Steroids. CCVI.[1] Ring A Modified Hormone Analogs. Part II. 2-Methylene Androstanes and 2-Methyl-Δ^1, Δ^2 and Δ^3-Androstenes[2]

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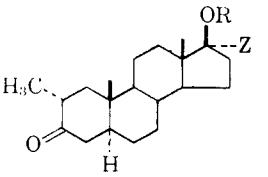
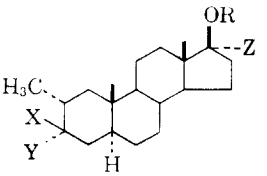
Syntheses are described of some 2-methyl-Δ^1, Δ^2 and Δ^3-androstenes as well as the isomeric 2-methylene androstanes. Several of these compounds display high myotrophic (anabolic) activities with favorable anabolic–androgenic ratios.

The discovery in the androstane series that a C-3 oxygen substituent was not an essential prerequisite of biological activity[3-7] led us to investigate "non-classical" androstane structures in which the broader requirement of an electron rich ring A was met by the presence of carbon–carbon double bonds.[1] In particular it was noted that unsaturation at C-2 and C-3 (Δ^1, Δ^2 or Δ^3 olefins) was compatible with a reasonable level of biological activity.[1]

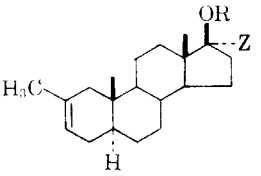
In view of the beneficial effect on biological activity of methyl substitution at C-2 in other androstanes, the effect of introducing a C-2 methyl group into a series of ring A olefins was investigated. Reduction of 2α-methylandrostane-17β-ol-3-one propionate[8] (Ia) with sodium borohydride afforded the corresponding 3β-alcohol (IIa), the tosylate IIb of which underwent elimination in boiling collidine to provide 2-methyl-Δ^2-androstene-17β-ol propionate (IIIa). Concomitant solvolysis of the tosylate by traces of moisture in the reaction mixture led to the isolation of 2α-methylandrostane-3α,17β-diol 17-propionate (IIc), different from the 3β-isomer IIa, oxidized by 8 *N* chromic acid[9] to the starting ketone Ia, and saponified to the known 2α-methylandrostane-3α,17β-diol (IId).[10] This diol IId with chromic acid[9] gave 2α-methylandrostane-3,17-dione.[11] Alkaline hydrolysis or lithium aluminum hydride reduction of 2-methyl-Δ^2-androstene-17β-ol propionate (IIIa) yielded the alcohol (IIIb), which was oxidized[9] readily to the derived ketone IV. Treatment of the latter with methylmagnesium bromide made available the 2,17α-dimethyl-Δ^2-androstene-17β-ol (IIIc). With ethynylmagnesium bromide only a small quantity of the pure 17α-ethynyl analog IIId was obtained, showing the expected infrared absorption band at 3310 cm.$^{-1}$ for acetylenic C–H. The Grignard adduct from two molecules of steroid ketone with one molecule of acetylene[12] also proved isolable, but in only trace amount. During chromic acid oxidation of the alcohol IIIb, failure to enforce strict temperature con-



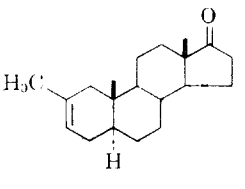
Ia, R = COC_2H_5, Z = H
b, R = $COCH_3$, Z = H
c, R = H, Z = C≡CH
d, R = H, Z = CH_3



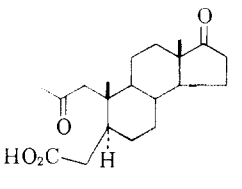
IIa, X = OH, Y = Z = H, R = COC_2H_5
b, X = $OSO_2C_6H_4CH_3$, R = COC_2H_5
c, X = Z = H, Y = OH, R = COC_2H_5
d, X = Z = R = H, Y = OH
e, X = OH, Y = Z = H, R = $COCH_3$
f, X = $OSO_2C_6H_4CH_3$, Y = Z = H, R = $COCH_3$
g, X = Z = H, Y = OH, R = $COCH_3$
h, X = OH, Y = R = H, Z = C≡CH
i, X = $OSO_2C_6H_4CH_3$, Z = C≡C—H
j, X = R = H, Y = OH, Z = C≡CH
k, X = Y = R = H, Z = CH_3



IIIa, R = COC_2H_5, Z = H
b, R = Z = H
c, R = H, Z = CH_3
d, R = H, Z = C≡CH
e, R = $COCH_3$, Z = H



IV



V

(1) Steroids CCV and Part I, A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada and E. Denot, *J. Med. Chem.*, **6**, 156 (1963).

(2) A preliminary account of part of this work has been reported, A. D. Cross, J. A. Edwards and A. Bowers, *ibid.*, **5**, 406 (1962).

(3) M. S. De Winter, C. M. Siegmann and S. A. Szpilfogel, *Chem. Ind.* (London), 905 (1959).

(4) N. E. Borglin, *Acta Endocrinologica*, Supplementum LVIII (1960).

(5) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts and A. J. Arnold, *J. Am. Chem. Soc.*, **81**, 1513 (1959); R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and D. C. Carabateas, *ibid.*, **83**, 1478 (1961); R. O. Clinton, A. J. Manson, F. W. Stonner, R. G. Christiansen, A. L. Beyler, G. O. Potts and A. J. Arnold, *J. Org. Chem.*, **26**, 279 (1961).

(6) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, H. C. Limon, L. Magaña, H. Jimenez, A. Bowers and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960).

(7) J. A. Edwards and A. Bowers, *ibid.*, 1962 (1961).

(8) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

(9) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(10) R. Mauli, H. J. Ringold and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5394 (1960).

(11) J. Iriarte and H. J. Ringold, *Tetrahedron*, **3**, 28 (1958).

(12) For similar examples see F. Sondheimer, O. Mancera, H. Flores and G. Rosenkranz, *J. Am. Chem. Soc.*, **78**, 1712 (1956).

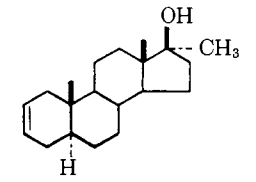
trol (<10°) leads to formation of appreciable quantities of the ring A oxidative cleavage product, 2-methyl-2,3-secoandrostane-2,17-dione-3-carboxylic acid (V). Throughout the series, the 2-methyl-Δ^2 compounds were identified easily by a characteristic =C—H deformation absorption band in the infrared spectrum at *ca.* 795 cm.$^{-1}$. Subsequently, during the preparation of the 2-methyl-Δ^2-androstenes in sufficient quantity for extended biological evaluation, it became necessary to utilize 2α-methylandrostane-17β-ol-3-one acetate (Ib) as a starting material. Its transformation to the 17β-alcohol IIIb, *via* the 3β-alcohol IIe, the derived tosylate IIf, and the elimination product IIIe followed the sequence outlined above. Again, 3α-alcohol IIg was a by-product from solvolysis of the crude tosylate IIf.

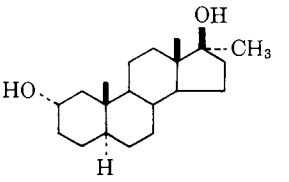
To circumvent the low-yield Grignard ethynylation of the ketone IV to the 17α-ethynyl analog IIId a second route was investigated. 2α-Methyl-17α-ethynylandrostane-17β-ol-3-one (Ic)[13] was reduced by sodium borohydride to the 3β-alcohol IIh and the latter converted to the 3β-tosylate IIi. Collidine elimination then afforded 2-methyl-17α-ethynyl-Δ^2-androstene-17β-ol (IIId). Again a 3α-alcohol IIj appeared by tosylate solvolysis during the elimination reaction.

A Wittig reaction upon 2-ketones appeared an attractive route to the isomeric 2-methylene androstanes. Hydroboration[14] of 17α-methyl-Δ^2-androstene-17β-ol (VI)[7] then alkaline hydrogen peroxide oxidation of the derived organoboron compound led to a mixture of the 2α-alcohol VII and the 3α-alcohol VIII.[15] Chromic acid oxidation[9] of these isomeric alcohols then gave, respectively, 17α-methylandrostane-17β-ol-2-one (IXa) and 17α-methylandrostane-17β-ol-3-one,[16] identical with an authentic sample. In the 17-desmethyl series the 2-ketone IXb was prepared by an alternative route[17] and then converted to the acetate IXc. Treatment of each of the 2-ketones IXa and IXc with the ylid prepared from triphenylmethylphosphonium bromide[18] afforded, respectively, 2-methylene-17α-methylandrostane 17β-ol (Xa) and 2-methyleneandrostane-17β-ol (Xb). The latter was acetylated immediately to the corresponding acetate Xc.

2-Methyl-Δ^1-androstene-3-one-17β-ol acetate[10] (XIa) was converted into the dithio-ketal XIb by reaction with ethane dithiol in the presence of boron trifluoride etherate. Desulfurization by means of deactivated Raney nickel[19] led to 2-methyl-Δ^1-androstene-17β-ol acetate (XIc), while desulfurization through the agency of sodium in liquid ammonia provided 2-methyl-Δ^2-androstene-17β-ol acetate (IIIe) identical with a sample prepared by the tosylate elimination procedure described above.

Sodium borohydride reduction of 4α-bromo-2α-methyl-androstane-3-one-17β-ol acetate (XIIa)[10] furnished


VI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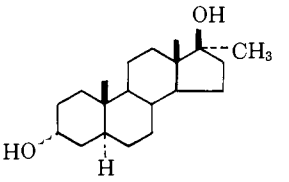
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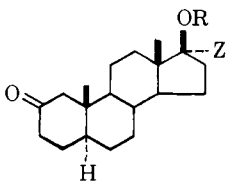
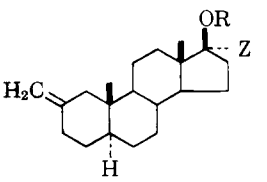
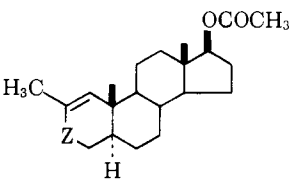
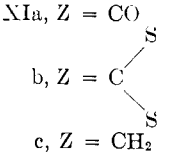
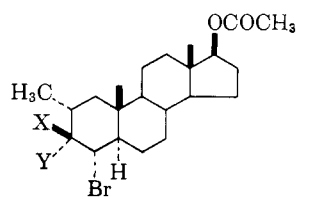

IXa, Z = CH_3, R = H
b, Z = R = H
c, Z = H, R = $COCH_3$

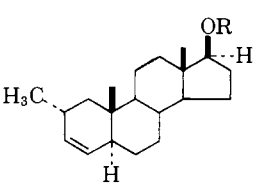

Xa, R = H, Z = CH_3
b, R = Z = H
c, R = $COCH_3$, Z = H

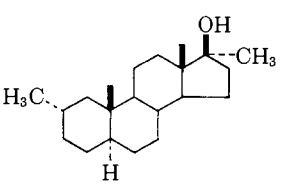

XIa, Z = CO


b, Z = C(S)(S)

c, Z = CH_2


IIIa, X and Y = O
b, X = OH, Y = H


XIIIa, R = H
b, R = $COCH_3$


XIV

(13) J. A. Zderic and H. Carpio of these laboratories (manuscript in preparation) prepared this compound from 2α-methyldihydrotestosterone by successively protecting the 3-ketone as a cycloethylene ketal, oxidation to the 17-ketone, 17α-ethynylation by *t*-butoxide–acetylene treatment, and, finally, hydrolytic cleavage of the ketal. We thank them for the details of this work in advance of publication.

(14) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6428 (1959).

(15) *Cf.* F. Sondheimer and M. Nussim, *J. Org. Chem.*, **26**, 630 (1961).

(16) C. Ruzicka, P. Meister and V. Prelog, *Helv. Chim. Acta*, **30**, 867 (1947).

(17) P. G. Holton and A. Bowers, unpublished results; ref. 2, footnote 9.

(18) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954).

(19) G. B. Spero, A. V. McIntosh and R. H. Levin, *J. Am. Chem. Soc.*, **70**, 1907 (1948).

the corresponding 3β-alcohol XIIb from which was obtained by a zinc–acetic acid elimination 2α-methyl-Δ^3-androstene-17β-ol (XIIIa). Acetylation of the latter led to the derived 17β-acetate XIIIb.

For purposes of comparative biological assay we also required a 2α-methylandrostane bearing neither an oxygen substituent nor unsaturation in ring A. In consequence a Wolff–Kishner reduction of 2α,17α-dimethylandrostane-3-one-17β-ol[20] (Id) was carried out to afford 2α,17α-dimethylandrostane-17β-ol (XIV).

Biological Activities.—The compounds were assayed as outlined in the previous paper,[1] and again the preliminary nature of the results (Table I) is emphasized. It can be seen that introduction of a methyl substituent at C-2 into Δ^2-androstenes affords compounds of good

(20) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956); H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959).

anabolic activity with a favorable androgenic–anabolic ratio.

TABLE I

ANDROGENIC AND ANABOLIC ACTIVITIES OF 2-METHYLANDROSTENES

(ACTIVITY OF TESTOSTERONE = 1.0)

Compound	Substitution in Ring A	Assay	Androgenic	Anabolic
IIIb	2-Me-Δ^2	Injection	0.5	1.5
Xb	2-CH_2=	Injection	0.1	0.2
Xa	2-CH_2=	Oral	1.0	4.0
XIc	2-Me-Δ^1	Injection	0.2	0.5
XIIIb	2-Me-Δ^3	Injection	<0.1	<0.1
IIIc	2-Me-Δ^2	Oral	2.0	10.0

Experimental[21]

Reductions of 3-Ketones

(i) **2α-Methylandrostane-3β,17β-diol 17β-propionate (IIa).**—To a solution of 80 g. of 2α-methyl dihydrotestosterone propionate[8] (Ia) in 500 ml. of dioxan was added slowly, with stirring, 40 g. of sodium borohydride in 80 ml. of water and 500 ml. of dioxan. After a further 3 hr. at room temperature 5 l. of water was added, and dilute hydrochloric acid to neutrality. The product was collected by filtration and crystallized from acetone and from hexane alternately to furnish 66 g. of pure IIa, m.p. 162–163°; $[\alpha]_D$ −12°; ν_{max} 3450 (m), 1747 (s), 1725 (s)[22] and 1195 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found C, 76.02; H, 10.60.

(ii) **2α-Methylandrostane-3β,17β-diol 17β-acetate (IIe).**—2α-Methyldihydrotestosterone (100 g.) was acetylated in the normal manner and the resultant 17-acetate Ib, m.p. 152–153°, was reduced immediately in 500 ml. of dioxan solution as described above for the propionate homolog. Thereby was obtained 110 g. of IIe, crystallized from hexane–methylene dichloride as prisms, m.p. 185–187°; $[\alpha]_D$ −10°; ν_{max} 3470 (m), 1730(s) and 1265 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41; O, 13.77. Found: C, 75.79; H, 10.14; O, 13.90.

(iii) **17α-Ethynyl-2α-methylandrostane-3β,17β-diol (IIh).**—A solution of 2.95 g. of 17α-ethynyl-2α-methyldihydrotestosterone[13] in 150 ml. of dioxan was treated dropwise with a solution of 2.5 g. of sodium borohydride in 20 ml. of water and 50 ml. of dioxan, and the whole was kept 4 hr. at room temperature. Successive addition of 2 l. of water and concd. hydrochloric acid, and filtration, afforded IIh (2.8 g.) which crystallized as prisms from acetone–hexane, m.p. 208–209°; $[\alpha]_D$ −52°; ν_{max} 3480 (m), and 3310 cm.$^{-1}$ (m).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; O, 9.68. Found: C, 80.01; H, 10.53; O, 9.77.

Tosylations

(i) **2α-Methylandrostane-3β,17β-diol 3β-Tosylate-17β-propionate (IIb).**—IIa (1.1 g.) and 1.1 g. of *p*-toluenesulfonyl chloride were added to 15 ml. of pyridine at room temperature and after 24 hr. the whole was poured into ice-water. The 3β-tosylate-17β-propionate IIb was isolated in the usual way and crystallized from hexane–ethanol as prisms (1.25 g.), m.p. 148–149°; $[\alpha]_D$ −33°; ν_{max} 1745 (s), 1605 (m), 1193 and 1180 cm.$^{-1}$ (broad and complex) propionate and tosylate.

Anal. Calcd. for $C_{30}H_{44}O_5S$: C, 69.74; H, 8.58; S, 6.20. Found: C, 69.93; H, 8.57; S, 6.27.

(ii) **2α-Methylandrostane-3β,17β-diol 3β-Tosylate-17β-acetate (IIf).**—Similarly, 110 g. of 2α-methylandrostane-3β,17β-diol 17β-acetate was tosylated to afford 95 g. of IIf, which separated from hexane–methylene dichloride as prisms, m.p. 135–136°; $[\alpha]_D$ −32°; ultraviolet, λ_{max} 226 mμ, log ε 4.09: ν_{max} 1732(s) and 1242 cm.$^{-1}$ (s) (acetate), and 1600, 1505, 1185, 1174 (s) and 668 cm.$^{-1}$ (s) (tosylate).

Anal. Calcd. for $C_{28}H_{40}O_5S$: C, 68.83; H, 8.25; O, 16.37. Found: C, 69.26; H, 8.19; O, 16.53.

(iii) **17α-Ethynyl-2α-methylandrostane-3β-17β-diol 3β-Tosylate (IIi).**—By the same experimental procedure there was prepared amorphous IIi, ultraviolet λ_{max} 225 mμ; ν_{max} 3460 (m), 3310 (m), 1600 (s), 1502 (m), 1185 (s) and 1175 cm.$^{-1}$ (s). The product was used immediately for an elimination reaction.

Elimination Reactions

(i) **2-Methyl-Δ²-androstene-17β-ol Propionate (IIIa).**—A solution of 2α-methylandrostane-3β,17β-diol 3β-tosylate-17β-propionate (8.0 g.) in 70 ml. of collidine was heated under reflux during 3 hr., cooled, and poured into ice-aqueous hydrochloric acid. Extraction with ether and washes of the extracts with dilute hydrochloric acid, bicarbonate solution and water afforded 5.9 g. of 2-methyl-Δ²-androstene-17β-ol propionate (IIIa) as leaflets from ethanol, m.p. 116.5–118°; $[\alpha]_D$ +46°; ν_{max} 1737 (s), 1183 (s), 3030 (w) and 798 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.18; H, 10.53. Found: C, 80.10; H, 10.41.

2α-Methylandrostane-3α,17β-diol 17β-Propionate (IIc).—In a separate experiment in which crude tosylate was subjected to the same elimination conditions, chromatography of the reaction product over alumina (Grade III) and elution with benzene–hexane (1:3) afforded the 2-methyl-Δ²-androstene-17β-ol propionate. With benzene–methylene chloride (5:1) there was eluted IIc, m.p. 168–170°; $[\alpha]_D$ +12°; ν_{max} 3550 (m), 1735 (s) and 1205 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57; O, 13.24. Found: C, 76.08; H, 10.63; O, 13.50.

Oxidation of this 3α-hydroxy compound (500 mg.) in acetone (10 ml.) with Jones reagent[9] at 0° gave, after the usual work up, 2α-methyldihydrotestosterone propionate (310 mg.), identical (infrared, m.p. and mixture m.p.) with authentic material.

(ii) **2-Methyl-Δ²-androstan-17β-ol Acetate (IIIe).**—From 95 g. of the 3β-tosylate-17β-acetate IIf there was obtained similarly IIIe, recovered from a solution in hexane as rods (68 g.), m.p. 130–131°; $[\alpha]_D$ +62°; ν_{max} 1732 (s), 1242 (s) and 794 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; O, 9.68. Found: C, 79.82; H, 10.35; O, 9.46.

The expected by-product also was isolated by chromatography over alumina (Grade III) and elution with benzene–methylene chloride (5:1 and 3:1), and crystallized from hexane–methylene chloride as 8.5 g. of prisms of 2α-methylandrostane-3α,17β-diol 17β-acetate (IIg), m.p. 204–205°; $[\alpha]_D$ ±0°; ν_{max} 3460 (s), 1735 (s) and 1250 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41; O, 13.77. Found: C, 75.72; H, 10.25; O, 13.79.

(iii) **17α-Ethynyl-2-methyl-Δ²-androsten-17β-ol (IIId).**—Employing the same experimental method, 2.5 g. of crude 17α-ethynyl-2α-methylandrostane-3β,17β-diol 3β-tosylate when kept 4 hr. in hot collidine afforded 0.7 g. of IIId, which after crystallization from methanol–water or hexane, had m.p. 100–101°; $[\alpha]_D$ ±0°; ν_{max} 3520 (m), 3310 (w) (≡C—H), and 793 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{22}H_{32}O$: C, 84.56; H, 10.32; O, 5.12. Found: C, 84.27; H, 10.44; O, 5.04.

From chromatography of the reaction products over alumina (Grade III) and elution with benzene–methylene chloride (3:1) there was also obtained 0.27 g. of 17α-ethynyl-2α-methylandrostane-3α,17β-diol which separated from hexane as prisms, m.p. 171–172°; $[\alpha]_D$ −41°; ν_{max} 3580 (m) and 3300 cm.$^{-1}$ (w).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; O, 9.68. Found: C, 79.76; H, 10.40; O, 10.05.

2-Methyl-Δ²-androsten-17β-ol (IIIb).—(i) To 5 g. of 2-methyl-Δ²-androsten-17β-ol propionate in 200 ml. of ethanol was added 3 g. of potassium hydroxide and after 24 hr. at room temperature the mixture was poured into water. By filtration there was collected 4.1 g. of IIIb which crystallized from hexane as prisms, m.p. 108–109° and 119–120°; $[\alpha]_D$ +78°; ν_{max} 3350 (m), 1690 (w) and 795 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 83.24; H, 11.18; O, 5.55. Found: C, 83.28; H, 11.16; O, 5.49.

(ii) Reduction of 2 g. of the propionate (IIIa) in 20 ml. of anhydrous ether was effected by 1 g. of lithium aluminum hydride during 3 hr. at reflux temperature. Work up in the normal

(21) Rotations are for solutions in chloroform, ultraviolet spectra for ethanol solutions and infrared spectra for KBr disks, except where otherwise stated. Microanalyses are by either Mid-West Micro Laboratories, Indianapolis 20, Indiana, or by Dr. A. Bernhardt, Mülheim (Ruhr), Germany. See also footnote 42 of preceding paper.

(22) The two peaks in the carbonyl region become one for a spectrum in chloroform solution. Duality of peaks in alkali halide disk spectra is well known.[23]

(23) *Cf.* A. D. Cross, "An Introduction to Practical Infrared Spectroscopy," Butterworths, London, 1960, p. 21.

manner, and ethyl acetate extraction yielded 1.7 g. of IIIb identical with a sample prepared from the propionate ester by alkaline hydrolysis.

The 17-acetate ester (68 g.) when reduced under the same conditions furnished 60 g. of the 17β-alcohol IIIb.

2α-Methylandrostane-3α,17β-diol (IId).—Alkaline hydrolysis of 500 mg. of 2α-methylandrostane-3α,17β-diol 17-propionate, under the same conditions as described above for saponification of the 17β-propionate IIIa, led to 410 mg. of IId, m.p. 248–250°; $[\alpha]_D$ +21° (lit.[10] m.p. 246–248°; $[\alpha]_D$ +22.2°).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.54; H, 11.28.

Oxidation of this diol (200 mg.) in 10 ml. of acetone solution by Jones reagent[9] at 0° furnished 2α-methylandrostane-3,17-dione, 160 mg. of prisms after crystallization from hexane–acetone, m.p. 151–152°; $[\alpha]_D$ +111°; ν_{max} 1710 (s) and 1745 cm.$^{-1}$ (s). (lit.[11] m.p. 152–153°; $[\alpha]_D$ +110°).

2-Methyl-Δ^2-androsten-17-one (IV).—A solution of 2-methyl-Δ^2-androsten-17β-ol (2 g.) in 100 ml. of acetone was treated dropwise at 0° with Jones reagent[9] until an excess was present. Chromatography of the oily product over alumina (Grade III) and elution with hexane and hexane–benzene (1:5) gave 1.4 g. of the ketone IV, prisms from hexane, m.p. 83–85°; $[\alpha]_D$ +148°; ν_{max} 1740 (s) and 795 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.49; H, 10.43.

In a separate experiment, in which a faster rate of addition of Jones reagent probably caused the solution temperature to rise several degrees, chromatography of the products over alumina (Grade III) afforded, besides the ketone IV, 2-methyl-2,3-seco-androstane-1,17-dione 3-carboxylic acid (V) from benzene–methylene dichloride (2:1) eluates, crystallizing from hexane–acetone as prisms, m.p. 173–175°; $[\alpha]_D$ +97°, ν_{max} 3500–3000 (broad absorption of CO_2H hydroxyl), 1735 (s), 1714 (s) and 1706 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; O, 19.14. Found: C, 72.11; H, 8.96; O, 19.02.

2,17α-Dimethyl-Δ^2-androsten-17β-ol (IIIc).—The 17-ketone IV (770 mg.) in 15 ml. of dry ether was kept under reflux during 3 hr. with 25 ml. of 4 *N* ethereal methylmagnesium bromide. Work up in the normal way gave, after chromatography over alumina (Grade III) an elution with benzene, 580 mg. of IIIc as prisms from hexane–ether, m.p. 112–114°; $[\alpha]_D$ +36°; ν_{max} 3480 (m) and 795 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.19; H, 11.22.

17α-Ethynyl-2-methyl-Δ^2-androsten-17β-ol (IIId).—Ethynylmagnesium bromide was prepared *in situ* from a stream of dry purified acetylene passed into 30 ml. of 4 *N* methylmagnesium bromide in tetrahydrofuran and 2-methyl-Δ^2-androsten-17-one (1.1 g.) in 100 ml. of tetrahydrofuran was added. The whole was kept at reflux temperature (6 hr.) prior to decomposition of the excess of reagent with ice-water. Ethyl acetate extraction, and chromatography over alumina (Grade III) afforded in the benzene eluates 100 mg. of IIId, crystallized from hexane, m.p. 98–101°, undepressed on admixture with a sample prepared by the alternate route (*vide supra*). A second component (80 mg.) eluted from the column with ethyl acetate crystallized from hexane in prisms, m.p. 258–261°; ν_{max} 3590 (m) and 794 cm^{-1} (s), but with no absorption for acetylenic hydrogen.

2-Methyleneandrostan-17β-ol Acetate (Xc).—A stirred suspension of 4.1 g. of methyltriphenylphosphonium bromide[18] in 150 ml. of dry ether was treated in a nitrogen atmosphere with 25.4 ml. of 0.48 *N* ethereal *n*-butyllithium. After stirring for 15 min. a solution of 1 g. of the acetate of androstan-17β-ol-2-one (IXb) in 200 ml. of dry ether was introduced into the reaction during 20 min. The reaction was stirred for an additional 4 hr. and then was kept standing overnight. Tetrahydrofuran (600 ml.) was added in several portions while the ether was removed by distillation. The reaction then was heated under reflux with stirring for 8 hr. Water was added and the product Xb, after isolation with methylene chloride, was acetylated overnight at room temperature with 60 ml. of acetic anhydride–pyridine (1:2). Water was added to the acetylation mixture and the product extracted with methylene chloride. The organic extracts were washed with cold 2.5% aqueous hydrochloric acid solution (v./v.), 5% sodium bicarbonate solution and with water. Removal of the solvent afforded 2.7 g. of thick oil which was dissolved in hexane–benzene (9:1) and adsorbed on 300 g. of alumina. The product was eluted with hexane–benzene (1:1) and crystallized from methanol to yield 0.4 g. of Xc, m.p. 139–142°. The pure sample melted at 141–143; $[\alpha]_D$ −26°; ν_{max} 3000 (w), 1650 (m), 892 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.11; H, 10.47.

17α-Methylandrostane-2α,17β-diol (VII).—A solution of 6.5 g. of 17α-methyl-Δ^2-androsten-17β-ol and 100 ml. of dry tetrahydrofuran was treated with an excess of diborane gas generated in a separate vessel by the addition of sodium borohydride dissolved in Diglyme to a mixture of boron trifluoride etherate and Diglyme. After being kept for 3 hr. the excess of diborane was destroyed by the cautious addition of water, the reaction was diluted with 200 ml. of tetrahydrofuran and then cooled in ice to 5°. An ice-cold solution of 6.3 g. of sodium hydroxide in 42 ml. of water was then added, with dropwise addition (during 15 min.) of 32 ml. of ice-cold 35% hydrogen peroxide. The reaction was stirred for 3 hr. without further cooling. Dilution of the reaction mixture with water and isolation with methylene chloride afforded 7 g. of crystalline product which was dissolved in benzene–hexane (4:1) and adsorbed on a column of 280 g of alumina. The less polar substance, eluted with mixtures of benzene–ether (4:1, 3:2, 1:1) and with pure ether, was crystallized from acetone–hexane and yielded 2.4 g. of 17α-methylandrostane-3α,17β-diol (VIII), m.p. 184–187°. A pure sample crystallized from the same solvent pair showed m.p. 187–189°; $[\alpha]_D$ −14°; reported[24] m.p. 185°.

Continued elution with methylene chloride and acetone afforded 3 g. of VII. Crystallization from acetone gave 2.1 g. of VII with m.p. 225–228°, raised to 231–232° after 3 additional crystallizations; $[\alpha]_D$ −4°.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.44; H, 11.23.

17α-Methyldihydrotestosterone.—An ice-cold solution of 0.3 g. of VIII in 20 ml. of acetone was treated with 0.5 ml. of 8 *N* chromium trioxide reagent.[9] After 5 min. the product was precipitated with water. Acetone crystallization furnished 0.2 g. of 17α-methyldihydrotestosterone, m.p. 197–200° and identical in all respects with an authentic specimen.

17α-Methylandrostan-17β-ol-2-one (IXa).—The oxidation of a solution of 1.7 g. of VII in 120 ml. of acetone and 20 ml. of dioxan at 5° with 2.1 ml. of 8 *N* chromium trioxide reagent[9] produced, after crystallization from acetone, 1.4 g. of the 2-ketone IXa, m.p. 179–181°. The analytical sample prepared from acetone exhibited m.p. 180–181°; $[\alpha]_D$ +19°; ν_{max} 1710 cm.$^{-1}$; R. D. in methanol (*c*, 0.06): peak at $[\alpha]_{305}$ +1359; R.D. in methanol and HCl (*c*, 0.06): peak at $[\alpha]_{305}$ +1195°.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.53; H, 10.37.

2-Methylene-17α-methylandrostan-17β-ol (Xa).—A solution of methylenetriphenylphosphorane was prepared in a nitrogen atmosphere by treating a stirred suspension of 3.8 g. of methyltriphenylphosphonium bromide[18] with 19.5 ml. of 0.5 *N* ethereal *n*-butyllithium solution. To this was added a solution of 0.8 g. of IXa in 140 ml. of dry ether and the reaction was carried out and processed exactly as described in the preparation of Xc with omission of the acetylation step. The crude product (2.4 g.) was dissolved in benzene–hexane (1:1) and adsorbed on a column of 70 g. of alumina. Elution with increasing concentrations of benzene afforded crystalline material. Crystallization from ether yielded 0.6 g. of the 2-methylene compound Xa, m.p. 149–152°. The analytical specimen from ether showed m.p. 150–153°; $[\alpha]_D$ −44°; ν_{max} 3300 (w), 1650 (m) and 890 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.21; H, 11.46.

2-Methyl-Δ^1-androsten-3-ethylene Dithioketal-17β-acetate (XIb).—To an ice-cooled solution of 37 g. of 2-methyl-Δ^1-androsten-3-one-17β-acetate (XIa) in 400 ml. of glacial acetic acid, were added 45 ml. of ethane dithiol and 35 ml. of boron trifluoride etherate complex, the mixture then being left at room temperature during 1.5 hr. The precipitate which formed was collected, washed with water, aqueous ammonia, water again, dried, and filtered through neutral, activated alumina. The solids which were eluted by benzene–hexane (1:1) were combined and crystallized from chloroform–heptane to afford 31 g. of XIb, m.p. 272-274°, raised by several recrystallizations from the same solvent system to m.p. 284-285°; $[\alpha]_D$ −1.0°; ν_{max} 1730 (s) and 1250 cm.$^{-1}$ (s).

(24) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp. New York, N. Y., 1959, p. 519.

Anal. Calcd. for $C_{24}H_{36}OS_2$: C, 68.52; H, 8.62; S, 15.24. Found: C, 68.21; H, 8.72; S, 14.92.

2-Methyl-Δ^2-androsten-17β-ol (IIIb) from the Dithioketal (XIb).—To 750 ml. of liquid ammonia 6.5 g. of metallic sodium was added with 5 g. of 2-methyl-Δ^1-androsten-3-ethylene-dithioketal-17β-acetate (XIb) in solution in 350 ml. of tetrahydrofuran. Thereafter the excess of sodium was discharged by the addition of ethanol. Ammonia was evaporated overnight and the organic solvents were evaporated under reduced pressure. The organic mixture then was dissolved in chloroform, washed with water, and dried over sodium sulfate. Filtration and solvent evaporation yielded an oil which was chromatographed through activated, neutral alumina. The fractions obtained with benzene were combined and 620 mg. of IIIb was obtained, identical by mixture m.p. and infrared spectrum with a sample prepared as described above.

2-Methyl-Δ^1-androsten-17β-ol-17-acetate (XIc).—A solution of 6 g. of 2-methyl-Δ^1-androsten-3-ethylene dithioketal-17β-acetate in 1000 ml. of acetone was refluxed with stirring for 48 hr. with 75 g. of Raney nickel, which was previously deactivated by several decantations from 600 ml. of acetone. After filtration and evaporation of the solvent, the gummy mixture was filtered through neutral, activated alumina. The fractions obtained by elution with hexane were combined to furnish 2.2 g. of XIc which was recrystallized from heptane. An analytical sample had m.p. 99-101°; $[\alpha]_D$ +84°; ν_{max} 1733 (s) and 1247 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; O, 9.68. Found: C, 79.80; H, 10.15; O, 9.44.

4α-Bromo-2α-methylandrostane-3β,17β-diol-17β-acetate (XIIb).—A solution of 3.74 g. of 4α-bromo-2α-methylandrostan-3-one-17β-ol acetate[7] in 150 ml. of tetrahydrofuran was mixed with a solution of 4 g. of sodium borohydride in 30 ml. of methanol and left overnight at room temperature. The solution was poured into water, extracted with ethyl acetate and the organic layer then was washed with water until neutral, dried with sodium sulfate, and evaporated to a crystalline mass. Four recrystallizations from methanol yielded 2.20 g. of XIIb, m.p. 213–215°; $[\alpha]_D$ −47°.

Anal. Calcd. for $C_{22}H_{35}BrO_3$: C, 61.80; H, 8.25; O, 11.21; Br, 18.70. Found: C, 61.62; H, 8.32; O, 10.60; Br, 19.33.

2α-Methyl-Δ^3-androsten-17β-ol (XIIIa).—The bromohydrin XIIb (1.18 g.) in 10 ml. of acetic acid was refluxed for 5 hr. with 4.0 g. of powdered zinc. The zinc was filtered off, and washed with hot ethanol (100 ml.). The combined ethanol and acetic acid solutions were poured into water, extracted with ethyl acetate, and the extract was washed with aqueous sodium bicarbonate and then with water until neutral. The ethyl acetate solution was evaporated to dryness, the residue dissolved in ethanol (50 ml.) containing potassium hydroxide (2 g.) and left at room temperature overnight. Working up by pouring into water, extracting into ethyl acetate, washing with water until neutral, and evaporating, chromatographing on 30 g. of alumina (activity I) and eluting with benzene yielded XIIIa, 430 mg. after four recrystallizations from hexane, m.p. 145-147°; $[\alpha]_D$ +129°; ν_{max} 3320 (s), 3030 (w), 1658 (w) and 698 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18; O, 5.55. Found: C, 83.71; H, 11.10; O, 5.49.

2α-Methyl-Δ^3-androsten-17β-ol Acetate (XIIIb).—Acetic anhydride-pyridine acetylation of 2α-methyl-Δ^3-androsten-17β-ol (XIIIa) at room temperature overnight led to the corresponding acetate XIIIb which was recrystallized several times from acetone, m.p. 150-152°; $[\alpha]_D$ −101°; ν_{max} 1732 (s), 1650 (w), 1250 (s) and 702 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.50; H, 10.55.

2α,17α-Dimethylandrostan-17β-ol (XIV).—A mixture of 6.0 g. of 2α,17α-dimethylandrostan-3-one-17β-ol (Id) and 20 ml. of hydrazine hydrate in 500 ml. of ethylene glycol was maintained under reflux during 3 hr. Potassium hydroxide (10.0 g.) was added and the internal temperature raised to 190° by distillation and held there for 5 hr. under reflux. On addition of 500 ml. of water a precipitate formed which was extracted into ethyl acetate and washed to neutrality with water. Evaporation of the dried extracts left a residue which was chromatographed over 400 g. of alumina. Elution with benzene–ether (4:1) afforded 3.81 g. of XIV, m.p. 119-122°. Recrystallization from methanol–water yielded prisms, m.p. 127-129°; $[\alpha]_D$ −12°; ν_{max} 3480 cm.$^{-1}$ (m).

Anal. Calcd. for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 82.68; H, 11.84.

Steroids. CCVII. Ring A Modified Hormone Analogs. Part III.[1] 2-Formyl-Δ^2-androstenes and Related Compounds. A New Class of Potent Anabolic Agents[2]

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The preparation of a series of 2-formyl, 2-hydroxymethyl, 2-carboxy and 2-acetyl-Δ^2-androstenes as well as the 4α-chloro, 4α-methyl and Δ^4-analogs of 2-formyl-Δ^2-androstene-17β-ol is described. Direct acylation of Δ^2-androstene-17β-ol afforded 3-acetyl-Δ^2-androstene-17β-ol. A number of these compounds possess high myotrophic activity with a favorable myotrophic–androgenic ratio.

As a continuation of our studies of compounds with variable electron density patterns around ring A[3] and particularly those possessing a Δ^2-double bond,[1,3] it appeared that a moiety which warranted attention was the 2-formyl-Δ^2-system.

As long ago as 1941, 2-formyl-Δ^2-cholestene[4] was prepared by pyrolysis of the α-ketolactone derived from 2-oxalyl cholestan-3ζ-ol. The preferred method for the introduction of the 2-formyl-Δ^2-grouping is, however, that used in the preparation of cyclohexene aldehyde from cyclohexanone,[5] and proceeds *via* the previously described[6] 2-hydroxymethylene-3-ketones.

2-Hydroxymethyleneandrostane-17β-ol-3-one[6] (Ia) was smoothly converted into its methyl ether Ib by treatment at room temperature with methanol containing a catalytic amount of hydrochloric or perchlo-

(1) Steroids. CCVI and Part II. A. D. Cross, J. A. Edwards, J. C. Orr, B. Berkóz, L. Cervantes, M. C. Calzada and A. Bowers, *J. Med. Chem.*, **6**, 162 (1963).

(2) For a preliminary account of a part of this work *cf.* J. C. Orr, O. Halpern and A. Bowers, *ibid.*, **5**, 409 (1962).

(3) For a general discussion of the considerations which govern our thinking in this work see Part I of this series: A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada and E. Denot, *ibid.*, **6**, 156 (1963).

(4) P. A. Plattner and L. M. Jampolsky, *Helv. Chim. Acta*, **24**, 1459 (1941).

(5) P. Seifert and H. Schinz, *ibid.*, **34**, 728 (1951).

(6) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959); see also B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, **11**, 139 (1960).