626. *Hydroaromatic Steroid Hormones. Part X.*[1] *Conversion of Œstrone into Androst-4-ene-3,17-dione.*

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

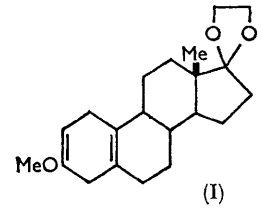
Reaction of dibromocarbene with two nor-steroids containing a 5,10-double bond and a potential carbonyl group in the 3-position, removal of the bromine by reduction with lithium in liquid ammonia, and acid fission of the cyclopropane ring led to introduction of a 10β-methyl group. Œstrone methyl ether 17-ethylene ketal was converted through its 1,4-dihydro-derivative eventually into androst-4-ene-3,17-dione.

Conversion of œstrone into 19-nortestosterone [2] completed the first total synthesis of a potent [3] steroid hormone other than an œstrogen. An attempt to introduce a 10-methyl group to complete a total synthesis of an authentic non-aromatic steroid was abandoned [4]

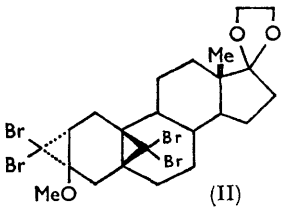
[1] Part IX, Birch, Graves, and Siddall, *J.*, 1963, 4234.
[2] Birch and Mukerjee, *J.*, 1949, 2531; Birch, *J.*, 1950, 367.
[3] Birch, *Ann. Reports*, 1950, 210.
[4] Birch, *Chem. and Ind.*, 1951, 615.

when the total syntheses of Cornforth [5] and Woodward [6] and their co-workers were announced. Although a number of total syntheses have since been carried out,[7] there has been no direct conversion of ring-A aromatic compounds into the 10β-methyl series. With the present ready availability of œstrone and some of its stereoisomers by total synthesis,[8] a simple method of introducing the missing carbon is highly desirable, and we report one which appears to be generally applicable.

Reaction of an excess of dibromocarbene on the steroid (I), obtained from œstrone, gave a mixture containing the mono-adduct previously reported [1] together with the bis-adduct (II) previously reported as a minor product.[1] This, after reduction with lithium in liquid ammonia, was treated with hydrogen chloride in chloroform, to give 2α-methyl-androst-4-ene-3,17-dione (III; R = Me).



(I)



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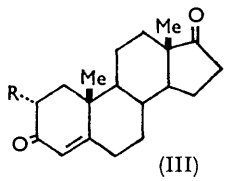

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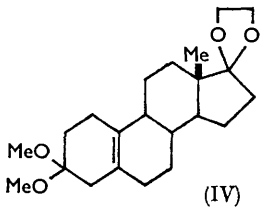

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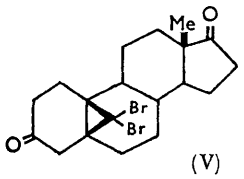
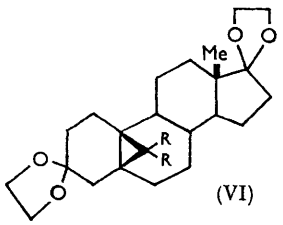


(V)



(VI)

There is no doubt that the 5,10-cyclopropane ring is β, as was expected in view of the β-epoxidation of 5,10-double bonds. Although the 2-methyl group of the product is α, this is the stable equatorial configuration and does not necessarily imply that the 2,3-cyclopropane ring of (II) is α. This appears probable, however, since in simpler cases the two rings are *trans*,[9] and the formula (II) is accordingly written in this way.

In order to avoid introduction of the 2-methyl group it was necessary to use a compound containing only the 5,10-double bond with a potential carbonyl at the 3-position. Attempts to produce a uniform bis-ketal from œstr-5(10)-ene-3,17-dione were unsuccessful, and the nuclear magnetic resonance spectrum of the product showed the presence of a considerable proportion of substance containing a trisubstituted double bond. 2,5-Dihydroanisole derivatives react very rapidly with methanol in the presence of toluene-*p*-sulphonic acid, to give the corresponding dimethyl ketal,[10] and this reaction with (I) gave the pure ketal (IV) in good yield. This compound reacted with dibromocarbene to give a mixed product which had lost to some extent the ketal groups. Their removal was completed by the action of toluene-*p*-sulphonic acid in acetone, to give the dibromo-compound (V). This compound was re-ketalised with ethylene glycol to yield the adduct (VI; R = Br) which was reduced with lithium in liquid ammonia to the methylene compound (VI; R = H). Removal of the ketal groups by the action of toluene-*p*-sulphonic acid in acetone gave 5,10-methyleneœstrane-3,17-dione undepressed in melting point by an authentic specimen synthesised from a steroid containing both angular methyl groups.[11] The action

[5] Cardwell, Cornforth, Duff, Holtermann, and Robinson, *Chem. and Ind.*, 1951, 389; *J.*, 1953, 361.
[6] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[7] For review, see Torgov, *Pure Appl. Chem.*, 1963, **2**, 525.
[8] Douglas, Graves, Hartley, Hughes, McLoughlin, Siddall, and Smith, *J.*, 1963, 5072.
[9] Birch and Brown, unpublished work.
[10] Birch and Smith, unpublished work.
[11] Bowers, personal communication.

of hydrogen chloride in chloroform on the ketal (VI; R = H) gave androst-4-ene-3,17-dione (III; R = H), m. p. 174—176°, undepressed by an authentic specimen and identical in infrared spectrum.

Taking into account the present efficient syntheses of œstrone, this constitutes the simplest total synthesis of a non-aromatic steroid so far reported.

Experimental

Conversion of Œstrone into 2α-Methylandrost-4-ene-3,17-dione.—A solution of 1,4-dihydro-œstrone methyl ether 17-ethylene ketal (1·1 g.) in benzene (30 ml.) and potassium t-butoxide (from potassium, 4 g.) was stirred at −10° and bromoform (21 g.) slowly added. Worked up as usual, the product (1·18 g.) was converted completely into the 17-ketone on shaking with chlofoform and aqueous ethanolic oxalic acid. Crystallisation of the crude mixture from acetone gave the pure *bisdibromocarbene adduct* (172 mg.), m. p. 194—196·5° (Found: C, 40·3; H, 4·2. $C_{21}H_{26}Br_4O_2$ requires C, 40·0; H, 4·0%). This adduct (140 mg.) was refluxed in benzene (40 ml.) with ethylene glycol (300 mg.) and toluene-*p*-sulphonic acid (20 mg.) for 4 hr. Worked up in the usual way, the 17-*ketal* (148 mg.) of the adduct had m. p. 180—183·5° (Found: C, 41·1; H, 4·4. $C_{23}H_{30}Br_4O_3$ requires C, 40·9; H, 4·4%).

A solution of this ketal (136 mg.) in tetrahydrofuran (5 ml.) was added to liquid ammonia (100 ml.) containing ethanol (5 ml.). Lithium (70 mg.) was added and working up gave a crude solid (75 mg.), which was difficult to obtain completely uniform. Purification gave some material, m. p. 135—139°. The crude material (62 mg.) was dissolved in dry chloroform, dry hydrogen bromide passed in, and the mixture set aside overnight. Water was added and the crude product (54 mg.) chromatographed on acidic alumina to give 2α-methylandrost-4-ene-3,17-dione (29 mg.), m. p. 157—159° (from light petroleum), $\lambda_{max.}$ 240 mμ (log ε 4·22) [lit., $\lambda_{max.}$ 242 mμ (log ε 4·22)], identical (mixed m. p. and optical rotatory dispersion, infrared, and proton magnetic resonance spectra) with an authentic sample.

3,3-*Dimethoxyœstr*-5(10)-*ene* 17-*Ketal.*—1,4-Dihydroœstrone 3-methyl ether 17-ketal (1 g.), in dry ether (50 ml.) and methanol (1 ml.), was cooled to 0° and a crystal of toluene-*p*-sulphonic acid was added. The mixture was left at 0° for 2 hr., refluxed for 30 min., neutralised with sodium methoxide, washed with water, and dried. Removal of the solvent deposited a semi-solid which crystallised from methanol as prisms, m. p. 108—110°, of the *ketal* (820 mg., 82%) (Found: C, 72·7; H, 9·6. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·4%), $\nu_{max.}$ (Nujol) 1058, 1110, 1170, and 1255 cm.$^{-1}$.

5,10-(*Dibromomethylene*)*œstra*-3,17-*dione.*—To a mixture of 3,3-dimethoxyœstr-5(10)-ene 17-ketal (800 mg.) and potassium t-butoxide (1 g.) in dry ether (30 ml.) was added dropwise a solution of bromoform (2·5 g.) in ether (10 ml.) at −20°, with stirring, under nitrogen. The mixture was stirred for 2 hr. and left to warm to room temperature. Water (50 ml.) was added and the contents were extracted with chloroform (3 × 30 ml.), washed thoroughly with water, and dried. Removal of the solvent deposited a gum consisting of ketone and the ketal ($\nu_{max.}$ 1740 and 1105 cm.$^{-1}$). It was deketalised with toluene-*p*-sulphonic acid and worked up in the usual way, to give a semi-solid mass which resisted crystallisation. This was purified through a column of " H " alumina to give the *dibromo-dione*, plates (103 mg.), m. p. 168—172° (from acetone) (Found: C, 52·5; H, 5·6; $C_{19}H_{21}Br_2O_2$ requires C, 51·4; H, 5·48%), $\nu_{max.}$ (CS_2) 1732, 825, and 784 cm.$^{-1}$.

5,10-*Methyleneœstrane*-3,17-*dione.*—5,10-(Dibromomethylene)œstrane-3,17-dione (100 mg.) was re-ketalised by refluxing with ethylene glycol and toluene-*p*-sulphonic acid in anhydrous benzene as above. Working up as usual gave a glassy mass of the diketal (92 mg.), which was reduced with lithium (20 mg.), liquid ammonia (30 ml.), and ethanol (2 ml.). The ammonia was allowed to evaporate and water (25 ml.) was added. The product was extracted with light petroleum (b. p. 40—60°; 3 × 10 ml.), washed thoroughly with water, and dried. Removal of the solvent gave a liquid which yielded 5,10-methyleneœstrane 3,17-diethylene ketal (60 mg.), m. p. 128—132° (from light petroleum). This was deketalised with toluene-*p*-sulphonic acid in acetone and the resulting 5,10-methyleneœstrane-3,17-dione had m. p. 132—134° (from ether), undepressed by an authentic specimen, m. p. 134—135°, kindly supplied by Dr. A. Bowers (Syntex).

Androst-4-*ene*-3,17-*dione.*—A stream of dry hydrogen chloride was passed through a solution

of 5,10-methyleneœstrane 3,17-diketal (50 mg.) in dry chloroform (10 ml.) for 1 hr. The mixture was left overnight, and working up as usual gave a brown gummy solid (30 mg.)

The gum was dissolved in benzene (20 ml.), applied to a column of " H " alumina (6 g.), and eluted with benzene–chloroform (10%). This, on evaporation, yielded a solid m. p. 160—170°, which gave the dione, needles (16 mg.), m. p. 168—170° (from methanol), $\lambda_{max.}$ 240 mμ (log ε 4·02), identified by mixed m. p. and infrared spectrum, $\nu_{max.}$ 1740, 1680, 1620, 1225, 1050, 1010, 870, and 780 cm.$^{-1}$.

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