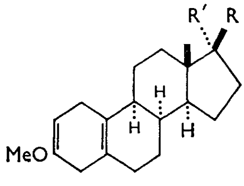
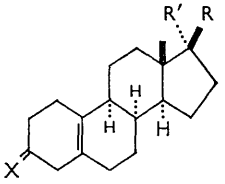
952. *Steroid Hormones. Part XV.*[1] *(±)-8α-Androst-4-ene-3,17-dione from 8α-Œstrone Methyl Ether*

By A. J. Birch and G. S. R. Subba Rao

The addition of dibromocarbene to a 5(10)-double bond in a hydro-œstrone derivative has led to a new total synthesis of non-aromatic steroids.[2] To test whether the method is applicable to any other stereoisomers, the reaction was applied to derivatives of 8α-œstrone. Addition of the carbene completely failed to occur. At this stage we were informed by Dr. A. D. Cross and Dr. R. Ginsig (Syntex, S.A., Palo Alto) of a successful experimental modification of the Simmons–Smith[3] methylene-addition process for difficult cases. This reaction has the great advantage of being sterically directed by an allylic or homoallylic hydroxyl group. The 8α-stereoisomers of œstrone methyl ether and œstradiol methyl ether, kindly presented by Dr. Herchel Smith (Wyeth Laboratories), were converted into compounds (I; R′ = H, R = OH) and (I; R,R′ = $O[CH_2]_2{\cdot}O$) by obvious methods. Acid hydrolysis under appropriate conditions gave compounds (II; R′ = H, R = OH) or (II; R,R′ = $O{\cdot}[CH_2]_2{\cdot}O$), reduced by sodium borohydride to compounds (III; R′ = H, R = OH) or (III; R,R′ = $O{\cdot}[CH_2]_2{\cdot}O$). The configuration of the 3β-OH is assigned as the result of the next step. Reaction of these compounds with methylene iodide and zinc under the Syntex reaction conditions caused addition of methylene to the 5(10)-double bond. Removal of the ketal group in the one case, followed by oxidation, and direct oxidation in the other, gave the diketone (IV), which on reaction with acid gave (±)-8α-androst-4-ene-3,17-dione (V). This compound, although optically inactive, was compared with (+)-8α-androst-4-ene-3,17-dione (kindly supplied by Professor Djerassi), the m. p. of which it did not depress. It was identical in infrared spectrum by comparison with the published[4] spectrum. The amount of natural material was too small to make further comparisons.

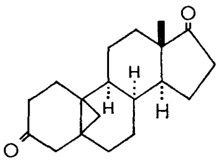


(I)

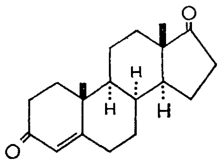


(II); X = O

(III); X = H···, HO ▬



(IV)



(V)

Experimental.—(±)-8α-*Œstr*-5(10)-*ene*-3,17-*dione* 17-*ethylene ketal*. (±)-3-Methoxy-8α-œstra-1,3,5(10)-trien-17-one, kindly given by Dr. Herchel Smith (Wyeth Laboratories), was converted into the 17-ethylene ketal, m. p. 106—108°, and thence into (±)-3-methoxy-8α-œstra-2,5(10)-dien-17-one 17-ethylene ketal, m. p. 134—135° by the usual methods, to be described by Dr. Smith.

To the latter ketal (1 g.), in tetrahydrofuran–methanol (1 : 1; 20 c.c.), was added oxalic acid (1·5 g.) in water (10 c.c.). After 1 hr. a saturated solution of sodium hydrogen carbonate was added to until the solution was neutral, and the product extracted with ether. Crystallisation from methanol gave (±)-8α-*œstr*-5(10)-*ene*-3,17-*dione* 17-*ethylene ketal* as needles (850 mg.), m. p. 119—120°, $\nu_{max.}$ 1700, 1603, and 1100 cm.$^{-1}$ (Nujol) (Found: C, 75·4; H, 8·4. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·8%).

(±)-5(10)-*Methylene*-8α-*œstra*-3,17-*dione*. (*a*) Sodium borohydride (0·5 g.) and the above ketone (0·5 g.) in methanol (20 c.c.) were left overnight. Addition of water and ether extraction,

---

[1] Part XIV, A. J. Birch, J. M. H. Graves, and G. S. R. Subba Rao, preceding Paper.

[2] A. J. Birch, J. M. Brown, and G. S. R. Subba Rao, *J.*, 1964, 3309.

[3] H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, 1959, **81**, 4256.

[4] C. Djerassi, A. J. Manson, and H. Bendas, *Tetrahedron*, 1957, **1**, 22.

followed by crystallisation from methanol gave (±)-3β-*hydroxy*-8α-*œstr*-5(10)-*en*-17-*one* 17-*ethylene ketal* (480 mg.) (Found: C, 75·1; H, 9·65. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·4%).

This carbinol (400 mg.), and reagent from zinc–copper couple (2 g.), and methylene iodide (0·5 c.c.) were heated in a sealed tube at 100° for 1 hr. The product was extracted with chloroform and the resulting gum oxidised with 8N-chromic acid. After passage of the product through alumina (±)-5(10)-*methylene*-8α-*œstra*-3,17-*dione* (35 mg.) was obtained and crystallised from hexane; it had m. p. 150—154° $\nu_{max.}$ (CS_2) 1715, 1240, 1110, 1065, 1038, 930, 820, and 750 cm.$^{-1}$; τ 9·08 (18-CH_3, 9·52 (–CH_2–) (Found: C, 80·0; H, 9·2. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·1%) (*b*) (±)-8α-œstra-diol methyl ether (2 g.), kindly given by Dr. Herchel Smith, was converted by lithium–ammonia reduction into its 1,4-dihydro-derivative, m. p. 135—136°, in a manner to be described in detail by Dr. Smith. This compound was hydrolysed with oxalic acid as above to give (±)-17β-*hydroxy*-8α-*œstr*-5(10)-*en*-3-*one* (1·12 g.) m. p. 148—150° (from methanol); $\nu_{max.}$ 3300, 1695, and 1603 cm.$^{-1}$ (Found: C, 78·4; H, 9·7. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%).

This ketone (1 g.) in methanol (30 c.c.) was allowed to react overnight with sodium borohydride (500 mg.). The product was a glass (920 mg.), which crystallised from methanol as plates (560 mg.), m. p. 130—132°, $\nu_{max.}$ 3250 cm.$^{-1}$, of (±)-8α-*œstr*-5(10)-*ene*-3β, 17β-*diol* (Found: C, 77·75; H, 10·5. $C_{18}H_{28}O_2$ requires C, 78·3; H, 10·2%).

The diol (500 mg.), zinc–copper couple (2·5 g.), and methylene iodide (0·5 g.) were heated in a sealed tube at 100° for 1 hr. The product was worked up and converted as above into the diketone, which was obtained (60 mg.) as crystals m. p. 150—154°, from hexane.

(±)-8α-*Androst*-5-*ene*-3,17-*dione*. A solution of the above diketone (50 mg.) in dry chloroform (5 c.c.) was saturated with dry hydrogen chloride and left overnight. The product was diluted with ether, and washed with hydrogen carbonate solution, and chromatographed on neutral alumina. The (±)-8α-*androst*-5-*ene*-3,17-*dione* (25 mg.), crystallised from methanol as prisms, m. p. 196—197°, $\lambda_{max.}$ 241 mμ (log ε 4·25); $\nu_{max.}$ 1740, 1668, and 1608 cm.$^{-1}$ (Nujol) (Found: C, 79·2; H, 9·3. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·1%). On admixture with an authentic (+)-specimen of this substance, m. p. 195—197°, the m. p. was undepressed.

We are indebted to Syntex, S.A. for financial assistance, and to Dr. Herchel Smith and Professor Carl Djerassi for specimens.

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