NOTES

Steroids. CLXXV. Further Steroidal Anabolic Agents[1]

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The high anabolic–androgenic ratios shown by 2α-methyl and 2-hydroxymethylene dihydrotestosterone (IV and I) and their 17α-methyl derivatives (V and II),[2] as well as by 17β-hydroxy-17α-methylandrostan[3,2,d]2′-methylthiazole (VIII),[3] prompted us to complete the preparation of the analogous compounds in the 17α-ethyl series. At the same time, to help define the necessary conditions for anabolic activity, we took the opportunity to prepare the 2-methyl-Δ^1-derivative.

The incorporation of a 6α-methyl group into testosterone and its 17α-methyl derivative has been reported by several groups.[4,5,6] In the corticoid[7] and progestational series[4,6,8] the 6α-methyl group has a potentiating effect on biological activity, but its influence in the androstane series is less clear. To gain information on this point we have synthesized 6α,17α-dimethyldihydrotestosterone, together with its 2α-methyl and 2-hydroxymethylene derivatives for comparison with the analogous 6-unsubstituted compounds.

For the synthesis of compounds in the 17α-ethyl series, 17α-ethynyl-androst-5-en-3β,17β-diol was hydrogenated over 5% palladium on charcoal to give the corresponding saturated diol in high yield. The conversion of the latter to 17α-ethyl-17β-hydroxy-5α-

(1) Steroids. CLXXIV. P. Crabbé and J. Zderic, *Bull. Soc. Chim. Belg.*, **70**, 403 (1961).

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

(3) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limón, L. Magaña, H. Jiménez, A. Bowers, and H. J. Ringold, *Chem. and Ind.*, 1625 (1960).

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

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

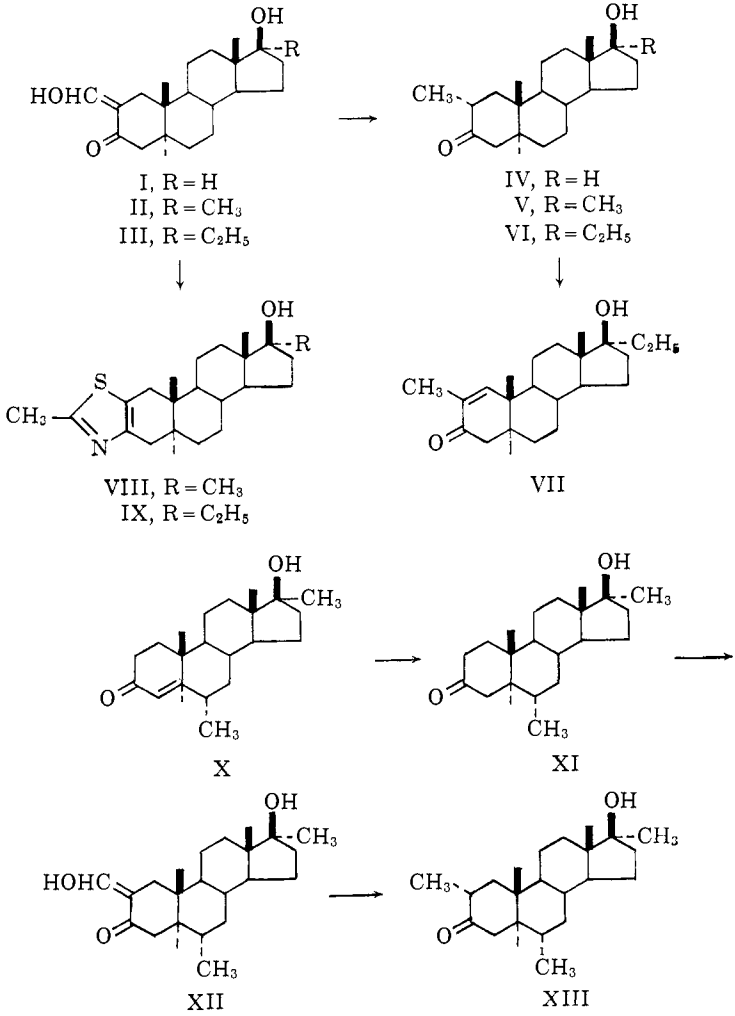
(6) J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 4717 (1958).

(7) G. B. Spero, J. L. Thompson, B. J. Nagerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956).

(8) *Inter alia:* A. David, F. Hartley, D. A. Millson, and V. Petrow, *J. Pharm. and Pharmacol.*, **9**, 929 (1957); H. J. Ringold, J. Pérez Ruelas, E. Batres, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959); S. Bernstein, E. W. Cantrall, and J. P. Duzza, *J. Org. Chem.*, **26**, 269 (1961).

androstan-3-one presented unexpected difficulties.[9] Attempts to effect the oxidation by means of 8 *N* chromium trioxide in acetone or dioxane were defeated by the insolubility of the diol, and the use of chromium trioxide in pyridine and Oppenauer oxidation similarly gave low yields. A number of experiments with N-bromoacetamide in aqueous pyridine eventually led to conditions whereby reproducible yields of 55% were obtained.

Condensation of 17α-ethyl-17β-hydroxy-5α-androstan-3-one with



(9) L. Ruzicka, P. Meister, and V. Prelog [*Helv. Chim. Acta*, **30**, 867 (1947)] obtained a 42% yield by the use of chromium trioxide in acetic acid.

ethyl formate by means of sodium methoxide led to the 2-hydroxymethylene compound III, previously uncharacterized, in excellent yield. Hydrogenation of the latter by an improved procedure over Adams catalyst in the presence of hydrochloric acid[10] gave the 2α-methyl-3-ketone VI in satisfactory yield and this, on bromination followed by dehydrobromination, led to the corresponding Δ^1-compound.

Bromination of the 2-hydroxymethylene-3-ketone III followed by treatment with alkali gave the 2α-bromoketone which, without purification, was condensed with thioacetamide to give the thiazole IX.

In the 6α,17α-dimethyl series, 6α,17α-dimethyltestosterone[6] (X) was reduced by lithium in liquid ammonia to the 4,5-dihydro-5α-compound (XI). Conversion of the latter to the 2-hydroxymethylene derivative (XII) and thence to the 2α-methyl-3-ketone (XIII) was carried out by procedures similar to those described above.

Compounds were tested for androgenic and myotrophic activity in the standard assay,[11] using immature castrate rats.

Compounds in the 17α-ethyl series displayed considerably less androgenic potency and to some extent reduced anabolic activity as compared with the corresponding compounds in the 17α-methyl and 17α-hydrogen series.[2,3]

In the 6α-methyl series, it was found that the introduction of this group did not contribute either to an over-all increase in activity or to a further separation of anabolic and androgenic effects, as compared with the corresponding 6-unsubstituted compounds.[2]

Experimental[12]

17α-Ethyl-5α-androstan-3β,17β-diol.—A solution of 17α-ethynylandrost-5-en-3β,17β-diol (140 g.) in methanol (4.9 l.) was hydrogenated over 5% palladium on charcoal (25 g.) at 2.07 kg./cm.^{2} pressure and 45°. The solution was filtered, washed with methanol and evaporated. The residue was crystallized from chloroform–methanol to give 121 g. of product with m.p. 219–221°. Concentration gave a further 17 g. of material which was crystallized as above to give 7 g. of m.p. 217–220° (total yield, 90%). The reported m.p. is 221–222°.[13,14]

(10) L. H. Knox and E. Velarde, *J. Org. Chem.*, in press.

(11) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Expt. Biol. Med.*, **85**, 175 (1953).

(12) All m.p.'s are corrected. Optical rotations were measured as 1% solutions in chloroform at 25°. Ultraviolet absorption spectra were determined in ethanol solution using a Beckman DK 2 spectrophotometer and infrared absorption spectra were determined in KBr pellets with a Perkin Elmer Model 21 Recording Spectrophotometer equipped with sodium chloride optics. Alumina for chromatography was neutralized by washing with ethyl acetate and activated by heating for 72 hr. at 120°.

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

(14) T. Reichstein and C. Meystre, *Helv. Chim. Acta*, **22**, 728 (1939).

17α-Ethyl-17β-hydroxy-5α-androstan-3-one.—A solution of the above diol (50.0 g.) in pyridine (1.0 l.) and water (100 ml.) was treated with N-bromoacetamide (70.0 g.) and set aside at 5° for 48 hr. The reaction mixture was poured into an iced salt solution (7.0 l.) and the crude product was collected, washed well with water, and dried. Chromatography on alumina (2.0 kg.) and elution with methylene chloride–hexane (3:1) gave 17α-ethyl-17β-hydroxy-5α-androstan-3-one which, after crystallization from acetone–hexane, had m.p. 142–145° (27.5 g., 55%). The reported m.p. is 147–148°.[13]

17α-Ethyl-17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (III).—Sodium methoxide (15.0 g.) was added to a stirred solution of 17α-ethyl-17β-hydroxy-5α-androstan-3-one (25.0 g.) in anhydrous thiophene-free benzene (220 ml.), followed by ethyl formate (25.0 ml.). The suspension was stirred at room temperature for 5 hr., after which the precipitated sodium salt of the hydroxymethylene derivative was collected, washed with benzene and hexane, and dried *in vacuo*. The powdered solid was added in portions with stirring to iced water (200 ml.) containing concd. hydrochloric acid (25 ml.). After 30 min., the product was collected, washed well with water, and dried to give 26.0 g. (95.6%) of material, m.p. 150–157°, λ_{max} 282–284 mμ, log ε 3.93, which was sufficiently pure for subsequent transformations. Crystallization from methylene chloride–hexane gave 22.0 g. (81%) of 17α-ethyl-17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one, m.p. 155–157°. The analytical sample had m.p. 157–159°, $[\alpha]_D$ + 31°, λ_{max} 284 mμ, log ε 3.95, ν_{max} 3540, 2790 (bonded OH), 1640 and 1620 cm.$^{-1}$ (bonded C=O).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89; O, 13.85. Found: C, 76.61; H, 9.74; O, 13.39.

17α-Ethyl-17β-hydroxy-2α-methyl-5α-androstan-3-one (VI).—A solution of the hydroxymethylene derivative III (5.0 g.) in ethanol (75 ml.) containing water (2.5 ml.) and concd. hydrochloric acid (0.25 ml.) was hydrogenated over 5% palladium on charcoal (0.8 g.) at atmospheric pressure and room temperature. Reduction was complete in 30 min. (negative ferric chloride test). The filtered solution was concentrated *in vacuo*, diluted with methylene chloride (100 ml.), washed with water, dried, and evaporated. Crystallization of the residue from hexane gave 1.46 g. of the 2α-methyl-3-ketone IX, m.p. 125–128°. Chromatography on alumina (20 g.) of the residue obtained from the mother liquors gave an additional 0.83 g., m.p. 126–128°, raising the total yield to 48%. For analysis the sample was crystallized further from hexane to m.p. 129–131°, $[\alpha]_D$ + 7°, ν_{max} 3700 (OH) and 1715 cm.$^{-1}$ (C=O).

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

Ringold, *et al.*,[2] report m.p. 128–131°, $[\alpha]_D$ + 6°.

17α-Ethyl-17β-hydroxy-2α-methyl-5α-androst-1-en-3-one (VII).—A solution of bromine (0.74 g.) in acetic acid (7.4 ml.) was added to a solution of the 2α-methyl-3-ketone IX (1.40 g.) in acetic acid (10 ml.) containing sodium acetate (0.35 g.). After 10 min., the solution was poured into iced water and the product was collected, washed with water and dried. The crude 2α-bromo compound, in dimethylacetamide (20 ml.) was added to a suspension of anhydrous calcium carbonate (1.0 g.) in dimethylacetamide (10 ml.) and the mixture was heated under reflux with stirring (45 min.). The cooled solution was filtered and the precipitate was washed with ethyl acetate. The filtrate and washings were evaporated *in vacuo* and poured into water. The product was collected, washed with water, dried and chromatographed on alumina (50 g.). Elution with benzene–hexane

(1:1) and crystallization of the product from pentane gave 300 mg. of VII, m.p. 112–115°, λ_{max} 240 mμ, log ε 3.95.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.94; H, 10.36; O, 9.68. Found: C, 79.72; H, 10.41; O, 9.74.

17α-Ethyl-17β-hydroxyandrostan[3,2,d]2′methylthiazole (IX).—A solution of bromine (2.5 g., 1.1 equiv.) in carbon tetrachloride (18.9 ml.) was added dropwise over 30 min. to a solution of the above hydroxymethylene derivative (5.0 g.) in methanol (65 ml.) containing anhydrous potassium acetate (0.93 g.). When addition was complete, a 1 *N* solution of sodium methoxide in methanol (20 ml.) was added and the mixture was refluxed for 10 min., before being poured into water (500 ml.). The crude 2α-bromo-3-ketone was collected, washed well with water, and dried. It was then dissolved in absolute ethanol (200 ml.), thioacetamide (5.0 g.) was added, and the solution was heated under reflux for 3 hr. After evaporation of the ethanol *in vacuo*, the residue was taken up in ethyl acetate (100 ml.) and washed well with water. Evaporation of the dried ethyl acetate solution and chromatography of the residue on alumina (150 g.) gave, on elution with benzene–hexane (9:1) and subsequent crystallization from acetone–hexane, 1.42 g. of IX (26.2%), m.p. 227–229°, $[\alpha]_D$ + 36°, λ_{max} 254–256 mμ, log ε 3.71. The analytical sample when crystallized from methylene chloride–ether (1:1) had m.p. 232–234°, λ_{max} 254–256 mμ, log ε 3.72, ν_{max} 3490 (OH), 1570 and 1492 cm.$^{-1}$ (thiazole).

Anal. Calcd. for $C_{23}H_{35}NOS$: C, 73.94; H, 9.46; N, 3.75; S, 8.58. Found: C, 73.68; H, 9.51; N, 3.73; S, 8.65.

17β-Hydroxy-6α,17α-dimethyl-5α-androstan-3-one (XI).—A solution of 17β-hydroxy-6α,17α-dimethylandrost-4-en-3-one[6] (5.0 g.) in a mixture of anhydrous dioxane (50 ml.) and ether (75 ml.) was added to a stirred solution of lithium (0.5 g.) in liquid ammonia (800 ml.). Ammonium chloride (1.0 g.) was immediately added and the ammonia was allowed to evaporate. After addition of water (200 ml.), the product was extracted with methylene chloride (3 × 100 ml.). The extracts were washed with water, dried (Na_2SO_4) and evaporated to give a crystalline residue which was chromatographed on alumina (250 g.). Elution with benzene–hexane (4:1), followed by crystallization of the product from acetone–hexane gave 2.80 g. (55.7%) of XI, m.p. 178–180°, $[\alpha]_D$ + 7.5°, ν_{max} 3550 (OH) and 1720 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.04. Found: C, 79.07; H, 10.71; C, 10.02.

17β-Hydroxy-2-hydroxymethylene-6α,17α-dimethyl-5α-androstan-3-one (XII).—Ethyl formate (4.0 ml.) was added to a solution of XI (2.50 g.) in anhydrous thiophene-free benzene (50 ml.), containing sodium methoxide (1.5 g.). The suspension was stirred at room temperature for 5 hr., after which the precipitated sodium salt of the 2-hydroxymethylene derivative was filtered, washed with benzene and hexane, and dried *in vacuo*. The salt was dissolved in water (300 ml.), the solution was extracted with methylene chloride (3 × 100 ml.) and the combined extracts were washed well with water, dried (Na_2SO_4) and evaporated. Crystallization of the residue from acetone–hexane gave 2.06 g. (75.7%) of XII, m.p. 197–199°, $[\alpha]_D$ + 50.3°. The analytical sample had m.p. 199–200° (methylene chloride–ether), $[\alpha]_D$ + 50.2°, λ_{max} 282–284 mμ, log ε 3.97, ν_{max} 3330, 2730 (bonded OH), 1700 (C=O) and 1622 cm.$^{-1}$ (bonded C=O).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89; O, 13.85. Found: C, 75.98; H, 9.99; O, 13.95.

17β-Hydroxy-2α,6α,17α-trimethyl-5α-androstan-3-one (XIII).—A solution of XII (1.5 g.) in ethanol (150 ml.) containing water (0.6 ml.) and concd. hydrochloric acid (0.08 ml.) was hydrogenated over 5% palladium on charcoal (0.5 g.) at room temperature and atmospheric pressure. Reduction was complete in 30 min. (negative ferric chloride test). The filtered solution was evaporated and the residue chromatographed on washed alumina (75 g.). Elution with benzene–hexane (70:30), and crystallization of the product from acetone–hexane gave 900 mg. (62.5%) of XIII, m.p. 138–140°, $[\alpha]_D$ + 7.2°. Further crystallization gave a product of m.p. 140–141°, $[\alpha]_D$ + 7.5°, ν_{max} 3690 (OH) and 1720 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91; O, 9.62. Found: C, 79.27; H, 10.76; O, 9.89.

Spasmolytic 1,2,5-Trisubstituted Pyrroles

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In previous papers,[1] it has been shown that 1,2,5-trisubstituted pyrroles bearing a basic radical in position 1 are endowed with spasmolytic activity, especially of the musculotropic type, the most active substance of that series so far encountered being 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-phenylpyrrole (I); this compound[2] has since proven to be a useful antispasmodic, especially in dysmenorrhea and spasms of Oddi's sphincter.

It was of interest to introduce variations in the nature of the substituent both in position 1 and in position 5, to see whether the main pharmacologic features would be maintained. Six new compounds of this type are now reported, of which five bear a dialkylaminoalkyloxy chain in the *ortho* position on the 1-aryl substituent; earlier studies had shown this structure to be the most favorable one for pharmacologic activity.

Knorr–Paal condensation[3] of 1-*p*-tolyl-1,4-pentanedione with *o*-aminophenol yielded 1-(*o*-hydroxyphenyl)-2-methyl-5-*p*-tolylpyrrole, whose β-diethylaminoethyl ether (II) is a methyl homolog of compound I. With 2-amino-4-chlorophenol, 1-phenyl-1,4-pentanedione

(1) N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, **1**, 23, 319 (1959); **2**, 335 (1960).

(2) Trademark Leioplegil®.

(3) C. Paal, *Ber.*, **18**, 2254 (1885); L. Knorr, *Ann.*, **236**, 313 (1886).