Studies in the Steroid Group. Part LXIII. Synthesis of Cortisone Acetate* via *5α-Hydroxy-steroids.*

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A route from ergosterol to cortisone, proceeding *via* a new series of 5α-hydroxy-steroid intermediates, has been completed.

THE intention of this work has been to explore the possibilities of synthesising cortical hormones *via* 3β : 5α-dihydroxy-steroids. Such diols virtually constitute a protected Δ^4-3-ketone system since the unsaturated ketone can be formed at a late stage in the synthesis by oxidation to a 5α-hydroxy-3-ketone followed by dehydration.

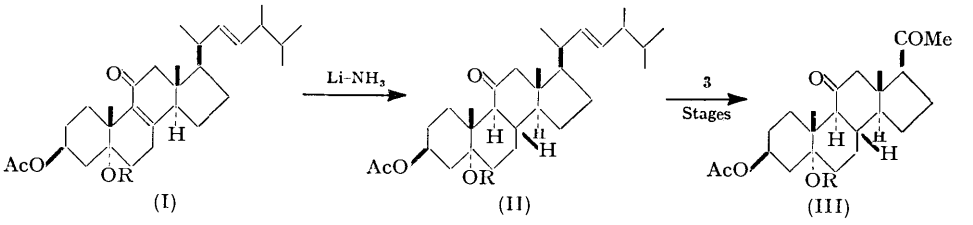
Earlier communications have recorded the preparation of 5α-hydroxy-compounds from the 5α : 8α-epidioxides of ergosterol (Part LX, Clayton, Henbest, and Jones, *J.*, 1953, 2015) and 9 : 11-dehydroergosterol (Part LVI, Bladon, Clayton, Greenhalgh, Henbest, Jones, Lovell, Silverstone, Wood, and Woods, *J.*, 1952, 4883). Further progress was reported in Part LVII (Bladon, Henbest, Jones, Wood, and Woods, *J.*, 1952, 4890), in which the side-chain degradation of a compound containing a 5α : 8α-epidioxy-$\Delta^{9(11)}$-grouping was described, leading eventually to a 5α-hydroxy-$\Delta^{7:9}$-20-ketone. Methods for conversion of 5α-hydroxy-$\Delta^{7:9}$-steroids into 5α-hydroxy-11-ketones (*via* 9α : 11α-epoxides, isomerisation to 11-oxo-9β-Δ^7-compounds, hydrogenation to 11-oxo-9β-steroids, and epimerisation at $C_{(9)}$) have been detailed in Parts LXI and LXII (*J.*, 1953, 2916, 2921, in collaboration with Dr. B. A. Hems and his colleagues of Glaxo Laboratories Ltd.) and were employed to effect a new synthesis of 11-oxoprogesterone.

In order to extend these approaches to the synthesis of cortisone and related hormones, a sufficient quantity of the key intermediate, the 11 : 20-diketone (III; R = H) was required. The diketone was first prepared as described in Part LXII (11 stages from ergosterol), but an alternative method (10 stages from ergosterol, improved overall yield) became available with the description of the lithium-ammonia reduction of 11-oxo-$\Delta^{8(9)}$-steroids to "natural" 11-ketones (Schoenewaldt, Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696; Sondheimer, Yashin, Mancera, Rosenkranz, and Djerassi, *ibid.*, p. 2696; 1953, **75**, 1282). Accordingly,

* Part LXII, *J.*, 1953, 2921.

this method of reduction was studied with the 3 : 5-diacetate (I; R = Ac, Part LXII), the reaction yielding the required nuclear saturated ketone (II; R = Ac) as the major product (after mild reacetylation). Smaller amounts of the corresponding 5α-hydroxy- (II; R = H) and 5α-hydrogen compound (II; OR replaced by H) were also formed in the reaction.

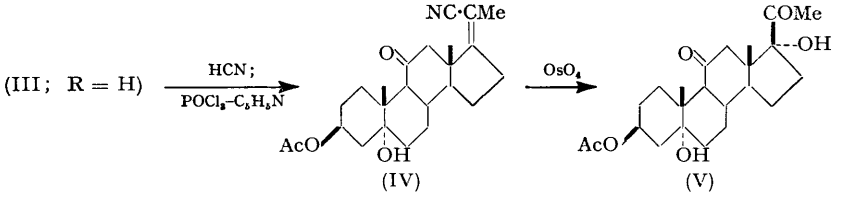
From (II; R = Ac) the way was now clear for shortening the side-chain. This was achieved by the methods described in detail in Parts LVII and LXI, ozonolysis giving



(I) (II) (III)

a C_{21} aldehyde (+ some acid), which on (potassium acetate-catalysed) enol acetylation and further ozonolysis yielded the 20-ketone (III; R = Ac). For the continuation of the synthesis it was advantageous to treat the reaction product from the second ozonolysis with alkali to hydrolyse both acetate groups, and then to reacetylate with acetic anhydride–pyridine at 20° to give the 5-hydroxy-compound (III; R = H). This procedure gave a better yield of 20-ketone than that involving isolation of the 3 : 5-diacetate, but more important, it was a convenient point at which to hydrolyse the 5-acetate. It was necessary to effect this replacement * at some stage in the synthesis, for, whereas 3β : 5α-diols are oxidised readily to 5α-hydroxy-3-ketones, the corresponding 5α-monoacetates (prepared in good yield by partial hydrolysis of 3β : 5α-diacetates, Part LVI) are relatively resistant to oxidation (Fudge and Shoppee, personal communication, and unpublished observations in these laboratories), probably owing to some interaction between the carbonyl group of the 5α-acetate and the 3α-hydrogen atom to be removed on oxidation.

Procedures for the introduction of hydroxyl groups at $C_{(17)}$ and at $C_{(21)}$ were now required. The widely used method of Koechlin, Garmaise, Kritchevsky, and Gallagher (*ibid.*, 1949, **71**, 3262) for inserting a 17α-hydroxyl group, involving enol acetylation of a 20-ketone to a 20-acetoxy-$\Delta^{17(20)}$-steroid followed by successive treatment with per-acid and with alkali, was considered first. Unfortunately, the conditions necessary to effect the (acid-catalysed) enol acetylation stage proved to be too drastic for the 5-hydroxy-compounds which, by experiments on simpler compounds (see Experimental section),



(IV) (V)

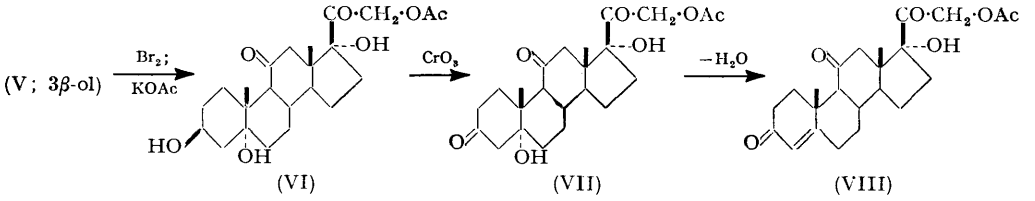
were shown to be readily dehydrated to Δ^5-steroids. This approach was therefore abandoned.†

The method devised by Sarett (*ibid.*, 1948, **70**, 1454) for elaborating the cortical side-chain appeared to be more suited to our series of compounds (some preliminary experiments

* An alternative approach appears to be to replace the 5-acetate in (II; R = Ac) by hydroxyl, ozonise, convert the aldehyde obtained into an " enamine " (Heyl and Herr, *ibid.*, 1952, **74**, 3627), and ozonise again.

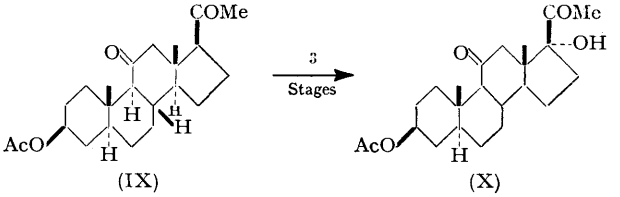
† In theory it would be possible to proceed with the synthesis *via* a Δ^5-compound [*e.g.*, that derived from (III; R = H)], but the unsaturated compounds would require protection at later stages. Besides the chemical advantages of retaining the 5-hydroxyl group, the synthesis led eventually to the 5-hydroxy-3-ketone (VII) which, in view of its close relation to cortisone, was required for clinical testing.

in the 5α-hydrogen series are discussed below). Addition of hydrogen cyanide to (III; R = H) (by a modified procedure) afforded one stereoisomer predominantly. This, on treatment with phosphorus oxychloride in pyridine at 20°, was dehydrated *selectively* to yield the conjugated unsaturated nitrile (IV)—experiments with simpler compounds had already established that 5α-hydroxy-steroids were recovered substantially unchanged when treated with this dehydrating reagent. Hydroxylation of the $\Delta^{17(20)}$-bond of (IV) led to the 3β : 5α : 17α-trihydroxy-compound, conveniently isolated as the 3-acetate (V), the 3-hydroxy-compound being relatively insoluble in organic solvents.



Hydrolysis of the 3-acetoxy-group of (V) was carried out with alkali in conditions mild enough to avoid structural alterations in the 17-hydroxy-20-ketone system. The resulting triol-diketone was sufficiently soluble in chloroform to permit bromination, the crude 21-bromo-compound then being treated with potassium acetate in acetone to afford (VI). Oxidation of this with chromic–sulphuric acid in acetone (cf. Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402) gave the penultimate compound (VII) of the synthesis. Dehydration of this 5-hydroxy-compound to cortisone acetate (VIII) was best achieved with hot acetic acid (cf. Lardon, *Helv. Chim. Acta*, 1949, **32**, 1517)—some deacetylation at $C_{(21)}$ appeared to take place during this treatment and a better yield of (VIII) was obtained after reacetylation with acetic anhydride. Treatment of (VII) with dilute alkali (Julia, Plattner, and Heusser, *ibid.*, 1952, **35**, 665) also gave cortisone, isolated as its acetate after reacetylation, but the hormone was more difficult to isolate from the reaction product probably owing to side-reactions in the somewhat alkali-sensitive cortical side-chain.

The cyanohydrin route to 17-hydroxy-steroids developed by Sarett (*loc. cit.*) with A–B-*cis*-compounds has been extended to compounds in the 5α-hydrogen series. Thus, the 11 : 20-diketone (IX) gave a cyanohydrin (mainly one isomer formed) which afforded a



good yield of unsaturated nitrile on dehydration. Hydroxylation led to (X) identical in properties with that prepared (by the enol-acetylation route) by Pataki, Rosenkranz, and Djerassi (*J. Amer. Chem. Soc.*, 1952, **74**, 5615).

Experimental

General directions are as given in Part LVI (*J.*, 1952, 4883).

3β : 5α-*Diacetoxyergost*-22-*en*-11-*one* (II; R = Ac).—Lithium (345 mg., 5 atoms), cut into small pieces, was added to a mixture of dry ether (200 c.c.) and liquid ammonia (500 c.c.) in a flask fitted with a soda-lime guard-tube. After 10 min., a solution of 3β : 5α-diacetoxyergosta-8 : 22-dien-11-one (5 g.) in dry ether (80 c.c.) at 0° was poured quickly into the flask which was swirled gently. Ammonium chloride was added immediately to discharge the blue colour of the mixture. The ammonia was removed by evaporation and the steroid isolated with ether. The products from 6 such experiments were combined and acetylated with acetic anhydride–pyridine at 20° overnight. Isolation with ether afforded a yellow gum, which in light petroleum–

benzene (10 : 3) was introduced on to acetic acid-deactivated alumina (800 g.). Elution with light petroleum–benzene (9 : 1) (3 l.) gave material, which after crystallisation from methanol and from hexane gave 3β-acetoxyergost-22-en-11-one (1·66 g.) as laths, m. p. 127—128·5°, $[\alpha]_D$ +14° (*c*, 1·85) (the m. p. and infra-red spectrum were identical with those of an authentic sample). Elution with light petroleum–benzene (4 : 1) (1·5 l.) yielded a gum. Development with light petroleum–benzene (2 : 3) gave, after crystallisation from methanol, 3β : 5α-*diacetoxyergost*-22-*en*-11-*one* (II; R = Ac) (10·9 g.), m. p. 134—137°; the pure product had m. p. 139—140°, $[\alpha]_D$ +37·5° (*c*, 1·27) (Found : C, 74·85; H, 9·55. $C_{32}H_{50}O_5$ requires C, 74·65; H, 9·8%). Infra-red spectrum (in Nujol) : main peaks at 1740, 1245 (acetate), 1700 (11-ketone), and 972 cm.$^{-1}$ (Δ^{22}). Elution with benzene–ether (3 : 1) (2 l.) yielded 3β-*acetoxy*-5α-*hydroxyergost*-22-*en*-11-*one* (II; R = H) (3·5 g.), which crystallised from methanol in leaflets, m. p. 216—221°, $[\alpha]_D$ +2° (*c*, 0·85) (Found : C, 76·5; H. 10·45. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%). Light absorption : Max. 2860 Å; ε = 41. Infra-red spectrum (in CCl_4); peaks at 3500 (hydroxyl), 1722, 1240 (acetate), and 1698 cm.$^{-1}$ (11-ketone).

3β : 5α-*Diacetoxy*-11-*oxobisnorcholan*-22-*al*.—3β : 5α-Diacetoxyergost-22-en-11-one (3·8 g.) in ethyl acetate (380 c.c.) at −70° was treated with a solution of ozone in ethyl acetate at −70° until a faint blue colour persisted. Nitrogen was bubbled for 10 min. through the solution, which was then warmed to 20° and shaken with aqueous ferrous sulphate until the organic layer gave no colour with starch–iodide paper. After being washed twice with 2% potassium hydroxide solution (see below), the organic solvent was removed under reduced pressure. Crystallisation of the product from acetone–*iso*propyl ether gave the *aldehyde* (2·3 g.) as blades, m. p. 150—152° (some decomp.), $[\alpha]_D$ +42·5° (*c*, 1·18) (Found : C, 69·0; H, 8·8; $C_{26}H_{38}O_6,CH_3{\cdot}CO{\cdot}CH_3$ requires C, 69·0; H, 8·8%). Infra-red spectrum (in CCl_4) : peaks at 2680 (aldehyde C–H stretching), 1730 and 1703 (carbonyl groups), and 1240 cm.$^{-1}$ (acetate).

Methyl 3β : 5α-*Diacetoxy*-11-*oxobisnorcholanate*.—The alkaline washings from the previous experiment gave a negligible precipitate on acidification, but from a previous experiment, in which excess of ozone was not removed by passage of nitrogen, starting material (2 g.) gave an acid fraction (150 mg.). Methylation with diazomethane and acetylation afforded the *methyl* ester (prisms from aqueous methanol), m. p. 188—192°, $[\alpha]_D$ +51·5° (*c*, 0·88) (Found : C, 67·95; H, 8·6. $C_{27}H_{40}O_7$ requires C, 68·05; H, 8·45%).

3β : 5α : 22-*Triacetoxybisnorchol*-20(22)-*en*-11-*one*.—The aldehyde (1·46 g.), fused potassium acetate (165 mg.), and redistilled acetic anhydride (3 c.c.) were heated together at 125° for 6 hr. The mixture was cooled, dissolved in pyridine (6 c.c.), poured on ice, and worked into ether. Crystallisation from acetone–*iso*propyl ether gave a product (1·2 g.), m. p. 168—172°. Crystallisation from methanol then gave the pure *enol-acetate* as platelets, m. p. 181—182°, $[\alpha]_D$ +51·5° (*c*, 1·07) (Found : C, 68·65; H, 8·25. $C_{28}H_{40}O_7$ requires C, 68·85; H, 8·25%). Infra-red spectrum (in Nujol) : 1742, 1225 (enol acetate), 1727, 1250 (acetate), 1698 (11-ketone), and 1665 cm.$^{-1}$ ($\Delta^{20(22)}$).

3β-*Acetoxy*-5α-*hydroxy*allo*pregnane*-11 : 20-*dione* (III; R = H).—A solution of the above enol acetate (1·64 g.) in ethyl acetate (160 c.c.) was cooled to −70° and treated with a solution of ozone in ethyl acetate at −70° until a permanent blue colour was obtained. Nitrogen was bubbled through the solution to remove excess of ozone, and the ozonide was decomposed as described above for the aldehyde preparation. The gummy product was treated with a 10% solution of potassium hydroxide in ethanol containing 5% of water under reflux for 15 hr. in nitrogen. About half of the solvent was removed under reduced pressure; water was added and the steroid (0·88 g.) extracted with ethyl acetate. Crystallisation of this material from methanol * gave solid (410 mg.), 100 mg. of which was crystallised from methanol and then from acetone to afford 3β : 5α-*dihydroxy*allo*pregnane*-11 : 20-*dione* as prismatic needles, m. p. 243—247°, $[\alpha]_D$ +108° (*c*, 0·75 in $CHCl_3$ containing 5% of EtOH) (Found : C, 72·35; H, 9·25. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%). Infra-red spectrum (in Nujol) : peaks at 3450 (hydroxyl) and 1690 cm.$^{-1}$ (11- and 20-ketones). The remainder of the diketone (360 mg.) (including that from the mother-liquors of the above crystallisations) was acetylated with acetic anhydride and pyridine. The product, isolated with ether, was crystallised from methanol, to give 3β-acetoxy-5α-hydroxy*allo*pregnane-11 : 20-dione (330 mg.), m. p. 254—260°, $[\alpha]_D$ +80°. The filtrate marked * above was evaporated to dryness and the residue heated under reflux in nitrogen for 2 hr. with a 5% solution of potassium hydroxide in methanol containing 5% of water. This product was reacetylated and then crystallised from the mother-liquors of the previous crystallisation of the 3-monoacetate, to give a product (157 mg.) with m. p. 253—256°, $[\alpha]_D$ +75°. Recrystallisation of the combined material from acetone–methanol yielded pure 3β-acetoxy-5α-hydroxy*allo*pregnane-11 : 20-dione as platelets, m. p. 261—263°, $[\alpha]_D$

+79° (*c*, 0·75) (Found: C, 70·45; H, 8·95. Calc. for $C_{23}H_{34}O_5$: C, 70·75; H, 8·8%). Infra-red spectrum (in Nujol): peaks at 3450 (hydroxyl), 1728, 1250 (acetate), and 1695 cm.$^{-1}$ (11- and 20-ketones). This compound is identical with that prepared by the alternative route (Part LXII, *loc. cit.*).

3β : 5α-*Diacetoxy*allo*pregnane*-11 : 20-*dione* (III; R = Ac).—The above enol acetate (0·64 g.) in ethyl acetate (60 c.c.) was cooled to −70° and treated with a solution of ozone in ethyl acetate at −70° until a permanent blue colour was produced. Nitrogen was bubbled through the solution for 10 min. The product was isolated as described above for the aldehyde; it was chromatographed on deactivated alumina (70 g.), elution with benzene–ether (19 : 1) yielding material (410 mg.) of m. p. 144—149°. Recrystallisation from *iso*propyl ether afforded the 11 : 20-*diketone* as prisms, m. p. 150·5—152°, $[\alpha]_D$ +107° (Found: C, 69·5; H, 8·45. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). Infra-red spectrum (in Nujol): peaks at 1725, 1697, and 1250 cm.$^{-1}$.

3β-*Acetoxy*-5α : 17α-*dihydroxy*allo*pregnane*-11 : 20-*dione* (V).—A mixture of 3β-acetoxy-5α-hydroxy*allo*pregnane-11 : 20-dione (96 mg.) in pyridine (1 c.c.), liquid hydrogen cyanide (5 c.c.), and 1-ethylpiperidine (4 drops) was kept at 20° overnight. Dilute hydrochloric acid was added and the product (112 mg.) isolated with ether. This material (dried *in vacuo*) in pyridine (1 c.c.) was treated with redistilled phosphorus oxychloride (0·12 c.c.) and kept overnight at 20°. Isolation with chloroform gave material (103 mg.) which showed $\lambda_{max.}$ 2210 Å (ε 13,500). This was dissolved in pyridine (2 c.c.), treated with osmium tetroxide (103 mg.), and kept overnight at 20°; some brown needles had then separated. Mannitol (1 g.) and potassium hydroxide (200 mg.) in water (2 c.c.) and methanol (2 c.c.) were added and the mixture was warmed at 40° for 10 min. After addition of dilute hydrochloric acid, the mixture was extracted eight times with chloroform, to give material (122 mg.), which was acetylated with acetic anhydride–pyridine overnight at 20° and then isolated with ether. Crystallisation of the product from methanol–*iso*propyl ether gave 3β-*acetoxy*-5α : 17α-*dihydroxy*allo*pregnane*-11 : 20-*dione* (58 mg.), m. p. 254—260° (decomp.), $[\alpha]_D$ +18° (*c*, 0·43) (Found: C, 68·1; H, 8·6. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·45%). On a larger scale, 1·28 g. of starting material afforded 1·04 g. of 17-hydroxy-compound (m. p. 255—258°)—in this experiment (repeated) extraction of the product from the (acidified) mixture obtained by hydrolysis of the osmium complex was performed with ethyl acetate, and this material (1·15 g.) (after mild acetylation) was twice passed in ethyl acetate solution through deactivated alumina (20-g. portions) to remove traces of dark osmium impurities.

21-*Acetoxy*-5α : 17α-*dihydroxy*allo*pregnane*-3 : 11 : 20-*trione* (VII).—The foregoing acetate (60 mg.) in dry methanol (5 c.c.) was mixed with a solution of sodium methoxide (70 mg.) in dry methanol, the mixture then being kept at 20° for 2 hr. Acetic acid was added and the steroid isolated with chloroform. It was treated in chloroform (40 c.c.) with bromine in chloroform (0·6 c.c. of 0·62N) and a trace of hydrogen bromide. The solution, illuminated with a 100-watt lamp, became colourless after 2½ hr. Evaporation under reduced pressure gave a solid which with dry potassium acetate (200 mg.) was heated under reflux in dry acetone solution (12 c.c.). The product (isolated with chloroform) was dissolved in acetone at 40°, and treated with a solution (0·15 c.c.) [prepared from chromic acid (6·7 g.) and sulphuric acid (5·3 c.c.), and made up to 25 c.c. with water] for 1½ min. The product was isolated with chloroform and crystallised from acetone and from ethyl acetate, to give the 3 : 11 : 20-*triketone* (22 mg.) as plates, m. p. 257—259° (decomp.), $[\alpha]_D$ +110° [*c*, 0·39 in EtOH–$CHCl_3$ (1 : 9)] (Found: C, 65·8; H, 7·65. $C_{23}H_{32}O_7$ requires C, 65·7; H, 7·65%). Infra-red spectrum (in Nujol): main peaks at 3460, 3320 (OH), 1740, 1242 (acetate), 1730 and 1700 cm.$^{-1}$ (keto-groups). From a larger-scale experiment, 180 mg. of triketone were obtained from 1 g. of starting material—in this experiment, the extractions were made with ethyl acetate in place of chloroform.

Cortisone Acetate (VIII) *from* (VII).—A solution of the 5α-hydroxy-compound (40 mg.) in acetic acid (5 c.c.) was heated under reflux (oil-bath) for 2 hr. The solvent was removed under reduced pressure and the residue treated with pyridine (2 c.c.) and acetic anhydride (1 c.c.) at 20° overnight. Four crystallisations of the product from ethanol gave pure cortisone acetate (18 mg.) as laths, m. p. and mixed m. p. 232—240°, $[\alpha]_D$ +218° (*c*, 0·44). The infra-red spectrum (in Nujol) was identical with that of an authentic sample: peaks at 3440, 1742, 1726, 1700, 1650, and 1610 cm.$^{-1}$. Dehydration of (VII) with 1% potassium hydroxide in methanol–water (40 : 1 v/v) under nitrogen at 20° for 100 min. gave (after evaporation, extraction of the dried residue with tetrahydrofuran, and reacetylation) somewhat less pure cortisone acetate, m. p. 225—233°, $[\alpha]_D$ +205°.

Dehydration of 3β-*Acetoxy*-5α-*hydroxyergostan*-11-*one*.—The steroid (86 mg.) in carbon

tetrachloride (2 c.c.) was treated with 60% perchloric acid (0·2 c.c.) in acetic anhydride (1 c.c.). After 1½ hr., the steroid was isolated (from the now dark solution) with ether. The product (91 mg.) was chromatographed on alumina (10 g.), benzene eluting a solid (63 mg.), which after 2 crystallisations from methanol gave 3β-*acetoxyergost*-5-*en*-11-*one* as needles, m. p. 121—123°, $[\alpha]_D$ −15·5° (*c*, 0·54) (Found: C, 78·75; H, 10·3. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Infra-red spectrum (supercooled melt): peaks at 1735, 1280, 1240 (acetate), 1690 (11-ketone), and 1663 cm.$^{-1}$ (Δ^5). When 3β-acetoxycholestan-5α-ol was subjected to these acidic conditions, a good yield of cholesteryl acetate was obtained.

3β-*Acetoxy*-20ξ-*cyano*-20ξ-*hydroxy*allo*pregnan*-11-*one*.—A mixture of 3β-acetoxy*allo*pregnane-11 : 20-dione (740 mg.) in dioxan (6 c.c.), liquid hydrogen cyanide (17 c.c.), and sodium cyanide (50 mg.) was kept at 20° overnight. Acetic acid was added, most of the hydrogen cyanide was removed by warming, and the steroid was isolated with ether. Recrystallisation from dioxan–*iso*propyl ether (containing a little acetic acid) gave the *cyanohydrin* (460 mg.) as needles, m. p. 185—187°, $[\alpha]_D$ +44° (*c*, 1·12) (Found: C, 71·45; H, 8·8; N, 3·7. $C_{24}H_{35}O_4N$ requires C, 71·8; H, 8·8; N, 3·5%).

3β-*Acetoxy*-20-*cyano*allo*pregn*-17-*en*-11-*one*.—A mixture of the cyanohydrin (850 mg.), pyridine (3·5 c.c.), and phosphorus oxychloride (0·55 c.c.) was kept overnight at 20°. The steroid was isolated with ether; crystallisation from methanol afforded the unsaturated *nitrile* (550 mg.) as needles (changing to hexagonal plates at 200—240°), m. p. 263—268°, $[\alpha]_D$ −6·5° (*c*, 0·9) (Found: C, 75·1; H, 8·4; N, 3·65. $C_{24}H_{33}O_3N$ requires C, 75·15; H, 8·7; N, 3·65%). Ultra-violet absorption (in ethanol): Maximum, 2210 Å (ε 12,300). Infra-red spectrum (in Nujol): peaks at 2220 (nitrile), 1720, 1250 (acetate), 1700 (11-ketone), and 1640 cm.$^{-1}$ ($\Delta^{17(20)}$).

3β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-11 : 20-*dione* (X).—The foregoing nitrile (191 mg.) in benzene (5·5 c.c.) was treated with osmium tetroxide (200 mg.) and pyridine (0·1 c.c.), the mixture being kept at 20° overnight. It was then shaken for 4 hr. with mannitol (2 g.) and potassium hydroxide (400 mg.) in water (20 c.c.), the brown colour being largely transferred from the organic to the aqueous phase, and some solid separating. The aqueous solution was twice extracted with chloroform, the organic extracts were evaporated, and the residue was dissolved in hot methanol (2 c.c.) and treated with potassium hydroxide (100 mg.) in methanol (0·5 c.c.) for 2 min.; some solid separated. Water was added, to give 3β : 17α-dihydroxy*allo*pregnane-11 : 20-dione (156 mg., 90%), m. p. 284—287°. This, with acetic anhydride and pyridine overnight at 20°, afforded the 3-acetate, m. p. 173—174° (melting and resolidifying at 160°), $[\alpha]_D$ +16° (*c*, 0·44) (Found: C, 70·8; H, 8·75. Calc. for $C_{23}H_{34}O_5$: C, 70·75; H, 8·8%). Infra-red spectrum (in Nujol): peaks at 3465 (hydroxyl), 1725 (acetate and 20-ketone), 1701 (11-ketone), and 1275 and 1250 cm.$^{-1}$ (acetate). Pataki *et al.* (*loc. cit.*) report m. p. 171—173°, $[\alpha]_D$ +8°.

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