57. *The Interconversion of Hexœstrol and* iso*Hexœstrol.*

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The dimethyl ethers of hexœstrol and *iso*hexœstrol are interconverted when heated at 305—310° in presence of hydrogen sulphide.

The important œstrogen hexœstrol (Campbell, Dodds, and Lawson, *Nature*, 1938, **142**, 1121; Dodds, Golberg, Lawson, and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 153; Campbell, Dodds, and Lawson, *ibid.*, 1940, *B*, **128**, 253) is conveniently prepared from its dimethyl ether obtained from *p*-α-bromopropylanisole by the action of sodium (Boots Pure Drug Co. Ltd., and W. F. Short, E.P. 523,320, 30.12.1938; Bernstein and Wallis, *J. Amer. Chem. Soc.*, 1940, **62**, 2871) or magnesium (Boots Pure Drug Co. Ltd. and W. F. Short, *loc. cit.*; Docken and Spielman, *J. Amer. Chem. Soc.*, 1940, **62**, 2163). Hexœstrol dimethyl ether prepared in this way is accompanied by *iso*hexœstrol dimethyl ether, which is demethylated to the relatively feeble œstrogen, *iso*hexœstrol. It was suggested by Dodds, Golberg, Lawson, and Robinson (*loc. cit.*) that hexœstrol and *iso*hexœstrol are the *meso-* and the racemic form respectively of γδ-di-*p*-hydroxyphenylhexane and this has been confirmed by the resolution of *iso*hexœstrol (Wessely and Welleba, *Naturwiss.*, 1940, **28**, 780).

*iso*Hexœstrol dimethyl ether remains unchanged when heated alone or in an atmosphere of sulphur dioxide or hydrogen chloride, whereas when heated to 250° in presence of 1% of iodine it is resinified. Traces of hexœstrol dimethyl ether are obtained when *iso*hexœstrol dimethyl ether is heated to 300—320° in presence of palladium–charcoal, and when heated at 300° with sulphur some isomerisation occurs but much of the material is resinified. When the *iso*-ether is heated at 300° in an atmosphere of hydrogen sulphide, it is partially isomerised to hexœstrol dimethyl ether, the yield being 50% when allowance is made for the recovered *iso*-ether. In the same way, hexœstrol dimethyl ether is partially isomerised to *iso*hexœstrol dimethyl ether, so the isomerisation is reversible. *iso*Hexœstrol remains unchanged when heated at 250° with pyridine–piperidine, is recovered unchanged, after hydrolysis, by heating with acetic anhydride at 250°, and is completely decomposed on heating with hydrogen sulphide at 300°.

These isomerisations provide a further addition to the small number of examples in which an interconversion of optical isomerides has been observed with compounds which are incapable of conversion into an unsaturated isomeride, for example, by enolisation of a carbonyl group adjacent to an asymmetric carbon atom. It is difficult to envisage the observed isomerisations except on the basis either of reversible dehydrogenation or of fission and recombination.

Experimental.

Isomerisation of Hexœstrol Dimethyl Ether.—Undried hydrogen sulphide was slowly passed through *iso*hexœstrol dimethyl ether (50 g.; m. p. 53—54°) at 305—310° (oil-bath) for 3 hours. The small distillate, which contained anethole and some hexœstrol dimethyl ether, was combined with the pale red residue, dissolved in light petroleum (150 c.c., b. p. 60—80°) and cooled to 0° overnight. The crystals were collected, washed with a little light petroleum, and recrystallised from boiling alcohol (150 c.c.). The dimethyl ether (5·1 g.) so obtained melted at 143·5—144°, undepressed by authentic hexœstrol dimethyl ether, and afforded hexœstrol, m. p. and mixed m. p. 185°, on demethylation with alcoholic potassium hydroxide. Evaporation of the mother-liquors and distillation of the residue afforded anethole (2·5 g.) and a fraction (40·3 g.), b. p. 184—187°/3 mm., which was practically pure *iso*hexœstrol dimethyl ether.

Isomerisation of iso*Hexœstrol Dimethyl Ether.*—Hexœstrol dimethyl ether (10 g.; m. p. 144°) was heated at 305—310° for 3 hours in a slow stream of undried hydrogen sulphide. The residue, which partly crystallised on cooling, was dissolved in boiling light petroleum (100 c.c.; b. p. 60—80°), cooled, and filtered from hexœstrol dimethyl ether; a further crop was obtained by concentrating the filtrate to 10 c.c. (total yield, 5·7 g.). The rest of the solvent was removed, and the residue distilled, giving (1) a fraction (1·2 g.) below 105°/20 mm., consisting mainly of anethole, and (2) a portion (1·2 g.), b. p. 215—225°/20 mm. Fraction (2) was dissolved in alcohol (6 c.c.), filtered from a small amount of hexœstrol dimethyl ether, and cooled to 0°. The crystals (0·45 g.) so obtained melted at 53—54° either alone or after admixture with authentic *iso*hexœstrol dimethyl ether.

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