32. *Synthetic Œstrogens. Part I. The Synthesis of* 2 : 3-*Di*-p-*hydroxyphenyl*-2 : 3-*dimethylbutane, an Isomer of Hexœstrol.*

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The diphenol named in the title has been synthesised by three methods, all involving dimerisation of free radicals. It has low solubility in aqueous alkalis, exhibits the unusual property of evolving methyl iodide under the conditions of the Zeisel determination, and is only weakly œstrogenic.

The "structural resemblance" theory of synthetic œstrogens (Dodds, Goldberg, Lawson, and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 140), although probably an over-simplification, stimulated the present research. The diphenyl-ethane and -ethylene series contain several patent synthetic hormones of wide clinical application (stilbœstrol, hexœstrol, dienœstrol). Substances of the type *p*-HO·C_6H_4·CHR·CHR′·C_6H_4·OH-*p* so far investigated have all contained the –CHR·CHR′– group corresponding to the B–C ring junction of natural steroids. If, however, a third or a fourth alkyl group were introduced, to give the grouping –CR^1R^2·CR^3R^4– (R^4 = H or alkyl), the structure would bear less resemblance to œstradiol. 2 : 3-Di-*p*-hydroxyphenyl-2-methylpentane (I; R = Me) and 3 : 4-di-*p*-hydroxyphenyl-3-methylhexane (I; R = Et) have been prepared (Huang, Thesis, Oxford, 1947) and found to be highly potent (full response in rats at dosages of 1 and 0·5 γ respectively). We therefore prepared the tetra-methyl homologue 2 : 3-di-*p*-hydroxyphenyl-2 : 3-dimethylbutane (II), which is isomeric with hexœstrol.

(I) *p*-HO·C_6H_4·CRMe·CHEt·C_6H_4·OH-*p* *p*-HO·C_6H_4·CMe_2·CMe_2·C_6H_4·OH-*p* (II)

Normal methods are not suited for the preparation of fully substituted dibenzyls typified by (II). For instance, in an approach to a Wurtz reaction, attempts to obtain pure 3-chloro-3-*p*-methoxyphenylpentane gave only the olefin (Huang, unpublished work). However, Kharasch, McBay, and Urry (*J. Org. Chem.*, 1945, **10**, 401) prepared 2 : 3-dimethyl-2 : 3-diphenylbutane, the unhydroxylated analogue of (II), by dimerisation of the radical obtained from *iso*propylbenzene by acetyl peroxide. We have prepared (II) by three methods, each involving dimerisation of a free radical which, however, we prepared by means of the safer di-*tert.*-butyl peroxide (Farmer and Moore, *J.*, 1951, 131).

First, 2-*p*-methoxyphenylpropan-2-ol was dehydrated by heat in the presence of a small quantity of quinol, and the resulting olefin reduced with sodium in ethanol to *p*-*iso*propylanisole. (The olefin polymerised readily in the presence of proton donors, *e.g.*, halogen or sulphuric acids, or free-radical initiators, *e.g.*, iodine.) Dimerisation of *p*-*iso*propylanisole by heating it with di-*tert.*-butyl peroxide at 140° under reflux or in a Carius tube (Farmer

and Moore, *loc. cit.*) and demethylation with hydrobromic acid, gave the desired diphenol (II). This product, although apparently pure, gave a small but definite value for methoxyl in the Zeisel determination. However, demethylation by hydriodic acid or methylmagnesium iodide yielded the same product as obtained above. Accordingly, the methoxyl group was then removed at an earlier stage : *p-iso*propylanisole was demethylated to *p-iso*propylphenol, the benzoate of which on dimerisation and subsequent hydrolysis afforded the same diphenol (II). Finally, in a synthesis avoiding the methoxyl group altogether, 2 : 3-dimethyl-2 : 3-diphenylbutane (Farmer and Moore, *loc. cit.*) was successively nitrated, reduced, and subjected to a diazo-reaction, once more yielding (II).

It has further been established that a number of fully methylated dibenzyls analogous to (II) yield methyl iodide under the conditions of the Zeisel determination (Huang and Morsingh, *Analyt. Chem.*, 1952, **24**, 1359).

The substance (II) is relatively insoluble in aqueous alkali. It is only weakly active as an œstrogen (10 mg. for full response in castrated rats).

Experimental

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford.

p-iso*Propylanisole*.—Crude 2-*p*-methoxyphenylpropan-2-ol (55 g.) (from *p*-methoxyphenylmagnesium bromide and acetone) was heated with quinol (0·1 g.) at 110°/vac. for 30 minutes. Water separated. Distillation afforded the olefin (40 g.), b. p. 86°/2 mm., n_D^{23} 1·5483. By this treatment the dimeric product reported by Behal and Tiffeneau (*Compt. rend.*, 1901, **132**, 561) was not encountered. The olefin (34 g.) was then reduced with sodium in ethanol in the usual manner, giving the required *p-iso*propylanisole (15 g.), b. p. 55—58°/2 mm., n_D^{23} 1·5032. Klages (*Ber.*, 1904, **37**, 3996) reports b. p. 95—96°/19 mm., n_D^{17} 1·5045.

2 : 3-*Di*-p-*methoxyphenyl*-2 : 3-*dimethylbutane*.—(*a*) *p-iso*Propylanisole (15 g.) and di-*tert*.-butyl peroxide (7·5 g.; Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205) were heated under reflux at 140—145° for 48 hours, under a slow stream of nitrogen. Distillation removed *tert*.-butanol, b. p. 44°/100 mm. (4 g.), and unchanged hydrocarbon, b. p. 55°/2 mm. (9·4 g.). The residue, a dark brown glass, freely soluble in benzene but sparingly soluble in light petroleum, was chromatographed in benzene, on alumina. Elution with benzene–light petroleum (1 : 4) gave 2 : 3-*di*-p-*methoxyphenyl*-2 : 3-*dimethylbutane* (3·0 g., crude) which recrystallised from benzene–ethanol in prisms, m. p. 183—185° (0·44 g.) (Found : C, 80·2; H, 8·7. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

(*b*) *p-iso*Propylanisole (4 g.) and di-*tert*.-butyl peroxide (2 g.) were heated under nitrogen in a sealed tube at 150—155° for 26 hours. After addition of a few drops of petroleum yellowish crystals were deposited during 24 hours. These on trituration with ethanol followed by three recrystallisations from benzene–ethanol afforded the butane derivative, m. p. 183—185° (0·40 g.).

2 : 3-*Di*-p-*hydroxyphenyl*-2 : 3-*dimethylbutane*.—The above product (87 mg.) was heated under reflux with hydrobromic acid (*d* 1·5; 1 ml.) and acetic acid (7 ml.) for 8 hours. The mixture was poured into water and extracted with ether. The ethereal solution was washed several times with sodium hydrogen carbonate solution, water, and finally 5% aqueous sodium hydroxide. After being washed with ether, the alkaline extract was acidified and the precipitated *diphenol* recovered in ether and crystallised from benzene as needles, m. p. 205—210° (50 mg.), raised to 210—212° by two recrystallisations from *cyclo*hexane (Found : C, 80·0; H, 8·2; OMe, 3·1. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·15; OMe, 0%). Approx. 0·1 g. dissolved in 100 ml. of 10% aqueous sodium hydroxide. The compound forms a *dibenzoate*, leaflets (from ethyl acetate–benzene), m. p. 251° (Found : C, 80·4; H, 6·4. $C_{32}H_{30}O_4$ requires C, 80·3; H, 6·3%).

Demethylation by hydriodic acid (*d* 1·7) and acetic acid (1 : 3) for 4 hours, or by methylmagnesium iodide at 180—190° for 1¼ hours, gave the same product, m. p. and mixed m. p. 210—212°. The latter product still gave an apparent methoxyl value (OMe, 3·8, 4·3%).

Dimerisation of p-iso*Propylphenyl Benzoate*.—*p-iso*Propylanisole (12·7 g.) was demethylated with hydrobromic–acetic acid, and the phenol converted into the benzoate which, recrystallised twice from ethanol, formed needles, m. p. 69—70° (6·0 g.). Behal and Tiffeneau (*Bull. Soc. chim.*, 1908, **3**, 318) report m. p. 70—71°. This (6·0 g.) was heated with di-*tert*.-butyl peroxide (3·2 g.) in a sealed tube as described above. The mixture on cooling deposited crystals which

were washed with ether (the dimer is sparingly soluble in contrast to the monomer). On recrystallisation from ethyl acetate, 2 : 3-di-*p*-benzoyloxyphenyl-2 : 3-dimethylbutane had m. p. 245—247° (2·3 g.), raised to m. p. 251° after further recrystallisation.

2 : 3-*Di*-p-*hydroxyphenyl*-2 : 3-*dimethylbutane*.—The above dibenzoate (1·14 g.) in warm benzene (20 ml.) was heated with 5% ethanolic sodium hydroxide (200 ml.) under reflux for 7 hours. The solvents were removed, leaving the solid sodium salt of the required diphenol. Water (70 ml.) was added, and the sparingly soluble sodium salt separated at the centrifuge. It was then acidified with hydrochloric acid and the liberated diphenol taken up in ether (80 ml.) and worked up in the usual way, yielding a pure product, m. p. 212° (0·41 g.).

2 : 3-*Dimethyl*-2 : 3-*di*-p-*nitrophenylbutane*.—2 : 3-Dimethyl-2 : 3-diphenylbutane (4·0 g.) was cautiously added to concentrated nitric acid (25 ml.; *d* 1·42), and the mixture heated with stirring at 70—80° for 7 hours, after which a yellowish-orange colour had developed. The cooled mixture was poured into ice-water, and the yellowish-orange solid which separated was washed with water by decantation, treated with a small quantity of hot ethanol, which removed most of the yellow colour, and repeatedly extracted with boiling chloroform. Thereby a chloroform-insoluble and a chloroform-soluble fraction were obtained. The former was 2 : 3-*dimethyl*-2 : 3-*di*-p-*nitrophenylbutane*, a yellowish powder (1·5 g.), m. p. 265° (decomp.) (Found : C, 65·5; H, 5·9; N, 8·45. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·1; N, 8·5%). The combined chloroform filtrates were concentrated to approx. 15 ml. Thereupon another yellowish solid, m. p. 230° (0·6 g.), separated, probably the op′-*isomer* (Found : C, 65·6; H, 6·0; N, 8·2%). Both compounds are sparingly soluble in ethanol, acetone, light petroleum, and ethyl acetate.

2 : 3-*Di*-p-*aminophenyl*-2 : 3-*dimethylbutane*.—The *pp*′-dinitro-compound (1·5 g.) was heated under reflux with ethanol (160 ml.) and concentrated hydrochloric acid (4 ml.) while iron filings (4 × 1·5 g.) were introduced during 20 minutes, and vigorous refluxing was continued for 10 hours. The mixture was then made neutral with alcoholic sodium hydroxide (excess being avoided) and filtered hot. The residue was washed with boiling ethanol. The combined filtrates on concentration afforded 2 : 3-*di*-p-*aminophenyl*-2 : 3-*dimethylbutane* (1·2 g.) which was washed with water. After four recrystallisations from benzene (charcoal) it was obtained as prisms, m. p. 235—236° (Found : C, 80·4; H, 8·7; N, 10·4. $C_{18}H_{24}N_2$ requires C, 80·6; H, 8·95; N, 10·45%), insoluble in water, but soluble in dilute hydrochloric acid. The Schotten–Baumann technique gave a dibenzoate, m. p. >270°.

2 : 3-*Di*-p-*hydroxyphenyl*-2 : 3-*dimethylbutane*.—Burger and Mosettig's method (*J. Amer. Chem. Soc.*, 1937, **59**, 1304) for conversion of an amine into a phenol was unsuitable. DeMilt and Van Zandt's method (*ibid.*, 1936, **58**, 2044) was used : Sodium nitrite (1·5 g.) was added to dilute sulphuric acid (15 ml. of concentrated acid in 7·5 ml. of water) and the mixture heated with stirring on a steam-bath until a clear solution of nitrosylsulphuric acid was obtained. This was then cooled to 0° and stirred mechanically as the diamine (220 mg.) in pyridine (5 ml.) was added during an hour, after which stirring was continued for another hour at 0°. The solution was then diluted to 200 ml. by ice-water, and treated with urea (1 g.) in water (25 ml.). After a further hour's stirring at 0°, more water (200 ml.) was added and the mixture boiled until decomposition was complete. A yellowish-orange solution was obtained which when cooled was extracted with ether, and the diphenol isolated from the ethereal extract in the usual manner. Recrystallisation from benzene yielded the pure substance, m. p. and mixed m. p. 210° (62 mg.).

The authors thank Professor E. C. Dodds, F.R.S., who made the biological tests on this compound, and the Shell Company of Singapore, Limited, for a research fellowship (to F. M.).

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