The Synthesis of Progesterone and Related Compounds.

By A. F. DAGLISH, J. GREEN, and V. D. POOLE.

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Ergosterol has been converted into pregnane-3 : 20-dione, progesterone, and 3α-acetoxypregnan-20-one.

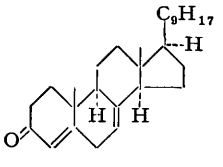
PREGNANE-3 : 20-DIONE, progesterone, and 3α-acetoxypregnan-20-one are useful intermediates in the synthesis of cortisone from readily available steroids and the object of the work described here is to provide a convenient route to these compounds from ergosterol. Preliminary announcements on this subject from the Upjohn Company (*Chem. Eng. News*, 1953, **31**, 3977), Johnson, Newbold, and Spring (*Chem. and Ind.*, 1953, 1230), and ourselves (*ibid.*, p. 1207) have already appeared.

Ergosterone (ergosta-4 : 7 : 22-trien-3-one) (I) was prepared by the Oppenauer oxidation of ergosterol with aluminium *iso*propoxide, *cyclo*hexanone, and benzene or toluene. The use of acetone as hydrogen acceptor gave products which contained unchanged ergosterol. When *iso*butyl methyl ketone and aluminium *iso*propoxide were used in the *absence* of the conventional inert solvent, good yields of ergosterone were obtained.

The direct isomerisation of ergosterone to *iso*ergosterone (ergosta-4 : 6 : 22-trien-3-one) (III) in 60% yield by treatment with a chloroform solution of hydrogen chloride has been carried out by Barton, Cox, and Holness (*J.*, 1949, 1771), but this yield is only obtained when the ergosterone has been carefully purified. In order to avoid this wasteful procedure, the crude product from the Oppenauer oxidation was acetylated directly, giving the enol acetate of ergosterone (II) (cf. Heilbron, Kennedy, Spring, and Swain, *J.*, 1938, 869), which in boiling aqueous-methanolic sulphuric acid afforded *iso*ergosterone in 66% overall yield from ergosterol. Other methods previously described for this conversion (Heilbron *et al.*, *loc. cit.*; Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, 1951, **16**, 1453) were found to give only low yields of highly coloured material. The hydrolysis proceeds through an intermediate compound believed from its analysis and ultra-violet absorption spectrum to be 3-methoxyergosta-3 : 5 : 7 : 22-tetraene. It has $\lambda_{max.}$ at 320 mμ (log ε 4·30), corresponding to a conjugated heteroannular triene, exhibiting the typical bathochromic shift due to methoxyl substitution (cf. Dorfman, *Chem. Reviews*, 1953, **53**, 47). It is easily isolated as it is precipitated from the reaction mixture during the early stages of the hydrolysis.

Hydrogenation of a dry ethanolic solution of *iso*ergosterone, in the presence of 10% palladised charcoal and relatively high concentrations of potassium hydroxide, ceased after the uptake of two mols. of hydrogen, yielding 5β-ergost-22-en-3-one (IV). Other

catalyst carriers such as calcium carbonate and barium sulphate were also successful. When a less active palladium catalyst (1% on charcoal) was used with a lower concentration of alkali, and when the hydrogenation was stopped after the uptake of one mol. of hydrogen, ergosta-4 : 22-dien-3-one (VI) (Barton *et al.*, *loc. cit.*) was isolated in good yield. However, this dienone was prepared more conveniently and in excellent yield by treating *iso*-ergosterone in liquid ammonia with lithium or sodium followed by ethanol, according to the general method of Wilds and Nelson (*J. Amer. Chem. Soc.*, 1953, **75**, 5360). This appears to be the first time that this reagent has been used for the selective reduction of a steroidal conjugated heteroannular dienone.



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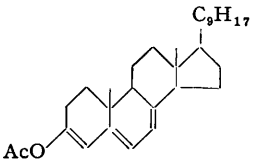

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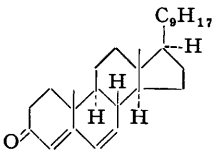

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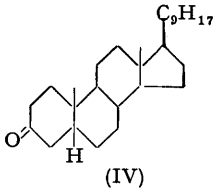

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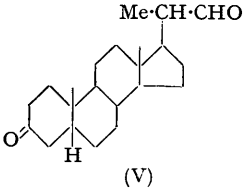

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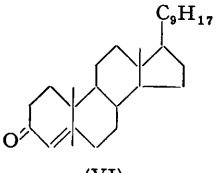

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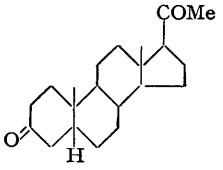

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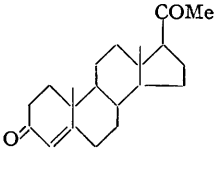

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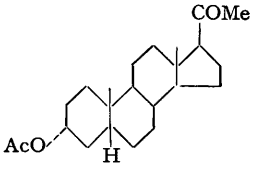

(IX)

Treatment of a chloroform solution of 5β-ergost-22-en-3-one at −70° with one mol. of ozone gave 3-oxobisnorcholan-22-al (V) in 92% yield. Ozonisation in other solvents was unsatisfactory. When two or more mols. of ozone were used, or when ozonisation was carried out at higher temperatures, the products contained large amounts of 3-oxobisnorcholanic acid. This acid was best obtained by permanganate oxidation of the ozonisation product. The cyclic ketal prepared from 5β-ergost-22-en-3-one and ethylene glycol was ozonised at 0° and gave a mixture from which, on esterification with diazomethane, methyl 3-ethylenedioxybisnorcholanate was isolated. The side chain of this compound could not be degraded further with phenylmagnesium bromide in the usual manner without hydrolysis of the ketal grouping. The only product isolated was 3 : 22 : 22-triphenylbisnorchola-3 : 20(22)-diene.

Treatment of a chloroform solution of ergosta-4 : 22-dien-3-one at −70° with one mol. of ozone gave 3-oxobisnorchol-3-en-22-al, which has been previously prepared from stigmasterol and converted into progesterone by Heyl and Herr (*loc. cit.*; *ibid.*, 1952, **74**, 3627).

3-Oxobisnorcholan-22-al was degraded by way of its enol acetate, prepared by the method of Bergman and Stevens (*J. Org. Chem.*, 1948, **13**, 10). The enol acetate was ozonised, without isolation, giving pregnane-3 : 20-dione (VII). Alternatively, degradation proceeded by way of the 22-piperidino-derivative (cf. Heyl and Herr, *loc. cit.*). This enamine, because of its instability, was difficult to obtain pure, and generally the crude condensation product was ozonised directly, to give the dione.

Hydrogenation of 5β-ergost-22-en-3-one in ethanol, containing potassium hydroxide, with Raney nickel gave 5β-ergost-22-en-3α-ol in 90% yield. (Barton *et al.*, *loc. cit.*, reduced this ketone with sodium and *n*-propanol.) The reduction was also carried out in high

yield with lithium in liquid ammonia, followed by addition of ethanol. 5β-Ergost-22-en-3α-ol was also obtained in good yield by the Raney nickel reduction of either ergost-4 : 22-dien-3-one or *iso*ergosterone, uptake of hydrogen ceasing at 2 and 3 mols. respectively. Acetic anhydride gave the 3α-acetate in 93% yield.

Treatment of a chloroform solution of 3α-acetoxy-5β-ergost-22-ene at −70° with one mol. of ozone gave over 90% of 3α-acetoxybisnorcholan-22-al. When larger amounts of ozone were used at higher temperatures, the main product isolated was the 3α-acetoxy-acid, also obtained in high yield by chromic acid oxidation of the total crude ozonisation product.

3α-Acetoxybisnorcholan-22-al was converted into its enol acetate, which, without isolation, was ozonised in chloroform, giving 3α-acetoxypregnan-20-one (IX). Alternatively, the 22-aldehyde gave a crystalline piperidino-derivative in good yield, which, on ozonolysis, also afforded 3α-acetoxypregnan-20-one.

Pregnane-3 : 20-dione, on bromination in methylene chloride–*tert.*-butanol, gave 4-bromopregnane-3 : 20-dione which, on dehydrobromination (cf. McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5813), gave progesterone (VIII).

Experimental

Optical rotations were determined on 0·5—1% solutions in $CHCl_3$ at 15—20°. Ultraviolet absorption measurements were made in ethanolic solution with a Hilger "Uvispek" instrument. Alumina for chromatography was Spence, Type "O."

3-Acetoxyergosta-3 : 5 : 7 : 22-tetraene (*Ergosterone Enol Acetate*) (II).—(*a*) A mixture of ergosterol (50 g.), *cyclo*hexanone (300 ml.), and benzene (500 ml.) was distilled until moisture had been removed azeotropically. Aluminium *iso*propoxide (40 g.) in dry benzene (250 ml.) was added, and the mixture refluxed for 6 hr. Rochelle salt (50 g.), dissolved in a minimum of water, was then added and the volatile solvents were removed by steam-distillation. While still warm, the residue was extracted with benzene, and the extract washed with water, dried, and evaporated, the last traces of volatile material being removed on a steam-bath under reduced pressure. The crude product, which was a yellow solid, was refluxed with acetic anhydride (50 ml.) and pyridine (50 ml.) for 3 hr. After cooling, the product crystallised from the reaction mixture, which was filtered. Crystallisation from ethyl acetate gave 3-acetoxyergosta-3 : 5 : 7 : 22-tetraene (41 g., 74%) as plates, m. p. 146—149°, $[\alpha]_D$ −143°, $\lambda_{max.}$ 315 mμ (log ε 4·36). Heilbron *et al.* (*loc. cit.*) give m. p. 146°, $[\alpha]_D$ −143·5°, $\lambda_{max.}$ 316·5 mμ (log ε 4·33).

(*b*) Repetition of (*a*) with toluene (1200 ml.) in place of benzene and refluxing for 20—30 min. gave the same yield of 3-acetoxyergosta-3 : 5 : 7 : 22-tetraene.

(*c*) Aluminium *iso*propoxide (15 g.) was refluxed in a dry solution of ergosterol (15 g.) in *iso*butyl methyl ketone (600 ml.) for 2 hr. When cool, the product was washed with dilute sulphuric acid, followed by water until neutral. The solvent was removed and the residue acetylated, affording 3-acetoxyergosta-3 : 5 : 7 : 22-tetraene (11·5 g., 70%) as plates, m. p. 144—147°.

Ergosta-4 : 6 : 22-triene-3-one (iso*Ergosterone*) (III).—A suspension of 3-acetoxyergosta-3 : 5 : 7 : 22-tetraene (100 g.) in methanol (5000 ml.), sulphuric acid (150 ml.), and water (125 ml.) was heated under reflux. The enol acetate dissolved rapidly, and during the reaction a white flocculent precipitate appeared, which slowly redissolved. Refluxing was continued for 1 hr. after the final clearing of the solution, the total reaction period being approx. 3 hr. The solution was cooled to room temperature and an equal volume of water added. The precipitated solid was collected and dissolved in ether, and the extract washed with water until free from acid. Evaporation left crude ergosta-4 : 6 : 22-trien-3-one which crystallised from methanol as faintly yellow needles (78 g., 87%), m. p. 106·5—108·5°, $[\alpha]_D$ −40°, $\lambda_{max.}$ 283 mμ (log ε 4·44). Heilbron *et al.* (*loc. cit.*) give m. p. 108°, $[\alpha]_D$ −30°, $\lambda_{max.}$ 280 mμ (log ε 4·52).

3-Methoxyergosta-3 : 5 : 7 : 22-tetraene.—The above hydrolysis was repeated and, after 1 hour's refluxing, a portion of the insoluble intermediate was filtered off, washed with hot methanol, and crystallised twice from ethyl acetate, yielding *3-methoxyergosta-3 : 5 : 7 : 22-tetraene* as needles, m. p. 137—140°, $\lambda_{max.}$ 320 mμ (log ε 4·30) (Found: C, 85·3; H, 11·0. $C_{29}H_{44}O$ requires C, 85·2; H, 10·9%). This substance is unstable, especially in chloroform solution, but an ether solution gave $[\alpha]_D$ −75°.

5β-Ergost-22-en-3-one (IV).—A solution of potassium hydroxide (50 g.) in pure, dry ethanol (5 l., distilled over Raney nickel) containing palladium catalyst (10% on charcoal; 20 g.) was

shaken in an atmosphere of hydrogen until the catalyst was saturated. *iso*Ergosterone (100 g.) was added and hydrogenation continued until there was no further uptake of hydrogen (2·0 mols. of hydrogen were absorbed in 2 hr.). After filtration, the solution was made just acid by addition of acetic acid, and the solvent removed under reduced pressure. The product from ether was crystallised from methanol, yielding 5β-ergost-22-en-3-one (81 g., 80%) as plates, m. p. 108—110°. After several recrystallisations from methanol, a sample for analysis had m. p. 114—115°, $[\alpha]_D$ −6° (Found: C, 83·9; H, 11·5. Calc. for $C_{28}H_{46}O$: C, 84·4; H, 11·6%). Barton *et al.* (*loc. cit.*) give m. p. 110·5°, $[\alpha]_D$ −2°.

Ergosta-4 : 22-*dien*-3-*one* (VI).—(*a*) A solution of potassium hydroxide (0·1 g.) in dry ethanol (250 ml.), containing palladium catalyst (1%, on charcoal; 1·25 g.), was shaken in an atmosphere of hydrogen until the catalyst was saturated. *iso*Ergosterone (5 g.) was added and reduction continued until 1 mol. of hydrogen had been absorbed, then the reaction was stopped. The product was isolated in the usual manner, affording ergosta-4 : 22-diene-3-one (3·0 g., 60%), m. p. 127—128°, $[\alpha]_D$ +42°, $\lambda_{max.}$ 242 mμ (log ε 4·21). Barton *et al.* (*loc. cit.*) give m. p. 127·5—128·5°, $[\alpha]_D$ +44°, $\lambda_{max.}$ 242 mμ (log ε 4·26).

(*b*) *iso*Ergosterone (1·0 g.) was dissolved in dry ether (50 ml.), and liquid ammonia (250 ml.) was added with stirring. Lithium (1·0 g.) was added in small pieces during 5 min. After a further 10 minutes' stirring absolute ethanol was added dropwise so that the solution became colourless after 15—20 min. The solvents were then evaporated and water was added to the residue. Extraction with ether and evaporation of the dried extract left a sticky solid which was dissolved in benzene and filtered through a small column of alumina. Removal of the benzene and crystallisation of the residue from methanol gave ergosta-4 : 22-dien-3-one (0·8 g.) as colourless needles, m. p. 129—130°, $\lambda_{max.}$ 241 mμ (log ε 4·23).

In this preparation, sodium could be used in place of lithium, a similar yield being obtained.

3-*Oxobisnorcholan*-22-*al* (V).—5β-Ergost-22-en-3-one (12 g.), dissolved in pure chloroform (250 ml.), was cooled to −70°, and treated with ozonised oxygen until the solution became faintly blue (this corresponded to an uptake of 1·0—1·05 mols. of ozone). Immediately, zinc dust (20 g.) was added, followed by glacial acetic acid (50 ml.), and the mixture was stirred at room temperature until it no longer gave a positive starch–iodide reaction (about 20 min.). The zinc residues were removed by filtration and the filtrate evaporated to a small bulk under diminished pressure. The residue was extracted with ether, and the extract was washed with potassium hydroxide solution (1%), water, and dried. Evaporation left 3-*oxobisnorcholan*-22-*al* (9·2 g., 93%), as a white crystalline solid, m. p. 140—145°. This material was sufficiently pure for the next stage. A portion crystallised twice from *iso*propyl ether had m. p. 142—145°, $[\alpha]_D$ +24° (Found: C, 80·0; H, 10·5. $C_{22}H_{34}O_2$ requires C, 80·0; H, 10·4%).

3-*Oxobisnorcholanic Acid*.—5β-Ergost-22-en-3-one (4 g.), dissolved in chloroform (200 ml.), was cooled to 0° and treated with 2 mols. of ozone. The solvents were removed under reduced pressure and the residue was dissolved in a mixture of acetic acid (24 ml.) and ether (50 ml.). Zinc dust (4 g.) was added and the mixture stirred at room temperature for 30 min. After dilution with water and extraction with ether, the extract was dried and evaporated. The residue was dissolved in acetone (50 ml.) containing acetic acid (5 ml.), and a saturated solution of potassium permanganate in acetone (40 ml.) was added. After 2 hours' stirring the solution was acidified with dilute sulphuric acid. Sodium metabisulphite was then added until the mixture was colourless. Extraction with ether and crystallisation from methanol gave 3-oxobisnorcholanic acid (2·0 g., 58%), m. p. 178—180°, $[\alpha]_D$ +8°. (Budenandt and Mamoli, *Ber.*, 1935, **68**, 1854, give m. p. 184°, $[\alpha]_D$ +4·55°.) Reaction with diazomethane in ether gave the *methyl ester*, which crystallised from methanol as plates, m. p. 168—169°, $[\alpha]_D$ +20° (Found: C, 76·3; H, 10·1. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%).

3-*Ethylenedioxy*-5β-*ergost*-22-*ene*.—A mixture of 5β-ergost-22-en-3-one (6 g.), dry benzene (60 ml.) and ethylene glycol (12 ml.) was refluxed for 12 hr., in the presence of toluene-*p*-sulphonic acid (100 mg.), with constant removal of the water with barium oxide. After cooling, potassium hydroxide (0·5 g.) in methanol (10 ml.) was added, and the lower phase was discarded. The benzene extract was washed with water, dried, and evaporated. Crystallisation from methanol–ethyl acetate gave 3-*ethylenedioxy*-5β-*ergost*-22-*ene* (6·0 g., 90%) as needles, m. p. 91—93°, $[\alpha]_D$ 0° (Found: C, 81·3; H, 11·2. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

Methyl 3-*Ethylenedioxybisnorcholanate*.—3-Ethylenedioxy-5β-ergost-22-ene (2 g.), in chloroform (100 ml.) and pyridine (2 ml.), was treated with 2 mols. of ozone at 0°. The solvents were removed under reduced pressure and the residue was dissolved in ether (25 ml.) and acetic acid (12 ml.). Zinc dust (2 g.) was added, and, after 10 minutes' stirring, the zinc residues were removed by filtration. The acid fraction was extracted from the filtrate by shaking it with potassium

hydroxide solution (1%). The alkaline liquors were acidified with acetic acid, and the liberated acid was extracted with ether and worked up in the usual manner. The crude acid was methylated with diazomethane, and the ester was purified by chromatography on alumina. The benzene eluate yielded a crystalline solid. *Methyl 3-ethylenedioxybisnorcholanate* (0·72 g., 40%) separated from methanol as needles, m. p. 100—102°, $[\alpha]_D$ +10° (Found: C, 74·2; H, 9·8. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

Further degradation of the side chain of this compound with phenylmagnesium bromide yielded 3 : 22 : 22-*triphenylbisnorchola*-3 : 20(22)-*diene*, which crystallised from methanol as needles, m. p. 234—236°, $[\alpha]_D$ +373° (Found: C, 91·3; H, 9·0. $C_{40}H_{46}$ requires C, 91·2; H, 8·8%).

3-*Oxobisnorchol*-4-*en*-22-*al*.—A solution of ergosta-4 : 22-dien-3-one (5 g.) in chloroform (25 ml.) at −70° was treated with ozonised oxygen until 1 mol. had been absorbed. Zinc dust (7·5 g.) and acetic acid (50 ml.) were added and the mixture was shaken at room temperature until it no longer gave a positive starch–iodide test. Zinc residues were removed by filtration, and the filtrate was extracted with ether. After removal of the acid fraction with potassium hydroxide solution (1%), evaporation of the extract left a white solid which, after crystallisation from *iso*propyl ether, gave 3-oxobisnorchol-4-en-22-al (2·9 g.) as needles, m. p. 152—159°. A sample crystallised several times from *iso*propyl ether had m. p. 159—160°, $[\alpha]_D$ +88°. Heyl and Herr (*loc. cit.*) give m. p. 160—161°, $[\alpha]_D$ +82·5°.

Pregnane-3 : 20-*dione* (VII).—3-Oxobisnorcholan-22-al (2 g.) in acetic anhydride (20 ml.), containing fused sodium acetate (2 g.), was refluxed for 6 hr. in an atmosphere of nitrogen. The product, a light yellow gum, was treated in chloroform (100 ml.) with ozonised oxygen (1·4 mols.) at −70°. Zinc dust (6 g.) and glacial acetic acid (50 ml.) were added and the mixture was stirred at room temperature for 20 min. The filtered solution was evaporated, and the residue was dissolved in ether and washed with potassium hydroxide solution (1%), followed by water. Crystallisation from light petroleum (b. p. 40—60°) afforded pregnane-3 : 20-dione (1·08 g., 56%), m. p. 121—123°, $[\alpha]_D$ +109° (Found: C, 79·5; H, 10·1. Calc. for $C_{21}H_{32}O_2$: C, 79·7; H, 10·2%).

22-*Piperidinobisnorchol*-20(22)-*en*-3-*one*.—A solution of 3-oxobisnorcholan-22-al (2 g.) in benzene (100 ml.), containing piperidine (0·8 ml.), was heated at the b. p. for 2·5 hr. The solvent was continuously dried with barium oxide during the reaction. After removal of the solvents, the product was chromatographed on alumina in benzene–light petroleum (1 : 10). The eluate, on evaporation, yielded a solid, which was crystallised several times from light petroleum, and then *iso*propyl ether, affording 22-*piperidinobisnorchol*-20(22)-*en*-3-*one* as needles, m. p. 111—130°, $[\alpha]_D$ +26°, $\lambda_{max.}$ 236 mμ (log ε 3·90) (Found: C, 81·7; H, 10·9. $C_{27}H_{43}ON$ requires C, 81·6; H, 10·9%). In an earlier communication (*Chem. and Ind.*, 1953, 1207) the m. p. and rotation of this compound were wrongly reported.

Pregnane-3 : 20-*dione from* 22-*Piperidinobisnorchol*-20(22)-*en*-3-*one*.—3-Oxobisnorcholan-22-al (2·8 g.) was converted into its 22-piperidino-derivative as described above, and the crude product was treated in pure chloroform (100 ml.) with ozonised oxygen at −70°, until a blue colour appeared. Zinc dust (4 g.) and acetic acid (50 ml.) were added and, after isolation in the usual manner, the product was chromatographed in benzene–light petroleum (1 : 1) on alumina. The first eluate afforded pregnane-3 : 20-dione (1·2 g., 54%), m. p. 119—122°, $[\alpha]_D$ +108°.

5β-*Ergost*-22-*en*-3α-*ol*.—(a) *From* 5β-*ergost*-22-*en*-3-*one*. (i) To a solution of potassium hydroxide (2 g.) in ethanol (200 ml.), Raney nickel sludge (2 ml.) was added, and the suspension was shaken in hydrogen until the catalyst was saturated. 5β-Ergost-22-en-3-one (2 g.) was then added and reduction continued until absorption was complete (122 ml.). After filtration, the solution was made acid with acetic acid and evaporated to dryness. Crystallisation from methanol afforded 5β-ergost-22-en-3α-ol (1·8 g., 90%), as needles, m. p. 149—150°, $[\alpha]_D$ −2° (Found: C, 83·9; H, 11·9. Calc. for $C_{28}H_{48}O$: C, 83·9; H, 12·1%). Refluxing with acetic anhydride for 1 hr. gave 3α-acetoxy-5β-ergost-22-ene (93%), m. p. 115—116°, $[\alpha]_D$ +11° (Found: C, 81·0; H, 11·2. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·3%). Barton *et al.* (*loc. cit.*) give m. p. 149—150°, $[\alpha]_D$ −2°, for the alcohol and m. p. 114—115°, $[\alpha]_D$ +16°, for the acetate.

(ii) To a solution of 5β-ergost-22-en-3-one (2 g.) in dry ether (60 ml.) was added redistilled liquid ammonia (200 ml.) with stirring, followed by lithium (1 g.), in small pieces, during 5 min. Stirring was continued for 10 min., and dry ethanol (25 ml.) was then added dropwise during 10 min., by which time the solution became colourless. The ammonia was evaporated and water added. Isolation with ether and crystallisation from methanol gave 5β-ergost-22-en-3α-ol, m. p. 140—144°, which was converted directly into its acetate (1·6 g., 72%), m. p. 115—117°.

(b) *From ergosta-4 : 22-dien-3-one.* Ergosta-4 : 22-dien-3-one (5 g.) in ethanol (300 ml.), containing potassium hydroxide (3 g.), was hydrogenated over Raney nickel. Absorption ceased when 2 mols. of hydrogen had been taken up. After isolation with ether, a sample of the crude solid did not give a precipitate with digitonin. Crystallisation from methanol gave 5β-ergost-22-en-3α-ol (3·5 g., 69%), m. p. 146—149°.

(c) *From* iso*ergosterone.* By the method previously described, *iso*ergosterone (8·7 g.) was hydrogenated over Raney nickel. Absorption ceased after 3 mols. of hydrogen had been taken up. After isolation in the usual way, the crude product was crystallised from methanol, yielding 5β-ergost-22-en-3α-ol (7·0 g., 79%), m. p. 145—148°.

3α-*Acetoxybisnorcholan-22-al.*—3α-Acetoxy-5β-ergost-22-ene (12 g.) in chloroform (250 ml.) was ozonised at −70°. The solution became blue after 1 mol. of ozone had been absorbed. Isolation in the usual manner gave 3α-acetoxybisnorcholan-22-al (9·4 g., 92%), m. p. 125—128°. Crystallisation from *iso*propyl ether gave plates, m. p. 127—128°, $[\alpha]_D$ +33° (Found : C, 77·0; H, 10·4. Calc. for $C_{24}H_{38}O_3$: C, 77·0; H, 10·2%).

3α-*Acetoxybisnorcholanic Acid.*—(a) *Using an excess of ozone.* 3α-Acetoxy-5β-ergost-22-ene (2 g.) in chloroform (200 ml.) was treated with 2 mols. of ozone at 0—5°. The solvents were evaporated under reduced pressure and the ozonide was decomposed with zinc dust (2 g.) and acetic acid (12 ml.). Isolation of the steroid acid fraction, treatment with diazomethane, and crystallisation of the product from methanol gave the *methyl* 3α-*acetoxybisnorcholanate* (0·84 g., 46%) as plates, m. p. 109—112°, $[\alpha]_D$ +40° (Found : C, 73·7; H, 9·8. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

(b) *By ozone, followed by chromic acid oxidation.* 3α-Acetoxy-5β-ergost-22-ene (2 g.) in chloroform (75 ml.) was treated with 1·25 mols. of ozone at 0°. Zinc dust (3 g.) and acetic acid (100 ml.) were added and the mixture stirred for 1 hr. The solids were filtered off and the filtrate was evaporated to dryness. The residue was dissolved in acetic acid (50 ml.), and chromic acid (1 g.) in water (1 ml.) was added. The solution was allowed to remain at room temperature for 17 hr. After removal of the excess of chromic acid with methanol, the product was isolated with benzene. Crystallisation from methanol–water gave 3α-acetoxybisnorcholanic acid (1·1 g., 62%) as colourless blades, m. p. 220—223°, $[\alpha]_D$ +22° (Found : C, 73·8; H, 9·7. Calc. for $C_{24}H_{38}O_4$: C, 73·8; H, 9·8%). Treatment with diazomethane afforded the methyl ester, m. p. 109—112°.

3α-*Acetoxypregnan-20-one.*—3α-Acetoxybisnorcholan-22-al (4·46 g.) was heated at reflux under nitrogen for 5 hr. in acetic anhydride (36 ml.) containing anhydrous potassium acetate (0·07 g.). After isolation in the usual manner, the product was dissolved in dry ether (100 ml.), cooled to −35°, and treated with 1 mol. of ozone. The product was dissolved in light petroleum and purified by chromatography on alumina. Crystallisation from ether gave 3α-acetoxypregnan-20-one, as prisms, m. p. 100—101°, $[\alpha]_D$ +123° (Found : C, 76·2; H, 10·1. Calc. for $C_{23}H_{36}O_3$: C, 76·6; H, 10·1%).

3α-*Acetoxy-22-piperidinobisnorchol-20(22)-ene.*—3α-Acetoxybisnorcholan-22-al (6·4 g.) was refluxed under nitrogen for 2½ hr. in benzene (150 ml.) containing piperidine (5 ml.). Barium oxide was used to remove water from the distilling solvent. Removal of the solvent left a solid which, on crystallisation from methanol, gave 3α-acetoxy-22-piperidinobisnorchol-20(22)-ene (4·1 g., 54%) as plates, m. p. 106—110°. After recrystallisation from methanol, the analytical sample had m. p. 114—115°, $[\alpha]_D$ +47° (this rotation was wrongly recorded in the preliminary communication) (Found : C, 79·0; H, 10·6; N, 3·2. Calc. for $C_{29}H_{47}O_2N$: C, 78·8; H, 10·7; N, 3·2%).

3α-*Acetoxypregnan-20-one from* 3α-*Acetoxy-22-piperidinobisnorchol-20(22)-ene.*—A solution of the acetoxy-enamine (5·7 g.) in dry ether (200 ml.) was treated at −35° with ozonised oxygen until absorption of ozone was complete, as shown by analysis of the effluent gas. The product was chromatographed in light petroleum on alumina. The first fractions gave 3α-acetoxypregnan-20-one (2·7 g., 58%), which crystallised from ether as prisms, m. p. 100—101°, showing no depression on admixture with the previously prepared sample.

4-*Bromopregnane-3 : 20-dione.*—Pregnane-3 : 20-dione (1·0 g.) was dissolved in a mixture of methylene chloride (5 ml. saturated at room temperature with hydrogen bromide) and *tert.*-butanol (5 ml.), and cooled in ice. Bromine (0·50 g.) in a mixture of methylene chloride (5 ml.) and *tert.*-butanol (5 ml.) was added during 15 min. The solution was then set aside at room temperature until the colour was discharged. Extraction with ether gave a solid which crystallised from chloroform–ether, affording 4-bromopregnane-3 : 20-dione (0·65 g., 52%), m. p. 178—182°. Butenandt and Schmidt (*Ber.*, 1934, **67**, 1901) give m. p. 186—187°.

Progesterone.—4-Bromopregnane-3 : 20-dione (1·0 g.) was dissolved in a mixture of *tert.*-

butanol (50 ml.) and chloroform (30 ml.), and the air above the solution was displaced by nitrogen. Semicarbazide base (300 mg.) was added, and the solution was allowed to stand under nitrogen for a further 3 hr. After 0·5 hr., the solution became deep orange and later colourless. Solvents were removed under reduced pressure, and the residue was triturated with ethanol (15 ml.) and water (20 ml.). The solid semicarbazone (0·92 g.) had m. p. 234—236°, $[\alpha]_D$ +192° (*c*, 0·2 in 1 : 1 chloroform–*tert.*-butanol), $\lambda_{max.}$ 270 mμ (log ε 4·46).

The semicarbazone was dissolved in acetic acid (15 ml.), containing water (5 ml.) and *p*-hydroxybenzaldehyde (1·6 g.), and sealed under nitrogen for 24 hr. Isolation with ether gave a product which was dissolved in benzene and chromatographed on alumina. A benzene–ether eluate gave progesterone (0·30 g., 38%), which crystallised from light petroleum as blades, m. p. and mixed m. p. 127—129°, $[\alpha]_D$ +220°.

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WALTON OAKS EXPERIMENTAL STATION, VITAMINS LIMITED,
DORKING ROAD, TADWORTH, SURREY.

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