TETRABROMOERGOSTENYL ACETATE AND DERIVATIVES

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T H E S I S

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A C K N O W L E D G M E N T S

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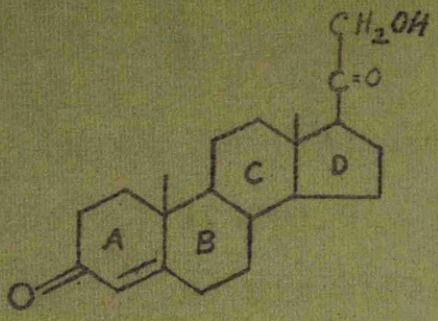
Tetrabromoergostenyl Acetate and Derivatives

C O N T E N T S

I N T R O D U C T I O N

In 1930 it was established[1,2] that extracts of the adrenal cortex will prolong the life of an adrenalectomised animal. This discovery promoted extensive research[3,4,5,6] into the isolation of the physiologically active functions. The initial achievements, allied to those from further investigations,[7,8,9] led to the isolation of twenty-nine crystalline compounds from the crude adrenal cortex extracts.

A variety of different techniques was required to isolate the active material. Extraction of the adrenal glands with cold acetone or alcohol and subsequent partition of the extracted material between various immiscible solvent pairs, yielded a concentrate. Separation of the component compounds and the investigation of their structures were undertaken by Reichstein,[3] Kendall,[4] Pfiffner,[5] and others. The methods of fractionation included the use of Girard reagents[10] for the separation of carbonyl from non-carbonyl material, partition techniques, and chromatography of acetates.[11,12]



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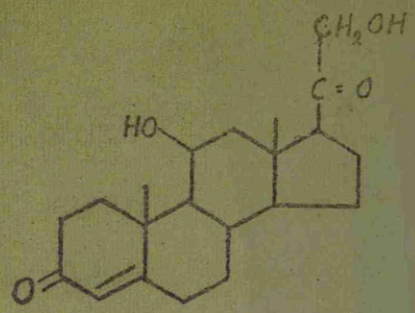

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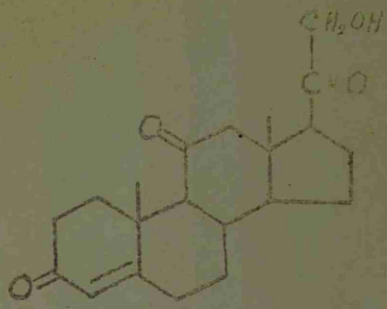

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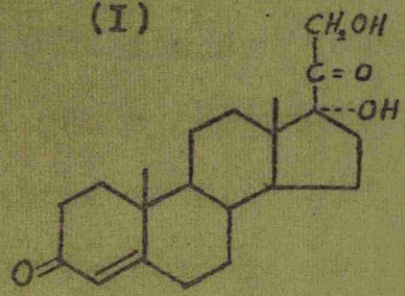

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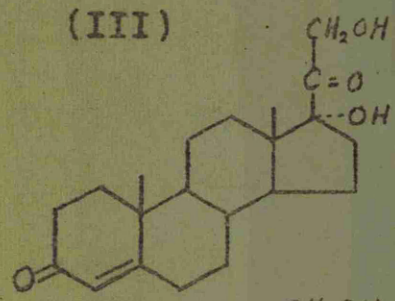

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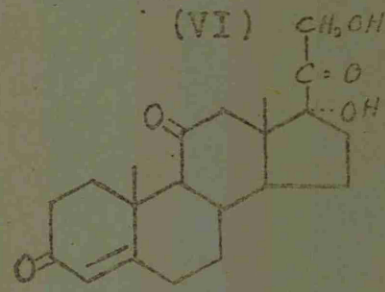
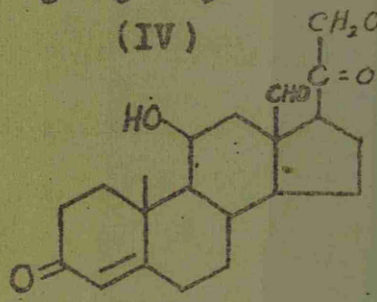


(VII)



(V)

Seven of the compounds (I-VII) proved capable of maintaining the life of an adrenalectomised animal. Examination of the compounds (I-VII) shows that they all possess an αβ-unsaturated ketonic function in ring A, and have an α-ketol side chain which is highly sensitive to acid or alkali. The hormone activity is associated with the presence of both these groupings in the molecule. Comparison of these seven active hormones indicated that the oxygen functions at $C_{(11)}$ and $C_{(17)}$ were not necessary for life maintenance activity, but are essential for exhibiting other physiological properties.

With the elucidation of the structure of cortisone, 17-hydroxy-11-dehydrocorticosterone,(VII), by Hench[12] and his colleagues in 1949, investigations leading to its synthesis were commenced since it appeared to possess a remarkable therapeutic value against rheumatoid arthritis. Although this initial promise was not fulfilled, the investigations yielded a number of corticosteroid intermediates having an 11-oxygen function, or a 9(11)-olefinic double bond which is readily convertible to an 11-oxygen function.

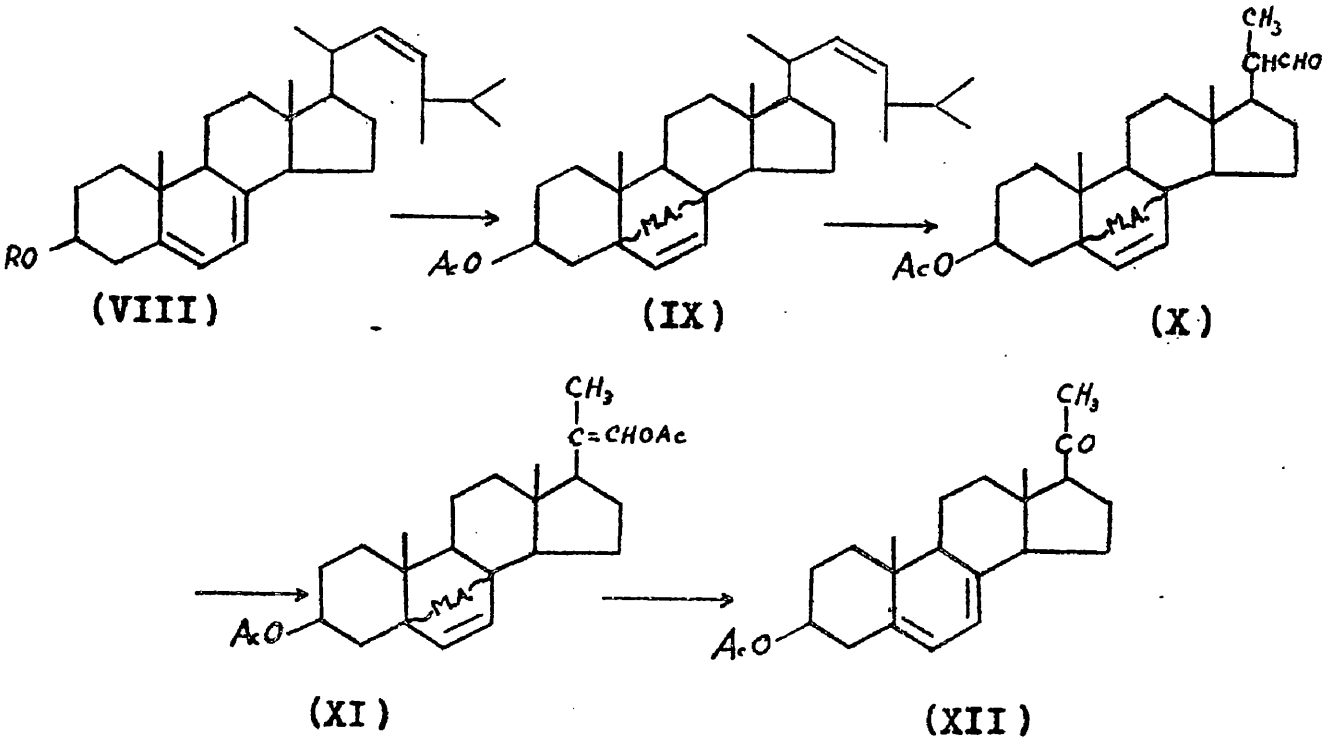
H I S T O R I C A L

The first part of this section describes some of the corticosteroid intermediates formed in projected partial syntheses of cortisone from ergosterol-D and dehydroergosterol.

Later the rearrangement of dehydroergosterol (or analogous $\Delta^{5:7:9(11)}$-steroids) to an anthrasteroid will be discussed and comparison made with the neosteroids and other aromatic compounds.

Ergosterol as a Starting Material for Adrenocortical Hormone Synthesis.

In 1948 Bergmann and Stevens[14] indicated the suitability of ergosterol (VIII; R = H) as a starting material for the partial synthesis of adrenal cortical steroids because of its probable facile conversion into derivatives like dehydroergosterol, having unsaturation at $C_{(11)}$, which might lend themselves to the introduction of oxygen at this position. In addition, it was pointed out that the $\Delta^{22(23)}$-double bond was ideally situated to facilitate cleavage of the side chain with subsequent formation of one of the typical adrenal cortical hormone side chains.



The same authors showed that the homoannular diene system of (VIII) may be protected by formation of the maleic anhydride adduct (IX) while the side chain is degraded by ozonolysis to the aldehyde (X). This is then converted into the enol-acetate (XI), ozonolysis of which followed by pyrolysis gives 20-oxopregna-5,7-dien-3β-yl acetate (XII). This degradation of the side chain became a standard method employed by later workers.[15,16]

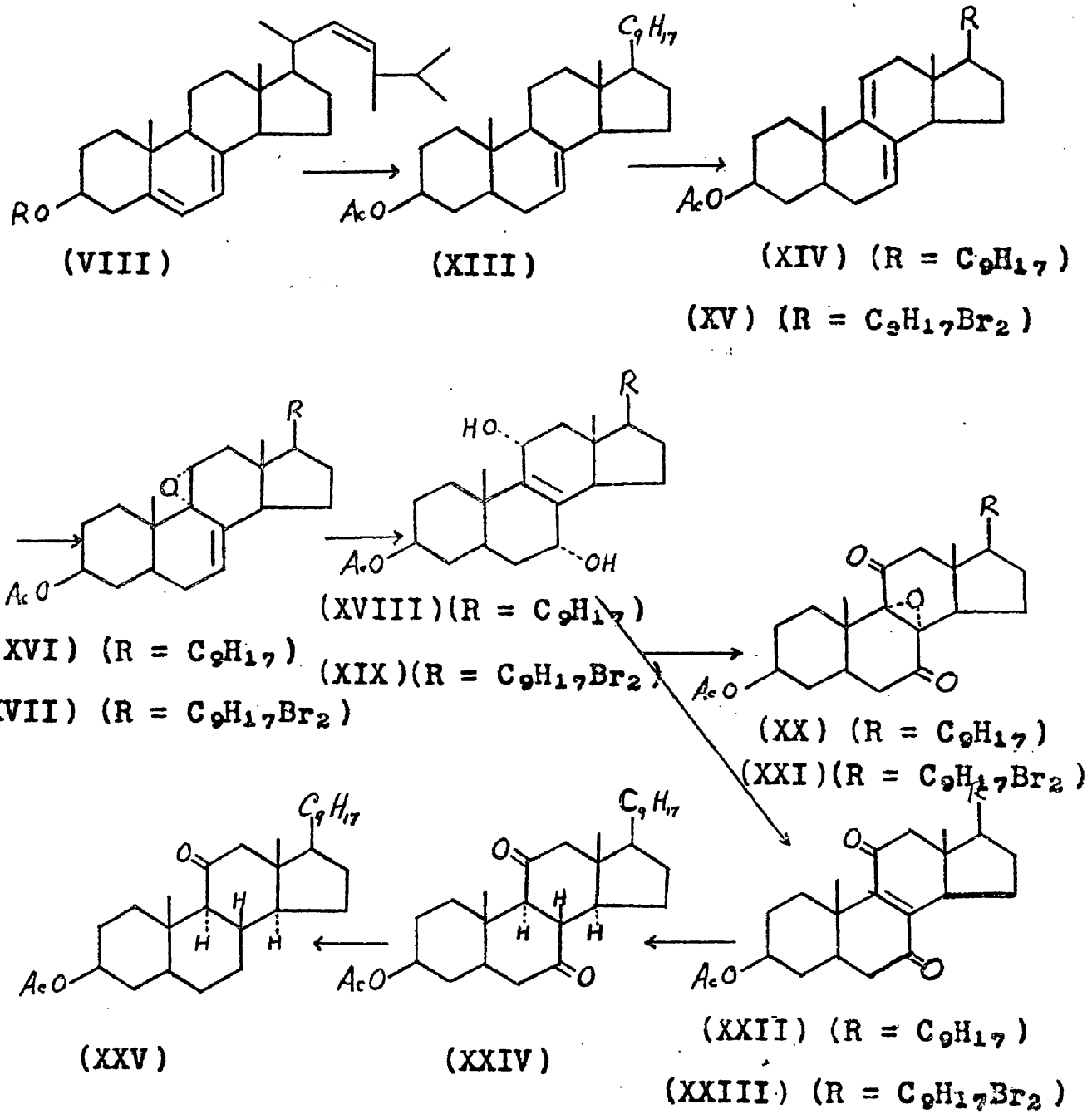
11-Oxo-steroids from Ergosterol-D.

In 1951 Tishler[16] and his co-workers achieved the synthesis of 11-oxygenated ergosterol derivatives.

Partial reduction[17] of ergosterol acetate (VIII;

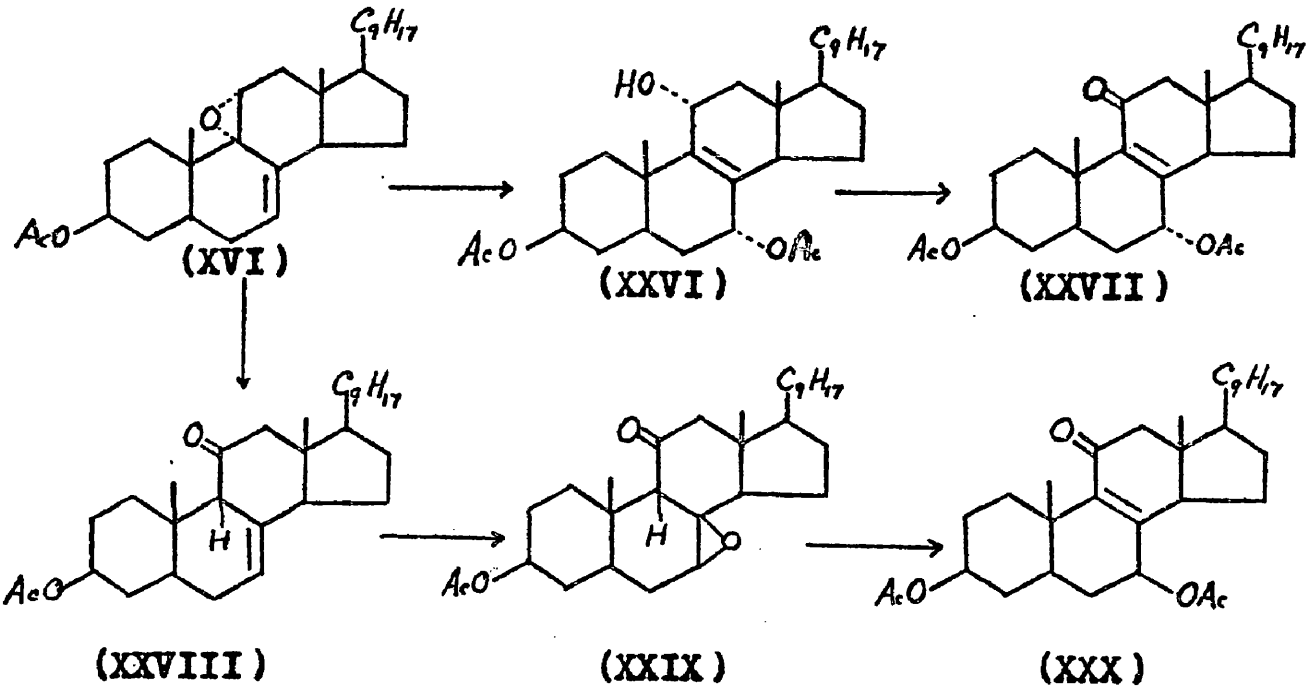
R = Ac) gave 5-dihydroergosteryl acetate (XIII) which was oxidised with mercuric acetate[18] to ergosterol-D acetate (ergosta-7,9(11),22-trien-3β-yl acetate) (XIV). Treatment of the triene (XIV) with one equivalent of perbenzoic acid gave a monoepoxide, 9α,11α-epoxyergosta--7,22-dien-3β-yl acetate (XVI), hydrolytic rearrangement of which yielded 7α,11α-dihydroxyergosta-8,22-dien-3β-yl acetate (XVIII). Chromic anhydride oxidation of (XVIII) gave 8α,9α-epoxy-7,11-dioxoergost-22-en-3β-yl acetate (XX) and 7,11-dioxoergosta-8,22-dien-3β-yl acetate (XXII). The latter was reduced to 7,11-dioxoergost-22-en-3β-yl acetate (XXIV) on treatment with zinc dust in acetic acid and further reduction of this product (XXIV) by the Huang--Minlon[19] modification of the Wolff-Kishner procedure yielded 11-oxoergost-22-en-3β-yl acetate (XXV). Similar transformations of diosgenin, cholesterol, and stigmasterol have also been described[16].

Immediately after the publication of this work Heusser[20,21] and his co-workers reported a partial synthesis which followed essentially the same pattern. The analagous products in the cholestane and androstane series were also synthesised.



The 7-hydroxyl group of the triol monoacetate (XVIII) was assigned the α-configuration by Henbest and Wagland[22]. Acetolysis of the epoxide (XVI) gave 3β,7α-diacetoxyergosta-8,22-dien-11α-ol (XXVI), which was

oxidised to 11-oxo-3β,7α-diacetoxyergosta-8,22-diene (XXVII) by treatment with chromic acid in acetic acid.



Treatment with the boron trifluoride-ether complex isomerised the epoxide (XVI) to 11-oxo-9β-ergosta-7,22--dien-3β-yl acetate (XXVIII) which was oxidised with monoperphthalic acid to 11-oxo-7β,8β-epoxy-9β-ergost-22--en-3β-yl acetate (XXIX). The β-configuration was assigned to the 7,8-epoxy-group in view of the similar stereochemical courses taken by hydrogenation and peracid reactions with other trisubstituted olefinic bonds in the steroid series. Alkaline rearrangement of the epoxide (XXIX) and acetylation yielded 11-oxo-3β,7β-diacetoxy-

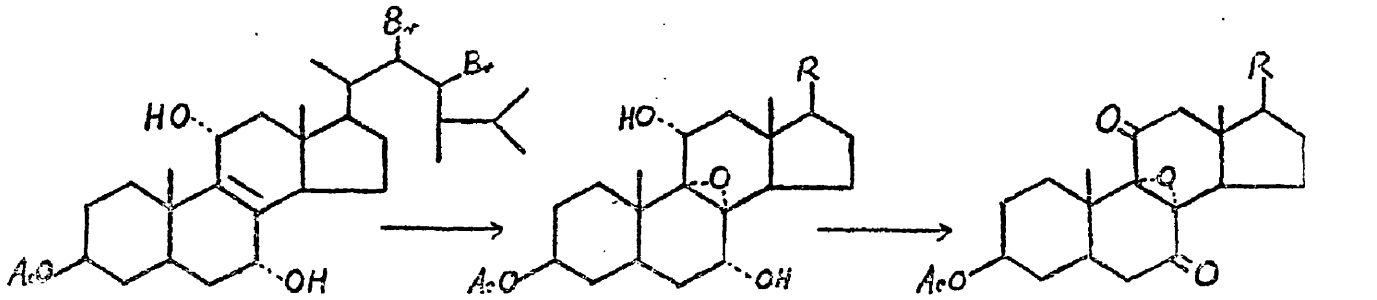
ergosta-8,22-diene (XXX).

During the years 1952-1955 Spring and his co-workers published a series of steroid papers[23-31] which contained, in addition to other work, a conclusive proof of the structures of the above compounds (XVI to XXX).

Treatment of 5-dihydroergosteryl acetate (XIII) with bromine yielded a tetrabromoergosteryl acetate which was partially debrominated by sodium iodide to 22,23-dibromoergosta-7,9(11)-dien-3β-yl acetate (XV), debromination of which with zinc dust yielded ergosterol-D acetate (XIV).[23] Treatment of the dihydro-acetate (XIII) with bromine followed by debromination of the reaction mixture (without isolation of intermediates) gave the conjugated diene (XV) in excellent yield.

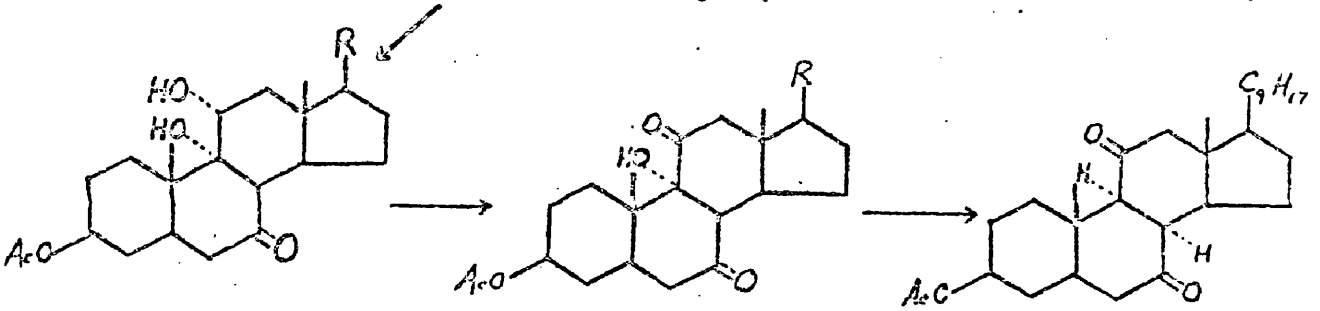
Oxidation[28] of the diene (XV) with perbenzoic acid yielded the epoxide (XVII) which was treated with sulphuric acid in dioxan to give 22,23-dibromo-7α,11α-dihydroxy-ergost-8-en-3β-yl acetate (XIX), oxidation of which with chromic anhydride gave a mixture of the epoxide (XXI) and the ene-dione (XXIII). Debromination using zinc dust related the compounds (XVII, XIX, XXI, and XXIII) to those in the analogous series described by Tishler[16] and Heusser[20,21] (page 6). In particular treatment of the enedione (XXIII) with zinc dust in acetic acid gave

7,11-dioxoergost-22-en-3β-yl acetate (XXIV).



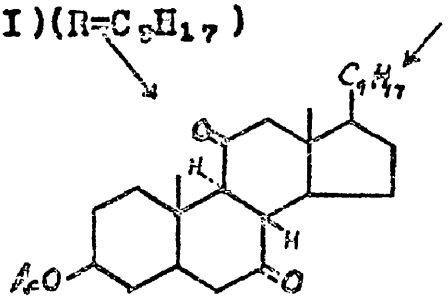
(XIX) (XXXI) (R=$C_9H_{17}Br_2$) (XXI) (R = $C_9H_{17}Br_2$)

(XXXV) (R = C_9H_{17}) (XX) (R = C_9H_{17})



(XXXII)(R=$C_9H_{17}Br_2$) (XXXIII)(R=$C_9H_{17}Br_2$) (XXXIV)

(XXXVI)(R=C_9H_{17}) (XXXVII)(R=C_9H_{17})



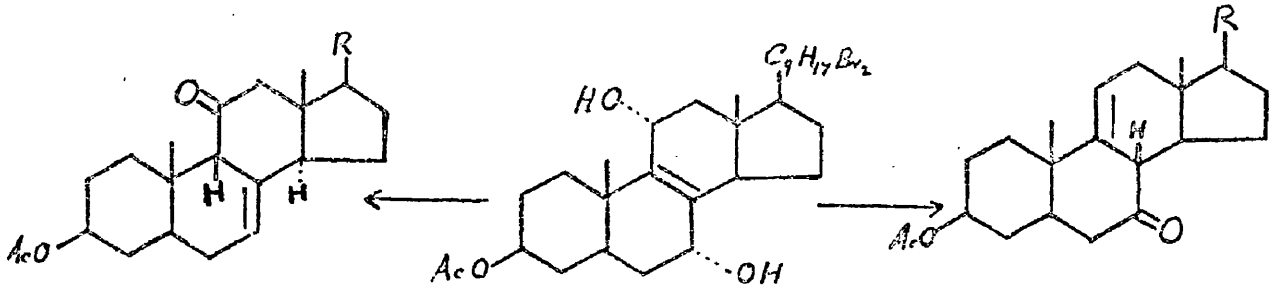
(XXIV)

Treatment[27] of the triol monoacetate (XIX) with perbenzoic acid gave 22,23-dibromo-8α,9α-epoxy-7,11--dihydroxyergostan-3β-yl acetate (XXXI) which was oxidised with chromic anhydride to 22,23-dibromo-8α,9α--epoxy-7,11-dioxoergostan-3β-yl acetate (XXI). Aqueous hydrogen bromide in acetic acid converted this saturated epoxide (XXXI) into 22,23-dibromo-9α,11α-dihydroxyergostan-

-7-one (XXXII) which was oxidised with chromium trioxide to 22,23-dibromo-9α-hydroxy-7,11-dioxoergost-8-en-3β-yl acetate (XXXIII), which in turn yields 7,11-dioxoergost--22-en-3β-yl acetate (XXIV) on treatment with zinc dust in acetic acid. Alternatively debromination of the hydroxy-anedione (XXXIII) with zinc dust in neutral solvent gave 7,11-dioxo-8α-ergost-22-en-3β-yl acetate (XXXIV), which was isomerised to the normal ane-dione (XXIV) on heating with acetic acid, suggesting that the hydrogen atoms at $C_{(8)}$ and $C_{(9)}$ in (XXXIV) are are α-oriented due to a cis-addition of hydrogen to the $\Delta^{8(9)}$-double bond. (A similar cis-addition of hydrogen to a 1,4-dioxo-2,3-ene by treatment with zinc and acetic acid has been described by Barton et al.[32]). This view was taken since addition of hydrogen at $C_{(9)}$ probably occurs from the rear (α) face of the molecule to give a 9α-hydrogen and consequently the isomer (XXXIV) differs from (XXIV) in configuration at $C_{(8)}$.

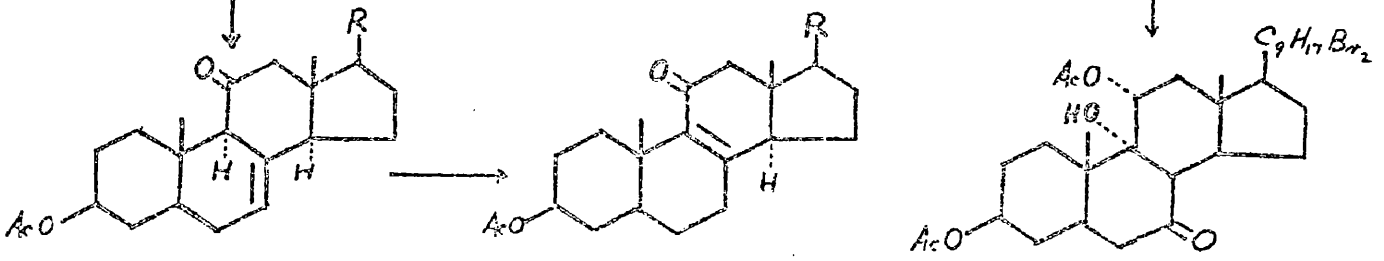
Debromination of the compounds (XXXI), (XXXII), and (XXXIII) gave the corresponding ergost-22-enyl derivatives (XXXV), (XXXVI), and (XXXVII).[27]

The α-configuration of the 9-hydroxyl group of the compound (XXXII) was established by MacLean and Spring[29]. Short treatment of 22,23-dibromo-7α,11α-



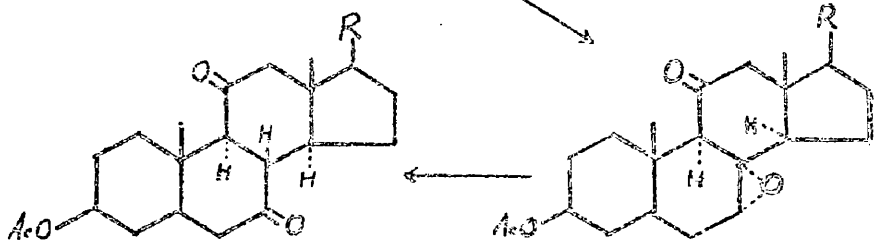
(XXVIII) (R=C_9H_{17}) (XIX) (XXXVIII) (R = $C_9H_{17}Br_2$)

(XXXIX) (R = $C_9H_{17}Br_2$) (XL) (R = C_9H_{17})



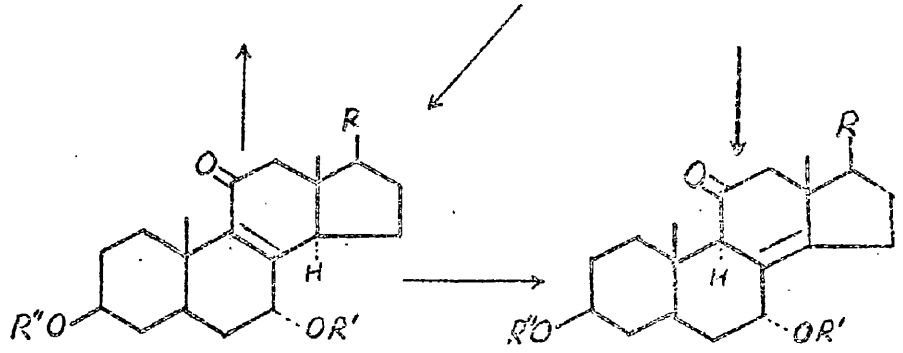
(XLII)(R = $C_9H_{17}Br_2$)(XLIV)(R = $C_9H_{17}Br_2$) (XLI)

(XLIII)(R = C_9H_{17}) (XLV) (R = C_9H_{17})



(XLVIII)(R = $C_9H_{17}Br_2$) (XLVI) (R = $C_9H_{17}Br_2$)

(XXIV) (R = C_9H_{17}) (XLVII) (R = C_9H_{17})



(XLIX)(R=$C_9H_{17}Br_2$,R'=H,R"=Ac) (LI)(R=$C_9H_{17}Br_2$,R'=H,R"=H)

(L)(R=$C_9H_{17}Br_2$,R'=R"=Ac) (LII)(R=$C_9H_{17}Br_2$,R'=R"=Ac)

(XXVII)(R=C_9H_{17},R'=R"=Ac)

dihydroxyergost-8-en-3β-yl acetate (XIX) with the boron trifluoride-ether complex gave a mixture of the βγ -unsaturated ketones, 22,23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (XXXVIII) and 22,23-dibromo-11-oxo-9β--ergost-7-en-3β-yl acetate (XXXIX). Debromination of these products (XXXVIII) and (XXXIX) gave the known βγ -unsaturated ketones (XL)[16,20,21,36] and (XXVIII)[33,34,35]. Hydroxylation of the βγ -unsaturated ketone (XXXVIII) with osmium tetroxide followed by acetylation gave the diacetate (XLI) which is consequently a cis-glycol and therefore has a 9α-hydroxyl group.

Spring et al.[30] also demonstrated that filtration of a benzene solution of the ketone (XXVIII) through alumina gave the 9α-epimer (XLII) (cf. Bladon et al.[34]), and that prolonged contact of the 9β-epimer (XXVIII) with alumina gave the αβ-unsaturated ketone (XLIV). This shows that the 9α-epimer is an intermediate in the conversion of (XXVIII) into (XLIV). Similarly it was demonstrated that the debromo-ketone (XLIII) is an intermediate in the conversion of (XXXIX) into (XLV).

In addition treatment of the ketone (XLII) with perbenzoic acid yielded 22,23-dibromo-7α,8α-epoxyergostan-3β-yl acetate (XLVI). The α-configuration for the 7,8-epoxide bridge was established by considering its mode of formation and the following sequence of reactions.

The epoxide (XLVI) rearranged readily on mineral acid treatment. With hydrogen bromide in chloroformic acetic acid 22,23-dibromo-7,11-dioxoergostan-3β-yl acetate (XLVIII) was formed and related to the known 7,11-dioxoergost-22-en-3β-yl acetate (XXIV) by debromination with zinc dust in a neutral solvent. Treatment of the epoxide (XLVI) with sulphuric acid in dioxan gave 22,23-dibromo-7α-hydroxy-11-oxoergost-8-en--3β-yl acetate (XLIX) which was acetylated to the diacetate (L) and debrominated to give the 11-oxoergosta--8,22-dien-3β,7α-diol diacetate (XXVII) previously described (p. 8) by Henbest and Wagland[22]. 22,23-Dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate (XLIX) is an intermediate in the conversion of the oxo-epoxide (XLVI) to the saturated diketone (XLVIII) since (XLIX) yields the last compound (XLVIII) on treatment with hydrogen bromide in chloroformic acetic acid.

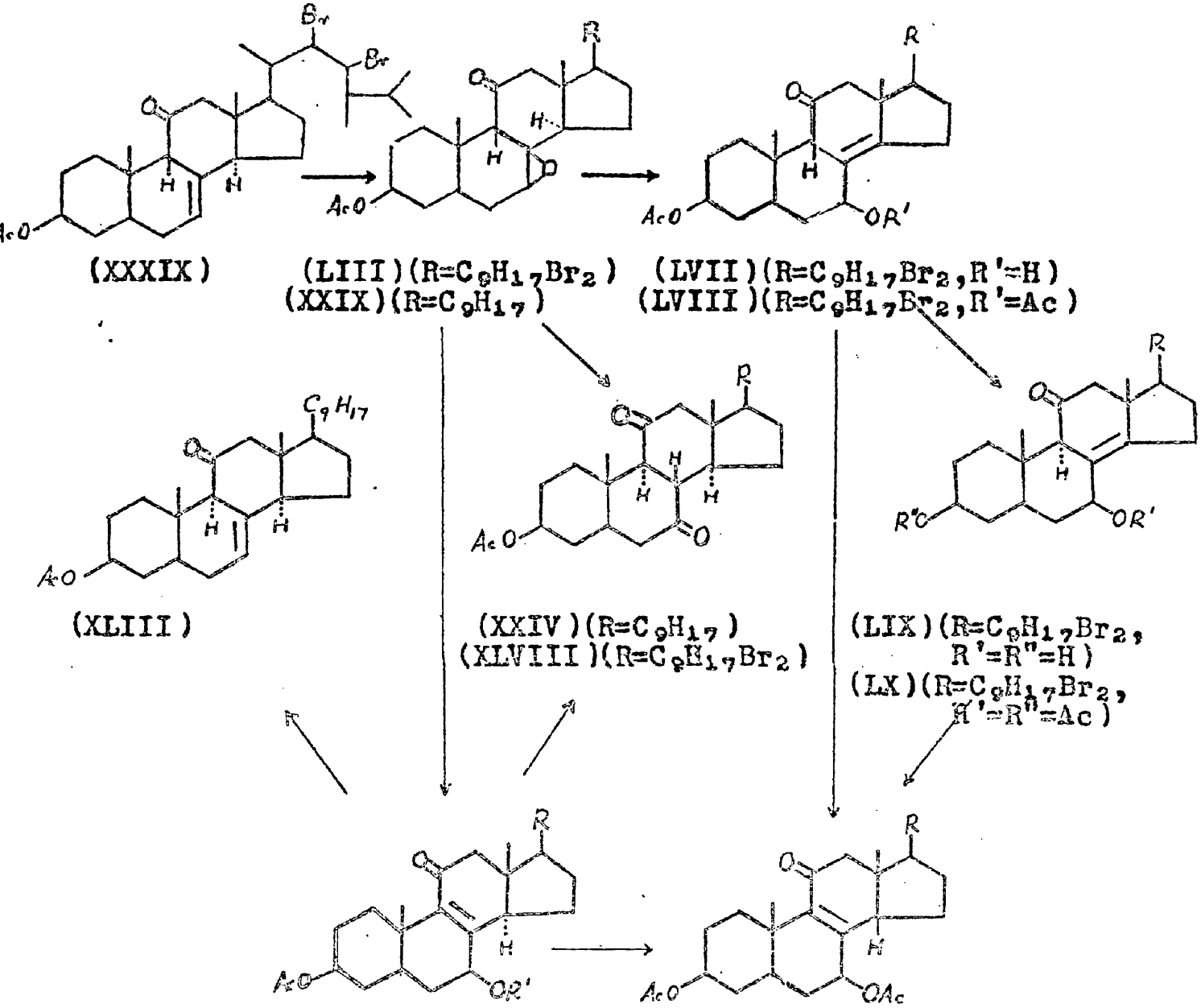
When the oxo-epoxide (XLVI) was treated with 1% methanolic potassium hydroxide at room temperature 22,23 dibromo-3β,7α-dihydroxyergost-8-en-11-one (XLIX) was formed, and acetylated to give the diacetate (L) described above. However, with refluxing methanolic potassium hydroxide the oxo-epoxide (XLVI) gave 22,23-dibromo-3β,7α-dihydroxy-ergost-8(14)-en-11-one (LI) which was acetylated to the

diacetate (LII). 22,23-Dibromo-3β,7α-diacetoxyergost-8-en--11-one (L) was shown to be an intermediate in the conversion of the oxo-epoxide (XLVI) to the diol (LI) as (L) was converted to the last compound (LI) by refluxing methanolic caustic potash.

The 7α,8α-configuration is assigned to the epoxide ring in view of the established attack from the rear (α) face of Δ^7-stenols by osmium tetroxide-acid. (Oxidation of cholest-7-en-3β-yl acetate with osmium tetroxide followed by hydrolysis yields 3β,7α,8α--trihydroxy-cholestane[37,38]). Consequently the hydroxyl groups of the unsaturated ketones (XLIX) and (LI) derived by cleavage of the epoxide ring are α-oriented.

Oxidation of 22,23-dibromo-11-oxo-9β-ergost-7-en--3β-yl acetate (XXXIX) with freshly prepared perbenzoic acid in mineral acid-free chloroform gave an almost quantitative yield of 22,23-dibromo-7β,8β-epoxy-11-oxo--9β-ergostan-3β-yl acetate (LIII), which was debrominated by zinc in neutral solvent to 7β,8β-epoxy-11-oxo-9β--ergost-22-en-3β-yl acetate (XXIX), previously obtained by Henbest and Wagland[22], and by Heusler and Wettstein.[35]

Treatment of the oxo-epoxide (LIII) in chloroform with a trace of hydrobromic acid gave 22,23-dibromo-7β--hydroxy-11-oxoergost-8-en-3β-yl acetate (LIV) which was



(XXXIX) (LIII)(R=$C_9H_{17}Br_2$) (LVII)(R=$C_9H_{17}Br_2$,R'=H)
(XXIX)(R=C_9H_{17}) (LVIII)(R=$C_9H_{17}Br_2$,R'=Ac)

(XLIII) (XXIV)(R=C_9H_{17})
(XLVIII)(R=$C_9H_{17}Br_2$)

(LIX)(R=$C_9H_{17}Br_2$, R'=R"=H)
(LX)(R=$C_9H_{17}Br_2$, R'=R"=Ac)

(LIV)(R=$C_9H_{17}Br_2$,R'=H)
(LV)(R=$C_9H_{17}Br_2$,R'=Ac)
(LVI)(R=C_9H_{17},R'=H)
(XXX)(R=C_9H_{17},R'=Ac)

(LXI)(R=$C_9H_{17}Br_2$)
(LXII)(R=C_9H_{17})

acetylated to the diacetate (LV). Debromination of the alcohol (LIV) yielded 7β-hydroxy-11-oxoergosta-8,22--dien-3β-yl acetate (LVI) which on acetylation gave the diacetate (XXX) previously prepared by Henbest and Wagland[22] (p. 8).

Apart from the orientation of the 7-hydroxyl group, structure (LIV) was established by oxidation with chromic anhydride followed by treatment with zinc dust in acetic acid to give the known 7,11-dioxoergost-22-en-3β-yl acetate (XXIV)[28]. Consequently the compound resulting from the action of hydrobromic acid on the oxo-epoxide (LIII) can only differ from 22,23-dibromo-7α-hydroxy-ergost-8-en-3β-yl acetate (XLIX) in configuration at $C_{(7)}$. Hence (LIV) includes a 7β-hydroxyl group and the epoxide ring of (LIII) has the β-configuration.

Treatment of the oxo-epoxide (LIII) with sulphuric acid in dioxan yielded 22,23-dibromo-7β-hydroxy-11-oxo-9β--ergost-8(14)-en-3β-yl acetate (LVII) which was acetylated to the corresponding diacetate (LVIII). Mild alkaline hydrolysis of this diacetate (LVIII) gave the unconjugated diol (LIX) which on acetylation gave 22,23-dibromo-3β,7β-diacetoxyergost-8(14)-en-11-one (LX). It was therefore concluded that the hydrolysis conditions caused epimerisation of the 9β-hydrogen atom to give the natural 9α-epimer. This simultaneously demonstrated that epoxidation of the unconjugated ketone (XXXIX) yielding (LIII) was not accompanied by inversion at $C_{(9)}$ (cf. Henbest and Wagland[22]).

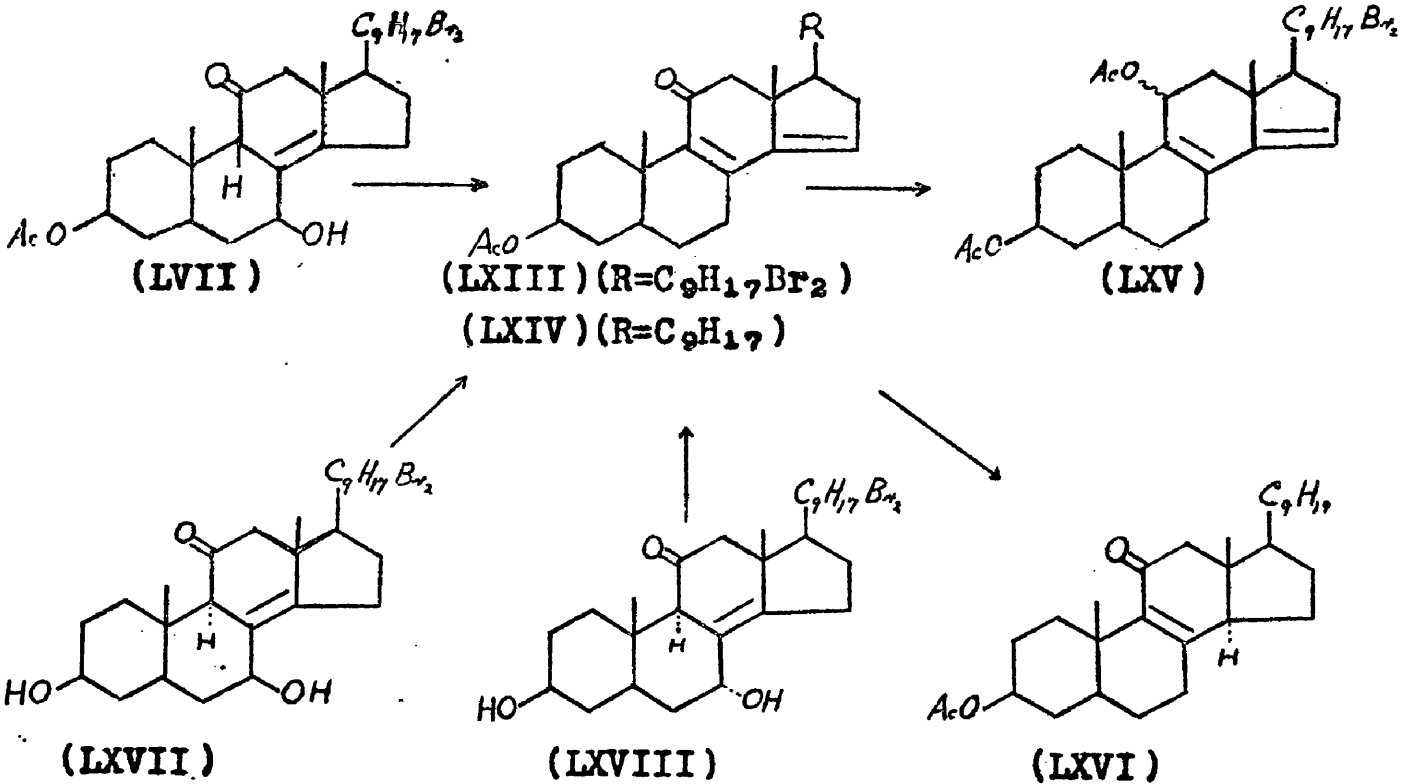
Short treatment of the oxo-epoxide (LIII) with

alcoholic alkali followed by acetylation yielded 22,23-dibromo-3β,7β-diacetoxyergost-8-en-11-one (LV). However prolonged treatment of (LIII) with alcoholic alkali and subsequent acetylation gave a mixture which yielded three homogeneous products, two of which were identified as the αβ-unsaturated ketone (LV) and the saturated diketone (XLVIII); the third product was another αβ-unsaturated keto- diacetate. Treatment of 22,23-dibromo-7β-hydroxy--11-oxo-ergost-8-en-3β-yl acetate (LIV) with alkali followed by acetylation yielded a mixture of the saturated diketone (XLVIII) and this keto-diacetate, which was also formed from 22,23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (LVII) by refluxing with alkali followed by acetylation. It was therefore deduced that this keto-diacetate is 22,23-dibromo-3β,7β-diacetoxy-14β-ergost-8--en-11-one (LXI), differing from (LIV) only in the configuration at $C_{(14)}$. It is noted that debromination of (LXI) proceeds smoothly with zinc dust in neutral solvent, while similar treatment of the 14α-isomer (LV) yields the βγ - unsaturated ketone (XLIII).

It is also pertinent to contrast the behaviour of 7α and 7β-hydroxy substituted 22,23-dibromo-11-oxoergost--8-en-3β-yl acetates in refluxing alkali. The 7α-hydroxy--derivative (XLIX) yields the non-conjugated 22,23-dibromo-

3β,7α-dihydroxyergost-8(14)-en-11-one (LI) in which the double bond has moved out of conjugation to give an alkali stable βδ -unsaturated ketone. Similar alkali treatment (followed by acetylation) of the 7β-hydroxy--derivative (LIV) results in the formation of the 14β--epimer (LXI).

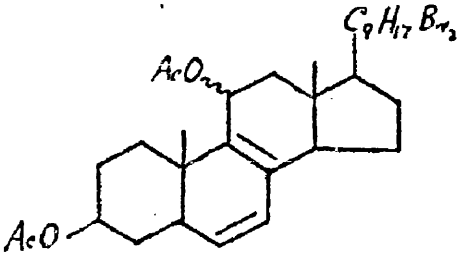
Treatment of 22,23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (LVII) with a trace of hydrobromic acid in chloroform yielded a dienone which was shown to be 22,23-dibromo-11-oxoergosta-8,14-dien-3β-yl acetate (LXIII) by Grigor, Newbold, and Spring[31], who carried out the following reactions. Reduction of the oxo-diene (LXIII) with lithium borohydride followed by acetylation



(LVII) (LXIII)(R=$C_9H_{17}Br_2$) (LXV)

(LXIV)(R=C_9H_{17})

(LXVII) (LXVIII) (LXVI)



(LXIX)

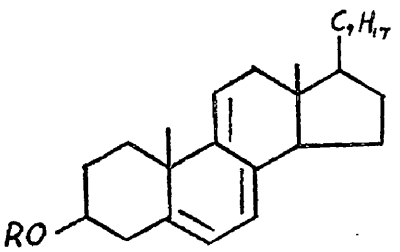
yielded 22,23-dibromo-3β,11ξ-diacetoxyergosta-8,14-diene (LXV), the ultraviolet spectrum of which was characteristic of the ergo-β$_5$ ($\Delta^{8,14}$) diene system as distinct from that expected for the $\Delta^{6,8}$-diene system of 22,23-dibromo-3β,11-diacetoxyergosta-6,8-diene (LXIX). Hydrogenation of the oxo-diene (LXIII) over Raney nickel gave the known 11-oxo--ergost-8-en-3β-yl acetate (LXVI)[25], formation of which verified the structure (LXIII) for the oxo-diene.

The conjugated oxo-diene (LXIII) was also prepared by sulphuric acid treatment (followed by acetylation) of 22,23-dibromo-11-oxoergost-8(14)-en-3β,7β-diol (LXVII) or of the 7α-isomer (LXVIII). In contrast it is noted that acid treatment of the $\Delta^{8(9)}$-isomer (L) with subsequent acetylation gave the saturated diketone (XLVIII) (p. 12).

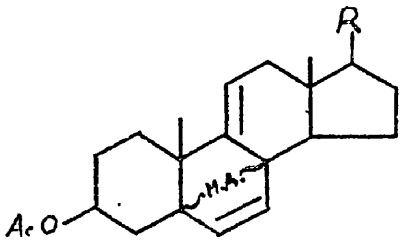
11-Oxo-steroids from Dehydroergosterol.

Bergmann and Stevens[14] further (cf. p. 4) suggested that dehydroergosterol (LXXI), prepared by mercuric acetate

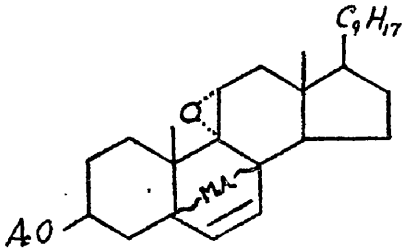
oxidation of ergosteryl acetate (VIII; R = Ac), appeared an attractive starting material for the synthesis of 11-oxo-ergosterol derivatives. The maleic anhydride adduct (LXXIII) of dehydroergosteryl acetate (LXXII) was formed and the side chain protected by bromination to give the dibromide (LXXIV). Treatment of the last compound (LXXIV) with perbenzoic acid followed by debromination with zinc dust gave a high yield of the monoepoxide (LXXV), pyrolysis of which caused aromatisation and no identifiable 11-oxosteroid was isolated.



(LXXI)(R = H)

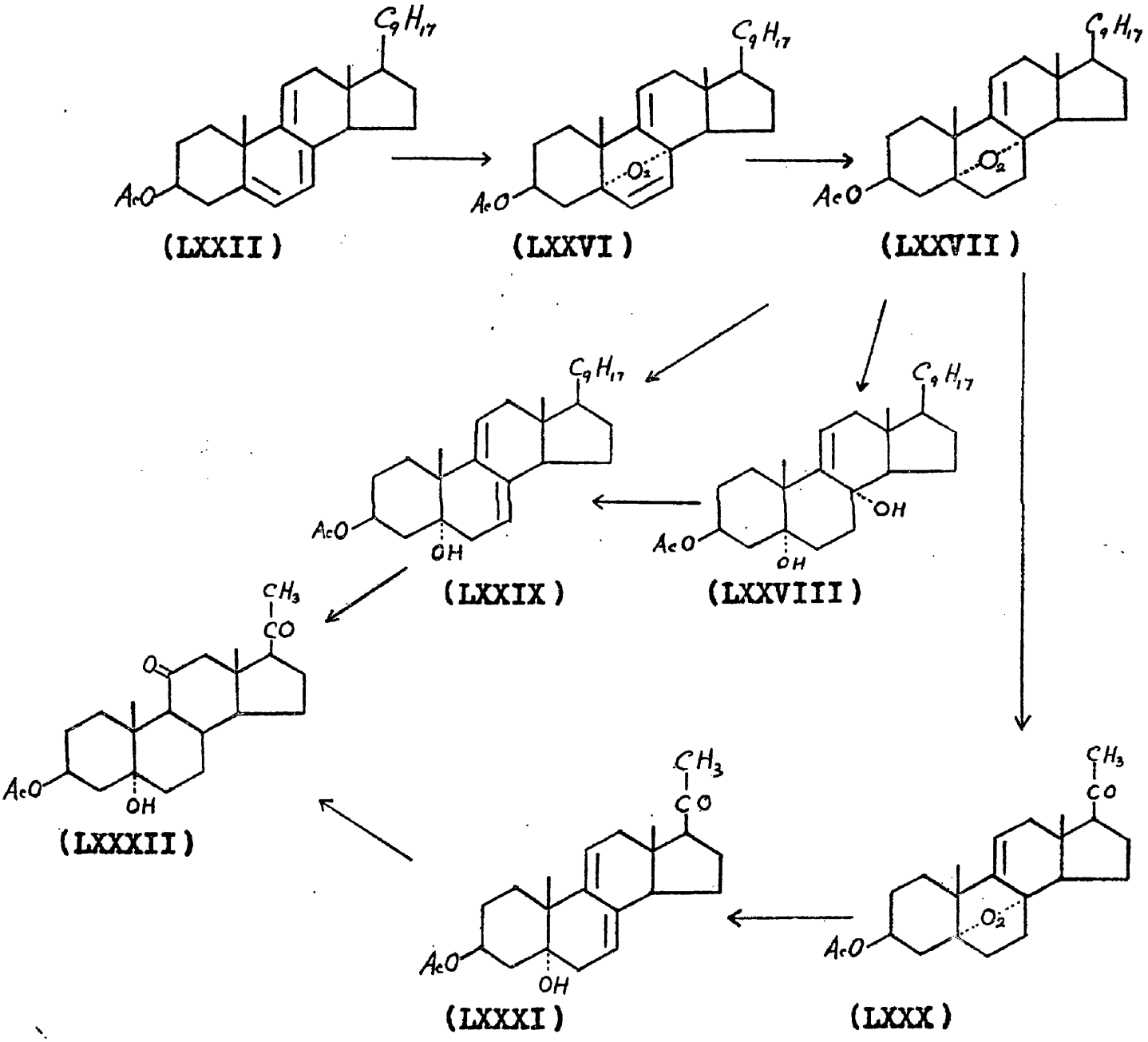


(LXXIII)(R=C_9H_{17})
(LXXIV)(R=$C_9H_{17}Br_2$)



(LXXV)

In 1952-1953 a series of publications by Jones et al.[41,42] described another approach to 11-oxo-steroids. Photoperoxidation of dehydroergosteryl acetate (LXXII) gave 5α,8α-epidioxydehydroergosteryl acetate (LXXVI), first prepared by Windaus and Linsert.[40] Jones and his co-workers preferentially reduced the Δ^6-double bond of (LXXVI) with a specially prepared platinum catalyst to give 5α,8α-epidioxyergosta-9(11),22-dien-3β-yl acetate (LXXVII), which



on hydrogenation with Raney nickel or palladium catalyst gave 5α-hydroxyergosta-7,9(11),22-trien-3β-yl

acetate (LXXIX). Since this compound is also prepared by platinum catalysed hydrogenation (2 moles) of the epidioxide (LXXVII) to give 5α,8α-dihydroxyergosta-9(11),22--dien-3β-yl acetate (LXXVIII) which is readily dehydrated to the conjugated 7,9(11)-diene (LXXIX) on mild acid treatment, the diol (LXXVIII) is an intermediate in the conversion of the transannular epidioxide (LXXVII) into this diene (LXXIX). The application of the standard method (p. 5) of degradation of the side chain of ergosterol derivatives to the epidioxide (LXXVII) gave 5α,8α-epidioxy-20-oxoallopregn-9(11)-en-3β-yl acetate (LXXX), hydrogenation of which yielded 5α-hydroxy-20-oxoallopregna-7,9(11)-dien-3β-yl acetate (LXXXI).

The $\Delta^{9(11)}$-ethylenic linkage of the epidioxide (LXXVII) proved only moderately reactive to oxidising agents and formed the 9,11-epoxide and 9,11-diol in poor yields. This was attributed to the steric hindrance of the $\Delta^{9(11)}$-double bond by the α-orientated epidioxide bridge.

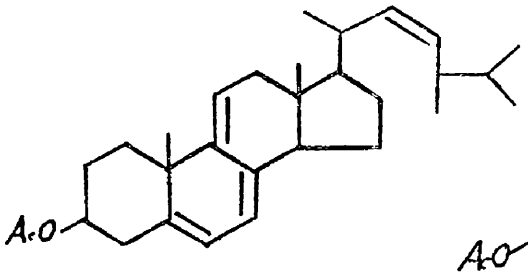
Following the well established routes described previously for $\Delta^{7,9(11)}$-dienes, both the bridge compounds (LXXVII) and (LXXX) can be converted into 5α-hydroxy-11,20-dioxoallopregnan-3β-yl acetate (LXXXII), and thence to cortisone.

It is observed that formation of cortisone <u>via</u>

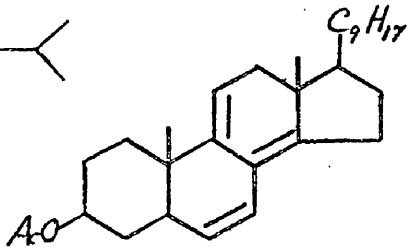
5α,8α-epidioxides is facilitated by the subsequent formation of a 5α-hydroxy-derivative which is readily dehydrated after oxidation of the 3β-hydroxyl group to give the Δ^4-3-oxo system of cortisone.

11-Oxo-steroids from Ergosta-6,8(14),9(11),22--tetraen-3β-yl Acetate.

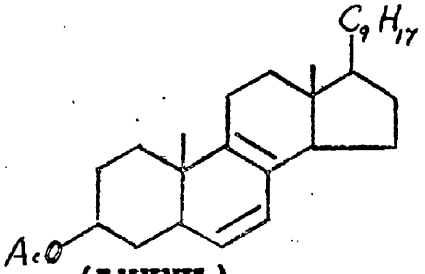
Laubach et al.[45a] demonstrated that dehydroergosteryl acetate (LXXII) rearranges in the presence of anhydrous sulphur dioxide and pyridine to the isomer ergosta-6,8(14), 9(11),22-tetraen-3β-yl acetate (LXXXIII), which proved a useful intermediate for corticosteroid synthesis. The structure



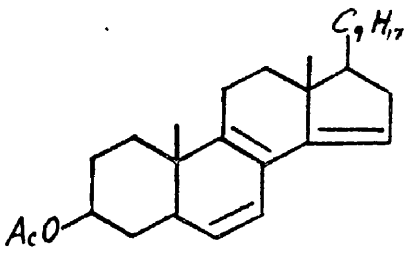
(LXXII)



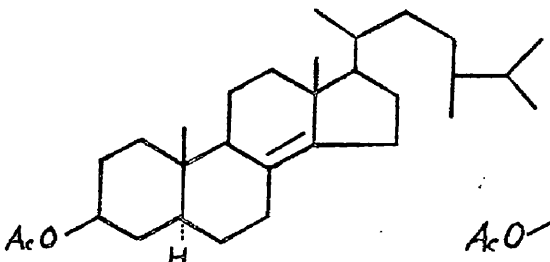
(LXXXIII)



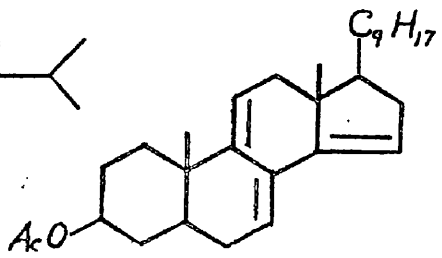
(LXXXV)



(LXXXVI)



(LXXXIV)

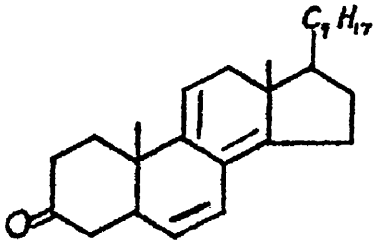


(LXXXVII)

(LXXXIII) was established by the following series of reactions.

Catalytic hydrogenation of the tetraene (LXXXIII)

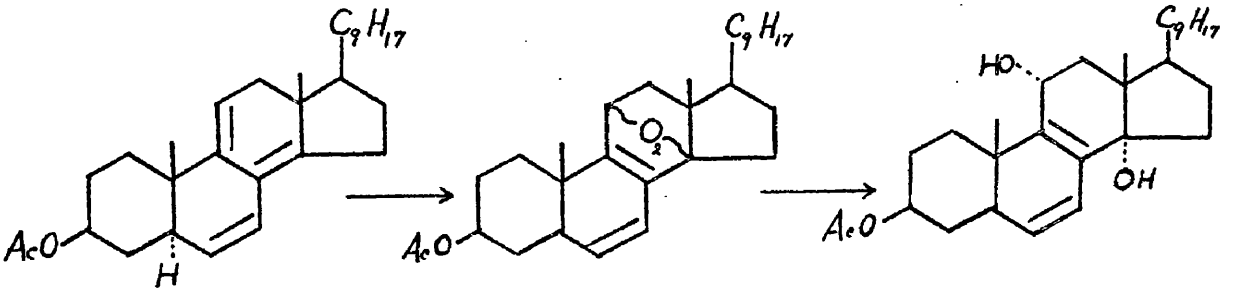
over platinum catalyst (3 moles of hydrogen) yielded ergost-8(14)-en-3β-yl acetate (LXXXIV). Formation of the maleic anhydride adduct of the tetraene (LXXXIII) gave a compound the ultraviolet absorption spectrum of which was consistent with that of the cisoid diene (LXXXV) and different from the absorption maxima expected for the $\Delta^{7,14}$ or $\Delta^{8(14),9(11)}$ diene systems derived from the adducts of the tetraenes (LXXXVI) and (LXXXVII) respectively.



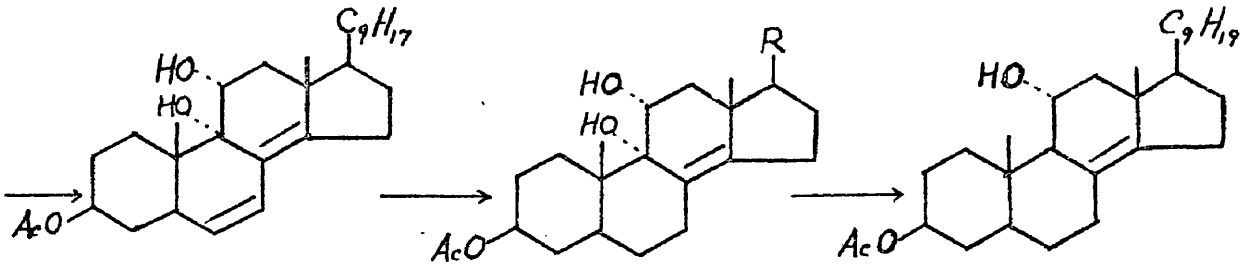
(LXXXVIII)

Saponification of the tetraene (LXXXIII) followed by oxidation yielded a non-conjugated ketone (LXXXVIII) having an unchanged ultraviolet absorption spectrum. The original $\Delta^{8(9)}$ double bond has therefore migrated away from its position adjacent to ring A in the sulphur dioxide-pyridine rearrangement.

The same workers[48b] formed the epidioxide (LXXXIX) by photoperoxidation of the tetraene (LXXXIII). The epidioxide system in the former (LXXXIX) was selectively

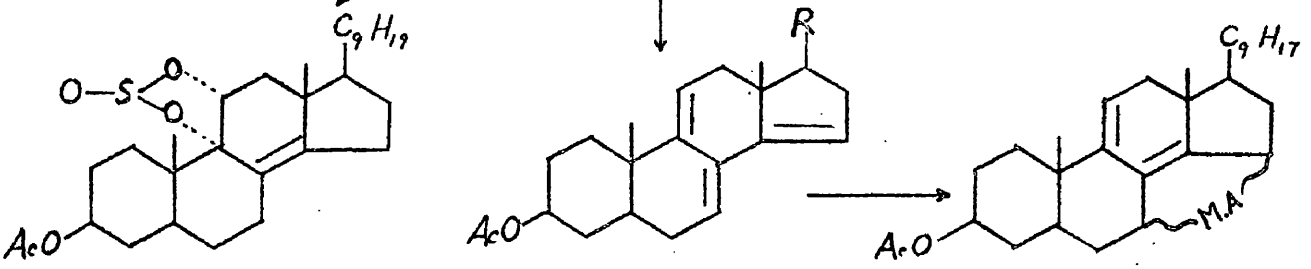


(LXXXIII) (LXXXIX) (XC)



(XCI) (XCII)(R=C_9H_{17}) (XCIV)

(XCIII)(R=C_9H_{19})



(XCV) (XCVI)(R=C_9H_{17}) (XCVIIIa) (R=C_9H_{17})

(XCVII)(R=C_9H_{19}) (XCVIIIb)(R=C_9H_{19})

cleaved by a highly deactivated palladium-lead catalyst to yield 11α,14α-dihydroxyergosta-6,8,22-trien-3β-yl acetate (XC). Attempted acid-catalysed dehydration of the 14α-hydroxyl group gave the isomeric 9α,11α-

-dihydroxyergosta-6,8(14),22-trien-3β-yl acetate (XCI), which was subsequently prepared in quantitative yield by very dilute aqueous acid treatment of the diene-diol (XC). The isomers (XC) and (XCI) each absorbed one mole of hydrogen over Raney nickel catalyst, the conjugated diene systems being partially reduced under conditions which were not adequate for the reduction of the isomeric $\Delta^{8,14}$-diene system in the ergostatriene series.[46] The hydrogenation (1 mole of hydrogen) of the diol (XCI) over Raney nickel gave 9α,11α-dihydroxyergosta-8(14),22-dien-3β-yl acetate (XCII), which in turn was hydrogenated (3 moles of hydrogen) over platinum catalyst to 11α-hydroxyergost-8(14)-en-3β-yl acetate (XCIV). In addition the diol (XCI) absorbed two moles of hydrogen over palladium-charcoal catalyst giving 9α-11α-dihydroxyergost-8(14)-en-3β-yl acetate (XCIII), the remaining $\Delta^{8(14)}$-double bond of which was completely inert to noble-metal hydrogenation in neutral media.

The α-configuration was assigned to the epidioxide ring upon considering the approach of the peroxidising attack and the stereochemistry of the subsequent derivatives. It has been well established that attack of $\Delta^{9(11)}$-unsaturated steroids[16,20,47-49] and of the $C_{(11)}$

carbon atom[50a] itself occurs from the rear (α) face of the molecule. Moreover transannular additions to the somewhat sterically comparable $\Delta^{5,7}$-diene steroids have generally been found to take place on the α-face[37].

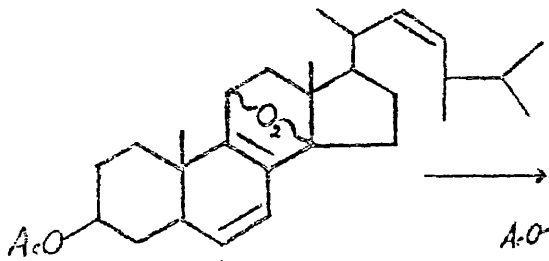
The non-rearranging 11-hydroxyl group of the diols (XCI) and (XCII) has the same configuration as the 11-hydroxyl function of the parent diol (XC). This secondary hydroxyl group is readily acetylated under conditions insufficient for the acylation of an 11β--hydroxyl group of a steroid with the normal (9α) B C-ring junction. That this B C ring fusion in (XCI) is normal seemed a reasonable deduction on consideration of acid--catalysed rearrangements of other Δ^{8}-unsaturated steroids[50b,52]. Experimental support for the 9,11-cis--orientation of the hydroxyl groups was gained from the facile formation of the cyclic sulphite ester (XCV). This reaction has a precedent[53d] in the analogous facile osterification of a 5,8-oxido-9α,11α-diol by the action of thionyl chloride in pyridine.

Treatment of the diols (XCII) and (XCIII) with boiling acetic anhydride yielded the corresponding $\Delta^{7,9(11),14}$-trienes (XCVI) and (XCVII), which formed the maleic anhydride adducts (XCVIIIa) and (XCVIIIb) respectively. Hydrogenation of ergosta-7,9(11),14-trien-3β-yl acetate

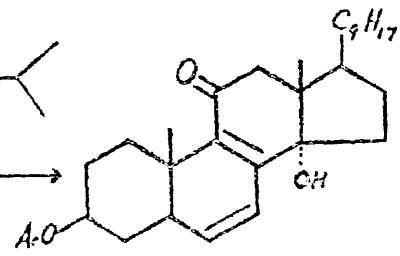
(XCVII) over platinum in acetic acid resulted in the absorption of two equivalents of hydrogen to yield ergost-8(14)-en-3β-yl acetate (LXXXIV) which is similarly prepared by hydrogenation of ergosteryl acetate (VIII; R = Ac). This indicated that there has been no rearrangement of the carbon skeleton. Although the ultraviolet absorption spectra of the adducts, (XCVIIIa) and (XCVIIIb) disagreed with the calculated maxima, it was found to coincide with the absorption exhibited by a $\Delta^{8(14),9(11)}$-diene which had been synthesised by Graber *et al.*[51] in the corticosteroid series.

With a view to obtaining a saturated 11α-hydroxyergostan-3β-yl acetate the monoacetates (XCII) and (XCIII) were reduced over platinum catalyst in acetic acid. These conditions (followed by acetylation) however, yielded 3β,11α-diacetoxyergost-8(14)-ene (XCIV) which remained unchanged under conditions which isomerised and hydrogenated the double bond of ergost-8(14)-en-3β-yl acetate (LXXXIV) to give ergostan-3β-yl acetate.[52]

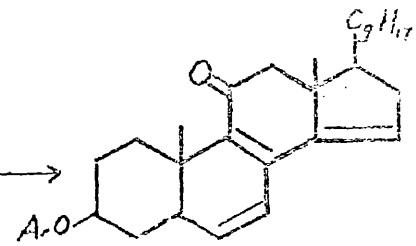
However the same workers prepared a nuclear-saturated 11-oxoergost-22-enyl derivative by a 'reduction-oxidation' cleavage of the epidioxide (XCIX) to give 14α-hydroxy--11-oxoergosta-6,8,22-trien-3β-yl acetate (CI) which was readily dehydrated by treatment with mineral acid followed by acetylation to give 11-oxoergosta-6,8,14,22-tetraen-3β-yl acetate (CII). Hydrogenation of the nuclear trienone (CII) over palladium in neutral medium gave 11-oxoergost-8-en-3β-yl acetate (CIII). However, if the tetraenone (CII) was reduced over a Raney nickel catalyst, 11-oxoergosta-8,14,22-trien-3β-yl acetate (LXIV) resulted. The analogous hydrogenation treatment of the trienone (CI) gave the unsaturated ketol (CV), subsequent acid-catalysed dehydration of which yielded the trienone (LXIV), previously prepared by Spring et al.[31] (p. 19). Partial hydrogenation of (LXIV) to 11-oxoergosta-8,22-dien--3β-yl acetate (CVI) was effected over a Raney nickel catalyst in a basic aqueous alcoholic medium. The remaining nuclear double bond of the ketone (CVI) was readily reduced by lithium metal in liquid ammonia to give 11-oxoergost-22-en-3β-yl acetate (CVII) in good yield as reported by Tishler[34] and Djerassi.[55]



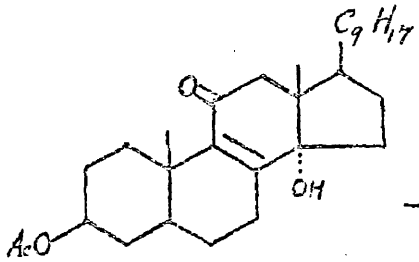
(XCIX)



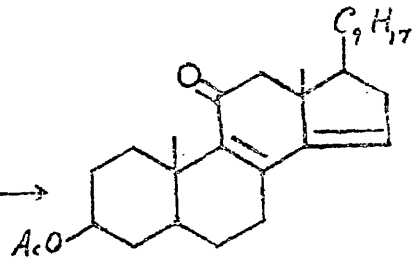
(CI)



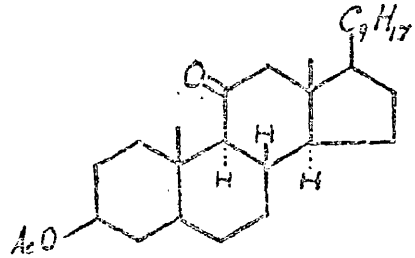
(CII)



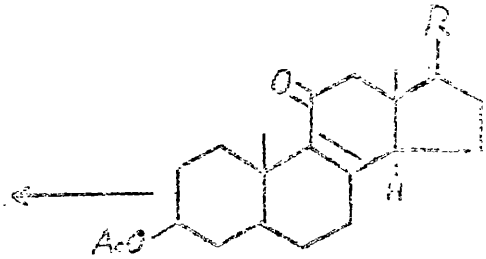
(CV)



(LXIV)



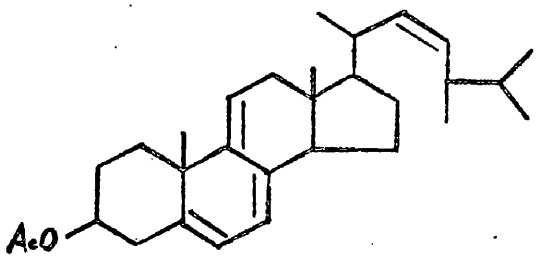
(CVII)



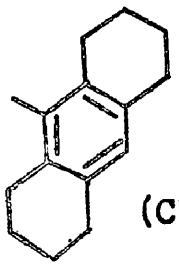
(CIII) (R = C_8H_{18})
(CVI) (R = C_9H_{17})

The Anthrasteroid Rearrangement.

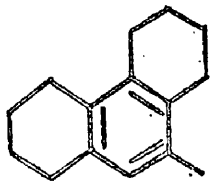
In 1953 Nes and Mosettig[56] discovered that treatment of dehydroergosteryl acetate (LXXII) with chloroformic hydrogen chloride promoted a rearrangement of the steroid nucleus giving a hydrocarbon anthraergostapentaene, which was shown to contain a benzene ring with a double bond in conjugation and an isolated double bond. These last non-aromatic double bonds were readily reduced to give a tetrahydro-derivative, the ultraviolet spectrum of which is very similar to that of 9-methyl-s-octahydroanthracene (CVIII) as distinct from 9-methyl-s-octahydrophenanthrene (CIX). Selenium dehydrogenation of anthraergostapentaene yielded an anthracene derivative which indicated the presence of



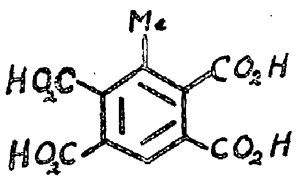
(LXXII)



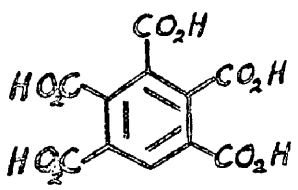
(CVIII)



(CIX)



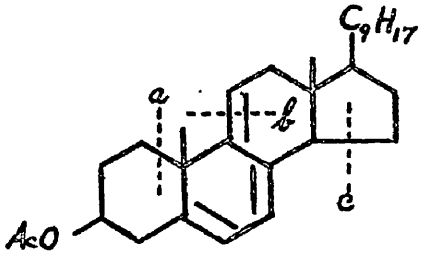
(CX)



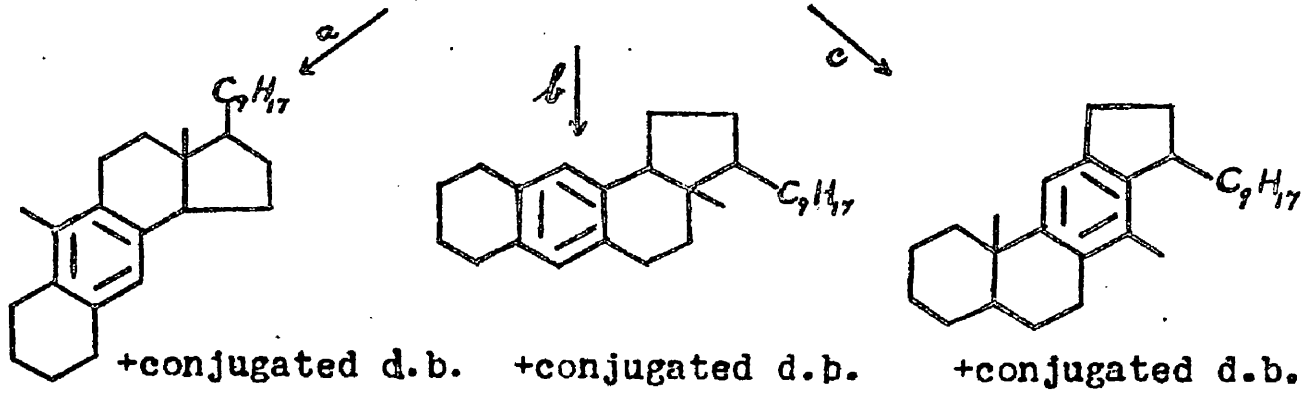
(CXI)

an octahydroanthracene nucleus in the carbon skeleton of the parent pentaene. In addition vigorous oxidation of the pentaene with concentrated nitric acid yielded 1-methyl-2,3,5,6-tetracarboxybenzene (CX).[58] This acid was also formed on similar oxidation of 9-methyl-s--octahydroanthracene (CVIII), whereas 9-methyl-s-octahydrophenanthrene (CIX) gave the pentacarboxylic acid (CXI).

The same workers remarked that a hydrocarbon having the 9-methyl-s-octahydroanthracene skeleton could arise from dehydroergosteryl acetate (LXXII) by only two types of carbon-carbon rupture i.e. (a) at $C_{(1)}$ and $C_{(10)}$, and (b) $C_{(9)}$ and $C_{(11)}$, leading to the aromatic compounds (CXII) and (CXIII) respectively. Scission at $C_{(14)}$ and $C_{(15)}$ could give the structure (CXIV) which, although



(LXXII)



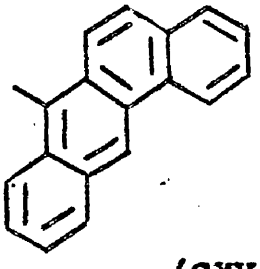
+conjugated d.b. +conjugated d.b. +conjugated d.b.

+ Me

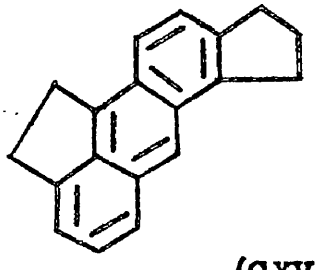
(CXII) (CXIII) (CXIV)

satisfying the spectroscopic and oxidation results, seemed unlikely to produce an anthracene derivative on dehydrogenation. The rearrangement of dehydrolumisteryl acetate (the $C_{(10)}$ epimer of LXXII) also yields the anthraergostapentaene which consequently cannot be represented by structure (CXIV).

These authors pointed out that this rearrangement of the steroid nucleus to an anthracene derivative may well be associated with part of a biogenetic route to endogenous carcinogens since many potent carcinogens are anthracene derivatives with a ring fused to the 1,2 - positions (e.g. 10-methyl-1,2-benzanthracene CXV). It was observed that the hydrocarbon (CXII) bears a skeletal resemblance to 1,2-cyclopenteno-5,10-anthracene (CXVI) which shows a definite carcinogenic activity[59].



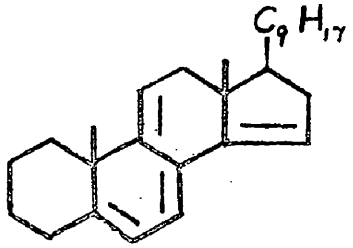
(CXV)



(CXVI)

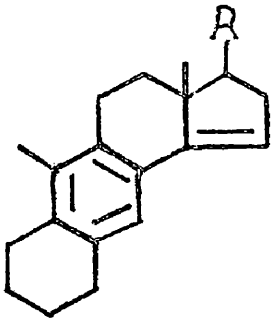
That the route[60a] to the anthrasteroid proceeded by dehydration followed by aromatisation was demonstrated by the isolation of an intermediate dehydration product

shown to be ergosta-5,7,9(11),14,22-pentaene (CXVII), which was subsequently isomerised to anthraergostapentaene (CXII) in high yield by chloroformic hydrogen chloride.

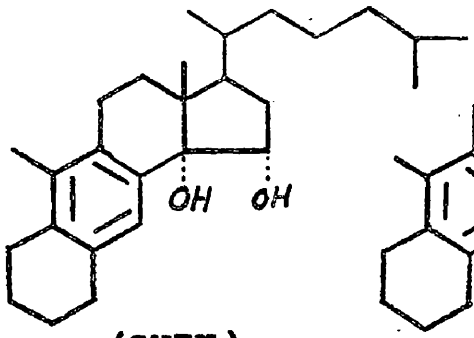


(CXVII)

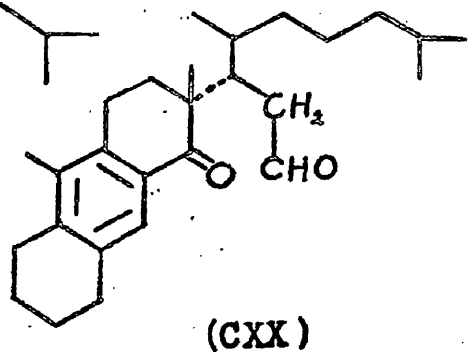
Burgstahler[61] demonstrated that the anthrasteroids are correctly represented by the cipher (CXVIII) as a result of the following sequence of degradative reactions.



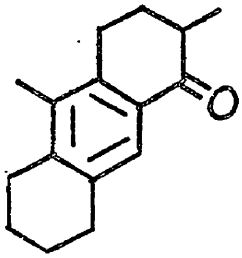
(CXVIII)



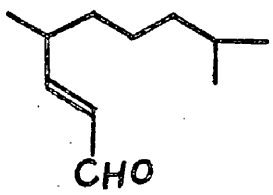
(CXIX)



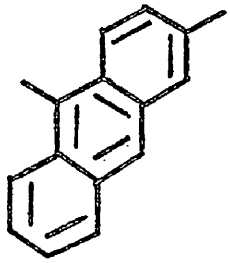
(CXX)



(CXXI)



(CXXII)



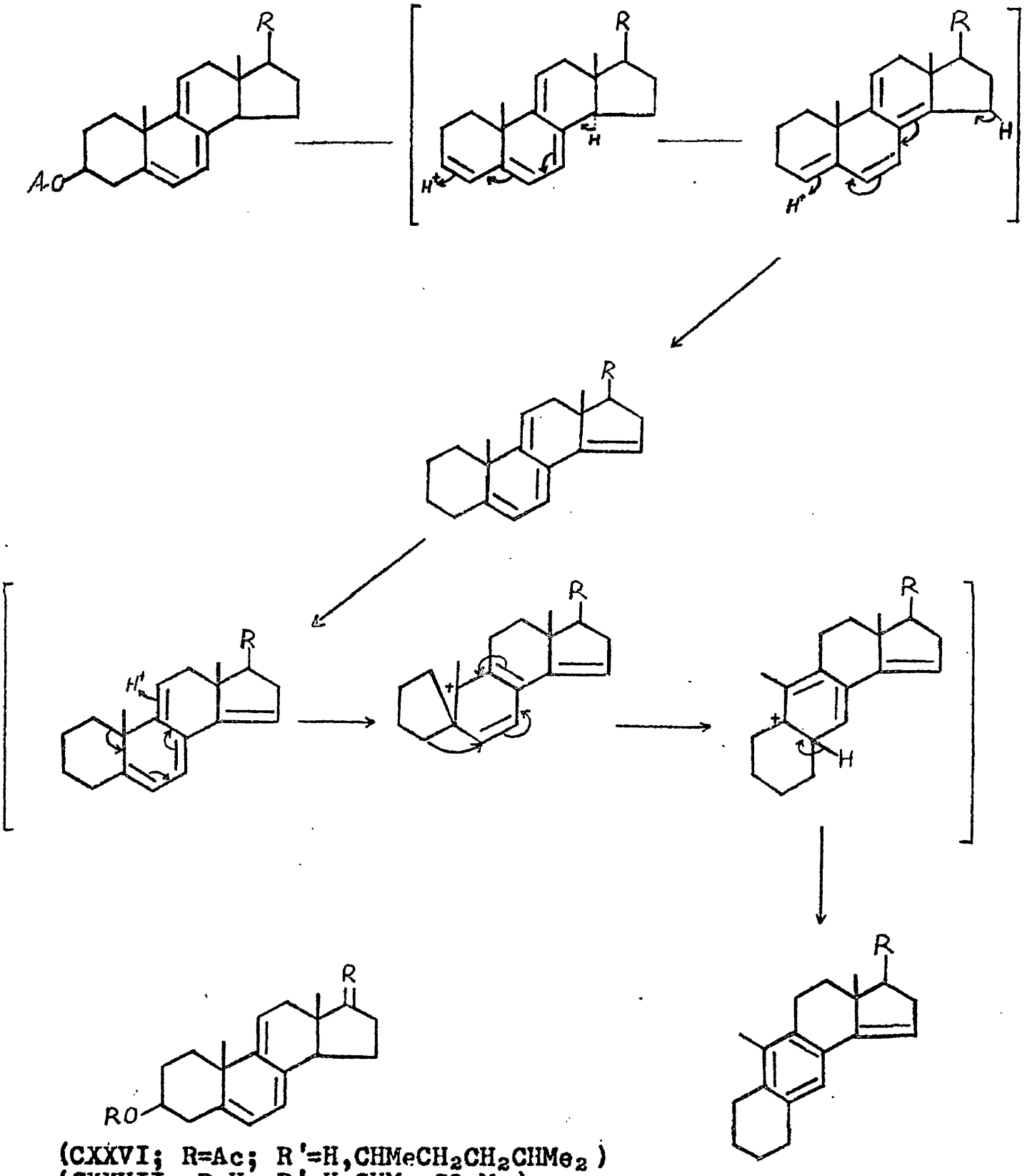
(CXXIII)

Treatment of anthracholestatetraene (CXVIII; R = C_8H_{17}) with osmium tetroxide yielded the cis-α--glycol (CXIX) which was cleaved with lead tetra-acetate giving the keto-aldehyde (CXX). Pyrolysis of (CXX) produced the volatile aldehyde (CXXII) and the non-volatile ketone (CXXI) which was dehydrogenated with palladium--charcoal to give 3;9-dimethylanthracene (CXXIII), identified by synthesis.

The following mechanism for the anthrasteroid rearrangement was outlined by Burgstahler[61] (page 37).

The anthrasteroids (CXXIV) and (CXXV) were prepared[60b] from cholesta-5,7,9(11)-trien-3β-yl acetate (CXXVI) and 3β-hydroxybisnorchola-5,7,9(11)-trienic acid methyl ester (CXXVII) respectively. The product from 17-oxoandrosta-5,7,9(11)-trien-3β-yl isocaproate (CXXVIII), however, was a mixture which probably contained the chloro-derivative (CXXIX).

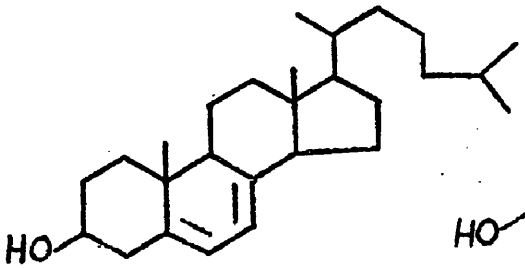
The irradiation of 7-dehydrocholesterol (CXXX), isodehydrocholesterol (CXXXI), or cholesta-5,8-dien-3β-ol (CXXXII) in the presence of p-toluenesulphonic acid and mercuric acetate, and in the absence of oxygen, to give an aromatic compound has been described by Tsuda and Hayatsu[62], who obtained an anthracene derivative from



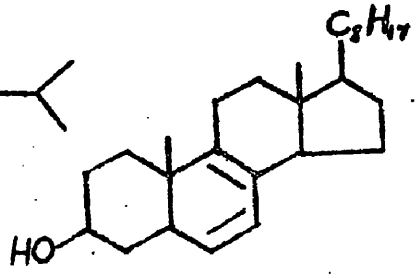
(CXXVI; R=Ac; R'=H,CHMeCH$_2$CH$_2$CHMe$_2$)
(CXXVII; R=H; R'=H,CHMe.CO$_2$Me)
(CXXVIII; R=i-C$_6$H$_{13}$O;R'=O)

(CXXIV; R=CHMe.CH$_2$CH$_2$CH$_2$CHMe$_2$)
(CXXV; R=CHMeCO$_2$Me)

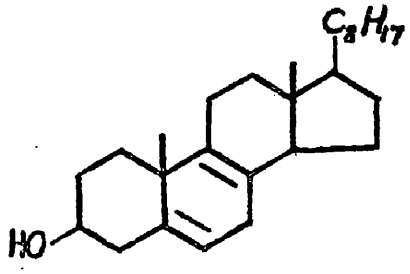
selenium dehydrogenation of the aromatic compound which was consequently formulated as (CXXXIII).



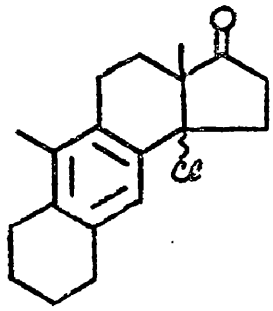
(CXXX)



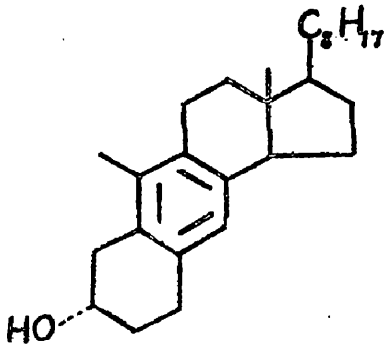
(CXXXI)



(CXXXII)



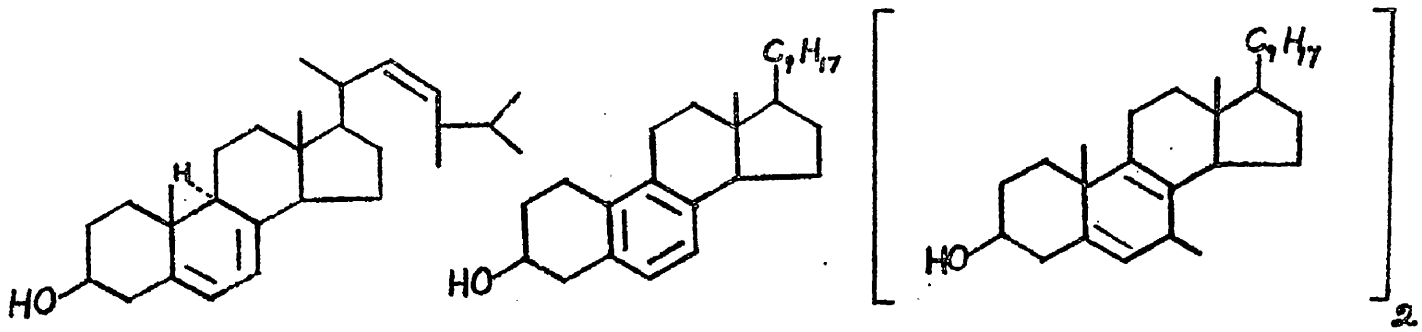
(CXXIX)



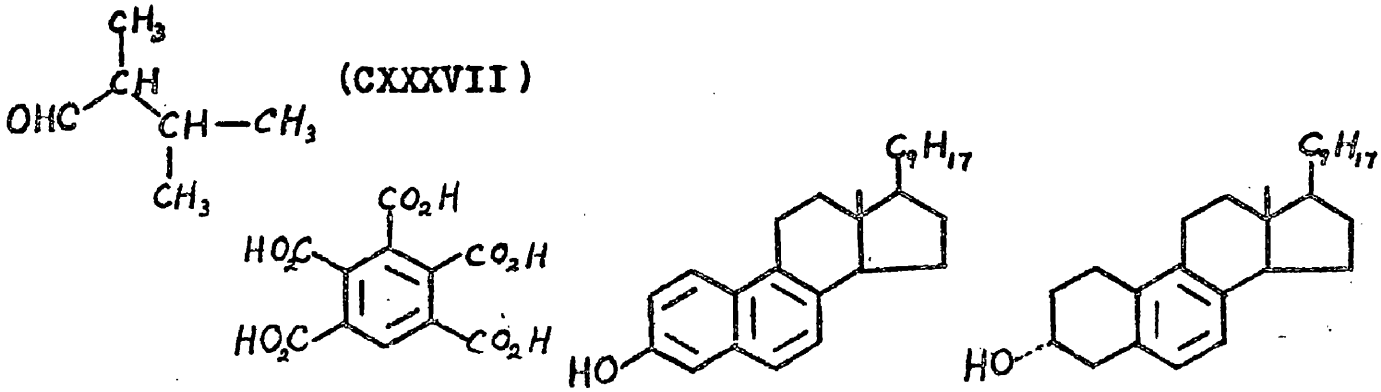
(CXXXIII)

The Neosteroids

It was discovered by Windaus[63] in 1928 that visible light, in the presence of eosin and the absence of oxygen, caused ergosterol (CXXXIV), to form the bisergostatrienol (CXXXV). High vacuum distillation of (CXXXV) results in the loss of methane to give a mixture of neoergosterol (CXXXVI) and the non-aromatic



(CXXXIV) (CXXXVI) (CXXXV)



(CXXXVII)

(CXXXVIII) (CXXXIX) (CXL)

"isoneoergosterol".[64]

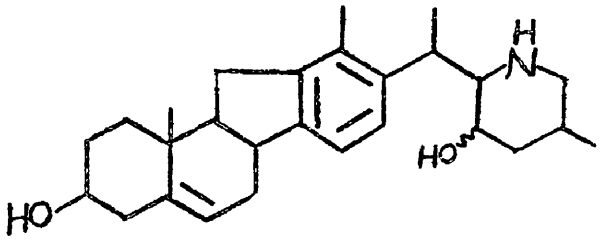
Neoergosterol (CXXXVI) contains only one reactive double bond which was located in the 22,23-position by isolation of methylisovaleraldehyde (CXXXVII) as a product of ozonolysis.[64] The presence of an aromatic ring in the nucleus was indicated by the elementary analysis and the ultraviolet absorption spectrum.[65] Oxidation of neoergosterol (CXXXVI) by concentrated nitric acid gave prehnitic acid (CXXXVIII) which originated from ring B and not ring C as the ready dehydrogenation of neoergosterol, without loss of methane, gave the naphthol (CXXXIX).[66]

The latter was reduced by sodium in amyl alcohol[67] to epineoergosterol (CXL). The 3β-hydroxyl group[68,69] in neoergosterol is epimerised by refluxing with sodium in amyl alcohol.

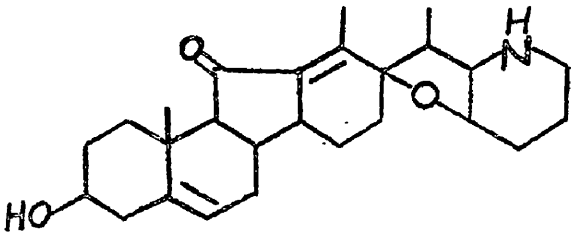
Further work on the formation of neosteroids has been carried out by later workers.[70]

Aromatic Ring-C or Ring-D.

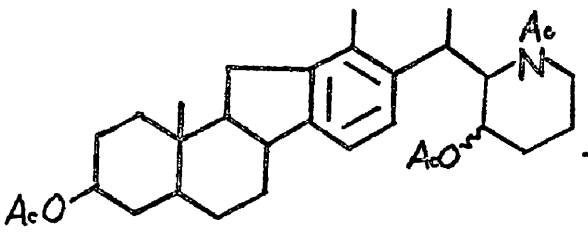
The steroidal alkaloid veratramine (CXLI) and certain derivatives of jervine (CXLIII) are analogous to a hypothetical D-homosteroid in which ring-D is aromatic.



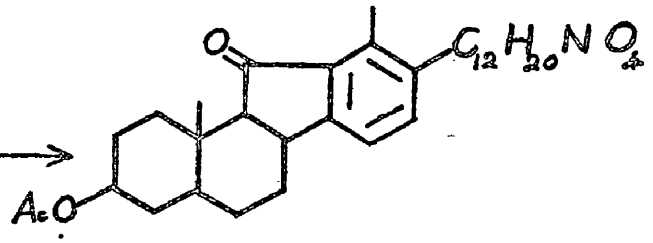
(CXLI)



(CXLIII)



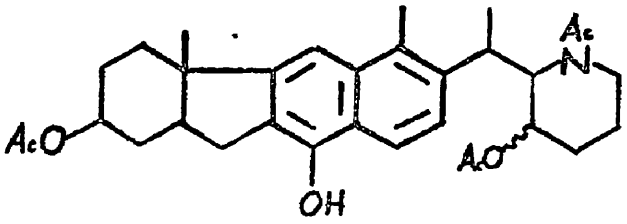
(CXLII)



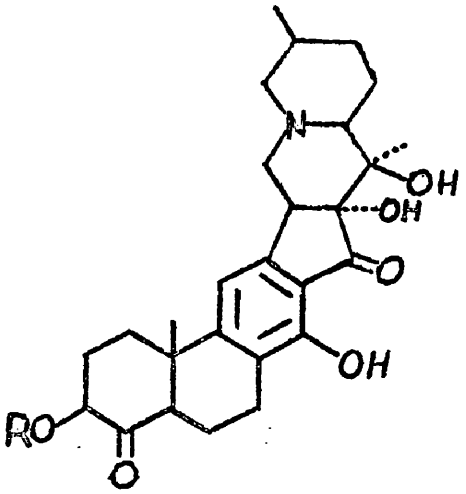
(CXLIV)

The structure (CXLI) for veratramine was proposed by Tamm and Wintersteiner[71] who obtained experimental support for this formulation by oxidation of triacetyldihydroveratramine (CXLII) to the indanone (CXLIV), which proved identical with a compound derived[72] from jervine (CXLIII).

In conclusion, the only aromatic ring-C compounds (CXLV)[71] and (CXLVI)[73] derived from steroidal substances possessed a carbon skeleton fundamentally different from that of the normal steroid nucleus.



(CXLV)



(CXLVI) ($R=CH_2CH=C(CH_3)CO$)

THEORETICAL

Introduction

During the investigation of the possible conversion of ergosterol (CXXXIV) into cortisone (VII), Anderson, Spring, and Stevenson,[23] required as an intermediate, 22,23-dibromoergosteryl-D acetate[76]. This was prepared in good yield by treatment of tetrabromoergostenyl acetate with sodium iodide. The structure of this tetrabromide, obtained by low temperature bromination of 5α,6-dihydroergosteryl acetate (XIII), was not established.

The work described in this thesis defines the constitutions of further products obtained from the tetrabromide, and utilises a knowledge of these derivatives to consider the character of the parent compound, which is subsequently shown to be a 7,11,22,23--tetrabromoergost-8-en-3β-yl acetate.

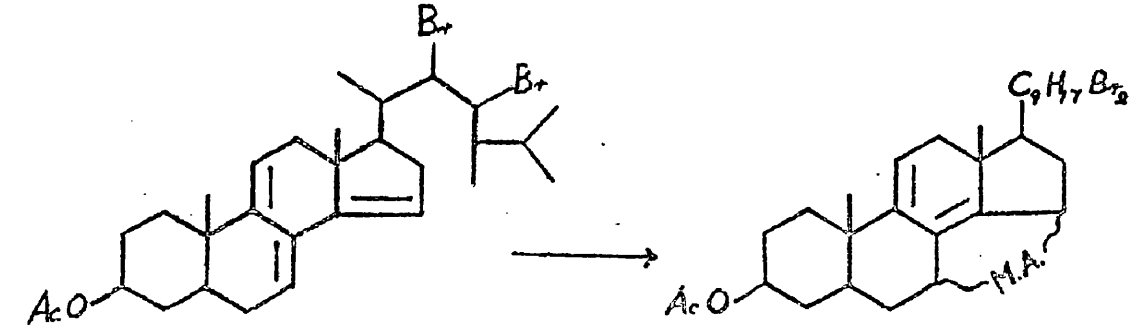
Chromatography of Tetrabromoergostenyl Acetate.

When a solution of the tetrabromide in benzene was filtered through a column of alumina, decomposition took place with the simultaneous production of a violet-green (ultimately brown) band at the top of the column. Elution with benzene gave two isomeric crystalline compounds, $C_{30}H_{44}O_2Br_2$, having distinct characteristics, and when the brown band was finally washed from the column with methanol, a third compound, $C_{31}H_{48}O_3Br_2$, crystallised slowly from the concentrated eluate.

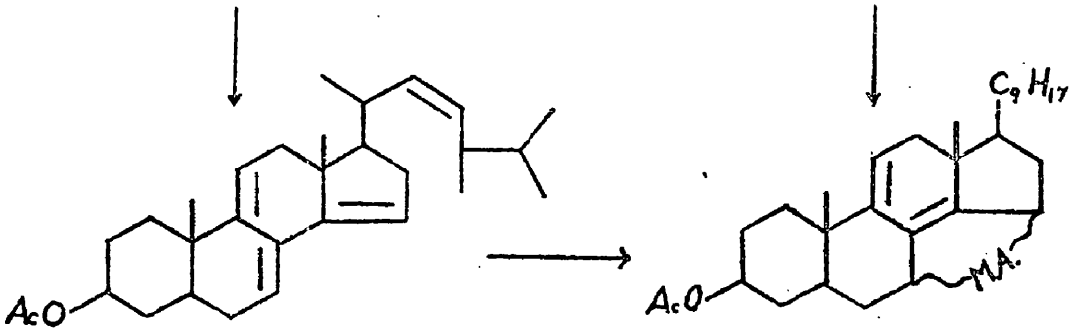
The first isomer, m.p. 211-212°, was obtained in high yield when a warm benzene solution of the tetrabromide was filtered quickly through the column, while the second isomer, m.p. 136-137°, was isolated in good yield when the column was allowed to stand overnight before elution. In each case a small amount of the third substance was isolated from the methanol fraction. The structure of this material is discussed in a later section (p. 86).

The isomer, m.p. 211-212°, gave a deep orange colour, fading to yellow, with tetranitromethane, and showed three maxima of medium intensity (ca.11,000) at 2280 Å, 2340 Å, and 2680 Å, in the ultraviolet region.

This spectrum corresponded exactly with that of ergosta-7,9(11), 14,22-tetraen-3β-yl acetate (XCVI), prepared by Laubach, Schreiber, Agnello, and Brunings[45b] (p. 26), who also formed the corresponding maleic anhydride adduct (XCVIIIa) absorbing at 2730 Å. (ϵ = 4570).



(CXLVII) (CXLVIII)



(XCVI) (XCVIIIa)

Debromination of the isomer, m.p. 211-212°, by treatment with zinc in ether-ethanol at 50°, gave a product having the same melting point and ultraviolet absorption spectrum as the tetraene (XCVI) prepared by Laubach et al.[45b], who published neither a specific rotation value nor an elementary analysis for the compound.

In order to confirm the structure (CXLVII)

for the parent dibromotriene the maleic anhydride adduct (CXLVIII) was formed and subsequently debrominated to a compound having the same constants as the corresponding adduct (XCVIIIa) prepared by Laubach et al.[45b] An identical maleic anhydride adduct (XCVIIIa) was prepared from the debromotriene (XCVI).

T A B L E I.

		m.p.	$[\alpha]_D$	Ultraviolet absorption spectra.
Laubach et al.				
Ergosta-7,9(11),14,22-tetraen-3β-yl acetate	(XCVI)	127-131°		2270Å (ϵ = 9120) 2350Å (ϵ = 6310 2680Å (ϵ = 10,000)
M.A. Adduct.	(XCVIIIa)	205-209°	-36.7°	2730Å (ϵ = 4570)
Author.				
Tetraene	(XCVI)	127-131°		2280Å (ϵ = 10,070), 2350Å (ϵ = 10,120), 2680Å (ϵ = 9180).
M.A. Adduct	(XCVIIIa)	205-208°	-36.5°	2730Å (= 4280).

From this comparison the first isomer, m.p. 211-212°, is identified as 22,23-dibromoergosta-7,9(11),14--trien-3β-yl acetate (CXLVII).

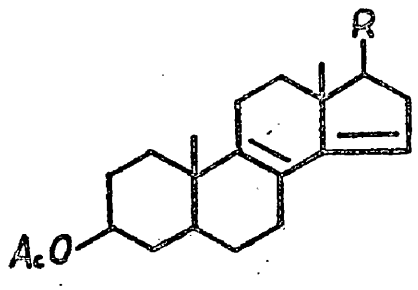
Alkaline hydrolysis of the acetate (CXLVII) yielded the corresponding alcohol which on reacetylation gave the original compound. Attempted dehydration of the

alcohol with phosphorus oxychloride yielded the 3α-chloro derivative which proved unstable on recrystallisation; this configuration assumes that Walden inversion has taken place.[75]

Treatment of the tetrabromide with collidine also gave the dibromotriene (CXLVII), but in this case contaminated with a dibromodiene, since subsequent treatment of the mixture with chloroformic hydrogen chloride destroyed the cross-conjugated triene system and 22,23-dibromoergosta--8,14-dien-3β-yl acetate (CXLIX) was isolated from the reaction product by chromatography. The last compound was previously prepared[76a] by low temperature bromination (2 moles) of 5α,6-dihydroergosteryl acetate (XIII), followed by chromatography on alumina. A comparison of the constants below of the two products showsthat they differ only in the intensity of absorption at 2480 Å. The author suggests that the extinction coefficient, (19,500), is correct as it is in excellent agreement with that, (19,800) reported for ergosteryl-B_1 acetate (CL) by Fieser et al.[77]

TABLE II

Dibromoergosteryl-B_1 Acetate	m.p.	$[\alpha]_D$	Ultraviolet Absorption Spectra.
R. C. Anderson	227-228°	-20.5°	2480Å. (ϵ = 14,000).
Author	225-226°	-20°	2480Å. (ϵ = 19,500).



(CXLIX) (R = $C_8H_{17}Br_2$)
(CL) (R = C_8H_{17})

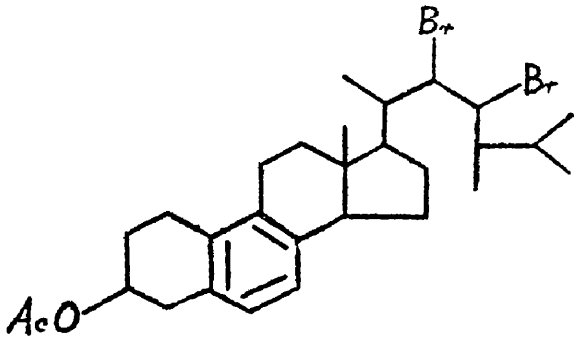
The second isomer, $C_{30}H_{46}O_2Br_2$, m.p. 136-137° (p.43) gives a deep yellow colour with tetranitromethane in chloroform. It was not reduced by Adam's catalyst[57] in glacial acetic acid, and displayed absorption characteristic of an aromatic ring in both the ultraviolet and infrared regions.

Hydrolysis of the acetate using either acid or alkali gave the corresponding alcohol, $[\alpha]_D$ + 5°, which yielded the original dibromo aromatic acetate on reacetylation. Oxidation of the alcohol with chromium trioxide in pyridine gave the 3-keto steroid, $[\alpha]_D$ + 23°, exhibiting absorption in the infrared region at 1721 $cm.^{-1}$ corresponding[80] to an isolated 6-ring carbonyl group, and still showing the presence of an unconjugated benzenoid ring in the ultraviolet absorption spectrum. The molecular rotation difference between the alcohol and the

ketone (+99°) is in fair agreement with the figure (+73 ±8°)[78] for the oxidation of 3β-hydroxy-steroids to 3-oxo-steroids.

The alcohol was not dehydrated by treatment with phosphorus oxychloride, but gave a 3α-chloro derivative.[75] Dehydration of the alcohol with phosphorus pentoxide, however, gave a mixture of two isomers, the 2-ene and the 3-ene, which were separated by fractional crystallisation. Both isomers displayed the characteristic ultraviolet absorption of an unconjugated aromatic ring and were unchanged after attempted isomerisation with strong mineral acid. This behaviour eliminates the possibility of an aromatic ring A or B, and hence eliminates an anthrasteroid structure (CXVIII; p. 35).

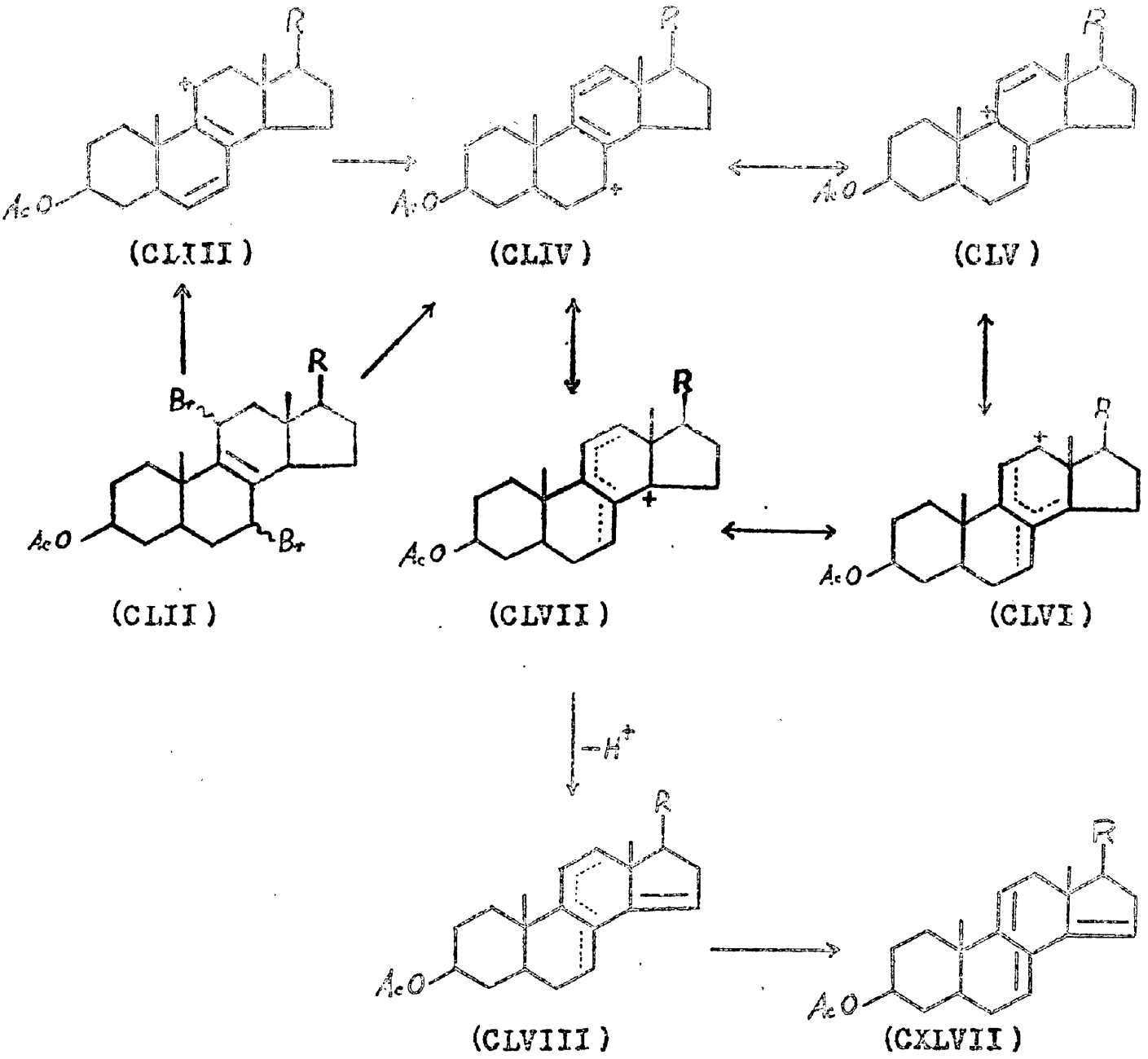
In addition the dibromoaromatic acetate does not correspond to a neosteroid since (a) no gaseous products were observed during its formation, (b) the elementary analysis of the acetate and its derivatives require all the carbon atoms of the original ergostane skeleton, and (c) it differs from 22,23-dibromoneoergosteryl acetate (CLI), m.p. 179-181°.[65]



(CLI)

In order to consider the possible mechanism of the aromatisation, tetrabromoergostenyl acetate will be represented by the structure (CLII), which is later (p. 95) shown to be correct. Nuclear dehydrobromination and protonation give the carbonium ions (CLIII) or (CLIV) which can exist in the resonance hybrid forms (CLV), (CLVI), and (CLVII), due to the unsaturated nature of the nucleus. As stated above, the dibromotriene (CXLVII) is obtained in high yield when an alumina column on which the tetrabromide (CLII) has been adsorbed is immediately washed with benzene. On the other hand when elution of the column is delayed for 20 hours, only a small proportion of the dibromotriene (CXLVII) is obtained and the major product is the dibromoaromatic acetate. This would suggest that the aromatic compound is formed preferentially at the expense of the triene (CXLVII) when a longer contact time with the alumina is allowed. This requires that

R = $C_8H_{17}Br_2$



(CLIII) (CLIV) (CLV)

(CLII) (CLVII) (CLVI)

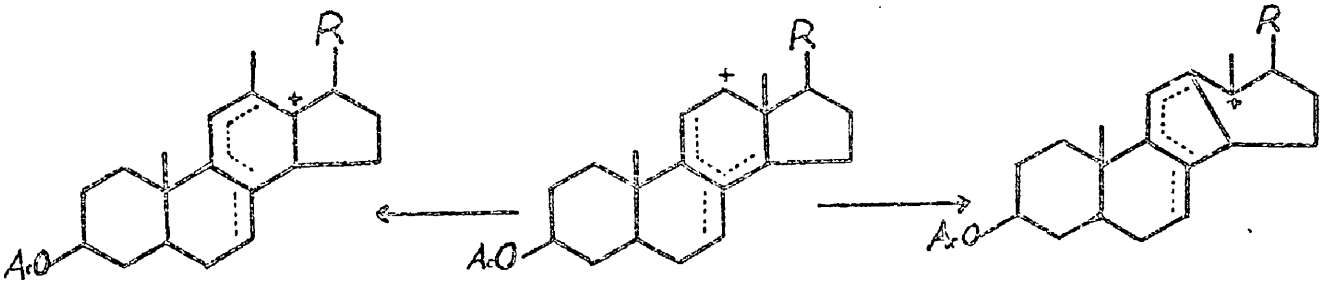
(CLVIII) (CXLVII)

there must be a common carbonium ion intermediate which may give rise to either the triene (CXLVII) or the aromatic compound. The triene (CXLVII) is considered to have been formed from the intermediate carbonium ion (CLVII) by loss of a proton from $C_{(18)}$ as shown above. Possible mechanisms for the formation of an aromatic

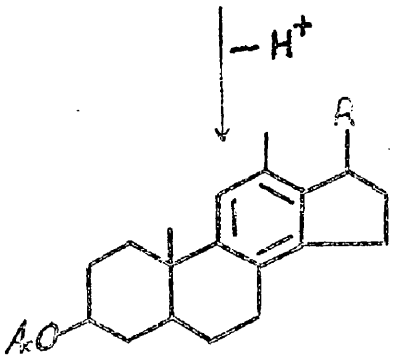
structure from the resonant carbonium ions (CLVI) and (CLVII) are outlined below.

In the first route from the carbonium ion (CLVI), a Wagner-Meerwein migration of the $C_{(13)}$-methyl group to $C_{(12)}$ is followed by loss of a proton from $C_{(14)}$ to give the benzenoid structure (CLIX). Alternatively, a rearrangement of the nucleus could result in the formation of the ring-D aromatic steroid (CLX).

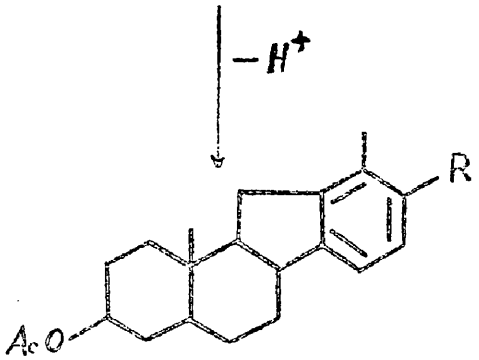
R = $C_9H_{17}Br_2$



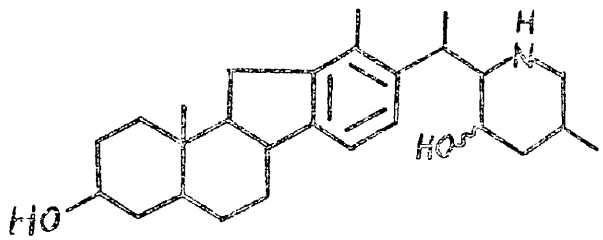
(CLVI)



(CLIX)

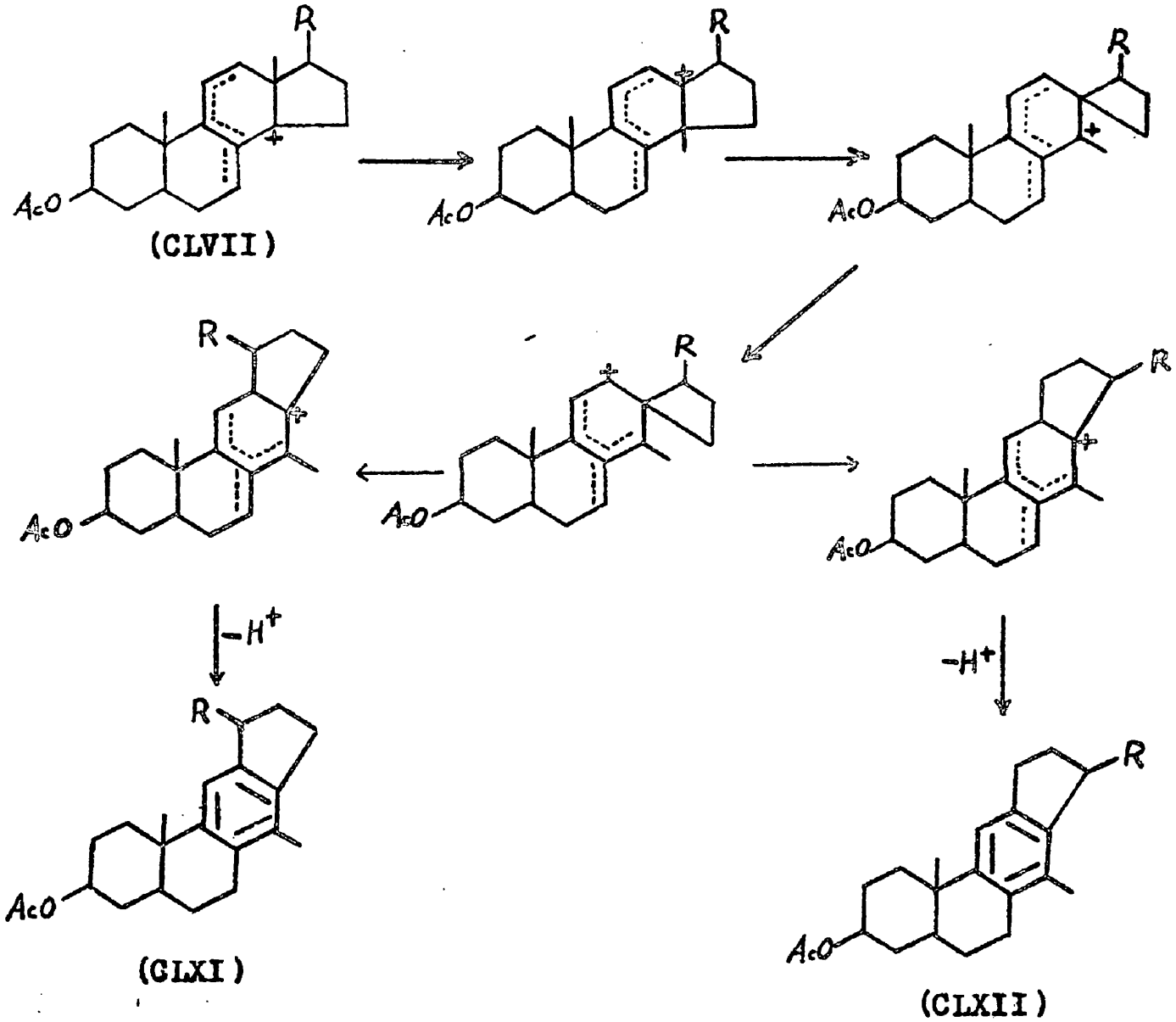


(CLX)



(CLXIII)

Another mechanism originates from the carbonium ion (CLVII) and leads to the aromatic compounds (CLXI) and (CLXII), which resemble the dihydroanthrasteroids (CLXV).



(CLVII)

(CLXI)

(CLXII)

However, treatment of the dibromotriene (CXLVII) with chloroformic hydrogen chloride did not yield the dibromoaromatic compound. In addition, the dibromotriene (CXLVII) was recovered quantitatively after having been left on a column of alumina mixed with aluminium bromide, and having a few drops of hydrobromic acid added as

catalyst. It is therefore unlikely that this last reaction mechanism is correct as protonation of the dibromotriene (CXLVII) should readily yield the carbonium ion (CLVII) and hence the aromatic structures (CLXI) and (CLXII).

Evidence in favour of structure (CLIX) for the dibromoaromatic acetate was obtained from a study of its spectroscopic properties.

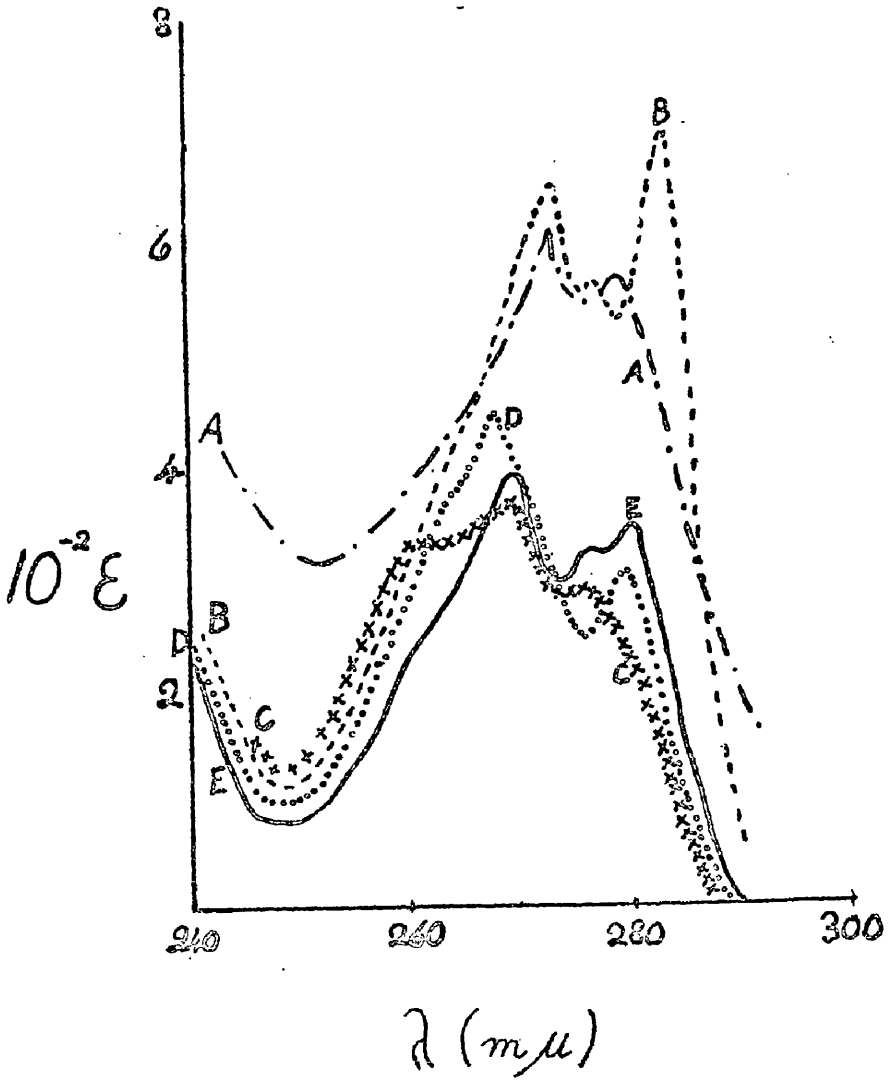
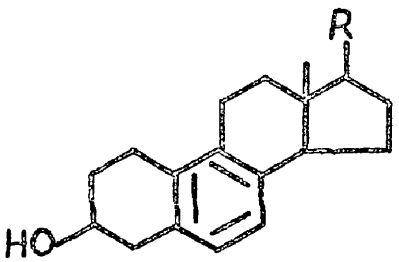
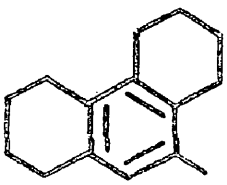


Fig. I

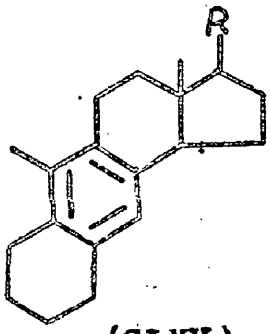
A study (Fig.I) of the ultraviolet absorption spectrum[79] (C) showed that it closely resembled the spectra of the neosteroids (CLXIV; D)[81] and 9-methyl-s-octahydrophenanthrene (CIX; E)[81] while differing markedly from the absorption of veratramine (CLXIII, A; [82,83] p.51) and of the dihydroanthrasteroids[81] (CLXV, B).



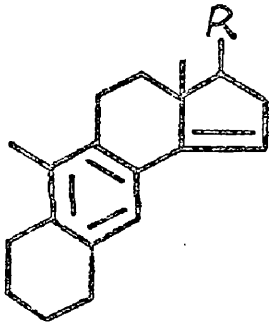
(CLXIV)



(CIX)



(CLXV)

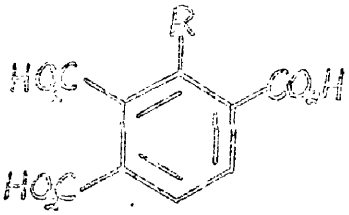


(CXVIII)

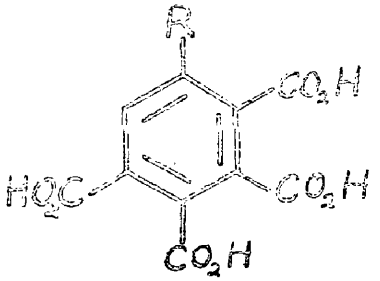
That is to say it displays an absorption consistent with the angular annulation contained in structure (CLIX).

Moreover, the infrared spectrum of the dibromo-aromatic acetate (in chloroform) shows bands at 1606 $cm.^{-1}$ and 1575 $cm.^{-1}$ and, (in carbon disulphide) at 869 $cm.^{-1}$. This absorption is attributed[81] to a pentasubstituted benzene ring, which is evident in structures (CLIX), (CLXI), and (CXLII). There is no strong absorption at 810 $cm.^{-1}$, nor is the absorption in the 1600 $cm.^{-1}$ region characteristic of a tetrasubstituted benzene ring, such as is present in structure (CLX).

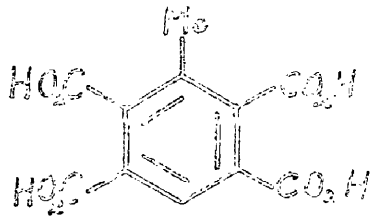
It has previously been reported that oxidation of the neosteroids[65] (CLXIV) with concentrated nitric acid degradates the nucleus to give benzene-1,2,3,4-tetracarboxylic acid (prehnitic acid, CLXVI), whereas similar oxidation of the anthrasteroid[67] (CXVIII) nucleus, having a pentasubstituted benzene ring, gives benzenepentacarboxylic acid (CXI).



(CLXVI) (R = COOH)
(CLXVII)(R = CH_3)



(CXI) (R = COOH)
(CLXVIII) R = CH_3)

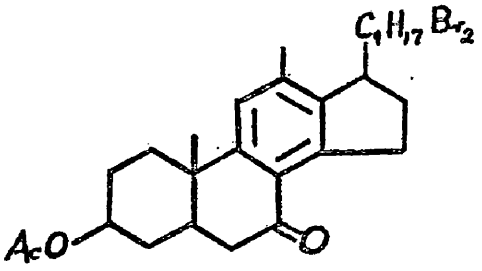


(CX)

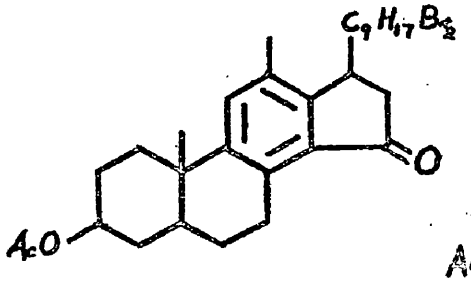
Similar oxidation of the aromatic ring-C compound (CLIX) would be expected to give (CXI) or toluene-2,3,4,5-tetracarboxylic acid (CLXVIII), whereas the D-homosteroid (CIX) should oxidise to toluene-2,3,6-tricarboxylic acid (CLXVII) or to benzene-1,2,3,4-tetracarboxylic acid (CLXVI). Application of this method to ergosterol gave the expected toluene-2,3,5,6-tetracarboxylic acid (CX), but the same treatment of the dibromoaromatic acetate (CLIX) yielded no crystalline material.

Oxidation of the dibromoaromatic acetate with chromium trioxide in acetic acid yielded a neutral compound

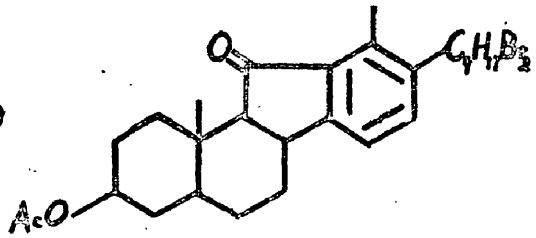
$C_{30}H_{42}O_3Br_2$, which did not give a 2,4-dinitrophenylhydrazone, but which exhibited a strong band at 1684 cm.$^{-1}$ (aromatic carbonyl stretching frequency; Table III). The corresponding absorptions of the aromatic ketones (CLXXII) and (CLXXIII)[84] at 1709 cm.$^{-1}$ and 1703 cm.$^{-1}$ are too similar to permit distinction of a five- from a six-membered ring ketone in conjugation with a benzene ring. However, the absorption falls to 1700 cm.$^{-1}$ when the indanone[71,84] system is included in the veratramine nucleus (CXLIV)[71], while the inclusion of the oxotetralin nucleus (CLXXIII) in 4-oxo-3,9-dimethyl-s-octahydroanthracene (CXXI) raises the wavelength of carbonyl absorption to 1680 cm.$^{-1}$. This favours the 6-ring ketone structure (CLXIX) for the dibromoaromatic keto-acetate, as against the indanone structure (CLXX).



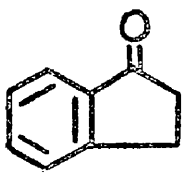
(CLXIX)



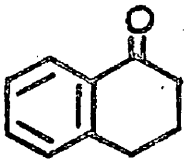
(CLXX)



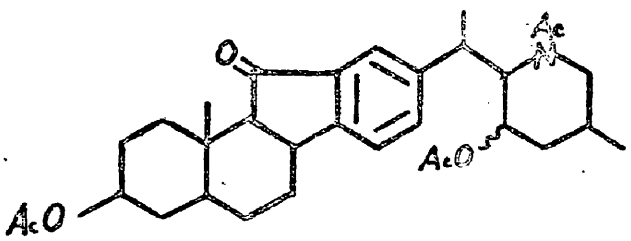
(CLXXI)



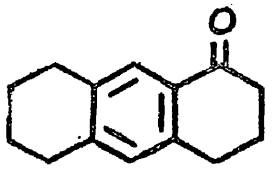
(CLXXII)



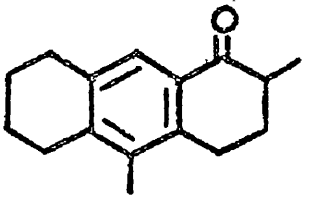
(CLXXIII)



(CXLIV)



(CLXXIV)



(CXXI)

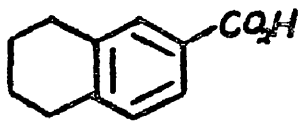
T A B L E III

	aromatic carbonyl stretching frequency ($cm.^{-1}$)	ultraviolet absorption.
Triacetyldihydroketo-veratramine (CXLIV)	1700	2510 Å (ϵ = 10,700) 3000 Å (ϵ = 3,000)
1-oxoindane (CLXXII)	1709	2510 Å (ϵ = 10,000) 3000 Å (ϵ = 3,200)
1-oxotetraline (CLXXIII)	1703	2490 Å (ϵ = 12,000) 2920 Å (ϵ = 3,200)
cyclohexenotetralone (CLXXIV)		2620 Å (ϵ = 15,800) 3050 Å (ϵ = 3,500)
dibromoaromatic keto-acetate (CLXIX)	1684	2650 Å (ϵ = 15,000) 3100 Å (ϵ = 3,000)

Examination of the ultraviolet absorption data (Table III) shows that the absorption of the indanone[71,84] system in triacetyldihydroketoveratramine (CXLIV) is almost identical with that of 1-oxoindane (CLXXII). It is therefore reasonable to deduce that the dibromoaromatic keto-acetate cannot be represented by structure (CLXXI) since its ultraviolet absorption spectrum is markedly

different from that of the ketoveratramine (CXLIV). It is also observed that fusion of a second ring to the benzene ring of 1-oxotetralin (CLXXIII), giving cyclohexenotetralone (CLXXIV),[79] involves a bathochromic shift of 13 Å, accompanied by an increase in the intensity of absorption. Since the absorption displayed by (CLXXIV) and the dibromoaromatic keto-acetate are of the same order, it is to be expected that the latter will contain a similar triannular chromophore and therefore may be represented by (CLXIX) or (CLXX) (p.56).

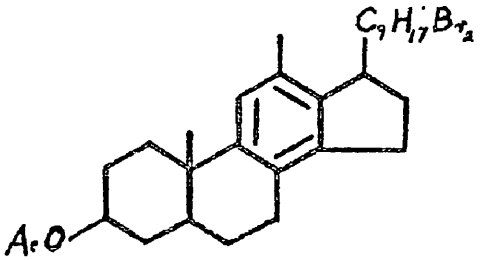
Prolonged oxidation of the dibromoaromatic acetate or of the derived keto-acetate with an excess of chromium trioxide in acetic acid, yielded an acidic product, whose elementary analysis and equivalent weight determination were consistent with a dicarboxylic acid, $C_{30}H_{42}O_6Br_2$. A broad infrared absorption band at 3300-2850 $cm.^{-1}$, and a secondary band at 1720-1710 $cm.^{-1}$, confirmed the presence of carboxyl groups, and the ultraviolet absorption at 2570 Å. (ϵ = 11,000) and 3000 Å. (ϵ = 3,000) bears a close relationship to that of 5,6,7,8-tetrahydro-2-naphthoic acid (CLXXV)[79]. Moreover, the acid product did not give



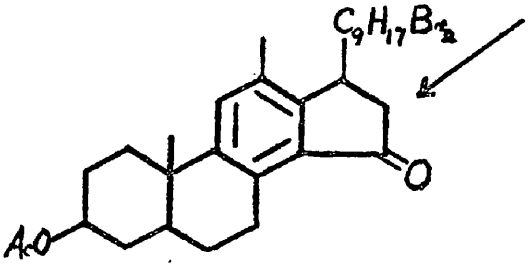
(CLXXV)

a 2,4-dinitrophenylhydrazone with Brady's reagent, even after prolonged refluxing. The acid proved difficult to crystallise and did not form a crystalline anhydride.

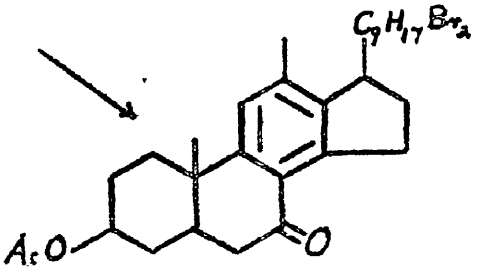
Alkaline hydrolysis of the acid-acetate, followed by acidification, gave the corresponding acid-alcohol, $C_{28}H_{40}O_5Br_2$, which was purified by repeated precipitation from its acetic acid solution by the addition of water. This alcohol did not yield a crystalline benzoate or 3,5-dinitrobenzoate.



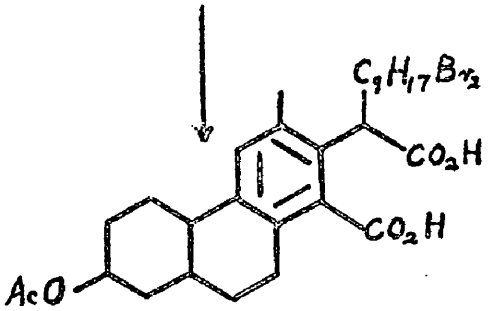
(CLIX)



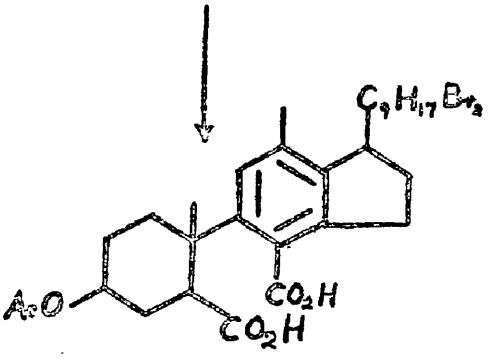
(CLXX)



(CLXIX)

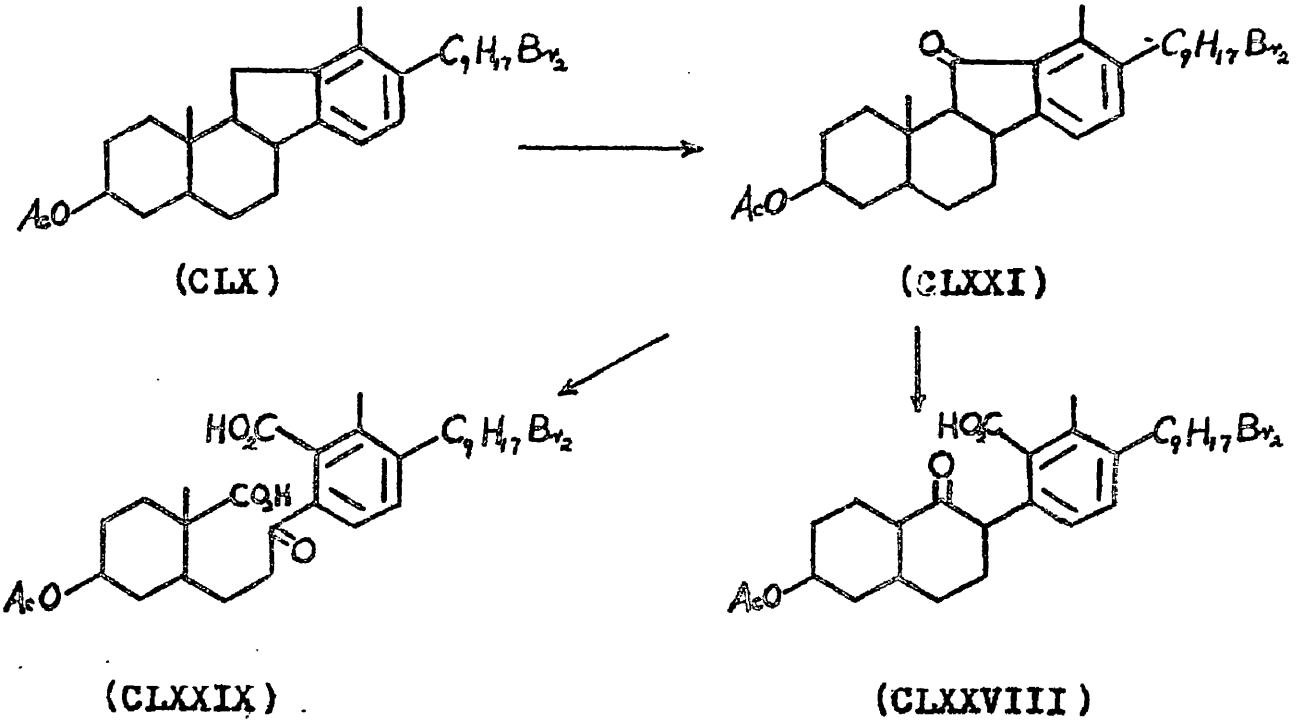


(CLXXVI)



(CLXXVII)

It is evident that oxidation of a compound having structure (CLIX) would give one of the intermediate ketones (CLXIX) or (CLXX) before subsequent formation of the corresponding dicarboxylic acids (CLXXVII) or (CLXXVI), whereas the hypothetical compound (CLX) would yield the ketone (CLXXI) which on further oxidation would give a keto-monocarboxylic acid (CLXXVIII) or a keto-dicarboxylic acid (CLXXIX).



(CLX) (CLXXI)

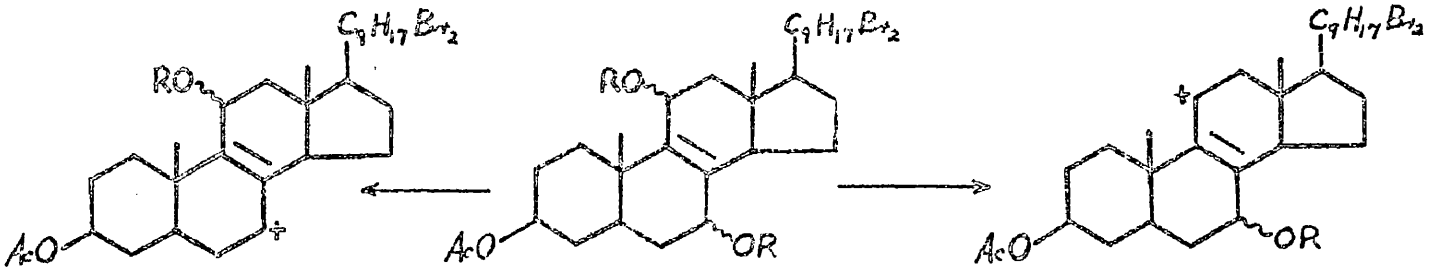
(CLXXIX) (CLXXVIII)

Since it has been established that the final oxidation product is a dicarboxylic acid having no carbonyl group, structures (CLXXVIII) and (CLXXIX) are eliminated. Hence, the intermediate aromatic keto-acetate has structure (CLXX) or (CLXIX). The dibromoaromatic acetate must therefore be 22,23-dibromo-12-methyl-18--norergosta-8(14),9(11),12-trien-3β-yl acetate (CLIX).

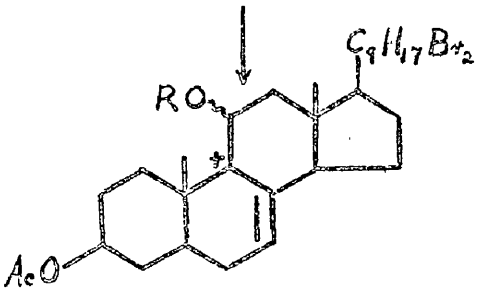
Action of Silver Acetate on Tetrabromoergostenyl Acetate.

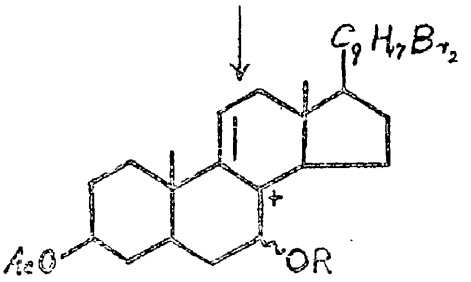
When a suspension of tetrabromoergostenyl acetate in ether is treated with silver acetate below -25°C, a yellowish solid is isolated, showing maxima at 2040 Å. (ϵ = 3680), 2330 Å. (ϵ = 5160), and 2400 Å. (ϵ =3540). Subsequent fractional crystallisation or chromatography of this material yields 11-oxo-22,23-dibromoergost-8-en-3β-yl acetate (CLXXXIII) as the major product, and 7-oxo-22,23-dibromoergost-8-en-3β-yl acetate (CLXXXIV), both of which absorb at 2330 Å.(ϵ = 9,500). Examination of the ultraviolet spectrum (above) of the intermediate mixture reveals that neither of the αβ--ketones (CLXXXIII) and (CLXXXIV) are present as components. It is therefore suggested that this immediate reaction product is a mixture of the dibromoergostenyl (CLXXX) and dibromoergostadienyl derivatives (CLXXXI) and (CLXXXII), which degrade readily and rearrange as shown to give the αβ-unsaturated ketones (CLXXXIII)[88] and (CLXXXIV)[89].

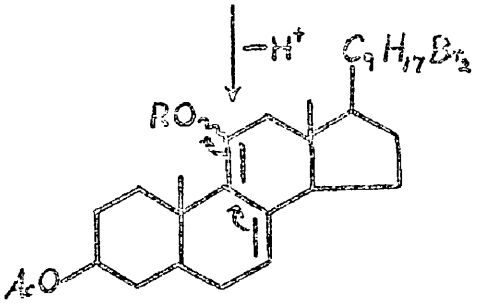
When the above reaction is carried out at room temperature and the product is carefully chromatographed, no pure material is, however, obtained. The intermediate product shows maxima at 2050 Å., 2360 Å., and 2450 Å., and the impure fractions of the chromatogram show similar



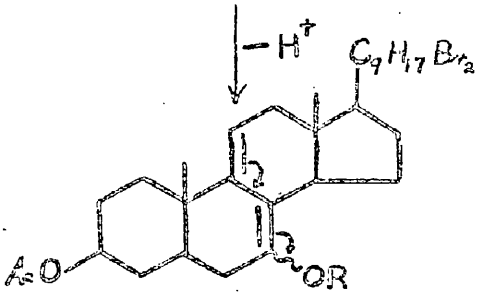
(CLXXX)





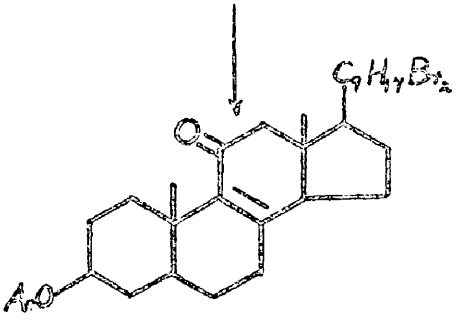


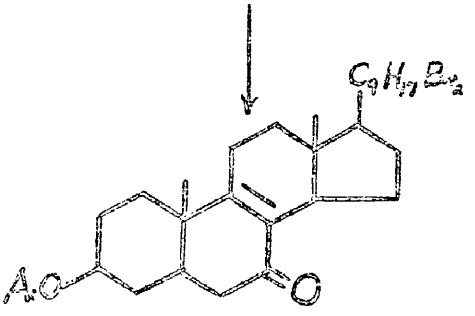
R = H or Ac.



(CLXXXI)

(CLXXXII)



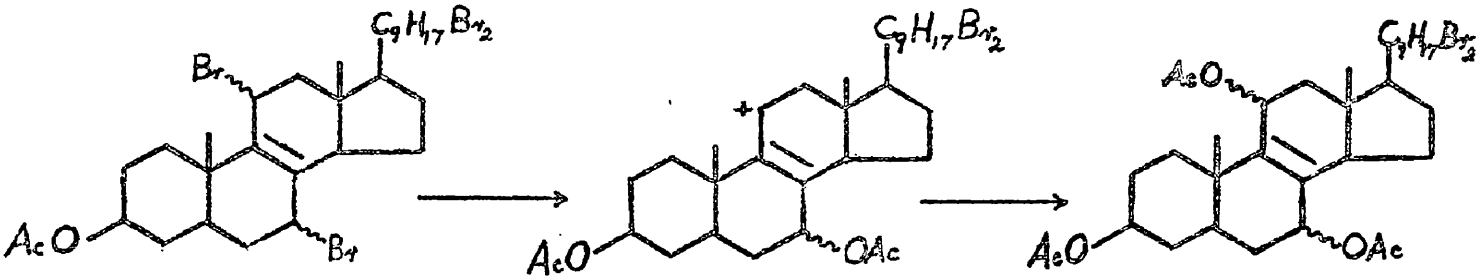


(CLXXXIII)

(CLXXXIV)

spectra. Hence, it may be deduced that the reaction gives a mixture of stable triacetoxydibromoergostenes and dibromoergostadienol acetates, which prove inseparable by chromatography or fractional crystallisation.

The purpose of treating the tetrabromide with silver acetate was to replace, without rearrangement, the two nuclear bromine atoms by acetate groups. As the tetrabromide was formed in the presence of acetic acid, and is known to exist in the acid-stable allyllic form,[7cd] it was then treated with silver acetate in acetic acid. An immediate precipitate of the yellow silver bromide was evident, suggesting that the reaction was of the ionic nature outlined below (cf. p. 91).



(CLII) (CLXXXV) (CLXXXVI)

The solution was filtered and a white solid was precipitated from the acetic acid solution by the addition of water. This product could be taken up in petrol and chromatographed, or worked up through ether, and the neutral product chromatographed, to give the same four compounds in each case i.e.

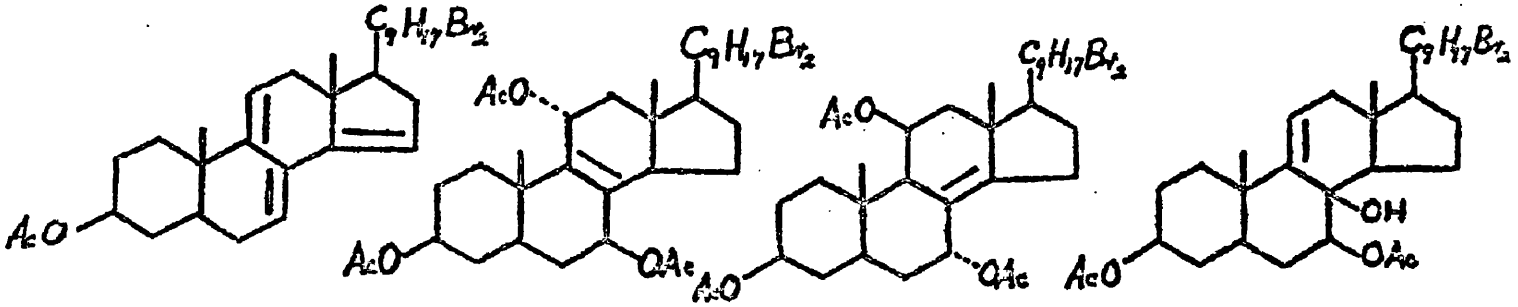
22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate (CXLVII),

3β,7β,11α-triacetoxy-22,23-dibromoergost-8-ene (CLXXXVIII),

3β,7α.11β-triacetoxy-22,23-dibromoergost-8(14)-ene (CLXXXIX), and

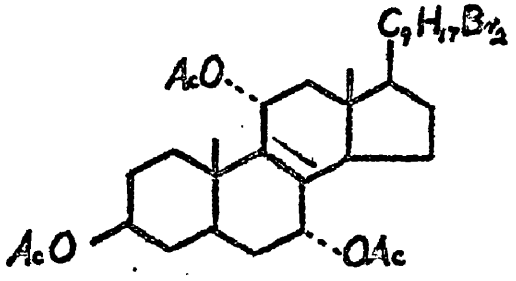
3β,7β-diacetoxy-22,23-dibromoergost-9(11)-en-8β-ol (CXC).

The cross-conjugated triene (CXLVII) has been described (p. 44).



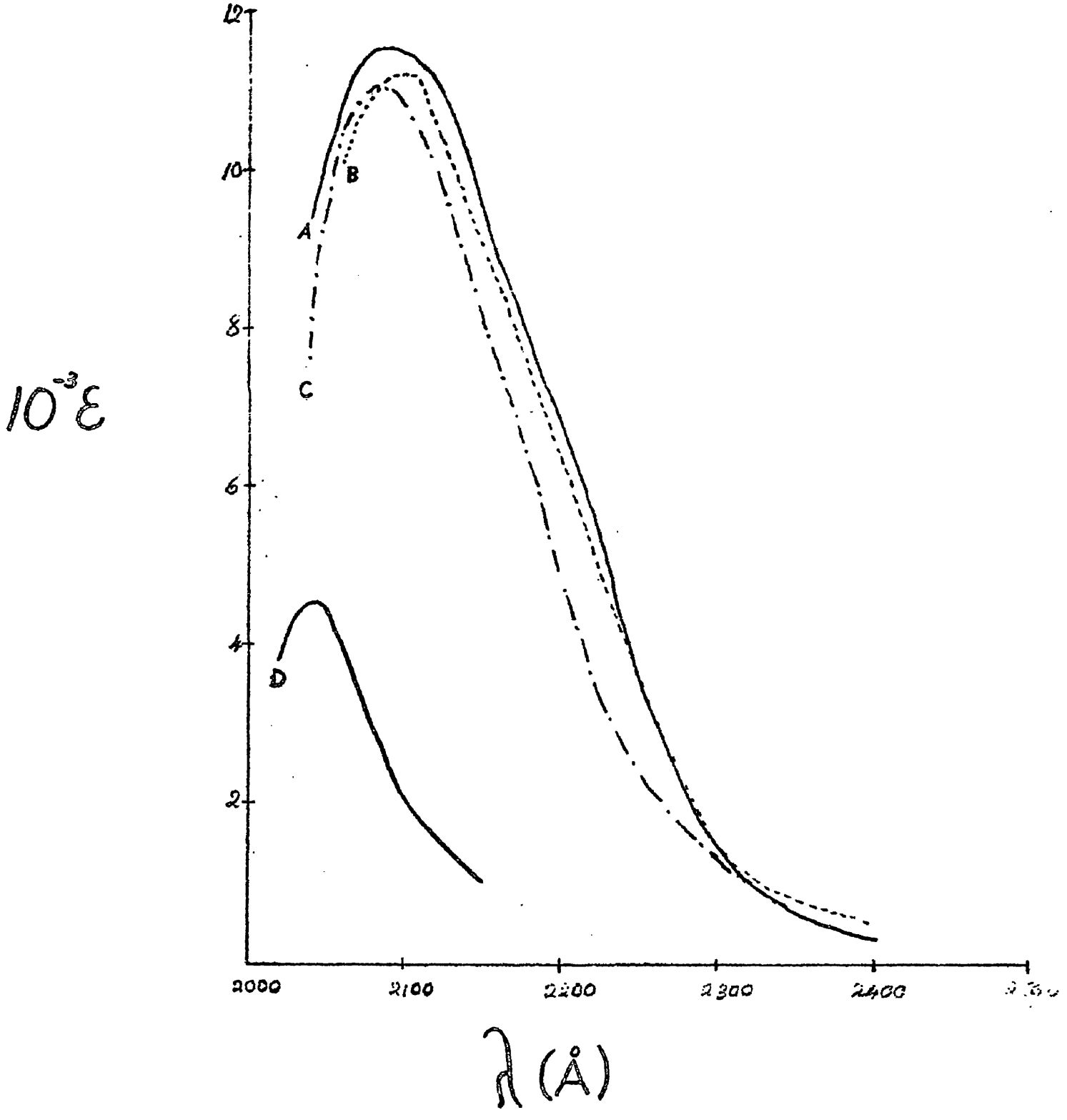
(CXLVII) (CLXXXVIII) (CLXXXIX) (CXC)

Before considering the elucidation of the structures (CLXXXVIII), (CLXXXIX), and (CXC), it is pertinent to compare the ultraviolet absorption spectra of these compounds with that of the known 3β,7α,11α-triacetoxy--22,23-dibromoergost-8-ene (CXCI).



(CXCI)

(Fig. II)

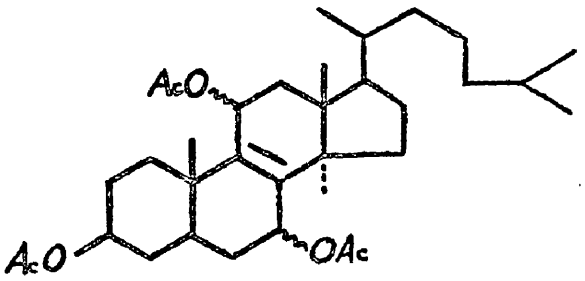

12
10
8
6
4
2
A
B
C
D
2000
2100
2200
2300
2400
$10^{-3}\varepsilon$
λ (Å)

It is observed (Fig. II) that, while the triacetates (CLXXXVIII), (CLXXXIX), and (CXCI), exhibit maxima in the 2080-2100 Å. region having extinction coefficients of ca. 11,000, the diacetate (CXC) absorbs at the lower wavelength 2040 Å. and with a smaller intensity of absorption, i.e. 4,500. This similarity in the ultraviolet absorption spectra of the triacetates (CLXXXVIII), (CLXXXIX), and (CXCI), is consistent with each molecule having a tetrasubstituted[86] double bond allyl to an acetate group. Further, the spectrum of the diacetate (CXC) is in good agreement with that exhibited by a steroid having a trisubstituted $\Delta^{9(11)}$-olefinic linkage.[86]

3β,7β,11α-Triacetoxy-22,23-Dibromoergost-8-ene.

This compound was eluted with light petroleum-benzene mixtures and gives an elementary analysis consistent with a triacetoxydibromoergostene, $C_{34}H_{52}O_6Br_2$. The ultraviolet absorption spectrum (C, Figure II) indicates the presence of a tetrasubstituted double bond, whilst broad 'acetate' bands are exhibited in the infrared region.

The acetate groups were located by the following series of reactions. Debromination with zinc dust in ether-ethanol gave a crystalline triacetoxyergostadiene, $C_{34}H_{52}O_6$, which was hydrolysed with lithium aluminium hydride to give an impure triol product, which proved unstable to recrystallisation techniques. This instability is comparable with the impure triol product obtained from the alkaline hydrolysis of 3,7,11-triacetoxy-lanost-8-ene[87] (CXCII), and the instability is probably due to the labile nature of the allyllic alcohol groups at $C_{(7)}$



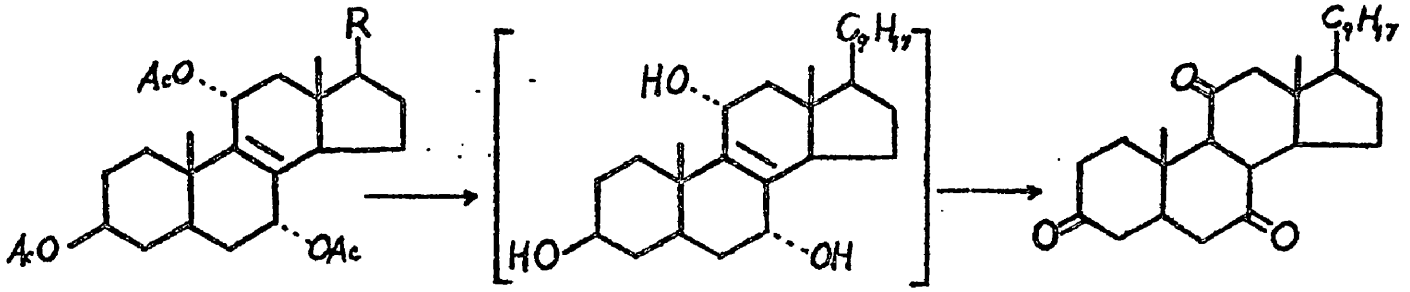
(CXCII)

and $C_{(11)}$. The impure ergostadienetriol showed no absorption in the infrared region corresponding to the presence of acetate, and was subsequently oxidised with chromium trioxide in pyridine (specific oxidation of hydroxyl[88]) to give a yellow crystalline compound, $C_{28}H_{40}O_3$. The absorption at 2680 Å. (ϵ = 8,000) in the ultraviolet region, and 1718 cm.$^{-1}$ (isolated 6-ring carbonyl) and 1675 cm.$^{-1}$ (ene-dione) in the infrared region, is consistent with the structure of 3,7,11-trioxoergosta-8,22-diene (CXCIV)(p.70).

Debromination of the known 3β,7α,11α-triacetoxy--22,23-dibromoergost-8-ene (CXCI)[26] yielded 3β,7α,11α--triacetoxyergosta-8,22-diene (CXCIII) which was hydrolysed with lithium aluminium hydride and oxidised with the chromium trioxide-pyridine complex to give 3,7,11-trioxoergosta-8,22-diene (CXCIV), identical with the oxidation product described above.

It would therefore appear that the unknown compound is a 3,7,11-triacetoxy-22,23-dibromoergost--8-ene and only the configuration of the acetate groups at $C_{(7)}$ and $C_{(11)}$ remains to be determined. A portion of the impure triol was reacetylated and chromatographed on alumina.

The product was eluted with light petroleum--benzene mixtures. It showed no hydroxyl absorption in the infrared region, was free from αβ-unsaturated ketonic material and proved to be identical with the original triacetate, 3β,7ξ,11ξ-triacetoxyergosta-8,22-diene. Since the conditions of acetylation were insufficient[81] for acylation of an 11β-hydroxyergost-8-ene, the 11-acetate group must be α-orientated, and hence this triacetoxy-ergostadiene, which can only differ from the triacetate (CXCIII) in configuration at $C_{(7)}$ is 3β,7β,11α-triacetoxy-ergosta-8,22-diene (CXCV). The parent product is therefore 3β,7β,11α-triacetoxy-22,23-dibromoergost-8-ene (CLXXXVIII):



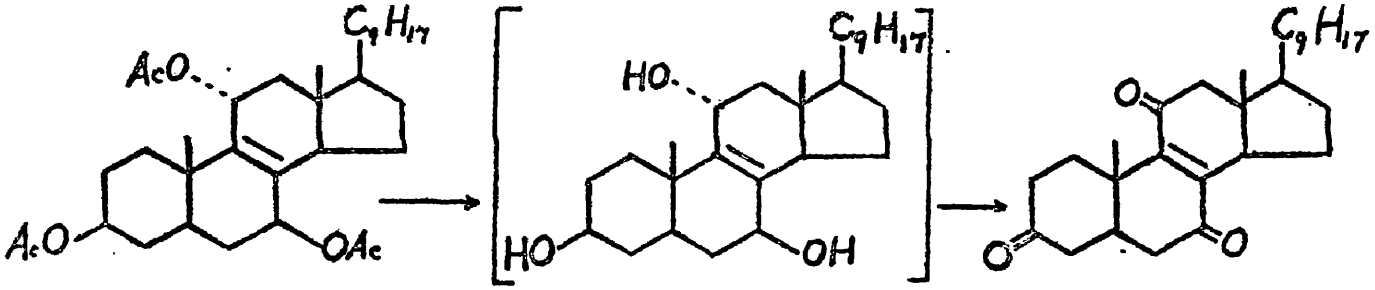
(CXCI) (R = $C_9H_{17}Br_2$)

(CXCIII)(R = C_9H_{17})

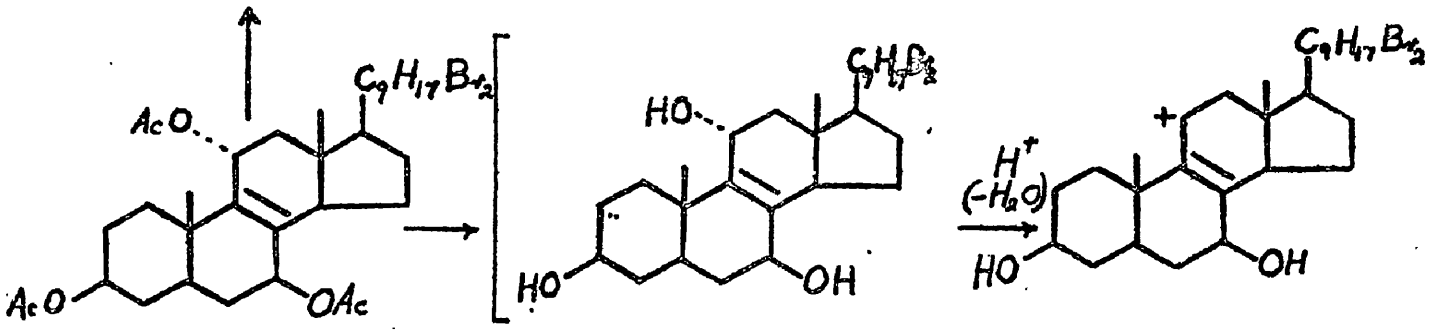
(CXCIV)

Alkaline hydrolysis of the triacetate (CLXXXVIII) again gave an impure triol product showing no absorption corresponding to acetate in the infrared region.

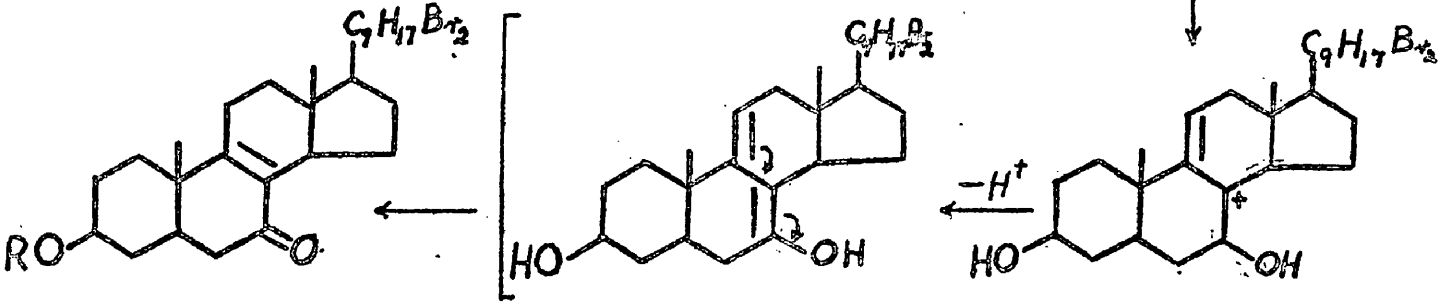
Mild acid hydrolysis of the triacetate (CLXXXVIII) followed by acetylation yielded 7-oxo-22,23-dibromoergost-8-en-3β-yl acetate (CLXXXIV). The reaction probably proceeds by acid-catalysed dehydration to the dienol (CXCVI), which rearranges to the αβ-unsaturated ketone (CXCVII), identified as the corresponding acetate (CLXXXIV).



(CXCV) (CXCIV)



(CLXXXVIII)



(CXCVII) (R = H) (CXCVI)
(CLXXXIV) (R = Ac)

3β,7α,11β-Triacetoxy-22,23-dibromoergost-8(14)-ene.

This substance was eluted from the column of alumina with benzene and displayed absorption in the ultraviolet region (B, Fig.II) typical of a tetrasubstituted double bond, and absorption in the infrared region corresponding to more than one acetate group. These characteristics again indicated a 3,7,11-triacetoxy-22,23-dibromoergost-8-ene.

Debromination with zinc dust in a neutral solvent gave a crystalline triacetoxyergostadiene, which was hydrolysed with lithium aluminium hydride to an ergostadientriol, $C_{28}H_{46}O_3$, treatment of which with the chromium trioxide-pyridine complex yielded 3,7,11-trioxoergosta-8,22-diene (CXCIV). This located the three acetate groups in the original compound at $C_{(3)}$, $C_{(7)}$, and $C_{(11)}$.

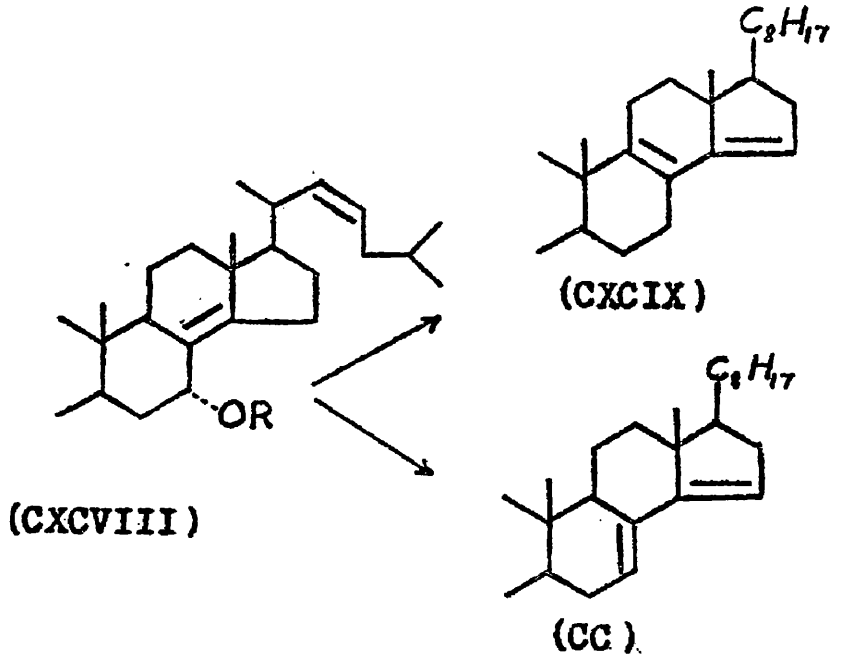
Since the elementary analyses obtained for the dibromo-triacetate and the debromo-triacetate did not distinguish a triacetate from a triol-diacetate or a triol-monoacetate, the dibromo-compound was treated with chromium trioxide in pyridine. The substance was recovered quantitatively and it is therefore concluded that the oxysubstituents attached to the secondary carbon atoms $C_{(7)}$ and $C_{(11)}$ are acetate groups. It remains to

establish the configuration of these groups and the position of the tetrasubstituted double bond.

Alkaline hydrolysis of the dibromo-triacetate gave an impure product which was not purified by crystallisation techniques.

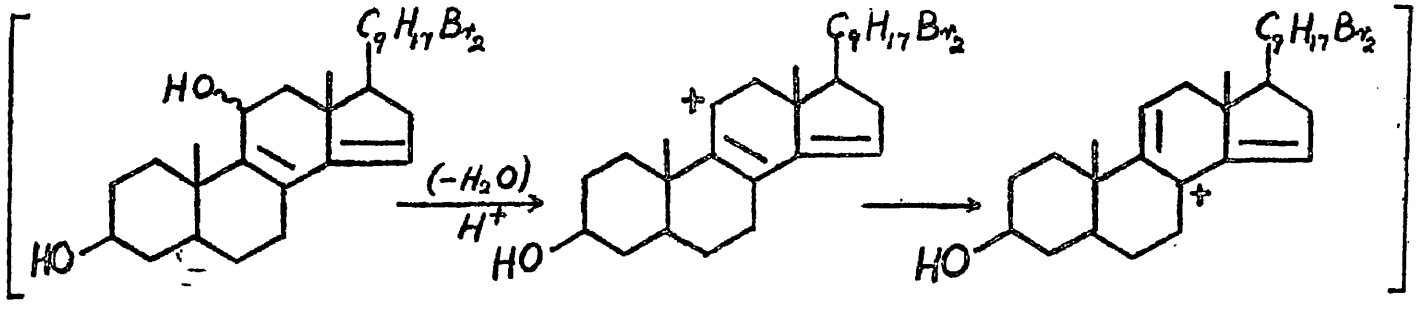
Acid hydrolysis of the dibromo-triacetate and acetylation of the product, yielded 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate (CXLVII). The same product (CXLVII) was obtained when the dibromotriacetate was boiled under reflux with acetic anhydride. Similar treatment of 3β,7β,11α-triacetoxy-22,23-dibromoergost--8-ene (CLXXXVIII) with acetic anhydride gave a quantitative recovery of starting material.

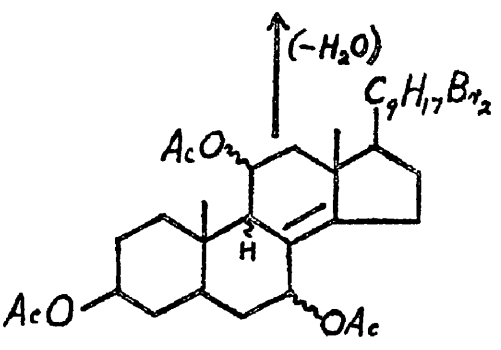
Laubach et al.[45b] (p.26) have obtained this $\Delta^{7,9(11),14}$-triene system by the ready dehydration of a 9α,11α-dihydroxyergost-8(14)-ene derivative. In addition, Fieser and Ourisson[37] have demonstrated that 7α-acyl-cholest-8(14)-ene derivatives (CXCVIII) are readily converted into either $\Delta^{8,14}$- (CXCIX) or $\Delta^{7,14}$- (CC) cholestadienes depending on the conditions employed.



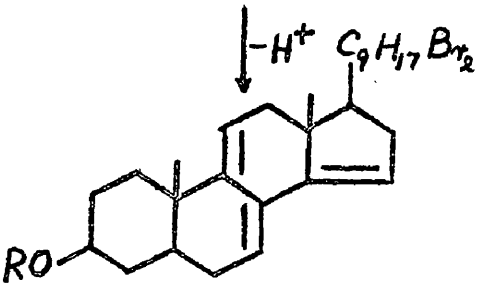
(CXCVIII) (CXCIX) (CC)

It would therefore appear that the dibromotriacetate has a $\Delta^{8(14)}$-double bond as in structure (CCII) and that the acid-catalysed dehydration follows a route similar to that shown below, (cf. p. 70) to give the trienol (CCIII), identified as the corresponding acetate (CXLVII).





(CCII).



(CCIII) (R = H)
(CXLVII) (R = Ac)

Further evidence for structure (CCII) for the dibromotriacetate was obtained when attempts were made to establish the configuration of the acetate groups at $C_{(7)}$ and $C_{(11)}$. Debromination of the dibromotriacetate followed by hydrolysis with lithium aluminium hydride yielded the ergostadientriol as before.

Reacetylation of this material yielded, instead of the original triacetate, a slightly impure diacetate, the infrared absorption spectrum of which [3425 $cm.^{-1}$ (hydroxyl), 1733 $cm.^{-1}$, 1706 $cm.^{-1}$, 1255 $cm.^{-1}$, and 1248 $cm.^{-1}$ (acetate)], corresponded to that of a 3β:7ξ-diacetoxyergosta-8(14),22-dien-11β-ol. That dehydration at $C_{(7)}$ or $C_{(11)}$ had occurred to only a minor extent to give a conjugated diene system was indicated by the ultraviolet absorption spectrum of this product ($\lambda_{max.}$ 2100 Å, ϵ = 9000, with inflexion at 2500 Å, ϵ = 1,000). Attempts to purify this crystalline material led to further degradation.

In order to establish the presence of an 11β-hydroxyl group, the material was oxidised with the chromium trioxide-pyridine complex. The oxidation product was isolated in ether and crystallised from cold methanol as stout blades. These were, however, shown to be of mixed composition from their absorption at 2120 Å (ϵ = 4860), 2430 Å (ϵ = 6120), and 2960 Å (ϵ = 4100) in the

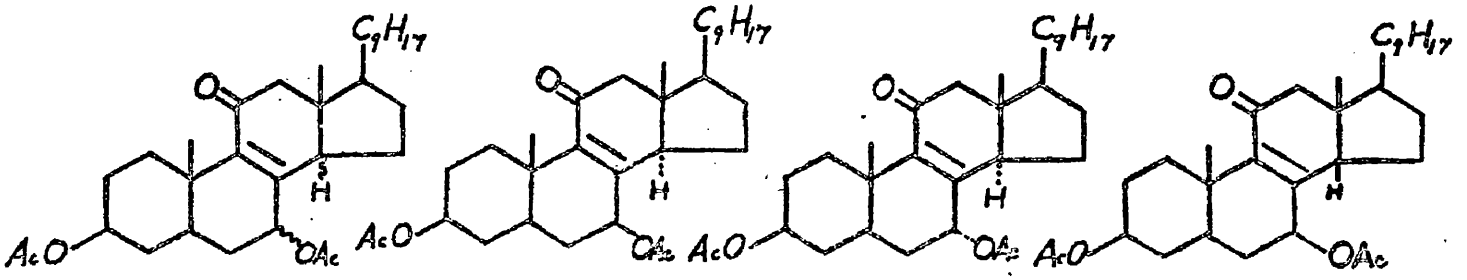
ultraviolet region. The intensity of absorption at 2430 Å. corresponds to 75% of αβ-unsaturated ketone. Careful chromatography and crystallisation of this oxidation product (110 mg.) gave two compounds in very poor yield.

Light petroleum-benzene (2:1) eluted a fraction which crystallised in yellow blades (7 mg.) the characteristics of which compared favourably with the constants of 11-oxoergosta-8,14-dien-3β-yl acetate (LXIV) previously prepared by Spring et al.[31] (p. 19), and by Laubach et al[45b] (p. 31)

	m.p.	$[\alpha]_D$	Ultraviolet absorption spectra.
Spring et al.	144-145°	0° ± 1°	2100 Å. (ϵ = 8,900), 2960 Å. (ϵ = 12,500)
Author	136-142°	+ 5°	2100 Å. (ϵ = 7,800) 2960 Å. (ϵ = 8,000)

Shortage of material prevented further purification. Elution with benzene-ether yielded a second fraction which crystallised as colourless needles showing absorption at 2440 Å. (ϵ = 8,000). From the ultraviolet absorption spectrum of the original reaction product, it appears that the major component, absorbing at 2440 Å. (ϵ = 6120), is readily decomposed either by recrystallisation or by contact with alumina since only a small amount (14 mg.) could be obtained in pure crystalline form. This compound

absorbs at 1739 cm.$^{-1}$, 1239 cm.$^{-1}$ (acetate) and 1677 cm.$^{-1}$ (αβ-unsaturated ketone) in the infrared region and this, together with the elementary analysis, is consistent with that of an 11-oxo-14ξ-ergosta-8,22-diene-3β,7ξ-diacetate (CCIII).



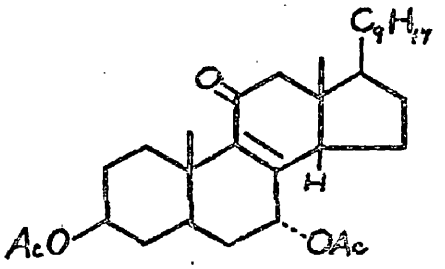
(CCIII) (XXX) (XXVII) (LXII)

TABLE IV

	m.p.	$[\alpha]_D$	Ultraviolet absorption	Carbonyl Absorption in I.R
(XXX)	152-153°	+ 82°	2490 A (ε = 8,800)	1658 cm.$^{-1}$
(XXVII)	102-103°	+109°	2490 A (ε = 8,800)	1670 cm.$^{-1}$
(LXII)	82-84°	+103°	2440 A (ε = 8,400)	1689 cm.$^{-1}$
(CCIII)	186-188°	+ 77°	2440 A (ε = 8,000)	1677 cm.$^{-1}$

In Table IV, the constants of this αβ-unsaturated ketone are compared with those of the three known compounds of the series: viz: 11-oxo-ergosta-8,22-dien-3β,7β--diacetate (XXX), 11-oxoergosta-8,22-dien-3β,7α-diacetate (XXVII), and 11-oxo-14β-ergosta-8,22-dien-3β,7β-diacetate (LXII). From this comparison, it is evident that the new

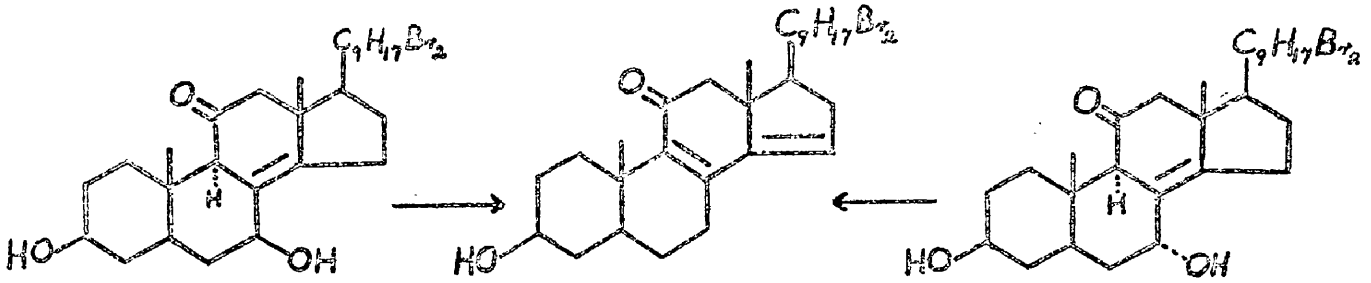
compound is not identical with the isomers (XXX), (XXVII) and (LXII), and consequently it must be 11-oxo-14β-ergosta-8,22-dien-3β,7α-diacetate (CCIV). It will be noted that this compound, like the other 14β-isomer (LXII) shows maximum absorption at 2440 Å. in the ultra violet region whereas the 14α-isomers (XXX) and (XXVII)



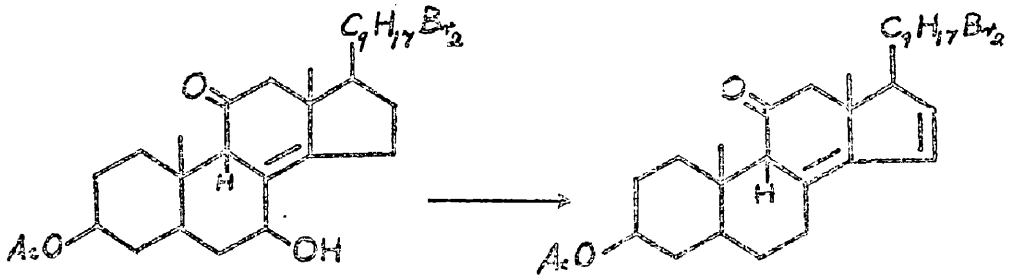
(CCIV)

both exhibit absorption maxima at the slightly higher wavelength 2490 Å.

It has been shown by Spring et al.[91] that while acid treatment of the βγ- unsaturated ketones (LIX) and (LI) gives 22,23-dibromo-11-oxoergosta-8,14-dien-3β-ol (CIV), similar treatment of the βγ-unsaturated ketone (LVII) having the unnatural (β) configuration at $C_{(9)}$ gives a "non--conjugated" oxo-diene which was tentatively assigned the structure (CCV).

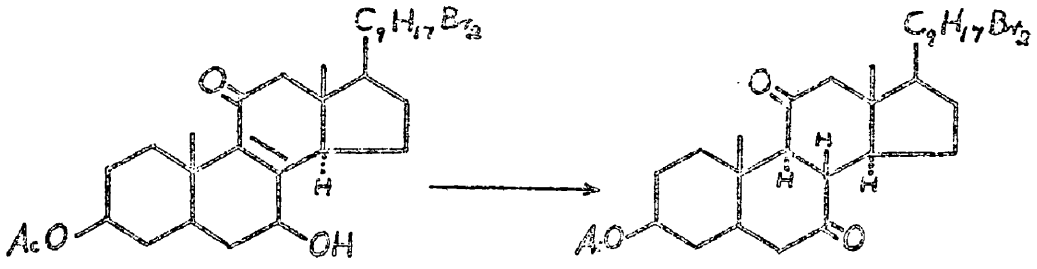


(LIX) (CIV) (LI)

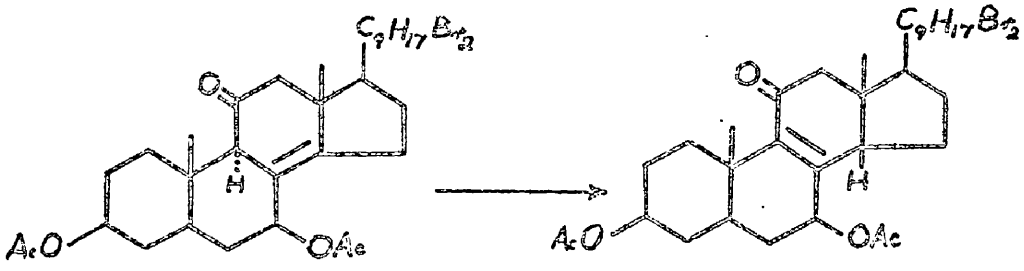


(LVII) (CCV)

It is also noted[31] that acid treatment of the αβ-unsaturated ketone (LIV), having a Δ^{8}-double bond, gives the saturated diketone (XLVIII).



(LIV) (XLVIII)

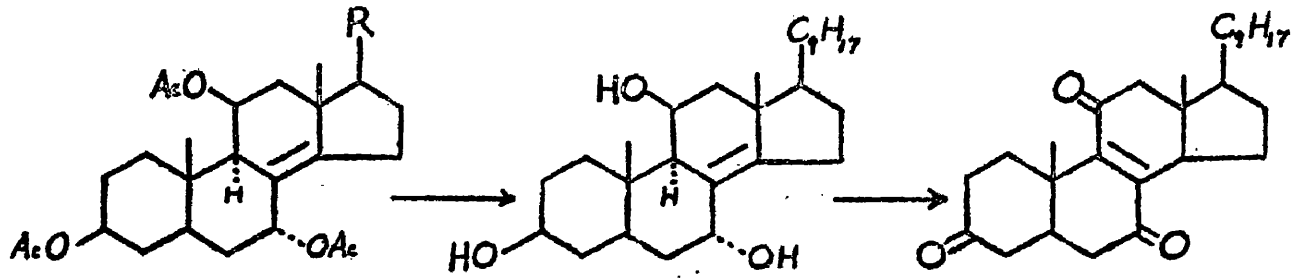


(LX) (LXI)

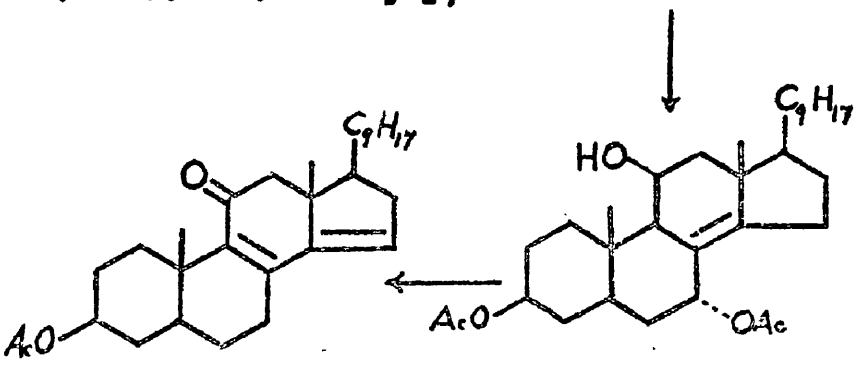
Hence it is reasonable to deduce that the triol diacetate, which is partially oxidised by the chromium trioxide-pyridine complex to give the $\Delta^{8,14}$-dienone (LXIV), has the natural (α) configuration at $C_{(9)}$ and a $\Delta^{8(14)}$-double bond as in structure (CCVIII).

The second product of this oxidation has been assigned the structure (CCIV). The formation of this αβ-unsaturated ketone from the triol-diacetate (CCVIII) is analogous to the formation of 22,23-dibromo-11-oxo--14β-ergost-8-en-3β,7β-diacetate (LXI) from the βγ-unsaturated ketone (LX) by isomerisation of the double bond from the $\Delta^{8(14)}$- to the Δ^{8}-position.[30] (p. 16)

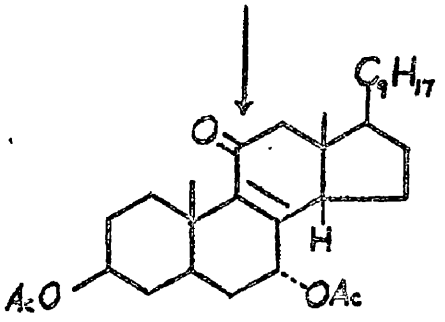
The assignment of structure (CCVIII) to the triol--diacetate requires that the parent triacetate be 3β,7α,11β-triacetoxy-22,23-dibromoergost-8(14)-ene (CLXXXVIII), debromination of which gives 3β,7α,11β-triacetoxyergosta--8(14),22-diene (CCVI). This in turn is hydrolysed with lithium aluminium hydride to the triol (CCVII) which, on oxidation with the chromium trioxide-pyridine complex, yields 3,7,11-trioxoergosta-8,22-diene (CXCIV). Reacetylation of the triol (CCVII) with acetic anhydride in pyridine at room temperature yields the unstable triol-diacetate (CCVIII). Oxidation of this triol-diacetate (CCVIII)



(CLXXXVIII)(R = $C_9H_{17}Br_2$) (CCVII) (CXCIV)
(CCVI) (R = C_9H_{17}



(LXIV) (CCVIII)



(CCIV)

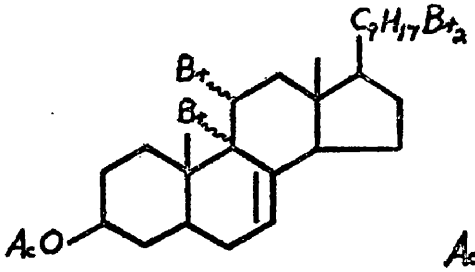
yields the two products identified as the dienone(LXIV) and the αβ-unsaturated ketone (CCIV).

3β,7β-Diacetoxy-22,23-dibromoergost-9(11)-en-8β-ol.

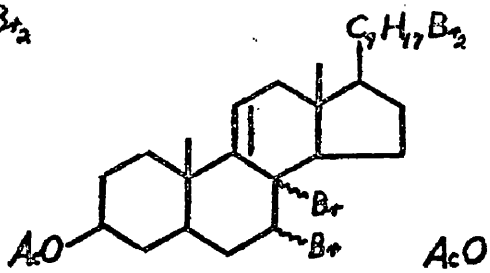
The fourth product, $C_{32}H_{50}O_5Br_2$, formed by the action of silver acetate on a suspension of the tetrabromide in acetic acid, was eluted from the alumina column with benzene-ether mixtures. The infrared absorption spectrum showed the presence of hydroxyl (3636 $cm.^{-1}$) and acetate groups (1733, 1718, 1261 and 1239 $cm.^{-1}$). The absorption in the ultraviolet region (p.65, D, Fig. II) was consistent with the presence of a trisubstituted double bond, as distinct from a tetrasubstituted olefinic linkage Debromination, with zinc dust in boiling ethanol, yielded a crystalline diacetoxyergostadienol, $C_{32}H_{50}O_5$.

That the dibromoalcohol was not acetylated under normal conditions indicated the presence of a hindered hydroxyl group, which was shown to be tertiary when the dibromoalcohol was recovered unchanged after attempted oxidation with the chromium trioxide-pyridine complex.

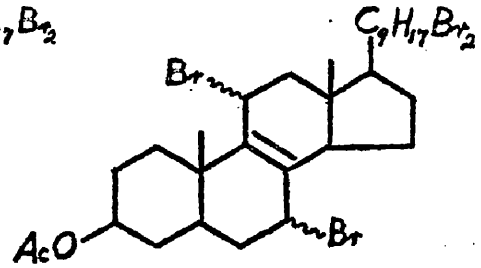
From the data described and the fact that the 22,23-dibromotriol diacetate was prepared from the tetrabromide which must be a 1,2 (CCIX,CCX) or a 1,4 (CLII) nuclear dibromide,[73b] the structure of this diacetate must be represented by (CCXI) or (CCXII), the latter having the unhindered α-configuration at $C_{(11)}$.



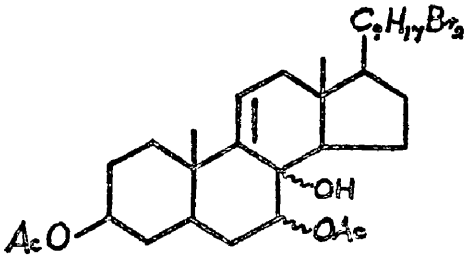
(CCIX)



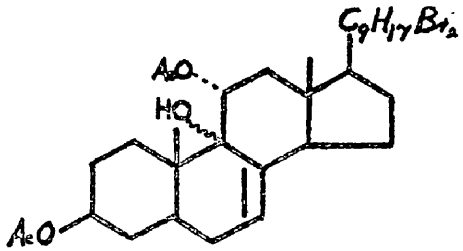
(CCX)



(CLII)



(CCXI)

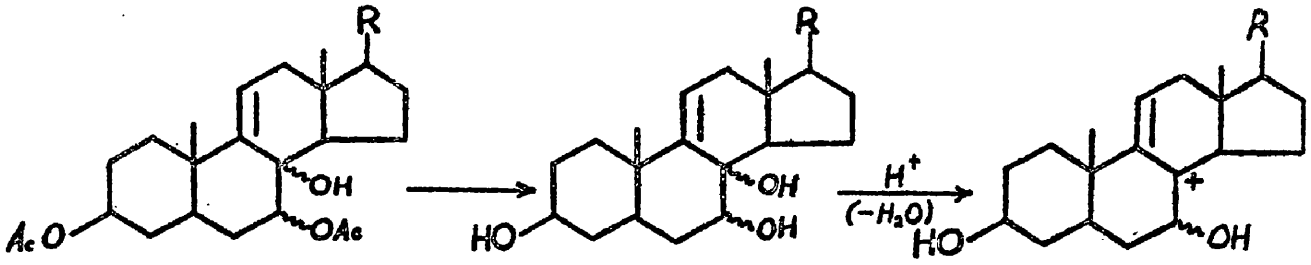


(CCXII)

Alkaline hydrolysis of this diacetate yielded the corresponding triol which readily regenerated the original diacetate on acetylation.

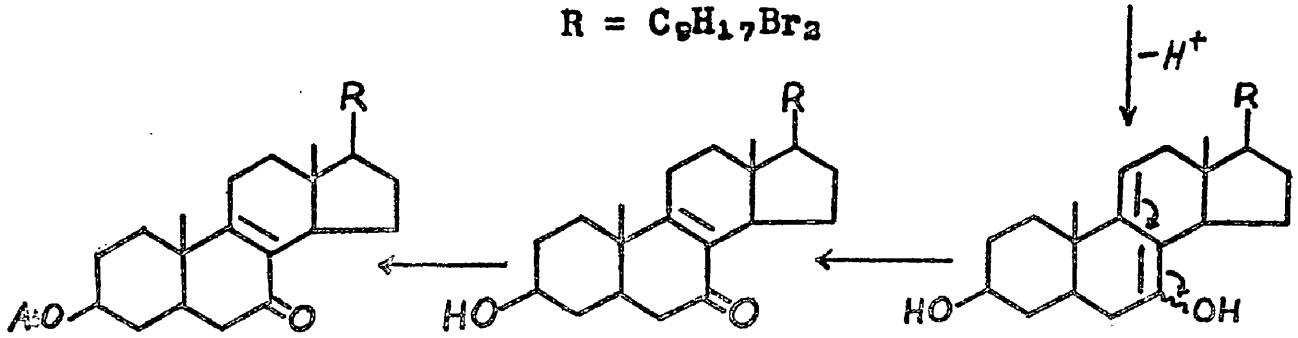
Acid hydrolysis of the parent diacetate followed by crystallisation of the product gave a material showing maximum absorption at 2550 Å. (ϵ = 7,200) in the ultra-violet region. Acetylation of this product gave 7-oxo-22,23-dibromoergost-8-en-3β-yl acetate (CLXXXIV).

This acid dehydration to the αβ-unsaturated ketone (CCXIII) favours the structure (CCXI) for the triol-diacetate which may hydrolyse, dehydrate and rearrange as shown.



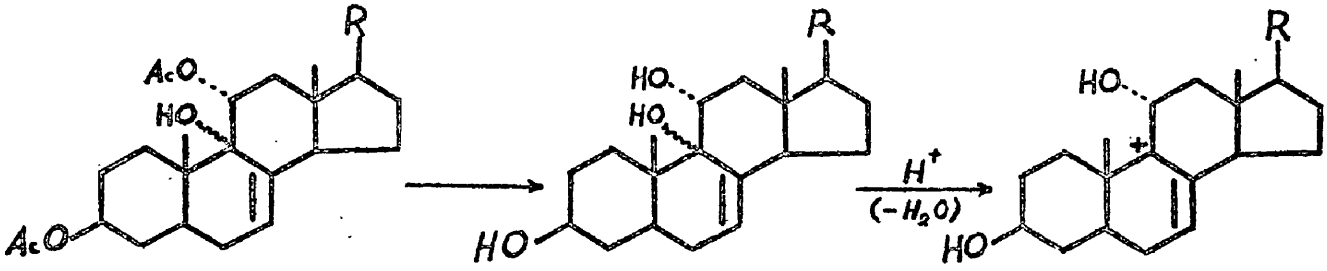
(CCXI)

R = $C_9H_{17}Br_2$



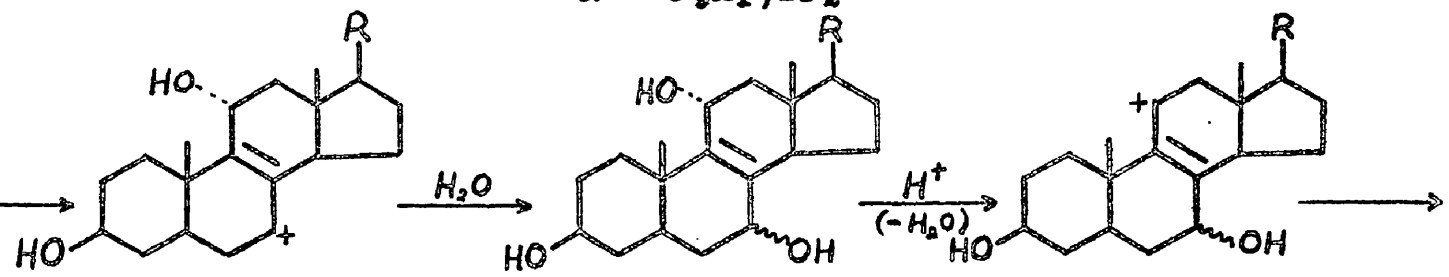
(CLXXXIV) (CCXIII)

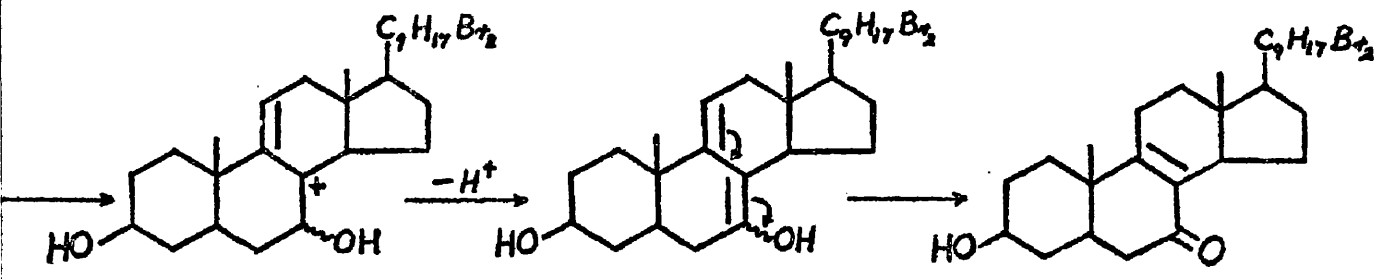
However it is possible that the hypothetical 3β,11α-diacetate (CCXII) may follow a path similar to that outlined below to give the same αβ-unsaturated ketone (CCXIII).



(CCXII)

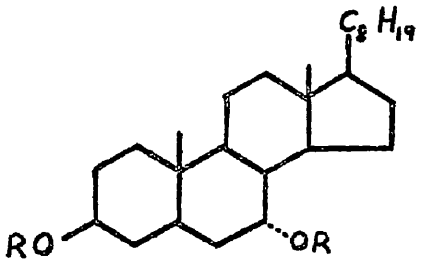
R = $C_9H_{17}Br_2$





(CCXIII)

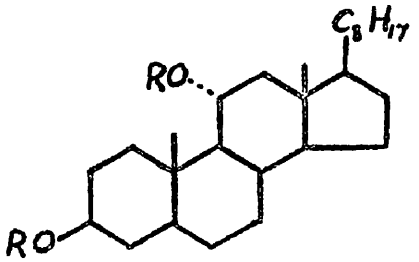
In order to make a decision between the possible structures (CCXI) and (CCXII) for the triol-diacetate, the molecular rotation change which accompanies the formation of the last compound from the corresponding triol was compared with the molecular rotation differences observed on acetylation of the saturated 3,7- and 3,11-diols (CCXIV), (CCXV), (CCXVI), and (CCXVII).[37]



(CCXIV) Diol M_D + 33

(CCXVIII) 3,7-Diacetate M_D -84

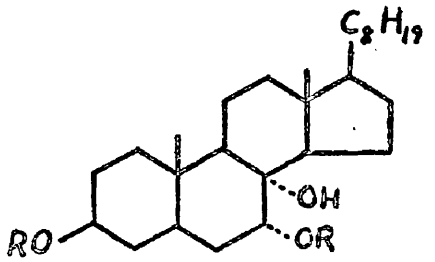
ΔM_D -117°



(CCXV) Diol M_D -67

(CCXIX) 3,11-Diacetate M_D -180

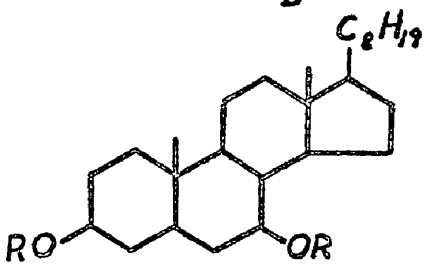
ΔM_D -113°



(CCXVI) Triol M_D - 54

(CCXX) 3,7-Diacetate M_D -201

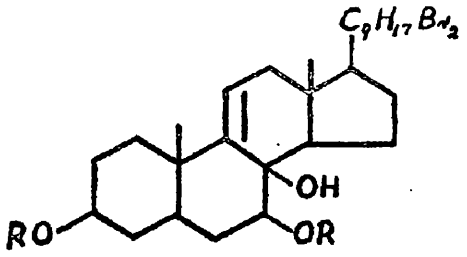
ΔM_D -147°



(CCXVII) Diol M_D + 214

(CCXXI) 3,7-Diacetate M_D + 267

ΔM_D + 53°



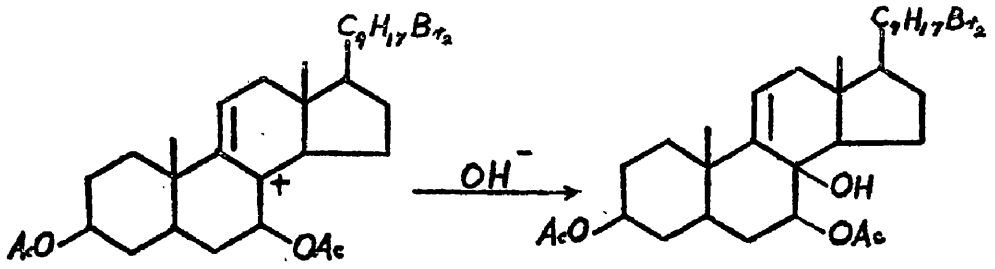
(CCXXII) Triol M_D -294

(CCXXIII) 3,7-Diacetate M_D -182

ΔM_D + 112°

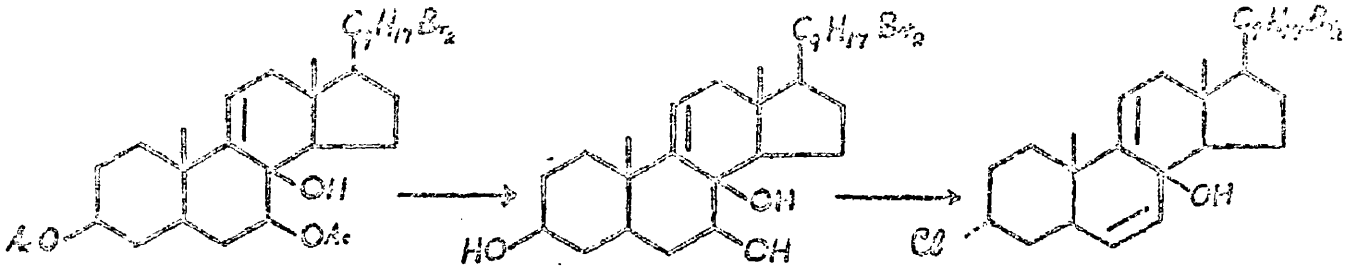
While the conversions of the 3β,7α-diol (CCXIV) and the 3β,11α-diol (CCXV) into the diacetates (CCXVIII) and (CCXIX) respectively are accompanied in each case by a negative change in molecular rotation, the corresponding change which occurs on acetylation of the 3β,7β-diol (CCXVII) is positive (+53), and compares favourably with that (+112) for the acetylation of the dibromotriol (CCXXII) to the dibromodiacetate (CCXXIII). The apparent discrepancy between the figures (+112) and (+53) may possibly be attributed to the presence of a $\Delta^{9(11)}$-double bond and a tertiary hydroxyl group in the triol-diacetate (CCXXIII).

Further, since this triol-diacetate (CCXXIII) was most probably formed by hydroxylation of the carbonium ion (CCXXIV; p. 86), the tertiary hydroxyl group may reasonably be expected to adopt the normal β-configuration to form 3β,7β-diacetoxy-22,23-dibromoergost-9(11)-en-8β-ol (CCXXIII)

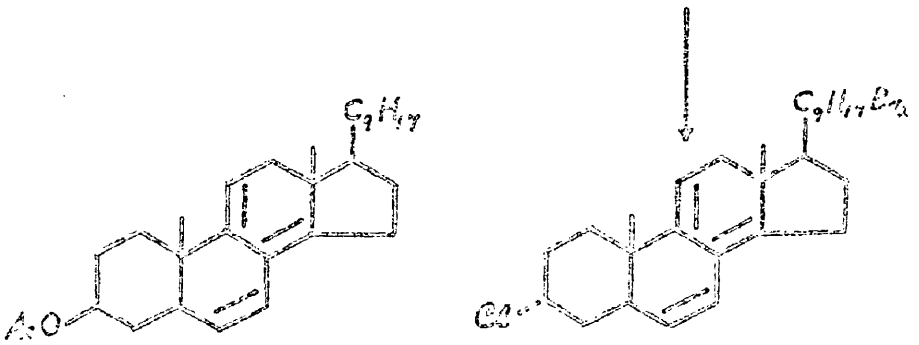


(CCXXIV) (CCXXIII)

Attempted dehydration of the triol-diacetate (CCXXIII) with thionyl chloride, phosphorus oxychloride, or acetic anhydride, under vigorous conditions proved unsuccessful and only unchanged starting material was recovered. However, alkaline hydrolysis to give the triol (CCXXII), followed by relatively milder treatment with phosphorus oxychloride, yielded an impure yellow solid, showing an absorption maximum at 2320 Å (ϵ = 12,000) with an inflexion at 2300 - 2900 Å (ϵ = 4,450). This absorption spectrum is comparable with that of the 6,8(14), 9(11)-triene[45a] system in ergosta-6,8(14),9(11)-22-tetraen--3β-yl acetate (LXXXIII), λ_{max} 2320 Å, (ϵ = 18,500) and 2370 Å., (ϵ = 6,500). Although no firm conclusion can be reached as to the structure of the impure dehydration product, it is considered to be the 3α-chloro-triene (CCXXV) since treatment of a 3β-alcohol with phosphorus oxychloride gives the 3α-chloro derivative.[75]



(CCXXIII) (CCXXII)

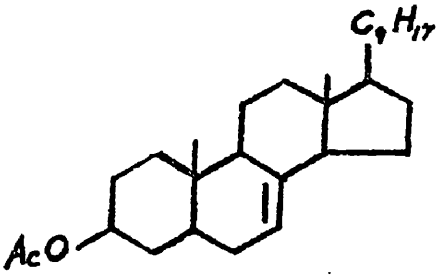


(LXXXIII) (CCXXV)

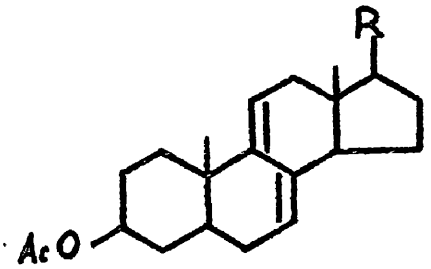
It is significant that the triol-diacetate (CCXXIV) is not easily dehydrated when the 7β-acetate is present in the molecule. This suggests that attack of the 8β-hydroxyl group is hindered by the neighbouring acetate function. However, basic hydrolysis to the triol (CCXXII) permits dehydration at the $C_{(7)}$-position, and leaves the tertiary 8β-hydroxyl group open to attack with the subsequent formation of the 3α-chlorotriene (CCXXV).

The Location and Configuration of the Nuclear Bromine Atoms in Tetrabromoergostenyl Acetate.

Anderson prepared[76c] tetrabromoergostenyl acetate by low temperature bromination of 5α,6-dihydroergostenyl acetate (XIII), ergosteryl-D acetate, (XIV), and dibromo-ergosteryl-D acetate (XV). The bromination of the ergosteryl-D acetates (XV) and (XIV) gives an immediate separation of the ether-insoluble tetrabromide, while in the bromination of the dihydro compound (XIII), the tetrabromide is only precipitated after 15 to 30 minutes.



(XIII)

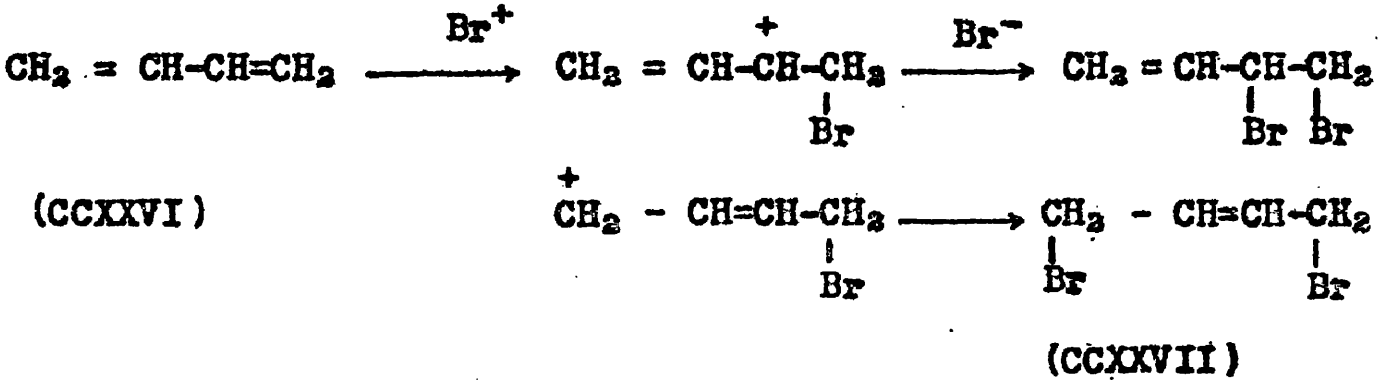


(XV) (R = $C_9H_{17}Br_2$)
(XIV) (R = C_9H_{17})

It was deduced therefore that bromination of the side chain double bond and of the conjugated diene system, takes place rapidly while the initial oxidation of the dihydro compound (XIII) by the bromine to produce a $\Delta^{9(11)}$-ethylenic linkage, takes place slowly.

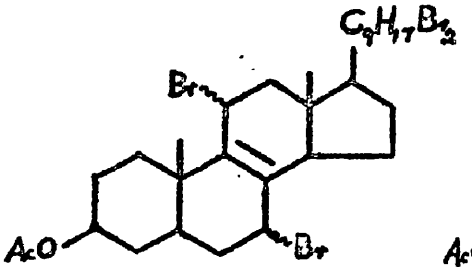
Bromination of the ergosteryl-D diene system is analogous to the addition of bromine to buta-1,3-diene (CCXXVI), a reaction which is known[91,92] to give <u>trans</u>-

1,4-dibromobut-3-ene (CCXXVII) as the major product. The reaction is formulated[91] as a two step reaction involving a resonant carbonium ion as an intermediate.

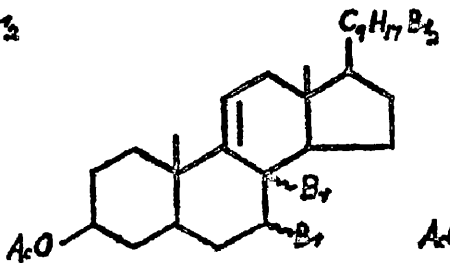


(CCXXVI) (CCXXVII)

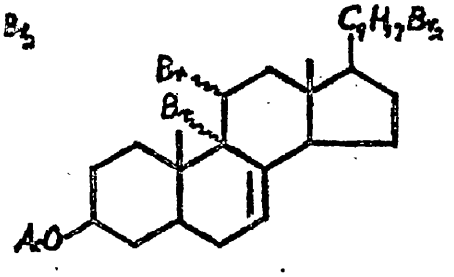
Application of this mechanism to the ergosteryl-D conjugated diene system in (XV) and (XIV), favours the formation of a 7,11,22,23-tetrabromoergost-8-ene (CLII), i.e. a 1,4-nuclear dibromo compound, as against the 1,2-nuclear dibromides (CCX) and (CCIX), which are regarded as unlikely since they also require the attachment of a large bromine atom to a hindered tertiary position, i.e. at $C_{(8)}$ or $C_{(9)}$.



(CLII)



(CCX)

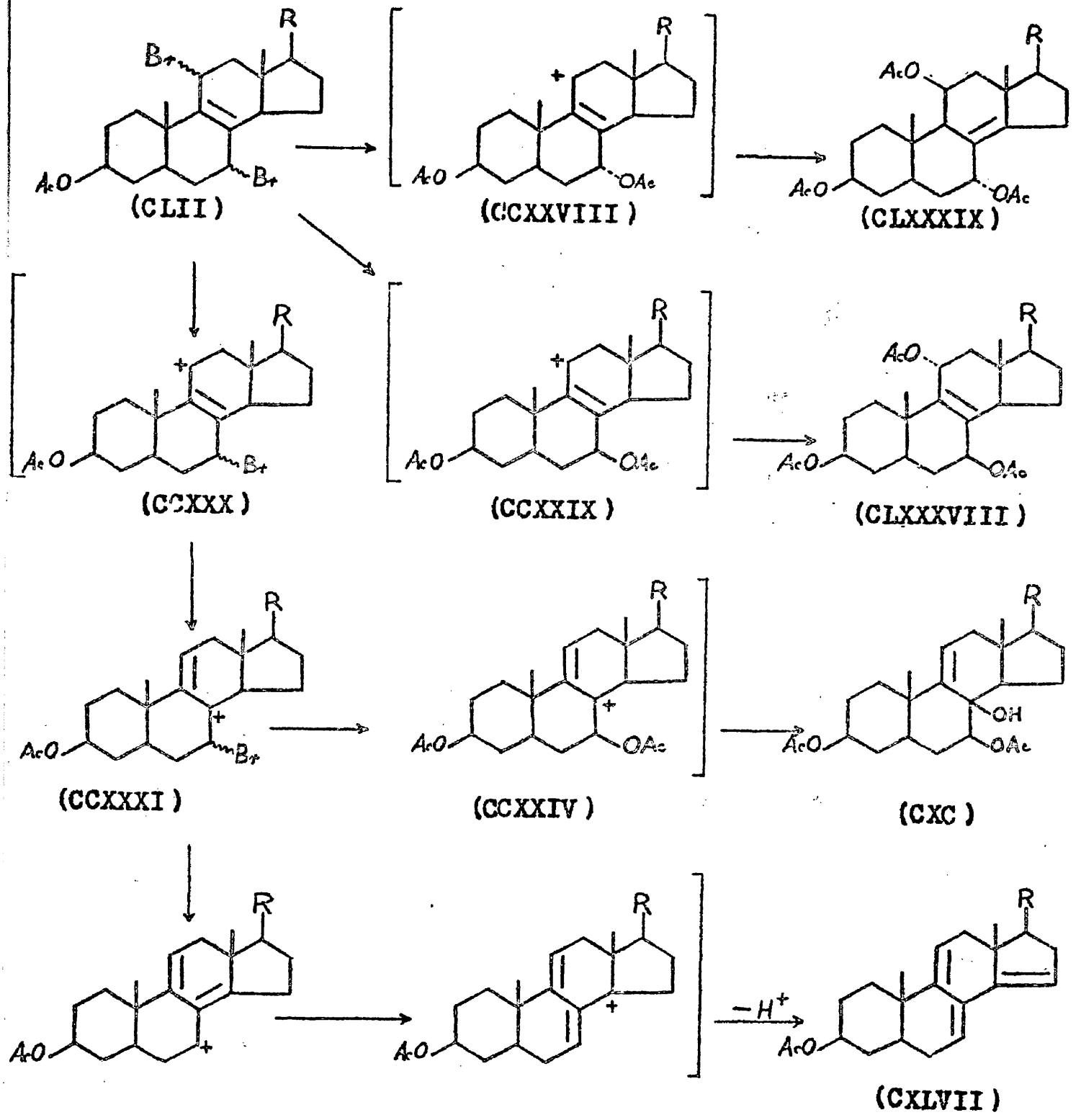


(CCIX)

From the work described in this section, it is observed that the tetrabromide, subsequently referred to as (CLII), is unstable in the presence of alkali. Treatment of the tetrabromide (CLII) with collidine leads to the removal of two moles of hydrogen bromide from the steroid nucleus and gives 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate (CXLVII) as the major product.

When the tetrabromide (CLII) is treated with hydrobromic acid, under conditions known to promote allylic rearrangement,[7ed] it is recovered unchanged. It would therefore appear to exist in the acid stable allylic form.

In order to prove that the nuclear bromine atoms are in fact located at positions 7 and 11 (CLII) an attempt was made to replace these bromine atoms by acetate groups. To prevent possible rearrangement of the molecule, the reaction was carried out under acidic conditions in acetic acid. An immediate precipitate of yellow silver bromide was formed. This was removed by filtration and four compounds (CXLVII), (CLXXXVIII), (CLXXXIX), and (CXC), were isolated from the acetic acid solution.


R
Br
AcO
Br
(CLII)
(CCXXVIII)
(CLXXXIX)
(CCXXX)
(CCXXIX)
(CLXXXVIII)
(CCXXXI)
(CCXXIV)
OH
(CXC)
$-H^+$
(CXLVII)

$R = C_8H_{17}Br_2$

A possible mechanism for the formation of these four compounds is outlined above.

Facile replacement of the bromine atom at $C_{(7)}$ from both sides of the molecule (CLII) results in the formation of a 7α- or 7β-acetate, and since substitution at $C_{(11)}$ is relatively hindered this may give rise to the transitory carbonium ions (CCXXVIII) and (CCXXIX). To give a trans-7,11-diacetate (CLXXXIX), (CCXXVIII) requires an acetate ion to take up the hindered 11β-configuration. It has been deduced by Wendler et al.[51] that an 11β-hydroxyl group attached to a $\Delta^{8(14)}$-steroidal skeleton assumes an equatorial conformation and is therefore less hindered than the allyl (Δ^{8})11β-hydroxyl group which proved[51] more resistant to acetylation. It is therefore reasonable to assume that the approach of an acetate ion from the β-face of the molecule may induce migration of the Δ^{8}-double bond to the 8(14)-position with subsequent formation of 3β,7α,11β--triacetoxy-22,23-dibromoergost-8(14)-ene (CLXXXIX).

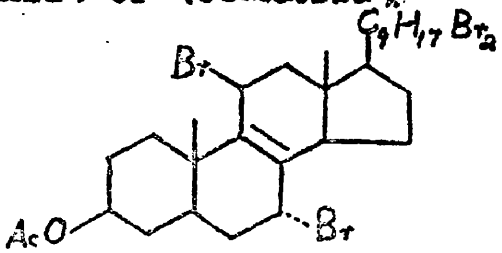
In the case of the carbonium ion (CCXXIX), a second trans-7:11-diacetate, i.e. 3β,7β,11α-triacetoxy-22,23-dibromoergost-8-ene (CLXXXVIII), is formed by the attachment of an α-orientated acetate group to the carbon atom $C_{(11)}$ which is open to attack on the rear (α) face of the molecule.

Attempts to rearrange either of the dibromo-triacetates (CLXXXVIII) or (CLXXXIX) on alumina in the presence of acetic acid proved unsuccessful and led to quantitative recovery of starting material. From this it is deduced that (CLXXXVIII) and (CLXXXIX) are not intermediates in the conversion of the tetrabromide (CLII) into 3β,7β-diacetoxy-22,23-dibromoergost-9(11)-en-8β-ol (CXC). A suggested mechanism for this conversion proceeds through the carbonium ion (CCXXX) which undergoes allylic rearrangement to the tertiary carbonium ion (CCXXXI). Substitution of the bromine atom at $C_{(7)}$ by an acetate group yields the carbonium ion (CCXXIV) which would preferentially take up a hydroxyl group at the hindered tertiary $C_{(8)}$ carbon atom rather than a larger acetate group, to give the diacetate (CXC) having the normal β-configuration at $C_{(8)}$.

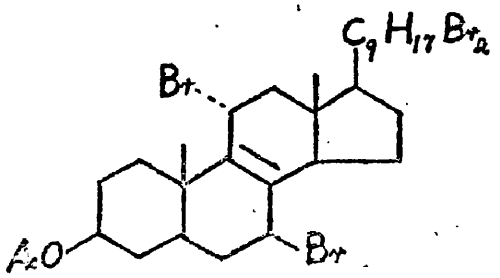
As is usual with the reactions of the tetrabromide a small amount of 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate (CXLVII) was formed as a by-product of the reaction. The mechanism may proceed via the carbonium ion (CCXXXI) as shown, (cf. p. 50)

It has been reported[92] that bromination of butadiene (CCXXVI) yields principally a trans-1,4-dibromide (CCXXVII).

If 22,23-dibromoergosteryl-D acetate (XV) is considered to be a butadiene derivative, then the addition of bromine to its diene system will yield a tetrabromoergostenyl acetate which may be represented by (CCXXXII) or (CCXXXIII).



(CCXXXII)



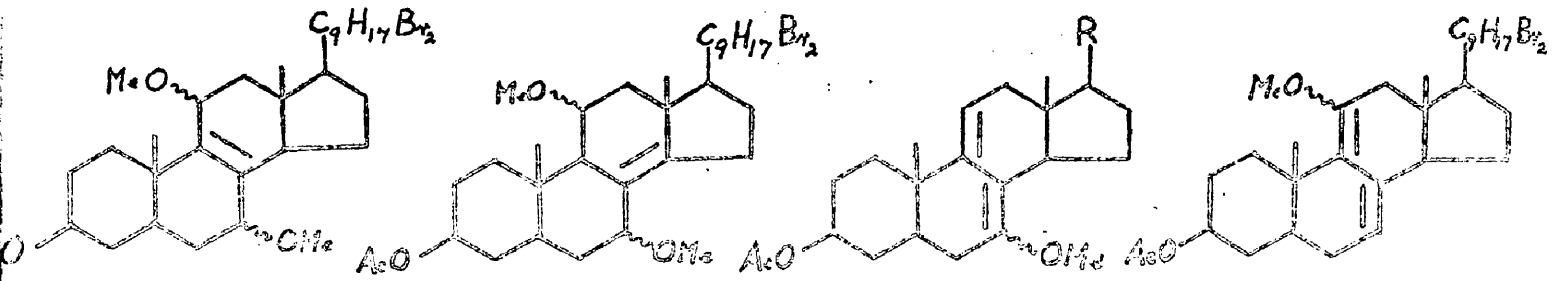
(CCXXXIII)

It is significant that only two triacetates (CLXXXVIII) and (CLXXXIX), having 7,11-trans-diacetate groups, are formed by the action of silver acetate-acetic acid on the tetrabromide. This would suggest that the two nuclear (trans) bromine atoms of the tetrabromide (CCXXXII) or (CCXXXIII) undergo replacement by two separate reaction mechanisms, (a) by direct substitution, (b) by substitution with Walden inversion, to give the 7,11-trans-diacetates (CLXXXVIII) and (CLXXXIX). Should the tetrabromide include two nuclear (cis) bromine atoms, it is unlikely that the two 7,11-trans-diacetates (CLXXXVIII) and (CLXXXIX) would be the sole products obtained by replacement of the nuclear bromine atoms with acetate groups. Similarly the formation of these two 7,11-trans-diacetates (CLXXXVIII) and (CLXXXIX) precludes a nuclear 1,2-dibromide structure for tetrabromoergostenyl acetate, and it is therefore

concluded that the last compound is either 7α,11β,22,23--tetrabromoergost-8-en-3β-yl acetate (CCXXXII) or 7β,11α,22,23-tetrabromoergost-8-en-3β-yl acetate (CCXXXIII).

The Action of Methanol on Tetrabromoergostenyl Acetate.

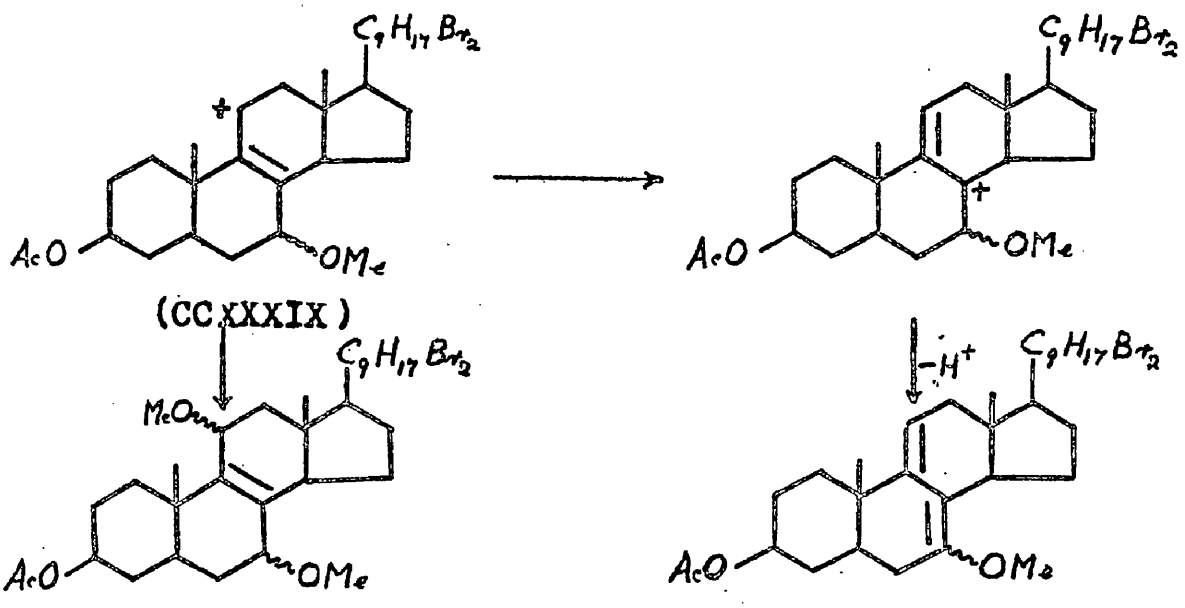
When tetrabromoergostenyl acetate is treated with calcium carbonate in boiling methanol two products are obtained. The first of these was shown to contain two methoxyl groups (Zeisel) and the elementary analysis indicated the molecular formula, $C_{30}H_{46}O_2Br_2(OMe)_2$. In addition the ultraviolet absorption spectrum (λ_{max} 2060 Å. ϵ = 9750) indicated the presence of a tetrasubstituted double bond, which is most probably $\Delta^{8(9)}$ or $\Delta^{8(14)}$ as in the analogous products (CLXXXVIII) and (CLXXXIX) respectively (p. 91) obtained from the tetrabromide by the substitution of the two nuclear bromine atoms. This compound is therefore represented by either (CCXXXIV) or (CCXXXV). It displays a strong band at 1081 cm.$^{-1}$ which may be due to the vinyl ether system.



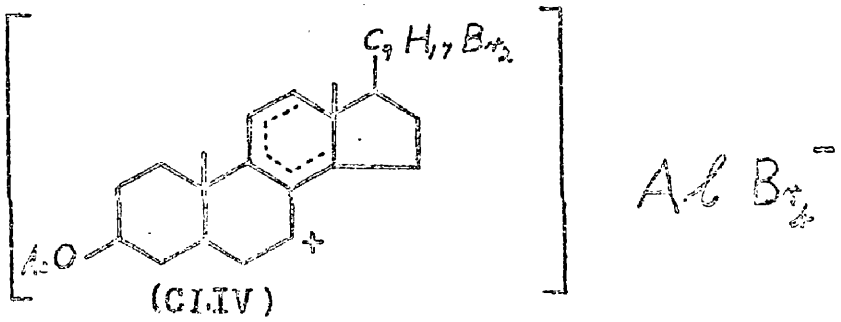
(CCXXXIV) (CCXXXV) (CCXXXVI) (R = $C_9H_{17}Br_2$) (CCXXXVIII)
(CCXXXVII) (R = C_9H_{17})

Zeisel estimation and analysis of the second product showed that it contained only one methoxyl group and had the molecular formula $C_{30}H_{46}O_2Br.OMe$. The ultraviolet absorption spectrum ($\lambda_{max.}$ 2460 Å, ϵ = 18,000) corresponded to that expected of the ergosta-7,9(11)-dienol ether systems in formulae (CCXXXVI) and (CCXXXVIII), (cf. Djerassi et al.[85])

Considering the possible mechanism of formation of the above products from tetrabromoergostenyl acetate (CCXXXII or CCXXXIII) it is reasonable to assume that the carbonium ion (CCXXXIX) is an intermediate. This carbonium ion (CCXXXIX) can then become stabilised in two ways (a) by taking up a methoxyl group to give the dimethoxy-ergostene (CCXXXIV) or (CCXXXV), and (b) by allylic rearrangement and loss of a proton from $C_{(7)}$ to give the methoxydiene (CCXXXVI).



The conjugated diene (CCXXXVI) was also isolated from the methanol fraction of the tetrabromide chromatogram (p.43), having resisted elution by the non-polar solvents. However since the methoxydiene, once formed, is not strongly adsorbed on alumina but is readily eluted with light petroleum-benzene mixtures, it is suggested that a stable complex of the type (CCXXXX), exists on the tetrabromide column and on elution with



(CLIV)

(CCXXXX)

methanol this complex is decomposed to give the methoxydiene (CCXXXVI).

It has already been postulated (p.50) that the resonating carbonium ions (CLIII), (CLIV), (CLV), (CLVI), and (CLVII) are formed on contact of the tetrabromide with alumina. Considering the large dimensions of the anion $(AlBr_4)^-$ and the location of the positive charge in these carbonium ions it is evident that the carbonium ion most likely to participate in complex formation is (CLIV), the bulky anion $(AlBr_4)^-$ being more readily attached to the relatively unhindered 7-position to give the complex (CCXXXX).

An attempt to prepare the methoxydiene (CCXXXVI), by filtration of an ether-methanol solution of the tetrabromide through a column of alumina, gave a mixture of 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate (CXLVII) and 7-oxo-22,23-dibromoergost-8-en-3β-yl acetate (CLXXXIV).

Alkaline hydrolysis of the methoxydiene (CCXXXVI) gave the corresponding alcohol, from which the original acetate was regenerated on acetylation. Debromination of the methoxydiene (CCXXXVI), with zinc dust in refluxing ether:ethanol solution, yielded 7-methoxyergosta-7,9(11), 22-trien-3β-yl acetate (CCXXXVII).

EXPERIMENTAL

All melting points are uncorrected. Specific rotations were determined in chloroform solution, (unless otherwise stated), in a 1 dm. tube at approximately 15°C. Ultraviolet absorption spectra were measured in ethanol solution, using a Unicam SP.500 spectrophotometer. Infrared absorption spectra were measured in Nujol mulls, (unless otherwise stated), with a Grubb Parsons S.4 double beam spectrophotometer with sodium chloride optics. Grade II alumina and light petroleum (b.p. 60-80°) were used for chromatography.

The author wishes to thank Dr. A. C. Syme and Mr. W. McCorkindale for the microanalyses and the ultraviolet absorption measurements, and Dr. G. T. Newbold for the infrared absorption spectra.

Tetrabromoergosteryl Acetate. - Bromine (16 g.; 4.4 moles) in glacial acetic acid (50 ml.) was added to a solution of 5α,6-dihydroergosteryl acetate (10 g.) in dry ether (1000 ml.) at -30°, and the solution was cooled rapidly to -75° by acetone-"drikold". The orange solution was shaded from sunlight and gradually allowed to attain room temperature during 3 hr. The crystalline material was collected and washed white with dry ether

before drying *in vacuo* at room temperature (1 hr.). Crystallisation of this product (7 g.) from benzene-light petroleum (b.p. 60-80°) yielded tetrabromoergostenyl acetate as colourless needles, m.p. 126-127° (decomp.), $[\alpha]_D$ + 260° (*c*,1.5, in benzene) [Found: C,47.7; H,6.4; Br,42.5. Calc. for $C_{30}H_{46}O_2Br_4$: C,47.5; H,6.1; Br,42.2%].

The Action of Alumina on Tetrabromoergostenyl Acetate. - (a) A solution of the tetrabromide (21 g.) in *WARM* benzene (400 ml.) was percolated through a column (21 x 4 cm.) of alumina (200 g.). Elution with benzene (600 ml.) yielded a fraction (14.1 g.), which crystallised from chloroform-methanol to give *22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate* as pale yellow leaflets, m.p. 211-212° (decomp.), $[\alpha]_D$ - 54° (*c*,1.1). Recrystallisation did not remove the yellow colour, but filtration through a short column of alumina yielded colourless leaflets, m.p. 211-212° (decomp.), $[\alpha]_D$ - 53° (*c*,1.2), $\lambda_{max.}$ 2280 Å. (ϵ = 11,730), 2340 Å. (ϵ = 11,080), 2680 Å. (ϵ = 10,090); infrared absorption at 1733cm.$^{-1}$ and 1250 cm.$^{-1}$ (O-acetyl). The triene gives an orange-red colour, going to deep yellow, with tetranitromethane in chloroform [Found: C,60.6; H,7.5. $C_{30}H_{46}O_2Br_2$ requires: C,60.4; H,7.4%].

Further elution with benzene, benzene-ether, and ether yielded no pure material. However, elution with methanol (250 ml.) removed the dark brown band from the head of the column, the methanol eluate being repeatedly concentrated to yield crops of a crystalline solid (400 mg.). Recrystallisation of this product from ether-methanol gave 22,23-dibromo-7-methoxyergosta-7,9(11)-dien-3β-yl acetate as large prisms, m.p. 180-182°, $[\alpha]_D$ + 94° (c,1.8), giving a brown colour with tetranitromethane in chloroform; $\lambda_{max.}$ 2460 Å. (ϵ = 18,000); infrared absorption at 1740 $cm.^{-1}$ and 1240 $cm.^{-1}$ (O-acetyl), 1068 $cm.^{-1}$ (C = C - O - C). [Found: C,59.3; H,7.8; OMe,5.5. $C_{30}H_{48}O_2Br_2.OMe$ requires: C,59.2; H,7.7; OMe,4.9%].

The methoxydiene was recovered unchanged after filtration through alumina, recrystallising from ether-methanol as large prisms, m.p. 181-182°, $[\alpha]_D$ + 96° (c,1.5).

(b) A solution of tetrabromoergostenyl acetate (18 g.) in COLD benzene (500 ml.) was adsorbed on a column of alumina (500 g.) and left overnight. Elution with benzene (600 ml.) yielded a fraction (1.9 g.) which crystallised from acetone-methanol to give 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate as pale yellow leaflets (650 mg.), m.p. 204-206° (decomp.); $[\alpha]_D$ - 54° (c,1.2).

Further elution with benzene (2 l.) gave a second fraction (15.1 g.) which crystallised slowly from acetone-methanol to yield 22,23-dibromo-12-methyl-13-nor-ergosta-3(14),9(11),12-trien-3β-yl acetate as colourless needles (5.2 g.), m.p. 136-137°, $[\alpha]_D$ - 4.1° (c,1.6), $\lambda_{max.}$ (in iso-octane): 2090 Å. (ϵ = 31,200), 2700 Å. (ϵ = 363), 2760 Å. (ϵ = 283), inflexion at 2620 Å. (ϵ = 288); infrared absorption at 1740 $cm.^{-1}$ and 1241 $cm.^{-1}$ (O-acetyl); 1606 $cm.^{-1}$ and 1575 $cm.^{-1}$ ($CHCl_3$) (aromatic ring vibration); 869 $cm.^{-1}$ (penta-substituted benzene ring) (CS_2). The compound gave a deep yellow colour with tetranitromethane in chloroform. [Found: C,60.4; H,7.5. $C_{30}H_{44}O_2Br_2$ requires C,60.4; H,7.4%].

Elution with benzene-ether (1 l.) and ether (1 l.) gave intractible gums (1.5 g.). Elution with ether-methanol (1 l.) and methanol (500 ml.) gave a fraction (2.5 g.), which crystallised slowly from methanol as a light brown solid. Recrystallisation of this material from ether-methanol furnished 22,23-dibromo-7-methoxy-ergosta-7,9(11)-dien-3β-yl acetate (125 mg.), m.p. 180-182°, $[\alpha]_D$ + 92° (c,0.9).

(c) A saturated solution of the tetrabromide (2 g.) in ether-methanol (250 ml. 1:1) was percolated through a column of alumina (17 g.). Concentration of the eluate

(250 ml.) yielded a mixture of yellow needles (150 mg.), m.p. 198-202° (decomp.) and 217-220° (decomp.), which was dissolved in light petroleum (10 ml.) and chromatographed on alumina (5 g.). Elution with light petroleum benzene mixtures (300 ml.) yielded a fraction (60 mg.) which crystallised from ether-methanol to give colourless leaflets of 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate, m.p. 198-200° (decomp.). Elution with benzene and then with ether gave a yellow-white solid (85 mg.) which crystallised from ether-methanol as needles, m.p. 228-233°, $[\alpha]_D$ - 25.4° (c,1.6). Recrystallisation of this material from ether-methanol furnished pale yellow needles, m.p. 244-245°, $[\alpha]_D$ - 27° (c,1.0), $\lambda_{max.}$ 2530 Å. (ϵ = 9000), identical (m.p. and mixed m.p., and infrared absorption) with 22,23-dibromo-7-oxoergost-8-en-3β-yl acetate. [Found: C,58.86; H,7.8. Calc. for $C_{30}H_{46}O_3Br_2$: C,58.6; H,7.55%].

The Action of Alumina-Aluminium Bromide on 22,23-Dibromoergosta-7,9(11),14-trien-3β-yl Acetate. - A solution of the dibromo-triene (250 mg.) in benzene (30 ml.) was filtered through a column containing an intimate mixture of alumina (9 g.) and anhydrous aluminium bromide (1 g.), to which a few drops of concentrated hydrobromic acid had been added. After three days at room temperature, elution

with benzene (1 l.), gave a fraction which crystallised to yield the dibromo-triene as colourless leaflets (200 mg.), m.p. 198-200° (decomp.), $[\alpha]_D$ - 54° (c,2.5). No colour developed on the column as in the aromatisation of tetrabromoergostenyl acetate.

Debromination of 22,23-Dibromoergosta-7,9(11),14-trien-3β-yl Acetate. - A solution of the dibromo-triene (450 mg.) in ether ethanol (100 ml.) at 50°, was stirred vigorously for 4 hr. in the presence of activated zinc dust (4 g.). The product was worked up through ether in the usual way and dried (Na_2SO_4). On concentration of the ether solution a white solid was obtained which on recrystallisation from acetone gave ergosta-7,9(11),14,22-tetraen-3β-yl acetate as plates, m.p. 134-139°, $\lambda_{max.}$ 2280 Å. (ϵ = 10,070), 2350 Å. (ϵ = 10,120), 2680 Å. (ϵ = 9180). After drying under high vacuum the constants of the material were m.p. 128-131°, $[\alpha]_D$ - 88.2° (c,1.8). [Found: C,82.7; H,10.45. $C_{30}H_{44}O_2$ requires C,82.5; H,10.2%].

Laubach et al.,[45b] gave m.p. 127-131°, $\lambda_{max.}$ 2270 Å. (ϵ = 9120) 2350 Å. (ϵ = 6310), 2680 Å. (ϵ = 10,000). No specific rotation or analysis was recorded by these workers.

The Maleic Anhydride Adduct of 22,23-Dibromoergosta-7,9(11),14-trien-3β-yl Acetate. - A solution of the dibromo-triene (550 mg.) in dry benzene (50 ml.) was boiled under reflux for 7 hr. with maleic anhydride (550 mg.) Concentration of the solution yielded fine

white needles, m.p. 226-227°, $\lambda_{max.}$ 2060 Å. (ϵ = 4320), 2750 Å. (ϵ = 3950). Four recrystallisations from acetone furnished the adduct as needles, m.p. 234°, $[\alpha]_D$ + 28° (c,1.6) [Found: C,58.6; H,6.9. Calc. for $C_{34}H_{46}O_5Br_2$: C,58.8, H,6.7%].

The Maleic Anhydride Adduct of Ergosta-7,9(11),14,22-tetraen-3β-yl Acetate. - (a) The maleic anhydride adduct of the dibromo-triene (70 mg.) was dissolved in ether-ethanol (100 ml.) and the solution was boiled under reflux for 2 hr. with activated zinc dust (3 g.). The product was isolated in ether worked up in the usual manner, and the solvent evaporated to give a yellow-white solid (30 mg.) which was taken up in methanol, boiled with charcoal, and the solution filtered. Recrystallisation from methanol gave the adduct as stout needles, m.p. 205-208°, $[\alpha]_D$ - 36.5° (c,1.3), $\lambda_{max.}$ 2040 Å. (ϵ = 3970), 2750 Å (ϵ = 3720); Infrared absorption at 1730 $cm.^{-1}$ and 1224 $cm.^{-1}$ (O-acetyl), 1842 $cm.^{-1}$, 1779 $cm.^{-1}$, 1263 $cm.^{-1}$, and 1202 $cm.^{-1}$ (acid anhydride). Laubach et al. gave m.p. 205-209°, $[\alpha]_D$ - 36.7°, $\lambda_{max.}$ 2730 Å. (ϵ = 4570).

(b) A solution of ergosta-7,9(11),14,22-tetraen-3β-yl acetate (22 mg.) in dry toluene (8 ml.) was refluxed (3 hr.) with maleic anhydride (34 mg.). The solution was evaporated to dryness and the product recrystallised from methanol

to give the adduct as stout needles, m.p. 205-206°, $\lambda_{max.}$ 2040 Å. (ϵ = 4870), 2730 Å. (ϵ = 4280); identical (m.p., mixed m.p., and infrared absorption) with the debrominated adduct prepared above.

22,23-Dibromoergosta-7,9(11),14-trien-3β-ol. - The dibromo-trienyl acetate (119 mg.) was refluxed for 1 hr. with 2% methanolic sodium hydroxide (25 ml.) The product was worked up through ether in the usual manner and recrystallised from chloroform-methanol to give 22,23-dibromoergosta-7,9(11),14-trien-3β-ol, as leaflets (50 mg.), m.p. 190-191°, $[\alpha]_D$ - 59° (c,1.6), $\lambda_{max.}$ 2280 Å. (ϵ = 10,500), 2350 Å. (ϵ = 9170), 2670 Å. (ϵ = 10,200); infrared absorption at 3360-3135 $cm.^{-1}$ (alcoholic hydroxyl). [Found: C,60.9; H,7.9. $C_{28}H_{42}OBr_2$ requires C,60.7; H,7.65%].

Acetylation of the alcohol regenerated the dibromo--trienyl acetate m.p. 205-206°; $\lambda_{max.}$ 2280 Å. (ϵ = 11,100), 2350 Å. (ϵ = 10,200), 2690 Å. (ϵ = 9860). Identical infrared absorption.

The Action of Phosphorus Oxychloride-Pyridine on 22,23-Dibromoergosta-7,9(11),14-trien-3β-ol. - A solution of the dibromo-trienol (125 mg.) in pyridine (13 ml.) was heated for 1.5hr. with phosphorus oxychloride (1.3 ml.) at 100° and the solution was allowed to cool overnight. The product, isolated by means of ether was crystallised from

chloroform-methanol to give white needles of 22,23-dibromo--3α-chloroergosta-7,9(11),14-triene, m.p. 199-200°, $[\alpha]_D$ -28.2° (c,1.7), $\lambda_{max.}$ 2280 Å. (ε = 11,350), 2340 Å. (ε = 10,760), 2680 Å. (ε = 8,750) [Found: C,58.4; H,7.4. $C_{28}H_{41}Br_2Cl$ requires C,58.7; H,7.2%]

The Action of Collidine on Tetrabromoergosteryl Acetate. - A solution of the tetrabromide (11 g.) in dry benzene (400 ml.) and collidine (75 ml.), (purified by distillation over sodium), was maintained at 100° for 20 min. A buff-coloured precipitate (5.12 g.; theoretical for collidine hydrobromide: 5.85 g.) was filtered off and washed with dry benzene (30 ml.). The combined filtrate and washings were washed with dilute sulphuric acid, saturated sodium hydrogen carbonate solution, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded a white solid, which was dissolved in a minimum of cold chloroform. Methanol was then added and small needles of impure 22,23-dibromoergosta-7,9(11),14-trienyl acetate, m.p. 205-206° were precipitated. $\lambda_{max.}$ 2220 Å (ε = 9,330), 2350 Å. (ε = 8820), 2680 Å. (ε = 9020). Recrystallisation from chloroform-methanol yielded blades, m.p. 205-206°, $[\alpha]_D$ -55° (c,2.1) [Found: C,60.6; H,7.8. Calc. for $C_{30}H_{44}O_2Br_2$: C,60.4; H,7.4%].

Debromination of the above material by treatment with zinc dust in ether-ethanol at 50° for 4 hr., followed by

chromatography of the product gave only impure ergosteryl-D acetate in poor yield. Several similar debrominations, in which the temperature varied between 40° and 60°, also failed to yield pure ergostatetraene.

The Action of Chloroformic Hydrogen Chloride on the Impure 22,23-Dibromoergosta-7,9(11),14-trien-3β-yl Acetate.- Chloroformic hydrogen chloride (10 ml.; 0.26N) was added to a solution of the impure dibromo-triene (800 mg.) in dry chloroform (40 ml.) and the green solution was maintained at 30° for 12 hr., before being washed with saturated aqueous sodium bicarbonate solution and water. Evaporation of the dried solution under reduced pressure gave a brown gum (800 mg.) which was dissolved in light petroleum (30 ml.) and adsorbed on a column of alumina (24 g.). Elution with light petroleum (300 ml.) yielded the dibromo-triene (30 mg.), m.p. 205-206°. Further elution with the same solvent (1100 ml.) yielded a white crystalline solid (150 mg.) which on recrystallisation from ether-methanol gave 22,23-dibromoergosta-8,14-dien-3β-yl acetate, as colourless needles, m.p. 222-223°, $[\alpha]_D$ - 17.2° (c,1.7). Two further recrystallisations from the same solvent gave needles, m.p. 225-226°, $[\alpha]_D$ - 20° (c,1.3), $\lambda_{max.}$ 2480 Å. (ϵ = 19,500). [Found: C,60.5; H,8.1. $C_{30}H_{46}O_2Br_2$ requires C,60.2; H,7.8%].

The Attempted Catalytic Hydrogenation of the Dibromoaromatic Acetate. - Platinum catalyst (prepared by hydrogenation of 250 mg. platinum oxide) was added to a solution of the dibromoaromatic acetate (250 mg.) in glacial acetic acid (50 ml.) and the mixture was shaken for 24 hr. with hydrogen at atmospheric pressure. No uptake of hydrogen was observed and starting material was recovered quantitatively after working up the acetic acid solution in the normal manner.

The Dibromoaromatic Alcohol. - (a) The dibromoaromatic acetate (250 mg.) was boiled under reflux for 1 hr. with 2% methanolic sodium hydroxide (25 ml.). The product was worked up through ether and crystallised from light petroleum to give felted needles (90 mg.) of 22,23-dibromo-12-methyl-18-norergosta-8(14),9(11),12-trien-3β-ol, m.p. 111-113°, $[\alpha]_D$ + 5° (c,1.1), $\lambda_{max.}$ 2080 Å. (ϵ = 30,000), 2680 Å. (ϵ = 400), 2760 Å. (ϵ = 260); infrared absorption at 3390 $cm.^{-1}$ (hydroxyl group), 1598 $cm.^{-1}$ (aromatic ring vibration), 865 $cm.^{-1}$ (pentasubstituted benzene ring). [Found: C,60.2; H,7.6. $C_{28}H_{42}OBr_2$ requires: C,60.6; H,7.6%]. (b) The dibromoaromatic acetate (497 mg.) was boiled under reflux for 1 hr. with 18% aqueous methanolic sulphuric acid (100 ml.) and left overnight to crystallise as colourless needles (450 mg.), m.p. 90-98°. Further recrystallisation from aqueous methanol yielded the dibromoaromatic alcohol

as colourless needles, m.p. 108-110°, $[\alpha]_D$ + 5°, identical (m.p., mixed m.p., ultraviolet and infrared spectra) with the alkaline hydrolysis product. Acetylation of this alcohol regenerated the dibromoaromatic acetate, m.p. 136-137°, $[\alpha]_D$ - 2° (c,1.2).

Dibromoaromatic 3-Ketone. - A slurry of chromium trioxide (100 mg.) in pyridine (2 ml.) was added to a solution of the dibromoaromatic alcohol (100 mg.) in pyridine (1 ml.) and the mixture was allowed to stand for 20 hr. at room temperature with occasional agitation. Methanol (5 ml.) was added and then 2% aqueous sodium hydroxide solution (20 ml.). The product was worked up through ether in the normal manner and evaporation of the solvent gave a pale yellow gum which crystallised slowly from methanol as rosettes of colourless needles, m.p. 102-105°. Further recrystallisation from chloroform-methanol yielded 3-oxo-22,23-dibromo-12-methyl-18-norergosta-8(14),9(11),12-triene, m.p. 139-140°, $[\alpha]_D$ + 23° (c,1.1), $\lambda_{max.}$ 2080 Å. (ϵ = 30,000), 2680 Å. (ϵ = 500), 2760 Å. (ϵ = 260); infrared absorption at 1721 $cm.^{-1}$ (six-ring carbonyl), 1597 $cm.^{-1}$ (aromatic ring vibration), 872 $cm.^{-1}$ (penta-substituted benzene ring). [Found: C,60.7; H,7.2. $C_{28}H_{40}OBr_2$ requires: C,60.9; H,7.3%].

The Action of Phosphorus Oxychloride-Pyridine on the Dibromoaromatic Alcohol. - A solution of the dibromoaromatic alcohol (85 mg.) in pyridine (10 ml.) was heated for 1.5 hr. with phosphorus oxychloride (1 ml.) at 100° and allowed to cool overnight before working up through ether in the normal manner. The resultant white solid (60 mg.) was recrystallised from chloroform-methanol to give 22,23--dibromo-3α-chloro-12-methyl-18-norergosta-8(14),9(11),12-triene as colourless needles, m.p. 195-197°, $[\alpha]_D$ + 13° (c,1.7), $\lambda_{max.}$ 2150 Å. (ϵ = 25,000), 2580 Å.(ϵ = 467), 2670 Å.(ϵ 476), 2760 Å. (ϵ = 400). [Found: C,58.65; H,7.3; Br,27.2; Cl,6.05. $C_{28}H_{41}Br_2Cl$ requires C,58.7; H,7.2; Br,27.9; Cl,6.2%].

Dehydration of the Dibromoaromatic Alcohol. - A solution of the dibromoaromatic alcohol (160 mg.) in dry benzene (5 ml.) was shaken (22 hr.) with phosphorus pentoxide (160 mg.) at room temperature. The product was worked up in the normal manner yielding a pale yellow gum (140 mg.), $\lambda_{max.}$ 2080 Å. (ϵ = 27,000), 2690 Å. (ϵ = 370), which crystallised from acetone as colourless blades (70 mg.) m.p. 124-125°, $[\alpha]_D$ + 53° (c,0.7), $\lambda_{max.}$ 2080 Å. (ϵ = 30,000), 2690 Å (ϵ = 370) [Found: C,62.65; H,7.7. $C_{28}H_{40}Br_2$ requires C,62.7; H,7.5%]. This compound must be the 2-ene or the 3-ene. The other isomer, or a mixed crystal of the two, crystallised from the mother liquors as needles

(30 mg.), m.p. 123-128°. Further crystallisation from chloroform-methanol furnished colourless needles, m.p. 128-131°, $[\alpha]_D$ + 41° (c,0.6), $\lambda_{max.}$ 2080 Å. (ϵ = 30,000) 2690 Å. (ϵ = 370) [Found: C,62.5; H,7.5. $C_{28}H_{40}Br_2$ requires C,62.7; H,7.5%]. Both isomers gave a strong yellow colour with tetranitromethane in chloroform. They showed no marked difference in their infrared spectra and a mixture of the two had m.p. 124-125°.

Both isomers, after refluxing (1 hr.) with concentrated hydrochloric acid and acetic acid (1:5), showed no change in their ultraviolet absorption spectra (n-hexane).

Treatment of Ergosterol with Concentrated Nitric Acid. - Concentrated nitric acid (s.g. 1.42, 45 ml.) was added carefully to ergosterol (2 g.) and, after the initial vigorous reaction, the solution was gently warmed until the evolution of nitrous fumes had ceased. The solution was refluxed gently for 17 hr. and concentrated (35 ml. distillate collected). The solution was allowed to cool and deposit a crystalline precipitate which was collected, washed with ether, and recrystallised from water to give prisms of toluene-2,3,5,6-tetracarboxylic acid (180 mg.), m.p. 238-241°, the crystalline form changing to blades at 210°

The acid was treated with excess diazomethane in ether to yield the tetramethyl ester, m.p. 118-122°. (Inhoffen[57] gives m.p. 121-123°).

Treatment of the Dibromoaromatic Acetate with Concentrated Nitric Acid. - Concentrated nitric acid (s.g. 1.42; 45 ml.) was added carefully to the dibromoaromatic acetate (2 g.) and the solution gently warmed. When the evolution of nitrous fumes had ceased, the solution was refluxed gently for 16 hr., concentrated, (35 ml. of distillate collected), and allowed to cool. No solid material appeared and addition of water precipitated an uncrystallisable gum. The aqueous phase was extracted with ether yielding a gum which was combined with the precipitated gum and treated with excess diazomethane in ether. Careful chromatography of the product yielded only intractible material.

The Action of Chromium Trioxide in Acetic Acid on the Dibromoaromatic Acetate. - A solution of chromium trioxide (222 mg.; 2 atoms oxygen per mole) in stabilised acetic acid (5 ml.) was mixed intimately with a solution of the dibromoaromatic acetate (1 g.) in stabilised acetic acid (80 ml.). After 2.5 hr., a further quantity of chromium trioxide (333 mg.; 3 atoms oxygen per mole) in

stabilised acetic acid (10 ml.) was added to the reaction mixture and the whole maintained at room temperature for 19 hr. The addition of water precipitated a white solid which was collected, and washed with water. Crystallisation of this product from acetone-methanol gave the dibromoaromatic keto-acetate (600 mg.), as colourless rods, m.p. 133-138°. Recrystallisation from methanol furnished long needles, m.p. 135-138°, $[\alpha]_D$ - 10° (c,1.9), $\lambda_{max.}$ 2190 Å (ϵ = 31,000), 2650 Å (ϵ = 15,000), 3100 Å. (ϵ = 3,000); infrared absorption at 1736 cm.$^{-1}$ (O-acetyl), 1684 cm.$^{-1}$ (carbonyl group adjacent to a benzene ring), 1592 cm.$^{-1}$ (aromatic ring vibration) [Found: C,59.2; H,7.2. $C_{30}H_{42}O_3Br_2$ requires C,59.0; H,6.9%].

The ketone did not form a 2,4-dinitrophenylhydrazone even after prolonged refluxing with Brady's reagent.

The keto-acetate (200 mg.) was hydrolysed by treatment with 2% methanolic potassium hydroxide to the corresponding alcohol (150 mg.), m.p. 199-201°, $[\alpha]_D$ - 5° (c,0.9) [Found: C,59.3; H,7.4; Br,23.8. $C_{28}H_{40}O_2Br_2$ requires C,59.2; H,7.1; Br,28.1%].

Acetylation of this alcohol regenerated the original keto-acetate.

The keto-acetate was refluxed for 2.5 hr. with sodium

borohydride in methanol, the product, which crystallised from the reaction mixture, was a dibromoaromatic diol, m.p. 115-117°, $[\alpha]_D$ + 11° (c,1.2), $\lambda_{max.}$ 2080 Å. (ϵ = 35,000) 2690 Å. (ϵ = 400); infrared absorption at 3236 $cm.^{-1}$ (alcoholic hydroxyl groups). [Found: C,58.7; H,7.2. $C_{28}H_{42}O_2Br_2$ requires: C,58.95; H,7.4%].

Further Action of Chromium Trioxide in Acetic Acid on the Dibromoaromatic Acetate. - A solution of chromium trioxide (1.05 g.; 12 atoms oxygen per mole) in stabilised glacial acetic acid (15 ml.) was added to a solution of the dibromoaromatic acetate (900 mg.) in stabilised acetic acid (50 ml.) and allowed to stand for 50 hr. at room temperature. The product was worked up through ether in the usual manner to give an acid and a neutral fraction.

The neutral fraction crystallised from acetone-methanol as colourless rods (200 mg.), m.p. 135-138°, $[\alpha]_D$ - 10° (c,1.0), identical (m.p., mixed m.p. and infrared) with dibromoaromatic keto-acetate.

The acid fraction was an amorphous, white solid (500 mg.) which was purified by repeated precipitation from its solution in acetic acid by the addition of water. It could not be recrystallised from the usual solvents but was obtained as fine crystals on evaporation to dryness,

at room temperature, of its concentrated acetic acid solution. It had m.p. 150-170° (decomp); $\lambda_{max.}$ 2570 Å. (ϵ = 11,000), 3000 Å. (ϵ = 3,000); Infrared absorption at 3300-2850 cm.$^{-1}$ and 1720-1710 cm.$^{-1}$ (carboxyl groups) [Found: C,54.6; H,6.7. $C_{30}H_{42}O_5Br_2$ requires C,54.7; H,6.4%]. (Equivalent weight: Found 357, $C_{28}H_{40}O_5Br_2$ $(COOH)_2$ requires: 329).

The acid did not give a 2,4-dinitrophenylhydrazone after prolonged refluxing with Brady's reagent, nor did it form a crystalline anhydride after refluxing for 1 hr. with acetic anhydride. It also failed to give a pure product on treatment with diazomethane.

Alkaline hydrolysis of the acid acetate followed by acidification gave an amorphous material which was again purified by precipitation with water from an acetic acid solution to yield the dibromoaromatic dicarboxylic acid alcohol, m.p. 140-170° (decomp.) [Found: C,54.9; H,6.8. $C_{28}H_{40}O_5Br_2$ requires C,54.6; H,6.5%]. This alcohol formed neither a pure benzoate nor a 3,5-dinitrobenzoate.

The dibromoaromatic keto-acetate was converted into the dibromoaromatic dicarboxylic acid by oxidation with excess chromium trioxide in acetic acid, using the method described above.

Debromination of the Dibromoaromatic Acetate. - A solution of the dibromoaromatic acetate (400 mg.) in ether-ethanol (100 ml.) was refluxed for 4 hr. with zinc dust (4 g.). The product was worked up through ether in the usual manner and yielded 12-methyl-18-norergosta-8(14), 9(11),12,22-tetraen-3β-yl acetate, as a clear gum (290 mg.), $[\alpha]_D$ + 60° (c,1.6); it could not be crystallised.

Alkaline hydrolysis gave the corresponding alcohol as a gum, $[\alpha]_D$ + 77° (c,1.1) $\lambda_{max.}$ 2080 Å. (ϵ = 31,000) 2680 A. (ϵ=490). This alcohol was treated overnight at room temperature with 3,5-dinitrobenzoyl chloride in pyridine. Crystallisation of the product from chloroform-methanol gave the 3,5-dinitrobenzoate as yellow blades, m.p. 156-157°, $[\alpha]_D$ - 52° (c,2.5). [Found: C,71.4; H,7.2; N,4.6. $C_{35}H_{44}N_2O_6$ requires: C,71.4; H,7.5; N,4.8%]. The alcohol was regenerated by alkaline hydrolysis of this material or by filtration of a solution of the 3,5-dinitrobenzoate in benzene through a column of alkaline alumina.

The Action of Calcium Carbonate in Methanol on Tetrabromoergostenyl Acetate. - The tetrabromide (1.5 g.) was refluxed for 2 hr. with analar calcium carbonate (3.9 g.) in methanol (100 ml.). The hot solution was filtered free from solid which was washed with chloroform, and the washings concentrated. Needles (110 mg.) were precipitated from

the chloroform washings by the addition of cold methanol These needles were identical (m.p., mixed m.p. and ultra-violet absorption) with 22,23-dibromoergosta-7,9(11),14--trien-3β-yl acetate.

The warm methanolic filtrate on standing overnight deposited a white solid (600 mg.), which was collected, dissolved in light petroleum-benzene (1:1, 20 ml.) and chromatographed on alumina (20 g.). Elution with benzene-ether (3:1, 300 ml.) yielded a fraction (285 mg.), which crystallised from chloroform-methanol as white needles of 22,23-dibromo-7ξ,11ξ-dimethoxyergosta-8-en-3β-yl acetate, m.p. 177-179°, $[\alpha]_D$ + 17° (c,1.8) $\lambda_{max.}$ 2060 Å. (ϵ = 9750); infrared absorption at 1730 cm.$^{-1}$, 1250 cm.$^{-1}$ (O-acetyl), 1081 cm.$^{-1}$ (C - O - C). [Found: C,58.35; H,8.1; OMe,8.3. $C_{30}H_{46}O_2Br_2.(OMe)_2$ requires: C,58.2; H,7.9; OMe,9.4%].

The methanol mother liquors were evaporated to dryness to yield a dark yellow gum (800 mg.), which was taken up in light petroleum and adsorbed on a column of alumina (20 g.). Benzene eluted a fraction (150 mg.) which crystallised from acetone-methanol as prisms, m.p. 181-182°, $\lambda_{max.}$ 2450 Å. (ϵ = 16,200); identical (m.p. mixed m.p., and infrared absorption) with 22,23-dibromo-7ξ-methoxyergosta--7,9(11)-dien-3β-yl acetate.

Alkaline Hydrolysis of the Dibromomethoxydienyl Acetate. - The methoxydienyl acetate (157 mg.) was

refluxed for 1 hr. with 2% methanolic sodium hydroxide (15 ml.). The product was worked up through ether in the normal manner and crystallised from chloroform-methanol to give the dibromomethoxydiene alcohol as needles, m.p. 169-170°, $[\alpha]_D$ + 82° (c, 1.8), $\lambda_{max.}$ 2450 Å. (ϵ = 16,000); infrared absorption at 3450 $cm.^{-1}$ (alcoholic hydroxyl), 1068 $cm.^{-1}$ (C - O - C = C). [Found: C,59.6; H,7.9. $C_{29}H_{48}O_2Br_2$ requires: C,59.4; H,7.9%]. Acetylation regenerated the original acetate (m.p., mixed m.p., infrared absorption).

Debromination of the Dibromomethoxydienyl Acetate. - The dibromo-dienyl acetate (256 mg.) was refluxed for 2.5 hr. with activated zinc dust (5 g.) in ether-ethanol (1:2, 60 ml.). The product was worked up through ether in the normal manner and the resultant gum (165 mg.) crystallised from ether-methanol to give 7-methoxyergosta-7,9(11),22-trien-3β-yl acetate, as blades, m.p. 101-102°, $[\alpha]_D$ + 134° (c, 2.2), $\lambda_{max.}$ 2460 Å. (ϵ = 16,000). [Found: C,79.7; H,10.3. $C_{31}H_{48}O_2$ requires: C,79.4; H,10.3%].

Treatment of Tetrabromoergostenyl Acetate with Silver Acetate in Ether Followed by Chromatography of the Product on Alumina. - A suspension of the tetrabromide (850 mg.) and silver acetate (1.5 g.) in ether (100 ml.) was stirred for 1 hr. below -25°. The ethereal solution was filtered, dried (Na_2SO_4), and evaporated to give a yellow-white solid (700 mg.); $\lambda_{max.}$ 2040 Å. (ϵ = 6680), 2330 Å. (ϵ = 3160), 2400 A. (ϵ = 3450). The solid was dissolved in light petroleum benzene (20 ml., 2:1) and chromatographed on alumina (21 g.). Light petroleum benzene (600 ml., 1:1) eluted a fraction (200 mg.) which crystallised from chloroform-methanol to yield 11-oxo-22,23--dibromoergost-8-en-3β-yl acetate as blades, m.p.191-192°, $[\alpha]_D$ + 83° (c,1.7); $\lambda_{max.}$ 2520 Å. (ϵ = 9,330). [Found: C,58.7; H,7.55. Calculated for $C_{30}H_{46}O_3Br_2$: C,58.6; H,7.55%].

Further elution with benzene-ether (150 ml., 4:1) yielded a fraction (50 mg.) which crystallised from chloroform-methanol to give 7-oxo-22,23-dibromoergost-8-en-3β-yl acetate as blades, m.p. 234-235°, $[\alpha]_D$ - 27° (c,1.5), $\lambda_{max.}$ 2520 Å. (ϵ = 9080).

Both αβ-unsaturated ketones proved identical (m.p., mixed m.p. and infrared absorption) with authentic specimens.

The above reaction was repeated and fractional recrystallisation of the yellow white solid also gave the two αβ-unsaturated ketones in similar yields.

Treatment of Tetrabromoergostenyl Acetate with Silver Acetate in Glacial Acetic Acid. - The tetrabromide (3.9 g.) was shaken vigorously for 5 min. with silver acetate (4 g.) in glacial acetic acid (100 ml.) and the solution was filtered. A white flocculent solid (4 g.) was precipitated from the filtrate by the addition of water. This slightly acid solid was taken up in light petroleum (40 ml.) and adsorbed on a column of alumina (145 g.). Elution with light petroleum (1.5 l.), light petroleum-benzene (1 l., 9:1; 500 ml. 4:1) yielded no material. Light petroleum-benzene (500 ml.; 2:1) eluted 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate, m.p. 208-210°; identical (m.p., mixed m.p. and ultraviolet absorption) with an authentic specimen.

Light petroleum-benzene (1 l., 1:2) yielded a fraction (750 mg.) which was crystallised from chloroform-methanol to yield 3β,7β,11α-triacetoxy-22,23-dibromoergost-8-ene as large prisms, m.p. 204-206°, $[\alpha]_D$ + 19° (c,2.0) λ_{max} 2080 Å. (ϵ = 10,930); infrared absorption at 1730 $cm.^{-1}$ and 1250-1225 $cm.^{-1}$ (O-acetyl). [Found: C,56.9; H,7.7. $C_{34}H_{52}O_6Br_2$ requires: C,57.0; H,7.3%].

Light petroleum-benzene (500 ml., 1:6) and benzene (2.2 l.) eluted a fraction (900 mg.) crystallisation of which from acetone-water gave 3β,7α,11β-triacetoxy-22,23-dibromoergost-8(14)-ene as fine needles, m.p. 152-156°, $[\alpha]_D$ - 15.5° (c,1.0); $\lambda_{max.}$ 2090 A. (ϵ = 11,200); infrared absorption at 1739 cm.$^{-1}$ and 1250-1221 cm.$^{-1}$ (O-acetyl) [Found: C,57.2; H,7.7. $C_{34}H_{52}O_6Br_2$ requires: C,57.0; H,7.3%].

Elution with benzene-ether (900 ml., 6:1; 500 ml., 1:1) gave a yellow gum (700 mg.) which crystallised from acetone-water to give 3β,7β-diacetoxy-22,23-dibromoergost--9(11)-en-8β-ol as stout blades, m.p. 210-212°, $[\alpha]_D$ - 29° (c,1.8); $\lambda_{max.}$ 2030 Å. (ϵ = 7,700), infrared absorption at 3597 cm.$^{-1}$ (alcoholic hydroxyl), 1733 cm.$^{-1}$, 1724 cm.$^{-1}$ 1262 cm.$^{-1}$ and 1240 cm.$^{-1}$ (O-acetyl). [Found: C,57.1; H,7.7. $C_{32}H_{50}O_6Br_2$ requires: C,57.0; H,7.5%].

The Preparation of 3,7,11-Trioxoergosta-8,22-diene from 3β,7α,11α-Triacetoxy-22,23-dibromoergost-8-ene. - A solution of the dibromotriacetate (300 mg.) in ether-ethanol (100 ml.) was refluxed for 4 hr. with activated zinc dust (2 g.). Working up through ether in the usual manner and evaporation of the solvent gave the corresponding triacetate as a white solid (250 mg.).

Lithium aluminium hydride (200 mg.) was added to a solution of the triacetate (250 mg.) in dry ether (60 ml.)

and the resultant mixture was allowed to stand for 10 min. at room temperature before being boiled under reflux for 20 min. The excess of lithium aluminium hydride was destroyed by the addition of ice-water and the resultant mixture was extracted with ether (3 x 100 ml.). The ethereal solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water and dried (Na_2SO_4). Evaporation of the solvent gave the triol (180 mg.) as a white crystalline solid.

A slurry of chromium trioxide (500 mg.) in pyridine (5 ml.) was added to a suspension of the triol (180 mg.) in pyridine (2 ml.) and the mixture was kept at room temperature for 16 hr. with occasional agitation. The product was precipitated with water, extracted with ether, washed with 2% aqueous sodium hydroxide, dilute hydrochloric acid, saturated sodium bicarbonate solution, and dried (Na_2SO_4). Evaporation of the solution gave a yellow solid (150 mg.) which crystallised from methanol to yield 3,7,11-trioxoergosta-8,22-diene as fine needles, m.p.175-178°, $[\alpha]_D$ + 61° (c,1.3); $\lambda_{max.}$ 2670 Å.(ϵ = 7600); infrared absorption at 1718 $cm.^{-1}$ (6-ring carbonyl), 1675 $cm.^{-1}$ (ene-dione). [Found: C,76.6; H,9.4. $C_{28}H_{40}O_3 \cdot CH_3OH$ requires: C,76.3; H,9.7%].

3β,7β,11α-Triacetoxy-22,23-dibromoergost-8-ene

3β,7β,11α-Triacetoxyergosta-8,22-diene. - A solution of the dibromotriacetate (104 mg.)in ethanol (70 ml.) was refluxed for 3 hr with activated zinc dust (1 g.). The product was worked up through ether in the normal manner. The dried ethereal solution was concentrated and the product crystallised from ether-methanol to give 3β,7β,11α-triacetoxyergost-8,22-diene as prismatic needles, m.p. 123-125°, (softening at 110-114°), $[\alpha]_D$ + 5° (c,1.8), $\lambda_{max.}$ 2080 Å. (ϵ = 10,500); infrared absorption at 1733 cm.$^{-1}$ and 1250-1225 cm.$^{-1}$. [Found: C,72.35; H,9.55. $C_{34}H_{52}O_6 \cdot \frac{1}{2}$ (CH_3OH) requires: C,72.35; H,9.5%].

Hydrolysis of 3β,7β,11α-Triacetoxyergost-8,22-diene Followed by Oxidation. - Lithium aluminium hydride (180 mg.) was added to a solution of the triacetoxyergostadiene (200 mg.) in ether and the suspension was kept for 20 min. at room temperature and then boiled under reflux for 30 min. The product was worked up through ether in the normal manner to give a white solid (120 mg.), crystallisation of which from methanol gave the impure triol, m.p. 178-185°; $\lambda_{max.}$ 2090 Å (ϵ = 5,300), 2520 Å (ϵ = 1600).

A fraction of the white solid (80 mg.) in pyridine (0.8 ml.), was mixed intimately with a slurry of chromium trioxide (300 mg.) in pyridine (3 ml.), and the mixture

was kept at room temperature for 18 hr. The product was worked up through ether as before to give a yellow solid (60 mg.) which crystallised from acetone-methanol to yield 3,7,11-trioxoergosta-8,22-diene as yellow plates, m.p. 175-178°, $[\alpha]_D$ + 63.5° (c,1.4); $\lambda_{max.}$ 2680 A. (ϵ = 8,000); identical (mixed m.p., infrared absorption), with the trione derived from 3β,7α,11α-triacetoxyergosta-8,22-diene (p.122).

Reacetylation of 3β,7β,11α-Trihydroxyergosta-8,22-diene. - A solution of 3β,7β,11α-trihydroxyergosta-8,22-diene in pyridine (2 ml.) and acetic anhydride (2 ml.) was kept for 20 hr. at room temperature. The acetylated product was worked up through ether in the normal manner to yield a clear gum (480 mg.), which was dissolved in light petroleum (2 ml.) and adsorbed on a column of alumina (16 g.). Light petroleum-benzene mixtures eluted several fractions (400 mg.) having melting ranges 100-110° and 170-180°, $\lambda_{max.}$ 2030 Å. (ϵ = 6,000), 2540 Å (ϵ=1220); infrared absorption at 1733 $cm.^{-1}$, 1247 $cm.^{-1}$ (O-acetyl) and a weak band 1667 $cm.^{-1}$ (αβ-unsaturated ketone); there was no absorption corresponding to the presence of a hydroxyl group. Fractional recrystallisation of this material (50 mg.) yielded the original triacetoxyergosta-diene as blades, identical (m.p., mixed m.p., and infrared absorption) with an authentic specimen.

Treatment of 3β,7β,11α-Triacetoxy-22,23-dibromo-ergost-8-ene with Acetic Acid on Alumina. - A solution of the dibromo-triacetate (140 mg.) in benzene (2 ml.) and acetic acid (2 ml.) was adsorbed on a column of alumina (6 g.) and allowed to stand for 48 hr. Elution with benzene yielded a fraction (135 mg.) which recrystallised from methanol in needles, identical (m.p., mixed m.p., and infrared absorption) with starting material.

Hydrolysis of 3β,7β,11α-Triacetoxy-22,23-dibromoergost-8-ene. - (a) A solution of the dibromotriacetate (280 mg.) in methanolic sodium hydroxide (2%; 100 ml.) was boiled under reflux for 3 hr. The product was precipitated by the addition of water and worked up through ether in the normal manner. Evaporation of the ether yielded a white solid (220 mg.) $\lambda_{max.}$ 2060 Å. (ϵ = 8820), 2500 Å (ϵ = 883); infrared absorption at 3448-3279 cm.$^{-1}$ (alcoholic hydroxyl). This material could not be purified by recrystallisation. (b) A solution of the dibromotriacetate (80 mg.) in aqueous methanolic hydrochloric acid (5%; 50 ml.) was refluxed for 1 hr. The solution was concentrated and the product was precipitated by the addition of water. Working up through ether in the usual way and evaporation of the dried solvent yielded a yellowish solid (50 mg.), m.p. 182-188°, $\lambda_{max.}$ 2510 A. (ϵ = 7830). A solution of the yellow solid (40 mg.) in pyridine (1.5 ml.) and acetic

anhydride (1.5 ml.) was kept overnight at room temperature. The acetylated product, isolated by means of ether, was obtained as a yellow-white solid (46 mg.), crystallisation of which from chloroform-methanol gave 7-oxo-22,23-dibromoergost-8-en-3β-yl acetate as blades, m.p. 231-234°; $\lambda_{max.}$ 2530 A (ϵ = 8760), identical (m.p., mixed m.p. and infrared absorption) with an authentic specimen.

3β,7α,11β-Triacetoxy-22,23-dibromoergost-8(14)-ene.

3β,7α,11β-Triacetoxyergosta-8(14),22-diene. - A solution of the dibromotriacetate (770 mg.) in ethanol (100 ml.) was refluxed for 3 hr. with activated zinc dust. The product was worked up through ether in the normal manner. Evaporation of the ethereal solution and crystallisation of the residue from acetone-water gave 3β,7α,11β-triacetoxyergosta-8(14),22-diene as large plates, m.p. 90-92°, $[\alpha]_D$ - 17° (c, 2.1); $\lambda_{max.}$ 2100 Å.(ϵ = 9,500); infrared absorption at 1739 $cm.^{-1}$ and 1250-1225 $cm.^{-1}$ (O-acetyl). [Found: C,72.1; H,9.55. $C_{34}H_{52}O_6 . \frac{1}{2}H_2O$ requires: C,72.2; H,9.45%].

3β,7α,11β-Trihydroxyergosta-8(14),22-diene. - The triacetoxy-diene (140 mg.) in dry ether (75 ml.) was treated with lithium aluminium hydride (100 mg.) in the usual way. The product, isolated by means of ether,

crystallised from acetone-ether as light plates, m.p. 175-187°. Two further crystallisations of this material from acetone furnished 3β,7α,11β-trihydroxyergosta-8(14),22-diene as fine needles, m.p. 161-165°, $[\alpha]_D$ + 35° (c,0.7, pyridine); $\lambda_{max.}$ 2040 A. (ϵ = 11,400); infrared absorption at 3226 $cm.^{-1}$ (alcoholic hydroxyl). [Found: C,78.1; H,11.0. $C_{28}H_{46}O_3$ requires: C,78.1; H,10.8%].

3,7,11-Trioxoergosta-8,22-diene. - A slurry of chromium trioxide (90 mg.) in pyridine (1 ml.) was added to a solution of the triol(90 mg.) in pyridine (1 ml.) and the mixture was allowed to stand for 18 hr at room temperature. The product was worked up through ether in the normal manner to give a yellow frothy solid (70 mg.) $\lambda_{max.}$ 2680 Å (ϵ = 8,000), which was dissolved in benzene, adsorbed on a short column of alumina, and eluted with ether. Crystallisation of the product from methanol yielded 3,7,11-trioxoergosta-8,22-diene as felted needles, m.p. 176-178°, $[\alpha]_D$ + 65° (c,1.0); $\lambda_{max.}$ 2690 Å. (ϵ=8,000); identical (m.p., mixed m.p. and infrared absorption) with an authentic specimen.

Treatment of 3β,7α,11β-Triacetoxy-22,23-dibromoergost-8(14)-ene with Chromium Trioxide in Pyridine. - A solution of the dibromotriacetate (85 mg.) in pyridine (0.85 ml.) was mixed intimately with a slurry of chromium trioxide (100 mg.) in pyridine (100 ml.) and the reaction mixture was left for

20 hr. at room temperature. Working up through ether in the normal way gave a frothy gum (72 mg.) which crystallised from methanol to give unchanged dibromotriacetate, as needles, m.p. 148-152°, identical (m.p., mixed m.p., and infrared absorption), with an authentic specimen.

3β,7α-Diacetoxy-14β-ergosta-8,22-dien-11-one. - A solution of 3β,7α,11β-trihydroxyergosta-8(14),22-dione (150 mg.) in pyridine (11ml.), and acetic anhydride (11 ml.) was kept for 12 hr. at room temperature. The product was isolated in the usual way to give 3β,7α-diacetoxyergost--8(14),22-dien-11β-ol as a white crystalline solid (160 mg.) m.p. 151-161°; $\lambda_{max.}$ 2060 A (ϵ = 8830), inflexion at 2400-2700 Å. (ϵ = 1,000); infrared absorption at 3425 cm.$^{-1}$ (hydroxyl), 1733 cm.$^{-1}$, 1706 cm.$^{-1}$, 1255 cm.$^{-1}$ and 1248 cm.$^{-1}$ (O-acetyl).

A slurry of chromium trioxide (290 mg.) in pyridine (2.9 ml.) was added to a solution of the triol-diacetate (150 mg.) in pyridine (1.5 ml.) and the mixture was left for 24 hr. at room temperature. The product was precipitated by the addition of water and extracted with ether. The extract was washed with sodium hydroxide solution (2%), dilute hydrochloric acid, saturated sodium bicarbonate solution, and dried (Na_2SO_4). The solution was evaporated to dryness under reduced pressure at room temperature to give a gum (130 mg.) which crystallised from cold methanol

as stout blades, m.p. 143-163°. $\lambda_{max.}$ 2120 Å. (ϵ = 4,860), 2430 Å. (ϵ = 6,120), 2960 Å. (ϵ = 4,100). A solution of this material (110 mg.) in light petroleum-benzene (3:1; 8 ml.) was chromatographed on a column of alumina (6 g.).

Elution with light petroleum-benzene (2:1; 100 ml.) yielded a fraction which crystallised from acetone-methanol to yield 11-oxoergosta-8,14,22-trien-3β-yl acetate as flat yellow blades (7 mg.), m.p. 135-141°, $[\alpha]_D$ + 5.4° (c,0.7); $\lambda_{max.}$ 2110 Å. (ϵ = 7820) 2960 Å. (ϵ = 7920). Shortage of material prevented further purification and characterisation of this compound.

A further fraction (14 mg.) was eluted with pure ether and crystallised from methanol to give 3β,7α-diacetoxy-14β-ergosta-8,22-dien-11-one as needles, m.p. 186-188°, $[\alpha]_D$ + 77° (c,0.6). Recrystallisation from methanol gave needles, m.p. 186-188°, $[\alpha]_D$ + 77.5°(c,0.9); $\lambda_{max.}$ 2440 Å. (ϵ = 8020); infrared absorption at 1739 cm.$^{-1}$ and 1239 cm.$^{-1}$ (acetate), 1677 cm.$^{-1}$ (αβ-unsaturated ketone). [Found: C,74.7; H,8.9. $C_{32}H_{48}O_5$ requires: C,74.95; H,9.4%].

These were the only two crystalline fractions obtained although careful elution removed all the material (102 mg.) which was adsorbed on the column.

The Behaviour of 3β,7α,11β-Triacetoxy-22,23-dibromo-ergost-8(14)-one under Dehydration Conditions. - A solution

of the dibromotriacetate (29 mg.) in acetic anhydride (10 ml.) was refluxed for 1½ hr. and left overnight. The product was precipitated by the addition of water and worked up through ether in the usual manner. Crystallisation from ether-methanol yielded 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate in clusters of small needles, m.p. 197-199°: $\lambda_{max.}$ 2270 Å. (ϵ = 11,730), 2340 Å. (ϵ = 11,030), 2680 Å. (ϵ = 10,090).

Hydrolysis of 3β,7α,11β-Triacetoxy-22,23-dibromo-ergost-8(14)-one. - (a) A solution of the dibromotriacetate (140 mg.) in aqueous methanolic hydrochloric acid (5%; 21 ml.) was refluxed for 1 hr., allowed to cool and poured into water. The product was isolated using ether as a greenish-white solid (103 mg.), $\lambda_{max.}$ 2280 Å. (ϵ = 8830), 2360 Å. (ϵ = 8280), 2630 Å. (ϵ = 8130), 3150 Å. (ϵ = 1600).

A solution of this material in pyridine (2 ml.) and acetic anhydride (2 ml.) was allowed to stand at room temperature overnight. The crystalline product which precipitated was removed by filtration, washed with dilute hydrochloric acid and water and recrystallised from acetone to give 22,23-dibromoergosta-7,9(11),14-trien-3β-yl acetate as needles (93 mg.), m.p. 205-206°, $\lambda_{max.}$ 2280 Å. (ϵ = 11,100), 2350 Å. (ϵ = 10,200), 2690 Å.

(ϵ = 9360); the m.p. was undepressed on admixture with an authentic specimen.

(b) A solution of the dibromotriacetate in aqueous methanolic sodium hydroxide (2%) was boiled under reflux for 1 hr. The solution was concentrated and the product, precipitated by the addition of water; was extracted with ether and isolated in the usual manner as a white solid, $\lambda_{max.}$ 2060 Å. (ϵ=9730), inflexion 2500 Å. (ϵ = 1,000). Crystallisation from acetone-methanol gave an impure white material, m.p. 203-206°, $\lambda_{max.}$ 2120 Å. (ϵ = 9570); infrared absorption at 3533 cm.$^{-1}$ (alcoholic hydroxyl), 1706 cm.$^{-1}$ and 1259 cm.$^{-1}$ (O-acetyl).

Treatment of 3β,7α,11β-Triacetoxy-22,23-dibromoergost-8(14)-ene with Acetic Acid on Alumina. - Glacial acetic acid (2 ml.) was added to a solution of the dibromo-triacetate (150 mg.) in light petroleum-benzene (8:1; 6 ml.) and the mixture was adsorbed on a column of alumina (8 g.) and allowed to stand for 3 days. Elution with benzene (100 ml.) yielded a fraction (150 mg.) which crystallised from acetone-water as fine needles, m.p. 148-152°, identical (m.p., mixed m.p. and infrared absorption) with the starting material.

3β,7β-Diacetoxy-22,23-dibromoergost-9(11)-en-8β-ol.

3β,7β-Diacetoxyergosta-9(11),22-dien-8β-ol. - A solution of the dibromotriol-diacetate (80 mg.) in ether-ethanol (40 ml.) was refluxed for 3 hr. with activated zinc dust (3 g.). The solution was filtered and the product, precipitated with water, was extracted with ether. The extract was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water. The dried solution was evaporated and the residue crystallised from acetone-water as long needles, m.p. 153-157°, $[\alpha]_D$ - 28° (c,1.2). Further recrystallisation from acetone-water yielded 3β,7β-diacetoxyergosta-9(11),22-dien-3β-ol as blades, m.p. 161-163°, $[\alpha]_D$ - 41° (c,0.9); $\lambda_{max.}$ 2040 Å. (ϵ = 4500); infrared absorption at 3636 cm.$^{-1}$,(hydroxyl), 1733 cm.$^{-1}$, 1718 cm.$^{-1}$, 1261 cm.$^{-1}$, 1239 cm.$^{-1}$(O-acetyl). [Found: C,74.70; H,10.0. $C_{32}H_{50}O_5$ requires: C,74.65; H,9.8%].

Attempted Acetylation of 3β,7β-Diacetoxy-22,23-dibromoergost-9(11)-en-8β-ol. - A solution of the dibromotriol-diacetate (40 mg.) in acetic anhydride (2 ml.) and pyridine (2 ml.) was maintained for 1 hr. at 100°. The acetylated product was worked up through ether in the usual way and crystallised from acetone-water to give unchanged starting material, (m.p., mixed m.p. and

infrared absorption).

Acid Hydrolysis of 3β,7β-Diacetoxy-22,23-dibromo-ergost-9(11)-en-8β-ol. - A solution of the dibromotriol-diacetate (40 mg.) in aqueous methanolic hydrochloric acid (5%, 21 ml.) was refluxed for 1 hr. The solution was concentrated, the product was precipitated with water, and worked up through ether in the normal manner. Crystallisation from ether-methanol yielded an amorphous solid, $\lambda_{max.}$ 2550 Å. (ϵ = 7,200) and a second crop of micro-crystalline needles, m.p. 191-206°, $\lambda_{max.}$ 2520 Å. (ϵ = 9,000).

The needles (11 mg.) were acetylated in acetic anhydride-pyridine at 100° for 2 hr. and crystallised from chloroform-methanol to yield 7-oxo-22,23-dibromoergost-8-en-3β-yl acetate as plates, m.p. 232-233°, $\lambda_{max.}$ 2530 Å. (ϵ = 8,000); infrared absorption at 1748 cm.$^{-1}$ and 1237 cm.$^{-1}$ (O-acetyl), 1666 cm.$^{-1}$ and 1592 cm.$^{-1}$ (unconjugated carbonyl); identical (m.p. mixed m.p. and infrared absorption) with an authentic specimen.

Basic Hydrolysis of 3β,7β-Diacetoxy-22,23-dibromo-ergost-9(11)-en-8β-ol. - The dibromotriol-diacetate (73 mg.) was refluxed for 1 hr. with aqueous methanolic sodium hydroxide (2%). The product was worked up through ether in the usual way, and crystallised from

acetone-methanol to give 3β,7β,8β-trihydroxy-22,23--dibromoergost-9(11)-ene as plates, m.p. 201-204°, $[\alpha]_D$ - 51° (c,1.9, pyridine); $\lambda_{max.}$ 2030 Å. (ϵ = 5,850); infrared absorption at 3300 cm.$^{-1}$ (hydroxyl). [Found: C,56.2; H,8.4. $C_{28}H_{46}O_3Br_2.CH_3OH$ requires: C,56.0; H,8.1%].

Reacetylation of the triol (18 mg.) in acetic anhydride and pyridine at room temperature for 16 hr. regenerated the original dibromotriol-diacetate (m.p., mixed m.p. and infrared absorption).

The Attempted Dehydration of 3β,7β-Diacetoxy-22,23--dibromoergost-9(11)-en-8β-ol. - (a) Thionyl chloride (0.1 ml.) was added to a solution of the dibromotriol-diacetate (40 mg.) in pyridine (1 ml.) and the solution was allowed to stand for 2 hr. at room temperature. The dark brown solution was poured into water, extracted with ether and worked up in the usual way. Evaporation of the dried (Na_2SO_4) solution yielded a clear gum, which was triturated with methanol to give a white crystalline solid (23 mg.); m.p. 204-208°; $\lambda_{max.}$ 2050 Å. (ϵ = 4620); 2420 Å. (ϵ = 1730).

(b) Phosphorus oxychloride (6 ml.) was added to a solution of the dibromotriol-diacetate (210 mg.) in pyridine (20 ml.) and the resulting solution was maintained

for 2½ hr. at 100°. After the careful addition of water the product was worked up through ether in the normal manner. Evaporation of the ether gave a yellow gum (170 mg.); $\lambda_{max.}$ 2060 Å. (ϵ = 4500), 2220 Å. (ϵ = 3,000), 2460 Å. (ϵ = 1800), which could not be crystallised.

(c) The dibromotriol-diacetate (40 mg.) in pyridine (1 ml.) and acetic anhydride (20 ml.) was boiled under reflux for 40 min. The solution was concentrated, diluted with water and, after 1 hr., the product was extracted with ether. Evaporation of the ether yielded a clear gum (20 mg.) which crystallised from acetone-water as fine blades, m.p. 211-212°; identical (m.p., mixed m.p.) with starting material.

(d) Alkaline hydrolysis of the dibromotriol-diacetate (80 mg.) yielded 3β,7β,8β-trihydroxy-22,23-dibromo-ergost-9(11)-ene as a white solid (70 mg.). A solution of this material in pyridine was treated with phosphorus oxychloride (2.2 ml.) and the resulting yellow solution was heated for 1 hr. at 100° and then allowed to stand overnight. Water was added carefully and the product was worked up through ether in the usual way. Evaporation of the ether yielded a yellow solid (28 mg.) $\lambda_{max.}$ 2320 A. (ϵ = 11,750) with inflexion at 2800-2900 Å.

(ϵ = 4,450); cf. ergosta-6,8(14),9(11),22-tetraen-3β-yl acetate,[45a] $\lambda_{max.}$ 2310 Å. (ϵ = 18,150), 2800 Å. (ϵ = 6030).

Treatment of 3β,7β-Diacetoxy-22,23-dibromoergost--9(11)-en-8β-ol with the Chromium Trioxide-Pyridine Complex. - A slurry of chromium trioxide (80 mg.) in pyridine (0.8 ml.) was added to a solution of the dibromotriol-diacetate (53 mg.) in pyridine (0.5 ml.) and the reaction mixture was allowed to stand for 16 hr. at room temperature. The product was precipitated by the addition of water and worked up through ether in the usual manner. Evaporation of the ether yielded a white solid (48 mg.), which crystallised from methanol as blades, m.p. 211-212°, identical (m.p., mixed m.p. and infrared absorption) with starting material.

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