Hypocholesterolemic Agents. II.[1] 2β-Halo-5α-androstane Derivatives

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Received May 18, 1962

The synthesis of a number of 2β-halo-5α-androstan-3α-ol-17-ones and their derivatives is described. Physical data have been obtained to confirm the chemical evidence for the axial orientation of the fluorine in the 2β-fluoro-3-keto-5α-androstanes. Preliminary biological studies have shown some of these compounds to possess interesting physiological properties.

A recent report by Hellman and associates[2] describing the hypocholesterolemic effect produced by parenterally administered androsterone (5α-androstan-3α-ol-17-one) stimulated our interest in 2β-halo-5α-androstan-3α-ol-17-ones and their derivatives. It was hoped that the introduction of a 2β-halogen into the androsterone molecule would not only enhance the cholesterol-lowering effect, but also produce compounds possessing oral activity.

A search of the literature revealed that the synthesis of 2β-bromo-5α-androstan-3α-ol-17-one had been described by Fajkos, *et al.*[3] By using a slight modification of this procedure, the 2β-chloro, bromo, and iodo-5α-androstan-3α-ol-17-one analogs (IIb-d) were prepared by diaxial cleavage of 2α,3α-epoxy-5α-androstan-17-one (I). An attempt to prepare the corresponding 2β-fluoro-5α-androstan-3α-ol-17-one (IIa) from I with boron trifluoride etherate in a benzene-ether solution[4] led mainly to a high melting product with analysis for $C_{38}H_{57}FO_4$.[5] A fair yield of IIa was obtained, however, when a chloro-

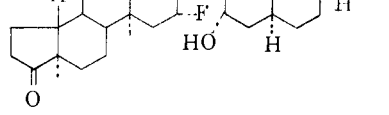
(1) Paper I, R. E. Counsell, P. D. Klimstra, R. E. Ranney and D. L. Cook, *J. Med. Pharm. Chem.*, **5**, 720 (1962).

(2) L. Hellman, H. L. Bradlow, B. Zumoff, D. K. Fukushima, and T. F. Gallagher, *J. Clin. Endocrinol. and Metab.*, **19**, 936 (1959).

(3) J. Fajkos and F. Sorm, *Coll. Czechoslov. Chem. Comm.*, **24**, 3115 (1959).

(4) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957).

(5) This product, m.p. 267–269°, $[\alpha]^{21}D$ + 91°, was tentatively assigned the structure:



form solution of I was added slowly to a large excess (20–30-fold) of anhydrous hydrogen fluoride in chloroform-tetrahydrofuran.

The 17-carbonyl group in the above halohydrins was reduced smoothly and in good yield with lithium-tri-*tert*-butoxyaluminohydride to give the corresponding 2β-halo-5α-androstane-3α,17β-diols (IIIa-d). The reduction of IIc with sodium borohydride, on the other hand, gave 2α,3α-epoxy-5α-androstan-17β-ol due to the basicity of the reducing media. Similar treatment of IIb, however, gave the desired 2β-chloro-3α,17β-diol (IIIb). The acetates (IIe-g) of the 2β-halohydrins were prepared by conventional methods.

The observation[6] that 2α-fluoro-5α-androstan-17β-ol-3-one acetate (X) caused marked inhibition of methylcholanthrene-induced rat mammary cancer as well as a strong anabolic response in the young female rat prompted us to prepare the corresponding 2β-fluoro epimer. Diaxial fission of 2α,3α-epoxy-5α-androstan-17β-ol acetate (VII) with anhydrous hydrogen fluoride as described above gave the desired fluorohydrin (VIII). Chromic acid oxidation of VIII furnished 2β-fluoro-5α-androstan-17β-ol-3-one acetate (IX). A similar oxidation of IIa gave 2β-fluoro-5α-androstane-3,17-dione (IV). Treatment of IV and IX with hydrobromic acid in acetic acid led to the previously described 2α-fluoro epimers, V[6] and X.[6,7]

An interest in the possible myotrophic activity of the 2-fluoro steroids prompted us to prepare some 2-fluoro-5α-androst-1-ene derivatives.[8] Bromination and dehydrohalogenation of V gave 2-fluoro-5α-androst-1-ene-3,17-dione (VI). The preparation of 2-fluoro-5α-androst-1-en-17β-ol-3-one acetate (XII) involved treating XI in glacial acetic acid with anhydrous hydrogen fluoride.

Except for a recently issued patent,[9] this is the first description of 2β-fluoro-3-ketosteroids. Consequently, spectroscopic and other physical data were obtained to confirm the chemical evidence for the axial orientation of the fluorine group in compounds IV and IX. In contrast with 2-bromo- and 2-chloro-3-ketosteroids,[10] the infrared spectrum was of no value for differentiating the equatorial and axial 2-fluoro-3-keto-5α-androstane epimers. For example, the C-3 carbonyl stretching region of both IV and IX was displaced by about 24 cm.$^{-1}$ to a higher frequency. In the ultraviolet, however, the presence of the axial fluorine in compound IX produced a bathochromic

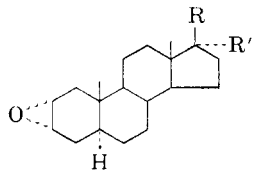
(6) S. Nakanishi, K. Morita, and E. V. Jensen, *J. Am. Chem. Soc.*, **81**, 5259 (1959).

(7) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5262 (1959).

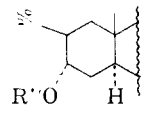
(8) The preparation and myotrophic activity of 2-bromo and 2-chloro-5α-androst-1-ene derivatives was included in a previous publication, R. E. Counsell and P. D. Klimstra, *J. Med. Pharm. Chem.*, **5**, 477 (1962).

(9) R. E. Counsell and P. D. Klimstra, U. S. Patent 2,980,710 (1961).

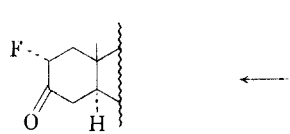
(10) E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).



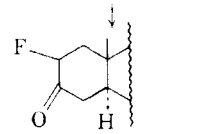
I, RR′ = O
VII, R = OAc, R′ = H



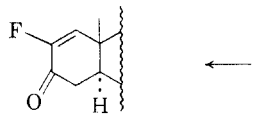
IIa, X = F, RR′ = O, R″ = H
b, X = Cl, RR′ = O, R″ = H
c, X = Br, RR′ = O, R″ = H
d, X = I, RR′ = O, R″ = H
e, X = F, RR′ = O, R″ = Ac
f, X = Cl, RR′ = O, R″ = Ac
g, X = I, RR′ = O, R″ = Ac
IIIa, X = F, R = OH, R′ = R″ = H
b, X = Cl, R = OH, R′ = R″ = H
c, X = Br, R = OH, R′ = R″ = H
d, X = I, R = OH, R′ = R″ = H
VIII X = F, R = OAc, R′ = R″ = H



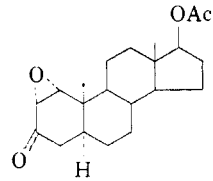
V, RR′=O
X, R=OAc, R′=H



IV, RR′=O
IX, R=OAc, R′=H



VI, RR′=O
XII, R=OAc, R′=H



XI

shift in the low intensity carbonyl absorption band of about +9 mμ. This shift is slightly less than that reported (*i.e.*, +15) for other axial α-fluoroketosteroids.[11] As expected, the introduction of the equatorial 2α-fluoro group left the ultraviolet absorption maximum unaffected.

Additional evidence for the axial configuration of the fluorine group in 2β-fluoro-5α-androstane-3,17-dione (IV) was obtained by nuclear magnetic resonance measurements.[12] The C-19 methyl protons of IV displayed a split peak (63 and 65 c.p.s.) possibly due to a 5 bond

(11) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Company, Inc., New York, N. Y., 1960, pp. 115–131; C. Djerassi and W. Klyne, *J. Am. Chem. Soc.*, **79**, 1506 (1957).

(12) The n.m.r. spectra were furnished by Dr. R. T. Dillon and Mr. J. Damascus of our Analytical Division. Measurements were obtained on the Varian model A-60 at 60 Mc. in deuteriochloroform using tetramethylsilane as an internal standard.

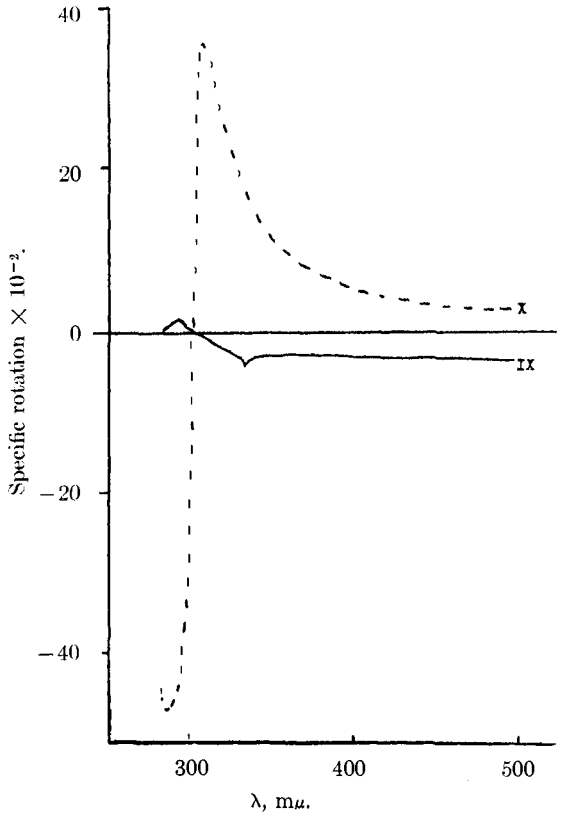


Fig. 1.—Rotatory dispersion curves (methanol) of 2β-fluoro-5α-androstan-17β-ol-3-one acetate (IX) and 2α-fluoro-5α-androstan-17β-ol-3-one acetate (X).

spin-spin coupling between the C-19 methyl protons and the C-2 axial fluorine.[13] In contrast, the 2α-fluoro isomer (V) gave the usual C-19 methyl group singlet (68 c.p.s.). The possibility that the split peak is due to a mixture of A-ring conformers, however, cannot be completely eliminated. The fact that the fluorohydrin (IIa) also gave a split peak (56 and 58 c.p.s.) for the C-19 methyl protons would tend to discount this latter possibility.[14]

Recently, optical rotatory dispersion measurements have been very useful in determining the configuration of α-haloketones.[11] As shown in Fig. 1, the ORD curve[15] of X is not sufficiently different from that of

(13) D. R. Davis, R. P. Lutz, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 246 (1961).

(14) We are indebted to Dr. R. H. Bible of our Chemical Research Division for his assistance in the interpretation of the n.m.r. data.

(15) We are greatly indebted to Prof. W. Klyne, Westfield College, London, England, for determining the ORD curves of these compounds for us.

5α-androstan-17β-ol-3-one acetate,[11] thus confirming the equatorial configuration of the fluorine atom. In contrast with axial α-bromo and α-chloroketones, however, IX gave a negative curve. This anomalous behavior of axial fluorines has been noted previously.[11]

A recent report by Allinger and associates[16] described the use of dipole moment data to prove the equatorial orientation of 2α-fluorocholestan-3-one by direct correlation with calculated values. Preliminary measurements gave dipole moment values which primarily prove the axial configuration of the fluorine in 2β-fluoro-5α-androstane-3,17-dione (IV) when compared with its calculated value.[17]

Biological Activity.[18]—The assay used to evaluate the hypocholesterolemic activity of the 2β-halo-5α-androstan-3α-ol-17-ones was an adaptation of that used by Garattini and coworkers.[19] The compounds were administered intraperitoneally to Triton-stimulated adult male rats. At a dose of 100 mg./kg., 2β-iodo-5α-androstan-3α-ol-17-one (IId) and 2β-chloro-5α-androstan-3α-ol-17-one (IIb) exhibited significant inhibition of the Triton-induced hypercholesterolemia. These compounds possessed 2 and 0.75 times the activity of the standard diphenylethylacetic acid (Liosol), respectively. By comparison, androsterone was inactive in this assay under similar conditions.

None of the 2β-halo-5α-androstane derivatives was effective in reducing the plasma cholesterol level when administered orally to rats made hypercholesterolemic with 0.2% propylthiouracil. Compounds IId and IIe, however, did show some activity in this assay when administered subcutaneously.

In comparing compounds IX and X, interesting biological results were noted. While 2α-fluoro-5α-androstan-17β-ol-3-one acetate (X) exhibited anabolic activity in the immature rat as measured by the increase in weight of the levator ani muscle, the 2β-fluoro isomer (IX) was inactive at the same dose level. Both compounds, however, exhibited antiestrogenic activity. Studies are now in progress to evaluate 2β-fluoro-5α-androstan-17β-ol-3-one acetate as an inhibitor of mammary fibroadenoma.

(16) N. L. Allinger, H. M. Blatter, M. A. DaRooge, and L. A. Freiberg, *J. Org. Chem.*, **26**, 2550 (1961).

(17) We are extremely grateful to Dr. Norman L. Allinger of Wayne State University for determining and interpreting the dipole moment data for this compound. These data will be reported by Dr. Allinger in *J. Org. Chem.*, in press.

(18) We are grateful to Drs. Francis J. Saunders, Robert E. Ranney, Donald L. Cook, and Mr. E. F. Nutting of our Biological Research Division for furnishing us with this information.

(19) S. Garattini, C. Morpurgo, B. Murelli, R. Paoletti, and N. Passerini, *Arch. Int. Pharmacodyn. Therap.*, **109**, 400 (1957).

Experimental[20]

2β-Fluoro-5α-androstan-3α-ol-17-one (IIa).—To a solution of anhydrous hydrogen fluoride (20.8 g.) in purified tetrahydrofuran (38 ml.) and chloroform (14 ml.) cooled in a Dry Ice–isopropyl alcohol bath was added dropwise and with rapid stirring 2α,3α-epoxy-5α-androstan-17-one[4] (I, 12.0 g.) in chloroform (64 ml.). The addition required 2.5 hr. The reaction mixture remained 1.5 hr. in the cold and was then allowed to come to room temperature. The contents were poured slowly into 15% aqueous potassium carbonate solution (800 ml.). Chloroform (100 ml.) was added and the solution stirred rapidly. Additional 15% aqueous potassium carbonate solution (250 ml.) was added and the organic layer separated. The aqueous layer was extracted with chloroform and the combined organic layers were washed successively with water, 5% sodium bicarbonate solution and water. The extract was dried over anhydrous potassium carbonate containing Darco and the solvent removed *in vacuo*. The resulting glass was taken up in benzene and adsorbed onto silica gel (1 kg.). Elution with benzene–ethyl acetate (7:1) gave IIa (6.6 g.), m.p. 184–185°, $[\alpha]^{26}D$ +97°.

Anal. Calcd. for $C_{19}H_{29}FO_2$: C, 73.99; H, 9.48; F, 6.16. Found: C, 74.10; H, 9.53; F, 5.90.

2β-Chloro-5α-androstan-3α-ol-17-one (IIb). General Method.—A heterogeneous mixture of 2α,3α-epoxy-5α-androstan-17-one[4] (I, 4.0 g.), concd. hydrochloric acid[21] (110 ml.), and chloroform (250 ml.) was placed on a mechanical shaker for 20 min. The chloroform layer was separated and washed successively with 5% sodium bicarbonate solution and water. The extract was dried over anhydrous sodium sulfate containing Darco. Removal of the solvent *in vacuo* left a white solid which was recrystallized from ethanol-water to give IIb (2.7 g.), m.p. 197–199° dec., $[\alpha]^{26}D$ +92°.

Anal. Calcd. for $C_{19}H_{29}ClO_2$: C, 70.24; H, 9.00; Cl, 10.92. Found: C, 70.13; H, 8.89; Cl, 10.81.

2β-Fluoro-5α-androstan-3α-ol-17-one Acetate (IIe). General Method.—A solution of 2β-fluoro-5α-androstan-3α-ol-17-one (IIa, 0.4 g.) in acetic anhydride (2.0 ml.) and dry pyridine (4.0 ml.) was stirred at room temperature for 3.5 hr. The solution was poured into ice and water (30 ml.). An oil separated which was extracted with ether. The extract was washed successively with 5% hydrochloric acid, 5% sodium bicarbonate solution, and water. The organic phase was dried over anhydrous potassium carbonate containing Darco. Removal of the solvent *in vacuo* left an oil which crystallized from ethanol–water to give IIe (0.32 g.), m.p. 123–125°, $[\alpha]^{26}D$ + 113.5°.

Anal. Calcd. for $C_{21}H_{31}FO_3$: C, 71.97; H, 8.92. Found: C, 72.18; H, 8.65.

2β-Fluoro-5α-androstane-3α,17β-diol (IIIa). General Method.—A solution of lithium-tri-*tert*-butoxyaluminohydride[22] (2.5 g.) in tetrahydrofuran (15 ml.) was added to 2β-fluoro-5α-androstan-3α-ol-17-one (IIa, 1.0 g.) in tetrahydrofuran (15 ml.) cooled in an ice bath. After stirring for 3 hr. the colution was poured into a mixture of ice and water (150 ml.) containing acetic acid (15 ml.). The

(20) Optical rotations, spectra, and analytical data were furnished by our Analytical Department under the supervision of Dr. R. T. Dillon. Optical rotations and infrared spectra were obtained in chloroform and ultraviolet spectra in methanol unless otherwise indicated. Melting points are uncorrected.

(21) Substitution of 48% aqueous hydrobromic acid (80 ml.) and 47% aqueous hydriodic acid (50 ml.) in this procedure afforded compounds IIc and IId, respectively.

(22) Obtained commercially from Metal Hydrides, Inc.

TABLE I
2β-HALO-5α-ANDROSTANE DERIVATIVES

	Recrystallization media	Yield, %	M.p., °C.	$[\alpha]^{25}D$	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
IIa	Me_2CO–hexane	51.5	184–185	+97°	$C_{19}H_{29}FO_2$	73.99	9.48	74.10	9.53
IIb	EtOH	60	204–205 dec.	+92°	$C_{19}H_{29}ClO_2$	70.24	9.00	70.13	8.89
IIc	MeOH	62.6	186–186.5[a] dec.	+93°	$C_{19}H_{29}BrO_2$	61.78	7.91	61.97	8.06
IId	MeOH–H_2O	55.5	139.5 dec.	+102°	$C_{19}H_{29}IO_2$	54.81	7.02	54.89	7.17
IIe	MeOH–H_2O	70.5	123–125	+113.5[c]	$C_{21}H_{31}FO_3$	71.97	8.92	72.18	8.65
IIf	MeOH	73.4	161–164	+96.5°	$C_{21}H_{31}ClO_3$	68.74	8.52	68.79	8.60
IIg	MeOH	77	135–136	+144°	$C_{21}H_{31}IO_3$	55.02	6.82	54.83	6.73
IIIa	EtOH–H_2O	79.4	242–244	[b]	$C_{19}H_{31}FO_2$	73.51	10.07	73.68	10.07
IIIb	Me_2CO	80.7	249.5 dec.	+34°[c]	$C_{19}H_{31}ClO_2$	69.80	9.56	69.56	9.67
IIIc	Me_2CO–MeOH	83.5	220–221[d] dec.	+44°[c]	$C_{19}H_{31}BrO_2$	61.45	8.42	61.40	8.33
IIId	Me_2CO	59.6	141–142	+54°	$C_{19}H_{31}IO_2$	54.54	7.47	54.63	7.54

[a] Fajkos[3] reports m.p. 196–197°. [b] Too insoluble to determine optical rotation. [c] Dioxane was used as the solvent. [d] Fajkos[3] reports m.p. 250–251°.

precipitate was collected, washed with water, and air dried. Recrystallization from ethanol–water gave IIIa (0.8 g.), m.p. 242–244°.

Anal. Calcd. for $C_{19}H_{31}FO_2$: C, 73.51; H, 10.07. Found: C, 73.68; H, 10.07.

2β-Iodo-5α-androstane-3α,17β-diol (IIId).—A heterogeneous mixture of 2α,3α-epoxy-5α-androstan-17β-ol[4] (2.0 g.) and 47% aqueous hydriodic acid (23 ml.) in chloroform (75 ml.) was agitated mechanically for 20 min. at room temperature. A small amount of dark brown precipitate which formed was collected and discarded. The tan-colored chloroform layer was separated and washed successively with dil. sodium thiosulfate solution (20 ml., 0.004 *N*), 5% aqueous sodium bicarbonate solution and water. The extract was dried over anhydrous sodium sulfate containing Darco. Removal of the solvent *in vacuo* left a solid which was recrystallized from acetone to give IIId (1.2 g.), m.p. 141–142°, dec., $[\alpha]^{26}D$ +54° (dioxane).

Anal. Calcd. for $C_{19}H_{31}IO_2$: C, 54.54; H, 7.47. Found: C, 54.63; H, 7.54.

2β-Fluoro-5α-androstane-3,17-dione (IV).—To a solution of 2β-fluoro-5α-androstan-3α-ol-17-one (IIa, 0.5 g.) in acetone (20 ml.) was added dropwise and with stirring a standard chromic acid solution[23] until the color of the reagent persisted. The excess of chromic acid was decomposed by adding a drop of isopropyl alcohol. The organic layer was decanted from its inorganic salts and poured into ice and water. The precipitate was collected, washed with water, and air dried. Recrystallization from methanol-water gave IV (320 mg.), m.p. 142–143°, ϵ_{max}^{292} 42, λ_{max} 3.4, 5.75 μ, $[\alpha]^{27}D$ +123°.

Anal. Calcd. for $C_{19}H_{27}FO_2$: C, 74.47; H, 8.88. Found: C, 74.16; H, 8.93.

2α-Fluoro-5α-androstane-3,17-dione (V).—A solution of 2β-fluoro-5α-androstane-3,17-dione (IV, 100 mg.) in glacial acetic acid (3.5 ml.) and 48% aqueous hydrobromic acid (0.5 ml.) was allowed to stand for 20 hr. at room temperature. The reaction mixture was poured into ice and water and the precipitate collected, washed with water, and air dried to give V, m.p. 203–205° dec. (reported[6] m.p. 204–205°), ϵ_{max}^{291} 60, λ_{max} 3.4, 5.75 μ, $[\alpha]^{27}D$ +138°.

2-Fluoro-5α-androst-1-en-3,17-dione (VI).—To 2α-fluoro-5α-androstane-3,17-dione (V, 3.0 g.) in glacial acetic acid (25 ml.) and 48% aqueous hydrobromic acid (0.1 ml.) cooled to 10–15° was added dropwise with stirring over 0.5 hr. a solution of bromine (1.6 g.) and sodium acetate (0.82 g.) in glacial acetic acid (15 ml.). The reaction was stirred for 2 hr. and poured into ice and water (250 ml.) containing sodium acetate (0.8 g.). The precipitate was collected and washed successively with water and 5% sodium bicarbonate solution. The crude 2-bromo derivative (1.3 g.) in dimethylformamide (10 ml.) containing lithium chloride (0.45 g.) and lithium carbonate (0.27 g.) was refluxed for 2.5 hr. in a nitrogen atmosphere. Ether (20 ml.) was added and the total solution poured into cold water. The aqueous layer was extracted with ether and the combined extract washed successively with 5% hydrochloric acid, 5% sodium bicarbonate solution, and water. The extract was dried over anhydrous potassium carbonate containing Darco and the solvent removed *in vacuo*. The oily residue was dissolved in benzene and adsorbed onto silica gel (50 g.). Crystallization of the benzene-ethyl acetate (19:1) eluate from acetone–hexane gave VI (0.3 g.), m.p. 188–190°, $\epsilon_{max}^{236\text{-}237.5}$ 8600, $[\alpha]^{27}D$ +122°.

Anal. Calcd. for $C_{19}H_{25}FO_5$: C, 74.97; H, 8.23. Found: C, 74.74; H, 8.55.

(23) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

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°, $[\alpha]^{26}D$ +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

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Received June 15, 1962

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