[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CV.[1] 2-Methyl and 2-Hydroxymethylene-androstane Derivatives

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RECEIVED AUGUST 6, 1958

Treatment of 3-ketoandrostanes or 3-keto-Δ^4-androstenes successively with ethyl oxalate, methyl iodide and alkoxide yielded the 2α-methyl derivatives. Alternately 2α-methyl androstanes were synthesized by hydrogenation of 2-hydroxymethylene-3-ketoandrostanes. Direct alkylation of 3-ketoandrostanes yielded mainly the 2,2-dimethyl derivatives. A number of the described compounds were found to have favorable anabolic–androgenic ratios.

As part of a systematic study of the effects of alkyl substitution on biological activity in the androstane and 17α-alkylandrostane series we have prepared androstane and 19-norandrostane derivatives with alkyl substituents at C-1,[2] C-2,[3] C-4[4–6] and C-6.[7,8] Such an approach may offer insight into the steric requirements for biological activity[9] of steroids.

This paper is concerned with the synthesis and activity of a number of 2-methyl, 2,2-dimethyl and 2-hydroxymethylene steroid derivatives, some of which already have been reported in a preliminary communication.[3]

2-Monomethyl and 2-Hydroxymethylene Derivatives.—The 2-monomethyl testosterone derivatives were prepared by two general methods. Condensation of testosterone or methyltestosterone or their 4,5-dihydroallo derivatives with excess ethyl oxalate gave the enolic 2-ethoxyoxalates as amorphous solids.[10] Condensation was in general effected in benzene solution with an excess of sodium hydride as the base. Alkylation of the ethoxyoxalates with methyl iodide in acetone solution in the presence of potassium carbonate gave the corresponding 2-methyl-2-ethoxyoxalates which underwent reversal of oxalate condensation with alcoholic alkoxide to give the 2α-methyltestosterone (Ia, Ib) or dihydrotestosterone (IIa, IIb) derivatives. While yields in the testosterone series were of the order of 40%, the reactions proceeded poorly with the 4,5-dihydro compounds yielding only 10 to 20% of the requisite 2-methyl compounds.

More convenient for the preparation of the dihydrotestosterone derivatives was a sequence involving condensation at C-2 with ethyl formate. The 2-hydroxymethylene derivatives thus obtained were hydrogenated[11] in methanol solution over a palladium–carbon catalyst at one to three atmospheres pressure and room temperature, presumably yielding as an intermediate the thermodynamically unstable 2β-methyl (axial) derivatives.[12] Passage of a benzene solution of the total hydrogenation mixture over alkaline alumina gave the 2α-methyl (equatorial) derivatives IIa and IIb in *ca.* 50% over-all yield. Hydrogenation of the diacetate or dipropionate rather than the free 2-hydroxymethylenedihydrotestosterone offered no particular advantage.

2α-Methyldihydrotestosterone (IIa) was also

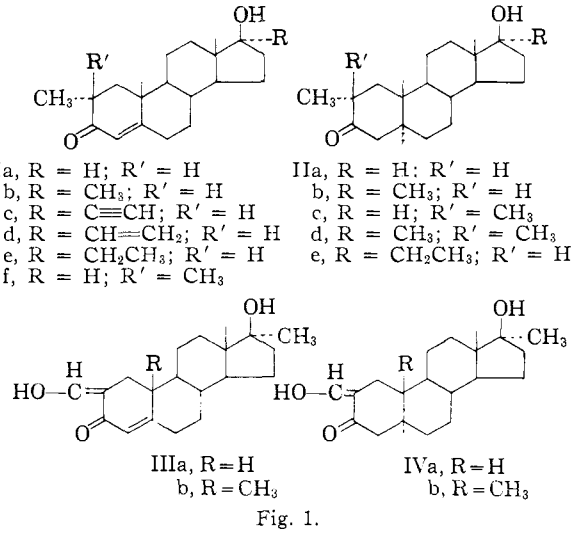

Fig. 1.

obtained by catalytic hydrogenation of the 3-cycloethylene ketal (V) of 2α-methyltesterone in methanol solution over a palladium–carbon catalyst thus interrelating the two series.

When it was found that a number of members of this series, particularly the dihydrotestosterone derivatives, exhibited interesting anabolic as well as anti-tumor activity and that furthermore the intermediate 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one (IVb) was particularly striking as a potent oral anabolic agent with minimal androgenic activity, our study was expanded to include the preparation of other potentially biologically interesting 2-hydroxymethylene derivatives. Thus by conventional means 17α-methyltestosterone, 17α-methyl-19-nortestosterone and 17α-methyl-19-norandrostan-17β-ol-3-one were also converted to the crystalline 2-hydroxymethylene compounds, IIIb, IIIa and IVa.

It was of further interest to prepare the 2α-methyl-17α-alkyltestosterone derivatives where

(1) Paper CIV, A. Bowers and H. J. Ringold, THIS JOURNAL, **81**, 424 (1959).

(2) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 2477 (1956).

(3) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(4) H. J. Ringold and G. Rosenkranz, *ibid.*, **22**, 602 (1957).

(5) F. Sondheimer and Y. Mazur, THIS JOURNAL, **79**, 2906 (1957).

(6) J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, *ibid.*, **78**, 5662 (1956).

(7) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(8) M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 4099 (1957).

(9) For the specificity of enzyme and coenzyme-steroid interactions see P. I. Marcus and P. Talalay, *Proc. Roy. Soc. (London)*, **144B**, 116 (1955) and A. Munck, J. F. Scott and L. L. Engel, *Biochim. Biophys. Acta*, **26**, 397 (1957).

(10) The preparation of 2α-methyl cortical hormones by this route has been described by J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955).

(11) *Cf.* Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, *ibid.*, **75**, 2567 (1953).

(12) The isolation and independent preparation of 2β-methylandrostanes will be the subject of a further communication.

the 17-alkyl group was ethyl, vinyl and ethynyl. For this purpose, the aforementioned ethylene ketal (V) of 2α-methyltestosterone was oxidized with pyridine–chromium trioxide to the 17-ketone VI which was converted to the 17α-ethynyl derivative VII by reaction with potassium acetylide. Acid hydrolysis regenerated the Δ^4-3-ketone system yielding 2α-methyl-17α-ethynyltestosterone (VIII). Catalytic hydrogenation of VIII over a palladium–calcium carbonate catalyst in pyridine solution stopped with the absorption of one molecular equivalent of hydrogen and gave 2α-methyl-17α-vinyltestosterone (IX). Hydrogenation of VIII in dioxane, over the same catalyst, interrupted at two moles, gave 2α-methyl-17α-ethyltestosterone (X). It was found

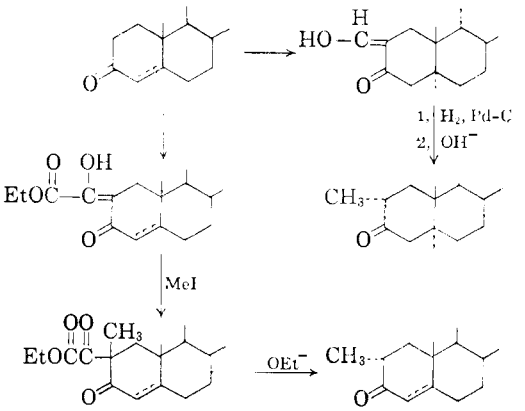

Fig. 2.

that VIII could be synthesized alternatively by condensation of 17α-ethynyltestosterone with ethyl oxalate, followed by alkylation at C-2 with methyl iodide and ethoxide reversal of oxalate condensation.

2α-Methyl-17α-ethylandrostan-17β-ol-3-one (IIe) was prepared from 17α-ethylandrostan-17β-ol-3-one, condensation with ethyl formate yielding the 2-hydroxymethylene derivative which was then hydrogenolyzed as in the other cases furnishing the desired IIe.

Previously we reported the synthesis of 6β-methylandrostan-17β-ol-3-one.[7] This compound, by ethyl formate condensation and hydrogenation of the intermediate hydroxymethylene compound gave 2α,6β-dimethylandrostan-17β-ol-3-one (XI).

2,2-Dimethyl Derivatives.—The 2,2-dimethylandrostane derivatives IIc and IId were prepared by direct alkylation of androstan-17β-ol-3-one (or its esters) and of 17α-methylandrostan-17β-ol-3-one. Treatment of the former with excess methyl iodide and potassium *t*-butoxide in *t*-butyl alcohol at room temperature gave, after chromatographic separation, the 2,2-dimethyl derivative IIc in about 50% yield and approximately 10% of the 2-monomethyl derivative IIa. Superior yields of IIc were obtained by alkylation of dihydrotestosterone propionate, followed by saponification, whereupon almost a 60% yield of IIc was obtained by direct crystallization. The direct alkylation of 17α-methyldihydrotestosterone proceeded satisfactorily yielding 2,2,17α-trimethyldihydrotestosterone (IId).

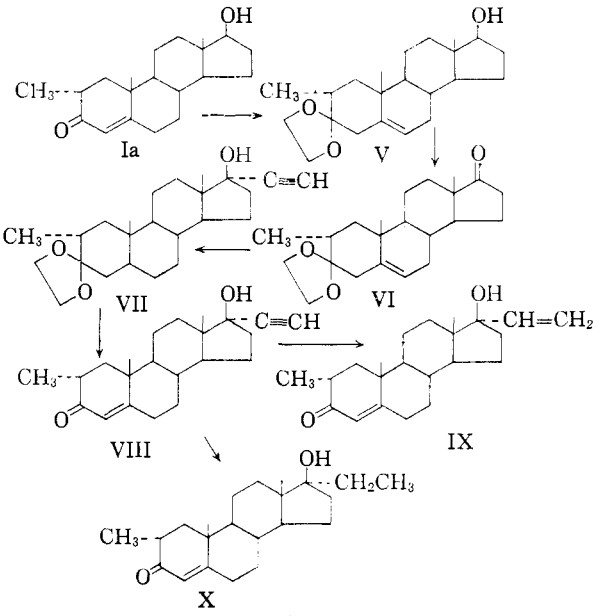

Fig. 3.

It was necessary to establish that dimethylation had indeed occurred at 2,2′. This was readily demonstrated by bromination–dehydrobromination experiments conducted with the 17-acetate (IIc acetate) of 2,2-dimethyldihydrotestosterone. Titration with bromine in acetic acid showed the uptake of just two moles of bromine and gave a crystalline dibromo compound (XII). Collidine dehydrobromination yielded a compound still containing one bromine atom and with an ultraviolet maximum at 262 mμ, log ε 4.07, characteristic of a 4-bromo-Δ^4-3-ketone,[13] establishing that this compound (XIII) is 2,2-dimethyl-4-bromotestosterone acetate. Bromination of IIc acetate with one equivalent of bromine gave 4-bromo-2,2-dimethyldihydrotestosterone acetate (XIV) which was converted by collidine dehydrobromination to 2,2-dimethyltestosterone acetate (XV), λ_{max} 240 mμ, log ε 4.19.

Biological Activity.—As reported in our preliminary communication, a number of these compounds were found by Huggins and Mainzer[14] to be potent inhibitors of the development

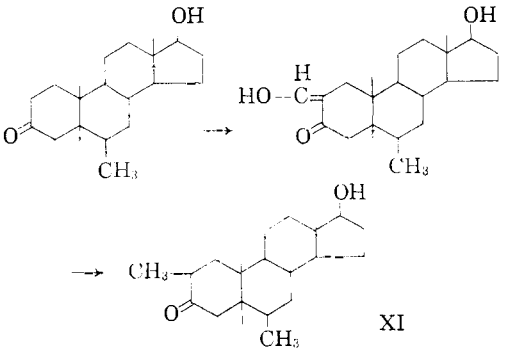

Fig. 4

(13) J. I. Shaw and R. Stevenson, *J. Chem. Soc.*, 3549 (1955); D. N. Kirk, D. K. Patel and V. Petrow, *ibid.*, 627 (1956); H. J. Ringold, E. Batres, O. Mancera and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956).

(14) C. Huggins and K. Mainzer, *J. Exptl. Med.*, **105**, 485 (1957).

of a transplantable rat mammary tumor. This activity was particularly marked in the case of 2α-methyldihydrotestosterone (IIa) and 2α,17α-dimethyldihydrotestosterone (IIb), both compounds being more effective than testosterone or dihydrotestosterone. One possible explanation of the increased activity of the 2α-methyl- compounds lies in the known *in vivo* conversion of androgens to estrogens,[15] the C-2 unsubstituted compounds being converted in some degree to the highly potent estrone or estradiol which have a tumor stimulatory effect[14] partially counteracting the anti-tumor effect of the androgens. The 2-methyl-derivatives, if they do undergo such *in vivo* aromatization, are converted to much weaker estrogens, 2-methylestrone for example being only 1/200 as active[16] as estrone.

In the seven day anabolic–androgenic assay with 21-day old castrate male rats,[17] subcutaneous route, 2α-methyldihydrotestosterone propionate (IIa propionate) exhibited approximately 2× the anabolic and 0.5× the androgenic activity of testosterone propionate, as measured by levator ani, prostate and seminal vesicle response.[18] Unesterified 2α-

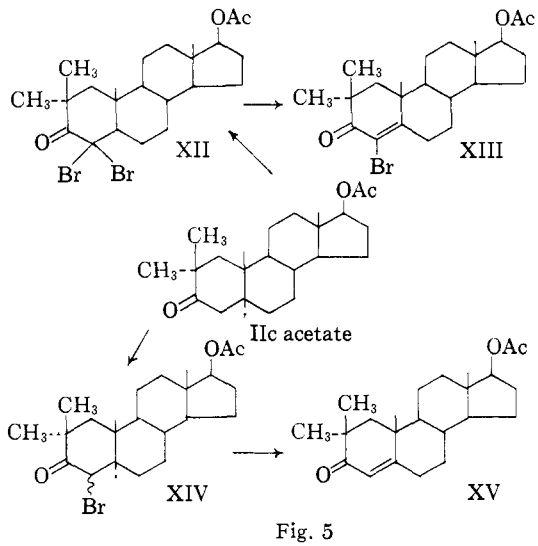

Fig. 5

methyldihydrotestosterone (IIa), 2α,17α-dimethyldihydrotestosterone (IIb) and 2-hydroxymethylene-17α-methyldihydrotestosterone (IVb) were found in the experimental animal to be potent orally active anabolic agents exhibiting only relatively weak androgenic activity.[18]

Experimental[19]

2α-Methyltestosterone (Ia).—In a nitrogen atmosphere, a mixture of testosterone (50 g.) in anhydrous thiophene-free benzene (1 l.), ethyl oxalate (50 ml.) and sodium hydride (15 g.) was stirred for 4 hours. The precipitated sodium salt of the 2-ethoxyoxalate and the excess sodium hydride was filtered, washed with benzene, then hexane, and dried for several hours *in vacuo*. The product was cautiously added in portions to a stirred ice-cold hydrochloric acid solution (100 cc. 35% acid–2 l. ice-water) liberating the free ethoxyoxalate which was extracted with methylene dichloride, the extract washed with water, dried and evaporated. The residue was taken up in 1.1 liters of acetone, finely powdered anhydrous potassium carbonate (50 g.) and methyl iodide (150 ml.) were added and the mixture boiled under condenser for 48 hr. The filtered solution was evaporated almost to dryness, water was added, the oily residue extracted with methylene dichloride and the extract washed with 1% sodium hydroxide, water, dried and evaporated to dryness. The residue was dried at 90° for 2 hr. *in vacuo* (1 mm.) and then treated with the solution of sodium ethoxide prepared from 5 g. of sodium and 500 ml. of absolute ethanol. The solution was allowed to stand for 48 hr. at room temperature and then poured into 5 l. of water. Without neutralization, the mixture was extracted with methylene dichloride (occasionally emulsions formed during extraction and it was necessary to add salt), the organic extract was washed with water to neutrality, dried and evaporated. The residue was taken up in benzene and chromatographed on 2 kg. of ethyl acetate-washed alumina (1-l. eluate fractions). Acetone–hexane crystallization of the benzene–ether (9:1) fractions gave 19.07 g. (36%) of 2α-methyltestosterone (Ia), m.p. 149–153°. The analytical specimen from the same solvent exhibited m.p. 155–157°, $[\alpha]_D$ +116°, λ_{max} 242 mμ, log ε 4.19.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.33; H, 10.28.

2α-17α-Dimethyltestosterone (Ib).—17α-Methyltestosterone (5 g.) was treated successively with ethyl oxalate, methyl iodide and sodium ethoxide as described for Ia. The residue, after chromatography on 250 g. of neutral alumina and acetone–hexane crystallization of the benzene–ether (9:1) fractions gave 1.96 g. (37%) of 2α,17α-dimethyltestosterone (Ib), m.p. 150–152°, $[\alpha]_D$ +182°, λ_{max} 240 mμ, log ε 4.21.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.68; H, 10.03.

2α-Methylandrostan-17β-ol-3-one (IIa). (a) **By Oxalate Sequence.**—Androstan-17β-ol-3-one (50 g.) in anhydrous thiophene-free benzene (600 cc.) was condensed with ethyl oxalate (50 cc.) in the presence of 11.5 g. of sodium hydride as described for Ia. The product, after treatment with methyl iodide and then sodium ethoxide as described above, was purified by chromatographic separation on 1 kg. of alkaline alumina (500-ml. eluates). The benzene–ether (9:1) fractions were crystallized from acetone–hexane yielding 9.0 g. (17%) of 2α-methyl-dihydrotestosterone (IIa), m.p. 149–153°; analytical sample from ether, m.p. 152–154°, $[\alpha]_D$ +32° (ethanol).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.70; H, 10.77.

(b) **By Hydrogenation of 2-Hydroxymethylene Derivative.**—A mixture of androstan-17β-ol-3-one (50 g.) in anhydrous thiophene-free benzene (400 cc.), ethyl formate (20 ml.) and sodium hydride (15 g.) was stirred for 8 hours under nitrogen.[20] The sodio salt of the resultant 2-hydroxymethylene derivative and the excess hydride were filtered, washed with benzene, then hexane and dried *in vacuo*. Cautious precipitation in excess ice-cold dilute hydrochloric acid gave the crude free 2-hydroxymethylenedihydrotestosterone which was filtered, washed with water and air-dried. The product (50.5 g.) was hydrogenated for 24 hr. in methanol (750 ml.) over 20 g. of prehydrogenated 10% palladium-carbon catalyst at 25° and 570 mm. pressure (hydrogen uptake 9 liters). The mixture was filtered, the catalyst washed with hot methanol and the combined solutions evaporated to dryness. The residue, taken up in one liter of benzene, was absorbed on 1.5 kg. of alkaline alumina in a column and then eluted by passage of 15 liters of benzene. Evaporation of the extract and crystallization from acetone–hexane yielded 22.7 g. (43%) of IIa, m.p. 146–150°; one recrystallization raised the melting point to that of the an-

(15) For leading references see R. Dorfman and R. A. Shipley, "Androgens," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 89.

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

(17) L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exper. Biol. and Med.*, **83**, 175 (1953).

(18) Bioassays by Dr. R. Dorfman, The Worcester Foundation and The Endocrine Laboratories, Madison, Wis.

(19) Melting points are uncorrected. Unless specified otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 96% ethanol. Thanks are due A. Mijares for able technical assistance and Dr. L. Throop for determinations of rotations and spectra.

(20) This procedure for ethyl formate condensation is a minor modification of the method used in the case of testosterone and cholestenone by F. Weisenborn, D. Remy and T. Jacobs, THIS JOURNAL, **76**, 552 (1954).

alytical sample with which this sample was identical in all respects.

(c) **By Hydrogenation of 2α-Methyltestosterone Cycloethylene Ketal.**—The ketal V (130 mg.) was hydrogenated for 5 hr. at 25° and 570 mm. in 20 ml. of methanol over 120 mg. of prehydrogenated 10% palladium—carbon catalyst (uptake 8 ml.). The filtered solution, after the addition of water (5 ml.) and concentrated hydrochloric acid (1 ml.), was boiled for 30 minutes, concentrated *in vacuo* and precipitated with water. Filtration and crystallization from acetone–hexane gave 40 mg. of authentic IIa, m.p. 150–152°.

2α-Methylandrostan-17β-ol-3-one 17-Propionate (IIa Propionate).—A solution of 1 g. of IIa, 3.3 ml. of propionic anhydride and 1.1 ml. of pyridine after being heated for 2 hr. at 90° was cooled and treated with 50 ml. of water. The mixture was heated to hydrolyze excess anhydride, then cooled and extracted with methylene dichloride, the extract being washed successively with dilute hydrochloric acid, bicarbonate and water. Evaporation and crystallization of the residue from hexane gave 900 mg. of IIa propionate, m.p. 126–130°, $[\alpha]_D$ +24°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.61; H, 10.07. Found: C, 76.48; H, 10.01.

IIa Phenylpropionate.—2α-Methyldihydrotestosterone (1 g.) in 5 cc. of cold pyridine was treated with 0.8 g. of phenylpropionyl chloride and the solution then allowed to stand for 18 hr. at room temperature and finally heated for 30 minutes at 90.° The cooled solution was worked up as in the case of the propionate and the residue chromatographed on 50 g. of neutral alumina, the hexane–benzene (1:1 and 2:3) fractions yielding after crystallization from acetone–hexane, 740 mg. of phenylpropionate, m.p. 132–135°, $[\alpha]_D$ +33°, λ_{max} 254 mμ and 258 mμ, log ε 2.33 and 2.38.

Anal. Calcd. for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23. Found: C, 79.50; H, 9.12.

IIa Cyclopentylpropionate.—Cyclopentylpropionyl chloride was substituted for phenylpropionyl chloride in the preparation above. Chromatography and methanol–water crystallization of the hexane–benzene (3:1) fractions gave 2α-methylandrostan-17β-ol-3-one cyclopentylpropionate, m.p. 96–100°, $[\alpha]_D$ +34°.

Anal. Calcd. for $C_{28}H_{44}O_3$: C, 78.45; H, 10.34. Found: C, 78.70; H, 9.95.

2α,17α-Dimethylandrostan-17β-ol-3-one (IIb). (a) By Oxalate Sequence.—17α-Methylandrostan-17β-ol-3-one (10 g.) was condensed with excess ethyl oxalate exactly as described for Ia. Acidification of the sodium salt of the 2-ethoxyoxalate gave an amorphous solid which was filtered, washed, dried and treated successively with methyl iodide and sodium ethoxide as in Ia. The crude product (4.0 g.) remaining after reversal of oxalate condensation was chromatographed on 300 g. of neutral alumina. Crystallization of the benzene–ether (19:1) fractions from ether–hexane gave 0.89 g. (9%) of IIb, m.p. 151–154°, $[\alpha]_D$ +8°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.29; H, 10.82.

(b) **By Hydrogenation of 2-Hydroxymethylene Derivative.**—17α-Methylandrostan-17β-ol-3-one (20 g.) in anhydrous thiophene-free benzene (700 ml.) was treated with ethyl formate (40 ml.), sodium hydride (12 g.) and the mixture stirred for 5 hr. under nitrogen. The sodio salt of the hydroxymethylene derivative was filtered, washed first with benzene, then hexane and dried *in vacuo*. Precipitation in dilute cold hydrochloric acid liberated crude 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one (IVb) (20 g.). The filtered, washed and dried product was added to 700 ml. of methanol containing 16 g. of pre-hydrogenated 5% palladium–carbon catalyst and the product hydrogenated at 25° and 570 mm. Hydrogen uptake (1.8 molar equivalents) ceased in 2 hr., the solution was filtered and concentrated to dryness. The residue (negative ferric chloride test) was purified by chromatography on 950 g. of alkaline alumina. The benzene–ether (9:1) fractions crystallized from acetone–hexane to yield 11.06 g. (55%) of IIb, m.p. 147–151°.

2-Hydroxymethylene-17α-methylandrostan-17β-ol-3-one (IVb).—Ethyl acetate crystallization of the crude 2-hydroxymethylene derivative above (preparation of IIb part (b)) gave pure IVb, m.p. 178–180°, $[\alpha]_D$ +38°, λ_{max}. 285 mμ, log ε 3.99. In a number of runs the average yield of purified material was 65%.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.71; H, 9.64.

IVb enol acetate, hexane crystallization, m.p. 144–148°, $[\alpha]_D$ +27° (ethanol), λ_{max} 255 mμ, log ε 4.09. *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.49; H, 9.07.

IVb enol propionate, hexane crystallization, m.p. 135°, $[\alpha]_D$ +26 ° (ethanol), λ_{max}. 257 mμ, log ε 4.11. *Anal.* Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.74; H, 9.14.

IVb enol benzoate, acetone–water crystallization, m.p. 188–190°, $[\alpha]_D$ ± 0°, λ_{max}. 230 mμ, log ε 4.19. *Anal.* Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.37; H, 8.06.

2-Hydroxymethylene-17α-methyl-19-nortestosterone (IIIa).—17α-Methyl-19-nortestosterone[21] was condensed with ethyl formate as described above. Crystallization from acetone–ether gave the analytical specimen of IIIa, m.p. 146–147°, $[\alpha]_D$ −74°, λ_{max}. 252 mμ and 305 mμ, log ε 4.06 and 3.75.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 75.95; H, 8.86. Found: C, 75.52; H, 8.65.

2-Hydroxymethylene-17α-methyltestosterone (IIIb) was prepared from 17α-methyltestosterone and ethyl formate as described above; analytical sample from acetone–ether, m.p. 179–181°, $[\alpha]_D$ +6°, λ_{max}. 251 and 309 mμ, log ε 4.07 and 3.73.

Anal. Calcd. for $C_{21}H_{30}O_3 \cdot {}^1/_2C_3H_6O$: C, 75.16; H, 9.25. Found: C, 74.81; H, 9.08.

2-Hydroxymethylene-17α-methyl-19-norandrostan-17β-ol-3-one (IVa) was prepared from 17α-methyl-19-norandrostan-17β-ol-3-one[22] and ethyl formate as described above. Crystallization from methanol yielded pure IVa, m.p. 195–197°, $[\alpha]_D$ +95°, λ_{max}. 281 mμ, log ε 3.96.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.43; H, 9.50. Found: C, 74.87; H, 9.55.

2α-Methyl-3-cycloethylenedioxy-Δ⁵-androsten-17β-ol (V).—A mixture of 2α-methyltestosterone (Ia) (2 g.), ethylene glycol (20 ml.), benzene (100 ml.) and *p*-toluenesulfonic acid·$1H_2O$ (200 mg.) was boiled for 22 hr. with continuous separation of water. The cooled solution, after potassium carbonate wash, was evaporated to dryness. Crystallization of the residue from acetone–hexane yielded 1.1 g. of V, m.p. 173–177°, and a second crop of 400 mg., m.p. 164–171°. Recrystallization from the same solvent gave the pure material, m.p. 175–178°, $[\alpha]_D$ +41° (pyridine), no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.11; H, 9.78.

2α-Methyl-3-cycloethylenedioxy-Δ⁵-androsten-17-one (VI).—A stirred solution of 1.5 g. of V, in 20 cc. of pyridine was cooled to 10° and treated under nitrogen, with 900 mg. of chromium trioxide. The mixture was then allowed to stand at room temperature for 18 hr. before being diluted with 100 ml. of ethyl acetate and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue chromatographed on 20 g. of alkaline alumina. The hexane–benzene (1:1) fractions were crystallized from acetone–hexane yielding the 17-ketone VI (930 mg.), m.p. 201–210°. A sample crystallized from acetone to constant melting point exhibited m.p. 206–210°, $[\alpha]_D$ +51° (pyridine).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.92; H, 9.38.

2α-Methyl-17α-ethynyl-3-cycloethylenedioxy-Δ⁵-androsten-17β-ol (VII).—A solution of the preceding ketal-ketone VI (2.0 g.) in 45 ml. of anhydrous benzene was added, under nitrogen, to the solution prepared from dissolving 2 g. of potassium in 40 ml. of *t*-amyl alcohol. A slow current of purified acetylene was passed through the solution for 40 hours, whereupon the solution was poured into ice-water and extracted with benzene. Evaporation of solvent and chromatographic separation of the residue on 100 g. of alkaline alumina gave in the hexane–benzene (2:3) fractions 510 mg. of 17α-ethynyl compound VII. The analytical sample, from acetone–hexane melted at 224–227°, $[\alpha]_D$ −63° (pyridine).

(21) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer THIS JOURNAL, **76**, 4092 (1954).

(22) A. Bowers, H. J. Ringold and R. I. Dorfman, *ibid.*, **79**, 4556 (1957).

Anal. Calcd. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.85; H, 9.31.

2α-Methyl-17α-ethynyltestosterone (VIII). (a) **By Hydrolysis of VII.**—A solution of 100 mg. of ketal VII, methanol (3 ml.), water (1 ml.) and concentrated hydrochloric acid (0.2 ml.) was allowed to stand for 18 hours at 25° and then precipitated with water yielding 50 mg. of 2α-methyl-17α-ethynyltestosterone, m.p. 172–177°. Crystallization from acetone–hexane raised the m.p. to 175–178°, $[\alpha]_D$ +3°, $\lambda_{max.}$ 240 mμ, log ε 4.19.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.02; H, 9.33.

(b) **From 17α-Ethynyltestosterone.**—A mixture of ethynyltestosterone (5 g.), benzene (150 ml.), anhydrous tetrahydrofuran (100 ml.), ethyl oxalate (10 ml.) and sodium hydride (2 g.) was stirred for 5.5 hours under nitrogen. Work-up in the usual manner followed by alkylation (methyl iodide, potassium carbonate, acetone) and sodium ethoxide treatment as already described yielded 2.5 g. of semi-crystalline material. Chromatography on 250 g. of neutral alumina yielded in the hexane–benzene (1:9) fractions (acetone–hexane crystallization) 1.03 g. of VIII, m.p. 174–177°, identical with the product obtained in (a) and a second crop of 440 mg., m.p. 169–175°.

2α-Methyl-17α-vinyltestosterone (IX).—The ethynyl compound VIII (1.0 g.) was added to a mixture of 250 mg. of pre-hydrogenated 10% palladium–calcium carbonate catalyst in 35 ml. of pyridine and hydrogenated at 25° and 570 mm. until 96 ml. (1 molar equivalent) of hydrogen had been absorbed. The solution was filtered, evaporated to dryness *in vacuo* and the product crystallized from acetone–hexane yielding 680 mg. of IX, m.p. 157–162°. The analytical specimen from the same solvent melted at 159–162°, $[\alpha]_D$ +89°, λ_{max} 240 mμ, log ε 4.20.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.43; H, 9.88. Found: C, 80.54; H, 9.60.

2α-Methyl-17α-ethyltestosterone (X).—Compound VIII (1 g.) was hydrogenated at 25° and 570 mm. over 200 mg. of pre-hydrogenated 5% palladium–carbon catalyst in 100 ml. of dioxane (freshly distilled from Raney nickel). The hydrogenation was interrupted after the uptake of 200 ml. (1.5 hr.), the solution filtered, evaporated to dryness *in vacuo*, and the product crystallized from acetone–hexane, yielding 600 mg. of X, m.p. 139–143°. Further crystallization raised the m.p. to 141–143°, $[\alpha]_D$ +88°, $\lambda_{max.}$ 240 mμ, log ε 4.21.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.95; H, 10.23.

2α-Methyl-17α-ethylandrostan-17β-ol-3-one (IIe).—17α-Ethyl-androstan-17β-ol-3-one[23] (3.5 g.) was condensed with ethyl formate in the usual manner yielding 3.3 g. of crude 2-hydroxymethylene derivative. This product in 150 ml. of methanol was hydrogenated over 1.42 g. of pre-hydrogenated 10% palladium–carbon catalyst at 25° and 570 mm. Hydrogen uptake was extremely slow with the absorption of only 97 ml. in 3 hours; therefore the hydrogenation vessel was heated to and kept at 45° whereupon an additional 400 ml. of hydrogen was absorbed in 2 hours. The mixture was filtered, the solvent evaporated and the residue chromatographed on 100 g. of alkaline alumina. The benzene–ether (8:2) fractions were crystallized from acetone–hexane, yielding 1.43 g. of IIe, m.p. 128–131°, $[\alpha]_D$ +6°.

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.69; H, 10.85.

2α,6β-Dimethylandrostan-17β-ol-3-one (XI).—6β-Methyl-androstan-17β-ol-3-one[7] (0.8 g.) in 50 ml. of benzene was treated with 1 ml. of ethyl formate and 0.3 g. of sodium hydride. The mixture, after stirring for 5 hours under nitrogen, was filtered, washed with hexane and dried *in vacuo*. Precipitation of the sodio salt in dilute hydrochloric acid yielded 730 mg. of crude 2-hydroxymethylene-6β-methyl-androstan-17β-ol-3-one, which was hydrogenated in 50 ml. of methanol over 1.6 g. of pre-hydrogenated palladium–carbon catalyst. Hydrogen uptake ceased with the absorption of 92 ml. (theor. at 25°, 570 mm., 144 ml. for 2 equiv.). The solution was filtered, evaporated and the residue chromatographed on 35 g. of alkaline alumina, the benzene–ether (7:3) fractions, after crystallization from acetone–hexane, yielding 230 mg. of XI, m.p. 177–180°; analytical sample, m.p. 181–183°, $[\alpha]_D$ +9°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.33; H, 10.53.

2,2-Dimethylandrostan-17β-ol-3-one (IIc). (a) **By Alkylation of Dihydrotestosterone.**—To the solution of potassium *t*-butoxide prepared from 2 g. (3 equiv.) of potassium in 100 ml. of *t*-butyl alcohol was added 5 g. of androstan-17β-ol-3-one. The mixture was stirred under nitrogen for 30 minutes whereupon solution was complete and 6.4 ml. (6 equiv.) of methyl iodide was added dropwise and the reaction stirred an additional 4 hours. Water (100 ml.) and acetic acid to neutrality were added and the mixture concentrated *in vacuo*. The resultant semi-solid gum was filtered, washed with water and chromatographed on 300 g. of neutral alumina. The hexane–benzene (1:4) fractions were pooled and crystallized from acetone–water yielding 2.34 g. (43%) of 2,2-dimethylandrostan-17β-ol-3-one (IIc). m.p. 128–133°, while the benzene fractions yielded 510 mg. (10%) of 2α-methylandrostan-17β-ol-3-one (IIa). A purified sample of IIc melted at 134–136°, $[\alpha]_D$ +72°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.84; H, 10.43.

IIc acetate,[24] methanol–water crystallization, m.p. 138–140°, $[\alpha]_D$ +56°. *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.68; H, 10.14.

IIc propionate, methanol–water crystallization, m.p. 66–67°, $[\alpha]_D$ +47°. *Anal.* Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.78; H, 10.19.

IIc cyclopentylpropionate, hexane crystallization, m.p. 131–132°, $[\alpha]_D$ +80°. *Anal.* Calcd. for $C_{29}H_{48}O_3$: C, 78.68; H, 10.48; O, 10.84. Found: C, 79.21; H, 10.60; O, 10.51.

(b) **By Alkylation of Dihydrotestosterone Propionate.**—A solution of 10 g. of androstan-17β-ol-3-one propionate in 80 ml. of anhydrous *t*-butyl alcohol was added under nitrogen to the solution of potassium *t*-butoxide prepared from 4.5 g. (4 equiv.) of potassium and 150 ml. of *t*-butyl alcohol. Methyl iodide (14.4 ml., 8 equiv.) was added dropwise with cooling and the mixture stirred for 4 hours under nitrogen at 25–30°. Water and acetic acid were added as in (a), the solution was concentrated and the residue, a gum, taken up in 500 ml. of ethanol. Potassium hydroxide (5 g.) was added, the solution was then boiled for 3 hours to hydrolyze the 17-propionate, neutralized with acetic acid and concentrated. Water was added, the residue extracted with methylene dichloride, the extract washed, dried and concentrated. Crystallization from acetone–hexane gave 5.6 g. (61%) of IIc, m.p. 130–133°, identical with the product obtained in (a).

2,2,17α-Trimethylandrostan-17β-ol-3-one (IId).—17α-Methylandrostan-17β-ol-3-one (10 g.) was condensed with 3 equiv. of potassium *t*-butoxide and 6 equiv. of methyl iodide exactly as described for IIc, preparation (a). The reaction product was chromatographed on 500 g. of neutral alumina, the hexane–benzene (1:4) fractions yielding, after crystallization from acetone–hexane, 3.5 g. (32%) of 2,2-17α-trimethylandrostan-17β-ol-3-one (IId), m.p. 114–116°, while the benzene fractions yielded 1.4 g. of impure 2α, 17α-dimethyl-androstan-17β-ol-3-one (IIb), m.p. 125–130°. Pure IId was obtained by acetone–hexane recrystallization, m.p. 117–120°, $[\alpha]_D$ +53°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.92; H, 11.12.

2,2-Dimethyl-4,4-dibromoandrostan-17β-ol-3-one Acetate (XII).—A solution of 1 g. of 2,2-dimethylandrostan-17β-ol-3-one acetate (IIc acetate) in 15 ml. of glacial acetic acid was treated dropwise at 25° with bromine in acetic acid (100 mg./ml.) until a permanent bromine color persisted for at least 15 minutes. Uptake stopped with the addition of 9 ml. (2.02 equiv.). The solution was poured into water and the crude XII (1.34 g.), m.p. 165–168°, was filtered, washed and dried. Crystallization from acetone–methanol yielded 920 mg. (64%) of XII, m.p. 174–177° dec. The same product was obtained by 24-hour treatment of IIc acetate with 3 equivalents of bromine; analytical sample, m.p. 180–181° dec., $[\alpha]_D$ +100°.

Anal. Calcd. for $C_{23}H_{34}Br_2O_3$: C, 53.29; H, 6.61; Br, 30.84. Found: C, 53.60; H, 6.83; Br, 30.15.

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

(24) Esters of IIc were prepared by Dr. J. Zderic of these laboratories.

2,2-Dimethyl-4-bromotestosterone Acetate (XIII).—Dibromo compound XII (820 mg.) was heated in boiling γ-collidine (5 ml.) for 40 minutes. The cooled mixture was diluted with ethyl acetate, washed with dilute sulfuric acid and the solution evaporated. Methanol–acetone crystallization of the residue yielded 2,2-dimethyl-4-bromotestosterone acetate (XIII), m.p. 151–153°, $[\alpha]_D$ +82°, λ_{max} 262 mμ, log ε 4.07

Anal. Calcd. for $C_{23}H_{33}BrO_3$: Br, 18.27. Found: Br, 17.92.

2,2-Dimethyl-4-bromoandrostan-17β-ol-3-one Acetate (XIV).—IIc acetate (700 mg.) in glacial acetic acid (10 ml.) was brominated with one equivalent of bromine (310 mg. in 3.1 ml. of acetic acid), uptake being complete in 5 minutes. Water precipitation gave the crude 4-bromo compound XIV which was crystallized from acetone–hexane to yield 470 mg. (55%) of XIV, m.p. 142–144° dec.; analytical sample, m.p. 146–148° dec., $[\alpha]_D$ +13° (ethanol).

Anal. Calcd. for $C_{23}H_{35}BrO_3$: C, 62.87; H, 8.02; Br, 18.19. Found: C, 62.59; H, 7.86; Br, 18.47.

2,2-Dimethyltestosterone Acetate (XV).—Treatment of 420 mg. of XIV with 2 ml. of boiling γ-collidine for 1.5 hours followed by ethyl acetate dilution and sulfuric acid wash yielded an oil with λ_{max} 240 mμ, log ε 4.03. The product, in hexane (25 ml.), was absorbed on 20 g. of neutral alumina and then eluted with 50-ml. portions of hexane. Fractions 6 to 13 were recrystallized from acetone–hexane, furnishing XV, m.p. 171–173°, $[\alpha]_D$ +44°, λ_{max} 240 mμ, log ε 4.19.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.23; H, 9.81.

APARTADO POSTAL 2679
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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CVI.[1] Synthesis of 7β-Methyl Hormone Analogs

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RECEIVED AUGUST 6, 1958

The preparation of 7β-methylcortisone *via* addition of methyl Grignard reagent to 7-ketocortisone bisethylene ketal acetate is described. The resulting addition product after hydrolysis and dehydration provided the corresponding 7-methyl-$\Delta^{4,6}$-dienone which upon hydrogenation was converted to 7β-methylcortisone. Alternately 7β-methylcortisone was prepared by hydrolysis of the coupling product of methyl Grignard reagent with 7-bromocortisone bisethylene ketal acetate. Hydride reduction of the Grignard coupling product followed by acid hydrolysis led to 7β-methylhydrocortisone. The synthesis of 7β-methyltestosterone by addition of methyl Grignard to 7-ketotestosterone ethylene ketal acetate is also described.

Previous reports from this Laboratory and others have described the substitution of methyl groups at position 2,[2] 4,[3] 6[4] and 11[5] of the steroid nucleus as well as position 1[6] in the 19-norsteroid series.

In continuation of the general program directed toward the relationship of structural modification to biological activity we now report the preparation of some 7-methyl analogs in the testosterone and cortical hormone series.

Although no 7-methyl-Δ^4-3-ketones have been previously reported, the 7-methylene and 7-methyl-7-hydroxy derivatives of cholesterol have been prepared[7] by the addition of methyl Grignard reagent to the corresponding 7-ketone. In our present work this general method was utilized, but as will be seen the method became impractical in the preparation of the 7-methylcorticoids, forcing employment of an alternate route.

Starting with cortisone bisethylene ketal acetate (Ia) the Lenhard and Bernstein procedure[8] was used to prepare the unstable 7-bromo compound Ib which was then hydrolyzed and oxidized to form 7-ketocortisone bisethylene ketal acetate (Ic) in overall yields of 50 to 60% based on Ia. Reaction of this 7-keto compound with methylmagnesium bromide proceeded in tetrahydrofuran solvent at room temperature and after 5–6 hours appeared almost complete on the basis of ultraviolet spectroscopy.

Treatment of the resulting 7-methyl-7-hydroxy compound Id with a methanolic acetone solution of perchloric acid directly yielded 7-methyl-Δ^6-dehydrocortisone (IIa). The use of perchloric acid catalyst for hydrolysis of the two ethylene ketal groups with concomitant dehydration of the 7-hydroxy groups invariably gave better yields of the dienone IIa than the methanol–sulfuric acid ketal hydrolysis method.[9]

The hydrogenation of the dienone IIa to 7β-methylcortisone (IIIa) was carried out under a variety of conditions, but in no case could a completely selective reduction of the Δ^6-double bond be achieved. When the reductions were stopped after one mole of hydrogen had been consumed, the product was a three-component mixture of IIa, IIIa and presumably 7β-methyldihydroallocortisone which we did not attempt to obtain pure. Only by using 1.2 moles of hydrogen for the reduction was the dienone totally reduced and even so chromatography and recrystallization did not yield a completely pure sample of 7β-methylcortisone. On the basis of the ultraviolet maximum the above product was estimated to be only 80% pure.

The preparation of pure 7β-methylcortisone (IIIa) was accomplished by our second general route which involved the coupling of methylmagnesium bromide and 7-bromocortisone bisethylene ketal acetate (Ib). The product of this reaction

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