The fraction obtained with 25% ethyl acetate in benzene gave, after recrystallization from acetone, VIII, m.p. 205–208° $[\alpha]^{20}D$ −16° (*c* 10.310); infrared maxima ν_{max} 3500 (hydroxyl), 1045, 1040 (equatorial 3β- and 17α-OH groups), 1103 cm.$^{-1}$ (methoxy group).

Anal. Calcd. for $C_{23}H_{40}O_3$: C, 75.77; H, 11.06. Found: C, 75.91; H, 11.09.

16α-Methoxy-17a,17a-dimethyl-D-homoandrostane-3,-17-dione (IX) from V and VI.—To the solution of 150 mg. of V in 50 ml. of methylene chloride was added the solution of 200 mg. of chromic trioxide in 2 ml. of 80% acetic acid, and the reaction mixture was shaken for 24 hours at room temperature. The excess chromic oxide was reduced with a few drops of saturated aqueous sodium hydrogen sulfite solution and then the methylene chloride solution was washed with water to neutrality, dried and evaporated. The noncrystalline residue was chromatographed and the fractions with 5% ethyl acetate–benzene gave, after recrystallization from ether, 120 mg. of IX, m.p. 216–221° (transformation 195–205°); infrared absorption maxima: ν_{max} 1710 (keto groups), 1400, 1386, 1380, 1335, 1170, 955 (isopropyl group), 1122 cm.$^{-1}$ (methoxy group). The oxidation of VI gave the same product.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.47; H, 10.21.

16α-Methoxy-17a,17a-dimethyl-D-homoandrostane-3,-17-dione (IX) from VII.—The oxidation was carried out in exactly the same way with double the amount of chromic acid solution, and after chromatography and recrystallization, the product was identical with IX, described above.

2,2-Dibromo-17a,17a-dimethyl-D-homoandrostane-3,-17-dione (XII) from XI.—To the solution of 150 mg. of XI[2] in 50 ml. of anhydrous ether was added a few drops of 38% hydrobromic acid in acetic acid, the solution cooled to 0°, and the solution of 0.047 ml. of bromine in 2 ml. of acetic acid was added dropwise under vigorous stirring. After one mole-equivalent of bromine was added, further addition caused the precipitation of dibromide XII. After all the bromine was added, the resulting suspension was stirred for an additional half-hour. The precipitated product was filtered off and washed with ether, m.p. 233–234°, λ_{max} 318 and 291 mμ; infrared absorption maxima: ν_{max} 1728 (3-ketone), 1705 (17-ketone), 1394, 1384, 1379, 1163, 965 (isopropyl group), 762 (bromine).

2-Chloro-17a,17a-dimethyl-D-homoandrost-1-ene-3,17-dione (XIII) from XII.—To the solution of 150 mg. of XII in 10 ml. of dimethylformamide was added 100 mg. of anhydrous lithium chloride and the reaction mixture was then heated for 2 hours at 100°. After cooling, the reaction mixture was poured into a large excess of water, the crystalline precipitate was filtered off, washed with water, and dried. The product was chromatographed and the fractions with 1 and 2% ethyl acetate in benzene gave, after recrystallization from ether, XIII, m.p. 244–248°, λ_{max} 247 mμ; infrared absorption maxima ν_{max} 1730 (3-ketone); 1705 (17-ketone), 797 cm.$^{-1}$ (chlorine).

Anal. Calcd. for $C_{22}H_{31}O_2Cl$: C, 72.80; H, 8.62. Found: C, 72.97; H, 8.62.

17a,17a-Dimethyl-D-homoandrostane-3,17-dione (XI) from XIII.—To the solution of 50 mg. of XIII in 10 ml. of glacial acetic acid was added 50 mg. of zinc powder and the reaction mixture was refluxed for two hours under nitrogen. After cooling, the zinc was filtered off, washed with a large excess of ethyl acetate, then the filtrate was washed with water, 2 *N* sodium hydroxide solution, and again with water, dried over sodium sulfate and evaporated. The noncrystalline residue was chromatographed and the fraction with 1 and 2% ethyl acetate in benzene gave, after recrystallization from methanol, XI, m.p. 202–205°, which had the infrared spectrum identical with the spectrum from authentic material.[2]

Quinoxalo[2,3-b]-17a,17a-dimethyl-D-homoandrostan-17-one (XIV) from XIII.—To the solution of 5 mg. of XIII in 1 ml. of glacial acetic acid was added 2 mg. of *o*-phenylenediamine, and the reaction mixture was refluxed for 2 hours under nitrogen. After cooling, 50 ml. of chloroform was added, the chloroform solution was washed with 2 *N* hydrochloric acid and water, dried over sodium sulfate and evaporated. The residue crystallized from ether, giving XIV, m.p. 230–233°, λ_{max} 238 and 332 mμ.

WORCESTER, MASS.

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

Steroids. CXXXIII.[1] B-Homo-androstane Derivatives

BY H. J. RINGOLD

RECEIVED JULY 20, 1959

Platinum reduction of the cyanohydrin of 7-ketoandrostane-3β,17β-diol diacetate gave the aminomethyl compound which underwent ring expansion on treatment with nitrous acid. The resultant B-homoketone IV, on Wolff–Kishner reduction, gave B-homoandrostane-3β,17β-diol (Va) oxidized to the dione VII, while selective saponification of V-diacetate followed by oxidation and hydrolysis gave B-homodihydrotestosterone (VI). Biological activities of VI and VII are described.

As a continuation of the investigation in these laboratories of the relationship of structural changes to biological activity in the androgen series it was of interest to prepare an androstane derivative with a seven-membered ring B, a hitherto unknown structure. A-Homo-[2] and D-homo-dihydrotestosterone[3] have been reported, the former exhibiting a very low order of androgenic activity[2] while the latter compound was found to be about as androgenic as dihydrotestosterone.[3] We and others have described the synthesis of 2-[4], 4-[5], 6-[6] and 7-[7] alkyltestosterone derivatives.

This paper presents the synthesis of B-homoandrostane-3β,17β-diol (Va), B-homodihydrotestosterone (VI) and B-homoandrostane-3,17-dione (VII) from Δ[5]-androstene-3β,17β-diol diacetate (I) by a straight-forward route.[8] Treatment of I with N-bromosuccinimide in boiling carbon tetrachloride gave the allylic 7-bromo compound which was hydrolyzed to the 7-hydroxy derivative(s) by stirring with alumina and finally con-

(1) Paper CXXXII, J. Edwards and H. J. Ringold, THIS JOURNAL, **81**, 5262 (1959).

(2) M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta*, **26**, 288 (1943).

(3) M. W. Goldberg and R. Monnier, *ibid.*, **23**, 376, 840 (1940).

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

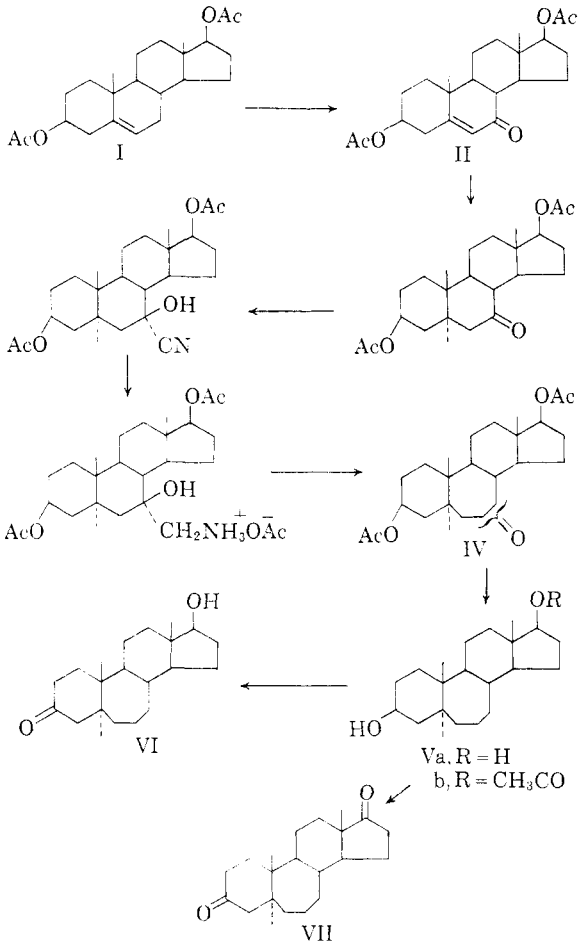
(5) J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, *ibid.*, **78**, 5662 (1956); F. Sondheimer and Y. Mazur, *ibid.*, **79**, 2906 (1957); N. W. Atwater, *ibid.*, **79**, 5315 (1957); H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957).

(6) H. J. Ringold, E. Batres and G. Rosenkranz, *ibid.*, **22**, 99 (1957); J. A. Campbell, J. C. Babcock and J. A. Hogg, THIS JOURNAL, **80**, 4717 (1958); G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957), and earlier references therein.

(7) J. A. Zderic, H. Carpio and H. J. Ringold, THIS JOURNAL, **81**, 432 (1959).

(8) Presented in part at the 129th Meeting of the American Chemical Society, Dallas, Tex., April, 1956.

verted to the known 7-keto-Δ^5-androstene-3β,17β-diol diacetate[9a,b] (II) in 57% over-all yield by chromic acid oxidation of the allylic alcohol.[10] Stereospecific hydrogenation of II to the dihydro-allo (5α)-derivative III over a palladium–carbon catalyst in methanol solution offered an initial difficulty which was overcome by the addition of a small amount of pyridine to the hydrogenation mixture. Under these conditions up to a 90% yield of 7-keto-androstane-3β,17β-diol diacetate[9b] (III) was obtained while in the absence of pyridine the yield was only of the order of 50%, cursory examination of the product under the latter conditions indicating some reduction of the 7-keto function.



Treatment of III with acetone cyanohydrin in the presence of a few drops of 10% sodium hydroxide gave the 7-cyanohydrin. Ercoli and de Ruggieri[11] reported the preparation of 17-cyanohydrins by this exchange procedure either in the absence of catalyst or in the presence of a small amount of base such as ammonium hydroxide or potassium carbonate. It was of interest that no reaction occurred in our case with carbonate catalysis but reaction was smooth in the presence of sodium hydroxide.

The assignment of the 7β-hydroxy-7α-cyano structure to the cyanohydrin is based on the assumption that C–N would add from the less hindered α-face of the molecule to give the 7β-equatorial alcohol. The opposite cyanohydrin configuration or the possibility that the product is a mixture of two isomers cannot be definitely excluded.

The crude cyanohydrin in glacial acetic acid was hydrogenated over a platinum catalyst at atmospheric pressure and room temperature and the acetic acid solution of the intermediate amine acetate directly treated with sodium nitrite to give the B-homoketone IV by Tiffeneau rearrangement.[2,12] On the basis of available information the ketone function cannot be definitely assigned to the 7- or 7a-position of ring B. Although in the first reactions, IV was separated by reaction with Girard reagent T[13] it was later found possible to isolate the compound in about 50% yield by direct crystallization.

Modified Wolff–Kishner reduction of IV in a mixture of ethylene glycol–diethylene glycol[14] gave B-homoandrostane-3β,17β-diol (Va).[15] Conversion of the diol to its 3,17-diacetate (an oil) followed by mild hydrolysis with methanolic potassium hydroxide at 0° gave a mixture of the 17-monoacetate Vb and recovered diol, a mixture readily separated by chromatography. Oxidation of Vb with chromic acid gave B-homodihydrotestosterone acetate as an oil, but saponification gave crystalline B-homodihydrotestosterone (VI). Oxidation of the diol V gave B-homoandrostane-3,17-dione (VII).

In the 21-day old castrate rat (7 day assay, *subcutaneous route*) B-homodihydrotestosterone exhibited androgenic activity equal to testosterone, as measured by the prostate and seminal vesicles, while the myotrophic activity (levator ani increase) was twice that of testosterone.[16] In the same assay, B-homoandrostanedione (VII) exhibited an activity characteristic of androstane-3,17-dione, namely, marked stimulation of the ventral prostate with very little stimulation of the seminal vesicles. It may be concluded thus that in the androstane series the change from a six- to a seven-membered B ring exerts minimal influence on androgenic activity. Since molecular models of B-homodihydrotestosterone and B-homoandrostanedione reveal considerable distortion of rings B and C and none of ring A it would appear that, in the presence of the proper steric environment in ring A, distortion in the center of the steroid molecule and hence lack of close enzyme "fit" in the center does not significantly influence androgenic and myotrophic activity.

(9) (a) A. Butenandt, E. Hausmann and J. Paland, *Ber.*, **71**, 1316 (1938); (b) K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **35**, 284 (1952).

(10) This three-step procedure has been previously utilized for the preparation of 7-ketodiosgenin acetate (H. J. Ringold, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3318 (1952)), while R. H. Lenhard and S. Bernstein, *ibid.*, **78**, 989 (1956), have prepared 7-keto-Δ^5-3-cycloethylenedioxy derivatives by the same sequence.

(11) A. Ercoli and P. de Ruggieri, THIS JOURNAL, **75**, 650 (1953).

(12) M. Tiffeneau, P. Weill and B. Tchoubar, *Compt. rend.*, **205**, 54 (1937); B. Tchoubar, *ibid.*, **212**, 195 (1941); B. Tchoubar, *Bull. soc. chim.*, 160 (1949).

(13) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936); T. Reichstein, *ibid.*, **19**, 1107 (1936).

(14) *Cf.* Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(15) The possibility cannot be excluded that inversion occurred at C-8 during the ring enlargement or during the Wolff–Kishner step yielding compounds with the abnormal 8α-hydrogen configuration.

(16) Bioassays by The Endocrine Laboratories, Madison, Wisc.

Experimental[17]

Δ^5-Androstene-3β,17β-diol-7-one Diacetate (II).—To a solution of 10 g. of Δ^5-androstene-3β,17β-diol diacetate[18] (I) in 100 ml. of hot carbon tetrachloride 5.05 g. of N-bromosuccinimide was added and the mixture boiled for 10 min. under reflux with exposure to strong light. The mixture was rapidly cooled in an ice-bath, the succinimide (2.64 g.) filtered and 75 g. of ethyl acetate-washed alumina added to the solution which was then stirred for 2 hours at room temperature. The solution was filtered, the alumina thoroughly washed with acetone and the combined filtrates evaporated to dryness *in vacuo*. The residue was dissolved in 200 ml. of 85% acetic acid, treated dropwise over a 30-min. period with a solution of 1.89 g. of chromium trioxide in 45 ml. of 85% acetic acid and the mixture allowed to stand for 48 hours before pouring into ice-water. The crude II was filtered, washed, dried and crystallized from methanol yielding 5.9 g. (57%) of pure Δ^5-androstene-3β,17β-diol-7-one diacetate, m.p. 224–226°, λ_{max} 236 mμ, log ϵ 4.14, $[\alpha]_D$ −128° (reported[9b] m.p. 219–221°, λ_{max} 237 mμ, log ϵ 4.15, $[\alpha]_D$ −125°).

Androstane-3β,17β-diol-7-one Diacetate (III).—A suspension of 10 g. of II and 3 g. of 10% palladium–carbon catalyst containing 0.5 ml. of pyridine was hydrogenated at 570 mm. and 25° until hydrogen uptake ceased which occurred in various runs with the absorption of 0.98 to 1.05 equivalents in 2 to 4 hours. The mixture was filtered, the catalyst washed with a few ml. of chloroform and the filtrate concentrated to incipient crystallization and cooled, yielding 8.6 g. of III, m.p. 195–197°, $[\alpha]_D$ −45°, no selective absorption in the ultraviolet region (reported[9b] m.p. 192–193°, $[\alpha]_D$ −39°).

B-Homoandrostane-3β,17β-diol-ξ-one Diacetate (IV).—A solution of 10 g. of III in 30 ml. of acetone cyanohydrin and 0.5 ml. of 10% aqueous sodium hydroxide was allowed to react at room temperature for 2 hours and then poured into 1 l. of ice-water containing 2 ml. of acetic acid. The mixture was vigorously stirred whereupon the oil which had separated slowly solidified. After standing overnight at room temperature, the precipitate subsequently was filtered, washed with water and dried, yielding 10.5 g. of crude cyanohydrin (m.p. 137–142° dec. *Anal.* Calcd. for $C_{24}H_{35}NO_5$: N, 3.4. Found: N, 3.6) which was taken up in 200 ml. of glacial acetic acid and hydrogenated over 3 g. of pre-reduced Adams[19] catalyst at 570 mm. and 25°. Uptake of hydrogen ceased after 70 min. with the absorption of 1.9 molar equivalents. The mixture was diluted with 1 l. of water, filtered through Celite and the clear solution of intermediate aminomethyl acetate cooled to −5° and treated dropwise with stirring with a cold solution of 20 g. of sodium nitrite in 100 ml. of water, care being taken that the temperature of the reaction mixture did not exceed 0°. The solution was then allowed to warm to room temperature and stand overnight. The resultant precipitate was filtered, washed and recrystallized from methanol yielding 5.4 g. of pure B-homo ketone IV, m.p. 200–203°, $[\alpha]_D$ −67°, infrared maxima 1700 and 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 70.92; H, 8.98.

B-Homoandrostane-3β,17β-diol (Va).—A solution of 5 g. of IV, 15 ml. of hydrazine hydrate, 50 ml. of ethylene glycol and 50 ml. of diethylene glycol was boiled for 2 hours and then cooled. Potassium hydroxide (12 g.) in water (12 ml.) was added, the solution slowly distilled until the internal temperature of the reaction mixture reached 195° and the boiling solution, then, under condenser, kept at 195–200° for 2.5 hours. The cooled solution was poured into salt water and the crude B-homoandrostane-3β,17β-diol filtered, dried and crystallized from acetone and then ethyl acetate yielding 2.7 g. of Va as a hydrate, m.p. 153–155°, $[\alpha]_D$ +33°, hydroxyl only in the infrared.

Anal. Calcd. for $C_{20}H_{34}O_2 \cdot H_2O$: C, 74.02; H, 11.19. Found: C, 74.50; H, 11.11.

B-Homoandrostane-3β,17β-diol 17-Monoacetate (Vb).—The diol Va (5.25 g.) in 50 ml. of pyridine–acetic anhydride (1:1) was heated for 2 hours at 90° and the cooled solution then poured into water. Extraction with methylene dichloride followed by successive washes with dilute hydrochloric acid, bicarbonate and water gave the 3,17-diacetate (6.1 g.) as an oil which did not exhibit hydroxyl band in the infrared. The oil was taken up in 100 ml. of methanol, cooled to 0°, treated with 2.0 g. of potassium hydroxide in 10 ml. of water and allowed to stand for 8 hours at 0–5°. The solution was neutralized with acetic acid, concentrated *in vacuo* and then poured into water. The reaction product, after isolation by methylene dichloride extraction, was chromatographed on 100 g. of silica, whence elution with benzene–ether (4:1) gave 2.27 g. of the desired 17-monoacetate Vb, m.p. 115–120°, while benzene–ether (3:2) gave 730 mg. of recovered diol Va. The analytical specimen of Vb, from ethyl acetate crystallization, exhibited m.p. 117–120°, $[\alpha]_D$ +25°, and exhibited both acetate (1736 cm.$^{-1}$) and hydroxyl in the infrared.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41; O, 14.06. Found: C, 75.54; H, 10.45; O, 14.07.

B-Homodihydrotestosterone (VI).—A solution of 0.5 g. of B-homoandrostane-3β,17β-diol 17-acetate (Vb) in 20 ml. of 80% acetic acid was treated with 250 mg. of chromium trioxide in 10 ml. of 80% acetic acid. The solution was allowed to stand for 1 hour at 25° before pouring into water. Extraction with chloroform gave B-homodihydrotestosterone acetate as an oil which, without purification, was saponified by 1-hour treatment with 50 ml. of boiling 1% methanolic potassium hydroxide. The solution was neutralized with acetic acid, the solvent removed *in vacuo* and water added. The crude VI was filtered, dried and purified by chromatography on 20 g. of neutral alumina. The benzene–ether (9:1) fractions were pooled and crystallized first from acetone–water and then acetone–hexane to give 60 mg. of B-homodihydrotestosterone (VI) melting at 142–146°, $[\alpha]_D$ +37°, infrared maximum 1712 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 79.09; H, 10.57.

B-Homoandrostane-3,17-dione (VII).—A solution of 1.95 g. of B-homodiol Va in 200 ml. of 90% acetic acid was treated over a 10-min. period with 1.5 g. of chromium trioxide in 50 ml. of 90% acetic acid. After standing for 3 hours at 25°, the solution was poured into water, the product extracted with methylene dichloride, the extract washed to neutrality with water and bicarbonate and concentrated to dryness. The residue crystallized from acetone–hexane to yield 1.43 g. of B-homoandrostane-3,17-dione (VII), m.p. 109–115°. The analytical specimen, obtained from the same solvent, exhibited m.p. 113–116°, $[\alpha]_D$ +119°, infrared maxima 1718 and 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.65; H, 9.67.

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(17) Melting points are uncorrected. Rotations were determined in chloroform, ultraviolet absorption spectra in 96% ethanol and infrared spectra in carbon disulfide solution. Thanks are due Mr. P. Lehmann for technical assistance and to Mr. E. Avila for determination of physical constants.

(18) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

(19) R. Adams, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 452.