800. *Hydroaromatic Steroid Hormones. Part IX.* Tropone Analogues of Œstrone.*

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By addition of dibromocarbene, followed by the action of silver nitrate or perchlorate, the 1,4- and 1,2-dihydroœstrone derivatives (I) and (V) are converted into analogues (IV) and (VIII) of œstrone with a tropone ring A. The action of potassium t-butoxide in dimethyl sulphoxide on the 1,4-dihydro-derivative (I) produces the 1,2-isomer.

In Part I[1] was described the first total synthesis of a 19-nor-steroid hormone, 19-nortestosterone, which was also the first active[2] androgen made by total synthesis. The process, which has since been developed into industrially important syntheses of other 19-norsteroids, particularly oral contraceptives, by addition of an appropriate side-chain in the

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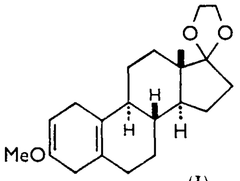
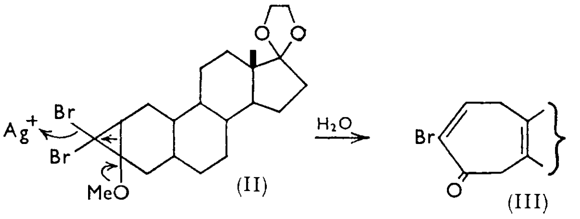
* Part VIII, Birch, Kocor, and Smith, *J.*, 1962, 782.

[1] Birch, *J.*, 1950, 367.

[2] Birch, *Ann. Reports*, 1950, 210.

17-position,[3] involves reduction of an aromatic ring A by means of metal–ammonia solutions in the presence of an alcohol.[4] Hitherto, the intermediate dihydrobenzenes, *e.g.*, (I), have been utilised only by conversion into ketones by acid treatment. We have been exploring other ways of utilising such intermediates and now report an efficient conversion into troponoid steroids by a process which, although devised with this end in view, has a more general application.


(I)



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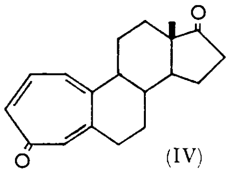
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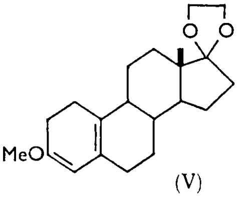
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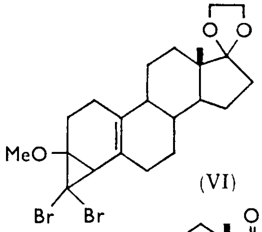
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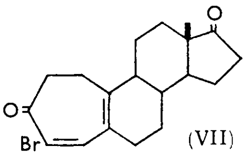
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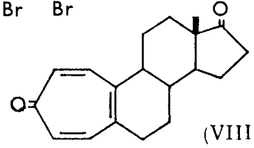
(VIII)

It has been briefly noted [5] that halogenocarbenes react in good yields with 2,3- or 2,5-dihydroanisole derivatives mainly on the double bond carrying the methoxyl group, in accord with the electrophilic reactivity of these reagents. The bromocarbene adducts on reaction with soluble silver salts,[5] preferably the perchlorate, are converted efficiently into tropones. Addition of dibromocarbene to the compound (I) gave mainly the adduct (II) with a minor proportion of the adduct involving both double bonds. The product also contained some of the monoadduct which had lost the 17-ketal group. Refluxing this product (II), or the crude mixed product, with aqueous methanol containing silver nitrate gave the A-homo-steroid (IV) in good yield. The expected tropone structure was supported by characteristic infrared and ultraviolet spectra (cf. ref. 6). The exact pathway of the reaction has not been defined, but the first step is thought to be that shown in (II) ⟶ (III), being facilitated by the methoxyl group. Further loss of hydrogen bromide presumably involves initial shift of a double bond by enolisation.

Conjugation of the double bonds in 2,5-dihydroanisole derivatives can be brought about by strong bases such as potassamide in liquid ammonia,[7] the enol-ether double bond pivoting about the end carrying the methoxyl group. Treatment of compound (I) in this way gave evidence from ultraviolet spectra of some conjugation, but possibly because of solubility difficulties conversion was low. A more recent reagent for similar base-catalysed isomerisation of double bonds is potassium t-butoxide in dimethyl sulphoxide,[8] and under the influence of this reagent smooth isomerisation (I) ⟶ (V) occurred.

[3] L. F. and M. Fieser, "Steroids," p. 591 *et seq.*, Reinhold Publ. Corpn., New York, 1959.

[4] Birch, *J.*, 1944, 430; *Quart. Rev.*, 1950, 69; Birch and Smith, *Quart. Rev.*, 1958, 17.

[5] Birch and Graves, *Proc. Chem. Soc.*, 1962, 282.

[6] Nozoe in "Non-benzenoid Aromatic Compounds," ed. Ginsburg, Interscience Publ., Inc., New York and London, 1959, p. 372.

[7] Birch, *J.*, 1947, 1642.

[8] Schriesheim, Hofmann, and Rowe, *J. Amer. Chem. Soc.*, 1962, **84**, 3164.

Reaction of the 1,2-dihydro-compound (V) with dibromocarbene gave the adduct (VI). Some loss of the ketal group occurred during the reaction and to obtain maximum yields of the tropone (VIII) it was advisable to treat the crude material directly with silver perchlorate in aqueous acetone. An intermediate (VII) in the conversion could be obtained by refluxing the 17-ketone from (VI) with silver perchlorate in almost anhydrous acetone. Further refluxing of this intermediate (VII), or of the 17-ketone obtained by acid hydrolysis of the initial crude adduct, with silver perchlorate in aqueous acetone gave the tropone (VIII) in high yield.

Biological activities will be published elsewhere, but it may be noted now that compound (IV) has no œstrogenic activity.

EXPERIMENTAL

Addition of Dibromocarbene to 1,4-*Dihydroœstrone Methyl Ether* 17-*Ethylene Ketal.*—Potassium t-butoxide was prepared by dissolving potassium (0·24 g.) in t-butyl alcohol (20 c.c.). This solution was diluted with benzene (20 c.c.), 1,4-dihydroœstrone methyl ether 17-ethylene ketal (1 g.) in benzene (10 c.c.) added, and the mixture cooled to 0°. Bromoform (1·53 g.) in benzene (5 c.c.) was then added during 20 min. and the whole stirred for a further hour. Working up by addition of water and extraction with ether gave a pale yellow gum which crystallised from benzene–ethanol in three fractions. The first consisted of colourless rods of the *mono-adduct* (II) (0·62 g., 41%), m. p. 159—161° (Found: C, 52·45; H, 6·2. $C_{22}H_{30}Br_2O_3$ requires C, 52·6; H, 6·0%). The infrared spectrum was in accord with the expected formula, and in particular the enol-ether band (1690 cm.$^{-1}$) of the starting material had disappeared. The second fraction consisted of mixed crystals (87 mg.), its reactions indicating that it was a mixture of the monoadduct and the bisdibromocarbene adduct (87 mg.), to be discussed in a subsequent paper. The third fraction was identified as the dibromocarbene *adduct* of 1,4-dihydroœstrone (56 mg.), m. p. 155·5—156·5° (Found: C, 52·4; H, 5·95. $C_{20}H_{26}Br_2O_2$ requires C, 52·4; H, 5·7%), $\nu_{max.}$ 1728 cm.$^{-1}$ (C=O).

A-*Homoœstra*-2,4a(10)-*triene*-4,17-*dione* —The adduct (II) (190 mg.) was refluxed in aqueous methanol (50 c.c.) containing silver nitrate (4 mol.) for 3 hr. After dilution with water and extraction with benzene the product was a brown gum which was chromatographed on neutral alumina. The first eluate (4 : 1 light petroleum–benzene) was recovered starting material (60 mg.); the second eluate (1 : 4 benzene–ether) was the required *homoœstratrienedione* which, crystallised from ethyl acetate–light petroleum, had m. p. 143—146° (66 mg., 51%) (Found: C, 80·45; H, 8·0. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%), $\nu_{max.}$ (in Nujol) 1727, 1630, 1588, 1528, 1267, 1150, 1076, 1024, 892, 882, 832, 817, 730, and 703 cm.$^{-1}$,$\lambda_{max.}$ (in EtOH) 231, 234, 237, and 313 mμ (ε 26,600, 27,100, 27,800, and 10,200, respectively).

1,2-*Dihydroœstrone Methyl Ether* 17-*Ethylene Ketal.*—To a solution of re-sublimed potassium t-butoxide (5·8 g.) in pure anhydrous dimethyl sulphoxide (235 g.) under dry nitrogen was added 1,4-dihydroœstrone methyl ether 17-ethylene ketal (9·9 g.), and the mixture was shaken for 6 hr. Portions containing ~5 mg. of steroid were removed at intervals of 30 min. and examined by ultraviolet spectroscopy. The absorption at $\lambda_{max.}$ 274 mμ reached a maximum extinction after about 5 hr. The mixture was poured into water (1·25 l.) and extracted with ether. Evaporation of the extract gave a colourless gum, $\lambda_{max.}$ 274 mμ (ε 4300, indicating about 65% conjugation on the basis of ε 6800 for the pure compound). The product crystallised from ether, and the isomeric dienes were separated by crystallisation from ether containing dry methanol by selective seeding. 1,2-*Dihydroœstrone methyl ether* 17-*ethylene ketal* (6·9 g.) had m. p. 86—87·5° (Found: C, 76·5; H, 9·1. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·05%). In addition, pure starting material (2·53 g.) was recovered. The overall yield on material consumed was 93%.

Addition of Dibromocarbene to 1,2-*Dihydroœstrone Methyl Ether* 17-*Ethylene Ketal.*—Resublimed potassium t-butoxide (1·36 g.) was suspended in a solution of 1,2-dihydroœstrone methyl ether 17-ketal (4·69 g.) in dry ether (40 c.c.) at −20° under nitrogen. A solution of bromoform (4·31 g.) in dry ether (10 c.c.) was added dropwise with vigorous stirring in 20 min. After a further 65 min. the mixture was left to warm to room temperature, poured into water (50 c.c.), and extracted with ether. The extracted gum was shown by means of its infrared spectrum to contain 40—50% of material with a free 17-carbonyl group. The mixed product was therefore hydrolysed in 15 : 85 aqueous acetone (90 c.c.) containing oxalic acid (1·5 g.) for 1 hr. Working up in the usual way gave a gum (7·14 g.) which partially crystallised but was best purified by chromatography in benzene on neutral alumina. The first eluate (4·84 g.) was the dibromocarbene *adduct*, m. p. 159—161°, of 1,2-dihydroœstrone methyl ether (Found: C, 51·9; H, 6·5. $C_{20}H_{26}Br_2O_2$ requires C, 52·4; H, 5·7%).

4-*Bromo*-A-*homoœstr*-4,5(10)-*diene*-3,17-*dione*.—To a solution of the above adduct (275 mg.) in acetone (30 c.c.) containing water (0·5 c.c.) was added at the b. p. a solution of silver perchlorate (0·55 g., 5 mol.) in acetone (2 c.c.). Silver bromide was rapidly precipitated and was removed after 25 min. (111 mg., 1 mol.). Dilution with water, chloroform extraction, and crystallisation from ethyl acetate gave the *bromohomoœstradienedione* (210 mg.), m. p. 95—155° (decomp.) (Found: C, 63·4; H, 6·2. $C_{19}H_{23}BrO_2$ requires C, 62·8; H, 6·4%). The rather unsatisfactory analysis was probably due to instability, but the structure is supported by spectra: $\nu_{max.}$ 1735, 1662, 1615, and 1550 cm.$^{-1}$; $\lambda_{infl.}$ 228; $\lambda_{max.}$ 325 mμ (ε 5750 and 7300).

A-*Homoœstra*-1,4,5(10)-*triene*-3,17-*dione*.—The preceding bromo-ketone (200 mg.) was heated to the b. p. in 1 : 4 aqueous acetone (30 c.c.) containing silver perchlorate (0·5 g.) for 30 min., then silver bromide (105 mg.) was removed by filtration. After dilution with water the product was extracted with chloroform and crystallised from ethyl acetate, to give the *homoœstratrienedione* (165 mg.), m. p. 193—196·5°, $\lambda_{max.}$ 232 and 318·5 mμ (ε 25,200 and 14,050), $\nu_{max.}$ 1730, 1627, 1570, and 1512 cm.$^{-1}$ (Found: C, 81·0; H, 7·7. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%). The same compound (431 mg.) was obtained directly from the dibromocarbene adduct of dihydroœstrone methyl ether (704 mg.) in refluxing 1 : 4 aqueous acetone (30 c.c.) containing silver perchlorate (1·4 g.) in 30 min.

We are indebted to D.S.I.R. for research scholarships (to J. M. H. G. and J. B. S.) and to Syntex S.A. for a gift of œstrone and for arranging biological tests.

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