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CHEMISTRY OF 11-OXYGENATED ERGOSTEROL DERIVATIVES.

The author wishes to express his appreciation for the guidance and encouragement given during these investigations by Professor F.S.Spring, F.R.S. He is also deeply indebted to Dr. G.T.Newbold for invaluable advice and assistance.

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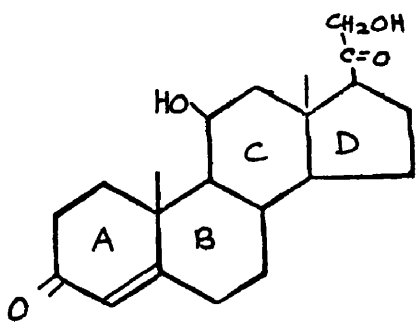
* Experimental corresponding to the section mentioned in Theoretical (contents).

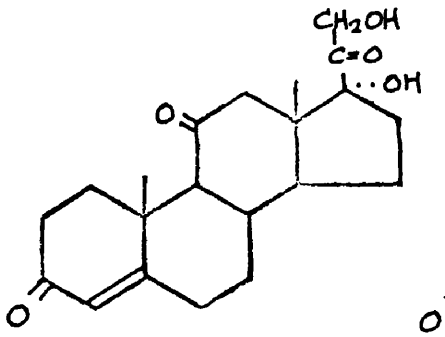
HISTORICAL

HISTORICAL

The chemistry of ergosterol (1, 2) investigated extensively during the 1930's was further extended in consequence of its use as a starting material for the synthesis of adrenocortical hormones, particularly those, e.g. corticosterone (I), cortisone (II), and cortisol (III) having a substituent oxygen atom at $C_{(11)}$,(71)



(I)



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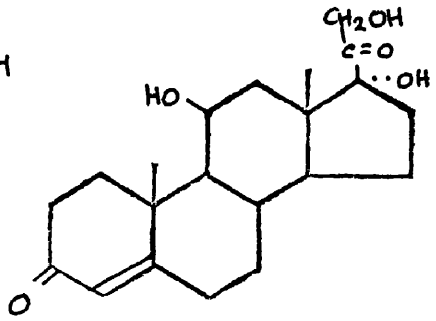
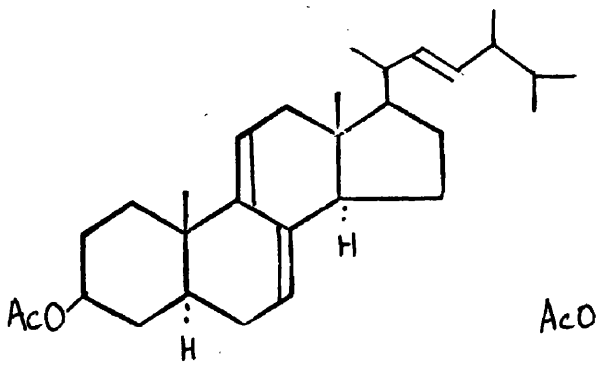


(III)

Because they offer a route for the introduction of oxygen into ring C and the side-chain double bond allows a degradation to a pregnane derivative, ergosta-7:9(11):22--trien-3β-yl acetate (IV) and ergosta-5:7:9(11):22-tetraen--3β-yl acetate (V) became important intermediates.



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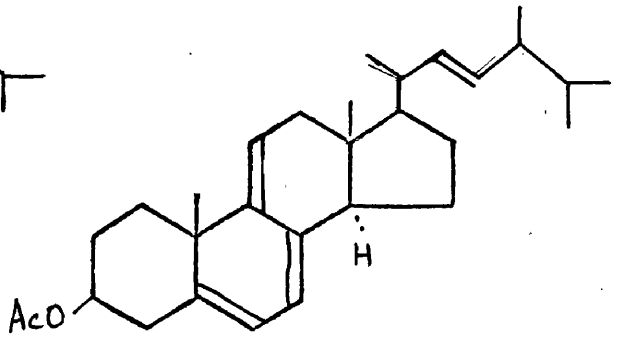
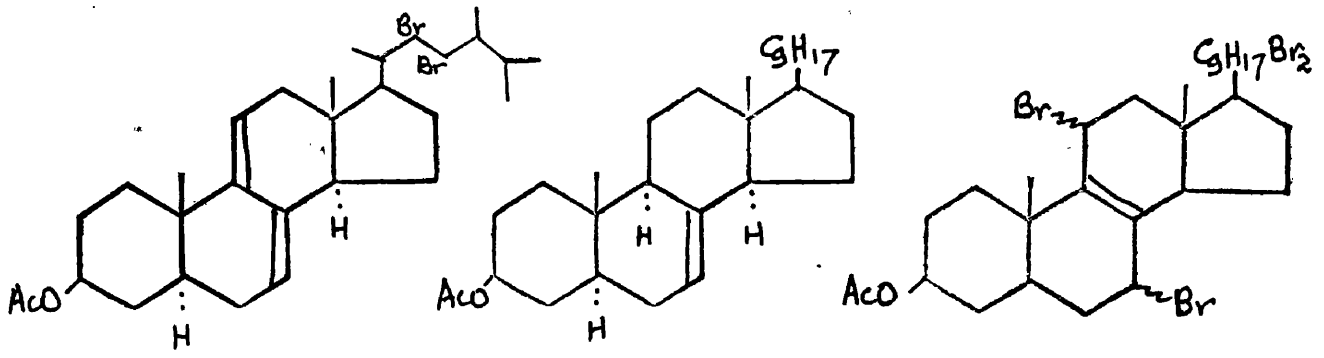


(V)

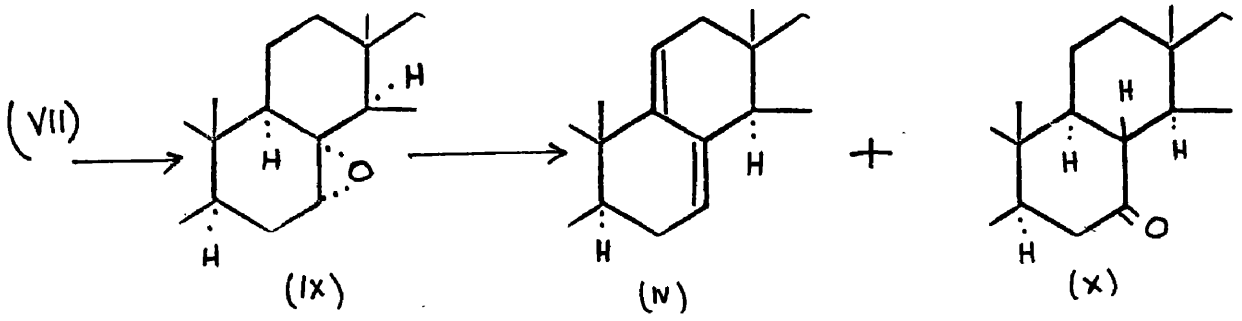
Ergosterol.

Recently an improved method for the preparation of ergosteryl-D acetate (IV) has been described by Anderson, Budziarek, Newbold, Stevenson and Spring (3). The 7:9(11)--diene (IV) is thereby obtained in good yield and of superior purity to that from the original mercuric acetate process (4,5). In addition 22:23-dibromoergosta-7:9(11)--dien-3β-yl acetate (VI) became available in which the side chain double bond is protected. Treatment of 5--dihydroergosteryl acetate (VII) with bromine under controlled conditions gives a tetrabromergostenyl acetate; partial debromination with sodium iodide affords 22:23--dibromoergosta-7:9(11)-dien-3β-yl acetate (VI) the structure of which is established by debromination with zinc in ether-ethanol to ergosteryl-D acetate (IV).



It has been suggested (6) that this tetrabromergostenyl acetate may be formulated as 7:11:22:23-tetrabromoergost--8-en-3β-yl acetate (VIII).

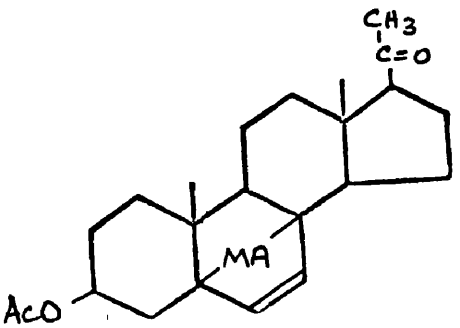
Recently, Barton and Alt (7) have shown that the oxidation of 5-dihydroergosteryl acetate (VII) with monoperphthalic acid gives 7α:8α-epoxyergost-22-en-3β-yl acetate (IX). Controlled acid catalysed dehydration gave, as the main product, a mixture of dienes from which



ergosteryl-D acetate (IV) was separated on treatment with maleic anhydride. The minor product was identified as 7-oxoergost-22-en-3β-yl acetate (X).

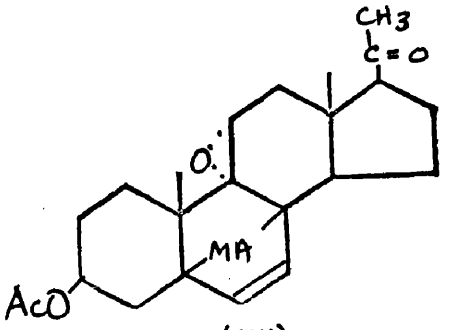
Dehydroergosterol and its Derivatives.

In 1948 Bergmann and Stevens (5), appreciating the importance of ergosterol in the synthesis of adrenocortical hormones, were successful in degrading the side chain to CH_3CO - (XI) by protection of the nuclear double bonds by maleic anhydride. Attempts at the preparation of 11-oxygenated derivatives were disappointing. The 9α:11α--epoxide (XII) was prepared but pyrolysis to regenerate the 5:7-diene system led to aromatisation of ring-B.



(XI)

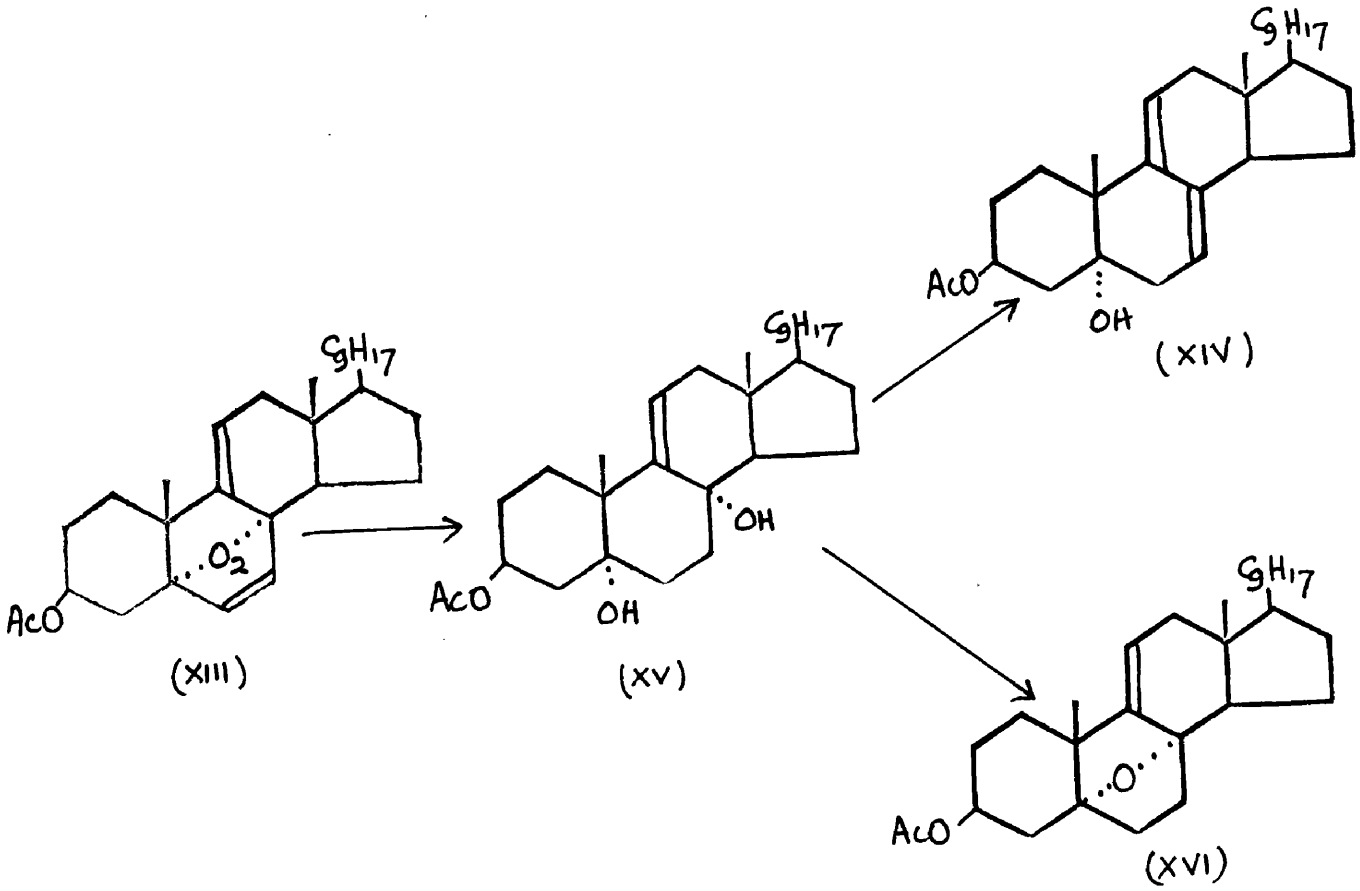
MA= CH·CO
CH·CO
O



(XII)

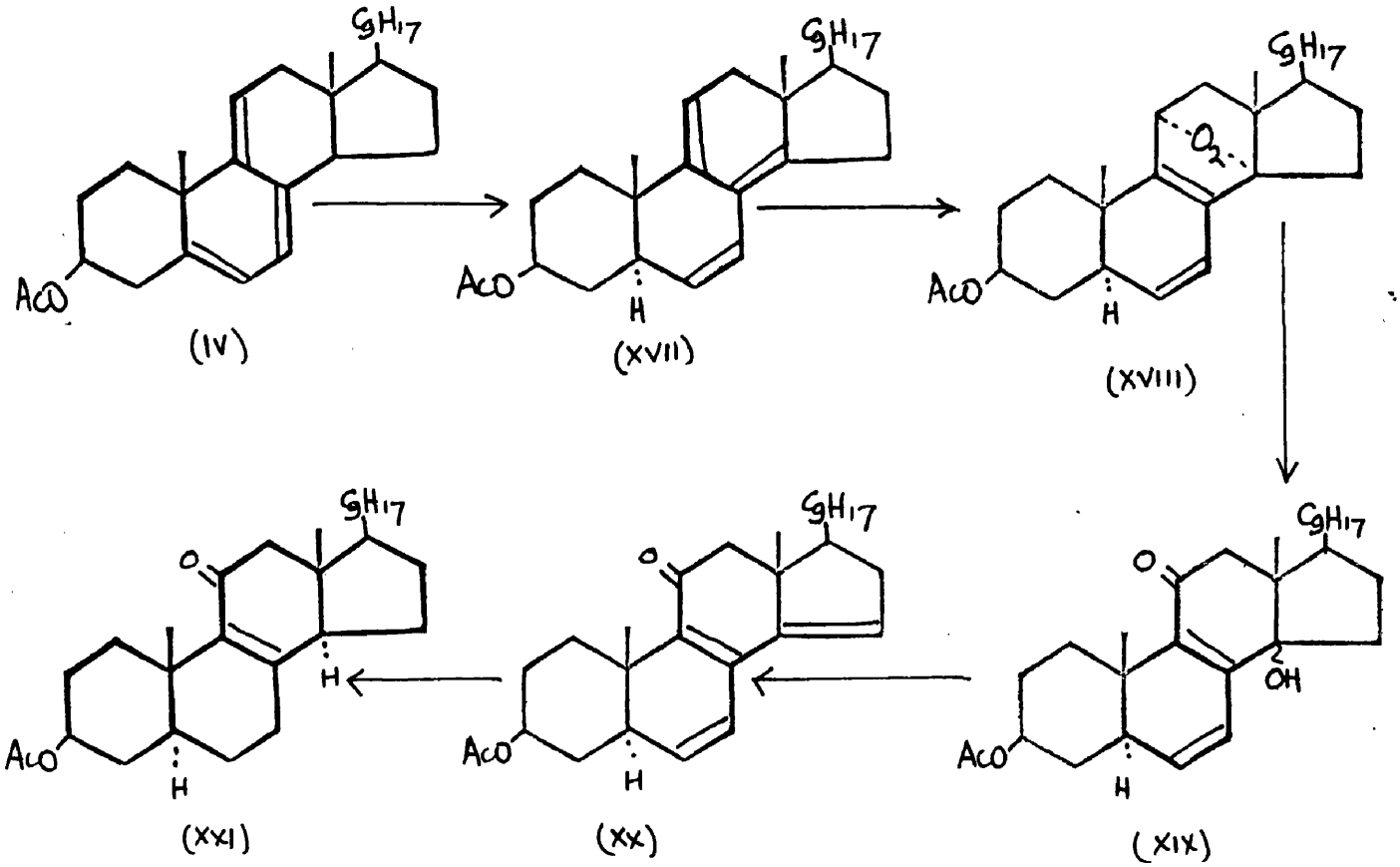
E.R.H. Jones and coworkers (8) in their approach to the problem aimed at preserving - during other structural alterations - a potential 4:5-double bond in the form of a 5α-hydroxyl group. Dehydroergosterol epidioxide acetate (XIII), obtained from ergosteryl acetate by photoperoxidation, was hydrogenated over Raney nickel to give the 5α-hydroxy--7:9-diene (XIV) which is also formed by dehydration of

an intermediate 8α-ol (XV) with mineral acid. The tertiary alcohol (XV), on treatment with acetic acid, gives the transannular 5:8-epoxide (XVI). In both the epidioxide (XIII) and the 5:8-epoxide (XVI) the



9(11)-double bond is shielded from attack on the rear (α) face, and consequently attempts to prepare 11-oxygenated steroids were disappointing. Attention was therefore directed to the oxidation of the 5α-hydroxy-7:9(11)-diene (XIV) and this route is discussed later.

Laubach, Schrieber, Agnello, Lightfoot and Brunings (9) in a preliminary note, describe the successful conversion of C-ring unsaturated steroids to 11-oxoergosta--8:22-dien-3β-yl acetate (XXI) which has been converted to cortisone.



Isomerisation of dehydroergosteryl acetate (V) in liquid sulphur dioxide gave in high yield ergosta-6:8(14):9(11):22--tetraen-3β-yl acetate (XVII) which on photoperoxidation afforded 11:14-epidioxyergosta-6:8:22-trien-3β-yl acetate

(XVIII). Mild base catalysed rearrangement of (XVIII) led to 3β-acetoxy-11-oxoergosta-6:8:22-trien-14ξ-ol (XIX) which, when treated with acid yielded 11-oxoergosta-6:8:14:22--tetraen-3β-yl acetate (XX). Catalytic hydrogenation gave 11-oxoergosta-8:22-dien-3β-yl acetate (XXI) via the intermediate 8:14-diene.

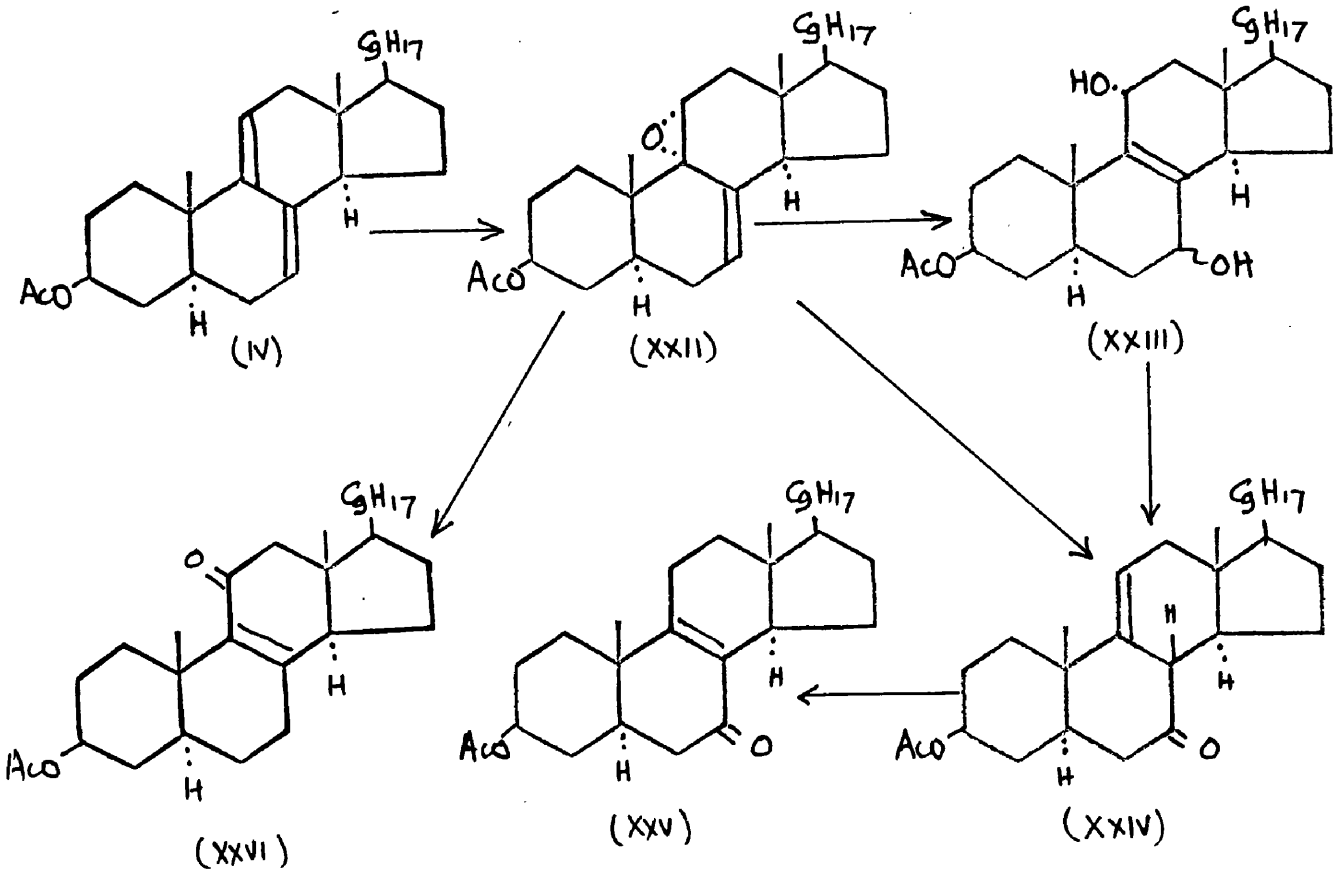
A novel approach by Rees and Shoppee (10) consisted in attempts to induce anionotropic rearrangement of a 6-substituted steroid 7:9(11)-diene [cf. Barton, Robinson (11)] to an 11-substituted 6:8-diene. 3:5-cycloErgosta--7:9(11):22-trien-6β-ol (i-dehydroergosterol) was prepared, but attempts to rearrange it to 3:5-cycloergosta--6:8:22-trien-11ξ-ol were unsuccessful.

The Formation of 11-Oxygenated Steroids from 7:9(11)-Dienes.

The first successful introduction of 11-oxygen functions in the steroid nucleus, from ergosterol, was outlined by Tishler (12) in May 1951. This announcement led to a series of preliminary communications describing the conversion of 7:9(11)-dienes into 11-oxygenated steroids (3, 14, 15, 16).

The Peraromatic Acid Route.

9α:11α-Epoxyergosta-7:22-dien-3β-yl Acetate. - Ergosteryl-D acetate (IV) with one molecular proportion of perbenzoic acid gives 9α:11α-epoxyergosta-7:22-dien-3β--yl acetate (XXII) (12, 17). Ambiguity arose as to the location of the epoxide grouping since treatment with dilute sulphuric acid gave the 8(9)-en-7ξ-11α-diol (XXIII), the 9(11)-en-7-one (XXIV) and the 8-en-7-one (XXV) depending on the conditions (17-20). The structure of the epoxide was established by its rearrangement with boron

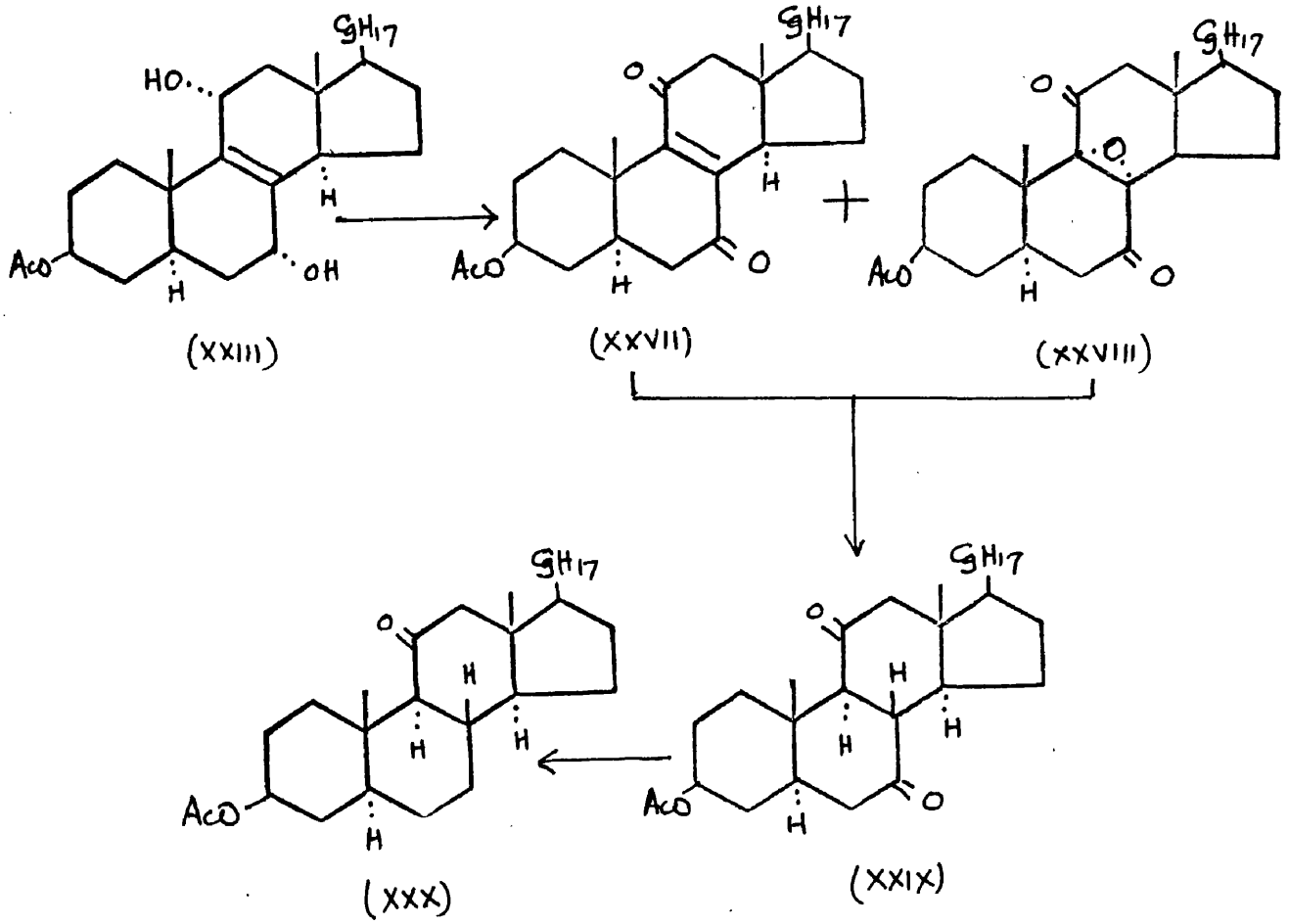


trifluoride-etherate (17, 18) or ferric chloride (19) in benzene to the 8-en-11-one (XXVI) which can be reduced to the saturated 11-ketone (XXX) (20) by lithium in liquid ammonia [cf. Birch (21)]; when ethanol is present the reaction proceeds to the 11α-ol (22).

Oxidation of 22:23-dibromoergosta-7:9(11)-dien-3β-yl acetate (VI) and 5α-hydroxyergosta-7:9(11):22-trien-3β--yl acetate (XIV) give the corresponding 9:11-epoxides [(23) and (24) respectively].

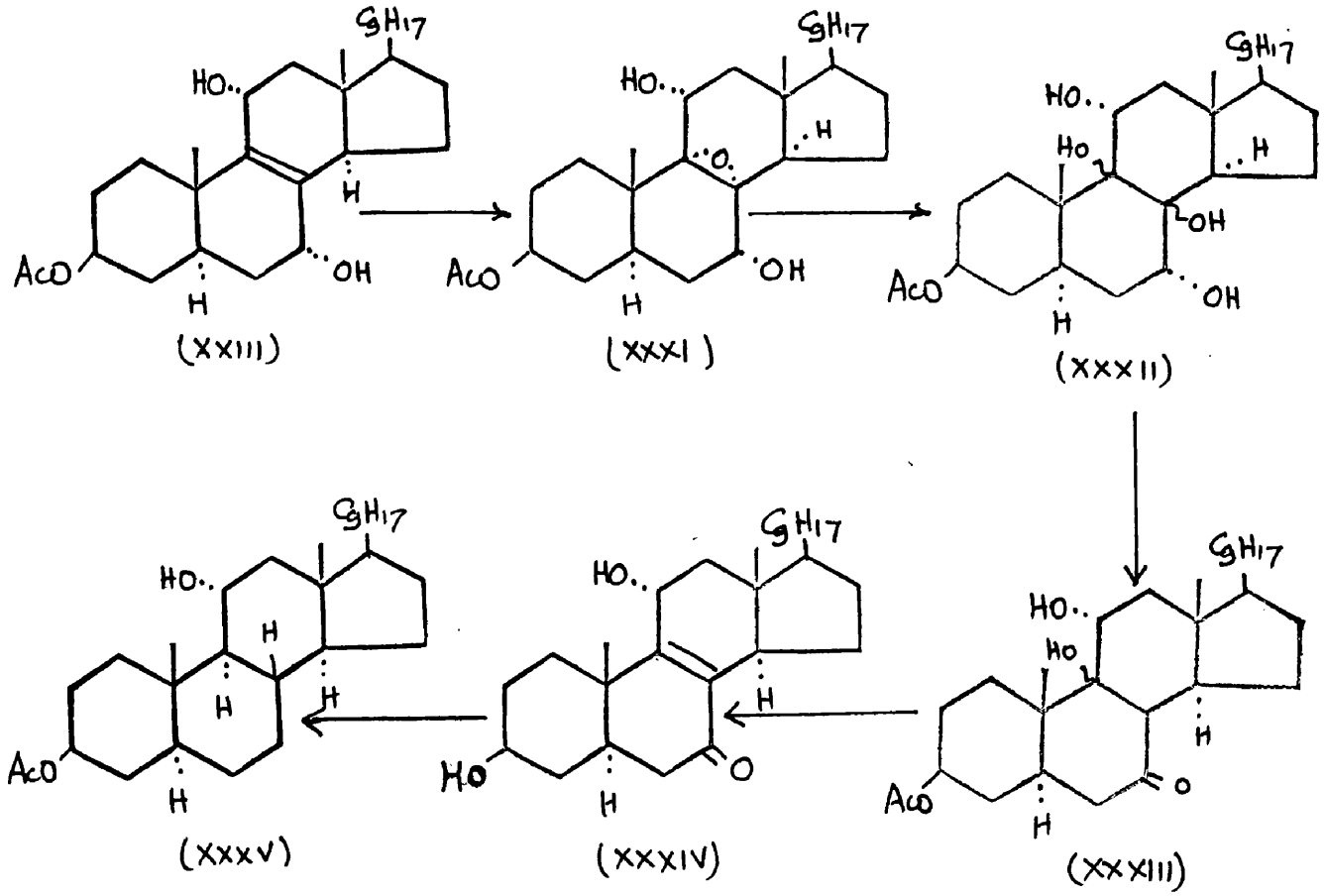
7α:11α-Dihydroxyergosta-8:22-dien-3β-yl Acetate. - Tishler's method (12, 25) consisted in the hydrolytic rearrangement of the epoxide (XXII) to 7α:11α-dihydroxy-ergosta-8:22-dien-3β-yl acetate (XXIII). The α-orientation for the 7-hydroxyl group has been suggested by Fieser (26) from molecular rotation studies and has been established by Henbest and Wagland (27).

Oxidation of the ene-diol (XXIII) with chromic acid gives 7:11-dioxoergosta-8:22-dien-3β-yl acetate (XXVII) which on treatment with zinc and acetic acid yields 7:11-dioxoergost-22-en-3β-yl acetate (XXIX). Wolff-Kishner reduction of the dione (XXIX) gave 11-oxoergost-22-en-3β--yl acetate (XXX).

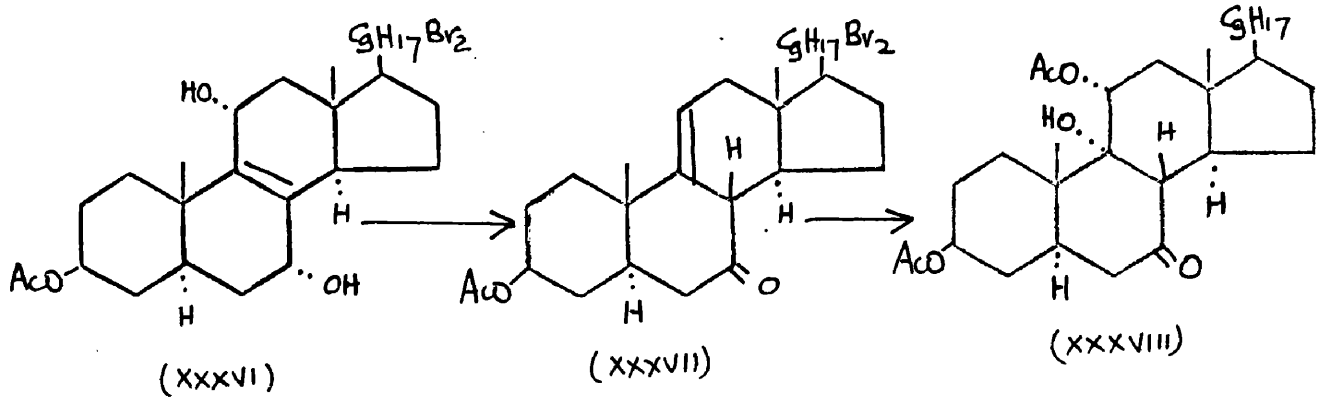


Heusser, Jeger et al. (17) described the same route (XXIII) ⟶ (XXX). Under their conditions, 8α:9α-epoxy-7:11-dioxoergost-22-en-3β-yl acetate (XXVIII) was isolated as well as (XXVII) from the chromic acid oxidation. Both (XXVII) and (XXVIII) give the ane-dione (XXIX) on reduction with zinc in acetic acid. In a later communication, Heusser, Anliker, Eichenberger and

Jeger (19) describe variations in the above method. Treatment of 7α:11α-dihydroxyergosta-8:22-dien-3β-yl acetate (XXIII) with monoperphthalic acid gives the 8α:9α-epoxide (XXXI) which was converted into (XXXIII) either directly or through the intermediate tetrol (XXXII). Treatment of (XXXIII) with alkali yielded 3β:11α-dihydroxy-ergosta-8:22-dien-7-one (XXXIV) which was converted into (XXXV) by selective reduction of the 8(9)-double bond followed by Wolff-Kishner reduction.

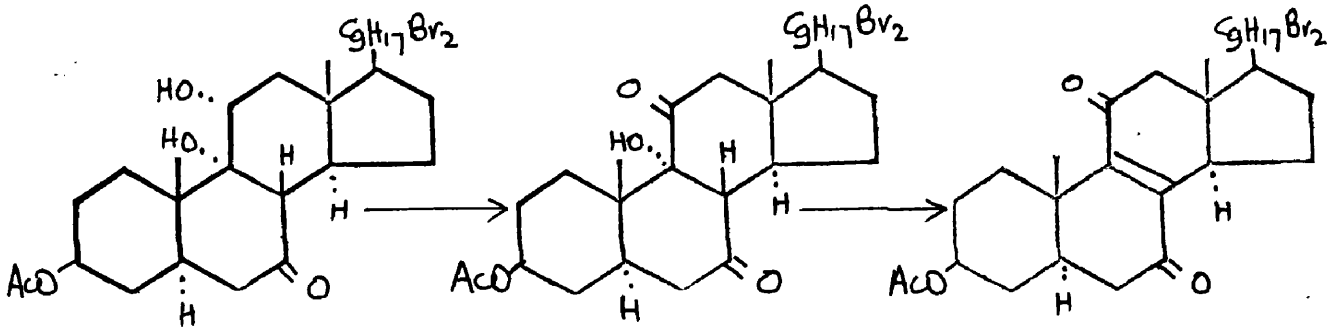


The orientation of the hydroxyl group at C(8) in (XXXIII) and related compounds has been shown to have the α-configuration by Maclean and Spring (28). Short treatment of 22:23-dibromo-7α:11α-dihydroxyergost-8-en--3β-yl acetate (XXXVI) with boron trifluoride etherate gives a mixture of 22:23-dibromo-7-oxoergost-9(11)-en--3β-yl acetate (XXXVII) and 22:23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate. Oxidation of the former with



osmium tetroxide followed by acetylation and debromination gives (XXXVIII) identical with the product obtained by acetylation of (XXXIII). It follows that the hydroxyl groups at C(8) and C(8) in the tetrol (XXXII) are β and α respectively. Budziarek and Spring (29) have described similar experiments starting from 22:23-dibromo-7α:11α--dihydroxyergost-8-en-3β-yl acetate (XXXVI).

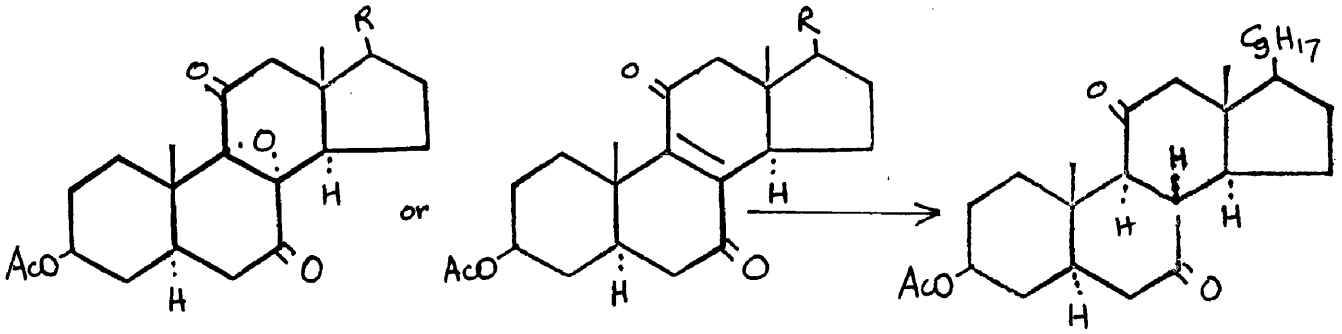
7:11-Dioxo-8α-ergost-22-en-3β-yl Acetate. - Budziarek and Spring (30) oxidised 22:23-dibromo-9α:11α-dihydroxy-7-oxo-ergostan-3β-yl acetate (XXXIX) with chromium trioxide to the corresponding 9α-hydroxy-7:11-dione (XL); vigorous treatment of which with alkali, followed by acetylation, yielded the ene-dione (XLI). These authors made the



(XXXIX) (XL) (XLI)

interesting observation that whereas treatment of (XXVII) or (XXVIII) or their dibrom analogoues with zinc in acetic acid gives 7:11-dioxoergost-22-en-3β-yl acetate (XXIX) with zinc in ether-methanol the 8α-isomer, 7:11-dioxo--8α-ergost-22-en-3β-yl acetate (XLII), was obtained. It is readily isomerised to (XXIX) on heating with acetic acid.

This cis addition of hydrogen to the double bond was later confirmed by Barton (31) who had shown that



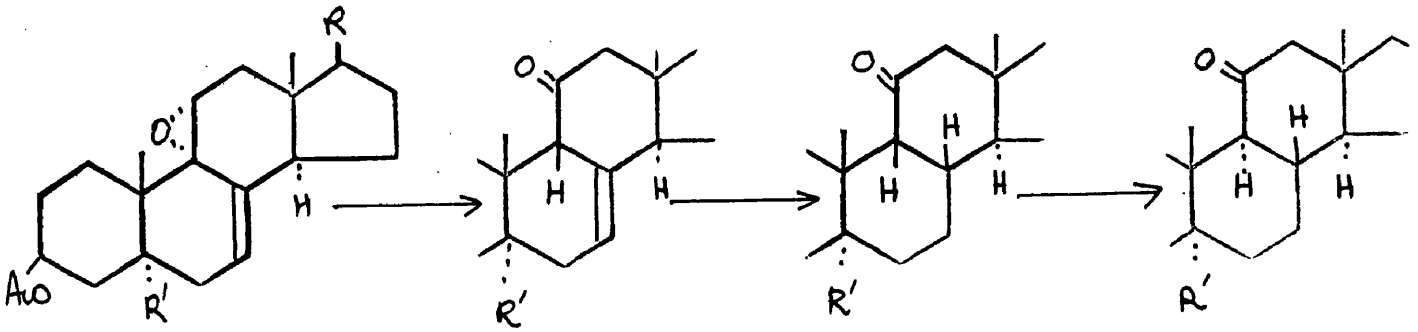
$R = C_9H_{17}$; $C_9H_{17}Br_2$.

(XLII)

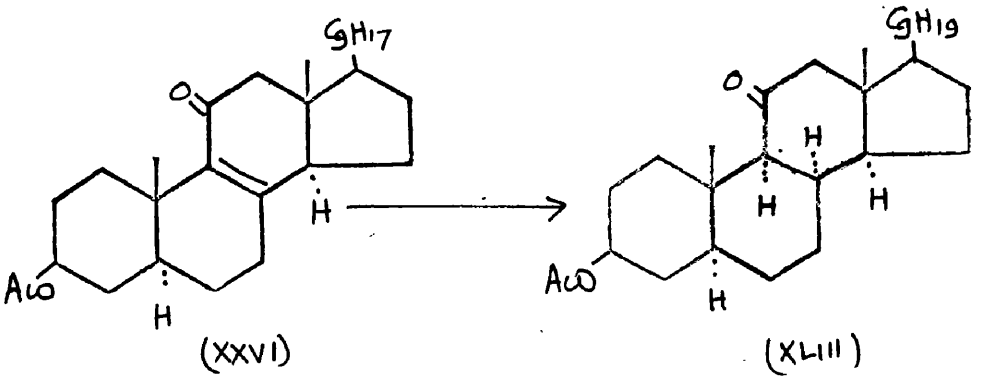
selenium dioxide oxidation of ane-1:4-diones to ene-1:4--diones requires a cis-relation for the eliminated hydrogen atoms. The 8α-isomeric 7:11-dione (XLII) gave the ene--dione (XXVII) while 7:11-dioxoergost-22-en-3β-yl acetate (XXIX) was recovered unchanged from treatment with selenium dioxide.

11-Oxo-9β-ergosta-7:22-dien-3β-yl Acetate and Related Compounds. - E.R.H.Jones et al. (32) have described the controlled rearrangement of 9α:11α-epoxy-Δ^7-compounds, in the allo-steroids, with boron trifluoride to 11-oxo--Δ^7-9β-steroids. These βγ-unsaturated ketones can be isomerised successively to the 11-oxo-Δ^7-9α-compounds and 11-oxo-$\Delta^{8(9)}$-isomers. The unconjugated 7:8-double bond, in contrast to the 9α-compounds, can be hydrogenated to 11-oxo-9β-compounds which are isomerised by alkali to

11-ketones of 9α-configuration. These reactions were



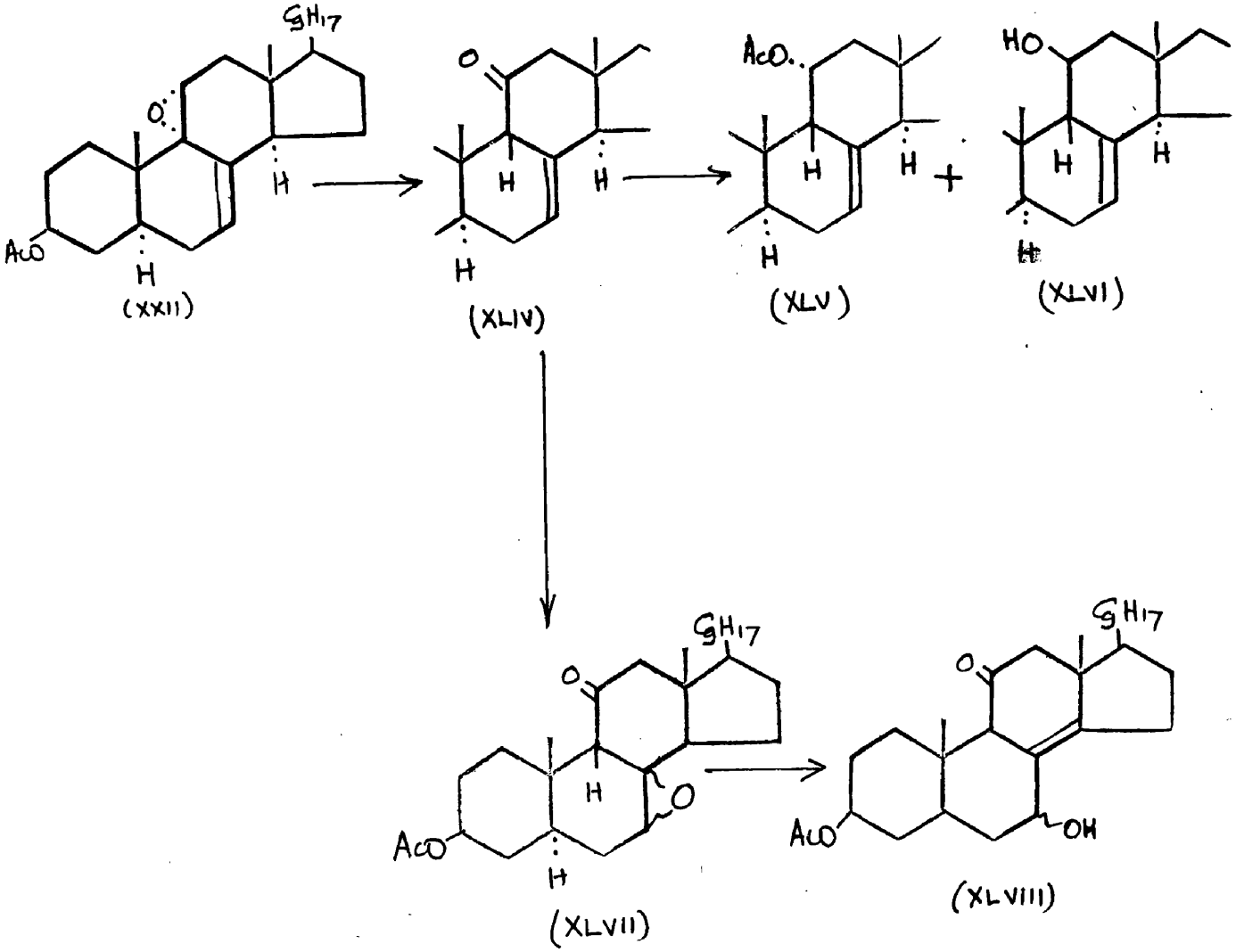
performed in the ergostane, bisnorallocholanic acid and allopregnane series with hydrogen, hydroxyl or acetoxyl substituents at $C_{(5)}$. In the ergosterol series hydrogenation of 11-oxoergosta-8:22-dien-3β-yl acetate (XXVI) in the presence of palladium gave 11-oxo-8α-ergostan--3β-yl acetate (XLIII).



(XXVI) (XLIII)

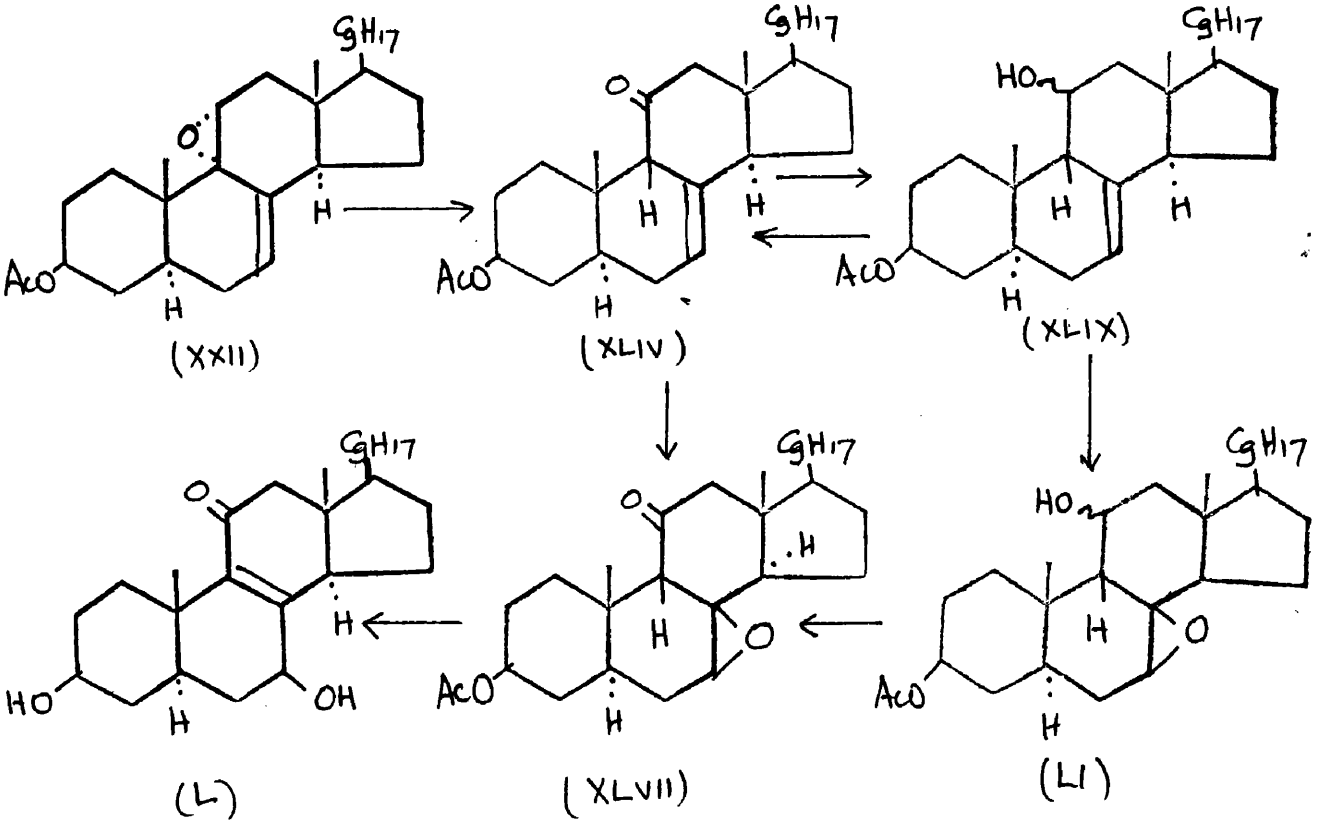
Similar conversions have been reported (33) starting from 22:23-dibromo-9α:11α-epoxyergost-7-en-3β-yl acetate and also in the allopregnane series (34). Heusler and

Wettstein have reported (35) the same rearrangement to 11-oxo-9β-ergosta-7:22-dien-3β-yl acetate (XLIV), which isomerises with mineral acid or boron trifluoride in benzene to the known Δ^{a}-11-ketone (XXVI). Treatment of (XLIV) with lithium aluminium hydride, followed by acetylation, gave compounds (XLV) and (XLVI) retaining the 9β-configuration. Oxidation with monoperphthalic acid affords the oxo-epoxide (XLVII) which rearranges with boron trifluoride in

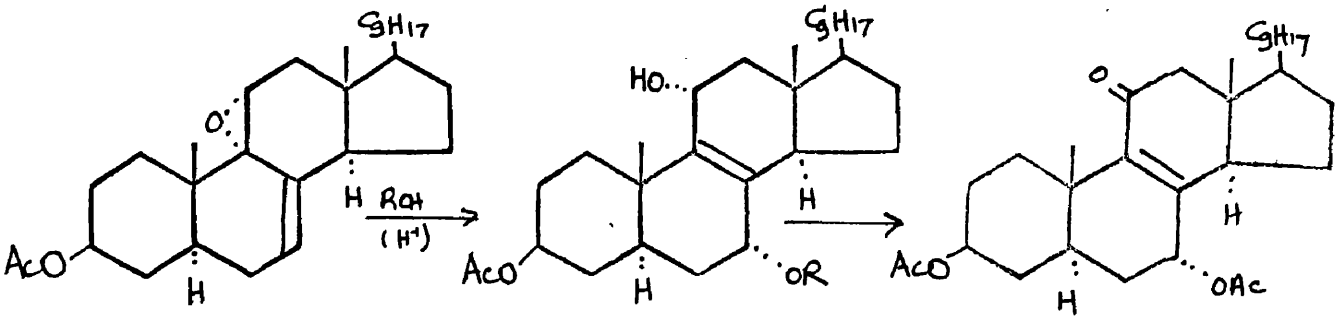


dioxan to a 7ξ-hydroxy-8(14)-en-11-one (XLVIII).

Henbest and Wagland (27) have carried out essentially similar experiments although they do not ascribe any configuration to the 11-hydroxyl group on lithium aluminium hydride reduction of (XLIV). The 9β-centre in (XLIX) is confirmed by oxidation back to the parent ketone (XLIV). The oxo-epoxide (XLVII), assigned the 7β:8β-configuration in analogy with the direction of attack on hydrogenatioh, on treatment with alkali gives 11-oxoergosta--8:22-dien-3β:7β-diol (L).

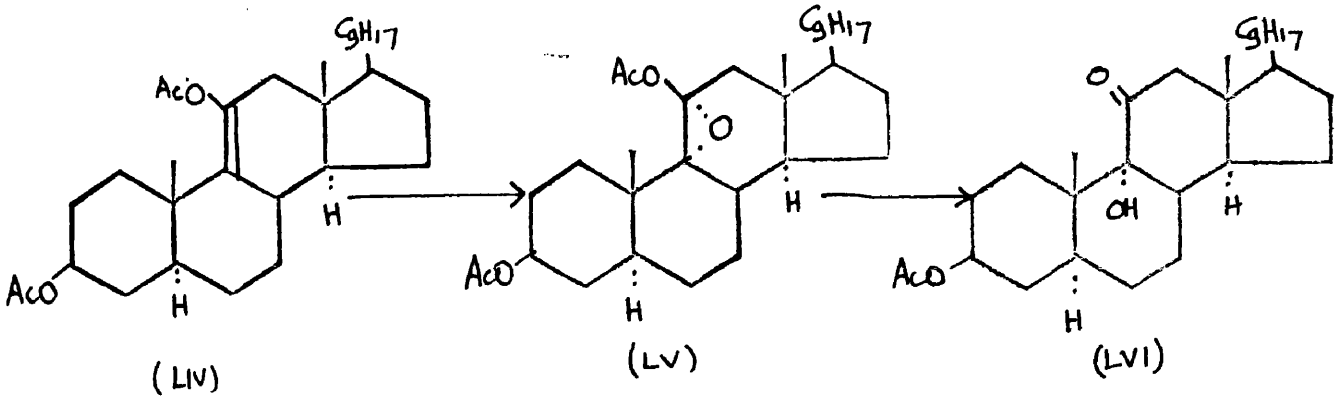


Henbest and Wagland assign the α-orientation to the 7-hydroxyl group in (XXIII), since acetolysis of the epoxide (XXII) followed by oxidation affords 7α--hydroxy-8(9)-en-11-ketone (LIII) differing from the diacetate of (L) only in the configuration at $C_{(7)}$.



11-Oxoergost-22-en-3β-yl Acetate. - Crawshaw, Henbest and Jones (36) investigating the reduction of 11-oxo-5α-steroids to 11α and 11β-hydroxy compounds [cf. (22)] showed that the hindered 11β--hydroxyl group could be acetylated with acetyl chloride [cf. (38)]. These authors also showed that the direction of enol acetylation in 11-oxo--5α-steroids was towards $C_{(9)}$ (cf. Barton (39)) by oxidation of the enol acetate (LIV) to the 9α:11α--epoxide (LV) which on treatment with alkali followed by acetylation gives the ketol (LVI) dehydrated with

thionyl chloride to the Δ^{8}-11-ketone (XXVI). This



is an extension of the method employed by Hirschmann and Wendler (40) in the normal (5β) series.

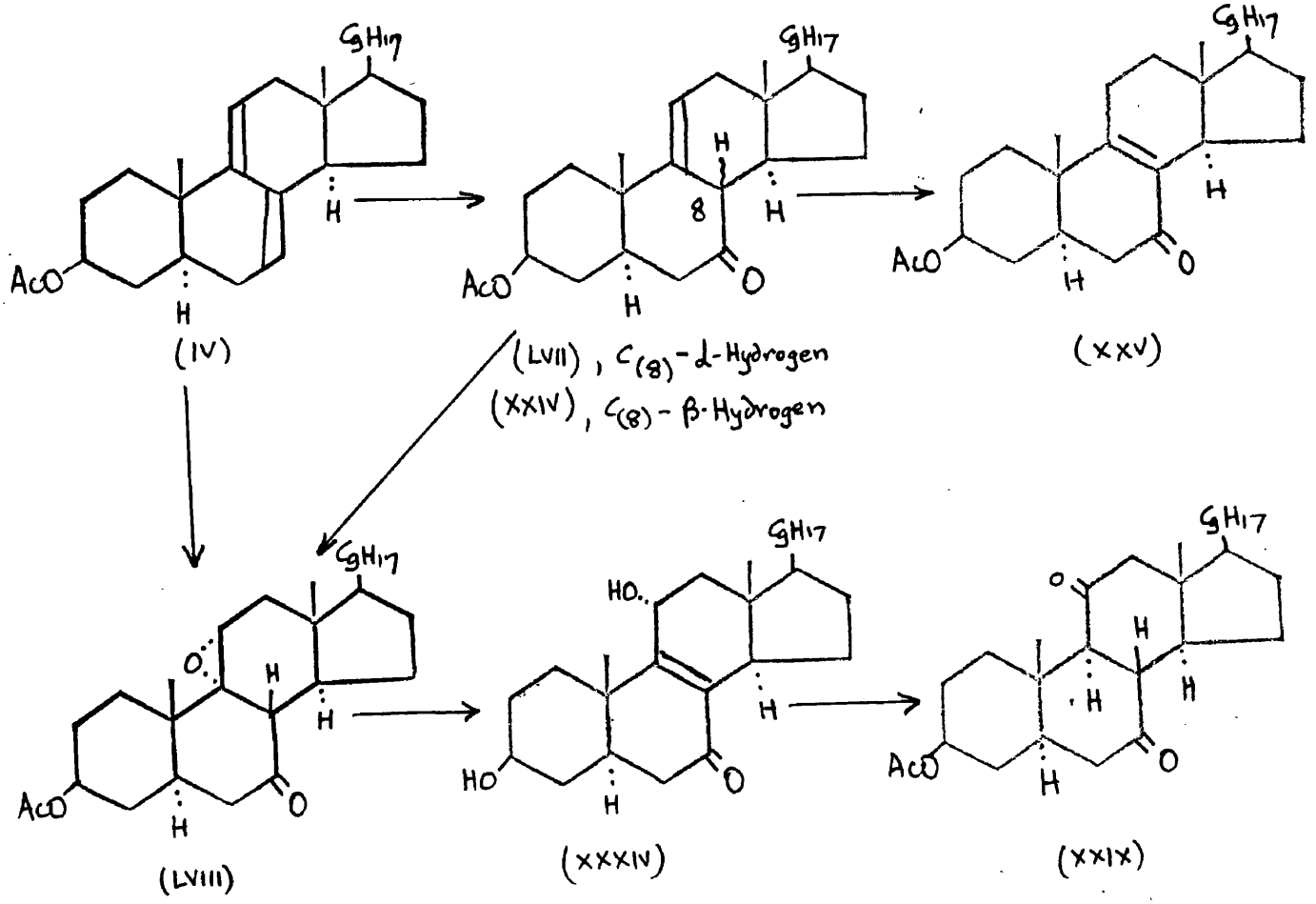
The Peraliphatic Acid Route.

These peraliphatic oxidations are confined to allo-steroids only, and are extensions of the method originally developed by Djerassi et al. (14, 41) in the allopregnane series.

Budziarek, Newbold, Stevenson and Spring (42, 43) isolated from the action of one mol. of performic acid on ergosteryl-D acetate (IV) the βγ-unsaturated ketone, 7-oxo-8α-ergosta-9(11):22-dien-3β-yl acetate (LVII), $[\alpha]_D$ + 20°, while Heusser et al. (19) obtained the normal C(8)-epimer, 7-oxoergosta-9(11):22-dien-3β-yl acetate (XXIV), $[\alpha]_D$ - 55°, by reaction with hydrogen

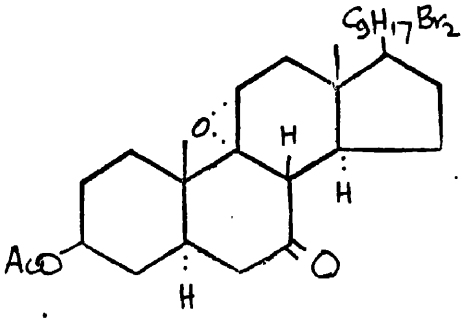
peroxide in acetic acid. The 8β-compound (XXIV) is also obtained by controlled mineral acid treatment of 9α:11α-epoxyergosta-7:22-dien-3β-yl acetate (XXII). Both these βγ-unsaturated ketones give 7-oxoergosta--8:22-dien-3β-yl acetate (XXV) on treatment with alkali followed by acetylation.

Treatment of ergosteryl-D acetate with two molecular proportions of performic acid gave 9α:11α--epoxy-7-oxoergost-22-en-3β-yl acetate (LVIII) also

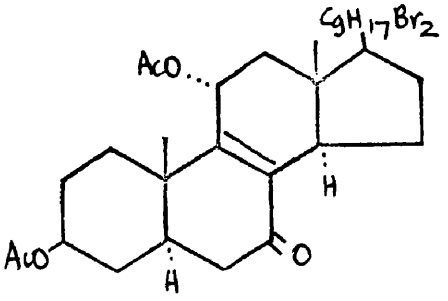


obtained from each of the $C_{(8)}$-epimeric $\beta\gamma$-unsaturated ketones (42). This oxo-epoxide (LVIII) although stable to mineral acid is readily converted to 3β:11α-dihydroxy-ergosta-8:22-dien-7-one (XXXIV) by mild alkali; more vigorous treatment of the oxo-epoxide (LVIII) or the derived diol (XXXIV) with alkali gives 7:11-dioxoergost--22-en-3β-yl acetate (XXIX).

22:23-Dibromo-9α:11α-epoxy-7-oxoergostan-3β-yl acetate (LXII) has been prepared and its rearrangement products studied (43). An interesting conjugated

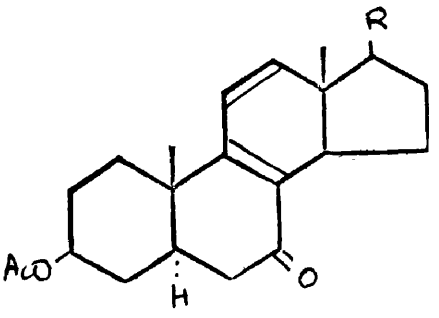


(LXII)

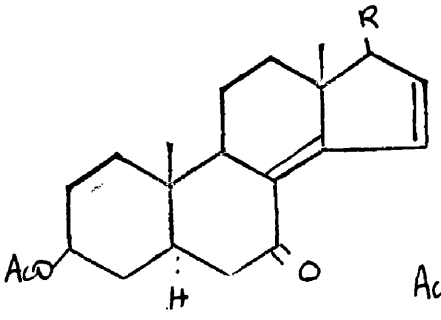


(LXIII)

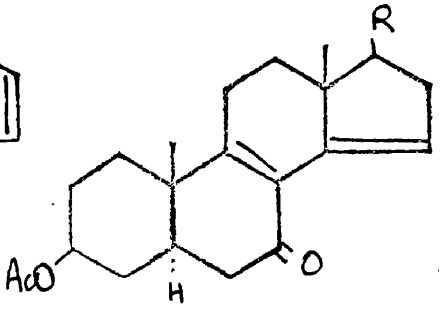
oxo-diene was obtained by hydrolysis of 22:23-dibromo--3β:11α-diacetoxyergost-8-en-11-one (LXIII) with methanolic hydrogen chloride, analogous to one, obtained by Djerassi (41) in the allopregnane series, to which



(LIX)



(LX)



(LXI)

the formula (LIX) was assigned but later amended (44) to (LX). It has been suggested by Fieser, Nakanishi and Huang (45) that both these oxo-dienes possess a 7-oxo-8:14-diene system, (LXI).

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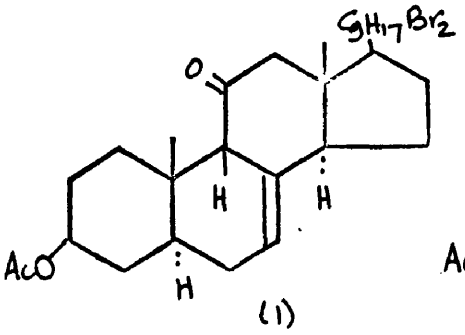
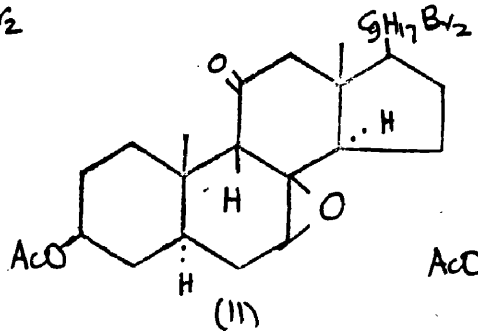
THEORETICAL

Introduction.

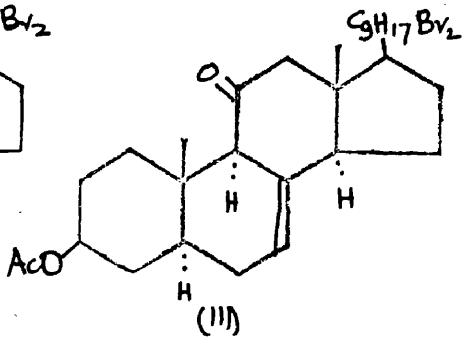
This work began in 1952 with the preparation of 22:23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (I) and its oxidation with peraromatic acids. The behaviour of the resulting oxo-epoxide (II) with acids and alkali was examined in detail, and the constitution



(I)



(II)

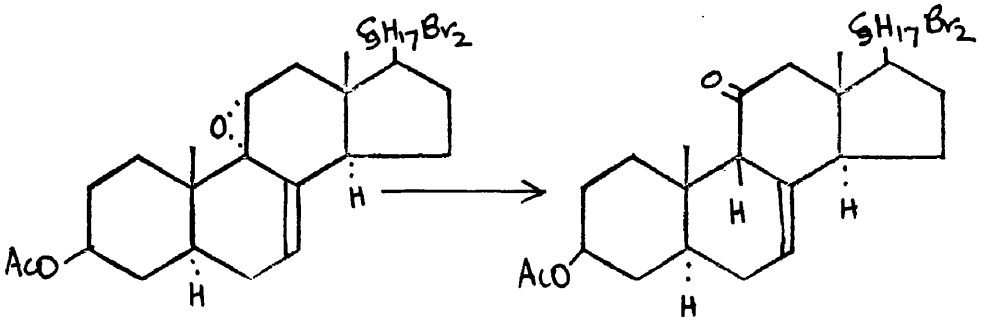


(III)

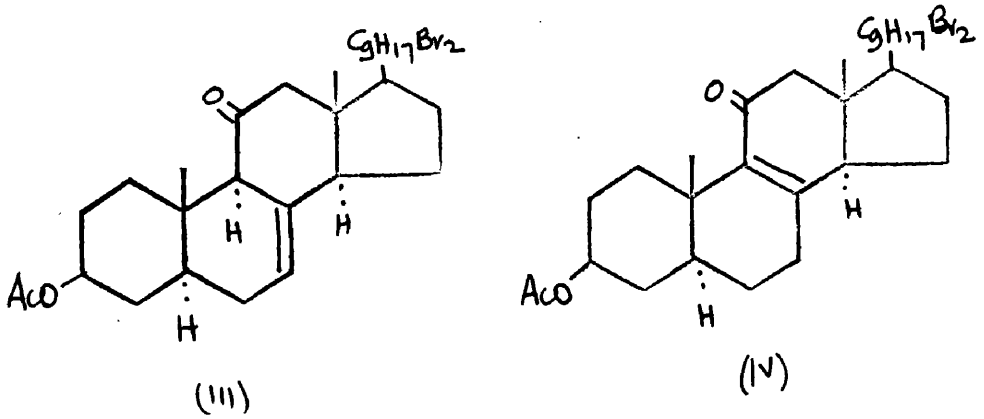
of the rearrangement products elucidated. The investigation led to the extension of the problem to include the preparation and oxidation of the 9α--epimer, 22:23-dibromo-11-oxoergost-7-en-3β-yl acetate (III) for comparison of the steric course of addition of peracids at the 7:8-double bond in natural (9α) and unnatural (9β)-steroids. Most of the work described has been published (46, 61).

11-Oxo-Δ^7-Ergostenyl Derivatives.

An attempt to prepare the enol acetate of an 11-ketone by treatment of 22:23-dibromo—9α:11α--epoxyergost-7-en-3β-yl acetate (I) with boron trifluoride etherate in acetic anhydride-ether gave instead 22:23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (II) identical with a specimen prepared by Maclean and Spring (28). In connection with studies of the oxidation of this βγ-unsaturated ketone (II) with peraromatic acids it became



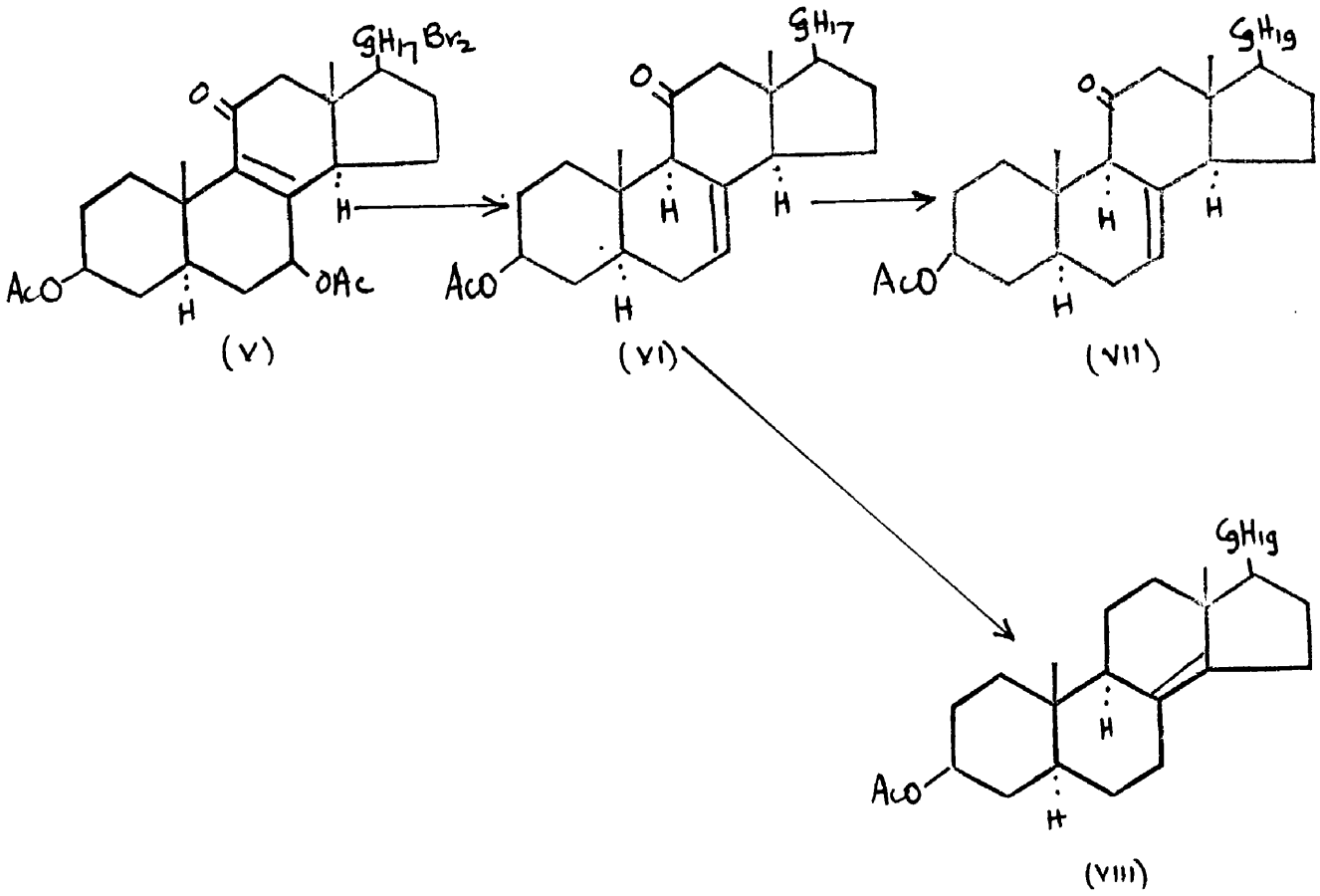
desirable to isolate the 9α-epimer (III) to examine parallel reactions in a natural (9α) steroid.



Attempted epimerisations at $C_{(9)}$ in (II) in acetic acid-chloroform and acetic acid alone gave successively unchanged material or mixtures showing high intensity absorption at 2540 Å and finally the αβ--ketone (IV); polarimetric investigations of the rearrangement of (II) with boron trifluoride etherate in benzene-ether mixtures did not support the view that conversion of (II) into (IV) proceeds via (III).

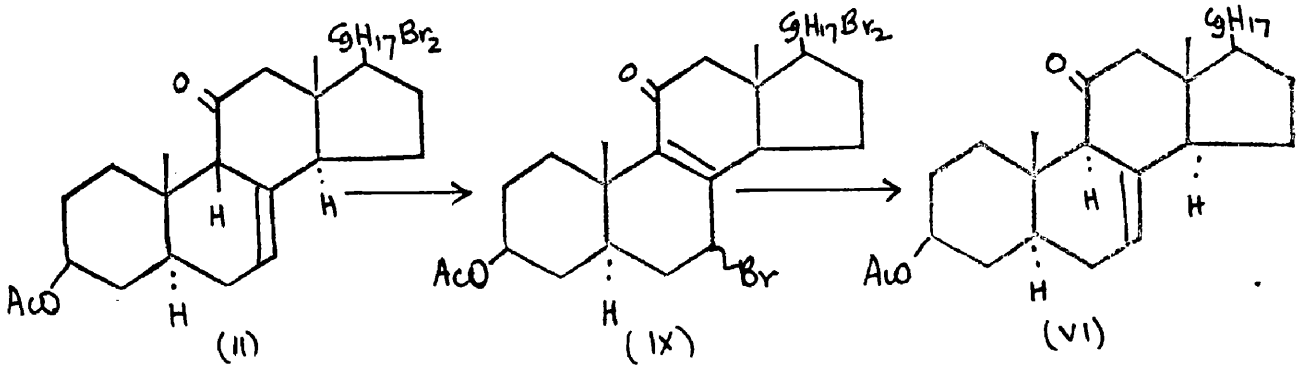
11-Oxoergosta-7:22-dien-3β-yl acetate (VI), the debrominated 9α-epimer, became available from an unexpected source. Attempted debromination with activated zinc in neutral solvent of 22:23-dibromo-3β:7β-diacetoxyergost-8-en-11-one (V), whose preparation is discussed in the next section, gave instead a compound $C_{30}H_{46}O_3$ (or possibly $C_{30}H_{48}O_3$) giving a yellow colour with tetranitromethane in chloroform and showing ultra-violet absorption at 2040 Å (ε 3,400). In order to determine whether the compound contained a nuclear double bond, hydrogenations were carried out in glacial acetic acid, and ethyl acetate respectively, in the presence of platinum as catalyst. The former gave a compound identified as ergost-8(14)-en-3β-yl acetate (VIII) indicating that hydrogenolysis and migration

of the nuclear double bond had occurred. Hence the compound $C_{30}H_{46}O_3$ is 11-oxoergosta-7:22-dien-3β-yl acetate (VI). The product from the hydrogenation in



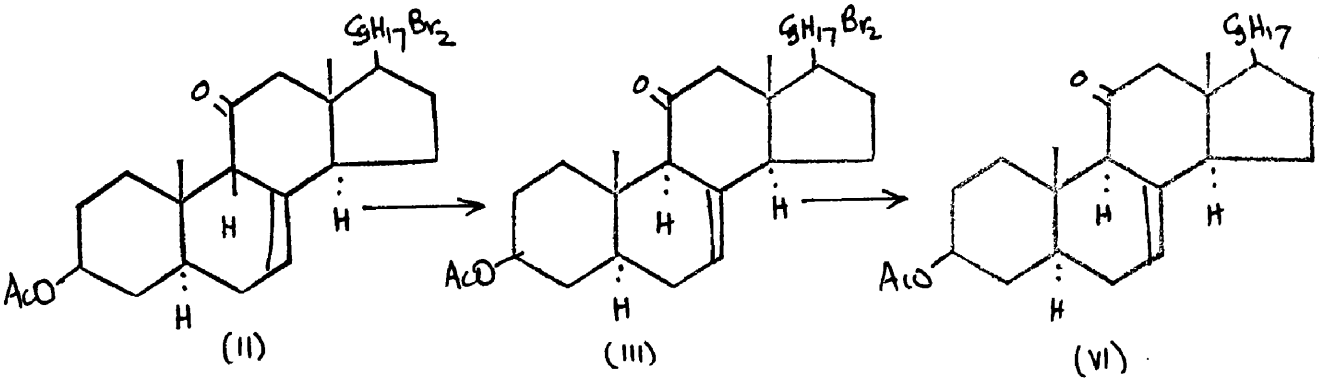
ethyl acetate is 11-oxoergost-7-en-3β-yl acetate (VII). These investigations confirm the investigations of Bladon et al. (32) who had previously prepared (VI) and reduced it to (VIII) in acetic acid, using dioxan as solvent 11-oxoergost-7-en-3β-yl acetate (VII) was obtained by these authors in crude form.

Bromination (46) of the βγ-unsaturated ketone (II) gave a tribromo derivative, 7ξ:22:23-tribromo-11-oxo-ergost-8-en-3β-yl acetate (IX) which on debromination with zinc in neutral solvent gave 11-oxoergosta-7:22--dien-3β-yl acetate (VI). Since (VI) is obtained from the 7β-acetoxy compound (V) and not from the 7α-isomer, described later, the β-configuration is suggested for



the bromine atom attached to $C_{(7)}$ in (IX).

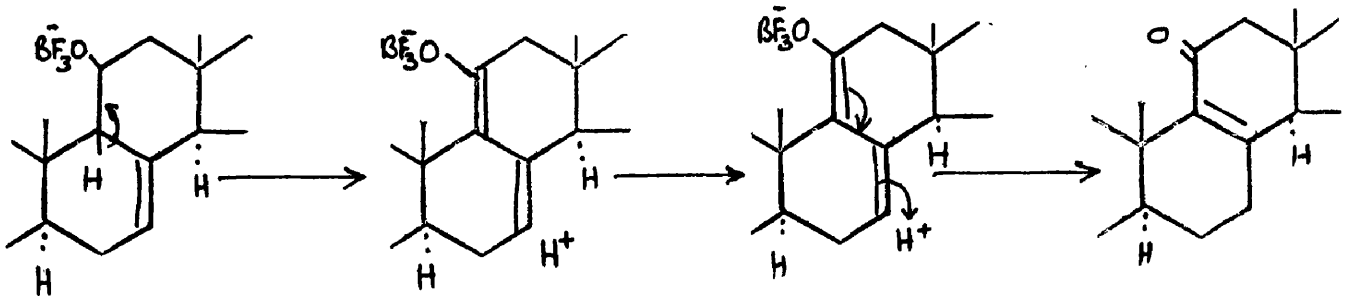
22:23-Dibromo-11-oxoergost-7-en-3β-yl acetate (III) was eventually prepared by rapid filtration of (II)



through a column of specially treated alumina [cf. Bladon *et al.* (32)]; its structure was confirmed by debromination to 11-oxoergosta-7:22-dien-3β-yl acetate (VI). Elks, Evans, Robinson, Thomas and Wyman (33) described the preparation of a compound to which the structure (III) was ascribed; this claim was later withdrawn since their preparation gives a 2:4-dinitrophenylhydrazone in good yield (70). The molecular rotation change associated with the conversion of (II) into the 9α-epimer (III) (Δ + 930°) is similar to that associated with the conversion of 11-oxo-9β--ergosta-7:22-dien-3β-yl acetate into the 9α-epimer (VI) (Δ + 970°).

Believing that they had isolated the 9α-epimer (III), Elks *et al.* (33) suggested that the rearrangement of 22:23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (II) into the Δ^{8}-11-ketone (IV) involves as its first stage inversion at $C_{(9)}$. There is now no experimental evidence for this opinion which is in accord with our experience in rearrangements with boron-trifluoride etherate in benzene-ether mixtures, mentioned earlier. We suggest that rearrangement with

Lewis acids proceeds as below.

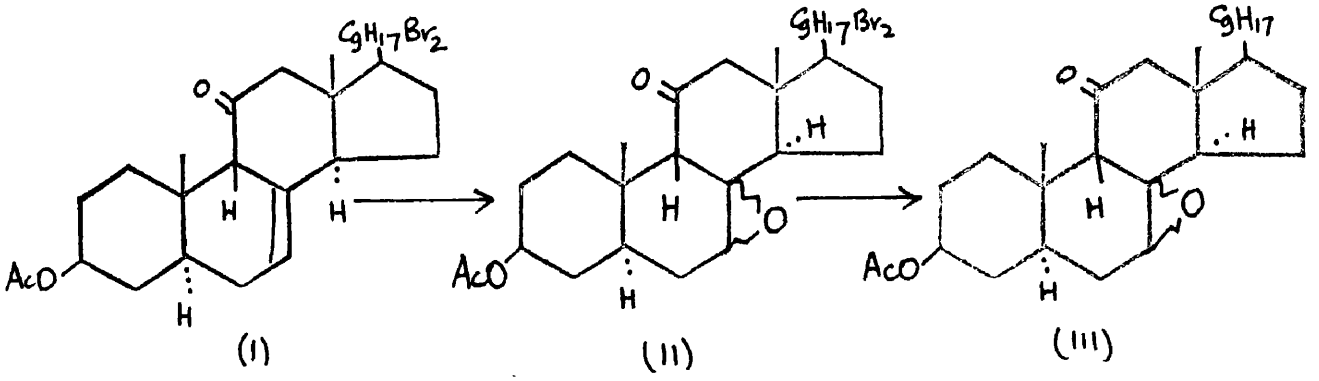


This mechanism is in contrast to the rearrangement under alkaline conditions where the 9α-epimer has been shown to be intermediate (46).

22:23-Dibromo-7β:8β-epoxy-11-oxo-9β-ergostan-3β-yl Acetate.

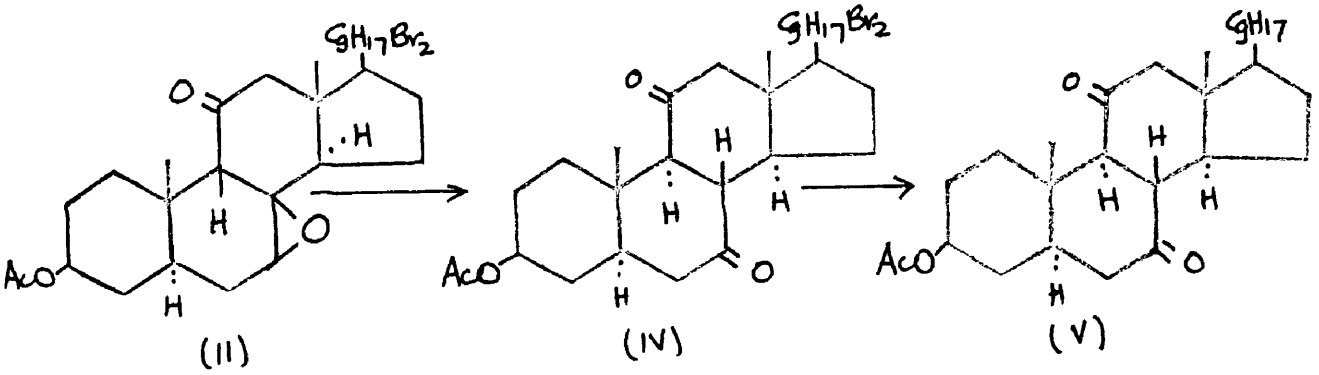
The oxidation of 22:23-dibromo-11-oxo-9β-ergost--7-en-3β-yl acetate (I) with perbenzoic acid was examined; by using freshly prepared reagent and mineral acid-free chloroform, an almost quantitative yield of a compound $C_{30}H_{46}O_4Br_2.\frac{1}{2}CHCl_3$ was obtained. The unsolvated crystal $C_{30}H_{46}O_4Br_2$ was prepared by oxidation of (I) with monoperphthalic acid in ether followed by crystallisation from benzene-light petroleum. Attempts to remove the solvent of crystallisation at 135° *in vacuo* were accompanied by a change towards dextrorotation and the appearance of high intensity absorption at 2540 Å. The solvated modification is obtained from the unsolvated crystal on crystallisation

from chloroform-methanol. The compound $C_{30}H_{46}O_4Br_2$ ($.\frac{1}{2}CHCl_3$) gave no colour with tetranitromethane in chloroform and did not show intense selective absorption in the ultra-violet above 2000 Å; the absence of a hydroxyl group was confirmed by its infra-red absorption spectra. This compound is either 22:23-dibromo-7:11-dioxoergostan-3β-yl acetate (IV) or 22:23-dibromo-7ξ:8ξ-epoxy-11-oxo--9β-ergostan-3β-yl acetate (II). The former possibility being eliminated when debromination with zinc in neutral solvent gave a compound $C_{30}H_{46}O_4$ different from the known (12, 17) 7:11-dioxoergost--22-en-3β-yl acetate (V). The debromination product is therefore 7ξ:8ξ-epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (III); this compound was later described by



Heusler and Wettstein (35) and Henbest and Wagland (27).

Treatment of the dibromo-oxo-epoxide (II) with aqueous hydrogen bromide in acetic acid-chloroform gave an isomer $C_{30}H_{46}O_4Br_2$ showing no intense absorption in the ultra-violet above 2000 Å. and giving no colour with tetranitromethane in chloroform. Debromination with zinc in neutral solvent gave 7:11--dioxoergost-22-en-3β-yl acetate (V). The natural

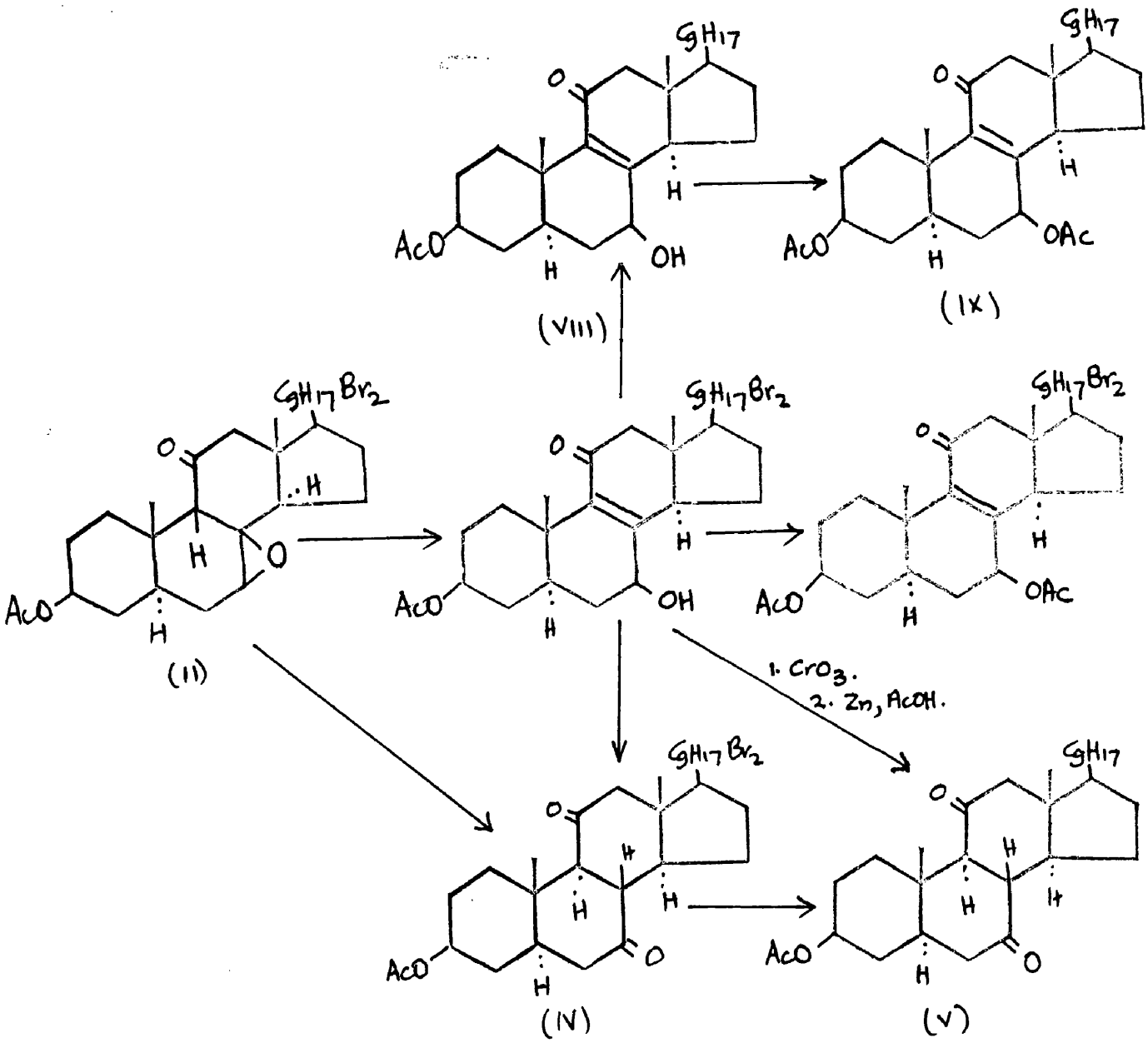


configuration at $C_{(8)}$ and $C_{(9)}$ in (IV) follows both from this reaction and its recovery unchanged after alkaline hydrolysis followed by reacetylation. This permits location of the epoxide group at $C_{(7)}$ and $C_{(8)}$; the β-configuration is assigned to the oxo-epoxide (II) and (III) for reasons which will appear in the sequel.

When 22:23-dibromo-7β:8β-epoxy-11-oxo-9β-ergostan--3β-yl acetate (II) is treated with a trace of hydrogen

bromide in chloroform, a second isomer is obtained which shows the characteristic ultra-violet absorption spectrum of an αβ-unsaturated ketone; its infra-red spectrum shows peaks characteristic of an αβ-unsaturated ketone, hydroxyl and acetoxyl groups. The presence of a hydroxyl group was confirmed by acetylation to the diacetate (VII). The isomer is therefore 22:23-dibromo-7β-hydroxy-11-oxoergost-8-en--3β-yl acetate (VI). Apart from the orientation of the hydroxyl group, the correctness of the formulation (VI) was established by oxidation with chromic acid followed by treatment with zinc dust in acetic acid to 7:11-dioxoergost-22-en-3β-yl acetate (V). 22:23-Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (VI) is an intermediate in the conversion of the oxo-epoxide (II) into the saturated diketone (IV) since it is converted into the last compound by treatment with hydrogen bromide in acetic acid-chloroform. Treatment of the diol-monoacetate (VI) with zinc in neutral solvent gave 7β-hydroxy-11-oxoergosta-8:22-dien-3β-yl acetate (VIII) acetylation of which gave 3β:7β-diacetoxyergosta--8:22-dien-11-one (IX), prepared by Henbest and Wagland

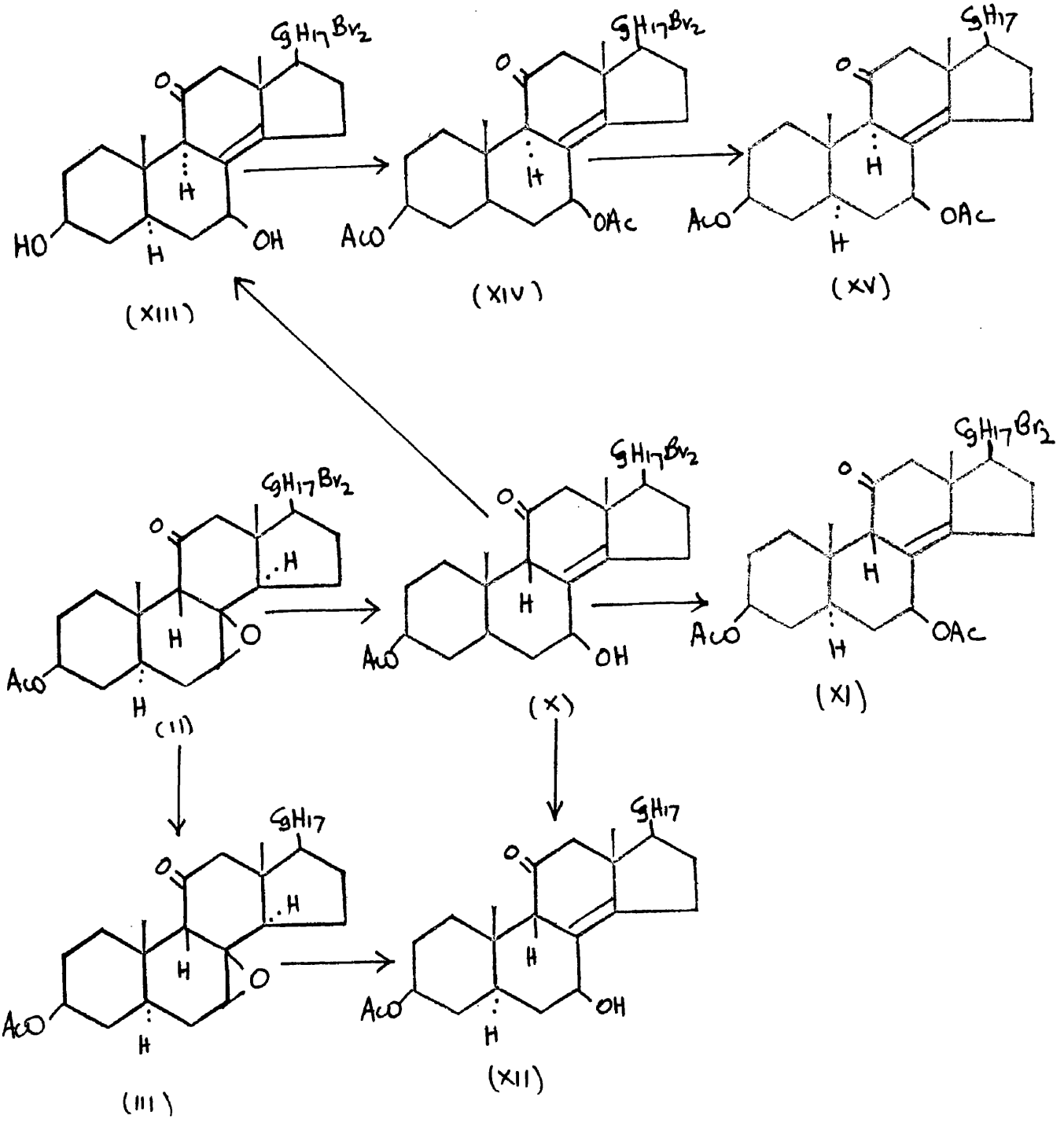
(27) by acetylation of the corresponding diol.



Attempted debromination of 22:23-dibromo-3β:7β--diacetoxyergost-8-en-11-one (VII) gave 11-oxoergosta--7:22-dien-3β-yl acetate discussed in the previous section.

When the oxo-epoxide (II) is treated with dioxan containing dilute sulphuric acid, a third isomer $C_{30}H_{46}O_4Br_2$ was obtained; this shows the ultra-violet absorption spectra of a $\Delta^{8(14)}$-stenol and the presence of a hydroxyl was confirmed by the infra-red absorption spectrum and by acetylation to a diacetate (XI). This third isomer is therefore 22:23-dibromo-7β-hydroxy-11--oxo-9β-ergost-8(14)-en-3β-yl acetate (X) which is smoothly debrominated by zinc in neutral solvent to 7β-hydroxy-11-oxo-9β-ergosta-8(14):22-dien-3β-yl acetate (XII). The 9β-configuration is assigned to (X), (XI) and (XII) because alkaline hydrolysis of the first compound at room temperature gives a diol (XIII), the ultra-violet absorption spectrum of which established the presence therein of the 8:14-double bond. Acetylation of the diol gives a diacetate which differs from (XI) and is consequently considered to be 22:23-dibromo-3β:7β-diacetoxyergost-8(14)-en-11-one (XIV) differing from the previous diacetate solely in configuration at $C_{(8)}$. It therefore follows that formation of the oxo-epoxide (II) from 22:23-dibromo--11-oxo-9β-ergost-7-en-3β-yl acetate is not accompanied

by inversion at $C_{(8)}$. For different reasons the same conclusion was reached by Henbest and Wagland (27)

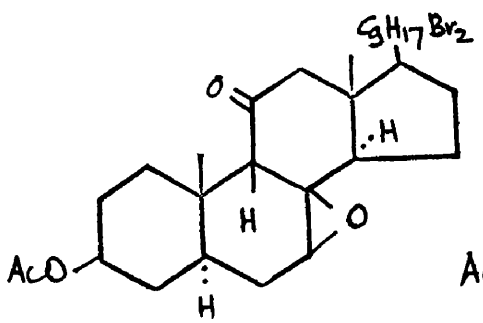


concerning the structure of the related bromine-free oxo-epoxide (III). Debromination of the 9α-diacetate (XIV) by zinc in neutral solvent gives 3β:7β-diacetoxy-ergosta-8(14):22-dien-11-one (XV).

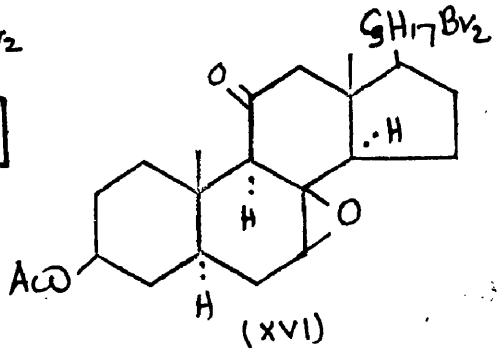
A compound designated 7ξ-hydroxy-11-oxoergosta--8(14):22-dien-3β-yl acetate has been obtained by Heusler and Wettstein (35) by treatment of the de-brominated oxo-epoxide (III) with boron trifluoride--etherate in hot dioxan. Although the m.p. of this compound is similar to that of 7β-hydroxy-11-oxo-9β--ergosta-8(14):22-dien-3β-yl acetate (XII), the rotations of the two preparations are markedly different (+ 76°, + 216° respectively). We have not prepared 7β-hydroxy-11-oxoergosta-8(14):22-dien-3β-yl acetate; the related diacetate m.p. 113°, $[\alpha]_D$ + 34° again differs appreciably from the diacetate (m.p. 153-155°) obtained by Heusler and Wettstein who appreciated that their preparation was not pure. Repetition of their experiment did not give a homogeneous product; the sample obtained by us had m.p. 187-190°, $[\alpha]_D$ + 147°, Max. at 2480 Å (ε 1700). Modification of the experi-mental conditions to boron trifluoride-etherate in

dioxan at room temperature for 18 hours gave 7β--hydroxy-11-oxo-9β-ergosta-8(14):22-dien-3β-yl acetate (XII), $[\alpha]_D$ + 211°. This experiment, followed spectroscopically and polarimetrically, failed to show the existence of a 9α-oxo-epoxide (XVI) as intermediate confirming the postulated 9β-centre in (XII).

In spite of many attempts, it was not possible to convert the 9β-oxo-epoxide (II) to the 9α-epimer (XVI). Attempted rearrangement of (II) on previously

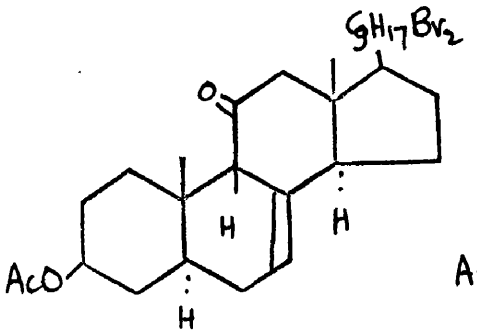


(II)

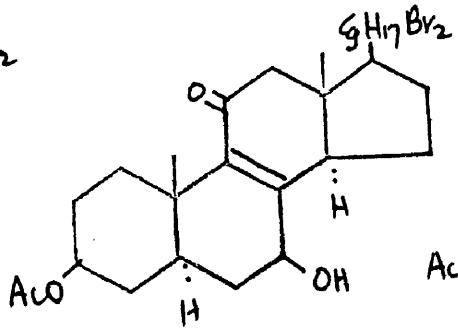


(XVI)

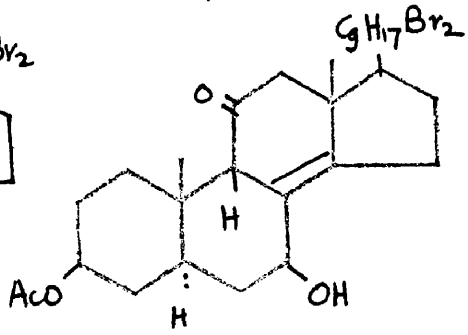
treated alumina, used successfully in the epimerisation at C(α) in the βγ-unsaturated ketone (I),



(I)

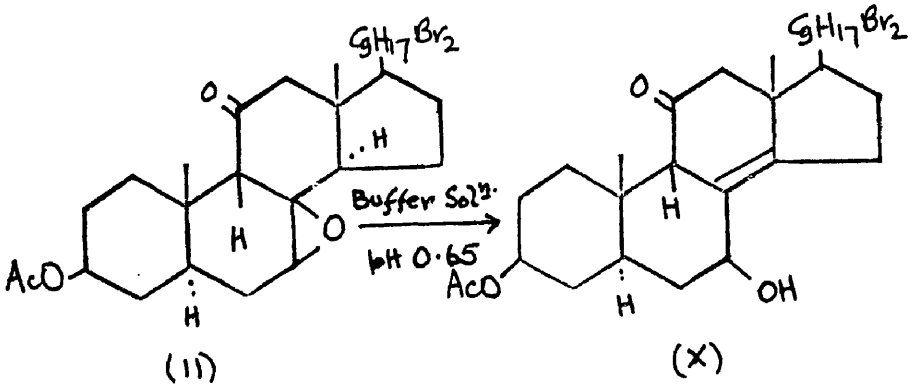


(VI)



(X)

led to its recovery unchanged. The action of alkali is later discussed. Various acid conditions were employed but these were unsuccessful. A

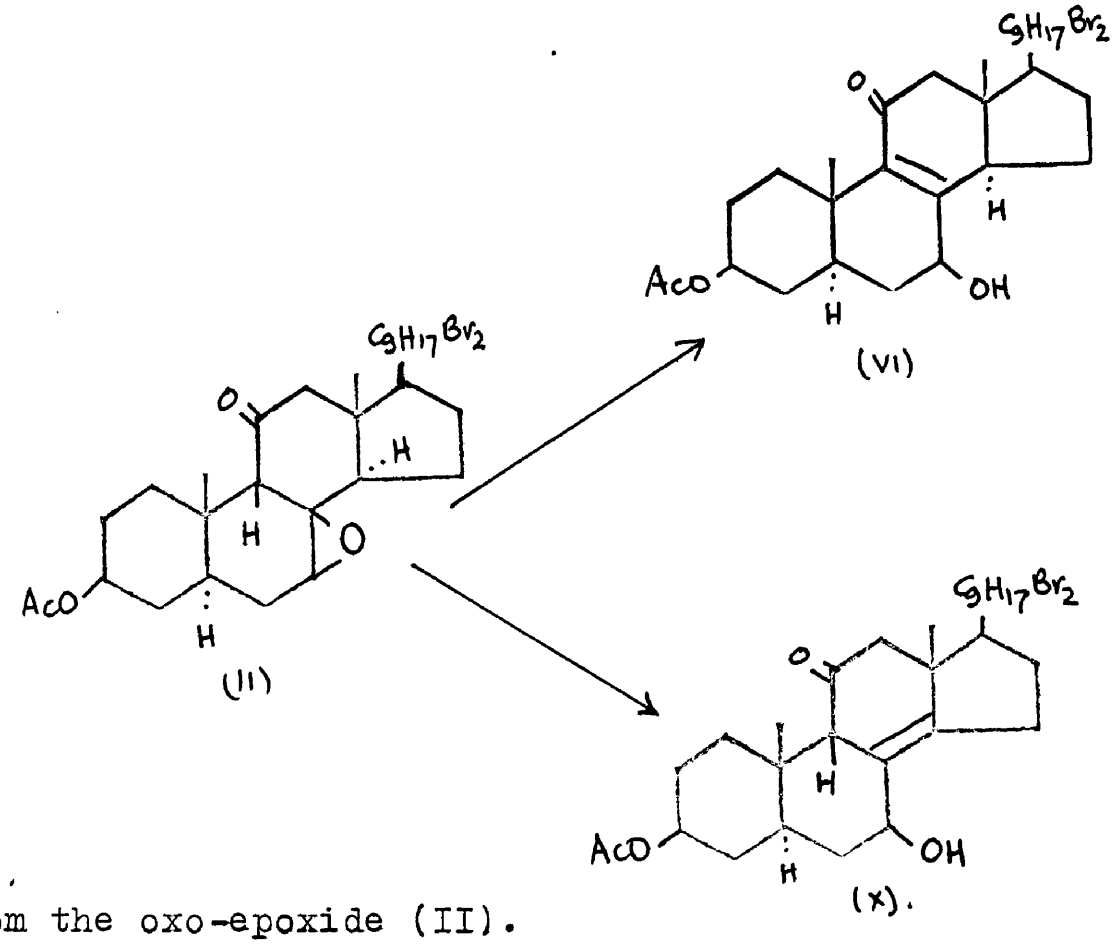


(II) (X)

systematic approach in which the behaviour of the oxo-epoxide (II) was studied at various pHs was carried out. It was found that rearrangement occurred between pH 1.09 and 1.42; at pH 0.65 (II) is converted into the 9β-7-hydroxy-8(14)-ene (X) demonstrating that fission of the epoxide group occurs before attack at C(9). In view of this result, attempts to carry out the epimerisation were suspended. It is unlikely that conversion of the oxo-epoxide (II) to the diol monoacetate (VI) proceeds via the 9α-oxo-epoxide (XVI); since oxidation of the βγ-unsaturated ketone (I) by perbenzoic acid which had been stored for

several days and contained a trace of hydrogen chloride gave a mixture of the oxo-epoxide (II) and the diol mono-acetate (VI).

The diol monoacetate (VI) is recovered unchanged after treatment with sulphuric acid in dioxan under conditions which convert the oxo--epoxide into the 7β-hydroxy-8(14)-en-9β-compound (X); it follows that (X) is not an intermediate in the conversion into (VI) by mineral acid; this conclusion is in agreement with the established 9β-configuration in (X). When treated with a trace of hydrobromic acid under conditions which convert the oxo-epoxide (II) into the diol monoacetate (VI) 22:23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (X) is not converted into (VI) but is dehydrated to give a "non-conjugated" oxo-diene whose structure is discussed in a later section. This proves that the Δ8(14)-9β-compound (X) is not an intermediate in the conversion of the oxo-epoxide to 22:23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (VI). Consequently compounds (VI) and (X) are the primary and independent rearrangement products



from the oxo-epoxide (II).

It is now pertinent to discuss the orientation of the epoxide grouping. The lack of information of the influence of the unnatural (β) configuration at $C_{(9)}$ did not permit any prediction for the steric course of addition at the 7:8-double bond. If the direction of attack by peracids is assumed to be the same as in hydrogenation of 9β-Δ^7-steroids (32) then the β-configuration is suggested.*

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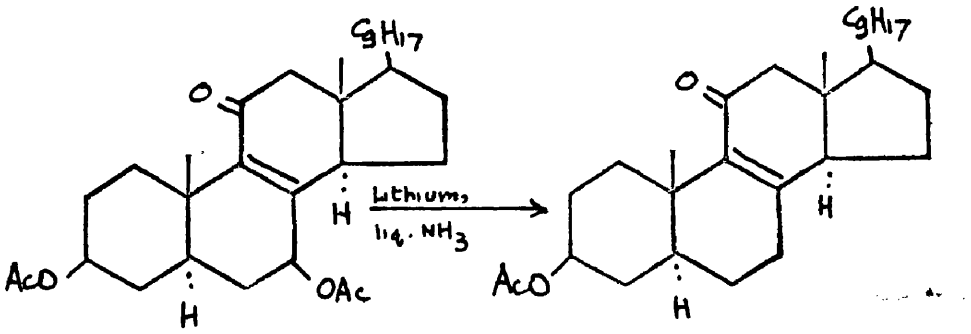
* Henbest and Wagland (27) assigned the β-configuration to 7β:8β-epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate on these grounds.

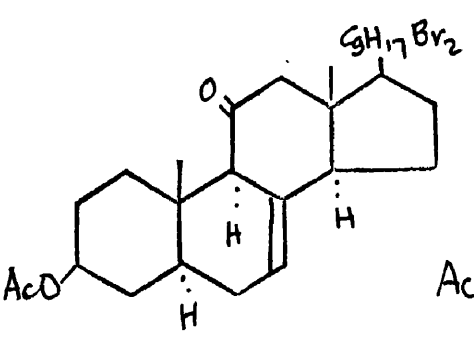
It was believed that application of molecular rotation methods had limitations in that comparison of compounds possessing nuclear unsaturation was undesirable. Hence attempts were made to obtain a saturated 7-hydroxyl derivative. An attempt to hydrogenate 22:23-dibromo-3β:7β-diacetoxyergost--8-en-11-one over platinum in ethanolic alkali (cf. Chemerda, Chamberlin, Wilson and Tishler (53) and Budziarek et al. (43)) and subsequent acetylation gave 3β:7β-diacetoxyergosta-8:22-dien-11-one (IX) the αβ-ketone moiety being retained. The action of lithium in liquid ammonia (cf. Birch (21) and Tishler (20)) was next investigated. Treatment of 3β:7β--diacetoxyergosta-8:22-dien-11-one (IX) with this reagent followed by acetylation gave a compound identified as 11-oxoergosta-8:22-dien-3β-yl acetate (XVII); this removal of the 7-substituent is comparable with the preparation of 11-oxoergosta-7:22-dien-3β-yl



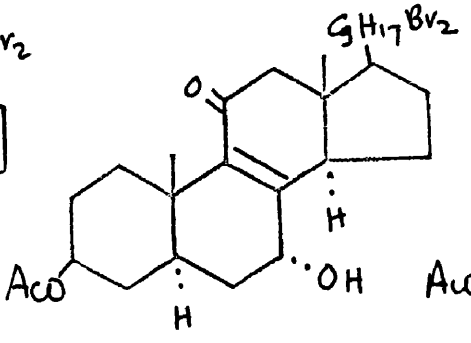
acetate from the corresponding dibromo-3β:7β-diacetate previously described.

Attempted hydrogenation of the oxo-epoxide (II) and (III) by D.Maclean (54) using a variety of catalysts and solvents led to rearrangements to the compounds previously obtained from acid-catalysed reactions. No saturated 7-hydroxyl compound was isolated from these experiments.

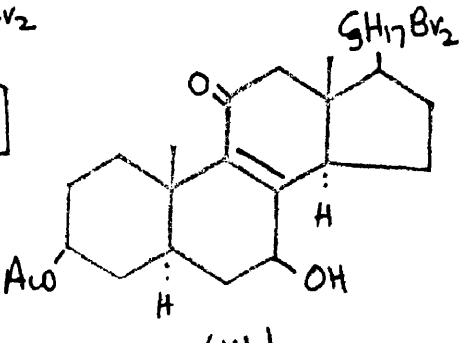
An approach from 22:23-dibromo-11-oxoergost-7--en-3β-yl acetate (XVIII) was initiated and forms the subject of the next section. 22:23-Dibromo-7α-hydroxy--11-oxoergost-8-en-3β-yl acetate (XIX) was prepared



(XVIII)



(XIX)

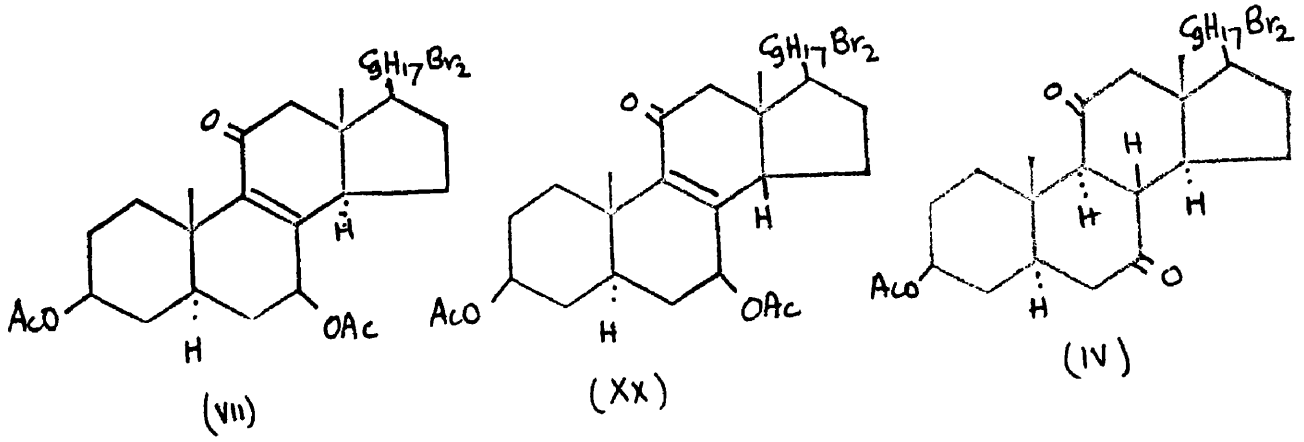


(VI)

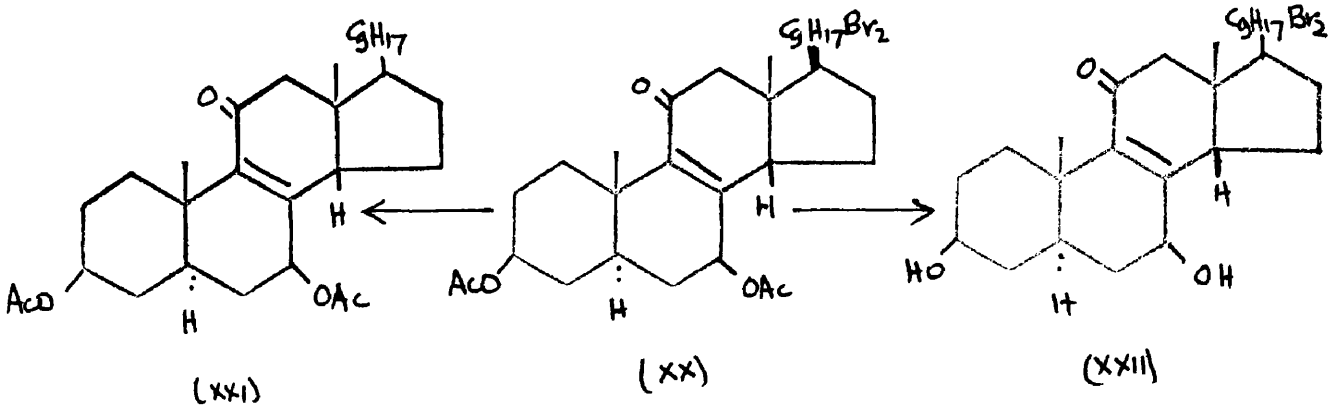
and found to be different from the diol-monoacetate (VI) obtained from the oxo-epoxide (II). This difference can only be at $C_{(7)}$ and consequently the diol monoacetate (VI) and the parent oxo-epoxide (II) must have the β-configuration.

The action of alkali on 22:23-dibromo-7β:8β--epoxy-11-oxo-9β-ergostan-3β-yl acetate (II) and its two primary acid rearrangement products 22:23--dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (VI) and 22:23-dibromo-7β-hydroxy-11-oxo-9β-ergost--8(14)-en-3β-yl acetate (X) has been examined. Short treatment of the oxo-epoxide (II) with alcoholic alkali followed by acetylation gave 22:23-dibromo--3β:7β-diacetoxyergost-8-en-11-one (VII) in good yield. Prolonged treatment of the oxo-epoxide (II) with alkali and subsequent acetylation gives a mixture from which three homogeneous reaction products have been isolated. One of these is the 3β:7β--diacetate (VII), a second is 22:23-dibromo-7:11--dioxoergostan-3β-yl acetate (IV), and the third is a diacetate $C_{32}H_{48}O_5Br_2$ m.p. 187°. Similar protracted treatment of 22:23-dibromo-7β-hydroxy-11--oxoergost-8-en-3β-yl acetate (VI) with alkali followed by acetylation gives a mixture of the 7:11--dione (IV) and the diacetate, m.p. 187°. This diacetate shows the light absorption properties of an αβ-ketone both in the ultra-violet and the infra-red. It is also obtained by treatment of 22:23-dibromo-7β-

-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (X) and 22:23-dibromo-11-oxoergost-8(14)-en-3β:7β-diol (XIII) with alkali and reacetylation. These relationships, we believe, show that the diacetate m.p. 187°

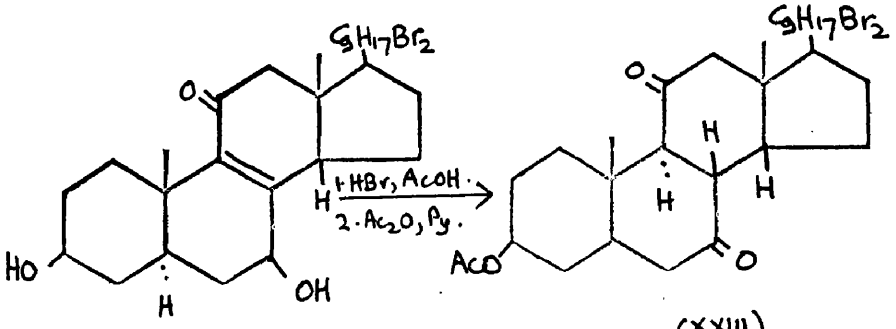


is 22:23-dibromo-3β:7β-diacetoxy-14β-ergost-8-en-11--one (XX) differing from (VII) solely in configuration at $C_{(14)}$. In contrast to the behaviour of the 14α--isomer, debromination of (XX) with zinc in neutral solvent proceeds normally to give 3β:7β-diacetoxy--14β-ergost-8-en-11-one (XXI). Hydrolysis of (XX)



gives 22:23-dibromo-11-oxo-14β-ergost-8-en-3β:7β--diol (XXII). In the 14β-compounds there is a characteristic hypsochromic shift of 50 Å., compared with the 14α-epimer, in absorption maxima in the ultra-violet.

This behaviour of the 7β-hydroxy-Δ^{8}-11-ketone is the same as that of a related Δ^{9}-11-ketone of the sapogenin series which epimerises at C$_{(14)}$ on treatment with alkali (48). Treatment of the diol (XXII) with aqueous hydrogen bromide in acetic acid-chloroform followed by acetylation gave a compound $C_{30}H_{46}O_4Br_2$ giving no colour with tetranitromethane in chloroform and showing no absorption in the ultra-violet. This compound is accordingly provisionally formulated as 22:23-dibromo-7:11-dioxo-14β-ergostan-3β-yl acetate (XXIII). The preparation of this 14-isomeric dione (XXIII) is analogous to the formation of the 7:11--dione (IV) from 22:23-dibromo-7β-hydroxy-11-oxoergost--8-en-3β-yl acetate (VI). The configuration at C$_{(8)}$

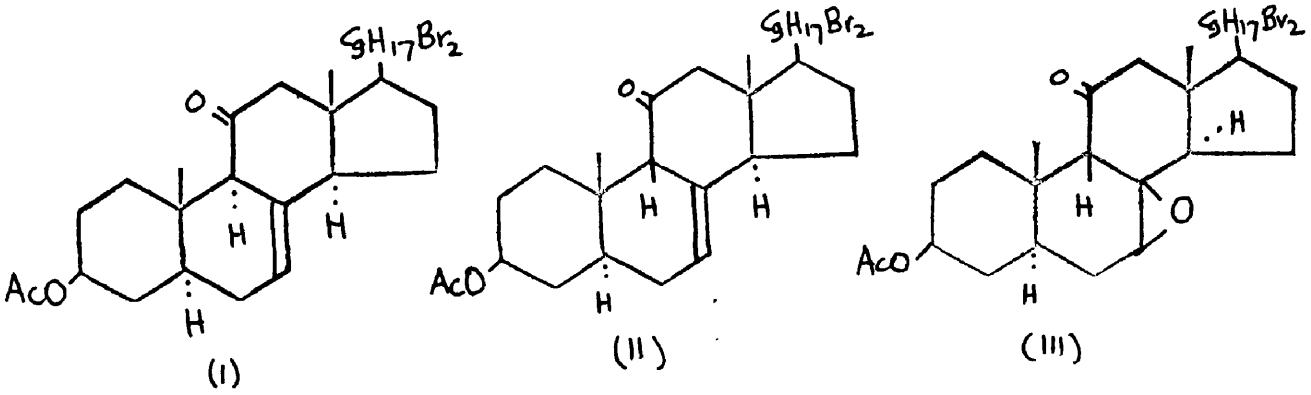


(XXII) (XXIII)

and $C_{(8)}$ is assumed to be β and α respectively from its mode of formation , and since Djerassi (49) has shown this to be the stable configuration in 14β-steroids.

22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl Acetate.

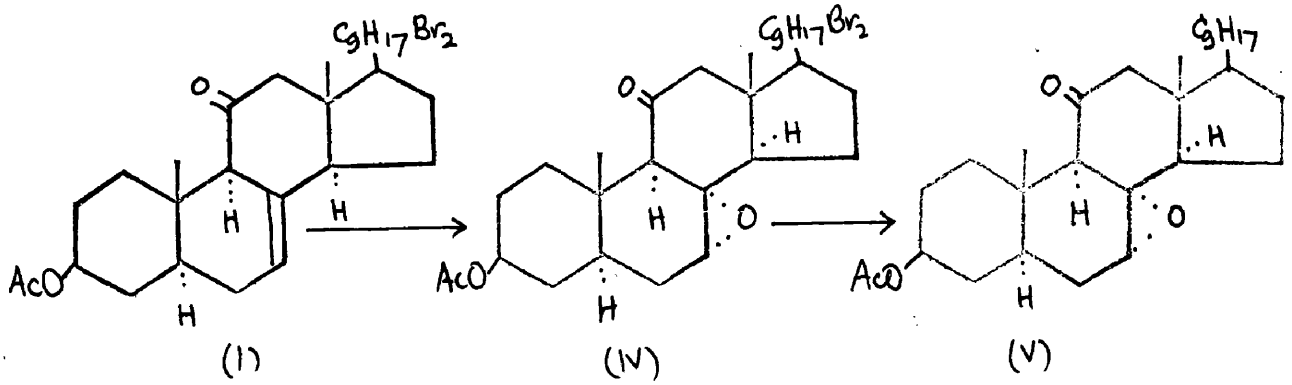
The oxidation of 22:23-dibromo-11-oxoergost-7-en--3β-yl acetate (I) was undertaken to compare its behaviour with that of the 9β-epimer (II) and to obtain information concerning the orientation of the epoxide group in the iso-oxo-epoxide (III). Treatment of



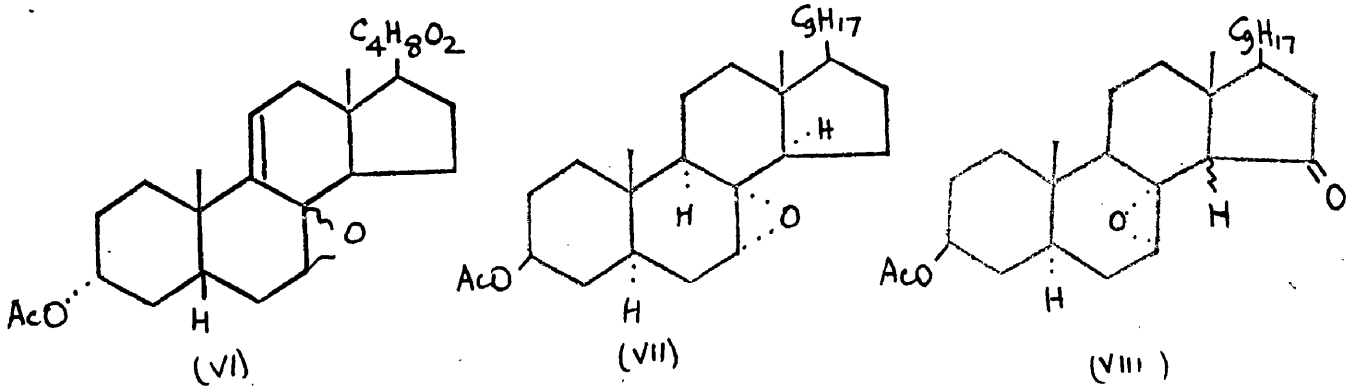
(I) (II) (III)

22:23-dibromo-11-oxoergost-7-en-3β-yl acetate (I) with perbenzoic acid in chloroform gives, in high yield, 22:23-dibromo-7α:8α-epoxy-11-oxoergostan-3β--yl acetate (IV). The structure of which follows from its method of preparation and from the following reactions. The oxo-epoxide (IV) does not show intense selective absorption in the ultra-violet above 2000 Å., and the absence of a hydroxyl group was confirmed by its infra-red absorption spectrum. When treated with zinc dust in neutral solvent, it is smoothly debromin-

ated to 7α:8α-epoxy-11-oxoergost-22-en-3β-yl acetate (V).

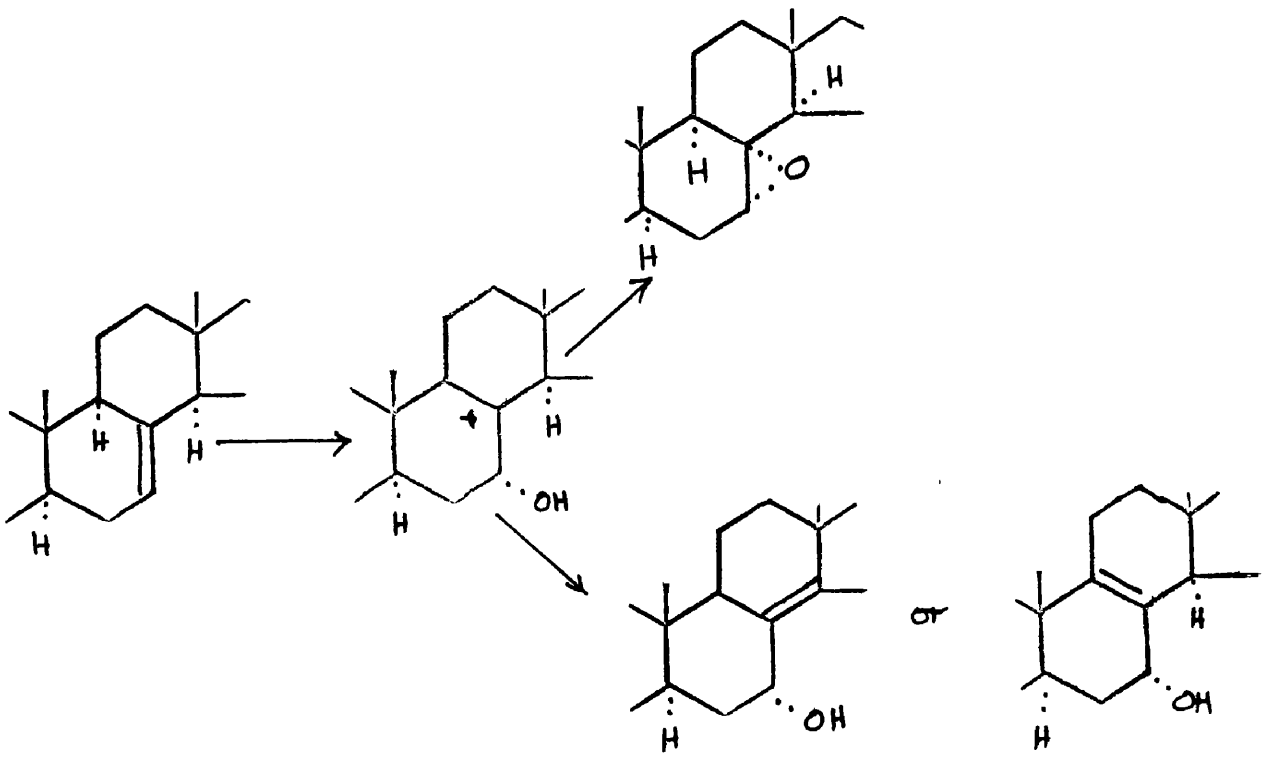


The epoxidation of the isolated Δ^7-bond in a natural steroid had not been observed previously. Before the commencement of this problem only one 7:8-epoxide had been described in the literature (19), methyl 3α-acetoxy-7ξ:8ξ-epoxychol-9(11)--enate (VI) prepared from the corresponding 7:9(11)--diene by treatment with monoperphthalic acid. A number of steroid 7:8-9:11-diepoxides have been described by Budziarek (6), Djerassi (55), Jones (24) and Tishler (25) and recently, Barton has described



the preparation (7) of 7α:8α-epoxyergost-22-en-3β-yl acetate (VII) and of the oxo-epoxide, 7α:8α-epoxy--15-oxo-14ξ-ergost-22-en-3β-yl acetate (VIII) by the photo-oxidation (50) of ergosta-7:14:22-trien-3β-yl acetate (ergosteryl-B_3 acetate). According to Fieser (56, 26) oxidation of a Δ^7-5α-stenol with peracid proceeds by initial hydroxylation at $C_{(14)}$, followed by allylic rearrangement to a $\Delta^{8(14)}$-7-hydroxy compound. This mechanism does not account for the formation of a 7:8-epoxide. It has therefore, been suggested (54) that peracid attack on Δ^7-stenols results in initial hydroxylation at $C_{(7)}$ (OH^+ attack) with the elimination of a proton in one of two ways, as shown, according to the conditions of the reaction i.e. either formation of a 7:8-epoxide or one or both of the allylic alcohol systems. This implies that the 7:8-epoxide and the $\Delta^{8(14)}$-7-hydroxy compound are not interconvertible. To test this postulate, a sample of Barton's epoxide (VII) was prepared; it was found that this epoxide is stable to benzoic acid in chloroform, so providing some support for the mechanism postulated. Benzoic acid in chloroform was chosen since the use of per-

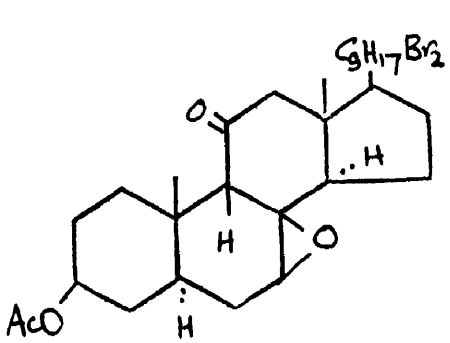
benzoic acid (58) gave the 8(14)-en-7α-hydroxy compound (which was then further oxidised to the 8:14-epoxide) suggesting the possibility in this



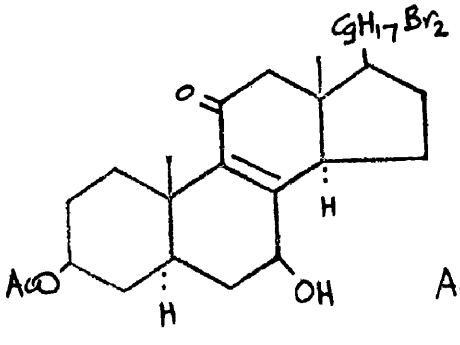
reaction of an acid-catalysed rearrangement to the allylic alcohol system.

22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (IV) is rearranged with mineral acids although it is somewhat more stable than the iso-oxo-epoxide (III). It is recovered unchanged after treatment with dilute sulphuric acid in dioxan at room temperature, and a trace of hydrogen bromide in chloroform, conditions which convert (III) into (X) and

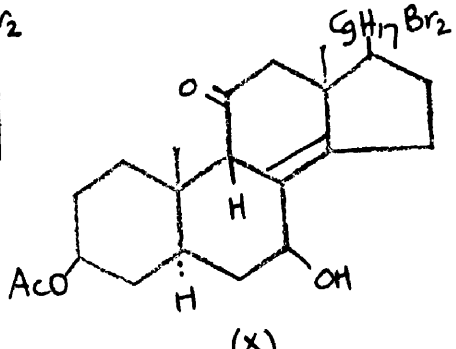
(IX) respectively. With aqueous hydrogen bromide in acetic acid-chloroform the oxo-epoxide (IV) gave 22:23-dibromo-7:11-dioxoergostan-3β-yl acetate (XI) hence confirming the location of the epoxide group at $C_{(7)}$: $C_{(8)}$. Treatment of the oxo-epoxide (IV) with dilute sulphuric acid in dioxan at 80° gives 22:23-dibromo-7α-hydroxy-11-oxoergost-8-en-3β--yl acetate (XII) which shows the characteristic ultra-violet absorption spectrum of an αβ-ketone.



(III)



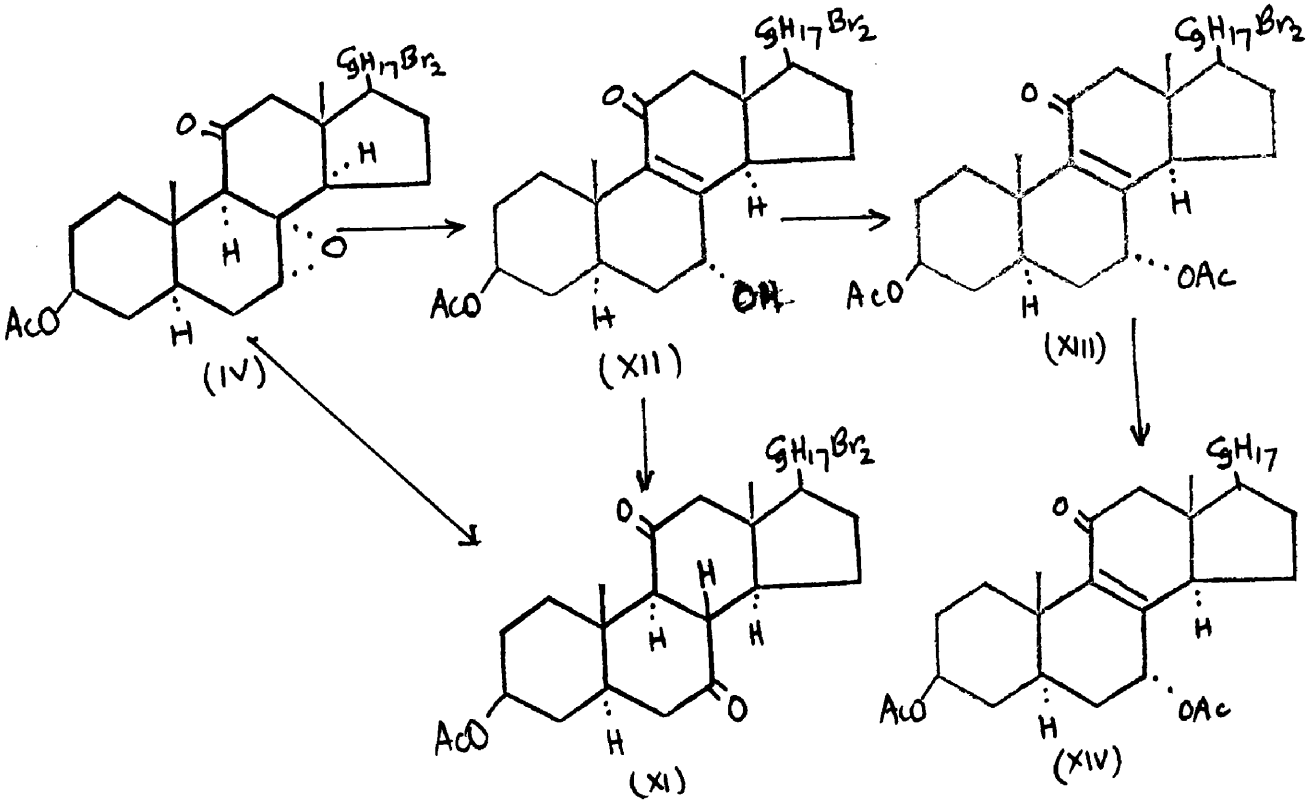
(IX)



(X)

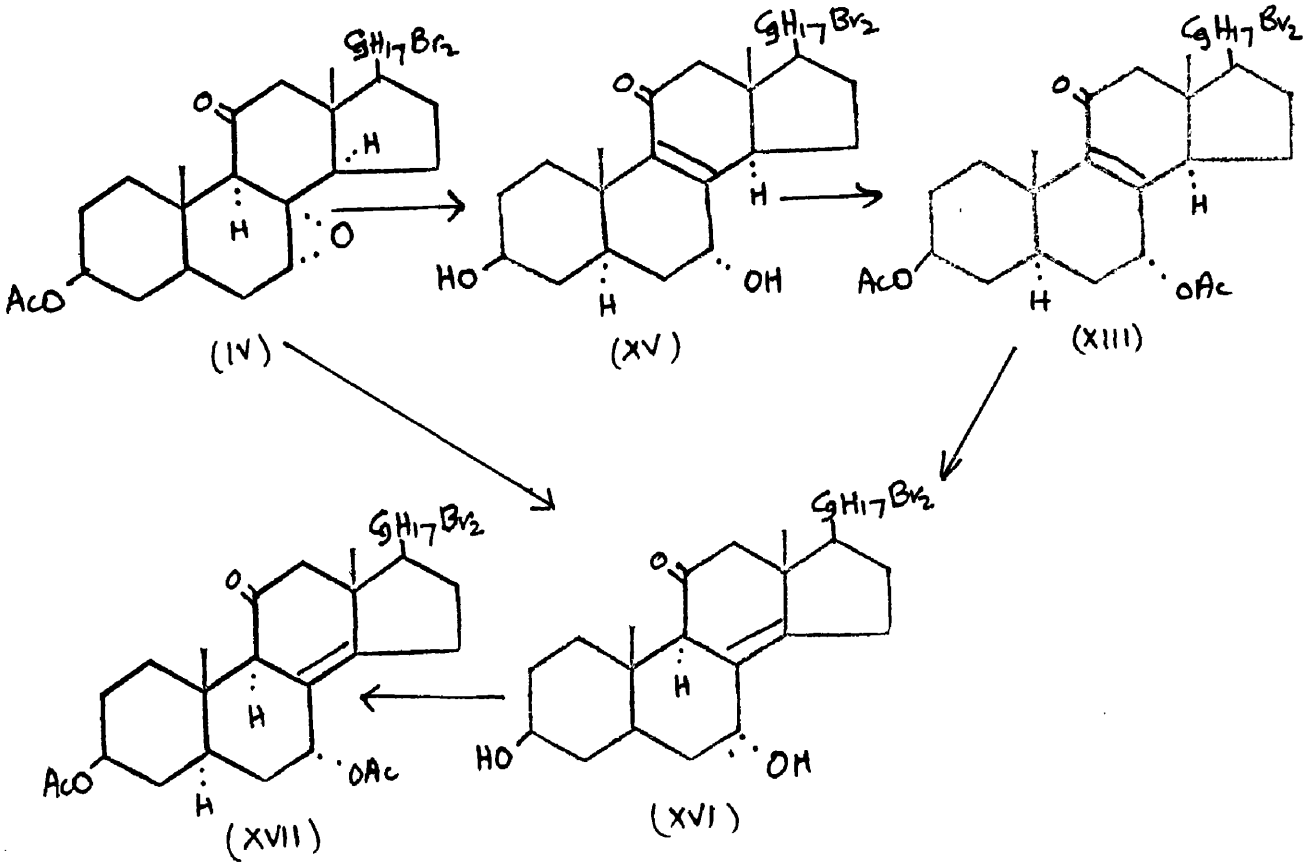
The presence of a hydroxyl group was established by acetylation which yielded a diacetate (XIII). Both (XII) and (XIII) differ from (IX) and its di-acetate respectively, and this difference can only be in the orientation of the hydroxyl group at $C_{(7)}$. This permitted the assignment of the β-orientation to the epoxide grouping in the iso-oxo-epoxide (III).

The diol monoacetate (XII) is converted into the saturated dione (XI) by aqueous hydrogen bromide in acetic acid-chloroform and is consequently an intermediate in its preparation from (IV). With hydrogen bromide in chloroform an impure specimen of 22:23--dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate (XII) was obtained (Max. at 2490 Å, ε 7300) which could not be purified. Debromination of 22:23--dibromo-3β:7α-diacetoxyergost-8-en-11-one (XIII) with zinc gave 3β:7α-diacetoxyergosta-8:22-dien-11--one (XIV) also described by Henbest and Wagland (27) who obtained it from the acetolysis of 9α:11α-epoxyergosta-7:22-dien-3β-yl acetate followed by oxidation



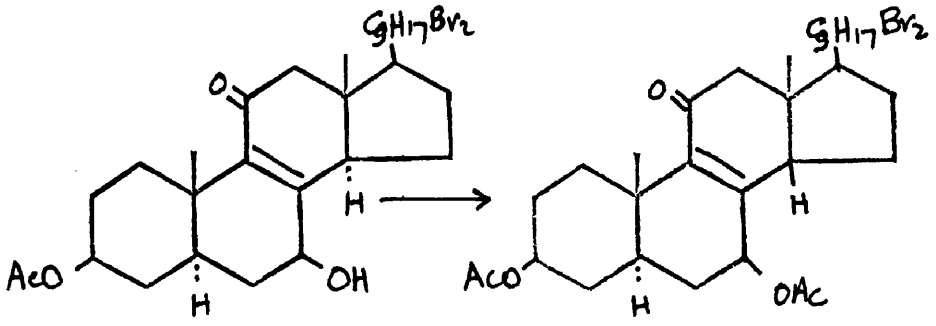
of the intermediate 11α-hydroxy compound with chromic acid.

The behaviour of the oxo-epoxide (IV) with alkali was next examined. In 1% methanolic potassium hydroxide at <u>room temperature</u> it gives 22:23-dibromo-3β:7α--dihydroxyergost-8-en-11-one (XV) acetylation of which gives the diacetate (XIV) mentioned above.



When treated with <u>refluxing</u> methanolic potassium hydroxide the oxo-epoxide (IV) gives 22:23-dibromo--3β:7α-dihydroxyergost-8(14)-en-11-one (XVI) which

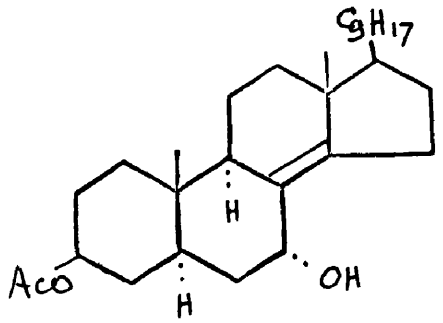
shows the light absorption characteristic of the isolated 8:14-double bond and is readily acetylated to the diacetate (XVII). It was shown that 22:23--dibromo-3β:7α-diacetoxyergost-8-en-11-one (XIII) is an intermediate in the conversion of (IV) into the $\Delta^{8(14)}$-isomer (XVI) since it is converted into the last compound by refluxing methanolic potassium hydroxide. The difference in behaviour of the 7α- and 7β-hydroxy substituted 22:23-dibromo-11-oxoergost--8-en-3β-yl acetates is noteworthy. The 7α-hydroxy derivative (XV) is converted into an alkali-stable βγ-unsaturated ketone (XVI). In the case of 22:23--dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (IX), treatment with alkali followed by acetylation gave the 14β-epimer (XVIII).



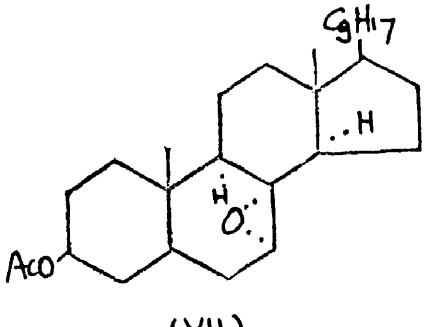
(IX) (XVIII)

The 7α:8α-configuration is ascribed to the

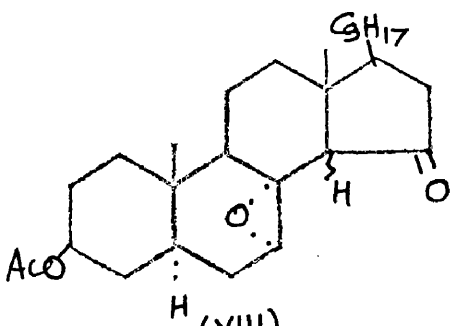
epoxide ring in the oxo-epoxide (IV) in analogy with the established attack from the rear (α) face of Δ^7-stenols by osmium tetroxide acid. Oxidation of cholest-7-enyl acetate with osmium tetroxide followed by hydrolysis yields cholestane--3β:7α:8α-triol (Fieser (26, 27), Wintersteiner and Moore (58)); it follows that the hydroxyl groups in the unsaturated alcohols (XII), (XV), (XVI) are 7α-orientated. Since the completion of this work



(XIX)



(VII)

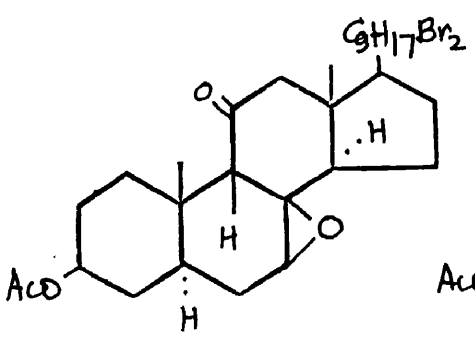


(VIII)

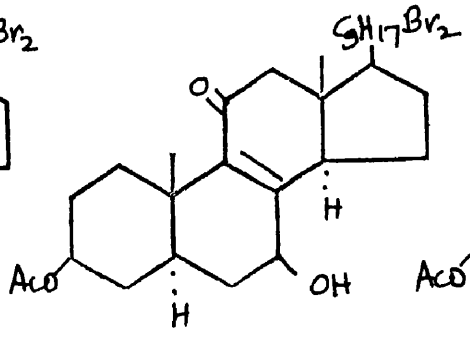
further support for rear (α) attack on Δ^7-stenols by oxidising agents has been obtained from the selenium dioxide oxidation of 5-dihydroergosteryl acetate (59) to products including 7α-hydroxyergosta-8(14):22-dien--en-3β-yl acetate (XIX) and the preparation of the 7α:8α-epoxides (VII) and (VIII) by Barton (7, 50).

22:23-Dibromo-11-oxoergosta-8:14-dien-3β-yl Acetate and Related Compounds.

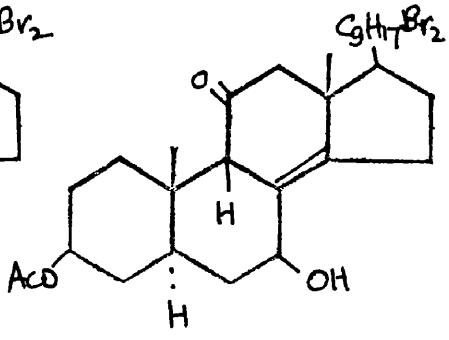
Some aspects of the rearrangement of 22:23--dibromo-7β:8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (I) with acid have been discussed. Mild acidic conditions on the oxo-epoxide (I) gave 22:23-dibromo--7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (II) and 22:23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en--3β-yl acetate (III) by treatment with a trace of hydrogen bromide in chloroform and by the action of dilute sulphuric acid in dioxan respectively; the



(I)



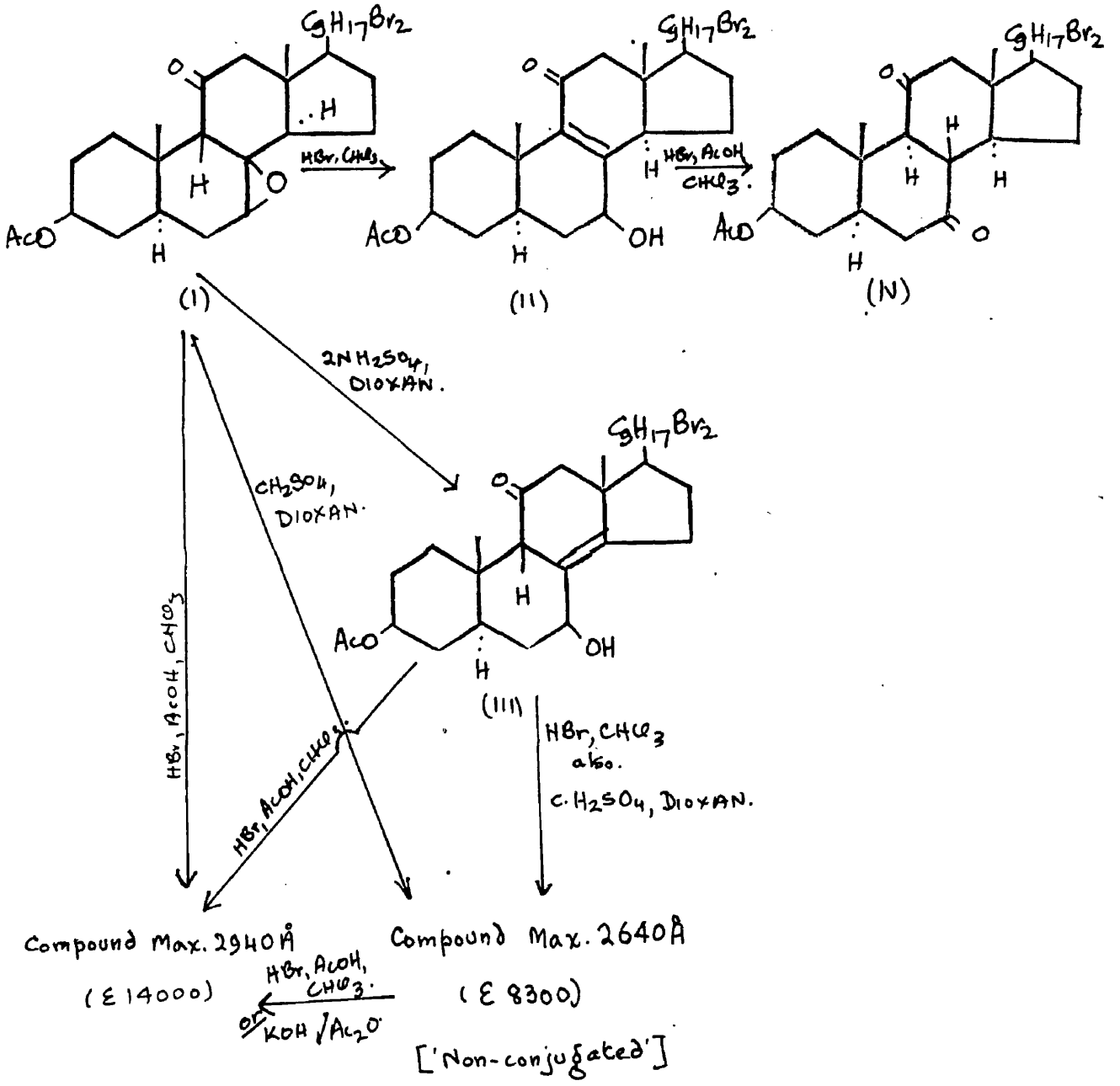
(II)



(III)

former compound with aqueous hydrogen bromide in acetic acid-chloroform gives 22:23-dibromo-7:11-dioxo-

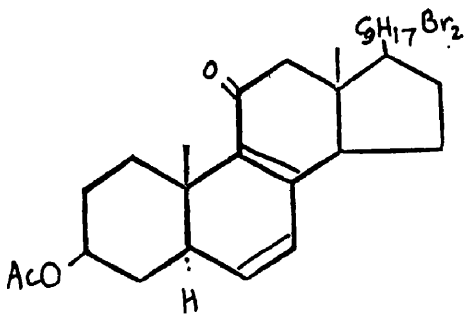
ergostan-3β-yl acetate (IV) while the latter gives a conjugated oxo-diene (Max. 2940 Å ε14,000) under identical conditions. This oxo-diene was also isolated along with the 7:11-dione (IV) from treatment of the oxo-epoxide (I) with this reagent. In experiments to determine whether the $\Delta^{8(14)}$-11--ketone (III) was an intermediate in the preparation of the Δ^{8}-11-ketone (II) 22:23-dibromo-7β-hydroxy-11--oxo-9β-ergost-8(14)-en-3β-yl acetate (III) was treated with a trace of hydrogen bromide in chloroform [conditions which gave (II) from (I)]. This led to dehydration and the formation of an isomeric oxo--diene (Max. 2640 Å. ε 8,300); the position of the ultra-violet absorption maxima shows that it cannot contain a fully conjugated dienone system and the compound was designated the "non-conjugated" oxo--diene. It was isomerised to the fully conjugated compound (Max. 2940 Å. ε 14,000) by alkaline hydrolysis, followed by acetylation, and by treatment with aqueous hydrogen bromide in acetic acid-chloroform. This "non-conjugated" oxo-diene was also obtained from the oxo-epoxide (I) by treatment with (a) dry



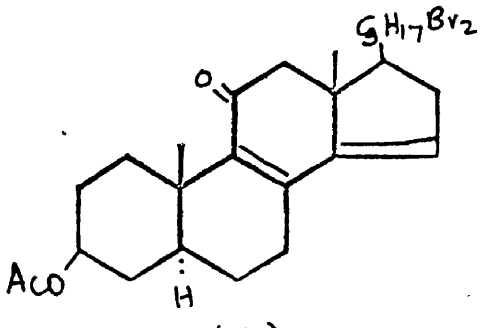
hydrogen chloride in chloroform, (b) concentrated sulphuric acid in dioxan, (c) acetic acid. De-bromination of the "non-conjugated" oxo-diene with

zinc in neutral solvent gave the corresponding Δ^{22}--compound (Max. 2640 Å. ε 8300), also obtained from the dibromo-oxo-epoxide (I) by treatment with zinc in acetic acid. Treatment of the dibromo-conjugated oxo-diene with zinc in ether-ethanol gave the Δ^{22}--compound (Max. 2940 Å. ε14000) also obtained from the debrominated oxo-epoxide (V) along with 7:11--dioxoergost-22-en-3β-yl acetate (VI) by rearrangement with aqueous hydrogen bromide in acetic acid--chloroform.

The conjugated oxo-diene (Max. 2940 Å.) contains a fully conjugated dienone system and only two formulations are possible - either the 6:8-dien-11-one (VII) or the 8:14-dien-11-one (VIII). It was appreciated that reduction of the 11-ketone to a



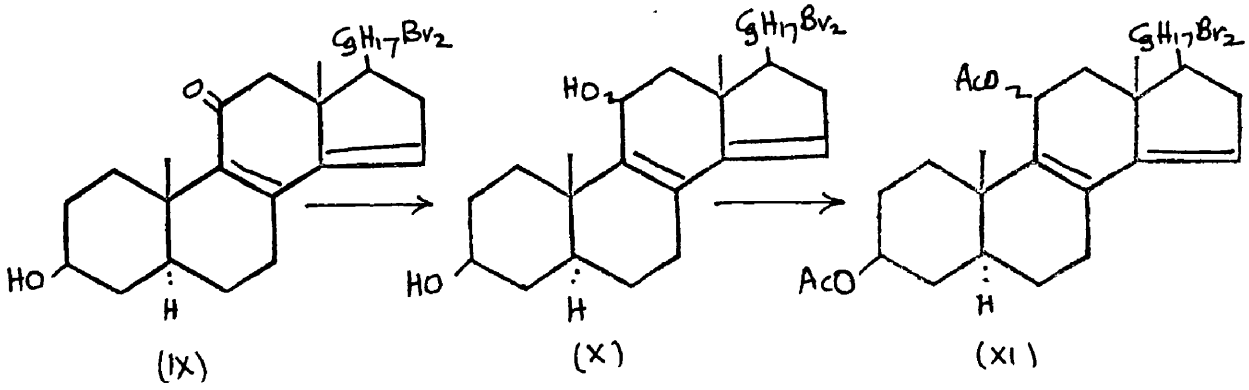
(VII)



(VIII)

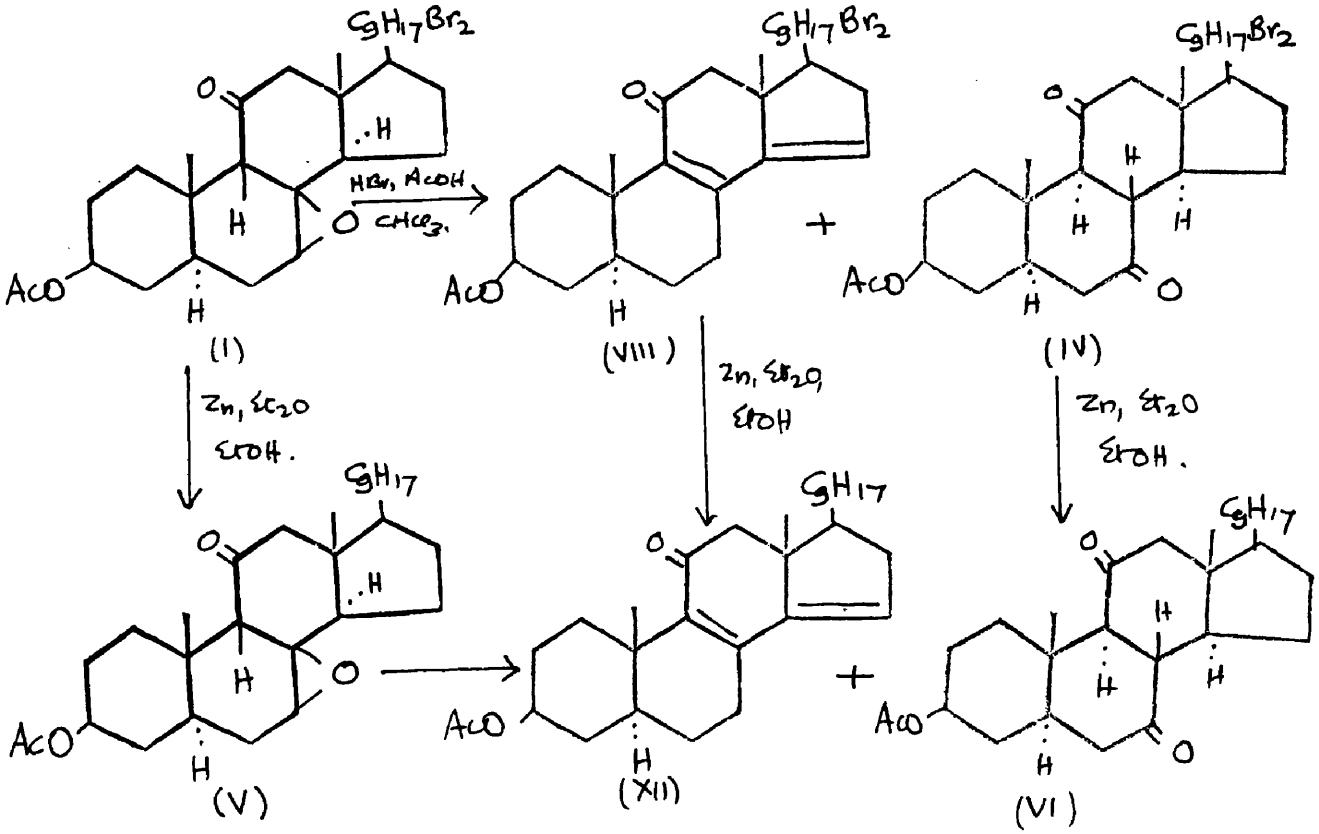
hydroxyl group would leave either a homo-annular 6:8-diene system (Max. 2750-2800 Å.) from formula (VII) or the heteroannular 8:14-diene system (Max. 2500 Å. ε 19,000) from formula (VIII) and thus permit a distinction between these formulations. Accordingly, the use of several metallic hydrides for this reduction was investigated avoiding the use of acid in the isolation procedure. The first to be employed, lithium aluminium hydride in ether, followed by acetylation, gave an intractable mixture from which a small amount of a mixed crystal (Max. 2500 Å, ε 3500) was isolated. Reduction of the 3--alcohol (IX) with sodium borohydride also gave a mixed crystal [Maxima at 2500(15,000) and 2940 Å. (ε 5000)]. Under suitable conditions, reduction with lithium borohydride in tetrahydrofuran afforded a quantitative yield of a compound formulated as 22:23--dibromoergosta-8:14-dien-3β:11ξ-diol (XX). The position of the dienic chromophore is deduced from its ultra-violet absorption maximum at 2500 Å, (ε 19,400) closely corresponding to that of ergosterol-B_2 (ergosta-8:14:22-trien-3β-ol) [Fieser (60)] which has

maximum at 2500 Å. (ε 19400). This differs



considerably from that of a steroid homoannular--6:8-diene which would be expected to absorb at 2750-2800 Å. (ε ca. 10,000). Consequently the conjugated oxo-diene is 22:23-dibromo-11-oxoergosta--8:14-dien-3β-yl acetate (VIII). Attempts to regenerate the parent oxo-diene (IX) by selective oxidation of the 11-hydroxyl group in (X) with manganese dioxide (67) were unsuccessful. Acetylation at room temperature of 22:23-dibromoergosta-8:14--dien-3β:11ξ-diol (X) gave a <u>diacetate</u> (XI) (absence of hydroxyl group in the infra-red). It would be expected that reduction of the 11-ketone under these

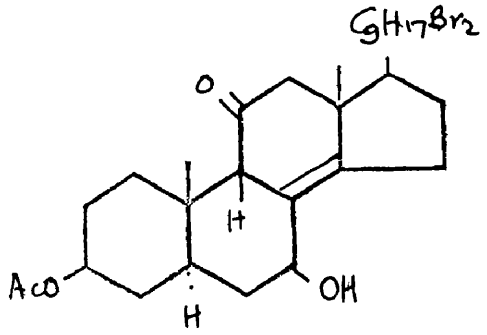
conditions would give a β-orientated hydroxyl group



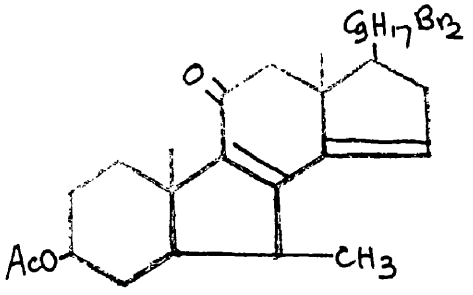
at $C_{(11)}$ which would not acetylate under these mild conditions, however, the vicinal effect of the 8:14--diene system may modify the reactivity at $C_{(11)}$ and so invalidate any attempt to assign a configuration to this hydroxyl group.

The debrominated conjugated oxo-diene is, therefore, 11-oxoergosta-8:14:22-trien-3β-yl acetate (XII). This formulation has been given to a compound by Laubach, Schreiber, Agnello, Lightfoot and Brunings

(9) obtained by the selective hydrogenation of 11-oxoergosta-6:8:14:22-tetraen-3β-yl acetate. The constants of their compound differ considerably from our preparation, viz. m.p. 127-128.2°, $[\alpha]_D$ + 20°, Max. 2910 Å. (log. 4.06 in ether) compared with our constants m.p. 145-6°, $[\alpha]_D$ -2°, Max. 2940 Å. (ε14000). It was possible that dehydration of the oxo-epoxide (I) and of the $\Delta^{8(14)}$-diol mono-acetate (III) was accompanied by B-ring contraction in which case, our compound is a different compound (e.g. XIII)



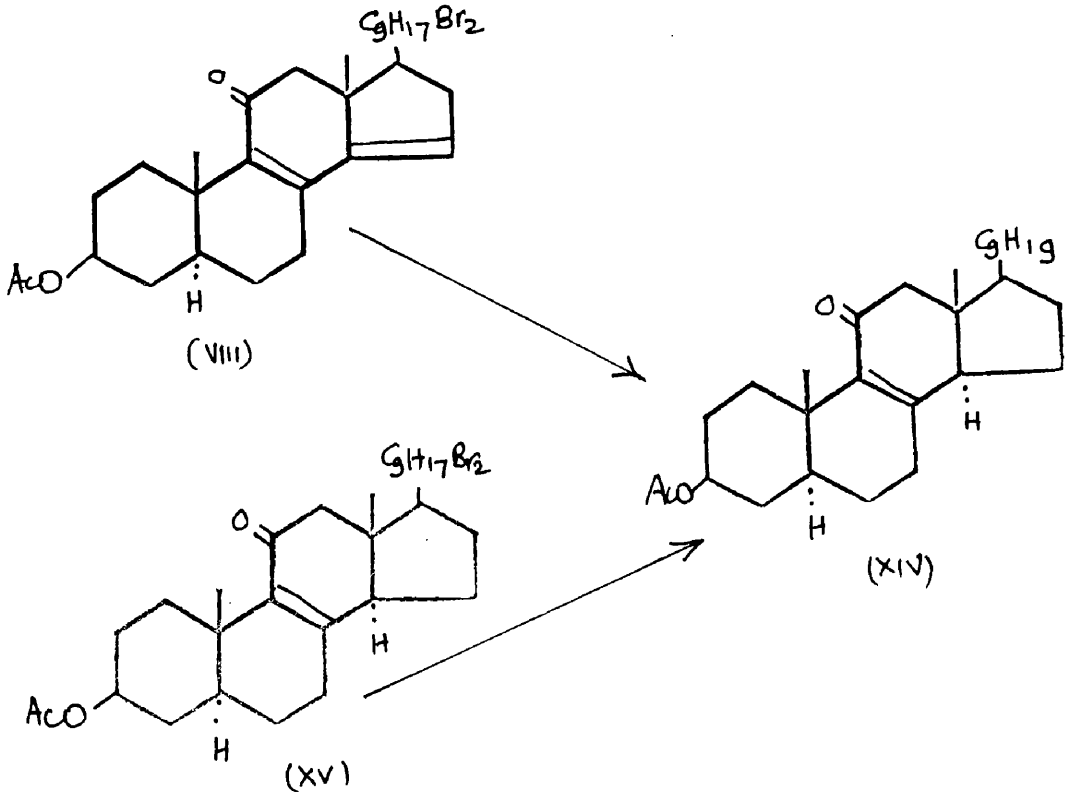
(III)



(XIII)

from that described by Laubach et al. (9). Hydrogenation experiments were therefore carried out to see if the subsequent products possessed a steroid

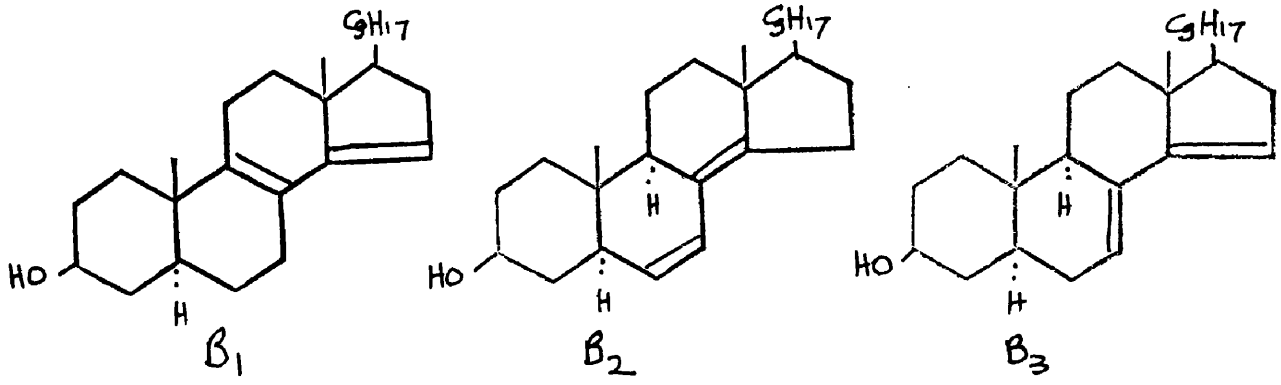
nucleus. Hydrogenation of 22:23-dibromo-11-oxoergosta--8:14-dien-3β-yl acetate (VIII) with Raney nickel in dioxan gave a compound identified as 11-oxoergost--8-en-3β-yl acetate (XIV) previously obtained by Bladon et al. (32) and by Laubach et al. (9) and confirmed by direct comparison with a specimen obtained by hydrogenation of 22:23-dibromo-11-oxoergost-8-en--3β-yl acetate (XV) with Raney nickel. It follows



that our conjugated oxo-diene is correctly represented by (VIII) and (XII). In a private communication to

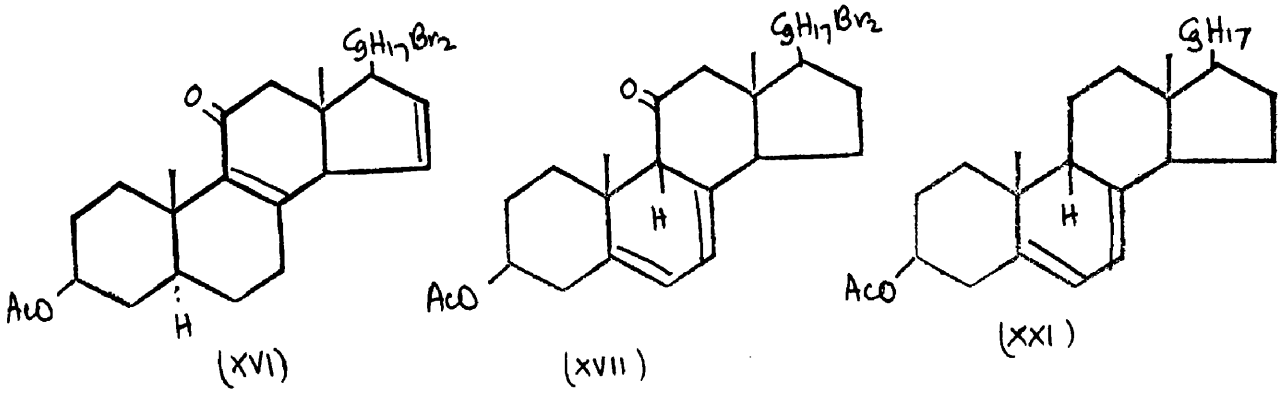
Professor Spring, Dr. Laubach reports that he and his colleagues have observed some variation in the physical properties of later preparations probably due to the not entirely selective course of the hydrogenation and a sample of a subsequent preparation which he kindly included had m.p. 140-141°, $[\alpha]_D$ + 1° in close agreement with our figures. Direct comparison with our preparation gave no depression in m.p.

22:23-dibromoergosta-8:14-dien-3β:11ξ-diol (X) and its diacetate (XI) are extremely labile in the presence of acids. Treatment with dry hydrogen chloride gave an intractable gum with no absorption above 2200 Å. and attempted debrominations with zinc in neutral solution led to similar intractable gums with no absorption above 2200 Å. This rearrangement of 11-hydroxyergosterol-B_1 to mixtures with no absorption above 2200 Å. is in marked contrast to the rearrangement (62,63)of ergosterol-B_1 which yields a separable mixture of ergosterol-B_1, B_2, and B_3 respectively.

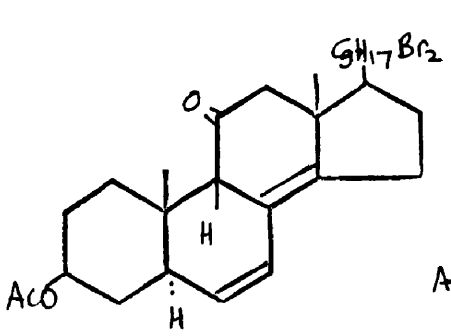


Ergosterol Isomers.

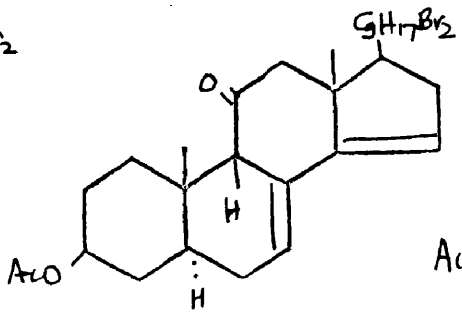
The structure of the "non-conjugated" oxo-diene may now be considered. It was believed that five possibilities existed (XVI-XX). The position of the maxima at 2640 Å. necessitated consideration of the $\alpha\beta$-ketone (XVI) with an isolated double bond, possibly at $C_{(15)} - C_{(16)}$.



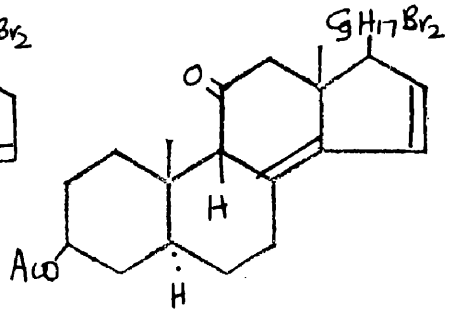
This was excluded since the "non-conjugated" oxo--diene gave a deep brown colour with tetranitromethane in chloroform and by the preparation of the related 11-alcohol with absorption maximum at 2610 Å (ε 11,000) by reduction of the oxo-diene with lithium borohydride in tetrahydrofuran. This leaves four possibilities (XVII-XX) all of which



(XVIII)



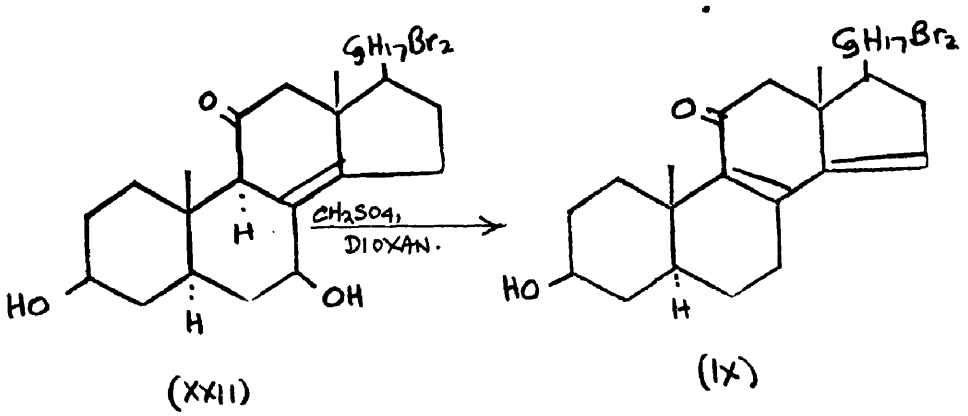
(XIX)



(XX)

have a hydrogen atom at $C_{(8)}$ and it was considered necessary to determine the orientation of this hydrogen atom. It was noted that the "non-conjugated" oxo-diene was prepared from parent compounds (I) and (III) each possessing a β-hydrogen atom at $C_{(8)}$ and it was believed that this configuration was retained

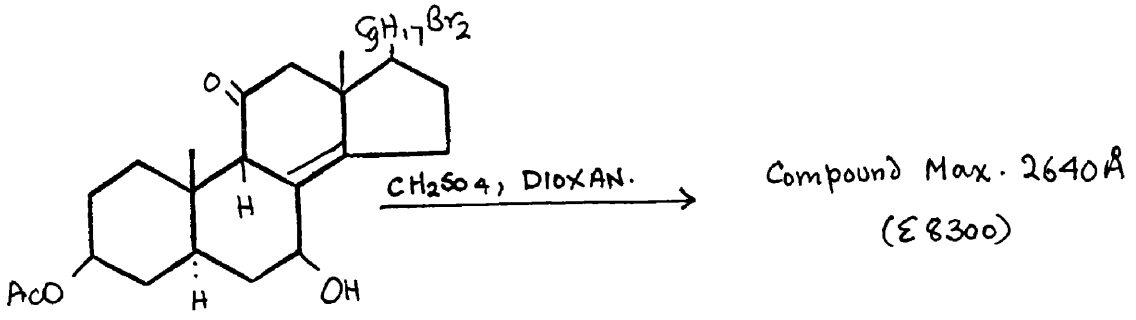
in the oxo-diene. Accordingly, the dehydration of the 9-epimeric 7β-hydroxy-8(14)-en-11-ones was investigated, using identical conditions, and the products compared. The 9α-epimer-22:23-dibromo-11--oxoergost-8(14)-en-3β:7β-diol (XXII) was dehydrated with concentrated sulphuric acid in dioxan to the



(XXII) (IX)

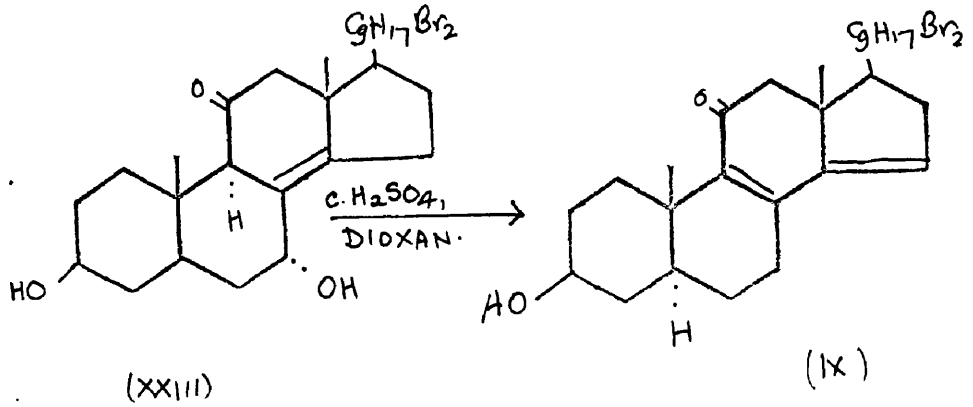
conjugated oxo-diene-(IX); whereas identical treatment of the 9β-compound 22:23-dibromo-7β-hydroxy-11--oxo-9β-ergost-8(14)-en-3β-yl acetate (III) gave the "non-conjugated" oxo-diene. Difference in configuration at $C_{(7)}$ does not appear to affect the dehydration since the 7α-hydroxy compound 22:23-dibromo--11-oxoergost-8(14)-en-3β:7α-diol (XXIII) also gives the conjugated oxo-diene (IX) under these conditions.

The difference in behaviour on dehydration is attributed to the difference in configuration at



(III)

$C_{(9)}$ and in consequence, since the "non-conjugated" oxo-diene is obtained only when the parent compound has a 9β-centre, then the hydrogen at $C_{(9)}$ in the

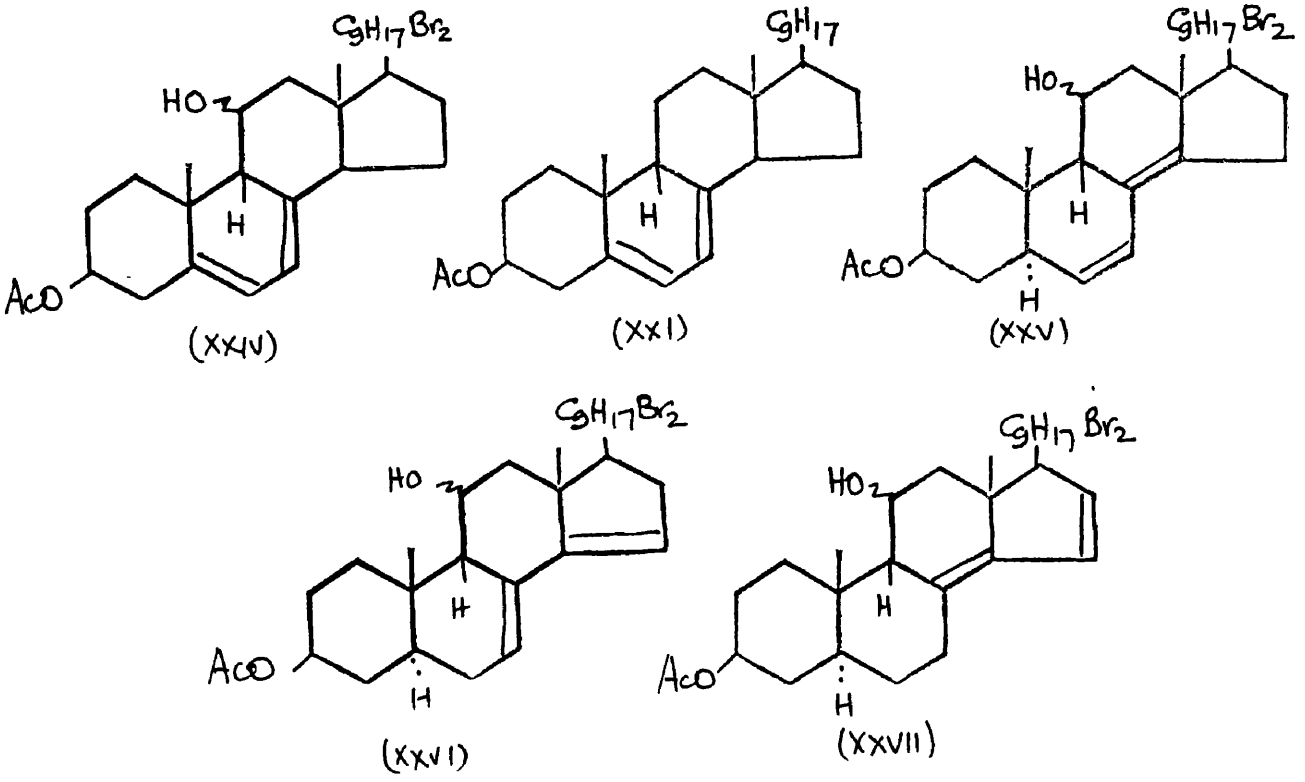


(XXIII) (IX)

"non-conjugated" oxo-diene has the β-configuration. A number of attempts to convert the "non-conjugated" oxo-diene into its 9α-epimer with piperidine and specially prepared alumina [cf. Similar conversions by Bladon et al. (32) and on p. 28 of this thesis] were unsuccessful; either unchanged material was recovered or isomerisation to the conjugated oxo--diene occurred.

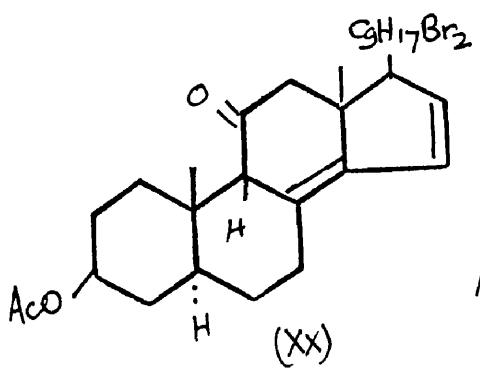
Considering the corresponding formulae (XXIV--XXVII) for the 11-hydroxy diene, obtained by reduction of the "non-conjugated" oxo-diene with lithium borohydride, as a better comparison with known steroid dienic chromophores than the parent oxo-diene, we are forced to reject formula (XXIV) corresponding to 11ξ-hydroxy-isopyrocalciferol from consideration of ultra-violet absorption data (Max. 2610 Å. ε 11,000) compared with isopyrocalciferol which absorbs at 2800 Å. (ε 10,000) (65). We do not believe that the unnatural (β) configuration at $C_{(9)}$ has a marked effect on the ultra-violet absorption of these dienic chromophores and this view is supported by comparison of the absorption data of

ergosterol compared with its 9β-isomer-isopyrocalciferol (XXI); which have principal maxima

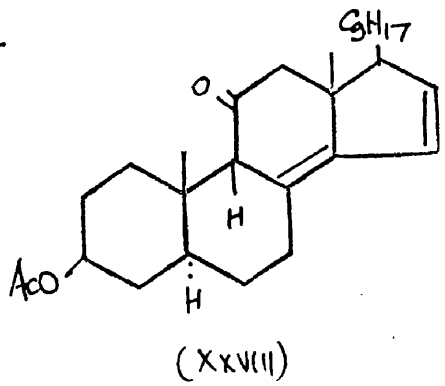


at 2820 and 2800 Å. respectively (64, 65). The transoid diene (XXV) [Max. 2550 Å. ε 17,000 (66)] is precluded by the characteristic cisoid intensity (ε11,000) of our hydroxydiene. Consequently, the 7:14-diene (XXVI) or the 8(14):15-diene (XXVII) are to be considered. In favour of (XXVI) is the apparently simple mechanism for formation of the conjugated oxo-diene (VIII) from the "non-conjugated" oxo-diene and the low intensity of absorption (ε9900)

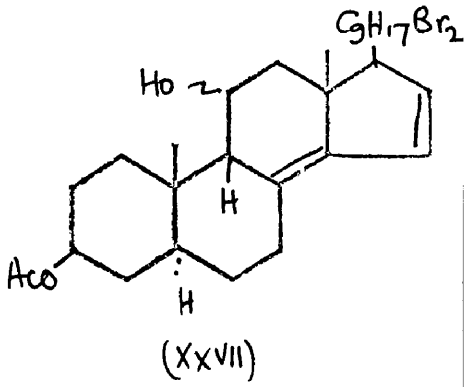
(63), but against this formulation is the wide difference in the position of the absorption maxima at 2420 Å., compared with our compound at 2610 Å., a difference which cannot be attributed solely to the unnatural (β) configuration at C(9); also the non-conjugated oxo-diene did not form an adduct with maleic anhydride under conditions whereby ergosteryl-B_3 acetate (ergosta-7:14:22-trien-3β-yl acetate) formed an adduct (66). We believe that the unconjugated oxo-diene and the hydroxy diene contain an 8(14):15--diene system, and this <u>cisoid</u> type diene is consonant with the low intensity of absorption in the hydroxy-diene (ε 11,000), and the oxo-diene (ε 8,300). No authentic steroid 8(14):15-diene has been previously described. Djerassi's claim (44) to such a compound has been rejected by Fieser (45).



(XX)



(XXVIII)

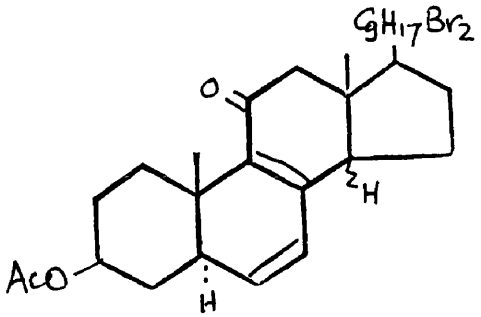


(XXVII)

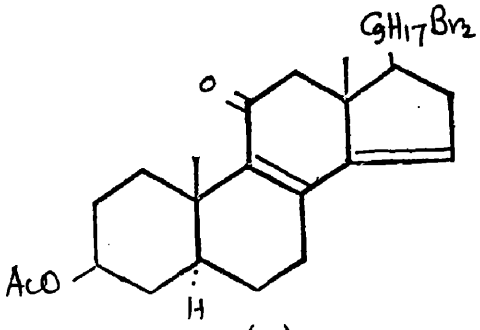
Consequently the "non-conjugated" oxo-diene is formulated as 22:23-dibromo-11-oxo-9β-ergosta--8(14):15-dien-3β-yl acetate (XX) the Δ^{22}-compound is 11-oxo-9β-ergosta-8(14):15:22-trien-3β-yl acetate (XXVIII) and the hydroxy-diene is 22:23-dibromo-11ξ--hydroxyergosta-8(14):15-dien-3β-yl acetate (XXVII). Attempted acetylation of the diol monoacetate (XXVII) at 0° gave unchanged starting material; it would be expected that the hydroxyl group in this compound would have the β-orientation, but again vicinal effects of the diene system make any assignment of configuration hazardous.

11-Oxo-Δ^{8}-Steroids.

During a study of the stability of the α--hydrogen atom at $C_{(14)}$ to hydrogen bromide in acetic acid-chloroform, which was of interest in investigations of the conjugated dienone (II) when the structure (I) was considered a possibility. 22:23-dibromo-11-oxoergost-8-en-3β-yl acetate (III) was treated with this reagent and an isomeric αβ--ketone (Max. at 2480 Å ε 8600) obtained. This is



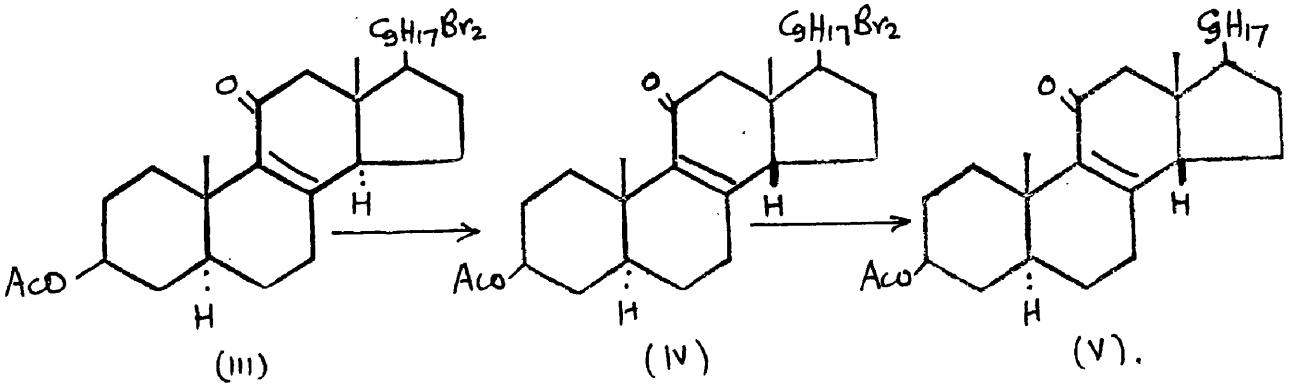
(I)



(II)

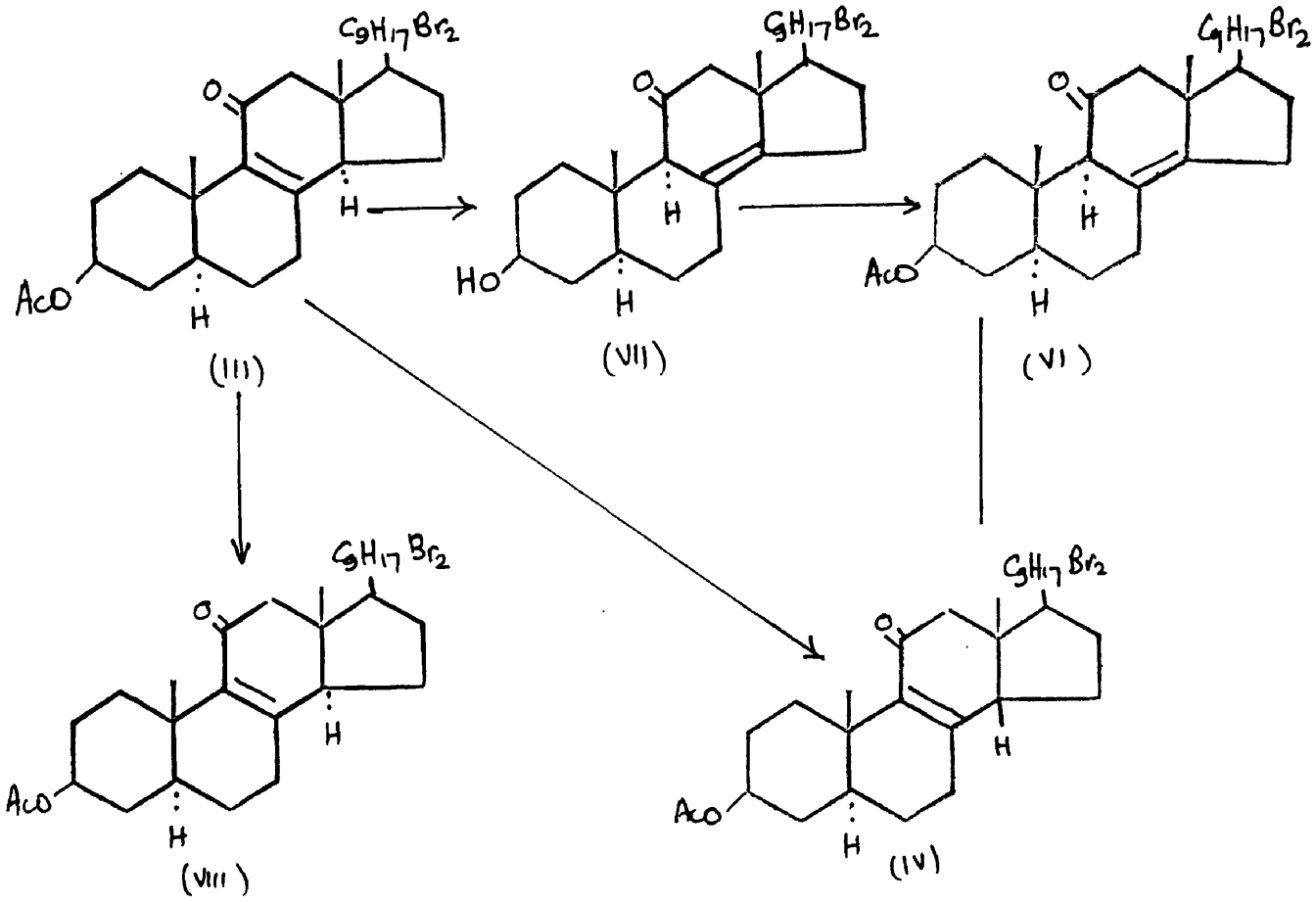
assigned the structure 22:23-dibromo-11-oxo-14β-ergost--8-en-3β-yl acetate (IV) and is smoothly debrominated with zinc in ether-methanol to 11-oxo-14β-ergosta--8:22-dien-3β-yl acetate (V). These 14β-epimers

(IV and V) were prepared by Johnson (47) independently

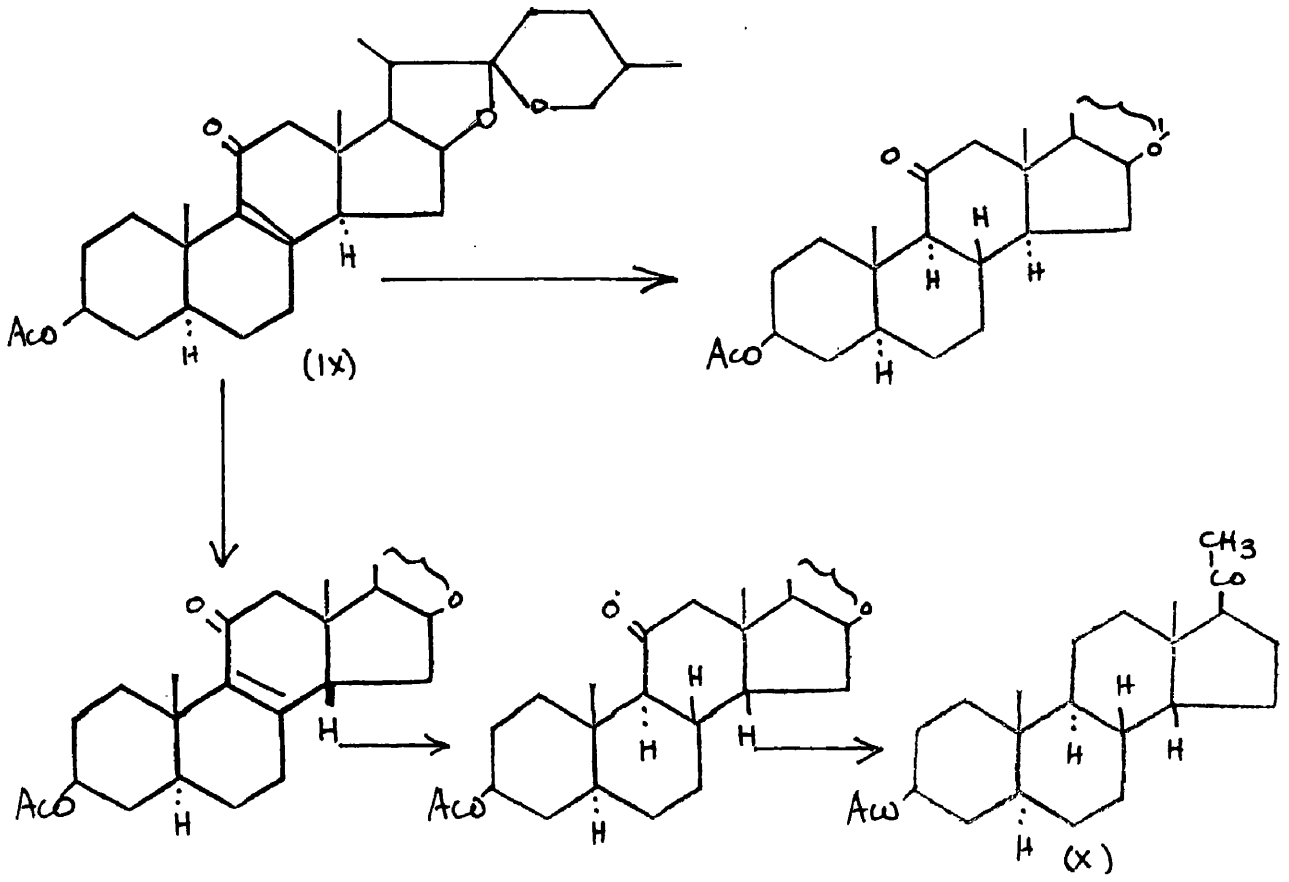


during attempts to prepare the alcohol corresponding to (III). These experiments led to a study of the behaviour of 22:23-dibromo-11-oxoergost-8-en-3β-yl acetate (III) with alkali. Short treatment of (III) with 12% ethanolic potash, and acetylation, gave a βγ-unsaturated ketone whose ultra-violet and infra--red absorption spectra are in agreement with its formulation as 22:23-dibromo-11-oxoergost-8(14)-en--3β-yl acetate (VI); prolonged treatment of (III) or the intermediate βγ-uhsaturated ketone (VI) with alkali, followed by acetylation, gave the 14β-isomeric αβ-ketone (IV). Djerassi et al. (48) have prepared

corresponding epimers in the 5α-spirostane series and have prepared (49) the parent 14β-compound (X)

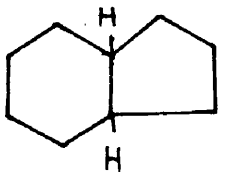


by lithium-liquid ammonia reduction of (IX) followed by removal of the 11-ketone by Wolff-Kishner reduction under forcing conditions and conversion to pregnane side-chain, thus confirming the presence of the unnatural (β) hydrogen at $C_{(14)}$ and showing that the trans-locking (8β:9α) of rings B/C is the stable configuration in 14β-steroids.

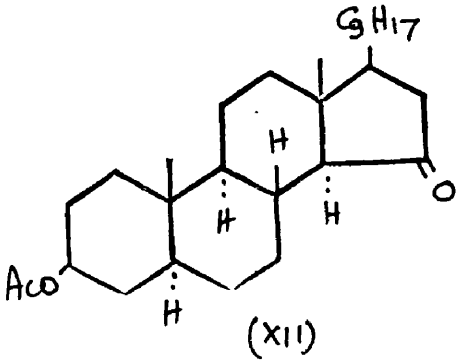


It is pertinent to consider the stability of the hydrogen atom at the C/D ring-junction. Barton and Laws (50) have shown that it is more stable in the trans than in the cis configuration by recovery of 3β-acetoxyergost-22-en-15-one (XII) unchanged from vigorous treatment with alkali. This contrasts with the observation that cis-hydrindane (XI) is somewhat more stable than trans-hydrindane. It is suggested from our experiments that the trans-con-

figuration at $C_{(13)}$, $C_{(14)}$ is the more stable.

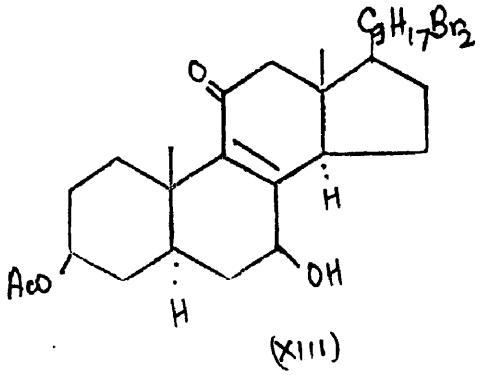


(XI)

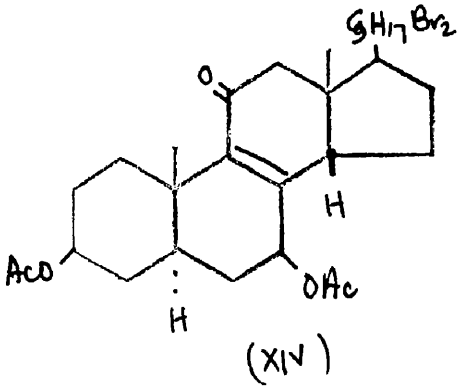


(XII)

in unsaturated steroids. Epimerisation at $C_{(14)}$ also occurs in the preparation of 22:23-dibromo--3β:7β-diacetoxy-14β-ergost-8-en-11-one (XIV) from the corresponding natural (14α)-diol monoacetate (XIII) previously discussed.



(XIII)



(XIV)

EXPERIMENTAL

Melting points are uncorrected.
Specific rotations were determined in chloroform solutions (unless otherwise stated) in a 1-dm. tube at room temperature.

Ultra-violet absorption spectra were measured in absolute ethanol solution (except where otherwise stated) with a Unicam SP. 500 spectrophotometer.

Micro-analyses were by Dr. A.C.Syme and Mr. Wm. McCorkindale, and the infra-red absorption spectra by Mr. A. Pajaczkowski, B.Sc., to whom grateful acknowledgements are due.

Finally, we thank Glaxo Laboratories Ltd., Greenford, for gifts of 22:23-dibromo-9α:11α--epoxyergost-7-en-3β-yl acetate.
For chromatography, activated alumina (supplied by Savory and Moore), Grade II (except where stated otherwise) standardised according to Brockmann, was employed.

"Working up in the usual manner" means addition of water, extraction with ether, washing with sodium hydrogen carbonate solution, and water, drying (Na_2SO_4) and evaporation under reduced pressure.

11-Oxo-Δ^7-Ergostenyl Derivatives.

22:23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl Acetate. - A suspension of 22:23-dibromo-9α:11α--epoxyergost-7-en-3β-yl acetate (500 mg.) [Budziarek, Johnson and Spring (23)] in dry ether (20 c.c.) and acetic anhydride (15 c.c.) was shaken at room temperature with boron trifluoride etherate (10 drops). Dissolution was complete after 10 minutes, whereafter solid began to separate. After 1 hour the solid (220 mg.), m.p. 198° was collected and crystallised from acetone from which 22:23-dibromo-11--oxo-9β-ergost-7-en-3β-yl acetate separated as prismatic needles or prisms, m.p. 200° undepressed when mixed with a specimen prepared as described by Maclean and Spring (28), $[\alpha]_D$ - 122° (c,1.1) (Found: C,58.3; H,7.5. Calc. for $C_{30}H_{46}O_3Br_2$: C,58.6; H,7.55%).

11-Oxo-9β-ergosta-7:22-dien-3β-yl Acetate. - 22:23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (3.0 g.) in ether-ethanol-benzene (150 c.c.; 1:1:1) was refluxed with ammonium chloride-activated zinc

(10 g.) for 6 hours. The zinc was removed by filtration, the filtrate concentrated to small bulk and extracted with ether. The ethereal extract was washed well with water and dried (Na_2SO_4). The residue was crystallised twice from methanol to give 11-oxo-9β-ergosta-7:22--dien-3β-yl acetate (1.40 g.) as hexagonal plates m.p. 156-8°, $[\alpha]_D$ - 186° (c,1.3) Maclean and Spring (28) give m.p. 159-161°, $[\alpha]_D$ - 206° and Bladon et al. (32) m.p. 159-161°, $[\alpha]_D$ - 191° for this compound.

Behaviour of the βγ-Unsaturated Ketone in Acid Media.

(a) 22:23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (290 mg.) was recovered unchanged from chloroform-acetic acid (15 c.c.; 1:2) at room temperature for 1 hour.

(b) Treatment as above but heated on the steam bath for 1 hour gave crude 22:23-dibromo-11--oxoergost-8-en-3β-yl acetate, $[\alpha]_D$ + 65° (c,1.3). Light absorption: Max. at 2540 Å (ε 7300).

(c) The βγ-unsaturated ketone was refluxed in glacial acetic acid for 2 hours to give 22:23--dibromo-11-oxoergost-8-en-3β-yl acetate, m.p. and mixed m.p. 200-202° $[\alpha]_D$ + 86° (c,0.7) Max. 2540 Å (ε 8700).

11-Oxoergosta-7:22-dien-3β-yl Acetate from 22:23--Dibromo-3β:7β-Diacetoxyergost-8-en-11-one. - Treatment of 22:23-Dibromo-3β:7β-diacetoxyergost-8-en-11--one (226 mg.) (see p.93) in refluxing benzene--methanol-ether (1:1:1; 75 c.c.) with freshly activated zinc (2 g.) for 5 ½ hours gave 11-oxoergosta-7:22--dien-3β-yl acetate (120 mg.) separating from methanol as plates, m.p. 174-176°, $[\alpha]_D$ + 29° (c,1.1). (Found: C,79.1; H,10.1. Calc. for $C_{30}H_{46}O_3$: C,79.2; H,10.2%). It gives a pale yellow colour with tetranitromethane in chloroform. Light absorption: Max. at 2040 Å (ε 3400).

11-Oxoergost-7-en-3β-yl Acetate. - A solution of 11-oxoergosta-7:22-dien-3β-yl acetate (250 mg.) in ethyl acetate (200 c.c.) was shaken in hydrogen for 48 hours with platinum (from 60 mg. PtO_2). Crystallisation of the product from methanol gave

11-oxoergost-7-en-3β-yl acetate (160 mg.) as needles m.p. 162-164°, $[\alpha]_D$ + 47° (c,1.5). For a crude (not analysed) specimen of this compound, Bladon et al. (32) give m.p. 145-156°, $[\alpha]_D$ + 32°. (Found: C,79.15; H,10.8. $C_{30}H_{48}O_3$ requires C,78.9; H,10.6%). Light absorption: Max. at 2050 Å (ε 3500).

Ergost-8(14)-en-3β-yl Acetate ('α'-Ergostenyl Acetate). - 11-Oxoergosta-7:22-dien-3β-yl acetate (150 mg.) in glacial acetic acid (70 c.c.) was shaken in hydrogen for four hours with platinum (from 50 mg. PtO_2). Isolation in the usual manner and crystallisation from methanol gave ergost-8(14)-en-3β-yl acetate m.p. 107-9°, undepressed when mixed with an authentic specimen prepared by Budziarek et al. (68), $[\alpha]_D$ + 0° (c,1.2). Light absorption: Max. at 2990 Å (ε 8800).

7ξ:22:23-Tribromo-11-oxoergost-8-en-3β-yl Acetate. - (cf. 46) - 22:23-Dibromo-11-oxo-9β--ergost-7-en-3β-yl acetate (1 g.) in dry ether (200 c.c.) was treated with a solution of bromine in glacial acetic acid (9.3 c.c.; 0.0316 g./c.c.). After stirring for a further 10 minutes the colourless

solution was washed successively with 1% sodium hydroxide solution, then with water, and dried (Na_2SO_4). Crystallisation of the product from chloroform-methanol gave 7ξ:22:23-tribromo-11--oxoergost-8-en-3β-yl acetate as plates, m.p. 194-195° (decomp.), $[\alpha]_D$ + 67° (c,1.7). Light absorption: Max. 2610 Å (ε 9080).
A later preparation (46) had constants, m.p. 198-199°, $[\alpha]_D$ + 78°. Light absorption: Max. at 2620 Å (ε 9500).

11-Oxoergosta-7:22-dien-3β-yl Acetate from 7ξ:22:23-Tribromo-11-oxoergost-8-en-3β-yl Acetate (46). - A solution of the tribromo compound (1.18 g.) in methanol-ether (150 c.c.; 1:1) was refluxed with activated zinc (6 g.) added in portions over 3 hours. Isolation using ether gave 11-oxoergosta-7:22-dien--3β-yl acetate (340mg.) as plates from methanol, m.p. and mixed m.p. 175-177°, $[\alpha]_D$ + 30° (c,1.2).

Epimerisation of 22:23-Dibromo-11-oxo-9β-ergost-7-en--3β-yl Acetate on an Alumina Column.

The alumina was prepared as follows:
Spence Type 'H' alumina (1 kg.) was stirred for 3

hours with aqueous acetic acid (1.5 l.; 10%), filtered, and washed with distilled water (2 l.), methanol (2 l.) and distilled water (2 l.) and then reactivated by heating at 400° for 5 hours.

22:23-Dibromo-11-oxoergost-7-en-3β-yl Acetate. - A solution of 22:23-dibromo-11-oxo-9β-ergost-7-en--3β-yl acetate (700 mg.) on light petroleum-benzene (1:1; 70 c.c.) was adsorbed rapidly on an alumina column (10 x 1.5 cm.). The column was immediately eluted with benzene (100 c.c.) again under pressure; these operations took 5 minutes. Evaporation of the filtrate under reduced pressure and crystallisation from chloroform-methanol gave 22:23-dibromo-11-oxo-ergost-7-en-3β-yl acetate (620 mg.) as felted needles m.p. 189-190°, $[\alpha]_D$ +29° (c,1.1).
Light absorption: Max. at 2060 Å. (ε 1550).
(Found: C,58.7; H,7.55. $C_{30}H_{46}O_3Br_2$ requires C,58.6; H,7.55%).

Debromination with zinc in neutral solvent (by W.Laird) gave 11-oxoergosta-7:22-dien-3β-yl acetate identical with previous preparations.

22:23-Dibromo-7β:8β-epoxy-11-oxo-9β-ergostan-3β-yl Acetate.

22:23-Dibromo-7β:8β-epoxy-11-oxo-9β-ergostan--3β-yl Acetate. -

(a) A solution of 22:23-dibromo-11-oxo-9β-ergost--7-en-3β-yl acetate (5.9 g.) in chloroform (70 c.c.) was treated over 1 hour at 0° with a freshly prepared solution of perbenzoic acid (Org.Syn., 13, 86) in mineral acid-free chloroform (23 c.c.; 62.5 mg./c.c.). After overnight storage at 0° the solution was diluted with chloroform (150 c.c.) and washed successively with saturated sodium hydrogen carbonate solution, water, and dried (Na_2SO_4) and the chloroform solution concentrated under reduced pressure below 35° and diluted with methanol to give 22:23-dibromo-7β:8β-epoxy-11-oxo-9β--ergostan-3β-yl acetate (5.0 g.) separating from chloroform-methanol as needles m.p. 218-221° (decomp.), $[\alpha]_D$ - 29° (c,0.7). (Found: C,52.7; C, 52.8; H,6.9, 7.1; Cl + Br, 30.75. $C_{30}H_{46}O_4Br_2.\frac{1}{2}CHCl_3$ requires C,53.1; H,6.8; Cl, 7.7; Br,23.15%).

The solvent of crystallisation was not expelled by heating at 100° *in vacuo*; heating at 135° *in vacuo* was accompanied by decomposition as shown by a marked change to dextrorotation, $[\alpha]_D$ + 95° (*c*,0.9) and the appearance of high intensity ultra-violet absorption at 2530 Å. [Max. at 2530 (ε 5360) and 2050 Å (ε 4600)].

Infra-red Spectrum: Peaks at 1730 and 1241 (acetate), 1717 (ketone) and 750 cm^{-1} (asymmetrical stretching frequency of C-Cl bond). The compound gave no colour with tetranitromethane in chloroform.

(b) A suspension of 22:23-dibromo-11-oxo-9β--ergost-7-en-3β-yl acetate (1.7 g.) in dry ether (200 c.c.) was treated with freshly prepared monoperphthalic acid in ether (*Org.Syn.*, *20*, 70) (8.4 c.c.; 91 mg./c.c.) and the mixture refluxed for 5½ hours. The suspended solid (1.2 g.), m.p. 198-199.5°, $[\alpha]_D$ - 122° (*c*,0.5) was unchanged starting material. The ethereal mother liquor on storage deposited needles (240 mg.), m.p. 206-215°, $[\alpha]_D$ - 36° (*c*,0.5) which on crystallisation from benzene-light petroleum

(b.p. 60-80°) gave 22:23-dibromo-7β:8β-epoxy--11-oxo-9β-ergostan-3β-yl acetate (200 mg.) as rosettes of fine needles, m.p. 225-226°, $[\alpha]_D$ - 29° (c,0.7) (Found: C,57.4; H,7.5. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.35%). Infra-red spectrum: Peaks at 1731 and 1245 (acetate) and 1715 $cm.^{-1}$ (ketone). It was undepressed in m.p. when mixed with the solvated specimen described above and on crystallisation from chloroform-methanol it gave needles, m.p. 226-227° containing chloroform of crystallisation.

7β:8β-Epoxy-11-oxo-9β-ergost-22-en-3β-yl Acetate. - A solution of 22:23-dibromo-7β:8β-epoxy-11-oxo-9β--ergostan-3β-yl acetate (1.5 g.) in benzene (50 c.c.), moist ether (50 c.c.) and methanol (50 c.c.) was heated under reflux for 5 hours with zinc dust (5 g.) previously activated by treatment with ammonium chloride. The product, isolated by means of ether, was crystallised from methanol to give 7β:8β-epoxy--11-oxo-9β-ergost-22-en-3β-yl acetate (1.0 g.) as needles, m.p. 185° $[\alpha]_D$ - 64°, - 67° (c,0.5, 1.2) (Found: C,76.3; H,10.0. Calc. for $C_{30}H_{46}O_4$:

C,76.55; H,9.85%).

It gives a pale yellow colour in chloroform with tetranitromethane and does not exhibit high intensity ultra-violet light absorption. Heusler and Wettstein (35) give m.p. 170.5-171.5°, $[\alpha]_D$ -74° for this compound: Henbest and Wagland (27) record m.p. 175-177°, $[\alpha]_D$ -63°.

7:11-Dioxoergost-22-en-3β-yl Acetate from 7β:8β--Epoxy-11-oxo-9β-ergost-22-en-3β-yl Acetate. - 7β:8β--Epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (800 mg.) in chloroform (30 c.c.) and glacial acetic acid (60 c.c.) containing aqueous hydrogen bromide (12 drops; 46%) was kept overnight at room temperature. The crude product was crystallised once from methanol and a solution of the crystalline solid (500 mg.) in benzene-light petroleum (b.p. 60-80°) (100 c.c.; 2:1) was filtered through a column of Grade II-III alumina (15 x 2 cm.); the column was washed with benzene (200 c.c.). Thereafter, benzene (100 c.c.) and benzene-ether (200 c.c.; 19:1) eluted a solid (130 mg.), m.p. 198°, crystallisation of which from aqueous methanol gave 7:11-dioxoergost-22-en-3β-yl

acetate as felted needles, m.p. 198-200°, either alone or mixed with a reference specimen; $[\alpha]_D$ -30° (c,1.7).

(Found: C,76.6; H,9.5. Calc. for $C_{30}H_{46}O_4$: C,76.55; H,9.85%).

22:23-Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl Acetate. - (a) 22:23-Dibromo-7β:8β-epoxy-11-oxo-9β--ergostan-3β-yl acetate (500 mg.) in chloroform (10 c.c.) was treated with a solution of aqueous hydrogen bromide (0.05 c.c.; 46%) in chloroform (10 c.c.). The mixture was kept at room temperature for 3 days. The crystalline solid (185 mg.) which had separated, was collected and crystallised from chloroform-methanol to yield 22:23-dibromo-7β-hydroxy--11-oxoergost-8-en-3β-yl acetate, m.p. 232-234°, $[\alpha]_D$ +85° (c,0.4)

(Found: C,57.05; H,7.55. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.35%).

Light absorption: Max. at 2540 Å (ε = 9000).

(b) 22:23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (1.2 g.) in chloroform (40 c.c.) was treated

with perbenzoic acid in chloroform (4.8 c.c.; 59 mg./c.c.) which had been kept at 0° for three weeks prior to use. The solution was concentrated under reduced pressure to approximately half bulk, diluted with methanol and the solid (0.8 g.) collected and crystallised from chloroform to give 22:23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (250 mg.) as plates, m.p. 232° alone or mixed with the specimen prepared by method (a); $[\alpha]_D$ +78° (c,0.35)
(Found: C,57.15; H,7.5%). It does not give a colour with tetranitromethane in chloroform. Light absorption: Max. at 2550 Å (ε = 10,000). Infra-red spectrum: Peaks at 3461 (hydroxyl), 1737 and 1245 (acetate) and 1661 cm.$^{-1}$ (αβ-unsaturated ketone). From the chloroform mother liquor 22:23-dibromo-7β:8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (200 mg.) was isolated; after crystallisation from chloroform-methanol it separated as needles, m.p. 218-220° undepressed by the specimen previously described; $[\alpha]_D$ -28° (c,0.5) (Found: C,52.8; H,6.9%).

7:11-Dioxoergost-22-en-3β-yl Acetate from 22:23--Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl Acetate. - 22:23-Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (85 mg.) suspended in glacial acetic acid (10 c.c.) was treated with stirring at room temperature with a solution of chromium trioxide in acetic acid (0.45 c.c.; N) diluted with acetic acid (5 c.c.) added in five equal portions over 1 hour. After a further hour, the mixture was heated at 50-60° for 1 hour and stored overnight at room temperature. The reaction solution was worked up using ether, the product dissolved in glacial acetic acid (10 c.c.) and stirred with zinc dust on the steam bath for 4 hours. Isolation using ether followed by percolation through a short column of Grade II alumina and crystallisation from aqueous methanol gave 7:11-dioxoergost-22-en-3β-yl acetate as felted needles, m.p. 195-197° alone or mixed with an authentic specimen; $[\alpha]_D$ -31° (c,0.5).
(Found: C,76.6; H,10.0. Calc. for $C_{30}H_{46}O_4$: C,76.55; H,9.85%).

7β-Hydroxy-11-oxoergosta-8:22-dien-3β-yl Acetate. - A solution of 22:23-dibromo-7β-hydroxy-11-oxoergost-

-8-en-3β-yl acetate (250 mg.) in a mixture of benzene (15 c.c.), methanol (15 c.c.) and ether (15 c.c.) was heated under reflux with activated zinc (1.25 g.) for 5 hours. The product was crystallised from chloroform-methanol from which 7β-hydroxy-11-oxoergosta-8:22-dien-3β-yl acetate (150 mg.) separated as plates, m.p. 245-246°, $[\alpha]_D$ + 104° (c,1.7).

(Found: C,76.5; H,9.9. $C_{30}H_{46}O_4$ requires C,76.55; H,9.85%).

Light absorption: Max. at 2540 Å. (ε 10,500).

11-Oxoergosta-8:22-dien-3β:7β-diol Diacetate. - 11-Oxoergosta-8:22-dien-3β:7β-diol diacetate was prepared by treatment of the monoacetate with acetic anhydride and pyridine at room temperature; it separated from aqueous methanol as needles, m.p. 152-153°, $[\alpha]_D$ + 82° (c,0.7)

(Found: C,74.8; H,9.4. Calc. for $C_{32}H_{48}O_5$: C,75.0; H,9.4%).

Light absorption: Max. at 2490 Å (ε = 8800).

Henbest and Wagland (27) record m.p. 149-152°, $[\alpha]_D$+83°.

22:23-Dibromo-11-oxoergost-8-en-3β:7β-diol Diacetate. - (a) 22:23-Dibromo-7β-hydroxy-11--oxoergost-8-en-3β-yl acetate (90 mg.) in pyridine (3 c.c.) and acetic anhydride (3 c.c.) was heated on the steam bath for 1½ hours. Crystallisation of the product from methanol gave 22:23-dibromo-11--oxoergost-8-en-3β:7β-diol diacetate as felted needles, m.p. 169-170°, $[\alpha]_D$ +70° (c,1.2). (Found: C,57.3; H,7.3. $C_{32}H_{48}O_5Br_2$ requires C,57.1; H,7.2%).

The diacetate does not give a colour with tetranitromethane. Light absorption: Max. at 2500 Å. (ε = 9200).

(b) A solution of 22:23-dibromo-7β:8β-epoxy-11--oxo-9β-ergostan-3β-yl acetate (200 mg.) in benzene (10 c.c.) and methanolic potassium hydroxide (20 c.c.; 5%) was heated under reflux for 10 minutes. The precipitated solid was separated, washed with methanol, dried and heated on the steam bath for 1 hour with pyridine (10 c.c.) and acetic anhydride (5 c.c.). Isolation using ether gave 22:23-dibromo-11-oxoergost--8-en-3β:7β-diol diacetate (100 mg.) which separates

from aqueous methanol as felted needles, m.p. and mixed m.p. 170-171°, $[\alpha]_D$ +69° (c,0.6)
(Found: C,56.7; H,7.15%).

(c) 22:23-Dibromo-7β:8β-epoxy-11-oxo-9β-ergostan--3β-yl acetate (500 mg.) in chloroform (10 c.c.) was treated with a portion (10 c.c.) of a solution prepared by dissolving aqueous hydrogen bromide (5 drops; 46%) in chloroform (100 c.c.) and kept at room temperature for 3 days. The crystalline solid (185 mg.) was acetylated on the steam-bath. Isolation from ether and crystallisation from aqueous methanol gave 22:23-dibromo-11-oxoergost--8-en-3β:7β-diol diacetate (120 mg.) as felted needles, m.p. and mixed m.p. 170-2°, $[\alpha]_D$ +69° (c,1.7).
(Found: C,57.1; H,7.25%).

22:23-Dibromo-7β-hydroxy-11-oxo-9β-ergost--8(14)-en-3β-yl Acetate. - A solution of 22:23--dibromo-7β:8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (1.19 g.) in dioxan (230 c.c.) was treated with sulphuric acid (8 c.c.; 2N) and stored at

room temperature for 4 hours. The solution was diluted with water, the product isolated by means of ether, and crystallised from methanol. The first crop (40 mg.) which showed high intensity absorption at 2540 Å was rejected. Concentration of the mother liquor and crystallisation of the solid obtained from aqueous methanol gave 22:23--dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (940 mg.) as plates, m.p. 201-202°, $[\alpha]_D$ +196° (c,1.5).

(Found: C,57.0; H,7.6. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.35%). It gives a yellow colour with tetranitromethane in chloroform. Light absorption: $\varepsilon_{2110} = 9000$.

Infra-red spectrum: Peaks at 3470 (hydroxy), 1740 and 1250 (acetate) and 1710 $cm.^{-1}$ (ketone).

Acetylation with acetic anhydride-pyridine at room temperature gave 22:23-dibromo-11-oxo-9β-ergost-8(14)--en-3β:7β-diol diacetate which separated from methanol as plates, m.p. 170-171°, $[\alpha]_D$ +142° (c,1.0).

(Found: C,57.1; H,7.5. $C_{32}H_{48}O_5Br_2$ requires C,57.1; H,7.2%). Light absorption: $\varepsilon_{2100} = 8400$.

Treatment of 22:23-Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl Acetate with Sulphuric Acid in Dioxan.

22:23-Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (39 mg.) was dissolved in dioxan (50 c.c.) containing sulphuric acid (2 c.c.; 2N) and kept at room temperature for 12 hours. Isolation from chloroform gave unchanged starting material, m.p. and mixed m.p. 234-6°, $[\alpha]_D$ +82° (c,0.25).
Light absorption: Max. at 2540 Å. (ε 8300).

Treatment of 22:23-Dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl Acetate with Hydrogen Bromide in Chloroform.

A solution of the acetate (420 mg.) in chloroform (10 c.c.) was treated with a solution of aqueous hydrogen bromide (0.05 c.c.; 46%) in chloroform (10 c.c.) and kept at 15° for 4 days. The mixture was diluted with chloroform and the product isolated in the usual manner. Crystallisation from chloroform-methanol gave an oxo-diene (80 mg.) - later shown to be 22:23-dibromo-11-oxo-9β-ergosta-8(14):15-dien-3β-yl acetate (see p. 66) - as plates, m.p.

215-217°, $[\alpha]_D$ +24° (c,1.25).
(Found: C,58.8; H,7.6. $C_{30}H_{44}O_3Br_2$ requires C,58.8; H,7.2%).
Light absorption: Max. at 2640 Å (ε 8300); it gives a red brown colour with tetranitromethane in chloroform.

7β-Hydroxy-11-oxo-9β-ergosta-8(14):22-dien-3β--yl Acetate.- (a) 22:23-Dibromo-7β-hydroxy-11--oxoergost-8(14)-en-3β-yl acetate (250 mg.) was debrominated with activated zinc dust in benzene--ether-methanol and the product crystallised from aqueous acetone to give 7β-hydroxy-11-oxo-9β-ergosta--8(14):22-dien-3β-yl acetate (130 mg.) as plates, m.p. 192-195°, $[\alpha]_D$ + 216° (c,1.45)
(Found: C,75.35; H,9.9. $C_{30}H_{46}O_4.C_3H_6O$ requires C,75.0; H, 9.9%). It gives a yellow colour in chloroform with tetranitromethane. Light absorption: ε_{2090} = 8000.
(b) 7β:8β-Epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (290 mg.) in absolute dioxan (25 c.c.) containing freshly distilled boron trifluoride etherate (4 drops) was kept at room temperature overnight. The solution

was poured into sodium hydrogen carbonate solution, washed successively with water, saturated sodium hydrogen carbonate solution, and water and dried (Na_2SO_4). Crystallisation of the residue from aqueous methanol gave 7β-hydroxy-11-oxo-9β-ergosta--8(14):22-dien-3β-yl acetate as plates, m.p. and mixed m.p. 194-7°, $[\alpha]_D$ + 211° (c,0.5).
Light absorption: Max. at 2100 Å (ε 7,300).

This experiment followed polarimetrically and spectroscoptically failed to indicate the existence of an 9α-oxoepoxide or other intermediate.

Repeat of Heusler and Wettstein's Experiment.

Following the method of Heusler and Wettstein (35) 7β:8β-Epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (227 mg.) in absolute dioxan (15 c.c.) was heated with boron trifluoride etherate (3 drops) at 80°. Isolation from ether followed by chromatography on alumina (5 g.) failed to yield a homogeneous compound. The material obtained had m.p. 187-190°, $[\alpha]_D$ +147° (c,0.4) showing absorption max. at 2480 Å (ε 1700).

Heusler and Wettstein (35) claimed 7ξ-hydroxy-

-11-oxoergosta-8(14):22-dien-3β-yl acetate, m.p. 190-193°, $[\alpha]_D$ + 76° (cf. our rotation of +216°).

22:23-Dibromo-11-oxoergost-8(14)-en-3β:7β-diol. (with D.Maclean). - A solution of 22:23-dibromo-7β--hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (1.8 g.) in methanol (150 c.c.) was treated with potassium hydroxide (2.0 g.) in water (5 c.c.) and kept at room temperature for 16 hours. The crystalline solid was separated at -50°, washed with water, and crystallised from chloroform-methanol from which 22:23-dibromo-11-oxoergost-8(14)-en--3β:7β-diol (1.25 g.) separated as elongated plates, m.p. 207-209°, $[\alpha]_D$ +85° (c,0.5).
(Found: C,55.6; H,7.9. $C_{28}H_{44}O_3Br_2.2CH_3OH$ requires C,55.2; H,8.0%). Light absorption: ε_{2090} = 10,500.

22:23-Dibromo-7:11-dioxoergostan-3β-yl Acetate. - (a) A solution of 22:23-dibromo-7β-hydroxy-11-oxo-ergost-8-en-3β-yl acetate (250 mg.) in chloroform (15 c.c.) containing aqueous hydrogen bromide (8 drops; 46%) was kept overnight. The product was

isolated in the usual manner and crystallised from chloroform-methanol to give 22:23-dibromo-7:11--dioxoergostan-3β-yl acetate (170 mg.) as fine needles, m.p. 263° (decomp.), $[\alpha]_D$ -5° (c,1.3) (Found: C,57.4; H,7.4. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.35%). The diketone does not give a colour with tetranitromethane in chloroform and does not show high intensity ultra-violet absorption.

(b) A solution of 22:23-dibromo-7β:8β-epoxy-11-oxo--9β-ergostan-3β-yl acetate (400 mg.) in chloroform (25 c.c.) was treated with glacial acetic acid (50 c.c.) containing aqueous hydrobromic acid (10 drops; 46%) and kept overnight at room temperature. After dilution with water, the product was isolated by means of chloroform and the solid crystallised from chloroform-methanol to give 22:23-dibromo-7:11--dioxoergostan-3β-yl acetate (90 mg.) as fine needles, m.p. and mixed m.p. 263° (decomp.), $[\alpha]_D$ -2° (c,1.3) (Found: C,56.75; H,7.5).

7:11-Dioxoergost-22-en-3β-yl Acetate. - 22:23--Dibromo-7:11-dioxoergostan-3β-yl acetate (200 mg.)

was treated with activated zinc dust in benzene--ether-methanol. The product, isolated by means of ether, separated from methanol giving 7:11--dioxoergost-22-en-3β-yl acetate as felted needles, m.p. and mixed m.p. 197-199°, $[\alpha]_D$ -30° (c,0.8) (Found: C,76.45; H,9.9. Calc. for $C_{30}H_{46}O_4$: C,76.55; H,9.85%).

Treatment of 22:23-Dibromo-7β:8β-epoxy-11-oxo--9β-ergostan-3β-yl Acetate with Alkali. - A solution of 22:23-dibromo-7β:8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (1.0 g.) in benzene (25 c.c.) and methanolic potassium hydroxide (55 c.c.; 10%) was refluxed for 4 hours. The solution was concentrated under reduced pressure, diluted with water and extracted with ether to give an extract and an ether--insoluble solid (147 mg.), m.p. 235° which were separated. Acetylation of the solid using acetic anhydride and pyridine gave 22:23-dibromo-11-oxo-ergost-8-en-3β:7β-diol diacetate which separated from aqueous methanol as felted needles, m.p. 170-171°; $[\alpha]_D$ +70° (c,0.5).
(Found: C,57.0; H,7.4%. $C_{32}H_{48}O_5Br_2$ requires

C,57.1; H,7.2%). Infra-red spectrum: Peaks at 1734 and 1235 (acetate) and 1682 cm.$^{-1}$ (αβ-unsaturated ketone).

The ether solution was evaporated and the residue acetylated with acetic anhydride-pyridine by heating on the steam bath for 1 hour. The solid product, isolated by means of ether was digested with methanol and the insoluble fraction (80 mg.; m.p. 240°) collected and crystallised from chloroform--methanol to give 22:23-dibromo-7:11-dioxoergostan--3β-yl acetate as fine needles, m.p. and mixed m.p. 263° (decomp.), $[\alpha]_D$ -3° (c,1.5).
(Found: C,57.4; H,7.6%. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.35%).

22:23-Dibromo-11-oxo-14β-ergost-8-en-3β:7β-diol Diacetate. - (a) On standing, the methanol digest described above deposited prismatic needles (350 mg.), m.p. 175°, crystallisation of which from aqueous acetone gave 22:23-dibromo-11-oxo-14β-ergost-8-en--3β:7β-diol diacetate (250 mg.) as needles, m.p. 187°, $[\alpha]_D$ +61°, +62° (c, 1.0, 0.9).
(Found: C,57.5; H,7.3. $C_{32}H_{48}O_5Br_2$ requires C,57.1; H,7.2%).

Light absorption: Max. at 2440 Å (ε = 9200).
Infra-red spectrum: Peaks at 1737 and 1241 (acetate) and 1689 cm.$^{-1}$ ($\alpha\beta$-unsaturated ketone).

(b) A solution of 22:23-dibromo-3β:7β-dihydroxy-ergost-8(14)-en-11-one (215 mg.) was refluxed with methanolic potash (65 c.c.; 1%) for 2 hours. The solution was poured into water, extracted with ether and the extract washed with water and dried (Na_2SO_4). Acetylation of the residue on the steam bath for 1 hour followed by isolation from ether and crystallisation from aqueous acetone gave 22:23-dibromo-11--oxo-14β-ergost-8-en-3β:7β-diol diacetate (100 mg.) m.p. and mixed m.p. 185-186°, $[\alpha]_D$ +61° (c,0.9).
Light absorption: Max. at 2440 Å. (ε 9000).

11-Oxo-14β-ergosta-8:22-dien-3β:7β-diol--Diacetate. - Debromination of 22:23-dibromo-11-oxo--14β-ergost-8-en-3β:7β-diol diacetate (100 mg.) using activated zinc in benzene-ether-methanol gave 11-oxo--14β-ergosta-8:22-dien-3β:7β-diol diacetate (40 mg.) separating from methanol as needles, m.p. 82-84° (softening at 65°), $[\alpha]_D$ +103° (c,0.9).

(Found: C,72.9; H,9.3. $C_{32}H_{48}O_5$.MeOH requires C,72.75; H,9.8%). Light absorption: Max. at 2460 Å (ε = 8400).

22:23-Dibromo-3β:7β-dihydroxy-14β-ergost-8-en-11-one. - Hydrolysis of 22:23-dibromo-3β:7β-diacetoxy-14β-ergost-8-en-11-one (300 mg.) in benzene (6 c.c.) with methanolic potash (50 c.c.; 2%) at reflux for 1 hour gave 22:23-dibromo-3β:7β-dihydroxy-14β-ergost-8-en-11-one as needles from chloroform-methanol, m.p. 206-7°, $[\alpha]_D$ +85° (c,1.0). Light absorption: Max. at 2490 Å (ε 8400). (Found: C,55.8; H,8.0. $C_{28}H_{44}O_3Br_2$.MeOH requires C,56.1; H,7.8%).

Rearrangement of 22:23-Dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl Acetate with Alkali. - A solution of 22:23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (250 mg.) in benzene (20 c.c.) and methanolic potassium hydroxide (40 c.c.; 5%) was heated under reflux for 4 hours. The product was isolated using ether and heated with acetic

anhydride (4 c.c.) and pyridine (4 c.c.) on the steam bath for 1 hour. Isolation using ether gave a gum which crystallised from chloroform-methanol to give 22:23-dibromo-7:11-dioxoergostan-3β-yl acetate (40 mg.) as needles, m.p. and mixed m.p. 263° (decomp.), $[\alpha]_D$ -5° (c,1.8).
(Found: C,57.4; H,7.6%). Concentration of the first chloroform-methanol mother liquor gave a solid which after recrystallisation from aqueous acetone yielded 22:23-dibromo-11-oxo-14β-ergost--8-en-3β:7β-diol diacetate as needles, m.p. 187-188°, $[\alpha]_D$ +64° (c,1.2).
(Found: C,56.9; H,7.5%).
Light absorption: Max. at 2430 Å (ε 9000).

22:23-Dibromo-7:11-dioxo-14β-ergostan-3β-yl Acetate. - A solution of 22:23-dibromo-3β:7β--dihydroxy-14β-ergost-8-en-11-one (100 mg.) in chloroform-acetic acid (30 c.c.; 1:2) and aqueous hydrogen bromide (5 drops; 46%) was kept at room temperature overnight. Isolation from chloroform and acetylation of the residue in pyridine gave a

white solid on trituration with methanol. Crystallisation from methanol gave 22:23-dibromo--7:11-dioxo-14β-ergostan-3β-yl acetate (65 mg.) as needles m.p. 217-219°, $[\alpha]_D$ -42° (c,1.3). The compound gave no colour with tetranitromethane and did not exhibit any absorption in the ultra-violet above 2000 Å. Infra-red spectrum confirmed the carbonyl grouping (1700 $cm.^{-1}$).
(Found: C,57.6; H,7.7. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.35%).

Attempted Epimerisation of 22:23-Dibromo-7β:8β--epoxy-11-oxo-9β-ergostan-3β-yl Acetate.

(a) Alumina. - Recovered unchanged from rapid filtration through column of specially prepared alumina (cf. epimerisation of 22:23--dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate p. 83).

(b) Buffer Solutions. - Vogel (69).
pH range:- 2.2 —— 6.8 NaH_2PO_4/citric acid buffer.
:- 0.65 —— 3.09 NaOAc/HCl buffer.

Method:- 22:23-Dibromo-7β:8β-epoxy-11-oxo-9β--ergostan-3β-yl acetate (100 mg.) in dioxan (10 c.c.) and the buffer solution (1 c.c.) were kept at room temperature overnight and the product isolated from ether.

pH Range.	$[\alpha]_D$	U.V.Absorption.	
1.42 — 6.8	-29°	-	unchanged starting material
1.09	+109°	High intensity at 2100 A°.	Not purified further.
0.65	+168°	Max. 2080 A° (ε 8000)	

Attempted Reduction of 22:23-Dibromo-3β:7β-diacetoxy-ergost-8-en-11-one.

(a). Platinum in Ethanolic Potash. - The diacetate (230 mg.) in ethanolic potash (130 c.c.; 0.1N) was shaken overnight with hydrogen in the presence of platinum (from 60 mg. PtO_2). Isolation from ether followed by acetylation and isolation as before

gave a gum. Trituration with methanol followed by crystallisation from the same solvent gave 3β:7β-diacetoxyergosta-8:22-dien-11-one m.p. and mixed m.p. 152-3°. Light absorption: Max. at 2490 Å. (ε 8,900).

(b). Lithium in Liquid Ammonia. - To a solution of lithium (510 mg.) in liquid ammonia (340 c.c.) was added with vigorous stirring over 2 minutes a solution of the diacetate (1.7 g.) in ether (50 c.c.). Stirring was continued for a further 3 minutes and the reaction quenched by the cautious addition of acetone. The ammonia was allowed to evaporate at room temperature overnight, and the product isolated from ether. The residue was dissolved in benzene-light petroleum (80 c.c.; 1:1) and chromatographed over alumina (39 g.). Elution with benzene-light petroleum (500 c.c.; 1:1) and crystallisation from methanol-chloroform gave 11-oxoergosta-8:22-dien-3β-yl acetate (910 mg.) m.p. and mixed m.p. 132-3°. Light absorption: - Max. at 2540 Å. (ε 9000).

22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl Acetate.

22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl Acetate. - A solution of 22:23-dibromo-11-oxoergost-7-en-3β-yl acetate (8.35 g.) in chloroform (100 c.c.) at 0° was treated with a freshly prepared solution of perbenzoic acid in mineral acid-free chloroform (2.5 mols.; 40 c.c.) and the solution kept at 0° for 8 days. The solution was diluted with chloroform (500 c.c.) and washed successively with saturated sodium hydrogen carbonate solution, water, and dried (Na_2SO_4). The chloroform solution was concentrated under reduced pressure below 35° and diluted with methanol to give 22:23-dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (6.9 g.) separating from chloroform-methanol as needles, m.p. 210-212°, $[\alpha]_D$ -17.5° (c,1.7). (Found: C,57.3; H,7.6. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.4%). The oxo-epoxide does not show high intensity light absorption above 2000 Å., and it does not give a colour with tetranitromethane in chloroform; it was recovered unchanged after

treatment at room temperature with acetic anhydride and pyridine. Infra-red spectrum: Peaks at 1747 and 1250 (acetate) and 1717 cm.$^{-1}$ (ketone); no hydroxyl peak.

7α:8α-Epoxy-11-oxoergost-22-en-3β-yl Acetate. (With W. Laird). - 22:23-Dibromo-7α:8α-epoxy-11--oxoergostan-3β-yl acetate (320 mg.) in benzene--methanol was debrominated in the usual way using zinc. 7α:8α-Epoxy-11-oxoergost-22-en-3β-yl acetate (190 mg.) separates from chloroform-methanol as elongated plates, m.p. 190-191°, $[\alpha]_D$ -15.5° (c,1.3) (Found: C,76.4; H,9.8. $C_{30}H_{46}O_4$ requires C,76.55; H,9.85%). Light absorption: ε_{2040} = 2100. It gives a pale yellow colour with tetranitromethane in chloroform.

22:23-Dibromo-7:11-dioxoergostan-3β-yl Acetate. - 22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (300 mg.) in chloroform-acetic acid (20 c.c.; 1:1) was treated with aqueous hydrogen bromide (46%; 10 drops) and the solution kept at room temperature overnight. Isolation from chloroform

in the usual manner and crystallisation of the residue from chloroform-methanol gave 22:23-dibromo--7:11-dioxoergostan-3β-yl acetate (80 mg.) as needles m.p. 262° (dec.) undepressed with previous preparations. $[\alpha]_D$ -3° (c,1.1).
(Found: C,57.2; H,7.4. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.4%).

22:23-Dibromo-7α-hydroxy-11-oxoergost-8-en-3β--yl Acetate. - (a) 22:23-Dibromo-7α:8α-epoxy-11--oxoergostan-3β-yl acetate (220 mg.) in dioxan (45 c.c.) was heated with sulphuric acid (1.5 c.c.; 2N) on the steam bath for 2¼ hours. Isolation from ether and crystallisation of the residue from chloroform--methanol gave 22:23-dibromo-7α-hydroxy-11-oxoergost--8-en-3β-yl acetate (85 mg.) as needles, m.p. 217-218°, $[\alpha]_D$ +95° (c,0.7). Light absorption: Max. at 2490 Å. (ε 9000). A solution of the compound in chloroform gave no colour with tetranitromethane.
(Found: C,56.9; H,7.1. $C_{30}H_{46}O_4Br_2$ requires C,57.1; H,7.4%).
(b) 22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (160 mg.) in dioxan (30 c.c.) was kept at

room temperature for 8 days in the presence of sulphuric acid (0.8 c.c.; 2N). Isolation as above gave 22:23-dibromo-7α-hydroxy-11-oxoergost-8-en-3β--yl acetate (65 mg.), m.p. and mixed m.p. 217-218°, $[\alpha]_D$ +97° (c,0.9). Light absorption: Max. at 2490 Å. (ε 9000).

Note:- 22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β--yl acetate was recovered unchanged on treatment with dilute sulphuric acid in dioxan at room temperature for 5 hours. This is of interest when contrasted to the reactivity of 22:23-dibromo-7β:8β-epoxy-11--oxo-9β-ergostan-3β-yl acetate under identical conditions.

Treatment of 22:23-Dibromo-7α:8α-epoxy-11-oxoergostan--3β-yl Acetate with Aqueous Hydrogen Bromide in Chloroform.

22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (320 mg.) in chloroform (5.5 c.c.) was treated with aqueous hydrogen bromide (46%; 5 drops). The hydrobromic acid remained partly in suspension and mixing was promoted by occasional shaking. After

30 minutes a sample was isolated and showed absorption at 2490 Å. (ε ca. 3000). After 90 minutes, the product was isolated from chloroform and the residue dissolved in benzene (50 c.c.) and filtered through alumina (10 g.). Elution with benzene-ether (400 c.c.; 7:3) and crystallisation from chloroform-methanol gave crude 22:23-dibromo-7α-hydroxy-11-oxoergost-8--en-3β-yl acetate (137 mg.) as short needles, m.p. 217-218° (decomp.), $[\alpha]_D$ +81° (c,0.9). Light absorption: Max. at 2490 Å. (ε 7,300). These constants were unchanged on further crystallisation or chromatography.

Note:- In contrast to the preparation of the corresponding 7β-hydroxy compound, under somewhat milder conditions, the 7α-hydroxy compound above did not separate from the reaction solution at any stage.

22:23-Dibromo-11-oxoergost-8-en-3β:7α-Diol. - A solution of 22:23-dibromo-7α:8α-epoxy-11-oxoergostan--3β-yl acetate (300 mg.) in benzene (6 c.c.) was kept at room temperature for 3½ hours with methanolic potash (50 c.c.; 1%). Isolation from ether followed by crystallisation from chloroform-methanol gave

22:23-dibromo-11-oxoergost-8-en-3β:7α-diol (260 mg.) as felted needles, m.p. 213-214°, $[\alpha]_D$ +112° (c,0.7). Light absorption: Max. at 2500 Å. (ε 9,500). (Found: C,56.0; H,7.5; $C_{28}H_{44}O_3Br_2$.MeOH requires C,56.1; H,7.8%).

22:23-Dibromo-3β:7α-diacetoxyergost-8-en-11-one. - (a) Acetylation of the corresponding 3β:7α-diol in pyridine on the steam bath for 1 hour gave 22:23--dibromo-3β:7α-diacetoxyergost-8-en-11-one as plates from methanol, m.p. 212-213°, $[\alpha]_D$ +102° (c,1.2). Light absorption: Max. at 2460 Å. (ε 9400). (Found: C,57.2; H,7.3. $C_{32}H_{48}O_5Br_2$ requires C,57.1; H,7.2%).

(b) Acetylation of 22:23-dibromo-7α-hydroxy-11-oxo ergost-8-en-3β-yl acetate in pyridine gave the diacetate m.p. and mixed m.p. 211-212°, $[\alpha]_D$ +100° (c,0.8).

22:23-Dibromo-11-oxoergost-8(14)-en-3β:7α-Diol. - 22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (540 mg.) in benzene (50 c.c.) was refluxed with methanolic potash (150 c.c.; 2%) for 1½ hours.

The solution was concentrated under reduced pressure and extracted with chloroform. The extract was washed well with water and dried (Na_2SO_4). Crystallisation from chloroform-methanol gave 22:23--dibromo-11-oxoergost-8(14)-en-3β:7α-diol (340 mg.) as needles, m.p. 201-202°, $[\alpha]_D$ +35° (c,0.2 in pyridine). Light absorption: ε_{2060} = 8,000. (Found: C,57.2; H,7.3. $C_{28}H_{44}O_3Br_2$ requires C,57.15; H,7.5%).

Treatment of 7α:8α-Epoxyergost-22-en-3β-yl Acetate with Benzoic Acid in Chloroform. - 7α:8α--Epoxyergost-22-en-3β-yl acetate (100 mg.), prepared according to Barton and Alt (7), was treated with a solution of benzoic acid (40 mg.) in chloroform (2 c.c.) and kept at room temperature for 24 hours. The solution was diluted with chloroform and washed well with sodium hydrogen carbonate solution and water and dried (Na_2SO_4). The solvent was removed under reduced pressure at 30°. The residue was dissolved in light petroleum (30 c.c.) and chromatographed over ethyl acetate washed alumina (10 cm. x 1 cm.). The column was washed

with light petroleum (250 c.c.) and eluted with benzene (80 c.c.) to give a white solid (55 mg.) which gave unchanged 7α:8α-epoxyergost-22-en-3β-yl acetate as needles, m.p. and mixed m.p. 156-158°. Light absorption: Max. 2060 Å. (ε 3600).

The Structure of 22:23-Dibromo-11-oxoergosta-8:14--dien-3β-yl Acetate and Related Compounds.

22:23-Dibromo-11-oxo-9β-ergosta-8(14):15-dien--3β-yl Acetate. - (a) 22:23-Dibromo-7β:8β-epoxy--11-oxo-9β-ergostan-3β-yl acetate (200 mg.) in dioxan (25 c.c.) at 15° was treated with sulphuric acid (1 c.c.; d,1.84) and kept for 40 mins. Water (10 c.c.) was added and after one hour the precipitate was collected and washed with methanol. Crystallisation from chloroform-methanol gave 22:23-dibromo-11-oxo-9β--ergosta-8(14):15-dien-3β-yl acetate (90 mg.) as plates, m.p. 216-217°, $[\alpha]_D$ +25° (c,1.1).
(Found: C,59.15; H,7.3. $C_{30}H_{44}O_3Br_2$ requires C,58.8; H,7.2%).
Light absorption: Max. at 2640 Å. (ε 8400).
It gives a red-brown colour with tetranitromethane in chloroform rapidly fading to yellow.
(b) A solution of 22:23-dibromo-7β:8β-epoxy-11-oxo--9β-ergostan-3β-yl acetate (1.0 g.) in dry chloroform (20 c.c.) at -5° was treated with dry hydrogen

chloride for 15 minutes and the solution kept for $3\frac{1}{2}$ hrs. The product, isolated using chloroform, was recrystallised from chloroform-methanol to give 22:23-dibromo-11-oxo-9β-ergosta-8(14):15-dien-3β-yl acetate (220 mg.), m.p. and mixed m.p. 216-217°, $[\alpha]_D$ +25° (c,1.1). Light absorption: Max. at 2640 Å. (ε 8500).

(Found: C,58.85; H,7.4%).

(c) 22:23-Dibromo-7β:8β-epoxy-11-oxo-9β-ergostan--3β-yl acetate (500 mg.) was treated with boiling glacial acetic acid (25 c.c.) for 2-3 minutes, the solution cooled, and the product precipitated by addition of water and isolated using ether. The solid was crystallised from chloroform-methanol (mother liquor A) to give 22:23-dibromo-11-oxo-9β--ergosta-8(14):15-dien-3β-yl acetate (200 mg.) as plates, m.p. 214-215°, alone or mixed with the specimens above, $[\alpha]_D$ +24° (c,1.2).

(Found: C,59.0; H,7.35%). Light absorption: Max. at 2640 Å. (ε 8500).

(d) 22:23-Dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)--en-3β-yl acetate (100 mg.) in dioxan (10 c.c.) was

treated with sulphuric acid (10 drops; d,1.84) and kept at 15° for 40 minutes. Water (5 c.c.) was added and after 3 hrs. the mixture gave 22:23--dibromo-11-oxo-9β-ergosta-8(14):15-dien-3β-yl acetate (40 mg.) crystallising from chloroform-methanol as plates, m.p. and mixed m.p. 217-128°, $[\alpha]_D$ +25° (c,1.3).

(Found: C,58.75; H,7.5%). Light absorption Max. at 2640 Å. (ε 8500).

11-Oxo-9β-ergosta-8(14):15:22-trien-3β-yl Acetate. - (a) 22:23-Dibromo-11-oxo-9β-ergosta--8(14):15-dien-3β-yl acetate (250 mg.) in a mixture of benzene (20 c.c.), ether (30 c.c.), and ethanol (30 c.c.), was refluxed with activated zinc (1.5 g.) for 4 hours. The product was isolated in the usual manner and crystallised from chloroform-methanol to give 11-oxo-9β-ergosta-8(14):15:22-trien-3β-yl acetate as plates, m.p. 180-182°, $[\alpha]_D$ -28° (c,1.1). Light absorption: Max. at 2660 (ε 8300) and 2140 Å. (ε 3600).

(Found: C,79.3; H,10.0. $C_{30}H_{44}O_3$ requires C,79.6; H,9.8%).

(b) A solution of 22:23-dibromo-7β:8β-epoxy-11--oxo-9β-ergostan-3β-yl acetate (550 mg.) in glacial acetic acid (50 c.c.) was heated on the steam bath with zinc (6 g.) and stirred vigorously for 2½ hrs. Isolation from ether, followed by crystallisation from chloroform-methanol gave 11-oxo-9β-ergosta--8(14):15:22-trien-3β-yl acetate (120 mg.) as translucent plates, m.p. and mixed m.p. 180-182°, $[\alpha]_D$ -29° (c,1.8). Light absorption: Max. at 2640 Å. (ϵ 8200). A solution in chloroform gave a red-brown colour with tetranitromethane. (Found: C,79.4; H,9.9%).

22:23-Dibromo-11-oxoergosta-8:14-dien-3β-yl Acetate. - (a) A solution of 22:23-dibromo-7β:8β--epoxy-11-oxo-9β-ergostan-3β-yl acetate (400 mg.) in chloroform (25 c.c.) was treated with glacial acetic acid (50 c.c.) containing aqueous hydrobromic acid (10 drops; 46%) and kept overnight at room temperature. The product was crystallised from chloroform-methanol to give 22:23-dibromo-7:11--dioxoergostan-3β-yl acetate, m.p. 263° (decomp.).

Evaporation of the crystallisation mother liquors gave a residue, m.p. ca. 210° (strong yellow colour with tetranitromethane in chloroform) which was dissolved in light petroleum (b.p. 60-80°)-benzene (1.1) and adsorbed on a column of Grade II alumina (10 x 1.5 cm.). The column was washed with the same solvent (250 c.c.) and then with benzene (400 c.c.) which eluted a solid (120 mg.) seven crystallisations of which from chloroform-methanol gave 22:23-dibromo-11-oxoergosta-8:14-dien-3β-yl acetate (50 mg.) as plates, m.p. 221-223°, $[\alpha]_D$ +35°, +34° (c,2.1).

(Found: C,59.2; H,7.4. $C_{30}H_{44}O_3Br_2$ requires C,58.8; H,7.2%).

It gives a bright yellow colour with tetranitromethane in chloroform. Light absorption: Max. at 2140 Å. (ε 11,700) and 2920 Å. (ε 13,700).

(b) Treatment of 22:23-dibromo-7β:8β-epoxy-11-oxo--9β-ergostan-3β-yl acetate with acetic acid gave a mixture from which 22:23-dibromo-11-oxo-9β-ergosta--8(14):15-dien-3β-yl acetate was isolated in 40%

yield as described on p.118. Evaporation of the mother liquor A from this compound gave a solid (300 mg.) which was dissolved in benzene-light petroleum (b.p. 60-80°) (100 c.c.; 1:3) and adsorbed on a column of Grade II alumina (15 x 2 cm.). The column was washed with benzene-light petroleum (b,p. 60-80°) (320 c.c.; 1:3, 250 c.c.; 1:2, 100 c.c.; 1:1) and then with benzene-ether (220 c.c.; 19:1) which eluted 22:23-dibromo-11-oxoergosta-8:14-dien-3β-yl acetate (50 mg.) separating from methanol as prisms, m.p. and mixed m.p. 221-223°, $[\alpha]_D$ +35° (c,0.4). Light absorption: Max. at 2130 (ϵ 10,000) and 2940 Å. (ϵ 13,000). Further elution of the column with benzene-ether (370 c.c.; 19:1, 100 c.c.; 17:3, 150 c.c.; 4:1, 150 c.c.; 3:2, 250 c.c.; 1:2) and ether (200 c.c.) followed by evaporation of the combined eluates and crystallisation of the residue from methanol gave 22:23-dibromo-7:11-dioxoergostan-3β-yl acetate (40 mg.), m.p. and mixed m.p. 262° (decomp.), $[\alpha]_D$ -3° (c,0.8).

(c) 22:23-Dibromo-11-oxo-9β-ergosta-8(14):15-dien-3β-yl acetate (100 mg.) in benzene (10 c.c.) and

methanolic potassium hydroxide (10 c.c.; 10%) was heated under reflux for 1 hr. The product was isolated using ether and heated on the steam bath with acetic anhydride and pyridine for 1 hr. 22:23--Dibromo-11-oxoergosta-8:14-dien-3β-yl acetate (50 mg.), isolated from ether, crystallised from chloroform--methanol as plates, m.p. and mixed m.p. 222-223°, $[\alpha]_D$ +36° (c,0.7).

(Found: C,59.1; H,7.1%). Light absorption: Max. at 2090 (ϵ 8000) and 2920 Å. (ϵ 13000). Repetition of this experiment and isolation of the intermediate alcohol gave 22:23-dibromo-11-oxoergosta-8:14-dien--3β-ol as plates from chloroform-methanol, m.p. 208°, $[\alpha]_D$ +47° (c,1.3). Light absorption: Max. at 2940 Å. (ϵ 13,000).

(Found: C,57.1; H,7.9. $C_{28}H_{42}O_3Br_2.2MeOH$ requires C,56.8; H,7.9%). Acetylation gave the acetate separating from chloroform-methanol as plates, m.p. and mixed m.p. 220-221°, $[\alpha]_D$ +35° (c,0.9).

(d) 22:23-Dibromo-11-oxo-9β-ergosta-8(14):15-dien--3β-yl acetate (100 mg.) in chloroform (5 c.c.) and glacial acetic acid (10 c.c.) containing aqueous

hydrogen bromide (10 drops; 46%) was kept at room temperature for 24 hrs. Isolation by means of chloroform gave 22:23-dibromo-11-oxoergosta-8:14--dien-3β-yl acetate (60 mg.) crystallising from chloroform-methanol as plates, m.p. and mixed m.p. 222-223°, $[\alpha]_D$ +35°, (c,0.4).
(Found: C,59.0; H,7.5%). Light absorption: Max. at 2100 (ε 9000) and 2940 Å (ε 13,000).

(e) 22:23-Dibromo-7β-hydroxy-11-oxo-9β-ergost--8(14)-en-3β-yl acetate (250 mg.) in chloroform (20 c.c.) was treated with glacial acetic acid (40 c.c.) containing aqueous hydrogen bromide (8 drops; 46%) and allowed to stand at room temperature overnight. Isolation from chloroform and crystallisation from chloroform-methanol gave a solid (110 mg.), m.p. 208-211° showing absorption at 2100 (ε 9800) and 2940 Å (ε 11,100). Filtration through an alumina column followed by repeated crystallisation from chloroform-methanol gave 22:23-dibromo-11-oxo-ergosta-8:14-dien-3β-yl acetate as plates, m.p. and mixed m.p. 219-220°, $[\alpha]_D$ +35° (c,2.0). Light absorption: Max. at 2110 (ε 10,000) and 2920 Å (ε 12,500).

22:23-Dibromo-11-oxoergosta-8:14-dien-3β-ol. - (a) A solution of 22:23-dibromo-11-oxoergost-8(14)-en-3β:7α-diol (100 mg.) in redistilled dioxan (52 c.c.) and sulphuric acid (2 c.c., d, 1.84) was kept at room temperature for 40 minutes. Isolation of the product in the usual manner followed by crystallisation from chloroform-methanol gave 22:23-dibromo-11-oxoergosta-8:14-dien-3β-ol (25 mg.) as plates, m.p. and mixed m.p. 208-209°, $[\alpha]_D$ +45° (c,1.5). Light absorption: Max. at 2100 (ε 10,000) and 2920 Å (ε 12,000).

(b) 22:23-Dibromo-11-oxoergost-8(14)-en-3β:7β-diol (80 mg.) was dissolved in dioxan (10 c.c.) and sulphuric acid (0.4 c.c.; d, 1.84) and kept at room temperature for 40 minutes. Isolation as above gave 22:23-dibromo-11-oxoergosta-8:14-dien-3β-ol (35 mg.), m.p. and mixed m.p. 208-209°, $[\alpha]_D$ +47° (c,0.7). Light absorption: Max. at 2100 (ε 9,600) and 2910 Å (ε 11,800).

11-Oxoergosta-8:14:22-trien-3β-yl Acetate. - (a) 22:23-Dibromo-11-oxoergosta-8:14-dien-3β-yl

acetate (160 mg.) was debrominated with activated zinc (750 mg.) in ether-ethanol (50 c.c.). 11-Oxoergosta-8:14:22-trien-3β-yl acetate (90 mg.) separated from aqueous methanol as flat needles, m.p. 145-146°, m.p. 141-142° when mixed with a specimen (m.p. 140°, $[\alpha]_D$ +1°) kindly supplied by Dr. Laubach, $[\alpha]_D$ -2° (c,1.6).

(Found: C,79.7; H,9.8. $C_{30}H_{44}O_3$ requires C,79.6; H,9.8%).

The compound gives a deep yellow colour with tetranitromethane in chloroform. Light absorption: Max. at 2120 (ϵ 8900) and 2940 Å (ϵ 12,500).

(b) 7β:8β-Epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (800 mg.) in chloroform (30 c.c.) and glacial acetic acid (60 c.c.) containing aqueous hydrobromic acid (12 drops; 46%). was stored overnight at room temperature. Isolation from chloroform followed by crystallisation of the residue from methanol gave a solid (500 mg.), m.p. ca. 130°, a solution of which in benzene-light petroleum (b.p. 60-80°)(100 c.c.; 2:1) was adsorbed on a column (15 x 2 cm.) of Grade II-III alumina. The column was washed with benzene (50 c.c.)

which eluted a solid (228 mg.), m.p. 143-144°. Crystallisation from aqueous methanol gave 11--oxoergosta-8:14:22-trien-3β-yl acetate (180 mg.) as flat needles, m.p. and mixed m.p. 144-145°, $[\alpha]_D$ -3° (c,3.0).
(Found: C,79.5; H,9.8%). Light absorption: Max. at 2120 (ε 9000) and 2950 Å. (ε 14,000). Max. at 2910 Å (ε 15,000) in ether.

The column was washed with benzene (150 c.c.; trace of oily elute) and then with benzene (100 c.c.) and benzene-ether (200 c.c.; 19:1) to give a solid (130 mg.), m.p. 198°. Crystallisation from aqueous methanol yielded 7:11-dioxoergost-22-en-3β-yl acetate (100 mg.) as felted needles, m.p. and mixed m.p. 198-200°, $[\alpha]_D$ -30° (c,1.7).
(Found: C,76.6; H,9.85. Calc. for $C_{30}H_{48}O_4$: C,76.55; H,9.85%).

22:23-Dibromo-ergosta-8:14-dien-3β:11ξ-Diol. - 22:23-Dibromo-11-oxoergosta-8:14-dien-3β-ol (150 mg.) in dry tetrahydrofuran (12 c.c.) was added dropwise with stirring over 40 minutes to lithium borohydride

(150 mg.) in tetrahydrofuran (15 c.c.) at 20°. Stirring was continued for a further seven hours and the solution kept overnight.

Excess lithium borohydride was destroyed by cautious addition of water. Extraction with ether followed by repeated washing with water, drying (Na_2SO_4) and evaporation of the solvent at 40° gave a residue (150 mg.) which showed absorption at 2500 Å. (ε 18,000). (N.B. all traces of acid were avoided in the isolation procedure). Recrystallisation from chloroform-methanol gave 22:23--dibromoergosta-8:14-dien-3β:11ξ-diol (120 mg.) m.p. 187-188° (decomp.), $[\alpha]_D$ -18° (c,1.2); -17° (c,1.0). Light absorption: Max. at 2500 Å (ε 19,400). (Found: C,56.35; H,8.2. $C_{28}H_{44}O_2Br_2.2MeOH$ requires C,56.6; H,8.2%).

Acetylation of the diol at room temperature gave the diacetate separating from chloroform-methanol as needles, m.p. 178-179° (the m.p. varies widely with rate of heating), $[\alpha]_D$ -35° (c,1.3).
(Found: C,58.5; H,7.4. $C_{32}H_{48}O_4Br_2$ requires C,58.5;

H,7.4%).

Light absorption: Max. at 2500 Å. (ε 19,600).

Infra-red absorption: Acetate peaks at 1730, 1240 $cm.^{-1}$

11-Oxoergost-8-en-3β-yl acetate. - (a) A solution of 22:23-dibromo-11-oxoergost-8-en-3β-yl acetate [Budziarek et al., (23)]; (1 g.) in Analar benzene (150 c.c.) was treated with a suspension of freshly prepared Raney nickel sludge in ethanol (Org.Synth., 29, 25) (W7; 1 c.c.) and the mixture shaken at room temperature with hydrogen at slight positive pressure until absorption was complete. Filtration of the solution followed by removal of the solvent under reduced pressure gave a residue which in crystallisation from aqueous methanol gave 11-oxoergost-8-en-3β-yl acetate (420 mg.) as blades m.p. 137-139°; $[\alpha]_D$ +122° (c,0.7).

(Found: C,79.2; H,10.9. Calc. for $C_{30}H_{48}O_3$: C,78.9; H,10.6%).

Light absorption: Max. at 2540 Å. (ε 8,600).

Bladon et al. (32) report m.p. 138-140°, $[\alpha]_D$ +119°: Laubach et al. (9) report m.p. 137.8-138.6; $[\alpha]_D$ +125°).

(b) A solution of 22:23-dibromo-11-oxoergosta--8:14-dien-3β-yl acetate (1 g.) in dioxan (150 c.c.) was shaken with Raney nickel (W.7; 1 c.c.) as above. Isolation as before gave 11-oxoergost--8-en-3β-yl acetate (400 mg.) as blades m.p. and mixed m.p. 137-139°; $[\alpha]_D$ +119° (c,1.7). Light absorption: Max. at 2540 Å (ε 8,500).

3β-Acetoxy-22:23-dibromo-9β-ergosta-8(14):15--dien-11ξ-ol. - 22:23-Dibromo-11-oxo-9β-ergosta--8(14):15-dien-3β-yl acetate (300 mg.) in tetrahydrofuran (60 c.c.) was treated with a solution of lithium borohydride (320 mg.) in tetrahydrofuran (25 c.c.) during 5 minutes. The solution was kept at room temperature overnight and isolated as in the previous borohydride reduction. Crystallisation from benzene-light petroleum gave 3β-acetoxy-22:23--dibromo-9β-ergosta-8(14):15-dien-11ξ-ol (130 mg.) as needles, m.p. 232° (decomp.), $[\alpha]_D$ -51°, (c,1.1). Light absorption: Max. at 2610 Å (ε 11,400). (Found: C,58.7; H,7.8. $C_{30}H_{46}O_3Br_2$ requires C,58.6; H,7.55%). A solution of the material in chloroform gave a red-brown colour with tetranitro-

methane fading to yellow.

Attempted acetylation. - The diol-monoacetate (200 mg.) in pyridine (3 c.c.) at 0° was treated with acetic anhydride (5 c.c.) at 0° and the solution kept at 0° for 48 hours. Isolation from ether and crystallisation from benzene-light petroleum gave unchanged starting material m.p. and mixed m.p. 232°, $[\alpha]_D$ -53° (c,0.4).

Attempted Epimerisation of 22:23-Dibromo-11-oxo-9β--ergosta-8(14):15-dien-3β-yl Acetate.

(a) Mild Alkali. - 22:23-Dibromo-11-oxo-9β-ergosta--8(14):15-dien-3β-yl acetate (190 mg.) in benzene (8 c.c.) was recovered unchanged from treatment with methanolic potash (10 c.c.; 0.36%) at room temperature for 4 hours.

By increasing the volume of alkali (to 50 c.c.) and the time to 24 hours, an intractable mixture showing maximal absorption at 2070, 2450, 2940 Å., of approximately equal intensities, was obtained.

(b) On Alumina. - 22:23-Dibromo-11-oxo-9β-ergosta--8(14):15-dien-3β-yl acetate (320 mg.) in benzene-

-light petroleum (3:1; 80 c.c.) was adsorbed on Spence alumina (10 g.), prepared as described on p.83. Elution with ether (150 c.c.) under a slight positive pressure gave unchanged starting material m.p. and mixed m.p. 217° (decomp.). Light absorption: Max. at 2640 Å (ε 8000).

(c) In Presence of Piperidine. - 22:23-Dibromo--11-oxo-9β-ergosta-8(14):15-dien-3β-yl acetate (100 mg.) in benzene (10 c.c.) was recovered unchanged from standing at room temperature with piperidine (4 drops; $K_b = 1.6 \times 10^{-4}$) for 6 days.

Increasing the quantity of piperidine (to 3.5 c.c.) again gave unchanged starting material.

Attempted Preparation of the Maleic Anhydride Adduct of 22:23-Dibromo-11-oxo-9β-ergosta-8(14):15--dien-3β-yl Acetate. - 22:23-Dibromo-11-oxo-9β--ergosta-8(14):15-dien-3β-yl acetate (200 mg.) in benzene (20 c.c.) was refluxed with freshly distilled maleic anhydride (90 mg.) for 17 hours. Removal of the benzene under reduced pressure gave a gum which was refluxed in methanolic potash

(2 g./24 c.c.) for 2½ hours. The solution poured into water was extracted with ether and the aqueous extract retained. The ether extract was washed well with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The residual brown gum (120 mg.) could not be induced to crystallise. The aqueous extract was then examined. Acidification followed by isolation from ether gave an acid fraction (130 mg.). [Calculation for weight of unreacted maleic acid present ca. 110 mg.].

Treatment of 22:23-Dibromoergosta-8:14-dien-3β:11-diol with:-

(a) Manganese Dioxide. - The diol (100 mg.) in chloroform (20 c.c.) was shaken for 20 hours with manganese dioxide (67) (1.25 g.). Isolation in the usual manner gave unchanged starting material.

(b) Hydrogen Chloride. - Dry hydrogen chloride gas was bubbled through a solution of the diol (140 mg.) in chloroform (40 c.c.) at room temperature. The solution was kept at room temperature overnight and isolated in the usual manner. The residual gum

showed no absorption above 2200 Å and gave no crystalline product on chromatography over alumina.

(c) Zinc in Ethanol-Ether. - Attempted debromination with activated zinc in the usual manner on both the diol and the diacetate gave intractable mixtures with no ultra-violet absorption above 2200 Å.

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22:23-Dibromo-11-oxo-14β-ergost-8-en-3β-yl Acetate. - 22:23-Dibromo-11-oxoergost-8-en-3β-yl acetate (275 mg.) in chloroform (10 c.c.) and glacial acetic acid (20 c.c.) was treated with aqueous hydrogen bromide (10 drops; 46%) and kept at room temperature for 3 days. Dilution with chloroform (50 c.c.) and washing successively with water, sodium hydrogen carbonate solution, and water and drying (Na_2SO_4) gave a gummy residue on evaporation. Several crystallisations from chloroform--methanol gave 22:23-dibromo-11-oxo-14β-ergost-8--en-3β-yl acetate as plates (120 mg.) m.p. 173-175°, $[\alpha]_D$ +92° (c,0.9).
Light absorption: Max. at 2470 Å. (ε 8300).
(Found: C,59.0; H,7.8. $C_{30}H_{46}O_3Br_2$ requires C, 58.6; H,7.55%).

11-Oxo-14β-ergosta-8:22-dien-3β-yl Acetate. - 22:23-Dibromo-11-oxo-14β-ergost-8-en-3β-yl acetate (1.5 g.) in ether-ethanol (75 c.c.) was refluxed with activated zinc (7.5 g.) for 5 hours. Isolation from ether in the usual manner gave 11-oxo-14β--ergosta-8:22-dien-3β-yl acetate (720 mg.) as needles

m.p. 111-112°, $[\alpha]_D$ +135° (c,1.7).

(Found: C,79.1; H,10.3. Calc. for $C_{30}H_{46}O_3$ C,79.3; H,10.3%).

Light absorption: Max. at 2480 (ε 8900).

Johnson (47) gives m.p. 113-114°, $[\alpha]_D$ +134° (c,1.3) for this compound.

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