2β-Fluoro-5α-androstane-3α,17β-diol 17-Monoacetate (VIII).—Treatment of 2α,3α-epoxy-5α-androstan-17β-ol acetate[4] (VII, 5.6 g.) with hydrogen fluoride as described above gave pure VIII (2.8 g.), m.p. 204.5–205.5°, $[\alpha]^{25}D$ +12°.

Anal. Calcd. for $C_{21}H_{33}FO_3$: C, 71.56; H, 9.44. Found: C, 71.67; H, 9.47.

2β-Fluoro-5α-androstan-17β-ol-3-one 17-Acetate (IX).—Chromic acid oxidation of 2β-fluoro-5α-androstane-3α,17β-diol 17-monoacetate (VIII, 1.0 g.) as described above gave IX (0.4 g.), m.p. 153–154°, ϵ_{max}^{289} 24.6, λ_{max} 3.38, 5.75, 7.91 μ, $[\alpha]D^{25}$ +38°.

Anal. Calcd. for $C_{21}H_{31}FO_3$: C, 71.97; H, 8.92. Found: C, 71.91; H, 9.20.

2α-Fluoro-5α-androstan-17β-ol-3-one 17-Acetate (X).—A sample of 2β-fluoro-5α-androstan-17β-ol-3-one 17-acetate (IX, 100 mg.) was epimerized as described above to give X as white needles (70 mg.), m.p. 192–194° (reported[6] m.p. 190–193°), ϵ_{max}^{280} 18.5, λ_{max} 3.38, 5.75, 7.92 μ, $[\alpha]^{26}D$ +46.5°.

2-Fluoro-5α-androst-1-en-17β-ol-3-one 17-Acetate (XII).—To a solution of anhydrous hydrogen fluoride (7.0 g.) in glacial acetic acid (60 ml.) was added with rapid stirring during 20 min. a solution of 1α,2α-epoxy-5α-androstan-17β-ol-3-one 17-acetate[24] (XI, 4.0 g.) in glacial acetic acid (140 ml.). The solution warmed to 40° and was controlled by means of a water bath. After allowing the solution to stand at room temperature for 17 hr., it was poured into ice and water (650 ml.). The resulting semi-solid was extracted with ether. The extracts were washed with 5% sodium bicarbonate solution and dried over anhydrous potassium carbonate containing Darco. Solvent removal *in vacuo* left a solid which was recrystallized twice from acetone-hexane to give XII (2.05 g.), m.p. 172–175°, $\epsilon_{max}^{236-237.5}$ 8200, $[\alpha]^{28}D$ +59°.

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.39. Found: C, 72.84; H, 8.45.

(24) W. M. Hoehn, *J. Org. Chem.*, **23**, 929 (1958).

Hypocholesterolemic Agents. III.[1] N-Methyl-N-(dialkylamino)alkyl-17β-aminoandrost-5-en-3β-ol Derivatives

R. E. COUNSELL, P. D. KLIMSTRA AND R. E. RANNEY

Division of Chemical Research of G. D. Searle & Co., Chicago 80, Illinois

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A series of N-methyl-N-(dialkylamino)alkyl derivatives of 17β-aminoandrost-5-en-3β-ol sterically similar to cholesterol was synthesized by the Leuckart reductive amination of readily available 3β-hydroxyandrost-5-en-17-one followed by reduction with lithium aluminum hydride. The ability of 17-ketosteroids to form stable Schiff bases when condensed with primary amines afforded an alternate path to these compounds. Several compounds in this series were found to exhibit pronounced oral hypocholesterolemic activity when evaluated in rats.

One approach to the development of hypocholesterolemic agents has involved the synthesis and biological evaluation of compounds

that inhibit the endogenous synthesis of cholesterol. In an earlier paper[2] the potent hypocholesterolemic action of a number of 22,25-diaza analogs of cholesterol was described. The rationale for investigating structures of this type was based on the known inhibitory action of cholesterol itself upon its own biosynthesis (*i.e.*, feedback control).[3] It was reasoned that various nitrogen isosteres of cholesterol would possess a greater inhibitory action upon cholesterol biosynthesis by being more firmly bound to the surface of the feedback-inhibited enzyme. The ability of 20α-(2-dimethylaminoethyl)-amino-5α-pregnan-3β-ol dihydrochloride (22,25-diazacholestanol dihydrochloride) to markedly reduce cholesterol levels in both *in vitro*[4] and *in vivo*[2,5] assays has served to confirm the validity of this approach. A series of 20,25-diaza analogs of cholesterol which also possess potent hypocholesterolemic activity forms the subject of this paper.

The Leuckart reductive amination of readily available 17-ketosteroids appeared to offer the most direct route to the desired substituted 17-aminosteroids. Previous studies by Tanabe and Onda[6] and later by Joska and Sorm[7] had shown that 17β-formamidoandrost-5-en-3β-ol could be obtained in good yield by allowing 3β-hydroxyandrost-5-en-17-one (Ia) to react with formamide and formic acid.[8] In order to evaluate the scope of this reaction with 17-ketosteroids, the reaction of Ia with N-methylformamide and N,N-dimethylformamide was investigated. As expected, N-methyl-17β-formamidoandrost-5-en-3β-ol formate (II) was obtained in 62.5% yield when N-methylformamide was employed. This material was accompanied by N-methyl-17β-aminoandrost-5-en-3β-ol (III) which was isolated in 18.6% yield as its hydrochloride salt. The latter product also was obtained from II by acid hydrolysis followed by liberation of the free base. When Ia was treated with N,N-dimethylformamide under similar conditions, however, only the formate ester of starting material was isolated. This result is in contrast with the good yields of 3β-dimethylaminocholestane obtained from the reaction of N,N-di-

(1) Paper II, P. D. Klimstra and R. E. Counsell, *J. Med. Pharm. Chem.*, **5**, 1216 (1962).

(2) R. E. Counsell, P. D. Klimstra, R. E. Ranney, and D. L. Cook, *J. Med. Pharm. Chem.*, **5**, 720 (1962).

(3) M. D. Siperstein, *Am. J. Clin. Nutrition*, **8**, 645 (1960).

(4) R. E. Ranney and R. E. Counsell, *Proc. Soc. Exper. Biol. and Med.*, **109**, 820 (1962).

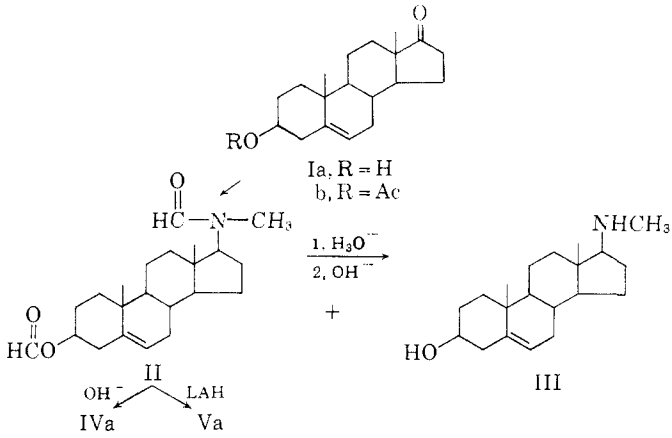
(5) R. E. Ranney and R. E. Counsell, *Fed. Proc.*, **21**, 96 (1962).

(6) S. Tanabe and M. Onda, *J. Pharm. Soc. Japan*, **72**, 944 (1952).

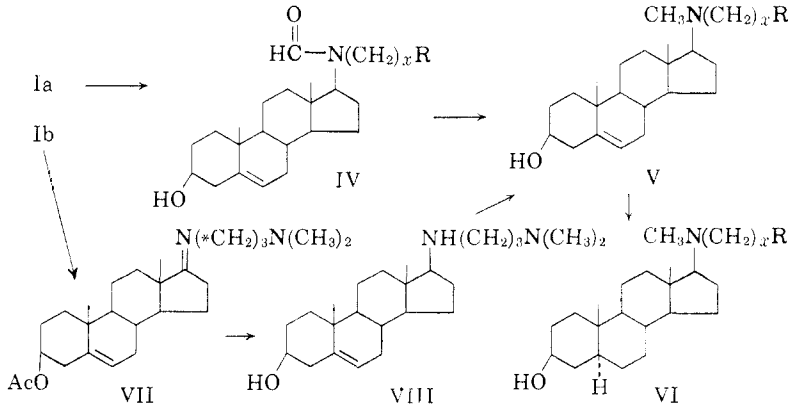
(7) J. Joska and F. Sorm, *Coll. Czechoslov. Chem. Comm.*, **21**, 754 (1958).

(8) When this reaction was repeated using commercial 98–100% formic acid in place of the reported 80% formic acid, the major product isolated was 17β-formamidoandrost-5-en-3β-ol formate, m.p. 250–251.5° dec., $[\alpha]^{25}D$ − 109.3°, infrared $\nu_{max}^{CHCl_3}$ 2.91, 3.39, 5.80, and 5.92 μ. *Anal.* Calcd. for $C_{21}H_{33}NO_3$: C, 73.00; H, 9.05; N, 4.06. Found: C, 73.48; H, 9.10; N, 3.92.

methylformamide with cholestan-3-one,[9] but in agreement with the reported inertness of 17-ketosteroids toward enamine formation.[10]



As shown by molecular models, the approach of secondary amines or their amides to the β-face of the C-17 carbonyl group is markedly hindered by the angular C-18 methyl group.



The β-orientation of the introduced amino function was proved by methylation of known 17β-aminoandrost-5-en-3β-ol with formaldehyde and formic acid as described by Julian and coworkers.[11] This afforded N,N-dimethyl-17β-aminoandrost-5-en-3β-ol (Va) identical

(9) R. R. Sauers, *J. Am. Chem. Soc.*, **80**, 4721 (1958).
(10) M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.*, **75**, 5927 (1953).
(11) P. L. Julian, H. C. Printy, and E. W. Meyer, U. S. Patent 2,705,238 (1955).

in all respects with that obtained by lithium aluminum hydride reduction of II. This high degree of stereospecificity for the Leuckart reaction with 17-ketosteroids is consistent with the current views[9,12] on the stereochemistry and mechanism of formic acid reductions (*i.e.*, the most favorable approach of the formate ion is from the less hindered α-face of the steroid molecule).

Substitution of various N,N-dialkylaminoalkylamines for N-methylformamide in the reductive amination step led to the intermediate N-(dialkylamino)alkyl-17β-formamidoandrost-5-en-3β-ol derivatives[13] (IV, see Table I) in yields as high as 80%. Reduction of these products with lithium aluminum hydride in dioxane gave the desired N-methyl-N-(dialkylamino)alkyl-17β-aminoandrost-5-en-3β-ols (V, see Table II). Catalytic hydrogenation of these latter products over platinum oxide in acidic ethanol furnished the corresponding 5α-androstane derivatives (VI). Although the initial assignment of the A/B *trans* configuration for VI was based on the normal steric course of hydrogenation of Δ^5-steroids,[14] this was later confirmed when substitution of 5α-androstan-3β-ol-17-one for Ia in the synthetic sequence afforded the same products.

The discovery that 17-ketosteroids readily formed stable imines when condensed with primary amines in the presence of a catalytic amount of *p*-toluenesulfonic acid furnished an alternate route to compounds of type V. Condensation of 3-dimethylaminopropylamine with 3β-acetoxyandrost-5-en-17-one (Ib) in benzene and removal of the water formed by azeotropic distillation gave 3β-acetoxy-17-(3-dimethylaminopropyl) iminoandrost-5-ene (VII) in essentially quantitative yield. Lithium aluminum hydride reduction of VII gave the corresponding substituted 17β-amine (VIII) which when methylated with formaldehyde and formic acid afforded Vc identical with that obtained by the reductive amination sequence.

Biological Activity.—Table IV shows the oral hypocholesterolemic activities for the diazacholesterol analogs as determined in rats made hypercholesterolemic with 6-propylthiouracil.[2] In this assay, compound Vc was found to have a potency of about fifteen times that of triparanol,[15] a well characterized hypocholesterolemic agent. Departure from the isosteric dimethylamino end group markedly low-

(12) N. J. Leonard and R. R. Sauers, *J. Am. Chem. Soc.*, **79**, 6210 (1957).

(13) In all cases studied, the products isolated were unesterified at C-3 when a diamine was used for reductive amination.

(14) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 272.

(15) Triparanol (MER-29) is 1-[4-(diethylaminoethoxy)phenyl]-1-(*p*-tolyl)-2-(*p*-chlorophenyl)-ethanol, and was generously supplied by Dr. D. Holtkamp, Richardson–Merrill, Inc.

TABLE I

N-(DIALKYLAMINO)ALKYL-17β-FORMAMIDO-ANDROST-5-EN-3β-OL DERIVATIVES

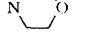
IV	R	x	Recrystallization media	M.p., °C.	$[\alpha]^{25}D$	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	H	1	MeOH–H_2O	218–220	−81°	61	$C_{21}H_{33}NO_2$	76.09	10.03	4.23	75.95	9.99	4.17
b	$N(CH_3)_2$	2	Me_2CO	158–159	−76°	63	$C_{24}H_{40}N_2O_2 \cdot C_3H_6O$	72.60	10.38	7.21	72.70	10.36	7.52
c	$N(CH_3)_2$	3	EtOAc	116–118	−67.5°	72	$C_{25}H_{42}N_2O_2$	74.58	10.52	6.96	74.28	10.87	7.04
d	$N(CH_3)_2$	4	MeOH–H_2O	181–184	−57°	66.5	$C_{26}H_{44}N_2O_2$	74.95	10.65	6.72	74.84	10.55	6.50
e	$N(C_2H_5)_2$	3	Hexane-Me_2CO	124–126	−61°	82.4	$C_{27}H_{46}N_2O_2$	75.29	10.71		75.21	10.74	
f		3	Me_2CO–H_2O	135–138	−62°	57	$C_{27}H_{44}N_2O_2$	75.35	10.35	6.54	75.45	10.52	6.21
g		3	Me_2CO	131–133	−63.5°	60	$C_{28}H_{46}N_2O_2$	75.97	10.47	6.33	76.15	10.10	6.27
h		3	EtOAc	130.5–132.5	−62°	80	$C_{27}H_{44}N_2O_3 \cdot 0.5C_4H_8O_2$	71.27	9.90		71.31	9.95	
i		3	Me_2CO	174–177	−56.5°	56.8	$C_{28}H_{47}N_3O_2$	73.47	10.35	9.18	73.72	10.48	9.06

TABLE II

N-METHYL-N-(DIALKYLAMINO)ALKYL-17β-AMINO-ANDROST-5-EN-3β-OL DERIVATIVES

V	R	x	Recrystallization media	M.p., °C.	$[\alpha]^{25}D$	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	H	1	EtOH	211–212.5	−77°	61	$C_{21}H_{35}NO$	79.44	11.11	4.41	78.96	10.82	4.39
b	$N(CH_3)_2$	2	Me_2CO	125–128	−64°	58.2	$C_{24}H_{42}N_2O$	76.95	11.30	7.48	77.27	11.37	7.19

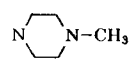
c	$N(CH_3)_2$	3	$MeOH–Me_2CO$	146–148	−54.5°	78	$C_{25}H_{44}N_2O$	77.26	11.41		77.14	11.39	
d	$N(CH_3)_2$	4	Me_2CO	107–110	−56.5°	87	$C_{26}H_{44}N_2O$	77.55	11.52		77.57	11.39	
e	$N(C_2H_5)_2$	3	Me_2CO	90–91.5	−52.5°	67.3	$C_{27}H_{48}N_2O$	77.82	11.61	6.72	78.01	11.37	6.84
f		3	$MeOH–Me_2CO$	158–160	−52°	72.5	$C_{27}H_{46}N_2O$	78.20	11.18	6.76	77.72	10.75	7.12
g		3	Me_2CO	136–136.5	−54°	55	$C_{28}H_{48}N_2O$	78.45	11.29	6.54	78.39	10.78	6.54
h		3	$MeOH–Me_2CO$	169–171	−49.5°	74	$C_{27}H_{46}N_2O_2$	75.30	10.77	6.51	75.77	10.68	6.53
i		3	Me_2CO	148–149	−44°	61.7	$C_{28}H_{49}N_3O$	75.79	11.13	9.47	75.53	11.04	9.93

TABLE III

N-METHYL-N-(DIALKYLAMINO)ALKYL-17β-AMINO-5α-ANDROSTAN-3β-OL DERIVATIVES

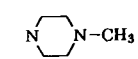
								Analyses, %					
								Calcd.			Found		
VI	R	x	Recrystallization media	M.p., °C.	$[\alpha]^{25}D$	Yield, %	Formula	C	H	N	C	H	N
a	$N(CH_3)_2$	3	$MeOH–Me_2CO$	134.5–135.5	+17°	84	$C_{25}H_{46}N_2O$	76.86	11.87	7.17	76.91	11.92	7.44
b	$N(C_2H_5)_2$	3	Me_2CO	91.5–93	+9.5°	83.4	$C_{27}H_{50}N_2O$	77.45	12.04	6.69	77.37	11.85	6.98
		3	$MeOH–Me_2CO$	143.5–145	+5°	92	$C_{27}H_{48}N_2O$	77.82	11.61	6.72	78.09	11.52	6.68
d		3	Me_2CO	134	+9°	80.5	$C_{28}H_{50}N_2O$	78.08	11.70	6.50	78.45	11.43	6.45
e		3	$MeOH–Me_2CO$	164–166	+4.5°	79.5	$C_{27}H_{48}N_2O_2$	74.95	11.18	6.48	74.45	10.95	6.79
f		3	Me_2CO	126–128	+9°	87.5	$C_{28}H_{57}N_3O$	75.45	11.53	9.42	75.47	11.15	9.50

TABLE IV
ORAL HYPOCHOLESTEROLEMIC ACTIVITY OF SEVERAL DIAZA ANALOGS OF CHOLESTEROL

Compound[a]	C-17 Substituent	Dose, mg./kg.	% Reduction[b]
Va[c]	CH_3NCH_3	10	Inactive
b	$CH_3N(CH_2)_2N(CH_3)_2$	3	28
		0.5	26
c	$CH_3N(CH_2)_3N(CH_3)_2$	3	35
		0.5	15
d	$CH_3N(CH_2)_4N(CH_3)_2$	10	Inactive
e	$CH_3N(CH_2)_3N(C_2H_5)_2$	10	Inactive
f	$CH_3N(CH_2)_3NC_4H_8$	10	15
g	$CH_3N(CH_2)_3NC_5H_{10}$	10	10
h	$CH_3N(CH_2)_3NC_4H_8O$	10	Inactive
i	$CH_3N(CH_2)_3NC_4H_3NCH_3$	10	Inactive
VIa	$CH_3N(CH_2)_3N(CH_3)_2$	10	28
		3	14
VIII	$HN(CH_2)_3N(CH_3)_2$	10	Inactive
Tripara-nol		10	21
		5	10
		3	Inactive

[a] All compounds were evaluated as their hydrochloride salts unless specified otherwise. [b] Values refer to the per cent reduction of serum cholesterol. [c] Evaluated as the free base.

ered activity in this series. Moreover, while lengthening, the side chain was found to destroy activity (Vd), decreasing the length of the side chain by one methylene group (Vb) had little effect upon the hypocholesterolemic potency. These results confirm and extend the previous findings regarding the activity of certain diazasterols in blocking cholesterol synthesis in a "cholesteromimetic" fashion.[2,4] Whereas lengthening the side chain or departing from the dimethylamino end group appears to impede adsorption at the receptor site, shortening the side chain does not diminish the hypocholesterolemic response. The activities of VIa and VIII also indicate that a 5,6 double bond and a tertiary nitrogen function at C-17 are essential for optimal activity.

Experimental[16]

N-Methyl-17β-formamidoandrost-5-en-3β-ol Formate (II).—A solution of 3β-hydroxyandrost-5-en-3-one (Ia, 10 g.) in N-methylformamide (20 g.) and formic acid[17] (20 ml.) was heated for 20 hr. under reflux in an oil-bath maintained at 170–180°. The solution was allowed to cool and poured slowly into ice water.

(16) The elemental analyses, infrared spectra, and optical rotations were furnished by our Analytical Department under the supervision of Dr. R. T. Dillon. The optical rotations and infrared spectra were obtained in chloroform unless stated otherwise. Melting points are uncorrected.

(17) Commercial 98–100% formic acid was used throughout the experimental.

The resulting mixture was neutralized with 20% sodium hydroxide solution and extracted with methylene chloride (3 × 100 ml.). The extract was washed successively with water (2 × 50 ml.), *N* hydrochloric acid (2 × 50 ml.), and water (50 ml.). A solid material appeared in the acid wash which was collected by filtration (2.2 g.). Treatment of a methanol–water (3:2, 25 ml.) solution of this material (1 g.) with a solution of potassium carbonate (250 mg.) in water (5 ml.) and then further dilution with water (15 ml.) afforded crude N-methyl-17β-aminoandrost-5-en-3β-ol (III, 0.83 g.), m.p. 199–204°. Recrystallization from ethanol gave an analytical sample, m.p. 213–214°, $[\alpha]^{26}D$ −51°.

Anal. Calcd. for $C_{20}H_{33}NO$: C, 79.15; H, 10.93; N, 4.62. Found: C, 78.66; H, 10.77; N, 4.45.

The methylene chloride solution was dried over anhydrous sodium sulfate and the solvent removed by distillation under reduced pressure. The oily residue crystallized from ethyl acetate–ether to give crude II (7.75 g.), m.p. 176–180°. Recrystallization from ethanol gave an analytical sample, m.p. 190.5–193°, $[\alpha]^{25}D$ −84.5°, infrared $\lambda_{max}^{CHCl_3}$ 3.38, 5.79, and 6.0 μ.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.09; H, 9.34; N, 3.75.

N-Methyl-17β-aminoandrost-5-en-3β-ol (III).—A solution of II (1.0 g.) in methanol (8 ml.) and concd. hydrochloric acid (2 ml.) was refluxed for 1 hr. on the steam bath. The hydrochloride salt which separated upon cooling was collected. Liberation of the free base gave N-methyl-17β-aminoandrost-5-en-3β-ol (0.43 g.) identical with that obtained above.

N-Methyl-17β-formamidoandrost-5-en-3β-ol (IVa).—A mixture of II (1.0 g.) and anhydrous potassium carbonate (0.5 g.) in 90% methanol (20 ml.) was stirred at room temperature for 1 hr. Water was added and the precipitate collected by filtration and washed with water. Recrystallization of the crude product from methanol–water gave pure IVa (0.9 g.), m.p. 218–220°, $[\alpha]^{25}D$ −81°, infrared $\lambda_{max}^{CHCl_3}$ 2.76, 3.40, and 6.02 μ.

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.95; H, 9.99; N, 4.17.

N-(3-Dimethylamino)propyl-17β-formamidoandrost-5-en-3β-ol (IVc). **General Method.**—Formic acid (60 ml.) was added slowly with external cooling and stirring to Ia (30 g.) in 3-dimethylaminopropylamine (60 g.) contained in a 500 ml. three-necked flask. After the addition of formic acid was completed, the mixture was heated in an oil bath maintained between 170–180°. After 8 hr., the reaction mixture was allowed to cool and water (200 ml.) added to the solidified reaction mixture. The resulting suspension was poured slowly into 15% sodium hydroxide solution (500 ml.) containing cracked ice. The insoluble product (too gelatinous to isolate by filtration) was extracted with chloroform containing a small amount of isopropyl alcohol to aid solution. The chloroform layer was washed several times with water and dried over anhydrous sodium sulfate. Solvent removal *in vacuo* gave a quantitative yield of crude IVc which was suitable for subsequent reduction. However, recrystallization at this stage from ethyl acetate gave pure IVc (30 g.), m.p. 116–118°, $[\alpha]^{25}D$ −67.5°.

Anal. Calcd. for $C_{25}H_{42}N_2O_2$: C, 74.58; H, 10.52; N, 6.96. Found: C, 74.28; H, 10.87; N, 7.04.

N,N-Dimethyl-17β-aminoandrost-5-en-3β-ol (Va).—A suspension of II (2.0 g.) in hot purified dioxane[18] (55 ml.) was added to a refluxing slurry of lithium alu-

(18) The purified dioxane was obtained from Pierce Chemical Company.

minum hydride (1.0 g.) in purified dioxane (25 ml.). The mixture was refluxed with stirring for 16 hr. and the excess hydride decomposed by the successive dropwise addition of aqueous dioxane (1:19, 20 ml.), 20% sodium hydroxide solution (0.75 ml.), and water (3.5 ml.). The salts were removed by filtration and washed with dioxane. The filtrate was concentrated to dryness *in vacuo* and the residue dissolved in methanol (10 ml.). Anhydrous ether (100 ml.) was added followed by a solution of hydrogen chloride in isopropyl alcohol until precipitation was complete. The hydrochloride salt (1.75 g.) was collected by filtration and washed with ether. To a solution of the hydrochloride salt (1.0 g.) in methanol (15 ml.) and water (10 ml.) was added a solution of potassium carbonate (0.25 g.) in water (5 ml.). Addition of more water (10 ml.) and collection of the precipitated product by filtration gave crude Va (0.62 g.), m.p. 207–211°. Recrystallization from ethanol afforded an analytical sample, m.p. 211–212.5° (reported[11] m.p. 208–213°), $[\alpha]^{25}D$ −77°. This product was identical with that obtained by methylating 17β-aminoandrost-5-en-3β-ol with formaldehyde and formic acid as described by Julian, *et al.*[11]

Anal. Calcd. for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 78.96; H, 10.82; N, 4.39.

N-Methyl-N-(3-dimethylamino)propyl-17β-aminoandrost-5-en-3β-ol (Vc). General Method.—A solution of crude IVc (42 g.) in purified dioxane (500 ml.) was added with stirring to a refluxing slurry of lithium aluminum hydride (10 g.) in purified dioxane (500 ml.). The mixture was stirred at the reflux temperature for 18 hr., and the excess hydride decomposed by the successive dropwise addition of aqueous dioxane (1:9, 100 ml.), 20% sodium hydroxide solution (7.5 ml.), and water (35 ml.). The insoluble salts were removed by filtration of the hot reaction mixture. After washing the salts with isopropyl alcohol, the filtrate was concentrated to dryness *in vacuo* and the solid residue recrystallized from acetone-methanol to give Vc (31.7 g.), m.p. 142–145°. One additional recrystallization afforded an analytical sample, m.p. 146–148°, $[\alpha]^{25}D$ −54.5°.

Anal. Calcd. for $C_{25}H_{44}N_2O$: C, 77.26; H, 11.41. Found: C, 77.14; H, 11.39.

Dihydrochloride Salts.—The crystalline free bases obtained as described above were dissolved in anhydrous ether containing sufficient isopropyl alcohol for solubilization. Addition of a solution of hydrogen chloride in isopropyl alcohol precipitated the dihydrochloride salts which were recrystallized from either aqueous ethanol or aqueous isopropyl alcohol. All salts gave satisfactory elemental analyses.

N-Methyl-N-(3-dimethylamino)propyl-17β-amino-5α-androstan-3β-ol (VIa). A. General Method.—A solution of Vc (3 g.) in 95% ethanol (200 ml.) containing concd. hydrochloric acid (1.2 ml.) was hydrogenated at atmospheric pressure (Parr shaker) and 25° using platinum oxide (1.75 g.) as catalyst.[19] The catalyst was removed by filtration and washed with 95% ethanol. The filtrate was concentrated to dryness *in vacuo*. Recrystallization of the solid residue from isopropyl alcohol-water afforded pure VIa dihydrochloride (3.0 g.), $[\alpha]^{27}D$ + 9° (80% EtOH).

Anal. Calcd. for $C_{25}H_{46}N_2O \cdot 2HCl$: N, 6.04; Cl, 15.30. Found: N, 5.81; Cl, 14.90.

To a stirred solution of the dihydrochloride (1.0 g.) in methanol (1.5 ml.) and

(19) We are indebted to Messrs. W. M. Selby and M. G. Scaros for performing the catalytic hydrogenations.

water (10 ml.) was added a 10% aqueous solution of potassium carbonate (5 ml.). More water (15 ml.) was added and the product collected by filtration. This afforded a quantitative yield of VIa (0.85 g.), m.p. 132.5–133.5°. Recrystallization from acetone–methanol gave an analytical sample, m.p. 134.5–135.5°, $[\alpha]^{24}D$ +17°.

Anal. Calcd. for $C_{25}H_{46}N_2O$: C, 76.86; H, 11.87; N, 7.17. Found: C, 76.91; H, 11.92; N, 7.44.

B. From 3β-Hydroxy-5α-androstan-17-one.—Reductive amination of 3β-hydroxy-5α androstan-17-one with 3-dimethylaminopropylamine and formic acid as described above gave a 56% yield of N-(3-dimethylamino)propyl-17β-formamido-5α-andostan-3β-ol, m.p. 148–150°, $[\alpha]^{26}D$ − 5.5°.

Anal. Calcd. for $C_{26}H_{44}N_2O_2$: C, 74.21; H, 10.96; N, 6.92. Found: C, 73.69; H, 10.72; N, 6.84.

Lithium aluminum hydride reduction of this material in the usual manner gave a 73% yield of pure VIa identical in all respects with that described above.

3β-Acetoxy-17-(3-dimethylaminopropyl)iminoandrost-5-ene (VII).—A solution of 3β-acetoxyandrost-5-en-3-one (Ib, 33 g.), 3-dimethylaminopropylamine (20.4 g.) and *p*-toluenesulfonic acid monohydrate (3.6 g.) in benzene (400 ml.) was refluxed and the water removed with the aid of a Dean-Stark trap. When the reaction was complete (2 hr.), the reaction mixture was allowed to cool to room temperature. The solution was washed with water (3 × 100 ml.) and dried over anhydrous potassium carbonate. Removal of the solvent *in vacuo* and crystallization of the oily residue from pentane gave VII (37.5 g., 90.5%), m.p. 81–86°.[20] Recrystallization from hexane furnished an analytical sample, m.p. 86.5–88.5°, $[\alpha]^{26}D$ −37°, infrared $\nu_{max}^{CHCl_3}$ 3.39, 3.58, 5.78, 5.95, 7.94 and 9.70 μ.

Anal. Calcd. for $C_{26}H_{42}N_2O_2$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.64; H, 9.98; N, 6.68.

17-(3-Dimethylaminopropyl)aminoandrost-5-en-3β-ol (VIII).—A solution of VII (20.7 g.) in purified dioxane (140 ml.) was added dropwise with stirring to a refluxing mixture of lithium aluminum hydride (10 g.) in purified dioxane (160 ml.). The mixture was refluxed with stirring for 16 hr. whereupon the excess hydride was decomposed by the successive dropwise addition of aqueous dioxane (1:4, 50 ml.), 20% sodium hydroxide solution (7.5 ml.), and water (35 ml.). The inorganic salts were removed by filtration of the warm reaction mixture and washed with dioxane. Concentration of the filtrate to dryness *in vacuo* and crystallization of the residue from ethanol-water afforded VIII (14.8 g., 79%), m.p. 150–155°.[20] Recrystallization from methanol–acetone furnished an analytical sample, m.p. 159–161°, $[\alpha]^{26}D$ −39.5°.

Anal. Calcd. for $C_{24}H_{42}N_2O$: C, 76.95; H, 11.30; N, 7.48. Found: C, 76.77; H, 11.04; N, 7.48.

Methylation of VIII.—A solution of VIII (2.0 g.), formic acid (1.1 ml.), and formalin (1 ml.) was heated on a steam bath for 20 hr. The resulting semi-solid was dissolved in methanol (30 ml.) and the solution made basic with 25% aqueous sodium hydroxide solution (2 ml.). The solution was refluxed for 5 min. and poured into ice and water (150 ml.). The mixture was extracted with chloroform and the extract washed with water. The chloroform solution was dried over anhydrous potassium carbonate and the solvent removed *in vacuo*. The solid residue was recrystallized from methanol–acetone to give pure Vc (1.6 g.) identical in all respects with that described above.

(20) The yield reported here was that obtained by R. J. Dexheimer of our laboratories.