Amino-steroids. Part II.[1] 6-Amino-androstanes and -pregnanes

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Condensation of 3β-acetoxy-5α,6α-epoxy-androstanes and -pregnanes with ammonia and primary and secondary amines, and subsequent alkaline hydrolysis, gives 6β-amino-3β,5α-dihydroxy-steroids; water catalyses the epoxide cleavage. When condensation with ammonia is carried out in aqueous dioxan solution a 6β-acetamido-5α-hydroxy-steroid is obtained. Condensation of a mixture of 5α,6α- and 5β,6β-epoxides with aqueous morpholine at 115° gives the cleavage product of the α-oxide only and the β-oxide is recovered unchanged. Condensation of 5β,6β-epoxy-3β-hydroxyandrostan-17-one with piperidine and morpholine at 190° gives abnormal ring opening to the diequatorial 6α-amino-3β,5β-dihydroxyandrostan-17-one, the infrared spectra of which show intramolecular hydrogen bonding between the 3β-hydroxyl group and the oxygen atom of the 5β-hydroxyl group, which in turn bonds to the 6α-nitrogen atom. Oxidation of 3β,5α-dihydroxy-6β-piperidinoandrostan-17-one or the 5β,6α-epimer, and subsequent dehydration of the product, gives 6α-piperidinoandrost-4-ene-3,17-dione.

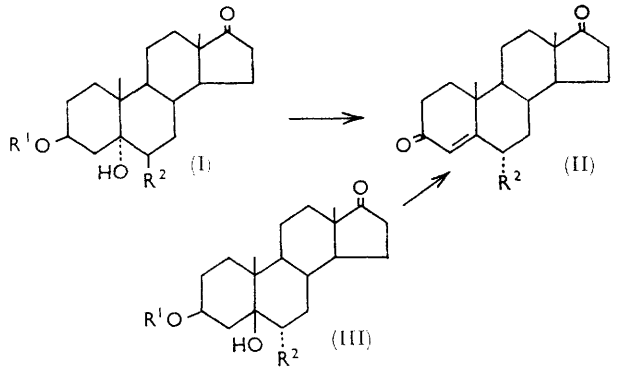
In Part I [1] the preparation of 16-amino-17-hydroxy- (or keto-)androstanes and -oestra-1,3,5(10)-trienes was described; these compounds have been shown to possess tranquillising and anticonvulsant activities.[2]

It was therefore of interest to examine steroids containing the β-amino-alcohol grouping at other positions in the steroid nucleus to study the effect of position on these activities. The present Paper concerns the preparation

[1] Part I, C. L. Hewett and D. S. Savage, *J. Chem. Soc.* (*C*), 1966, 484.

[2] G. A. Overbeek and I. L. Bonta, *Hormonal Steroids*, 1964, **1**, 496.

of 6β-amino-5α-hydroxy- and 6α-amino-5β-hydroxy-derivatives of androstanes and pregnanes. Since this work [3] was carried out several other groups of workers have reported [4-8] 6-amino-steroids, two of which, 6β-aminoandrostane-3β,5α,17β-triol [6,7] and 6α-acetamidoprogesterone,[8] are reported to have anaesthetic properties.



6β-Amino-5α-hydroxy-steroids were prepared by cleaving the corresponding 5α,6α-epoxide with ammonia or a primary or secondary amine at temperatures varying from 80 to 120° in the presence of water. Previous workers had not observed the influence of water in this reaction but we find, for example, that 3β-acetoxy-5α,6α-epoxyandrostan-17-one is completely cleaved in 3 days by boiling with morpholine containing 10% of water to give compound (I; R^1 = H, R^2 = morpholino); even after 5 hr., 50% opening of the epoxide ring has taken place, although in the absence of water only a 2% yield of compound (I; R^1 = Ac, R^2 = morpholino) is obtained. The presence of water in this reaction causes partial loss of the 3β-acetoxy-group so that complete hydrolysis is necessary to simplify purification. Condensation of the epoxide with boiling n-propylamine containing 10% of water or with a solution of ammonia in aqueous methanol and subsequent alkaline hydrolysis yielded 3β,5α-dihydroxy-6β-propylaminoandrostan-17-one (I; R^1 = H, R^2 = NHPr) and 6β-amino-3β,5α-dihydroxyandrostan-17-one (I; R^1 = H, R^2 = NH_2), respectively; the latter on acetylation gave 6β-acetamido-3β-acetoxyandrostan-5α-ol-17-one (I; R^1 = Ac, R^2 = NHAc). However, when the epoxide was condensed with a solution of ammonia in aqueous dioxan 6β-acetamido-3β,5α-dihydroxyandrostan-17-one (I; R^1 = H, R^2 = NHAc) was isolated; acetylation gave the diacetate (I; R^1 = Ac, R^2 = NHAc).

Since it was possible that ammonia removed the 3β-acetate to form acetamide or ammonium acetate, which in turn cleaved the 5α,6α-epoxide to give a 5α-hydroxy-6β-acetamide, 5α,6α-epoxy-3β-hydroxy-androstan-17-one was condensed with acetamide and ammonium acetate in dioxan solution. However, the acetamide (I; R^1 = H, R^2 = NHAc) was not produced in either case; the ammonium acetate condensation yielded 6β-acetoxy-3β,5α-dihydroxyandrostan-17-one (I; R^1 = H, R^2 = OAc). The mechanism of formation of the acetamide (I; R^1 = H, R^2 = NHAc) was not investigated further.

Reduction of 3β,5α-dihydroxy-6β-morpholino-androstan-17-one (I; R^1 = H, R^2 = morpholino) and its acetate (I; R^1 = Ac, R^2 = morpholino) with sodium borohydride gave the corresponding 17β-alcohols, The triol together with the 17-monoacetate and the 3β,17β-diacetate were isolated from the condensation of 3β, 17β-diacetoxy-5α,6α-epoxyandrostane with aqueous morpholine. The triol was most readily separated on account of its sparing solubility in ether; the monoacetate and diacetate were separated by chromatography of the ethereal mother-liquor on alumina.

The structure of the amines (I) was demonstrated in the case of (I; R^1 = H, R^2 = morpholino or piperidino) by oxidation with Kiliani [9] reagent to the corresponding 3-ketones which, under the acid conditions used, dehydrated and epimerised to the 6α-aminoandrost-4-ene-3,17-diones (II; R^2 = morpholino or piperidino). Batres *et al.*[4] have shown that the 6β-piperidino group in 6β-piperidinotestosterone epimerised to the thermodynamically more stable 6α-isomer under the influence of acid.

Epoxidation of Δ^5-steroids with peracids usually gives a mixture from which the 5α,6α-epoxide, the major component,[10] can be isolated in fair yield by crystallisation, but the remaining mixture of 5α,6α- and 5β,6β-epoxides cannot be separated by crystallisation. We have found that condensation of a mixture of α and β epoxides with aqueous morpholine at 115° for 5 days results in the cleavage of only the α-epoxide, and the β-epoxide can be obtained pure in about 15% yield based on the original mixture of α and β epoxides.

5β,6β-Epoxy-3β-hydroxyandrostan-17-one reacts with aqueous morpholine or piperidine at a very much higher temperature; after 2 days at 190° there was obtained 3β,5β-dihydroxy-6α-morpholinoandrostan-17-one (III; R^1 = H, R^2 = morpholino) and 3β,5β-dihydroxy-6α-piperidinoandrostan-17-one (III; R^1 = H, R^2 = piperidino). In contrast with the epimeric dihydroxy-amines derived from the 5α,6α-epoxides neither of these compounds showed absorption due to a free hydroxyl group in their infrared spectra. The piperidino-derivative (III; R^1 = H, R^2 = piperidino) showed a band at 3497 $cm.^{-1}$ arising from the 3β-hydroxyl group bonding to the oxygen atom of the 5β-hydroxyl group, which in turn bonds to the 6α-nitrogen atom to give an absorption at 3413 $cm.^{-1}$. In the morpholino-compound (III; R^1 = H, R^2 = morpholino) the corresponding absorptions are at 3497 and 3436 $cm.^{-1}$; this

[3] C. L. Hewett and D. S. Savage, B.P. 1,042,291; 1,042,292.
[4] E. Batres, G. Monroy, and H. J. Ringold, *J. Org. Chem.*, 1961, **26**, 878.
[5] E. Batres and H. J. Ringold, U.S.P. 2,985,650.
[6] K. Sasaki, B.P. 992,997.
[7] K. Sasaki, U.S.P. 3,156,710.
[8] K. Sasaki, U.S.P. 3,123,623.
[9] H. Kiliani, *Ber.*, 1901, **34**, 3564.
[10] In the epoxidation of 21-acetoxy-3,20-bisethylenedioxy-pregna-5,9(11)-dien-17α-ol with perbenzoic acid (1 mole), the 5β,6β-epoxide has been reported as the major epimer by S Bernstein and R. Littell, *J. Org. Chem.*, 1961, **26**, 3610.

latter band indicates that the 5β-hydroxyl group is not as strongly bound to the 6α-nitrogen atom of the morpholino-substituent as to the 6α-nitrogen of the stronger piperidino-base which absorbs at 3413 cm.$^{-1}$. The amino-diols (I) arising from the cleavage of the 5α,6α-epoxides with amines exhibit no hydrogen bonding at all, showing that cleavage of the 5α,6α-epoxides proceeds normally. In the case of the 5β,6β-epoxide abnormal cleavage takes place giving the 3,5-diaxial diol (with respect to ring A) and the 5,6-diequatorial hydroxy-amine (with respect to ring B).

Acetylation of the 3β-hydroxyl group of the diol (III; R^1 = H, R^2 = piperidino) gave the 3β-monoacetate (III; R^1 = Ac, R^2 = piperidino) which absorbed at 3448 cm.$^{-1}$, corresponding with a hydrogen-bonded 5β-hydroxyl group. Oxidation of the diol (III; R^1 = H, R^2 = piperidino) with Kiliani reagent gave 5β-hydroxy-6α-piperidinoandrostane-3,17-dione in which the 5β-hydroxyl group still bonded to the 6α-nitrogen atom. On treatment with 2% potassium hydroxide in aqueous methanol dehydration to 6α-piperidinoandrost-4-ene-3,17-dione (II; R^2 = piperidino) took place; this was identical with the product obtained from the oxidation of 3β,5α-dihydroxy-6β-piperidinoandrostan-17-one (I; R^1 = H, R^2 = piperidino).

Since pregnanes appear to be a better platform on which to build for anaesthetic properties,[11-13] these reactions were extended to the pregnane series. 3β-Acetoxy-5α,6α-epoxypregnan-20-one condensed with boiling aqueous morpholine for 5 days to give 3β,5α-dihydroxy-6β-morpholinopregnan-20-one and its 3β-acetate, which were separated by fractional crystallisation and chromatography on alumina. When a mixture of 5α,6α- and 5β,6β-epoxides, obtained from the monoperphthalic oxidation of pregnenolone acetate, was similarly treated, there was obtained, besides the 6β-morpholino-compound, 5β,6β-epoxy-3β-hydroxypregnan-20-one, which has been reported by Ellis and Petrow.[14]

The condensation of the α-epoxide with aqueous piperidine, piperazine, n-butylamine, and ammonia all gave the corresponding 6β-amino-3β,5α-dihydroxypregnan-20-ones after complete hydrolysis. The condensation with ammonia is in contrast with the findings of Sasaki,[6] who reported that he was unable to open the α-epoxide with ammonia.

Oxidation of 3β,5α-dihydroxy-6β-morpholinopregnan-20-one with Kiliani reagent gave 6α-morpholinoprogesterone. Oppenauer oxidation of this diol gave a mixture of 6α-morpholinoprogesterone and 5α-hydroxy-6β-morpholinopregnane-3,20-dione, the latter of which was dehydrated to 6β-morpholinoprogesterone with thionyl chloride and epimerised under the acid conditions to the thermodynamically more stable 6α-isomer.

Condensation of 3β,20β-diacetoxy-5α,6α-epoxypregnane with boiling aqueous morpholine and chromatography of the product on alumina gave 3β,20β-diacetoxy-6β-morpholinopregnan-5α-ol, 20β-acetoxy-6β-morpholinopregnane-3β,5α-diol, and 6β-morpholinopregnane-3β,5α,20β-triol.

The hydrochlorides of 3β,5α-dihydroxy-6β-morpholinoandrostan-17-one (I) and its 3β-acetate induced a state of sedation in mice at doses of 100 mg./kg. by the intravenous route.

The hydrochlorides of 3β,5α-dihydroxy-6β-morpholinopregnan-20-one and the 20β-ol induced prolonged sedation when administered intravenously in mice at 100 mg./kg. At the same dose level these compounds also showed anticonvulsant activity by protecting mice against electrically induced seizures. In marked contrast to these results the 3β-acetate of 3β,5α-dihydroxy-6β-morpholinopregnan-20-one is almost equipotent with leptazol as a convulsant.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Infrared spectra were determined with a Perkin-Elmer Infracord Spectrometer, and are for solutions in methylene chloride. Optical rotations were measured in ethanol solutions at room temperature, unless otherwise stated.

Acetates were prepared by dissolving the amino-alcohol in pyridine (20 vol.) and acetic anhydride (20 vol.) and keeping at room temperature for 18 hr. Water was then added and the solution basified with 5N-potassium hydroxide solution, the precipitate extracted with ether, the ethereal solution washed, dried (Na_2SO_4), evaporated to dryness, and the residue crystallised from a suitable solvent.

The hydrolysis of acetates was carried out by dissolving the acetate (1 part) in methanol (10 parts); 5N-potassium hydroxide solution (2 parts) was added, and the solution boilded under reflux for 30 min., cooled, and the product precipitated by the addition of water.

Epoxidation of 3β-*Acetoxyandrost-5-en-17-one with Monoperphthalic Acid.*—A solution of monoperphthalic acid (3 moles) in ethyl acetate (500 ml.) was added to a solution of 3β-acetoxyandrost-5-en-17-one (50 g.) in ethyl acetate (500 ml.) and the reaction mixture kept at 7° for 20 hr. A crystalline deposit was filtered off, washed with cold ethyl acetate, and crystallised from acetone to give 3β-acetoxy-5α,6α-epoxyandrostan-17-one in prisms (22 g.), m. p. 222—224°, $[\alpha]_D$ −5° (*c* 0·3).

The ethyl acetate filtrate was washed with saturated sodium hydrogen carbonate solution, water, and dried (Na_2SO_4). The solution was evaporated to dryness to give a mixture of 5α,6α- and 5β,6β-epoxide as a white solid (21 g.).

3β,5α-*Dihydroxy*-6β-*morpholinoandrostan*-17-*one* (I; R^1 = H, R^2 = morpholino).—(*a*) A solution of 3β-acetoxy-5α,6α-epoxyandrostan-17-one (5 g.) in morpholine (30 ml.) and water (5 ml.) was boiled under reflux for 5 days, cooled, and water added to precipitate a white solid. The product was filtered off and hydrolysed. The precipitate, which was completely soluble in dilute hydrochloric acid, was collected, dried (4·5 g.) and crystallised from acetone in

[11] S. Selye, "Encyclopaedia of Endocrinology," Section 1, The Steroids, Synoptic Charts, IV, 19.
[12] K. W. Wheeler, in "Medicinal Chemistry," 1963, vol. VI, p. 222.
[13] R. M. Atkinson, B. Downs, M. A. Pratt, H. M. Sharpe, and E. G. Torrich, *J. Medicin. Chem.*, 1965, **8**, 426.
[14] B. Ellis and V. Petrow, *J. Chem. Soc.*, 1956, 4417.

needles, m. p. 282—286° (decomp.), $[\alpha]_D$ −9° (*c* 0·3); $\nu_{max.}$ 3597 (3β,5α-diol), 1730 (17-ketone), and 1115 cm.$^{-1}$ (−CH_2OCH_2) (Found: C, 70·1; H, 9·35; N, 3·6. $C_{23}H_{37}NO_4$ requires C, 70·5; H, 9·5; N, 3·6%). 3β-*Acetate* (from acetone), m. p. 177—179°, $[\alpha]_D$ −15° (*c* 0·4); $\nu_{max.}$ 3584 (5α-OH), 1727 (17-ketone and 3β-OAc), and 1117 cm.$^{-1}$ (−CH_2−O−CH_2−) (Found: C, 68·3; H, 8·8; N, 3·1. $C_{25}H_{39}NO_5$, 0·5 CH_3COCH_3 requires C, 68·5; H, 9·1; N, 3·0%).

(*b*) When the reaction described under (*a*) was carried out for 5 hr. and the product separated into neutral and basic fractions, there was obtained 5α,6α-epoxy-3β-hydroxyandrostan-17-one and 3β,5α-dihydroxy-6β-morpholinoandrostan-17-one (1·4 g.).

(*c*) A solution of the epoxide (5 g.) in morpholine (30 ml.) was boiled under reflux for 5 hr. in the absence of water and worked up as under (*a*). Only 120 mg. of compound (I; R^1 = H, R^2 = morpholino) were obtained, the main product (4·0 g.) being 5α,6α-epoxy-3β-hydroxyandrostan-17-one.

(*d*) The mixture of epoxide epimers (10 g.), described above, was dissolved in morpholine (40 ml.) and water (10 ml.) and the solution boiled under reflux for 5 days. The product was worked up in the usual manner, hydrolysed with aqueous methanolic sodium hydroxide solution, and the non-basic fraction crystallised from acetone in prisms (3·0 g.), m. p. 160—162°; recrystallisation from ether gave 5β,6β-epoxy-3β-hydroxyandrostan-17-one, m. p. 166—168° $[\alpha]_D$ ($CHCl_3$) +57° (*c* 0·7) (Found: C, 74·7; H, 9·15. Calc. for $C_{19}H_{28}O_3$: C, 74·95; H, 9·3%). The basic fraction, after crystallisation from acetone, gave compound (I; R^1 = H, R^2 = morpholino), m. p. 280—284°.

3β,5α-*Dihydroxy*-6β-*piperidinoandrostan*-17-*one* (I; R^1 = H, R^2 = piperidino).—Condensation of the epoxide (5 g.) with boiling piperidine (30 ml.) and water (5 ml.) for 24 hr., followed by hydrolysis of the product, gave 3β,5α-*dihydroxy*-6β-*piperidinoandrostan*-17-*one* as a crystalline solid (4 g.). Crystallisation from ether gave needles, m. p. 205—207°, $[\alpha]_D$ +3·5° (*c* 2) (Found: C, 74·1; H, 10·1; N, 3·4. $C_{24}H_{39}NO_3$ requires C, 74·0; H, 10·1; N, 3·6%). A similar condensation gave anhydrous conditions with subsequent hydrolysis of the product yielded compound (I; R^1 = H, R^2 = piperidino) (300 mg.) and the 3β-hydroxy-5α,6α-epoxide (4·2 g.).

6α-*Piperidinoandrost*-4-*ene*-3,17-*dione* (II; R^2 = piperidino).—To a suspension of 3β,5α-dihydroxy-6β-piperidinoandrostan-17-one (I; R^1 = H, R^2 = piperidino) (2·8 g.) in acetone (20 ml.) was added concentrated sulphuric acid (0·25 ml.) and then water (4 ml.) to give a clear solution. Kiliani reagent (6·8 ml.; 1·5 atoms of oxygen) was added with stirring and the reaction mixture set aside at room temperature for 2 hr. The clear supernatant liquid was then decanted, made alkaline by the careful addition of saturated potassium hydrogen carbonate solution, and the precipitate extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4), and separated from unchanged material (1·6 g.) by percolating down a column (1 × ½ in.) of alumina. The ether eluate was evaporated and the residue crystallised twice from ether to give compound (II; R^2 = piperidino) in needles (380 mg.), m. p. 216—220°, $[\alpha]_D$ ($CHCl_3$) +185° (*c* 0·9); $\lambda_{max.}$ 240 mμ (ε 13,600); $\nu_{max.}$ 1740 (17-ketone), 1665 (3-ketone), and 1610 cm.$^{-1}$ (Δ^4-double bond) (Found: C, 78·1; H, 9·35; N, 3·9. $C_{24}H_{35}NO_2$ requires C, 78·0; H, 9·55; 3·8%).

6α-*Morpholinoandrost*-4-*ene*-3,17-*dione* (II; R^2 = morpholino).—A similar oxidation of 3β,5α-dihydroxy-6β-morpholinoandrostan-17-one (I; R^1 = H), R^2 = morpholino) (700 mg.) gave 6α-*morpholinoandrost*-4-*ene*-3,17-*dione* (prisms from ether; 100 mg.), m. p. 185—188°; $\lambda_{max.}$ 238 mμ (ε 14,200) (Found: C, 74·35; H, 8·95; N, 3·7. $C_{23}H_{33}NO_3$ requires C, 74·3; H, 8·9; N, 3·2%).

3β,5α-*Dihydroxy*-6β-*n*-*propylaminoandrostan*-17-*one* (I; R^1 = H, R^2 = n-propylamino).—A suspension of the epoxide (5 g.) in n-propylamine (15 ml.) and water (5 ml.) was boiled under reflux for 22 hr. The product was isolated, hydrolysed, and the basic material isolated in the usual manner. Crystallisation from ether gave 3β,5α-*dihydroxy*-6β-*propylaminoandrostan*-17-*one* in needles (2·3 g.), m. p. 162—164°, which after crystallisation had m. p. 168—170°, $[\alpha]_D$ +26° (*c* 2); $\nu_{max.}$ 3610 (3β,5α-diol) and 1733 cm.$^{-1}$ (17-ketone) (Found: C, 71·1; H, 10·0; N, 3·6. $C_{22}H_{37}NO_3$, 0·5H_2O requires C, 71·0; H, 10·3; N, 3·8%).

6β-*Amino*-3β,5α-*dihydroxyandrostan*-17-*one* (I; R^1 = H, R^2 = NH_2).—A solution of the expoxide (10 g.) in methanol (400 ml.), liquid ammonia (30 g.), and water (50 ml.) was boiled under reflux for 150 hr., the solution evaporated to dryness under reduced pressure, and the residue separated into neutral and basic materials. The basic product (2·2 g.) was crystallised from acetone to give 6β-*amino*-3β,5α-*dihydroxyandrostan*-17-*one* in prisms, m. p. 278—281°, $[\alpha]_D$ +70° (*c* 0·5) (Found: C, 69·9; H, 9·7; N, 3·9. $C_{19}H_{31}NO_3$, 0·5CH_3COCH_3 requires C, 70·25; H, 9·8; N, 4·0%).

6β-*Acetamido*-3β-*acetoxyandrostan*-5α-*ol*-17-*one* (I; R^1 = Ac, R^2 = NHAc) (in plates from ether), m. p. 175—178°, $[\alpha]_D$ 0° (*c* 1·4); $\nu_{max.}$ (Nujol) 3378 (5α-OH), 1739 (17-ketone), 1715 (3β-OAc), 1669, and 1529 cm.$^{-1}$ (amide) (Found: C, 67·9; H, 9·0; N, 3·15. $C_{23}H_{35}NO_5$ requires C, 68·1; H, 8·7; N, 3·45%).

6β-*Acetamido*-3β,5α-*dihydroxyandrostan*-17-*one* (I; R_1 = H, R_2 = NHAc).—A stream of ammonia was bubbled through a solution of the epoxide (10 g.) in dioxan (125 ml.) and water (40 ml.) at 100° for 100 hr. The solution was evaporated to dryness under reduced pressure and the residue separated into neutral and basic material. The basic product was extracted with ethyl acetate, the extract well washed with water, dried (Na_2SO_4), and concentrated to give a crystalline solid (2·8 g.), which after crystallisation from acetone gave 6β-*acetamido*-3β,5α-*dihydroxyandrostan*-17-*one* in needles, m. p. 268—270°, $[\alpha]_D$ (EtOH) −9° (*c* 2); $\nu_{max.}$ 3497 (3β-OH), 3378 (5α-OH), 1739 (17-ketone), and 1669 cm.$^{-1}$ (amide) (Found: C, 72·7; H, 9·7; N, 4·3. $C_{21}H_{33}NO_4$ requires C, 72·6; H, 9·6; N, 4·0%).

Acetylation of this compound gave 6β-*acetamido*-3β-*acetoxyandrostan*-5α-*ol*-17-*one* (I; R^1 = Ac, R^2 = NHAc) identical with the specimen described above.

Treatment of 5α,6α-*Epoxyandrostan*-3β-*ol*-17-*one*.—(*a*) With *acetamide*. Acetamide (1 g.) was added to a solution of the 3β-hydroxy-5α,6α-epoxide in dioxan and the solution boiled under reflux for 80 hr.; no 6β-acetamido-3β,5α-dihydroxyandrostan-17-one (I; R^1 = H, R^2 = NHAc) was produced.

(*b*) With *ammonium acetate*. A solution of ammonium acetate (1 g.) and the 3β-hydroxy-5α,6α-epoxide (1 g.) in dioxan (20 ml.) was boiled under reflux for 2 hr. and ammonium acetate (6 × 0·5 g.) added portionwise to the boiling solution over the next 60 hr. The product was precipitated by the addition of water, extracted with ether, the extract dried (Na_2SO_4) and concentrated to yield 6β-acetoxy-3β,5α-dihydroxyandrostan-17-one (I; R^1 = H, R^2 = OAc) in prisms (560 mg.), m. p. 280—283°, $[\alpha]_D$ (MeOH)

+14° (*c* 1); $\nu_{max.}$ (KCl) 3465 and 3330 (3β,5α-diol), 1725—1740 cm.$^{-1}$ (6β-acetate and 17-ketone) (Found: C, 69·3; H, 9·1. Calc. for $C_{21}H_{32}O_5$: C, 69·2; H, 8·85%), cf. Ehrenstein,[15] m. p. 276—277°, $[\alpha]_D$ (MeOH) +24°.

6β-*Morpholinoandrostane*-3β,5α,17β-*triol*.—Sodium borohydride (250 mg.) was added portionwise over 15 min. to a stirred solution of 3β,5α-dihydroxy-6β-morpholinoandrostan-17-one (1 g.) in methanol (60 ml.) and stirring continued for 2 hr. Addition of 10N-potassium hydroxide solution precipitated a white solid which was filtered off, washed neutral with water, and dried. Crystallisation from acetone gave the *triol* in needles (700 mg.), m. p. 233—236°, $[\alpha]_D$ −59° (*c* 1) (Found: C, 67·3; H, 9·6; N, 3·0. $C_{23}H_{39}NO_4,H_2O$ requires C, 67·1; H, 10·0; N, 3·4%).

3β-*Acetoxy*-6β-*morpholinoandrostane*-5α,17β-*diol*.—Reduction of 3β-acetoxy-6β-morpholinoandrostan-5α-ol-17-one (I; R^1 = Ac, R^2 = morpholino) (3 g.) in methanol solution (20 ml.) with sodium borohydride gave the *triol* 3β-*acetate* (2·7 g.). Crystallisation from aqueous acetone gave a sample, m. p. 185—189°, $[\alpha]_D$ −70° (*c* 2) (Found: C, 68·1; H, 10·0; N, 3·2. $C_{25}H_{41}NO_5,0{\cdot}5CH_3COCH_3$ requires C, 68·5; H, 9·55; N, 3·0%).

Condensation of 3β,17β-*Diacetoxy*-5α,6α-*epoxyandrostane with Aqueous Morpholine*.—A solution of 3β,17β-diacetoxy-5α,6α-epoxyandrostane (10 g.) in morpholine (32 ml.) and water (8 ml.) was boiled under reflux for 3 days, cooled, and the product precipitated as a brown crystalline solid by the addition of water. The solid was dried, finely ground, washed with ether, and the sparingly soluble crystals (4·5 g.) crystallised from acetone to give 6β-morpholinoandrostane-3β,5α,17β-triol in needles, m. p. 233—236°.

The ether filtrate was concentrated (to 50 ml.) and filtered down a column (6 × 1 in.) of alumina. Elution with ether (70 ml.) gave a fraction (3 g.), m. p. 138—145°, which was crystallised from ether to give 3β,17β-*diacetoxy*-6β-*morpholinoandrostan*-5α-*ol* in needles, m. p. 145—149°, $[\alpha]_D$ −68° (*c* 2) (Found: C, 67·6; H, 8·75; N, 2·8. $C_{27}H_{43}NO_6$ requires C, 67·8; H, 9·1; N, 2·9%).

Further elution with ether gave a fraction which was crystallised from ether to give 17β-*acetoxy*-6β-*morpholinoandrostane*-3β,5α-*diol* in micro-needles, m. p. 238—240°, $[\alpha]_D$ −58° (*c* 0·8) (Found: C, 68·4; H, 9·7; N, 2·8. $C_{25}H_{41}NO_5$ requires C, 68·9; H, 9·5; N, 3·2%).

3β,5β-*Dihydroxy*-6α-*piperidinoandrostan*-17-*one* (III; R^1 = H, R^2 = piperidino).—A solution of 5β,6β-epoxy-3β-hydroxyandrostan-17-one (5 g.) in piperidine (30 ml.) was maintained in an autoclave at 190—200° for 42 hr. The solution was evaporated to dryness under reduced pressure and the residual gum separated into neutral and basic material. The basic product was crystallised from ether to give 3β,5β-*dihydroxy*-6α-*piperidinoandrostan*-17-*one* in prisms (1·8 g.), m. p. 184—185°, $[\alpha]_D$ (EtOH) +118° (*c* 2); $\nu_{max.}$ (CCl_4) 3497 (3β-OH bonded to the 5β-OH), 3413 (5β-OH bonded to the 6α-N atom), and 1745 cm.$^{-1}$ (17-ketone); the spectrum was also recorded in dilute solution to show the same absorption in the hydroxyl region (Found: C, 74·1; H, 10·2; N, 3·8. $C_{24}H_{39}NO_3$ requires C, 74·0; H, 10·1; N, 3·6%).

The 3β-*acetate* had m. p. 208—209°, $\nu_{max.}$ 3448 (H-bonded 5β-OH), 1742 (3β-OAc and 17-ketone), 1261, and 1241 cm.$^{-1}$ (3β-OAc) (Found: C, 72·6; H, 9·2; N, 3·0. $C_{26}H_{41}NO_4$ requires C, 72·4; H, 9·6; N, 3·2%).

3β,5β-*Dihydroxy*-6α-*morpholinoandrostan*-17-*one* (III; R^1 = H, R^2 = morpholino).—A solution of the epoxide (5 g.) in morpholine (20 ml.) and water (5 ml.) was maintained in an autoclave for 44 hr. at 180—190°. The basic fraction was isolated in the usual way and crystallised twice from ether to give 3β,5β-*dihydroxy*-6α-*morpholinoandrostan*-17-*one* in blades (1·5 g.), m. p. 195—197°, $[\alpha]_D$ +105° (*c* 2); $\nu_{max.}$ (CCl_4) 3497 (3β-OH bonded to 5β-OH), 3436 (5β-OH bonded to 6α-N atom), 1745 (17-ketone), and 1119 cm.$^{-1}$ (−CH_2−O−CH_2−) (Found: C, 70·3; H, 9·3; N, 3·1. $C_{23}H_{37}NO_4$ requires C, 70·5; H, 9·5; N, 3·6%).

5β-*Hydroxy*-6α-*piperidinoandrostane*-3,17-*dione*.—Oxidation of 3β,5β-dihydroxy-6α-piperidinoandrostan-17-one (III; R^1 = H, R^2 = piperidino) (1 g.) was carried out as described under 6α-piperidinoandrost-4-ene-3,17-dione. The ethereal solution was concentrated, hexane added, and the crystalline material (900 mg.), m. p. 195—199°, recrystallised from ether. 5β-*Hydroxy*-6α-*piperidinoandrostane*-3,17-*dione* formed prisms (600 mg.), m. p. 203—205°, $[\alpha]_D$ +135° (*c* 2); $\nu_{max.}$ 3460 (5α-OH bonded to 6α-N atom), 1721 (3-ketone), and 1748 cm.$^{-1}$ (17-ketone) (Found: C, 74·6; H, 9·95; N, 3·7. $C_{24}H_{37}NO_3$ requires C, 74·4; H, 9·7; N, 3·6%).

6α-*Piperidinoandrost*-4-*ene*-3,17-*dione* (II; R^2 = piperidino).—A solution of 5β-hydroxy-6α-piperidinoandrostane-3,17-dione (500 mg.) in 2% aqueous methanolic potassium hydroxide solution (10 ml.) was boiled under reflux for 5 min. and allowed to cool over 45 min. The product was precipitated by the addition of water and extracted with ether. The ether extract was washed neutral with water, dried (Na_2SO_4), and concentrated to give 6α-*piperidinoandrost*-4-*ene*-3,17-*dione* in blades (250 mg.), m. p. 218—220°, $[\alpha]_D$ +70°; $\lambda_{max.}$ 2400 Å (ε 13,100); $\nu_{max.}$ (CCl_4) 1740 (3-ketone) and 1613 cm.$^{-1}$ (Δ^4-double bond) (Found: C, 78·1; H, 9·6; N, 4·0. $C_{24}H_{35}NO_2$ requires C, 78·0; H, 9·55; N, 3·8%).

Epoxidation of 3β-*Acetoxypregn*-5-*en*-20-*one*.—A solution of monoperphthalic acid (2 moles) in ethyl acetate (600 ml.) was added to a solution of pregnenolone acetate (100 g.) in ethyl acetate (1 l.) and the solution kept at 5° for 20 hr. The solution was worked up in the usual manner and the product crystallised from acetone–hexane to give the 5α,6α-epoxide (49 g.), m. p. 162—165°. The mother-liquors were evaporated to dryness to give a mixture of 5α,6α- and 5β,6β-epoxides.

3β,5α-*Dihydroxy*-6β-*morpholinopregnan*-20-*one*.—(*a*) A solution of 3β-acetoxy-5α,6α-epoxy-pregnan-20-one (20 g.) in morpholine (50 ml.) and water (10 ml.) was boiled under reflux for 5 days. Water was then added and the precipitated white solid, which was a mixture of the 3β-alcohol and its acetate, was hydrolysed. After crystallisation from acetone the product (16·0 g.) gave 3β,5α-*dihydroxy*-6β-*morpholinopregnan*-20-*one*, m. p. 276—280° (decomp.), $[\alpha]_D$ −11° (*c* 0·2); $\nu_{max.}$ (Nujol) 3356 (3β,5α-diol), 1701 (20-ketone), 1105 cm.$^{-1}$ (−CH_2−O−CH_2) (Found: C, 71·55; H, 9·7; N, 3·1. $C_{25}H_{41}NO_4$ requires C, 71·6; H, 9·85; N, 3·3%).

The 3β-*acetate*, prisms from ether–acetone, had m. p. 228—230° (decomp.), $[\alpha]_D$ −12° (*c* 0·4); $\nu_{max.}$ 3584 (5α-OH), 1727 and 1245 (3β-OAc), 1701 (20-ketone), 1117 cm.$^{-1}$ (−CH_2−O−CH_2) (Found: C, 69·6; H, 9·5; N, 3·1. $C_{27}H_{43}NO_5,0{\cdot}5CH_3COCH_3$ requires C, 69·8; H, 9·4; N, 2·85%).

3β-*Phenylpropionate*, needles from ethyl acetate, m. p. 207—210°, $[\alpha]_D$ (EtOH) −10° (*c* 1); $\nu_{max.}$ 3580 (5α-OH), 1720 (3β-phenylpropionate), 1700 (20-ketone), 1605 (phenyl),

[15] M. Ehrenstein, *J. Org. Chem.*, 1941, **6**, 626.

and 1120 cm.$^{-1}$ ($-CH_2-O-CH_2$) (Found: C, 74·2; H, 8·8; N, 2·7. $C_{34}H_{49}NO_5$ requires 74·0; H, 8·95; N, 2·55%).

(*b*) The mixture (43 g.) of 3β-acetoxy-5α,6α-epoxypregnan-20-one and 3β-acetoxy-5β,6β-epoxypregnan-20-one described above was boiled under reflux in morpholine (75 ml.) and water (25 ml.) for 40 hr., concentrated under reduced pressure, and the product precipitated by the addition of water. The brown gum was hydrolysed and then separated into basic and neutral components. Recrystallisation of the basic product (20 g.) from acetone gave 3β,5α-dihydroxy-6β-morpholinopregnan-20-one, m. p. 275—277°.

The neutral fraction after crystallisation from ether and then acetone gave needles (7·0 g.), m. p. 193—195°, $[\alpha]_D$ +69° (*c* 2) of 5β,6β-epoxy-3β-hydroxypregnan-20-one (cf. Ellis and Petrov [14] who report m. p. 188—189°, $[\alpha]_D$ +71°) (Found: C, 75·9; H, 9·7. Calc. for $C_{21}H_{32}O_3$: C, 75·9; H, 9·7%).

Reduction of this substance (1 g.) in methanol (20 ml.) with sodium borohydride (300 mg.) at room temperature for 2 hr. gave 5β,6β-epoxypregnane-3β,20β-diol (220 mg.) in needles, m. p. 210—212° (lit.,[16] m. p. 216—217·5°), $[\alpha]_D$ ($CHCl_3$) −18° (*c* 2) (Found: C, 75·6; H, 10·1. Calc. for $C_{21}H_{34}O_3$: C, 75·4; H, 10·2%).

3β,5α-*Dihydroxy*-6β-*piperidinopregnan*-20-*one*.— 3β-Acetoxy-5α,6α-epoxypregnan-20-one (10 g.) was condensed with aqueous piperidine for 70 hr. and the product hydrolysed. Crystallisation from ether gave 3β,5α-*dihydroxy*-6β-*piperidinopregnan*-20-*one* in fine needles (5·3 g.), m. p. 170—174°, $[\alpha]_D$ −18° (*c* 1) (Found: C, 74·9; H, 10·4; N, 2·8. $C_{26}H_{43}NO_3$ requires C, 74·6; H, 10·35; N, 3·3%).

3β-*Acetate*, needles from ether, m. p. 188—190°, $[\alpha]_D$ −21·5° (*c* 2) (Found: C, 73·3; H, 9·6; N, 3·1. $C_{28}H_{45}NO_4$ requires C, 73·1; H, 9·9; N, 3·05%).

3β,5α-*Dihydroxy*-6β-*piperazinopregnan*-20-*one*.— A suspension of 5α,6α-epoxy-3β-hydroxypregnan-20-one in piperazine hexahydrate was boiled under reflux for 72 hr. Water was added to the cooled suspension and the product filtered off, washed with water, and dried. This white solid was extracted with boiling acetone, filtered off, and crystallised from methanol–acetone to give 3β,5α-*dihydroxy*-6β-*piperazinopregnan*-20-*one* in plates, m. p. 260—275° (decomp.), $[\alpha]_D$ −9° (*c* 0·3); $\nu_{max.}$ (Nujol) 3356 (3β,5α-diol), 3333—3175 (secondary amine), 1701 (20-ketone) (Found: C, 71·5; H, 10·0; N, 6·4. $C_{25}H_{42}N_2O_3$ requires C, 71·7; H, 10·0; N, 6·7%).

6β-*n-Butylamino*-3β,5α-*dihydroxypregnan*-20-*one*.— A solution of 3β-acetoxy-5α,6α-epoxypregnan-20-one (10 g.) in n-butylamine (30 ml.) and water (10 ml.) was boiled under reflux for 3 days. The product was hydrolysed, dissolved in benzene (40 ml.), and percolated down a column (3 × 1 in.) of alumina. The benzene eluate was evaporated to dryness to give a yellow gum, which crystallised from ether to give 6β-*n-butylamino*-3β,5α-*dihydroxypregnan*-20-*one* in prisms (7 g.), m. p. 198—202°, $[\alpha]_D$ +24° (*c* 2) (Found: C, 74·1; H, 10·6; N, 3·4. $C_{25}H_{43}NO_3$ requires C, 74·0; H, 10·7; N, 3·45%).

6β-*Amino*-3β,5α-*dihydroxypregnan*-20-*one*.— Ammonia was bubbled through a refluxing solution of 3β-acetoxy-5α,6α-epoxypregnan-20-one (10 g.) in methanol (180 ml.), and water (20 ml.) for 100 hr., the methanol distilled off, and the aqueous supernatant liquor decanted and the brown gum separated into basic and neutral products. The basic fraction crystallised from aqueous methanol to give prisms (1·5 g.), m. p. 230—235°; recrystallisation from ether gave 6β-*amino*-3β,5α-*dihydroxypregnan*-20-*one* in prisms, m. p. 235—239°, $[\alpha]_D$ +55° (*c* 1·4) (Found: C, 72·2; H, 10·2; N, 3·7. $C_{21}H_{35}NO_3$ requires C, 72·2; H, 10·1; N, 4%).

6α-*Morpholinopregn*-4-*ene*-3,20-*dione*.—(*a*) Kiliani reagent (1·5 ml.; 2 atoms of oxygen) was added to a solution of 3β,5α-dihydroxy-6β-morpholinopregnan-20-one (500 mg.) in acetone (50 ml.), and 30% hydrobromic acid in acetic acid (0·25 ml.). After stirring the solution for 5 min., methanol (2 ml.) was added to destroy excess of oxidising agent. After a further 5 min. 10N-potassium hydroxide solution (10 ml.) was added carefully to precipitate the product, which was extracted with ether. The ether extract was washed neutral with water, dried (Na_2SO_4), and percolated through a column (1 × ½ in.) of alumina; concentration of the ether eluate yielded small prisms (170 mg.), m. p. 200—209°. Recrystallisation from ether–acetone gave 6α-*morpholinopregn*-4-*ene*-3,20-*dione* in prisms, m. p. 205—210°, $[\alpha]_D$ +122° (*c* 0·2); $\lambda_{max.}$ 2380 Å (ε 14,000); $\nu_{max.}$ 1701 (20-ketone), 1675 (3-ketone), 1618 (Δ^4-double bond), and 1120 cm.$^{-1}$ ($-CH_2-O-CH_2-$) (Found: C, 74·4; H, 9·5; N, 3·2. $C_{25}H_{37}NO_3$,0·5CH_3COCH_3 requires C, 74·3; H, 9·4; N, 3·3%).

(*b*) A solution of 3β,5α-dihydroxy-6β-morpholinopregnan-20-one (20 g.) and aluminium isopropoxide (10 g.) in toluene (200 ml.) and cyclohexanone (150 ml.) was slowly distilled for 50 min., cooled, and a solution of Rochelle salt (20 g.) in water (50 ml.) added. The solution was distilled with steam to remove all volatile solvent, the aqueous supernatant decanted, and the residual yellow gum triturated with ether. A white crystalline solid (5·78 g.), m. p. 200—210°, was obtained, which proved to be a mixture of 6α-morpholino-Δ^4-3-ketone and 6β-morpholino-5α-ol-3-one. It was dissolved in pyridine (80 ml.), thionyl chloride (3 ml.) added, and the solution stirred for 5 min. Excess of thionyl chloride was then destroyed by the careful addition of water, the precipitated crystalline solid (4·25 g.) filtered off and crystallised from acetone, yielding 6α-*morpholinopregn*-4-*ene*-3,20-*dione* in prisms, m. p. 214—218°, $[\alpha]_D$ ($CHCl_3$) +132° (*c* 0·5); $\lambda_{max.}$ 2390 Å (ε 12,530); $\nu_{max.}$ 1709 (20-ketone), 1683 (3-ketone), 1615 (Δ^4-double bond), and 1121 cm.$^{-1}$ ($-CH_2-O-CH_2-$) (Found: C, 75·3; H, 9·3; N, 3·2. $C_{25}H_{37}NO_3$ requires C, 75·15; H, 9·3; N, 3·5%).

3β-*Acetoxy*-6β-*morpholinopregnane*-5α,20β-*diol*.— Sodium borohydride (1 g.) was added portionwise over 20 min. to a solution of 3β-acetoxy-6β-morpholinopregnan-5α-ol-20-one (2·8 g.) in methanol (100 ml.) and the solution stirred for 1 hr. Addition of water precipitated a crystalline solid which was filtered off, washed with water, dried, and crystallised from acetone to give 3β-*acetoxy*-6β-*morpholinopregnane*-5α,20β-*diol* in small prisms (1·85 g.), m. p. 268—270°, $[\alpha]_D$ −70° (*c* 0·5) (Found: C, 69·6; H, 9·9; N, 3·0. $C_{27}H_{45}NO_3$ requires C, 69·9; H, 9·8; N, 3·0%).

Hydrolysis with potassium carbonate in aqueous methanol gave 6β-morpholino-5α-pregnane-3β,5α,20β-triol, needles from acetone, m. p. 234—238°, $[\alpha]_D$ −62° (*c* 1) (Found: C, 71·6; H, 10·0; N, 3·5. $C_{25}H_{34}NO_4$ requires C, 71·2; H, 10·3; N, 3·3%).

Condensation of 3β,20β-*Diacetoxy*-5α,6α-*epoxypregnane with Aqueous Morpholine*.—A solution of the epoxide (7·9 g.), in morpholine (34 ml.), and water (8 ml.) was boiled under reflux for 42 hr., concentrated almost to dryness, cooled, and water added to precipitate a buff-coloured solid which was filtered off, washed neutral with water, and dried.

[16] A. T. Rowland and H. R. Nace, *J. Amer. Chem. Soc.*, 1960, **82**, 2833.

This solid was dissolved in ether (50ml.) and the solution filtered down a column (6 × 1½ in.) of alumina. Elution with ether (125 ml.) yielded a fraction which crystallised from ether–light petroleum (b. p. 40—60°) to give 3β,20β-*diacetoxy*-6β-*morpholinopregnan*-5α-*ol* in large prisms (3·4 g.), m. p. 206—208°, $[\alpha]_D$ −37° (*c* 2) (Found: C, 69·1; H, 9·8; N, 2·7. $C_{29}H_{47}NO_6$ requires C, 68·9; H, 9·35; N, 2·8%).

Further elution with ether (1·5 l.) yielded a fraction (2·8 g.) which crystallised from ether to give 20β-*acetoxy*-6β-*morpholinopregnane*-3β,5α-*diol* in fine needles, m. p. 243—245°, $[\alpha]_D$ −32° (*c* 1·7) (Found: C, 69·9; H, 9·9; N, 3·1. $C_{27}H_{45}NO_5$ requires C, 69·9; H, 9·8; N, 3·0%).

Elution with methanol (250 ml.) gave a fraction which crystallised from acetone to give 6β-morpholinopregnane-3β,5α,20β-triol in small needles (250 mg.), m. p. 234—238°, which was identical with the specimen described above.

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