

**857. *Totally Synthetic Steroid Hormones. Part III.*<sup>1</sup>  
(±)-9 $\alpha$ -Hydroxy $\alpha$ estr-4-ene-3,17-dione.**

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An account is given of the total synthesis of (±)-9 $\xi$ -hydroxy-10 $\xi$ - $\alpha$ estr-4-ene-3,17-dione and the evidence allowing its formulation as the 9 $\alpha$ ,10 $\beta$ -isomer.

IN Part I<sup>2</sup> a total synthesis of (±)-D-homoc $\alpha$ strone by way of the intermediates (1—3;  $n = 2$ ) \* was described. No evidence was offered as to the stereochemistry at C-9 and C-10 in the ketone (3;  $n = 2$ ). Results bearing on the question, derived from analogous experiments starting from the ketol (1;  $n = 1$ ),<sup>2,3</sup> are now recorded. Reduction with lithium and ethanol in liquid ammonia, acetic acid hydrolysis, and oxidation with chromic acid in acetone, converted the ketol into the trione (2;  $n = 1$ ). Adsorption on Florex then induced an aldol-like reaction<sup>2</sup> to give a 9-hydroxy-dione isomeric with one made from the  $\alpha$ estradienone (4)<sup>4</sup> as follows. Oxidation with monoperphthalic acid in ether-chloroform gave, by selective attack at the 9,10-bond (cf. *e.g.*, ref. 5), an epoxide to which the structure (5; X = CO) is assigned from the close agreement in physical constants of its benzoate with one<sup>6</sup> shown by X-ray diffraction<sup>7</sup> and circular-dichroism measurements<sup>8</sup> to have the structure (5; X = CO, R = Bz). The molecular rotational difference (MeOH solutions) between the ketol (5; X = CO, R = H) and 19-nortestosterone is +33°. That between the benzoate (5; X = CO, R = Bz) and 19-nortestosterone benzoate (MeOH solutions) is +37° or +96° depending on whether our value or that previously recorded<sup>6</sup> for the former compound is used. Sodium borohydride reduction of the epoxide (5; X = CO, R = H) gave the 3,17-diol (5; X = CHOH, R = H) converted with lithium aluminium hydride into a triol and thence with chromic acid into a hydroxy-dione which is formulated as the *d*-enantiomorph (as defined by Lardon *et al.*<sup>9</sup>) of the 9 $\alpha$ ,10 $\beta$ -isomer of the dione (3;  $n = 1$ ) on the following grounds. Being derived from a 9 $\alpha$ ,10 $\alpha$ -epoxide the substance must be a 9 $\alpha$ - or 10 $\alpha$ -ol. A 10 $\beta$ ,9 $\alpha$ -structure, which would be favoured by the

\* These structures depict the enantiomorph in each racemic substance having the 13-methyl group in the  $\beta$ -configuration.

<sup>1</sup> Part II, Buzby, Douglas, Edgren, Fisher, Foell, Gadsby, Hartley, Herbst, Hughes, Jansen, Ledig, McLoughlin, McMenamin, Pattison, Phillips, Rees, Siddall, H. Smith, L. L. Smith, Tokolics, Watson, and Wendt, preceding Paper.

<sup>2</sup> Douglas, Graves, Hartley, Hughes, McLoughlin, Siddall, and H. Smith, *J.*, 1963, 5072.

<sup>3</sup> H. Smith, Hughes, and McLoughlin, *Experientia*, 1963, **19**, 177.

<sup>4</sup> Farkas, Fornefeld, Kraay, Perelman, and Rapala, *J. Amer. Chem. Soc.*, 1960, **82**, 2402; Farkas and Perelman, *S. African P.* 61/208.

<sup>5</sup> Knox, Zderic, Ruelas, Djerassi, and Ringold, *J. Amer. Chem. Soc.*, 1960, **82**, 1230.

<sup>6</sup> Nominé, Bucourt, and Pierdet, *Compt. rend.*, 1962, **254**, 1823.

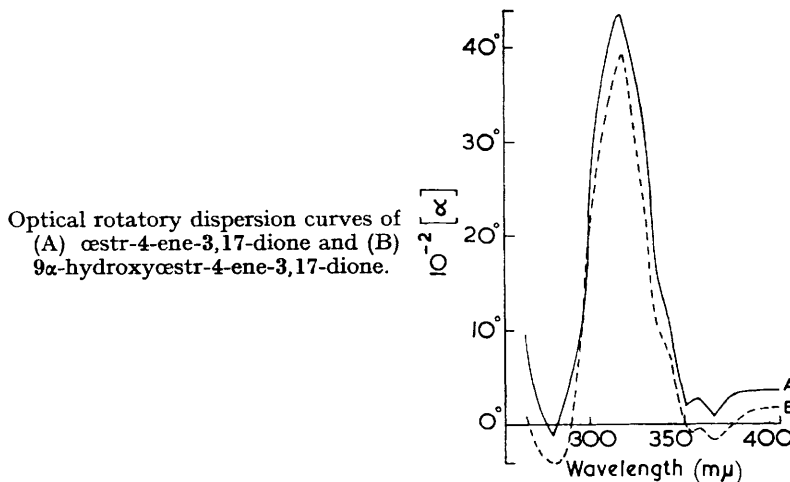
<sup>7</sup> Ayphassorho and Legrand, *Compt. rend.*, 1961, **253**, 684.

<sup>8</sup> Legrand, Viennet, and Caumartin, *Compt. rend.*, 1961, **253**, 2378.

<sup>9</sup> Lardon, Schindler, and Reichstein, *Helv. Chim. Acta*, 1957, **40**, 666.

rule of diaxial opening of oxiran rings,<sup>10</sup> is strongly supported by the close similarity in the optical rotatory dispersion curves of the hydroxy-dione and œstr-4-ene-3,17-dione (see Figure). The molecular rotational difference,  $-72^\circ$  ( $\text{CHCl}_3$  solutions), is to be compared with the value,  $-18^\circ$ , reported<sup>11</sup> for the corresponding androstane derivatives from measurements in the same solvent.

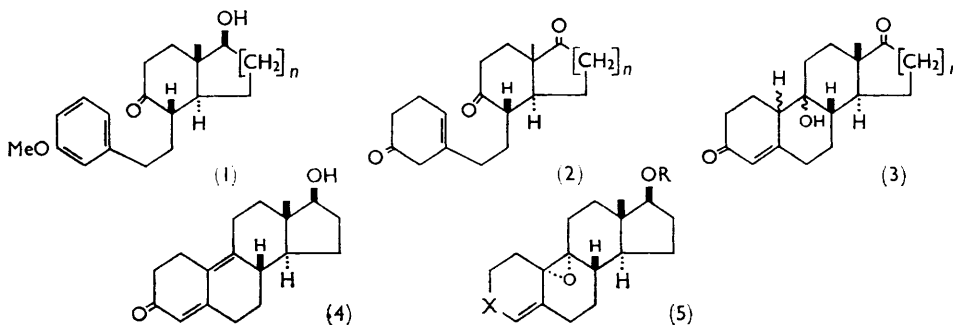
Since the hydroxy-dione (3;  $n = 1$ ) and the ( $\pm$ )-isomer made from the ketol (1) have



identical infrared spectra, we assign the 10 $\beta$ ,9 $\alpha$ -ol structure to the second substance and by analogy, to its D-homologue (3;  $n = 2$ ) reported in Part I.<sup>2</sup>

The (+)-10 $\beta$ ,9 $\alpha$ -hydroxy-dione (3;  $n = 1$ ) was also identical with a 9-hydroxyœstr-4-ene-3,17-dione<sup>12</sup> obtained by fermenting œstr-4-ene-3,17-dione with a *Nocardia* sp.

The proton magnetic resonance (p.m.r.) spectra of the ketone (5; X = CO, R = Bz) and the alcohol (5; X = CHO, R = Bz) each show a singlet associated with the C-4 protons at 3.93 and 4.21  $\tau$ , respectively. Ringold and Graves<sup>13</sup> observed diamagnetic displacements of the resonance signals of the C-4 protons of 0.22–0.25, and 0.39–0.44  $\tau$ ,



respectively, in going from a range of steroidal  $\Delta^4$ -3-ketones to the corresponding 3 $\alpha$ - and 3 $\beta$ -ols. The evidence therefore favours the  $\alpha$ -configuration for the 3-hydroxy group in the steroids (5; X = CHO, R = H, Bz).

<sup>10</sup> Barton and Cookson, *Quart. Rev.*, 1956, **16**, 67.

<sup>11</sup> Dodson and Muir, *J. Amer. Chem. Soc.*, 1961, **83**, 4627.

<sup>12</sup> Sih, unpublished work.

<sup>13</sup> Ringold and Graves, unpublished work.

## EXPERIMENTAL

General instructions are as for Part II. P.m.r. spectra were measured for deuteriochloroform solutions on a Varian Associates A-60 spectrometer. Chemical shifts were determined in  $\tau$  units relative to tetramethylsilane as an internal reference.

( $\pm$ )-9 $\alpha$ -Hydroxy $\alpha$ estr-4-ene-3,17-dione.—17 $\beta$ -Hydroxy-3-methoxy-9,10-seco $\alpha$ estra-1,3,5(10)-trien-9-one <sup>2</sup> (1.85 g.) was reduced with sodium borohydride (1.85 g.) in ethanol (45 c.c.). The product (1.84 g.) was reduced with lithium (0.5 g.) and ethanol (10 c.c.) in liquid ammonia (100 c.c.)–tetrahydrofuran (30 c.c.) to give 3-methoxy-9,10-seco $\alpha$ estra-2,5(10)-diene-9 $\xi$ ,17 $\beta$ -diol which formed a gum (1.84 g.),  $\nu_{\max}$  3420, 1689, 1661  $\text{cm}^{-1}$ . This diol was kept for 1 hr. at room temperature in ethanol (180 c.c.)–water (36 c.c.) containing oxalic acid [from the dihydrate (2.8 g.)]. The product formed a gum (1.68 g.),  $\nu_{\max}$  3440, 1703  $\text{cm}^{-1}$ . 8N-Chromic acid <sup>14</sup> was added dropwise to a portion (0.99 g.) in acetone (100 c.c.) until the solution had a permanent slightly yellow colour. After 2 min. ethanol (5 c.c.) was added, and the solution was concentrated, diluted with water, and extracted with ether. Distillation of the product gave slightly impure 9,10-seco $\alpha$ estra-5(10)-ene-3,9,17-trione (2;  $n = 1$ ) (0.9 g.),  $\nu_{\max}$  (a) 1735, 1705, 1660sh,  $\text{cm}^{-1}$  (Found: C, 75.1; H, 8.95.  $\text{C}_{18}\text{H}_{24}\text{O}_3$  requires C, 75.0; H, 8.4%). The foregoing trione (0.85 g.) in benzene was adsorbed on Florex (40 g.). Benzene–chloroform (4:1) eluted a product (205 mg.) which gave the *alcohol*, m. p. 193–198° (from benzene),  $\nu_{\max}$  3400, 1734, 1677, 1615  $\text{cm}^{-1}$ ,  $\lambda_{\max}$  (e) 242  $\text{m}\mu$  ( $\epsilon$  14,900) (Found: C, 75.6; H, 8.4.  $\text{C}_{18}\text{H}_{24}\text{O}_3$  requires: C, 75.0; H, 8.9%).

9 $\alpha$ ,10 $\alpha$ -Epoxy-17 $\beta$ -hydroxy $\alpha$ estr-4-en-3-one (5; X = CO, R = H).—Monoperphthalic acid (17.4 g.) in ether (220 c.c.) was added to 17 $\beta$ -hydroxy $\alpha$ estra-4,9-dien-3-one <sup>4</sup> (20.17 g.) in chloroform (800 c.c.) at  $-30^\circ$ . The solution was kept overnight at room temperature, water was added, and the organic layer was washed and dried. The product was recrystallised from acetone–hexane to give the *epoxide* (15.6 g.), m. p. 147–150°,  $\lambda_{\max}$  245  $\text{m}\mu$  ( $\epsilon$  13,700),  $\nu_{\max}$  (d) 3400, 1665, 1615, 1050, 897  $\text{cm}^{-1}$  (Found: C, 75.05; H, 8.35.  $\text{C}_{18}\text{H}_{24}\text{O}_3$  requires: C, 75.0; H, 8.4%). The mother-liquors gave further epoxide, m. p. 143–146° (3.32 g., total 88.7%). In our hands, 19-nortestosterone had  $[\alpha]_{\text{D}} + 45^\circ$  (MeOH) [lit., <sup>14</sup> + 55° (CHCl<sub>3</sub>)].

The benzoate had m. p. 173–174.5° (from ether–hexane),  $[\alpha]_{\text{D}} + 98^\circ$  (MeOH) {lit., <sup>6</sup> m. p. 174°,  $[\alpha]_{\text{D}} + 114^\circ$  (MeOH)} (Found: C, 76.7; H, 7.2. Calc. for  $\text{C}_{25}\text{H}_{28}\text{O}_4$ : C, 76.5; H, 7.2%). The p.m.r. spectrum showed signals at 3.93 (singlet, intensity 1, H-4), 5.0 (multiplet, intensity 1, C<sub>17</sub>-H) and 8.9  $\tau$  (singlet, intensity 3, H-18). 19-Nortestosterone benzoate had  $[\alpha]_{\text{D}} + 91^\circ$  (MeOH) [lit., <sup>15</sup> + 97.3° (CHCl<sub>3</sub>)].

9 $\alpha$ ,10 $\alpha$ -Epoxy $\alpha$ estr-4-ene-3 $\alpha$ ,17 $\beta$ -diol (5; X = CO, R = H).—Sodium borohydride (2 g.) was added piecemeal over 2 hr. to 9 $\alpha$ ,10 $\alpha$ -epoxy-17 $\beta$ -hydroxy $\alpha$ estr-4-en-3-one (2 g.) in ethanol–methanol (50 c.c.) at room temperature. Water (200 c.c.) was added slowly with stirring and the product was filtered off, dried, and recrystallised from acetone–hexane to give the *diol* (1.4 g.), m. p. 198–200.5°,  $\nu_{\max}$  (d) 3300, 1640, 1053, 1030, 898  $\text{cm}^{-1}$ ,  $[\alpha]_{\text{D}} + 32^\circ$  (CHCl<sub>3</sub>),  $[\alpha]_{\text{D}} + 56.5^\circ$  (MeOH).

17 $\beta$ -Benzoyloxy-9 $\alpha$ ,10 $\alpha$ -epoxy $\alpha$ estr-4-en-3 $\alpha$ -ol (5; X = CHOH, R = Bz), obtained by reduction of 17 $\beta$ -benzoyloxy-9 $\alpha$ ,10 $\alpha$ -epoxy $\alpha$ estr-4-en-3-one with sodium borohydride in ethanol–methanol, had m. p. 201–203° (from ether–hexane),  $\lambda_{\max}$  230  $\text{m}\mu$  ( $\epsilon$  15,900),  $\nu_{\max}$  (c) 3400, 1706, 1654, 1604, 1585  $\text{cm}^{-1}$ ,  $[\alpha]_{\text{D}} + 84^\circ$  (CHCl<sub>3</sub>);  $[\alpha]_{\text{D}} + 106^\circ$  (EtOH) {lit., <sup>16</sup> m. p. 204°,  $[\alpha]_{\text{D}} + 116^\circ$  (EtOH)} (Found: C, 76.1; H, 7.6.  $\text{C}_{25}\text{H}_{28}\text{O}_4$  requires C, 76.1; H, 7.7%). The p.m.r. spectrum showed signals at 4.21 (singlet, intensity 1, H-4), 5.08 (triplet, intensity 1, H-17), 5.77 (multiplet, intensity 1, H-3), 7.3 (doublet, intensity 1, OH), and 8.95  $\tau$  (singlet, intensity 3, H-18).

9 $\alpha$ -Hydroxy $\alpha$ estr-4-ene-3,17-dione.—9 $\alpha$ ,10 $\alpha$ -Epoxy $\alpha$ estr-4-ene-3 $\alpha$ ,17 $\beta$ -diol (1 g.) in tetrahydrofuran (30 c.c.) was added with stirring over 30 min. to lithium aluminium hydride (1.5 g.) in tetrahydrofuran (40 c.c.). The mixture was stirred overnight at room temperature and refluxed for 3 hr. to give a gummy product (0.7 g.). A portion (0.5 g.) was oxidised with 8N-chromic acid in acetone to give the *alcohol*, m. p. 217–219° (from tetrahydrofuran–ether),  $\lambda_{\max}$  245  $\text{m}\mu$  ( $\epsilon$  15,800),  $\nu_{\max}$  (c) 3440, 1734, 1660, 1618  $\text{cm}^{-1}$ ,  $[\alpha]_{\text{D}} + 106^\circ$  (Found: C, 74.9; H, 8.55.  $\text{C}_{18}\text{H}_{24}\text{O}_3$  requires C, 75.0; H, 8.4%).

(Estr-4-ene-3,17-dione had  $[\alpha]_{\text{D}} + 137^\circ$  (CHCl<sub>3</sub>).<sup>14</sup>

<sup>14</sup> Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

<sup>15</sup> Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5366.

<sup>16</sup> Hartman, Tomaszewski, and Dreiding, *J. Amer. Chem. Soc.*, 1956, **78**, 5662.

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