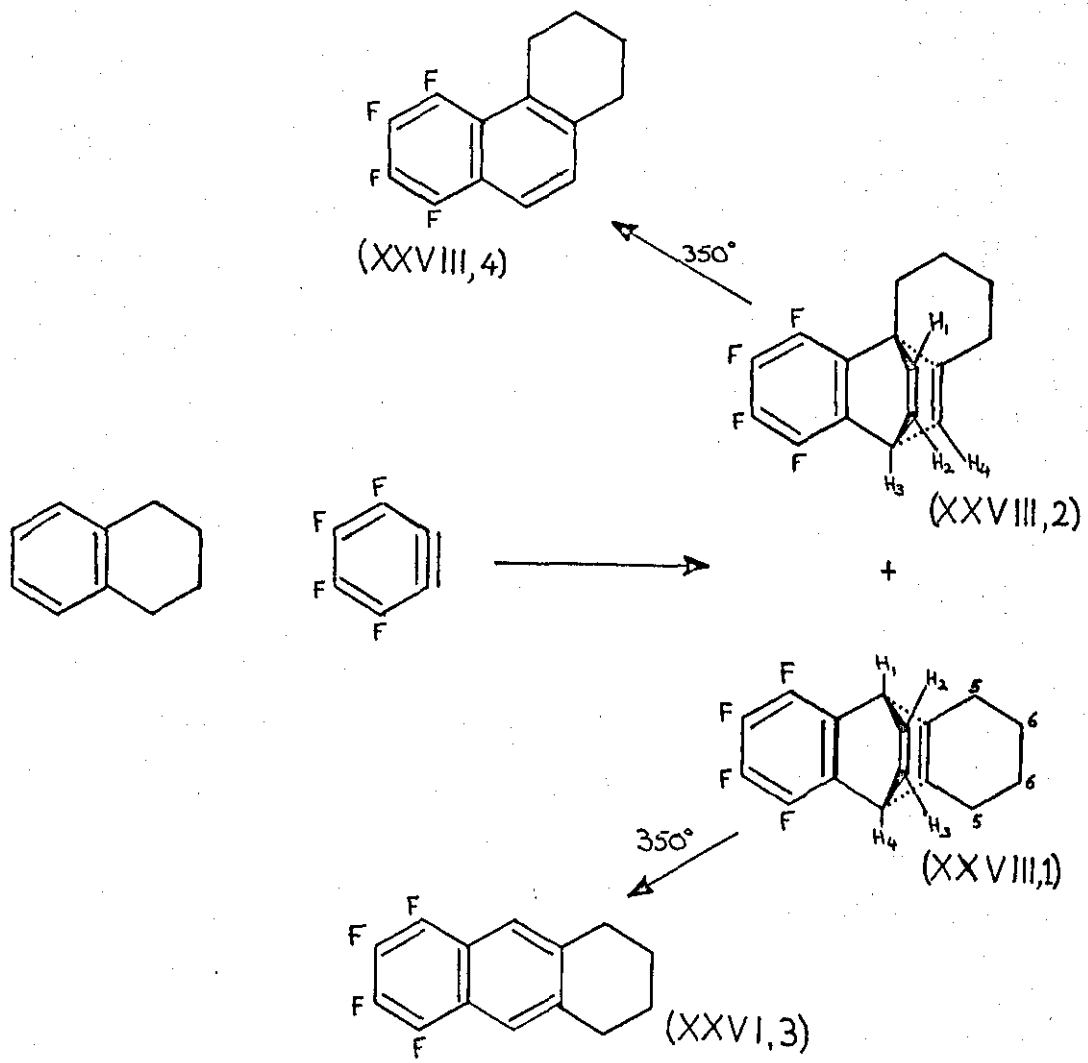
since most of the compounds appeared to be unstable. ^{19}F n.m.r. of mixtures of the products showed that fluorine was present. It is thought that under the strong basic conditions before the tetrafluorobenzyne is formed, the cis-diene is isomerised to the trans-9(10),11-diene (a reaction which has been observed previously with n-butyl lithium). Tetrafluorobenzyne then reacts with the trans-diene to give a number of ene-products whose double bonds might then isomerise into conjugation.

This reaction could not be investigated further since no other method for generating tetrafluorobenzyne is available at present.

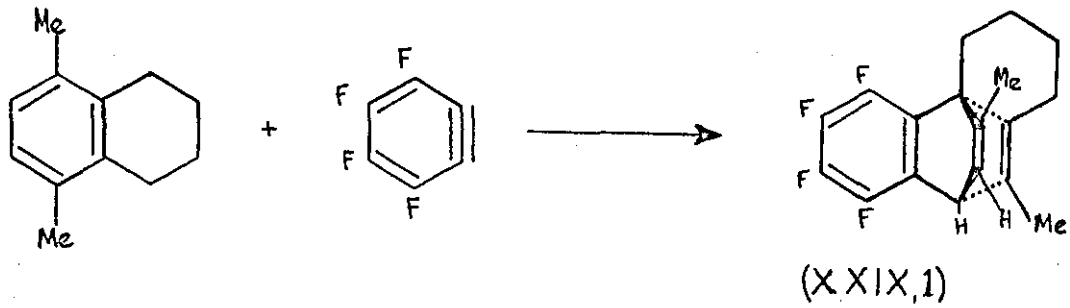
The reactions of tetrafluorobenzyne with tetralin, 5,8-dimethyltetralin, and 6-methoxytetralin were investigated, preparatory to the reactions of aromatic-A-ring-steroids with arynes.

Tetrafluorobenzyne, generated from the pentafluorophenyl-magnesium chloride, reacted with tetralin (Scheme XXVIII) to give the expected two adducts (XXVIII,1) and (XXVIII,2), in the ratio 2.7:1. Compound (XXVIII,1) was separated by preparative g.l.c. but the second component decomposed during chromatography and was therefore isolated by preparative t.l.c. on silica impregnated with silver nitrate. On pyrolysis both adducts readily lost acetylene to give 1,2,3,4-tetrafluoro-5,6,7,8-tetrahydroanthracene (XXVIII,3) and 1,2,3,4-tetrafluoro-5,6,7,8-tetrahydrophenanthrene(XXVIII,4)

Scheme XXVIII



Scheme XXIX



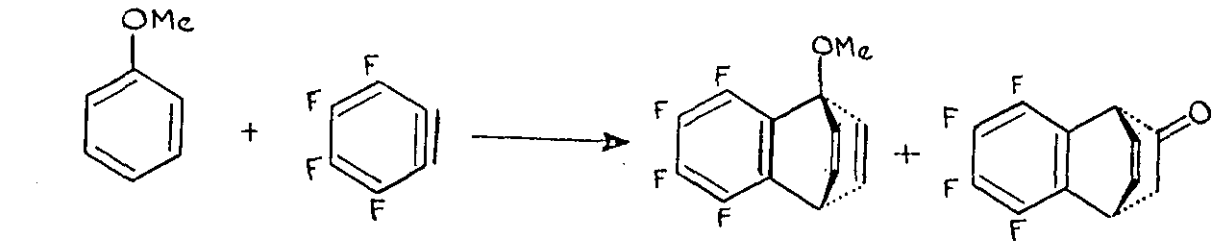
respectively. In addition a small amount of 1,2,3,4-tetrafluoronaphthalene (2%) was obtained, identified by comparison of its retention time by g.l.c. with an authentic sample. This could only have arisen by the loss of cyclohexyne.

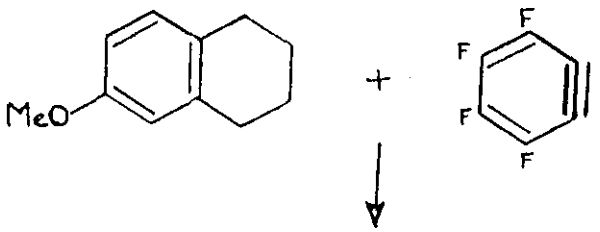
5,8-Dimethyltetralin, prepared from p-xylene and succinic anhydride in four steps,[99] reacted with tetrafluorobenzyne (Scheme XXIX) to give only one adduct (XXIX,1) which was shown to have no methyl group at the bridgehead position. The absence of any other adducts may be due to steric strain in their transition states.

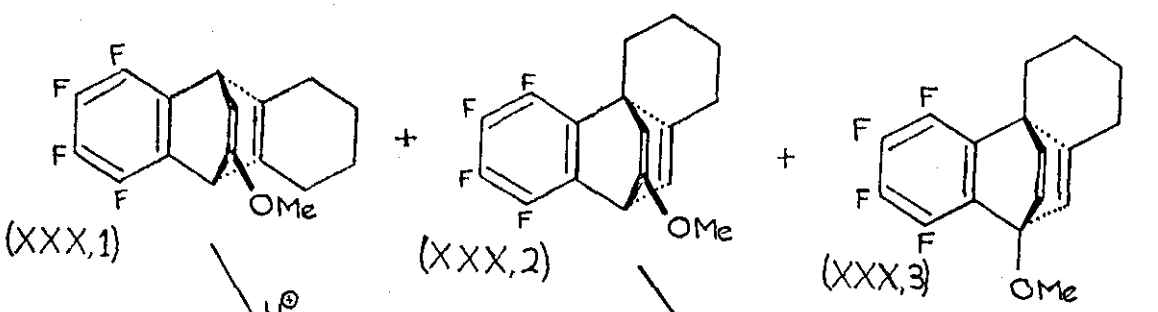
The final model compound chosen was 6-methoxytetralin. Attempts to prepare the latter from β-naphthyl methyl ether by high pressure hydrogenation using Raney nickel catalyst[100] gave inseparable mixtures of 6-methoxy-tetralin and 2-methoxy-1,2,3,4-tetrahydronaphthalene. The model compound was eventually prepared by methylation of 5,6,7,8-tetrahydro-2-naphthol with dimethyl sulphate.

Tetrafluorobenzyne reacted with 6-methoxytetralin to give three products (Scheme XXX). Examination of the infra-red spectrum of the crude product immediately after hydrolysis of the reaction mixture with water showed no carbonyl absorption. However after a few minutes an absorption at 1745 $cm.^{-1}$ started to appear. This was due to the slow decomposition of the enol-ethers (XXX,1 and 2)

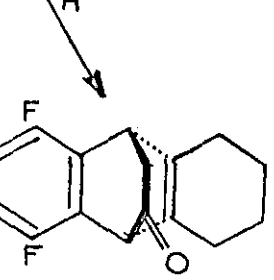
Scheme XXX



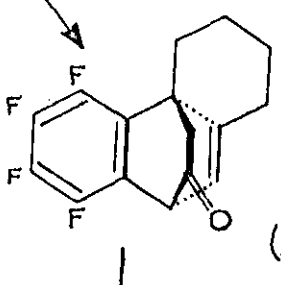




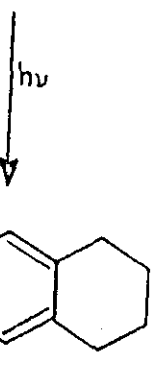
(XXX,1) (XXX,2) (XXX,3)



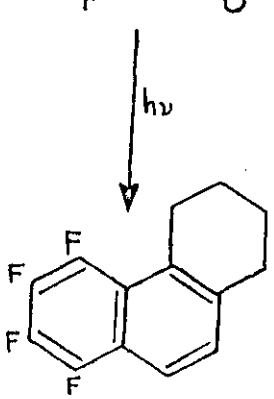
(XXX,4)



(XXX,5)



(XXX,6)



(XXX,7)

into their carbonyl compounds (XXX,4 and 5) respectively. Treatment of the crude mixture with mineral acid converted the enol-ethers into their corresponding ketones. Removal of the excess 6-methoxy tetralin by high vacuum distillation followed by column chromatography gave adduct (XXX,3) and a mixture of adducts (XXX,4 and 5). The two ketones were separated from each other by preparative t.l.c. on silica impregnated with silver nitrate.

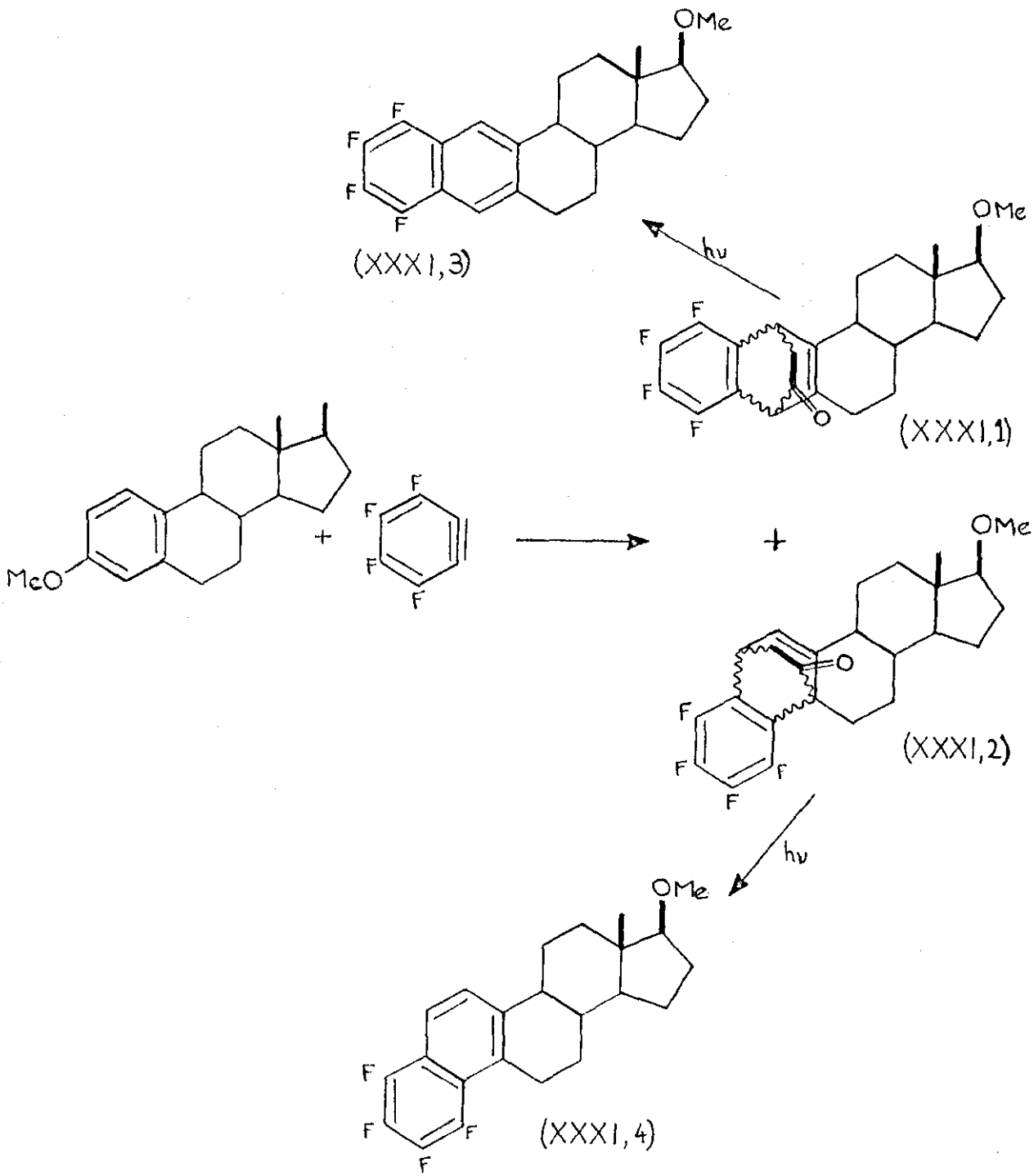
The mass spectra of the ketones (XXX,4) and (XXX,5) showed no molecular ion peaks even a low e.v. The loss of ketene in the mass spectrometer was by electron impact and was not a thermal loss, since on heating the ketones in vacuo for 48 hours at 200° starting material was recovered quantitatively. On pyrolysis of (XXX,4 and 5) at 300° ketene was slowly lost (65% after 24 hours) but on photolysis in ether the conversion of (XXX,4) into (XXX,6) and (XXX,5) into (XXX,7) was greater than 95% after 1 hour. If the reaction was a simple retro-Diels-Alder (a reverse 2 + 4 cycloaddition) then the loss of ketene should be concerted and the reaction should go easily thermally.[45] This is clearly not the case since ketene was readily lost photochemically. Thus in concerted reactions when dealing with cycloadditions which involve carbonyl compounds, it is necessary to include the electrons of the carbonyl group in the electron count in order to be able to predict the course of the reaction.[101]

The first aromatic-A-ring steroid chosen for reaction with tetrafluorobenzyne was oestradiol dimethyl ether. This was best prepared from oestradiol using n-butyl lithium and methyl iodide in dimethyl sulphoxide. Attempts to prepare the dimethyl ether using diazomethane and boron trifluoride diethyletherate[88] succeeded in methylating the phenolic hydroxyl group only, while trimethyl orthoformate and perchloric acid[89] gave a mixture of 17α- and β-methoxy- and 17β-formyl-oestra-1,3,5(10)-triene-3-ol.

The reaction of tetrafluorobenzyne, generated from pentafluorophenyl lithium, with oestradiol dimethyl ether (Scheme XXXI) gave, after acid hydrolysis, two adducts (XXXI,1) and (XXXI,2) in the ratio 6.5:3.5. These were separated with some difficulty by preparative t.l.c., since they readily photolysed in daylight and under the ultra-violet lamp used to detect the compounds on the t.l.c. plate.

The ^{1}H n.m.r. spectrum of adduct (XXXI,1) showed absorptions at τ 5.42 (m,C-1H), τ 5.64(d,C-4H, J_{F-H}= 3.0 Hz.), τ 6.74 (s, OMe), τ 6.60-7.00 (m,MeOCH) and τ 9.33 (s, C-18Me). The tetrafluorophenyl group is too remote to have any significant anisotropic effect on the C-18 methyl group. It is therefore impossible to tell if the adduct has the α or β stereochemistry, or even if it is a mixture of both. The ^{1}H n.m.r. spectrum of the adduct (XXXI,2) showed absorptions at τ 3.85(d,C-1H, J_{1-2}= 6.0 Hz.),

Scheme XXXI


OMe
F
F
F
(XXXI,3)
hν
OMe
F
F
F
O
(XXXI,1)
MeO
+
F
F
F
+
OMe
O
F
F
F
(XXXI,2)
hν
OMe
F
F
F
F
(XXXI,4)

τ5.37 (d of d, C-2H, J_{2-1}= 6.0 Hz., $J_{F-H}\simeq$ 2.0 Hz.), τ6.75 (s, OMe), τ 6.55-7.03 (m, MeOCH) and τ 9.25 (s, C-18Me). It was again impossible to ascertain the stereochemistry of the tetrafluorophenyl group for the reasons outlined above. Both adducts showed no molecular ion in the mass spectrum, losing ketene by electron impact, and they were readily photolysed in ether solution to the naphthalene derivatives (XXXI,3) and (XXXI,4). No adduct with a methoxyl group at the bridgehead position was isolated. This is surprising since tetrafluorobenzyne reacts with anisole (Scheme XXX) to give the adduct with a methoxyl-group at the bridgehead in higher yield than the enol-ether,[83] and an adduct with a bridgehead methoxyl-group was obtained in a reaction of tetrafluorobenzyne with 6-methoxytetralin.

The final steroid selected for reaction with tetrafluorobenzyne was 9(11)-dehydro-oestradiol dimethyl ether (3,17β-dimethoxyoestra-1,3,5(10),9(11)-tetraene). Recent reports[102] indicated that 9(11)-dehydro-oestrone methyl ether was easily prepared from oestrone methyl ether by dehydrogenation at room temperature in dioxan with the high potential quinone, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (referred to as DDQ). Several attempts to prepare 9(11)-dehydro-oestradiol dimethyl ether from oestradiol dimethyl ether under identical reaction conditions gave a large number of products. It was eventually found that the required steroid could be obtained

by treating small quantities of oestradiol dimethyl ether (not more than 100 mg. at a time) with DDQ (2 equivalents) in chloroform. Separation of the steroidal styrene from unreacted starting material was achieved by preparative t.l.c. For some unknown reason, when the reaction was carried out on a larger quantity of the steroid (e.g. 2 g.) or in different solvents (e.g. benzene, ether, D.M.F. etc.) a number of products were detected by t.l.c., and very small yields of the steroidal styrene were obtained.

Tetrafluorobenzyne, generated from pentafluorophenyl lithium, reacted with 9(11)-dehydro-oestradiol dimethyl ether to give a number of products. T.l.c., immediately after hydrolysis with water, showed at least eight compounds and some starting material, to be present. It is thought that the major initial products were the 1,4- and 2,5-adducts. After standing in contact with dilute hydrochloric acid overnight four new products had appeared and four of the product detected immediately after hydrolysis had disappeared; also a carbonyl-group absorption was found in the infra-red spectrum of the mixture. Presumably this was due to the conversion of the enol-ether adducts into their respective ketones. Attempts to separate the latter failed since they readily photolysed in daylight and under the ultra-violet lamp used to detect the compounds. A thorough search of the reaction mixture was made for

phenanthrene and dihydrophenanthrene adducts but none were found. It would be useful to compare the reactions of methoxy-styrenes with those of the 9(11)-dehydro-oestradiol dimethyl ether.

2. (c) Experimental.

All experimental conditions are as in Section 1 (c).

Cholesta-2,4-diene (Scheme (XXIII). A stirred solution of cholesterol (20 g.) in p-cymene (300 ml.), together with freshly activated alumina (40 g., heated for 24 hours at 600°) was heated under reflux using a Dean and Stark apparatus, for 16 hours. The mixture was filtered and the crude product was crystallised from acetone. Preparative t.l.c. on silica impregnated with silver nitrate (10%) (1.0 mm layer, eluting (x2) with benzene:light petroleum (1:9)) gave cholesta-2,4-diene (XXIII,2) (10 g.) m.p. 66-68° (from acetone), $\lambda_{max.}$ 266, 275 (ϵ 6,100) nm. (lit.[103] m.p. 68.5°, $\lambda_{max.}$ 267, 275 (ϵ 6,300) nm.)

Reaction of benzyne with cholesta-2,4-diene (Scheme XXIV). A.- A suspension of magnesium (0.9 g.) in a solution of cholesta-2,4-diene (1.9 g.) in tetrahydrofuran (50 ml.) and dibromoethane (2 drops) was gently warmed and stirred. A solution of o-bromofluorobenzene (5.8 g.) in tetrahydrofuran was added dropwise, and after addition was completed the mixture was heated under reflux for 1 hour. After hydrolysis the crude product was chromatographed on alumina and elution with light petroleum gave a fraction (300 mg.) from which aromatic by-products were removed by steam distillation. The residue (215 mg.), after t.l.c. on silica impregnated with silver nitrate (10%) (eluting (x3) with benzene:light petroleum (1:1), gave the α-adduct (XXXIV,1) (60 mg.),

m.p. 99-100.5° (from acetone-methanol), $\nu_{max.}$ 700, 750, 1620, and 3050 cm.$^{-1}$, $\lambda_{max.}$ 216 (ε 5,000), and 232 (inflexion, ε 1,600) nm., ^{1}H n.m.r. see discussion, (Found: C, 88.9; H, 10.75%, M.Wt. 444 (mass spectrometry). $C_{33}H_{48}$ requires C, 89.1; H, 10.9% M.Wt. 444), and the β-adduct (XXIV,2) (20 mg.), m.p. 125-126° (from acetone, ^{1}H n.m.r. see discussion, M.Wt. 444 (mass spectrometry).

B. A solution of anthranilic acid (5.5 g.) in methylene chloride (200 ml. was added over ½ hour to a stirred solution of cholesta-2,4-diene (3.7 g.) and isoamyl nitrite (14 g.) in methylene chloride (150 ml.), and was heated under reflux. After 4 hours, the solvent was removed and the crude product was extracted repeatedly with light petroleum. The resultant solution was filtered through alumina and gave a pale yellow syrup (1.0 g.). Preparative t.l.c. on silica (eluting with benzene:light petroleum (1:19)) gave a mixture of α-adduct (XXIV,1) and β-adduct (XXIV,2) in the ratio 4:1 (300 mg.), which was separated by preparative t.l.c. on silica impregnated with silver nitrate (10%) as in A.

Reaction of tetrafluorobenzyne with cholesta-2,4-diene (Scheme XXV). n-Butyl lithium (5.8 ml. of a 2.57M solution in hexane) was slowly added to a stirred solution of cholesta-2,4-diene (1.8g.) and bromopentafluorobenzene 4.6g.) in light petroleum (200 ml.) at -30° under nitrogen. The solution was allowed to warm to room temperature and after 4 hours was hydrolysed and extracted with ether to

give a pale yellow syrup (3.5 g.). Preparative t.l.c. on silica impregnated with silver nitrate (10%) (eluting (x2) with benzene:light petroleum (1:19)) gave the α-adduct(XXV,1) (400 mg.) a gum. $\nu_{max.}$ 735, 1070, 1625, 3060 cm.$^{-1}$, $\lambda_{max.}$ 217 (ϵ 6,800), and 265 (inflexion, ϵ 770) nm., ^{1}H n.m.r. see discussion. (Found: C, 76.4; H, 8.55; F, 15.0%, M.Wt. 516 (mass spectrometry). $C_{33}H_{44}F_4$ requires C, 76.7; H, 8.6; F, 14.7%, M.Wt. 516), and two unidentified fractions with molecular weight 660 and 812 (mass spectrometry).

3β,6β-Diacetoxy-5β-methyl-19-norcholesta-1(10),9(11)diene. Scheme (XXVI). A suspension of cholesterol (40 g.) in formic acid (400 ml. 98% solution) containing hydrogen peroxide (30 ml. of 30% solution) was stirred overnight. The resulting thick slurry was poured into water (ca. 1l.) and the precipitated solid was separated and dissolved in methanol (600 ml.). Sodium hydroxide (25% aqueous solution) was added until the solution was alkaline followed by acetic acid in order to precipitate cholestane-3β,5α,6β-triol(XXVI,1) (38 g.), m.p. 222-224° (from aq. acetone) (lit.[104] m.p.224°). Acetylation of the triol (XXVI,1) (38 g.) with acetic anhydride (100 ml.) in pyridine (300 ml.) gave 3β,6β-diacetoxy-cholestane-5α-ol(XXVI,2) (40 g.) m.p. 165-166° (from aq. acetone) (lit.[104] m.p. 166°). Acetic anhydride (120 ml.) containing concentrated sulphuric acid (4.0 ml.) was added to a solution of the diacetate (XXVI,2) (20 g.) in glacial

acetic acid (400 ml.) and acetic anhydride (100 ml.). The mixture was stirred for 10 minutes, keeping the temperature below 40°, then poured into brine (1.1) and extracted twice with ether. Removal of the solvent and fractional crystallisation from acetone gave 3β,6β-diacetoxy-5β-methyl-19-norcholesta-9(10)-ene (XXVI,3) (10 g.) m.p. 125-127° (lit.[105] m.p. 128°). The Westphalen diacetate (XXVI,3) (10 g.) was stirred overnight with monoperphthalic acid (200 ml. of ca. 0.45M solution in ether) and after filtration, the ethereal solution was neutralised with aq. sodium hydrogen carbonate. Removal of the solvent gave a colourless syrup (10 g.) which slowly crystallised. T.l.c. (eluting with benzene:ethyl acetate (4:1)) showed the presence of two compounds which were assumed to be the 9,10-α- and β-epoxides of 3β,6β-diacetoxy-5β-methyl-19-norcholesta-9(10)-ene (XXVI,4).. The mixed epoxides (XXVI,4) (10 g.) were dissolved in hot ethanol (100 ml. at 60°) and hydrochloric acid (5 ml.) was added. The solution was kept near its boiling point for 10 minutes, poured into water (200 ml.), and extracted with ether. After removal of the solvent the product was dissolved in chloroform, the solution cooled to 0°, and dry, hydrogen chloride passed through for 10 minutes. The product was re-acetylated with acetic anhydride in pyridine and preparative t.l.c. on silica impregnated with silver nitrate (10%) gave 3β,6β-diacetoxy-5β-methyl-19-norcholesta-9(10),11-diene (XXVI,5) (3.0 g.) m.p. 127-129° (from aq. methanol) $\lambda_{max.}$ 248 (ε 30,000), (lit.[97b] m.p. 127°, $\lambda_{max.}$ 247

(ε 29,000)), and 3β,6β-diacetoxy-5β-methyl-19-norcholesta-1(10),9(11)-diene (XXVI,6) (1.0 g.) m.p. 163-165° (from aq. methanol), $\lambda_{max.}$ 243 (ε 9,300), lit.[97b] m.p. 168° $\lambda_{max.}$ 242 (ε 9,200). Treatment of the trans-diene (XXVI,5) with dry, hydrogen chloride in chloroform at 0° for 10 minutes, gave the cis-diene (XXVI,6) (20%) which was separated from the starting material as described above. n-Butyl lithium (4.2 ml. of 2.5M solution in hexane) was slowly added to a suspension of 3β,6β-diacetoxy-5β-methyl-19-norcholesta-9(10),11-diene (XXVI,5) (1.0 g.) in dry dimethyl sulphoxide (50 ml.). After 30 minutes methyl iodide (2.0 g.) was added and after 10 minutes the resultant mixture was poured into water and extracted with ether. Preparative t.l.c. (eluting with benzene) gave 3β,6β-dimethoxy-5β-methyl-19-norcholesta-9(10),11-diene (XXVI,7) (0.6 g.) a gum, $\nu_{max.}$ 760, 1100, 1375, 1470, 1620 and 2940 cm.$^{-1}$, $\lambda_{max.}$ 238 (ε 25,000), 251 (ε 30,000), and 260 (ε 20,000) nm., ^{1}H n.m.r. τ 3.70-4.05 (m,2H olefinic), 6.74 (s, OMe), 6.76 (s,OMe), 6.45 (m, 2MeO.CH), 8.80 (s, C-5Me), 9.15 (d, side chain Me), and 9.22 (s, C-18Me), (Found: C, 81.7; H, 11.05. $C_{29}H_{46}O_2$ requires C, 81.6; H, 10.9%), and 3β,6β-dimethoxy-5β-methyl-19-norcholesta-1(10),9(11)-diene (XXVI,8) (0.2 g.) a gum, $\nu_{max.}$ 810, 1100, 1380, 1460, and 2950 cm.$^{-1}$, $\lambda_{max.}$ 245 (ε 9,800)nm., ^{1}H n.m.r. τ 4.20-4.60 (m, 2H olefinic) 6.71 (s, OMe), 6.76 (s,OMe), 6.60-7.10 (m, 2MeO.CH), 8.99 (s, C-5Me), 9.15

(d, side chain Me), and 9.31 (s, C-18Me). (Found: C, 81.6; H, 11.05. $C_{29}H_{46}O_2$ requires C, 81.6; H, 10.85%).

A small quantity of 3β-methoxy-5β-methyl-19- norcholesta-9(10),11-diene-6-ol (200 mg.) a gum, ^{1}H n.m.r. τ 3.63-4.10 (m, 2H olefinic), 6.40-6.90 (m, MeO.CH and HO.CH), 6.75 (s, OMe) 8.73 (s, C-5Me), and 9.08-9.20 (m, C-18Me and side chain Me), was isolated, which was converted to the dimethyl ether (XXVI,7) by re-treatment with n-butyl lithium and methyl iodide in dimethyl sulphoxide.

Reaction of benzyne with 3β,6β-diacetoxy-5β-methyl-19-norcholesta-1(10)9(11)-diene (Scheme XXVII). Benzenediazonium-2-carboxylate (ca. 1.0 g.), prepared in tetrahydrofuran,[106] was added to a warm, stirred solution of the steroid (XXVI,6) (0.8 g.) in methylene chloride (20 ml.). The product was eluted through a short column of alumina with chloroform. Preparative t.l.c. (eluting (x2) with benzene:ethyl acetate (9:1)) gave the α-adduct (XXVII,1)(200 mg., 20%) m.p. 150-151° (from acetone) $\nu_{max.}$ 750, 1030, 1240, 1475, 1740 and 2955 cm.$^{-1}$, ^{1}H n.m.r. see discussion, (Found: C, 79.7; H, 9.25%, M.Wt. 560 (mass spectrometry). $C_{37}H_{50}O_4$ requires C, 79.5; H, 9.02%, M.Wt. 560), and starting material (XXVI,8) (0.4g.).

Reaction of tetrachlorobenzyne with 3β,6β-diacetoxy-5β-methyl-19-norcholesta-1(10),9(11)-diene.(Scheme XXVII).

A solution of tetrachloroanthranilic acid (0.3 g.) in acetone (5 ml.) was added to a stirred solution of the steroid (XXVI,6) (0.3 g.) and 3-methylbutyl nitrite (0.5 ml.)

in methylene chloride (25 ml.) which was heated under reflux. After 30 minutes, octachloroacridone (32 mg.) was removed by filtration and the product (0.6 g.) eluted through a short column of alumina with benzene. Preparative t.l.c. (eluting (x4) with benzene) gave the α-adduct (XXVII,2) (32 mg.) m.p. 223-224° (from acetone), $\nu_{max.}$ 1040, 1240, 1740, and 2960 cm.$^{-1}$, ^{1}H n.m.r. see discussion, (Found: C, 63.6 ; H, 6.8 % M.Wt. 696 (mass spectrometry) $C_{37}H_{46}Cl_4O_4$ requires C, 63.8; H, 6.66% M.Wt. 696).

Reaction of tetrafluorobenzyne with tetralin (Scheme XXVIII). Chloropentafluorobenzene (20.2g.), magnesium (3.65g.), dibromoethane (9.39 g.) and tetralin (100 g.) gave a crude product (15.6 g.). Analytical g.l.c. (5ft., S.E.30 (10%) on firebrick at 200°)showed the presence of two adducts in the ratio 2.7:1. Preparative g.l.c. (5ft., SE30 (30%) on Chromosorb W at 150°) gave 5,6,7,8-tetrafluoro-1,2,3,4,9,10-hexahydro-9,10-etheno-anthracene (XXVIII,1) (40%), m.p. 57-59° (from ethanol), $\nu_{max.}$ 762, 1380, 1490, 1630, and 2930 cm.$^{-1}$, ^{1}H n.m.r. τ 3.20 (t, H_2 and H_3 olefinic, J_{2-1}= 5.9 Hz., J_{2-3}= 7.2 Hz.), 5.0-5.3 (m, H_1 and H_4, J_{1-3}= 1.5 Hz.), 7.6-8.0 (m, $4H_5$ methylenes), and 8.2-8.6 (m, $4H_6$ methylenes). (Found: C, 68.7; H, 4.4; F, 26.8. $C_{16}H_{12}F_4$ requires C, 68.6; H, 4.3; F, 27.1%). The second component decomposed during preparative g.l.c. and was therefore isolated by preparative t.l.c. on silica impregnated

with silver nitrate (10%) (eluting (x3) with benzene:light petroleum (4:1)) to yield 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9H-4a,9-ethenophenanthrene (XXVIII,2) (15%), $\nu_{max.}$ 1068, 1485, 1600, 1628, and 2940 cm.$^{-1}$, ^{1}H n.m.r. τ 3.3-3.55 (q, H_1, J_{1-2}= 6.7, J_{1-3}=J_{3-F}= 1.5 Hz.), 3.0-3.3 (q, H_2, J_{2-3}= 6.3 Hz.), 3.55 (d of t, H_4, J_{3-4}= 5.5 Hz.), 4.7-5.1 (m, H_3), and 6.8-9.4 (m, 8H methylenes). (Found: C, 69.4; H, 4.9; F, 26.5%).

5,8-Dimethyl tetralin. Powdered, anhydrous aluminium chloride (293 g.) was added to a solution of p-xylene (100 g.) and succinic anhydride (100 g.) in methylene chloride (800 ml.). After hydrolysis and extraction with ether, the product (200 g., 97%) was heated under reflux for 8 hours with hydrazine hydrate (98%, 75 g.) and potassium hydroxide (160 g.) in diethylene glycol (800 ml.). Acidification followed by ether extraction gave a brown solid (198 g.) which was distilled under vacuum to yield a colourless acid product (168 g. 87%). Cyclisation was achieved by heating the acid with polyphosphoric acid (450 g.) for 15 minutes. Addition of water (1. 1) and ether extraction gave a product (142 g.) which was refluxed with hydrazine hydrate (64%, 60 g.) and potassium hydroxide (135 g.) in digol (600 ml.). Dilution with water fdlowed by ether extraction gave 5,8-dimethyl-tetralin (90 g., 70%, b.p. 99-101°/ 3m.m.) (lit.[99] b.p. 120° at 1 m.m.).

Tetrafluorobenzyne and 5,8-dimethyltetralin (Scheme XXIX). Chloropentafluorobenzene (20.2 g.), magnesium (3.65 g.), dibromoethane (9.39 g.) and 5,8-dimethyltetralin (90 g.) gave a crude product (17.6 g.). Analytical g.l.c. (5 ft., SE30 (10%) on firebrick at 190°) showed the presence of only one adduct. Distillation under reduced pressure gave 10,12-dimethyl-5,6,7,8-tetrafluoro-9H,4a,9-ethenophenanthrene (XXIX,1)(53%), b.p. 159-161°/3.5 mm., $\nu_{max.}$ 800, 1055, 1380, 1480, 1625 and 2940 cm.$^{-1}$, ^{1}H n.m.r. τ 3.5-3.8 (m, H_4, J_{4-5}= 6.2, $J_{4-Me(2)}$= 1.9 Hz.), 5.38 (q, H_5, J_{5-F}=1.9 Hz.) 7.85 (sx., H_1, J_{1-F}= 4.8 Hz.), and 7.2-8.8 (m, methylenes), (Found: C, 70.0; H, 5.5; F, 24.5. $C_{18}H_{16}F_4$ requires C, 70.15; H, 5.2; F, 24.65%).

6-methoxytetralin. Dimethyl sulphate (63.8 ml.) was added to a solution of 5,6,7,8-tetrahydro-2-naphthol (200 g.) in methanol (400 ml.). The mixture was cooled and potassium hydroxide (84 g.) in water (400 ml.) was added. The temperature of the solution rose and a brown oil was thrown out of solution. The mixture was poured onto ice (400 g.) and extracted with ether. Distillation through a vigreux column (15 cm.) gave 6-methoxytetralin (70 g., 32%) b.p. 102-104°/ 3.2mm. Unreacted starting material (100 g.) was recovered.

Reaction of tetrafluorobenzyne and 6-methoxytetralin(Scheme XXX). Chloropentafluorobenzene (20.2 g.), magnesium (3.65 g.), 1.2-dibromoethane (9.39 g.) and 6-methoxytetralin (70 g.) were refluxed for 5 hours, then hydrolysed with water.

A carbonyl-group absorption (1745 cm.$^{-1}$) was observed to appear in the I.R. spectrum of the crude product after a few minutes, and g.l.c. indicated that the initially formed products were slowly hydrolysing. The mixture was treated with mineral acid and a portion (8.2 g.) column chromatographed on alumina (Grade I, 200 g.). Elution with benzene:light petroleum (1:9) gave 1,2,3,4-tetrafluoro-10-methoxy-4b,5,6,7,8,10-hexahydro-4b,10-ethenophenanthrene (XXX,3) (1.45 g.) an oil, $\nu_{max.}$ 760, 1110, 1230, 1330, 1490, 1630 and 2960 cm.$^{-1}$, ^{1}H n.m.r. τ 2.96 (broad d, H_2, J_{1-2}=7.8 Hz.) 3.44 (d, H_1), 3.43 (broad s, H_3), 6.30 (m, MeO), and 6.8-8.8 (m, methylenes), (Found: C, 65.65; H, 4.45%, M.Wt. 310 (mass spectrometry); $C_{17}H_{14}F_4O$ requires C, 65.80; H, 4.55%, M.Wt. 310). Elution with benzene:light petroleum (1:5.7) gave 1,2,3,4-tetrafluoro-5,6,7,8,9,10-hexahydro-9,10-oxoethanoanthracene (XXX,4) (2.0 g.) m.p. 117-119° (from light petroleum), $\nu_{max.}$ 680, 890, 1020, 1080, 1510, 1745 and 2950 cm.$^{-1}$, ^{1}H n.m.r. τ 5.62 (d, H_1, J_{1-F}=1.8 Hz.), 5.78 (m, H_2), and 7.50-8.60 (m, methylenes); the mass spectrum showed no molecular ion, highest peak at m/e 254, (Found: C, 64.6; H, 4.2. $C_{16}H_{12}F_4O$ requires C, 64.85; H, 4.1%). Elution with ether:light petroleum (1:19) gave a mixture of adducts (XXX,4 and 5) (3.4 g.). Preparative t.l.c. on silica impregnated with silver nitrate (10%) (eluting with benzene:light petroleum (1:1)) gave more of the adduct

(XXX,4) (2.0 g.) and 1,2,3,4-tetrafluoro-4b,5,6,7,8,10-hexahydro-11-oxo-4b,10-ethanophenanthrene (XXX,5), (1.4 g.) m.p. 119-120° (from light petroleum), $\nu_{max.}$ 815, 940, 1030, 1500, 1740, 2900 and 2960 cm.$^{-1}$, ^{1}H n.m.r. τ 3.81 (d, H_1, J_{1-2}= 7.2 Hz.), 5.39 (d of d, H_2, J_{1-F}= 1.0 Hz.) and 7.0-8.5 (m, methylenes); the mass spectrum again showed no molecular ion, highest peak at m/e 254. (Found: C, 64.55; H, 3.95%).

Oestradiol dimethyl ether. n-Butyl lithium (3 equivalents, 7.2 ml. of a 2.5M solution in hexane) was slowly added to a stirred suspension of oestradiol (1.64 g.) in dimethyl sulphoxide (50 ml.) under nitrogen. After 30 minutes, methyl iodide (2.6 g.) was added, and stirring continued for 15 minutes. The product was poured into water (200 ml.) and the precipitated solid was separated to give oestradiol dimethyl ether (1.7 g., 95%), m.p. 158-158.5° (lit.[107] m.p. 161°).

Reaction of tetrafluorobenzyne and oestradiol dimethyl ether (Scheme XXXI). n-Butyl lithium (10 ml.) was added to a stirred suspension of oestradiol dimethyl ether (2.5 g.) in ether (200 ml.) containing bromopentafluorobenzene (6.2 g.) at -10°. The solution was allowed to warm to room temperature and left for 16 hours. Extraction with ether, followed by steam distillation to remove aromatic by-products gave a pale yellow crystalline solid (3.5 g.). Preparative t.l.c. (eluting (x4) with benzene) gave the 1,4-adduct (XXXI,1)

(1.36 g.) a gum, $\nu_{max.}$ 880, 990, 1110, 1500, 1740 and 2930 cm.$^{-1}$, ^{1}H n.m.r. τ 5.42 (m, 1H bridgehead), 5.64 (d, 1H bridgehead, J_{H-F}= 2.4 Hz.), 6.74 (s, OMe), 6.5-7.0 (m, MeO.CH) and 9.33 (s, C-18Me), the mass spectrum showed no molecular ion, highest peak at m/e 392, and the 2,5-adduct (XXXI,2) (0.88 g.) a gum, $\nu_{max.}$ 860, 1020, 1420, 1740 and 2950 cm.$^{-1}$, ^{1}H n.m.r. τ 3.85 (broad d, H_1 olefinic, J_{1-2}= 6.0 Hz.), 5.37 (d of d, H_2 bridgehead, J_{F-H}= 2.4 Hz.), 6.75 (s, OMe), 6.68-7.03 (m, MeO.CH), and 9.25 (s, C-18Me), the mass spectrum again showed no molecular ion, highest peak at m/e 392. A small quantity of oestradiol dimethyl ether (1.08 g.) was recovered.

9(11)-Dehydrooestrone dimethyl ether. DDQ (150 mg.) suspended in chloroform (10 ml.) was added to a stirred solution of oestradiol dimethyl ether (100 mg.) in chloroform (50 ml.) at room temperature. The solution turned green and the hydroquinone was precipitated. The reaction was repeated 18 times and the chloroform solutions combined and filtered. After removal of the solvent and elution through a short column of alumina with benzene the colourless syrup (1.7 g.) was separated by preparative t.l.c. (eluting (x2) with benzene:chloroform (3:1)) to give 9(11)-dehydrooestrone dimethyl ether (0.9 g.) $\nu_{max.}$ 810, 1075, 1120, 1280, 1395, 1608 and 2950 cm.$^{-1}$, $\lambda_{max.}$ 266 (ϵ 19,000), 276 (inflexion, ϵ 15,000), 296 (ϵ 3,000)

and 308 (ε 2,150) nm., ^{1}H n.m.r. τ 2.53 (d, H_1, J_{1-2}= 9.0 Hz.), 3.44 (q, H_2, J_{2-4}= 3.0 Hz.), 3.53 (broad s, H_4), 3.81 (broad d, H_{11}, J = 6.0 Hz.), 6.35 (s, C-3 OMe), 6.76 (s, C-17β OMe), 7.10-7.45 (m, C-5 hydrogens) and 9.30 (s, C-18Me), (Found: C, 80.2; H, 9.25. $C_{20}H_{26}O_2$ requires C, 80.5; H,8.75%). Oestradiol dimethyl ether (0.6 g.) was recovered.

Pyrolysis of adducts. The adduct was heated in a nitrogen purged evacuated Carius tube (ca. 500 ml. capacity) at the temperature and for the period specified.

Adduct (XXIV,1) (60 mg.) after 12 hours at 250° gave the naphthalene (XXIV,5) (58 mg.) m.p. 88-89° (from ethanol), $\nu_{max.}$ 780, 800, 890, 1650 and 3080 cm.$^{-1}$, $\lambda_{max.}$ 226 (ε 72,500), 263 (ε 3,500), 273 (ε 6,000), 283 (ε7,300), and 294 (ε 4,800) nm., ^{1}H n.m.r. τ 1.8 - 2.8 (m, aromatic), 5.13 (broad s, $=CH_2$), 6.8 - 7.4 (m, $Ar.CH_2$), 8.34 (s, Me-C=), 9.12 (d, side chain methyls), and 9.25 (C-18Me), (Found: C, 89.2; H, 10.85. $C_{33}H_{48}$ requires C, 89.1; H, 10.9%).

Adduct (XXV,1) (150 mg.) after 12 hours at 250° gave the naphthalene (XXV,3) (96 mg.), m.p. 112-113° (from ethanol), $\nu_{max.}$ 760, 890, 1060, 1645, 1670, and 3080 cm.$^{-1}$, $\lambda_{max.}$ 220 (ε 78,800), 262 (ε 3,260), 274 (ε 5,990), 283 (ε 7,040), and 293 (ε 3050) nm., ^{1}H n.m.r. τ 1.9-2.2 (m. aromatic), 2.35-2.8 (m, aromatic), 5.22 (broad s,$=CH_2$) 8.35 (s, Me-C=), 9.12 (d, side chain methyls), and 9.25 (C-18Me), (Found: C, 76.3; H, 8.4; F, 14.9. $C_{33}H_{44}F_4$ requires C, 76.7; H, 8.6; F, 14.7%).

Adduct (XXVIII,1) (100 mg.) after 12 hours at 350° gave 1,2,3,4-tetrafluoro-5,6,7,8-tetrahydroanthracene (XXVIII,3) (80 mg.) m.p. 86-87° (from ethanol), $\nu_{max.}$ 663, 780, 860, 980, 1010, 1150, 1355, 1465, 1625, 1680 and 2940 cm.$^{-1}$, $\lambda_{max.}$ 226 (ε 56,300), 272 (inflexion, ε 3,390), 277 (ε 4,360), 286 (ε4,270), and 297 (inflexion,ε2,670) nm., ^{1}H n.m.r. τ 2.16 (d, 2 aromatic hydrogens, J_{H-F}= 0.9 Hz.), 6.8-7.25 (m, 4 methylenes), and 7.95-8.30 (m, 4 methylenes) (Found: C, 66.05; H, 3.85; F, 29.8. $C_{14}H_{10}F_4$ requires C, 66.15; H, 3.95; F, 29.9%).

Adduct (XXVIII,2) (100 mg.) after 12 hours at 350° gave 1,2,3,4-tetrafluoro-5,6,7,8-tetrahydrophenanthrene (XXVIII,4) (83 mg.) m.p. 111-113° (from ethanol), $\lambda_{max.}$ 226 (ε 50,100), 262 (inflexion, ε 3,200), 274 (ε 4,700), 281 (ε 5,050), 292 (inflexion, ε 3,850), 310 (ε 1,340), 324 (ε 2,000) nm., ^{1}H n.m.r. τ 2.37 (broad d, H_{10}, J_{10-9}= 8.4 Hz.), 2.88 (d, H_9 aromatic), 6.5-7.0 (broad m, 2 H_5 methylenes), 6.9-7.3 (m, 2H_8 methylenes), and 7.95-8.3 (m, 4 methylenes), (Found: C, 66.25; H, 3.90. $C_{14}H_{10}F_4$ requires C, 66.15; H, 3.95%).

Adduct (XXX,4) (100 mg.) was recovered unchanged after 48 hours at 200°. After 24 hours at 300°, g.l.c. (5 ft., S.E.30 (10%) on firebrick at 240°) showed 65% conversion to compound (XXX,6). Separation by preparative t.l.c. (eluting with benzene:light petroleum (1:1)) gave (XXX,6) identical to compound (XXVIII,3).

Hydrogenation of adducts. A solution of the adduct in ethyl acetate was stirred with 10% palladium on charcoal catalyst in an atmosphere of hydrogen until the gas uptake ceased. The solution was filtered and removal of the solvent gave the dihydro-compound.

α-Adduct (XXXIV,1) (48 mg.) gave the dihydro-α-adduct (XXIV,3) (47 mg.), a gum, $\nu_{max.}$ 665, and 752 cm.$^{-1}$, ^{1}H n.m.r. τ 2.6-3.2 (m, aromatic), 7.0-7.3 (m, Ph.CH), 8.85 (s,C-19Me), 9.15 (d, side chain methyls), and 9.36 (s,C-18Me), (Found: C, 88.65; H, 11.2. $C_{33}H_{50}$ requires C, 88.7; H, 11.3%).

β-Adduct (XXIV,2) (5 mg.) gave the dihydro-β-adduct (XXIV,4) m.p. 116-118° (from ethanol), ^{1}H n.m.r. τ 2.6-3.2 (m, aromatic), 7.0-7.2 (m, Ph CH), 9.14 (d, side chain methyls), 9.32 (s, C-18Me), and 9.69 (s, C-19Me), M.Wt.(mass spectrometry) 446.

Adduct (XXV,1) (80 mg.) gave the dihydro-adduct (XXV,2) (79 mg.), a gum, $\nu_{max.}$ 1080, and 2960 cm.$^{-1}$, ^{1}H n.m.r. τ 6.5-6.8 (m, $C_6F_4R.CH$), 8.90 (s, C-19Me), 9.15 (d, side chain methyls), and 9.35 (s, C-18Me). (Found: C, 76.2; H, 8.15. $C_{33}H_{46}F_4$ requires C, 76.4; H, 8.9).

The naphthalene (XXIV,5) (25 mg.) gave the dihydro compound (XXIV,6) (27 mg.),a gum, ^{1}H n.m.r. τ 1.9-2.8 (m, aromatic), 6.9-7.4 (m, Ar.CH_2), 8.9-9.3 (m, side chain and 9-$(Me)_2CH$), and 9.32 (s, C-18Me).

The naphthalene (XXV,3) (44 mg.) gave the dihydro compound (XXV,4) m.p. 96-97° (from ethanol), $\nu_{max.}$ 760, 980, 1060, 1500, 1670, and 2950 cm.$^{-1}$, ^{1}H n.m.r. τ 1.9-2.8 (m, aromatic), 6.7-7.2 (m, Ar.CH_2), 8.9-9.3 (m, side chain methyls and 9-$(Me)_2CH$), and 9.32 (s, C-18Me). (Found:C, 76.35; H, 8.6; F, 14.8. $C_{33}H_{46}F_4$ requires C, 76.4; H, 8.95; F, 14.65%).

Photolysis of adducts. The adduct was dissolved in ether (25 ml.) and photolysed in a quartz flask under nitrogen for 1 hour with a medium pressure mercury lamp emitting radiation predominantly of wavelengths 254, 265, 297, 313 and 366 nm. Removal of the solvent gave the product.

Adduct (XXX,4) (30 mg.) gave compound (XXX,6) (28 mg.) m.p. 86-87° (from ethanol) identical to compound (XXVIII,3).

Adduct (XXX,5) (30 mg.) gave compound (XXX,7) (28 mg.) m.p. 111-113° (from ethanol), identical to compound (XXVIII,4).

Adduct XXXI,1) (50 mg.) gave a yellow gum. Preparative t.l.c. (eluting with benzene) gave compound (XXXI,3) (40 mg.) m.p. 133-135° (from acetone), $\nu_{max.}$ 890, 1110, 1360, 1505, 1620, and 2940 cm.$^{-1}$, $\lambda_{max.}$ 226 (ε 57,400), 265 (inflexion, ε 5,080), 275 (ε 4,580), 285 (ε 4,360), and 297 (inflexion, ε 2,870) nm., ^{1}H n.m.r. τ 2.15 and 2.32 (broad s, H_1 and H_4 aromatic), 6.70 (s, MeO), and 9.23 (s, C-18Me).

Adduct (XXXI,2) (50 mg.) gave a yellow gum. Preparative t.l.c. (eluting with benzene) gave compound XXXI,4) (40 mg.) m.p. 172-174° (from acetone), $\nu_{max.}$ 820, 1110, 1420, 1455, 1500, 1620, 1670, and 2950 cm.$^{-1}$, $\lambda_{max.}$ 226 (ε 69,000),

264 (inflexion, ε 2,500), 275 (ε 3,450), 283 (ε 3,690), 293 (inflexion, ε 2,850), 310 (ε 1,070), 324 (ε 1,070) nm., ^{1}H n.m.r. τ 2.30 (broad d, H_2J_{1-2}= 9.0 Hz.), 2.56 (d, H_1 aromatic), 6.73 (s, MeO), and 9.25 (C-18Me). (Found: C, 70.25; H, 6.05. $C_{23}H_{24}F_4O$ requires C, 70.4; H, 6.15%).

Appendix

The Photoisomerisation of 5,6,7,8-tetrafluoro-1,4-dihydro-1,4-ethanonaphthalene.

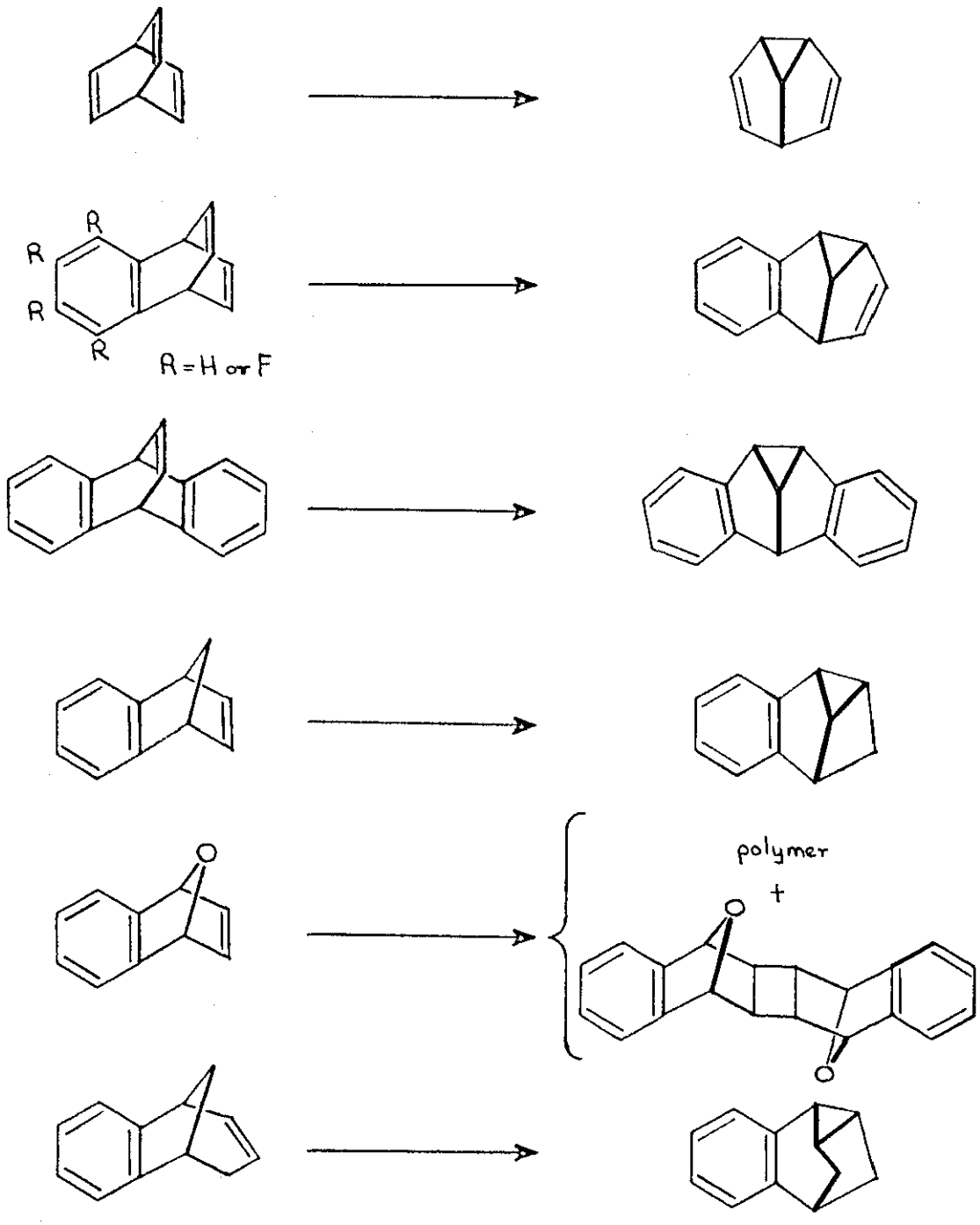
Introduction

In 1966 it was shown by Zimmerman and Grunewald[108] that barrelene, in the presence of a triplet sensitiser, was readily photoisomerised to semibullvalene, an interesting fluxional molecule, but that in the absence of a sensitiser the product was cyclooctatetraene. Since this first discovery, several groups of research workers have intensively studied the photochemical rearrangements of many other divinylmethanes (di-π-methanes)[109] both in the presence and absence of sensitisers. Some examples include substituted barrelenes,[110] benzobarrelene,[111] tetrafluorobenzobarrelene,[112] dibenzobarrelene [113,114] and its derivatives,[114] benzonorbornadiene,[115] 1,4-dihydro-1,4-epoxynaphthalene,[116] and benzo[6,7]bicyclo[3.2.1]octa-2,6-diene.[117]

Some general conclusions have been made concerning the reaction mechanisms. All of the above compounds, with the exception of 1,4-dihydro-1,4-epoxynaphthalene, when photolysed in the presence of a sensitiser (acetone, benzophenone or acetophenone) gave the expected vinyl- or benzo-cyclopropane compounds (Scheme XXXII). The products are thought to arise from a triplet diradical species[108c] which reacts via non-concerted vinyl-vinyl bridging in the case of benzobarrelenes, and via non-concerted benzo-vinyl bridging in all the other cases. The intermediates then rearrange to give benzocyclopropanes. The exception, 1,4-dihydro-1,4-epoxynaphthalene, on photolysis gave a large amount of polymer and a little

Scheme XXXII

Reactions in the presence of a triplet sensitiser.



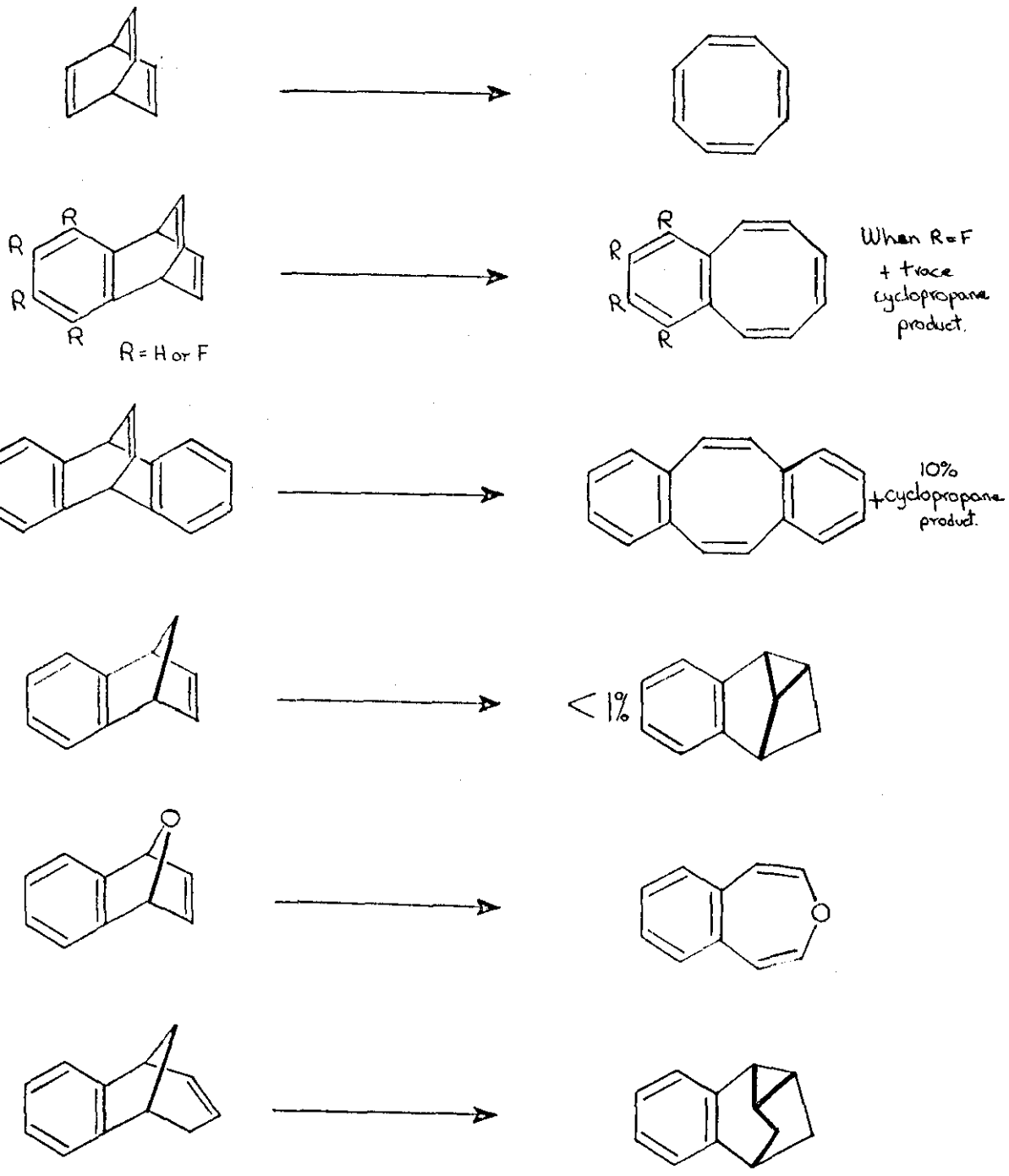
head-to-head trans-dimer. The former may have arisen through the instability of the benzo-oxa-cyclopropane under the reaction conditions, and the latter probably arose from dimerisation of the triplet species before benzo-vinyl bridging had occurred.[118]

In the absence of a sensitiser, a singlet diradical species is thought to be generated[111b] which leads to the different products shown in (Scheme XXXIII). It has been suggested that the photoisomerisation proceeds via quadricyclane-like intermediates.[108] These are formed by a symmetry allowed,[119] concerted, intramolecular, '2+2' cycloaddition process which is facilitated by the geometry of the bicyclic system. The small amounts of di-π-methane rearrangement products found in the case of tetrafluorobenzobarrelene and dibenzobarrelene probably arose from a triplet species formed by a singlet to triplet intersystem crossing reaction.[112] In the cases where no benzocyclopropane products were isolated, it is assumed that the intersystem crossing is too inefficient compared with the more facile, competing, singlet, cycloaddition process.

On photolysis of benzo[6.7]bicyclo[3.2.1]octa-2,6-diene, the benzocyclopropane product was isolated in the absence of a sensitiser.[117] The geometry of the former compound is such that '2+2' cycloaddition cannot take place since the double-bond is unable to approach the benzene-π-cloud for complete overlap. However, one end of the double-bond is just close enough for overlap, so the di-π-methane rearrangement might be directly initiated by an excited singlet. Alternatively,

Scheme XXXIII

Reactions in the absence of a triplet sensitiser.



intersystem crossing and triplet rearrangement could predominate.

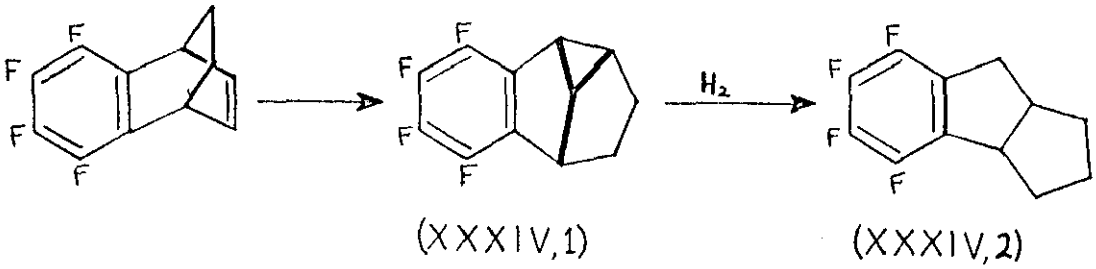
The photoisomerisation of benzonorbornadiene in the absence of a sensitiser gave less than 1% of the di-π-methane rearrangement product, presumably again because of inefficient intersystem crossing. However, no explanation can be offered for the complete absence of any benzocycloheptatriene, especially since norbornadiene[120] and its derivatives[121] are readily photoisomerised to quadricyclane and its derivatives by direct or triplet sensitised photolysis.

Discussion.

In view of the current interest in di-π-methane photoisomerisations, we have investigated the photolysis of 5,6,7,8-tetrafluoro-1,4-dihydro-1,4-ethanonaphthalene (tetrafluorodihydrobenzobarrelene) (Scheme XXXIV). Irradiation of a 0.3% solution of the latter in diethyl ether containing acetone (5%) gave, after 2 hours, a 56% conversion to 5,6-tetrafluorobenzotricyclo[5,1,0,$0^{4,8}$]oct-5-ene (XXXIV,1). The same major product was also isolated in 26% yield in the absence of triplet sensitisers after irradiation for 4 hours. No tetrafluorobenzocyclooctatriene was found.

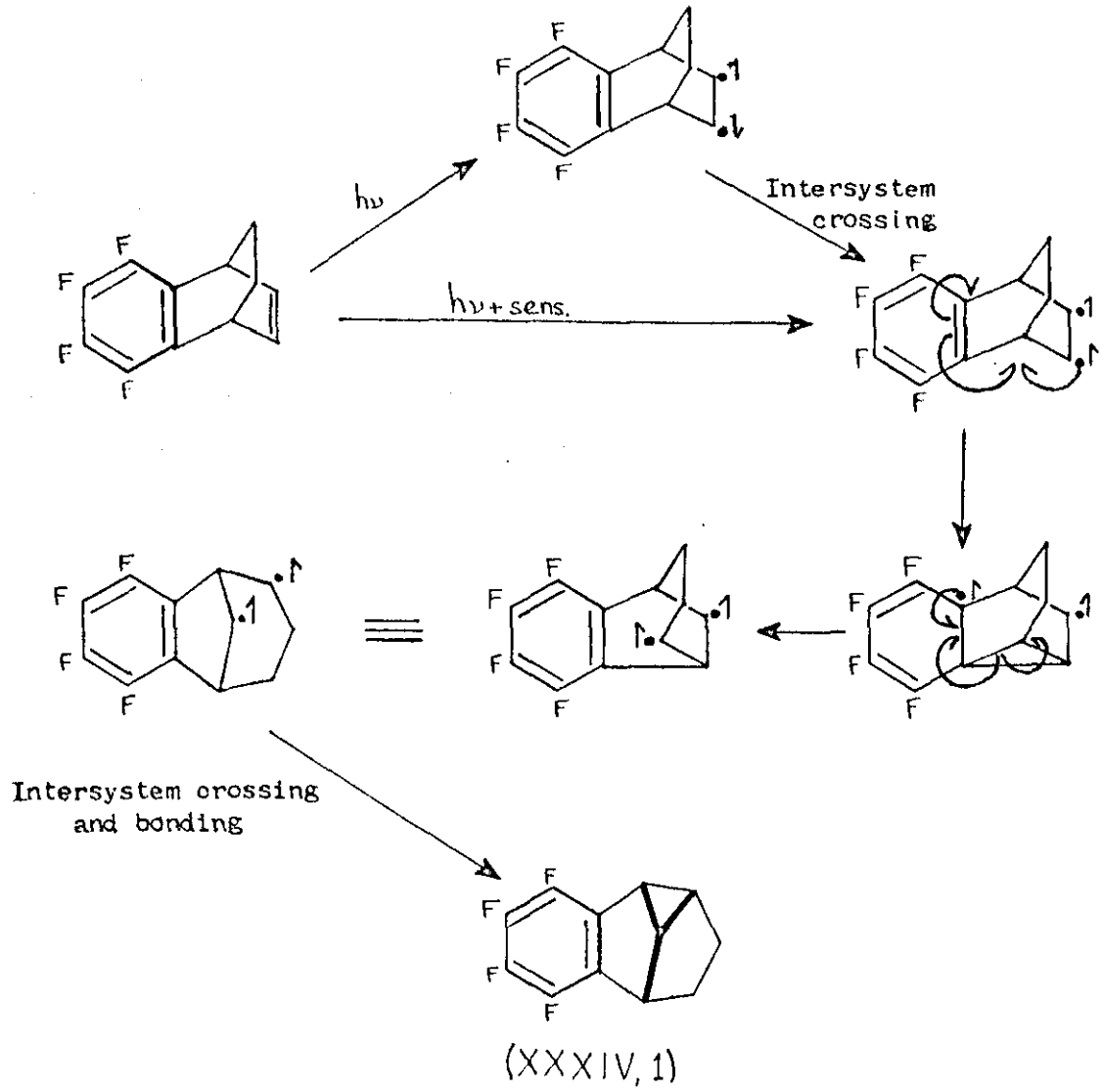
The product was separated from starting material by preparative t.l.c. on silica impregnated with silver nitrate followed by preparative g.l.c. to remove the final impurities. Its structure was assigned from the following evidence:

Scheme XXXIV



(XXXIV,1) (XXXIV,2)

Scheme XXXV



(XXXIV,1)

analysis and molecular weight determination (mass spectrometric) showed the compound to be isomeric with the starting material. The u.v. spectrum showed no strong chromophore associated with a conjugated double bond but the infra-red spectrum showed a strong absorption at 3050 $cm.^{-1}$ The ^1H n.m.r. spectrum, which could not be interpreted by first order methods, showed no olefinic absorptions, but multiplets were observed at τ 6.24(1H), 7.14 (1H) 7.49 (1H), 8.05 (4H), and 8.78(1H). These results indicated the presence of a non-conjugated, cyclopropane ring in which the protons are strongly deshielded, probably by a fluorinated aromatic ring. Final proof of the structure of compound (XXXIV,1) was obtained by showing that its infra-red, ^1H n.m.r., and g.l.c. retention time were identical to the reduction product obtained from the controlled hydrogenation of tetrafluorobenzosemibullvalene.[112] Further reduction of compound (XXXIV,1) gave 4,5,6,7-tetrafluoro-1,2,3,3a,8,8a-hexahydrocyclopent[a]indene(XXXIV,2). The ^1H n.m.r. spectrum of the latter is very similar, apart from the aromatic region, to the spectrum of the compound obtained from the complete reduction of benzosemibullvalene,[111b] namely 1,2,3,3a,8,8a-hexahydrocyclopent[a]indene.

It should be noted here that benzobicyclo[2.2.2]octadienols have recently been shown to photoisomerise in the presence of a sensitiser to benzodihydrohydroxysemibullvalenes.[122]

We feel that our isomerisation results are best explained by assuming that tetrafluorodihydrobenzosemibullvalene(XXXIV,1)

arises by a triplet mechanism which involves benzo-vinyl bridging (Scheme XXXV). In the absence of a sensitiser, the rate of production of the compound (XXXIV,1) is slower than in the presence of a sensitiser. It is thought in this case that a fairly efficient singlet to triplet intersystem crossing reaction takes place, which may be assisted to some extent by the presence of fluorine in the molecule. The result is that no tetrafluorobenzocyclooctatriene is formed. Alternatively, benzocyclooctatriene may be formed from the singlet, 2+2 cycloaddition reaction but is itself rapidly photoisomerised to (XXIV,1).

Experimental.

(i) A solution of 5,6,7,8-tetrafluoro-1,4-dihydo-1,4-ethanonaphthalene (300 mg.) was irradiated at room temperature in diethyl ether (100 ml.) containing acetone (5%) for 2 hours by means of a Hanovia medium pressure mercury lamp. The solvents were removed and the mixture shown to consist of two major components in the ratio 1:2.2 in order of increasing retention time by g.l.c. (5 ft., P.E.G.A (10%) on firebrick at 140°). Preparative t.l.c. on silica impregnated with silver nitrate (10%) (eluting with light petroleum) gave starting material (62.5 mg.) and impure 5,6-tetrafluorobenzotricyclo[5,1,0,$0^{4,8}$]oct-5-ene(XXIV,1) (85.0 mg.) a liquid. The compound was purified by preparative g.l.c.(10 ft. D.E.G.S.(20%) on Chromosorb W). $\nu_{max.}$ 650, 685, 720, 760, 800, 850, 900, 920,

965, 1020, 1070, 1130, 1240, 1330, 1420, 1500, 1650, 2870, 2960, and 3050 cm.$^{-1}$, $\lambda_{max.}$ 210 (ϵ 6,100) and 262 (ϵ 300) nm., ^{1}H n.m.r. see discussion, peaks observed in mass spectrum at m/e 228 (mol.ion), 213, 200 (base peak), and 187. (Found: C, 63.35; H, 3.8. $C_{12}H_8F_4$ requires C, 63.15; H, 3.55%).

(ii) Unsensitised irradiation of 5,6,7,8-tetrafluoro-1,4-dihydro-1,4-ethanonaphthalene (300 mg.) in diethyl ether (100 ml.) gave compound (XXXIV,1) (26%) after 4 hours, which was isolated as above.

(iii) Reduction of (XXXIV,1). (100 mg.) in ethanol (40 ml.) with palladium (10%) on charcoal (20 mg.) gave, 4,5,6,7-tetrafluoro-1,2,3,3a,8,8a-hexahydrocyclopent[a]indene (XXXIV,2) (70 mg.) a colourless liquid, $\nu_{max.}$ 970, 1410, 1500, 2880 and 2960 cm.$^{-1}$, ^{1}H n.m.r. 6.0-6.4 (m, $C_6F_4.C\underline{H}$), 6.4-6.75 (m, remaining methine), 6.75-7.5 (m, $C_6F_4.C\underline{H}_2$), and 7.6-8.8 (m, remaining 6 methylenes), M.Wt.(mass spectrometry) 230, ($C_{12}H_{10}F_4$ requires M.Wt. 230).

REFERENCES

1. E.Dreher and R.Otto, Annalen, 1870, 154, 93.

2. J.D.Roberts, H.E.Simmons jr., L.A.Carlsmith, and C.W.Vaughan, J.Amer.Chem.Soc., 1953, 75, 3290.

3.(a) G.Wittig, Angew.Chem., 1957, 69, 245.

(b) E.F.Jenny, M.C.Caserio, and J.D.Roberts, Experientia, 1958, 14, 349.

(c) J.D.Roberts, Chem.Soc.Symposium, Bristol 1958, Spec.Publ.No.12, The Chemical Society, London, 1958, p.115.

(d) J.F.Bunnett, Quart.Rev., 1958, 12, 1.

(e) R.Huisgen, Theoretical Organic Chemistry (Kekulé Symposium), Butterworth Scientific Publ., London, 1959, p.158.

(f) V.Franzen, Chemiker Ztg., 1960, 84, 3.

(g) R.Huisgen in Organometallic Chemistry, H.Zeiss, Reinhold Publ.Co., New York, 1960, p.36.

(h) R.Huisgen and J.Sauer, Angew.Chem., 1960, 72, 91.

(i) J.F.Bunnett, J.Chem.Educ., 1961, 38, 278.

(j) H.Heaney, Chem.Rev., 1962, 62, 81.

(k) G.Wittig, Angew.Chem., 1962, 74, 479; Angew.Chem. Internat.Edn., 1962, 1, 415.

(l) J.Sauer, Chem.Weekblad, 1963, 59, 57.

(m) G.Wittig, Pure and Appl.Chem., 1963, 7, 173.

(n) G.Wittig, Angew.Chem., 1965, 77, 752; Angew.Chem. Internat.Edn., 1965, 4, 731.

(o) R.W.Hoffmann, Naturwiss., 1965, 52, 655.

(p) R.W.Hoffmann, "Dehydrobenzene and Cycloalkynes", Academic Press, New York, 1967.

(q) T.L.Gilchrist and C.W.Rees, "Carbenes, Nitrenes and Arynes", Nelson, London, 1969.

4. C.A.Coulson, Chem.Soc.Spec.Publ., The Chemical Society, London, 1958, 12, 100.

5. (a) R.S.Berry, J.Clarby, and M.E.Schafer, J.Amer.Chem.Soc., 1964, 86, 2738.

(b) M.E.Schafer and R.S.Berry, ibid., 1965, 87, 4497.

6. G.Porter and J.I.Steinfeld, J.Chem.Soc.(A), 1968, 877.

7. (a) R.S.Berry, G.N.Spokes, and R.M.Stiles, J.Amer.Chem.Soc., 1960, 82, 5240.

(b) R.S.Berry, G.N.Spokes, and R.M.Stiles, ibid., 1962, 84, 3570.

8. R.Hoffmann, A.Imamura, and W.J.Hehre, J.Amer.Chem.Soc., 1968, 90, 1499.

9. E.W.Gowling, S.F.A.Kettle, and G.M.Sharples, Chem.Comm., 1968, 21.

10.(a) R.Huisgen and L.Zirngibl, Chem.Ber., 1958, 91. 1438.

(b) H.Gilman, W.Langham, and F.W.Moore, J.Amer.Chem.Soc., 1940, 62, 2327.

11. G.Wittig and L.Pohmer, Chem.Ber., 1956, 89, 1334.

12. R.Huisgen, J.Sauer, and A.Hauser, Chem.Ber., 1958, 91, 2366.

13.(a) M.E.Kuehne, J.Amer.Chem.Soc., 1962, 84, 837.

(b) H.E.Zieger and G.Wittig, Annalen, 1959, 623, 17.

(c) G.Ehrhart and G.Seidl, Chem.Ber., 1964, 97, 1994.

(d) R.Huisgen, W.Mack, and L.Möbius, Tetrahedron, 1960,9,29.

14.(a) C.H.Horning and F.W.Bergstrom, J.Amer.Chem.Soc., 1945, 67, 2110

(b) H.Gilman and H.W.Melvin jr., ibid., 1950, 72, 995.

15.(a) T.Kauffmann, and H.Henkler, Chem.Ber., 1963, 96, 3159.

(b) W.Strubell, Annalen, 1960, 631, 100.

16.(a) J.Sauer, R.Huisgen, and A.Hauser, Chem.Ber., 1958, 91, 1461.

(b) J.F.Bunnett and T.K.Brotherton, J.Amer.Chem.Soc., 1956, 78, 155, 6265.

(c) J.F.Bunnett, T.Kato, R.R.Flynn and J.A.Skorcz, J.Org.Chem., 1962, 27, 3836, 4152; 1963, 28, 1.

17.(a) J.D.Roberts, D.A.Semenow, H.E.Simmons, jr., and L.A.Carlsmith, J.Amer.Chem.Soc., 1956, 78, 601.

(b) J.F.Bunnett and B.F.Hrutfiord, ibid., 1962, 27, 4152.

(c) R.A.Benkeser and G.Schroll, ibid., 1953, 75, 3196.

18. R.G.Jones and H.Gilman, Org.Reactions, 1957, 9, 1.

19. H.Gilman and R.D.Gorsich, J.Amer.Chem.Soc., 1956, 78, 2217.

20. H.Gilman and R.D.Gorsich, J.Amer.Chem.Soc., 1957, 79, 2625.

21. E.Wolthius, J.Org.Chem., 1961, 26, 2216.

22. G.Wittig and L.Pohmer, Chem.Ber., 1956, 89, 1334.

23. G.Wittig and H.Härle, Annalen, 1959, 623, 17.

24. G.Wittig and E.Benz, Chem.Ber., 1959, 92, 1999.

25. H.Hellmann and D.Eberle, Annalen, 1963, 662, 188.

26. L.Friedman and F.M.Logullo, J.Amer.Chem.Soc., 1963, 85, 1549.

27. F.M.Logullo and L.Friedman, Org.Syntheses, in press.

28. H.Heaney and J.M.Jablonski, Chem.Comm., 1968, 1139.

29. R.Gompper, G.Seybold, and B.Schomolke, Angew.Chem. Internat.Edn., 1968, 7, 389.

30. G.Wittig and R.W.Hoffmann, Chem.Ber., 1962, 95, 2718.

31. C.D.Campbell and C.W.Rees. Proc.Chem.Soc., 1964,296.

32. N.Kharasch and R.K.Sharma, Chem.Comm., 1967, 492.

33. G.Wittig and H.F.Ebel, Annalen, 1961, 650, 20.

34. E.LeGoff, J.Amer.Chem.Soc., 1962, 84, 3786.

35. R.Huisgen and R.Knorr, Tetrahedron Letters, 1963,1017.

36. B.H.Klanderman and T.R.Criswell, J.Amer.Chem.Soc., 1969, 91, 510.

37. L.Friedman, J.Amer.Chem.Soc., 1967, 89, 3071.

38. R.W.Atkin and C.W.Rees, Chem.Comm., 1969, 152.

39. R.G.Miller and R.M.Stiles, J.Amer.Chem.Soc., 1963, 85, 1798.

40. M.Stiles and R.G.Miller, J.Amer.Chem.Soc., 1960, 82, 3802.

41. D.Bryce-Smith, Chem.Comm., 1969, 806.

42. O.Diels and K.Alder, Annalen, 1928, 460, 98.

43. For some reviews see:

(a) B.S.Thyagarajan, Chem.Rev., 1954, 54, 1038.

(b) K.Alder, "Newer Methods of Preparative Organic Chemistry", Interscience, New York, 1948, p. 381.

(c) A.S.Onischenko, "Diene Synthesis", S.Morrison, Jerusalem, 1964.

(d) J.G.Martin and R.K.Hill, Chem.Rev., 1961, 61, 537.

(e) Yu.A.Titov, Russ.Chem.Rev., 1962, 31, 267.

(f) S.B.Needleman and M.C.Chang Kuo, Chem.Rev., 1962, 62, 405.

(g) A.Masserman, "Diels-Alder Reactions", Elsevier, New York, 1965.

(h) J.Sauer, Angew.Chem.Internat.Edn., 1966, 5, 211 and 1966, 6, 16.

44. K.Alder and G.Stein, Angew.Chem., 1937, 50, 510.

45. R.Hoffmann and R.B.Woodward, Accounts of Chem.Res., 1968, 1, 17.

46. (a) H.E.Stavely and W.Bergmann, J.Org.Chem., 1937, 1, 567, 575.

(b) E.L.Skau and W.Bergmann, ibid., 1938, 3, 166.

47. Fr.Schenk, K. Bucholz, O.Wiese, Chem.Ber., 1936, 69, 2696.

48. I.M.Heilbron, G.L.Moffet, and F.S Spring, J.Chem.Soc., 1937, 411.

49. A.Windhaus and A.Luttringhaus, Chem.Ber., 1931, 64, 850.

50. A.Windhaus, Chem.Zentr., 1930, 1, 3194.

51. H.H.Inhoffen, Annalen, 1934, 508, 81.

52. E.M.Hicks, C.J.Berg, and E.S.Wallis, J.Biol.Chem., 1946, 162, 654.

53. L.F.Fieser and M.Fieser, "Steroids", Reinhold, New York, 1959, p.109.

54. (a) W.Bergmann, F.Hirschmann, and E.L.Skau, J.Org.Chem., 1939, 4, 29.

(b) R.J.Conca and W.Bergmann, ibid., 1953, 18, 1104.

55. F.Dalton and G.D.Meakins, J.Chem.Soc., 1961, 1880.

56. K.Schubert and K.H.Bohme, Chem.Ber., 1960, 85, 1131.

57. D.N.Jones and I.Thomas, J.Chem.Soc., 1964, 5206.

58. D.N.Jones, P.F.Greenhalgh, and I.Thomas, Tetrahedron, 1968, 24, 297.

59. (a) K.Alder and H.von Brachel, Annalen, 1962, 651, 141.

(b) W.R.Roth, Chimica (Switz.), 1966, 20, 229.

60. A. van der Gen, J.Lakeman, M.A.M.P.Gras, and H.O.Huisman, Tetrahedron, 1964, 20, 2521.

61. J.Lakeman, W.N.Speckamp, and H.O.Huisman, Tetrahedron Letters, 1967, 3699.

62. A. van der Gen, J.Lakeman, U.K.Pandit, and H.O.Huisman, Tetrahedron, 1965, 21, 3641.

63. J.Lakeman, W.N.Speckamp, and H.O.Huisman, Tetrahedron, 1968, 24, 5151.

64. A.Windhaus and R.Langer, Annalen, 1933, 508, 105.

65. A.van der Gen, W.A.Zunnebeld, U.K.Pandit,and H.O.Huisman, Tetrahedron, 1965, 21, 3651.

66. A.M.Lautzenheiser and P.W.LeOuesne, Tetrahedron Letters, 1969, 207.

67. D.N.Jones, P.F.Greenhalgh, and I.Thomas, Tetrahedron, 1968, 24, 5215.

68. K.D.Bingham, G.D.Meakins and J.Wicha, J.Chem.Soc.(C), 1969, 671.

69. A.J.Solo, H.S.Sachder, and S.S.H.Gilani, J.Org.Chem., 1965, 30, 769.

70. A.J.Solo and B.Singh, J.Med.Chem., 1966, 9, 957.

71. A.J.Solo and B.Singh, J.Med.Chem., 1967, 10, 1048.

72. A.J.Solo, B.Singh, Shefter, and A.Cooper, Steroids, 1968, 11, 637.

73. T.L.Popper, F.E.Carlon, H.M.Marigliano, and M.D.Yudis, Chem.Comm., 1968, 1434.

74. B.Ellis and V.Petrow, J.Chem.Soc., 1952, 2246.

75.(a) L.H.Knox, E.Valarde, S.Berger, D.Cuadriello, P.W.Landis, and A.D.Cross, J.Amer.Chem.Soc., 1963, 85, 1861.

(b) A.J.Birch and G.S.R.Subba Rao, Tetrahedron, 1966, supp.7, 391.

(c) M.S.Nazer, J.Org.Chem., 1965, 30, 1737.

(d) F.T.Bond and R.H.Cornelia, Chem.Comm., 1968, 1189.

76. R.H.Cornelia, Diss.Abs., 1968, 29, 933-B.

77. A.J.Birch, J.M.Brown, and G.S.R.Subba Rao, J.Chem.Soc., 1964, 3309.

78. E.Nield, R.Stephens, and J.C.Tatlow, J.Chem.Soc., 1959, 166.

79. P.L.Coe, R.Stephens, and J.C.Tatlow, J.Chem.Soc., 1962, 3227.

80.(a) G.Wittig and L.Pohmer, Angew.Chem., 1955, 67, 348.

(b) G.Wittig and L.Pohmer, Chem.Ber., 1956, 89, 1334.

81.(a) C.R.Patrick and G.S.Prosser, Nature, 1960, 187, 1021.

(b) J.Burdon, Tetrahedron, 1963, 21, 1101.

82. J.M.Jablonski, Ph.D.thesis, Loughborough, 1968.

83. J.P.N.Brewer, I.F.Eckhard, H.Heaney, and B.A.Marples, J.Chem.Soc.(C), 1968, 664.

84. H.Heaney and J.M.Jablonski, J.Chem.Soc.(C), 1968, 1895.

85. K.Ziegler, A.Spath, E.Schaaf, W.Schumann, and E.Winkelmann, Annalen, 1942, 551, 104.

86. (a) G.Wittig, Angew.Chem.Internat.Edn., 1965, 4, 731.

(b) H.E.Simmons, J.Amer.Chem.Soc., 1961, 83, 1657.

87. R.J.Gell, P.S.Littlewood, B.A.Marples, and B.Lythgoe, J.Chem.Soc., 1964, 4914.

88. M.Neeman, M.C.Caserio, J.D.Roberts, and W.S.Johnson, Tetrahedron, 1959, 6, 36.

89. J.P.Dusza, J.P.Joseph, and S.Bernstein, Steroids, 1966, 8, 495.

90. N.L.Wendler, "Molecular Rearrangements", Ed.P.de Mayo, Interscience, New York, 1964, p.1077.

91. I.F.Eckhard, H.Heaney, and B.A.Marples, Tetrahedron Letters, 1967, 4001.

92. I.F.Eckhard, H.Heaney, and B.A.Marples, J.Chem.Soc.(C), in press.

93. L.J.Morris, J.Lipid Res., 1966, 7, 717.

94. W.L.Dilling, Tetrahedron Letters, 1966, 939.

95. R.Harrison, H.Heaney, J.M.Jablonski, K.G.Mason, and J.M.Sketchley, J.Chem.Soc.(C),1969, 1684.

96. C.R.Butt, D.Cohen, L.Hewitt, and I.T.Millar, Chem.Comm., 1967, 309.

97.(a) V.Petrow, O.Rosenheim, and W.W.Starling, J.Chem.Soc., 1938, 677.

(b) B.Ellis and V.Petrow, J.Chem.Soc., 1939, 998.

98. (a) T.Westphalen, Chem.Ber., 1965, 48, 1064.

(b) J.W.Blunt, A.Fischer, M.P.Hartshorn, F.W.Jones, D.N.Kirk, and S.W.Yoong, Tetrahedron, 1965, 21, 1567.

99. E. de B.Barnett and F.G.Sanders, J.Chem.Soc., 1933, 434.

100. G.Stork, J.Amer.Chem.Soc., 1947, 67, 576.

101. R.K.Murray, Jr. and H.Hart, Tetrahedron Letters, 1968, 4995.

102. W.Brown, J.W.A.Findlay, and A.B.Turner, Chem.Comm., 1968, 10.

103. See ref. 53, p. 265.

104. See ref. 53, p. 192.

105. See ref. 53, p. 326.

106. Personal Communication, L.Friedman and F.M.Logullo, 1967.

107. Y.Urusibara and T.Nitta, Bull.Chem.Soc.Japan, 1941, 16, 179.

C.A. 1941, 35, 8210[1]. See also ref. 88.

108. (a) H.E.Zimmerman and G.L.Grunewald, J.Amer.Chem.Soc., 1966, 88, 183.

(b) H.E.Zimmerman and H.Iwamura, ibid., 1968, 90, 4763.

(c) H.E.Zimmerman, R.W.Binkley, R.S.Givens, G.L.Grunewald, and M.A.Sherwin, ibid., 1969, 91, 3316.

109. H.E.Zimmerman and P.S.Mariano, J.Amer.Chem.Soc., 1969, 91, 1718.

110. R.S.H.Liu, J.Amer.Chem.Soc., 1968, 90, 215.

111. (a) H.E.Zimmerman, R.S.Givens, and R.M.Pagni, J.Amer.Chem.Soc., 1968, 90, 6096.

(b) idem., ibid., 1968, 90, 6096.

112. J.P.N.Brewer and H.Heaney, Chem.Comm., 1967, 811.

113. E.Ciganek, J.Amer.Chem.Soc., 1966, 88, 2882.

114. P.W.Rabideau, J.B.Hamilton, and L.Friedman, J.Amer.Chem.Soc., 1968, 90, 4465.

115. (a) J.R.Edman, J.Amer.Chem.Soc., 1966, 88, 3454.

(b) R.S.H.Liu and J.R.Edman, ibid., 1969, 91, 1492.

116. (a) G.R.Ziegler and G.S.Hammond, J.Amer.Chem.Soc., 1968, 90, 513.

(b) G.R.Ziegler, ibid., 1969, 91, 446.

117. R.C.Hahn and L.J.Rothman, J.Amer.Chem.Soc., 1969, 91, 2409.

118. N.J.Turro, 'Molecular Photochemistry', W.A.Benjamin Inc., New York, 1965, p.200.

119. (a) R.Hoffmann and R.B.Woodward, J.Amer.Chem.Soc., 1965, 87, 2046.

(b) H.E.Zimmerman, ibid., 1966, 88, 1564.

(c) idem., Science, 1966, 153, 837.

120. G.S.Hammond, N.J.Turro, and A.Fischer, J.Amer.Chem.Soc., 1961, 83, 4674.

121. P.G.Gassman, D.H.Aue, and D.S.Patton, J.Amer.Chem.Soc., 1964, 86, 421.

122. H.Hart and R.K.Murray, J.Amer.Chem.Soc., 1969, 91, 2183.