Synthetic Œstrogens. Part III. The Free-radical Dimerisation of Arylacetic Acids and Arylacetones.*

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The synthesis of *meso*- and racemic αα′-di-*p*-hydroxyphenylsuccinic acid (I) by free-radical dimerisation of *p*-methoxyphenylacetic acid and its ethyl ester and subsequent hydrolysis is described. The dimerisation of some related acids and of certain arylacetones has also been studied.

The succinic acid derivative (I), prepared in one (presumably racemic) stereomodification only, has been reported to be biologically highly active (Hoch, *Compt. rend.*, 1950, **231**, 625). In a study of the stereochemical effect on biological activity, both *meso*- and racemic forms of this acid have now been prepared, by a free-radical dimerisation. Attempts to synthesise the higher homologues (II), (III), and (IV) by the same method were unsuccessful.

$$(p\text{-HO}\cdot C_6H_4\cdot \overset{\displaystyle R}{\overset{|}{C}}\cdot CO_2H)_2$$

(I): R = H (II): R = Me (III): R = Et (IV): R = Pr^n

"Dimerisation" (see footnote, Part II) of ethyl *p*-methoxyphenylacetate with di-*tert*.-butyl peroxide at 140°, as previously described, gave diethyl *meso*-αα′-di-*p*-methoxyphenylsuccinate. (In this work the higher-melting and less-soluble isomer is assigned the *meso*-configuration.) Treatment of this diester with alcoholic potassium hydroxide at 180° in a sealed tube resulted in hydrolysis, as well as isomerisation, to the racemic αα′-di-*p*-methoxyphenylsuccinic acid, m. p. 214—215° (acid A). Hydrolysis with the same reagent at 80°, however, was attended by partial isomerisation only, giving a mixture of the *meso*-acid, m. p. 272—273°, and an acid of m. p. 202—203°, resolidifying, and remelting at 238—239° (acid B); prolonged boiling with the reagent gave the acid B only. Since acid B has ultraviolet absorption ($\lambda_{max.}$ 277 mμ; ε 28,000) identical with that of the racemic acid A, it is believed to be a polymorphic form of the latter, rather than a mixture with the *meso*-form. Demethylation of acid B with hydrobromic acid furnished the required racemic hydroxy-acid (I).

Dimerisation of *p*-methoxyphenylacetic acid led to the *meso*-succinic acid whose stereochemical relation with the ester series was established by its complete isomerisation to the racemic acid A by potassium hydroxide in ethanol at 180° or in boiling diethylene glycol. (No demethylation took place under these conditions.) Demethylation of the *meso*-ester, by a modified method, furnished the *meso*-succinic acid (I).

The predominant formation of one stereomodification (*meso* in both cases) during free-radical dimerisation of both acid and ester was unexpected, but not without precedent. *E.g.*, Kharasch, McBay, and Urry (*J. Org. Chem.*, 1945, **10**, 394) in their dimerisation of dimethyl succinate with acetyl peroxide obtained a product containing $\lesssim$98% of the *meso*-isomer. Isomerisation of diastereoisomers of related acids under the action of alkalis is well known (see, *e.g.*, Wren and Still, *J.*, 1915, 107).

From the melting points, it appears that the diester, m. p. 145°, obtained by Hoch (*loc. cit.*) is the *meso*-form but that his methoxy- and hydroxy-acids, m. p. 220° and 230° respectively, consisted mainly, but not entirely, of the racemic diastereoisomers.

p-Methoxyphenylacetic acid was best prepared by a modification (see Experimental section) of the method of Levine, Eble, and Fischbach (*J. Amer. Chem. Soc.*, 1948, **70**, 1930). Other methods (Cain, Simonsen, and Smith, *J.*, 1913, 1035; Kondo and Oshima, *J. Pharm. Soc. Japan*, 1931, **51**, 979; Kindler, Metzendorf, and Dschi-yin-Kwok, *Ber.*, 1943, **76**, 308) involve difficultly accessible starting materials or give low yields.

meso-Di-*p*-methoxyphenylsuccinic acid (VI) is insoluble in the usual organic solvents,

* Part II, *J.*, 1954, 2570.

and demethylation by the usual procedures failed, but hydrogen bromide in glacial acetic acid gave the *meso*-hydroxy-acid (I) in satisfactory yield.

In attempted synthesis of the homologues (II), (III), and (IV), α-phenyl-propionic and -butyric acid and their ethyl esters, and ethyl α-phenylvalerate, were treated with di-*tert.*-butyl peroxide in the usual way, but the expected dimers were not obtained. (The *p*-hydroxy-groups were to be introduced subsequently *via* the dinitro-compounds, as in Part II.) Since ethyl phenylacetate reacts normally under similar conditions (Huang and Morsingh, unpublished results), presumably the α-alkyl substituents prevent the reaction, rendering disproportionation possible. A difference also exists between these acids and esters and the corresponding alkylated benzyl cyanides reported in Part II, but a parallel is found in the contrasting properties of the free 2-cyano-2-propyl and 2-ethoxycarbonyl-2-propyl radicals, the latter showing much greater tendency to disproportionation (Bickel and Waters, *Rec. Trav. chim.*, 1950, **69**, 312, 1490). Among aliphatic acids, *iso*butyric acid dimerises normally, though not in high yields, when treated with diacetyl peroxide at 80° (Kharasch and Gladstone, *J. Amer. Chem. Soc.*, 1943, **65**, 15) and *cyclo*hexanecarboxylic acid behaves similarly with di-*tert.*-butyl peroxide at 140°.

Another approach to the acids (II), (III), and (IV) was suggested by the work of Kharasch, McBay, and Urry (*J. Amer. Chem. Soc.*, 1948, **70**, 1269) who obtained diphenylsuccinic acid in unspecified yields by hypobromite oxidation of the dimer obtained from phenylacetone and diacetyl peroxide. 3-Phenylbutan-2-one with di-*tert.*-butyl peroxide gave a fair yield of mixed isomeric " dimers," which could not be separated; 3-*p*-methoxyphenylbutan-2-one also gave low yields of a mixture which on oxidation with sodium hypochlorite afforded small quantities of chlorine-containing acids. On the other hand, *p*-methoxyphenylacetone under the same conditions gave good yields of *meso*- and racemic 3 : 4-di-*p*-methoxyphenylhexane-2 : 5-dione. Oxidation of these with alkaline hypochlorite, however, also proved unsatisfactory: both isomers were unstable to alkali, being converted readily by 1% potassium hydroxide in aqueous alcohol into the same diaryl*cyclo*pentenone.

Both *meso*- and racemic αα'-di-*p*-hydroxyphenylacetic acid (I) were inactive in doses of 5 and 10 mg., respectively, when injected in aqueous solution into ovariectomised rats. This is not surprising in view of the total inactivity of *meso*- and racemic βγ-di-*p*-hydroxyphenyladipic acid (Dodds, Huang, Lawson, and Robinson, *Proc. Roy. Soc.*, 1953, *B*, **140**, 470; Lawson, personal communication).

Experimental

Ethyl p-*Methoxyphenylacetate.*—*p*-Anisaldehyde bisulphite compound (from 150 g. of anisaldehyde; cf. Levine *et al.*, *loc. cit.*) was added with stirring to an ice-cold solution of potassium cyanide (170 g. in *ca.* 250 c.c. of water), covered with ether (400 c.c.), to which had been added potassium hydroxide (4 g.) (essential for a good yield). The ether layer was separated, washed with a solution of sodium metabisulphite and then water, and dried. On removal of the ether and addition of light petroleum (b. p. 50—60°), the cyanohydrin crystallised (m. p. 61—63°; 148 g.). A portion (50 g.) was reduced and hydrolysed by 3 hours' refluxing with stannous chloride (100 g.) in acetic acid (100 c.c.), concentrated hydrochloric acid (100 c.c.), and hydriodic acid (7 c.c.; *d* 1·7). After cooling, the stannic chloride which separated was filtered off, and the filtrate diluted with water, extracted with carbon tetrachloride, and distilled, giving *p*-methoxyphenylacetic acid, b. p. 138—140°/2—3 mm., m. p. 82° (45 g.). This gave, with ethanol and sulphuric acid, the ethyl ester (27 g.), b. p. 100—102°/1 mm., n_D^{23} 1·5780.

Ethyl meso-αα'-*Di*-p-*methoxyphenylsuccinate.*—(*a*) Ethyl *p*-methoxyphenylacetate (18·2 g.) and di-*tert.*-butyl peroxide (10 g.) were heated in a sealed tube at 140—150° for 24 hr. After distillation of the volatile fractions and unchanged ester (12 g.), addition of methanol gave ethyl *meso*-αα'-di-*p*-methoxyphenylsuccinate (2·2 g.), m. p. 143—144° after recrystallisation from methanol (Hoch, *loc. cit.*, reports m. p. 145°).

(*b*) Ethyl *p*-methoxyphenylacetate (27 g.) and di-*tert.*-butyl peroxide (15 g.) were heated under reflux for 48 hr. After removal of unchanged ester (16 g.) and addition of methanol, the same dimeric *meso*-ester separated (m. p. 143—144°; 2·1 g.), and was filtered off. The filtrate was refluxed with 10% aqueous sodium hydroxide (50 c.c.) for 8 hr., cooled, extracted twice with ether, and acidified with 5N-sulphuric acid, and the precipitated acid was taken up in

ether. Removal of ether afforded the racemic *acid B*, which crystallised from ethanol in prisms, m. p. 202—203°, resolidifying, and remelting at 238—239° (2·1 g.) (Found: C, 65·1; H, 5·5. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%).

Hydrolysis and Isomerisation.—(*a*) The above succinic ester (0·50 g.) was heated in 15% alcoholic potassium hydroxide (15 c.c.) in a sealed tube at 180—190° for 6 hr. Water was added, and the product worked up as described above, giving racemic *αα'-di*-p-*methoxyphenylsuccinic acid A*, which crystallised from methanol in prisms, m. p. 214—215° (0·33 g.) (Found: C, 65·5; H, 5·6; OMe, 19·1. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5; OMe, 18·8%).

(*b*) The above ester (0·42 g.) was heated with 5% alcoholic sodium hydroxide (20 c.c.) for 1·5 hr. The product gave (i) racemic αα'-di-*p*-methoxyphenylsuccinic acid B, double m. p. 202—203°, 238—239° (0·22 g.) (Found: C, 65·7; H, 5·7%), and (ii) a small quantity of the *meso*-acid (*ca.* 30 mg.).

Demethylation.—The above racemic acid B (0·5 g.) was heated in acetic acid (5 c.c.) and hydrobromic acid (3 c.c.; *d* 1·47) at 80° for 5 hr. Water was added, and the acetic acid removed under a partial vacuum, the resulting solution being then extracted once with chloroform before exhaustive extraction with ether. Removal of ether afforded racemic *αα'-di*-p-*hydroxyphenylsuccinic acid*, m. p. 201—210° (0·18 g.) raised to 225—226° (decomp.) after six recrystallisations from benzene–ethanol (Hoch reports m. p. 230° for his impure acid) (Found: C, 63·0, 63·0; H, 4·9, 5·1. $C_{16}H_{14}O_6$ requires C, 63·5; H, 4·7%). The m. p. gradually dropped to 217—220° after a few weeks. The product was soluble in water. Demethylation with acetic and hydriodic acids was not successful.

meso-*αα'-Di*-p-*methoxyphenylsuccinic Acid.*—*p*-Methoxyphenylacetic acid (28 g.) and di-*tert.*-butyl peroxide (17·5 g.), heated for 48 hr. at 140°, deposited a solid, m. p. *ca.* 267° (5·1 g.), which was filtered off. It was practically insoluble in all the usual organic solvents, but when crystallised from much dioxan, gave the required *meso*-succinic acid, m. p. 272—273° (Found: C, 65·0; H, 5·4%). The filtrate was concentrated, and treated with ethanol to induce crystallisation. This failing, the mixture was esterified with ethanol (100 c.c.) and concentrated sulphuric acid (4 c.c.) to give, on distillation, the *meso*-ester obtained previously, m. p. 142—143° (*ca.* 1·7 g.). Thus no racemic acid was obtained in the above dimerisation.

Isomerisation.—(*a*) The above *meso*-succinic acid (0·50 g.), when heated at 190—200° for 16 hr. with a 15% alcoholic solution of potassium hydroxide (12 c.c.) in a sealed tube, gave the racemic acid, m. p. 207—209° (0·40 g.), raised to 214—215° after recrystallisation from ethanol, alone or mixed with the acid A obtained above.

(*b*) Heating with a solution of the same reactants in ethylene glycol under reflux for 4·5 hr. (210—220°) gave a lower yield (35%) of the racemic acid A. In each case no demethylation occurred.

Demethylation.—The above *meso*-acid (0·65 g.) was dissolved in boiling acetic acid (*ca.* 300 c.c.), cooled to *ca.* 70°, then saturated with dry hydrogen bromide, kept at this temperature for 36 hr., and finally heated at 100° for 5 hr. Water was added, and the solution concentrated under reduced pressure. This being repeated, the resulting aqueous solution was extracted once with chloroform, then four times with ether. The ethereal extracts, after drying, were concentrated, and the solid which separated (0·45 g.) was recrystallised from ethanol–benzene, giving *meso-αα'-di*-p-*hydroxyphenylsuccinic acid*, m. p. 284° (decomp.), becoming slightly yellow at *ca.* 260° (Found: C, 63·5; H, 5·0. $C_{16}H_{14}O_6$ requires C, 63·5; H, 4·7%). It is soluble in cold water.

Dimerisation of cyclo*Hexanecarboxylic Acid.*—This acid (25 g.) and di-*tert.*-butyl peroxide (17 g.), after refluxing for 48 hr., gave on distillation (i) unchanged acid (15 g.), (ii) *di*cyclo*hexyl-1 : 1'-dicarboxylic anhydride*, b. p. 140—143°/0·5 mm. (3·6 g.), m. p. 144—145° (from methanol) (Found: C, 71·5; H, 8·55. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%), and (iii) a residue (3·2 g.), sparingly soluble in ethanol, but soluble in benzene, and decolorising bromine in carbon tetrachloride. The anhydride was insoluble in aqueous sodium carbonate, but dissolved in aqueous sodium hydroxide by which it was hydrolysed to the *acid*, m. p. 255° after recrystallisation from ethanol–benzene (Found: C, 66·1; H, 8·7. $C_{14}H_{22}O_4$ requires C, 66·6; H, 8·5%).

Dimerisation of 3-*Phenylbutan*-2-*one.*—This ketone (33 g.) (Suter and Weston, *J. Amer. Chem. Soc.*, 1942, **64**, 533) and the peroxide (20 g.) were heated at 140° for 48 hr., and the product distilled, giving (i) unchanged ketone (20 g.), (ii) a viscous oil, b. p. 156—159°/2 mm. (6·5 g.), probably a mixture of *meso*- and racemic 3 : 4-dimethyl-3 : 4-diphenylhexane-2 : 5-dione (Found: C, 82·0; H, 7·2. Calc. for $C_{20}H_{22}O_2$: C, 81·6; H, 7·5%). It was soluble in methanol and ethyl acetate, but attempts at recrystallisation failed.

Dimerisation of p-*Methoxyphenylacetone.*—The ketone (55 g.) (Shepard, Noth, Porter, and

Simmans, *ibid.*, 1952, **74**, 4611) and di-*tert.*-butyl peroxide (30 g.), after 48 hr. under reflux, deposited a mixture of *meso*- and racemic **3 : 4-*di*-p-*methoxyphenylhexane*-2 : 5-*dione*** which was filtered off. Boiling methanol removed the racemic isomer, which separated from this solvent in light yellow prisms, m. p. **153—154°** (6·7 g.) (Found : C, 73·4; H, 6·7. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%). The meso-*isomer*, which was sparingly soluble in methanol, crystallised from dioxan in prisms, m. p. **201—202°** (8·4 g.) (Found : C, 73·7; H, 7·0%). The filtrates were concentrated and distilled, giving unchanged starting material (30 g.), and more of the racemic isomer, m. p. **140—150°** (4·1 g.).

Cyclisation (cf. Hunsdiecker, *Ber.*, 1942, **75**, 455).—The above *meso*-diketone (6·4 g.) in dioxan (50 c.c.) was refluxed with potassium hydroxide (2 g.) in 50% aqueous ethanol (180 c.c.) for 5 hr., during which a cherry-red colour developed. Water was added, and the product taken up in ether, washed with water, and dried. Removal of the ether gave **4 : 5-*di*-p-*methoxyphenyl*-3-*methyl*cyclo*pent*-2-*en*-1-*one***, m. p. **132—135°** (4·8 g.), raised to **134—135°** by recrystallisation from methanol, from which it separated in rectangular prisms (Found : C, 77·6; H, 6·5. $C_{20}H_{20}O_3$ requires C, 77·9; H, 6·5%). The *semicarbazone*, obtained in poor yield in aqueous ethanol, crystallised in pale yellow needles, m. p. 184° (Found : N, 11·6. $C_{21}H_{23}O_3N_3$ requires N, 11·5%).

The racemic diketone (5 g.) gave, on similar treatment with alcoholic potassium hydroxide (dioxan being omitted), the same *cyclo*pentenone (4·5 g.).

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