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STUDIES IN ERGOSTEROL CHEMISTRY

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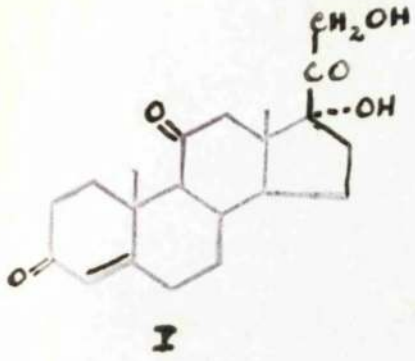
INTRODUCTION

INTRODUCTION

The dramatic clinical effects obtained with cortisone and ACTH in recent years have stimulated efforts to solve long standing problems connected with the partial and total synthesis of adrenocortical hormones. When, in 1929, Rogoff and Stewart(1), and in 1930, Swingle and Pfiffner(2), and Hartmann and Brownell(3) reported that extracts of cortical tissue would maintain life in the adrenalectomised animal, extensive investigations of the constituents of this gland were initiated. The active adrenal cortical agent was originally referred to as "cortin" or the "life-maintenance hormone".

The specific physiological activity of an adrenocortical hormone is difficult to define in that a substance may show a positive response in one method of assay and a negative response in another. It is essential, therefore, in reporting biological activity, to specify the assay method used. The most important of the symptoms which follow adrenalectomy and which provide quantitative methods of assay (besides survival tests) are:-

1. Disturbance of the Na^+, Cl^- and water balance (all increased excretion) and K^+ (retention).
2. Increase of the urea content of the blood.
3. Asthenia (inefficiency of muscle).
4. Disturbance of carbohydrate metabolism (decrease in liver glycogen).
5. Reduction in resistance to traumata (cold, mechanical shock, etc.).



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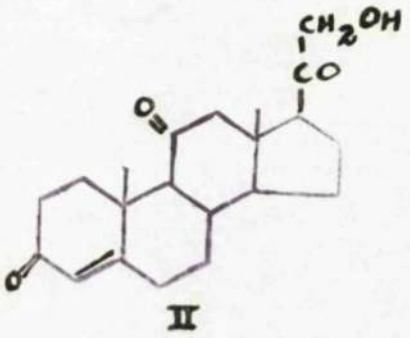

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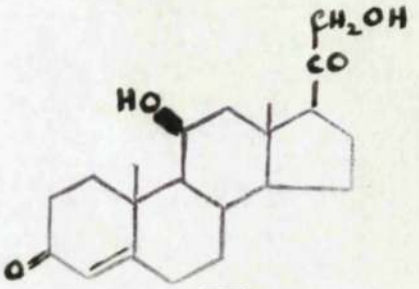

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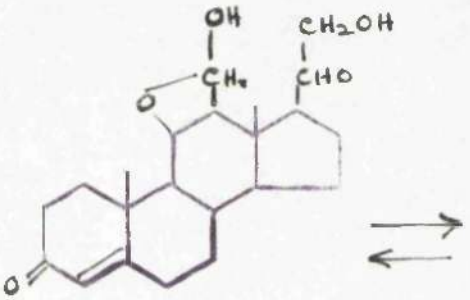

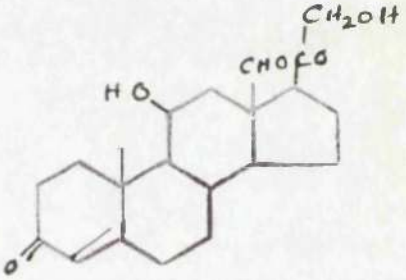

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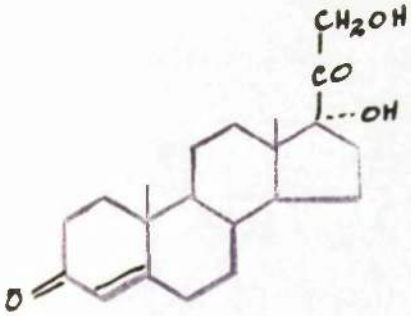

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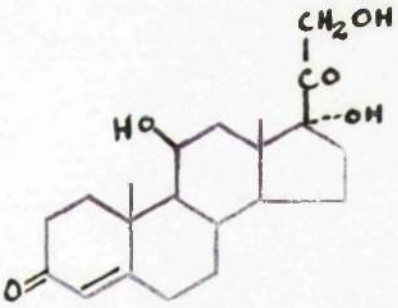

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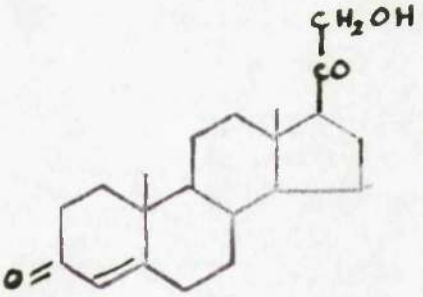

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Intensive research, conducted mainly by E.C.Kendall, J.J.Pfiffner T.Reichstein and O.Wintersteiner, and aimed at the isolation and chemical characterisation of cortical hormones, has resulted in the isolation from glandular extracts of twenty-eight crystalline steroids, six of which (I-VI) are capable of maintaining life in adrenalectomised animals. The residual amorphous fraction remaining, after removal of all crystalline material,

retained 14-30% of the activity of the whole extract. Recently there has been isolated from this amorphous fraction(4), a twenty-ninth crystalline steroid electro-cortin to which the structure (VII) has been ascribed. It has physiological activity about 30-100 times greater than 11-deoxy-corticosterone(VI).

Physiological activity was first clearly associated with a crystalline product when Mason, Myers and Kendall(5), established the effectiveness of their compound E (I, cortisone) in the work performance test of Ingle. The same compound has also been isolated by Wintersteiner and Pfiffner(6) who called it compound F, by Reichstein(7) who called it compound Fa, and later by Kuizenga and Cartland(8).

A detailed description of the chemical procedures involved in the isolation of the individual cortical steroids would be superfluous. In general, whole beef glands are extracted with acetone or alcohol which precipitate protein constituents. Advantage is taken of the relatively high water solubility of the hormones(9) whereby certain of the highly oxygenated hormones partition from ether or benzene to water on repeated extraction to give a fat-free aqueous concentrate. The Girard procedure is used for the separation of reactive ketones from non-ketonic or inert ketonic material(7). For separation of the individual components chromatography of the more stable acetates is used.

Nearly all the substances isolated are $C_{(21)}$ steroids, those exhibiting cortin activity all having the $\alpha\beta$-unsaturated ketonic grouping in ring A, characteristic of testosterone and progesterone, and possessing a ketol grouping in the side chain which is highly sensitive to both acids

and alkalies. At $C_{(11)}$ where substitution can exist, the ketone or the hydroxyl group (orientated in the β-configuration(6)) are subjected to very pronounced steric hindrance from the angular methyl groups at $C_{(10)}$ and $C_{(13)}$, a feature which is reflected in chemical behaviour. The carbonyl group at $C_{(11)}$ is inert to phenylhydrazine, hydroxylamine and to normal Wolff-Kishner conditions, Girard's reagents, and is resistant to catalytic hydrogenation in a neutral medium,. Hydrogenation can be accomplished in acetic acid solution, or by means of lithium aluminium hydride to give exclusively the hindered 11β-hydroxy derivative (i.e., hydrogen attacks the molecule at the unhindered rear face and opens the rear bond of the carbonyl group). The 11β-hydroxyl group is susceptible to dehydration even by dilute mineral acids and resists acylation under normal conditions, although methods of enforcing this acetylation have been described(104).

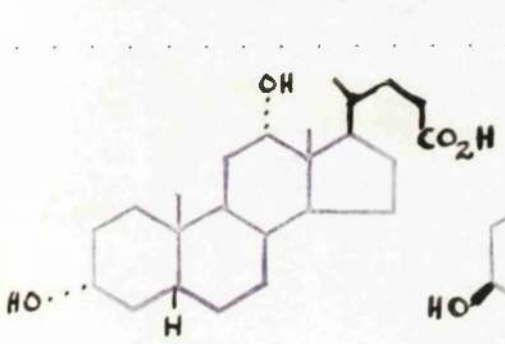
17-Hydroxy-11-dehydrocorticosterone (or "Cortisone")(I) isolated by Kendall(5) and often designated as Kendall's compound E, appears to be a particularly important member of the series from the point of view of physiological actions, matched only in part by compounds lacking either the tertiary hydroxyl group at C_{17} or an oxygen function at C_{11}.

Apart from the development of synthetic methods required for structural elucidation, and in particular of accomplishing the difficult task of the introduction of oxygen functions at C_{11} and C_{17}, it was imperative to obtain sufficient quantities of the adrenocortical hormones for clinical evaluation, since only minute amounts could be isolated from beef adrenal glands. In 1943 Reichstein(11) achieved the important feat of introducing oxygen at the 11-position and synthesised a substance

identical with natural 11-dehydrocorticosterone(II). In 1946 Sarett completed the synthesis of cortisone starting from deoxycholic acid. Within an extremely short time Hench and Kendall announced the anti-arthritic effect of cortisone(13). Eventually further results of the influence of cortisone on some of the collagen diseases have been reported and also on conditions associated with allergy, e.g., asthma and hayfever. The profound effect of cortisone on rheumatoid arthritis appeared to be highly specific(14), no other compound apart possibly from 17-hydroxy-corticosterone having comparable potency. Recent publications(15), however have reported that cortisone has no curative properties but merely suppresses the symptoms of rheumatoid arthritis, and radiological progressio of joint damage has been observed in patients under cortisone therapy. Evidence has also been published that cortisone and aspirin have comparable effects in arthritic patients(16). Electrocortin (or aldosterone), the recently isolated steroid adrenocortical hormone, is presently under clinical investigation(17).

In 1946, however, the apparent anti-arthritic effect of cortisone made it desirable that adequate supplies should be made available and partial synthesis from naturally occurring steroids seemed the most rational approach. Although most of the cortisone available until 1952 was prepared from deoxycholic acid(VIII), the difficulties attending this route have been appreciated for a considerable time and much attention has been given to routes starting from steroids other than bile acids. These investigations have been successful and cortisone can now be prepared

from a number of steroids, e.g., from ergosterol(XI), cholesterol(IX), stigmasterol(X), and the sapogenins diosgenin(XII) and hecogenin(XIII).



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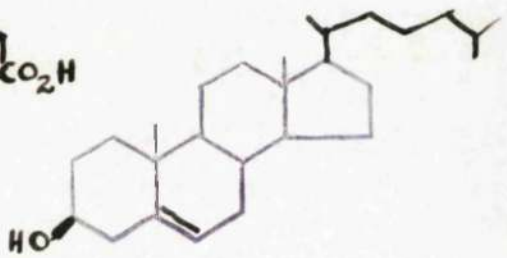

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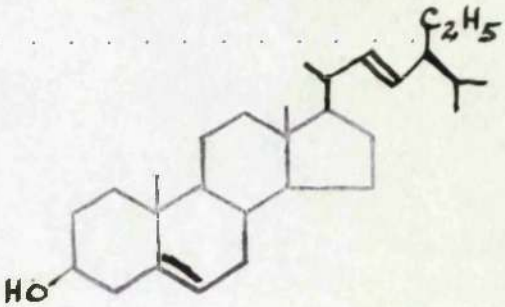

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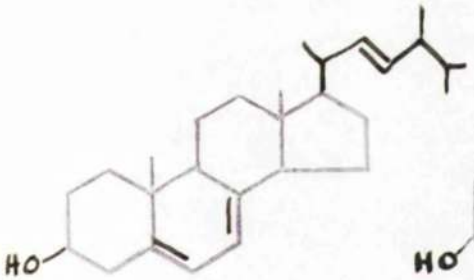

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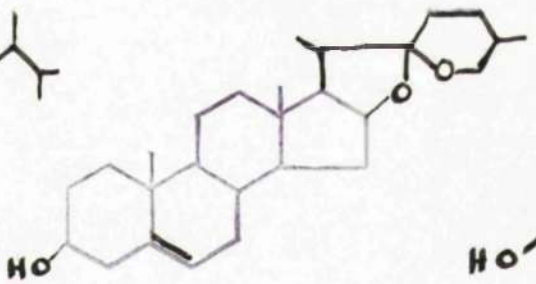

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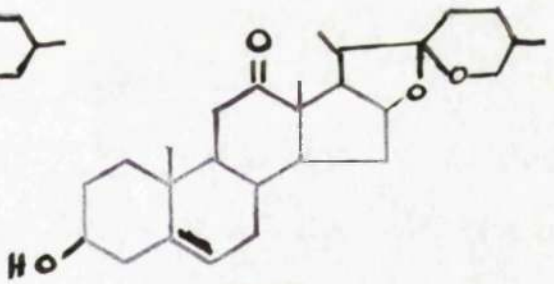
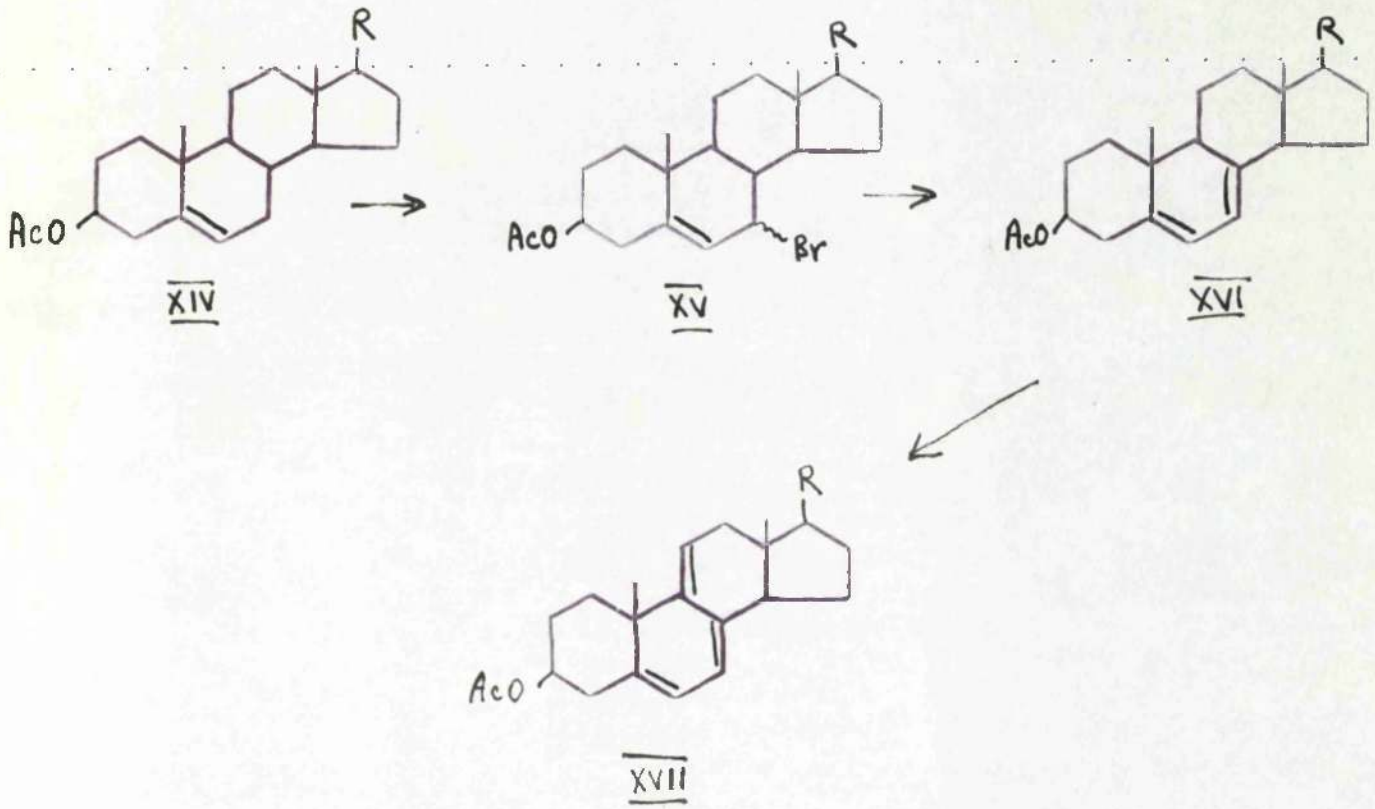


XIII

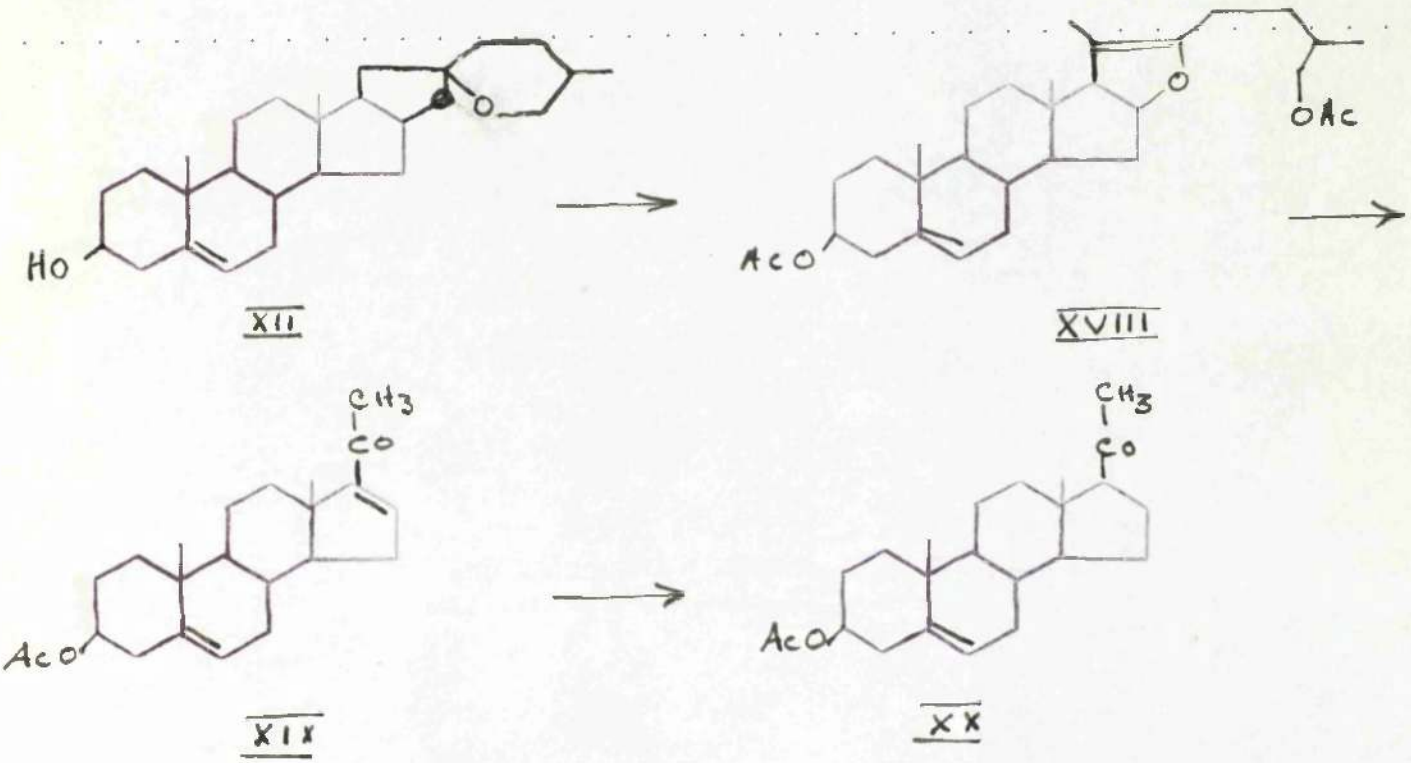
The principal disadvantage in the use of cholesterol(IX) is the difficulty of side chain degradation. The specific problem of devising a method for the introduction of an 11-oxygen function into steroids devoid of oxygen function in ring C but possessing a Δ^5-ethylenic linkage has been overcome by the general procedures of allylic bromination at C_7, dehydrobromination and mercuric acid oxidation to introduce the $\Delta^{9(11)}$-ethylenic bond, which serves as the necessary point of attack (XIV-XVII).



XIV XV XVI XVII

In ergosterol (XI) the side-chain double bond facilitates degradation (also a feature of stigmasterol) and the $\Delta^{9(11)}$-ethylenic bond can be introduced in one step.

Diosgenin (XII) is an attractive steroid as regards the synthesis of intermediate pregnane derivatives. Marker and his co-workers (18) have shown that treatment with acetic anhydride gives pseudodiosgenin acetate (XVIII) which can be oxidised to the pregna-5:16-diene derivative (XIX) which can be converted to pregnenolone acetate (XX) by hydrogenation.



This last compound is easily converted to progesterone and in view of the recent microbiological hydroxylation(20) of progesterone at C_{11}, diosgenin is gaining in importance as a starting material.

The total synthesis of cortisone has also been accomplished by several groups (21,22,23) and recent improvements (24) have suggested that this route might become as economic as partial synthesis.

Excellent reviews of the synthesis of cortisone and related steroids have recently been published by F.S. Spring (99) and by C. Djerassi (100).

The work described in this thesis is concerned with the utilisation of ergosterol as a starting material for cortisone synthesis.

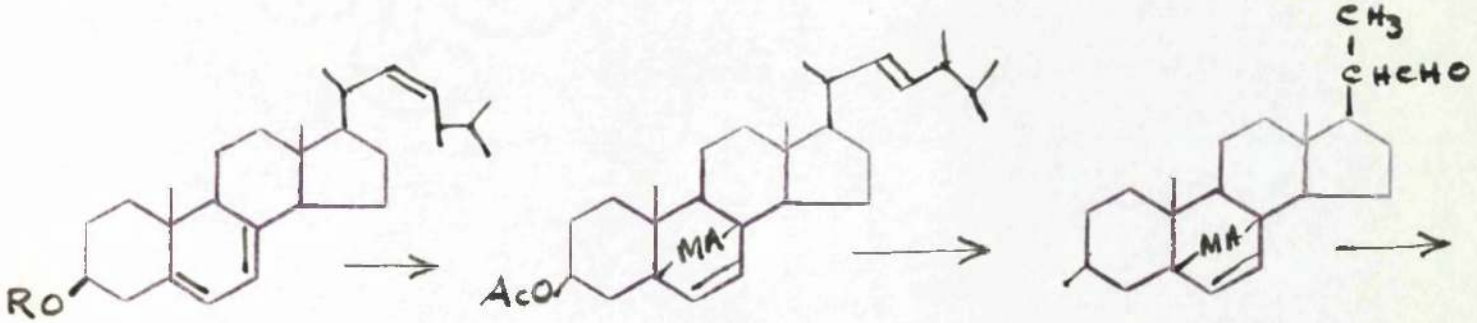
HISTORICAL.

HISTORICAL

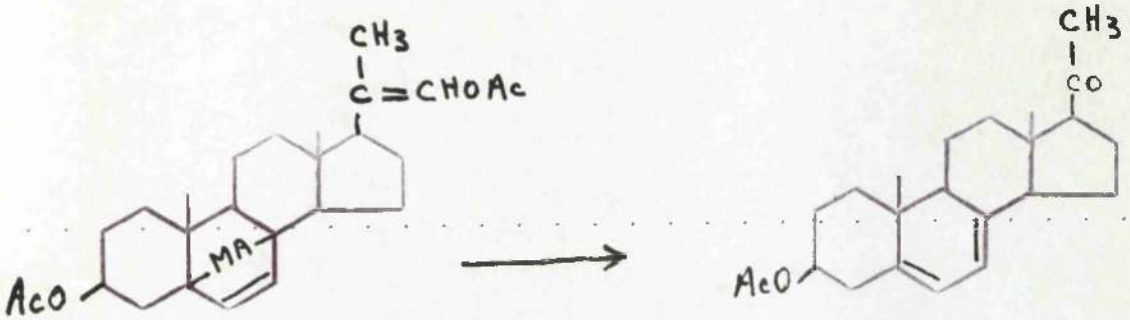
This section deals with the conversion of ergosterol to cortisone and therefore is principally confined to the methods which have been applied to the oxidation of the derived ergosterol-D (or analogous $\Delta^{7:9(11)}$ steroids) and dehydroergosterol.

I. Ergosterol as a Starting Material for Adrenocortical Hormone Synthesis.

In 1948, Bergmann and Stevens (25) suggested that ergosterol (XXI; R=H) might be used as a starting material for the partial synthesis of adrenal cortical steroids, "because of the comparative ease with which it may be converted to derivatives like dehydroergosterol which possess unsaturation at C_{11} and which might lend themselves to the introduction of oxygen at this point. In addition, the 22:23-double bond was expected to facilitate removal of the side chain to permit its replacement by one of the typical side chains of the adrenal cortical hormones." In this latter direction, considerable progress was made by these authors, who showed that protection of the ring B conjugated diene system of ergosteryl acetate (XXI; R=Ac) with maleic annydride permitted preferential attack on the side chain double bond.



XXI XXII XXIII



XXIV XXV

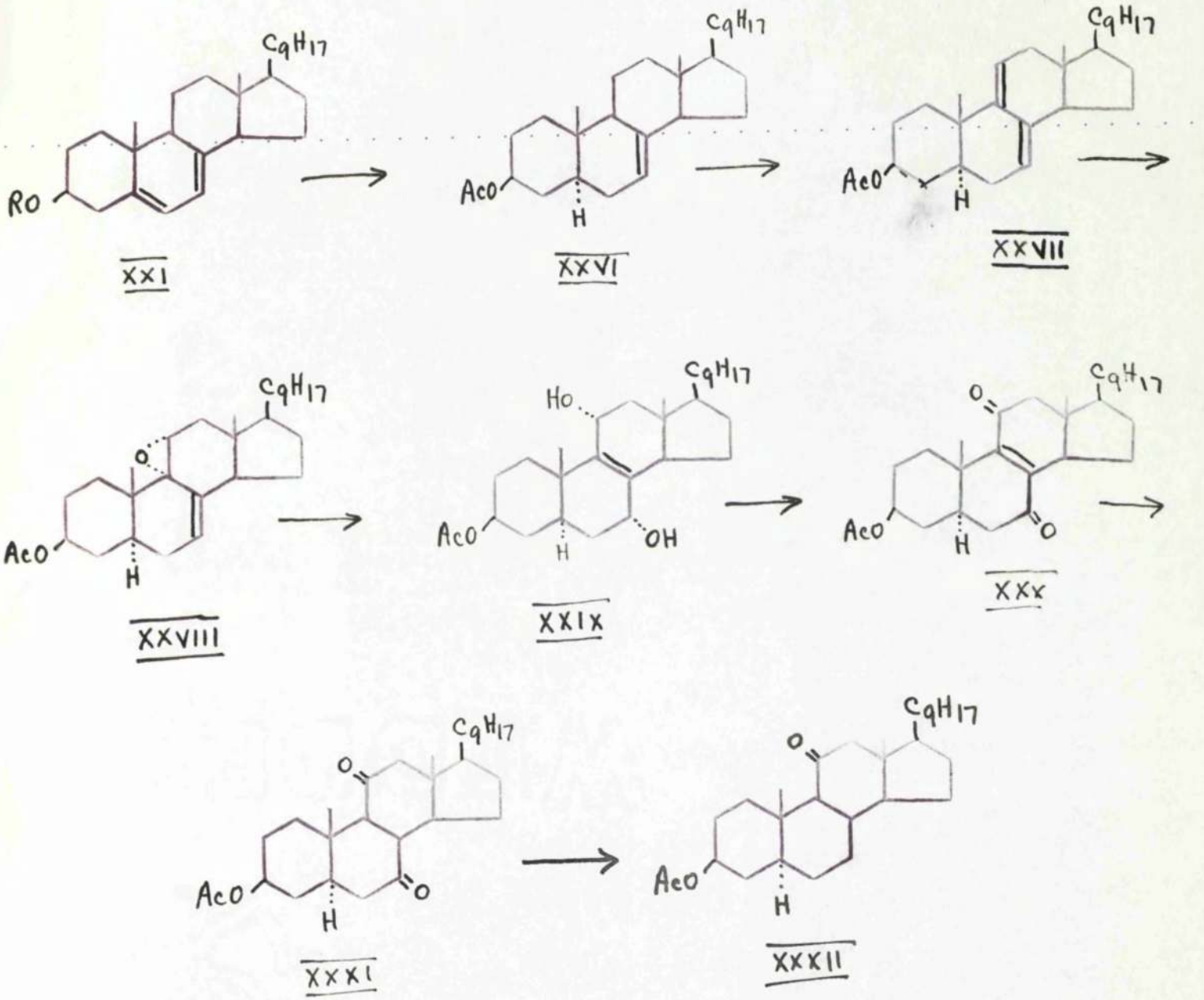
Thus treatment of the maleic anhydride adduct (XXII) with ozone gave an aldehyde (XXIII) which was converted into the enol acetate (XXIV), ozonolysis of which followed by pyrolysis gave 20-oxopregna-5:7-dien-3β-yl acetate (XXV). This ozonolysis procedure for side chain degradation has been substantiated by later workers (26,27).

II. 11-Keto-steroids from $\Delta^{7,9(11)}$-dienes.

(a) Oxidation with Peraromatic Acids.

In May, 1951, the successful introduction of 11-oxygen functions into ergosterol derivatives was announced by Tishler and his co-workers(27). This communication describes essentially a general scheme for the synthesis of 11-keto-steroids from steroids containing a Δ^5-ethylenic linkage such as ergosterol, diosgenin, stigmasterol and cholesterol. The three latter steroids must initially be converted into the $\Delta^{5:7}$ derivatives. This can be accomplished by allylic bromination of the Δ^5-steroid at C_7 followed by dehydrobromination.(XIV-XVI). (See Introduction).

The subsequent general procedure can be exemplified by reference to ergosterol. Partial reduction of ergosteryl acetate (XXI, R=Ac) gave 5-dihydroergosteryl acetate (XXVI)(28) oxidation of which with mercuric acetate gave ergosteryl-D acetate (ergosta-7,9(11),22-trien-3β-yl acetate) (XXVII)(29). Treatment of ergosteryl-D acetate with one equivalent of perbenzoic acid gave a monoepoxide 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate(XXVIII), hydrolytic rearrangement of which yielded 7ξ,11α-dihydroxy ergosta-8,22-dien-3β-yl acetate(XXIX). Henbest and Wagland (see Theoretical section V) have recently shown that the 7-hydroxyl group in (XXIX) has the α-orientation. Oxidation of (XXIX) by chromic anhydride yielded 7,11-dioxoergosta-8,22-dien-3β-yl acetate(XXX) which was reduced on treatment with zinc dust and acetic acid to 7,11-dioxoergost-22-en-3β-yl acetate(XXXI). Using the Huang-Minlon modification of the Wolff-Kishner procedure, the last compound was converted into 11-oxoergost-22-en-3β-yl



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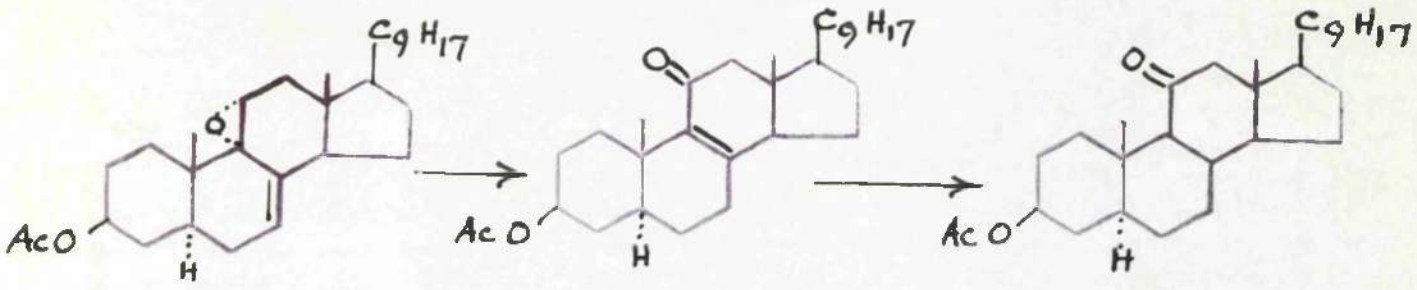
acetate (XXXI). Using the Huang-Minlon modification of the Wolff-Kishner procedure, the last compound was converted into 11-oxoergost-22-en-3β-yl acetate (XXXII). Heusser and his co-workers describe essentially the same route (30) and similar transformations in the cholestane and androstane series (31) and it was they who first ascribed the 9α:11α-epoxide structure to the monoepoxide (XXVIII).

An alternative route to 11-oxoergost-22-en-3β-yl acetate through the monoepoxide(XXVIII) has also been described(30). Treatment of the latter compound with boron trifluoride etherate in absolute benzene gave in high yield 11-oxoergosta-8,22-dien-3β-yl acetate (XXXIII)(30) which has subsequently been selectively reduced with lithium in liquid ammonia

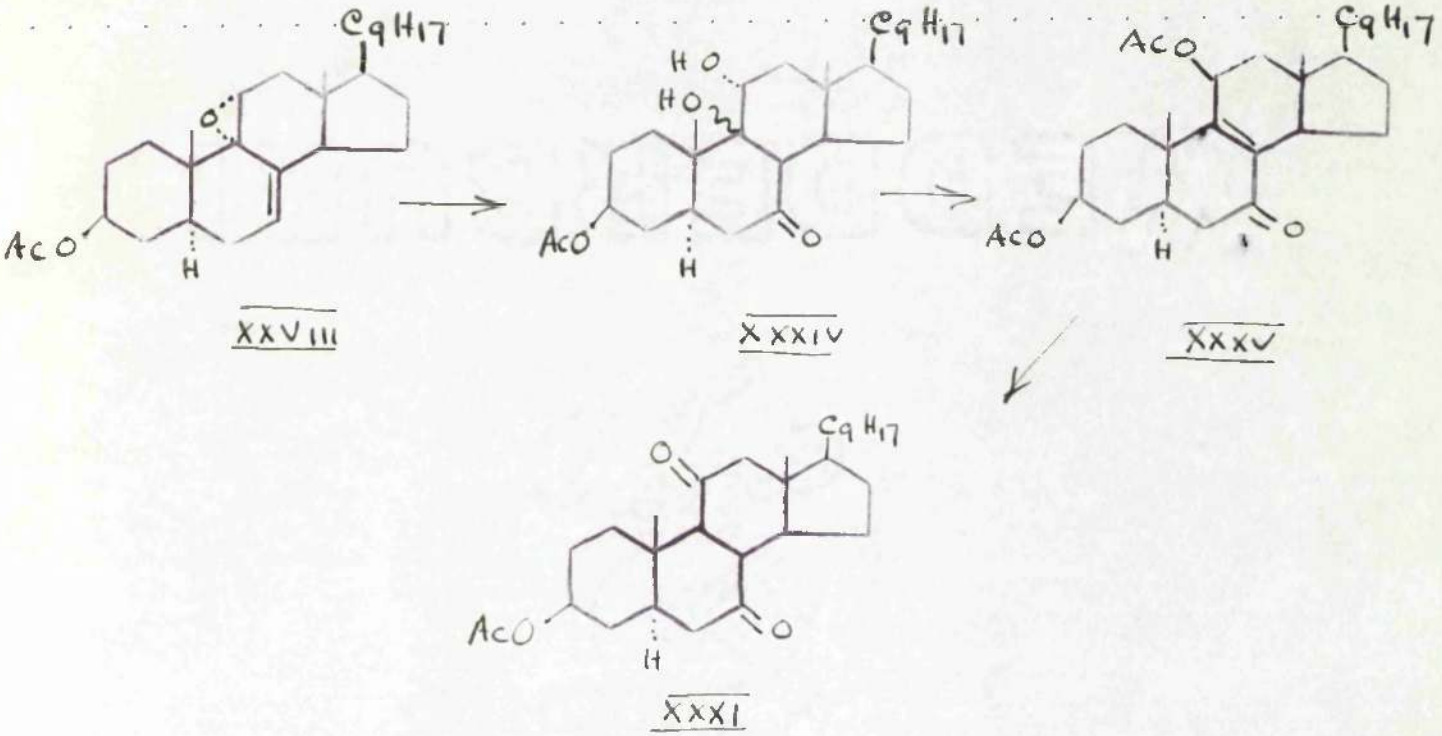


XXXVII XXXIII XXXII

to 11-oxoergost-22-en-3β-yl acetate (XXXII)(33). It has also been shown that reduction of Δ^{8}-11-ketones by lithium in liquid ammonia can produce 11α-hydroxy-steroids under certain conditions(34).

A further route to 11-oxoergost-22-en-3β-yl acetate has been described(35) in which 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (XXVIII) was treated successively with one mole of bromine, excess perbenzoic acid, and zinc dust and acetic acid to give 9ξ,11α-dihydroxy-7-oxoergost-22-en-3β-yl acetate (XXXIV)(this has subsequently been shown to be a 9α,11α-glycol, see theoretical section and(36)). Treatment of (XXXIV) with alkali followed by acetylation gave 3β,11α-diacetoxyergosta-8,22-dien-7-one (XXXV) which on treatment with strong base followed by re-acetylation

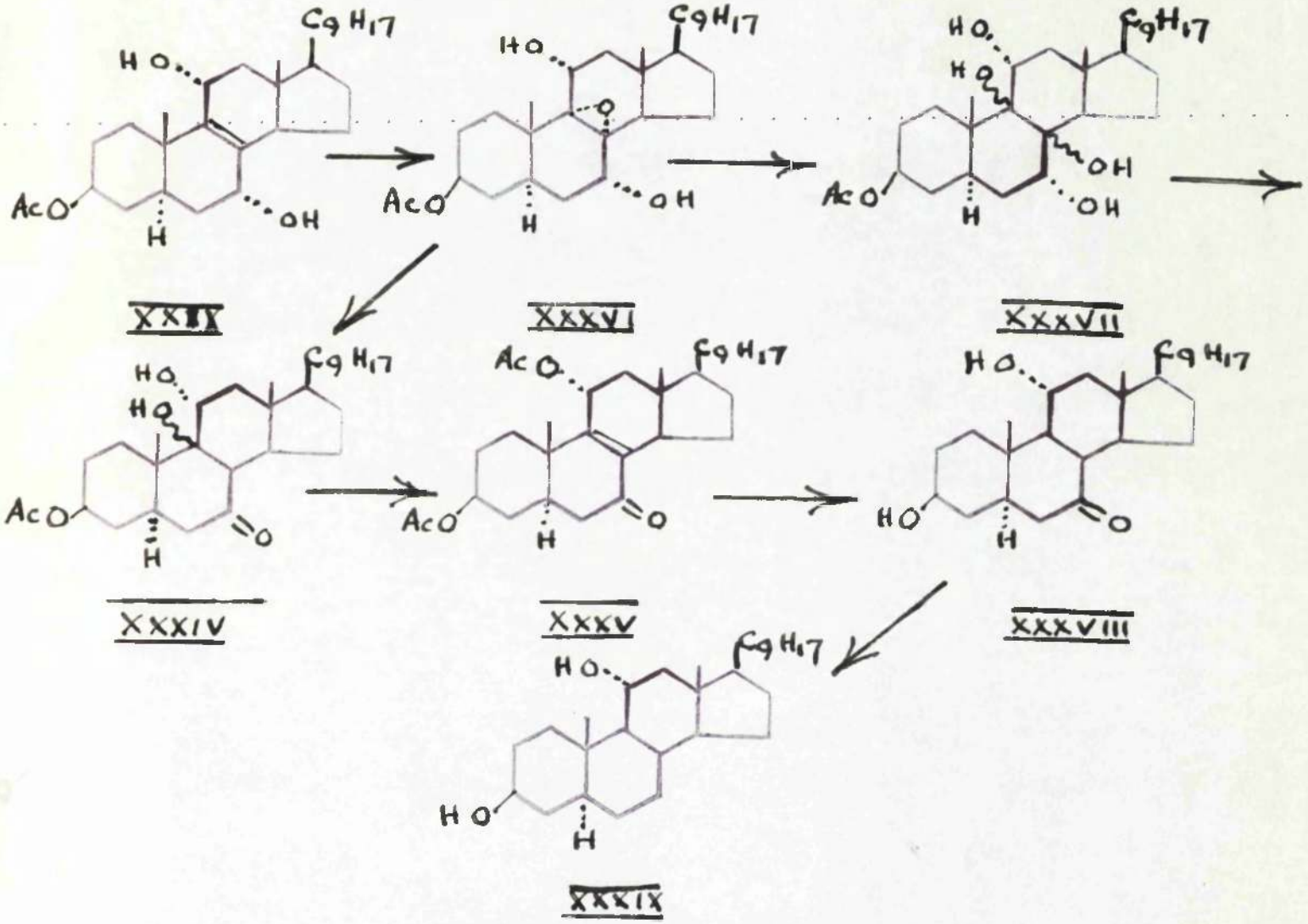
gave 7:11-dioxoergost-22-en-3β-yl acetate (XXXI).



XXVIII XXXIV XXXV

XXXI

9α:11α-Dihydroxy-7-oxoergost-22-en-3β-yl acetate (XXXIV) has been obtained by another route (37) starting from 7α:11α-dihydroxyergosta-8:22-dien-3β-yl acetate (XXIX). Partial oxidation of the latter with monoperphthalic acid gave the ditertiary epoxide (XXXVI). The 8α:9α-configuration is given to the epoxide group (30) since it has not been found possible to form the corresponding epoxide of the related methyl 3α-acetoxy-7α:11α-dihydroxy chol-8-enate. It is reasoned that a ready explanation for this marked difference is to be found if the epoxide group in (XXXVI) is α-orientated since addition of an α-epoxide group to the chol-8-ene derivative is considerably hindered by the cis fusion configuration of the rings A/B. The epoxide (XXXVI) is extremely liable to mineral acids and isomerises with hydrogen bromide or boron trifluoride

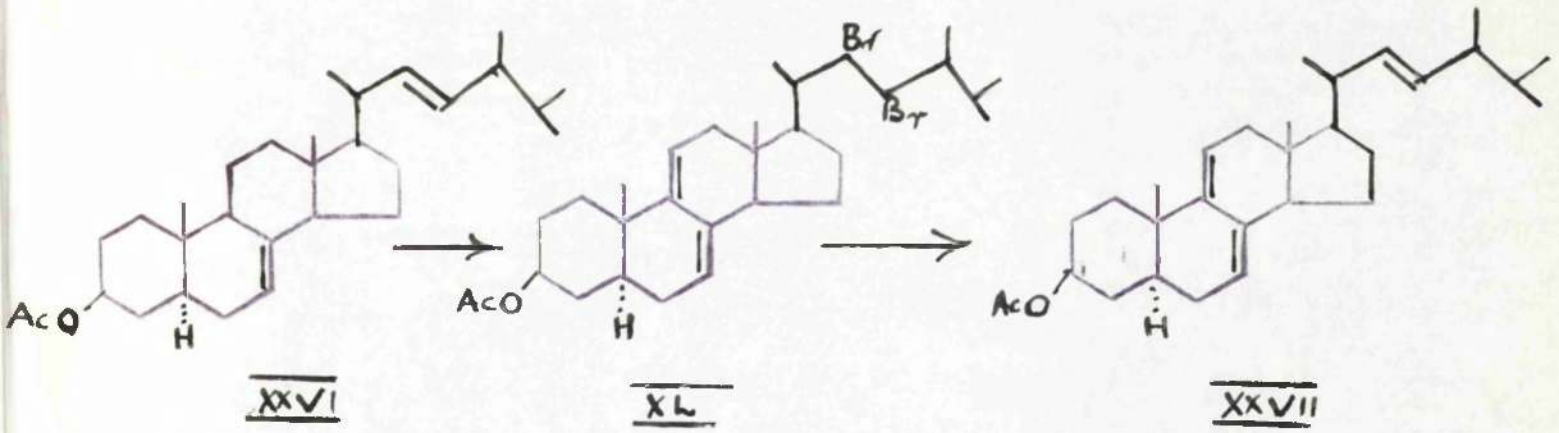


to 9α,11α-dihydroxy -7-oxoergost-22-en-3β-yl acetate (XXXIV). Treatment of the epoxide (XXXVI) with aqueous sulphuric acid converted it into 7ξ,8ξ,9ξ,11α -tetrahydroxyergost-22-en-3β-yl acetate(XXXVII)(37) which in turn on treatment with hydrogen bromide in acetic acid gave 9ξ,11α-dihydroxy-7-oxoergost-22-en-3β-yl acetate (XXXIV).

Catalytic hydrogenation of the diacetate (XXXV) in the presence of alkali effects saturation of the Δ^{8}-ethylenic linkage with formation of 3β,11α-dihydroxy ergost-22-en-7-one (XXXVIII)(37), Wolff-Kishner reduction

of which gives 3β,11α-dihydroxyergost-22-ene(XXXIX).

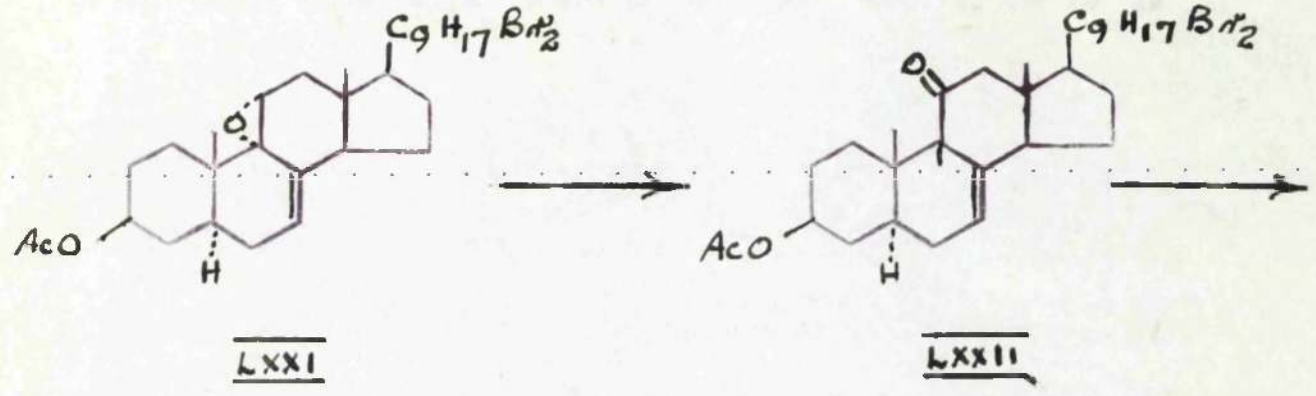
An approach to cortisone through ergosteryl-D acetate 22,23-dibromide has been described(38). Treatment of 5-dihydroergosteryl acetate (XXVI) with bromine under specific conditions gave a tetrabromo ergostenyl acetate, which on treatment with sodium iodide was partially debrominated to give 22,23-dibromoergosta-7,9(11)-dien-3β-yl acetate (XL)(ergosteryl-D acetate 22,23-dibromide), the structure of which was established by its debromination with zinc dust to ergosteryl-D acetate (XXVII).



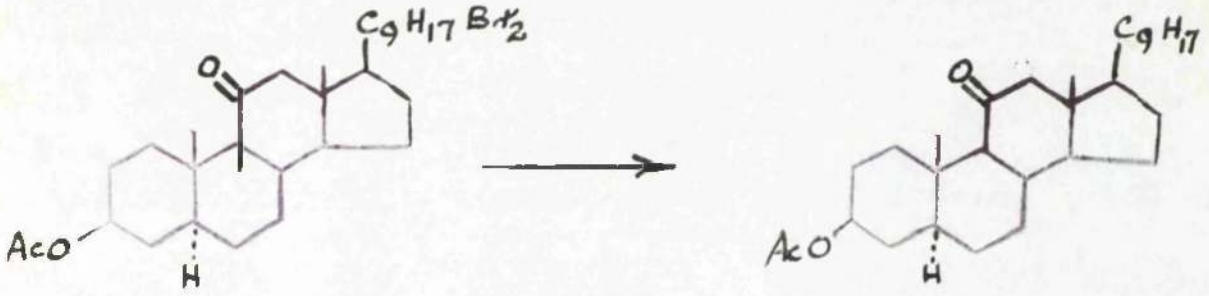
XXVI XL XXVII

The reaction series (XXVII) - (XXXII) (p.11) has been carried out with the related dibromides, reduction of the dibromo-Δ^{8}-7,11-diketone being accompanied by debromination to (XXXI)(39).

Another very efficient method of obtaining 11-oxoergost-22-en-3β-yl acetate has been described by Elks et al(54) being a method first described by Jones and his co-workers)(54), whereby the dibromo-epoxide (LXXI obtained by perbenzoic acid treatment of ergosteryl-D acetate 22,23-dibromide (XL) (39), was treated with boron trifluoride etherate in ether to give 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (LXXII).



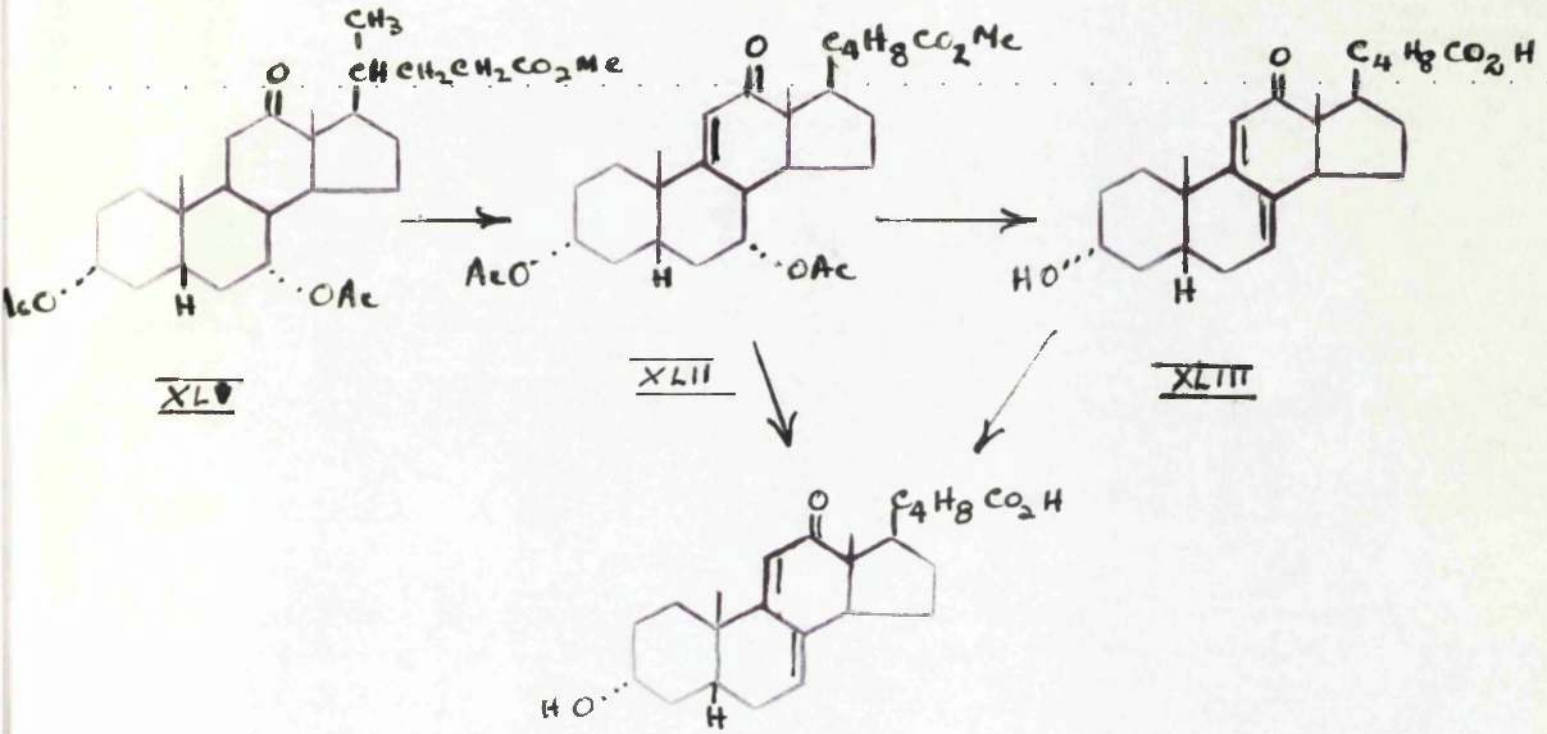
LXXI LXXII



LXXIII XXXII

Catalytic hydrogenation of the latter compound gave an excellent yield of 22,23-dibromo-11-oxo-9β-ergostan-3β-yl acetate (LXXIII). The 9β-hydrogen atom of (LXXIII) isomerised to the natural α-configuration with strong alkali treatment, debromination of the product giving 11-oxoergost-22-en-3β-yl acetate (XXXII).

In addition to ergosterol, cholesterol, stigmasterol and diosgenin, this general route to 11-oxygenated steroids has been applied to cholane, bisnorallocholane, androstane and cholestane derivatives. A $\Delta^{7:9(11)}$-diene was prepared from cholic acid as follows(30):- methyl 3α,7α-diacetoxy-12-oxocholanate (XLI) was oxidised with selenium dioxide to methyl 3α,7α-diacetoxy-12-oxochol-9-enate(XLII) which on treatment with alkali gave 3α-hydroxy-12-oxochola-7,9(11)-dienic acid(XLIII). Reduction of



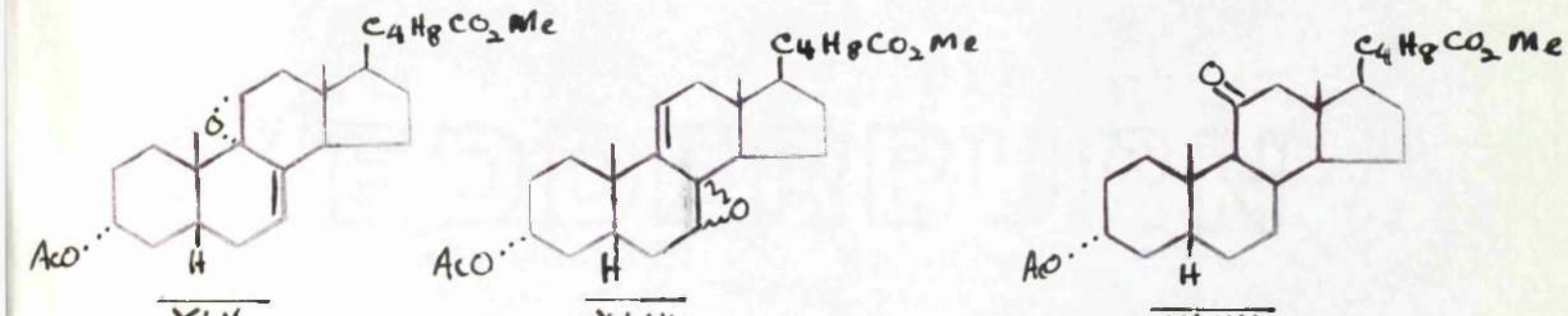
XLI

XLII

XLIII

XLIV

the latter compound by the Wolff-Kishner method gave the required 3α-hydroxychola-7,9(11)-dienic acid(XLIV), also obtainable directly from (XLII) by the Wolff-Kishner technique. Treatment of the 3-acetate methyl ester of (XLIV) with monoperphthalic acid gave as major product, an epoxide which by analogy with the corresponding ergosterol derivative was formulated as the 9α,11α-epoxide (XLV) from which the saturated 11-keto



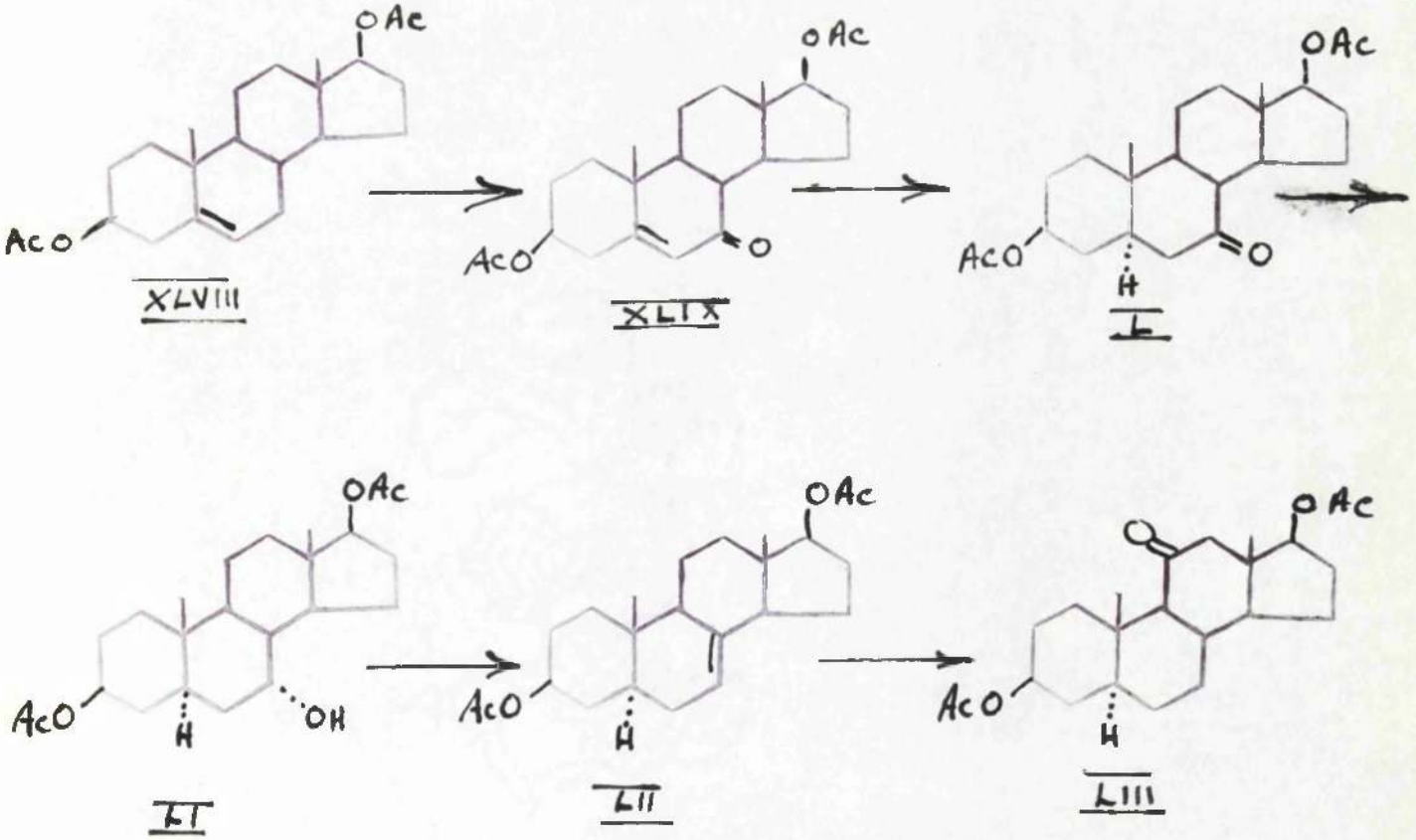
XLV

XLVI

XLVII

methyl ester (XLVII) can be prepared by a series of steps exactly similar to these for ergosterol derivatives, i.e., (XXVIII) -- (XXXII)(p.11). Doubts have been expressed(30) concerning the structure ascribed to the epoxide (XLV). Consideration of molecular rotation differences and of the fact that the epoxide with boron trifluoride etherate in absence of water isomerises to methyl 3α-acetoxy-7-oxochol-8-enate and not to the 11-keto isomer, suggest that the epoxide may have the 7,8-oxide structure (XLVI).

In the androstane series, 3β,17β-diacetoxyandrost-5-ene(XLVIII) was converted by a novel route(45) into 3β,17β-diacetoxyandrost-7-ene(LII). Oxidation of the diacetate (XLVIII) with t-butyl chromate(46) gave 3β,17β-diacetoxyandrost-5-en-7-one (XLIX), catalytic hydrogenation of which

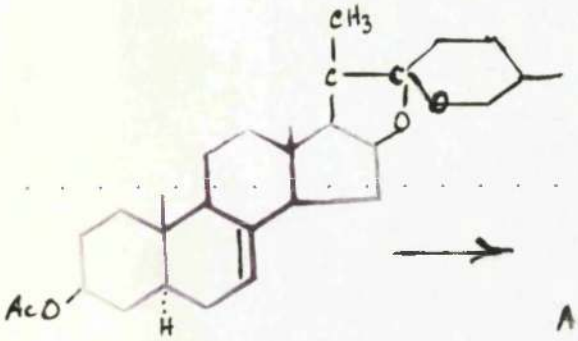


in ethyl acetate gave 3β,17β-diacetoxyandrostan-7-one(L). Further hydrogenation of (L) in acetic acid gave 3β,17β-diacetoxy-7α-hydroxyandrostane (LI), which was dehydrated to 3β,17β-diacetoxyandrost-7-ene(LII). Using essentially the same procedure(27,30), as that described above for 5-dihydro-ergosteryl acetate (through ergosteryl-D acetate) the compound (LII) was converted into 3β-17β-diacetoxy-11-oxoandrostane (LIII)(32).

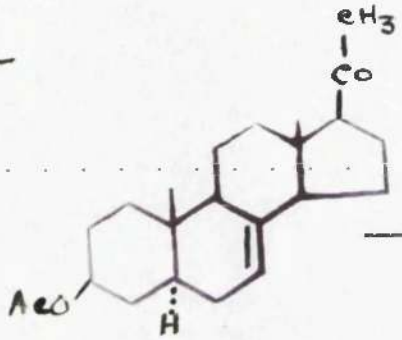
(b) Oxidation with Peraliphatic Acids.

This method is applicable only to compounds of the allo series, it does not apply to the 5β-series.

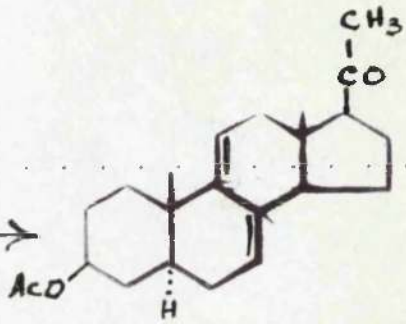
Diosgenin (XII) can be converted by general established methods as previously described into 22a-allospirost-7-en-3β-yl acetate (LIV) and thence to 20-oxoallopregn-7-en-3β-yl acetate (LV). Djerassi et al (47) described the mercuric acetate oxidation of the latter compound to give 20-oxoallopregna-7,9(11)-dien-3β-yl acetate (LVI). Treatment of (LV) with lithium aluminium hydride followed by acetylation gave 3β-20β-diacetoxyallopregn-7-ene (LVII) which was converted to the $\Delta^{7,9(11)}$-diene (LVIII) by mercuric acetate oxidation(48). Oxidation of (LVIII) with performic acid gave 3β,20β-diacetoxy-9α,11α-epoxy allopregnan-7-one (LIX) (49) which isomerised on treatment with alkali to give 3β,11α,20β-trihydroxyallopregn-8-en-7-one (LX). Catalytic hydrogenation of (LX) followed by Wolff-Kishner reduction gave 3β,11α,20β-trihydroxyallopregnane (LXI). Chromic anhydride oxidation of the latter gave the known triketone (LXII) which was reduced



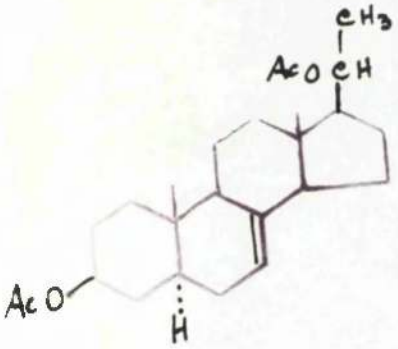
LIV



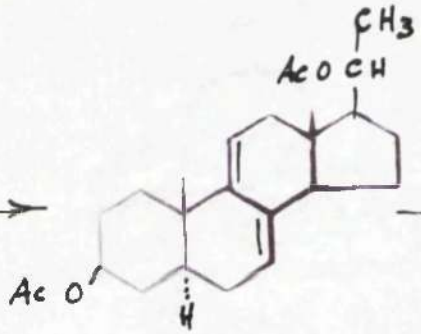
LV



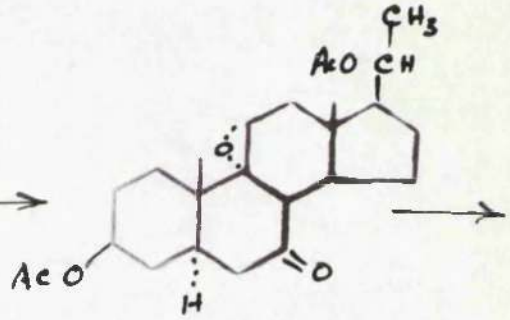
LVI



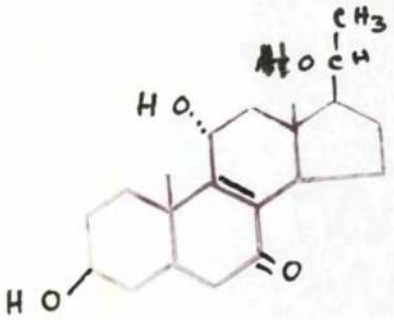
LVII



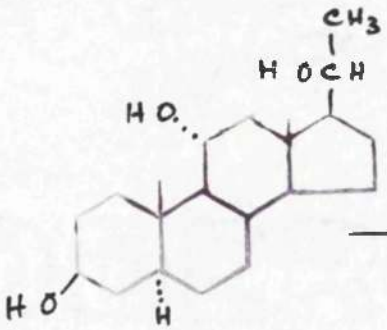
LVIII



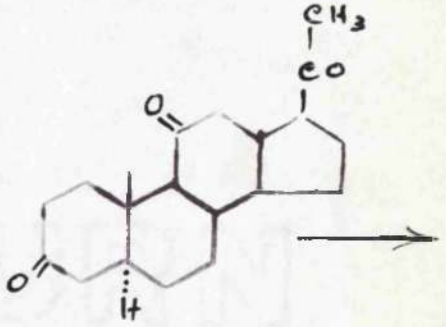
LIX



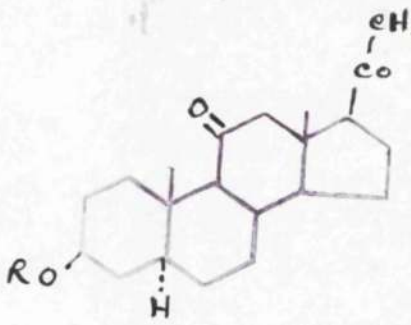
LX



LXI

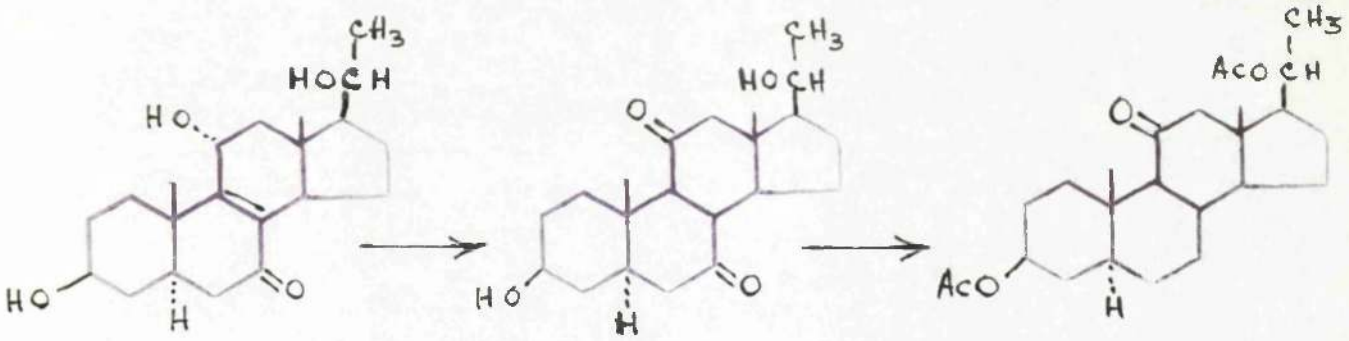


LX II



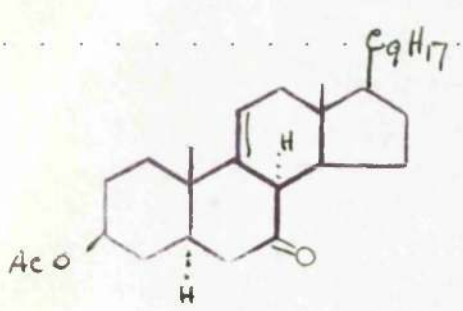
LXIII

by Raney nickel hydrogenation to 11:20-dioxoallopregnan-3β-ol (LXIII; R=H)(50). Another route has been described by Djerassi et al (51) whereby 3β:11α:20β-trihydroxyallopregn-8-en-7-one (LX) was isomerised into 3β:20β-dihydroxyallopregn-7:11-dione (LXIV) by refluxing with potassium t-butoxide in t-butanol. The diacetate of (LXIV) forms the 7-ethylene-dithioketal which on desulphurisation with Raney nickel gave 3β:20β-diacetoxyallopregnan-11-one (LXV).

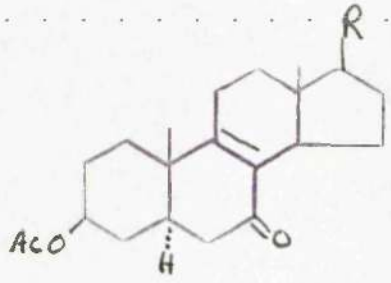


This general performic acid oxidation procedure has also been applied to allopregna-7:9(11)-dien-20-one(LVI) (52), to 22a-allospirosta-7:9(11)-dien-3β-yl acetate (53,49) obtained from diosgenin, and to ergosteryl-D acetate (35,38).

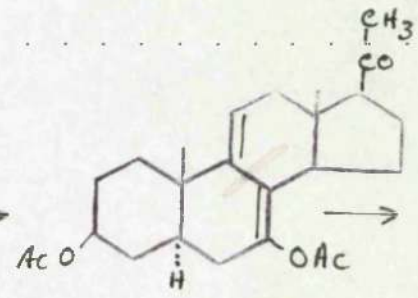
An interesting feature of these performic acid oxidations is that oxidation of ergosteryl-D acetate with 1 mole of performic acid (35,38) gave 7-oxo-8(-ergosta-9(11):22-dien-3β-yl acetate (LXVI) which can easily



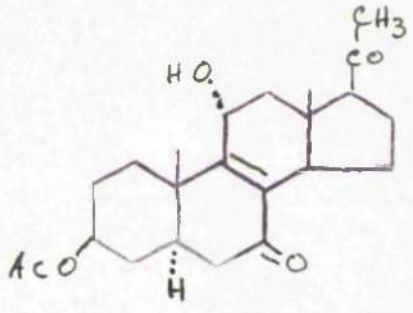
LXVI



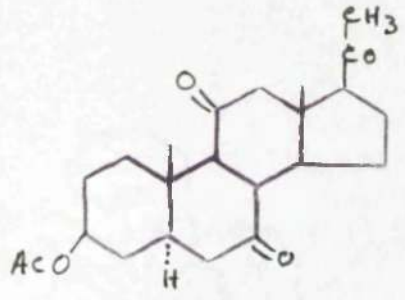
LXVII



LXVIII



LXIX

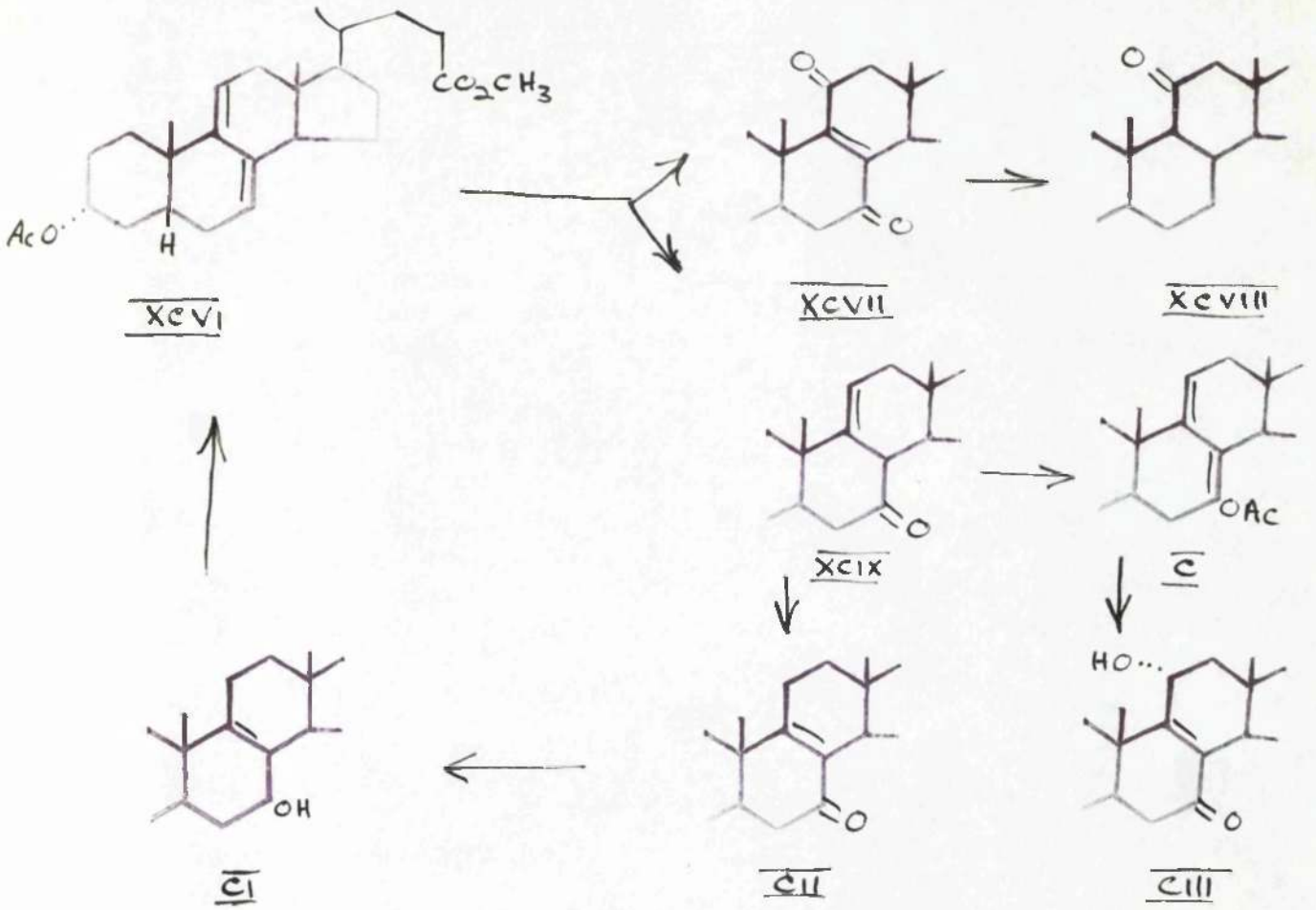


LXX

be isomerised with acid or alkali to 7-oxoergosta-8,22-dien-3β-yl acetate (LXVII; R=C_9H_{17}). From the mother liquors of the performic acid oxidation of 20-oxoallopregna-7,9(11)-dien-3β-yl acetate (LVI) and analogous αβ-unsaturated ketone 7,20-dioxoallopregn-8-en-3β-yl acetate (LXVII; R=$COCH_3$) has been isolated(52). Enol acetylation of the latter with isopropenyl acetate(52) gave (LXVIII) which on treatment with 1 mole of perbenzoic acid yielded 11α-hydroxy-7,20-dioxoallopregn-8-en-3β-yl acetate (LXIX). Catalytic hydrogenation of the latter followed by chromic acid oxidation gave 7,11,20-trioxoallopregnan-3β-yl acetate (LXX).

(c) Oxidation with Sodium Dichromate and N-bromsuccinimide.

Further methods for the production of 11-oxygenated steroids from $\Delta^{7,9(11)}$-dienes have been reported by Fieser and his co-workers (89,90,91), who investigated the oxidation of $\Delta^{7,9(11)}$-dienes with sodium dichromate and with N-Bromsuccinimide.

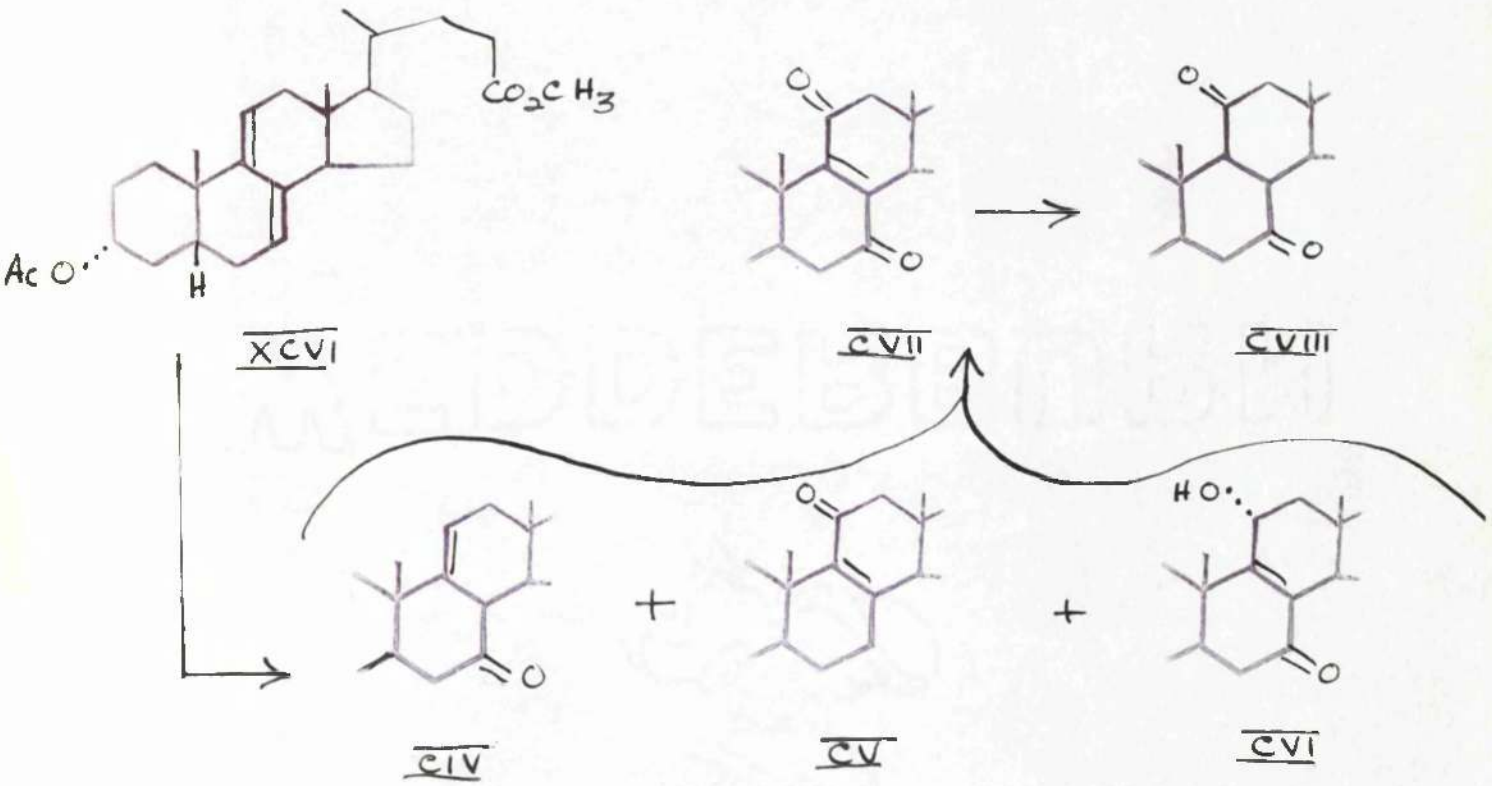


Oxidation of methyl 3α-acetoxychola-7,9(11)-dienate (XCVI) with sodium dichromate in acetic acid (92,89) gave the $\Delta^{9(11)}$-7-ketone (XCIX) and the Δ^{8}-7,11-diketone (XCVII). Reduction of the latter with zinc followed by removal of the 7-carbonyl group by the Wolff-Kishner method gave the methyl ester acetate of 11-ketolithocholic acid (XCVIII). The $\beta\gamma$-unsaturated ketone (XCIX) was easily isomerised to the conjugated

ketone (CII) which can be converted back to the diene (XCVI) by reduction with sodium and amyl alcohol to the alcohol (CI) followed by dehydration. Enol acetylation of the non-conjugated ketone (XCIX) gave the enol acetate (C) which was converted into (CIII) by treatment with perphthalic acid.

This dichromate oxidation method also applies to 5α-steroids. Dichromate oxidation of cholesta-7:9(11)-dien-3β-yl benzoate, (90) gave the related cholesterol products shown above (cf. also 93).

Another method for use with $\Delta^{7:9(11)}$-dienes with either a cis or trans A/B junction has been described (36,91)(102). Dienes of the bile acid, cholesterol and ergosteral series have been converted into the saturated 7:11-diketones (CVIII) by reaction with N-bromosuccinimide in t-butanol-dilute sulphuric acid, followed by further oxidation with

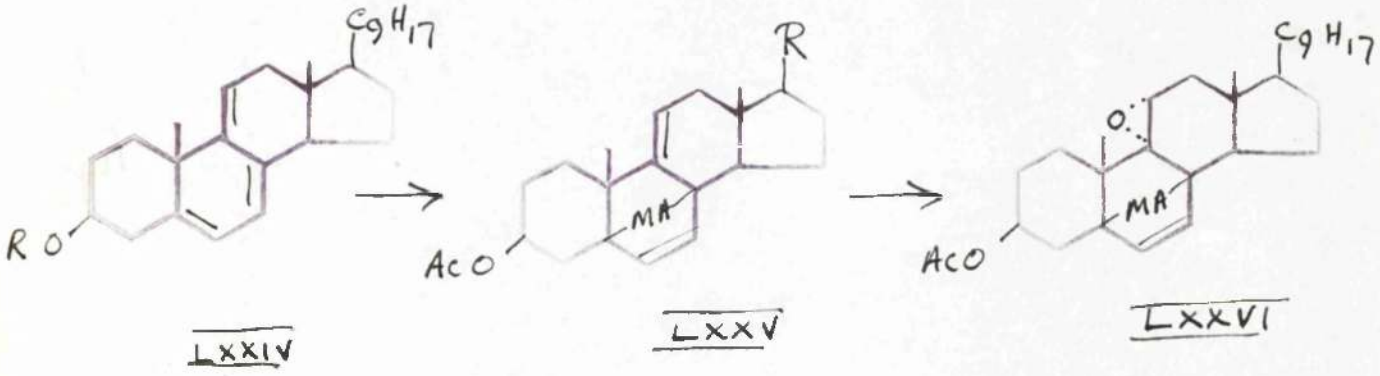


silver chromate and reduction with zinc and acetic acid. In the bile acid series, initial products of reaction with the bromoimide have been characterised(91) as the 9(11)-en-7-one(CIV), 8-en-11-one (CV), and 8-en-11α-ol-7-one (CVI). Silver chromate oxidation of these led to (CVII) which was reduced by treatment with zinc dust and acetic acid to (CVIII).

11-Keto-steroids from dehydroergosterol.

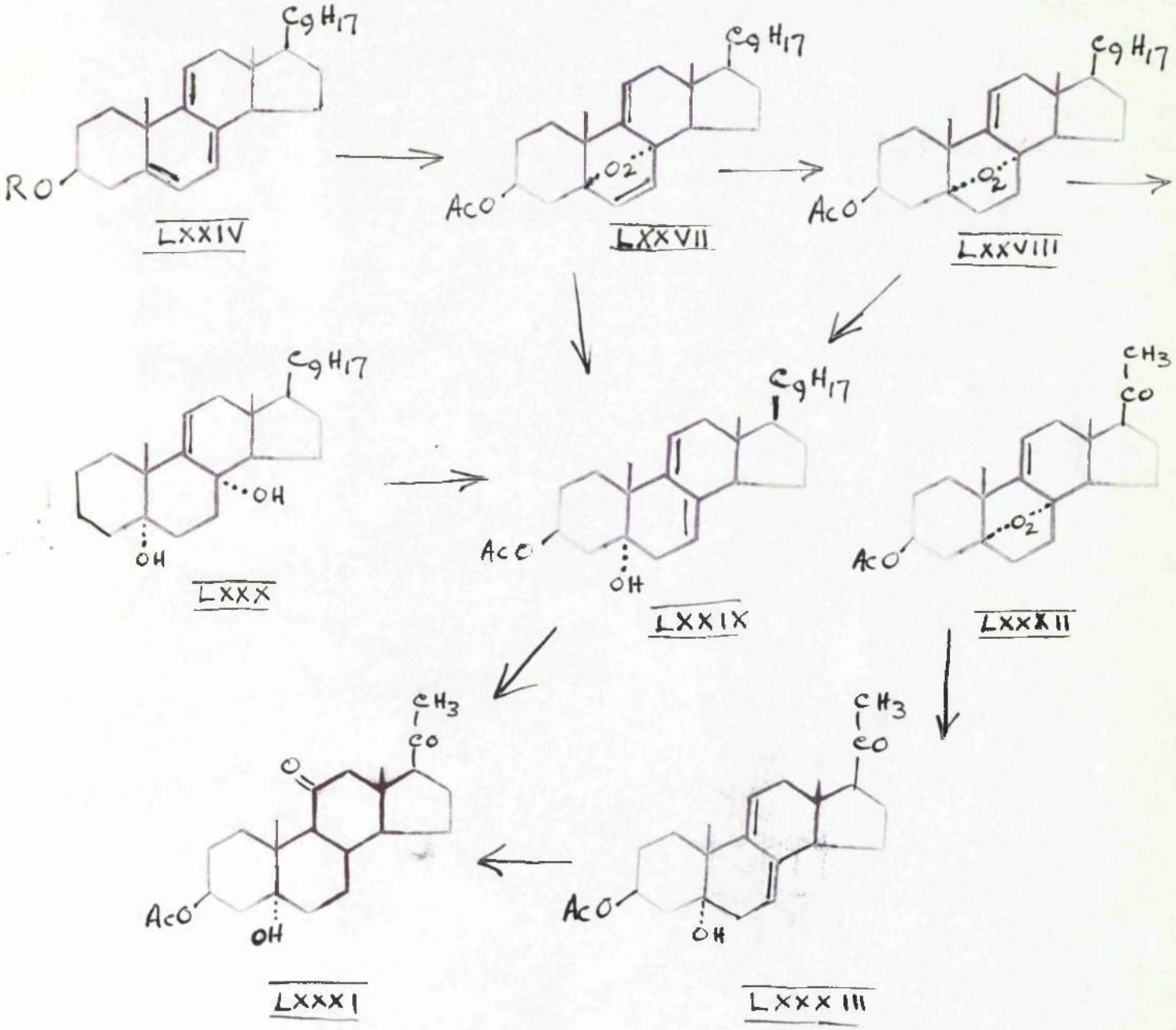
(a) Peroxidation in Ring B.

As mentioned before dehydroergosterol (LXXIV; R=H) prepared by mercuric acetate oxidation of ergosteryl acetate, seemed an attractive starting material for the synthesis of 11-keto ergosterol derivatives. Bergmann and Stevens(25) approached the problem by forming the maleic anhydride adduct (LXXV; $R=C_9H_{17}$) of dehydroergosteryl acetate (LXXIV; R=Ac),



LXXIV LXXV LXXVI

protecting the sidechain ethylenic linkage by addition of bromine to give (LXXV; R=$C_9H_{17}Br_2$) thus leaving the $\Delta^{9(11)}$-ethylenic linkage open to oxidative attack. Treatment of (LXXV; R=$C_9H_{17}Br_2$) with perbenzoic acid followed by debromination with zinc gave a high yield of the monoepoxide (LXXVI). Pyrolysis of (LXXVI), however, caused aromatisation in ring B and no identifiable 11-keto-steroid was isolated.



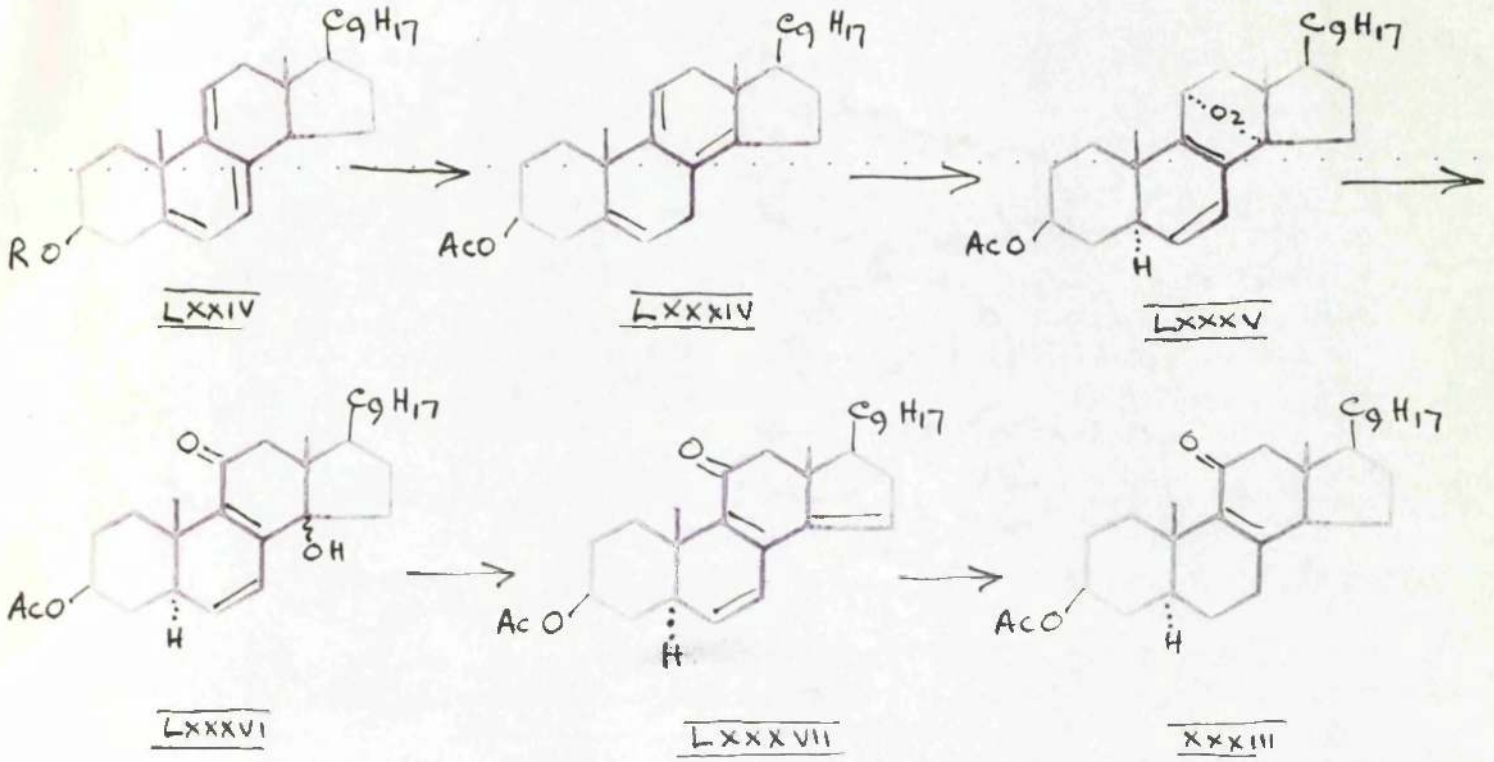
In 1952, a new approach to 11-keto-steroids from dehydroergosteryl acetate was described by Jones et al in a series of publications (55). Windaus and Linsert(57) in 1928 first prepared 5α,8α-epidioxydehydroergosteryl acetate (LXXVII) by photoperoxidation of dehydroergosteryl acetate (LXXIV;R=Ac). Jones and his co-workers(55a) preferentially reduced (LXXVII) with a specially prepared platinum catalyst to give 5α,8α-epidioxyergosta-9(11),22-dien-3β-yl acetate (LXXVIII). Catalytic hydrogenation of (LXXVII) with Raney nickel or palladium catalyst gave 5α-hydroxyergosta-7,9(11),22-trien-3β-yl acetate (LXXIX) which was also obtained from (LXXVIII) by Raney nickel or palladium catalysed hydrogenation. The formation of (LXXIX) probably proceeds through 5α,8α-dehydroxyergosta-9(11),22-dien-3β-yl acetate (LXXX) since this intermediate has been isolated by platinum catalysed hydrogenation (2 moles) of (LXXVIII) and readily dehydrates to (LXXIX) on mild acid treatment. The standard 3-stage degradation procedure for the side chain of ergosterol derivatives (25) (ozonolysis, enol acetylation, and ozonolysis) on (LXXVIII) gave 5α,8α-epidioxy -20-oxoallopregn-9(11)-en-3β-yl acetate (LXXXII)(55b) which was converted to 5α-hydroxy-20-oxoallopregna-7,9(11)-dien-3β-yl acetate (LXXXIII) by hydrogenation. The $\Delta^{9(11)}$-ethylenic linkage of 5α,8α-epidioxyergosta-9(11),22-dien-3β-yl acetate (LXXVIII) and related compounds was shown to be only moderately reactive towards oxidising agents although a 9,11-epoxide and a 9,11-diol have been formed, albeit in poor yield. This was attributed to steric hindrance of the $\Delta^{9(11)}$-ethylenic bond by the α-orientated epidioxy bridge. Following well established routes as described previously for $\Delta^{7,9(11)}$-dienes, both (LXXXIII) and (LXXIX)

can be converted into 5α-hydroxy-11,20-dioxoallopregnan-3β-yl acetate (LXXXI)(56,54)) and thence to cortisone.

A very important feature of this approach to cortisone through 5α,8α-epidioxy derivatives was that rupture of this 5α,8α-epidioxy system led to 5α-hydroxy derivatives which after oxidation of the 3β-hydroxyl group, led readily to the 3-keto-Δ^{4}-system (see p.32) the formation of which is one of the most formidable of the problems in the partial synthesis of cortisone.

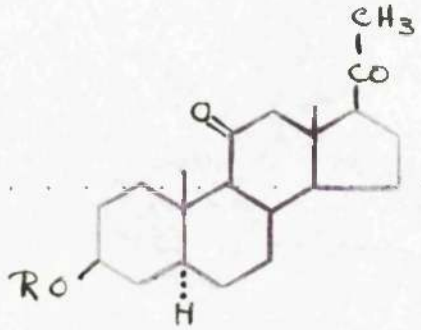
(b) Peroxidation in ring C.

In 1953, Laubach and Brunings(58) described without experimental detail, a novel route from dehydroergosterol to 11-oxygenated steroids and thence to cortisone. Dehydroergosteryl acetate (LXXIV; R=Ac) was catalytically isomerised with liquid sulphur dioxide to ergosta-6,8(14),9(11),22-tetraen-3β-yl acetate (LXXXIV). Photo-peroxidation of this latter compound afforded 11,14-epidioxyergosta-6,8,22-trien-3β-yl acetate (LXXXV) which under mild basic conditions rearranged to 3β-acetoxy-11-oxoergosta-6,8,22-trien-14-ol (LXXXVI). Acid hydrolysis of (LXXXVI) gave 11-oxoergosta-6,8,14,22-tetraen-3β-yl acetate (LXXXVII) which was partially hydrogenated to the known 11-oxoergosta-8,22-dien-3β-yl acetate (XXXIII).

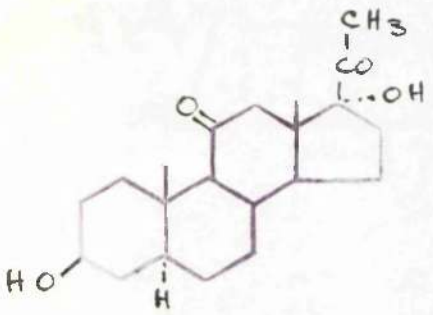


IV. Conversion of 11-oxygenated Steroids into Cortisone.

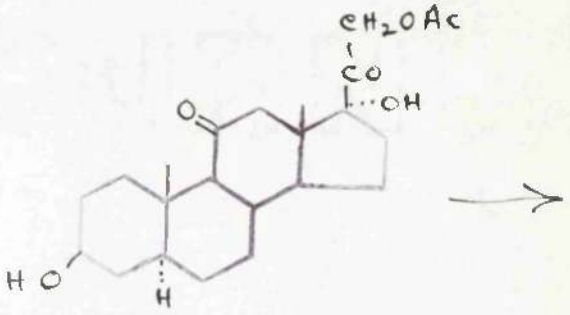
11,20-Dioxoallopregnan-3β-yl acetate (LXIII; R=Ac) is a common intermediate in many partial syntheses of cortisone from 5α-series steroid starting materials. The transformation of (LXIII; R=H) to cortisone acetate includes the introduction of two hydroxyl groups in positions C_{17} and C_{21} and of the αβ-unsaturated ketone in ring A. Using the Gallagher method (59), the 11,20-diketone (LXIII; R=Ac) is converted into its 11,20-dienol-acetate, oxidation of which with perbenzoic acid followed by alkaline hydrolysis gives 3β,17α-dihydroxy-11,20-dioxoallo pregnane (LXXXVIII). Bromination of the latter followed by treatment of the 21-bromo derivative with sodium acetate (60) or with sodium iodide followed by potassium acetate (61) gives 3β,17α- dihydroxy-11,20-dioxoallo pregnan-21-yl acetate (LXXXIX). Oxidation of (LXXXIX) with



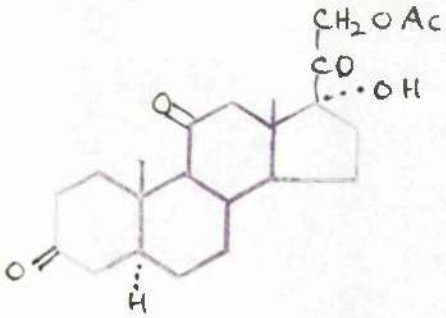
LXIII



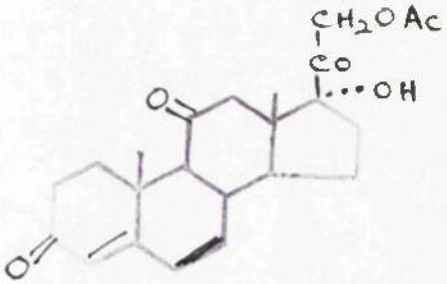
LXXXVIII



LXXXIX



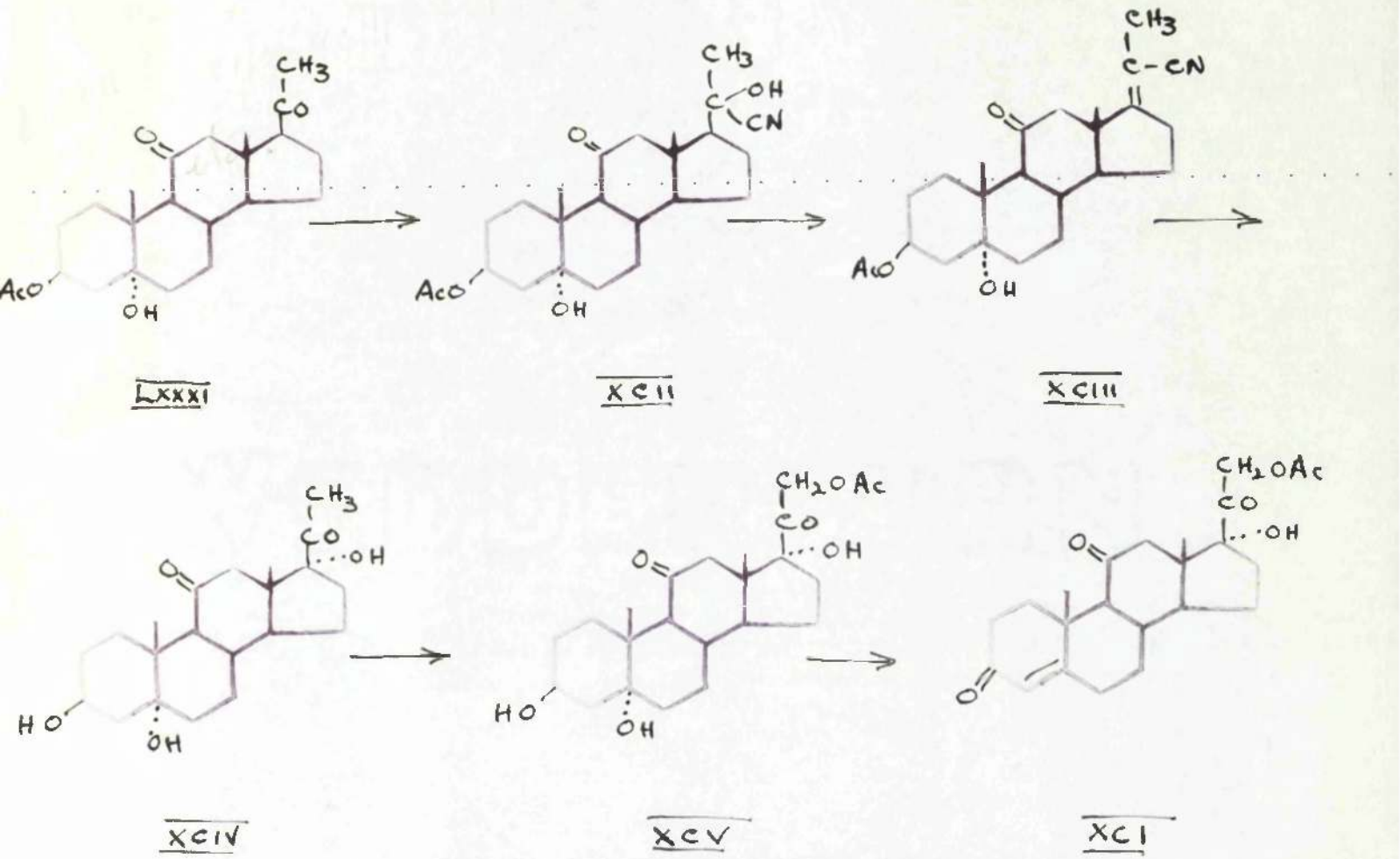
XC



XCI

N-bromoacetamide yields 17α-hydroxy-3,11,20-trioxoallopregnan-21-yl acetate (XC)(60,61). Bromination of the latter followed by dehydrobromination (60) or using a method previously used with other 3-keto allo steroids (62) gives cortisone acetate (XCI).

Gallagher's procedure however was found to be unsuitable(56) for 5α-hydroxy-11,20-dioxoallopregnan-3β-yl acetate (LXXXI), which, under the reaction conditions readily dehydrated to Δ^5-steroids. The method



LXXXI XCII XCIII

XCIV XCV XCI

of elaboration used in this case was that described by Sarett (62) whereby the 5α-hydroxy-11,20-diketone (LXXXI) was treated with hydrogen cyanide to give the cyanohydrin (XCII)(56). Selective dehydration at C_{20} of the latter compound with phosphorus oxychloride in pyridine gave (XCIII) which on osmium tetroxide oxidation gave a 17α,20-diol, which yielded(XCIV)on treatment with base. Treatment of (XCIV) with bromine followed by treatment of the 21-bromo derivative with potassium acetate as described before gave the 21-acetate (XCV). Oxidation of the latter gave the 3-ketone which was dehydrated to cortisone acetate (XCI).

THEORETICAL.

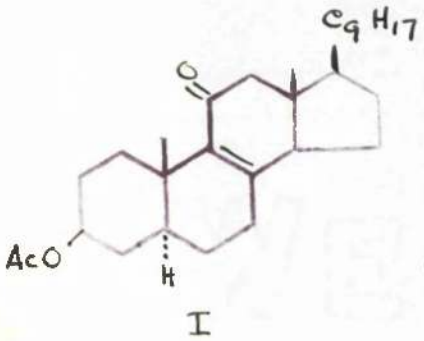
THEORETICAL.

The work described in this thesis had as its object the conversion of ergosterol into 11-oxygenated steroids, with a view to a partial synthesis of cortisone; the chemistry of some intermediates encountered is discussed in detail. The investigation was commenced in October, 1951, when a general scheme for the synthesis of 11-keto-steroids from Δ^5-steroids such as ergosterol, diosgenin and stigmasterol had already been reported by Tishler et al(27) and by Heusser et al (30).

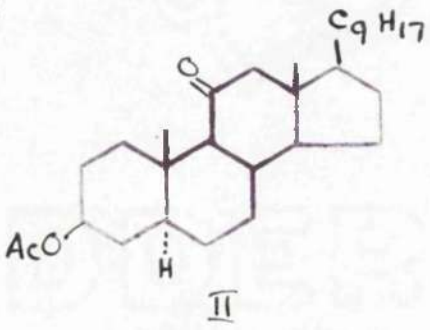
The experiments described have in part been reported in a series of publications (65-69).

I. The Preparation and Attempted Selective Hydrogenation of 11-Oxoergosta-8,22-dien-3β-yl Acetate.

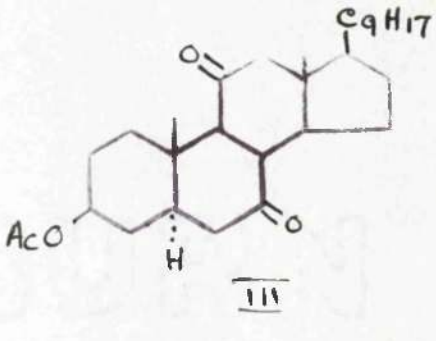
Heusser and his co-workers had described(30) (see Historical Section) the preparation of 11-oxoergosta-8,22-dien-3β-yl acetate(I) from ergosterol.



I



II

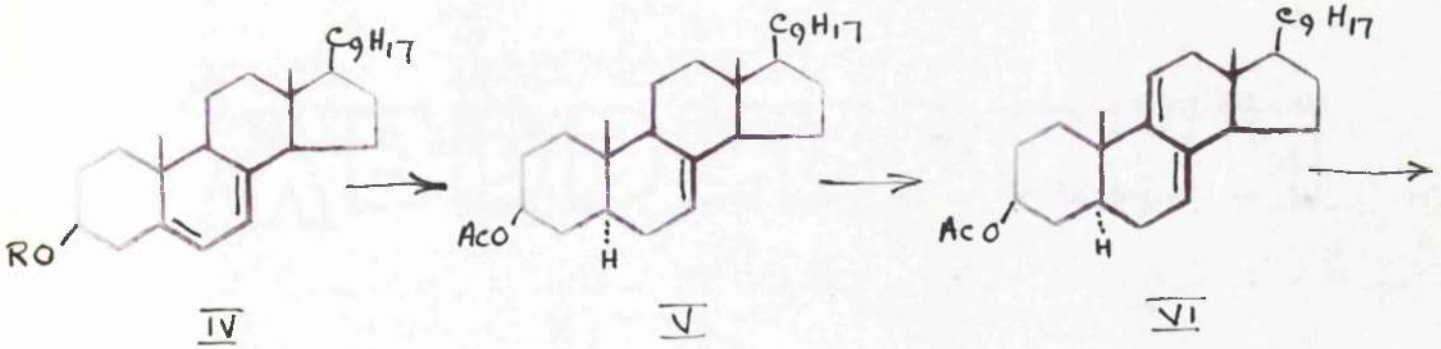


III

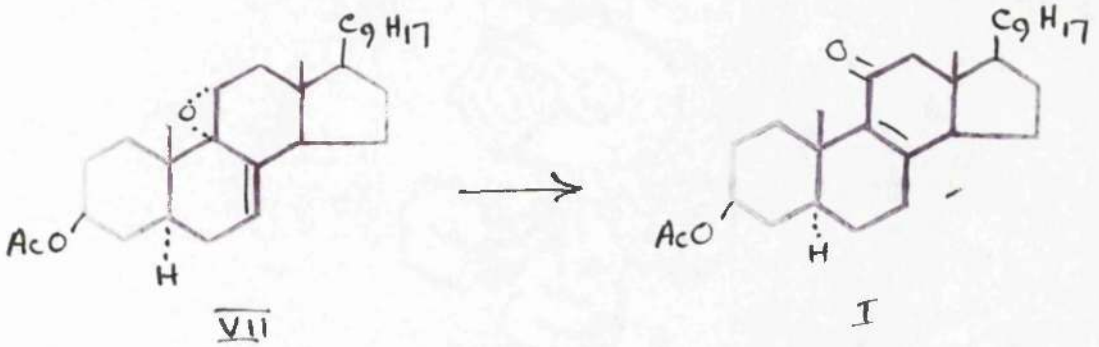
It was obvious that if this compound(I) could be selectively reduced to 11-oxoergost-22-en-3β-yl acetate (II), an attractive synthesis of cortisone from ergosterol could be envisaged. The latter compound (II) was known,

having been obtained by Heusser et al(30) by the removal of the 7-carbonyl group from the less readily accessible 7,11-dioxoergost-22-en-3β-yl acetate (III) either by the Wolff-Kishner method or by desulphurisation of the 7-ethylenedithioketal of (III). Attempts were therefore made to reduce selectively the Δ^{8}-ethylenic lead of (I).

11-oxoergosta-8,22-dien-3β-yl acetate was produced from ergosterol by the method of Heusser et al(30) which involved acetylation of ergosterol (IV;R=H) to ergosteryl acetate (IV;R=Ac). Selective hydrogenation of the latter compound gave 5-dihydroergosteryl acetate (V) (28) which was treated with mercuric acetate to give ergosteryl-D



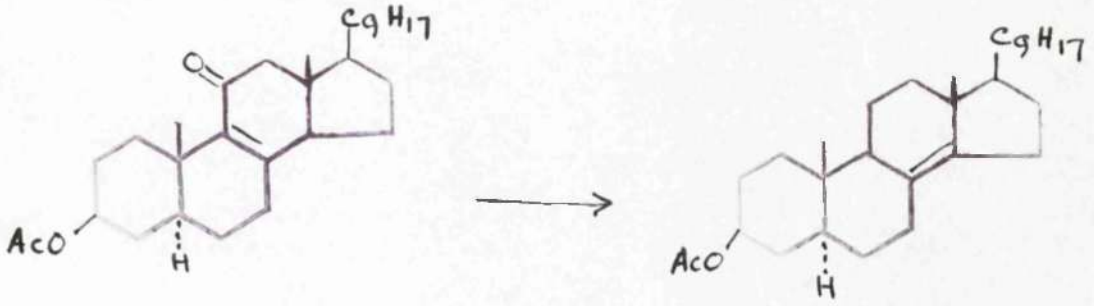
IV V VI



VII I

acetate(VI) in about 30% yield, after tedious separation from unchanged starting material. A much improved yield of ergosteryl-D acetate was obtained by the debromination of ergosteryl-D acetate 22,23-dibromide, prepared by the method of Anderson, Stevenson and Spring(28) by bromination of 5-dihydroergosteryl acetate (V) under specified conditions. Treatment of ergosteryl-D acetate (VI) with perbenzoic acid gave a mono-epoxide to which Heusser et al have ascribed the structure 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (VII). Rearrangement of the latter (VII) with boron trifluoride-etherate gave 11-oxoergosta-8,22-dien-3β-yl acetate (I).

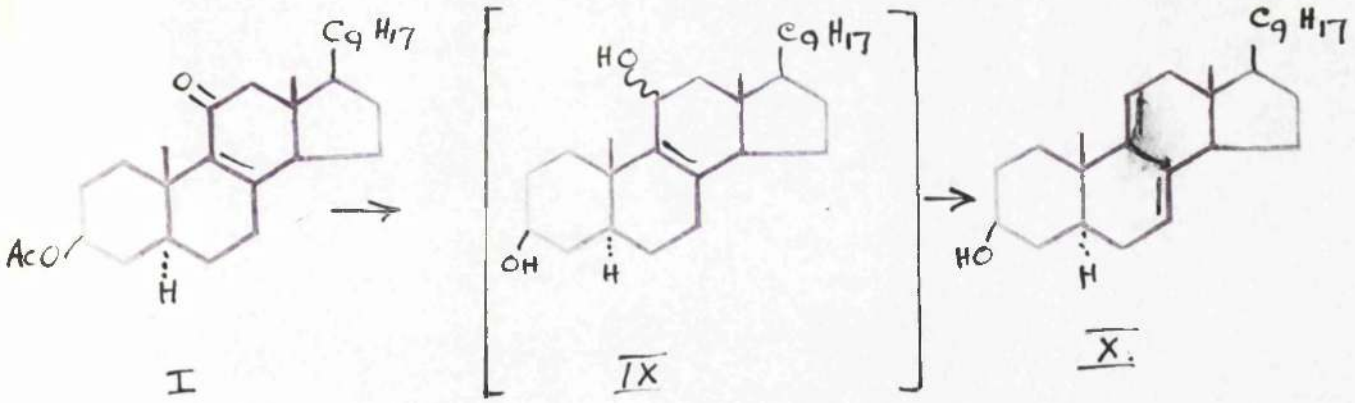
Direct catalytic hydrogenation of (I) was unsuccessful, however, in the attempted selective reduction of the Δ^{8}-bond. Hydrogenolysis of the 11-carbonyl group resulted with migration of the Δ^{8}-ethylenic bond giving ergost-8(14)-en-3β-yl acetate (α-ergosteryl acetate)(VIII),



I VIII

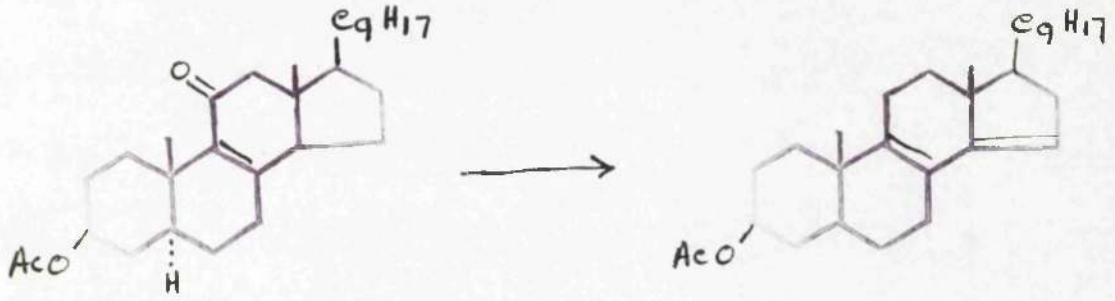
identical with a specimen prepared by Budziarek, Johnson and Spring (73) by hydrogenation of ergosteryl-D acetate.

Another approach was made to the problem by attempting to reduce the 11-carbonyl group of 11-oxoergosta-8,22-dien-3β-yl acetate(I) to the corresponding alcohol and to examine the possibility of reduction of the Δ^{8}-ethylenic bond of the derived allylic alcohol. Treatment of (I) with lithium aluminium hydride or with sodium borohydride, however, gave an inseparable mixture, the presence of a $\Delta^{7\cdot9(11)}$-diene impurity being indicated by the ultra-violet absorption spectrum. The lithium aluminium hydride product was considered to be a mixture of the desired allylic alcohol (IX)



and ergosterol-D the latter being a dehydration product of the former. Evidence that some carbonyl reduction had indeed occurred to yield a dienediol (IX or isomer) was adduced by the observation that dehydration of the mixture with boron trifluoride gave a high yield of ergosterol-D (X).

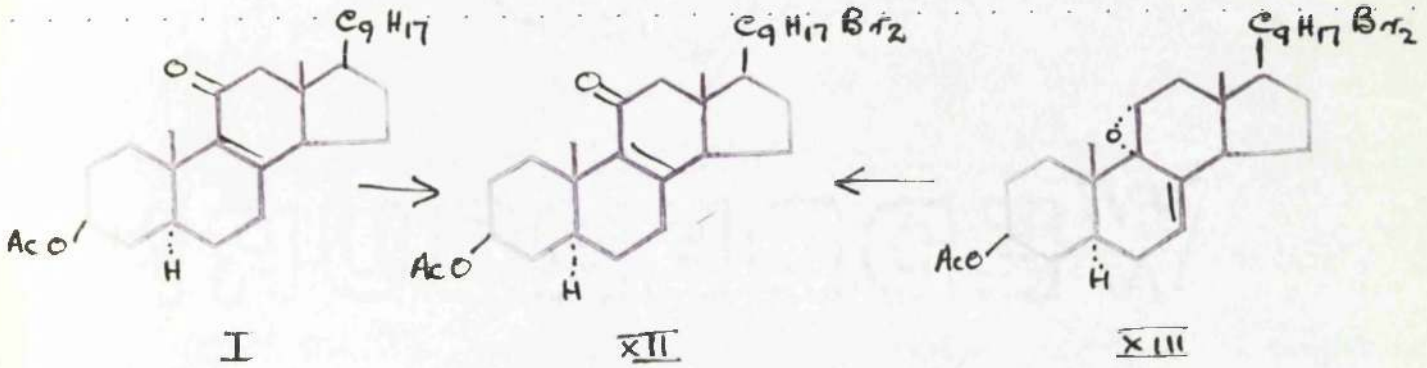
Prolonged treatment of the crude reduction mixture with boron trifluoride etherate followed by acetylation gave ergosteryl-B,



I XI

acetate (XI) in poor yield, the initially formed $\Delta^{7\cdot9(11)}$-diene having isomerised to the $\Delta^{8\cdot14}$-diene. The reduction product was not further examined.

Of primary importance in these experiments aimed at saturation of the Δ^{8}-ethylenic bond in 11-oxoergosta-8,22-dien-3β-yl acetate (I), was the protection and maintenance of the Δ^{22}-ethylenic linkage in order to facilitate subsequent side chain degradation. Accordingly a number of experiments were undertaken in order to examine the possibility of forming a 22,23-dibromide as a means of protection of the Δ^{22}-ethylenic linkage. Bromination of 11-oxoergosta-8,22-dien-3β-yl acetate (I) gave 22,23-dibromo-11-oxoergost-8-en-3β-yl acetate (XII),

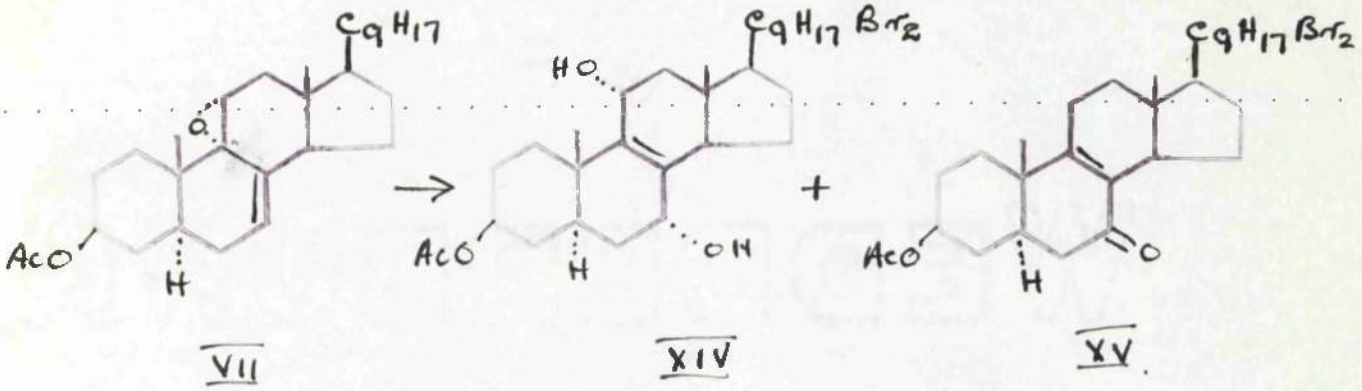


I XII XIII

which has also been obtained in this laboratory by Budziarek et al(39) by treatment of 22,23-dibromo -9α,11α-epoxyergost-7-en-3β-yl acetate (XIII) in absolute benzene with boron trifluoride-ether complex.

An attempt to hydrogenate the Δ^8-ethylenic bond of 22,23-dibromo 11-oxoergost-8-en-3β-yl acetate (XII) by the method of Kleiderer and Hornfeld(75) involving hydrogen exchange with cyclohexanol in the presence of Raney nickel in a fairly high boiling inert solvent such as toluene was unsuccessful. 11-Oxoergosta-8,22-dien-3β-yl acetate(I) was obtained as the product and no evidence of reduction of the Δ^8-ethylenic bond was found.

It is noteworthy that bromination of 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (VII) gave 22,23-dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (XIV) which was also obtained by Budziarek et al(39) and a second product, 7-oxoergosta-8,22-dien-3β-yl acetate (XV) which has previously



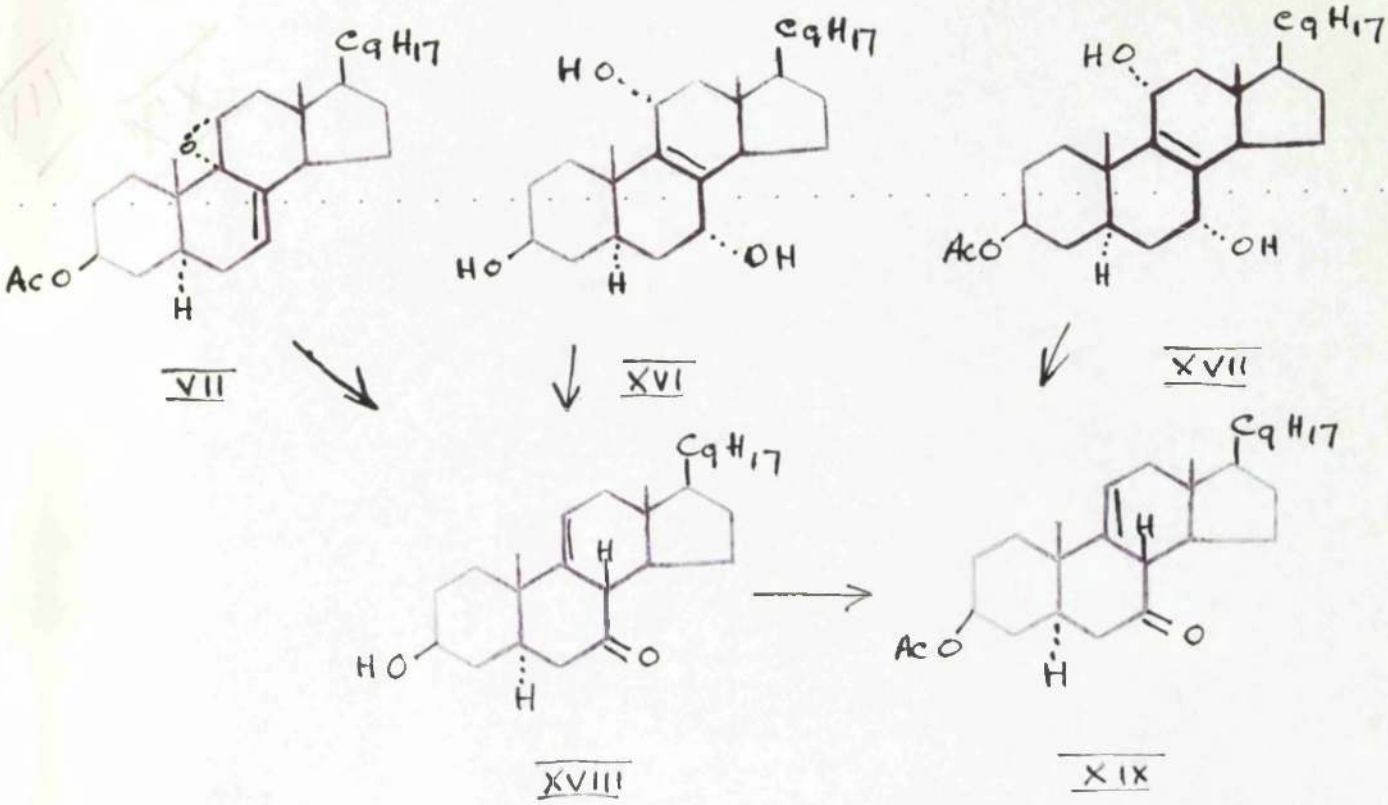
VII XIV XV

been obtained by prolonged treatment of the epoxide (VII) with mineral acid (27). Traces of hydrogen bromide in the bromine probably converted (VII) into (XV).

At this time, before an outlined programme of research was completed, Tishler(33) and Djerassi(34) and their co-workers reported the reduction of the Δ^{8}-11-ketone system to the saturated 11-ketone in high yield, using lithium metal in liquid ammonia, and no further experiments were carried out.

II. The Stereochemistry of $\Delta^{9(11)}$-7-Keto and Δ^{7}-11-Keto-steroids and some of their Derivatives.

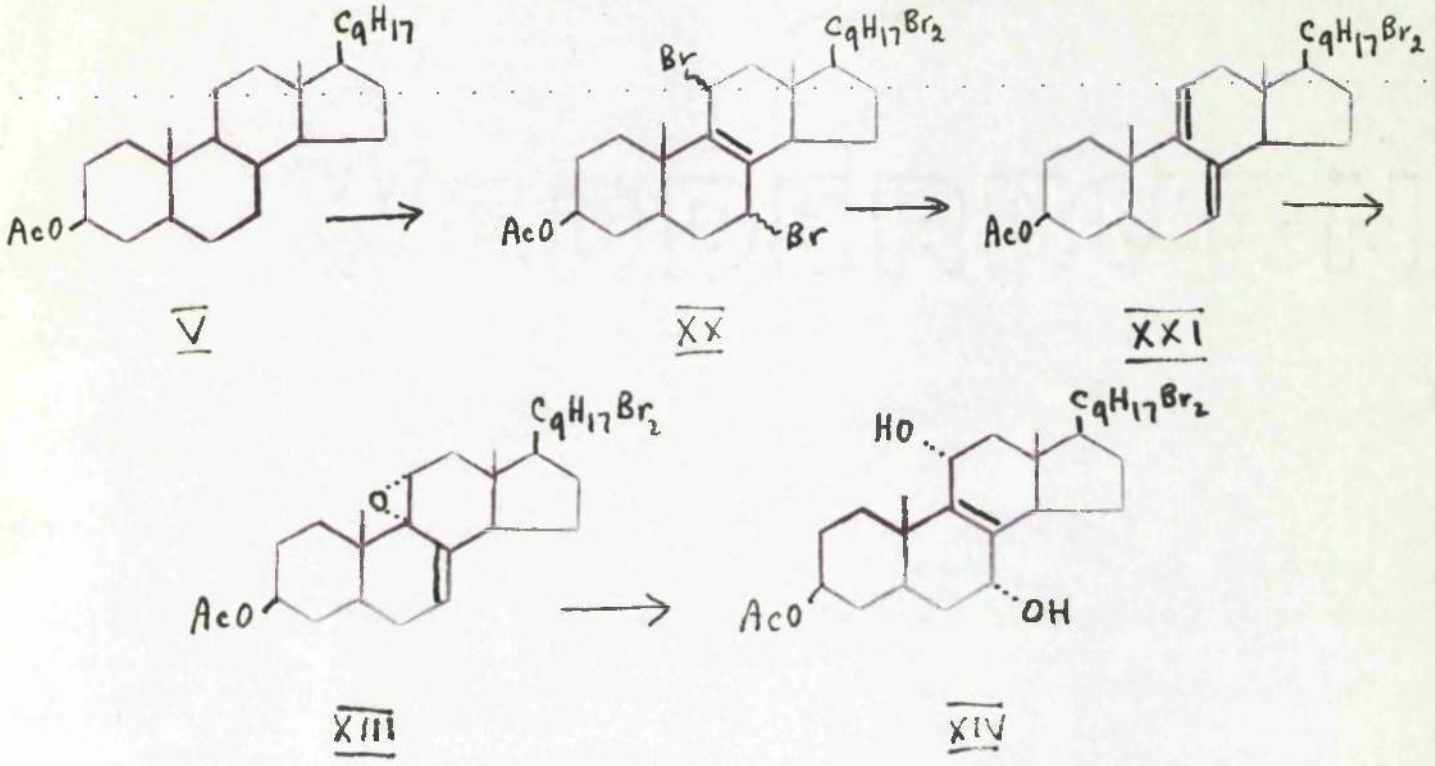
Budziarek et al(65) in this laboratory had prepared a compound, by oxidation of ergosteryl-D acetate with one mole of performic acid, to which they ascribed the structure 7-oxoergosta-9(11),22-dien-3β-yl acetate (XIX). This differed from the product, to which the same structure was given by Heusser et al(31), who obtained it by a dehydration of 7α,11α-dihydroxyergosta-8,22-dien-3β-yl acetate (XVII), and by Tishler et al(33)



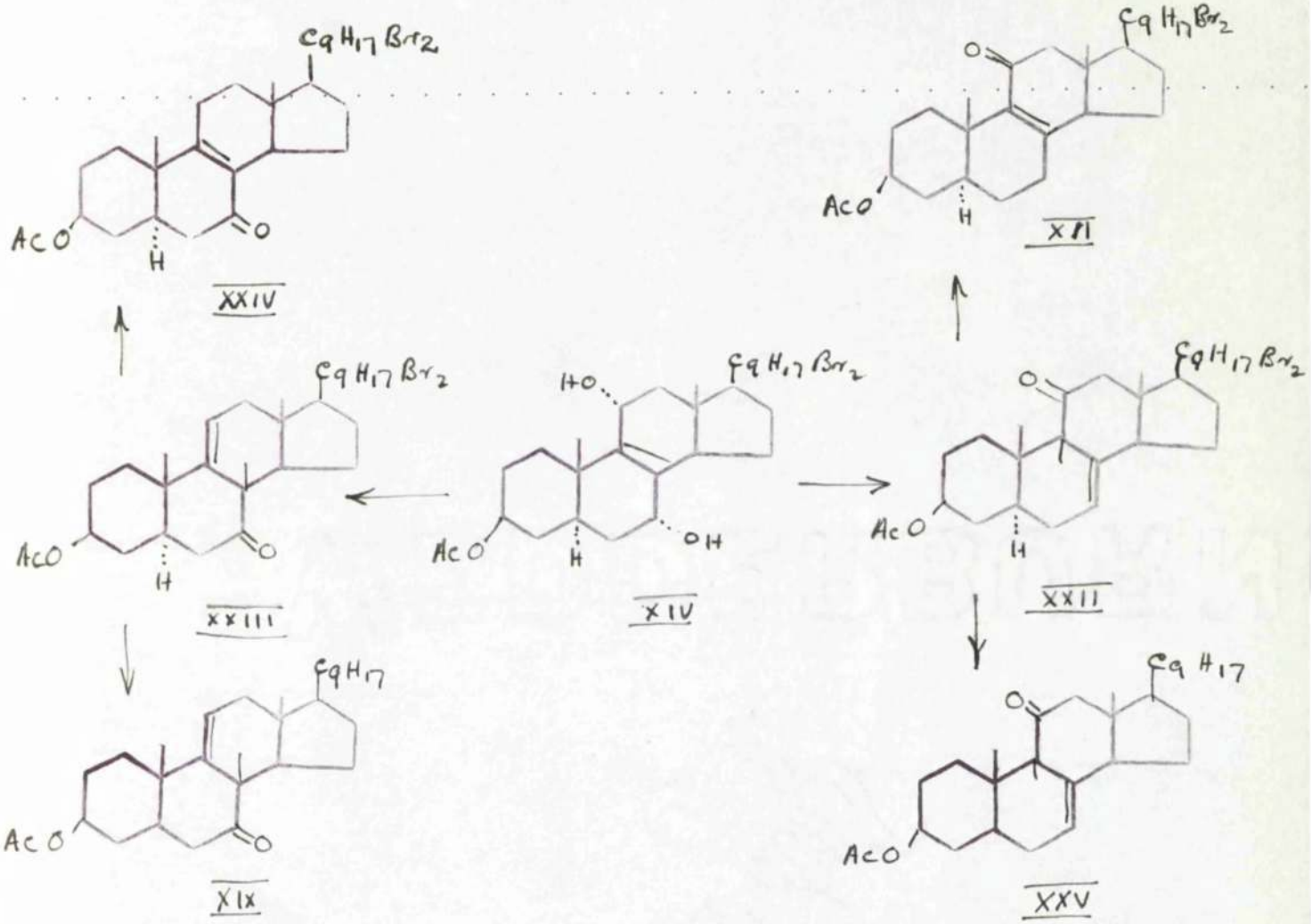
who obtained it by acidic rearrangement of both 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (VII) and of 3β,7α,11α-trihydroxyergosta-8,22-diene (XVI) under critical control followed by acetylation. A specimen of the compound described by Budziarek et al was prepared and its infra-red absorption spectrum determined. Two well resolved bands were evident, one at 1740 cm^{-1} ascribed to the 3β-acetate group, and the other at 1715 cm^{-1} ascribed to the 7-carbonyl group. This ruled out the possibility of an epoxide structure, and as the compound differed from 11-oxoergosta-7,22-dien-3β-yl acetate and its 9β-isomer and is converted into 7-oxoergosta-8,22-dien-3β-yl acetate by treatment with acid or base(65), it evidently possessed a $\Delta^{9(11)}$-7-carbonyl system. As a result Budziarek et al(66) concluded that their β γ-unsaturated ketone differed from that described by Heusser et al and Tishler et al in orientation around C_8. It was therefore desirable to examine and compare the reactions of these two isomers.

As prolonged mineral acid treatment of the triol-mono acetate(XVII) gave the $\alpha\beta$-unsaturated ketone, 7-oxoergosta-8,22-dien-3β-yl acetate to which the $\beta\gamma$-unsaturated ketone (XIX) is also converted by treatment with acid it is very probable that (XIX) is an intermediate in the conversion of (XVII) into 7-oxoergosta-8,22-dien-3β-yl acetate. For two reasons the line of investigation chosen was controlled acid treatment of 22,23-dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (XIV). Firstly, the sparing solubility of (XIV) rendered it valuable for controlling the reaction, because as the soluble $\beta\gamma$-unsaturated ketone was formed the completion of the reaction would be indicated by the dissolution of the insoluble (XIV); and secondly, protection of the Δ^{22}-olefinic bond as the dibromide permitte examination of the $\Delta^{9(11)}$-7-ketone system by oxidative attack.

22,23-Dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (XIV) was prepared by methods reported from this laboratory. Bromination of 5-dihydr ergosteryl acetate (V)(28) at -60° gave a tetrabrom oergosteryl acetate which is believed to be 7ξ,11ξ,22,23-tetrabromoergost-8-en-3β-yl acetate(XX) (Private communication of Merck and Co.; cf. R.C.Anderson thesis). Partial debromination of the latter compound with sodium iodide gave ergosteryl-D acetate 22,23-dibromide (XXI) which showed the characteristic ultra-violet absorption spectrum of a $\Delta^{7:9(11)}$-diene and which on treatment with zinc gave ergosteryl-D acetate. Treatment of ergosteryl-D acetate 22,23-dibromide with one mole of perbenzoic acid(39) gave 22,23-dibromo-9α,11α-epoxyergost-7-en-3β-yl acetate (XIII) which on treatment in tetrahydrofuran with sulphuric acid gave 22,23-dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (XIV).



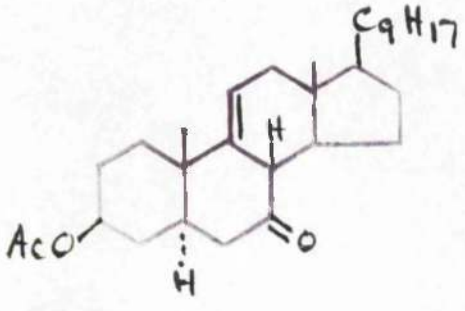
When 22:23-dibromo-7α:11α-dihydroxyergost-8-en-3β-yl acetate (XIV) was treated in absolute benzene with boron trifluoride-ether complex for a short time, two isomeric non-conjugated unsaturated ketones were obtained. One of these was 22:23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XXII), the structure being established by debromination with zinc dust in benzene-ethanol to yield 11-oxo-9β-ergosta-7:22-dien-3β-yl acetate (XXV). This had previously been prepared by Bladen et al (54) and Heusser et al (64), by brief treatment of 9α:11α-epoxyergosta-7:22-dien-3β-yl acetate (VII) with boron trifluoride, the unnatural 9β-configuration being ascribed to (XXV) because filtration of a solution of (XXV) through a column of alumina converted it into the 9α-isomer(54).



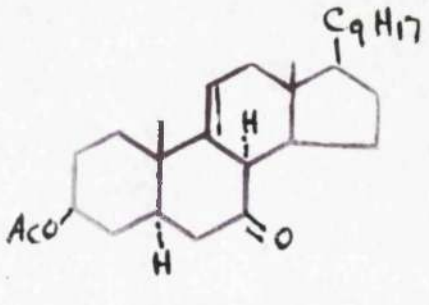
The structure (XXII) is further supported by the ultra-violet absorption spectrum and by the fact that filtration of a solution of (XXII) through a column of alumina converted it into the conjugated isomer 22:23-dibromo-11-oxoergost-8-en-3β-yl acetate (XII) previously obtained by Budziarek et al (39) by treatment of 22:23-dibromo-9α:11α-epoxyergost-7-en-3β-yl acetate in absolute benzene with boron trifluoride. The second (major) product of the reaction of (XIV) with boron trifluoride was 22:23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (XXIII), treatment of which with dilute alkali followed by acetylation gave the isomeric α:β-unsaturated ketone(XXI

previously obtained by Budziarek et al(39) by prolonged sulphuric acid treatment of the dibromo-epoxide (XIV). Elks et al(93)have subsequently prepared (XXIII) by dichromate oxidation of 22,23-dibromo ergosta-7,9(11)-dien-3β-yl acetate (XXI). Treatment of (XIV) with boron trifluoride for a short time followed directly by chromatography of the reaction mixture on alumina yielded the α,β -unsaturated ketones (XII) and (XXIV) in one operation, the initially formed β,γ-unsaturated ketones having been isomerised by the chromatographic alumina. The structure of (XXIII) follows from the following reasons.

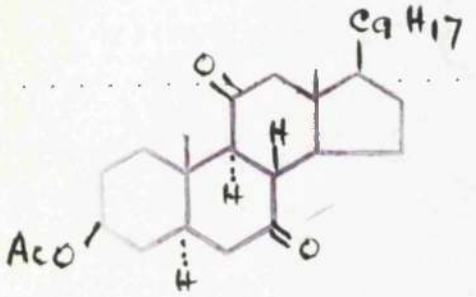
Debromination of 22,23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (XXIII) by zinc dust in ether ethanol gave 7-oxoergosta-9(11),22-dien-3β-yl acetate (XIX) $[\alpha]_D$-55°, identical with the product obtained by Heusser et al (31) and Tishler et al (33) as described earlier. Comparison of the latter compound with that $[\alpha]_D$+20° described by Budziarek et al (65) had led to the conclusion that they differed in orientation at C_8. Budziarek et al have also prepared a C_8-epimer(XXVIII) of 7,11-dioxoergost-22-en-3β-yl acetate (XXVII)(77) and a comparison of the molecular rotations



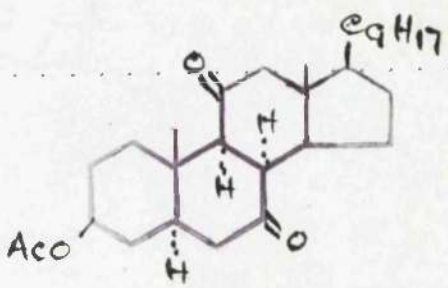
XIX



XXVI



XXVII

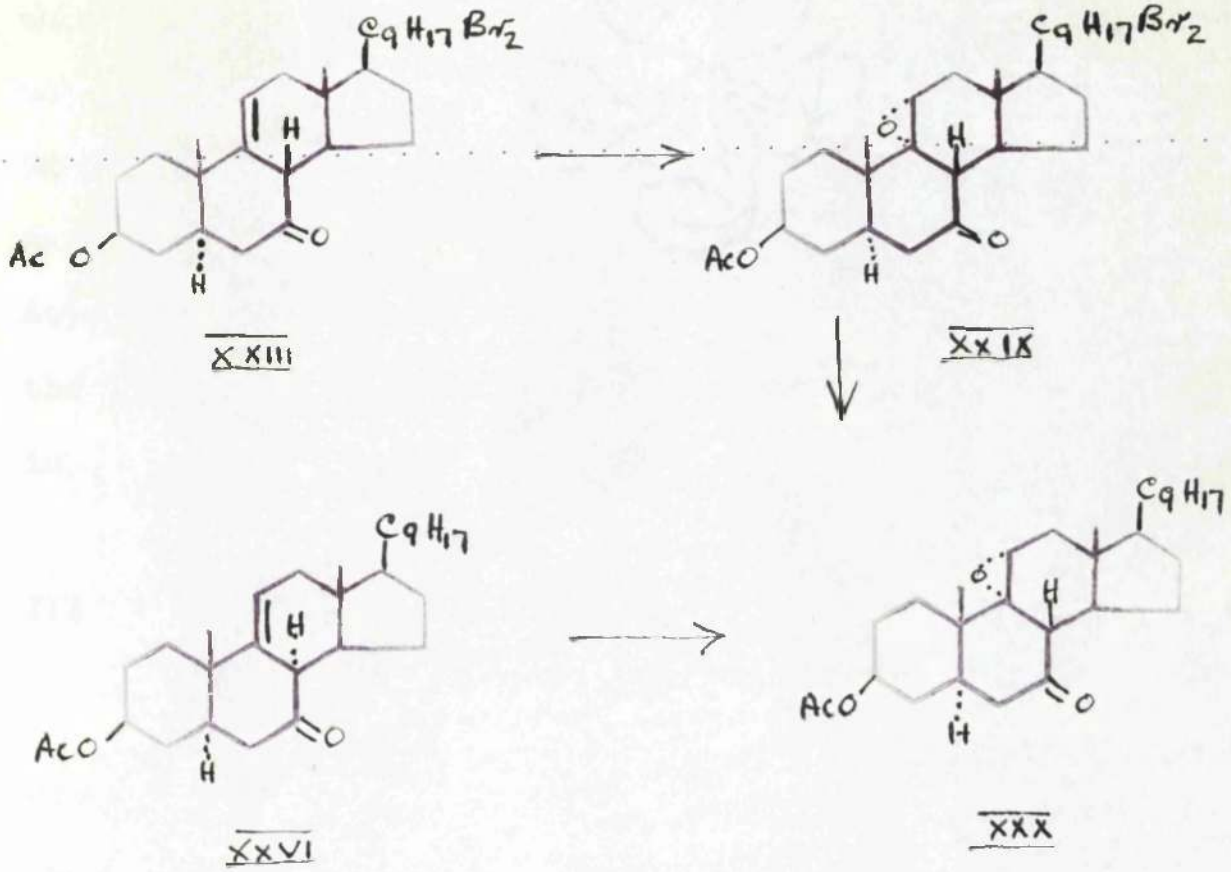


XXVIII

of the two diketones (XXVII) and (XXVIII) with those of the two $\beta\delta$-unsaturated ketones (XIX) and (XXVI) supports the original view and suggests that the isomer prepared by Budziarek et al ($[\alpha]_D$ +20°) is 7-oxo-8α-ergosta-9,(11)-dien-3β-yl acetate (XXVI) and that the isomer prepared by Heusser et al and Tishler et al ($[\alpha]_D$ -55°) has the natural 8β-configuration.

$[\alpha]_D$ -55° has the natural 8β-configuration.	$[\alpha]_D$	$[M]_D$
7,11-Dioxoergost-22-en-3β-yl acetate	-28°	-132°
7,11-Dioxo-8α-ergost-22-en-3β-yl acetate	+30	+141
8β----------→8α =		+273
7-oxoergosta-9(11),22-dien-3β-yl acetate	-55	-250
7-oxo-8α-ergosta-9(11),22-dien-3β-yl acetate	+20	+91
8β----------→8α =		+341

Oxidation of 22,23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (XXIII) with one mole of perbenzoic acid gave 22,23-dibromo-9α-11α-epoxy-7-oxoergosta-3β-yl acetate (XXIX) previously obtained by oxidation of ergosteryl-D

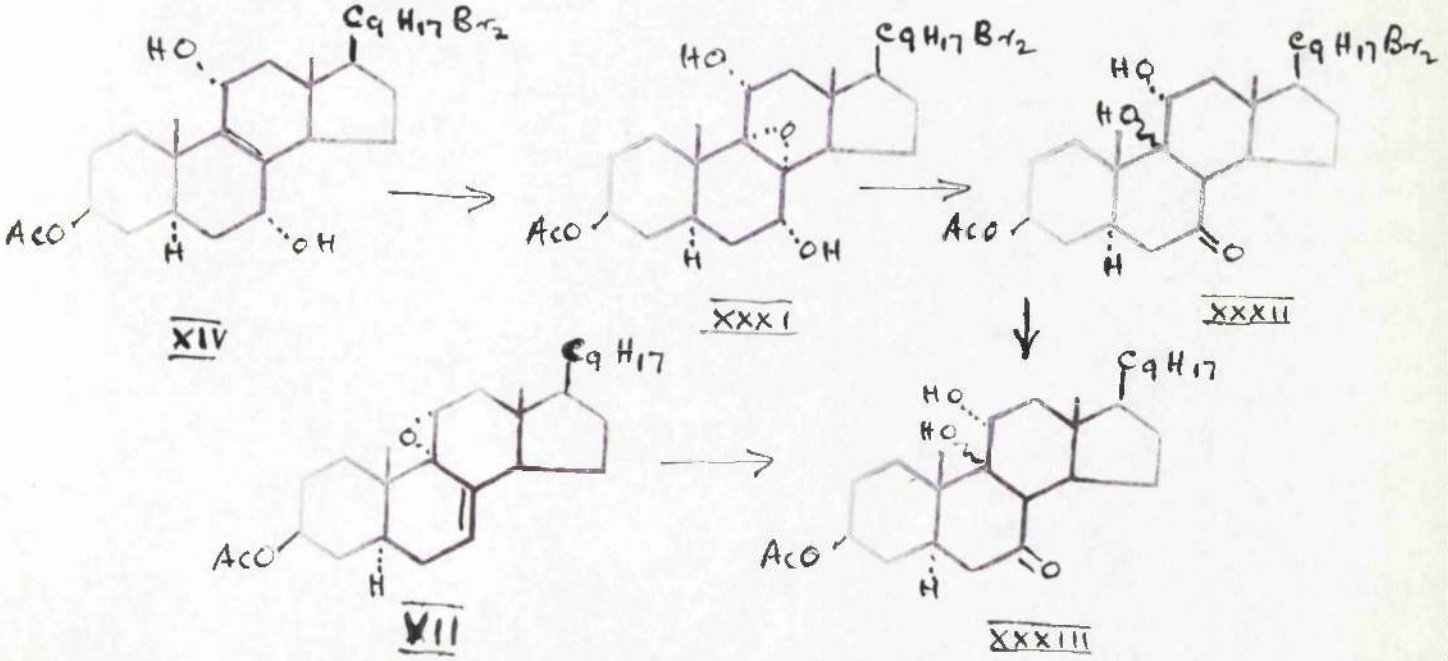


acetate 22,23-dibromide with 2 moles of performic acid(38). Debromination of (XXIX) with zinc dust gave 9α,11α-epoxy-7-oxoergost-22-en-3β-yl acetate (XXX). Budziarek et al(65) have reported the preparation of (XXX) by treatment of 7-oxo-8α-ergosta-9(11),22-dien-3β-yl acetate (XXVI) successively with one mole of bromine, perbenzoic acid and zinc dust. Therefore, one of these reactions, either the conversion of (XXIII) into (XXIX) or the conversion of (XXVI) into (XXX), must have involved inversion at C_8. This probably occurred in the latter case, since although 9α,11α-epoxy-7-oxoergost-22-en-3β-yl acetate (XXX) is very sensitive to alkali(66) forming 11α-hydroxy-7-oxoergosta-8,22-dien-3β-yl acetate, when it was treated with acetic acid or hydrogen bromide in acetic acid under which

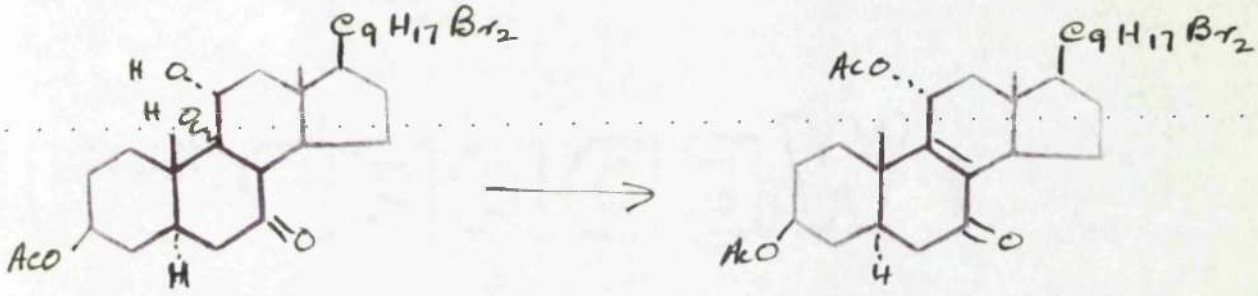
conditions 7,11-dioxo-8α-ergost-22-en-3β-yl acetate is converted into the more stable 8β-epimer, it was recovered unchanged. For this reason 9α,11α-epoxy-7-oxoergost-22-en-3β-yl acetate (XXX) is believed to have the natural 8β-configuration (i.e., the more stable trans linked B/C system). Attempts made to convert the unnatural βγ-unsaturated ketone (XXVI) into the 8β-epimer using the methods for converting the 8α-diketone (XXVIII) into (XXVII) failed.

III. The Sterochemistry of 9α,11α-dihydroxy-7-oxoergost-22-en-3β-yl acetate and of 7α,8α,9α,11α-tetrahydroxyergost-22-en-3β-yl acetate

Budziarek et al have reported (78,79) the preparation of 22,23-dibromo-8α,9α-epoxy-7α,11α-dihydroxyergostan-3β-yl acetate (XXXI) by the perbenzoic acid oxidation of 22,23-dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (XIV). Treatment of (XXXI) with hydrogen bromide in acetic acid (79) gave a compound which was ascribed the structure 22,23-dibromo-9ξ,11α-dihydroxy-7-oxoergostan-3β-yl acetate (XXXII), debromination of which gave 9ξ,11α-dihydroxy-7-oxoergost-22-en-3β-yl acetate (XXXIII).

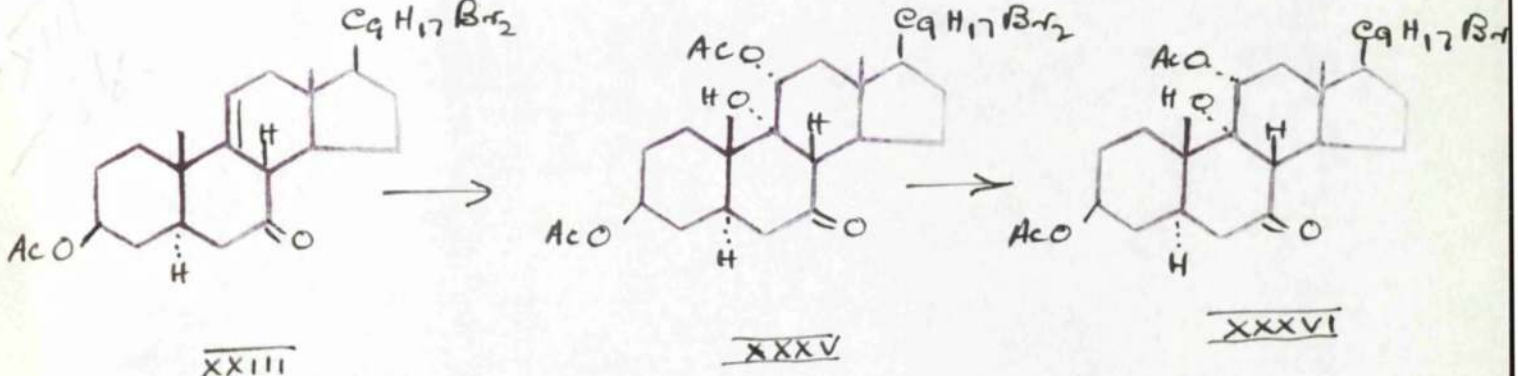


This compound (XXXIII) has also been obtained from 7α,11α-dihydroxyergost-22-en-3β-yl acetate under similar conditions by Heusser et al(31) and was first described by Budziarek et al(65) who obtained it by treatment of 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (VII) successively with one mole of bromine, excess perbenzoic acid, followed by zinc dust treatment. The latter authors(65) originally ascribed the β-orientation to the 9-hydroxyl group in (XXXII) the two hydroxyl groups being considered as trans orientated with respect to each other "since they almost certainly originate by a hydrolytic cleavage of a 9α,11α-epoxide intermediate". This argument does not appear satisfactory in view of the fact that addition of bromine to 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (VII) (page 4) results in hydrolytic rearrangement to give in part 22,23-dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (XIV) which may thus be the precursor (XXXIII) in Budziarek et al's conversion from (VII). As a result of this observation the 9β-hydroxyl assignment in (XXXIII) was later withdrawn(79). Further evidence on the stereochemistry of this group was therefore sought. The formation of 22,23-dibromo-9ξ,11α-dihydroxy-7-oxoergostan-3β-yl acetate (XXXII) from 22,23-dibromo-8α,9α-epoxy-7α,11α-dihydroxyergostan-3β-yl acetate (XXXI) and the ease of dehydration of the former compound to give 3β,11α-diacetoxy-22,23-dibromoergost-8-en-7-one (XXXIV) after re-acetylation, seem to indicate that the 9-hydroxyl group in (XXXII) and related compounds has the α-orientation (trans elimination of water). This view has been established in the following way.



XXXII XXXIV

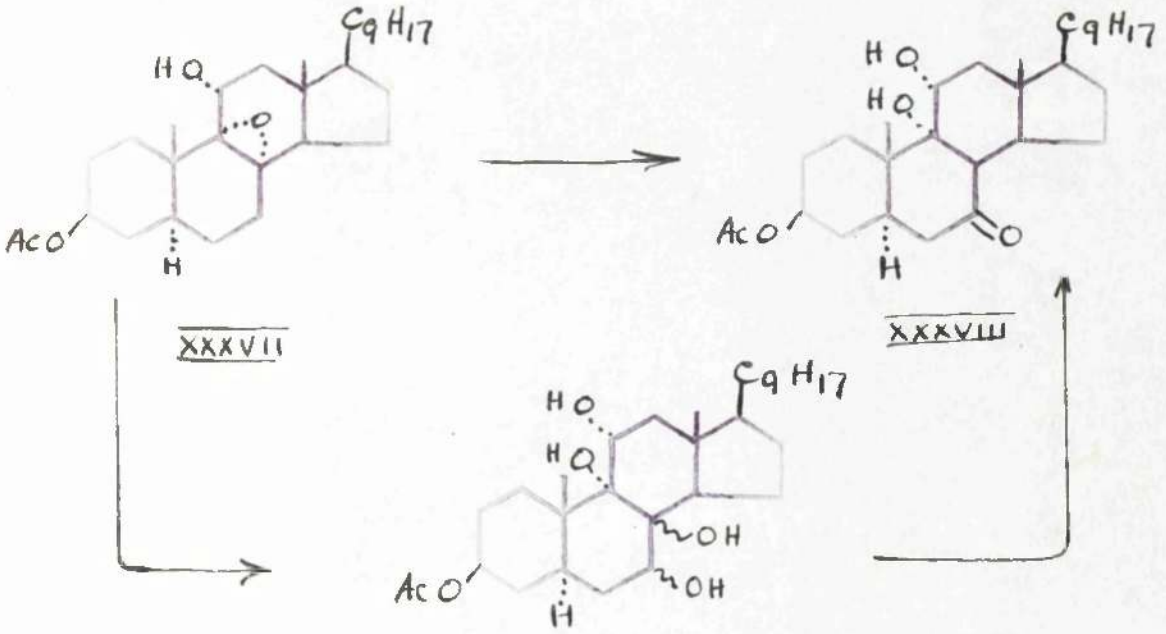
Oxidation of 22,23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (XXIII) with osmium tetroxide, followed by decomposition of the osmic acid complex by hydrolysis and subsequent re-acetylation gave a diacetate 3β,11α-diacetoxy-22,23-dibromo-9α-hydroxyergostan-7-one (XXXV) identical with a compound obtained by acetylation of 22,23-dibromo-9ξ,11α-dihydroxy-7-oxoergostan-3β-yl acetate (XXXII) as prepared by Budziarek et al(78,79). Debromination of this diacetate (XXXV) gave 3β,11α-diacetoxy-9α-hydroxyergost-22-en-7-one (XXXVI) identical with a specimen prepared by acetylation of 9ξ,11α-dihydroxy-7-oxoergost-22-en-3β-yl acetate (XXXIII) prepared by Budziarek et al(65). The 9α,11α-cis-glycol structure was ascribed to



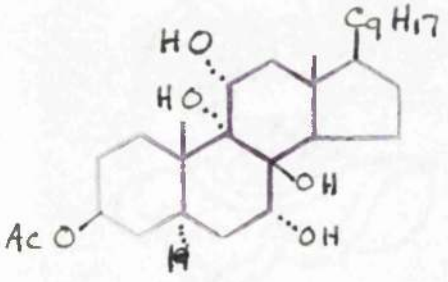
XXIII XXXV XXXVI

(XXXV) and (XXXVI) for the following reasons. Since oxidation with osmium tetroxide yields cis-glycols(80), since the $\Delta^{9(11)}$-double bond is invariably attacked from the rear(α) face, and the 11-hydroxyl group is readily acetylated and therefore has the α-orientation, it follows that the 9-hydroxyl group in (XXXV) and (XXXVI) and hence in (XXXIII) and (XXXII) related compounds is also α-orientated.

In addition to the formation of 9α,11α-hydroxy-7-oxoergost-22-en-3β-yl acetate (XXXVIII) from 8α,9α-epoxy-7α,11α-dihydroxyergost-22-en-3β-yl acetate, by treatment with hydrogen bromide in acetic acid, or boron trifluoride in absolute benzene, Heusser et al(31) describe the treatment of the latter compound (XXXVII) with aqueous sulphuric acid to get a 7,8,9,11-tetrahydroxyergost-22-en-3β-yl acetate (XXXIX) which in its turn gave 9α,11α-dihydroxy-7-oxoergost-22-en-3β-yl acetate (XXXVIII) on treatment with hydrogen bromide in acetic acid.



An allocation of configurations of the hydroxyl groups in (XXXIX) can be made in the following way. Starting from the view that the 9- and 11-hydroxyl groups in (XXXVIII) are α-orientated and as the tetrahydric alcohol (XXXIX) is converted into (XXXVIII) with hydrogen bromide it follows that the 9- and 11-hydroxyl groups in (XXXIX) are also α-orientated. Since the 8- and 9-hydroxyl groups in (XXXIX) result from an acid fission of the 8α,9α-epoxide bridge in (XXXVII), they will be <u>trans</u> orientated with respect to each other (in the cleavage of oxides a Walden inversion occurs at the carbon atom at which a carbon-oxygen bond is ruptured) from which it follows that the 8-hydroxyl group in (XXXIX) is β-orientated (i.e., Diaxial opening). Since Henbest and Wagland(63) are established the α-orientation of the 7-hydroxyl group in 7α,11α-dihydroxyergosta-8,22-dien-3β-yl acetate, it follows that the 7-hydroxyl group in (XXXVII) and hence in (XXXIX) is also α-orientated.

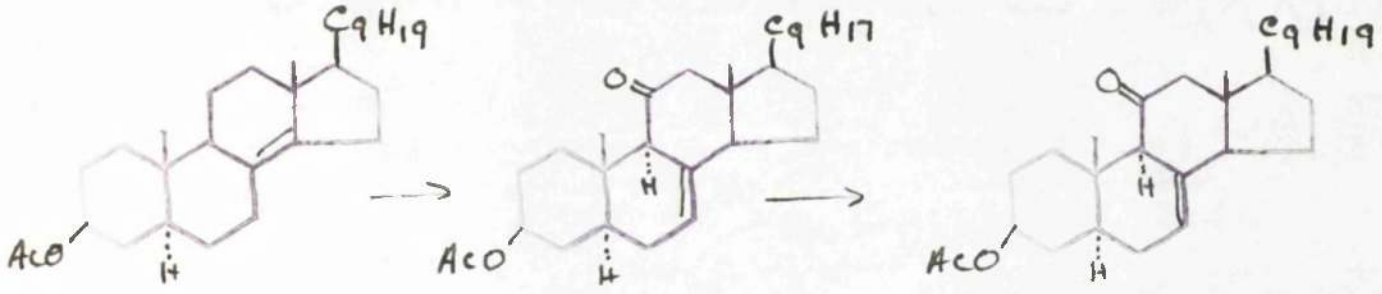


XL

The structure of the tetrahydric alcohol is therefore 7α,8β,9α,11α-tetrahydroxyergost-22-en-3β-yl acetate (XL). Heusser et al(31) for different reasons had tentatively ascribed the configuration of (XXXIX) as a 7β,8β,9α,11α-tetrahydric alcohol. They argued that if it is assumed the 8α,9α-epoxide bridge in (XXXVII) is α orientated, since (XXXVII) is converted into (XXXVIII) by boron trifluoride in the absence of water then the epoxide bridge in (XXXVII) is ruptured between C_8 and the oxygen with the consequence that the 9-hydroxyl group in (XXXVIII) is α -orientated. Therefore by reasoning similar to that above the 8-hydroxyl group in (XXXIX) is β -orientated and the 9- and 11-hydroxyl groups are α -orientated. Concerning the orientation of the 7-hydroxyl group, it was argued (31) that the ready dehydration of (XXXIX) to the 7-ketone (XXXVIII) connotes a cis-glycol (trans elimination of water) in which case the 7-hydroxyl group in (XXXIX) would be β -orientated. This conclusion, though apparently valid is erroneous as the 7-hydroxyl group has been shown(65) to be α -orientated (see Section V).

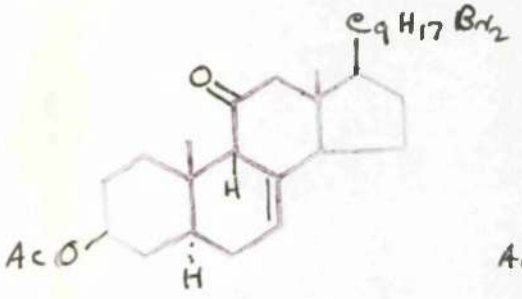
IV. Bromination of 22,23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl Acetate.

Bladon et al have found that hydrogenation of 11-oxoergosta-7,22-dien-3β-yl acetate (XLII) in acidic medium gave ergost-8(14)-en-3β-yl acetate (VIII) (α-ergosteryl acetate)(54), presumably by hydrogenolysis of the 11-oxygen function followed by migration of the double-bond.

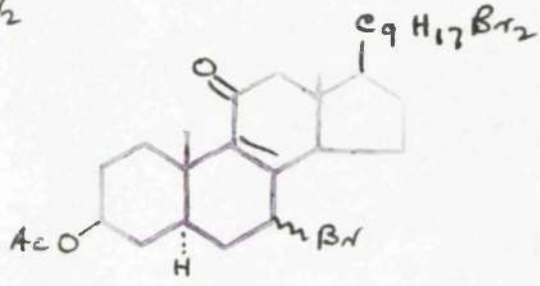


This behaviour has been confirmed and furthermore it was found that hydrogenation of (XLII) in ethyl acetate gave 11-oxoergost-7-en-3β-yl acetate (LXVIII) previously obtained only in crude form by Bladon et al. These authors and Elks et al(54) have described the hydrogenation of Δ^7-olefinic-9β-steroids when hydrogenation took place by frontal attack on position C_8 to give saturated 9β-steroids. Frontal peracid attack on Δ^7-olefinic-9β-steroids has also been described (63,64,69 Section VI this thesis). It was considered of interest to compare the action of bromine on Δ^7-olefinic-9β-steroids.

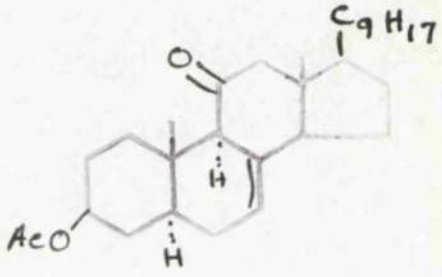
Treatment of 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XXII) with bromine gave a tribromo compound 7ξ,22,23-tribromo-11-oxoergost-8-en-3β-yl acetate (LXIX) which shows the characteristic ultra-violet



XXII



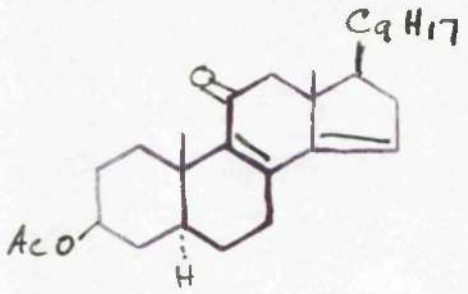
LXIX



XLII

light absorption of an αβ-unsaturated ketone. (No trace of a 7,8-dibromide was found). Treatment of the tribromo-ketone (LXIX) with zinc in a neutral solvent gave unexpectedly 11-oxoergosta-7,22-dien-3β-yl acetate (XLII). This last compound has also been obtained(69) from an attempted debromination of 3β,7β-diacetoxy-22,23-dibromo-ergost-8-en-11-one (Section VI; LXVI) with zinc in a neutral solvent. In view of the fact that side chain dehalogenatio of the last compound involves this remarkable formation of the βδ-unsaturated ketone (XLII) whereas the 7α-epimer (section V; XLIX) undergoes normal side chain dehalogenation, it is considered likely that the bromine atom at C_7 has the β-orientation.

Treatment of the tribromo-ketone (LXIX) with alkali followed by acetylation of the product gave a keto-diene which was identical with a keto-diene prepared by Mr. J.Grigor of this department by alternative methods. Mr. Grigor has subsequently proved the structure of this compound to be 22,23-dibromo-11-oxoergosta-8,14-dien-3β-yl acetate (LXX)

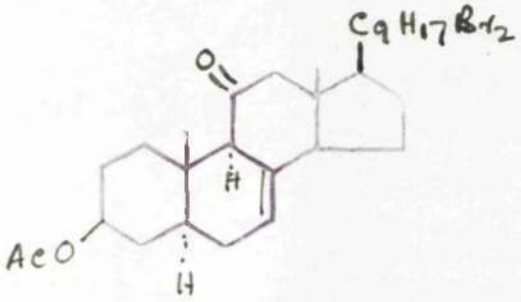


LXX

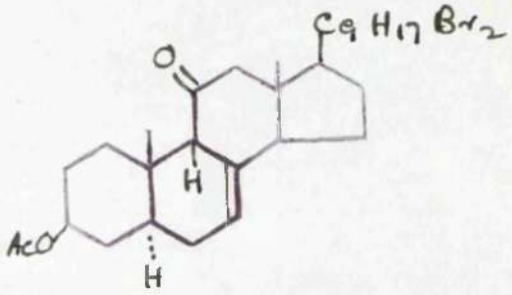
V. The Structure and Reactions of 22,23-Dibromo-7α,8α-epoxy-11-oxoergostan-3β-yl Acetate.

A number of oxidation products derived from steroidal $\Delta^{7,9(11)}$-dienes have been described during the last three years. In particular it has been established that oxidation of ergosteryl-D acetate with peraromatic acids gives a 9α,11α-epoxide(27,30) whereas with performic acid the β,γ-unsaturated ketone 7-oxo-8α-ergosta-9(11),22-dien-3β-yl acetate is produced (65,66,67). The natural C_8 epimer of the last compound, viz., 7-oxoergosta-9(11),22-dien-3β-yl acetate is obtained by the methods described earlier (page 44). These C_8-epimeric β,γ-unsaturated ketones have each been converted into 9α,11α-epoxy-7-oxoergost-22-en-3β-yl acetate (inversion

having occurred in the former case)(page46). This and the following subsections describe the nature and behaviour of the oxidation products derived from a further two β,γ-unsaturated ketones obtained from steroidal



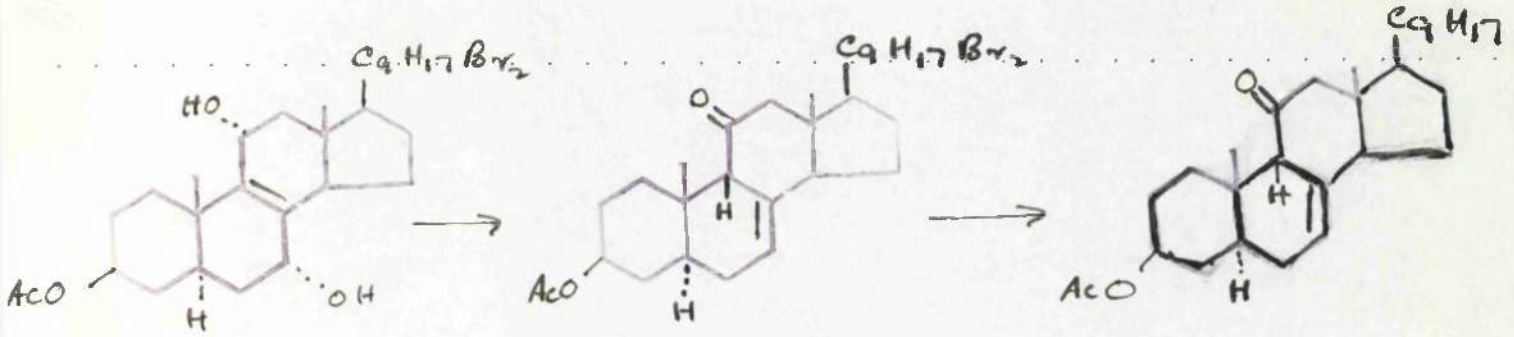
XLI



XXII

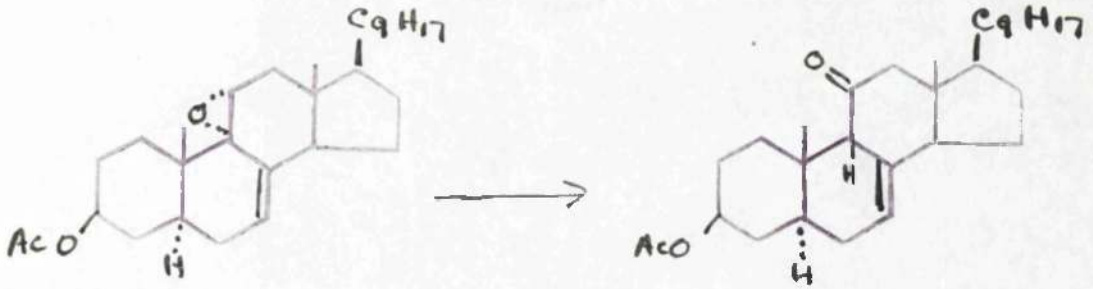
$\Delta^{7,9(11)}$-dienes, viz., 22,23-dibromo-11-oxoergost-7-en-3β-yl acetate (XLI) and 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XXII).

It has been shown earlier (Section II) that treatment of 22,23-dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (XIV) with boron trifluoride in absolute benzene gave a mixture from which 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XXII) was isolated, debromination of which yielded the corresponding 11-oxo-9β-ergosta-7,22-dien-3β-yl acetate (XXV). This same non-conjugated ketone (XXV) has been obtained by Bladon et al(54) and by Heusler and Wettstein(64) by controlled treatment of 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate in ether with boron



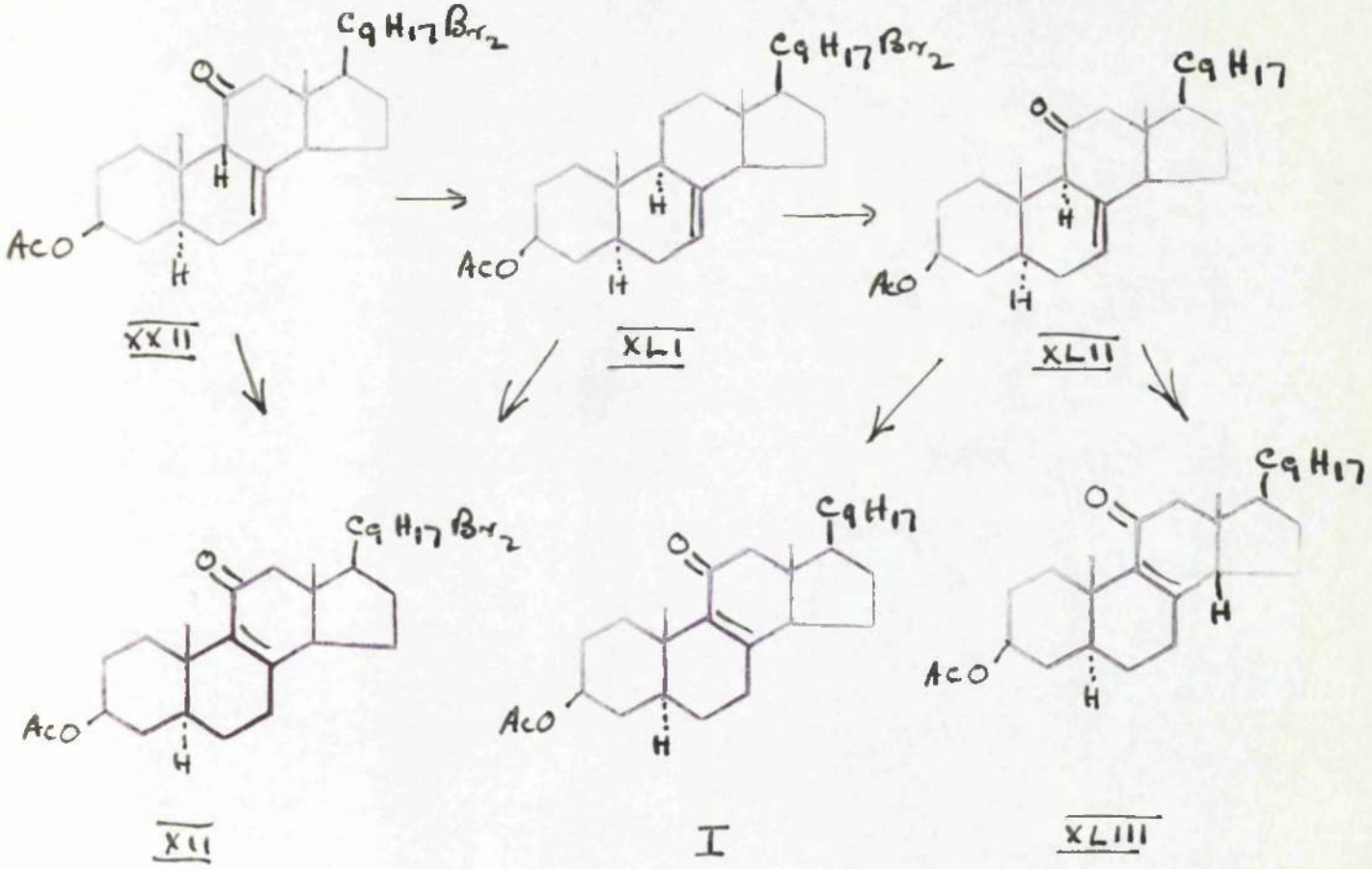
XIV XXII XXV

trifluoride-et ether complex, and Elks et al(54) have carried out a similar isomerisation of the related dibromide compound 22,23-dibromo-9α,11α-epoxyergost-7-en-3β-yl acetate to get (XXII). Spring and his co-workers also(69), in an attempt to form the enol acetate of 22,23-dibromo-11-oxoergost-8-en-3β-yl acetate by treating 22,23-dibromo-9α,11α-epoxyergost-7-en-3β-yl acetate with boron trifluoride in the presence of acetic anhydrid unexpectedly obtained instead of the β γ-unsaturated ketone (XXII).



VII XXIII

Bladon et al(54) have shown that filtration of a benzene solution of 11-oxo-9β-ergosta-7,22-dien-3β-yl acetate (XXV) through specially treated alumina caused inversion at C_9 giving 11-oxoergosta-7,22-dien-3β-yl acetate (XLII). Similar treatment of 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XXII) gave 22,23-dibromo-11-oxoergost-7-en-3β-yl acetate (XLI) in good yield. The structure of (XLI) was established by its conversion into

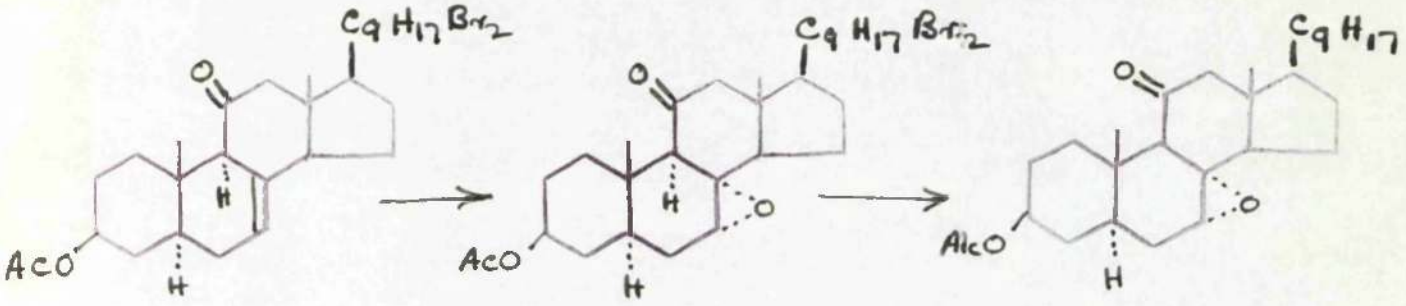


11-oxoergosta-7,22-dien-3β-yl acetate (XLII) by treatment with zinc dust. If the alumina treatment of 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XXII) was prolonged or if ordinary Spence grade H alumina was used (not specially treated as above) (Section II) then (XXII) was isomerised to 22,23-dibromo-11-oxoergost-8-en-3β-yl acetate (XII),

indicating that (XLI) is an intermediate in the rearrangement of (XXI) into (XII). In the same way, prolonged contact with alumina (not specially treated) converted 11-oxoergosta-7,22-dien-3β-yl acetate (XLII) into 11-oxoergosta-8,22-dien-3β-yl acetate (I) although in poor yield. The poor yield of this last reaction prompted a further attempt to be made on the conversion of (XLII) into (I). Treatment of (XLII) in acetic acid with hydrogen chloride gas gave 11-oxo-14β-ergosta-8,22-dien-3β-yl acetate (XLIII identical with a specimen prepared in this laboratory by treatment of 11-oxo-ergosta-8,22-dien-3β-yl acetate (I) with alkali or with hydrogen chloride gas(94). Presumably the Δ^{7}-ethylenic bond of (XLII) has migrated firstly to the 8,9-position with consequent enolisation causing inversion at C_{14}. The motivating force for this inversion of configuration at C_{14} probably lies in the fact that greater strain is associated with trans hydrindane than with the cis isomer (95,105) and therefore it would be expected that the $\Delta^{8\cdot9}$-14β-system (cis with respect to methyl group at C_{13}) would be more thermodynamically stable than the $\Delta^{8\cdot9}$-14α-system (trans with respect to methyl group at C_{13}). This behaviour has also been observed by Djerassi et al(87). A fuller discussion of this epimerisation at C_{14} is contained in Section (VI). The poor yield in the conversion of 11-oxoergosta-7,22-dien-3β-yl acetate (XLII) into 11-oxoergosta-8,22-dien -3β-yl acetate (I) by treatment with alumina is attributed to the slightly alkaline condition of the alumina which could partially induce epimerisation at C_{14}.

Treatment of 22,23-dibromo-11-oxoergost-7-en-3β-yl acetate (XLI) with perbenzoic acid gave in high yield 22,23-dibromo-7α,8α-epoxy-11-

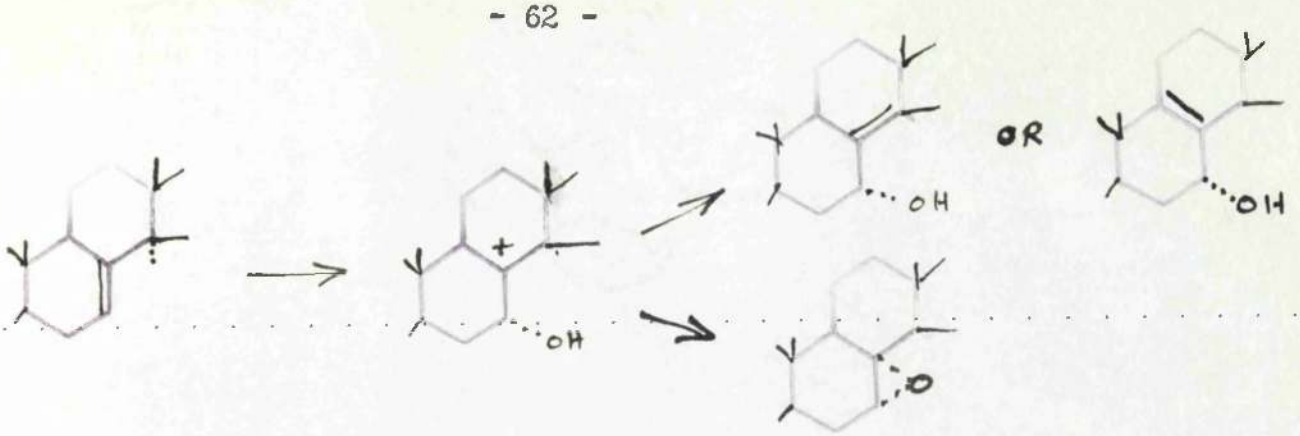
oxoergosta -3β-yl acetate (XLIV) the structure of which follows from the following reasons.



XLI XLIV XLV

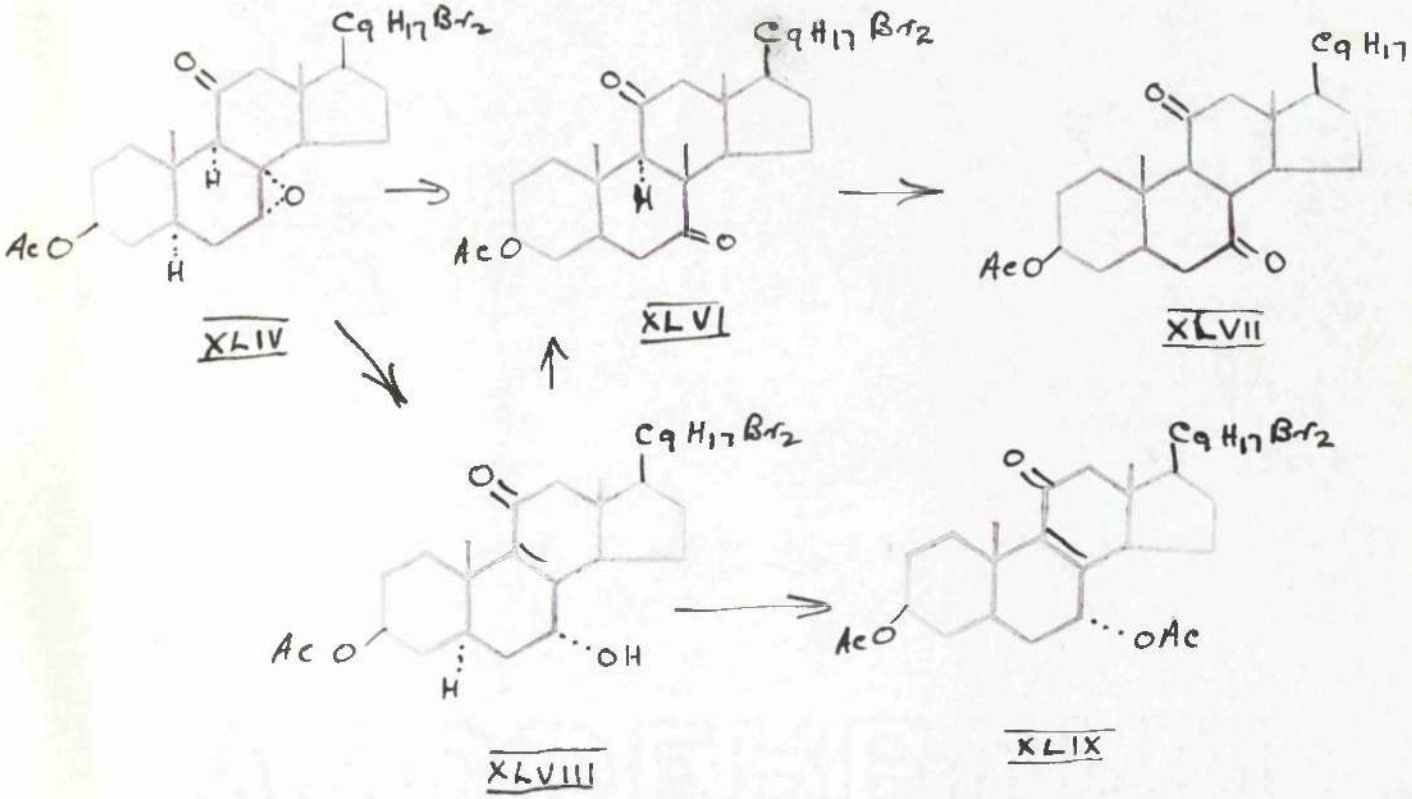
Empirical analysis of the compound (XLIV) was in agreement for $C_{30}H_{46}O_4Br_2$; it did not show intense selective light absorption in the ultra violet above 2000Å and the absence of a hydroxyl group confirmed by its infra-red absorption spectrum, (XLIV) must accordingly possess a 7:8-epoxide function. Fieser and Ourisson(82) had oxidised cholest-7-en-3β-yl acetate with osmium tetroxide acid to obtain a 3β:7α:8α-triol and also oxidised a Δ^{7}-stenol with selenium dioxide and obtained the $\Delta^{8\cdot14}$-7α-alcohol, the 7-hydroxyl group of which was proved to have the same orientation (α) as the 8:14-epoxide-7-alcohol obtained by Wintersteiner and Moore(86) by peracid oxidation of a Δ^{7}-stenol. This indicates that peracid attack on Δ^{7}-stenols proceeds by the suggested general rear (α) attack(85) on Δ^{7}-ethylenic bonds of natural steroids. Accordingly the 7α:8α-configuration was ascribed to the epoxide group in (XLIV),

The epoxidation of the isolated 7,8-double bond in a natural steroid had not been observed previously. Two steroid 7,8-epoxides had been described in the literature; one of these, prepared by Henbest and Wagland (63) by oxidation of 11-oxo-9β-ergosta-7,22-dien-3β-yl acetate (XXV) with monoperphthalic acid was 7β,8β-epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (unnatural configuration at C_9) which is discussed in some detail later. The second, methyl 3α-acetoxy-7ξ,8ξ-epoxychol-9(11)-enate is obtained by oxidation of methyl-3α-acetoxychola-7,9(11)-dienate with monoperphthalic acid(31). The vicinal effect of the $\Delta^{9(11)}$-ethylenic linkage may possibly play some part in the formation of the latter 7,8-epoxide. A number of 7,8,9,11-diepoxides have recently been described, viz., 7α,8α,9α,11α-diepoxy-22a-spirostan-3β-5α-diol by Djerassi et al(106), 7α,8α,9α,11α-diepoxy-5α-hydroxyergost-22-en-3β-yl acetate by Jones et al (55a) and 7ξ,8ξ,9α,11α-diepoxyergost-22-en-3β-yl acetate by Tishler et al (27). According to Fieser (81,82) peracid oxidation of a 5α-st-7-enol proceeds by initial hydroxylation at C_{14} which undergoes an allylic rearrangement to give a $\Delta^{8(14)}$-7-hydroxy compound. This mechanism does not account for epoxide formation. In view of the 7,8-epoxide formation in (XLIV) it is alternatively suggested that peracid attack on Δ^{7}-steols results in initia hydroxylation at C_7 (OH^+ attack) with the elimination of a proton in one of two ways as shown above according to the conditions of the reaction; i.e., either with the formation of a 7α,8β-epoxide or, with the formation of one or both the allylic alcohol systems. Support for this mechanism has been forthcoming from Barton et al(83) who very recently have obtained a 7,8-epoxide of 5-dihydroergosteryl acetate by perphthalic acid oxidation.



When treated with zinc dust in a neutral solvent 22:23-dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (XLIV) was smoothly debrominated to give 7α:8α-epoxy-11-oxoergost-22-en-3β-yl acetate (XLV).

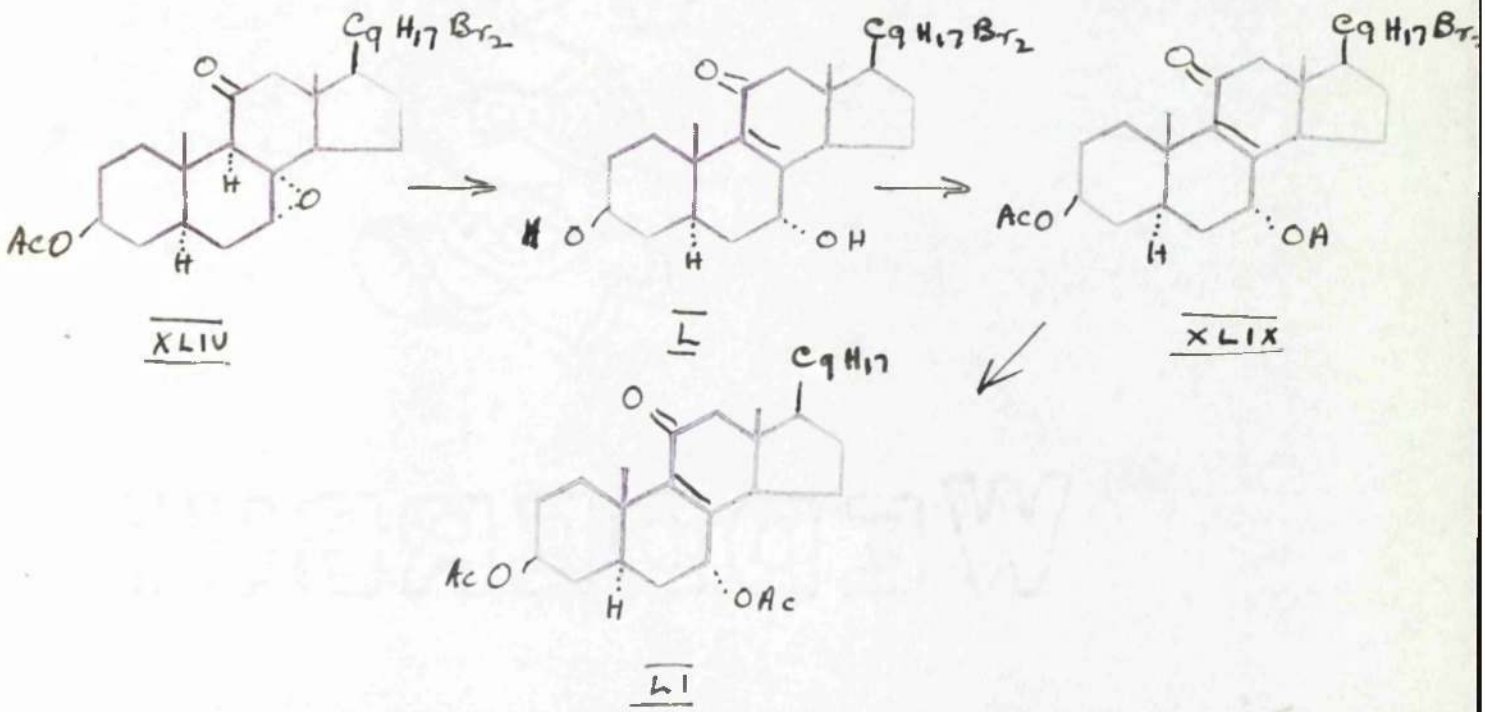
The behaviour of the keto-epoxide(XLIV) with acids was now examined. With hydrogen bromide in chloroform-acetic acid, it gave 22:23-dibromo-7:11-dioxoergostan-3β-yl acetate (XLVI) the structure of which followed from its ready conversion into the known 7:11-dioxoergost-22-en-3β-yl acetate (XLVII) by treatment with zinc in a neutral solvent. The natural configuration at C_8 and C_9 in (XLVI) follows from its conversion into (XLVII) and from



XLIV XLVI XLVII XLVIII XLIX

the fact that it was recovered unchanged after alkaline hydrolysis followed by acetylation. Treatment of the keto-epoxide (XLIV) with sulphuric acid in dioxane(69) gave 22,23-dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate (XLVIII) which showed the characteristic ultra-violet absorption spectrum of an α,β-unsaturated ketone. The presence of a hydroxyl group in (XLVIII) was confirmed by its acetylation to 3β,7α-diacetoxy-22,23-dibromoergost-8-en-11-one (XLIX) and its 7α-configuration follows from the fact that it is formed by acid cleavage of a 7α,8α-epoxide bridge. (XLVIII) is intermediate in the conversion of the keto-epoxide (XLIV) into the saturated diketone (XLVI) since it is converted into the last compound by treatment with hydrogen bromide in chloroform-acetic acid.

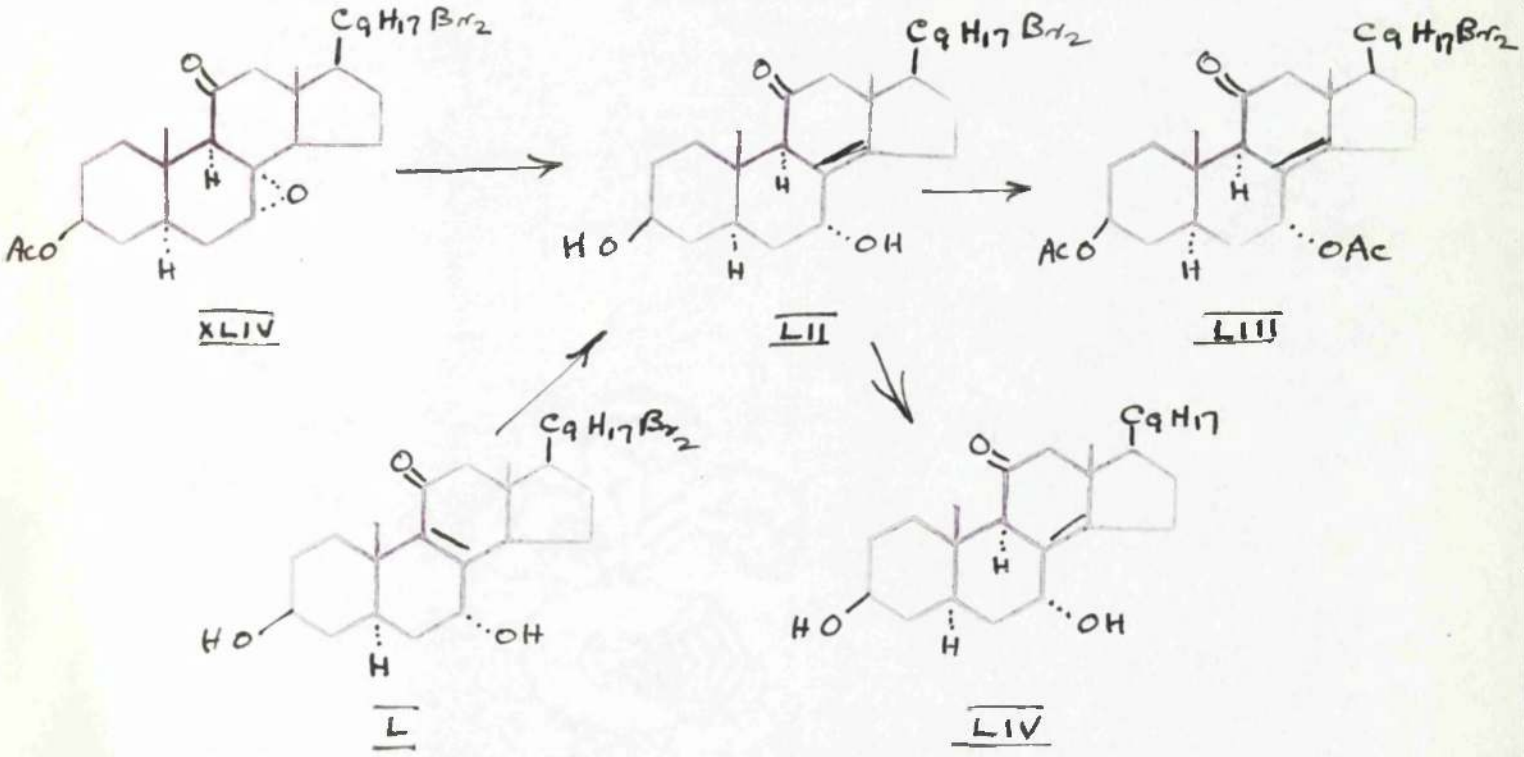
The behaviour of the keto-epoxide (XLIV) with alkali was next examined. Using 1% methanolic potassium hydroxide at <u>room temperature</u>, the keto-epoxide (XLIV) gave 22,23-dibromo-11-oxoergost-8-en-3β,7α-diol(I) acetylation of which yielded the diacetate (XLIX) identical with that



XLIV L XLIX LI

obtained by the action of sulphuric acid on the keto-epoxide (XLIV) followed by acetylation of the product (XLVIII). Treatment of the diol(L) with zinc dust followed by acetylation gave 3β,7α-diacetoxyergosta-8,22-dien-11-one (LI), also obtained by debromination of (XLIX) with zinc. This diacetate has also been obtained by Hunbest and Wagland(63) by the rear (α) attack by acetic acid on the Δ^{7}-ethylic bond of 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate followed by oxidation of the intermediate 3β,7α-diacetoxyergosta-8,22-dien-11α-ol with chromic acid.

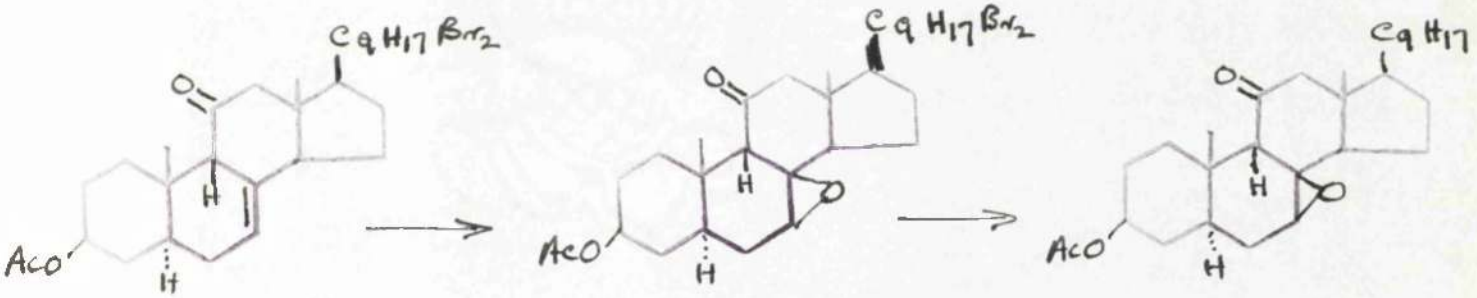
When treated with refluxing methanolic potassium hydroxide the keto-epoxide (XLIV) gave 22,23-dibromo-11-oxoergost-8(14)-en-3β,7α-diol (LII) which shows the ultra-violet light absorption characteristic of an isolated tetra-substituted double bond (84), and which is readily acetylated to give the diacetate (LIII). Debromination of the diol (LII) yielded 11-oxoergosta-8(14),22-dien-3β,7α-diol(LIV). The 7α-configuration of the hydroxyl group



in (LII) is further established by the fact that 22,23-dibromo-11-oxoergost-8-en-3β,7α-diol(L), obtained from XLIV) by treatment with cold alkali, was converted into (LII) by refluxing methanolic potassium hydroxide, also indicating that (L) is an intermediate in the conversion of (XLIV) into (LII). This migration, under alkaline conditions, of a Δ^{8}-ethylenic bond in a Δ^{8}-11-ketone to the 8,14-position has been observed previously by Djerassi et al(87) and in this department by Mr. F. Johnson(94). The configuration of the C_9 hydrogen atom in (LII) is considered to be 9α since it is formed from (L) under equilibrating conditions and might therefore be expected to assume the natural configuration. This is supported by the fact that 22,23-dibromo-11-oxo-9β-ergost-8(14)-en-3β-7β-diol was isomerised with alkali to 22,23-dibromo-11-oxoergost-8(14)-en-3β,7α-diol indicating the greater stability of the latter system. This last reaction is discussed later (Section VI).

VI. The Structure and Reactions of 22,23-Dibromo-7β,8β-epoxy-11-oxo-9β-ergostan-3β-yl Acetate.

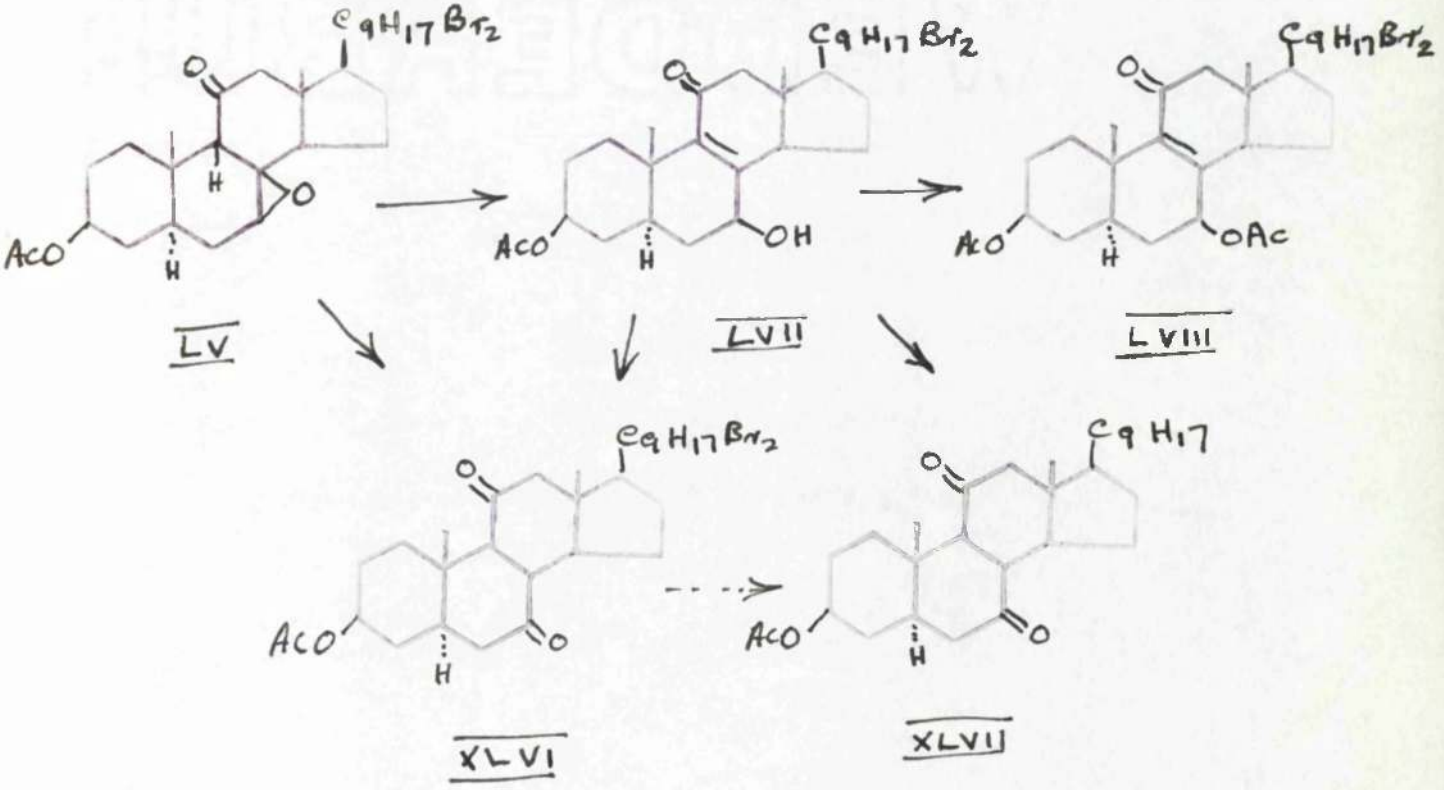
This section describes the examination of the oxidation products of the epimoic βδ -unsaturated ketone 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (XXII), Oxidation of which, using a freshly prepared peracid reagent and mineral acid free chloroform gave an almost quantitative yield of 22,23-dibromo-7β,8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (LV).



XXII LV LVI

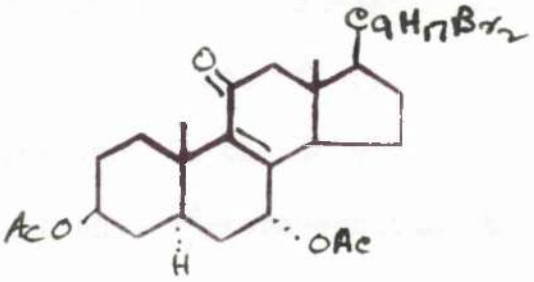
Debromination of (LV) with zinc in a neutral solvent gave 7β,8β-epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (LVI) previously obtained by Hunbest and Wagland(63) and by Heusler and Wettstein(64) by direct oxidation of 11-oxo-9β-ergosta-7,22-dien-3β-yl acetate with monoperphthalic acid. The configuration of the oxide and the maintenance of the 9β-centre in (LV) was proven by subsequent reactions which are described below.

Attempted reductive cleavage of the 7:8-epoxide bridge of (LV) by catalytic hydrogenation resulted in the isolation of two isomers, the first of which was assigned the structure 22:23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (LVII) on the basis of its method of preparation and its light absorption spectra, and which was also obtained by treatment of the keto-epoxide (LV) with a trace of hydrobromic acid in chloroform(69). (LVII) shows the characteristic ultra-violet absorption spectrum of an α,β-unsaturated ketone and its infra-red absorption spectrum reveals the presence of α,β-unsaturated ketone, hydroxyl and acetoxyl groups. The presence of a hydroxyl group was confirmed by acetylation of (LVII) which yielded the diacetate (LVIII). The second catalytic hydrogenation product was the known 22:23-dibromo-7:11-dioxoergostan-3β-yl acetate (XLVI) which established the epoxide bridge in (LV) as a 7:8-epoxide. Since the

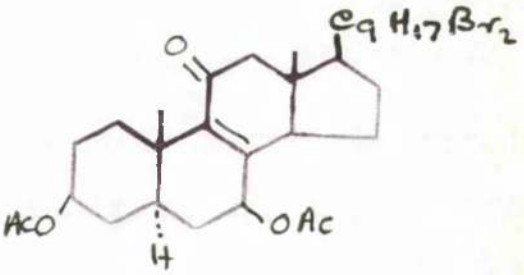


hydroxyl group in (LVII) was acylable and it resulted from a 7,8-epoxide bridge in (LV) it follows that it is situated at position C_7. This was firmly established (69) by the conversion of (LVII) into 7,11-dioxoergost-22-en-3β-yl acetate (XLVII) by treatment with chromic acid followed by debromination with zinc dust. Many attempted hydrogenations of (LV) were unsuccessful, isomerisation products always being isolated.

The configuration of the 7-hydroxyl group in (LVII) follows from these following reasons. The two diacetates (LVIII) and (XLIX) might conceivably differ in configuration at C_{14}. Since (LVIII) has the 14α-configuration, (it differs from the 14β-epimer described later), and since 22,23-dibromo-11-oxoergost-8-en-3β-7α-diol(L) is an intermediate in the conversion of the keto-epoxide (XLIV) into 22,23-dibromo-11-oxoergost-8(14)-



XLIX

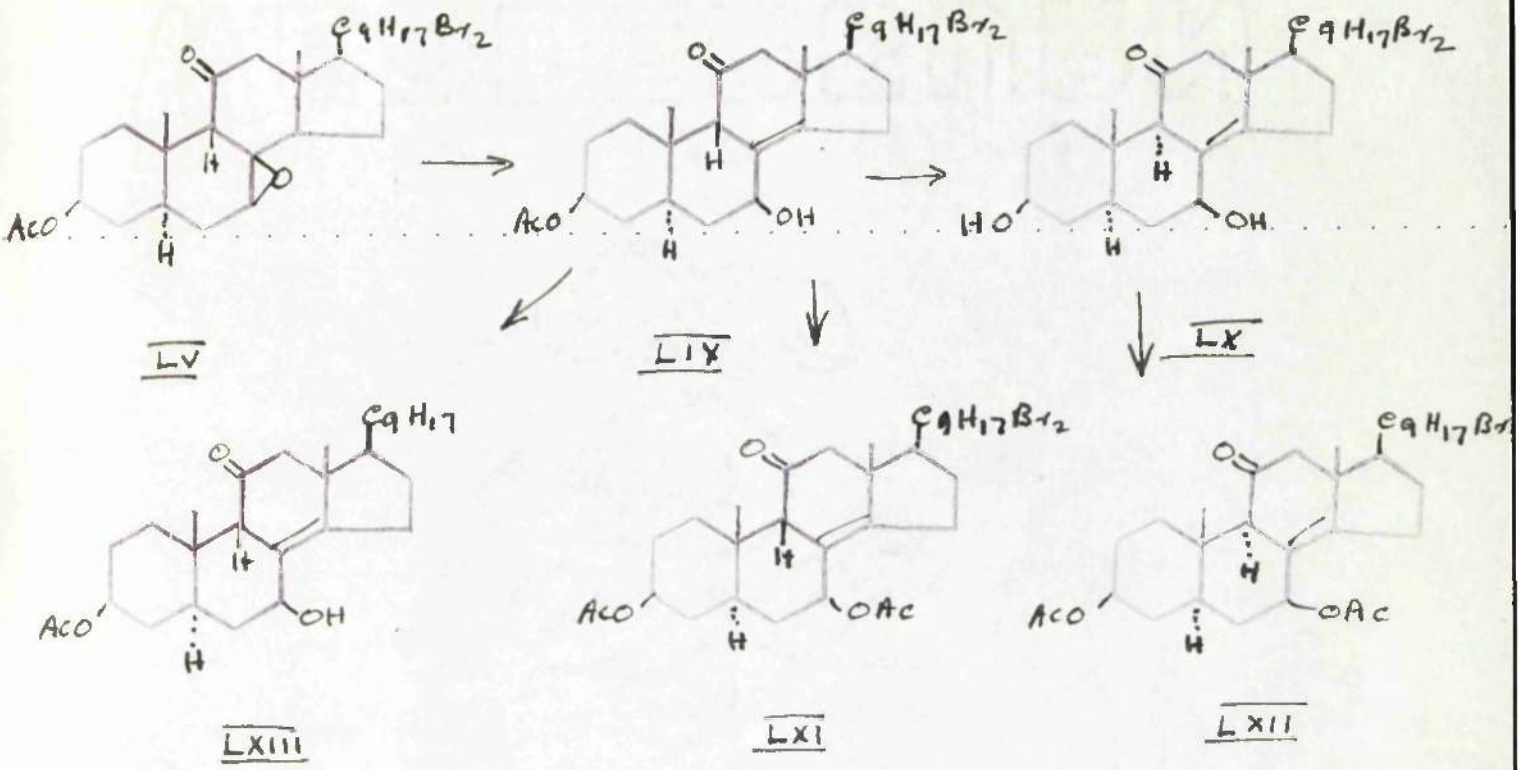


LVIII

en-3β,7α-diol(LII) and therefore the 14-centre is <u>not</u> involved in the formati of (L) and (XLIX) from the keto-epoxide (XLIV) it follows that (XLIX) has also the 14α-configuration. Therefore, (XLIX) and (LVIII) can only differ in their orientation at C_7. As it is established that (XLIX) has a 7α-acetoxyl group, therefore (LVIII) has 7β-acetoxyl group and as a corollary the epoxide bridge in (LV) has the β-configuration. Hunter and Wagland(63)

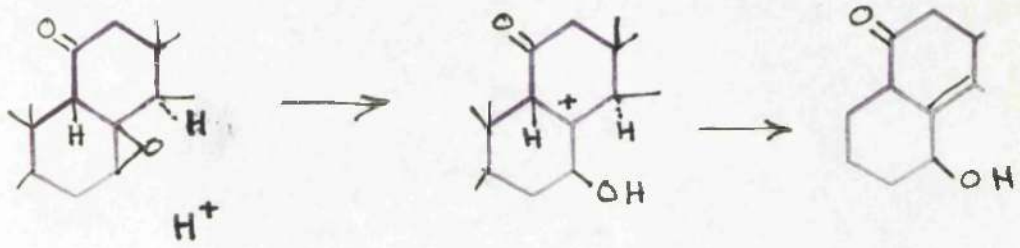
also ascribed the 7β,8β-epoxide configuration to the epoxide bridge in (LVI) reasoning that as trisubstituted olefinic bonds in natural steroids were normally attacked in a similar steric manner by both peracids and hydrogen and that as hydrogenation of 11-oxo-9β-ergosta-7,22-dien-3β-yl acetate gave 11-oxo-9β-ergostan-3β-yl acetate(54) a reaction which must proceed by frontal (β) attack on the Δ^7 -ethylenic bond, and therefore peracid attack on 11-oxo-9β-ergosta-7,22-dien-3β-yl acetate would give a 7β,8β-epoxide. An inspection of models shows that in (LV) and (LVI) the 7,8-olefinic bond is considerably more accessible for attack on the β face than is the case with the 9α-epimers (XLI) and (XLII).

At this stage in view of the necessity of utilising mineral acid free conditions in the formation of the keto-epoxide (LV) (the slightest trace of acid resulting in a mixture which consisted largely of 22,23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (LVII)(69))it was considered likely that in the formation of this keto-epoxide (LV) the hydrogen atom at C_9 had been maintained in the β orientation. Consequently many attempts were made to convert the 9β-keto-epoxide (LV) into the 9α-isomer, all of which were unsuccessful. One of these attempts, however, did indirectly furnish a proof of the 9β-structure of (LV). When 22,23-dibromo-7β,8β-epoxy-11-oxo-9β-ergosta 3β-yl acetate (LV) was treated with dioxane containing dilute sulphuric acid, a compound was formed to which the structure 22,23-dibromo-7β-hydroxy-11-oxo-9β ergost-8(14)-en-3β-yl acetate (LIX) was ascribed. This compound shows the ultra-violet absorption spectrum characteristic of a doubly exocyclic tetra-substituted olefinic bond (84); the presence of a hydroxyl group was confirmed by its infra-red absorption spectrum and also by acetylation which gave a diacetate (LXI); the hydroxyl group is situated at C_7 and has the



β-configuration because it is acylable and has been formed from a 7β,8β-epoxide bridge. The 9β-configuration was assigned to (LIX) for the following reasons. Alkaline hydrolysis of (LIX) at room temperature gave a diol (LX) the ultra violet absorption of which established the maintenance of the 8(14)-olefinic bond. Acetylation of this diol gave a diacetate which differed from (LXI) and which was consequently considered to be 3β,7β-diacetoxy-22,23-dibromo ergost-8(14)-en-11-one (LXII). The diacetates (LXI) and (LXII) can only differ in configuration at C_9. The latter is considered to have the 9α-configuration in view of the fact that it was produced under equilibrating conditions and might therefore be expected to have the natural (9α) configurati The compound (LIX) therefore possesses the 9β-orientation and so also must the keto-epoxide (LV) and therefore it follows that the formation of (LV) from the 9β-Δ^7-unsaturated-11-ketone (XXII) is not accompanied by inversion at C_9.

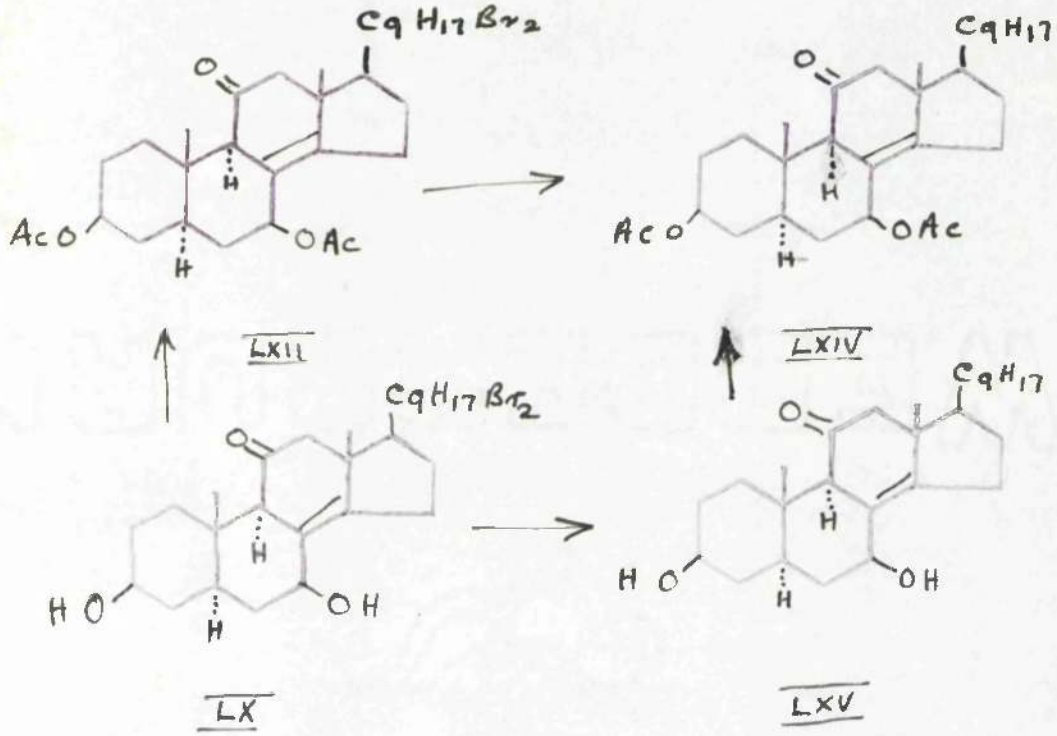
The interesting feature of the conversion of the keto-epoxide (LV) into (LIX) is that while the mechanism of the reaction probably follows the route outlined schematically below, viz., acid fission of the epoxide followed



by elimination of a proton to give an olefinic bond, which is formed preferentially in the $\beta\gamma$-position [$\Delta^{8(14)}$] to the 11-carbonyl function, instead of in the expected $\alpha\beta$-position [Δ^{8}]. It was considered possible that (LIX) was an intermediate in the formation of 22,23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (LVII) from the 9β-keto-epoxide (LV). When (LIX), however, was treated with a trace of hydrobromic acid in chloroform using conditions which convert the keto-epoxide (LV) into (LVII), it was not converted into (LVII) but gave a dienone of unknown structure. It appears unlikely, therefore that 22,23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (LIX) is an intermediate in the conversion of (LV) into (LVII). Similarly 22,23-dibromo-7β-hydroxy-11-oxo-ergost-8-en-3β-yl acetate (LVII) was recovered unchanged on treatment with sulphuric acid and dioxane using the conditions under which the keto-epoxide (LV) is converted into (LIX). It follows that (LVII) is not an intermediate in the conversion of (LV) into (LVII).

Debromination of 22,23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (LIX) with zinc in a neutral solvent yielded 7β-hydroxy-11-oxo-9β-ergosta-8(14),22-dien-3β-yl acetate (LXIII). Similarly debromination

of 3β,7β-diacetoxy-22,23-dibromoergost-8(14)-en-11-one(LXII) gave 3β,7β-diacetoxy -11-oxoergosta-8(14),22-diene(LXIV) which was also obtained by

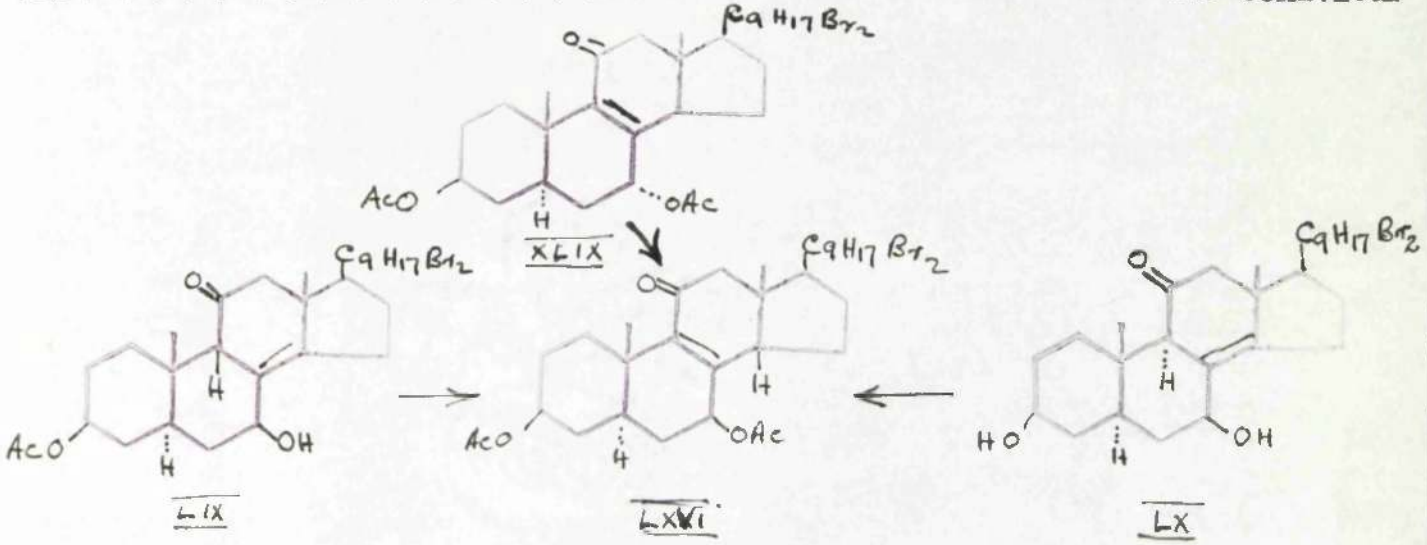


debromination of 22,23-dibromo-11-oxoergost-8(14)-en-3β,7β-diol(LX) to give 11-oxoergosta-8(14),22-dien-3β,7β-diol(LXV) followed by acetylation. A compound designated 7ξ-hydroxy-11-oxoergosta-8(14),22-dien-3β-yl acetate has been obtained by Heusler and Wettstein(64) by treatment of the 7β,8β-epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (LVI) in hot dioxane with boron trifluoride. 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 (LXIII) the rotations of the two preparation (+76°, +216° respectively) are markedly different. We have not prepared 7β-hydroxy-11-oxoergosta-8(14),22-dien-3β-yl acetate; the related diacetate (LXIV) m.p. 111-113° $[\alpha]_D$ +34°, again differs appreciably from the diacetate (m.p. 153-155°; $[\alpha]_D$ not given) obtained by Heusler and Wettstein . The last authors appreciated that their preparation was not pure. Repetition of the experiment of Heusler and Wettstein did not give a homogeneous product.

When 22,23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (LIX) or 22,23-dibromo-11-oxoergost-8(14)-en-3β,7β-diol (LX) were treated with refluxing alkali followed by acetylation they were converted into diacetoxy-22,23-dibromo-14β-ergost-8-en-11-one (LXVI). This compound shows the light absorption properties of an αβ-unsaturated ketone both in the ultra-violet and the Infra-red regions. As it must have the same configuration at C_7 as 3β,7β-diacetoxy-22,23-dibromoergost-8-en-11-one (LVIII) it can only differ from this last compound in configuration at C_{14}. Since greater strain is associated with trans hydrindane than with the cis isomer and since (LXVI) is formed under equilibrating conditions and will therefore take the less strained configuration, (LXVI) must be the 14β-epimer of (LVIII). Treatment of (LVIII) with refluxing alkali(69) followed by acetylation also gave the 14β-epimer (LXVI) .

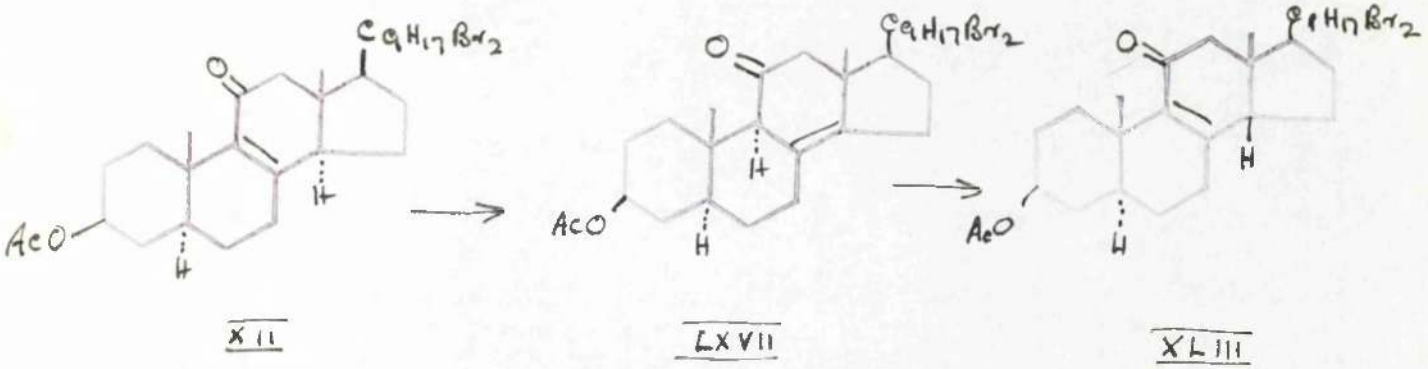
It is of interest at this point to compare the behaviour of 7α- and 7β-hydroxy substituted 22,23-dibromo-11-oxoergost-8-en-3β-yl acetates when treated with alkali. The 7α-hydroxy derivative (XLVIII) is converted by alkali into the non-conjugated 22,23-dibromo-11-oxoergost-8(14)-en-3β,7α-diol (LII), the double bond moving out of conjugation to give a βγ-unsaturated ketone. In the case of the 7β-hydroxy derivative (LVII), however, similar alkali treatment (followed by acetylation) leads to the 14β-epimer (LXVI). This C_{14} epimerisation has been observed by Djerassi et al (87) with a related Δ^8-11-ketone of the sapogenin series. A close examination of this behaviour with 22,23-dibromo-11-oxoergost-8-en-3β-yl acetate (XII) has recently been carried out by Johnson and Spring (94) who also isolated the intermediate 22,23-dibromo-11-oxoergost-8(14)-en-3β-yl acetate (LXVII) by refluxing (XII)

with 12% alkali. LXVII could be converted into the 14β-epimer of (XII), viz., XLIII by treatment with dilute alkali, which also could be obtained from (XII) by treatment with dilute alkali. It is therefore believed that the behaviour



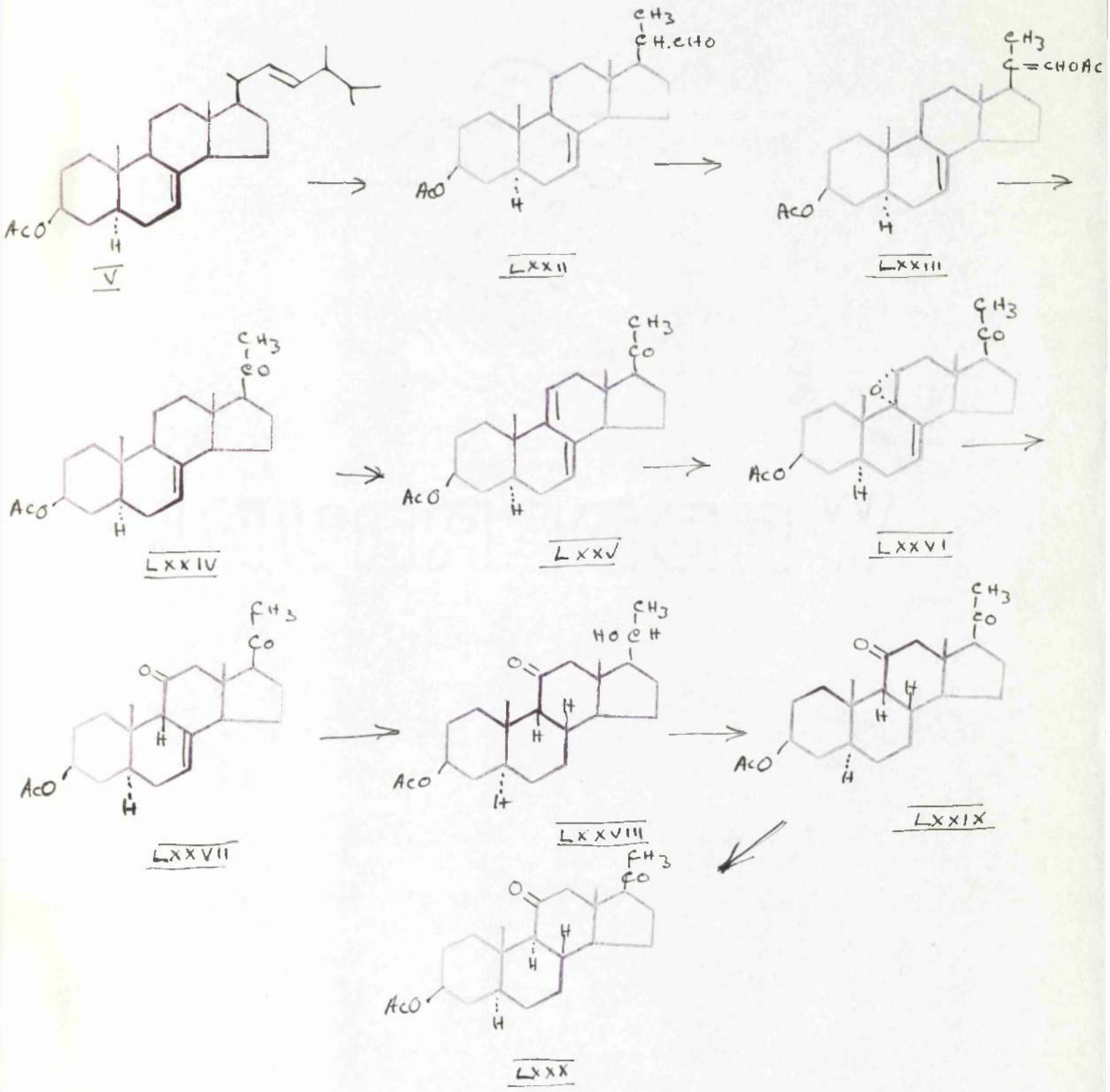
of both the 7α- and 7β-hydroxy derivatives (XLVIII) and (LVII) is similar to that observed by Johnson and Spring, the critical factor being the greater stability of a C/D cis. fusion system and that the configuration of the 7-hydroxy group exerts an influence on the bond migration.

It is of interest to note at this point that recently Barton and Laws(96) have shown that 3β-hydroxy-15-oxoergostane is apparently more stable when the C/D ring fusion is trans and a suggested rationalisation of these apparently contradictory results has been published by Dreiding (107).



VII. A Partial Synthesis of Cortisone from Ergosterol

The conversion of ergosterol into 11,20-dioxoallopregnan-3β-yl acetate (LXXX) has been achieved by the route (V) ⟶ (LXXX) as shown . . . .



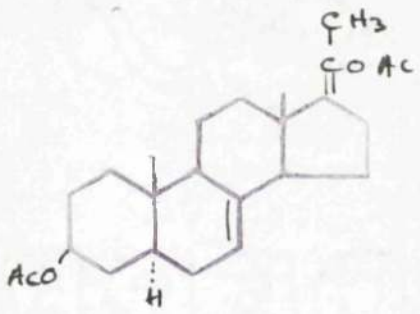
11:20-Dioxoallopregnan-3β-yl acetate (LXXX) is a common intermediate in the synthesis of cortisone starting from various natural products (49,97), and its conversion into cortisone follows well established routes (see Historical Section).

It has been shown earlier that ergosterol can be converted in high yield into 5-dihydroergosteryl acetate (V). In 1948, Bergmann and Stevens (25) first used ozanolysis to degrade the ergosterol side chain, a procedure which has later been shown by Jones and his co-workers(98) and by a Glaxo Laboratories group(102). Investigation of the action of ozone on 5-dihydroergosteryl acetate (V) at -50° showed that there was preferential attack of the side chain olefinic bond. An ozonide was formed which, on decomposition with zinc dust and acetic acid, gave 3β-acetoxy bisnorallochol-7-en-22-al (LXXII) in 85% overall yield. The ultra-violet absorption spectrum of (LXXII) showed the presence of a tri-substituted olefinic bond (84). The aldehyde (LXXII) was characterised by the very ready formation of a dimethyl acetal (formed even on crystallisation of the aldehyde from slightly impure methanol), and of a 2:4-dinitrophenylhydrazone. The side chain degradation product, separated from the crude reaction product by steam distillation was isolated as its 2:4-dinitrophenylhydrazone, identical with that from methyl isopropylacetaldehyde.

Enol acetylation of the aldehyde (LXXII) yielded 3β:22-diacetoxy bisnorallochola-7:20(22)-diene(LXXIII), selective ozanolysis of which at -50° followed by decomposition of the product with zinc dust and acetic acid gave 20-oxoallopregn-7-en-3β-yl acetate (LXXIV). Djerassi and his co-workers have prepared this compound from diosgenin(47). (LXXIV) was smoothly converted with alkali to the alcohol 20-oxoallopregn-7-en-3β-ol, which in turn was

benzoylated to 20-oxoallopregn-7-en-3β-yl benzoate.

Attempts to introduce a 17α-hydroxy function at this stage by the method of Kritchevsky and Gallagher(59) were not successful. Enol acetylation of (LXXIV) according to the method of these authors gave an oily mixture which probably consisted of the possible cis and trans isomers of an enol acetate of a C_{20}-ketone. Chromatography of this oil gave a specimen of a low melting compound, the empirical analysis of which was in agreement with 3β,20-diacetoxyallopregna-7,17(20)-diene(LXXXI). Treatment of the crude



LXXXI

oil with perbenzoic acid followed by alkaline hydrolysis by the method of Kritchevsky and Gallagher did not introduce a 17α-hydroxy function but gave 20-oxoallopregn-7-en-3β-ol, i.e., starting material. The use of excess perbenzoic acid was not any more successful but led to the formation of some $\Delta^{7,9(11)}$-diene as an impurity. Djerassi and his co-workers(88) have reported the introduction of the 17α-hydroxy function into (LXXIV) using this method but in very low yield. In view of these discouraging results, the introduction of a 17α-hydroxy function was postponed to a later stage.

Oxidation of 20-oxoallopregn-7-en-3β-yl acetate (LXXIV) with mercuric acetate according to the method of Djerassi and his co-workers(47) gave a poor yield of 20-oxoallopregna-7,9(11)-dien-3β-yl acetate (LXXV), no more than 10% of pure dienone being obtained after extensive purification.

The yield was greatly improved by carrying out the oxidation according to the method of Anderson Stevenson and Spring(28), who treated 5-dihydroergosteryl acetate at -50° with bromine followed by treatment with zinc dust to obtain ergosteryl-D acetate. Bromination of 20-oxoallopregn-7-en-3β-yl acetate (LXXIV) at -50° followed immediately by debromination of the product with zinc dust gave a 78% yield of pure 20-oxoallopregna-7,9(11)-dien-3β-yl acetate (LXXV). This compound shows the characteristic ultra-violet light absorption spectrum if a $\Delta^{7,9(11)}$-diene system. Alkaline hydrolysis of (LXXV) gave 20-oxoallopregna-7,9(11)-dien-3β-ol.

The introduction of an 11-oxogen function into (LXXV) was accomplished in the following way. Treatment of 20-oxoallopregna-7,9(11)-dien-3β-yl acetate (LXXV) with perbenzoic acid at 0° gave 9α,11α-epoxy-20-oxoallopregn-7-en-3β-yl acetate (LXXVI). This structure was ascribed in accordance with known behaviour of (30) of $\Delta^{7,9(11)}$-dienes of natural steroids with perbenzoic acid. Treatment of the keto-epoxide (LXXVI) with boron trifluoride-ether complex in ether as solvent using the method of Bladon et al (54) gave 11,20-dioxo-9β-allopregn-7-en-3β-yl acetate (LXXVII). Catalytic hydrogenation of the last compound (LXXVII) yielded 20β-hydroxy-11-oxo-9β-allopregnan-3β-yl acetate (LXXVIII), the structure of which was confirmed by its infra-red absorption spectrum which shows well resolved hydroxyl, carbonyl and acetoxyl bands. Sarett(89) has selectively reduced 20-ketone groups in 11,20-diketones of the pregnane (rings A/B cis fused) series, obtaining a preponderant amount of the 20β-isomer. Since the effects of an allopregnane (A/B trans fused) or 9β-hydrogen (B/C cis) system on reduction at C_{20} have not yet been established, the hydrogenation product (LXXVIII) is provisionally

assigned the 20β-hydroxyl configuration. Oxidation of 20β-hydroxy-11-oxo-9β-allopregnan-3β-yl acetate (LXXVIII) with chromic anhydride gave 11,20-dioxo-9β-allopregnan-3β-yl acetate (LXXIX). Alternatively catalytic hydrogenation of 11,20-dioxo-9β-allopregnan-3β-yl acetate (LXXVII) followed by oxidation of the crude reaction product with chromic anhydride gave 85% overall yield of 11,20-dioxo-9β-allopregnan-3β-yl acetate (LXXIX). Treatment of the last compound (LXXIX) with 20% methanolic potassium hydroxide converted it into 11,20-dioxoallopregnan-3β-ol, the identity of which was confirmed by comparison with an authentic specimen prepared by hydrolysis of a sample of 11,20-dioxo-allopregnan-3β-yl acetate (LXXX), kindly supplied by Dr. B.A.Hems, Glaxo Laboratories Limited, Greenford. Acetylation of 11,20-dioxoallopregnan-3β-ol gave 11,20-dioxoallopregnan-3β-yl acetate (LXXX) which was also identified by comparison with an authentic specimen.

EXPERIMENTAL.

EXPERIMENTAL.

All m.p's were determined using a standard N.P.L. thermometer.

Specific rotations were determined in chloroform solution (except where otherwise stated) in a 1 dm. tube at room temperature.

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

Infra-red absorption spectra were determined by M.A.Pajasckowski, B.Sc.

The alumina used for chromatography was that supplied by Peter Spence grade "H" (grade II standardised according to Brockmann).

I. The Preparation and Attempted Selective Hydrogenation of 11-oxoergosta-8,22-dien-3β-~~diones~~ yl Acetate.

Ergosteryl Acetate.

Acetic anhydride (300 c.c.) was added to a solution of ergosterol (300 g.) in warm pyridine (1800 c.c.), the air in the flask displaced by nitrogen, and the mixture kept in the dark at room temperature for 18 hours. The product, which had separated, was removed by filtration, washed with hot water and dried at 50°. Crystallisation from chloroform-methanol gave ergosteryl acetate as large lustrous leafs.

m.p. 173-175°. $[\alpha]_D$ -93° (c, 1·2).

5-Dihydroergosteryl Acetate.
[cf. Anderson Stevenson and Spring(38)]

Raney nickel sludge (Org.Synth.29,25) (15-20 c.c.), washed twice by decantation with benzene (2 x 50 c.c.), was added to a solution of ergosteryl

acetate (35 g.) in benzene (300 c.c.; Analar), and the mixture shaken at room temperature in an atmosphere of hydrogen until 2140 c.c. had been absorbed (about 15 minutes). A blank experiment had shown that the solvent absorbs about 150 c.c. of hydrogen in this time. The filtered reaction solutions from five such experiments were combined and the solvent removed under reduced pressure. Crystallisation from chloroform-methanol gave 5-dihydroergosteryl acetate (160 g.; 1st and 2nd crops) as plates

m.p. 180-182° $[\alpha]_D$ -19·5°

The compound gave a yellow colour with tetranitromethane in chloroform and did not show high intensity light absorption above 2200Å.

Ergosteryl - D Acetate
[Bergman and Stevens (25)]
[Anderson et al (38)]
[Heusser et al (37)]

A warm solution of mercuric acetate (96 g., 1·5 mols.) in stabilised glacial acetic acid (1300 c.c.) was added to a solution of 5-dihydroergosteryl acetate (44 g.) in dry chloroform (500 c.c.) and the mixture shaken for 17 hours. The precipitated mercurous acetate was removed by filtration and the filtrate concentrated under reduced pressure (below 50°) to about 300-400 c.c. The resulting precipitate was filtered and washed with cold methanol. Recrystallisation from chloroform-methanol gave ergosteryl-D acetate (18 g.) as blades, m.p. 168-172°, $[\alpha]_D$ +19°(c, 1·0). Recrystallisation gave a pure specimen which had m.p. 176°, $[\alpha]_D$ +30° (c, 2·0).
Light absorption : maxima at 2350 (ε = 15,500) and 2420 (ε = 17,000) and an inflection at 2510Å (ε = 12,500).
It shows a dark brown colour with tetranitromethane in chloroform.

9α,11α-epoxyergosta-7,22-dien-3β-yl acetate.
[cf. Budziarek et al (65)].

A solution of perbenzoic acid (1·1 mols.) in chloroform (80 c.c.) was added dropwise with stirring over 5 hours to a solution of ergosteryl-D acetate (9.0 g.) in chloroform (35 c.c.) maintained between -5° and 0°. After 24 hours at 0°, the solvent was completely removed from the reaction mixture under reduced pressure (below 35°). The solid residue was dissolved in boiling acetone and the solution concentrated until crystals started to separate. On cooling, 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate was deposited as plates (6 g.)

m.p. 211-213° $[\alpha]_D$ = -38° (c, 2.0)

Found: c, 79.5; H, 10.3

Calc. for $C_{30}H_{46}O_3$: C, 79.4; H, 10.2 %

It shows a yellow colour with tetranitromethane in chloroform and does not show selective high intensity light absorption above 2200Å.

Chamberlin et al(27) report m.p. 202-205° $[\alpha]_D$ -35° .
Heusser et al (30) report m.p. 205-207° $[\alpha]_D$ -39.5°.
Budziarek et al (loc.cit.) report m.p. 211-213° $[\alpha]_D$ -38°.

7α,11α-Dihydroxyergosta-8,22-dien-3β-yl Acetate.
[Cf. Heusser et al(30)].

A solution of 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (200 mg. in dioxan (150 c.c.) was treated with 2N sulphuric acid (27 c.c.) by shaking at 20° for exactly three minutes. The mixture was poured into a separating funnel containing sodium bicarbonate solution and ether. The ethereal extract was washed once more with sodium bicarbonate solution and

twice with water, dried (Na_2SO_4) and the ether removed under reduced pressure. Three crystallisations from acetone gave 7α,11α-dihydroxyergosta-8,22-dien-3β-yl acetate (140 mg.) as prismatic needles.

m.p. 230-232°, $[\alpha]_D$ = +85° (c, 0.7)

Crystallisation from Methanol gave prismatic needles

m.p. 248-250° $[\alpha]_D$ = +83° (c, 0.4)

Found: C, 76.0; H, 10.4

Calc. for $C_{30}H_{48}O_4$: C, 76.2; H, 10.2%

It gives a pale yellow colour with tetranitromethane in chloroform and does not show high intensity selective light absorption above 2200Å.

Chamberlin et al (loc.cit.) give m.p. 248-252°, $[\alpha]_D$ + 85°

Heusser et al (loc.cit.) give, m.p. 270-272° $[\alpha]_D$ + 82°

for this compound.

Ergosta-8,22-dien-3β,7α,11α-triol.

7α,11α-Dihydroxyergosta-8,22-dien-3β-yl acetate (200 mg.) was refluxed for 1 hour with 2% methanolic potash (75 c.c.). Treatment with water extraction with chloroform followed by washing the extract with water, drying (Na_2SO_4) and removal of the chloroform under reduced pressure gave a solid white residue which gave on crystallisation from chloroform-methanol ergosta-8,22-dien-3β,7α,11α-triol, as fine needles m.p. 240-242°.

The specific rotation was not determined because of the insolubility of the triol in most solvents at 20°.

Found: C, 77.6; H, 10.8

Calc. for $C_{28}H_{46}O_3$: C, 78.1; H, 10.8%

Light absorption: $\varepsilon_{2120} = 6,000$.

It gives a pale yellow colour with tetranitromethane in chloroform.

Chamberlin et al. give m.p. 273-274°.

7,11-Dioxoergost-22-en-3β-yl Acetate.
[cf. Heusser et al (30)]

A stirred solution of 7α,11α-dihydroxyergosta-8,22-dien-3β-yl acetate (300 mg.) in glacial acetic acid (35 c.c.) was treated dropwise over 15 minutes with 1.125 N chromic anhydride solution in acetic acid (8 c.c., 4 mols.) with external ice-cooling. Stirring was continued for a further 15 minutes and the mixture left at room temperature overnight. The excess chromic anhydride was destroyed with methanol and the mixture treated with water and extracted with ether. The ether extract was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the ether removed under reduced pressure to give a brown gum (250 mg.). (Heusser et al have isolated 8α,9α-epoxy-7-oxoergost-22-en-3β-yl acetate and 7,11-dioxoergosta-8,22-dien-3β-yl acetate, from this gum by chromatography).

A solution of the gum (250 mg.) in glacial acetic acid (25 c.c.) was treated with zinc dust (250 mg.) added at room temperature with stirring. The mixture was heated to 100° with constant stirring and more zinc dust (500 mg.) added over 30 minutes. The mixture was left to cool overnight after which the zinc was filtered, the filtrate treated with water and extracted with ether.

The extract was washed with saturated sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the ether removed under reduced pressure to leave a colourless gum (175 mg.). A solution of this gum in benzene (30 c.c.) was filtered through a column of alumina (6 x 2 cm.). Continued elution with benzene (250 c.c.) gave 7,11-dioxoergost-22-en-3β-yl acetate (40 mg.) which crystallised from methanol as fine needles,

m.p. 196 - 198°, $[\alpha]_D$ - 31° (c, 0.5).

Light absorption, maximum at 2900Å (ε, 110).

Found.	C, 76.4;	H, 10.0
Calc. for $C_{30}H_{42}O_4$,	C, 76.55;	H, 9.85%

It gives a faint yellow colour with tetranitromethane in chloroform.

Heusser et al (loc.cit.) give m.p. 195.5-196 $[\alpha]_D$ -27°.

11-Oxoergosta-8,22-dien-3β-yl Acetate.
[cf. Heusser et al (30)].

A solution of 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (500 mg.) in dry benzene (20 c.c.) was treated with redistilled boron trifluoride etherate complex (20 drops) and the solution kept at room temperature for 70 hours. The solution was diluted with ether (50 c.c.), washed successively with water, saturated sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). The solvent was removed under reduced pressure. Crystallisation of the residue from methanol gave 11-oxoergosta-8,22-dien-3β-yl acetate (350 mg.) as needles.

m.p. 130 - 132° $[\alpha]_D$ + 105.5° (c, 1.16)

Light absorption, maximum at 2550Å (ε = 9,500).

Found: C, 78.8; H, 10.3

Calc. for $C_{30}H_{46}O_3$: C, 79.2; H, 10.2%

It shows a pale yellow colour with tetranitromethane in chloroform.

Heusser et al. (loc. cit.) give m.p. 122-123° $[\alpha]_D$ + 92° for this compound.

Hydrogenation of 11-Oxoergosta-8,22-dien-3β-yl acetate.

A solution of 11-oxoergosta-8,22-dien-3β-yl acetate (112 mg.) in stabilised glacial acetic acid (200 c.c.) was shaken with pre-reduced platinum oxide catalyst in an atmosphere of hydrogen for 2 hours. The filtered solution was concentrated in vacuo to 20-30 c.c., treated with water and extracted with ether. The extract was washed successively with water, sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the ether removed under reduced pressure. Crystallisation of the solid residue from methanol gave ergost-8(14)-en-3β-yl acetate (α-ergostenyl acetate) (50 m.g.) as plates

m.p. 110-111°, $[\alpha]_D$ - 4° (c, 0.5)

Light absorption: ε_{2100} = 8,600.

Found: C, 80.71; H, 11.4

Calc. for $C_{30}H_{50}O_2$: C, 81.4; H, 11.4%

The compound was undepressed in m.p. on admixture with an authentic specimen.

Treatment of 11-oxoergosta-8,22-dien-3β-yl acetate with Lithium Aluminium Hydride and Boron Trifluoride.

(a) Lithium Aluminium hydride (1 g.) was placed in the cone of a Soxhlet extractor and extracted with dry ether (80 c.c.) Into this solution

was added dropwise over 10 minutes a solution of 11-oxoergosta-8,22-dien-3β-yl acetate (500 mg.) in ether (20 c.c.). The mixture was allowed to stand for a further 10 minutes after which water (10 c.c.) was added slowly to decompose the excess lithium aluminium hydride. The lithium-aluminium complex which formed was decomposed with dilute sulphuric acid (10 c.c.; 10%). The ethereal solution was washed with water, twice with saturated sodium hydrogen carbonate solution, and twice with water, dried (Na_2SO_4) and the ether removed under reduced pressure. A white solid A (450 mg.) was obtained m.p. 140-160°.

Light absorption: maxima at 2360 (ε = 8,700), 2430 (ε = 10,000) and an inflection at 2520 Å (ε = 7,400).

Chromatography of the solid A did not give a homogeneous product. Elution with benzene - 5% methanol gave a solid which had a light absorption spectrum: max. at 2360 (ε = 6,100) 242 (ε = 6,850) and an inflexion at 2500Å (ε = 4,550).

(b) The solid was dissolved in benzene (75 c.c.) and treated with redistilled boron trifluoride etherate complex (15 drops) and kept at room temperature for 70 hours. The reaction mixture which coloured considerably during this time, was diluted with ether, washed successively with water, sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The gummy residue obtained was treated in pyridine (4 c.c.) with acetic anhydride (4 c.c.) at 100° for 2 hours. The product isolated in the usual manner was dissolved in benzene (50 c.c.) and the solution filtered through a column of alumina (5 x 2 cm.). Elution with benzene (200 c.c.) gave a gum (30 mg.) which crystallised from methanol as plates of ergosteryl-B, acetate.

m.p. 138-140°, $[\alpha]_D$ - 56° (c, 1.2).

Light absorption: maximum at 2500Å (ε = 17,000).

Found: C, 81.6; H, 11.0

Calc. for $C_{30}H_{46}O_2$ C, 82.1; H, 10.6%

It shows a red brown colour with tetranitromethane in chloroform.

(c) When the solid A described above was dissolved in benzene (50 c.c.) and treated with redistilled boron trifluoride (5 drops) at room temperature for 10 minutes, and worked up as in (b) but not acetylated, white residual solid (400 mg.) was obtained which on crystallisation from acetone gave ergosterol-D as needles.

m.p. 165-167° $[\alpha]_D$ + 30° (c, 1.5)

Light absorption: maxima at 2360 (ε = 16,200), 2420 (ε = 18,500) and an inflection at 2510Å (ε = 12,500).

Found: C, 82.9; H, 11.4

Calc. for $C_{28}H_{44}O_2 \frac{1}{2}CH_3OH$ C, 83.0; H, 11.2%

Ergosterol-D gives a brown colour with tetranitromethane in chloroform.

22:23-Dibromo-11-oxoergost-8-en-3β-yl Acetate.
[cf. Budziarek et al(39)]

(a) A solution of 22:23-Dibromo-8α,11α-epoxyergost-7-en-3β-yl acetate (500 mg.) in benzene (50 c.c.) was treated with redistilled boron trifluoride etherate (40 drops) and kept at room temperature for 72 hours. The solution was diluted with ether (50 c.c.) and washed successively with water, sodium hydrogen carbonate solution, water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue crystallised from methanol-chloroform to give 22:23-dibromo-11-oxoergost-8-en-3β-yl acetate (300 mg.) as elongated plates.

m.p. 201-202° $[\alpha]_D$ + 96° (c, 1.0)

Light absorption: maximum at 2530Å (ε = 9,500)

Found: C, 58.8 ; H, 7.7

Calc. for $C_{30}H_{46}O_3Br_2$ C, 58.6; H, 7.55%

It gives no coloration with tetranitromethane in chloroform.

Budziarek et al give 201-202°, $[\alpha]_D$ + 98°.

(b) A solution of 11-oxoergosta-8,22-dien-3β-yl acetate (100 gm.) in chloroform (10 c.c.) was treated with a solution of bromine (1 mol.) in chloroform (5 c.c.), added dropwise during 20 minutes with stirring at 0°. The colourless solution was kept overnight at -4° diluted with chloroform (50 c.c.) washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the solvent removed under reduced pressure. A solution of the residue in light petroleum (b.p. 60-80°) - benzene (7:3; 50 c.c.) was filtered through a column of activated alumina (2 x 10 cm.) Elution of the column with the same solvent gave a fraction m.p. 194-195° (50 mg.) which crystallised from methanol chloroform to give 22,23-dibromo-11-oxoergost-8-en-3β-yl acetate as blades,

m.p. 200-201°, $[\alpha]_D$ + 99° (c, 1.0)

Light absorption: Maximum at 2530Å (ε = 9,000).

Found: C, 58.4; H, 7.6

$C_{30}H_{46}O_3Br_2$ requires: C, 58.6; H, 7.55%

A mixture with a specimen described under (a) had m.p. 200-201°.

Treatment of 22,23-dibromo-11-oxoergost-8-en-3β-yl Acetate with Raney nickel-cyclohexanol/toluene.

Preparation of Raney nickel catalyst. Raney nickel was prepared by the method of Mozingo(103) and after the exhaustive washing the water was decanted and toluene added. The toluene was then distilled until no further water was removed. The catalyst was stored under toluene.

A solution of 22,23-dibromo-11-oxoergost-8-en-3β-yl acetate (640 mg.) in toluene (20 c.c.) and cyclohexanol (10 c.c.) was refluxed for 22 hours with Raney nickel catalyst (3 g.). The cooled solution was then filtered, concentrated to about 5 c.c., treated with water and extracted with ether. The ethereal extract was washed 3 times with water, dried (Na_2SO_4) and the solvent removed in vacuo (1 mm., 100°). Six crystallisation from methanol gave 11-oxoergosta-8,22-dien-3β-yl acetate (330 mg.) as flat needles.

m.p. 130-131° $[\alpha]_D$ + 107.5° (c, 1.2).

Light absorption: maximum at 2550Å (ε = 8,200).

Found: C, 79.0; H, 10.5

Calc. for $C_{30}H_{46}O_3$: C, 79.2; H, 10.2%

It did not depress in m.p. when mixed with an authentic specimen.

Concentration of the methanol mother liquors followed by chromatography of the residue on alumina did not yield any other homogeneous product.

Bromination of 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate

A solution of 9α,11α-epoxyergosta-7,22-dien-3β-yl acetate (500 mg.) in chloroform (20 c.c.) was treated dropwise with a solution of

bromine (1 mol.) in chloroform during 20 minutes at -4°. The solution was kept overnight at -5°. Chloroform was removed under reduced pressure at room temperature. The residue was separated into an acetone soluble fraction A (200 mg.) and an acetone insoluble fraction (250 mg.) which was collected and washed with methanol. This proved to be 22:23-dibromo-7α:11α-dihydroxyergost-8-en-3β-yl acetate m.p. 204-205°.

The acetone soluble fraction A (after removal of acetone) was dissolved in ether-ethanol (1:1, 60 c.c.) and refluxed with zinc dust for 2 hours. The filtered solution was concentrated, treated with water and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and the ether removed under reduced pressure. Crystallisation from methanol gave an amorphus solid (120 mg.) m.p. 185-186°. This solid was dissolved in light petroleum (b.p. 60-80°) - benzene (1:1; 50 c.c.) and filtered through a column of alumina (10 x 2 cm.). Elution with benzene (150 c.c.) gave 7-oxoergost-8-en-3β-yl acetate (100 mg.) which crystallised from methanol as plates,

m.p. 208-209°, $[\alpha]_D$ - 57° (c, 1.0)

Light absorption : Maximum at 2540Å (ε = 10,000)

Found: C, 79.1; H, 10.2

Calc. for $C_{30}H_{46}O_3$; C, 79.2; H, 10.2%.

It was undepressed in m.p. on admixture with a specimen prepared by the method of Budziarek, Johnson and Spring(39) who give m.p. 209-211° $[\alpha]_D$ -56°.

II. The Stereochemistry of $\Delta^{9(11)}$-7-Keto and Δ^{7}-11-Keto-steroids and some of their Derivatives.

7ξ,11ξ,22,23-Tetrabromoergost-8-en-3β-yl Acetate. [cf. Anderson et al(38)]

A solution of 5-dihydroergosteryl acetate (10g.) in dry ether (1,000 c.c.) was cooled to -20°. Bromine (5.1 c.c.) in glacial acetic acid (20 c.c.) was quickly added and the mixture cooled rapidly to -60° with shaking. The mixture was allowed to regain room temperature over 2 hours and the solid (9.1g) which separated was filtered, washed with ether and dried under reduced pressure. This tetrabromo compound decomposes on storage and its solutions in chloroform, acetone or acetic acid decompose with evolution of hydrogen bromide. It crystallises from benzene-light petroleum as felted needles,

m.p. 128°, $[\alpha]_D$ + 230° (c, 1.0 in benzene)

Anderson et al. give m.p. 128° $[\alpha]_D$ + 260° (in benzene)

Ergosteryl-D-acetate 22,23-dibromide. [cf. Anderson et al (38)]

A solution of tetrabromoergostenyl acetate (26 g.) in slightly warm benzene (1400 c.c.) was shaken with a solution of sodium iodide (100 g.) in ethanol (1200 c.c.). Iodine was immediately liberated. The reaction mixture was kept at room temperature for 20 hours, after which it was washed with aqueous sodium thiosulphate solution (10%) until the iodine colour disappeared. The benzene layer was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to 200-300 c.c., and passed down a short column of alumina (20 x 4 cm.). Elution with benzene (500 c.c.) gave ergosteryl-D-acetate 22,23-dibromide (14.1 g.) which

crystallised from chloroform-methanol as prismatic needles

m.p. 230-232° $[\alpha]_D$ + 30° (c, 1.4).

Light absorption: maxima at 2350 (ε =19,000), 2420 (ε = 21,000) and inflection at 2500Å (ε = 13,000).

Found: C, 60.2; H, 7.7.

Calc. for $C_{30}H_{46}O_2Br_2$: C, 60.2; H, 7.75%

It gives a brown colour with tetranitromethane in chloroform.

Anderson et al give m.p. 233-234° $[\alpha]_D$ + 32°.

22:23-Dibromo-9α:11α-epoxyergost-7-en-3β-yl Acetate
[cf. Budziarek et al (39)]

A solution of ergosteryl-D-acetate 22:23-dibromide (14 g.) in chloroform (300 c.c.) was treated dropwise with perbenzoic acid (1.2 mols) in chloroform with stirring and cooling in ice during 5 hours. The mixture was kept at 0° for 12 hours. The solution was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the chloroform removed under reduced pressure (temperature below 35°). Crystallisation from acetone gave 22:23-dibromo-9α:11α-epoxyergost-7-en-3β-yl acetate (8.5 g.) as needles

m.p. 216°, $[\alpha]_D$ − 26° (c, 1.0)

The compound did not absorb light selectively above 2200Å.

Budziarek et al gave m.p. 218° $[\alpha]_D$ - 26°.

22,23-Dibromo-7α,11α-dihydroxyergost-8-en-3β-yl Acetate. [cf. Budziarek et al (39)]

A solution of 22,23-dibromo-9α,11α-epoxyergost-7-en-3β-yl acetate (20 g.) in tetrahydrofuran (100-105 c.c.) was treated with aqueous sulphuric acid (2 N; 6 c.c.) added in one portion with shaking. The solution was kept at room temperature for 4 hours. The crystalline solid which separated was collected and washed well with methanol, to give 22,23-dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (16.5 g.) as a microcrystalline solid, m.p. 207-210° which is very imsoluble in most organic solvents.

22,23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate.

A suspension of 22,23-dibromo-7α,11α-dihydroxyergost-8-en-3β-yl acetate (500 mg.) in benzene (100 c.c.) was shaken with boron trifluoride-ether complex (1 c.c.). After 12 minutes dissolution was complete; the mixture was diluted with ether and washed with sodium hydrogen carbonate solution, water, dried (Na_2SO_4) and the solvent removed under reduced pressure. Twelve crystallisations of the residue from acetone yielded 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (25 mg.) as needles,

m.p. 200-203°, $[\alpha]_D$ - 118° (c, 0.5)

Found: C, 58.9; H, 7.85.

$C_{30}H_{46}O_3Br_2$ requires C, 58.6; H, 7.55%

It does not show selective absorption of high intensity above 2200Å.

22:23-Dibromo-7-oxoergost-9(11)-en-3β-yl acetate.

The combined mother liquors from the first eight crystallisations of the foregoing compound were concentrated. A crop of plates (400 mg. was obtained which was recrystallised twice more from acetone to give 22:23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate as rhombic plates,

m.p. 231-233° $[\alpha]_D$ − 36°, -34° (c, 2.2, 1.8).

Found: C, 58.85; H, 7.7

$C_{30}H_{46}O_3Br_2$ requires C, 58.6; H, 7.55%

It gives a pale yellow colour with tetranitromethane in chloroform and does not show selective absorption of high intensity above 2200Å.

22:23-Dibromo-11-oxoergost-8-en-3β-yl acetate.

(a) A solution of 22:23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (100 mg.) in benzene (25 c.c.) was filtered through a column of alumina (2 x 8 cm.). Elution with benzene (300 c.c.) gave 22:23-dibromo-11-oxoergost-8-en-3β-yl acetate (70 mg.) which separated from methanol as elongated plates,

m.p. 200-201°, $[\alpha]_D$ + 98°

Light absorption: Maximum at 2530Å (ε = 9,000)

It does not give a colour with tetranitromethane in chloroform and a mixture with a specimen prepared according to Budziarek, Johnson and Spring(39) was undepressed in m.p.

(b) A suspension of 22:23-dibromo-7α-11α-dihydroxyergost-8-en-3β-yl acetate in benzene was treated with boron trifluoride etherate as described. A solution of the product in light petroleum (b.p. 60-80°) - benzene, (4:1; 50 c.c.) was filtered through alumina (2 x 15 cm.). Elution with benzene

(350 c.c.) gave a fraction (100 mg.) which, after five recrystallisations from methanol gave 22:23-dibromo-11-oxoergost-8-en-3β-yl acetate as elongated plates,

m.p. 200-203°, $[\alpha]_D$ + 96° (c, 1.0)

Light absorption: maximum at 2540Å (ε = 9,000).

Found: C, 58.8; H, 7.7

Calc. for $C_{30}H_{46}O_3Br_2$: C, 58.6; H, 7.55%

It does not give a colour with tetranitromethane in chloroform and was undepressed in m.p. on admixture with an authentic specimen.

22:23-dibromo-7-oxoergost-8-en-3β-yl acetate.

(a) Continued washing of the column described in (b) above with ether (300 c.c.) gave a fraction (260 mg.) which crystallised from methanol-chloroform to give 22:23-dibromo-7-oxoergost-8-en-3β-yl acetate as plates,

m.p. 240-242°, $[\alpha]_D$ - 29° (c, 0.5).

Light absorption: Maximum at 2530Å (ε = 9,000).

Found: C, 58.8; H, 7.6.

Calc.for $C_{30}H_{46}O_3Br_2$: C, 58.6; H, 7.55%

It does not give a colour with tetranitromethane in chloroform. It is undepressed in m.p. when mixed with a specimen m.p. 240-242° $[\alpha]_D$ -28°, prepared as described by Budziarek, Johnson and Spring (39).

(b) A solution of 22:23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (170 mg.) in 2% aqueous methanolic potassium hydroxide (50 c.c.) was heated under reflux for 2 hours. The cooled solution was diluted with water and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and the ether removed under reduced pressure. The residue was acetylated with pyridine and acetic anhydride on the steam bath at 100° for 3 hours. Isolation

of the product by means of ether and crystallisation from chloroform-methanol gave 22:23-dibromo-7-oxoergost-8-en-3β-yl acetate (150 mg.)

m.p. 239-241°, $[\alpha]_D$ - 28° (c, 2.0).

Undepressed in m.p. when mixed with the specimen described above.

Light absorption: maximum at 2520Å (ε = 9,250).

11-Oxo-9β-ergosta-7:22-dien-3β-yl acetate.

A solution of 22:23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (1 g.) in benzene-ethanol (1:1; 200 c.c.) was heated under reflux for 3½ hours with zinc dust (3 g.) added portion wise. The filtered solution was treated with water and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and the ether removed under reduced pressure. The residu was crystallised from acetone to give 11-oxo-9β-ergosta-7:22-dien-3β-yl acetate (600 mg.) as hexagonal plates,

m.p. 159-161°, $[\alpha]_D$ - 206° (c, 2.55)

Found: C, 79.5; 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 and does not show selective absorption of high intensity above 2200Å.

Bladon et al (54) gave m.p. 159-161°, $[\alpha]_D$ - 191°.

7-Oxoergosta-9(11),22-dien-3β-yl acetate .

A solution of 22,23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (500 mg.) in ethanol-ether (1:1; 50 c.c.) was heated under reflux for 3 hours with zinc dust (2 g.) added portionwise. Treatment of the filtered solution with water, followed by extraction with ether and washing the extract with water, drying (Na_2SO_4) and removal of the ether under reduced pressure gave 7-oxoergosta-9(11),22-dien-3β-yl acetate(300 mg.) which crystallised from aceton as plates,

m.p. 177-178°, $[\alpha]_D$ - 55° (c, 1.3)

Found: C, 79.4; H, 10.2%

Calc. for $C_{30}H_{46}O_3$; C, 79.2; H, 10.2%

It gives a pale yellow colour with tetranitromethane in chloroform and does not show selective light absorption of high intensity above 2200Å.

Heusser et al (31) give m.p. 176-177° $[\alpha]_D$ - 58°, and Schvenewaldt et al (33) give m.p. 176-177° $[\alpha]_D$ - 43.5°.

7-oxo-8α-ergosta-9(11),22-dien-3β-yl acetate.
[cf. Budziarek et al (65)]

A mixture of ergosteryl-D acetate (2.2g) in benzene (20 c.c.) formic acid (20 c.c.; 90%), and hydrogen peroxide (0.65 c.c.; 30%) was stirred for 20 hours at 15°. The reaction mixture was evaporated under reduced pressure below 50° (bath temperature), and the residue crystallised from methanol to give flat needles of m.p. 170-175°, and giving a red brown colour with tetranitro methane in chloroform.

Light absorption: maxima at 2360 (ε = 3,900), 2440 (ε = 4,800) and an inflection at 2520Å (ε = 3,500).

Concentration of the methanol mother liquors gave an amorphos solid which crystallised from methanol to give 7-oxo-8α-ergosta-9(11),22-dien-3β-yl acetate as needles,

m.p. 194-196° $[\alpha]_D$ + 18° (c, 0.5).

Light absorption: ε_{2120} = 5,400 and showing no selective absorption of high intensity above 2200Å.

Infra-red spectrum: Peaks at 1740 and 1235 (acetate) and at 1715 cm^{-1} (saturated carbonyl).

Found: C, 78.9; H, 10.2.

Calc. for $C_{30}H_{46}O_3$; C, 79.2; H, 10.2%.

3β-Hydroxyergosta-8,22-dien-7-one.

(a) A solution of 7-oxoergosta-9(11),22-dien-3β-yl acetate (300 mg.) in 3% aqueous methanolic potassium hydroxide (50 c.c.) was heated under reflux for 2 hours. Treatment of this solution with water, extraction with ether, washing the extract with water, drying (Na_2SO_4) and removal of the ether under reduced pressure gave 3β-hydroxyergosta-8,22-dien-7-one, which crystallised from methanol as plates (200 mg.),

m.p. 175-177°, $[\alpha]_D$ - 45° (c, 1·0)

Light absorption: maximum at 2560Å (ε = 9,000).

Found: C, 81.4; H, 10.7

Calc. for $C_{28}H_{44}O_2$; C, 81.5; H, 10.75%

It gives a pale yellow colour with tetranitromethane in chloroform and was undepressed in m.p. when mixed with a specimen prepared as described by Schoenewaldt et al (33).

(b) A solution of 7-oxo-8α-ergosta-9(11),22-dien-3β-yl acetate (150 mg.) was refluxed with 3% aqueous methanolic potassium hydroxide as described above in (a). Crystallisation of the product from methanol gave 3β-hydroxyergosta-8,22-dien-7-one (100 mg.) as plates,

m.p. 176-177°, $[\alpha]_D$ - 43° (c, 1·2)

Light absorption: maximum at 2540Å (ε = 10,000)

The compound was undepressed in m.p. on admixture with a specimen prepared as described in (a) above.

Attempted isomerisation of 7-Oxo-8α-ergosta-9(11),22-3β-yl acetate.

[cf. Budziarek and Spring (77) for isomerisation of 7,11-dioxo-8α-ergost-22-en-3β-yl acetate].

(a) A solution of 7-oxo-8α-ergosta-9(11),22-dien-3β-yl acetate (150 mg.) in glacial acetic acid (10 c.c.) was heated on the steam bath for one hour. Treatment of the mixture with water, followed by extraction with ether, washing the extract with water, with sodium hydrogen carbonate solution and with water, drying (Na_2SO_4) and removal of the ether under reduced pressure gave a highly coloured gum which could not be crystallised.

(b) A solution of 7-oxo-8α-ergosta-9(11),22-dien-3β-yl acetate (150 mg.) in glacial acetic acid (10 c.c.) was left overnight at room temperature. Isolation of the product by means of ether as described above did not give a homogeneous product.

22,23-Dibromo-9α,11α-epoxy-7-oxoergostan-3β-yl Acetate

A stirred solution of 22,23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (4.35 g.) in chloroform (50 c.c.) was treated dropwise with

perbenzoic acid (1.1 mols.) in chloroform (14 c.c.) during 3 hours at 0°. The solution was kept at 0° overnight, and then washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4) and the chloroform removed under reduced pressure below 35°. Crystallisation of the residue from methanol-chloroform gave 22,23-dibromo-9α,11α-epoxy-7-oxoergostan-3β-yl acetate as plates (3.3 g.)

m.p. 228-230°, $[\alpha]_D$ - 44° (C, 2.5).

Two crystallisations from acetone gave elongated needles,

m.p. 222-224°, $[\alpha]_D$ - 44°

Found: C, 57.2; H, 7.4

Calc. for $C_{30}H_{46}O_4Br_2$: C, 57.1; H, 7.35%

It does not show selective absorption of high intensity above 2200Å. On admixture with a specimen (m.p. 222-224°, $[\alpha]_D$ - 49°) prepared according to Anderson et al (38) it was undepressed in m.p.

Attempted Acid Rearrangements of 22,23-dibromo-9α,11α-epoxy-7-oxo-ergostan-3β-yl acetate.

(a) With Boron trifluoride-ether complex.

A solution of 22,23-dibromo-9α,11α-epoxy-7-oxoergostan-3β-yl acetate (400 mg.) in benzene-ether (1:1; 50 c.c.) was treated with boron trifluoride-ether complex (15 drops) in acetic acid (2 c.c.) and allowed to stand for 3 days at room temperature. The solution was diluted with ether (30 c.c.) washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the solvent removed under reduced pressure. Crystallisation from acetone gave elongated needles (370 mg.) m.p. 222-224° $[\alpha]_D$ - 48° (C, 2.1) alone and mixed with starting material.

(b) With Hydrogen Bromide in Acetic acid.

A solution of 22,23-dibromo-9α,11α-epoxy-7-oxoergostan-3β-yl acetate (450 mg.) in acetic acid-chloroform (2:1; 50 c.c.) was treated with hydrogen bromide solution in water (2 c.c.; 48%) and kept at room temperature overnight. The solution was concentrated, treated with water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. Crystallisation of the residue from acetone gave elongated needles $[\alpha]_D$ - 48° (C, 2.0), m.p. 221-222° alone and when mixed with starting material.

III. The Stereochemistry of 9α,11α-dihydroxy-7-oxoergost-22-en-3β-yl acetate.

3β,11α-Diacetoxy-22,23-dibromo-9α-hydroxyergostan-7-one.

A solution of 22,23-dibromo-7-oxoergost-9(11)-en-3β-yl acetate (1.0g.) in ether-benzene (4,1 ; 50 c.c.) and pyridine (0.74 c.c.) was treated with osmium tetroxide (1.0g.); a brown colour rapidly developed. After 5 days at room temperature, the mixture was evaporated under reduced pressure and the residue refluxed for 5 hours with a solution of sodium sulphite (5g.) in aqueous ethanol (100 c.c., 50%). The mixture was concentrated under reduced pressure, acidified (Congo-red) with dilute hydrochloric acid, and extracted with ether (2 x 150 c.c.) and then with chloroform (2 x 150 c.c.). The washed and dried (Na_2SO_4) chloroform extract was evaporated under reduced pressure and the residue was treated with acetic anhydride and pyridine at room temperature overnight. The acetylated product was isolated by means of ether and crystallised from chloroform-methanol to give 3β,11α-diacetoxy-22,23-dibromo-9α-hydroxyergostan-7-one (550 mg.) as needles,

m.p. 247-250°, $[\alpha]_D$ - 27° (c, 1.0)

Found: C, 55.95; H, 7.4

Calc. for $C_{32}H_{50}O_6Br_2$; C, 55.65; H, 7.3%

The substance showed no high intensity light absorption above 2200Å and gave no colour with tetranitromethane in chloroform. Budziarek, Hamlet and Spring (79) give m,p. 259-260° $[\alpha]_D$ - 29°, - 27°. A mixture of the above compound with a specimen prepared according to Budziarek et al did not depress in m.p. The m.p. of the substance is dependent on the rate of heating.

The material extracted by means of ether was acetylated with acetic anhydride and pyridine at room temperature overnight. The acetylated product, isolated by means of ether, was purified by chromatography on alumina to give 3β,11α-diacetoxy-22,23-dibromo-9α-hydroxyergostan-7-one (300 mg.) as needles from chloroform-methanol

$[\alpha]_D$ - 27° m.p. 247-249° alone or mixed with the above specimen.

Found: C, 55.9; H, 7.5

Calc. for $C_{32}H_{50}O_6Br_2$: C, 55.65; H, 7.3%

3β,11α-Diacetoxy-9α-hydroxyergost-22-en-7-one.

A solution of 3β,11α-diacetoxy-22,23-dibromo-9α-hydroxy-ergostan-7-one (200 mg.) in methanol-benzene (1:1; 50 c.c.) was refluxed with zinc dust (3.0 g.) added portionwise over 4 hours. The filtered solution was concentrated, treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated under reduced pressure. Crystallisation of the residue from aqueous acetone gave 3β,11α-diacetoxy-9α-hydroxyergost-22-en 7-one- (120 mg.) as needles

m.p. 193-195°, $[\alpha]_D$ -46° (c, 1.0)

Found: C, 72.6; H, 9.8

Calc. for $C_{32}H_{50}O_6$; C, 72.4; H, 9.5%

The substance showed no selective light absorption of high intensity above 2200Å. It did not depress in m.p. when mixed with a specimen (m.p. 194-196°) prepared by Budziarek, Hamlet and Spring (loc. cit.)

IV. Bromination of 22,23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl Acetate.

Ergost-8(14)-en-3β-yl Acetate (α-ergostenyl Acetate).

A solution of 11-oxoergosta-7,22-dien-3β-yl acetate (150 mg.) in acetic acid (100 c.c.) was shaken in an atmosphere of hydrogen for 1 hour with Platinum (from 60 mg. PtO_2). The filtered acetic acid solution was concentrated, treated with water and extracted with ether. The extract was washed successively with sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the ether removed under reduced pressure. Crystallisation of the residue from methanol gave ergost-8(14)-en-3β-yl acetate as plates,

m.p. 107-109°, $[\alpha]_D$ + 3° (c, 1.4)

Found: C, 81.6; H, 11.4

Calc. for $C_{30}H_{50}O_2$: C, 81.4; H, 11.4%

The m.p. of a mixture with an authentic specimen m.p. 109-110° $[\alpha]_D$ + 4° (c, 2.0) was undepressed.

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 an atmosphere of hydrogen for 24 hours with Platinum (from 60 mg. PtO_2). The filtered solution was evaporated to dryness and the residue crystallised from methanol to give 11-oxoergost-7-en-3β-yl acetate (160 mg.) as needles,

m.p. 162-164°, $[\alpha]_D$ + 48°, + 47° (c, 1.1; 1.5)

Light absorption: $\varepsilon_{2050} = 3,500$.

Found: C, 79.15; H, 10.8

$C_{30}H_{48}O_3$ requires: C, 78.9 ; H, 10.6%

For a crude (not analysed) specimen of this compound, Bladon et al (54) give m.p. 145-156°, $[\alpha]_D$ + 32°

7β,22,23-Tribromo-11-oxoergost-8-en-3β-yl Acetate.

A solution of 22,23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (1.0g.) in dry ether (200 c.c.) was treated with a solution of bromine in glacial acetic acid (7.8 c.c. ; 0.0316 gm./c.c.) added dropwise with stirring at 15°. After standing for 10 minutes, the colourless solution was washed with 1% sodium hydroxide solution, water, and dried (Na_2SO_4). Crystallisation of the product from chloroform-methanol gave 7β,22,23-tribromo-11-oxoergost-8-en-3β-yl acetate (300 mg.) as plates,

m.p. 198-199° (decomp.) $[\alpha]_D$ + 78° (c, 1.0)

Light absorption: maximum at 2620Å (ε = 9,500).

Found:	C, 51.8;	H, 6.7.
$C_{30}H_{45}O_3Br_2$ requires:	C, 52.0;	H, 6.5%

11-Oxoergosta-7,22-dien-3β-yl Acetate.

A solution of 7β,22,23-tribromo-11-oxoergost-8-en-3β-yl acetate (490 mg.) in methanol-ether (70 c.c.; 1:1) was refluxed with activated zinc (2 g.) added in portions over three hours. The filtered solution was concentrated, treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue crystallised from methanol to give 11-oxoergosta-7,22-dien-3β-yl acetate as plates,

m.p. 175-177°, $[\alpha]_D$ + 30° (c, 1.1).

Light absorption: ε_{2040} = 3,400

Found:	C, 79.15;	H, 10.4
Calc. for $C_{30}H_{46}O_3$;	C, 79.2;	H, 10.2%

It gives a pale yellow colour with tetranitromethane in chloroform. Bladon et al

(54) gives m.p. 175-180° $[\alpha]_D$ + 25° for a specimen obtained by filtration of the 9β-epimer through alumina.

22:23-Dibromo-11-oxoergosta-8:14-dien-3β-yl acetate.

A solution of 7β:22:23-tribromo-11-oxoergost-8-en-3β-yl acetate (120 mg.) in 3% aqueous methanolic potassium hydroxide (40 c.c.) was refluxed for 2 hours. The solution was treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue acetylated with acetic anhydride and pyridine at room temperature. The product isolated in the usual manner by means of ether was crystallised from methanol to give plates (40 mg.) m.p. 196-200°. This was dissolved in benzene (10 c.c.) and filtered through a short column of alumina (4 x 2 cm.). Elution with benzene (100 c.c.) gave a white solid (30 mg.) which was crystallis from methanol to give 22:23-dibromo-11-oxoergosta-8:14-dien-3β-yl acetate as plates,

m.p. 214-215° $[\alpha]_D$ + 38° (c, 1.5)

Light absorption: maxima at 2140 (ε = 11,000) and at 2920Å (ε = 12,500).

Found:	C, 58.9;	H, 7.35
$C_{30}H_{44}O_3Br_2$ requires:	C, 58.8;	H, 7.2%

V. The Structure and Reactions of 22,23-Dibromo-7α,8α-epoxy-11-oxoergostan-3β-yl Acetate.

22,23-Dibromo-11-oxo-9β-ergost-7-en-3β-yl Acetate. [cf. Elks, Evans et al (54)]

A solution of 22,23-dibromo-8α,11α-epoxyergost-7-en-3β-yl acetate (10g.) in dry ether (500 c.c.) was treated with freshly distilled boron trifluoride-ether complex (2 c.c., 1 mol.). The solution was kept at 0° for 18 hours. A crystalline solid which separated was collected, washed well with methanol and recrystallised from acetone from which 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate separated as prismatic needles,

m.p. 200°, $[\alpha]_D$ - 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%

It did not absorb light selectively with high intensity above 2200Å. The compound was underpressed in m.p. when mixed with a specimen prepared by Maclean and Spring(67).

22,23-Dibromo-11-oxoergost-7-en-3β-yl Acetate.

The alumina used in this experiment was prepared as follows:- Spence 'Type H' alumina (1 kg.) was stirred for 3 hours with aqueous acetic acid (1.5 l; 10%), filtered, washed with distilled water (2 l.), methanol (2 l.) and distilled water (2 l.) and then reactivated by heating at 400° for 5 hours.

A solution of 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (700 mg.) in light petroleum (b.p. 60-80°) - benzene (1:1; 70 c.c.) was adsorbed rapidly under pressure on an alumina column (10 x 1.5 cm.). The column was immediately eluted with benzene (100 c.c.) containing pyridine

(1 c.c.) again under pressure; these operations took 5 minutes. Evaporation of the filtrate under reduced pressure and crystallisation of the residue from chloroform-methanol gave 22,23-dibromo-11-oxoergost-7-en-3β-yl acetate (620 mg.) as felted needles,

m.p. 189 - 190°, $[\alpha]_D$ + 29° (c, 0.4)

Light absorption: ε_{2060} = 1550

Found: C, 58.7; H, 7.55

$C_{30}H_{46}O_3Br_2$ requires: C, 58.6; H, 7.55%

It gives a pale yellow colour with tetranitromethane in chloroform.

11-oxoergosta-8,22-dien-3β-yl Acetate.

A solution of 11-oxoergosta-7,22-dien-3β-yl acetate (150 mg.) in benzene-chloroform (10 c.c. 99:1) was adsorbed on a column of grade II alumina (10 x 2 cm.) and left for 5 days. Elution with benzene (50 c.c.) and crystallisation from methanol gave 11-oxoergosta-8,22-dien-3β-yl acetate (30 mg.) as blades,

m.p. and mixed m.p. 125-127°, $[\alpha]_D$ + 102° (c, 0.5)

Light absorption: maximum at 2530Å (ε = 8,000)

11-Oxo-14β-ergosta-8,22-dien-3β-yl Acetate.

A solution of 11-oxoergosta-7,22-dien-3β-yl acetate (100 mg.) in glacial acetic acid (50 c.c.) was treated with a continuous stream of dry hydrogen chloride gas for 1 hour at room temperature. The solution was treated with water and extracted with ether. The extract was washed successively with sodium hydrogen carbonate solution, and water, dried (Na_2SO_4) and the ether removed under reduced pressure. The residue was treated with

acetic anhydride and pyridine at 100° for 1 hour. The product isolated in the normal manner by means of ether crystallised from aqueous acetone to give 11-oxo-14β-ergosta-8,22-dien-3β-yl acetate as flat needles,

m.p. 111-112.5°, $[\alpha]_D$ + 138.5° (c, 1.2)

Light absorption: maximum at 2480Å (ε = 9,300)

Found: C, 78.8; H, 10.4

$C_{30}H_{46}O_3$ requires: C, 79.2; H, 10.2%

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

A solution of 22,23-dibromo-11-oxoergost-7-en-3β-yl acetate (380 mg.) in chloroform (10 c.c.) at 0° was treated with freshly prepared perbenzoic acid solution in mineral acid-free chloroform, (2.5 c.c.; 2.5 mols.) and the solution kept at 0° for 8 days. The solution was then diluted with chloroform and washed successively with 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 (300 mg.) which was collected and recrystallised from chloroform-methanol as needles,

m.p. 210-212°, $[\alpha]_D$ - 175° (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 2000Å 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 1717cm^{-1} (ketone). No hydroxyl peak was evident.

22,23-Dibromo-7,11-dioxoergostan-3β-yl Acetate.
[This experiment was carried out by Mr. J.Grigor].

A solution of 22,23-dibromo-7α,8α-epoxy-11-oxoergostan-3β-yl acetate (300 mg.) in chloroform (25 c.c.) was treated with glacial acetic acid containing aqueous hydrogen bromide solution (10 drops, 46%) and kept overnight at room temperature. After dilution with water the product was extracted with chloroform. The washed and dried extract was evaporated to dryness and the residue crystallised from chloroform-methanol to give 22,23-dibromo-7,11-dioxoergostan-3β-yl acetate (90 mg.) as fine needles,

m.p. 261-263°, $[\alpha]_D$ -2° (c, 1.3)

Found: C, 56.75; H, 7.5

$C_{30}H_{46}O_4Br_2$ 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 light absorption,

7α,8α-Epoxy-11-oxoergost-22-en-3β-yl Acetate.

A solution of 22,23-dibromo-7α,8α-epoxy-11-oxoergostan-3β-yl acetate (320 mg.) in benzene-methanol (1,1; 50 c.c.) was refluxed for 3 hours with zinc dust (1 g.) added portionwise. The filtered solution was concentrated, treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated under reduced pressure and the residue crystallised from chloroform-methanol to give 7α,8α-epoxy-11-oxoergost-22-en-3β-yl acetate (190 mg.) 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: $\varepsilon_{2040} = 2,100$.

It gives a pale yellow colour with tetranitromethane in chloroform.

22:23-Dibromo-11-oxoergost-8-en-3β:7α-diol.
(with W. Laird).

22:23-Dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (275 mg.) in benzene (6 c.c.) was treated with methanolic potassium hydroxide (50 c.c.; 1%) and the solution kept for 3½ hours at room temperature. The mixture was treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated and the residue crystallised from chloroform-methanol to give 22:23-dibromo-11-oxoergost-8-en-3β:7α-diol (240 mg.) as felted needles,

m.p. 211°, $[\alpha]_D$ + 113°, + 112° (c, 0.6, 0.7).

Light absorption: Maximum at 2500Å (ε = 9,600)

Found: C, 56.0; H, 7.5

$C_{28}H_{44}O_3Br_2 . CH_3OH$ requires: C, 56.1; H, 7.8%.

3β:7α-Diacetoxy-22:23-dibromoergost-8-en-11-one.

Treatment of the above diol with acetic anhydride and pyridine at room temperature and isolation of the product by means of ether gave 3β:7α-diacetoxy-22:23-dibromoergost-8-en-11-one which separated from methanol as prismatic plates

m.p. 212-213°, $[\alpha]_D$ + 104° (c, 1.5)

Light absorption: Maximum at 2460Å (ε = 9,400), ε_{2040} = 2,700.

Found: C, 57.2; H, 7.3

$C_{32}H_{48}O_5Br_2$ requires: C, 57.1; H, 7.2%

3β,7α-Diacetoxyergosta-8,22-dien-11-one.
(With W. Laird).

A solution of 22,23-dibromo-11-oxoergost-8-en-3β,7α-diol diacetate (500 mg.) in ether-methanol (1:1 ; 50 c.c.) was refluxed with zinc dust added portionwise during 3 hours. The filtered solution was treated with water and extracted with ether. The washed and dried extract was evaporated to dryness and the residue crystallised from methanol to give 3β,7α-diacetoxyergosta-8,22-dien-11-one (200 mg.) as fine needles,

m.p. 102-103° $[\alpha]_D$ + 109° (c, 1.0)

Light absorption: Maximum at 2490Å (ε = 8,800); ε_{2040} = 3,800

Found: C, 74.9; H, 9.6.

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

Kenbest and Wagland(63) give m.p. 102-105°, $[\alpha]_D$ + 109°.

22,23-Dibromo-11-oxoergost-8(14)-en-3β,7α-diol.

(a) A solution of 22,23-dibromo-7α,8α-epoxy-11-oxoergostan-3β-yl acetate (320 mg.) in benzene (10 c.c.) and methanolic potassium hydroxide (60 c.c.; 20%) was refluxed for 1½ hours. The concentrated solution was treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated and the residue crystallised from chloroform-methanol to give 22,23-dibromo-11-oxo-ergost-8(14)-en-3β,7α-diol (200 mg.) as needles,

m.p. 202-203°, $[\alpha]_D$ + 33° (c, 0.3 in pyridine.)

Light absorption: ε_{2060} = 3,700.

Found: C, 57.2; H, 7.7

$C_{28}H_{44}O_3Br_2$ requires: C, 57.15; H, 7.5%

(b) Hydrolysis of 22:23-dibromo-11-oxoergost-8-en-3β:7α-diol (140 mg.) with aqueous methanolic potassium hydroxide as in (a) gave 22:23-dibromo-11-oxoergost-8(14)-en-3β:7α-diol (90 mg.), m.p. and mixed m.p. 202-203°, $[\alpha]_D$ + 31° (c, 0.2 in pyridine)

Light absorption: ε_{2060} = 10,200.

3β:7α-Diacetoxy-22:23-dibromoergost-8(14)-en-11-one.

Treatment of the above diol with acetic anhydride and pyridine at room temperature and isolation of the product by means of ether gave 3β:7α-diacetoxy-22:23-dibromoergost-8(14)-en-11-one which separated from methanol as needles,

m.p. 194-195°, $[\alpha]_D$ + 32° (c, 1.4).

Light absorption: ε_{2070} = 8,600

Found: C, 57.4; H, 7.3

$C_{32}H_{48}O_5Br_2$ requires: C, 57.1; H, 7.2%.

11-Oxoergosta-8(14):22-dien-3β:7α-diol.
(with W. Laird).

A solution of 22:23-dibromo-11-oxoergost-8(14)-en-3β:7α-diol (110 mg.) in benzene-methanol (1:1 ; 50 c.c.) was refluxed with zinc dust (2g.) added portionwise during 2½ hours. Isolation of the product by means of ether gave 11-oxoergosta-8(14):22-dien-3β:7α-diol (66 mg.) as needles from aqueous methanol

m.p. 179-181° $[\alpha]_D$ + 8° (c, 0.7)

Light absorption: ε_{2080} = 7,000

Found: C, 78.4; H, 10.4

$C_{28}H_{44}O_3$ requires: C, 78.45; H, 10.35%

22:23-Dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate. (with W. Laird).

A solution of 22:23-dibromo-7α:8α-epoxy-11-oxoergostan-3β-yl acetate (400 mg.) in benzene (10 c.c.) was treated with sulphuric acid (5 c.c.; 2 N) in methanol (50 c.c.) and the mixture refluxed for one hour. Treatment of the solution with water followed by extraction with ether, washing, drying (Na_2SO_4) and evaporation of the extract under reduced pressure gave 22:23-dibromo-7α-hydroxy-11-oxoergost-8-en-3β-yl acetate (130 mg.) as needles

m.p. 216-217° $[\alpha]_D$ + 97° (c, 1.8)

Light absorption: maximum at 2490Å (ε = 9,000); ε_{3030} = 3,1000.

Found:	C, 56.9;	H, 7.1
$C_{30}H_{46}O_4Br_2$ required:	C, 57.1;	H, 7.35%

Acetylation of the alcohol using acetic anhydride and pyridine at 100° gave 3β:7α-diacetoxy-22:23-dibromo ergost-8-en-11-one which separated from methanol as prismatic plates,

m.p. and mixed m.p. 212-213°, $[\alpha]_D$ + 100° (c, 0.8).

VI. The Structure and Reactions of 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 solution of 22,23-dibromo-11-oxo-9β-ergost-7-en-3β-yl acetate (5.9g.) in chloroform (70 c.c.) was treated during 1 hour at 0° with a freshly prepared solution of perbenzoic acid in chloroform (23 c.c., 62.5 mg./c.c. After overnight storage at 0°, the solution was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4) concentrated and diluted with methanol to give a crystalline solid which was recrystallised from methanol chloroform, giving 22,23-dibromo-7β,8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate as needles,

m.p. 218-219°, $[\alpha]_D$ - 29° (c, 0.7)

Found:	C, 52.7;	52.8;	H, 6.9, 7.1	Cl+Br 30.75
Calc. for $C_{30}H_{46}O_4Br_2.\frac{1}{2}CHCl_3$:	C, 53.1;		H, 6.8	Cl, 7.7) Br 23.15%

The solvent of crystallisation was not expelled by heating in vacuo at 100°. The compound gave no colour with tetranitromethane in chloroform and did not absorb light selectively with high inte sity above 2000A.

Infra-red Spectrum: Peaks at 1730 and 1241 (acetate) and 1717 cm^{-1} (ketone).

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.) ether (50 c.c.), and methanol (50 c.c.) was heated under reflux for 5 hours with zinc dust (3 g.) added portionwise. The filtered solution was treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue 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 with tetranitromethane in chloroform and does not exhibit high intensity ultra-violet light absorption. Henbest and Wagland (63) record m.p. 175-177°, $[\alpha]_D$ - 63°, for this compound. Heusler and Wettstein (64) give m.p.170.5-171.5°, $[\alpha]_D$ -74°.

22,23-Dibromo-7,11-dioxoergostan-3β-yl acetate.

22,23-Dibromo-7,11-dioxoergostan-3β-yl acetate.

A solution of 22,23-dibromo-5β,6β-epoxy-11-oxo-5β-ergostan-3β-yl acetate (1 g.) in redistilled ethyl acetate (350 c.c.) was shaken in an atmosphere of hydrogen for 24 hours with pre-reduced platinum catalyst (from 200 mg. PtO_2). A crystalline solid separated which was collected by filtration to give a mixture (A) of platinum and steroid. The ethyl acetate mother liquors were removed under reduced pressure and the residue was crystallized from methanol-chloroform to give 22,23-dibromo-7,11-dioxoergostan-3β-yl acetate (330 mg.) as needles,

m.p. 258-259°, $[\alpha]_D$ - 2° (c, 1.0)

Found: C, 57.4; H, 7.5.

$C_{30}H_{46}O_4Br_2$ requires: C, 57.1; H, 7.35%

The diketone did not give a colour with tetranitromethane in chloroform and did not show high intensity ultra-violet light absorption.

22:23-Dibromo-7β-hydroxy-11-oxoergost-3-en-3β-yl Acetate.

The mixture (A) of platinum and steroid described above was extracted by percolation of hot chloroform through the mixture in a filter funnel. The chloroform extract was evaporated to dryness and the residue crystallised from chloroform-methanol to give 22:23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (185 mg.) as plates,

m.p. 239-241°, $[\alpha]_D$ + 85° (c, 0.3)

Light absorption: maximum at 2540Å (ε = 9,000)

Found: C, 56.85; H, 7.5

$C_{30}H_{46}O_4Br_2$ requires: C, 57.1; H, 7.35%

The compound did not give a colour with tetranitromethane chloroform.

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 (1.19g.) in dioxan (230 c.c.) was treated with sulphuric acid (8 c.c.; 2 N.) and kept at room temperature for 4 hours. The solution was diluted with water, and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue crystallised from methanol. The first crop (40 mg.) which showed high intensity absorption at 2540Å was not further examined. 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).

Light absorption: ε_{2110} = 9,000

Found: C, 57.0; H, 7.6.

$C_{30}H_{46}O_4Br_2$ requires: C, 57.1; H, 7.35%

It gives a pale yellow colour with tetranitromethane in chloroform.

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

3β,7β-Diacetoxy-22,23-dibromo-9β-ergost-8(14)-en-11-one.

Acetylation of 22,23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate with acetic anhydride and pyridine at room temperature and isolation of the product by means of ether gave 3β,7β-diacetoxy-22,23-dibromo-9β-ergost-8(14)-en-11-one which separated from methanol as plates,

m.p. 170-171°, $[\alpha]_D$ + 142° (c, 1.0)

Light absorption: ε_{2100} = 8,400.

Found: C, 57.1; H, 7.5

$C_{32}H_{48}O_5Br_2$ requires: C, 57.1; H, 7.2%

7β-Hydroxy-11-oxo-9β-ergosta-8(14),22-dien-3β-yl Acetate.

22,23-Dibromo-7β-hydroxy-11-oxoergost-8(14)-en-3β-yl acetate (250 mg.) was debrominated with activated zinc dust (3 g.) by refluxing in benzene-ether-methanol (1:1:1; 60 c.c.) for 3 hours. The filtered solution was concentrated, treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue 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)

Light absorption: ε_{2090} = 8,000

Found: C, 75.35; H, 9.9

$C_{30}H_{46}O_4 \cdot C_3H_6O$ requires; C, 75.0; H, 9.9

It gives a yellow colour with tetranitromethane in chloroform.

22,23-Dibromo-11-oxoergost-8(14)-en-3β,7β-diol.

A solution of 22,23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (1.8g.) 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 solution was cooled to -50° and the crystalline solid which separated was collected and washed with water . Recrystallisation from chloroform-methanol gave 22,23-dibromo-11-oxoergost-8(14)-en-3β,7β-diol (1.25 g.) 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.

3β,7β-Diacetoxy-22,23-dibromoergost-8(14)-en-11-one.

Treatment of the above diol with acetic anhydride and pyridine at 100° for 3 hours followed by isolation of the product in the usual manner by means of ether gave 3β,7β-Diacetoxy-22,23-dibromoergost-8(14)-en-11-one which separated from methanol as prismatic needles

m.p. 183-185°, $[\alpha]_D$ + 55° (c, 1.0 on a specimen dried at room temperature; drying at 100° causes decomposition accompanied by a change in rotation).

Light absorption on air dried specimen. ε_{2060} = 11,000

Found. C, 56.8; H, 7.3

$C_{32}H_{48}O_5Br_2$ requires. C, 57.1; H, 7.2%

11-Oxoergosta-8(14):22-dien-3β:7β-diol.

A solution of 22:23-dibromo-11-oxoergost-8(14)-en-3β:7β-diol (500 mg.) in ether methanol (1:1; 70 c.c.) was refluxed with zinc dust (3 g.) added portion wise over 3 ½ hours. The filtered solution was concentrated, treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue crystallised from aqueous acetone to give 11-oxoergosta-8(14):22-dien-3β:7β-diol (320 mg.) as plates,

m.p. 166-168°, $[\alpha]_D$ + 76° (c, 1.4)

Light absorption: ε_{2080} = 11,500

Found: C, 78.3; H, 10.1

$C_{28}H_{44}O_3$ requires: C, 78.45; H, 10.35%

3β:7β-Diacetoxyergosta-8(14):22-dien-11-one.

(a) Treatment of 11-oxoergosta-8(14):22-dien-3β:7β-diol with acetic anhydride and pyridine at room temperature overnight gave the diacetate which separated from aqueous methanol as plates,

m.p. 111-113°, $[\alpha]_D$ + 34° (c, 2.0)

Light absorption : ε_{2120} = 9,000

Found: C, 74.6; H, 9.4.

$C_{32}H_{48}O_5$ requires: C, 75.0; H, 9.4%

(b) A solution of 3β:7β-diacetoxy-22:23-dibromo-ergost-8(14)-en-11-one (700 mg.) in ether-methanol (1:1; 100 c.c.) was refluxed with zinc dust (3 g.) added portionwise over 2 hours. The filtered solution was concentrated, treated with water and extracted with ether. The washed and

dried (Na_2SO_4) extract was evaporated to dryness and the residue crystallised from aqueous methanol to give 3β:7β-diacetoxyergosta-8(14):22-dien-11-one (480 mg.) as plates,

m.p. and mixed m.p. 111-113°, $[\alpha]_D$ + 35° (c, 2.0)

Light absorption: ε_{2120} = 9,200.

3β:7β-Diacetoxy-22:23-dibromo-14β-ergost-8-en-11-one.

(a) A solution of 22:23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (150 mg.) in methanolic potassium hydroxide (50 c.c.; 2%) was heated under reflux for 2 hours. The cooled solution was treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue treated with pyridine and acetic anhydride at room temperature. Isolation of the product in the usual manner by means of ether gave 3β:7β-diacetoxy-22:23-dibromo-14β-ergost-8-en-11-one (100 mg.) which crystallised from aqueous acetone as needles,

m.p. 184-186°, $[\alpha]_D$ + 63° (c, 1.3).

Light absorption: maximum at 2430Å (ε = 8,500).

Found: C, 57.4; H, 7.35%

$C_{32}H_{48}O_5Br_2$ requires: C, 57.1; H, 7.2%

Infra-red spectrum: Peaks at 1737 and 1241 (acetate) and 1689 cm^{-1} ($\alpha\beta$-unsaturated ketone).

(b) Alkali treatment of 22,23-dibromo-11-oxoergost-8(14)-en-3β,7β-diol exactly as in (a) followed by acetylation gave 3β,7β-diacetoxy-22,23-dibromo-14β-ergost-8-en-11-one which separated from aqueous acetone as needles

m.p. and mixed m.p. 185-186°, $[\alpha]_D$ + 62° (c, 0.9)

Light absorption: maximum at 2440Å (ε = 8,900).

VII. A Partial Synthesis of Cortisone from Ergosterol.

3β-Acetoxybisnorallochol-7-en-22-al

An ozonised stream of oxygen was bubbled through a solution of 5-dihydroergosteryl acetate (40 g.) in chloroform (600 c.c.) at -40° to -50° until ozone (1.5 mols) had been passed. When the solution attained room temperature (30 minutes), acetic acid (200 c.c.) and zinc dust (30 g.) were added and the mixture stirred for one hour. After filtration methylisopropyl acetaldehyde was removed by steam-distillation. The non-volatile fraction was extracted with ether and the extract washed successively with sodium carbonate solution (3%) and water, dried (Na_2SO_4) and the ether removed under reduced pressure. The residue was extracted with hot aqueous acetone (3x800 c.c., 30%). The combined extractions were concentrated until 3β-acetoxybisnorallochol-7-en-22-al (27 g.) separated as plates m.p. 133-134°. Two recrystallisations gave the pure aldehyde as plates, m.p. 136-138°. $[\alpha]_D$ - 18° (c, 2.0)

Light absorption: $\varepsilon_{2100} = 5,000$

Found:	C, 77.5;	H, 10.0
$C_{24}H_{36}O_3$ requires:	C, 77.4;	H, 9.7%

It gives a pale yellow colour with tetranitromethane in chloroform.

No acid product was isolated.

The aqueous acetone insoluble fraction was recrystallised from methanol chloroform to give 5-dihydroergosteryl acetate as plates m.p. and mixed m.p. 170-173°.

2:4 Dinitropheylhydrazone

Treatment of the aldehyde in methanol with Brady's reagent gave the 2:4-dinitrophenylhydrazone which crystallised from ethyl acetate as yellow needles,

m.p. 243-244°

Light absorption: maxima at 2270 (ε = 14,000) and at 3600Å (ε = 21,750).

Found: C, 65.2; H, 7.0

$C_{30}H_{40}O_6H_4$ requires: C, 65.2; H, 7.3%.

Dimethyl Acetal.

(a) The aldehyde (500 mg.) in warm methanol (50 c.c.) was treated with concentrated hydrochloric acid (0.02 c.c.). Immediately a white solid separated which was collected, washed well with water, and crystallised from methanol-methylene chloride to give the dimethyl acetal (450 mg.) as plates,

m.p. 210-212°, $[\alpha]_D$ - 10° (c, 2.4).

Light absorption: ε_{2080} = 4,400

Found: C, 74.8; H, 10.3.

$C_{26}H_{42}O_4$ requires: C, 74.6; H, 10.1%

It gives a pale yellow colour with tetranitromethane in chloroform.

(b) Crystallisation of the aldehyde from impure (technical) aqueous methanol gave the dimethyl acetal,

m.p. and mixed m.p. 210-212°, $[\alpha]_D$ - 9° (c, 2.5).

Methylisopropyl acetaldehyde 2:4-Dinitrophenylhydrazone.

The steam distillate described above was extracted with chloroform. The extract was washed successively with water, sodium hydrogen carbonate solution and water, dried (Na_2SO_4) and the chloroform removed under reduced pressure. The residue in methanol was treated with Brady's reagent to give a 2:4-dinitrophenylhydrazone which crystallised from methanol as needles,

m.p. 122-123°

[Lit. records 2:4-Dinitrophenylhydrazone of methylisopropyl acetaldehyde m.p. 122-123°].

3β:22-Diacetoxybisnorallochola-7:20(22)-diene.

A solution of well dried 3β-acetoxybisnorallochol-7-en-22-al (10 g.) in acetic anhydride (40 c.c.) was heated with freshly fused potassium acetate (2 g.) at 120-123° for six hours. On cooling a crystalline solid separated which was collected and washed well with water. Crystallisation from acetone gave 3β:22-diacetoxybisnorallochola-7:20(22)-diene as plate (5g.)

m.p. 163-165°, $[\alpha]_D$ -25° (c, 1.0)

Light absorption: $\varepsilon_{2080} = 5,000$

Found: C, 75.4; H, 9.2.

$C_{26}H_{38}O_4$ requires: C, 75.3; H, 9.2%

It gives a pale yellow colour with tetranitromethane in chloroform.

The acetic anhydride mother liquors were treated with water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4) and the ether removed under reduced pressure. The residue crystallised from acetone to yield

a further 2.7 g. of the enol acetate.

20-Oxoallopregn-7-en-3β-yl Acetate.

A solution of 3β:22-diacetoxybisnorallochola-7:20(22)-diene (5 g.) in chloroform (400 c.c.) was treated at -40° to -50° with ozone (1.5 mols.). When the solution had attained room temperature (30 minutes) acetic acid (150 c.c.) and zinc dust (10 g.) were added and the mixture stirred for 1½ hours. After filtration the solution was concentrated, treated with water and extracted with ether. The extract was washed successively with water, sodium carbonate solution (3%) and water, dried (Na_2SO_4) and the ether removed under reduced pressure. The residue crystallised from acetone to give 20-oxoallopregn-7-en-3β-yl acetate (3 g.) as blades,

m.p. 174-176°, $[\alpha]_D$ + 38° (c, 1.0)

Light absorption: ε_{2110} = 4,500 and maximum at 2900Å (ε = 48)

Found: C, 77.0; H, 9.6

Calc. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.6%

It gives a pale yellow colour with tetranitromethane in chloroform. Djerassi et al (loc. cit.) record m.p. 174-176°, $[\alpha]_D$ + 39° for this compound.

A second crop from the acetone mother liquors gave a further yield (1 g.) of the product m.p. 170-173°.

20-Oxoallopregn-7-en-3β-ol.

A solution of 20-oxoallopregn-7-en-3β-yl acetate in aqueous methanolic potassium hydroxide was refluxed for one hour. The solution was treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue crystallised from methanol to give 20-oxoallopregn-7-en-3β-ol as blades,

m.p. 213-215°, $[\alpha]_D$ + 39° (c, 1.3)

Light absorption: ε_{2010} = 5,600

Found: C, 79.4; H, 10.3.

Calc. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2%

It gives a pale yellow colour with tetranitromethane in chloroform.

Djerassi et al (loc.cit.) record m.p. 213-215°, $[\alpha]_D$ + 41°.

20-Oxoallopregn-7-en-3β-yl Benzoate.

Treatment of the alcohol in pyridine with benzoylchloride at 100° for 1 hour and the product isolated by means of ether gave 20-oxoallopregn-7-en-3β-yl benzoate as plates from methanol

m.p. 186-188° $[\alpha]_D$ + 39° (c, 1.0)

Light absorption: ε_{2040} = 10,000 and maximum at 2380Å (ε = 17,000).

Found: C, 79.85; H, 8.8

$C_{28}H_{36}O_3$ requires: C, 80.0; H, 8.6%

It gives a pale yellow colour with tetranitromethane in chloroform.

Application of Kritchewsky and Gallagher's procedure to 20-oxoallopregn-7-en-3β-yl Acetate.

(a) A solution of 20-oxoallopregn-7-en-3β-yl acetate (550 mg.) in acetic anhydride (15 c.c.) containing p-toluenesulphuric acid (50 mg.) was concentrated to ca 5 c.c. over 7 hours by distilling off the excess anhydride very slowly. The solution was poured into ice-water and extracted with ether. The washed and dried extract (Na_2SO_4) was evaporated to dryness and the residue A (450 mg.) dissolved in light petroleum (b.p. 60-80°) - benzene (30 c.c. ; 10:1) and chromatographed on alumina (2x10 cm). Elution of the column with petroleum-benzene and benzene did not give a homogeneous product. Elution with benzene-ether (50 c.c.; 1:1) gave 3β:20-diacetoxy-allopregna-7:17(20)-diene (100 mg.) which crystallised from aqueous methanol as plates,

m.p. 58-61°, $[\alpha]_D$ + 4.2° (c, 1.3).

Light absorption: ε_{2120} = 5,500.

Found: C, 75.54; H, 9.4.

Calc. for $C_{25}H_{36}O_4$: C, 75.0; H, 9.1%

This fraction was hydrolysed with 1% aqueous methanolic potassium hydroxide and re-acetylated with acetic anhydride and pyridine at room temperature to give 20-oxoallopregn-7-en-3β-yl acetate, m.p. and mixed m.p. 174-176°, $[\alpha]_D$ + 38° (c, 0.8).

(b) The residue A (450 mg.) obtained from a similar enol acetylation was treated with perbenzoic acid (1.1 mole) in chloroform (10 c.c. and kept at room temperature overnight. The chloroform solution was washed

with saturated sodium hydrogen carbonate solution, dried and evaporated to dryness. The residue was hydrolysed with 1% methanolic sodium hydroxide and the product isolated in the usual way to give 20-oxoallopregn-7-en-3β-ol, m.p. and mixed m.p. 213-215°, $[\alpha]_D$ + 39° (c, 1.0).

20-Oxoallopregna-7:9(11)-dien-3β-yl Acetate. (cf. Djerassi et al (47)).

(a) A solution of 20-oxoallopregn-7-en-3β-yl acetate (1 g.) in chloroform (30 c.c.) and acetic acid (30 c.c.) was shaken with mercuric acetate (3 g.) for 18 hours. The filtered solution was concentrated, treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue crystallised from methanol to give plates (300 mg.) m.p. 146-150°, $[\alpha]_D$ + 53°, several recrystallisations of which gave 20-oxoallopregna-7:9(11)-dien-3β-yl acetate (100 mg.) as plates,

m.p. 157-160°, $[\alpha]_D$ + 78°, (c, 1.0)

Djerassi et al record m.p. 139-141°, $[\alpha]_D$ + 78.9°.

(b) To a stirred solution of 20-oxoallopregn-7-en-3β-yl acetate (5 g.) in chloroform (200 c.c.) at -50° ± 5°, bromine (5.65 g., 2.5 mols.) in chloroform (180 c.c.) was added dropwise over two hours. Glacial acetic acid (100 c.c.) and zinc dust were added and stirring continued at -30 to -50° for two hours. The filtered solution was washed successively with water, with sodium hydrogen carbonate solution, and water, dried (Na_2SO_4) and the chloroform removed under reduced pressure. The residue was crystallised from methanol to give 20-oxoallopregna-7:9(11)-dien-3β-yl

acetate (3.9 g.) as elongated plates,

m.p. and mixed m.p. 159-162° $[\alpha]_D$ + 81° (c, 1.0)

Light absorption: maxima at 2360 (ε = 12,500), 2420 (ε = 14,200) and an inflection at 2500Å (ε = 9,300).

Found:= C, 77.2; H, 9.3

Calc. for $C_{23}H_{32}O_3$: C, 77.5; H, 9.05%

It gives a red brown colour with tetranitromethane in chloroform.

20-Oxoallopregna-7:9(11)-dien-3β-ol.

Hydrolysis of 20-oxoallopregna-7:9(11)-dien-3β-yl acetate with 2% aqueous methanolic potassium hydroxide gave the alcohol which separates from acetone as plates,

m.p. 200-202°, $[\alpha]_D$ + 73° (c, 1.0)

Light absorption: maxima at 2360 (ε = 11,000), 2420 (ε = 12,750) and an inflection at 2500Å (ε = 7,800).

It gives a red brown colour with tetranitromethane in chloroform.

Djerassi et al gave m.p. 201-203° $[\alpha]_D$ + 74.1°.

9α:11α-Epoxy-20-oxoallopregn-7-en-3β-yl Acetate.

A stirred solution of 20-oxoallopregna-7:9(11)-dien-3β-yl acetate (5 g.) in chloroform (150 c.c.) was treated with perbenzoic acid (1.1 mols.) in chloroform (25 c.c.) added dropwise at 0° over 4 hours. The solution was kept at 0° overnight. The solution was washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4) and the chloroform removed under reduced pressure (below35°). Crystallisation of the residue from acetone gave 9α:11α-epoxy-20-oxoallopregn-7-en-3β-yl

acetate (3.3 g.) as plates,

m.p. 191-192°, $[\alpha]_D$ - 2° (c, 1.4)

Light absorption: ε_{2080} = 5,600

Found: C, 74.3; H, 8.95.

$C_{23}H_{32}O_4$ requires: C, 74.2; H, 8.7%.

It gives a pale yellow colour with tetranitromethane in chloroform.

11:20-Dioxo-9β-allopregn-7-en-3β-yl Acetate.

A solution of 20-oxo-9α:11α-epoxyallopregn-7-en-3β-yl acetate (200 mg.) in dry ether (45 c.c.) was treated with boron trifluoride-ether complex (0.3 c.c.) and the solution kept at room temperature for 16 hours. The solution was washed with water, with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4) and the ether removed under reduced pressure. The residue was crystallised from acetone-distilled water to give 11:20-dioxo-9β-allopregn-7-en-3β-yl acetate (160 mg.) as plates,

m.p. 119-121°, $[\alpha]_D$ - 110° (c, 1.4)

Light absorption: ε_{2090} = 5,400

Found: C, 74.5; H, 9.0.

$C_{23}H_{32}O_4$ requires: C, 74.2; H, 8.7%

It gives a pale yellow colour with tetranitromethane in chloroform.

20β-Hydroxy-11-Oxo-9β-allopregnan-3β-yl acetate.

A solution of 11:20-dioxo-9β-allopregn-7-en-3β-yl acetate (300 mg.) in glacial acetic acid (200 c.c.) was shaken for 50 minutes in an atmosphere of hydrogen, with pre-reduced platinum catalyst (from 60 mg. PtO_2). The filtered solution was concentrated and the product isolated

by means of ether. Crystallisation from acetone-light petroleum (b.p. 60-80°) gave 20β-hydroxy-11-oxo-9β-allopregnan-3β-yl acetate (220 mg.) as needles,

m.p. 202-203°, $[\alpha]_D$ + 44°, + 44.5° (c, 1.5, 1.3).

Found: C, 73.7; H, 9.9

$C_{23}H_{36}O_4$ requires: C, 73.4; H, 9.6%

It does not show high intensity light absorption in the ultra-violet. Infra-red spectrum: Peaks at 3500 (hydroxyl), 1726 (ketone) 1720 and 1240 cm^{-1} (acetate).

11:20-Dioxo-9β-allopregnan-3β-yl Acetate.

A solution of 11-oxo-9β-allopregnan-3β:20β-diol 3-acetate (109 mg.) in stabilised glacial acetic acid (5 c.c.) was treated with chromic anhydride (29 mg.) in acetic acid (1 c.c.) and kept at room temperature for 16 hours. The excess oxidising agent was destroyed by treatment with methanol. The concentrated solution was treated with water and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to dryness and the residue crystallised from light petroleum (b.p. 60-80°) to give 11:20-dioxo-9β-allopregnan-3 -yl acetate (90 mg.) as plates,

m.p. 191-193° $[\alpha]_D$ + 154° (c, 1.6)

Found: C, 73.75; H, 9.3

$C_{23}H_{34}O_4$ requires: C, 73.8; H, 9.15%

It does not give a colour with tetranitromethane in chloroform and does not absorb light with high intensity in the ultra-violet region.

11:20-Dioxoallopregnan-3β-ol.

A solution of 11:20-dioxo-9β-allopregnan-3β-yl acetate (150 mg.) in aqueous methanolic potassium hydroxide (5.5. c.c., 20%) was refluxed for six hours. The cooled solution was treated with water and extracted with ether. The washed and dried extract was evaporated to dryness and the residue crystallised from acetone-light petroleum (b.p. 60-80°) to give 11:20-dioxoallopregnan-3β-ol (110 mg.) as elongated plates (or prisms depending on the rate of crystallisation),

m.p. 194-195°, $[\alpha]_D$ + 116, + 118° (C, 1.6, 1.3).

Found; C, 75.5; H, 9.7.

Calc.for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7%

It does not give a colour with tetranitromethane in chloroform and does not absorb light with high intensity in the ultra-violet region. It did not depress in m.p. on admixture with a specimen m.p. 194-195, $[\alpha]_D$ + 117° (c, 1.0) prepared by hydrolysis of 11:20-dioxoallopregnan-3β-yl acetate kindly supplied by Dr. B.A. Hems of Glaxo Laboratories.

Stork et al (49) record m.p. 192-194°, $[\alpha]_D$ + 99°.

11:20-Dioxoallopregnan-3β-yl Acetate.

Treatment of the alcohol with acetic anhydride and pyridine at room temperature gave 11:20-dioxoallopregnan-3β-yl acetate which separated as prismatic needles, (from aqueous acetone)

m.p. and mixed m.p. 143-144°, $[\alpha]_D$ + 88°(c,0.5).

Stark et al (49) gave m.p. 143-144° $[\alpha]_D$+ 89°

Chamberlin et al (97) gave m.p. 143-144° $[\alpha]_D$ + 88°

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