584. (*a*) *Studies in the Steroid Group. Part LXII.** (*b*) *Studies in the Synthesis of Cortisone. Part I.*

A Novel Route to 11-*Ketosteroids.*

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It has been shown that 11-keto-Δ^7-9β-steroids (II) are the initial products of isomerising 9α : 11α-epoxy-Δ^7-compounds (I) in the *allo*steroid series with the boron trifluoride–ether complex. These new unsaturated ketones are isolated in good yields and can be isomerised successively to 11-keto-Δ^7-9α-compounds and 11-keto-$\Delta^{8(9)}$-steroids. The unconjugated 7 : 8-bond in the 11-keto-Δ^7-9β-steroids, in contrast to that in the 9α-compounds, can be hydrogenated, and the resulting 11-keto-9β-compounds (III) can be isomerised by alkali to 11-ketones of natural (9α-)configuration (IV). These sequences of reactions have been carried out with compounds containing hydrogen, or a hydroxy- or acetoxy-substituent, at $C_{(5)}$ and having the ergostane, pregnane, or bisnorcholanic acid side-chain, and have led to a new synthesis of 11-ketoprogesterone. Some hydrogenation experiments with 11-keto-Δ^7-9α- and 11-keto-$\Delta^{8(9)}$-steroids are also described. Mention is made of the stereochemical implications of abnormal configuration at the 8 : 9-bridgehead, with particular reference to the structure of the 11-keto-stanol obtained by palladium-catalysed hydrogenation of 3β-acetoxyergosta-8(9) : 22-dien-11-one.

ONE of the most direct methods for introducing an 11-keto-group into the readily available steroids containing a 7 : 9-diene system is that first described by Heusser, Eichenberger, Kurath, Dällenbach, and Jeger (*Helv. Chim. Acta*, 1951, **34**, 2106; cf. Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696; and Sondheimer, Yashin, Rosenkranz, and Djerassi, *ibid.*, p. 2696). The first group of authors showed that small amounts of boron trifluoride–ether complex in benzene solution converted 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene (I; R = H, R′ = C_9H_{17}) into the isomeric 11-keto-$\Delta^{8(9)}$-compound (VI; R = H, R′ = C_9H_{17}). One of the first of our present observations was that the yield of unsaturated ketone from this reaction could be improved by using 1 mol. of boron trifluoride–ether complex and a shorter reaction time. A more detailed investigation of this isomerisation reaction led to the discovery that a βγ-unsaturated ketone was an intermediate in the rearrangement, the first evidence for this being obtained by two different methods.

The course of the reaction in benzene could be followed polarimetrically, and it was then observed that the rotation dropped rapidly from that of the epoxide ($[\alpha]_D$ −40°) to a minimum ($[\alpha]_D$ about −170°) and then increased more slowly to a constant value of approximately $[\alpha]_D$ +90°, corresponding to complete formation of the conjugated ketone (VI; R = H, R′ = C_9H_{17}). If the mixture was worked up when the rotation was at the most negative value, a new ketone, shown to be (II; R = H, R′ = C_9H_{17}), could be isolated in excellent yield. The other approach involved the substitution of ether for benzene as solvent; rearrangement was then very much slower, but the new βγ-unsaturated ketone

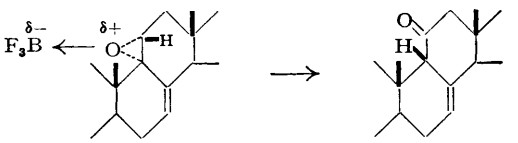
* Part LXI, preceding paper.

was obtained in excellent yield after 18 hours, no appreciable amount of further isomerisation to (VI; R = H, R′ = C_9H_{17}) taking place even in 14 days.

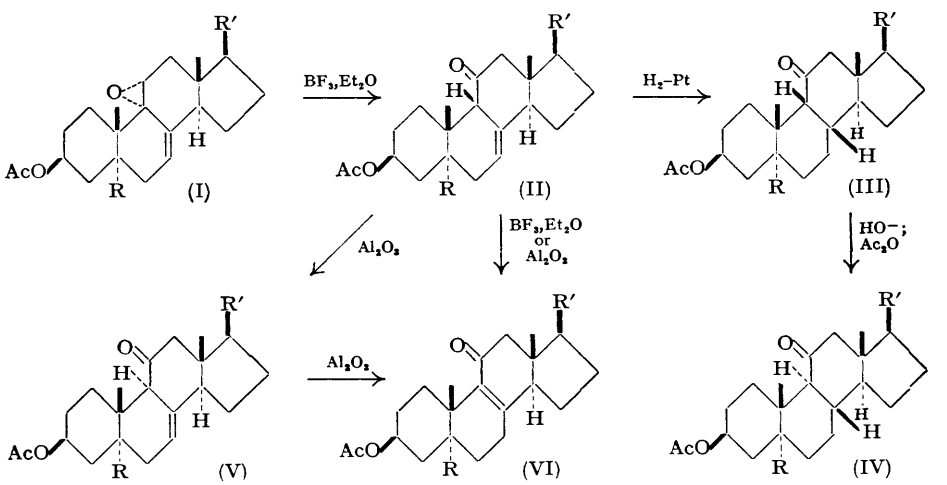
The formulation of the new compound as a βγ-unsaturated ketone followed from its ultra-violet and infra-red light absorption characteristics and from its ready isomerisation to the conjugated ketone (VI; R = H, R′ = C_9H_{17}) when treated with boron trifluoride–ether complex in benzene, or with hot acetic acid, or when passed in benzene through activated alumina; each of these three methods gave nearly quantitatively (VI; R = H, R′ = C_9H_{17}) of considerably better quality than that obtained by the direct method of the Swiss workers. Further chemical transformations of (II; R = H, R′ = C_9H_{17}) clearly indicated the presence at $C_{(9)}$ of a centre of unnatural configuration, a result readily explained by consideration of the mechanism of the rearrangement.

The first step in the isomerisation of the 9α : 11α-epoxide to the 11-keto-Δ^7-9β-steroid must be co-ordination of boron trifluoride with the epoxide group. On the assumption that partial dissociation of the boron trifluoride complex takes place, the reaction can be depicted as :

$$BF_3,Et_2O \rightleftharpoons Et_2O + BF_3$$



Co-ordination takes place rapidly in benzene, whereas in ether the slowness of the rearrangement results from repression of dissociation of the boron trifluoride–ether complex. The isomerisation can then be envisaged as a movement of the $C_{(9)}$-oxygen linkage electrons on to the now electron-deficient oxygen atom with simultaneous movement of the 11β-hydrogen along the β-face of the molecule to the unnatural β-position at $C_{(9)}$.



Evidence for the β-configuration of the hydrogen atom at $C_{(9)}$ in (II; R = H, R′ = C_9H_{17}) was provided by the observation that this ketone and its hydrogenation product (see below) could be epimerised to the corresponding 9α-compounds under alkaline conditions. The epimerisation of the 11-keto-Δ^7-9β-compound was complicated to some extent by the ease with which further isomerisation to the conjugated ketone occurred, but a good yield of 3β-acetoxyergosta-7 : 22-dien-11-one (V; R = H, R′ = C_9H_{17}) was obtained by passing a benzene solution of (II; R = H, R′ = C_9H_{17}) through a column of suitably acid-treated alumina. Inversion at $C_{(9)}$ is accompanied by a comparatively large positive increase in molecular rotation and this appears to be general for all the 11-keto-Δ^7-compounds studied. In view of the ease of inversion at $C_{(9)}$, the normal isomer

may feature as an intermediate in the rearrangement of (II; R = H, R′ = C_9H_{17}) to (VI; R = H, R′ = C_9H_{17}) and some evidence in support of this is presented in the next paper. An analogy for the fact that the kinetically controlled epimerisation of the $C_{(9)}$-β-hydrogen atom in (II; R = H, R′ = C_9H_{17}) takes precedence over the further isomerisation to the more stable conjugated ketone may be found in the experiments of Ingold, de Salas, and Wilson (*J.*, 1936, 1328), who showed that the rate of hydrogen exchange of the activated methylene group in *cyclo*hex-1-enylacetonitrile was much greater than the rate of isomerisation to the conjugated nitrile. This epimerisation at $C_{(9)}$ may be an example of a "concerted displacement reaction" of the type discussed by Swain and his co-workers (*J. Amer. Chem. Soc.*, 1952, **74**, 2534, 2538, and earlier papers); these authors consider that the rate-determining step in the mutarotation of certain sugars is the simultaneous addition and loss of a proton.

The difference in chemical properties between the two isomeric βγ-unsaturated ketones was particularly apparent in their behaviour on hydrogenation. The unnatural configuration at $C_{(9)}$ was first suspected when the ketone (II; R = H, R′ = C_9H_{17}) readily absorbed two mols. of hydrogen (one reducing the 22 : 23-bond) in the presence of platinum under neutral or acidic conditions, to afford a new saturated 11-ketostanol (III; R = H, R′ = C_9H_{19}). The unprecedented ease of hydrogenation of the 7 : 8-bond clearly indicated that some unusual stereochemical factor must be involved, and confirmation of the suspected abnormal β-configuration at $C_{(9)}$ in the hydrogenation product followed from its epimerisation to the 9α-isomer, although the conditions needed proved to be much more severe than those used in the conversion of (II; R = H, R′ = C_9H_{17}) into (V; R = H, R′ = C_9H_{17}). Thus the epimerisation of (III; R = H, R′ = C_9H_{19}) necessitated heating in strong alcoholic alkali for several hours; the isomeric ketone of natural configuration was then obtained in good yield, its structure being proved by comparison of its 3β-acetate (IV; R = H, R′ = C_9H_{19}) with an authentic sample prepared by hydrogenation of 3β-acetoxyergost-22-en-11-one (IV; R = H, R′ = C_9H_{17}) (Heusser *et al.*, *loc. cit.*). The conversion of (III; R = H, R′ = C_9H_{19}) into (IV; R = H, R′ = C_9H_{19}) clearly proves that the enolisable $C_{(9)}$-hydrogen atom in (III), and thus in (II), has the β-orientation. It also shows that the $C_{(8)}$-hydrogen atom introduced by hydrogenation of the 7 : 8-bond in (II) is normally (β-)orientated, and that this reduction must take place by frontal approach of the platinum catalyst rather than by attack on the α-face of the molecule as appears to be the general rule for hydrogenation in the B-, C-, and D-rings in sterols of natural configuration (Fieser, *Experientia*, 1950, **6**, 313).

Hydrogenation of (V; R = H, R′ = C_9H_{17}) took a course entirely different from that of the 9β-epimer. Platinum-catalysed reduction in neutral solution resulted in saturation of the side-chain bond, to give 3β-acetoxyergost-7-en-11-one (V; R = H, R′ = C_9H_{19}) whose structure was indicated by the absence from the infra-red absorption spectrum of a band associated with the side-chain double bond and also by its conversion into 3β-acetoxyergost-8(9)-en-11-one (VI; R = H, R′ = C_9H_{19}) on alumina. Hydrogenation in acidic medium, however, resulted in the formation of the $\Delta^{8(14)}$-compound, α-ergostenyl acetate, the reaction probably proceeding *via* the conjugated ketone, for (VI; R = H, R′ = C_9H_{17}), on hydrogenation, also yielded α-ergostenyl acetate, presumably by hydrogenolysis of the 11-keto-group and subsequent migration of the double bond.

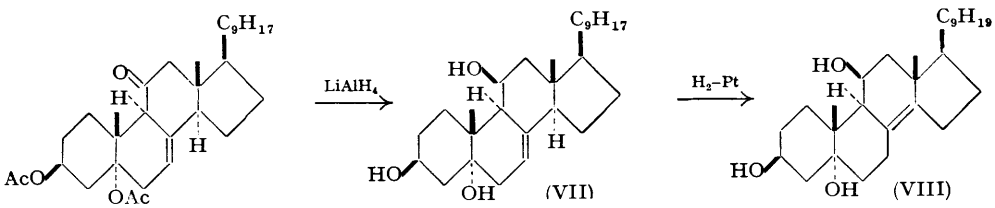
The difference in the course of hydrogenation of (II) and (V) must be related to the unusual conformation of the 9β-epimer. Ring C has approximately a *cyclo*hexanone boat conformation, and the effect of this is to move the angular 18- and 19-methyl groups further apart, thus enhancing the opportunity for frontal attack by the hydrogenation catalyst. Further evidence of the stereospecificity of the hydrogenation of Δ^7-9β-sterols is provided by Müller's observation (*Z. physiol. Chem.*, 1935, **233**, 224) that *iso*pyrocalciferol [identical in configuration at $C_{(9)}$ and $C_{(10)}$ with (II)] takes up 3 mols. of hydrogen, in contrast to the 2 mols. absorbed by pyrocalciferol [different from *iso*pyrocalciferol and (II) in configuration at $C_{(10)}$] or by ergosterol.

11-Keto-steroids of natural configuration containing 5α-hydroxy- or 5α-acetoxy-substituents have been prepared similarly. The monoepoxides (I; R = OH or OAc, R′ = C_9H_{17}) have been prepared by selective oxidation of the corresponding 7 : 9-dienes

with monoperphthalic acid, and the chemistry of these compounds provides unequivocal proof that the epoxy-group is located at 9 : 11. The epoxides (I; R = OH or OAc, R′ = C_9H_{17}) were isomerised to the corresponding 11-keto-Δ^7-9β-stenols (II) by the boron trifluoride–ether complex, although the rate of rearrangement was appreciably less than with the 5-hydrogen compounds—this indicates steric interference by the more bulky substituents at $C_{(5)}$. Rearrangement of (I; R = OAc, R′ = C_9H_{17}) has also been effected by use of the stannic chloride–ether complex in ether–benzene as an example of an alternative Lewis acid; the product being then chromatographed, the 9α-isomer (V; R = OAc, R′ = C_9H_{17}) was consequently obtained.

The reduction and isomerisation reactions could be carried out with these 5-hydroxy- and 5-acetoxy-compounds, although again the rates of the various reactions were considerably diminished. The strongly alkaline conditions required for epimerisation of (III; R = OAc, R′ = C_9H_{19}) to the corresponding 11-ketone of natural configuration resulted in hydrolysis of the 5α- as well as of the 3β-acetoxy-group, mild acetylation then giving the same product (IV; R = OH, R′ = C_9H_{19}) as was obtained in the 5-hydroxy-series. In no instance in this sequence of reactions was there any indication that the hydroxyl substituents at $C_{(5)}$ had been eliminated.

Isomerisation of the unconjugated ketone (II; R = OAc, R′ = C_9H_{17}) to the conjugated compound was readily effected by treatment with dilute alkali at room temperature; the monoacetate so obtained was evidently 5α-acetoxy-3β-hydroxyergosta-8(9) : 22-dien-11-one (VI; R = OAc, R′ = C_9H_{17}, 3-OH in place of 3-OAc), since it readily afforded a diacetate (VI; R = OAc, R′ = C_9H_{17}). Some difficulty, however, was encountered in obtaining the conjugated 5-hydroxy-ketone, treatment of the unconjugated isomer (II; R = OH, R′ = C_9H_{17}) with alkali or with acetic acid (or better zinc and acetic acid) leading to incomplete isomerisation (judged spectroscopically). However, the conjugated compound could be isolated by chromatography of such mixtures.

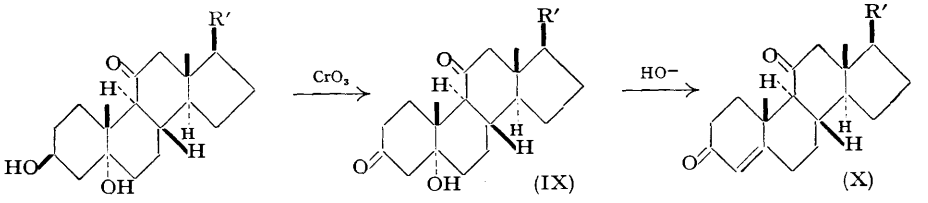


On reduction with lithium aluminium hydride, 3β : 5α-diacetoxyergosta-7 : 22-dien-11-one (V; R = OAc, R′ = C_9H_{17}), obtained by epimerisation of the 9β-isomer on alumina, gave an ergostadienetriol (VII); it must contain an 11β-hydroxyl group as only a monoacetate was formed on mild acetylation. Hydrogenation of (VII) with platinum in acetic acid resulted in saturation of the side-chain double bond and also in migration of the nuclear double bond from the 7(8)- to the 8(14)-position, to give ergost-8(14)-ene-3β : 5α : 11β-triol (VIII). Evidence for the location of the double bond in (VIII) is provided by its greater intensity of absorption in the 2050—2250-Å region compared with (VII) (Bladon, Henbest, and Wood, *J.*, 1952, 2737). Platinum-catalysed reduction of (V; R = OAc, R′ = C_9H_{17}) in acetic acid (at normal pressure or at 100 atmospheres) resulted only in saturation of the side-chain double bond. The product, 3β : 5α-diacetoxyergost-7-en-11-one (V; R = OAc, R′ = C_9H_{19}), was identical with that obtained from the epoxide (I; R = OAc, R′ = C_9H_{19}) by rearrangement with the boron trifluoride–ether complex and subsequent epimerisation.

The sequence of reactions (I)—(IV) opens up alternative routes to cortisone and also to its 9-*iso*-analogue. One such approach could involve the selective hydrogenation of the 7 : 8-bond in (II; R = H, R′ = C_9H_{17}), leaving the side-chain double bond intact for subsequent degradation. Catalytic hydrogenation with nickel, platinum, or palladium catalysts in neutral or acidic media indicated some preferential reduction of the side-chain rather than the nuclear double bond. However, by starting from ergosteryl-D acetate 22 : 23-dibromide or -dichloride (Anderson, Stevenson, and Spring, *J.*, 1952, 2901), a

similar series of reactions has been used to prepare (III; R = H, R′ = C_9H_{17}) (cf. following paper).

Alternatively, by using the procedures described above, the 20-ketone (I; R = OH, R′ = COMe) (cf. previous paper) has been converted into the 11 : 20-diketone (IV; R = OH, R′ = COMe). The strongly alkaline conditions necessary for epimerising the 9β-hydrogen atom in the intermediate compound (III; R = OH, R′ = COMe) are vigorous enough to cause equilibration at $C_{(17)}$ (cf. references given by Elks and Shoppee, *J.*, 1953, 241). However, as with compounds not containing an 11-keto-group, the compound with the side-chain in the natural configuration was the more stable and a good yield of (IV; R = OH, R′ = COMe) could be obtained. The intention in introducing and retaining the 5-hydroxyl group throughout this work has been to facilitate the eventual production of a 3-keto-Δ^4-grouping, and the usefulness of this approach was demonstrated by oxidation of (IV; R = OH, R′ = COMe) to the 3-keto-5-hydroxy-compound (IX; R′ = COMe), which, with dilute alkali, yielded 11-ketoprogesterone (X; R′ = COMe).



(R′ = COMe or CHMe·CO_2Me)

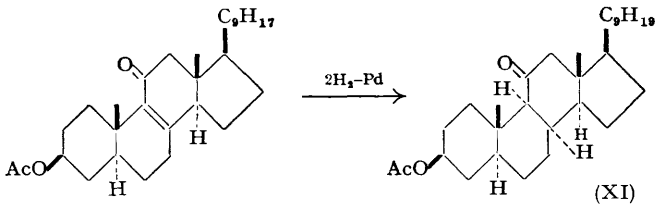
The production of a similar series of compounds containing a –CHMe·CO_2H side-chain started from 3β-acetoxy-5α : 8α-epidioxybisnor*allo*chol-9-enic acid, originally obtained as a by-product from the ozonolysis of 3β-acetoxy-5α : 8α-epidioxyergosta-9 : 22-diene (Bladon, Henbest, Jones, Wood, and Woods, *J.*, 1952, 4890). The yield of acid can be greatly improved (at the expense of the aldehyde) by decomposing the ozonide with permanganate in acetic acid. Zinc–acetic acid treatment of the acid yielded the corresponding 7 : 9-diene, which could be transformed by the new methods into methyl 3 : 11-diketobisnorchol-4-enate (X; R′ = CHMe·CO_2Me).

It is now accepted that the *cyclo*hexane ring is more stable in the chair than in the boat form and therefore that, of a number of possible conformations to represent a given steroid, the one having the most chair forms is to be preferred (Barton, *Experientia*, 1950, **6**, 316; *J.*, 1951, 1048; *J.*, 1953, 1027; Johnson, *Experientia*, 1951, **7**, 315). Comparison of models of the 9α- (IV) and 9β-steroids (III) shows that, whereas the 9α-compound will exist with rings A, B, and C in chair forms, the epimer must have either ring B or ring C in a boat form * (the conformation of the 9β-compounds will be discussed in more detail in a later paper); accordingly, conversion into the compound of natural configuration might be expected when epimerisation of the hydrogen at $C_{(9)}$ is possible (as in III). This example is superficially analogous to the well-known conversion of *cis*-α-decalones into *trans*-α-decalones, but the *trans*-ring fusion is not always more stable, as is exemplified by the failure to isomerise *cis-syn-trans*-perhydro-9-ketophenanthrene to the *trans-syn-trans*-compound (Linstead and Whetstone, *J.*, 1950, 1428). It is significant that the latter compound, unlike the *cis*-isomer, cannot exist with the central ring in a chair form and so has a chair-boat-chair conformation (Johnson, *loc. cit.*). Of interest in relation to these ideas is the palladium-catalysed hydrogenation of 3β-propionoxy-5α : 22*a*-spirost-8(9)-en-11-one to give a saturated steroid, formulated, presumably by virtue of its stability to alkali, as 3β-propionoxy-5α : 8α : 9β : 22*a*-spirostan-11-one (Sondheimer, Yashin, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 2696). However, this stability to alkali may not imply the existence of a *trans*-B–C ring fusion since inspection of models of steroids with

* A consequence is that the 18- and 19-methyl groups are further apart in the 9β-compounds (III) than in the 9α-isomers (IV), but the 11-keto-group in (III) is, nevertheless, still too hindered to allow the formation of an oxime or 2 : 4-dinitrophenylhydrazone.

8α-hydrogen atoms shows that the compound with a *cis*-B–C ring-fusion (8α : 9α; Fig. 1) * contains one less *cyclo*hexane boat conformation than the isomer with the unnatural *trans*-B–C ring-fusion (8α : 9β; Fig. 2) (it will be noted that these conformations both contain one more boat ring than the corresponding perhydrophenanthrene compounds discussed above—this is due to the increased rigidity imposed by the *trans*-fused ring D). On this basis the alkali-stable reduction product would, perhaps, best be formulated as 3β-propionoxy-5α : 8α : 22*a*-spirostan-11-one.

In view of the vigorously alkaline conditions required for epimerisation of (III), it was thought desirable to confirm the stability of the type of hydrogenation product prepared by Sondheimer *et al.* Palladium-catalysed hydrogenation of 3β-acetoxyergosta-8(9) : 22-dien-11-one (VI; R = H, R′ = C_9H_{17}), under conditions essentially those used by them, afforded a saturated 11-ketostanol, which differed in physical properties from (III) and



(XI)

(IV) (R = H, R′ = C_9H_{19}) and must therefore have either the 8α : 9α- or the 8α : 9β-configuration. The change in molecular rotation (ΔM_D −590°) accompanying saturation of the 8 : 9-bond of the intermediate (VI; R = H, R′ = C_9H_{19}) was similar to that of the sapogenin example (ΔM_D −525°), indicating that the configurations of the two hydro-

FIG. 1.

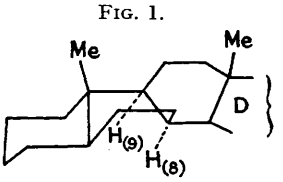
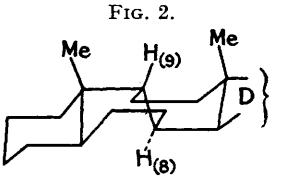


FIG. 2.



genation products about the 8 : 9-bridgehead are probably the same. The stability of the 11-ketostanol to alkali under conditions causing epimerisation at $C_{(9)}$ in (III) was then confirmed. This is best explained if the hydrogenation product is 3β-acetoxy-8α-ergostan-11-one (XI), saturation of the 8 : 9-bond having taken place by normal *cis*-addition of hydrogen.

On the other hand, hydrogenation of the similarly substituted 7-keto-$\Delta^{8(9)}$-system gives saturated ketones of natural configuration (8β : 9α) (cf. Stavely and Bollenback, *ibid.*, 1943, **65**, 1290). It is possible that *cis*-addition to give an 8α : 9α-compound first takes place and that this is succeeded by a ready epimerisation of the 8-hydrogen atom under the conditions of hydrogenation; alternatively, different steric factors may favour 1 : 4-addition of hydrogen to the unsaturated ketone system.

Addendum.—Since this paper was prepared for publication, Heusler and Wettstein (*Helv. Chim. Acta*, 1953, **36**, 398) have described the preparation of 3β-acetoxy-9β-ergost-7-en-11-one, m. p. 146—148°, $[\alpha]_D$ −144°, from the corresponding 9α : 11α-epoxide. They describe also the further isomerisation to the conjugated ketone.

EXPERIMENTAL

For general instructions see preceding paper. A Perkin–Elmer model 21 double-beam spectrophotometer equipped with rock-salt optics was used for the determination of infra-red spectra.

* Fig. 1 represents the most probable conformation for an 8α : 9α-compound, accounting for the ready conversion of 5α : 8α-dihydroxy-steroids into 5α : 8α-epoxides (Clayton, Henbest, and Jones, *J.*, 1953, 2015). On the assumption that ring A is in a chair form, Fig. 2 represents the only strainless conformation for an 8α : 9β-steroid.

The boron trifluoride–ether complex was freshly distilled before use, and the solvents used in conjunction with this reagent were thoroughly dried over sodium.

The 5α-hydrogen series.

3β-*Acetoxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (II; R = H, R′ = C_9H_{17}).*—(*a*) A solution of pure 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene (Heusser *et al.*, *Helv. Chim. Acta*, 1951, **34**, 2106) (5 g.; dried for 3 hr. *in vacuo*) in dry benzene (120 c.c.) was treated with boron trifluoride–ether complex (400 mg.). After 1 min. sodium hydrogen carbonate solution was added, the mixture shaken, and the benzene separated and evaporated under reduced pressure. Crystallisation from acetone afforded the 11-*ketone* (3·9 g.) as blades, m. p. 159—161°, $[\alpha]_D$ −191° (*c*, 1·16) (Found: C, 79·15; H, 10·05. $C_{30}H_{46}O_3$ requires C, 79·25; H, 10·2%). Light absorption: Max. 2950 Å; ε = 120. Infra-red spectrum (in CS_2): peaks at 1736 and 1240 (acetate), 1725 (11-ketone), 1660 (Δ⁷), 970 (Δ²²), 820 and 810 cm.⁻¹ ($C_{(7)}$–H bending).

(*b*) Boron trifluoride–ether complex (6·5 c.c.; 1·15 mols.) was added to a solution of the epoxide (20 g.) in dry ether (2 l.), the solution then being kept at 20° for 20 hr. Crystallisation of the product from chloroform–methanol gave the 11-ketone (17 g.), m. p. 158—160°, $[\alpha]_D$ −182°.

3β-*Acetoxyergosta*-7 : 22-*dien*-11-*one* (V; R = H, R′ = C_9H_{17}).—A solution of the foregoing ketone (2 g.) in light petroleum–benzene (2 : 1; 45 c.c.) was adsorbed on alumina (60 g.) (see below). Elution with the same solvent mixture (200 c.c.) and benzene (100 c.c.) gave a solid (1·75 g.) which, on crystallisation from methanol, afforded the 11-*ketone* as hexagonal plates, m. p. 175—180°, $[\alpha]_D$ +25° (Found: C, 79·2; H, 10·15. $C_{30}H_{46}O_3$ requires C, 79·25; H, 10·2%). Infra-red spectrum (in CS_2): peaks at 1735 and 1240 (acetate), 1710 (11-ketone), 1665 (Δ⁷), 970 (Δ²²), 830 and 800 cm.⁻¹ ($C_{(7)}$–H bending).

The alumina used above was prepared as follows: Peter Spence (Grade 0) alumina was treated with 10% aqueous acetic acid, then thoroughly washed with methanol, and reactivated (Brockmann grade II/III) at 100°/12 mm. It is important that the steroid is adsorbed on the column in a solvent of lower polarity than that required to elute the product. With other types of deactivated alumina, it is sometimes necessary to leave the column for several hours (or overnight) before eluting the 9α-isomer.

3β-*Acetoxyergosta*-8(9) : 22-*dien*-11-*one* (VI; R = H, R′ = C_9H_{17}).—(*a*) 3β-Acetoxy-9β-ergosta-7 : 22-dien-11-one (320 mg.; dried *in vacuo*) was dissolved in dry benzene (8 c.c.) and treated with boron trifluoride–ether complex (100 mg.; 1 mol.). The specific rotation of the solution changed from −186° to a constant value of +80° after 48 hr. at 20°. Isolation with ether and crystallisation from methanol yielded the conjugated ketone (250 mg.) as blunt needles, m. p. 136—136·5°, $[\alpha]_D$ +105° (*c*, 1·39) (Found: C, 79·3; H, 10·3. Calc. for $C_{30}H_{46}O_3$: C, 79·25; H, 10·2%). Light absorption: Max. 2540 Å; ε = 9200 (Heusser *et al.*, *loc. cit.*, record m. p. 122—123°, $[\alpha]_D$ +92°; $\lambda_{max.}$ 2530 Å, ε = 9500; Schoenewaldt *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 2696, give m. p. 131·5—134°, $[\alpha]_D$ +110°; $\lambda_{max.}$ 2540 Å, ε = 9140). Infra-red spectrum (in Nujol): peaks at 1732 and 1250 (acetate), 1655 and 1640 (11-ketone), 1590 ($\Delta^{8(9)}$), and 970 cm.⁻¹. (Δ²²).

(*b*) The 9β-unconjugated ketone (250 mg.) in acetic acid (8 c.c.) was heated under reflux for 2 hr. Isolation with ether, and recrystallisation from methanol, gave the conjugated ketone (195 mg.) as laths, m. p. 132—134°, $[\alpha]_D$ +95°.

(*c*) A solution of the 9β-unconjugated ketone (250 mg.) in benzene (5 c.c.) was adsorbed on alumina (25 g.). After 45 min. the column was eluted with ether (200 c.c.). Evaporation of the solvent gave a solid which afforded the conjugated ketone (180 mg.), m. p. 135—136°, $[\alpha]_D$ +105°, on crystallisation from methanol.

3β-*Acetoxy*-9β-*ergostan*-11-*one* (III; R = H, R′ = C_9H_{19}).—A solution of 3β-acetoxy-9β-ergosta-7 : 22-dien-11-one (250 mg.) in acetic acid (25 c.c.) was shaken with hydrogen and Adams catalyst (25 mg.). Hydrogenation ceased after the uptake of 2 mols. Isolation with ether, followed by crystallisation from methanol, afforded the saturated 11-*ketone* (200 mg.), m. p. 155—156°, $[\alpha]_D$ +43° (*c*, 1·39) (Found: C, 78·75; H, 10·75. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Light absorption: Max. 2920 Å; ε = 31. Infra-red spectrum (in CS_2): peaks at 1735 and 1245 (acetate), and 1720 cm.⁻¹ (11-ketone). On admixture with 3β-acetoxy-ergostan-11-one (see below) the m. p. was depressed to 113—145°. No derivative was formed with 2 : 4-dinitrophenylhydrazine.

Hydrogenation in dioxan, with Adams catalyst, yielded the same product.

3β-*Acetoxyergostan*-11-*one* (IV; R = H, R′ = C_9H_{19}).—A solution of the 9β-compound

* See addendum, p. 2926.

(1 g.) and potassium hydroxide (7·5 g.) in ethanol (50 c.c.) was heated under reflux for 18 hr. The product was isolated with ether and then reacetylated, to give (after crystallisation from aqueous methanol) 3β-acetoxyergostan-11-one (0·78 g.) as needles, m. p. 135—136°, $[\alpha]_D$ +33° (Found: C, 78·5; H, 10·95. Calc. for $C_{30}H_{50}O_3$: C, 78·55; H, 11·0%). The m. p. was not depressed on admixture with an authentic sample obtained by hydrogenation of 3β-acetoxyergost-22-en-11-one in acetic acid with Adams catalyst. Heusser *et al.*, *loc. cit.*, record m. p. 135—136°, $[\alpha]_D$ +32°.

Hydrogenation of 3β-*Acetoxyergosta*-7 : 22-*dien*-11-*one*.—(a) *In acetic acid.* The ketone (250 mg.), dissolved in acetic acid (25 c.c.), was shaken in hydrogen with prereduced Adams catalyst (100 mg.); three mols. were taken up in 2 hr. Filtration, evaporation under reduced pressure, and crystallisation from methanol, afforded 3β-acetoxyergost-8(14)-ene (α-ergostenyl acetate) (160 mg.) as plates, m. p. (and mixed m. p. with an authentic sample) 110—112°, $[\alpha]_D$ +1° (*c*, 2·2).

(b) *In dioxan.* Dioxan (25 c.c.) was substituted for acetic acid in experiment (a). Hydrogenation ceased after 5 hr., when 1 mol. of hydrogen had been absorbed. The product was crystallised from methanol, giving crude 3β-acetoxyergost-7-en-11-one, m. p. 145—156°, $[\alpha]_D$ +32°. Further crystallisation did not appreciably change these properties; the infra-red spectrum indicated the presence of acetate and 11-ketone groups and the virtual absence of the Δ^{22}-bond, and analytical data on the mixture were in agreement with $C_{30}H_{48}O_3$. A solution of this material (300 mg.) in benzene (5 c.c.) was adsorbed on alumina (P. Spence, Grade 0, 30 g.). After 15 hr. the column was eluted with benzene (150 c.c.) to give a gum; elution with ether (150 c.c.) gave solid (180 mg.) which crystallised from methanol, to yield 3β-*acetoxyergost*-8(9)-*en*-11-*one* as laths, m. p. 138—140°, $[\alpha]_D$ +119° (*c*, 0·8) (Found: C, 78·95; H, 10·5. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Light absorption: Max. 2540 Å; ε = 9010. Infra-red spectrum in Nujol: peaks at 1732 and 1247 (acetate), 1643 (11-ketone), and 1590 cm.$^{-1}$ ($\Delta^{8(9)}$).* On admixture with a sample of 3β-acetoxyergosta-8(9) : 22-dien-11-one, the m. p. was depressed to 123—133°.

Hydrogenation of 3β-*Acetoxyergosta*-8(9) : 22-*dien*-11-*one*.—(a) *In acetic acid.* The ketone (250 mg.) in acetic acid (25 c.c.) was shaken with prereduced Adams catalyst (100 mg.) in hydrogen. Three mols. were taken up in 4 hr. The product, crystallised from methanol, gave 3β-acetoxyergost-8(14)-ene (190 mg.) as plates, m. p. and mixed m. p. 110—112°, $[\alpha]_D$ 0°. The infra-red spectrum was identical with that of an authentic sample.

(b) *In ethanol.* The ketone (2·5 g.) in ethanol (150 c.c.) was shaken with 4% palladised charcoal (2·05 g.) under hydrogen for 18 hr. The gummy product was chromatographed on alumina (P. Spence, Grade 0, 60 g.). Elution with light petroleum–benzene (1 : 1) gave material (1·1 g.) which on crystallisation from methanol afforded 3β-*acetoxy*-8α-*ergostan*-11-*one* (XI) (705 mg.) as plates, m. p. 162—164°, $[\alpha]_D$ −11° (Found: C, 78·75; H, 10·95. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Infra-red spectrum (in CS_2): peaks at 1732 and 1240 (acetate) and 1698 cm.$^{-1}$ (11-ketone).

Attempted isomerisation of the above compound (500 mg.), by heating it with a solution of potassium hydroxide (4 g.) in ethanol (25 c.c.) for 18 hr., yielded unchanged material (after reacetylation).

The 5α-hydroxyl series.

3β-*Acetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene*-5α-*ol* (I; R = OH, R′ = C_9H_{17}).—An ethereal solution of monoperphthalic acid (1·4 mols.) was added to 3β-acetoxyergosta-7 : 9 : 22-trien-5α-ol (Bladon, Clayton, Greenhalgh, Henbest, Jones, Lovell, Silverstone, Wood, and Woods, *J.*, 1952, 4883) (1·75 g.) dissolved in dry ether (200 c.c.), and the mixture was kept at 0° for 24 hr. and then at 25° for 48 hr. The steroid was isolated with ether and then absorbed on deactivated alumina (200 g.) from benzene–light petroleum (1 : 1). Elution with the same solvent mixture (4·8 l.) gave crude diepoxide. Elution with benzene (5·2 l.) gave the 9α : 11α-*epoxide*, which crystallised from *iso*propyl ether as plates (570 mg.), m. p. 229—237°, $[\alpha]_D$ +2° (*c*, 1·06) (Found: C, 76·65; H, 10·0. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). The compound showed no significant absorption above 2200 Å. Infra-red spectrum (in CS_2): peaks at 3500 (hydroxyl), 1735 (acetate), and 968 cm.$^{-1}$ (Δ^{22}).

3β-*Acetoxy*-5α-*hydroxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (II; R = OH, R′ = C_9H_{17}).—The above epoxide (5·6 g.) in dry benzene (175 c.c.) was treated with boron trifluoride–ether complex

* The preparation of this compound by a different method has recently been described by Laubach, Schreiber, Agnello, Lightfoot, and Brunings (*J. Amer. Chem. Soc.*, 1953, **75**, 1514), who report m. p. 137·8—138·6° and α]$_D$ +125° (in $CHCl_3$).

(0·46 g.). The solution became slightly yellow during 5 min.; then aqueous sodium hydrogen carbonate was added with shaking. The steroid was crystallised from acetone to give the *hydroxy-ketone* (first crop, 4·35 g.; m. p. 173—182°, $[\alpha]_D$ −129°; second crop, 0·55 g., $[\alpha]_D$ −124°). Recrystallisation gave the pure product as blades, m. p. 181—187°, $[\alpha]_D$ −135° (*c*, 0·9) (Found: C, 76·3; H, 9·9. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption: Max. 2930 Å; $\varepsilon = 190$. Infra-red spectrum (in Nujol): peaks at 3530 (hydroxyl), 1725 (acetate), 1700 (11-ketone), and 1660 cm^{-1}. (Δ^7).

3β-*Acetoxy*-5α-*hydroxyergosta*-8(9) : 22-*dien*-11-*one* (VI; R = OH, R′ = C_9H_{17}).—The foregoing ketone (1 g.) in acetic acid (50 c.c.) was heated to boiling with zinc dust (3 g.). After 5 min., more zinc dust (7 g.) was added and the mixture heated under reflux for 3½ hr. The product (0·95 g.), isolated with ether, had $[\alpha]_D$ +53°; $\lambda_{max.}$ 2550 Å; $\varepsilon = 6300$. Crystallisation of this material raised the rotation slightly but did not raise the ε value at 2550 Å. The total product was chromatographed on deactivated alumina (100 g.), and material of $[\alpha]_D$ +20° to +60° was eluted with light petroleum–benzene (1 : 1), followed by a solid (0·43 g.) with $[\alpha]_D$ +80° eluted with benzene. Crystallisation of the latter product from methanol and then from acetone yielded the conjugated *ketone* as needles, m. p. 192—197°, $[\alpha]_D$ +81° (*c*, 0·89) (Found: C, 76·4; H, 9·8. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption: Max. 2570 Å; $\varepsilon = 9200$. The yield estimated by spectroscopic examination of the total reaction product was not altered by different reaction times (from 1 to 18 hr.), $\varepsilon_{max.}$ always being *ca.* 6500.

If the zinc was omitted from the experiment, the reaction proceeded more slowly and somewhat less completely, a constant ε value of 5100 being reached after about 5 hr.

3β-*Acetoxy*-5α-*hydroxy*-9β-*ergostan*-11-*one* (III; R = OH, R′ = C_9H_{19}).—3β-Acetoxy-5α-hydroxy-9β-ergosta-7 : 22-dien-11-one (250 mg.) in acetic acid (10 c.c.) was shaken in hydrogen with Adams catalyst (50 mg.); 2 mols. were taken up during 45 min. The product, dissolved in acetone (15 c.c.), was treated with 0·5 c.c. of 8N-chromic acid in dilute sulphuric acid for 10 min.; isolation with ether and crystallisation from methanol gave the *ketone*, m. p. 171—173°, $[\alpha]_D$ +88° (*c*, 0·95) (Found: C, 75·95; H, 10·55. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). Light absorption: Max. 2880 Å; $\varepsilon = 45$. Infra-red spectrum (in Nujol): peaks at 3400 (hydroxyl), 1730 (acetate), and 1690 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-5α-*hydroxyergostan*-11-*one* (IV; R = OH, R′ = C_9H_{19}).—A solution of the foregoing ketone (100 mg.) and potassium hydroxide (1 g.) in 95% methanol (10 c.c.) was heated under reflux for 18 hr. Isolation with ether, followed by crystallisation from acetone, gave the 3 : 5-diol (75 mg.) as needles, m. p. 228—231° (decomp.), $[\alpha]_D$ +39·5°. This diol, with acetic anhydride and pyridine at 20° overnight, afforded the 3-*acetoxy*-11-*ketone* (plates from methanol), m. p. 208—212°, $[\alpha]_D$ +24·5° (*c*, 1·02) (Found: C, 75·85; H, 10·75. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). Infra-red spectrum (in Nujol): peaks at 3490 (hydroxyl), 1735 (acetate), and 1693 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-5α : 8α-*epidioxybisnor*allo*chol*-9-*enic Acid*.—3β-Acetoxy-5α : 8α-epidioxyergosta-9(11) : 22-diene (Bladon *et al.*, *J.*, 1952, 4883) (20 g.) in ethyl acetate (1·5 l.) was treated with ozone at −70° until a blue colour persisted. After being allowed to warm to room temperature the solution was treated with potassium permanganate (10 g.) in water (170 c.c.) and acetic acid (200 c.c.). Air was passed through the mixture for 50 min. Excess of permanganate and manganese dioxide were removed by treatment with sodium hydrogen sulphite, the organic layer then being washed with water and then with 0·5N-sodium carbonate. Acidification of the alkaline washings precipitated 3β-acetoxy-5α : 8α-epidioxybisnor*allo*chol-9-enic acid (7·7 g.), m. p. 199—201°. For this compound Bladon *et al.* (*J.*, 1952, 4890) record m. p. 201—205°.

3β-*Acetoxy*-5α-*hydroxybisnor*allo*chola*-7 : 9(11)-*dienic Acid*.—The above acid (10 g.) was treated with zinc dust (20 g.) in refluxing acetic acid (200 c.c.). The steroid was isolated with chloroform; crystallisation from acetone yielded the *diene acid* (7·2 g.) as needles, m. p. 225—227°, $[\alpha]_D$ +54° (*c*, 1·1) (Found: C, 71·7; H, 8·4. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%). Light absorption: Max. 2425 Å; $\varepsilon = 15{,}500$. Infra-red spectrum (in Nujol): peaks at 3400 (hydroxyl), 1732 and 1250 (acetate), 1700 and 1275 cm.$^{-1}$ (carboxyl).

Treatment of the acid with diazomethane gave the methyl ester, which crystallised from methanol as needles, m. p. 193—195°, $[\alpha]_D$ +71° (*c*, 0·9) (Found: C, 72·3; H, 8·6. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%). (Bladon *et al.*, *J.*, 1952, 4890, give m. p. 191—193° $[\alpha]_D$ +69°). Infra-red spectrum (in Nujol): peaks at 3400 (hydroxyl), 1732 and 1250 cm.$^{-1}$ (acetate). Light absorption: Max. 2425 Å; $\varepsilon = 16{,}700$.

Methyl 3β-*Acetoxy*-9α : 11α-*epoxy*-5α-*hydroxybisnor*allo*chol*-7-*enate* (I; R = OH, R′ = CHMe·CO_2Me).—A solution of monoperphthalic acid in ether (99 c.c., containing 4·28 mg. of active oxygen per c.c.; 1·1 mols.) was added to methyl 3β-acetoxy-5α-hydroxybisnor*allo*chola-

7 : 9-dienate (10 g.) in dioxan (200 c.c.). After 24 hr. at 0°, and 48 hr. at 20° the solution was diluted with ethyl acetate and washed successively with water, sodium hydrogen carbonate solution, and water. After removal of the solvent *in vacuo*, crystallisation of the residue from acetone gave the *epoxide* (5·1 g.) as prisms, m. p. 204—206°, $[\alpha]_D$ +15° (*c*, 1·03) (Found : C, 69·4; H, 8·2. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). Infra-red spectrum (in Nujol) : peaks at 3300 (hydroxyl), 1730 and 1250 cm.$^{-1}$ (acetate).

Methyl 3β-*Acetoxy*-5α-*hydroxy*-11-*keto*-9β-*bisnor*allo*chol*-7-*enate* (II; R = OH, R′ = CHMe·CO_2Me).—The 9α : 11α-epoxide (500 mg.) in dry benzene (50 c.c.) was treated with boron trifluoride–ether complex (5 drops) and set aside for 5 min. Isolation with ether and crystallisation from methanol yielded needles of the 11-*ketone* (300 mg.), m. p. 171—172°, $[\alpha]_D$ −109° (*c*, 1·97) (Found : C, 69·55; H, 8·3. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). Infra-red spectrum (in CS_2) : peaks at 3520 (hydroxyl), 1735 and 1242 (acetate), 1708 (11-ketone), 1166 (ester), 830 and 810 cm.$^{-1}$ ($C_{(7)}$–H bending).

Methyl 3β-*Acetoxy*-5α-*hydroxy*-11-*keto*-9β-*bisnor*allo*cholanate* (III; R = OH, R′ = CHMe·CO_2Me).—A solution of the foregoing Δ^7-compound (200 mg.) in acetic acid (2 c.c.) was shaken in hydrogen with Adams catalyst (20 mg.), 1 mol. being taken up during 12 min. Filtration, evaporation under reduced pressure, and crystallisation of the residue from methanol gave the saturated *ketone* (120 mg.) as plates, m. p. 187°, $[\alpha]_D$ +84° (Found : C, 69·45; H, 8·85. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%). Infra-red spectrum (in CS_2) : peaks at 3420 (hydroxyl), 1734 and 1238 (acetate), 1734 and 1158 (ester) and 1703 cm.$^{-1}$ (11-ketone).

Methyl 3β-*Acetoxy*-5α-*hydroxy*-11-*ketobisnor*allo*cholanate* (IV; R = OH, R′ = CHMe·CO_2Me). —The corresponding 9β-compound (500 mg.) and potassium hydroxide (3·5 g.) in ethanol (25 c.c.) were heated under reflux for 15 hr. Acidification and extraction with ether gave the organic acid which was treated with diazomethane in ethereal solution, and then with acetic anhydride in pyridine, to yield the *ketone* (135 mg.), m. p. 215—218° (from methanol), $[\alpha]_D$ +18·5° (*c*, 0·65) (Found : C, 69·45; H, 8·9. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%). Infra-red spectrum (in CS_2) : peaks at 3600 (hydroxyl), 1732 and 1236 (acetate), 1735 and 1156 (ester), 1702 cm.$^{-1}$ (11-ketone). If the acetylation stage was omitted, the corresponding 3 : 5-*diol* was obtained as needles, m. p. 187—191°, $[\alpha]_D$ +46° (*c*, 0·92) (Found : C, 70·5; H, 9·25. $C_{23}H_{36}O_5$ requires C, 70·35; H, 9·25%). Infra-red spectrum (in Nujol) : peaks at 3600 and 3450 (hydroxyl), 1741 and 1160 (ester), and 1690 cm.$^{-1}$ (11-ketone).

Methyl 5α-*Hydroxy*-3 : 11-*diketobisnor*allo*cholanate* (IX; R′ = CHMe·CO_2Me).—Chromium trioxide in dilute sulphuric acid (0·5 c.c.; 7·5N, with respect to active oxygen) was slowly added to a solution of the above diol (400 mg.) in acetone (5 c.c.) at 40°. Isolation with ether, followed by crystallisation from aqueous acetone, gave the *diketone* (260 mg.) as plates, m. p. 222—226°, $[\alpha]_D$ +58° (Found : C, 70·9; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). Infra-red spectrum (in Nujol) : peaks at 3460 (hydroxyl), 1735 and 1170 (ester), 1710 and 1716 cm.$^{-1}$ (11- and 20-ketones).

The 2 : 4-dinitrophenylhydrazone formed rapidly with Brady's reagent as a yellow solid, quickly changing to a red solid shown to be the 2 : 4-*dinitrophenylhydrazone* of methyl 3 : 11-diketobisnorchol-4-enate. From a warm solution only the red solid was precipitated. The derivative crystallised from methanol–chloroform as needles, m. p. 248—250° (Found : C, 63·1; H, 6·4; N, 10·45. $C_{29}H_{36}O_7N_4$ requires C, 63·0; H, 6·6; N, 10·1%). Light absorption : Max. 2250 (ε = 18,500) and 3820 Å (ε = 33,000).

Methyl 3 : 11-*Diketobisnorchol*-4-*enate* (X; R′ = CHMe·CO_2Me).—The above diketone (95 mg.) in ethanol (30 c.c.) was treated with potassium hydroxide solution (33%; 0·45 c.c.) and then kept at 20° for 70 min. Isolation with ether gave solid (80 mg.) which, on crystallisation from aqueous methanol, afforded *methyl* 3 : 11-*diketobisnorchol*-4-*enate* as needles, m. p. 170°, $[\alpha]_D$ +86° (*c*, 0·6) (Found : C, 74·2; H, 8·6. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%). Light absorption : Max. 2370 Å; ε = 10,000. Infra-red spectrum (in Nujol) : peaks at 1742 and 1160 (ester), 1711 (11-ketone), 1678 (3-ketone), and 1620 cm.$^{-1}$ (Δ^4).

3β-*Acetoxy*-5α-*hydroxy*allo-9β-*pregn*-7-*ene*-11 : 20-*dione* (II; R = OH, R′ = COMe).—A solution of the corresponding 9α : 11α-epoxide (cf. preceding paper) (190 mg.; dried *in vacuo* at 80°) in dry benzene (10 c.c.) was treated with boron trifluoride–ether complex at 20°. After 5 min., the pale yellow solution was shaken with aqueous potassium hydrogen carbonate, dried, and evaporated. Crystallisation from methanol–*iso*propyl ether gave plates (140 mg.), m. p. 175—182°; the pure *ketone* had m. p. 182—183°, $[\alpha]_D$ −61° (*c*, 0·67) (Found : C, 71·1; H, 8·35. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). Infra-red spectrum (in Nujol) : peaks at 3480 (hydroxyl), 1717 (acetate and 20-ketone), 1705 (11-ketone), 1657 (Δ^7), and 1250 cm.$^{-1}$ (acetate).

3β-*Acetoxy*-5α-*hydroxy*allo-9β-*pregnane*-11 : 20-*dione* (III; R = OH, R′ = COMe).—The fore-

going Δ^7-compound (120 mg.) in acetic acid (12 c.c.) was shaken with hydrogen and prereduced Adams's catalyst (50 mg.). Between 2 and 3 mols. of hydrogen were taken up, and the mixture of dihydroxy(and possibly trihydroxy)-compounds was oxidised by treating the crude hydrogenation product in acetone (10 c.c.) at 40° with chromic acid solution [0·2 c.c. of a solution of chromic acid (6·7 g.) in sulphuric acid (5·35 c.c.) and water (20 c.c.)]. After 3 min., water was added and the steroid extracted with ether. The *diketone* (80 mg.) crystallised from methanol–*iso*propyl ether as needles, m. p. 177—179°, $[\alpha]_D$ +180° (*c*, 1·21) (Found: C, 71·0; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). Infra-red spectrum (in Nujol): peaks at 3390 (hydroxyl), 1730 (acetate and 20-ketone), 1690 (11-ketone), and 1250 cm.$^{-1}$ (acetate). In one experiment (3 mol. uptake), the product was crystallised from methanol–*iso*propyl ether, affording 3β-*acetoxy*-9β-allo*pregnane*-5α : 11ξ : 20ξ-*triol*, m. p. 240—250°, $[\alpha]_D$ +39° (*c*, 1·0) (Found: C, 70·1; H, 9·8. $C_{23}H_{38}O_5$ requires C, 70·0; H, 9·7%). The infra-red spectrum confirmed the presence of hydroxyl and acetate groups.

3β-*Acetoxy*-5α-*hydroxy*allo*pregnane*-11 : 20-*dione* (IV; R = OH, R′ = COMe).—The 9β-isomer (135 mg.) and potassium hydroxide (1 g.) in methanol (5 c.c.) and water (0·5 c.c.) were heated under reflux for 6 hr. Isolation with ether, followed by mild acetylation, gave a product which on crystallisation from chloroform–*iso*propyl ether afforded material (100 mg.), m. p. 240—250°. The pure *diketone* had m. p. 257—261°, $[\alpha]_D$ +79·5° (*c*, 0·66) (Found: C, 70·85; H, 8·85. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). Infra-red spectrum (in Nujol): peaks at 3485 (hydroxyl), 1720 (acetate and 20-ketone), 1690 (11-ketone), and 1245 cm.$^{-1}$ (acetate). Rehydrolysis of the material in the mother-liquor and reacetylation gave more material, probably owing to equilibration at $C_{(17)}$.

11-*Ketoprogesterone* (X; R′ = COMe).—3β-Acetoxy-5α-hydroxy*allo*pregnane-11 : 20-dione (70 mg.) was hydrolysed by hot 2% methanolic potassium hydroxide for 1 hr. The diol, obtained by ether-extraction of the acidified solution, was dissolved in acetone (7·5 c.c.) at 40° and treated with 0·15 c.c. of a solution of chromic acid (6·7 g.) in sulphuric acid (5·35 c.c.) and water (20 c.c.). After 2 min., the product was isolated with ether; crystallisation from methanol–*iso*propyl ether gave the 5-hydroxy-3-ketone (27 mg.) as prisms, m. p. 250°, $[\alpha]_D$ +123° (*c*, 0·41). This was dissolved in ethanol (10 c.c.) containing potassium hydroxide (0·2 g.) and kept at 20° for 1½ hr. Acidification and isolation with ether gave material that was absorbed on alumina (2 g.); the residue from the benzene eluates gave, after 3 crystallisations from methanol–*iso*propyl ether, 11-ketoprogesterone as needles, m. p. 170—173° (not depressed on admixture with a sample kindly supplied by Dr. C. Djerassi), $[\alpha]_D$ +234° (*c*, 0·63). Infra-red spectrum (in Nujol): peaks at 1700 (11- and 20-ketones), 1665 (3-ketone), 1615 (Δ^4), and 871 cm.$^{-1}$ ($C_{(4)}$–H bending); the spectrum was identical with that of Dr. Djerassi's sample.

The 5α-acetoxyl series.

3β : 5α-*Diacetoxy*-9α : 11α-*epoxyergosta*-7 : 22-*diene* (I; R = OAc, R′ = C_9H_{17}).—3β : 5α-Diacetoxyergosta-7 : 9(11) : 22-triene (Bladon *et al.*, *J.*, 1952, 4883) (7·63 g.) in ether (150 c.c.) was treated at 0° with monoperphthalic acid in ether (31·0 c.c.; 1·105N; 1·1 mols.), the solution then being kept at 0° for 24 hr. and at 20° for 48 hr. The solution was washed successively with water, sodium hydrogen carbonate solution, water, ferrous sulphate solution, and water, and then evaporated to dryness. Crystallisation of the residue from aqueous acetone gave the *epoxide* as needles (6·9 g.), m. p. 125—127°, $[\alpha]_D$ +57·5° (*c*, 0·7) (Found: C, 74·75; H, 9·4. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). The compound showed no significant absorption above 2200 Å. Infra-red spectrum (in CS_2): peaks at 1740—1730 and 1240 (acetates), 968 (Δ^{22}), and 807 cm.$^{-1}$ ($C_{(7)}$–H bending).

3β : 5α-*Diacetoxy*-9β-*ergosta*-7 : 22-*dien*-11-*one* (II; R = OAc, R′ = C_9H_{17}).—The above epoxide (10 g.) and boron trifluoride–ether complex (5 c.c.) in dry benzene (150 c.c.) and dry ether (350 c.c.) were kept at 20° for 3 hr. Treatment with sodium hydrogen carbonate solution, followed by evaporation of the organic solvent, yielded an oil which was dissolved in acetone (50 c.c.). Water (5 c.c.) was added and the solution was cooled to 0°, whereupon the *mono-acetone solvate* of the 11-ketone (8·5 g.) separated as rosettes of needles, melting at 77°, resolidifying by 115°, and melting again at 140—143°, $[\alpha]_D$ −45° (Found: C, 73·3; H, 9·3. $C_{32}H_{48}O_5$,C_3H_6O requires C, 73·65; H, 9·55%). The acetone was easily removed by warming the solvate *in vacuo* and the product then crystallised from methanol, affording the 11-*ketone* as rods, m. p. 140—143°, $[\alpha]_D$ −49° (Found: C, 74·75; H, 9·5. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Infra-red spectrum (in CS_2): peaks at 1730 (acetate and 11-ketone), 1664 (Δ^7), 1244 (acetate), 968 (Δ^{22}), and 805 cm.$^{-1}$ ($C_{(7)}$–H bending).

3β : 5α-*Diacetoxy*-9β-*ergostan*-11-*one* (III; R = OAc, R′ = C_9H_{19}).—The foregoing ketone

(4 g., of acetone solvate) in acetic acid (50 c.c.) was shaken in hydrogen with Adams catalyst (400 mg.); two mols. were absorbed in 10 min. The product, the 11-*ketone*, crystallised from methanol as plates (3 g.), m. p. 127—130°, $[\alpha]_D$ +64° (Found: C, 74·25; H, 10·0. $C_{32}H_{52}O_5$ requires C, 74·35; H, 10·15%). Infra-red spectrum (in CS_2): peaks at 1740, 1728 and 1240—1230 (acetates), and 1728 cm.$^{-1}$ (11-ketone).

3β-*Acetoxy*-5α-*hydroxyergostan*-11-*one* (IV; R = OH, R′ = C_9H_{19}).—A solution of the foregoing ketone (2 g.) and potassium hydroxide (10 g.) in ethanol (100 c.c.) was heated under reflux for 20 hr. Isolation with chloroform and crystallisation from ethanol gave a good yield of 3β : 5α-*dihydroxyergostan*-11-*one* as rods, m. p. 229—235°, $[\alpha]_D$ +37° (Found: C, 77·5; H, 10·9. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). Infra-red spectrum (in Nujol): peaks at 3500 and 3200 (hydroxyl), and 1700 cm.$^{-1}$ (11-ketone). Acetylation with acetic anhydride and pyridine at 20° gave the 3-acetate (IV; R = OH, R′ = C_9H_{19}) identical in a mixed m. p. determination and infra-red spectrum with a specimen prepared by the route described above.

3β : 5α-*Diacetoxyergosta*-7 : 22-*dien*-11-*one* (V; R = OAc, R′ = C_9H_{17}).—The isomeric 9β-compound (200 mg.) was adsorbed from light petroleum–benzene (1 : 1) solution on to alumina [acid washed, see preparation of (V; R = H, R′ = C_9H_{17})] (30 g.). The column was eluted with benzene to yield, after 2 crystallisations from ethanol, the 11-*ketone* (85 mg.) as needles, m. p. 174—178°, $[\alpha]_D$ +84° (Found: C, 74·65; H, 9·4. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Infra-red spectrum (in CS_2): peaks at 1735 and 1240 (acetate), 1710 (11-ketone), 1667 (Δ^7), 968 (Δ^{22}), and 805 cm.$^{-1}$ ($C_{(7)}$–H bending).

3β : 5α-*Diacetoxyergosta*-8 : 22-*dien*-11-*one* (VI; R = OAc, R′ = C_9H_{17}) (with D. C. Eaton).—3β : 5α-Diacetoxyergosta-7 : 22-dien-11-one (9α- or 9β-epimer) (1 g.), dissolved in methanol (50 c.c.), was treated with 2% methanolic sodium hydroxide (50 c.c.) The solution was kept at 20° for 1 hr., and the steroid then isolated with ether and reacetylated with acetic anhydride and pyridine at 20° overnight. The isomeric *diacetate* (0·8 g.) crystallised from methanol as laths, m. p. 150—153°, $[\alpha]_D$ +121° (*c*, 1·3) (Found: C, 74·85; H, 9·65. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Light absorption: Max. 2540 Å; ε = 9000. Infra-red spectrum (in CCl_4): peaks at 1735 (acetate), and 1665 cm.$^{-1}$ (11-ketone).

If the reacetylation was omitted, 5α-*acetoxy*-3β-*hydroxyergosta*-8 : 22-*dien*-11-*one* could be obtained by crystallisation from methanol. It formed needles, m. p. 128—131°, $[\alpha]_D$ +103° (*c*, 0·67) (Found: C, 76·5; H, 9·8. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). Light absorption: Max. 2540 Å; ε = 8800.

3β : 5α-*Diacetoxyergost*-7-*en*-11-*one* (V; R = OAc, R′ = C_9H_{19}).—(*a*) 3β : 5α-Diacetoxy-9α : 11α-epoxyergost-7-ene (cf. preceding paper) (500 mg.) in dry benzene (15 c.c.) was treated with 1 drop of boron trifluoride–ether complex. The measured rotation of the solution changed from +2·16° to +0·03° (constant) during 2 days. Isolation with ether, and chromatography of the product on deactivated alumina (50 g.), afforded the ketone (220 mg.) (eluted with 1 : 1 light petroleum–benzene). Recrystallisation from aqueous methanol gave the pure *ketone* as small needles, m. p. 143—147°, $[\alpha]_D$ +104° (*c*, 0·75) (Found: C, 75·0; H, 9·95. $C_{32}H_{50}O_5$ requires C, 74·65; H, 9·8%).

(*b*) 3β : 5α-Diacetoxyergosta-7 : 22-dien-11-one (500 mg.) in acetic acid (100 c.c.) was shaken with Adams catalyst (100 mg.) for 1 hr. under hydrogen at 100 atm. The product, isolated in the usual way, crystallised from methanol as needles, m. p. 153—157°, $[\alpha]_D$ +104° (*c*, 1·2) (Found: C, 74·5; H, 10·1. $C_{32}H_{50}O_5$ requires C, 74·65; H, 9·8%). Infra-red spectrum (in Nujol): peaks at 1740 and 1250 (acetate), and 1710 cm.$^{-1}$ (11-ketone).

Ergosta-7 : 22-*diene*-3β : 5α : 11β-*triol* (VII).—3β : 5α-Diacetoxyergosta-7 : 22-dien-11-one (0·8 g.) in ether (20 c.c.) was slowly added to a solution of lithium aluminium hydride (0·4 g.) in ether under nitrogen. The mixture was refluxed for 3 hr., then poured on ice, and the resulting aluminium hydroxide precipitate was dissolved in a small excess of aqueous tartaric acid. Isolation with chloroform, and crystallisation from acetone, gave the *triol* (0·6 g.) as plates, m. p. 235—236°, $[\alpha]_D$ −25° (*c*, 1·9) (Found: C, 77·5; H, 10·8. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·8%). Light absorption: Max. 2060 Å; ε = 6070. Infra-red spectrum (in Nujol): peaks at 3400 (hydroxyl), 968 (Δ^{22}), 829 and 809 cm.$^{-1}$ ($C_{(7)}$–H bending). The compound gave a yellow colour with tetranitromethane.

Acetylation gave the 3-*monoacetate*, which crystallised from alcohol as prisms, m. p. 217—218°, $[\alpha]_D$ −8° (*c*, 1·0) (Found: C, 76·3; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·25; H, 10·25%). Infra-red spectrum (in Nujol): peaks at 3600—3400 (hydroxyl), 1730 and 1275 (acetate), 966 (Δ^{22}), 834 and 806 cm.$^{-1}$ ($C_{(7)}$–H bending).

Ergost-8(14)-*ene*-3β : 5α : 11β-*triol* (VIII).—The preceding triol (300 mg.) in acetic acid (50 c.c.) was shaken with hydrogen in the presence of Adams catalyst (300 mg.) for 5 hr.

Removal of the catalyst, and evaporation of the solvent, gave a solid which was crystallised twice from acetone; *ergost*-8(14)-*ene*-3β : 5α : 11β-*triol* was obtained as plates, m. p. 193—196°, $[\alpha]_D$ +18° (*c*, 1·0) (Found : C, 78·0; H, 11·3. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). Light absorption : Apparent max. 2070—2080 Å; ε = 10,000.

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