

**415. Urinary Steroids and Related Compounds. Part V.<sup>1</sup>**  
**5 $\alpha$ ,17 $\alpha$ -Pregnan-20-ols.\***

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The epimeric 5 $\alpha$ ,17 $\alpha$ -pregnan-20-ols and their acetates have been prepared. Configurations have been allotted by the methods of asymmetric synthesis and partial resolution. Optical rotatory dispersion data are discussed.

GLICK and HIRSCHMANN<sup>2</sup> recently described the preparation of the 20-epimeric alcohols in the 17 $\alpha$ -pregnane (17-isopregnane) series † (5 $\alpha$ ,17 $\alpha$ -pregnane-3 $\beta$ ,20-diols) and allotted configurations at C-20 on the basis of mechanistic and rotational arguments. These authors obtained the 20 $\alpha$ (S)-isomer as the main product of reduction of the 17 $\alpha$ -20-ketone by sodium borohydride, whilst the 20 $\beta$ (R)-isomer was the main product isolated when Raney nickel was used.

During work on side-chain-substituted pregnanes with no nuclear substituents,<sup>3</sup> we obtained a new ketone showing a negative Cotton effect ( $a -114!$ ) as a by-product from the partial Clemmensen reduction of 5 $\alpha$ -pregnane-3,20-dione. This compound was formulated as 5 $\alpha$ ,17 $\alpha$ -pregnan-20-one (I), since it could easily be converted into 5 $\alpha$ -pregnan-20-one ( $a +192$ ) on mild acid or alkaline treatment. Compound (I) was also obtained on equilibration of 5 $\alpha$ -pregnan-20-one with methanolic hydrochloric acid (see refs. 2 and 4).

\* Note added in Proof.—A useful review on 17 $\alpha$ -pregnan-20-ones has recently appeared (Rubin, *Steroids*, 1963, **2**, 561).

† The nomenclature used here follows the I.U.P.A.C. Definitive Rules for Steroids ("Handbook for Chemical Society Authors," 1961, pp. 137—138), the symbols 17 $\alpha$  and 17 $\beta$  denoting the configuration of the side-chain.

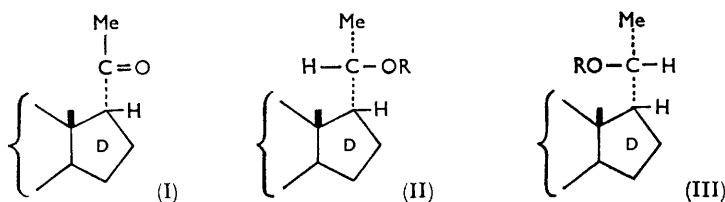
<sup>1</sup> Part IV, Danilewicz and Klyne, *J.*, 1964, 537.

<sup>2</sup> Glick and Hirschmann, *J. Org. Chem.*, 1962, **27**, 3212.

<sup>3</sup> Danilewicz and Klyne, *J.*, 1962, 4950.

<sup>4</sup> Butenandt and Mamoli, *Ber.*, 1935, **68**, 1847.

Optical rotatory dispersion measurements on the crude equilibration products showed that, under acid conditions, the proportions of the isomers were (in duplicate determinations) 73 and 68% of 17 $\beta$ , and 27 and 32% of 17 $\alpha$ ; under alkaline conditions (5% methanolic potassium hydroxide) the proportions were 74 and 70% of 17 $\beta$ , and 26 and 30% of 17 $\alpha$ .



5 $\alpha$ ,17 $\alpha$ -Pregnan-20-one was reduced with sodium borohydride to a mixture of the 20 $\alpha$ - and 20 $\beta$ -ols. Careful gradient elution on silica gel, and characterization of the fractions by thin-layer chromatography, separated the crude reduction product into two pure fractions. The less polar isomer B [m. p. 77–78°; subsequently shown to be the 20 $\beta$ (*R*)-ol] was eluted first, in 31% yield, followed by the isomer A [m. p. 128–129°; shown to be the 20 $\alpha$ (*S*)-ol] in 65% yield. Raney nickel reduction afforded the same products, but the 20 $\beta$ (*R*)-ol predominated [20 $\beta$ (*R*)-ol, 82%; 20 $\alpha$ (*S*)-ol, 15%].

We determined the configuration of isomer A by the atrolactic ester method<sup>5</sup> of Prelog and Tsatsas, and of both A and B by the partial-resolution method developed by one of us.<sup>6,7</sup> The results, which show that isomers A and B are 20 $\alpha$ (*S*) and 20 $\beta$ (*R*), respectively, agree with the findings of Glick and Hirschmann<sup>2</sup> on the 3,20-diols, based on mechanistic and rotational evidence. For comparison, the epimeric 20-alcohols of the 17 $\beta$ (normal)-series were also studied by the method of partial resolution.<sup>6,7</sup> The optical yields in the two series show marked differences (see Experimental section).

Optical rotatory dispersion data are given in Table I, which shows that rotation

TABLE I.

Molecular rotations,  $[\phi]$ , and their differences.

5 $\alpha$ ,17 $\alpha$ -Pregnane-3 $\beta$ ,20-diol derivatives <sup>2</sup>	3 $\beta$ ,20 $\alpha$ (589 m $\mu$ )	3 $\beta$ ,20 $\beta$ (589 m $\mu$ )
3-OAc .....	-32°	-115°
3,20-(OAc) <sub>2</sub> .....	-12	-89
$\Delta\phi$ (20-OAc - 20-OH) .....	+20	+26

5 $\alpha$ ,17 $\alpha$ -Pregnan-20-ols *	20 $\alpha$		20 $\beta$	
	589 m $\mu$	300 m $\mu$	589 m $\mu$	300 m $\mu$
20-OH .....	-17°	-20°	-120°	-450°
20-OAc .....	-3	-125	-108	-270
$\Delta\theta$ (20-OAc - 20-OH) .....	+14	-105	+12	+180

\* These measurements were obtained for methanol solutions, using a Rudolf photoelectric spectropolarimeter (model 200A).

differences at 300 m $\mu$  are more significant than those at 598 m $\mu$ . At 300 m $\mu$  the changes in rotation on acetylation ( $\Delta\phi$ ) of the 17 $\alpha$ -20 $\alpha$ - and -20 $\beta$ -ols are strongly negative and positive, respectively, in agreement with the general rule<sup>8</sup> for the 17 $\beta$ -series. Since we know little about the preferred conformations of side-chains, it may be unwise, without reserve, to apply to the 17 $\alpha$ -series rotational arguments based on the 17 $\beta$ -series, however

<sup>5</sup> Prelog and Tsatsas, *Helv. Chim. Acta*, 1953, **36**, 1178.

<sup>6</sup> Horeau, *Tetrahedron Letters*, 1961, 506, 654; cf. Bird, *ibid.*, 1962, 117.

<sup>7</sup> Horeau, *Tetrahedron Letters*, 1962, 965.

<sup>8</sup> Fieser and Fieser, *Experientia*, 1948, **4**, 285.

well-founded the arguments are in the latter series. Some interesting preliminary results obtained by Mr. J. P. Jennings (to whom we express our thanks) indicate that optical rotatory dispersion curves of acetates, which show Cotton effects in the region of 220  $m\mu$ , may be more significant than plain curves at longer wavelengths. Values obtained with the Bellingham and Stanley-Bendix Ericsson Polarmatic 62 recording spectropolarimeter are shown in Table 2. The rotatory dispersion curves of the phenylglyoxylates prepared

TABLE 2.

Optical rotatory dispersion curves and Cotton effects for 20-acetates, in hexane.

		First extremum		Rotation at lowest wavelength recorded		$a!^*$
		$\lambda$ ( $m\mu$ )	$\phi$	$\lambda$ ( $m\mu$ )	$\phi$	
17 $\beta$ -Series	20 $\alpha$ -OAc .....	234	-725°	208	+2750°	-35
	20 $\beta$ -OAc .....	232	+2650	217	+1160	+15
17 $\alpha$ -Series	20 $\alpha$ -OAc .....	234	-1280	208	+3320	-46
	20 $\beta$ -OAc .....	234	+790	208	-5100	+59

\* Incomplete amplitude.

for use in Prelog and Tsatsas's method<sup>5</sup> show an indication of a Cotton effect at about 380  $m\mu$ ; these may be worth further study for stereochemical purposes.

A detailed examination of the infrared hydroxyl stretching bands ( $\sim 3600$   $cm^{-1}$ ) exhibited by 5 $\alpha$ ,17 $\alpha$ -pregnan-20 $\beta$ -ol and -20 $\alpha$ -ol revealed an interesting anomaly. The spectra were taken for dilute carbon tetrachloride solutions (0.003M) using an Unicam S.P. 700 spectrophotometer and 1-cm. Infracell cell. The 20 $\beta$ -ol exhibited one band at 3622 ( $\epsilon$  50) with a slight inflection at about 3640  $cm^{-1}$ . For the 20 $\alpha$ -ol, however, two bands were clearly resolved: 3648 ( $\epsilon$  32) and 3622  $cm^{-1}$  ( $\epsilon$  32). The positions and relative intensities of the two bands were independent of concentration and of the conditions under which the sample was dried. The presence of two bands presumably results from different preferred conformations of the hydroxyl group about the C-O bond (cf. a very recent Paper by Aaron and Rader,<sup>9</sup> and references given there, especially Dalton *et al.*<sup>10</sup>).

## EXPERIMENTAL

Melting points are corrected, and optical rotations were measured in methanol unless otherwise stated ( $\phi$  = molecular rotation). Infrared spectra were taken in carbon disulphide solution using an Infracord spectrometer.

5 $\alpha$ ,17 $\alpha$ -Pregnan-20-one (I).—5 $\alpha$ -Pregnan-20-one was refluxed with methanolic hydrochloric acid.<sup>2,4</sup> Initial recrystallization from methanol, and chromatography of the mother-liquors, afforded 5 $\alpha$ ,17 $\alpha$ -pregnan-20-one as plates, m. p. 102.5–103.5°,  $\phi_{308}$  -6340,  $\phi_{265}$  +5030 ( $a$  = -114!) (Found: C, 83.6; H, 11.6.  $C_{21}H_{34}O$  requires C, 83.5; H, 11.3%).

5 $\alpha$ ,17 $\alpha$ -Pregnan-20 $\alpha$ -ol (II; R = H) and -20 $\beta$ -ol (III; R = H).—(a) 5 $\alpha$ ,17 $\alpha$ -Pregnan-20-one (176 mg.) was set aside with sodium borohydride (315 mg.) in propan-2-ol (20 c.c.) for 5 days at room temperature. The excess of reagent was destroyed with dilute hydrochloric acid, and the suspension extracted with ether. The ether extract was washed with saturated aqueous sodium hydrogen carbonate then water until neutral, dried ( $Na_2SO_4$ ), and evaporated to dryness. The residue (180 mg.) was chromatographed by gradient elution (with increasing proportions of benzene in light petroleum) on silica gel. Fractions were characterized by thin-layer chromatography, using silica gel G (prepared according to Stahl) and developing the plates with chloroform. The first material eluted (55 mg.) was a single pure substance ( $R_F$  0.49, thin-layer). Recrystallization from methanol afforded 5 $\alpha$ ,17 $\alpha$ -pregnan-20 $\beta$ -ol, m. p. 55–60°, resolidifying to plates, m. p. 77–78° (Found: C, 83.2; H, 11.9.  $C_{21}H_{36}O$  requires C, 82.9; H, 11.8%). The second material eluted ( $R_F$  0.38; 115 mg.) gave 5 $\alpha$ ,17 $\alpha$ -pregnan-20 $\alpha$ -ol as needles, m. p. 128–129° (Found: C, 82.6; H, 11.9%).

<sup>9</sup> Aaron and Rader, *J. Amer. Chem. Soc.*, 1963, **85**, 3046.

<sup>10</sup> Dalton, Meakins, Robinson, and Zaharia, *J.*, 1962, 1566.

(b)  $5\alpha,17\alpha$ -Pregnan-20-one (340 mg.) was shaken with Raney nickel (2 g.) in hydrogen at atmospheric pressure. After 2 hr., the catalyst was filtered off, and the filtrate evaporated to dryness. The crude product was separated as described previously, giving two pure fractions (20 $\beta$ -ol, 281 mg.; 20 $\alpha$ -ol, 52 mg.).

$5\alpha,17\alpha$ -Pregnan-20 $\alpha$ -ol Acetate (II; R = Ac).—The 20 $\alpha$ -ol, when treated in the usual manner with acetic anhydride in pyridine, afforded the acetate as needles, m. p. 151° (from methanol),  $\nu_{\max}$ . 1735  $\text{cm}^{-1}$  (Found: C, 79.6; H, 10.8.  $\text{C}_{23}\text{H}_{38}\text{O}_2$  requires C, 79.8; H, 11.0%).

$5\alpha,17\alpha$ -Pregnan-20 $\beta$ -ol Acetate (III; R = Ac).—The 20 $\beta$ -ol, acetylated as above, afforded the acetate as needles, m. p. 127–128° (from methanol),  $\nu_{\max}$ . 1735  $\text{cm}^{-1}$  (Found: C, 80.2; H, 11.4%).

*Asymmetric Synthesis.*<sup>5</sup>—Phenylglyoxyloyl chloride (490 mg.) was added to a solution of  $5\alpha,17\alpha$ -pregnan-20 $\alpha$ -ol (642 mg.) in dry redistilled benzene (15 c.c.) and pyridine (10 c.c.). The mixture was set aside at room temperature overnight, poured into iced water, and extracted with ether. The ether extract was washed with dilute acetic acid and water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated to dryness. The residue gave the phenylglyoxylate as plates (568 mg.), m. p. 140–144° (from light petroleum). A pure sample had m. p. 143–144° (from hexane),  $\nu_{\max}$ . 1695 and 1730  $\text{cm}^{-1}$ ,  $\phi_{800} + 228$ ,  $\phi_{380} + 1135$ ,  $\phi_{330} - 413$  (Found: C, 80.0; H, 9.5.  $\text{C}_{29}\text{H}_{40}\text{O}_3$  requires C, 79.8; H, 9.2%).

A solution of  $5\alpha,17\alpha$ -pregnan-20 $\alpha$ -ol phenylglyoxylate (303 mg.) in ether (8 c.c.) was added dropwise to an ice-cold solution of methylmagnesium iodide [from magnesium (70 mg.), methyl iodide (400 mg.), and dry ether (10 c.c.)]. The mixture was set aside at room temperature for 3 hr., refluxed for 1 hr., cooled, and a few drops of water and then dilute acetic acid were added. The ether layer was washed with 0.1N-sodium thiosulphate and water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated to dryness. The gummy residue (298 mg.) was hydrolysed by refluxing with potassium hydroxide (200 mg.) in 10% aqueous methanol (5 c.c.) for 5 hr. The solvent was removed *in vacuo* and the residue taken up in water and extracted with ether to remove neutral material. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated to dryness, affording atrolactic acid (98 mg., 85%) as a crystalline solid,  $[\alpha]_{\text{D}}^{24} + 6.8^\circ$ .

*Partial Resolution Method.*<sup>6,7</sup>—A solution of  $\alpha$ -phenylbutyric anhydride (33.7 mg.) in dry pyridine (226 mg.) was added to  $5\alpha,17\alpha$ -pregnan-20 $\alpha$ -ol (14 mg.), and the mixture was set aside at 0° for 16 hr. The excess of reagent was destroyed by adding a drop of water and heating the mixture on a water-bath for 30 min. A little water and benzene were added, and the free  $\alpha$ -phenylbutyric acid was estimated by titration with 0.1N-sodium hydroxide (phenolphthalein). (This estimation showed that the amount of anhydride used in the reaction corresponded to 65% esterification.) The benzene layer was removed, and the aqueous layer was extracted twice with chloroform and acidified with N-hydrochloric acid. The liberated  $\alpha$ -phenylbutyric acid was extracted with benzene and the benzene extract concentrated to 1.226 g. (1.4 c.c.). The rotation of the solution (1 dm. cell) was  $[\alpha]_{\text{D}} - 0.159$ , corresponding to an optical resolution of 47.5%. A similar determination using  $5\alpha,17\alpha$ -pregnan-20 $\beta$ -ol resulted in an optical resolution of 26% [(+)-acid predominating]. The values obtained in the 17 $\beta$ -series for  $5\alpha$ -pregnan-20 $\alpha$ -ol and -20 $\beta$ -ol were 28 and 52%, [(–)- and (+)-acids predominating, respectively].

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