762. *Some 7-Substituted Derivatives of the 5α-Pregnane * Series.*

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Some 3 : 7 : 20-substituted derivatives of pregn-5-ene and 5α-pregnane have been prepared by standard methods. The molecular optical rotations of these compounds are discussed.

THIS work was begun at a time when it was thought that the urane compounds reported by Marker, Kamm, Oakwood, Wittle, and Lawson (*J. Amer. Chem. Soc.*, 1938, **60**, 1061) might be 3 : 7-substituted derivatives of 5α-pregnane * or of an isomer of this compound. It is now known that the urane derivatives are D-homosteroids (Klyne, *Nature*, 1950, **166**, 559).

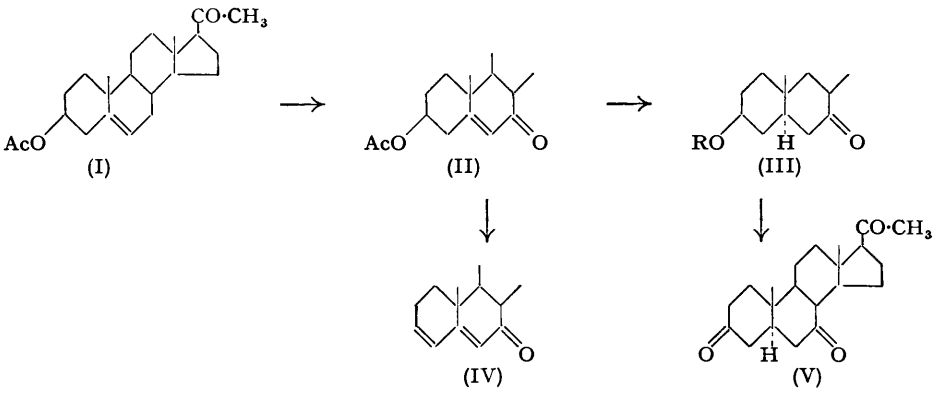
3β-Acetoxypregn-5-ene-7 : 20-dione (II), 3β-hydroxy-5α-pregnane-7 : 20-dione (III; R = H), 5α-pregnane-3 : 7 : 20-trione (V), and derivatives of these compounds have been prepared by standard methods previously used in the cholestane series.

The preparation of 5α-pregnane-3 : 7 : 20-trione completes the series of 5α-pregnanetriones most likely to be needed as reference compounds in work on naturally occurring steroids. The 3 : 6 : 20-trione has been described by Liebermann, Dobriner, Hill, Fieser, and Rhoads (*J. Biol. Chem.*, 1948, **172**, 263), the 3 : 11 : 20-trione by Steiger and Reichstein (*Helv. Chim. Acta*, 1938, **21**, 161), and the 3 : 12 : 20-trione by Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof (*J. Amer. Chem. Soc.*, 1947, **69**, 2167) and by Wagner, Moore, and Forker (*ibid.*, 1950, **72**, 1856).

The molecular rotations of the 7 : 20-diketones observed in the present work have been compared with those calculated from the rotations of previously known compounds (cf. Barton and Cox, *J.*, 1948, 783; Barton and Klyne, *Chem. and Ind.*, 1948, 755). The calculations were

* Nomenclature follows the proposals of a conference at the CIBA Foundation, London (*Chem. and Ind.*, 1951, p. SN1).

carried out on the assumption that the rotation contributions of groups in the $C_{(3)}$–C_{7}, area and of a $C_{(20)}$-keto-group are independent. The results, summarized in the table, show that this



assumption is not strictly correct. A keto-group at $C_{(20)}$ does not affect the rotation changes characteristic of acetylation and oxidation at $C_{(3)}$ (Barton and Cox, *loc. cit.*). It appears,

7 : 20-*Diketones. Comparison of observed and calculated rotations.*

	$[M]_D$ observed	$[M]_D$ calc.*	Difference (obs. − calc.)
3β-Acetoxypregn-5-ene-7 : 20-dione	−274°	−238°	−36°
3β-Hydroxy-5α-pregnane-7 : 20-dione	+ 8	+ 61	−53
3β-Acetoxy-5α-pregnane-7 : 20-dione	+ 2	+ 42	−40
5α-Pregnane-3 : 7 : 20-trione	+ 71	+139	−68

* From standard values given by Barton and Klyne (*loc. cit.*).

therefore, that keto-groups at $C_{(7)}$ and $C_{(20)}$ interfere with one another's rotation contribution—*i.e.*, exert vicinal action on each other. Barton and his colleagues have shown that olefinic double bonds at $C_{(7)}$ and $C_{(22)}$ show vicinal action (Barton, Cox, and Holness, *J.*, 1949, 1771; Barton and Brooks, *J. Amer. Chem. Soc.*, 1950, **72**, 1633). Rosenkranz, Romo, Batres, and Djerassi (*J. Org. Chem.*, 1951, **16**, 298), and Djerassi, Romo, and Rosenkranz (*ibid.*, p. 754), have reported vicinal action between an olefinic double bond at $C_{(7)}$ and a keto-group at $C_{(20)}$ or the *spiro*ketal chain of the sapogenins.

Experimental.

M. p.s are corrected for emergent stem.

Specific rotations were determined in chloroform for the sodium D line, using a 0·5-dm. micro-tube; the errors are calculated as described by Klyne, Schachter, and Marrian (*Biochem. J.*, 1948, **43**, 231), except that five pairs of readings with the solution and five pairs with a solvent blank were taken in each case.

Ultra-violet absorptions were determined by using a Beckman spectrophotometer, Model DU.

Microanalyses are by Drs. Weiler and Strauss, Oxford.

The expression "usual working-up" indicates the following operations: A solution of the reaction product in an organic solvent (usually ether) was washed with N-sodium carbonate, N-sulphuric acid, and three times with water; it was then dried (Na_2SO_4) and filtered, and the solution evaporated to dryness.

Chromatography was carried out with alumina supplied by Savory and Moore, Ltd., of activity II—III according to Brockmann and Schodder (*Ber.*, 1941, **74**, 73). Other details are as given by Paterson and Klyne (*Biochem. J.*, 1948, **43**, 614). The proportions of mixed solvents are given as % (v/v).

3β-Acetoxypregn-5-ene-7 : 20-dione (II) (following Windaus, Lettré, and Schenk, *Annalen*, 1935, **520**, 98).—3β-Acetoxypregn-5-en-20-one (I) (m. p. 140—142°; 1·00 g.) was dissolved in glacial acetic acid (40 c.c.) and the solution warmed to 55° and stirred mechanically. To this, chromium trioxide (0·80 g.), dissolved in water (0·8 c.c.) and acetic acid (8 c.c.), was added dropwise during 40 minutes and the mixture was then heated for a further hour with occasional shaking, the temperature being kept at 55° throughout. The mixture was then cooled to 20°, excess of chromium trioxide reduced with aqueous sodium hydrogen sulphite, and the bulk of the acetic acid evaporated off at 100°/15 mm. The residue was cooled, then treated with water and ether, and the aqueous solution extracted five times more with ether. The ethereal solutions after the removal of all acidic material with aqueous sodium carbonate

and the usual working-up yielded 0·47 g. of yellowish solid. Two recrystallisations from aqueous ethanol gave *3β-acetoxypregn-5-ene-7 : 20-dione* as rosettes of fine shining needles, m. p. 151—153°, $[\alpha]_D^{21}$ −73·8° ± 0·8° (*c*, 1·0) (Found, on sample dried *in vacuo* at 80° : C, 74·3; H, 8·5. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·6%). The compound gave no colour with tetranitromethane in chloroform. With concentrated sulphuric acid it gave an immediate yellow colour. In the Liebermann–Burchardt reaction it gave, in the sulphuric acid layer, an immediate yellow colour, which became orange after 1 hour; the chloroform layer remained colourless. The ultra-violet absorption (kindly determined by Mr. J. Glover, University of Liverpool) showed $\lambda_{max.}$ 234·5, 390 μ (log $\varepsilon_{max.}$ 4·26, 1·85).

The *monosemicarbazone* was prepared by treating the compound (14 mg., 0·038 millimole) in methanol (1·0 ml.) with a solution of semicarbazide hydrochloride (6·7 mg., 0·06 millimole) and sodium acetate (5·2 mg., 0·06 millimole; anhyd.), in water (0·03 ml.). The mixture was left for 3 hours at room temperature and the precipitate which formed was filtered off and recrystallized from methanol (cf. androsta-3 : 5-diene-7 : 17-dione, which gave a monosemicarbazone in similar conditions; Billeter and Miescher, *Helv. Chim. Acta*, 1948, **31**, 629). The product formed microscopic prisms, m. p. 231—234° (decomp.) (Found : N, 9·8. $C_{24}H_{35}O_4N_3$ requires N, 9·8%).

3β-Hydroxy-5α-pregnane-7 : 20-dione (III; R = H).—3β-Acetoxypregn-5-ene-7 : 20-dione (300 mg.) was reduced in ethyl acetate solution with hydrogen and Adams's platinum oxide catalyst at atmospheric pressure and temperature for 30 minutes. The product, after filtration and evaporation, was dissolved in glacial acetic acid (10 c.c.) and treated with chromium trioxide (80 mg.) in acetic acid (4 c.c.) for 8 hours at room temperature, to oxidize any secondary alcoholic groups to keto-groups. After working-up as described above for the unsaturated compound, the product formed needles (240 mg.). Chromatography of this material and recrystallization of the middle fractions (eluted with light petroleum–benzene, 80 : 20 and 50 : 50) from ethyl acetate–light petroleum (b. p. 40—60°) yielded the saturated acetoxy-diketone (III; R = Ac), m. p. 169—170°. The ultra-violet absorption of this product at 233 mμ showed that it contained about 2% of the unsaturated compound (II).

The saturated compound was finally freed from unsaturated impurities by taking advantage of the fact that 5-ene-3β-hydroxy-7-keto-compounds are decomposed when heated with hydrogen chloride (Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 567) to give 3 : 5-diene-7-ketones (IV), which can be readily separated from the 3β-hydroxy-7-ketones by chromatography. Crude 3β-acetoxy-5α-pregnane-7 : 20-dione (550 mg.) in methanol (30 c.c.) was treated with potassium carbonate (500 mg.) in water (5 c.c.), and the mixture refluxed for 3 hours. It was then cooled and made acid to litmus with concentrated hydrochloric acid (1·5 c.c.). A further 5 c.c. of concentrated hydrochloric acid were added and the mixture was refluxed again for 1·5 hours. Most of the methanol was evaporated, the residue was taken up in ether and water, and the usual working-up yielded a white solid (450 mg.; m. p. 180—195°). This was chromatographed on alumina. Light petroleum–benzene mixtures eluted a small quantity of gummy solid; benzene and benzene–ether (90 : 10 and 80 : 20) eluted 283 mg. of solid, m. p. 203—210°. Benzene–ether (60 : 40 and 20 : 80) eluted about 100 mg. of material of lower m. p., which has not been further investigated. The material of m. p. 203—210°, after recrystallization from ethyl acetate (8 c.c.) and light petroleum (15 c.c.; b. p. 40—60°), gave *3β-hydroxy-5α-pregnane-7 : 20-dione* as small glistening leaflets, m. p. 209—211°, $[\alpha]_D^{25}$ +2·3° ± 0·3° (*c*, 2·2). This material showed no selective absorption between 230 and 240 mμ (Found, on sample sublimed at 150—170°/0·5 μ : C, 76·0; H, 9·7. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%).

The compound gave no colour with tetranitromethane in chloroform; it dissolved in concentrated sulphuric acid to give a colourless solution which became very pale yellow after 30 minutes. In the Liebermann–Burchardt test the chloroform layer remained colourless throughout; the sulphuric acid layer was colourless on mixing, and became very pale yellow after 20 minutes.

The *acetate* (III; R = Ac) was prepared by treating the hydroxy-diketone with acetic anhydride in pyridine at 15—20° overnight. The product crystallised from ethanol as very fine needles, m. p. 173—174°, $[\alpha]_D^{25}$ +0·5° ± 0·3° (*c*, 2·1) (Found, on sample dried *in vacuo* at 110° : C, 73·6; H, 8·9. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1%).

The *disemicarbazone* was prepared by treating the hydroxy-diketone with a large excess of semicarbazide hydrochloride and sodium acetate in aqueous methanol at room temperature for 3 days. The product was precipitated with water, filtered, dried, and recrystallized from ethanol, giving a white amorphous powder. It did not melt up to 310° (Found : N, 19·2. $C_{23}H_{38}O_3N_6$ requires N, 18·8%).

5α-Pregnane-3 : 7 : 20-trione (V).—3β-Hydroxy-5α-pregnane-7 : 20-dione (134 mg., 0·4 millimole) in glacial acetic acid (5 c.c.) was treated with chromium trioxide (47 mg., 0·47 millimole) in glacial acetic acid (2 c.c.) and set aside at 15—20° for 24 hours. Excess of chromium trioxide was then reduced by the addition of a few drops of ethanol. The usual working-up gave *5α-pregnane-3 : 7 : 20-trione*, which after two recrystallisations from ethanol formed needles, m. p. 206—208°, $[\alpha]_D^{24}$ +22·5° ±0·4° (*c*, 2·0) (Found, on sample sublimed at 140—170°/0·5 μ : C, 75·8; H, 9·2. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·1%). In the Liebermann–Burchardt, concentrated sulphuric acid, and tetranitromethane colour reactions, the same results were obtained as with 3β-hydroxy-5α-pregnane-7 : 20-dione.

The *trisemicarbazone*, prepared as was the disemicarbazone of 3β-hydroxy-5α-pregnane-7 : 20-dione, was a white granular powder which became brown at 235—240° but did not melt up to 320° (Found : N, 24·6. $C_{24}H_{39}O_3N_9$ requires N, 25·1%).

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