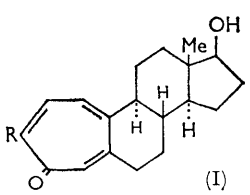
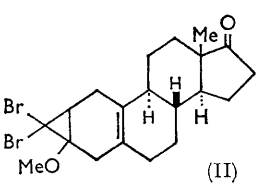
951. *Steroid Hormones. Part XIV.*[1] *Further Tropone and Tropolone Analogues*

By A. J. Birch, J. M. H. Graves, and G. S. R. Subba Rao

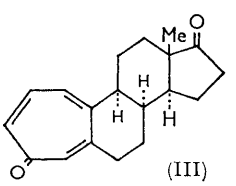
We recently reported[2] the synthesis of two tropone analogues of œstrone. The biologically important œstra-3,17β-diol differs from œstrone in the presence of two hydroxyl groups, and closer tropone analogues would possess one or both, one of them phenolic. Accordingly, we have synthesised compounds (I; R = H) and (I; R = OH). The compound (II) previously reported[2] was reduced with sodium borohydride and the product converted[2] into (I; R = H). The latter was also prepared by reduction of the corresponding 17-ketone already described,[2] since borohydride attacked this carbonyl preferentially. Since this work was carried out, the synthesis of the 17-acetyl derivative of (I; R = H), essentially by a modification of our original method,[2] has been reported.[3]



(I)



(II)



(III)

The action of hydroxylamine and alkali on (I; R = H), as described[4] for tropones in general, resulted in a tropolone, which is probably (I; R = OH), with the expected spectra

[1] Part XIII, A. J. Birch and G. S. R. Subba Rao, *J.*, 1965, 3007.
[2] A. J. Birch, J. M. H. Graves, and J. B. Siddall, *J.*, 1963, 4234.
[3] A. B. Font, *Bull. Soc. chim. France*, 1964, **5**, 906.
[4] T. Nozoe, T. Mukai, and J. Minegishi, *Proc. Japan Acad.*, 1952, **28**, 287.

and properties. The formula is written with the usual uncertainty in the position of the hydroxyl proton. The isomer with OH at position 4a is not ruled out but seems unlikely.

In view of the biological activity of some members of the 8α-series,[5] the tropone (III) has been prepared from (±)-8α-œstrone methyl ether[6] by the previous[2] sequence of reactions.

The biological properties of these compounds will be reported elsewhere.[7]

Experimental.—A-*Homo*-17β-*hydroxyœstra*-1(10),2,4a-*trien*-4-*one* (I; R = H). (*a*) The ketone (II)[2] (250 mg.) was left with sodium borohydride (200 mg.) in ethanol–tetrahydrofuran overnight. The resulting 17β-*carbinol* crystallised from ether, m. p. 148—150°, $\nu_{max.}$ 3380, 1242, 1074, and 1049 cm.$^{-1}$ (Found: C, 52·0; H, 6·2. $C_{20}H_{28}Br_2O_2$ requires C, 52·2; H, 6·1%). This compound (210 mg.) in acetone was refluxed with silver perchlorate (4 equiv.) for 2 hr. The resulting A-*homo*-17β-*œstra*-1(10),2,4a-*trien*-4-*one* was crystallised from benzene, m. p. 196—200°, $\nu_{max.}$ 3360, 1628, 1552, and 1527 cm.$^{-1}$, $\lambda_{max.}$ 230, 234, 238, and 314 mμ (ε 27,200, 28,700, 29,300, and 11,300) (Found: C, 80·7; H, 8·5. $C_{19}H_{24}O_2$ requires C, 80·4; H, 8·5%).

(*b*) Sodium borohydride (65 mg., 2 equiv.) and A-homoœstra-1(10),2,4a-trien-4,17-dione (100 mg.) in ethanol (20 c.c.) were left overnight. Working up as usual and crystallisation from benzene gave a pale yellow solid (60 mg.), m. p. 195—197°, $\nu_{max.}$ 3360, 1628, 1552, and 1527 cm.$^{-1}$, identical with the above compound.

A-*Homo*-3,17β-*dihydroxyœstra*-1(10),2,4a-*trien*-4-*one*. The above tropone (100 mg.) and hydroxylamine hydrochloride (100 mg.) in 2N-methanolic sodium hydroxide (10 c.c.) were refluxed for 6 hr., poured into water, and extracted with ether. The aqueous extract was acidified and extracted with chloroform. The *trienone* crystallised from ethanol, m. p. 141—142°, $\nu_{max.}$ 3300, 1615, 1590, and 1585 cm.$^{-1}$, $\lambda_{max.}$ 235 and 320 mμ (ε 16,980 and 6760) (Found: C, 76·25; H, 8·1. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%). It gave a strong green colour with ferric chloride.

(±)-3-*Methoxy*-8α-*œstra*-2,5(10)-*dien*-17-*one* 17-*ethylene ketal*. (±)-3-Methoxy-8α-œstra-trien-17-one (1 g.) ethylene glycol, and toluene-*p*-sulphonic acid (50 mg.) were refluxed in benzene (300 c.c.) using a Dean–Stark water separator. The 17-*ethylene ketal* crystallised from ether as colourless needles, m. p. 106—108°, $\nu_{max.}$ 1600, 1575, 1500, and 1100 cm.$^{-1}$ (Found: C, 77·0; H, 8·2. $C_{21}H_{27}O_3$ requires C, 76·8; H, 8·25%). The ketal (1 g.) was reduced in the usual way with lithium (0·65 g.) in liquid ammonia (150 c.c.), t-butyl alcohol (100 c.c.), and tetrahydrofuran (100 c.c.). The (±)-3-*methoxy*-8α-*œstra*-2,5(10)-*dien*-17-*one* 17-*ethylene ketal* (850 mg.) was crystallised from ether–methanol, m. p. 134—135°, $\nu_{max.}$ 1685, 1660, and 1100 cm.$^{-1}$ (Found: C, 76·4; H, 8·85. $C_{21}H_{30}O_3$ requires C, 76·4; H, 9·1%).

A-*Homo*-8α-*œstra*-2,4a,10-*trien*-4,17-*dione*. To the above ketal (1·0 g.), resublimed potassium *t*-butoxide (1·2 g.), and dry ether (10 c.c.) was added slowly a solution of bromoform (1·0 c.c.) in dry ether (5 c.c.) at −28° over 30 min. After stirring the mixture for 65 min. and pouring into water the bromocarbene adduct of the ketal slowly crystallised and was recrystallised from acetone, m. p. 156—157°, $\nu_{max.}$ 768 cm.$^{-1}$ (Found: C, 53·1; H, 6·0. $C_{22}H_{30}Br_2O_3$ requires C, 52·6; H, 6·0%). The mother-liquor gave the corresponding *ketone* (52 mg.) which could also be obtained by mild acid treatment of the ketal. It crystallised from acetone, m. p. 153—154°, $\nu_{max.}$ 1735 and 770 cm.$^{-1}$ (Found: C, 52·8; H, 6·05. $C_{20}H_{26}Br_2O_2$ requires C, 52·4; H, 5·7%).

The above ketone (400 mg.) in aqueous acetone (40 c.c.) was refluxed with silver perchlorate (500 mg.) for 3 hr. After filtration and addition to water, the ether extract was crystallised from ethyl acetate–light petroleum (b. p. 40—60°) to give A-*homo*-8α-*œstra*-2,4a,10-*trien*-4,17-*dione* (200 mg.), m. p. 120—140°, raised by crystallisation from ethyl acetate to 148—150°, $\nu_{max.}$ 1735, 1628, 1552, and 1527 cm.$^{-1}$, $\lambda_{max.}$ 235 and 312 mμ (ε 25,140 and 10,480) (Found: C, 81·3; H, 7·9. $C_{19}H_{22}O_2$ requires C, 80·85; H, 7·8%).

We are indebted to the D.S.I.R. for the award of a Scholarship (to J. M. H. G.) and to Syntex, S.A. for financial assistance and gifts of material.

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MANCHESTER. [*Received, March 3rd,* 1965.]

[5] C. Djerassi, A. J. Manson, and H. Bendas, *Tetrahedron*, 1957, **1**, 22.
[6] G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. B. Siddall, and Herchel Smith, *J.*, 1963, 5072.
[7] A. J. Birch, R. I. Dorfman, and F. Kincl, unpublished results.