943. *Urinary Steroids and Related Compounds. Part I. 11-Substituted Derivatives of Androsterone.*

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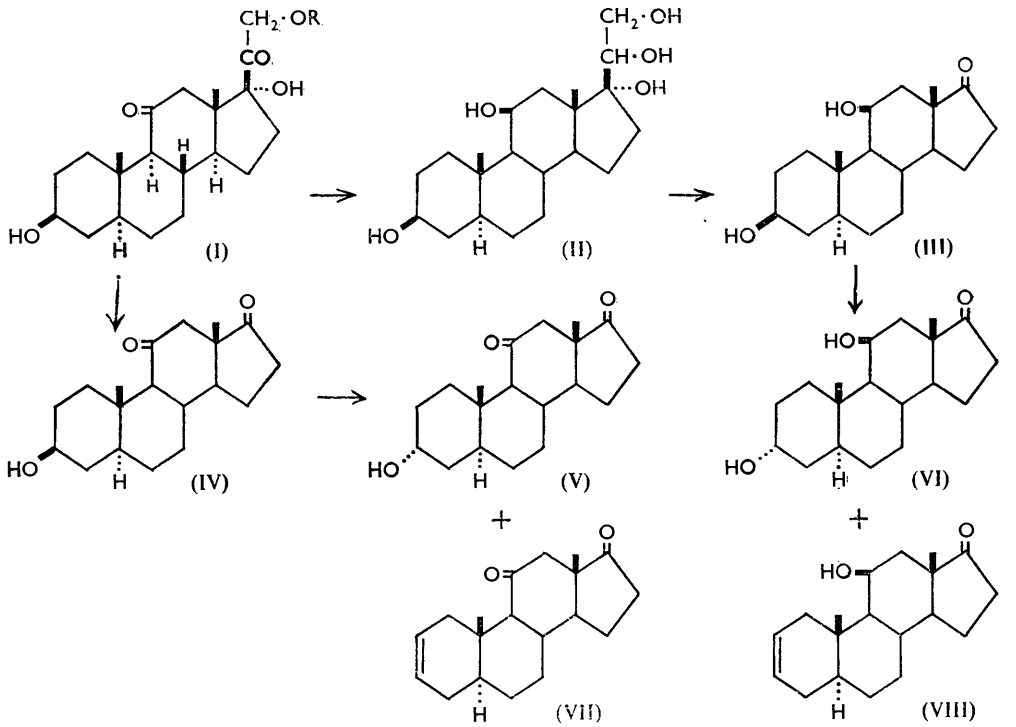
Partial syntheses of 11β-hydroxyandrosterone (3α : 11β-dihydroxy-5α-androstan-17-one) and 11-oxoandrosterone (3α-hydroxy-5α-androstane-11 : 17-dione) are described.

THE compounds commonly described in biochemical literature as 11-hydroxyandrosterone (VI) and 11-keto(or oxo)androsterone (V) are minor but common constituents of human urine. The 11-hydroxy-compound was first isolated by Mason [1] and the 11-oxo-compound by Lieberman, Fukushima, and Dobriner.[2] (For further references to the presence of these compounds in urine, see ref. 3.) No partial synthesis of these two urinary steroids has hitherto been described in the literature (except for the oxidation of the 11-hydroxy- to the 11-oxo-compound); syntheses from a member of the 5α-pregnane series are now reported.



3β : 17α : 21-Trihydroxy-5α-pregnane-11 : 20-dione (I; R = H) on oxidation with sodium bismuthate in glacial acetic acid [4] gave 3β-hydroxy-5α-androstane-11 : 17-dione [5] (IV) in 68% yield. The toluene-*p*-sulphonate of this, on solvolysis with sodium acetate in acetic acid, followed by alkaline hydrolysis,[6] yielded by inversion at $C_{(3)}$ the desired 3α-isomer (V) (25%) and by elimination the related 2-ene (VII) (49%).

[1] Mason, *J. Biol. Chem.*, 1945, **158**, 719; Mason and Kepler, *ibid.*, 1945, **161**, 235.
[2] Liebermann, Fukushima, and Dobriner, *ibid.*, 1950, **182**, 299.
[3] Dorfman and Shipley, "Androgens," John Wiley and Sons, Inc., New York, 1956.
[4] Brooks and Norymberski, *Biochem. J.*, 1953, **55**, 371.
[5] Steiger and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 817.
[6] Plattner and Furst, *ibid.*, 1943, **26**, 2266; Iriarte, Rosenkrantz, and Sondheimer, *J. Org. Chem.*, 1955, **20**, 542.

Solvolysis of the toluene-*p*-sulphonate of 3β : 11β-dihydroxy-5α-androstan-17-one [7] (III) [prepared from the 11 : 20-dione (I; R = Ac) by reduction with lithium aluminium hydride and oxidation with bismuthate] similarly yielded the 3α : 11β-dihydroxy-17-ketone (VI) accompanied by the 2-ene (VIII).

Samples of the partially synthetic 11-hydroxy- and 11-oxo-androsterone were kindly compared by Dr. A. E. Kellie (Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London) with samples isolated from urine, on the basis of the R_F values of the free 17-oxo-steroids and their Zimmermann complexes when run on paper chromatograms in the Bush B_1 system.[8] By these criteria, the corresponding compounds were identical. Comparisons of infrared spectra in carbon disulphide were also made. In the case of 11β-hydroxyandrosterone (run as the acetate) the records were identical. The 11-oxoandrosterone samples gave identical spectra in the carbonyl region; comparison in other regions confirmed the opinion that the material isolated from urine was impure.

Experimental

M. p.s were determined on a hot stage and are corrected.

Specific rotations were determined in chloroform (except where stated otherwise) for the sodium D line, in a 1 dm. micro-tube, at room temperature (18—25°). Analytical samples were dried at 80° (unless stated otherwise).

Chromatography was carried out with alumina supplied by Savory and Moore, Ltd., of activity II—III.[9]

Infrared spectra were determined with a Perkin-Elmer model 21 double-beam spectrophotometer, by kind permission of Dr. G. D. Meakins, Manchester.

"Working up in the usual manner" implies washing the organic layer with water, 2N-sulphuric acid, water, saturated sodium hydrogen carbonate solution, and then water until washings are neutral.

Light petroleum refers to the fraction of b. p. 60—80°.

5α-Pregnane-3β : 11β : 17α : 20β : 21-pentaol (II).—A solution of 21-acetoxy-3β : 17α-dihydroxy-5α-pregnane-11 : 20-dione (I; R = Ac) (1 g.) in dry tetrahydrofuran (25 c.c.) was added dropwise to a suspension of lithium aluminium hydride (0·5 g.) in dry tetrahydrofuran (100 c.c.) heated under reflux, further tetrahydrofuran (50 c.c.) was added, and heating continued for 2 hr. Excess of reagent was destroyed, and the reaction mixture acidified to *ca.* pH 4. After removal of solvent by evaporation, and addition of water, the product was isolated by continuous extraction with chloroform (3 hr.). Evaporation to dryness gave a gummy solid which on crystallization from alcohol, and then methyl alcohol, yielded the pentaol, m. p. 211—218°, $[\alpha]_D$ +16° (*c* 0·85 in EtOH), $[M]_D$ +59°. Reichstein [10] gives m. p. 221—222°, $[\alpha]_D$ +16° in EtOH, and Kemp *et al.*[7] m. p. 201—208°. Infrared spectrum (in Nujol): broad bands, $\nu_{max.}$ 3475 and 1020, 1049 cm.$^{-1}$ (OH).

3β : 11β-Dihydroxy-5α-androstan-17-one (III).—21-Acetoxy-3β : 17α-dihydroxy-5α-pregnane-11 : 20-dione (I; R = Ac) (5 g.) was reduced with lithium aluminium hydride (as described above) to yield crude pentaol (3·7 g.); to a solution of this, presumably a mixture of 20β- and 20α-epimers, in 50% aqueous acetic acid (1 l.) sodium bismuthate (50 g.) was added. The whole was protected from light and shaken for 1·5 hr. A solution of sodium metabisulphite (20 g.) in water (200 c.c.) was added and shaking continued for 30 min. After the addition of 3N-sodium hydroxide (1 l.) the steroid was isolated with ether–chloroform, and the organic layer washed with 3N-sodium hydroxide and water. Evaporation to dryness yielded a colourless solid (2·64 g.), which crystallized from acetone, to yield the diolone (1·65 g.), m. p. 228—233°; further material was obtained by crystallization, and chromatography from the mother-liquors. Further samples had m. p. 230—234° and 234—238°, $[\alpha]_D$ +81° (*c* 0·82), $[M]_D$ +249°, and $[\alpha]_D$ +83° (*c* 1 in EtOH), $[M]_D$ +254° {reported [7] m. p. 234—235°, $[\alpha]_D$ +84° (in EtOH)}. Infrared spectrum (in Nujol): $\nu_{max.}$ 3395, 3349 (OH), 1042 (equatorial OH), and 1720 cm.$^{-1}$ (CO). It is of interest that bands at *ca.* 1045 and 1000 cm.$^{-1}$ (3β equatorial, and 3α axial OH respectively) can be clearly distinguished in the spectra of compounds (III) and (VI), in spite of the presence in these compounds of an additional (axial) hydroxyl group at the 11β-position.

[7] Reichstein, *Helv. Chim. Acta*, 1936, **19**, 402; von Euw and Reichstein, *ibid.*, 1942, **25**, 988; Kemp, Kappas, Salamon, Herling, and Gallagher, *J. Biol. Chem.*, 1954, **210**, 123.
[8] Bush, *Biochem. J.*, 1952, **50**, 370; Kellie and Smith, *Nature*, 1956, **178**, 323.
[9] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.
[10] Reichstein, *Helv. Chim. Acta*, 1936, **19**, 29.

11β-*Hydroxy*-3β-*toluene*-p-*sulphonyloxy*-5α-*androstan*-17-*one*.—A solution of 3β : 11β-dihydroxy-5α-pregnan-17-one (1·76 g.) and freshly crystallized toluene-*p*-sulphonyl chloride (1·7 g.) in dry pyridine (8 c.c.) was kept at room temperature overnight. Excess of reagent was decomposed with iced water, and the steroid worked up *via* ether–chloroform in the usual manner; drying and evaporation of the solvent yielded a gum (2·55 g.). Trituration with ether afforded 11β-*hydroxy*-3β-*toluene*-p-*sulphonyloxy*-5α-*androstan*-17-*one* (1·41 g.) as prisms, m. p. 149—153°, and a second crop (460 mg.), m. p. 147—148°. The analytical sample had m. p. 150·5—153°, $[\alpha]_D$ +41° (*c* 1·64), $[M]_D$ +193° (Found : C, 67·95; H, 7·9. $C_{26}H_{36}O_5S$ requires C, 67·8; H, 7·9%).

11β-*Hydroxy*-5α-*androst*-2-*en*-17-*one* (VIII).—A solution of the foregoing ester (1·72 g.) and anhydrous sodium acetate (1·72 g.) in acetic acid (34 c.c.) was heated under reflux for 2 hr., then kept at room temperature for 24 hr. After removal of the acetic acid *in vacuo*, isolation *via* ether–chloroform yielded a gum, which was hydrolysed by hot 5% methanolic potassium hydroxide. The product was worked up in the usual manner in ether–chloroform, and evaporation to dryness yielded a partially crystalline gum (1·06 g.), which was chromatographed in benzene on alumina (30 g.). Elution with benzene and benzene–ether (50 : 1 and 20 : 1) yielded 11β-*hydroxy*-5α-*androst*-2-*en*-17-*one* (580 mg.) crystallizing from acetone–pentane as needles, m. p. 129—133°. Further recrystallizations gave a sample, m. p. 132·5—134°, $[\alpha]_D$ +118° (*c* 0·81), $[M]_D$ +342° (Found : C, 79·4; H, 10·0. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%). Infrared spectrum (in Nujol) : $\nu_{max.}$ 3440 (OH), 1714 (CO), and 1653, 777 cm.$^{-1}$ (2-ene). This compound gave a yellow colour with tetranitromethane.

3α : 11β-*Dihydroxy*-5α-*androstan*-17-*one* (VI).—Further elution of the foregoing chromatogram with benzene–ether (5 : 1 to 1 : 1) yielded the 3α : 11β-diol-17-one (430 mg.), crystallizing from acetone–ether–light petroleum as prisms, m. p. 197—200°, $[\alpha]_D$ +81° (*c* 0·9), $[M]_D$ +249°, and $[\alpha]_D$ +99° (*c* 0·8 in EtOH), $[M]_D$ +309° {Mason and Kepler [1] give m. p. 199—200°, $[\alpha]_D$ +98° (in EtOH)}. Infrared spectrum (in Nujol) : $\nu_{max.}$ 3492, 3344 (OH), 1000 (axial OH), and 1728 cm.$^{-1}$ (CO) (cf. Dobriner, Katzenellenbogen, and Jones,[11] compound 165).

3β : 17α : 21-*Trihydroxy*-5α-*pregnane*-11 : 20-*dione* (I; R = H).—Concentrated hydrochloric acid (10·5 c.c.) was added, with cooling, to a solution of 21-acetoxy-3β : 17α-dihydroxy-5α-pregnane-11 : 20-dione (I; R = Ac) (5 g.) in chloroform (50 c.c.), methyl alcohol (175 c.c.), and water (17 c.c.), and the mixture kept at room temperature for 48 hr. (cf. Mattox and Kendall [12]); after the addition of water (600 c.c.) the whole was kept at 4° for 24 hr., and the resulting precipitate was filtered off, washed with water and chloroform, and dried, to give the crude triol-dione (3·62 g.), crystallizing from acetone as prisms (1·95 g.), m. p. 237—244° (decomp.), $[\alpha]_D$ +70° (*c* 1·1 in EtOH), and a second crop (0·98 g.), m. p. 231—237° (decomp.) (Reichstein [7,10] gives m. p. 238—242°, $[\alpha]_D$ +66° in EtOH). Ether–chloroform extraction of the filtrate yielded a gum (0·86 g.), crystallizing to give further material (310 mg.), m. p. 222—228° (decomp.).

3β-*Hydroxy*-5α-*androstane*-11 : 17-*dione* (IV).—Sodium bismuthate (30 g.) was added to a solution of the foregoing triol-dione (1·95 g.) in 50% aqueous acetic acid (500 c.c.); and the reaction carried out in a similar manner to that described for 3β : 11β-dihydroxy-5α-androstan-17-one (above); evaporation to dryness of the ether–chloroform extract yielded the crude hydroxy-dione (1·34 g.), crystallizing from acetone–ether–pentane as prismatic needles, m. p. 168—171° (520 mg.), then needles, m. p. 164—167° (490 mg.) (lit.,[5] m. p. 166·5—168°). Chromatography of the mother-liquors (330 mg.) on alumina (10 g.) in benzene, and elution with benzene–ether (20 : 1 to 1 : 1) yielded a colourless solid (320 mg.), crystallizing from acetone–ether–pentane as needles (200 mg.), m. p. 167—168°, $[\alpha]_D$ +124° (*c* 1·47), $[M]_D$ +377°. Infrared spectrum (in Nujol) : $\nu_{max.}$ 3465, 1044 (equatorial OH), and 1695, 1732 cm.$^{-1}$ (CO).

3β-*Toluene*-p-*sulphonyloxy*-5α-*androstane*-11 : 17-*dione*.—A solution of the foregoing hydroxy-dione (1·23 g.) in dry pyridine (4·5 c.c.) was treated at room temperature with freshly crystallized toluene-*p*-sulphonyl chloride (1·23 g.); working up *via* ether–chloroform in the usual manner yielded a gum (1·86 g.), crystallizing from ether to give 3β-*toluene*-p-*sulphonyloxy*-5α-*androstane*-11 : 17-*dione* as laths (1·66 g.), m. p. 160—163° (depressed on admixture with initial hydroxy-diketone), and further material (50 mg.), m. p. 152—154°. The sample for analysis had m. p. 157·5—159° before, and 153—154·5° after, drying at 40°, $[\alpha]_D$ +64° (*c* 1·42), $[M]_D$ +295° (Found : C, 67·8; H, 7·6. $C_{26}H_{34}O_5S$ requires C, 68·1; H, 7·45%).

5α-*Androst*-2-*ene*-11 : 17-*dione* (VII).—Anhydrous sodium acetate (1·71 g.) was added to the foregoing ester (1·71 g.) in acetic acid (35 c.c.), and the solution heated under reflux for 2 hr.,

[11] Dobriner, Katzenellenbogen, and Jones, "The Infrared Absorption Spectra of Steroids—An Atlas," Interscience Publ. Corp., New York.

[12] Mattox and Kendall, *J. Biol. Chem.*, 1951, **188**, 287.

then kept at room temperature overnight. Removal of the acetic acid *in vacuo*, and working up the product *via* ether–chloroform, yielded a colourless solid (1·04 g.); this was hydrolyzed with 5% methanolic potassium hydroxide (60 c.c.). Working up the product in the usual manner gave a gummy solid (960 mg.), which was chromatographed in benzene on alumina (30 g.); elution with benzene gave crude 5α-*androst*-2-*ene*-11 : 17-*dione* (605 mg.), crystallizing from acetone as plates (496 mg.), m. p. 180—187°; a second crystallization gave material (421 mg.), m. p. 187—193°, $[\alpha]_D$ +202° (*c* 2·88), $[M]_D$ +581°. The analytical sample had m. p. 192—196° (Found: C, 79·25; H, 9·15. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%). Infrared spectrum (in Nujol): $\nu_{max.}$ 1699, 1734 (CO) and 1653, 773 cm.$^{-1}$ (2-ene). This compound gave a weak colour with tetranitromethane.

3α-*Hydroxy*-5α-*androstane*-11 : 17-*dione* (V).—Elution of the foregoing alumina column with benzene–ether (1 : 1; 1 : 3) gave the hydroxy-dione (357 mg.), crystallizing from acetone–ether–pentane as small laths (185 mg.), m. p. 150—151°, $[\alpha]_D$ +124° (*c* 0·95), $[M]_D$ +377°, and further material (90 mg.), m. p. 148—151°. Liebermann *et al.*[2] give m. p. 153—155°, $[\alpha]_D$ +127°. Infrared spectrum (in Nujol): $\nu_{max.}$ 3455, 999 (axial OH), 1699, 1720 cm.$^{-1}$ (CO) (cf. Dobriner, Katzenellenbogen and Jones,[11] compound 195; these authors comment that the purity of their sample was doubtful).

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