STUDIES IN
OLEFIN CYCLISATION

A Thesis presented by

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Abstract.

In the first part of this work the cation initiated cyclisation reactions of polyolefinic compounds are reviewed. The various initiators are described and a comparison is made of their efficiency in forming polycyclic systems. Particular emphasis is placed on the stereochemistry of cyclisation and the underlying mechanisms in an attempt to differentiate purely chemical influences from enzymic ones on the observed stereochemistry of biogenetic cyclisations.

In the second part a stereospecific transannular cyclisation of a cis,trans-cyclononadiene to a trans-hydrindanone is reported. Attempts to incorporate this reaction into a steroid synthesis, and in particular the closure of ring B by a 9,10 bond formation, are described. Model experiments were performed to test the possibility of achieving this ring closure via aromatic nitrenium ions, 1,5-dienes and epoxyolefins. The last of these proved successful. Finally the incorporation of the synthetic trans-hydrindanone, via an epoxyolefin cyclisation, into a mixture of epimeric double bond isomers of (±)-18-norandrostadien-3-one is described.

Acknowledgements.

I would like to thank Professor J.K. Sutherland and Dr. D.A. Widdowson for their interest, advice and encouragement during the course of this work.

Thanks are also due to my colleagues in the Tilden and Hofmann Laboratories for their friendship and helpful discussions.

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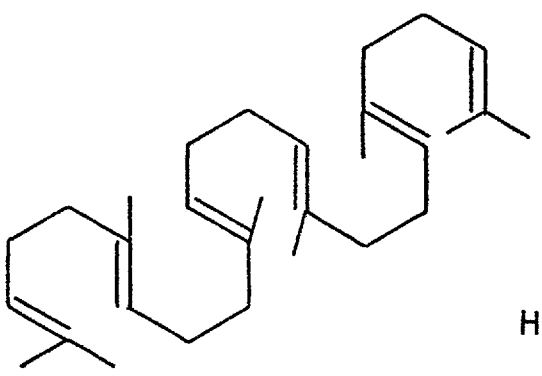
Contents

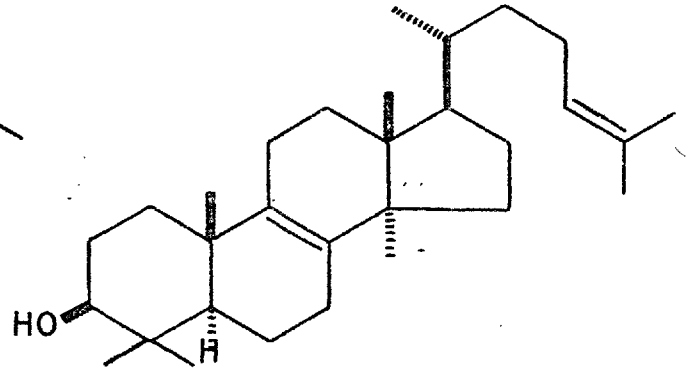
REVIEW.

Introduction.

Numerous investigations on the biosynthesis of terpenes and steroids have made it possible to rationalise their formation in terms of the coupling of isoprene units to form an acyclic precursor followed by structurally selective and stereospecific cyclisation. This well known 'Isoprene Rule' was formally proposed by Ruzicka[1] in 1953. Of particular interest was the demonstration by Bloch and Clayton that squalene (1), an acyclic polyisoprene containing no centres of asymmetry, was converted in mammalian tissue to cholesterol[2] via lanosterol (2)[3,4], a tetracyclic compound containing seven asymmetric centres. Squalene has also been shown to be the biological precursor of other polycyclic triterpenes e.g. β-amyrin[5], tetrahymanol[6].



(1)

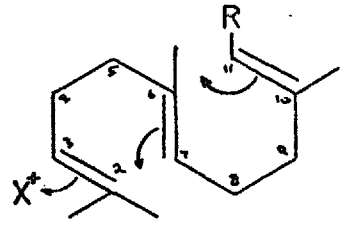


(2)

These cyclisations, which in vivo are under enzymic control, may be simulated by the cyclisation of polyolefins by the action of acids and other cationic initiators. A study of these model reactions provides an insight into the precise role of the enzyme. One view is that the enzyme plays an all important role, acting as a template to hold the substrate in the correct conformation for cyclisation. On the other hand there is much evidence that squalene-like molecules have an intrinsic susceptibility to cyclise stereospecifically to give

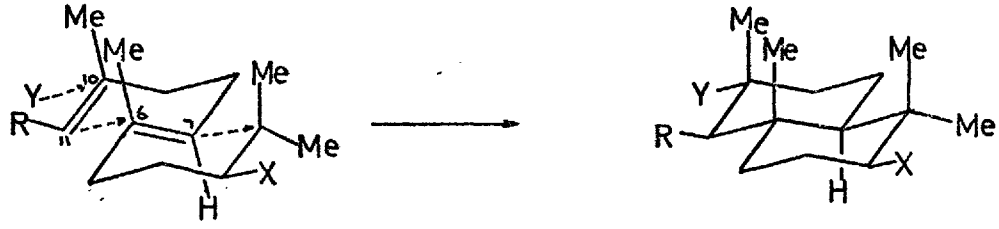
a product having the 'natural' configuration.[7] The true situation is somewhere between these extremes, as enzyme action is necessary to ensure essentially quantitative yields of fully cyclised products and to block other reactions leading to uncyclised and partially cyclised byproducts.[8]

In 1955 Stork[9] and Eschenmoser[10] independently set forth the hypothesis that the observed stereochemistry of polycyclic natural products could be rationalised in terms of concerted cyclisations of the corresponding acyclic polyenes.



(3)

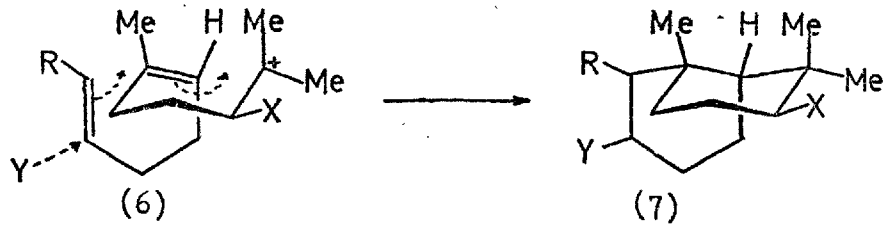
In the triisoprene unit (3) cyclisation is initiated by the generation of a carbonium ion at C-2. If the electrophilic attack on the 6,7-trans double bond is synchronous with nucleophilic attack by the 10,11 bond the resulting bicyclic system (5) will have a trans fused ring junction, i.e:-



(4) (5)

If Y represents a double bond on the side chain R the cyclisation continues.

A corollary to the Stork-Eschenmoser hypothesis is that if the 6,7 double bond has cis geometry as in (6) then the product (7) will have a cis fused ring junction[7].



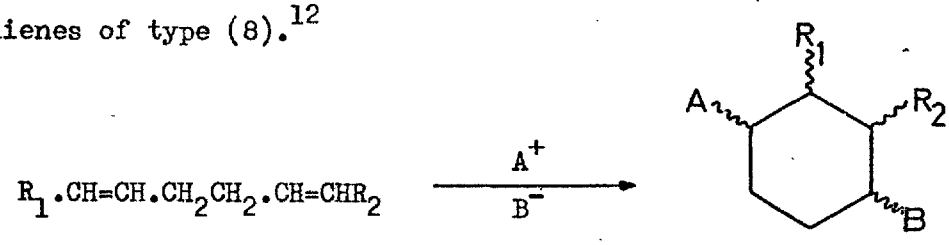
(6) (7)

Cyclisations Initiated by the Addition of a Cation to a Terminal Double Bond.

In the historical developement of the subject the first cyclisations studied were initiated by the addition of a proton to the terminal double bond. Subsequently a wide range of cationic initiators have been used e.g. Lewis acids (boron trifluoride), cation exchange resins, carbonium ions (RCO^+, $CH_3OCH_2^+$), I^+, Br^+ and mercury salts. These examples will be described in the text. All these initiators are considered in one section as the course of cyclisation is often independent of the initiating cation.

a. Monocyclic Systems.

The main requirements for in vivo cyclisations and their non-enzymic analogues are the conformation of the cyclising molecule and antiplanar addition to each double bond.[11,12] These then define both the relative configuration and the primary conformation of the cyclised molecule as shown by Table I, drawn up by Eschenmoser for dienes of type (8).[12]



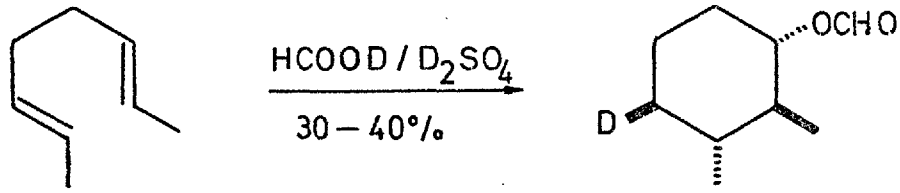
(8) (9)

Configuration of Double Bonds in (8)	Relative Configuration of Substituents in (9)	
	Via Chair type folding	Via Boat type folding
trans,trans	trans,trans,trans	trans,cis,trans
cis,trans	cis,cis,trans	cis,trans,trans
trans,cis	trans,cis,cis	trans,trans,cis
cis,cis	cis,trans,cis	cis,cis,cis

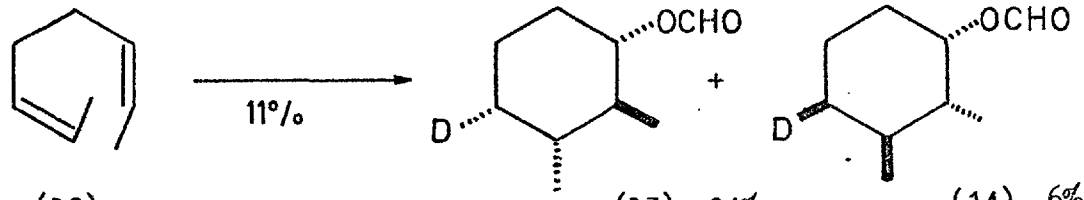
Table I

The stereospecificity of these reactions implies either a fully concerted mechanism or a stepwise reaction proceeding by the formation of cationic intermediates (e.g. bridged carbonium ions) in which the rate of attack by the next double bond is faster than conformational inversion or attack by an external nucleophile. The latter mechanism is the more reasonable in view of the high yields of polycyclic material obtained by Johnson[7] and the statistical improbability of obtaining a polyene folded in the correct conformation.

Trans,trans-2,6-octadiene (10) and its cis,cis isomer (12) were cyclised in a deuterated medium.[13]



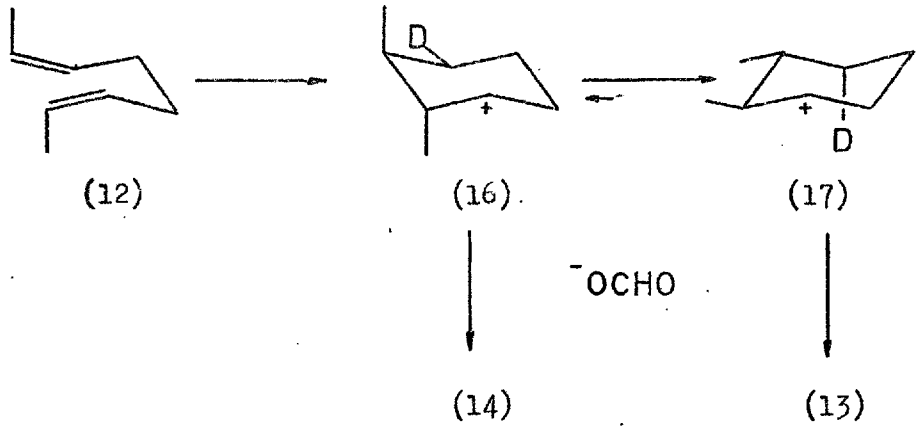
(10) (11), 100%



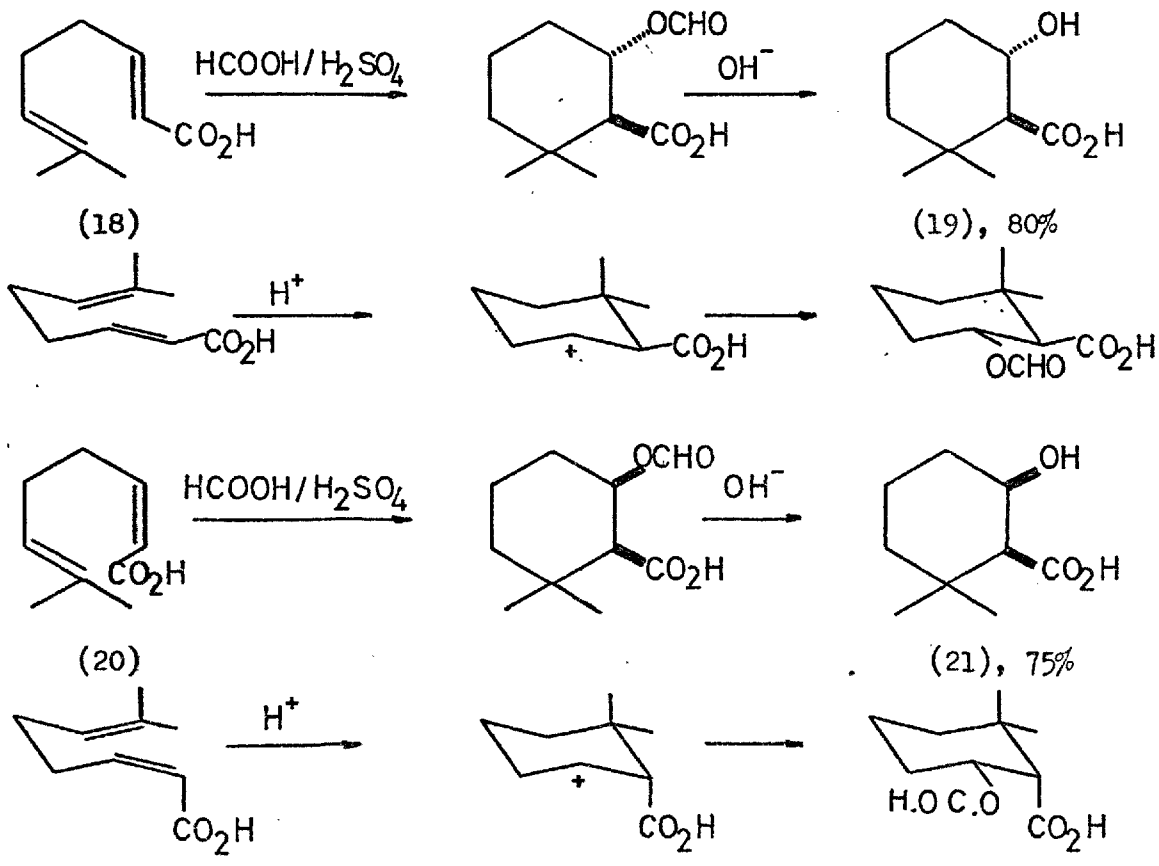
(12) (13), 94% (14), 6%

These results suggest that protonation and ring closure are synchronous giving the cyclohexyl carbonium ions (15) and (16). Equatorial attack of formate ion on the conformationally stable (15) gives the product (11). (16) however inverts to the more stable conformer (17) much faster than attack by formate ion, giving (13) as the major product. The minor product (14) is obtained by attack by formate ion on (16).

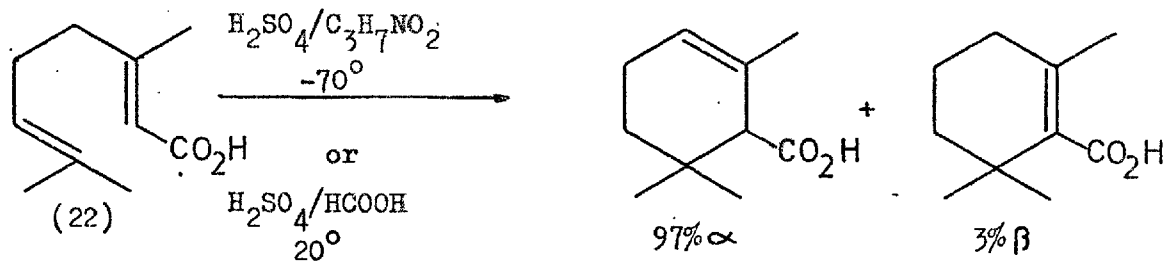
(10) (15)



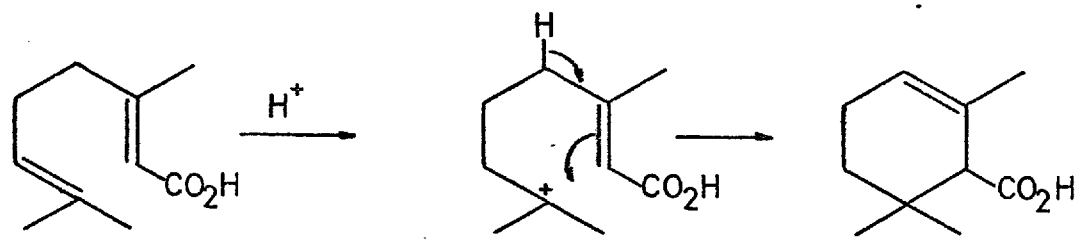
In the cyclisation of the isomeric 7-methyl-2,6-octadienoic acids (apogeranic acids) by a mixture of formic and sulphuric acids Schinz[14-16] demonstrated that the trans isomer (18) gave the trans-hydroxyacid (19) after saponification of the formate ester and the cis isomer (20) gave the cis-hydroxyacid (21). These results are consistent with cyclisation via an intermediate cyclohexyl carbonium ion in the chair conformation.



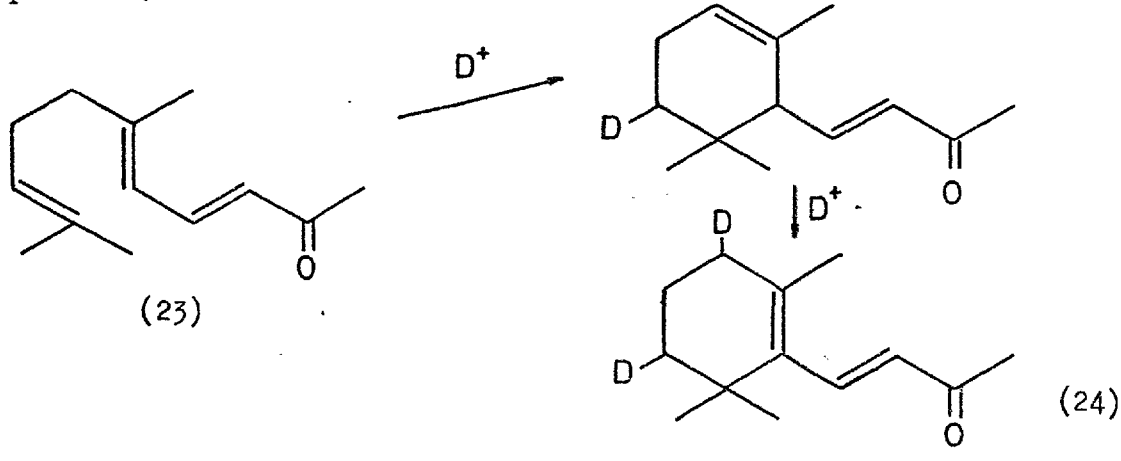
In systems with a methyl group in the β position of the second double bond cyclisation results in unsaturated products. Numerous examples of this type, in which the second double bond is conjugated, have been reported.[17-25] For instance geranic acid (22) was cyclised to a mixture of α- and β-monocyclogeranic acids.



It has been shown that in these cyclisations the initially formed product has the double bond in the α position.[20,24] This may isomerise under the reaction conditions to give the double bond in the β position which being both tetrasubstituted and conjugated is more stable. The elimination of the proton to give the α orientated double bond compensates to some extent for the low nucleophilicity of the conjugated double bond and facilitates its participation in ring closure :-

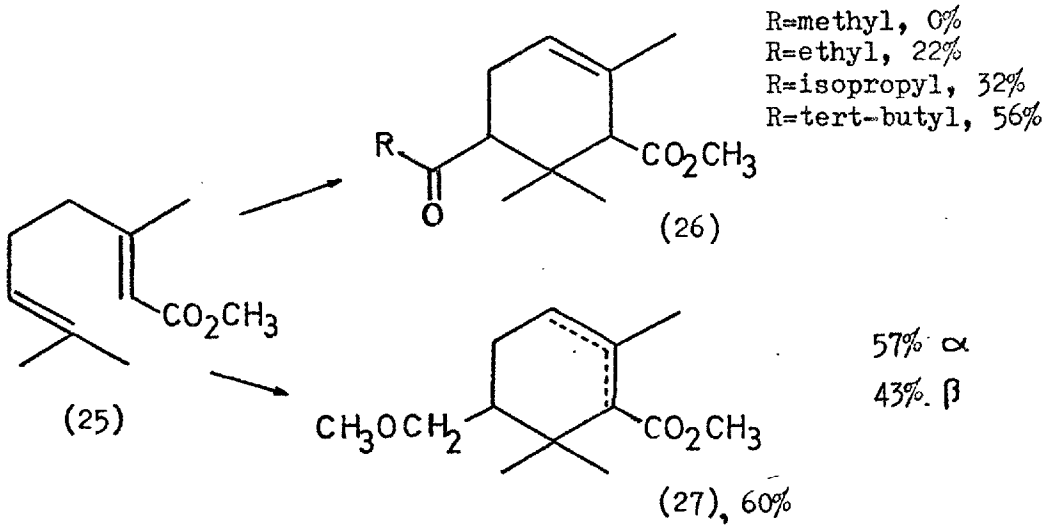


This view was supported by work of De Boer.[26] When the cyclisation of pseudoionone (23) was carried out in deuterosulphuric acid, deuterium was incorporated in β-ionone (24) in the allylic position.

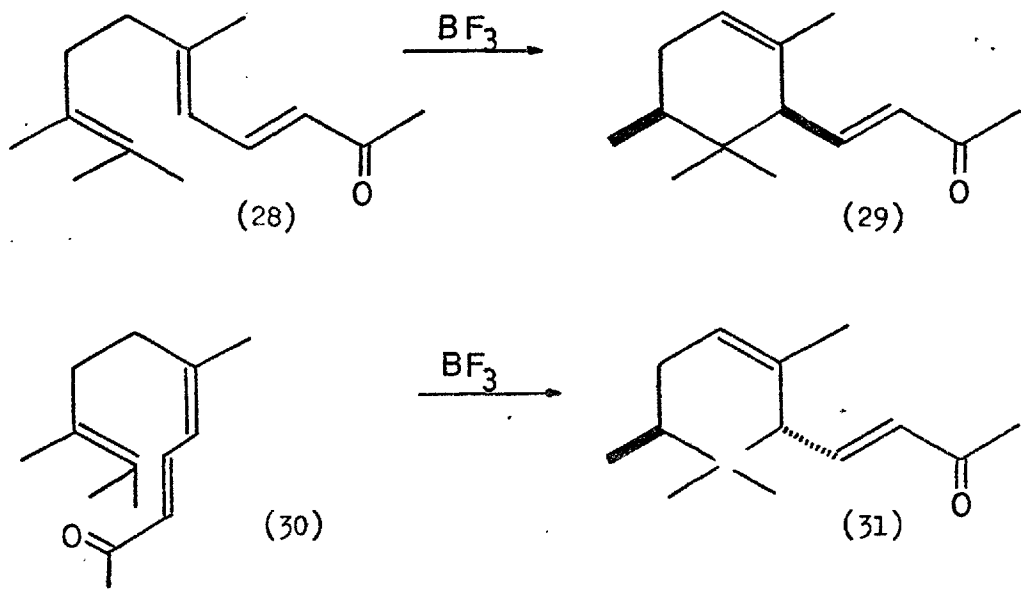


These cyclisations have also been initiated by other cations. Treatment of geranic acid (22) with Amberlite IR-120 cation exchange resin gave ∝-cyclogeranic acid in 70% yield.[27] Methyl geranate has been cyclised by iodine.[28]

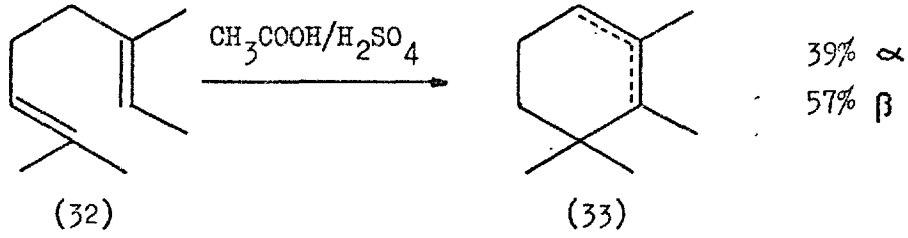
Stable carbonium ions are good cyclisation initiators and the yield of cyclised product increases with the stability of the initiating carbonium ion. Thus methyl geranate (25) on treatment with RCO^+ ($RCOCl/AgBF_4$) gave yields of cyclic products (26) varying from 0% (R=methyl) to 56% (R=tert-butyl)[29]. The methoxymethyl carbonium ion ($CH_3OCH_2Cl/AgBF_4$) also gave good yields of cyclic products (27).[29]



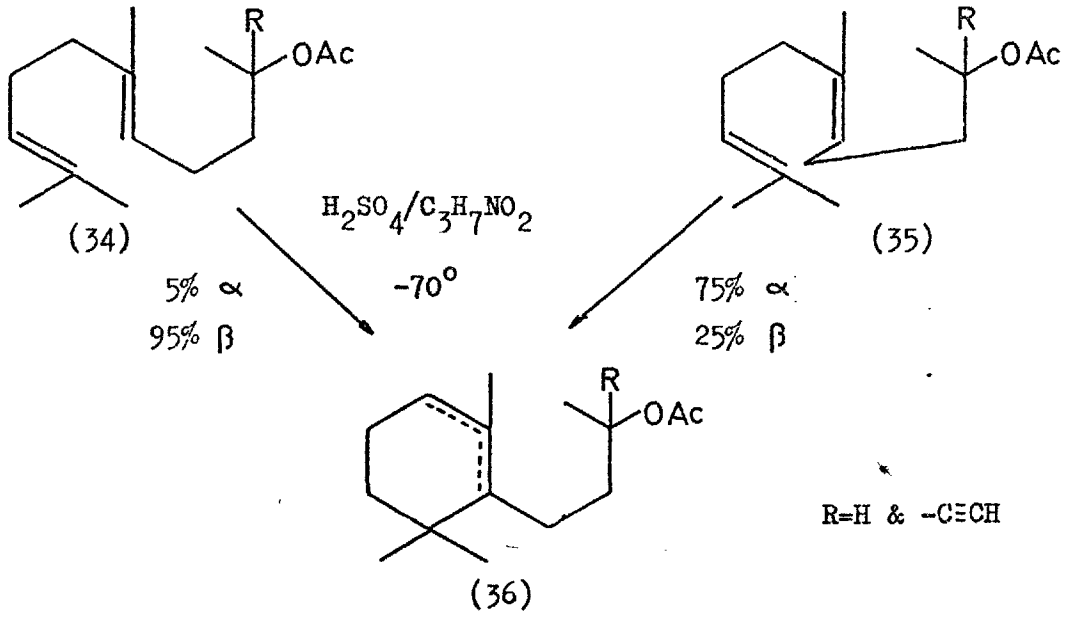
The pseudoirones (28) and (30) have been cyclised with boron trifluoride.[30]



Smit and Semenovskii have observed that when the second double bond is not conjugated the cyclisations proceed much faster. Also if the double bond is trans the product is predominantly β and if cis the product is initially ∝ although rapid isomerisation usually occurs giving the β form, e.g.[20,31,32] :-

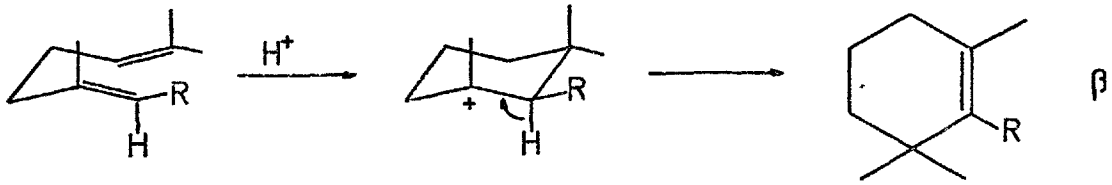


(32) (33)

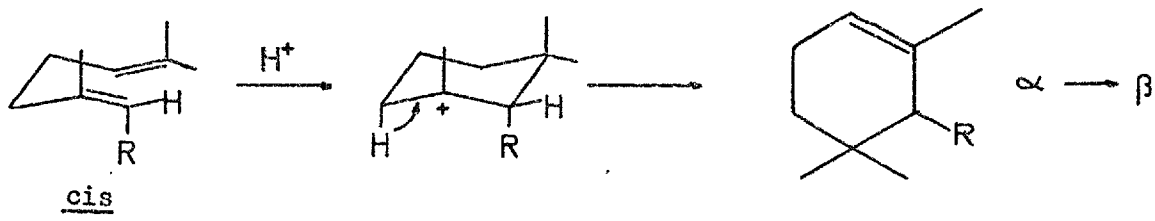


(34) (35) (36)

The greater nucleophilicity of the nonconjugated double bond accounts for the faster cyclisation and in these cases it appears that elimination of an allylic proton is not required as a driving force for ring closure. A cyclohexyl carbonium ion is formed which then eliminates the nearest axial proton to give the observed products :-



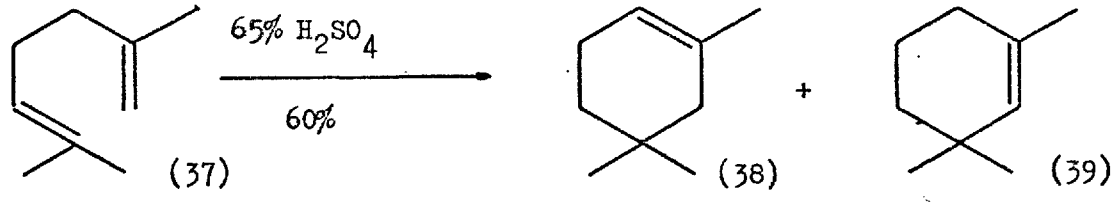
trans



cis

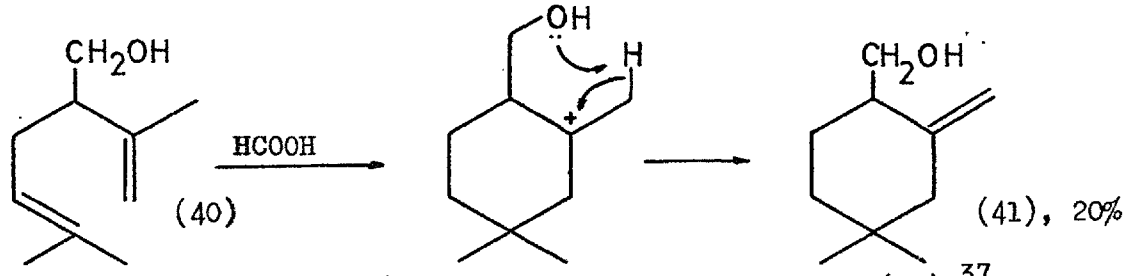
Three cyclisations are reported which do not conform to these observations. Geraniol[33], geranyl acetate[33] and geranyl methyl ether[34] all give α-cyclo products. A possible explanation of this is that the intermediate carbonium ion undergoes conformational inversion before elimination of a proton.

A number of cyclisations have been carried out on systems where the 1,5-diene has a geminal dimethyl group at one end but no substituents at the other. These follow essentially the same pattern as the substituted systems. Geraniolene (37) gave a mixture of α- and β-cyclogeraniolene.[35]



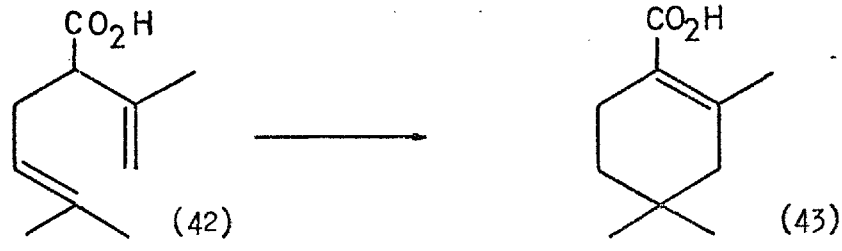
(37) (38) (39)

Lavandulol (40) cyclised to (41).[36] In this case anchimeric assistance in the collapse of the intermediate carbonium ion by the neighbouring hydroxymethyl group gives the exocyclic methylene.



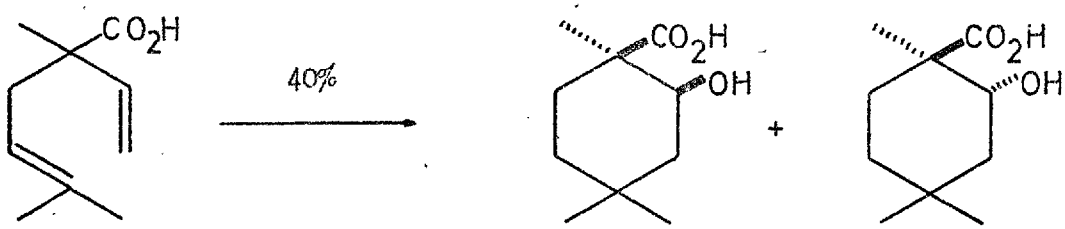
(40) (41), 20%

Lavandulic acid (42) gave β-cyclolavandulic acid (43).[37]



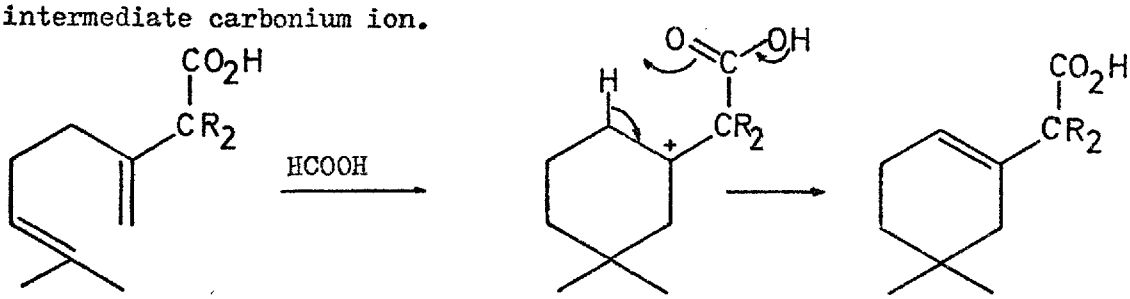
(42) (43)

Treatment of 3,6-dimethyl-3-carbohydroxyhepta-1,5-diene (44) with a formic-sulphuric acid mixture followed by alkaline hydrolysis gave a mixture of two epimeric hydroxyacids (45) and (46).[38]



(44) (45) (46)

Allogeranic acid (47)[39] and its dimethyl analogue (48)[40] cyclise to (49) in which the double bond is endocyclic rather than conjugated showing that anchimeric assistance controls the collapse of the intermediate carbonium ion.

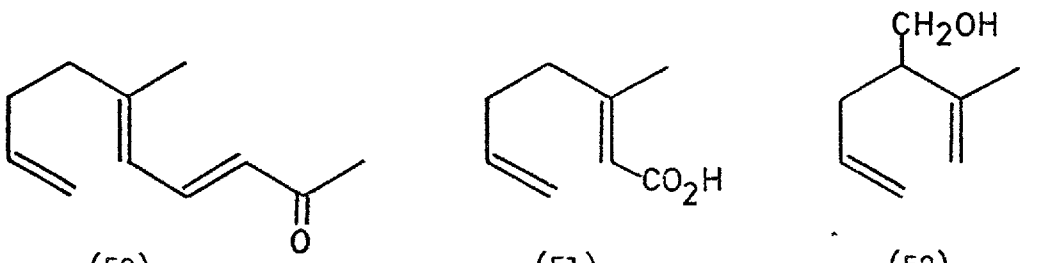


(47), R=H
(48), R=CH_3

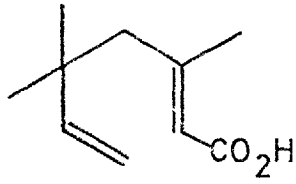
(49)

Schinz[41] showed that for analogues of geranic acid the substitution pattern was critical for cyclisation. Compounds without the lone methyl group do cyclise but less readily than geranic acid.
e.g. (18) ⟶ (19), (p. 6).

For compounds in which the geminal dimethyl group is entirely absent, formation of a five-membered ring would be theoretically possible but not that of a six-membered ring. However no cyclisation at all was observed in the dienes (50)-(54).



(50) (51) (52)



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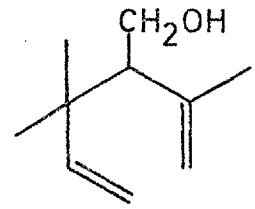
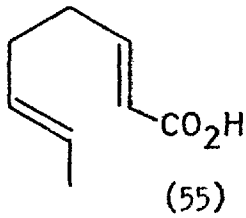


(54)

For compounds in which the geminal dimethyl group is replaced by a single methyl or ethyl group the formation of a six-membered ring cannot be excluded theoretically, but no cyclisation was observed in (55)-(57).



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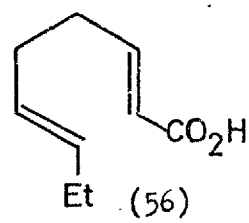

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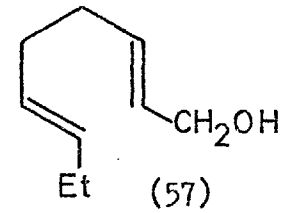
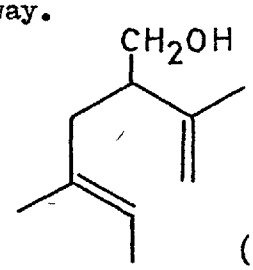


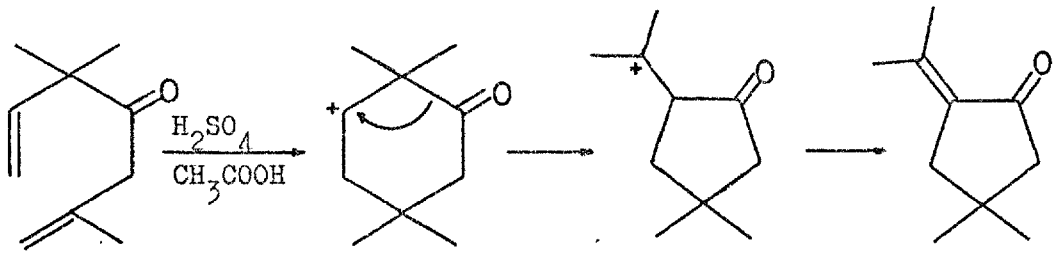
(57)

The poor nucleophilicity of these double bonds makes protonation more difficult and the poorly nucleophilic conjugated double bond is unable to assist protonation by a concerted attack (cf. reference 13). The failure of (58) to cyclise must be due entirely to the low tendency to form five membered rings as its isomer lavandulol (40) cyclises in the normal way.

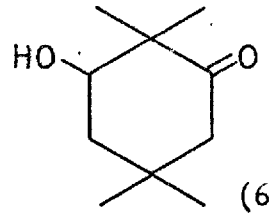


(58)

A few examples of cyclisation to five and seven membered rings have been reported. Eschenmoser[42] cyclised artemesiaketone (59) to (61) but showed that it was formed via an intermediate cyclohexyl carbonium ion (60). This mechanism was supported by the fact that the β-ketol (62) rearranges to (61) under the same conditions.

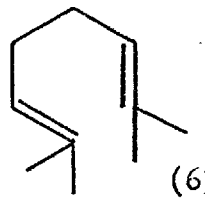


(59) (60) (61)



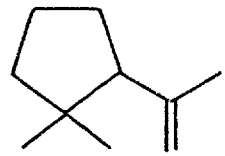
(62)

Stevens and Spalding[43] cyclised 2,7-dimethylocta-2,7-diene (63) to (64).



(63)

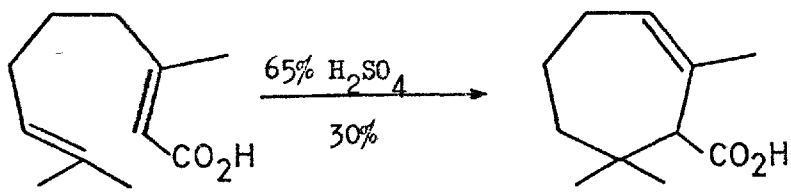
Phosphoric acid



(64)

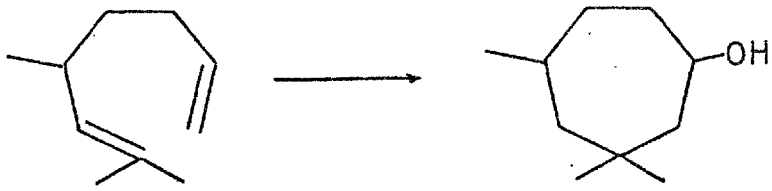
Two mechanisms are feasible for this reaction, either a Markownikov addition to give a cyclopentyl cation directly or a similar mechanism to the previous example via a cyclohexyl cation. No attempt was made to distinguish between these possible mechanisms.

3,8-Dimethyl-2,7-nonadienoic acid (65) was cyclised to the cycloheptenecarboxylic acid (66)[44], but the reaction was much slower and gave a lower yield than in the analogous cyclohexyl case (i.e. geranic acid ⟶ ∝-cyclogeranic acid).



(65) (66)

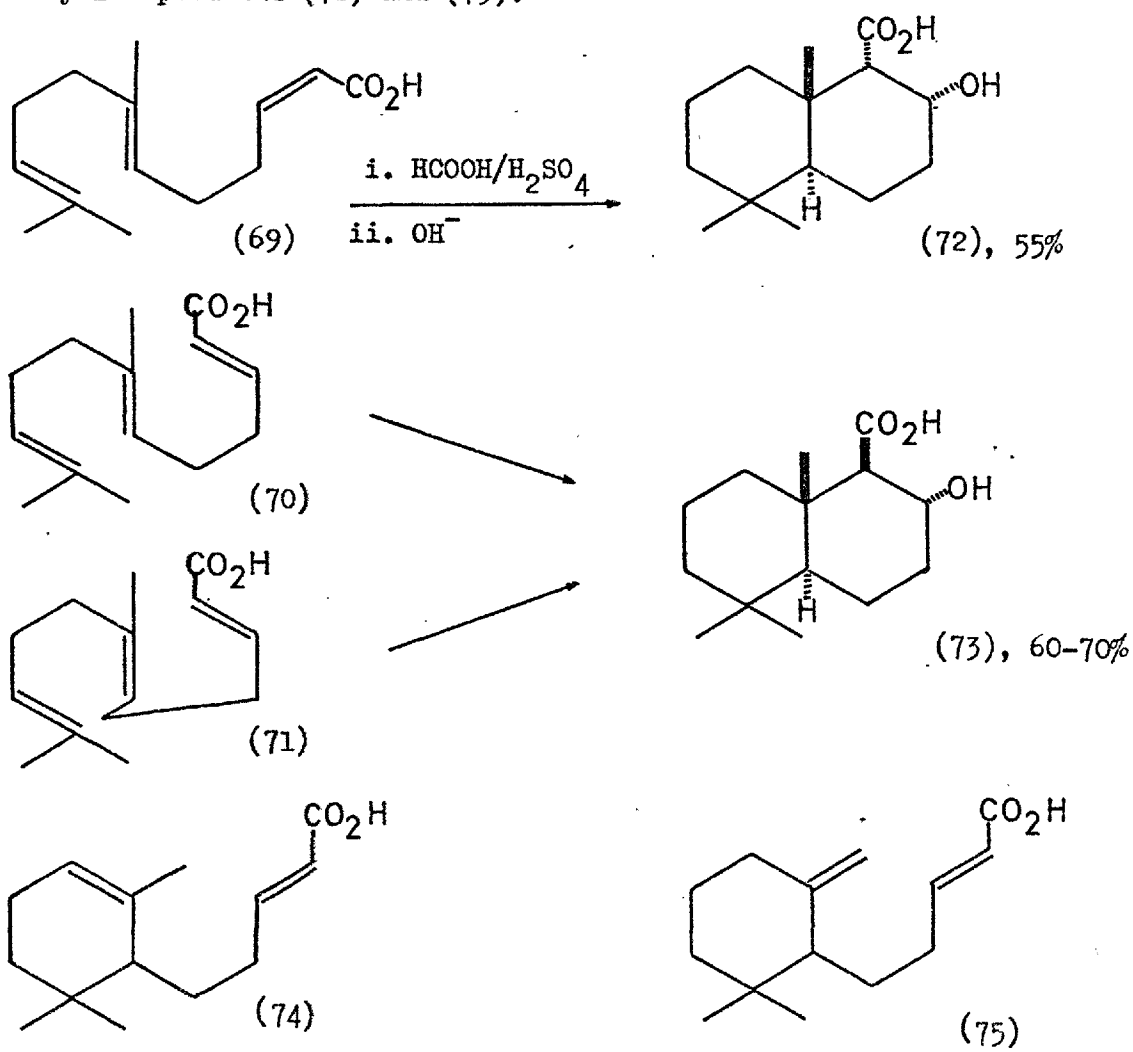
5,7-Dimethyl-1,6-octadiene (67) in a boron trifluoride-formic acid mixture gave after hydrolysis the cycloheptanol (68).[45]



(67) (68)

b. Bicyclic and Tricyclic Systems.

Treatment of the isomeric desmethylfarnesic acids (69), (70) and (71) with a formic-sulphuric acid mixture gave good yields of the bicyclic products (72) and (73).[11,12]



(69) (72), 55%

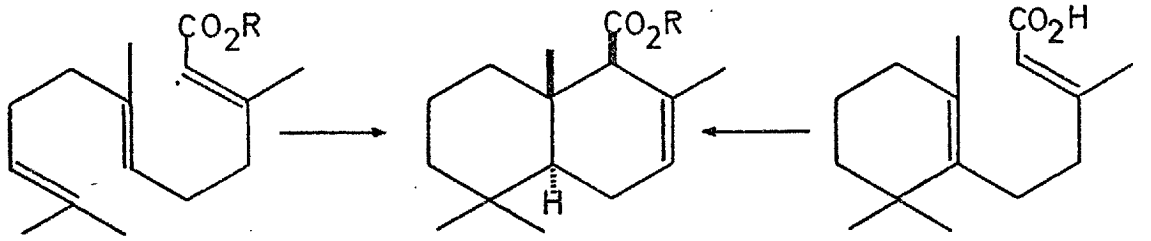
(70)

(71)

(73), 60-70%

(74) (75)

The formation of the same trans-decalin derivative (73) from both the cis- and trans-6,7 double bond isomers shows that the cyclisation is not a concerted process with respect to this double bond. Moreover the cyclisation of the monocyclic isomers (74) and (75) to (73) indicates that a discrete monocyclic intermediate is involved.[11] A similar result was observed in the cyclisation of farnesic acid (76).[46,47]



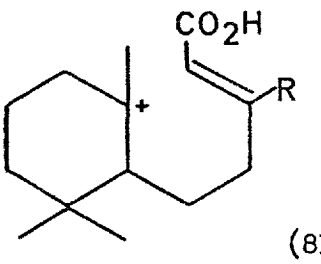
(76), R=H
(78), C_2H_5

(77), R=H
(79), R=C_2H_5

(80)

Ethyl farnesate (78) and its cis-6,7 double bond isomer were both cyclised to the trans-octalin (79) by sulphuric acid at -70°.[48]

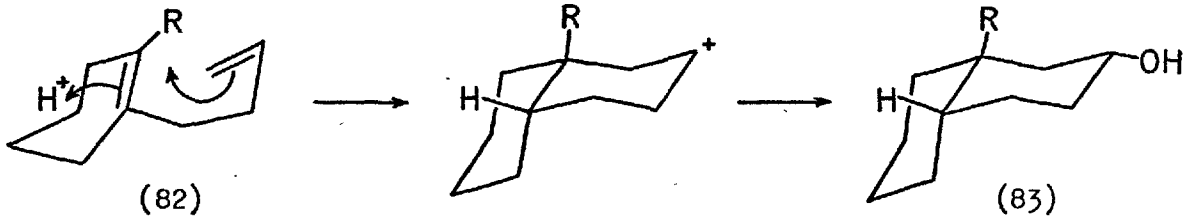
Controlled cyclisation of farnesic acid by boron trifluoride below 5°[9] and by Amberlite IR-120 cation exchange resin[27] gave the isolable monocyclic product (80), which was further cyclised to (77) under more vigorous conditions.[9] Although this points to a two stage process via a monocyclic intermediate, it cannot be via (80) since Caliezi and Schinz[49] showed that farnesic acid (76) cyclised to (77) much faster than the monocyclic isomer (80). The explanation for these observations, put forward by Johnson[50], is that the double bond conjugated to the carbonyl group is such a poor nucleophile that it does not react synchronously and the initial product of cyclisation is the carbonium ion (81).



(81), R=H & CH_3

Depending on the conditions (81) either collapses to a monocyclic diene or attack by the second double bond in an equatorial manner gives the thermodynamically more stable trans-bicyclic product.

A concerted antiplanar addition to the monocyclic olefin would give the cis-bicyclic product. A reaction of this type was observed by Linstead. Cyclisation of the butenylcyclohexenes (82) gave the cis-decalols (83)[51,52] but none of the isomeric trans-decalols.[50]

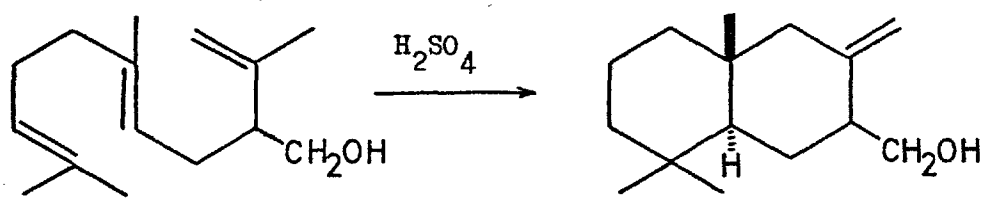


(82) (83)

R=H or CH_3

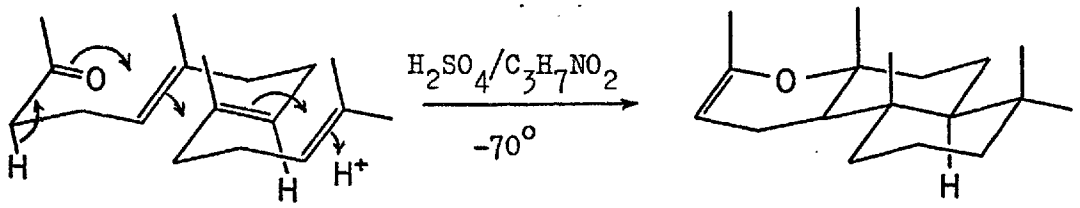
Farnesal[53], farnesylideneacetone[54] and farnesylidenemethyl isopropyl ketone[55], in which the 10,11-double bond is conjugated and methyl substituted also cyclised to α-bicyclo products with trans ring fusion.

Cyclisations have been effected in systems in which the 10,11-double bond is nonconjugated e.g. sesquilavandulol (84)[56] and sesquilavandulic acid[57] but no attempt has been made to determine whether or not a concerted mechanism obtains.

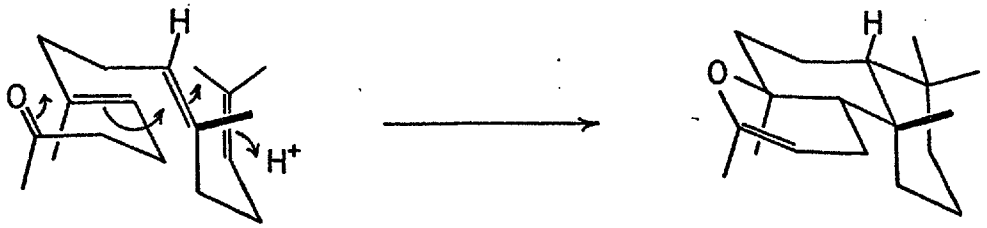


(84) (85)

The cyclisation of farnesylacetone[58] was shown to occur in a stereospecific manner as the trans,trans isomer (86) gave the trans,anti,trans tricyclic product (87) and the cis,trans isomer (88) gave cis,syn,cis (89).

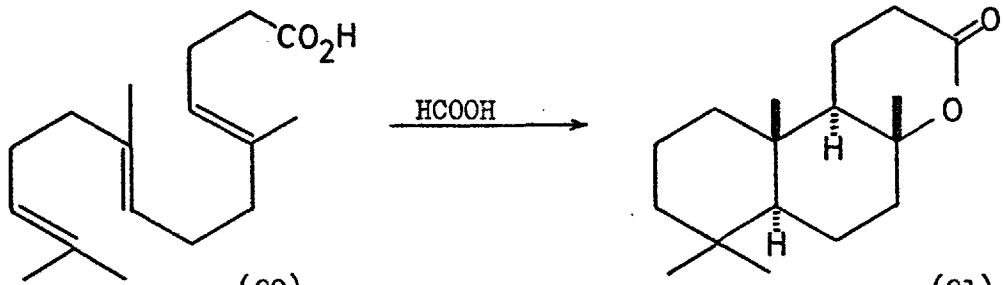


(86) (87)



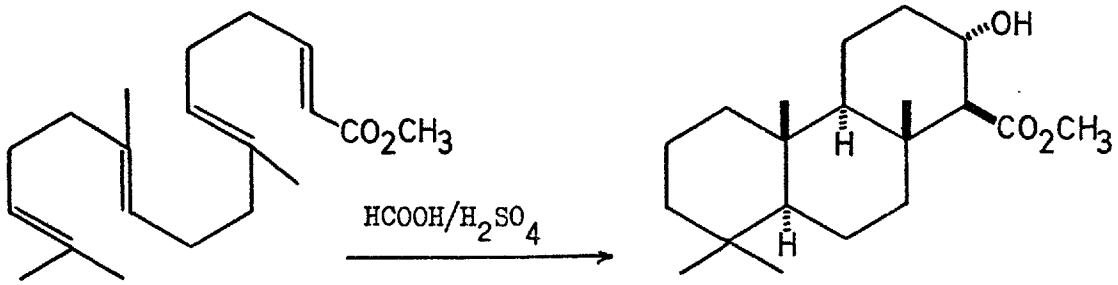
(88) (89)

Similarly farnesylacetic acid (90) gave (±)-ambreinolide (91).[59]

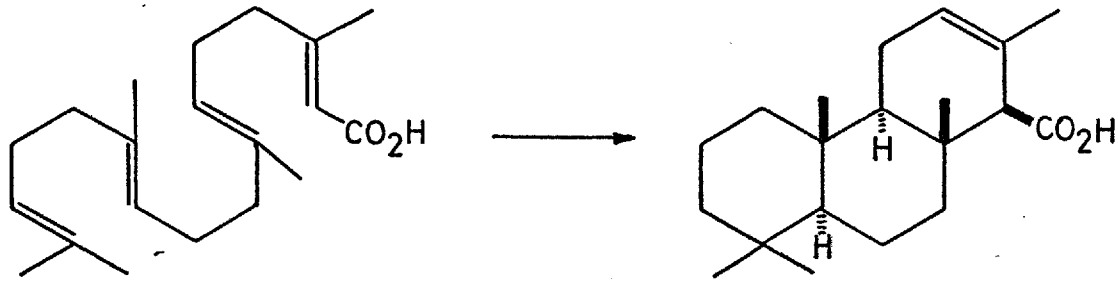


(90) (91)

The acid catalysed cyclisation of the tetraenic ester (92)[11] and acid (94)[55] have been reported, giving the trans,anti,trans cyclic products (93) and (95).



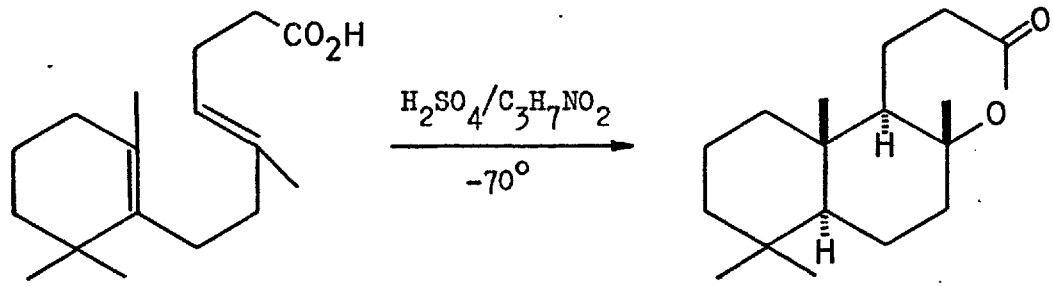
(92) (93)



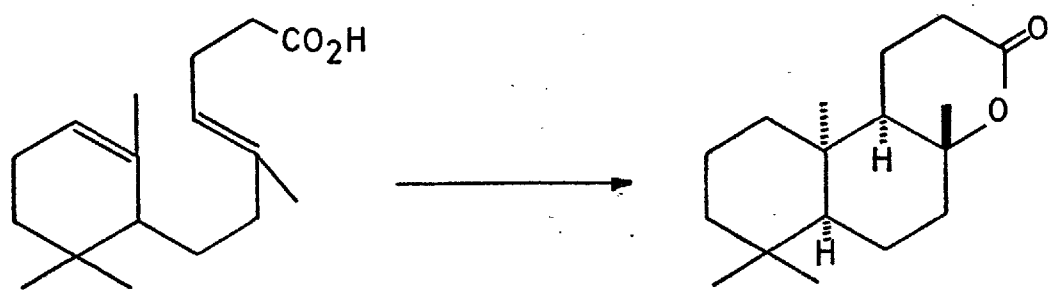
(94) (95)

The yields of tricyclic material were low (5-10%) and Eschenmoser concluded that in polyenes of this complexity, acid catalysed cyclisation ceases to be a useful reaction from the preparative point of view.[11]

A concerted mechanism for the cyclisation of the isomeric monocyclofarnesylacetic acids (96) and (97)[60] can be ruled out on the basis of the unusual stereochemistry observed.

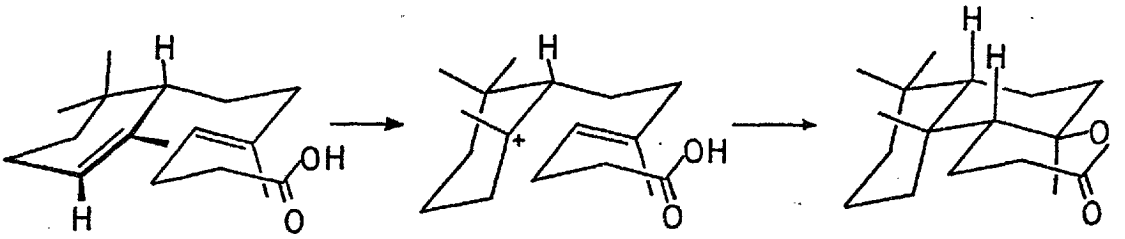


(96) (91), trans,anti,trans.



(97) (98), cis,syn,trans.

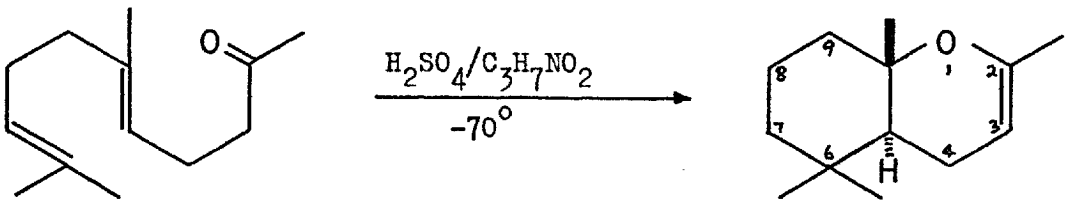
The product from the ∝-isomer can be explained in terms of the concept of Allylic Strain Interaction.[61] Due to this strain the most likely conformation for (97) is (99) with a pseudoaxial side chain. Protonation gives the cyclohexyl carbonium ion with an axial side chain which undergoes ring closure faster than inversion to the more stable conformer.



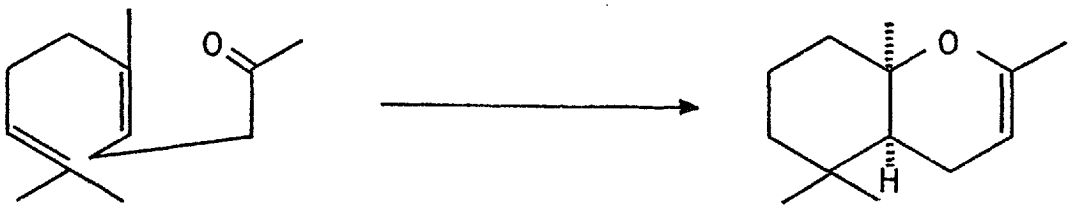
(99) (100)

Protonation of the β-isomer (96) gives a conformationally stable cyclohexyl carbonium ion which undergoes ring closure to the thermodynamically more stable trans-fused product (91). The same stereochemical behaviour was observed in the cyclisations of trans- and cis-monocyclofarnesylacetones[62,63] and the monocyclogeranylacetones[64].

The isomeric geranylacetones (101) and (103) gave the bicyclic ethers (102) and (104).[65] The stereochemistry of the products show the reaction to be antiplanar about the 6,7-double bond. A similar result was obtained with the isomers of geranylacetic acid giving bicyclic lactones.[66,67]

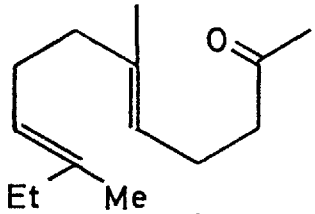


(101) (102)

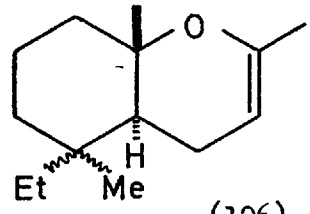


(103) (104)

In these cases ring closure is not concerted with protonation but goes via an intermediate tertiary carbonium ion. This is clear from the fact that when (101) is cyclised with deuterosulphuric acid, deuterium is incorporated at C-7 of the product in both the axial and equatorial positions.[68] Furthermore, cyclisation of the monoethyl analogue (105) of geranylacetone occured stereospecifically at the central double bond but gave a mixture of C-6 epimers.[69]



(105)

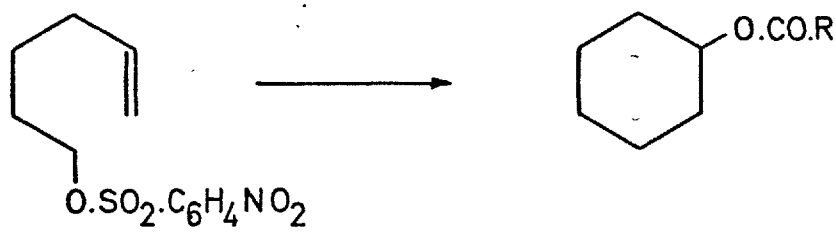


(106)

The stereospecific bicyclisation of geranylacetone has also been induced by other cations e.g. CH_3CO^+, $PhCO^+$, $CH_3OCH_2^+$,[70] mercuric nitrate and trifluoroacetate.[71]

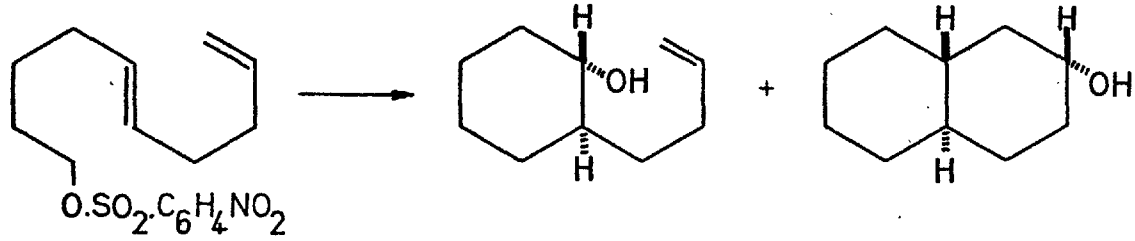
Cyclisation of Olefinic Sulphonate Esters.

With the aim of obviating the difficulties in acid catalysed cyclisations of polyolefinic compounds, Johnson has explored a number of other methods of initiation designed to define unequivocally the initial cationic centre. The first of these was based on the observation that the cyclohexyl esters (108) were obtained in up to 68% yield in the acetolysis[72] and formolysis[73] of 5-hexenyl p-nitrobenzenesulphonate (107).



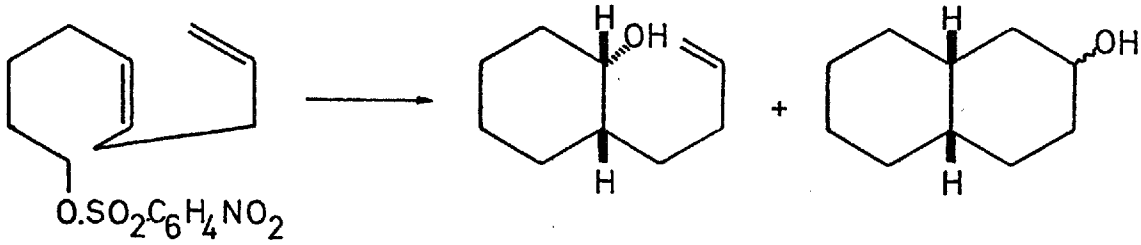
(107) (108), R=H, CH_3

Johnson extended this reaction to produce bicyclic and tricyclic systems. Formolysis of trans-5,9-decadienyl p-nitrobenzenesulphonate (109)[73] gave, after hydrolysis, the monocyclic trans-alcohol (110) (35%) and trans-bicyclic material (12%), the major product of which was (111). None of the corresponding cis products were found.



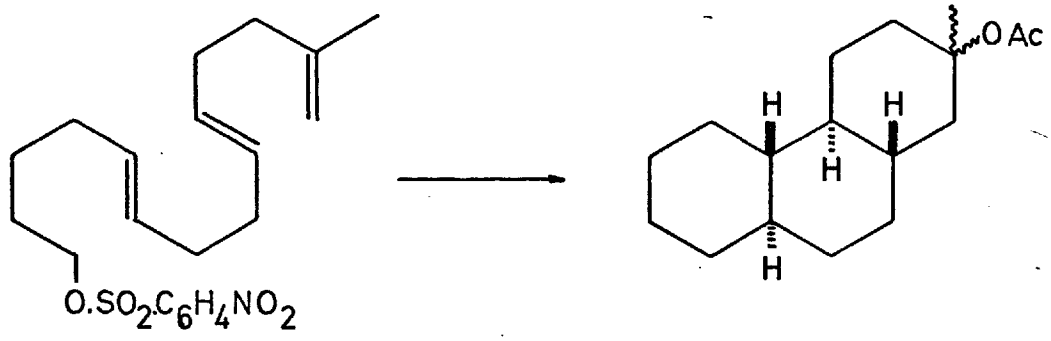
(109) (110) (111)

Similarly the cis isomer (112) gave the cis-monocyclic alcohol (113), (38%) and bicyclic material (16%) which was mainly a mixture of the epimeric cis-2-decalols (114).[74]



(112) (113) (114)

The trienyl sulphonate (115) cyclised to the tricyclic ester (116) but in only 2·8% yield.[75]



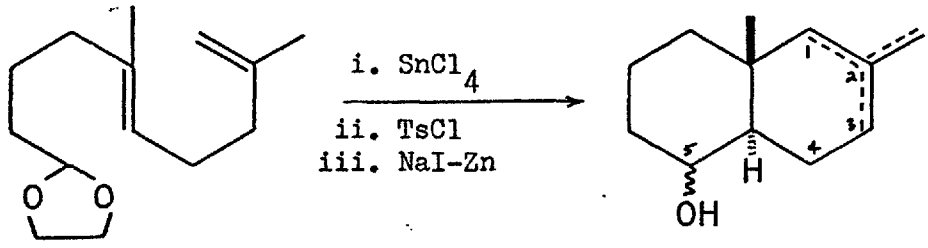
(115) (116)

Although the yields of polycyclic material are low these cyclisations are stereospecific, indicating a fully concerted mechanism. However Johnson, on kinetic evidence, favours the intermediacy of the nonclassical bridged carbonium ions (117) and (118).[76]

(117) (118)

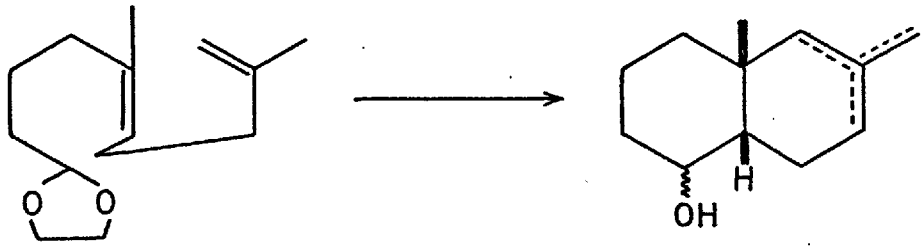
Cyclisation of Olefinic Acetals.

The treatment of polyolefinic ethyleneacetals with stannic chloride in benzene was found by Johnson to give polycyclic products in good yield. A 91% yield of trans-bicyclic products was obtained from the trans-dienic acetal (119).[77]



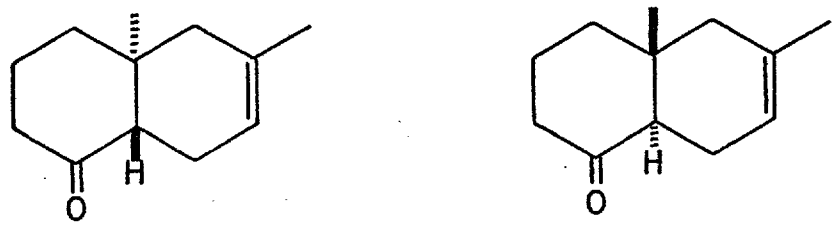
(119) (120), 91%

The predominant product (60%) was the 5β-OH, Δ^2 isomer of (120). When nitromethane was used as solvent this isomer was obtained in over 80% yield.[76] The cis-dienic acetal (121) also underwent cyclisation to give bicyclic products with cis ring fusion.[77]



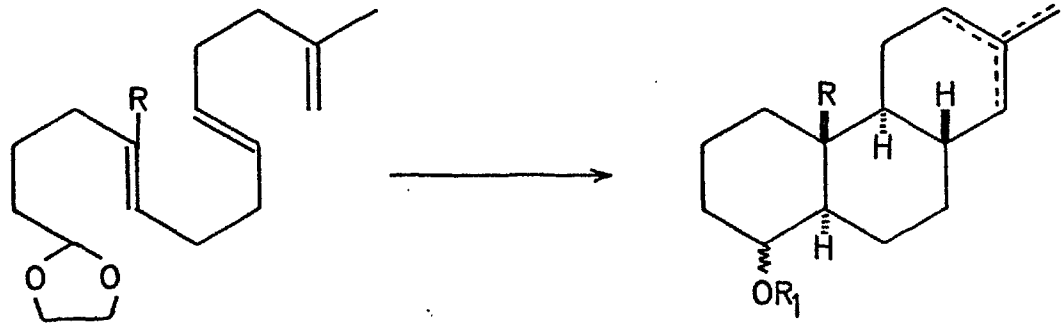
(121) (122), 88%

The optically active acetal of (119) from l-2,3-butandiol cyclised with a high degree of asymmetric induction to give, after oxidation, a product containing the enantiomeric ketones (123) and (124) in the ratio 92:8.[78]



(123), 92% (124), 8%

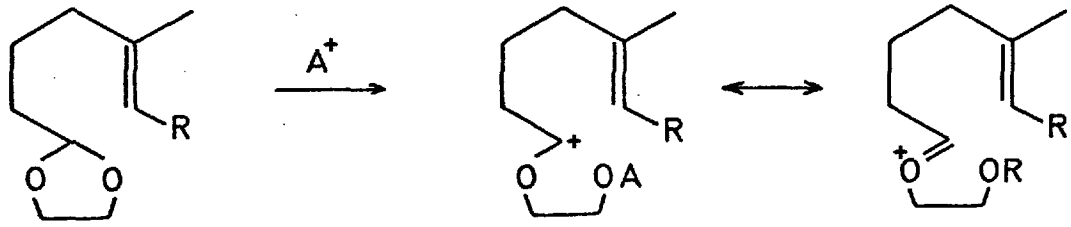
The trienic acetals (125) and (126) gave stereospecifically the trans,anti,trans tricyclic products (127) and (128).[7,75] In the latter case the faster reaction and higher yield reflect the greater nucleophilicity of the 5,6-double bond.



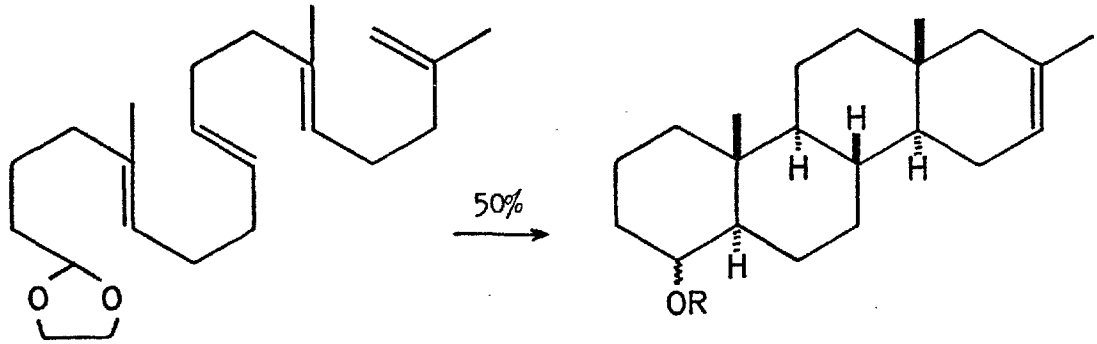
(125), R=H
(126), R=CH_3

(127), R=H
(128), R=CH_3

The high yields of polycyclic products are probably a result of both the stability of the initiating cation and the minimum of side reactions.



Moreover the high degree of stereoselectivity accords with the Stork-Eschenmoser hypothesis.[9,10] Even when the reaction is extended to the tetraenic acetal (129) a high yield of tetracyclic material (130) is obtained.[79]



(129)

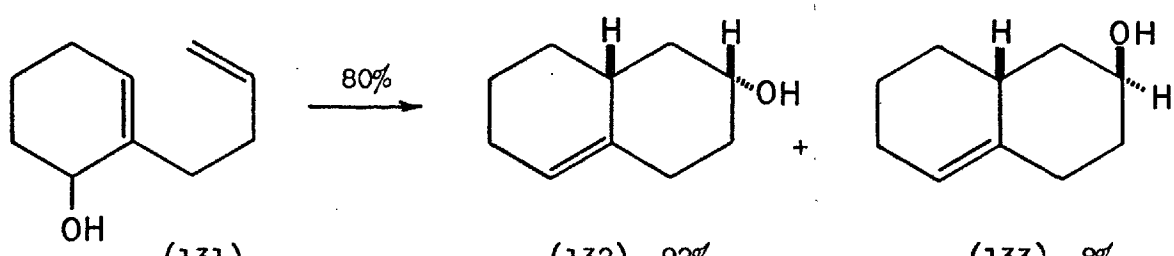
(130)

The kinetics of these reactions are quite different to those of the sulphonate solvolysis cyclisations and Johnson favoured a mechanism involving intermediate monocyclic carbonium ions which maintain their stereochemical integrity.[76]

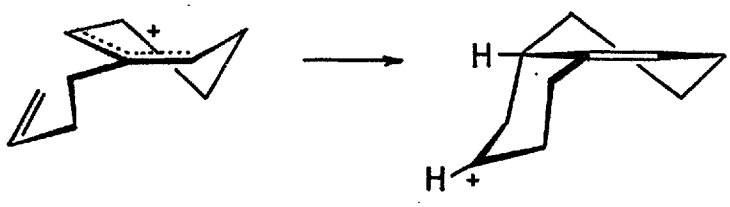
Cyclisation of Allyl Alcohols.

Another stabilised cation which is a good initiator of cyclisation is the allyl carbonium ion.

The butenylcyclohexenol (131) reacted rapidly with cold formic acid to give the octalols (132) and (133).[80] The mechanism involves the rapid formation of the allylic carbonium ion (134) which cyclises to (135). Preferential equatorial attack by solvent gives the observed product.

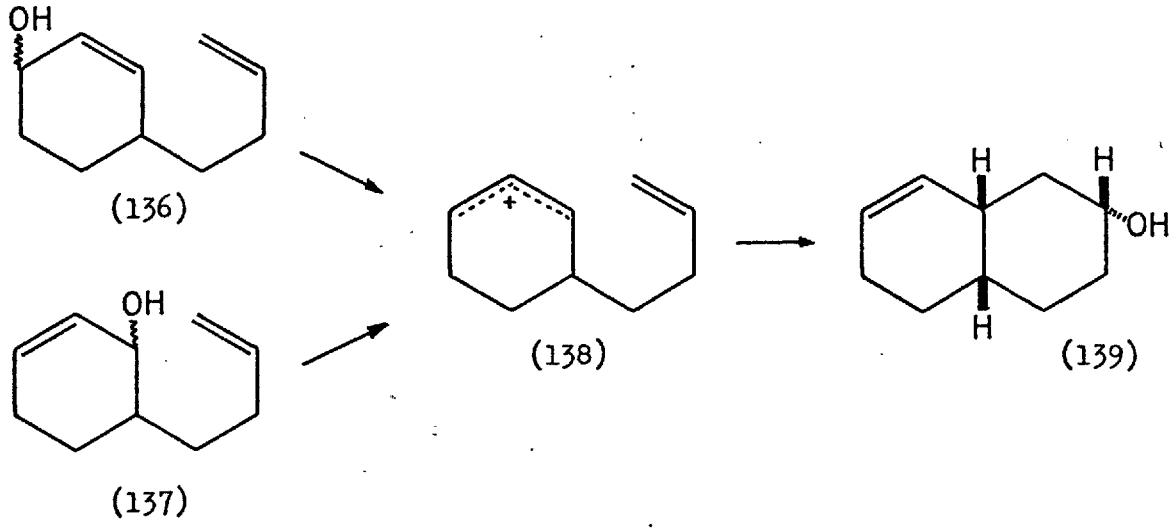


(131) (132), 92% (133), 8%

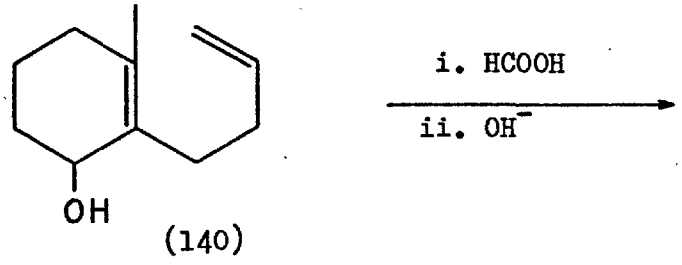


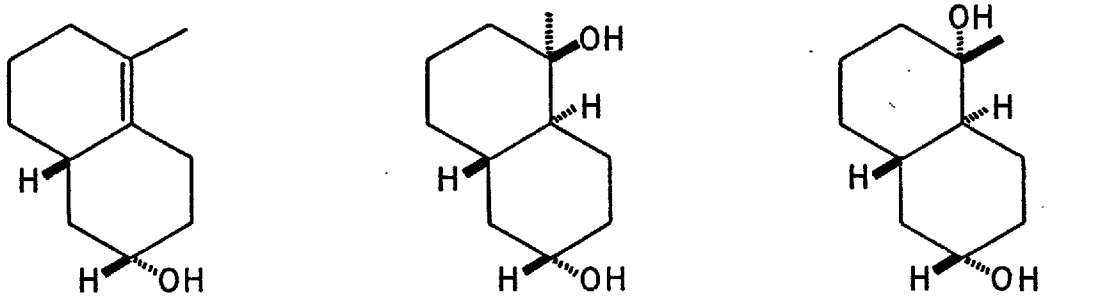
(134) (135)

Evidence to support this mechanism was obtained when the butenylcyclohexenols (136) and (137) both cyclised via the allylic carbonium ion (138) to give (139) as the major product.[80,81]

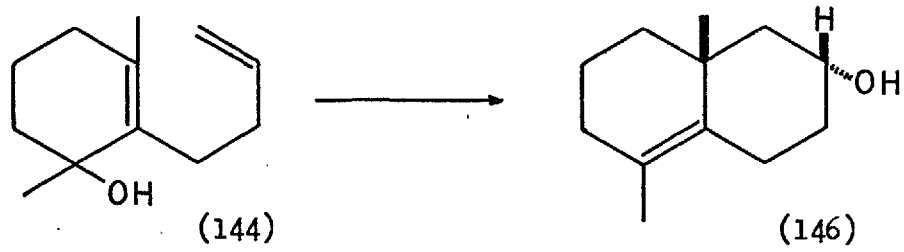


When the butenylmethylcyclohexenol (140) was cyclised none of the products had an angular methyl group, again favouring an allylic carbonium ion mechanism. In this case ring closure occurs at the least hindered site of the cation.[82]

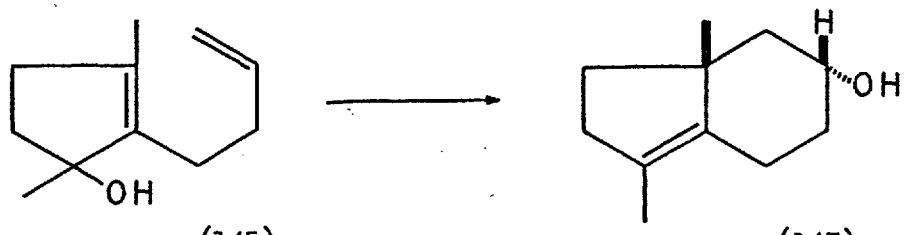




In the dimethyl analogues (144) and (145) cyclisation gave products with an angular methyl group.[83,84]

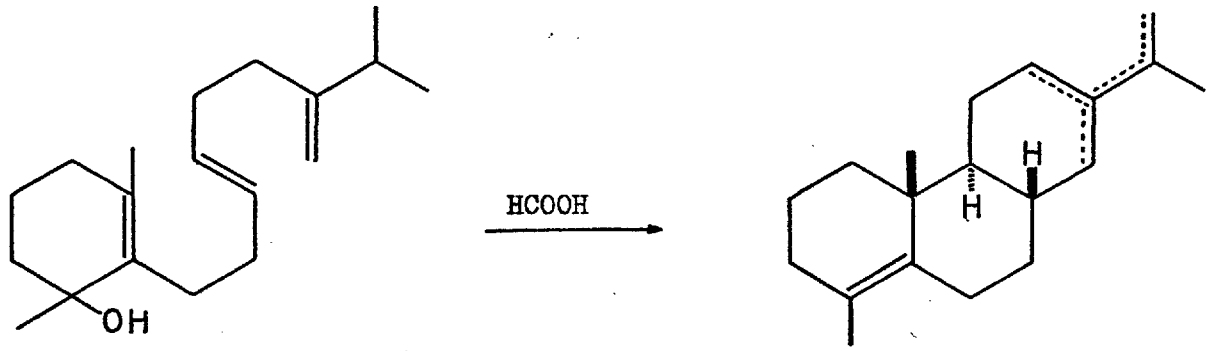


(144) (146)



(145) (147)

This method of initiation gives excellent yields of polycyclic material. For example, an essentially quantitative yield of tricyclic material was obtained from (148).[85]



(148) (149), 67%

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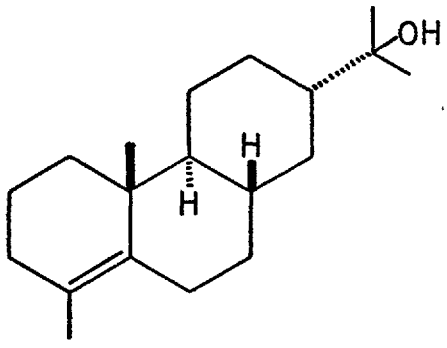
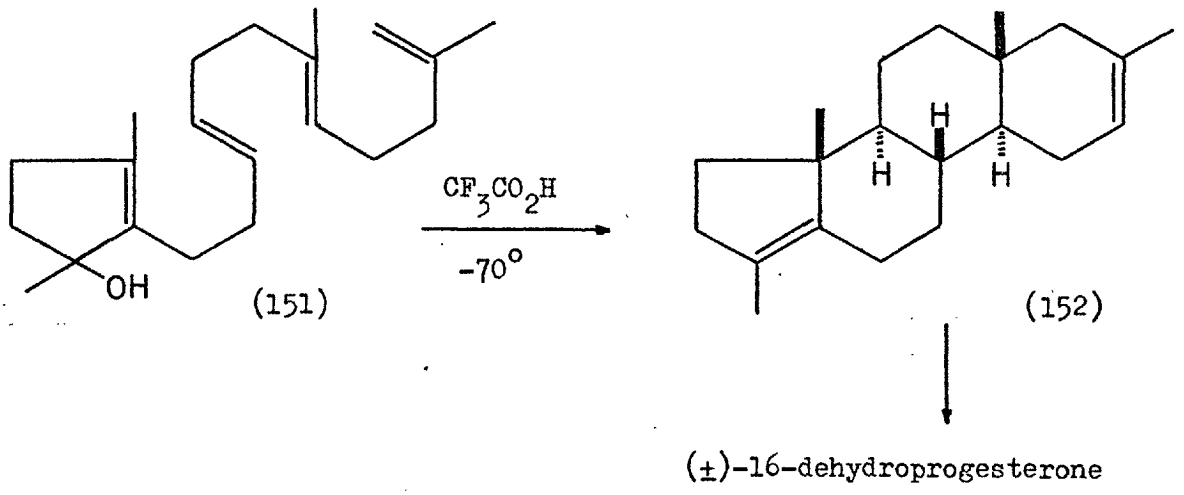
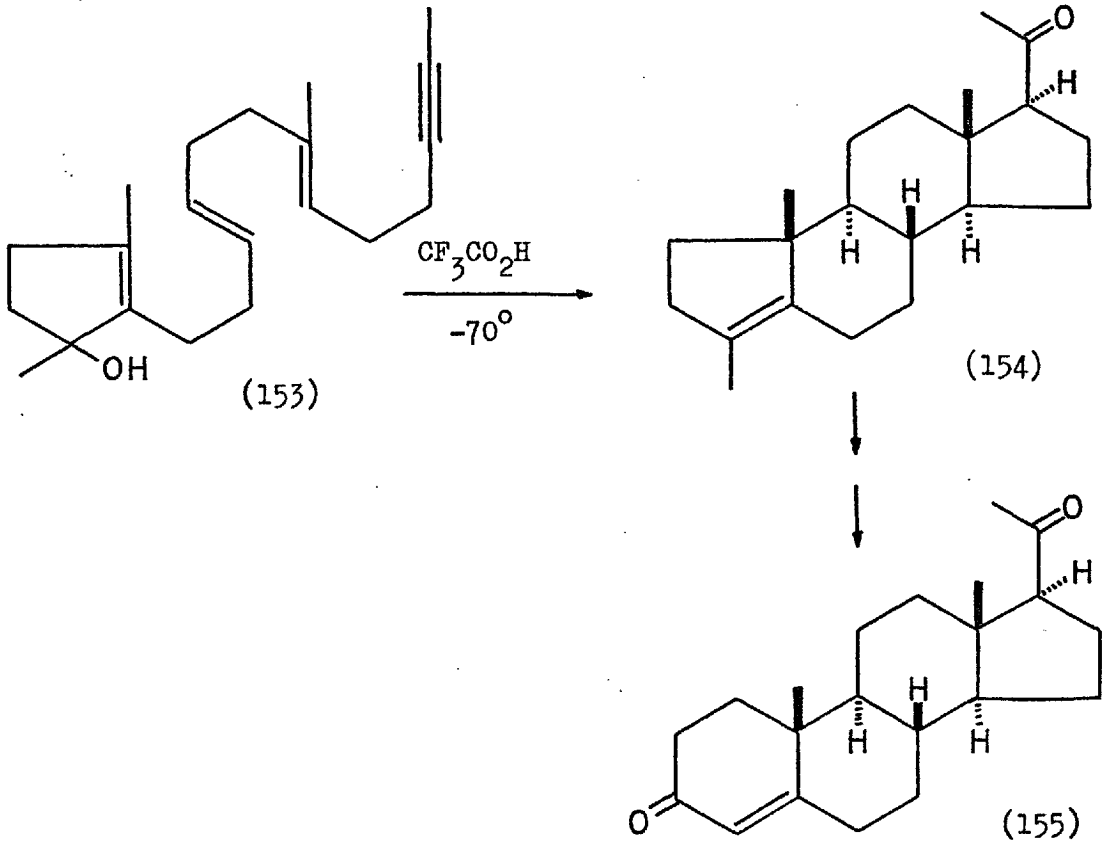


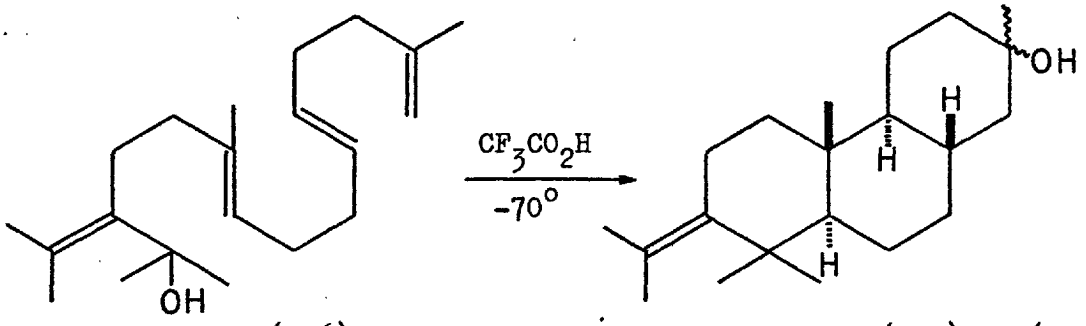
(150), 28%

Johnson has achieved the elegant total synthesis of (±)-16-dehydroprogesterone [84] and (±)-progesterone (155)[86] by cyclisations which involve the simultaneous generation of five asymmetric centres. These are the closest nonenzymic analogues so far to the biological formation of the steroid nucleus.





The trans,anti,trans tricyclic alcohol (157) was formed in good yield from the acyclic trienol (156).[87]

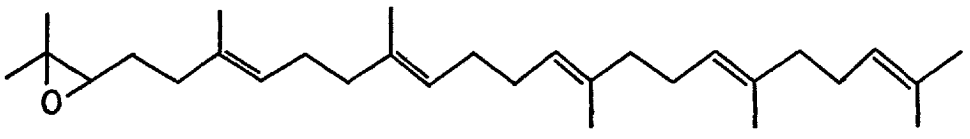


(156) (157), 52%

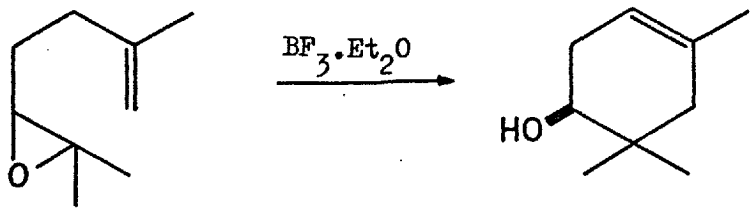
From the foregoing work the fact has emerged that in polyene cyclisations, as opposed to diene cyclisations, success is only achieved when a stable initiating cation is used (e.g. allyl and oxonium ions).

Cyclisation of Epoxyolefins.

Following the recognition of the central role of squalene-2,3-oxide (158) in sterol biosynthesis[88,89,90] Van Tamelen initiated an investigation into the nonenzymic cyclisation of model polyolefin terminal epoxides. A preliminary investigation by Goldsmith had shown that a monocyclic alcohol (160) resulted from the action of boron trifluoride etherate on geraniolene monoepoxide (159).[91]

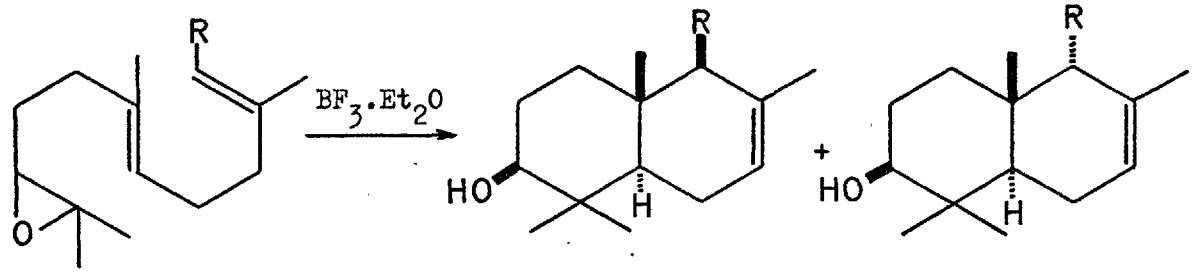


(158)



(159) (160)

Treatment of methyl trans,trans-10,11-oxidofarnesate (161)[8] and trans,trans-oxidofarnesyl acetate (162)[92] with this reagent produced the bicyclic esters (163) and (164) in varying proportions depending on the reaction conditions.

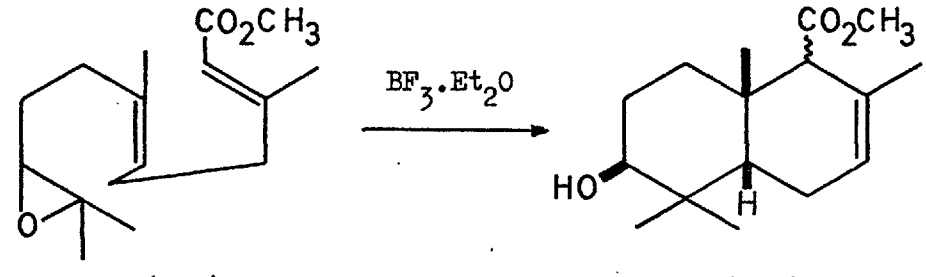


(161), R=CO_2CH_3
(162), R=$CH_2O.CO.CH_3$

(163)

(164)

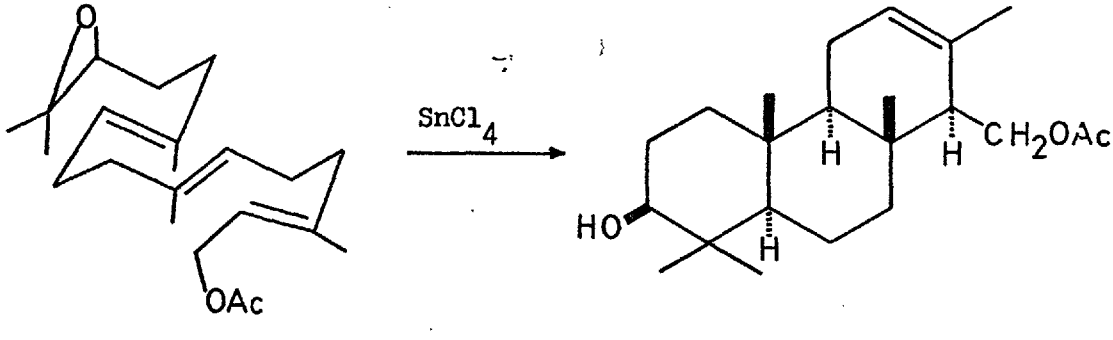
The corresponding cis-ester (165) gave a low yield of the cis-bicyclic ester (166).[8]



(165)

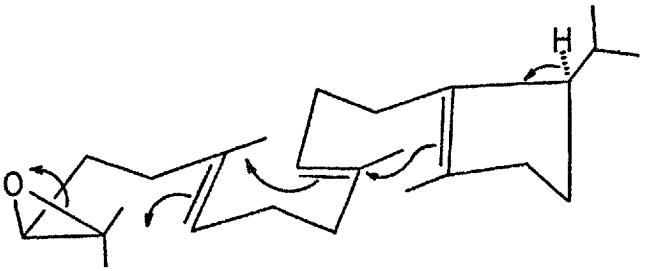
(166), 3%

Two further examples suggest that an all chair conformation is normally adopted for cyclisation. Stannic chloride induced cyclisation of the triene epoxide (167) produced the hydrophenanthrene (168)[93] and the epoxide (169) with a preformed D ring was converted (35% yield) to the isoeuphenol system (170).[94]



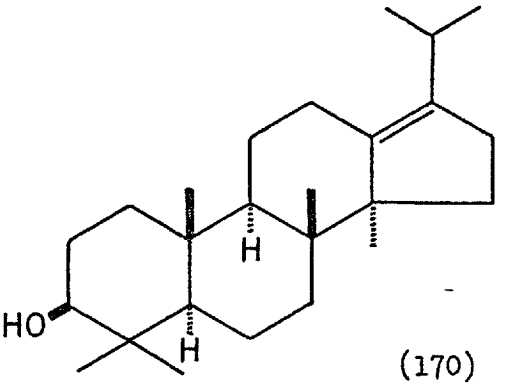
(167)

(168)



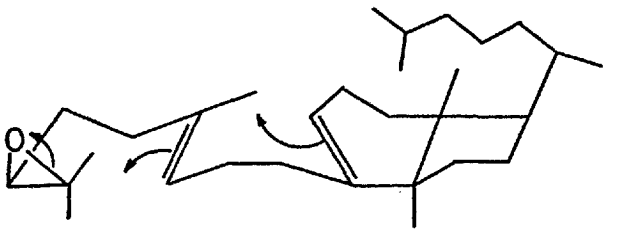
(169)

$SnCl_4$



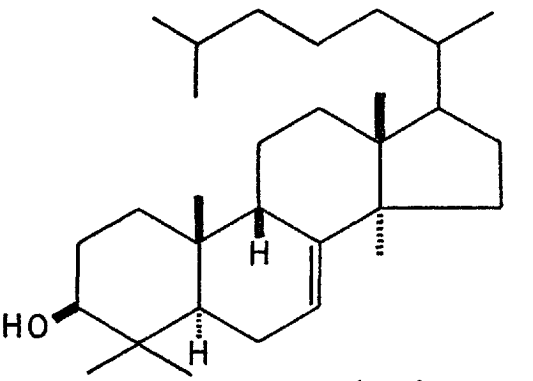
(170)

Cyclisation of the epoxide (171), with preformed CD rings, occured via a boat,chair type folding to give the 9,10-cis-sterol (172).[95] This stereochemical result is unusual in nonenzymic cyclisations but parallels the Zurich proposal[10] of the biosynthetic cyclisation of squalene oxide to yield a protosterol intermediate having the 9β,10β relationship.



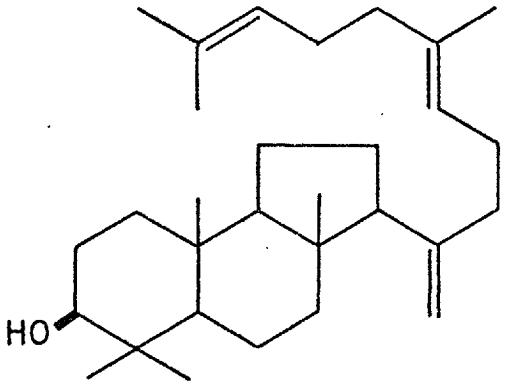
(171)

$SnCl_4$

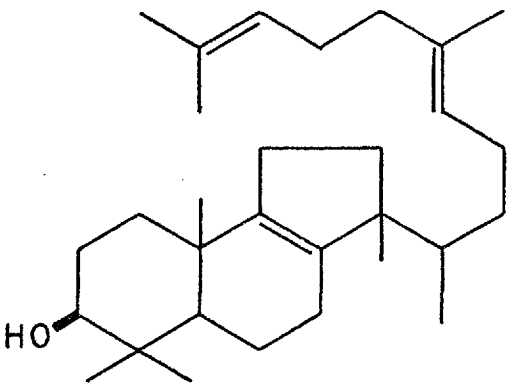


(172)

The nonenzymic cyclisation of squalene-2,3-oxide proved particularly instructive. The stannic chloride catalysed reaction gave partially cyclised products.[96,97] The two tricyclic components (25-30% yield) were identified as alcohols (173) and (174) formed by Markownikov controlled cyclisation followed in the latter case by a CH_3/H migration sequence.

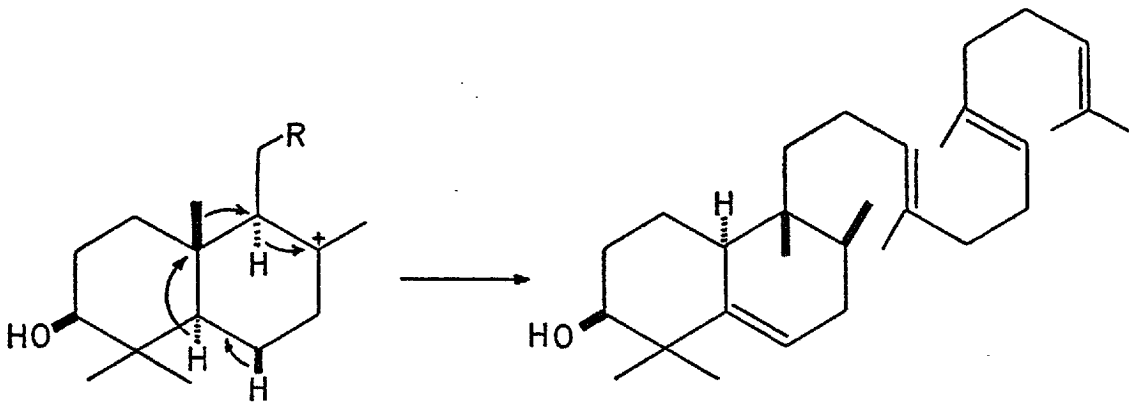


(173)



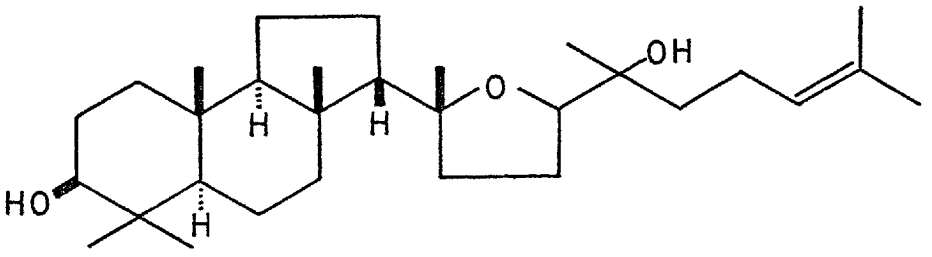
(174)

A bicyclic alcohol (20-25% yield) was shown to have the structure (176). This can be explained in terms of a series of CH_3/H migrations in the bicyclic carbonium ion (175).



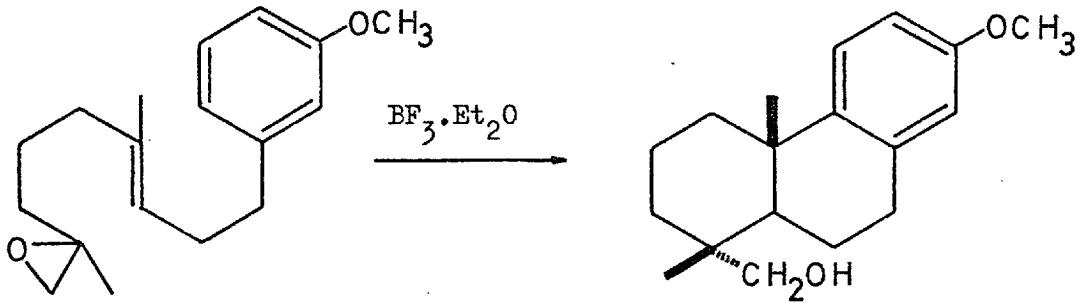
(175) (176)

The picric acid catalysed cyclisation of 18,19-dihydroxysqualene--2,3-oxide gave (±)-malabaricanediol (177).[98]



(177)

Van Tamelen was unable to distinguish between a fully synchronous process and a sequential formation of cyclic carbonium ions.[93] He did however prefer the view that anchimeric assistance by the 6,7-double bond in the epoxide ring opening closes the first ring in a concerted manner.[99] The cyclisation of the epoxide (178) to the alcohol (179) suggests that a discrete monocyclic carbonium ion forms, since none of the 4β-hydroxymethyl epimer was obtained.[100]



(178) (179)

Reactions of this type are potentially useful in the synthesis of terpenes and steroids as a high degree of stereoselectivity is obtained. However the yields are generally poor and work must be done to improve the efficiency of the cyclisation process.

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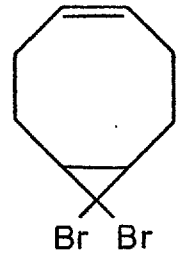
RESULTS AND DISCUSSION.

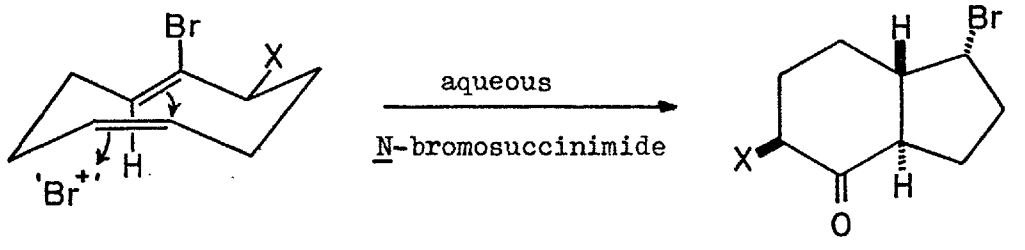
Introduction.

The stereospecific formation of ring junctions is one of the major problems in the design of a steroid total synthesis. Carbonium ion induced olefin cyclisations offer a way of achieving this. These reactions are stereospecific and in cases analogous to enzymic cyclisations often follow the same stereochemical course.

By utilising the highly stereospecific transannular cyclisation reactions of medium ring olefins, Duffin, Sutherland and Heggie[1,2] developed a synthesis of trans-hydrindanes from suitably substituted 1,5-cyclononadienes. They converted the dibromocarbene adduct (1) of 1,5-cyclooctadiene by cyclopropyl to allyl rearrangement to the cis,trans-1,5-cyclononadienes (2 a-d) which gave the trans-hydrindanones (3 a-d) on treatment with aqueous N-bromo--succinimide, stereospecifically generating four asymmetric centres.



(1)



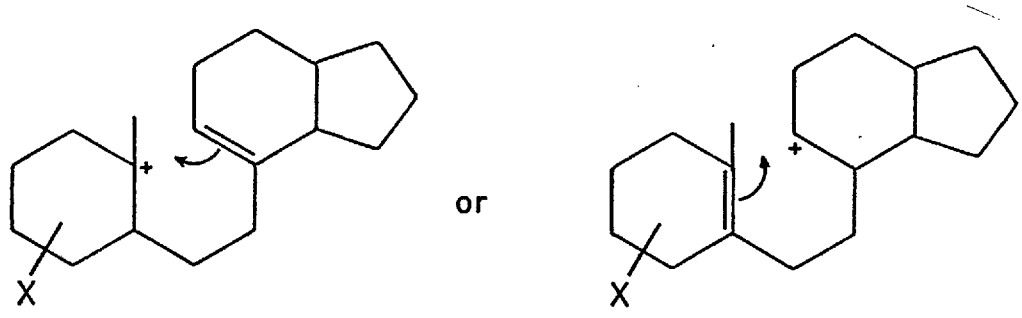
(2 a-d) (3 a-d)

a. X = OAc
b. X = OH
c. X = OTs
d. X = Br

Substituted trans-hydrindanes are difficult to prepare as they are in general thermodynamically less stable than the corresponding cis isomers[3] and hitherto only one direct method has been reported for their synthesis.[4]

The stereospecificity of the formation of the trans-hydrindanones (3 a-d) makes this an attractive basis for a steroid synthesis. To achieve this the AB ring system must be incorporated. The approach considered was to link a suitably substituted A ring precursor to the hydrindane via a two carbon unit followed by closure of the B ring by the nucleophilic attack of a double bond on a carbonium ion.

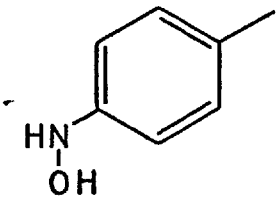
i.e.



A series of model experiments were carried out to devise such a method.

Attempted Cyclisation of Aromatic Nitrenium Ions.

In 1921 Bamberger[5] observed that when p-tolyl hydroxylamine (4) was treated with aqueous acid, dienone (5) was isolated.



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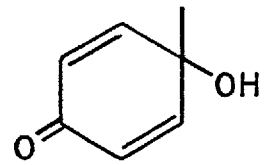
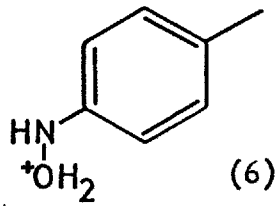
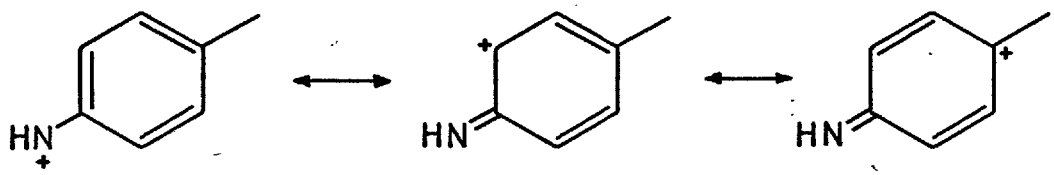


(5)

This result was explained[6] as the initial formation of nitrenium ion (7) in which the positive charge is localised predominantly in the para position - i.e. resonance form (9). Nucleophilic attack by water at this cationic centre gives, after hydrolysis, the observed product.

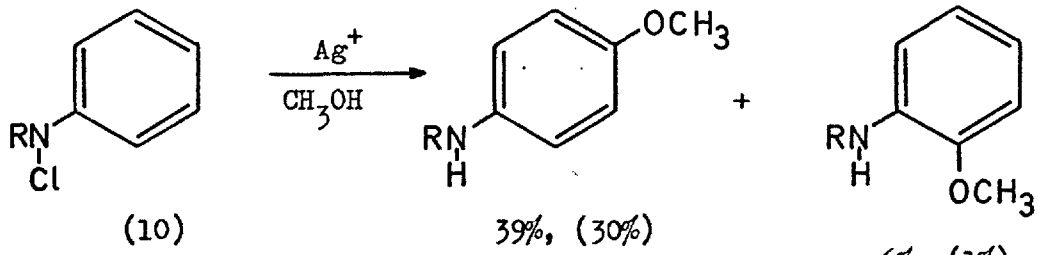


(6)



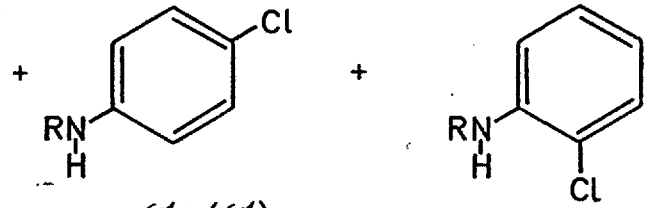
(7) (8) (9)

More recent evidence for nitrenium ion formation and reaction in the para position was obtained by Gassman, Campbell and Frederick.[7,8] Aromatic N-chloroamines were treated with silver ion in methanol.

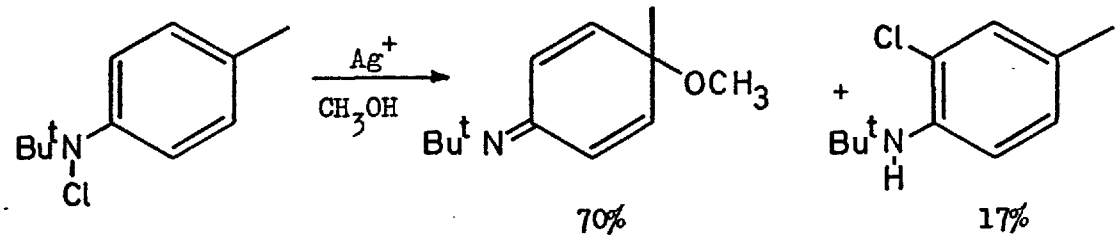


(10) 39%, (30%) 6%, (1%)

R = tert-butyl, (methyl)



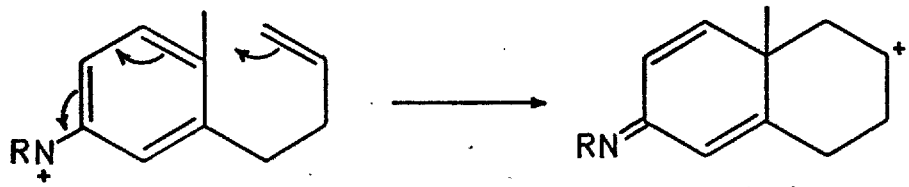
6%, (6%) 28%, (9%)



70% 17%

Heterolytic cleavage of the N-Cl bond occurs in the presence of Ag^+, followed by attack by methanol or chloride ion in the ortho and para positions of the resulting aromatic nitrenium ions.

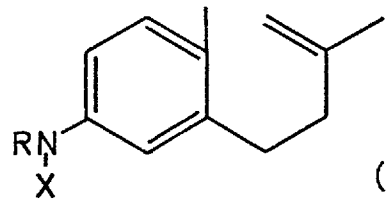
At the beginning of this work no investigation had been reported on intramolecular nucleophilic attack on aromatic nitrenium ions. If a reaction of the type (12) ⟶ (13)



(12) (13)

could be induced it would provide a novel method of obtaining the

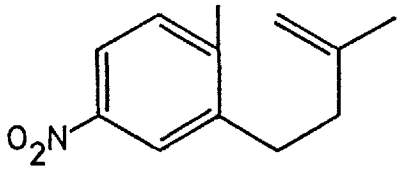
required cyclisation in the steroid synthesis. Consequently the synthesis of model compounds of the type (14) was undertaken.



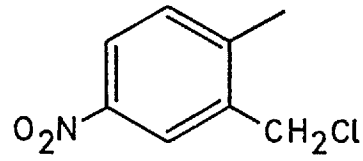
(14)

R = H or alkyl

X = OH or halogen

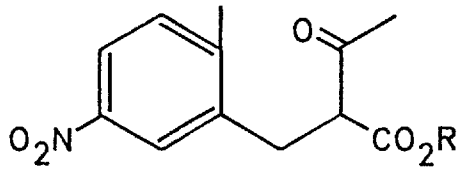


(15)

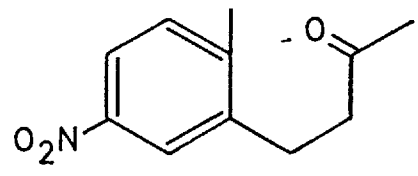


(16)

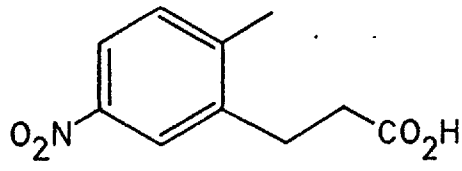
The initial objective was the preparation of 2-(3-methylbut-3--enyl)-4-nitrotoluene (15). The route proposed was to alkylate the anion of a β-ketoester with 2-chloromethyl-4-nitrotoluene (16)[9] to give (17) followed by hydrolysis to ketone (18) which could be converted to the olefin (15) by a Wittig reaction. Although the sodium enolate of ethyl acetoacetate alkylated smoothly to give the ester (17, R=ethyl) the hydrolysis to ketone (18) was not satisfactory. The optimum yield of (18) was 36%, obtained by hydrolysis of (17, R=ethyl) with acid. The p.m.r. spectrum of ketone (18) showed the two expected methyl singlets (τ 7·76 and τ 7·55) and an A_2B_2 type multiplet (τ 6·97 - 7·24).



(17)



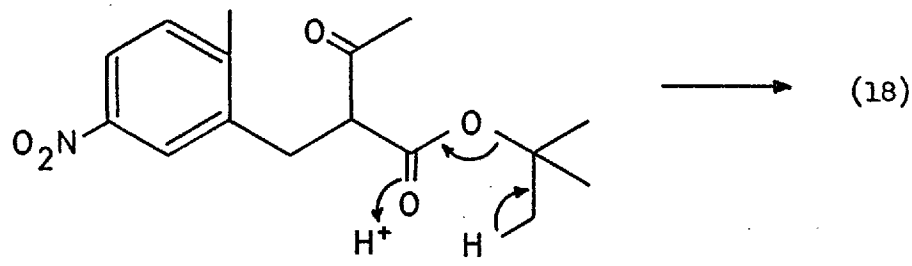
(18)



(19)

A crystalline acidic compound was also obtained from the hydrolysis. It was shown to be the product of 'acid hydrolysis' (19) (18% yield) by its p.m.r. spectrum - only one methyl singlet (τ 7·54), an A_2B_2 multiplet (τ 6·7-7·8) and a D_2O labile signal at τ 0·25.

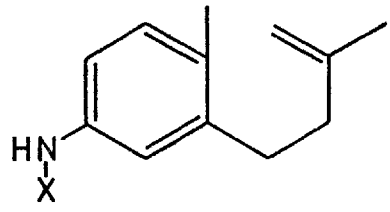
The yield of ketone (18) was greatly improved to 88% from chloride (16) by pyrolysis of (17, R=tert-butyl) with toluene-p-sulphonic acid. The acid catalysed elimination mechanism [10] of this reaction precludes the formation of byproduct (19).



(18)

Ketone (18) was converted to olefin (15) in 67% yield by a Wittig reaction. The p.m.r. spectrum confirmed the structure by the presence of a two proton signal at τ 5·2 and two methyl singlets at τ 7·55 and 8·20.

The first model prepared for the attempted cyclisation was the N-aryl hydroxylamine (20).



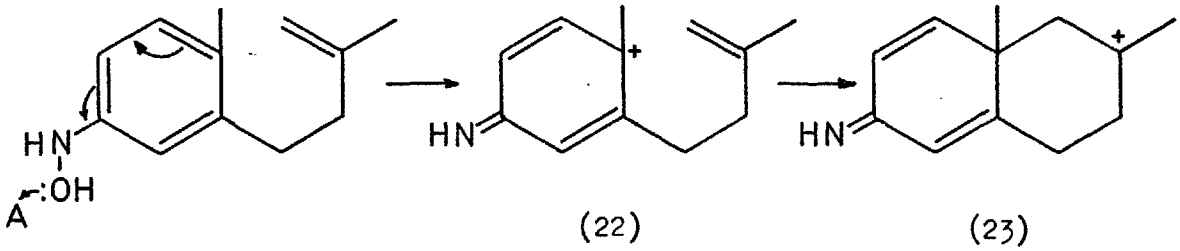
(20), X = OH

(21), X = H

The standard method of reducing aryl nitro compounds to the corresponding hydroxylamines is treatment with zinc dust in aqueous ammonium chloride.[11] When the nitro compound (15) was reacted under these conditions with the stoichiometric amount of zinc the oily product had ν_{max} 3300 cm^{-1}, but t.l.c. showed it to contain unreacted (15). Since spectroscopic evidence would not distinguish between the hydroxylamine (20) and the amine (21), the crystalline benzoyl derivative was prepared. Elemental analysis showed this to be the derivative of amine (21).

The obvious cause of this result is the low pH of the solution since aryl hydroxylamines readily undergo further reduction in acid solution. In an attempt to prevent this over-reduction the reaction was repeated using ammonium acetate as the proton source. The product was a waxy solid, ν_{max} 3300 cm^{-1}. It did not give a crystalline benzoate but was characterised as the required hydroxylamine (20) by its monotosylate, m.p. 119-21°.

In an attempt to induce cyclisation via cation (22) to (23), the hydroxylamine (20) was treated with several acids and Lewis acids but without success.



(22) (23)

The results are summarised in Table 1.

Reagent (Solvent)	Temp. (°C)	Reaction Time	Result	
			Neutral Fraction	Basic Fraction
H_2SO_4 (THF/H_2O)	25	Overnight	a	a
$BF_3.Et_2O$ (Ether)	i. -78 ii. 0	" "	b a	c a
Amberlyst 15 (CH_2Cl_2)	25	"	b	a,d
H_2SO_4 (Ether)	i. -78 ii. 25	" "	- a	c a
CF_3COOH ($CHCl_3$)	-60	2 hr., e	a	a
HCOOH (98%)	0	Overnight	a	a
$SnCl_4$ (Benzene)	0	"	a	a
$CuBF_4$ (EtOAc)	0	Immediate Work up	a	a

Table 1.

Key

a. Intractable tar.

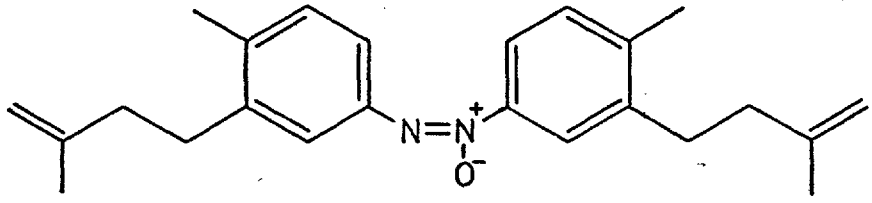
b. The only isolable product was the azoxy compound (24).

c. Starting material.

d. Obtained by extracting the resin with 2N HCl.

e. Reaction followed by p.m.r. - after 2 hr. no starting material remained.

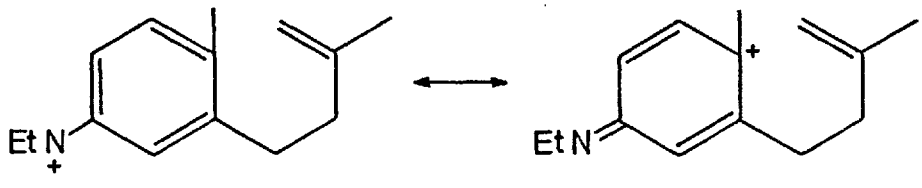
In each case the crude product was separated into a basic and a neutral fraction but these mainly consisted of intractable tars. The only characterisable product was the crystalline azoxy compound (24), identified by elemental analysis and the similarity of its p.m.r. spectrum to that of amine (21). Azoxy compounds are common decomposition products of aryl hydroxylamines.[12]



(24)

No positive evidence was obtained for the formation of the intermediate nitrenium ion but the results suggest that if it had formed the only reaction it underwent was polymerisation.

Having failed to obtain evidence of the required cyclisation in the hydroxylamine series, attention was turned to the model system (14) in which R=ethyl and X=chlorine. It was hoped that by analogy with Gassman's results [7,8] treatment of this with silver ion would produce the cation (25) which would undergo the required cyclisation.

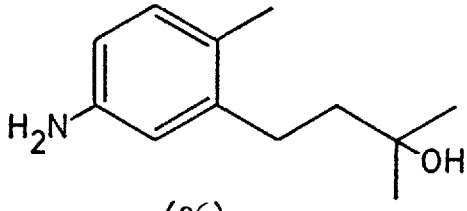


(25)

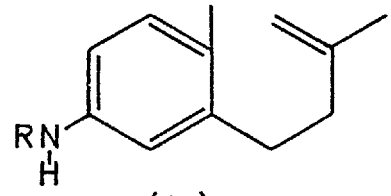
It was decided to use the N-ethyl group rather than the N-tert-butyl group in Gassman's work as the introduction of the latter requires heating the amine, tert-butanol and acid to $> 120^{\circ}$. These conditions would be too vigorous for the sensitive terminal

methylene group. This should not make any significant difference to the silver catalysed reactions as Gassman obtained similar results with both N-tert-butyl and N-methyl amines.

The synthesis of (14, R=ethyl, X=Cl) was undertaken. Reduction of the nitro compound (15) by stannous chloride and hydrochloric acid occured with concomitant hydration of the double bond giving the crystalline amine (26), identified by the six proton singlet at τ 8·76. However reduction of (15) under neutral conditions with aluminium amalgam gave the required amine (21) in 62% yield. Acetylation of (21) gave, in quantitative yield, the amide (27) which was smoothly reduced by lithium aluminium hydride to the N-ethylamine (28).



(26)



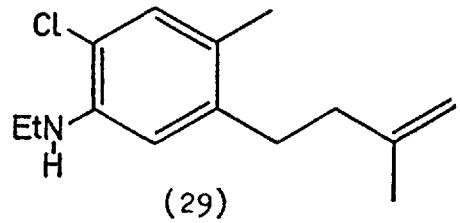
(27), R = $COCH_3$

(28), R = CH_2CH_3

Treatment of the N-ethylamine (28) with a large excess of calcium hypochlorite in carbon tetrachloride at 0° [8] gave a solution of the N-chloroamine (14, R=ethyl, X=Cl). This was not isolated but was treated immediately with the silver salt.

A number of different conditions were tried using both silver perchlorate and trifluoroacetate in various solvents at temperatures ranging from $+20^{\circ}$ to -20°. In each case a white precipitate formed immediately on addition of the silver salt but work up gave a tarry mixture from which only one pure compound could be isolated by p.l.c. This proved to be the ring chlorinated amine (29). The p.m.r. spectrum contained signals due to a 1,2,4,5-tetrasubstituted aromatic ring (two one proton singlets at τ 3·47 and 2·95) and a secondary amine (a D_2O labile proton at τ 6·23). The similarity of the rest of the spectrum to starting material (28) showed that cyclisation

had not occured.

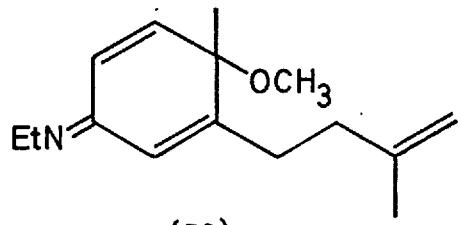


(29)

A control experiment was carried out keeping the chloroamine (14, R=ethyl, X=Cl) overnight in benzene/carbon tetrachloride solution. A 48% yield of (29) was obtained. This was in agreement with the general rearrangement of N-chlorinated aromatic amines involving migration of a positive chlorine ion from nitrogen to the aromatic ring.[13] This isomerisation was catalysed by water. Addition of a few drops of water to (14, R=ethyl, X=Cl) in an n.m.r. tube rapidly changed the spectrum to that of (29). Thus the presence of silver ion does not induce this migration. The formation of a siver chloride precipitate, however, indicates that some formation of nitrenium ion (25) occurs but it polymerises to an intractable tar.

To exclude the possibility of tarring of the products by perchloric or trifluoroacetic acids the reactions were repeated in the presence of triethylamine, but this failed to give a cleaner product.

Although the required cyclisation of cation (25) did not take place it was hoped to at least demonstrate its formation by trapping it as the methoxyazadienone (30) using Gassman's original conditions.[8]



(30)

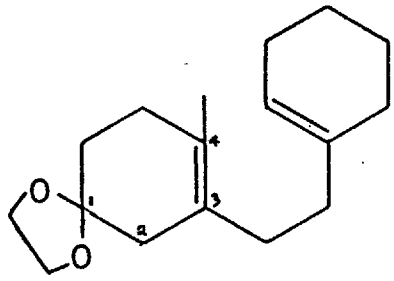
However treatment of (14, R=ethyl, X=Cl) with silver trifluoroacetate in methanol gave only the ring chlorinated amine (29) plus tar.

Finally an attempt was made to generate the cation (25) from the N-chloroamine formed in situ by a method recommended by Gassman for water sensitive N-chloroamines.[14] Treatment of the amine (28) with tert-butyl hypochlorite at 0° followed by silver trifluroacetate gave the usual tarry product containing mainly (29) but no trace of the required product.

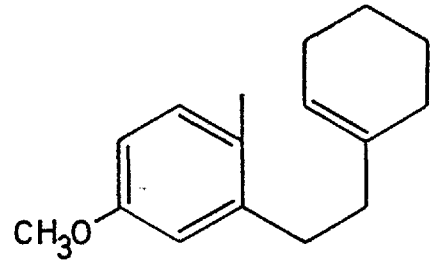
At this stage having obtained no promising results, attention was turned to possible alternative methods to achieve the desired cyclisation.

The Synthesis and Reactions of a Model 1,5-Diene.

The acid catalysed cyclisation of 1,5-dienes has been extensively studied (see pages 4-20). A reaction of this type could in principle be used to effect the formation of the steroid B ring in the desired manner. The model diene (31) with a suitably protected C-1 oxygen function was synthesised in order to explore this possiblity.



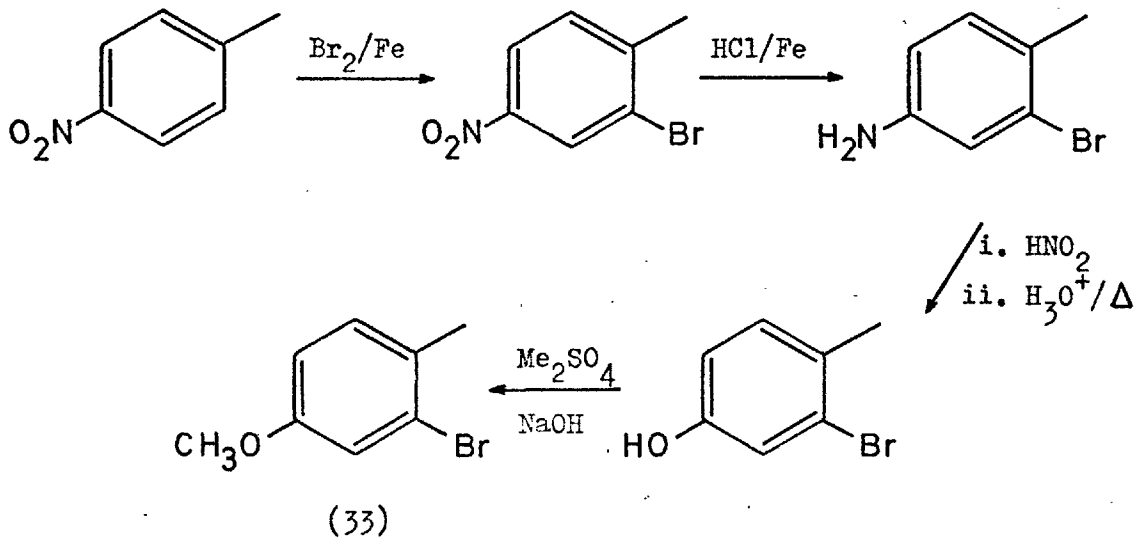
(31)



(32)

The aromatic precursor (32) of (31) is a known compound [15] but the reported method of preparation is inefficient giving (32) in only 15% yield from 2-bromo-4-methoxytoluene (33). Consequently an improved route to (32) was developed.

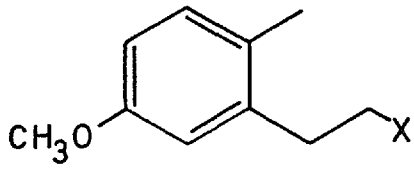
2-Bromo-4-methoxytoluene (33) was prepared from 4-nitrotoluene by the literature route [15] modified to give a purer product on a larger scale (Scheme 1).



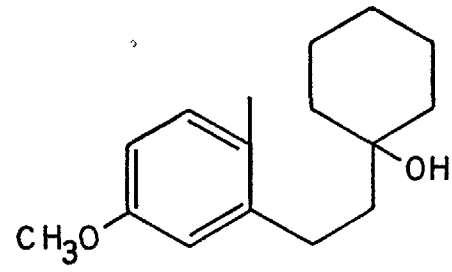
(33)

Scheme 1.

Treatment of the Grignard reagent of (33) with ethylene oxide gave the alcohol (34) in 75% yield. This was converted to both the chloride (35) by thionyl chloride/pyridine (87% yield) and the bromide (36) by phosphorus tribromide (60%).



(34), X = OH
(35), X = Cl
(36), X = Br

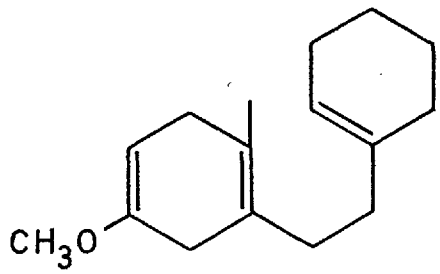


(37)

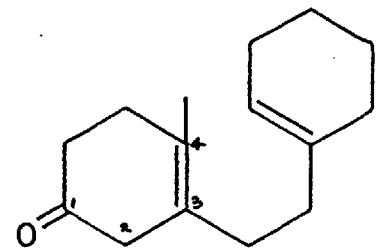
Both halides could be coupled, by Grignard reactions, to cyclohexanone giving the tertiary alcohol (37). The yield of (37) from the chloride (65%) was better than that (52%) from the bromide. This comparison therefore showed the chloride route to (37) to be the more efficient, giving an overall yield of 43% from (33). The alcohol (37) was dehydrated to olefin (32) in $>90\%$ yield by either the literature procedure [15] (pyrolysis with potassium hydrogen sulphate) or more conveniently by treatment with phosphoryl chloride in pyridine. In agreement with the assigned structure, the p.m.r. spectrum of (32) showed the characteristic 1,2,4-trisubstituted aromatic pattern of an AB system (τ 3·16 and 3·55) plus a singlet (τ 3·53). The remainder of the spectrum showed the methoxy (τ 6·25), aromatic methyl (τ 7·76) and vinyl (τ 4·55) signals.

Birch reduction of the olefin (32) gave the dihydro derivative (38) in quantitative yield. The p.m.r. spectrum revealed the presence of two vinyl protons at τ 4·66 and 5·58, confirming the assigned structure. Hydrolysis of (38) by aqueous oxalic acid gave ketone (39), ν_{max} 1720 cm^{-1}. The presence of only one vinyl proton in the p.m.r. spectrum (τ 4·66) verified that the Δ^3 double bond had not moved

into conjugation with the carbonyl group. The carbonyl group in (39) was protected as the ethyleneketal (31).

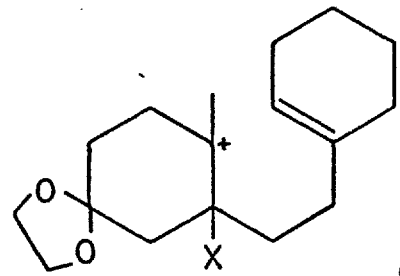


(38)



(39)

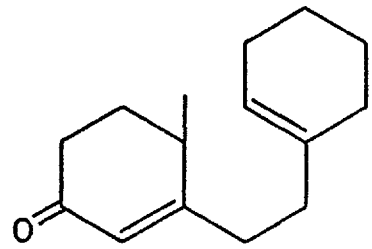
The model diene (31) was treated with a number of reagents in an attempt to induce cyclisation via a carbonium ion of type (40).



(40)

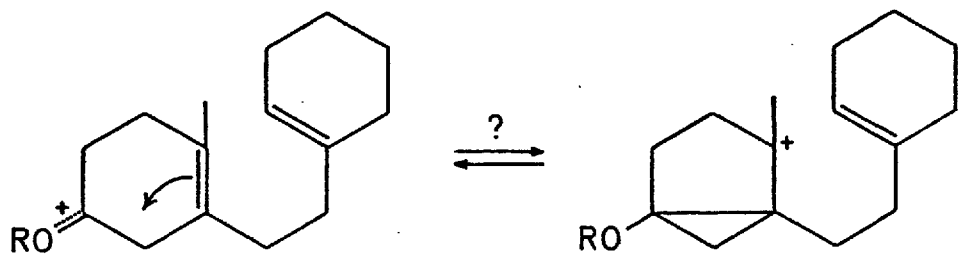
Aqueous N-bromosuccinimide, which has been used successfully in transannular cyclisations of medium ring dienes,[1,16] was the first reagent tried. Reaction of diene (31) with one equivalent of this reagent followed by mild acid hydrolysis gave a complex mixture of products which was not investigated. It is clear from this result that nonaqueous conditions are necessary to prevent the solvolysis of intermediate carbonium ions. It is likely that some cyclisation occurs in the reaction, as Van Tamelen [17] observed a small amount (ca. 4%) of cyclic material but mainly a mixture of acyclic bromohydrins when methyl farnesate was treated under the same conditions. Thus this reaction is only of synthetic utility in medium ring dienes where the π bonds interact due to the conformation of the ring.

Acids under anhydrous conditions have also been used to cyclise dienes. When diene (31) was treated with anhydrous trifluoroacetic acid at 0° no reaction was observed (t.l.c.) after 48 hours. With sulphuric acid in ether at 0° much tar was formed and t.l.c. showed one product plus some starting material. Work up gave the $\alpha\beta$-unsaturated ketone (41) as the only isolable product. The i.r. spectrum of this compound showed it to be a conjugated ketone (ν_{max} 1670 cm^{-1}) which was confirmed by the presence of two vinyl protons (τ 4·30 and 4·60).



(41)

An interesting possibility for cyclisation is the generation of carbonium ion (43) via homoallylic interaction of the Δ^3 double bond with the oxonium ion (42) (compare reference 18). In an attempt to achieve this (31) was treated with stannic chloride but gave only a mixture of ketones (39) and (41), indicating that (42) is sufficiently stabilised as such that double bond participation does not occur.

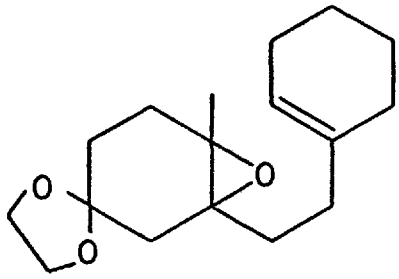


(42) (43)

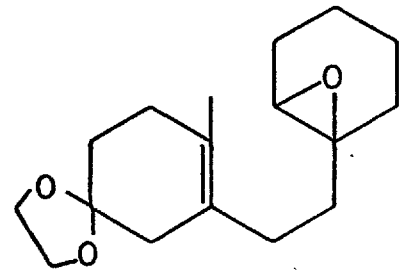
Cyclisation of a Model Epoxyolefin.

The possibility of cyclising (31) via the epoxy derivative (44) was then investigated, since Lewis acid catalysed cyclisations have been used successfully by several workers (see pages 29-33).

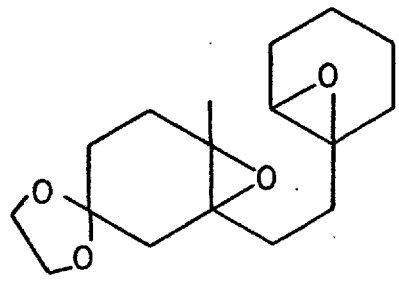
It was expected that when diene (31) was treated with a peracid the A ring epoxide (44) would form preferentially due to the greater nucleophilicity of the tetrasubstituted double bond. In the event, reaction with one equivalent of m-chloroperbenzoic acid was completely unselective giving the two possible monoepoxides (44) and (45) plus some bisepoxide (46). Separation was achieved with difficulty by p.l.c. on 10% silver nitrate in silica gel giving a 20% yield of pure epoxide (44). The two monoepoxides were clearly distinguished by their p.m.r. spectra. The A ring epoxide (44) showed both a vinyl proton (τ 4·70) and a methyl singlet (τ8·77) α to the epoxide. The C ring epoxide (45) had neither signal, but had a single methyl group (τ8·10).



(44)

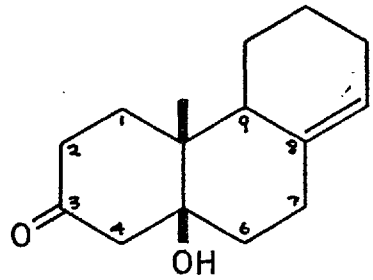


(45)

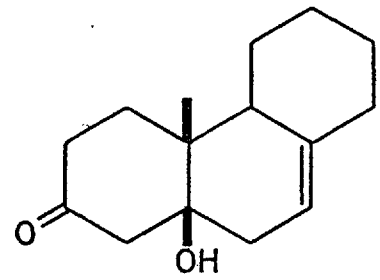


(46)

The action of Lewis acids on epoxide (44) achieved the required cyclisation. Treatment of (44) with boron trifluoride etherate, followed by mild acid hydrolysis of the ethyleneketal gave a crystalline product, ν_{max} 3360, 1700 cm^{-1}. This was shown to be a 1:1 mixture of the isomeric tricyclic ketols (47) and (48), obtained in 95% yield.



(47)

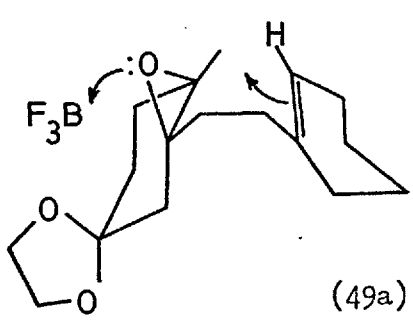


(48)

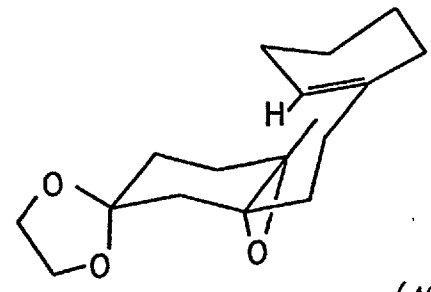
The p.m.r. spectrum showed the presence of angular methyl groups (singlets at τ 9·05 and 9·10 each integrating for 3/2 protons). It also showed two vinyl signals each of $\frac{1}{2}$ proton at τ 4·34 and 4·78 plus a sharp D_2O labile singlet at τ 8·20. The mass spectrum (M^+, 234 plus a strong M - 18 peak) and the microanalysis were in agreement with this assignment. A qualitative ultraviolet spectrum showed the appearance of a λ_{max} 234 nm on treatment with sodium ethoxide arising from dehydration to the corresponding $\alpha\beta$-unsaturated ketones.

The products were tentatively assigned the 9,10-<u>cis</u> stereochemistry on the basis of the stereoelectronic requirements for cyclisation. If it is assumed that the epoxide-Lewis acid complex undergoes opening in a diaxial antiperiplanar manner and that axial bond formation occurs to the nucleophilic centre then the molecule can adopt two conformations for cyclisation, the B ring boat (49a) and the B ring chair (49b) (Scheme 2.). An examination of a molecular model shows the boat conformation (49a) is sterically more favourable than the chair (49b). In the boat the two rings are parallel and the methyl

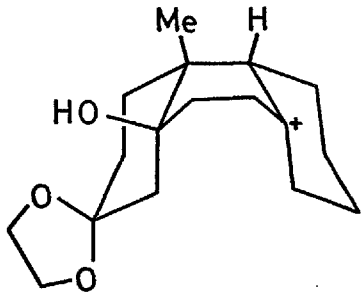
group is held away from the cyclohexene ring. In the chair form however the methyl group is held up against the cyclohexene ring, a less likely arrangement.



(49a)



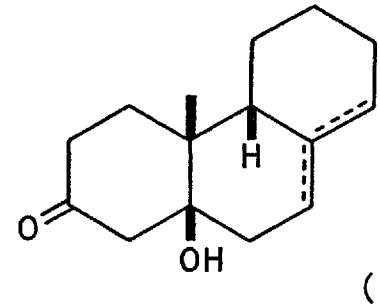
(49b)



(50)

i. Proton loss

ii. Hydrolysis



(51)

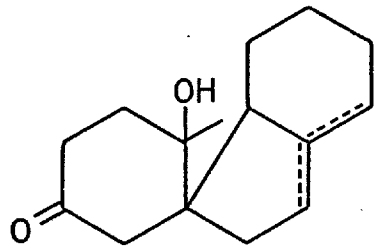
+ enantiomer

Scheme 2.

On this basis it was assumed that the cyclisation occured via the boat conformation (49a) giving the double bond isomers of (51). Evidence for the assigned stereochemistry came from the fact that none of the 8,9-double bond isomer was observed in the product. This isomer would be expected if the C-9 hydrogen in the intermediate carbonium ion (50) was in the axial position, which would obtain if cyclisation had occured via the chair conformation (49b).

No attempt was made to prove this stereochemical assignment in the model series as it was considered easier to do this on a similarly derived steroid. The approach to this will be described in a later section.

Stannic chloride and picric acid also cyclised (44) to (47) and (48) but in lower yield than boron trifluoride.

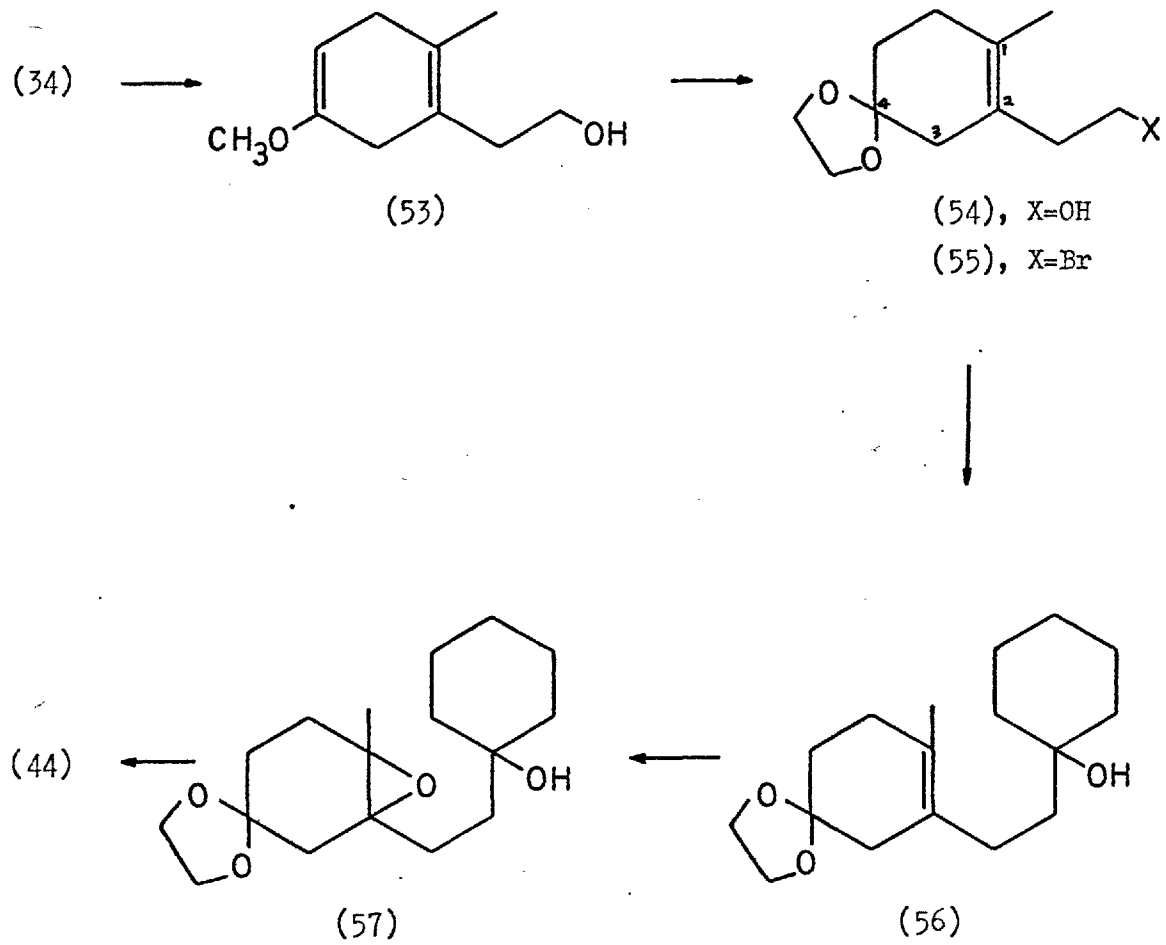


(52)

Since the epoxide ring in (44) can in principle open in two directions the formation of the spiro isomers (52) must be considered. However these can be ruled out as dehydration of the ketol gave an $\alpha\beta$-unsaturated ketone. To explain the absence of (52) the factors determining the course of the reaction must be considered. Since the epoxide is tetrasubstituted there is no overwhelming electronic preference for cleavage of either C-O bond. Thus the conformation of the cyclohexane ring dictates the preferred direction of opening, giving an axial oxygen atom.[19] If it is assumed that the A ring epoxide adopts the 'half chair' conformation as in (49a) (due to the simultaneous interaction of the two oxygen atoms on the β-face with the approaching Lewis acid) the the epoxide can only open in the observed manner. This ring opening may also be anchimerically assisted by the C ring double bond, closing the B ring in a concerted manner. The many examples of concerted rearrangements of steroidal epoxides [19] support this postulate.

Modifications to the Epoxyolefin Synthesis.

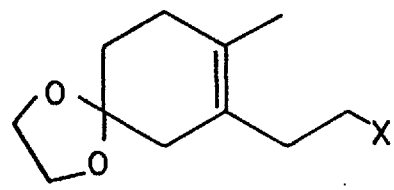
Having achieved the desired cyclisation on the model epoxyolefin (44), further consideration was given to the synthesis of these systems. In order to incorporate this cyclisation in a steroid synthesis it was necessary to devise a general route giving selectively the A ring epoxide. In addition a suitable AB precursor was required to minimise the number of steps after coupling to the CD rings. 1-Methyl-2-(2-bromoethyl)-4,4-ethylenedioxycyclohexene (55) was selected as a potential AB precursor since the A ring was functionalised so that only one step (epoxidation) would be required after this coupling. Scheme 3 was devised in an attempt to demonstrate this and also to provide an unequivocal synthesis of the model epoxyolefin (44).



Scheme 3.

Birch reduction of the alcohol (34) afforded the dihydro derivative (53) which was converted directly to the ethyleneketal (54) by reaction with ethanediol and toluene-p-sulphonic acid in benzene. Treatment of the alcohol (54) with carbon tetrabromide and tri-n-butylphosphine in the presence of pyridine gave the required bromide (55). The yield was optimised to 52% by the addition of two equivalents of lithium bromide to the reaction. The p.m.r. spectrum of (55) showed the expected A_2X_2 pattern (triplets at τ 6·74 and 7·52) plus the ethyleneketal singlet (τ6·15) and the allylic methyl group (τ8·35).

The Grignard reagent from bromide (55) readily formed in tetrahydrofuran if the magnesium was preactivated with methyl iodide. When this was treated with cyclohexanone the major product was the ketal (58), formed by premature work up of the reaction. Only a trace of the required tertiary alcohol (56) could be detected by a weak parent ion at m/e 280 in the mass spectrum. On increasing the reaction temperature and time a maximum yield of 10% of the alcohol (56) was isolated by p.l.c.



(58), X=H
(59), X=D

The possibility of moisture in the reaction was excluded by a control experiment. The Grignard reagent of (55) was quenched with D_2O. A single product was obtained, the deuterated derivative (59). The triplet at τ9·10 integrated for two protons and the triplet at

τ8·03 compared to the corresponding quartet in (58). The mass spectrum (M^+, 183) confirmed the deuterium incorporation.

The coupling of the Grignard reagent from bromide (55) to cyclohexanone is much slower than that of the aromatic analogue (36) although it is difficult to see why this should be so, as one would expect the steric hindrance to be the same in both cases. The inherent instability of the system precluded an extended reaction time.

Since it has been shown that it is not feasible to couple the AB precursor in the required oxidation level, this must be achieved with the aromatic precursor (35). An unequivocal synthesis of the model epoxyolefin (44) was therefore undertaken from the chloride (35).

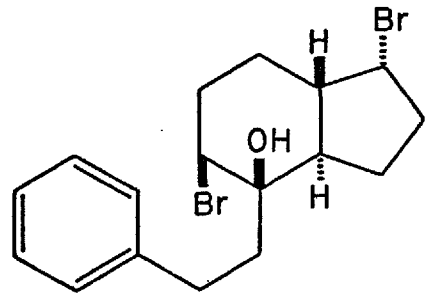
Birch reduction of the tertiary alcohol (37) followed by ketalisation afforded the tertiary alcohol (56). This was oxidised by m-chloroperbenzoic acid to the epoxide (57) which on treatment with methanesulphonyl chloride in pyridine gave the required epoxyolefin (44).

Incorporation of the Synthetic trans-Hydrindane.

The transannular cyclisation mentioned above (p. 41) of the substituted cyclononadienes gives not only a trans-hydrindane but the product is suitably functionalised for elaboration into a steroid. A study of this ring system was undertaken to find a way to attach the AB precursor and to modify the resulting 9,10-secosteroid to an epoxyolefin suitable for cyclisation.

Of the examples cyclised, the dibromocyclononadiene (2d) is the most attractive from the synthetic standpoint as Heggie [2] has shown that this is formed in high yield simply by the alumina catalysed rearrangement of the dibromocarbene adduct (1). The conditions for this rearrangement were optimised for large scale preparation to give a 60% yield of the pure dibromocyclononadiene (2d). The cyclisation of (2d) by aqueous N-bromosuccinimide to the dibromo-trans--hydrindanone (3d) proceeded efficiently on a large scale.

Initially 2-bromoethyl benzene was chosen as a simple model of the AB precursor. The addition of the Grignard reagent of this to the dibromoketone (3d) gave a 40% yield of the crystalline dibromohydrin (60).

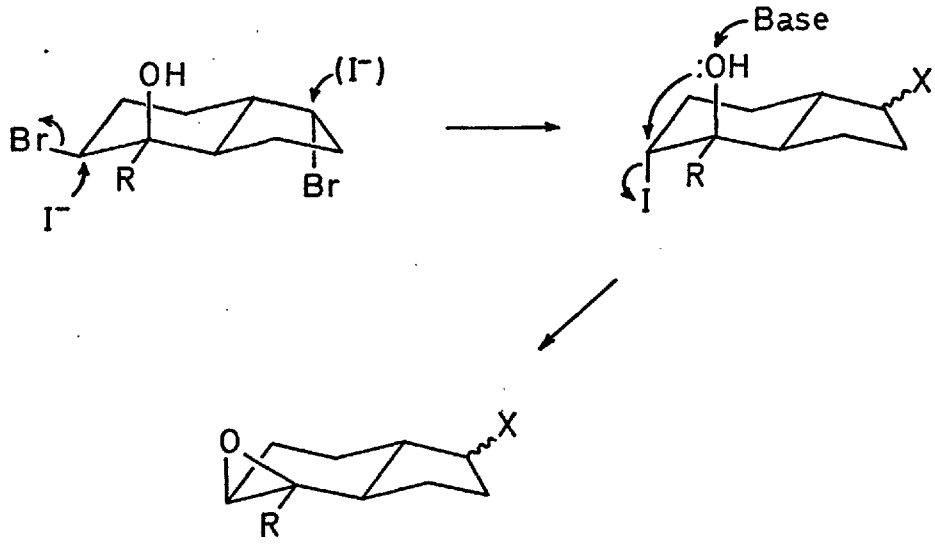


(60)

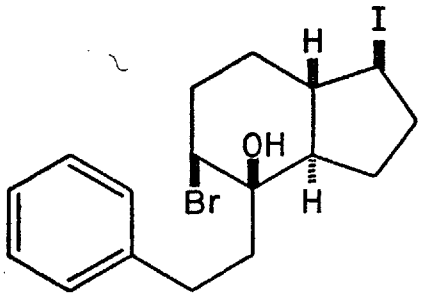
The stereochemistry of (60) was assigned on the basis of approach by the Grignard reagent on the least hindered face of the ketone (i.e. trans to the β-bromine) and on product developement control giving the more stable equatorial phenethyl group. The resistance of the vicinal bromohydrin to epoxide formation on treatment with base (see below) confirmed the cis relationship. The infrared spectrum showed the alcohol function, ν_{max} 3540 cm^{-1} and the two equatorial bromines 708 and 715 cm^{-1}. The p.m.r. spectrum showed a five proton singlet at τ2·97 and a two proton multiplet at τ5·5-6·1. The mass spectrum showed the characteristic dibromide parent ion triplet at m/e 400/402/404.

Although the epoxyolefin cyclisation had been achieved on the A ring epoxide model, it was thought to be of interest to examine the cyclisation of a C ring epoxide. Attempts were thus made to convert the bromohydrin function of (60) to the β-epoxide. In forming this the main problem was that the cis-bromohydrin would not eliminate HBr with base. The obvious way round this problem was to displace the bromine in an S_N2 reaction to give the trans-halohydrin which should readily eliminate to the β-epoxide.

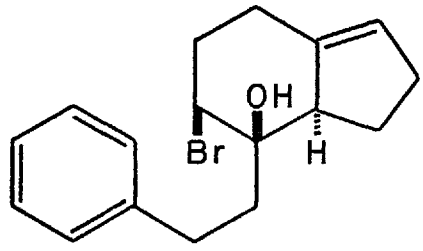
i.e.



Consequently the dibromohydrin (60) was treated with potassium iodide and triethylamine in refluxing acetone. This gave two products (61) and (62) but none of the required epoxide.



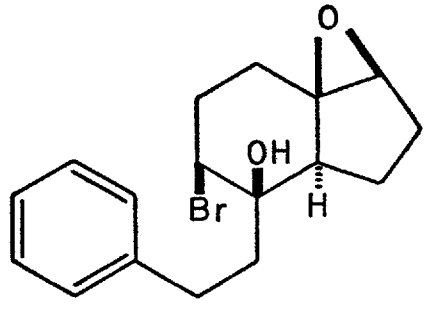
(61)



(62)

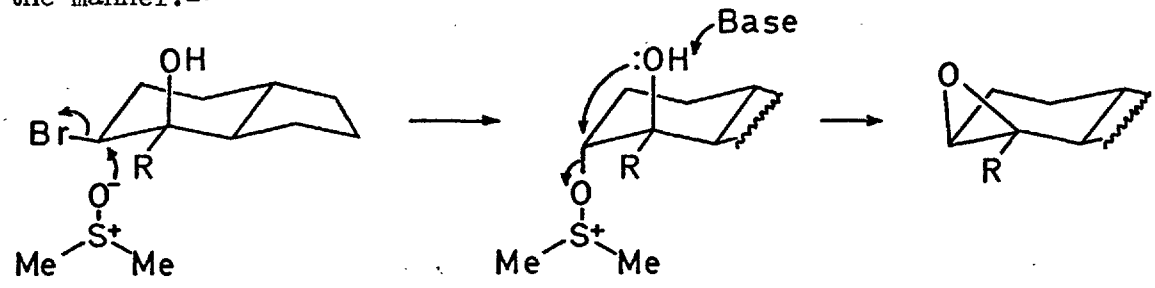
The stereochemistry of the crystalline iodobromohydrin (61) was assigned on the basis of it being the kinetic product of an S_N2 displacement of bromide by iodide since displacement by a second iodide ion would give the α-iodide which would readily undergo elimination to (62). The bromohydrin olefin (62) was shown to be a monobromide (M^+ doublet at m/e 320/322) and a one proton triplet at τ5·46 in the p.m.r. spectrum. This also showed a one proton olefin signal at τ4·70 indicating that the double bond had formed towards the ring junction.

Treatment of (62) with peracetic acid gave the crystalline monoepoxide (63).



(63)

Dimethylsulphoxide is known to displace secondary tosylates and halides in steroids.[20] Elimination of the resulting oxysulphonium ion gives either a ketone or an olefin depending on the base present. An attempt was made to form the epoxide from the bromohydrin (60) in the manner:-

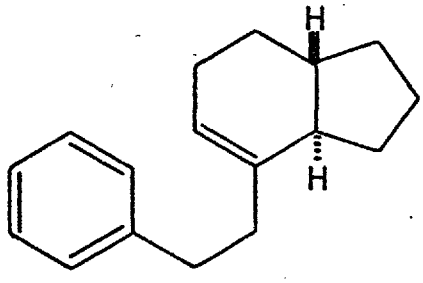


Treatment of the bromohydrin (60) with sodium methylsulphinyl--methide proved too destructive and gave an intractable tar. Collidine in dimethylsulphoxide gave the bromohydrin olefin (62) as the sole nonpolar product.

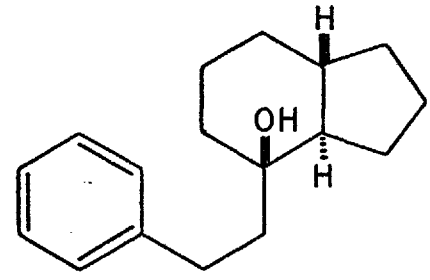
Thus the cis-bromohydrin cannot be converted directly to the C ring β-epoxide. If this approach were to be investigated an indirect synthesis of this epoxide from the olefin would be necessary. However these experiments proved profitable in that they demonstrated the resistance of the β-bromine in the model (60) to nucleophilic displacement. This suggests the possibility of introducing a side chain by selective displacement of the D ring bromine although no work has been done yet on this aspect.

An additional consequence of these experiments was the proof of the α-orientation of the C-1 bromine atom in the hydrindanones (3 a-d) previously assigned solely on the basis of trans addition to the double bond in (2a).[1]

The second objective in this model system was the introduction of the Δ^8 double bond of the secosteroid. This could be achieved by simple reductive elimination of the bromohydrin function in (60). The reduction of (60) with calcium in liquid ammonia gave the required olefin (64) (38%) plus the alcohol (65) (20%) as the two major products.



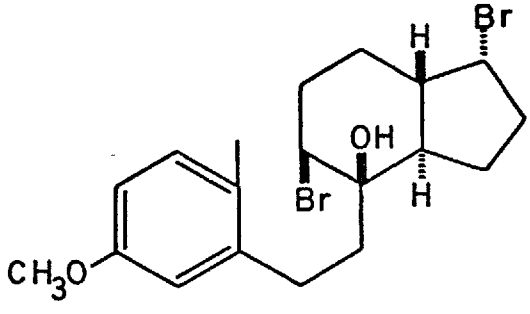
(64)



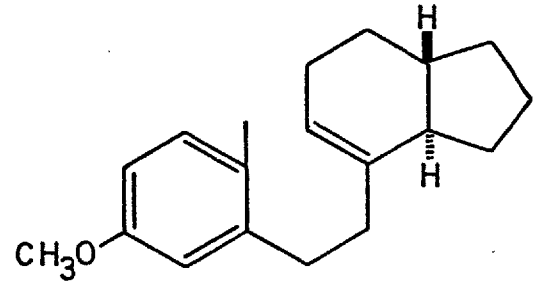
(65)

However treatment of (60) with zinc dust in glacial acetic acid gave the olefin (64) as the sole product.

The reaction sequence developed to give the model olefin (64) was applied to the synthesis of the analogous olefin (67) with a functionalised A ring. Grignard addition of the chloride (35) to the dibromoketone (3d) gave the dibromohydrin (66) which was reduced to the liquid olefin (67) in 75% yield on treatment with zinc in acetic acid.



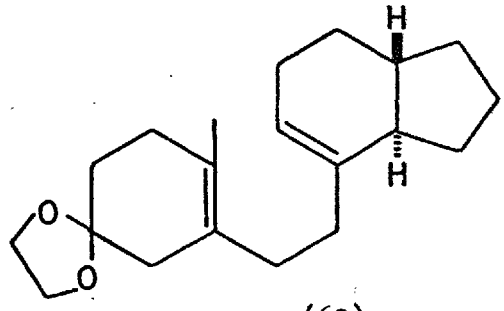
(66)



(67)

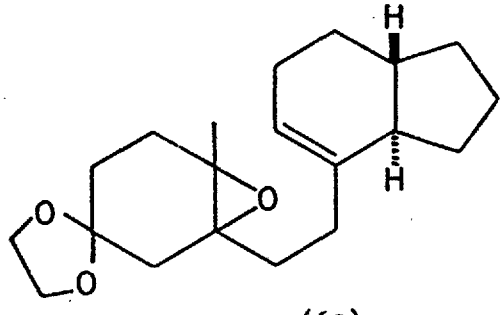
Birch reduction of the olefin (67) followed by ketalisation of the intermediate enol ether afforded the diene (68) with the protected

C-3 oxygen. The p.m.r. spectrum of (68) was identical, except for the methylene region, to that of the cyclohexenyl analogue (31).

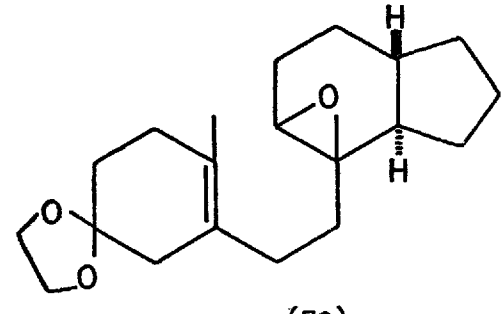


(68)

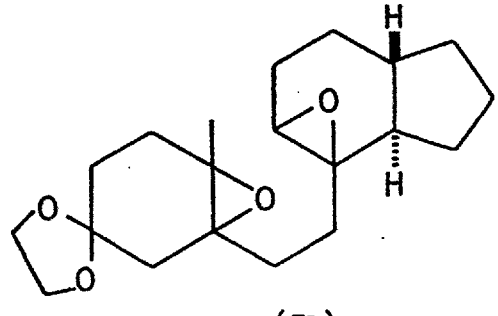
The diene (68) was the parent compound of the substituted secosteroids that could be derived from the dibromocyclononadiene (2d) and was useful in that the derived A ring epoxide (69) could be used to examine the effect of the trans-hydrindane ring system on the epoxyolefin cyclisation.



(69)



(70)



(71)

The preparation of the epoxyolefin (69) was initially undertaken by epoxidation of the diene (68). By analogy with the epoxidation of diene (31) complete specificity of formation of the A ring epoxide was not expected, but it was hoped that the C ring olefin in (68) would be more hindered than in (31) favouring a greater proportion of the A ring epoxide (69). Since the direct epoxidation of (31) with peracid was unselective, the indirect method via the bromohydrin was attempted on (68) in the hope of improving selectivity. However when (68) was treated with one equivalent of N-bromosuccinimide in aqueous tetrahydrofuran followed by ethanolic base, the monoepoxide fraction obtained was shown to contain at least 95% of the C ring epoxide (70). None of the required A ring epoxide (69) could be detected by p.m.r. In this case it would appear that steric rather than electronic factors influence the site of attack by the bromonium iom.

Treatment of diene (68) with m-chloroperbenzoic acid proved completely unselective giving both monoepoxides (69) and (70) each in 21% yield plus the bisepoxide (71) (14%), easily separated by chromatography.

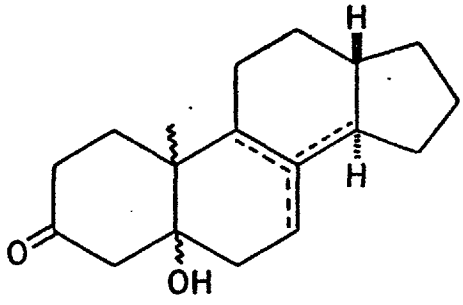
With the introduction of the trans-fused D ring the diene (68) becomes asymmetric. Hence each monoepoxide can have two epimeric forms and the bisepoxide, four epimeric forms. An examination of a molecular model of diene (68) shows no steric preferences and each monoepoxide can be expected to contain a 1:1 mixture of epimers.

The p.m.r. spectrum of the A ring epoxide (69) showed a vinyl proton (τ 4·70), a methyl singlet (τ 8·70) α to the epoxide and the ethyleneketal (singlet at τ 6·15). The C ring epoxide showed only the last of these.

Although the model diene (31) had been cyclised via the A ring epoxide, it was thought of interest to examine the action of a Lewis acid on the C ring epoxides (70). Treatment of the epoxides (70) with

boron trifluoride etherate, followed by mild acid hydrolysis gave a complex mixture of products which was not investigated.

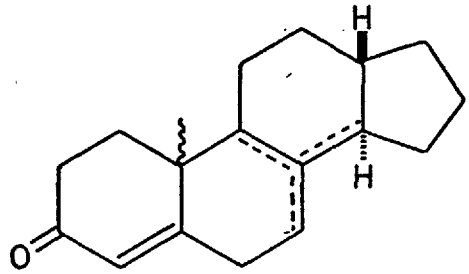
Treatment of the A ring epoxides (69) under these conditions gave a semicrystalline product, from which was obtained the crystalline ß-ketols (72), ν_{max} 3400, 1715 cm^{-1}, a mixture of at least three epimeric double bond isomers, containing the required steroid nucleus.



(72)

The small amount of material available precluded the separation of the isomers of (72). The isomeric mixture was homogeneous on t.l.c. in several solvent systems. However it was possible to show that the desired cyclisation had taken place by the presence of three angular methyl groups in the p.m.r. spectrum (τ9·00, 9·05 and 9·12) in approximately equal proportions. This spectrum also revealed a broad signal at τ4·70 integrating for ca. $\frac{1}{3}$ proton indicating that the steroid mixture contained ca. $\frac{1}{3}$ of Δ^7 isomers. Elemental analysis and the mass spectrum (M^+, 274 plus a strong M - 18 peak) confirmed the molecular formula.

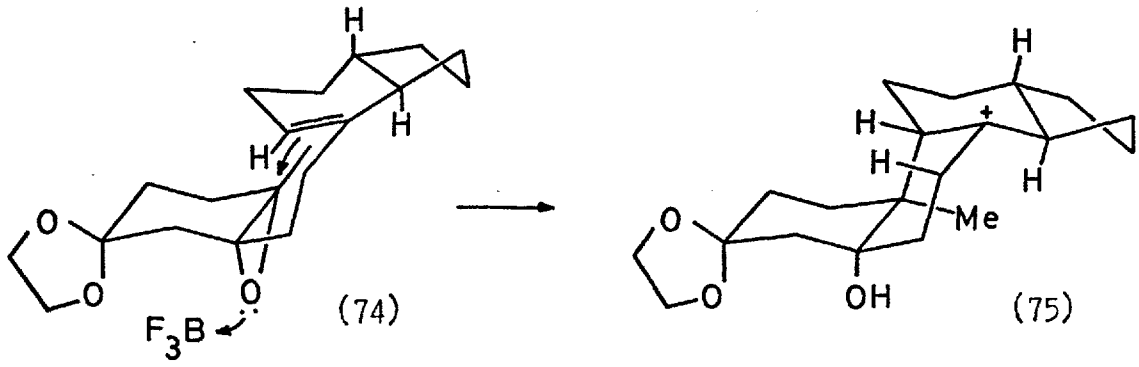
The ketols (72) underwent dehydration on treatment with sodium ethoxide to afford the corresponding mixture of αß-unsaturated ketones (73), ν_{max} 1660 cm^{-1}, λ_{max} 230 nm. A crystalline 2,4-dinitrophenylhydrazone of correct elemental composition was obtained from (73).



(73)

Thus it has been shown that the trans-hydrindane system, derived from the stereospecific transannulation of a cis,trans-1,5-cyclo--nonadiene can be incorporated into a steroid nucleus with a trans-fused CD ring junction. At this stage insufficient material was available to determine which of the possible epimeric double bond isomers are formed in the epoxyolefin cyclisation.

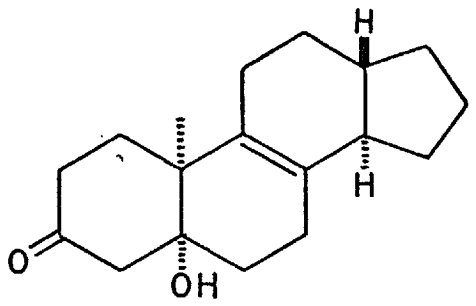
It is however possible to predict the more likely structures on theoretical grounds. The stereoelectronic requirements of diaxial antiperiplanar opening of the epoxide-Lewis acid complex and of axial bond formation to the olefin determine the conformation of the cyclising molecule. Thus the ∝-epimer of (69) can be expected to cyclise in the B ring chair conformation (74). The locked conformation of the C ring in (74) necessitates this mode of cyclisation despite the fact that the B ring boat conformation is sterically more favourable (see p. 58). The intermediate carbonium ion (75) can then eliminate an axial proton to give, after hydrolysis, the ketones (76), (77) and (78).



(74) (75)

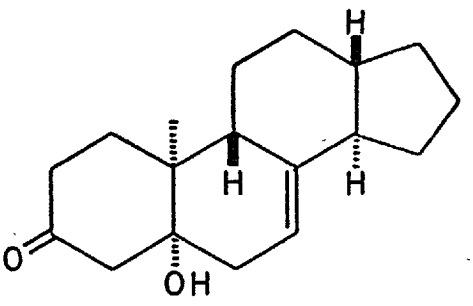
i. Proton loss

ii. Hydrolysis



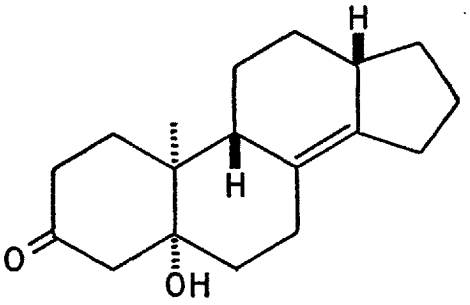
(76)

+



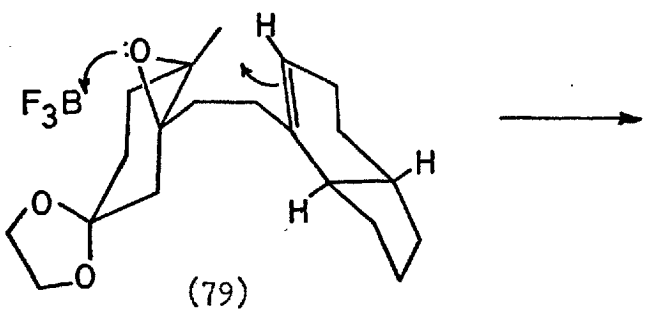
(77)

+

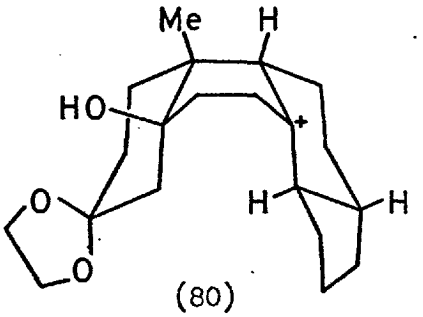


(78)

The ß-epimer of (69) should cyclise via the sterically more favourable B ring boat conformation (79) giving the ketones (81) and (82) as the two possible products.

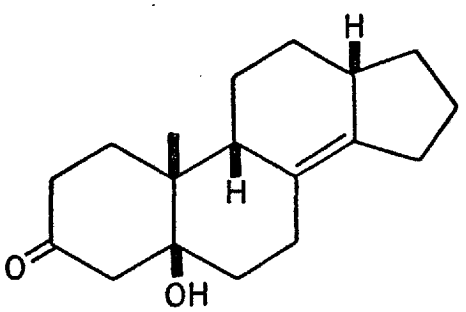


(79)



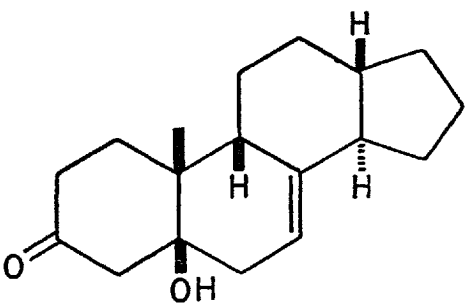
(80)

i. Proton loss
ii. Hydrolysis



(81)

+

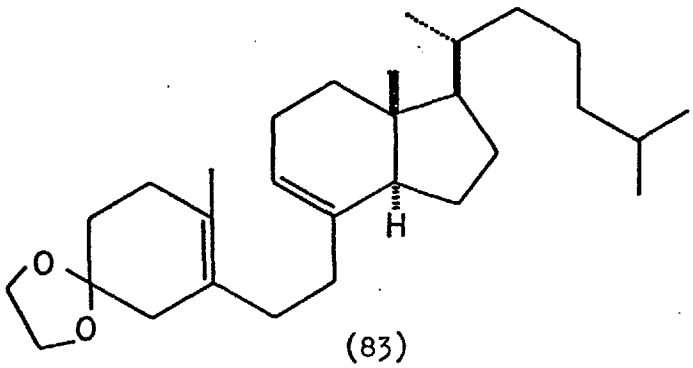


(82)

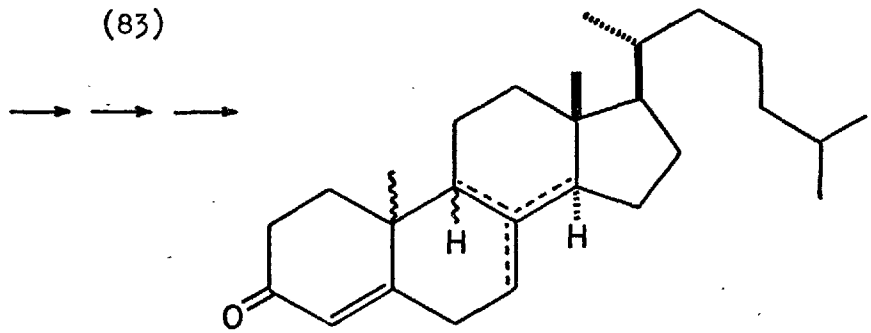
Approaches to Establish the Stereochemistry of Cyclisation.

The best way to establish the stereochemistry of this epoxyolefin cyclisation would be to achieve the cyclisation on a naturally derived secosteroid. The products could then be compared to the corresponding steroids of unequivocally defined stereochemistry.

Some preliminary experiments were conducted on the synthesis of the diene (83), with the CD rings and the side chain derived from cholesterol. This would give the isomeric steroids (84).

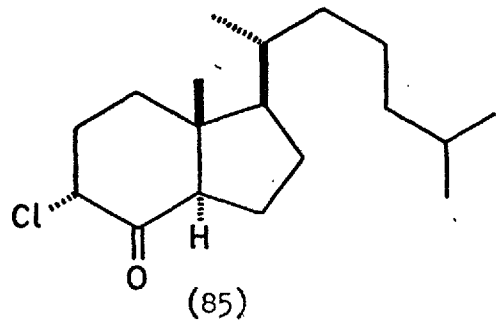


(83)



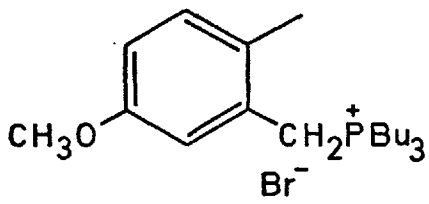
(84)

The obvious analogy of the ∝-chloroketone (85) [21] to the bromoketone (3d) suggested that this could be converted to the diene (83) by the same coupling/reduction sequence used in the synthesis of the diene (68). The chloroketone (85) was prepared by Lythgoe's method.[21] However it proved impossible to couple this to the Grignard reagent from the chloride (35), due probably to the steric hindrance of the axial ∝-chlorine atom.

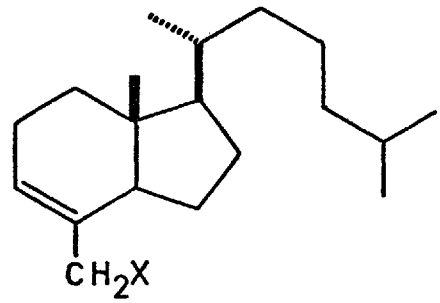


(85)

The synthetic route to the diene (83) at present under investigation is to couple the allylic bromide (88) to the phosphonium salt (86) by the method of Van Tamelen.[22] It is hoped to derive the bromide (88) from the allylic alcohol (87) [23] easily derived from cholesterol.



(86)



(87), X=OH
(88), X=Br

EXPERIMENTAL

All melting points were taken with a Kofler hot stage apparatus and are uncorrected. Proton magnetic resonance (p.m.r.) spectra were determined on Varian A60 or T60 instruments. Infrared spectra were recorded on a Unicam SP200 and ultraviolet spectra on a Unicam SP800 spectrophotometer. Mass spectra were determined on an A.E.I. MS9 mass specrometer .

Neutral alumina of Brockmann grades I or III and Silica Gel MFC (Hopkin and Williams) were used for column chromatography. Thin layer (t.l.c.) and preparative layer chromatography (p.l.c.) plates were prepared from Merck Kieselgel GF_{254}.

Organic solutions were dried over either anhydrous sodium sulphate or potassium carbonate.

Unless otherwise stated reactions were carried out at room temperature.

Unless aqueous solvents are specified reactions were conducted under anhydrous conditions.

Petrol refers to petroleum ether b.p. 40-60° which was redistilled before use. Benzene and diethyl ether were dried over sodium wire. Tetrahydrofuran was predried with sodium and distilled over lithium aluminium hydride. Methylene chloride was distilled over phosphorus pentoxide. Ethanol and methanol were refluxed over magnesium/iodine and distilled. tert-Butanol and 2-methylbutan-2-ol were distilled over calcium hydride. Pyridine was distilled from and stored over potassium hydroxide pellets. Acetone was stored over anhydrous potassium carbonate and distilled before use.

2-Chloromethyl-4-nitrotoluene (16).[9]

4-Nitrotoluene was converted by the literature method [9] to 2-chloromethyl-4-nitrotoluene, m.p. 53-4°.

2-(2-Ethoxycarbonyl-3-ketobutyl)-4-nitrotoluene (17, R=ethyl).

Ethyl acetoacetate (13·0 g.) was added to a warm solution of sodium ethoxide (from 2·30 g. sodium metal) in ethanol (50 ml.). After 15 min. 2-chloromethyl-4-nitrotoluene (16) (18·5 g.) in ethanol (50 ml.) was added and stirred overnight under reflux. The hot solution was filtered to remove the sodium chloride precipitate. Evaporation of the ethanol gave the crude β-ketoester (17, R=ethyl) (26·5 g.). Distillation of a portion gave a pale yellow liquid, b.p. 190°/2 mmHg.

ν_{max}(film) 1715, 1730, 1530, 1355, 750 cm^{-1}.

λ_{max}(EtOH) 274 nm (ϵ 10,650).

τ($CDCl_3$) 6·0-7·3 (3H, m), 1·5-3·0 (3H, m), 5·76 (2H, q, J=7 Hz), 8·76 (3H, t, J=7 Hz), 7·54 (3H, s), 7·69 (3H, s).

2-(3-Ketobutyl)-4-nitrotoluene (18).

Method 1.- The crude β-ketoester (17, R=ethyl) (23·7 g.) was stirred for three days in refluxing 15% aqueous sulphuric acid (500 ml.). On cooling the product was extracted with ether. The ether solution was washed with saturated aqueous sodium bicarbonate, brine, dried and the ether evaporated. Distillation of the residue in vacuo gave 2-(3-ketobutyl)-4-nitrotoluene (18) (6·34 g., 36%), b.p. 124-30°/0·04 mmHg, which crystallised on standing. Recrystallisation (ether/petrol) gave colourless needles, m.p. 54-5°.

ν_{max}(nujol) 1710, 1355, 1540 cm^{-1}.

λ_{max}(EtOH) 277 nm (ε 9,200).

τ($CDCl_3$) 1·5-3·0 (3H, m), 7·07 (4H, A_2B_2 system), 7·55 (3H, s), 7·76 (3H, s).

Found: C, 63·96%; H, 6·27%; N, 6·81%.

$C_{11}H_{13}NO_3$ requires C, 63·77%; H, 6·38%; N, 6·76%.

The aqueous sodium bicarbonate washings were acidified to precipitate 2-(2-carboxyethyl)-4-nitrotoluene (19) (3·70 g., 18%) which was recrystallised (ether/petrol) to give pale yellow needles, m.p. 123-4°.

ν_{max}(nujol) 1705, 1530, 1315, 1250, 820 cm^{-1}.

τ($CDCl_3$) 0.25 (1H, s, D_2O labile), 1·88 (1H, s), 1·96 (1H, d, J=9 Hz), 2·62 (1H, d, J=9 Hz), 6·7-7·8 (4H, A_2B_2 m), 7·54 (3H, s).

Found: C, 57·63%; H, 5.23%; N, 6·68%.

$C_{10}H_{11}NO_4$ requires C, 57·42%; H, 5·27%; N, 6·70%.

Method 2.- tert-Butyl acetoacetate (3·61 g.) was added to a warm solution of sodium ethoxide (from 0·52 g. sodium metal) in ethanol (10 ml.). After 15 min. 2-chloromethyl-4-nitrotoluene (16) (4·24 g.) in ethanol (10 ml.) was added and stirred overnight under reflux. The hot solution was filtered to remove the sodium chloride precipitate and the ethanol was evaporated to give 2-(2-tert-butoxycarbonyl-3--ketobutyl)-4-nitrotoluene (17, R=tert-butyl) (6·45 g., 92%), a yellow oil.

ν_{max}(film) 1726, 1710, 1530, 1355, 1250, 1150, 830, 750 cm^{-1}.

τ($CDCl_3$) 1·88 (1H, s), 1·96 (1H, d, J=9 Hz), 2·62 (1H, d, J=9 Hz), 5·6-7·0 (3H, m), 7·54 (3H, s), 7·70 (3H, s), 8·56 (9H, s).

The ester (17, R=tert-butyl) was not purified but used directly in the next stage. The ester (6·40 g.) was heated under nitrogen

with toluene-p-sulphonic acid (200 mg.) at 120° (bath) for 3 hr. The resulting yellow gum was dissolved in ether (40 ml.), washed with saturated aqueous sodium bicarbonate, brine and dried. Evaporation of the ether gave the ketone (18) (4·15 g., 95%). The p.m.r. spectrum showed the absence of unreacted ester in the crude product.

2-(3-Methylbut-3-enyl)-4-nitrotoluene (15).

Sodium hydride (6·25 g. of a 57% oil dispersion) was washed free of oil with benzene and suspended in benzene (600 ml.) under nitrogen. 2-Methylbutan-2-ol (24·0 g.) was added dropwise to the stirred suspension which was warmed to give a clear solution of sodium 2-methylbutan-2-oxide. Triphenylmethylphosphonium bromide (53·1 g.) was added and stirred 1 hr. to give a deep yellow solution. The ketone (18) (28·0 g.) in benzene (150 ml.) was added and stirred overnight under reflux. The solution was filtered, concentrated and chromatographed on grade I alumina (1 kg.). 9:1 petrol/methylene chloride eluted 2-(3-methylbut-3-enyl)-4-nitrotoluene (15) (18·83 g., 67%), a pale yellow oil, n_{23}^{D} 1·5466.

ν_{max}(film) 1530, 1355, 910 cm^{-1}.

λ_{max}(EtOH) 277 nm (ϵ 8,200).

τ($CDCl_3$) 1·8-2·8 (3H, m), 5·2 (2H, s), 6·95-7·85 (4H, A_2B_2 m), 7·55 (3H, s), 8·20 (3H, s).

Found: C, 70·55%; H, 7·19%; N, 6·85%.

$C_{12}H_{15}NO_2$ requires C, 70·25%; H, 7·32%; N, 6·83%.

Zinc/Ammonium Chloride Reduction of the Nitroolefin (15).

AnalaR zinc dust (200 mg.) was added during 5 min. to a vigorously stirred solution of the nitroolefin (15) (195 mg.) and ammonium chloride (100 mg.) in 4:1 ethanol/water (5 ml.) at 50° under nitrogen. After a further 5 min. the solution was filtered and the precipitate washed with ethanol (2 ml.). The combined ethanol solutions were stirred with sodium chloride (1 g.) and crushed ice, then extracted with ether. The dried ether solution was evaporated at 20° to give a yellow oil, ν_{max} 3300, 1610, 1500, 900 cm^{-1}. Attempts to crystallise the oil from several solvents were unsuccessful. T.l.c. showed it to be a mixture of the amine (21) and unreacted (15).

Benzoylation.- The crude oily product (31 mg.) in methylene chloride (5 ml.) was treated with benzoic acid (50 mg.) and dicyclohexylcarbo--diimide (100 mg.) for 3 hr. The solution was filtered, washed with aqueous sodium bicarbonate and dried. P.l.c. (silica gel, chloroform) of the crude product gave the benzoyl derivative (32 mg.) of 2-(3-methylbut-3-enyl)-4-aminotoluene (21). Recrystallisation (ether/petrol) gave colourless needles, m.p. 88-9°.

ν_{max}(nujol) 1645, 890, 830, 728 cm^{-1}.

Found: C, 81·63%; H, 7·20%; N, 4·80%.

$C_{19}H_{21}NO$ requires C, 81·72%; H, 7·53%; N, 5·02%.

2-(3-Methylbut-3-enyl)-4-hydroxyaminotoluene (20).

AnalaR zinc dust (150 mg.) was added during 15 min. to a vigorously stirred solution of the nitroolefin (15) (240 mg.) and ammonium acetate (1·0 g.) in 4:1 ethanol/water (25 ml.) under nitrogen. After a further 5 min., iced water and sodium chloride (1 g.) were added and the mixture was extracted with ether. The dried ether solution

was evaporated at 20° to give 2-(3-methylbut-3-enyl)-4-hydroxyamino--toluene (20) (155 mg.), a yellow waxy solid, ν_{max}(nujol) 3300, 1620, 1510, 900, 830 cm^{-1}. The solid crystallised from ether/petrol at -78° but redissolved above this temperature. Ca. 1 mg. of white crystalline solid, m.p. 35° was obtained by rapid filtration.

Tosylation.- The hydroxylamine (20) was treated with toluene-p-sulphonyl chloride in pyridine at 0° overnight. Evaporation of the pyridine at 20° (oil pump) and p.l.c. of the residue gave the tosylate, colourless plates, m.p. 119-21° from ether/petrol.

Found: C, 65·90%; H, 6·63%; N, 3·99%.

$C_{19}H_{23}NO_3S$ requires C, 66·08%; H, 6·67%; N, 4·06%.

Reactions of the Hydroxylamine (20).

The reactions attempted and conditions used are summarised on p. 48. The general technique used was to add the reagent to a solution of the hydroxylamine under nitrogen. The reactions were worked up by pouring into water and extracting with ether. The ether solution was washed with 2N hydrochloric acid, aqueous sodium bicarbonate, dried and evaporated to give a neutral fraction. The acid solution was basified with 4N sodium hydroxide and extracted with ether to give a basic fraction. In all cases t.l.c. showed both the neutral and basic fractions to consist mainly of intractable tars. In two cases (boron trifluoride etherate and Amberlyst 15), the crystalline azoxy compound (24) was isolated by p.l.c. Recrystallisation (ether/petrol) gave pale yellow microcrystals, m.p. 53-4°.

ν_{max}(nujol) 1650, 1500, 910, 830 cm^{-1}.

$\tau(CCl_4)$ 8·26 (6H, s), 7·61 (6H, s), 6·9-7·9 (8H, A_2B_2 m), 5·20 (4H, broad s), 1·8-2·8 (6H, m).

Found: C, 79·69%; H, 8·56%; N, 7·59%.

$C_{24}H_{30}N_2O$ requires C, 79·52%; H, 8·34%; N, 7·73%.

Stannous Chloride Reduction of the Nitroolefin (15).

The nitroolefin (15) (3·10 g.) was stirred in a solution of stannous chloride (10·0 g.) in 4N hydrochloric acid (75 ml.) and acetone (200 ml.). After 5 hr. an organic layer was still visible on the surface of the solution. A further 10.0 g. stannous chloride and 25 ml. hydrochloric acid was added and stirred 2 hr. The solution was diluted with water and extracted with ether. The aqueous layer was basified with sodium hydroxide and extracted with ether. This ether extract was washed with water, dried and the ether evaporated to give 2-(3-hydroxy-3-methylbutyl)-4-aminotoluene (26) (1·08 g.), a brown oil which crystallised on standing, m.p. 85-90°. Recrystallisation (ether/petrol) gave colourless plates, m.p. 93-5°.

ν_{max}(nujol) 3250, 3400, 1615, 1510, 830 cm^{-1}.

λ_{max}(EtOH) 237 nm (ϵ 7,300), 290 nm (ϵ 1,600).

τ($CDCl_3$) 3·1-3·7 (3H, m), 7·86 (3H, s), 7·97 (4H, A_2B_2 m), 8·76 (6H, s).

Found: C, 74·71%; H, 9·75%; N, 7·16%.

$C_{12}H_{19}NO$ requires C, 74·61%; H, 9·85%; N, 7·25%.

2-(3-Methylbut-3-enyl)-4-aminotoluene (21).

The nitroolefin (15) (6·00 g.) in ether (200 ml.) was stirred overnight with moist, freshly prepared aluminium amalgam (7·5 g.). Water (40 ml.) was added with vigorous stirring to coagulate the alumina precipitate, from which the solution was decanted. The precipitate was washed with ether (2 x 50 ml.), the combined ether solutions were washed with water, dried and the solvent evaporated. Distillation *in vacuo* of the crude product gave 2-(3-methylbut-3-enyl)--4-aminotoluene (21) (3·23 g., 62%), b.p. 98-100°/0·25 mmHg.

ν_{max}(film) 3350, 1620, 1510, 900, 820 cm^{-1}.

λ_{max}(EtOH) 237·5 nm (ε 7,700), 292 nm (ε 1,600).

τ($CDCl_3$) 3·44 (1H, d, J=8 Hz), 3·08 (1H, d, J=8 Hz), 3·50 (1H, s), 5·22 (2H, s), 6·60 (2H, broad s, D_2O labile), 7·1-8·0 (4H, m), 7·81 (3H, s), 8·22 (3H, s).

2-(3-Methylbut-3-enyl)-4-acetamidotoluene (27).

The amine (21) (671 mg.) was suspended in water (2 ml.) and stirred vigorously 1 hr. with acetic anhydride (1 ml.). The amide (27) precipitated as a white solid and was isolated by diluting with water (5 ml.) and extracting with methylene chloride. The extracts were washed with saturated aqueous sodium bicarbonate, water, dried and the solvent evaporated to give 2-(3-methylbut-3-enyl)-4-acetamidotoluene (27) (831 mg., 100%). Recrystallisation (ether/petrol) gave colourless plates, m.p. 112-3°.

ν_{max}(nujol) 3300, 1655, 1615, 900,835 cm^{-1}.

λ_{max}(EtOH) 247 nm (ε 19,000), 287 nm (ε 1,080).

τ($CDCl_3$) 2·60-3·33 (3H, m), 1·97 (1H, broad s, D_2O labile), 5·27 (2H, s), 7·76 (3H, s), 7·92 (3H, s), 8·25 (3H, s), all other protons in the region 7·1-8·0.

Found: C, 77·30%; H, 8·65%; N, 6·43%.

$C_{14}H_{19}NO$ requires C, 77·41%; H, 8·75%; N,6·45%.

2-(3-Methylbut-3-enyl)-4-ethylaminotoluene (28).

The amide (27) (337 mg.) in ether (40 ml.) was stirred 48 hr. with lithium aluminium hydride (760 mg.). Excess reagent was destroyed by the dropwise addition of N sodium hydroxide (2 ml.). The solution was decanted from the precipitate which was washed with ether (2 x 10 ml.). The combined, dried ether solutions were

evaporated to give 2-(3-methylbut-3-enyl)-4-ethylaminotoluene (28) (281 mg., 89%), a pale yellow oil.

ν_{max}(film) 3400, 1620, 1520, 1330, 900, 810 cm^{-1}.

λ_{max}(EtOH) 247nm (ϵ 10,200), 297·5 nm (ϵ 2,000).

τ($CDCl_3$) 3·55 (1H, d, J=8 Hz), 3·03 (1H, d, J=8 Hz), 3·50 (1H, s), 5·20 (2H, broad s), 6·90 (1H, s, D_2O labile), 7·79 (3H, s), 8·20 (3H, s), 6·85 (2H, q, J=7 Hz), 8·76 (3H, t, J=7 Hz).

Benzoyl Derivative.- The amine (28) (40 mg.) was shaken with benzoyl chloride (0·5 ml.) in aqueous sodium hydroxide. Extraction with methylene chloride and p.l.c. gave the benzoyl derivative, an oil, which was purified by short path distillation (100° bath/0·1 mmHg).

ν_{max}(film) 1645, 1605, 1505, 1320, 895, 830 cm^{-1}.

Found: C, 82·25%; H, 8·11%; N, 4·78%.

$C_{21}H_{25}NO$ requires C, 82·10%; H, 8·14%; N, 4·56%.

N-Chloro-N-ethyl-2-(3-methylbut-3-enyl)-4-aminotoluene (14, R=ethyl, X=Cl).

The N-ethylamine (28) (175 mg.) in carbon tetrachloride (20 ml.) was stirred with powdered calcium hypochlorite (2·0 g.) under nitrogen at 0° for 1 hr. T.l.c. (silica gel, chloroform) showed a single product. The solution of the N-chloroamine (14, R=ethyl, X=Cl) was filtered and used without isolation of the product for further experiments.

Cyclohexane and methylene chloride were used as alternative solvents in some experiments (see below).

τ(CCl_4) 3·0-3·8 (3H, m), 5·26 (2H, broad s), 6·84 (2H, q, J=7 Hz), 7·80 (3H, s), 8·20 (3H, s), 8·71 (3H, t, J=7 Hz), all other protons in the region 7·0-8·0.

Reaction of the N-Chloroamine (14, R=ethyl, X=Cl) with Silver Ion.

Experiment 1.- A solution of the N-chloroamine (14, R=ethyl, X=Cl) in carbon tetrachloride was prepared from the amine (28) (150 mg.) and cooled to -20°. A solution of silver perchlorate (297 mg.) in benzene (15 ml.) was added giving an immediate pale brown precipitate. The solution was stirred at -20° for 5 hr. then washed with water, dried and evaporated. P.l.c. (silica gel, 4:1 petrol/chloroform) of the dark brown oily residue gave the ring chlorinated amine (29) (54 mg., 30%), a pale yellow oil, as the only nonpolar product.

ν_{max}(film) 3420, 1610, 1520, 900, 810 cm^{-1}.

λ_{max}(EtOH) 247 nm (ϵ 9,270), 304·5 nm (ϵ 2,670).

$\tau(CDCl_3)$ 2·95 (1H, s), 3·51 (1H, s), 5·22 (2H, s), 5·8-6·4 (1H, broad absorption, D_2O labile), 7·83 (3H, s), 8·21 (3H, s), 6·80 (2H, q, J=7 Hz), 8·72 (3H, t, J=7 Hz).

Benzoyl Derivative.- The amine (29) (40 mg.) was shaken with benzoyl chloride (0·5 ml.) in aqueous sodium hydroxide. Extraction with methylene chloride and p.l.c. gave the benzoyl derivative (41 mg.), an oil, which was purified by short path distillation (100° bath/0·1 mmHg).

ν_{max}(film) 1655, 1600, 1500, 1320, 905, 805, 710 cm^{-1}.

Found: C, 73·68%; H, 7·02%; N, 3·95%.

$C_{21}H_{24}ClNO$ requires C, 73·75%; H, 7·07%; N, 4·10%.

Experiment 2.- A solution of the N-chloroamine (14, R=ethyl, X=Cl) was prepared from the amine (28) (138 mg.) in cyclohexane (20 ml.), and added dropwise under nitrogen to a stirred solution of silver trifluoroacetate (200 mg.) in benzene (20 ml.). A white precipitate formed immediately. After stirring overnight, the solution was washed

with water, dried and evaporated. P.l.c. of the brown oily residue gave (29) (38 mg.) as the only nonpolar product.

Experiment 3.- A solution of the N-chloroamine (14, R=ethyl, X=Cl) in methylene chloride was prepared from the amine (28) (300 mg.). The solution was evaporated at 20°, the residue was dissolved in benzene, added to a solution of silver perchlorate (614 mg.) in benzene (200 ml.) and stirred overnight. The solution was washed with water, dried and evaporated. T.l.c. of the residue showed a complex mixture.

Experiment 4.- A solution of the N-chloroamine (14, R=ethyl, X=Cl) was prepared from the amine (28) (200 mg.) and added to a benzene (20 ml.) solution of silver perchlorate (359 mg.) and triethylamine (1·0 g.) at 0°, and stirred overnight. The usual work up procedure gave the ring chlorinated amine (29) (65 mg.) as the only nonpolar product.

Control Experiment.- A solution of the N-chloroamine (14, R=ethyl, X=Cl) in carbon tetrachloride was prepared from the amine (28) (157 mg.). It was diluted with benzene and set aside overnight at room temperature. The usual work up procedure gave the ring chlorinated amine (29) (87 mg., 48%).

Reaction of the N-Chloroamine (14, R=ethyl, X=Cl) with Silver Trifluoroacetate and Methanol.

Experiment 1.- A solution of the N-chloroamine in carbon tetrachloride was prepared from the amine (28) (180 mg.) and added to silver trifluoroacetate (242 mg.) in methanol (30 ml.) at 0° and

stirred 3 hr. The usual work up procedure gave the ring chlorinated amine (29) (60 mg.) as the only nonpolar product.

Experiment 2.- The amine (28) (263 mg.) in carbon tetrachloride (5 ml.) was treated at 0° in the dark under nitrogen with tert-butyl hypochlorite (156 mg.) in carbon tetrachloride (5 ml.) for 15 min. Methanol (10 ml.) was added followed by silver trifluoroacetate (324 mg.) in methanol (10 ml.). A white precipitate formed almost immediately. After 2 hr. at 0°, the usual work up procedure gave a brown oil. The ring chlorinated amine (29) (136 mg.) was obtained by p.l.c. as the only nonpolar product.

2-Bromo-4-aminotoluene.

A modification of the literature procedure [15] was used.

4-Nitrotoluene (280 g.) and iron filings (12 g.) were stirred at 100° during the dropwise addition over 3 hr. of bromine (100 ml.). After a further 1 hr. at 100°, the hot mixture was poured with stirring into cold water (3 l.). The water was decanted from the crude solid 2-bromo-4-nitrotoluene which was dissolved in 95% ethanol (1 l.). Concentrated hydrochloric acid (25 ml.) was added and the boiling solution was stirred vigorously (mechanical paddle stirrer) during the addition of iron filings (300 g.) over 2 hr. The reaction mixture was stirred overnight under reflux. The hot solution was filtered, concentrated, added to water (3 l.), basified with 4N sodium hydroxide and boiled 3 hr. to disperse the ferrous hydroxide precipitate. On cooling, the lower layer was separated and distilled in vacuo to give 2-bromo-4-aminotoluene (278 g., 73%), a pale yellow liquid, b.p. 96-105°/2 mmHg.

2-Bromo-4-methoxytoluene.

A modification of the literature procedure [15] was used.

2-Bromo-4-aminotoluene (278 g.) in 6N hydrochloric acid (2 l.) was diazotised below 5° by the dropwise addition of sodium nitrite (120 g.) as a saturated aqueous solution.

Sodium hydrogen sulphate (200 g.) and 50% aqueous sulphuric acid (500 ml.) in a 5 l. flask were brought to boiling by the passage of a current of steam. The diazonium salt solution was added dropwise to this solution so that the phenol produced distilled over in the current of steam. The passage of steam was continued until no more phenol distilled over. The crude 2-bromo-4-cresol (128 g.) was isolated by extraction with methylene chloride.

2-Bromo-4-cresol (128 g.) and sodium hydroxide (55 g.) in water (500 ml.) were cooled to 0°. Dimethyl sulphate (130 ml.) was added dropwise over 1 hr. to the stirred solution whilst keeping the temperature below 10°. The mixture was then stirred 3hr. under reflux. The pH was checked at intervals and when necessary the solution was made alkaline by the addition of 4N sodium hydroxide. The cooled solution was extracted with methylene chloride (3 x 150 ml.), the extracts washed with brine, dried and concentrated. Distillation of the crude product *in vacuo* gave pure 2-bromo-4-methoxytoluene (92·6 g.), b.p. 88-90°/5 mmHg (lit. b.p. 103-5°/10 mmHg).

ν_{max}(film) 1605, 1500, 1300, 1245, 1050, 870, 815 cm^{-1}.

$\tau(CDCl_3)$ 2·8-3·4 (3H, m), 6·24 (3H, s), 7·67 (3H, s).

2-(2-Hydroxyethyl)-4-methoxytoluene (34).

A solution of the Grignard reagent was prepared under nitrogen from 2-bromo-4-methoxytoluene (28·0 g.) and magnesium turnings (6·0 g.) in tetrahydrofuran (100 ml.) and cooled to 0°. Freshly distilled ethylene oxide (ca. 24 g.) in ether (100 ml.) was added dropwise and stirred at 0° for 4 hr. The solvent was removed by warming to 70° and the magnesium salt was hydrolysed by 40% hydrochloric acid. The product was extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, water and dried. Evaporation of the ether and distillation of the residue in vacuo gave 2-(2-hydroxyethyl)--4-methoxytoluene (34) (17·2 g., 75%), b.p. 96-100°/0·2 mmHg.

ν_{max}(film) 3400, 1610, 1510, 1250, 1050, 820 cm^{-1}.

$\tau(CDCl_3)$ 2·8-3·5 (3H, m), 6·25 (3H, s), 7·76 (3H, s), 7·20 (2H, t, J=6·5 Hz), 6·20 (2H, t, J=6·5 Hz), 7·46 (1H, s, D_2O labile).

3,5-Dinitrobenzoate.- The alcohol (34) (221 mg.) and 3,5-dinitrobenzoyl chloride (200 mg.) were refluxed in benzene for 10 min. The solution was filtered, the benzene evaporated and the product recrystallised (benzene/ether) to give the 3,5-dinitrobenzoate, m.p. 148-51°.

Found: C, 56·83%; H, 4·61%; N, 7·76%.

$C_{17}H_{16}N_2O_7$ requires C, 56·66%; H, 4·44%; N, 7·78%.

2-(2-Chloroethyl)-4-methoxytoluene (35).

Thionyl chloride (10·0 ml.) was added dropwise over 1 hr. to a stirred solution of the alcohol (34) (20·0 g.) in pyridine (10·0 g.) whilst maintaining the temperature below 30°. The reaction mixture was stirred 1 hr. at 20°, then 30 min. at 80°, cooled and poured into water. The product was extracted into ether, the ether solution washed with aqueous sodium bicarbonate, dried and evaporated.

Distillation of the crude product in vacuo gave 2-(2-chloroethyl)--4-methoxytoluene (35) (19·36 g., 87%), b.p. 70-2°/0·2 mmHg (lit.[15] b.p. 126-34°/10 mmHg).

ν_{max}(film) 1612, 1510, 1255, 1050, 815, 705 cm^{-1}.

$\tau(CCl_4)$ 2·9-3·6 (3H, m), 6·32 (3H, s), 6·45 (2H, t, J=7 Hz), 7·05(2H, t, J=7 Hz), 7·76 (3H, s).

2-(2-Bromoethyl)-4-methoxytoluene (36).

Phosphorus tribromide (17 ml.) was added dropwise to a stirred solution of the alcohol (34) (14·5 g.) in carbon tetrachloride (100 ml.) and refluxed 2 hr. Excess reagent was destroyed by the careful addition of water and the organic layer was washed with aqueous sodium bicarbonate, water and dried. Evaporation of the solvent and distillation of the residue in vacuo gave 2-(2-bromoethyl)-4-methoxy--toluene (36) (12·0 g., 60%), b.p. 70-80°/0·15 mmHg.

ν_{max}(film) 1610, 1510, 1255, 1050, 825, 670 cm^{-1}.

$\tau(CDCl_3)$ 2·8-3·4 (3H, m), 6·25 (3H, s), 7·76 (3H, s), 6·30-7·10 (4H, A_2B_2 m).

Found: C, 52·00%; H, 5·81%; Br, 34·65%.

$C_{10}H_{13}BrO$ requires C, 52·42%; H, 5·72%; Br, 34·87%.

2-(2-Cyclohexenylethyl)-4-methoxytoluene (32).

A solution of the Grignard reagent was prepared from the bromide (36) (15·22 g.) and magnesium turnings (2·8 g.) in ether (100 ml.) under nitrogen. Cyclohexanone (15 g.) in ether (80 ml.) was added dropwise to the stirred solution which was then refluxed 30 min. On cooling, aqueous ammonium chloride was added. The ether solution was separated, washed with aqueous sodium bicarbonate, water and dried.

The ether and excess cyclohexanone were removed *in vacuo*. The residue was dissolved in pyridine (50 ml.) and treated overnight with phosphoryl chloride (7·6 ml.) at 0°. The solution was poured into excess ice cold 2N hydrochloric acid and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, water and dried. The residue was chromatographed on grade I alumina (750 g.). 19:1 petrol/chloroform eluted 2-(2-cyclohexenylethyl)--4-methoxytoluene (32) (8·02 g., 52%), b.p. 100-6°/0·1 mmHg (lit.[15] b.p. 150-5°/4 mmHg).

ν_{max}(film) 1610, 1510, 1255, 1050, 820, 810 cm^{-1}.

λ_{max}(EtOH) 284 (sh) (ϵ 1,910), 278 (ϵ 2,140), 205 nm (ϵ 17,000).

$\tau(CDCl_3)$ 7·76 (3H, s), 6·25 (3H, s), 4·55 (1H, broad), 2·8-3·5 (3H, m), all other protons in the region 7·2-8·5.

1-Methyl-2-(2- cyclohexenylethyl)-4-methoxy-1,4-cyclohexadiene (38).

Sodium metal (1·70 g.) was added in small portions to a stirred solution of the aromatic ether (32) (674 mg.) in distilled ammonia (ca. 50 ml.), tetrahydrofuran (25 ml.) and *tert*-butanol (25 ml.). Stirring was continued 5 hr., excess powdered ammonium chloride was added and the ammonia was allowed to evaporate overnight. The residue was partitioned between ether and water. The ether solution was washed with water, dried and evaporated to give 1-methyl--2-(2-cyclohexenylethyl)-4-methoxy-1,4-cyclohexadiene (38), (616 mg., 92%), a pale yellow oil. An analytically pure sample was obtained by chromatography on grade III alumina eluting with pentane.

ν_{max}(film) 1698, 1670, 798 cm^{-1}.

$\tau(CCl_4)$ 4·66 (1H, broad), 5·58(1H, broad), 6·55 (3H, s), 8·40 (3H, s), all other protons in the region 7·0-9·2.

Found: C, 82·77%; H, 10·30%.

$C_{16}H_{24}O$ requires C, 82·75%; H, 10·35%.

1-Methyl-2-(2-cyclohexenylethyl)cyclohexen-4-one (39).

A solution of the enol ether (38) (228 mg.) and oxalic acid (250 mg.) in ethanol (15 ml.) and water (3 ml.) was stirred overnight. Aqueous sodium bicarbonate was added to neutralise the acid and the solution was extracted with ether. The ether extracts were washed with water, dried and evaporated to give 1-methyl-2-(2-cyclohexenylethyl)cyclohexen-4-one (39) (193 mg.), a pale yellow oil.

ν_{max}(film) 1720, 1670 cm^{-1}.

$\tau(CCl_4)$ 4·74 (1H, broad), 7·67 (3H, s), all other protons in the region 7·0-9·0.

Semicarbazone.- Semicarbazide hydrochloride (16 mg.) and sodium acetate (24 mg.) were dissolved in a few drops of water and diluted with ethanol (3 ml.). This solution was added to the ketone (39) (28 mg.) and refluxed 10 min. On cooling the crystalline semicarbazone was obtained. Recrystallisation from ethanol gave colourless plates, m.p. 153-5°.

Found: C, 69·78%; H, 9·07%; N, 15·28%.

$C_{16}H_{25}N_3O$ requires C, 69·82%; H, 9·09%; N, 15·27%.

1-Methyl-2-(2-cyclohexenylethyl)-4,4-ethylenedioxycyclohexene (31).

A solution of the ketone (39) (114 mg.), ethanediol (1 ml.) and toluene-p-sulphonic acid (10 mg.) in benzene (10 ml.) was stirred overnight under reflux with a Dean-Stark separator to remove the water produced. The cooled solution was washed with water, aqueous sodium bicarbonate and dried. Removal of solvent gave 1-methyl--2-(2-cyclohexenylethyl)-4,4-ethylenedioxycyclohexene (31) (138 mg.), a colourless oil. P.l.c. (alumina, petrol) gave an analytically pure sample.

ν_{max}(film) 1090, 1065, 950 cm^{-1}.

$\tau(CCl_4)$ 4·60 (1H, broad), 6·10 (4H, s), all other protons in the region 7·5-9·0.

Found: C, 77·88%; H, 9·86%.

$C_{17}H_{26}O_2$ requires C, 77·85%; H, 9·92%.

Reaction of the Model Diene Ethyleneketal (31) with Aqueous N-Bromosuccinimide.

Recrystallised N-bromosuccinimide (272 mg.) was added to a solution of the model diene ethyleneketal (31) (400 mg.) in AnalaR acetone (200 ml.) and water (4 ml.). After overnight stirring the solution gave a negative starch iodide test. Toluene-p-sulphonic acid (100 mg.) was added and the solution refluxed 1 hr. followed by evaporation of the acetone. The residue was extracted with ether, the extracts were washed with aqueous sodium bicarbonate, dried and the solvent removed to give an oil, ν_{max} 1670, 3500 cm^{-1}. T.l.c. showed a complex mixture.

Reactions of the Model Diene (31) with Nonaqueous Acids.

1. Trifluoroacetic Acid.- The model diene (31) (10 mg.) in ether (0·5 ml.) was cooled to 0° and treated with trifluoroacetic acid (5 drops). After 48 hr. at 0° t.l.c. showed only starting material.

2. Sulphuric Acid.- The model diene (31) (96 mg.) in ether (5 ml.) was cooled to 0° and treated with sulphuric acid (10 drops). After 48 hr. at 0° the solution had become dark brown. T.l.c. (alumina, 19:1 petrol/chloroform) showed one nonpolar product. The solution was poured into aqueous sodium bicarbonate and extracted with ether. P.l.c. of the crude product gave the $\alpha\beta$-unsaturated ketone (41)(28 mg.).

ν_{max}(film) 1670 cm^{-1}.

$\tau(CCl_4)$ 4·30 (1H, s), 4·60 (1H, broad), 8·80 (3H, d, J=7 Hz), all other protons in the region 7·3-8·7.

Semicarbazone.- Treatment of the ketone (41) (28 mg.) under the conditions on p.93 gave the semicarbazone. Recrystallisation from aqueous ethanol gave colourless microcrystals, m.p. 178-80°.
Found: C, 69·57%; H, 9·20%; N, 15·29%.
$C_{16}H_{25}N_3O$ requires C, 69·82%; H, 9·09%; N, 15·27%.

Reaction of the Model Diene Ethyleneketal (31) with Stannic Chloride.

A solution of the diene (31) (115 mg.) in benzene (5 ml.) was stirred 20 min. with stannic chloride (0·1 ml.). A brown oily precipitate formed. Water was added and the mixture was extracted with methylene chloride. The extracts were washed with aqueous sodium bicarbonate, dried and evaporated. P.l.c. (silica gel, chloroform) of the crude oily product gave the ketone (41) (28 mg.) and the ketone (39) (8 mg.), identical in spectroscopic properties to authentic samples.

Epoxidation of the Diene (31).

m-Chloroperbenzoic acid (176 mg. of 88% w/w) was added to a stirred solution of diene (31) (236 mg.) in methylene chloride (5 ml.). Stirring was continued 1 hr. The solution was poured into aqueous sodium bicarbonate and extracted with methylene chloride. The dried extracts were evaporated and the crude product was separated by p.l.c. (10% silver nitrate on silica gel, 8:1 petrol/ethyl acetate).
The least polar product (R_f ca. 0·5) was the epoxyolefin (44) (50 mg., 20%), a colourless oil.

ν_{max}(film) 1080, 1040, 855 cm^{-1}.

$\tau(CCl_4)$ 4·70 (1H, broad), 6·22 (4H, s), 8·77 (3H, s), all other protons in the region 7·8-8·8.

Found: C, 73·23%; H, 9·50%.

$C_{17}H_{26}O_3$ requires C, 73·38%; H, 9·35%.

The second product (R_f ca. 0·3) was the epoxyolefin (45) (31 mg.), a colourless oil.

ν_{max}(film) 1075, 950, 855 cm^{-1}.

$\tau(CCl_4)$ 6·25 (4H, s), all other protons in the region 7·6-8·8.

Found: C, 73·47%; H, 9·10%.

$C_{17}H_{26}O_3$ requires C, 73·38%; H, 9·35%.

The most polar product (R_f ca. 0·1) was the bisepoxide (46) (26 mg.), a colourless oil.

ν_{max}(film) 1080, 850 cm^{-1}.

$\tau(CCl_4)$ 6·25 (4H, s), 8·77 (3H, s), all other protons in the region 7·5-8·8.

Found: C, 69·47%; H, 8·90%.

$C_{17}H_{26}O_4$ requires C, 69·39%; H, 8·85%.

Cyclisation of the Epoxyolefin (44).

1. With Boron Trifluoride Etherate.- Boron Trifluoride Etherate (2 drops) was added to a stirred solution of the epoxyolefin (44) (45 mg.) in methylene chloride (4 ml.) at 0° under nitrogen. After 40 min. water was added and the mixture was extracted with methylene chloride. The solvent was evaporated and the crude product was refluxed 1 hr. with toluene-p-sulphonic acid (20 mg.) in acetone (6 ml.) and water (4 ml.). The acetone was evaporated and the mixture extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, water, dried and evaporated to give a waxy solid

(36 mg.) which crystallised on trituration with petrol. Recrystallisation (chloroform/60-80° petrol) gave prisms, m.p. 136-43° of a 1:1 mixture of the ketones (47) and (48), homogeneous on t.l.c. (silica gel, 4:1 methylene chloride/ether).

ν_{max}(nujol) 3360, 1700, 1150, 825 cm^{-1}.

$\tau(CDCl_3)$ 4·34 ($\frac{1}{2}$H, broad), 4·78($\frac{1}{2}$H, broad), 9·05 (3/2H, s), 9·10 (3/2H, s), 8·20 (1H, D_2O labile), all other protons in the region 6·5-9·0.

M^+, 234.

Found: C, 76·60%; H, 9·39%.

$C_{15}H_{22}O_2$ requires C, 76·88%; H, 9·46%.

2. With Stannic Chloride.- Stannic chloride (10 drops) was added to a stirred solution of the epoxyolefin (44) (56 mg.) in benzene (4 ml.) under nitrogen. After 1 hr. the reaction was worked up and the crude product hydrolysed as above. T.l.c. of the product showed it to be a mixture of several compounds, one spot corresponding to the authentic mixture of the ketones (47) and (48).

3. With Picric Acid.- The epoxyolefin (44) (25 mg.) in nitromethane (1 ml.) was treated overnight with picric acid (50 mg.). Acetone (6 ml.), water (4 ml.) and toluene-p-sulphonic acid (20 mg.) were added, the solution was refluxed 1 hr. and worked up as above. T.l.c. of the product showed it to be a complex mixture with one spot corresponding to the authentic mixture of the ketones (47) and (48).

1-Methyl-2(2-hydroxyethyl)-4-methoxy-1,4-cyclohexadiene (53).

Sodium metal (48 g.) was added in small portions over 30 min. to a stirred solution of the alcohol (34) (17·0 g.) in distilled ammonia (ca. 500 ml.), tetrahydrofuran (200 ml.) and tert-butanol (200 ml.). After stirring for a further 5 hr. the reaction was worked up by the procedure on p. 92 to give the alcohol (53) (15·9 g., 93%), a pale yellow oil.

ν_{max}(film) 3450, 1690, 1670, 1220, 795 cm^{-1}.

$\tau(CCl_4)$ 5·55 (1H, broad), 6.50 (2H, t, J=6·5 Hz), 7·78 (2H, t, J=6·5 Hz), 6·58 (3H, s), 8·35 (3H, s), 6·80 (1H, D_2O labile).

1-Methyl-2-(2-hydroxyethyl)-4,4-ethylenedioxycyclohexene (54).

The alcohol (53) (13·3 g.) in benzene (350 ml.) was stirred overnight with ethanediol (70 ml.) and toluene-p-sulphonic acid (2 g.). The solution was poured into excess aqueous sodium bicarbonate, the benzene layer separated and washed with water. The combined aqueous solutions were extracted with a further 200 ml. benzene. The combined benzene solutions were dried and evaporated. Fractional distillation in vacuo of the crude product gave 1-methyl-2-(2-hydroxyethyl)-4,4--ethylenedioxycyclohexene (54) (7·12 g.), b.p. 110-4°/0·02 mmHg.

Losses on distillation were minimised by bulb to bulb distillation at 150° bath/5 x 10^{-4} mmHg. In a typical distillation 1·48 g. crude material gave 1·34 g. purified alcohol.

ν_{max}(film) 3450, 1080, 1065 cm^{-1}.

$\tau(CCl_4)$ 6·15 (4H, s), 6·50 (2H, t, J=6·5 Hz), 8·35 (3H, s), 6·90 (1H, D_2O labile), all other protons in the region 7·0-8·5.

3,5-Dinitrobenzoate.- The alcohol (54) (55 mg.) in pyridine (1 ml.) was treated overnight with 3,5-dinitrobenzoyl chloride (80 mg.).

Dilution with aqueous sodium bicarbonate and extraction with methylene chloride gave the crude 3,5-dinitrobenzoate which was purified to a colourless oil by p.l.c. (silica gel, methylene chloride).
Found: C, 55·41%; H, 5·22%; N, 7·23%.
$C_{18}H_{20}N_2O_8$ requires C, 55·11%; H, 5·10%; N, 7·14%.

1-Methyl-2-(2-bromoethyl)-4,4-ethylenedioxycyclohexene (55).

A solution of the alcohol (54) (713 mg.), carbon tetrabromide (1·20 g., 1·2 equiv.), pyridine (10 drops) in benzene (5 ml.) was stirred during the dropwise addition of tri-n-butylphosphine (800 mg., 1·1 equiv.) in benzene (5 ml.). The solution was stirred under reflux 2 hr., powdered lithium bromide (1·5 g.) was added and after a further 2 hr. reflux the solution was allowed to cool overnight. Water was added and the solution was extracted with benzene. The benzene solution was washed with brine, dried and concentrated. P.l.c. of the crude product (silica gel, 1:1 methylene chloride/petrol) gave 1-methyl-2-(2-bromoethyl)-4,4-ethylenedioxycyclohexene (55) (484 mg., 52%), a colourless oil.
ν_{max}(film) 1100, 1070 cm^{-1}.
$\tau(CCl_4)$ 6·15 (4H, s), 6·74 (2H, t, J=8 Hz), 7·52 (2H, t, J=8 Hz), 8·35 (3H, s), all other protons in the region 7·5-9·0.
Found: C, 50·81%; H, 6·54%.
$C_{11}H_{17}BrO_2$ requires C, 50·60%; H, 6·56%.

Reactions of the Grignard Reagent from the Bromide (55) with Cyclohexanone.

Experiment 1.- A solution of the bromide (55) (488 mg.) in tetrahydrofuran (5 ml.) was added in one portion to magnesium turnings (100 mg., activated by methyl iodide) under nitrogen and rapidly warmed to reflux temperature. A vigorous reaction occured. The solution was refluxed 30 min. and cooled. Cyclohexanone (230 mg.) in tetrahydrofuran (3 ml.) was added and the solution was stirred 1 hr. under reflux. The reaction was quenched by the addition of aqueous ammonium chloride. The solution was extracted with ether, the ether extracts washed with aqueous sodium bicarbonate, dried and evaporated to give an oil (462 mg.). Short path distillation of this oil at 150° bath/10^{-4} mmHg gave a colourless oil (280 mg.) shown by t.l.c. (silica gel, 1:1 methylene chloride/petrol) to be mainly the protonation product (58) plus several impurities at low R_f including the required alcohol (56) (shown by a weak m/e 280 in the mass spectrum and a weak ν_{max} 3500 cm^{-1}) but insufficient to isolate.

P.l.c. purification of the distillate gave 1-methyl-2-ethyl--4,4-ethylenedioxycyclohexene (58).

ν_{max}(film) 1255, 1155, 1135, 1100, 1068, 790 cm^{-1}.

$\tau(CCl_4)$ 6·15 (4H, s), 8·03 (2H, q, J=8 Hz), 9·10 (3H, t, J=8 Hz), all other protons in the region 7·6-8·6.

Found: M^+, 182. $C_{11}H_{18}O_2$ requires M, 182.

2,4-Dinitrophenylhydrazone.- The ethyleneketal (58) (30 mg.) in ethanol (3 ml.) and water (1 ml.) was refluxed 10 min. with 2,4-dinitrophenylhydrazine (30 mg.) and 6N hydrochloric acid (2 drops). Ether extraction and p.l.c. gave the 2,4-dinitrophenylhydrazone, orange-red plates (from cyclohexane), m.p. $159\text{-}61^{\circ}$.

Found: C, 56·59%; H, 5·22%; N, 17·62%.

$C_{15}H_{18}N_4O_4$ requires C, 56·61%; H, 5·66%; N, 17·61%.

Experiment 2.- A solution of the Grignard reagent was prepared by the method of Experiment 1. from the bromide (55) (470 mg.) and magnesium turnings (100 mg.) in tetrahydrofuran (10 ml.). Cyclohexanone (700 mg.) in tetrahydrofuran (5 ml.) was added and the solution was refluxed overnight under nitrogen. Aqueous ammonium chloride was added and the solution was extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, dried and evaporated. T.l.c. of the crude product showed a complex mixture. P.l.c. isolated the alcohol (56) (50 mg., 10%), a colourless oil.

ν_{max}(film) 3500, 1100, 1070, 975, 955, 845 cm^{-1}.

$\tau(CDCl_3)$ 6·05 (4H, s), all other protons in the region 7·5-9·0.

Found: M^+, 280. $C_{17}H_{28}O_3$ requires M, 280.

2,4-Dinitrophenylhydrazone.- Treatment of the ethyleneketal (56) (40 mg.) under the conditions on p.100 gave the 2,4-dinitrophenyl--hydrazone, orange-red needles (from methylene chloride/60-80° petrol), m.p. 151-2°.

Found: C, 60·48%; H, 6·78%; N, 13·33%.

$C_{21}H_{28}N_4O_5$ requires C, 60·57%; H, 6·73%; N, 13·46%.

Reaction of the Grignard Reagent from the Bromide (55) with D_2O.

A solution of the Grignard reagent was prepared from the bromide (55) (178 mg.) and magnesium turnings (100 mg.) in tetrahydrofuran (4 ml.) under nitrogen. D_2O (0·5 ml.) was added dropwise to the stirred solution. After 15 min. ether (10 ml.) was added, the solution was dried, filtered and the solvent evaporated to give the

deuterated compound (59) (118 mg.), a colourless oil.

ν_{max}(film) 1255, 1155,1135, 1100, 1068, 790 cm^{-1}.

$\tau(CCl_4)$ 6·15 (4H, s), 8·03 (2H, t, J=8 Hz), 9·10 (2H, t, J=8 Hz), all other protons in the region 7·6-8·6.

Found: M^+, 183. $C_{11}H_{17}DO_2$ requires M, 183.

1-(3-Methoxy-6-methylphenyl)-2-(1-hydroxycyclohexyl)ethane (37).

The Grignard reagent was prepared from the chloride (35) (3·14 g.), magnesium turnings (700 mg., activated by a few drops of 1,2-dibromo--ethane) in tetrahydrofuran (30 ml.) under nitrogen and cooled to 0°. Cyclohexanone (2·0 g.) in ether (30 ml.) was added dropwise to the vigorously stirred solution and stirring was continued overnight. Aqueous ammonium chloride was added, the ether layer was washed with aqueous sodium bicarbonate, dried and evaporated. The crude product was dissolved in ethanol (75 ml.) and refluxed 1 hr. with Girard Reagent 'T' (2·0 g.) and glacial acetic acid (2·0 ml.). The cooled solution was poured into water and extracted with ether. The ether solution was washed with water, dried and the solvent removed. Chromatography of the residue on silica gel, eluting with methylene chloride gave the alcohol (37) (2·74g., 65%), a colourless liquid.

ν_{max}(film) 3450, 1612, 1510, 1250, 1140, 1005, 970, 820 cm^{-1}.

$\tau(CCl_4)$ 3·0-3·8 (3H, m), 6·33 (3H, s), 7·80 (3H, s), 8·8 (1H, D_2O labile), all other protons in the region 7·0-8·8.

1-(2-Methyl-5,5-ethylenedioxycyclohexenyl)-2-(1-hydroxycyclohexyl)--ethane (56).

Sodium metal (9·0 g.) was added in small portions to a stirred solution of the alcohol (37) (2·73 g.) in distilled ammonia (ca. 200 ml.),

tetrahydrofuran (80 ml.) and tert-butanol (80 ml.). Stirring was continued 4 hr., and the reaction was worked up by the method on p. 92.

The intermediate enol ether (2·47 g.) in benzene (125 ml.) was stirred vigorously overnight with ethanediol (25 ml.) and toluene-p-sulphonic acid (250 mg.). The solution was poured into aqueous sodium bicarbonate, the benzene layer separated and washed with water. The combined aqueous solutions were extracted with a further 100 ml. benzene. The combined, dried benzene solutions were evaporated to give the ethyleneketal (56) (2·77 g., 90%).

1-(1,2-Epoxy-2-methyl-5,5-ethylenedioxycyclohexyl)-2-(1-hydroxycyclohexyl)ethane (57).

The ethyleneketal (56) (2·77 g.) in methylene chloride (150 ml.) was stirred overnight with m-chloroperbenzoic acid (2·13 g. of 88% w/w). The solution was washed with aqueous sodium bicarbonate, water, dried and evaporated to give the epoxide (57) (2·68 g.).

ν_{max}(film) 3500, 1110 cm^{-1}.

$\tau(CDCl_3)$ 6·10 (4H, s), 8·70 (3H, s), all other protons in the region 7·7-9·0.

1-(1,2-Epoxy-2-methyl-5,5-ethylenedioxy)-2-cyclohexenylethane (44).

The epoxyalcohol (57) (128 mg.) in pyridine (3 ml.) was treated overnight at 0° with redistilled methanesulphonyl chloride (0·6 ml.). The solution was poured into aqueous sodium bicarbonate and extracted with ether. The ether solution was washed with water, dried and evaporated. P.l.c. (silica gel, methylene chloride) of the residue gave the epoxyolefin (44) (66 mg.).

1,9-Dibromocyclonona-1-trans-5-cis-diene (2d).

The dibromide (1) (6·0 g.) in petrol (60 ml.) was adsorbed on a dry packed column of grade I alumina (150 g.). After 1 hr. the column was eluted with methylene chloride (300 ml.). Removal of solvent gave the dibromocyclononadiene (2d) (3·54 g., 60%), a colourless oil.

ν_{max}(film) 1630, 738, 720 cm^{-1}.

$\tau(CDCl_3)$ 4·05 (1H, t, J=7 Hz), 4·62 (2H, m), 5·4 (1H, dd), all other protons in the region 7·5-8·4.

The Dibromoketone (3d).

The dibromocyclononadiene (2d) (11·44 g.) was dissolved in AnalaR acetone (300 ml.) and water was added to the limit of miscibility. N-Bromosuccinimide (8·03 g., 1·1 equiv., freshly crystallised) was added in portions to the stirred solution whilst maintaining the temperature below 20° with an ice bath. Stirring was continued for a further 90 min., water (200 ml.) was added and the product extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, water and dried. Crystallisation of the residue gave the dibromoketone (3d) (6·74 g.) as colourless prisms, m.p. 69-70°. [2]

ν_{max}(nujol) 1720 cm^{-1}.

$\tau(CDCl_3)$ 5·36 (2H, m), all other protons in the region 7·2-8·4.

(±)-17α,9β-Dibromo-8β-hydroxy-9,10-secogona-1,3,5(10)-triene (6o).

The dibromoketone (3d) (761 mg.) in ether (10 ml.) was added dropwise to a stirred solution of the Grignard reagent from magnesium turnings (128 mg.) and excess 2-bromoethyl benzene in tetrahydrofuran (10 ml.) under nitrogen. Stirring was continued for

1 hr. Excess aqueous ammonium chloride was added and the solution was extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, brine, dried and evaporated. P.l.c. (silica gel, 2:3 methylene chloride/petrol) gave the dibromohydrin (60) (416 mg., 40%). Recrystallisation (ether/60-80°petrol) gave colourless prisms, m.p. 87-8°.

ν_{max}(nujol) 3540, 1275, 1215, 1100, 965, 895, 765, 715, 708 cm^{-1}.

$\tau(CDCl_3)$ 2·97 (5H, s), 5·5-6·1 (2H, m), all other protons in the region 7·2-8·8.

M^+, 400/402/404.

Found: C, 50·67%; H, 5·55%.

$C_{17}H_{22}Br_2O$ requires C, 50·75%; H, 5·47%.

Reaction of the Dibromohydrin (60) with Sodium Iodide and Triethylamine.

The dibromohydrin (60) (50 mg.), sodium iodide (400 mg.) and triethylamine (100 mg.) were refluxed overnight in acetone (1·5 ml.). Water was added to the cooled solution which was extracted with ether. The crude product was separated by p.l.c. (silica gel, 2:3 methylene chloride/petrol). The less polar component was the iodobromohydrin (61) (11 mg.). Recrystallisation (60-80° petrol) gave colourless prisms, m.p. 124·5-125°.

ν_{max}(nujol) 3540, 750, 715, 705 cm^{-1}.

$\tau(CDCl_3)$ 2·97 (5H, s), 5·95 (1H, m), 6·60 (1H, m), all other protons in the region 7·0-8·8.

M^+, 448/450.

Found: C, 45·35%; H, 4·93%.

$C_{17}H_{22}BrIO$ requires C, 45·41%; H, 4·90%.

The more polar component was the olefinic bromohydrin (62) (20 mg.), a colourless oil.

ν_{max}(film) 3550, 1605, 1500, 1095, 980, 815, 760, 705 cm^{-1}.

$\tau(CDCl_3)$ 2·97 (5H, s), 4·70 (1H, s), 5·40 (1H, t, J=8 Hz), all other protons in the region 6·7-8·5.

Found M^+, 320/322. $C_{17}H_{21}BrO$ requires M, 320/322.

The Epoxide (63).

The olefinic bromohydrin (62) (10 mg.) in methylene chloride (1 ml.) was treated with peracetic acid (ca. 2 equiv.) for 1 hr. The solution was diluted with methylene chloride, washed with aqueous sodium bicarbonate, dried and the solvent evaporated. P.l.c. of the residue gave the epoxide (63), colourless needles (from methylene chloride/60-80° petrol), m.p. 131-3°.

M^+, 354/356.

Found: C, 60·24%; H, 6·63%.

$C_{17}H_{21}BrO_2$ requires C, 60·53%; H, 6·24%.

Reactions of the Dibromohydrin (60) with Dimethylsulphoxide and Base.

1. Sodium Methylsulphinylmethide.- Sodium hydride (100 mg., as a 57% suspension in oil) was washed free of oil by petrol under nitrogen. Dimethylsulphoxide (5 ml.) was added and the mixture stirred at 70° until the evolution of hydrogen ceased. The dibromohydrin (60) (100 mg.) was added and maintained at 100° for 1 hr. Water was added and the solution extracted with ether. The ether solution was dried and evaporated to yield a black tar. T.l.c. showed no nonpolar material.

2. Collidine.- The dibromohydrin (60) (65 mg.) in dimethylsulph--oxide (1 ml.) was treated with distilled collidine (100 mg.) overnight at 100°. The solvent was removed in vacuo and the tarry residue separated by p.l.c. (silica gel, 1:1 methylene chloride/petrol) to yield the olefinic bromohydrin (62) (19 mg.) as the only nonpolar product.

Calcium in Liquid Ammonia Reduction of the Dibromohydrin (60).

Calcium metal (95 mg.) was added to a solution of the dibromo--hydrin (60) (100 mg.) in ether (10 ml.) and distilled ammonia (20 ml.). Stirring was continued 2 hr. Methanol (1 ml.) was added followed by excess powdered ammonium chloride. The ammonia was allowed to evaporate overnight and the residue was partitioned between ether and water. The ether layer was washed with brine, dried and evaporated. The crude product was separated by p.l.c. (silica gel, 1:1 methylene chloride/petrol). The less polar product was (±)-9,10-secogona-1,3,5(10),8-tetraene (64) (21 mg.), a colourless oil. An analytically pure sample was obtained by short path distillation (100° bath/0·2 mmHg).

ν_{max}(film) 1460, 755, 705 cm^{-1}.

$\tau(CDCl_3)$ 2·90 (5H, s), 4·80 (1H), all other protons in the region 7·0-9·2.

M^+, 226.

Found: C, 90·11%; H, 9·63%.

$C_{17}H_{22}$ requires C, 90·20%; H, 9·80%.

The more polar product was (±)-8-hydroxy-9,10-secogona-1,3,5(10)--triene (65) (12 mg.), a colourless oil.

ν_{max}(film) 3500, 965, 755, 705 cm^{-1}.

$\tau(CDCl_3)$ 2·90 (5H, s), all other protons in the region 7·2-9·4.

M^+, 242.

Found: C, 83·71%; H, 9·75%.

$C_{17}H_{24}O$ requires C, 83·60%; H, 9·83%.

Zinc in Acetic Acid Reduction of the Dibromohydrin (60).

Zinc dust (400 mg.) was added to a solution of the dibromohydrin (60) (166 mg.) in glacial acetic acid (8 ml.) which was stirred 1 hr. under reflux. The solution was filtered, cooled, diluted with water and extracted with pentane. The pentane solution was washed with water, aqueous sodium bicarbonate and dried. P.l.c. (silica gel, petrol) of the crude product gave the olefin (64) (30 mg.).

(±)-17α,9β-Dibromo-8β-hydroxy-3-methoxy-9,10-seco-18-norandrosta--1,3,5(10)-triene (66).

A solution of the Grignard reagent was prepared from magnesium turnings (360 mg., activated with a few drops of 1,2-dibromoethane) and the chloride (35) (2·80 g.) in refluxing tetrahydrofuran (50 ml.). It was filtered under nitrogen and added dropwise to a stirred solution of the dibromoketone (3d) (2·20 g.) in ether (50 ml.). Stirring was continued overnight, excess aqueous ammonium chloride was added and the product extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, dried and evaporated. The dibromohydrin (66) (1·424 g., 45%), a colourless viscous oil, was obtained by chromatography (silica gel, 1:1 methylene chloride/petrol).
An analytically pure sample was obtained by short path distillation (100° bath/10^{-4} mmHg).

$\nu_{max}(CHCl_3)$ 3550, 1610, 1510, 1285, 1115, 970, 900 cm^{-1}.

τ ($CDCl_3$) 2·8-3·6 (3H, m), 5·6-6·0 (2H, m), 6·28 (3H, s), 7·76 (3H, s), all other protons in the region 7·0-9·2.

M^+, 444/446/448.

Found: C, 51·23%; H, 5·77%.

$C_{19}H_{26}Br_2O_2$ requires C, 51·12%; H, 5·83%.

(±)-3-Methoxy-9,10-seco-18-norandrosta-1,3,5(10),8-tetraene (67).

AnalaR zinc dust (1·60 g.) was added to a solution of the dibromohydrin (66) (807 mg.) in glacial acetic acid (30 ml.) and stirred 1 hr. under reflux. The solution was filtered, the acetic acid was evaporated and the residue extracted with ether. The ether solution was washed with water, aqueous sodium bicarbonate, dried and evaporated. The residue was dissolved in petrol and passed through a short silica gel column. Evaporation gave the olefin (67) (361 mg., 74%), a colourless oil. An analytically pure sample was obtained by short path distillation (100° bath/0·02 mmHg).

ν_{max}(film) 1615, 1515, 1250, 1050, 810 cm^{-1}.

τ($CDCl_3$) 2·7-3·5 (3H, m), 4·64 (1H, broad), 6·20 (3H, s), 7·76 (3H, s), all other protons in the region 7·2-9·2.

M^+, 270.

Found: C, 84·40%; H, 9·46%.

$C_{19}H_{26}O$ requires C, 84·43%; H, 9·63%.

(±)-3,3-Ethylenedioxy-9,10-seco-18-norandrosta-5(10),8-diene (68).

Sodium metal (13·0 g.) was added in small portions to a stirred solution of the olefin (67) (3·37 g.) in distilled ammonia (ca. 200 ml.), tetrahydrofuran (85 ml.) and tert-butanol (85 ml.). Stirring was continued 5 hr. and the reaction was worked up by the method on p. 92.

The intermediate enol ether (3·13 g.), ethanediol (40 ml.) and toluene-p-sulphonic acid (400 mg.) were stirred vigorously overnight in benzene (200 ml.). Work up by the method on p.103 and chromatographic purification (silica gel, 4:1 petrol/methylene chloride) gave the ethyleneketal diene (68) (2·094 g., 60%), a colourless oil.

ν_{max}(film) 1155, 1110, 1100, 1070 cm^{-1}.

$\tau(CDCl_3)$ 4·76 (1H, broad), 6·06 (4H, s), all other protons in the region 7·3-9·0.

Found: M^+, 302. $C_{20}H_{30}O_2$ requires M, 302.

2,4-Dinitrophenylhydrazone.- The ethyleneketal (68) (10 mg.), 2,4-dinitrophenylhydrazine (14 mg.) and 6N hydrochloric acid were refluxed 15 min. in ethanol (5 ml.) and water (1 ml.). Ether extraction and p.l.c. gave the 2,4-dinitrophenylhydrazone, orange-red plates (from 60-80° petrol), m.p. 125-6°.

Found: C, 65·66%; H, 6·92%; N, 12·71%.

$C_{24}H_{30}N_4O_4$ requires C, 65·75%; H, 6·85%; N, 12·78%.

Epoxidation of the Diene (68).

Method 1.- Freshly crystallised N-bromosuccinimide (142 mg.) was added in small portions over 10 min. to a stirred solution of the diene (68) (230 mg.) in tetrahydrofuran (5 ml.) and water (1·5 ml.) at 5°. Stirring was continued 1 hr. at 5-10°. The tetrahydrofuran was removed at 20° and the residue was extracted with ether. The ether solution was washed with water, dried and evaporated at 20° to give the oily bromohydrin, ν_{max} 3500, 1070, 685 cm^{-1}.

A solution of the bromohydrin in methanol (8 ml.) was stirred overnight with potassium carbonate (1 g.). The methanol was evaporated at 20° and the residue partitioned between ether and water. The ether solution was dried and evaporated. P.l.c. (silica gel, 8:1 petrol/ethyl acetate) yielded unreacted diene (64 mg.) and a monoepoxide fraction, shown by p.m.r. to be > 95% of (±)-3,3-ethylene--dioxy-8,9-epoxy-9,10-seco-18-norandrosta-5(10)-ene (70) (56 mg.), a colourless oil.

ν_{max}(film) 1070, 950, 850 cm^{-1}.

$\tau(CDCl_3)$ 6·05 (4H, s), all other protons in the region 7·0-9·0.

M^+, 318.

Found: C, 75·42%; H, 9·55%.

$C_{20}H_{30}O_3$ requires C, 75·43%; H, 9·50%.

Method 2.- m-Chloroperbenzoic acid (824 mg. of 88% w/w, 4·2 mmole) was added in small portions to a stirred solution of the diene (68) (1·208 g., 4·0 mmole) in methylene chloride (40 ml.) whilst maintaining the temperature below 10°. It was warmed to 25°, stirred 1 hr. and poured into aqueous sodium bicarbonate. The methylene chloride solution was separated, dried and evaporated. P.l.c. (silica gel, 8:1 petrol/ethyl acetate) separated the crude product into four compounds. The least polar compound was recovered diene (68) (286 mg.).

The second compound was (±)-3,3-ethylenedioxy-5,10-epoxy-9,10--seco-18-norandrosta-8-ene (69) (265 mg.), a colourless oil.

ν_{max}(film) 1080, 1040, 855 cm^{-1}.

$\tau(CDCl_3)$ 4·70 (1H, broad), 6·15 (4H, s), 8·70 (3H, s), all other protons in the region 7·5-9·2.

Found: C, 75·70%; H, 9·39%.

$C_{20}H_{30}O_3$ requires C, 75·43%; H, 9·50%.

The third compound was the epoxyolefin (70) (277 mg.).

The most polar compound was the bisepoxide (71) (190 mg.), a colourless oil.

ν_{max}(film) 1080, 850 cm^{-1}.

$\tau(CDCl_3)$ 6·15 (4H, s), 8·70 (3H, s), all other protons in the region 7·0-9·2.

Found: C, 71·70%; H, 8.92%.

$C_{20}H_{30}O_4$ requires C, 71·82%; H, 9·04%.

Reaction of the Epoxyolefin (70) with Boron Trifluoride Etherate.

Boron trifluoride etherate (5 drops) was added to a stirred solution of the epoxyolefin (70) (277 mg.) in methylene chloride (24 ml.) at 0° under nitrogen. After 40 min. at 0° water was added and the mixture extracted with methylene chloride. The solvent was removed and the residue refluxed 1 hr. with toluene-p-sulphonic acid (100 mg.) in acetone (25 ml.) and water (15 ml.). The acetone was evaporated. Extraction with ether gave a product shown by t.l.c. to contain at least nine compounds.

Cyclisation of the Epoxyolefin (69).

Boron trifluoride etherate (5 drops) was added to a stirred solution of the epoxyolefin (69) (265 mg.) in methylene chloride (24 ml.) at 0° under nitrogen. After 2 hr. at 0° water was added and the mixture extracted with methylene chloride. The solvent was removed at 20° and the residue stirred overnight with toluene-p--sulphonic acid (50 mg.) in acetone (20 ml.) and water (10 ml.). Excess aqueous sodium bicarbonate was added and the acetone was removed at ca. 30°. Methylene chloride extraction yielded a

semicrystalline material which on recrystallisation (methylene chloride/60-80° petrol) gave the ketol mixture (72) (64 mg.), colourless needles m.p. 138-9°.

ν_{max}(nujol) 3400, 1715 cm^{-1}.

$\tau(CDCl_3)$ 4·70 (broad), 9·00 (s), 9·05 (s), 9·12 (s), all other protons in the region 7·0-9·2.

M^+, 274.

Found: C, 78·64%; H, 9·50%.

$C_{18}H_{26}O_2$ requires C, 78·79%; H, 9·55%.

P.l.c. (silica gel, 3:2 ether/petrol) of the mother liquors gave a colourless semicrystalline material (112 mg.), homogeneous on t.l.c., containing ca. 50% of (72) (by p.m.r.). It was shown to be a mixture of several ketones (ν_{max} 1730, 1720, 1715, 1695, 1660 cm^{-1}).

The Ketones (73).

A solution of the ketols (72) (5·1 mg.) in ethanol (1 ml.) was treated 1 hr. with sodium ethoxide (from 9·2 mg. sodium metal). The solution was poured into ether, washed with N hydrochloric acid, water and dried. Evaporation of the solvent yielded the ketones (73) (4·1 mg.), a colourless oil.

$\nu_{max}(CHCl_3)$ 1655 cm^{-1}.

λ_{max}(EtOH) 230 nm.

2,4-Dinitrophenylhydrazone.- The ketone (4·1 mg.), 2,4-dinitrophenyl--hydrazine (6 mg.) and 6N hydrochloric acid (0·5 ml.) were refluxed 30 min. in ethanol (1 ml.). Ether extraction and p.l.c. gave the 2,4-dinitrophenylhydrazone, orange plates (from 60-80° petrol), m.p. 225-7°.

Found: C, 66·00%; H, 6·52%; N, 12·88%.

$C_{24}H_{28}N_4O_4$ requires C, 66·05%; H, 6·43%; N, 12·86%.

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