80. *Hydroaromatic Steroid Hormones. Part I.* 10-*Nortestosterone.*

By Arthur J. Birch.

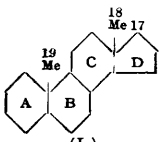
The problem of making physiologically active hormone substitutes is discussed, and the preparation of 10-nortestosterone (IV) is described.

One of the chief difficulties associated with the synthesis of steroid hormones is the quaternary nature of the carbon atoms which carry the angular methyl groups. This difficulty has contributed to prevent the synthesis of the non-aromatic hormones containing two such groups, and there is no known method of introducing the 19-Me (cf. I) into the synthetic aromatic hormones such as (+)-œstrone (ring A aromatic) to produce hydroaromatic compounds convertible into non-aromatic hormones such as testosterone. The only successful attempt on a model substance is that of Woodward (*J. Amer. Chem. Soc.*, 1940, **62**, 1208), but the reaction apparently failed with œstrone.

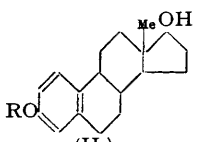
With the increasing importance of steroid hormones, it seems necessary to examine more closely the structural requirements for physiological activity, in particular whether this is retained by compounds lacking the angular methyl groups and therefore available by the reduction of aromatic systems. Œstrogenic activity is comparatively unspecific and is shown by compounds differing greatly in structure from the natural hormones, but for the androgenic, progestational, and cortical hormones even slight changes in the space-distribution of groups are sufficient to depress or abolish activity. Evidence is, however, available in several cases that the 19-Me (between rings A and B) is not absolutely essential for activity. Dirscherl, Kraus, and Voss (*Z. physiol. Chem.*, 1936, **241**, 1; cf. Schering-Kahlbaum A.-G., B.P. 423,287/1935) reported the reduction of (+)-œstrone to an octahydro-derivative (ring A fully reduced and hydroxyl in the 17-position) which is androgenic, and must be considered as the first synthetic compound with this activity; and Ehrenstein (*J. Org. Chem.*, 1944, **9**, 435) obtained a 19-norprogesterone which is claimed to be as active as progesterone itself. He also prepared a 19-nordeoxycorticosterone, which is, however, inactive. Neither of these last two products could be crystallised and they are probably mixtures of isomers.

The 18-Me (between rings C and D) appears to be essential for high activity, at least with the œstrogenic hormones equilenin and œstrone, but this effect may be due merely to the fact that it prevents the (natural) *trans*-junction of rings C and D from assuming the more stable *cis*-configuration. The methyl group can be replaced by ethyl or *n*-propyl without great diminution in activity (Bachmann and Holmes, *J. Amer. Chem. Soc.*, 1940, **62**, 2750). With two fused six-membered rings, the *trans*-junction is the more stable, and it is known that if ring D of the natural hormones is converted into a six-membered ring the compounds obtained are highly active (Goldberg and Wyndler, *Helv. Chim. Acta*, 1943, **26**, 1142; Goldberg and Studer, *ibid.*, 1941, **24**, 478), so it may be possible to omit the 18-Me in such cases.

The synthetic approach to nor-steroid hormones has now been greatly simplified by Birch and Mukherji's method of reduction (*Nature*, 1949, **163**, 766; *J.*, 1949, 2351), by which an aryl glyceryl or an aryl 2-hydroxyethyl ether is reduced with sodium and an alcohol in liquid ammonia, and the dihydro-derivative so obtained hydrolysed to an unsaturated ketone. "α"-Œstradiol 1'-glycerol ether [II; R = CH_2·CH(OH)·CH_2·OH] was thus reduced to (III), the constitution of which has now been further confirmed by its lack of a light-absorption



(I.)



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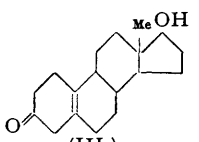

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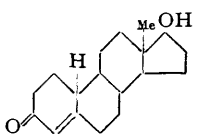

(IV.)

maximum in the region 2200—3000 A. This βγ-unsaturated ketone has now been isomerised by ethanolic sodium ethoxide to the αβ-unsaturated ketone (IV), which is a 10-*nortestosterone*. Although two stereoisomers are to be expected from the isomerisation, only one crystalline product (orientation at $C_{(10)}$–H unknown) could be isolated (in 60% yield), the remainder being a gum. The constitution assigned to the compound is confirmed by its light absorption in ethanol, with a maximum at 2400—2415 A., $\varepsilon_{max.}$ 17,000, and a low-intensity band at 3075 A., $\varepsilon_{max.}$ 92·5. Dannenberg (*Abhandl. preuss. Akad. Wiss.*, 1939, **21**, 3) gives for testosterone in ethanol a band at 2410 A., log $\varepsilon_{max.}$ 4·20.

The advantages of the reduction method are that ring A can be kept aromatic up to the last

stages, thus simplifying synthetic reactions on the other parts of the molecule; and that a *cyclo*hexenone ring is produced which is characteristic of hormones such as testosterone, progesterone, cortisone, and corticosterone. It is possible in many cases to protect groups such as carbonyl during the reduction (Birch, unpublished work).

This work is being pursued with the object of making further hormone analogues from (+)-œstrone in order to see whether the expenditure of effort necessary for the complete synthesis of such nor-steroids is likely to be justified.

Experimental.

10-*Nortestosterone* (IV).—The following method is somewhat better than that already given (Birch and Mukherji, *loc. cit.*) for the preparation of (III). " α "-Œstradiol 1'-glycerol ether (980 mg.) was dissolved in warm ethanol (30 c.c.) and stirred into liquid ammonia (300 c.c.). Potassium (3 g.) was rapidly added in small pieces with stirring and, after the reaction was complete, water (75 c.c.) was used to decompose the mixture. The ammonia was rapidly evaporated, finally under reduced pressure, and the solution just neutralised by the addition of hydrochloric acid, followed by sufficient acid to give a 5%-acid solution. This solution, containing a suspension, was then shaken with ethyl acetate (30 c.c.), which eventually dissolved the gummy solid as hydrolysis proceeded. The ethyl acetate solution was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was taken up in ethyl acetate (5 c.c.) and chromatographed on alumina (cf. Birch and Mukherji, *loc. cit.*) in the same solvent. The eluate was divided arbitrarily into fractions until evaporation under reduced pressure gave a non-crystallisable gum instead of a solid. The collected solid recrystallised from ethyl acetate as large flat prisms (215 mg.), m. p. 187—188°, $\lambda_{infl.}$ 2720—2940 A., $\varepsilon_{infl.}$ 51·4 (ethanol). This compound (III) (200 mg.) was dissolved in warm ethanol (10 c.c.) and added to a solution of sodium (15 mg.) in ethanol (4 c.c.). The mixture was kept at 50° for 5 minutes under nitrogen. After acidification with a few drops of acetic acid the solvent was removed under reduced pressure, and the residue washed with water, taken up in ethyl acetate (5 c.c.), and chromatographed on alumina (cf. Birch and Mukherji, *loc. cit.*) in the same solvent. The first fractions crystallised on removal of the solvent, and 10-*nortestosterone* (IV) was crystallised from light petroleum (b. p. 60—80°) containing a few drops of ethyl acetate, as large colourless prisms (120 mg.), m. p. 111°; $\lambda_{max.}$ 2400—2415 A., $\varepsilon_{max.}$ 17,000; $\lambda_{max.}$ 3075 A., $\varepsilon_{max.}$ 92·5 (ethanol) (Found: C, 78·5; H, 9·3. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%).

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