Amino-steroids. Part I. 16-Piperidino- and 16-Morpholino-androstanes and -œstra-1,3,5(10)-trienes

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The preparation of 16β-piperidino- and -morpholino-17-ketones of C_{18}- and C_{19}-steroids from 16α-bromo-17-ketones is described; reduction gives the corresponding *cis*-16β-amino-17β-ol the structure of which is confirmed by preparation from the *trans*-16α-bromo-17β-ol and by infrared spectroscopy. *trans*-16-Amino-17-ols were prepared from *cis*-16-bromo-17-ols and a 16α,17α-epoxide.

A NUMBER of steroidal amines [1-8] has been prepared and studied for non-hormonal biological activities, but very few of these,[5-8] contain the αβ-amino-alcohol grouping found in such biologically active compounds as choline and adrenaline. It seemed probable that the incorporation of such a grouping into C_{18}-, C_{19}-, or C_{21}-steroids might lead to complete suppression of hormonal activity and to the development of entirely new biological activities, depending upon the location and configuration of the amine and alcohol substituents. The present Paper deals with 16-amino-17-hydroxy-C_{18}- and -C_{19}-steroids.

The general method of preparation consists of heating a 16α-bromo-17-ketone, *e.g.*, (I),[9] with piperidine or morpholine to give the corresponding 16β-amino-17-ketone. This condensation parallels the nucleophilic displacement of a 16α-bromo-group in a 16α-bromo-17-ketone by thioacetate to give a 16β-acetylthio-17-ketone.[10] Reduction of the 16β-amino-17-ketone, *e.g.*, (II), with sodium borohydride gives the amino-alcohol (III).

The 16β-amino-17β-alcohol configuration of the products is deduced from infrared-spectral studies; 16β-piperidinoandrost-5-ene-3β,17β-diol (III) prepared by the above method shows an absorption band at 3333 cm.$^{-1}$ from which it can be deduced that the hydrogen of the 17β-hydroxyl group is bonded [11,12] to the 16-nitrogen atom, corresponding to the *cis*-configuration for the amino-alcohol grouping.

Condensation of 16α-bromoandrost-5-ene-3β,17β-diol (IV) with piperidine gave, together with the 16β,17β-epoxide, the same 16β-piperidino-17β-alcohol (III) as was obtained from the amino-ketone (II) by reduction with sodium borohydride.

Condensation of the 16α-bromo-17α-ol (V) with piperidine gave the 16β-piperidino-17α-ol (VII) in 6% yield and a quantitative return of unchanged starting material. Under the same condensation conditions the 16β-bromo-17β-ol (VI) yielded 43% of the 16α-piperidino-17β-ol, indicating that the bromohydrin (VI) is more readily attacked on the α-face of the molecule than the bromohydrin (V) is attacked on its β-face. Neither of the *trans*-16-piperidino-17-ols (VII) and (VIII) exhibited hydrogen bonding in their infrared absorption spectra.

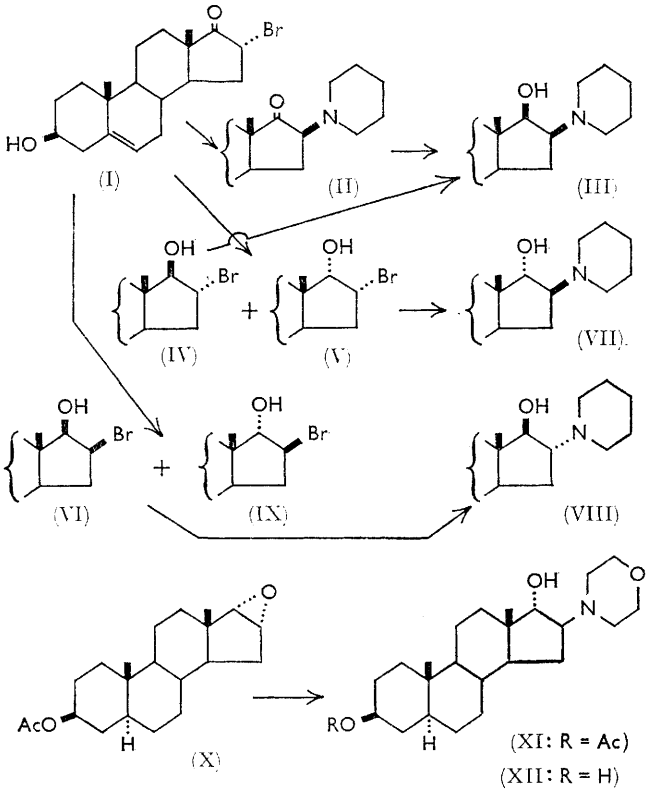
Condensation of 3β-acetoxy-16β-bromoandrost-5-en-

[1] E. J. Agnello and G. D. Laubach, U.S.P. 2,920,999.
[2] E. Batres and H. J. Ringold, U.S.P. 2,986,650.
[3] R. A. Lucas, D. F. Dickel, R. L. Dziemian, M. J. Ceglowski, B. L. Hensle, and H. B. MacPhillamy, *J. Amer. Chem. Soc.*, 1960, **82**, 5688.
[4] D. F. Morrow, M. E. Brokke, and G. W. Moersch, *Chem. and Ind.*, 1962, 1655.
[5] R. A. Micheli and C. K. Bradsher, *J. Amer. Chem. Soc.*, 1955, **77**, 4789.
[6] E. Batres, G. Monroy, and H. J. Ringold, *J. Org. Chem.*, 1961, **26**, 878.
[7] G. Drefahl and K. Ponsold, *Chem. Ber.*, 1958, **91**, 271.
[8] E. W. Warnhoff, *J. Org. Chem.*, 1962, **27**, 4587.
[9] B. Ellis, D. Patel, and V. Petrow, *J. Chem. Soc.*, 1958, 800.
[10] K. Takeda, and T. Toneno, *Chem. and Pharm. Bull. Japan*, 1964, **12**, 905.
[11] C. Hite, E. E. Smissman, and R. West, *J. Amer. Chem. Soc.*, 1960, **82**, 1207.
[12] N. A. Nelson, R. S. P. Hsi, J. M. Schuck, and L. D. Kahn, *J. Amer. Chem. Soc.*, 1960, **82**, 2573.

17β-ol [13] with morpholine gave 3β-acetoxy-16α-morpholinoandrost-5-en-17β-ol which showed no hydrogen-bonded hydroxyl present in its infrared spectrum. A similar condensation of 3β-acetoxy-16β-bromo-5α-androstane-3β,17β-diol with piperidine, followed by hydrolysis of the product, gave 16α-piperidino-5α-androstane-3β,17β-diol.

The epimeric bromohydrins (IV), (V), and (VI) were prepared by reduction of the 16α-bromo-ketone (I) with sodium borohydride under different conditions. In neutral medium (kept at pH 7 by slow addition of acetic acid) the 16α-bromo-17α-alcohol (V) was the main product with the epimeric 16α-bromo-17β-ol (IV) a by-product. The structures of these bromohydrins were confirmed by treatment with methanolic potassium hydroxide solution, when (V) gave 3β-hydroxyandrost-5-en-17-one and (IV) gave 16β,17β-epoxyandrost-5-en-3β-ol (cf. refs. 13 and 14); on treatment with zinc and acetic acid, (V) gave androsta-5,16-dien-3β-ol [15] and (IV) gave androst-5-ene-3β,17β-diol.

In alkaline medium, sodium borohydride reduction of the bromo-ketone (I) gave the expected 16β-bromo-17β-ol [14] (VI) as the main product, with the epimeric



16β-bromo-17α-ol (IX) as a by-product. The structure of the bromohydrin (IX) was confirmed by debromination with zinc–acetic acid to androst-5-ene-3β,17α-diol and by alkaline treatment of (IX) to give the 16α,17α-epoxide (cf. ref. 16).

The borohydride reductions at different pH values are of interest and in particular the isolation of the 16β-bromo-17α-ol (IX). Fajkoš [16] does not describe the isolation of this isomer on reduction of a 16-bromo-17-ketone, and Fishmann and Biggerstaff [17] showed that no 16β-bromo-17α-ol was produced when 16β-bromo-œstrone was reduced with lithium aluminium hydride.

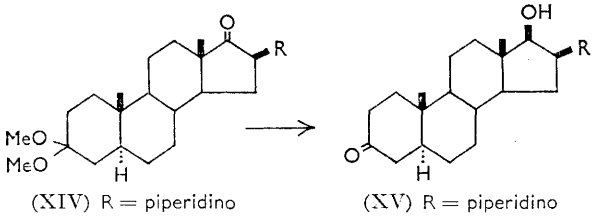
Condensation of 3β-acetoxy-16α,17α-epoxy-5α-androstane [13] (X) with morpholine likewise furnished a *trans*-isomer 3β-acetoxy-16β-morpholino-5α-androstan-17α-ol (XI) which showed no absorption corresponding to a bonded hydroxyl group in its infrared spectrum. This cleavage parallels the opening of the 16α,17α-epoxide with hydrobromic acid to give the 16β-bromo-17α-ol.[16] Alkaline hydrolysis of the acetate (XI) gave the 3β-alcohol (XII).

The configuration of the 16β-amino-17-ketones is confirmed by molecular-rotational evidence (Table 1). Shoppee *et al.*[18] have shown that the rotatory contribution of the 16α-bromine atom in 16α-bromo-17-ketones is −64 whereas that for a 16β-bromine is +170. The 16β-piperidino-ketone (II) shows an equivalent positive increment of +192 which is in good agreement with the 16β-configuration.

TABLE 1

Compound	$[\alpha]_D$	$[M]_D$	$_{16\alpha}\Delta\text{-Br}_{16\beta}$	Δ-Amino
5α-Androstan-17-one [18]	+98°	+268		
16α-Bromo- [18]	+58	+204	−64	
16β-Bromo- [18]	+124	+438		+170
3β-Hydroxy-5α-androstan-17-one	+90	+265		
16β-Piperidino-	+122	+457		+192

Preparation of 17β-hydroxy-16β-piperidino-5α-androstan-3-one (XV) was achieved by sodium borohydride reduction of the 3,3-dimethoxy-ketal (XIV) followed by deketalisation. 17β-Hydroxy-16β-morpholino-5α-androstan-3-one (XVII) was similarly prepared from the ketal (XVI).



(XIV) R = piperidino
(XVI) R = morpholino
(XV) R = piperidino
(XVII) R = morpholino

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.

16β-*Morpholino- and* 16β-*Piperidino*-17-*ketones*.—The

[13] J. Fajkoš, *Coll. Czech. Chem. Comm.*, 1955, **20**, 312.
[14] J. Fajkoš and F. Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 766.
[15] F. Sondheimer, O. Mancera, M. Urquiza, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1955, **77**, 4145.
[16] J. Fajkoš, *J. Chem. Soc.*, 1959, 3966.
[17] J. Fishmann and W. R. Biggerstaff, *J. Org. Chem.*, 1958, **23**, 1190.
[18] C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 1958, 3048.

appropriate 16α-bromo-17-ketones (5 g.), derived from œstrone acetate,[17] 3β-acetoxyandrost-5-en-17-one,[9] 3β-acetoxyandrostan-17-one,[13] 3α-acetoxy-5β-androstan-17-one,[19,20] 5α-androstane-3,17-dione,[21] or 5β-androstane-3,17-dione,[20] were boiled under reflux with six volumes of morpholine or piperidine for 1 hr. After removal of the majority of amines by distillation under reduced pressure the products were precipitated with water and the gummy solid washed with water. Except in the case of the diones the 3-acetates were completely hydrolysed by boiling under reflux with 10 volumes of 2% methanolic potassium hydroxide solution, and, after concentration, the crude free alcohols were precipitated by the addition of water.

The crude 16β-morpholino- and 16β-piperidino-17-ketones were dissolved in 1% hydrochloric acid, filtered from neutral material, and the clear filtrates basified to precipitate the amines; in the case of œstrone this was carried out by means of carbonate since the product is amphoteric. The amines were dissolved in ether, passed through a small column of alumina, distilled to dryness, and recrystallised to give the 16β-amino-17-ketones in 40—70% yields.

16β-*Morpholino- and* 16β-*Piperidino*-17β-*alcohols*.—Reduction of the 16β-amino-17-oxo-steroids (4 g.) with potassium borohydride (1 g.) in methanol solution (30—250 ml.) gave the corresponding *cis*-amino-alcohols in excellent yields.

17β-*Hydroxy*-16β-*piperidino- and* -16β-*morpholino*-3-*ketones*.— 17β-*Hydroxy*-16β-*piperidino*-5α-*androstan*-3-*one* (XV). A solution of 16β-piperidino-5α-androstane-3,17-dione (3 g.) and hydrogen chloride (1·1 mole) in anhydrous methanol (12·5 ml.) was boiled under reflux for 5 min. and then distilled almost to dryness. The residual crude 3-ketal was dissolved in fresh methanol (15 ml.), solid sodium hydrogen carbonate added to raise the pH to 7·0 and then the solution was stirred with potassium borohydride (1·5 g.). After 30 min., water was added to precipitate a white solid which was filtered off and crystallised from aqueous methanol to give the *androstanone* (XV) as a microcrystalline solid (1·8 g.), m. p. 177° (Found: C, 77·2; H, 10·6; N, 3·5. $C_{24}H_{39}NO_2$ requires C, 77·2; H, 10·5; N, 3·75%).

17β-*Hydroxy*-16β-*morpholino*-5α-*androstan*-3-*one* (XVII). In a similar manner 16β-morpholino-5α-androstane-3,17-dione (17·5 g.) gave 17β-*hydroxy*-16β-*morpholino*-5α-*androstan*-3-*one* (XVII) (15·5 g.), m. p. 209—210° (Found: C, 73·2; H, 10·1; N, 3·7. $C_{23}H_{37}NO_3$ requires C, 73·6; H, 9·9; N, 3·7%).

16-*Amino-steroids from* 16-*Bromo*-17-*ols*.—*Reduction of* 16α-*bromo*-3β-*hydroxy-androst*-5-*en*-17-*one* (I). (*a*) *Alkaline conditions*. To a solution of the androstenone (5 g.) in methanol (100 ml.) was added 10N-potassium hydroxide solution (0·1 ml.), followed by potassium borohydride (1 g.). The suspension was stirred for 40 min. and the product (4·5 g.) precipitated with water, collected, and dried, m. p. 165—170°. Recrystallisation from aqueous methanol gave pure 16β-bromoandrost-5-ene-3β,17β-diol [14] (VI) (3·2 g.), m. p. 182—183°.

The mother-liquors contained 16β-bromoandrost-5-ene-3β,17α-diol (IX) which was isolated in a crude form, m. p. 161—165°; debromination of this product with zinc–acetic acid gave androst-5-ene-3β,17α-diol, m. p. 191—192°, and treatment with methanolic potassium hydroxide solution gave 16α,17α-epoxyandrost-5-en-3β-ol, m. p. 168—172° (Found: C, 71·9; H, 9·7. Calc. for $C_{19}H_{30}O_3$,0·5H_2O: C, 72·3; H, 9·8%).

(*b*) *Neutral conditions*. To a solution of the androstenone (5 g.) in methanol (100 ml.), adjusted to pH 7·0 with acetic acid, was added portionwise, potassium borohydride (6·5 g.) over 45 min. with stirring and ice-cooling. The pH was maintained at 7·0 by the slow addition of a 10% solution of acetic acid in methanol. After 2 hr. at 0° more potassium borohydride (0·8 g.) was added, the suspension stirred for 30 min., diluted with water (100 ml.), and the product allowed to crystallise; repeated recrystallisation from methanol gave a *bromohydrin* (1·9 g.), m. p. 235—237° (Found: C, 61·9; H, 8·5; Br, 21·8. $C_{19}H_{29}BrO_2$ requires C, 61·8; H, 7·9; Br, 21·7%).

This product was shown (cf. Fajkoš [13,14]) to be 16α-bromoandrost-5-ene-3β,17α-diol (V) since treatment with methanolic potassium hydroxide solution gave 3β-hydroxyandrost-5-en-17-one, m. p. 145—148°, and debromination with zinc–acetic acid gave androsta-5,16-dien-3β-ol,[15] m. p. 140—141°.

Concentration of the mother-liquors gave first a mixture of bromohydrins and then 16α-*bromoandrost*-5-*ene*-3β,17β-*diol* (IV) (0·5 g.), m. p. 184—185° from aqueous methanol (Found: C, 61·8; H, 8·1; Br, 20·0. $C_{19}H_{29}BrO_2$ requires C, 61·8; H, 7·9; Br, 21·7%). Treatment of this bromohydrin with methanolic potassium hydroxide solution gave 16β,17β-epoxyandrost-5-en-3β-ol,[14] m. p. 144—145° (Found: C, 76·5; H, 9·45. Calc. for $C_{19}H_{28}O_2$,0·5H_2O: C, 76·7; H, 9·8%). Debromination with zinc dust in acetic acid gave androst-5-ene-3β,17β-diol.

16β-*Piperidinoandrost*-5-*ene*-3β,17β-*diol* (III). The 16α-bromo-17β-ol (IV) (250 mg.) was boiled under reflux with piperidine (2·5 ml.) for 16 hr. and separated into neutral and basic material. The latter crystallised from aqueous methanol to give 16β-*piperidinoandrost*-5-*ene*-3β,17β-*diol* (III) (80 mg.), m. p. 225—228°, identical with that prepared from the 16β-piperidino-17-ketone (II). The neutral fraction gave 16β,17β-epoxyandrost-5-en-3β-ol.

16β-*Piperidinoandrost*-5-*ene*-3β,17α-*diol* (VII). The 16α-bromo-17α-ol (V) (205 mg.) was boiled under reflux with piperidine (2·5 ml.) for 12 hr., the solution cooled, and the product precipitated by the addition of water. The solid precipitate was filtered and separated into unchanged starting material (190 mg.) and basic material. The base was crystallised from methanol to give 16β-*piperidinoandrost*-5-*ene*-3β,17α-*diol* (VII) (12 mg.), m. p. 239—241°, $\nu_{max.}$ (CCl_4) 3610 cm.$^{-1}$ (3β-OH), no absorption at 3600—3000 cm.$^{-1}$ (Found: C, 77·3; H, 10·4; N, 3·6. $C_{24}H_{39}NO_2$ requires C, 77·2; H, 10·5; N, 3·75%).

16α-*Piperidinoandrost*-5-*ene*-3β,17β-*diol*. The 16β-bromo-17β-ol (VI) (200 mg.) was boiled under reflux for 12 hr. with piperidine (5 ml.), the solution cooled, and a solid precipitated by the addition of water. This solid was filtered off and separated into neutral and basic material. The base recrystallised from methanol to give 16α-*piperidinoandrost*-5-*ene*-3β,17β-*diol* (VIII) (85 mg.), m. p. 239—241°, depressed by the 16β-isomer (III); $\nu_{max.}$ (CCl_4) 3610 cm.$^{-1}$ (3β-OH), no absorption at 3600—3000 cm.$^{-1}$ (Found: C, 77·0; H, 10·5; N, 3·6%).

3β-*Acetoxy*-16α-*morpholinoandrost*-5-*en*-17β-*ol*. A solution of 3β-acetoxy-16β-bromoandrost-5-en-17β-ol [13] (5 g.) in morpholine (30 ml.) was maintained at 80° for 48 hr.

[19] J. Fajkoš and V. Sanda, *Coll. Czech. Chem. Comm.*, 1962, **27**, 355.

[20] C. L. Hewett, U.S.P. 3,026,318/1962 (*Chem. Abs.*, 1962, **57**, 4731). B.P. 933,151/1963.

[21] H. Dannenberg, Thesis, Danzig, 1937.

TABLE 2

16β-Substituted 17-oxo-steroids

16β-Subst.*	Compound	M. p.	Recryst. from †	$[\alpha]_D$	$\nu_{max.}$ (cm.$^{-1}$)	Found (%) C	H	N	Formula	Required (%) C	H	N
P	3β-Hydroxy-5α-androstan-17-one	170—175°	A–W	+113°	3602, 1740	72·3	10·2	3·0	$C_{24}H_{39}NO_2,1{\cdot}5H_2O$	72·0	10·5	3·5
M	3β-Hydroxy-5α-androstan-17-one	192—197	M–W	+104	3600, 1740	70·2	9·3	3·6	$C_{23}H_{37}NO_3,H_2O$	70·2	10·0	3·55
P	5α-Androstane-3,17-dione	137	M–W	+132	1740, 1710	75·7	9·8	3·5	$C_{24}H_{37}NO_2,0{\cdot}5H_2O$	75·7	10·1	3·7
M	5α-Androstane-3,17-dione	220—223	M–W	+131	1740, 1710, 1118	74·5	9·0	3·85	$C_{23}H_{35}NO_3$	74·0	9·4	3·8
P	3β-Hydroxyandrost-5-en-17-one	170	M–W	+41		76·2	9·3	3·7	$C_{24}H_{37}NO_2,0{\cdot}5H_2O$	75·7	10·1	3·7
M	3β-Hydroxyandrost-5-en-17-one	200	M–W	+37		71·9	8·9	3·6	$C_{23}H_{35}NO_3,0{\cdot}5H_2O$	72·2	9·4	3·7
P	Androst-4-ene-3,17-dione	164—165	M–W	+182	1740, 1680—1660, 1620	78·0	9·5	3·7	$C_{24}H_{35}NO_2$	78·0	9·55	3·8
P	3α-Hydroxy-5β-androstan-17-one	212—214	M–W	+124	3603, 1740	73·4	10·5	3·9	$C_{24}H_{39}NO_2,H_2O$	73·6	10·55	3·6
M	3α-Hydroxy-5β-androstan-17-one	234—235	E	+113	3602, 1740, 1118	73·5	9·75	3·6	$C_{23}H_{37}NO_3$	73·6	9·9	3·7
P	5β-Androstane-3,17-dione	198—200	M–W	+131	1740, 1710	77·1	9·9	4·0	$C_{24}H_{37}NO_2$	77·6	10·0	3·8
M	5β-Androstane-3,17-dione	214—215	M–W	+124	1740, 1712	73·8	9·4	3·4	$C_{23}H_{35}NO_3$	74·0	9·45	3·75
P	Oestrone	215—217	B–M	+133	3584, 1740, 1614, 1597	75·0	9·0	3·3	$C_{23}H_{31}NO_2$,MeOH	74·8	9·15	3·6
M	Oestrone	225—228	B–M	+120		72·8	8·0	3·7	$C_{22}H_{29}NO_3,0{\cdot}5$MeOH	72·7	8·4	3·8

* P = Piperidino, M = morpholino. † A = Acetone, W = water, E = ether, B = benzene, M = ethanol.

TABLE 3

16β-Substituted dehydroxy-steroids

16β-Subst.*	Compound	M. p.	Recryst. from †	$[\alpha]_D$	$\nu_{max.}$ (cm.$^{-1}$)	Found (%) C	H	N	Formula	Required (%) C	H	N
P	5α-Androstane-3β,17β-diol	185°	M–W	+13°		76·2	10·7	3·9	$C_{24}H_{41}NO_2$	76·75	11·0	3·7
P	5α-Androstane-3β,17β-diol 3-acetate	135—137	M–W	+8	3333, 1721	74·8	10·3	3·6	$C_{26}H_{43}NO_3$	74·8	10·4	3·35
M	,, ,,	265	M–W	+19		73·1	10·1	3·2	$C_{23}H_{39}NO_3$	73·2	10·4	3·7
P	Androst-5-ene-3β,17β-diol	228—230	M–W	−32	3602, 3333—3000	77·4	10·3	3·7	$C_{24}H_{39}NO_2$	77·2	10·5	3·75
P	Androst-5-ene-3β,17β-diol diacetate	199—201	A–H	0	1721	73·0	9·4	2·6	$C_{28}H_{43}NO_4$	73·5	9·5	3·1
M	,, ,,	190	M–W	−41		73·1	9·7	3·6	$C_{23}H_{37}NO_3$	73·6	9·9	3·7
P	5β-Androstane-3α,17β-diol	185—186	M–W	+26	3602, 3420—2100	76·3	10·8	3·7	$C_{24}H_{41}NO_2$	76·75	11·0	3·7
M	,, ,,	210—212	M–W	+26	3602, 3580—3180	71·25	10·4	3·85	$C_{23}H_{39}NO_3{\cdot}0{\cdot}5H_2O$	71·5	10·4	3·6
P	Oestra-3,17β-diol	298	B–M	+83 C		77·1	9·3	3·7	$C_{23}H_{33}NO_2$	77·7	9·4	3·9
M	,,	295	B–M	+97 C		73·5	8·7	3·55	$C_{22}H_{31}NO_3$	73·9	8·7	3·9

* P = Piperidino, M = morpholino. † A = Acetone, H = n-hexane, B = benzene, M = methanol, C = chloroform.

and evaporated to dryness under reduced pressure. The product was separated into neutral and basic material. The latter was dissolved in ether and the ether solution percolated down a column (3 × 1 in.) of alumina. Concentration of the ether eluate yielded 3β-*acetoxy*-16α-*morpholinoandrost*-5-*en*-17β-*ol* as plates, m. p. 210—212°, $[\alpha]_D$ −70° (*c* 2·0); $\nu_{max.}$ (in CH_2Cl_2) 3610 (17β-OH), 1730, 1242 (3β-OAc), and 1117 cm.$^{-1}$ (–C–O–C–); there was no absorption in the 3450—3330-cm.$^{-1}$ region (N-bonded OH group) (Found: C, 72·45; H, 9·7; N, 3·3. $C_{25}H_{39}NO_4$ requires C, 71·9; H, 9·4; N, 3·35%).

16α-*Piperidino*-5α-*androstane*-3β,17β-*diol*. A solution of 3β-acetoxy-16β-bromo-5α-androstan-17β-ol (3·7 g.) in piperidine was boiled under reflux for 24 hr., the solution cooled, and a white solid precipitated by the addition of ice–water. This material was filtered off, well washed with water, dried, suspended in methanol (50 ml.), and a solution of potassium carbonate (2 g.) in water (12 ml.) added before refluxing for 1½ hr. The addition of water to the cooled solution precipitated a white solid which was filtered off and separated into neutral and basic fractions. Crystallisation of the neutral fraction (1·5 g.) from methanol yielded 3β-hydroxyandrostan-17-one, m. p. 176—178°, $[\alpha]_D$ +98° (*c* 2·0). Admixture with an authentic specimen gave no depression in melting point.

The basic fraction was crystallised from ether to give 16α-*piperidino*-5α-*androstane*-3β,17β-*diol* as needles, m. p. 274—279° (decomp.) (Found: C, 76·8; H, 11·1; N, 3·7. $C_{24}H_{41}NO_2$ requires C, 76·8; H, 11·0; N, 3·7%). The 16β-piperidino-epimer has m. p. 185°.

16-*Amino*-17-*alcohols from* 16α,17α-*Epoxides*.—3β-*Acetoxy*-16β-*morpholino*-5α-*androstan*-17α-*ol* (XI). A solution of 3β-acetoxy-16α,17α-epoxy-5α-androstane [13] (8 g.) (X) in morpholine (20 ml.) was boiled under reflux for 48 hr., the solution cooled, and the product separated into neutral and basic material. The basic fraction was crystallised from ether to give 3β-*acetoxy*-16β-*morpholino*-5α-*androstan*-17α-*ol* (XI) as a microcrystalline solid (4·5 g.), m. p. 236—240°, $\nu_{max.}$ (in CH_2Cl_2) 3610, 1028 (17α-OH), 1724, 1232 (3β-OAc), and 1119 cm.$^{-1}$ (–C–O–C–) (Found: C, 71·5; H, 9·7; N, 2·7. $C_{25}H_{41}NO_4$ requires C, 71·6; H, 9·8; N, 3·3%).

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