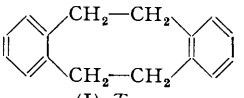
265. *Eight- and Higher-membered Ring Compounds. Part VII.* The Lactone of 2′-Hydroxydibenzyl-2-Carboxylic Acid.*

By WILSON BAKER, W. D. OLLIS, and T. S. ZEALLEY.

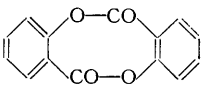
Compounds of the type of di-*o*-xylylene (I) might possibly exist in both *cis*- and *trans*-forms; di-*o*-xylylene is the *trans*-molecule, whilst disalicylide (II) possesses the *cis*-configuration. We have now prepared the 8-membered lactone of 2′-hydroxydibenzyl-2-carboxylic acid (III) in the hope that two stereoisomerides might be isolated, but only one lactone is formed and its dipole moment shows that it has the *cis*-configuration. The lactone is prepared from the hydroxy-acid by a variety of methods; *e.g.*, reaction with trifluoroacetic anhydride gives a 95% yield. Dehydration of *m*- and *p*-hydroxybenzoic acids has given only material of high molecular weight.

CONSIDERABLE interest attaches to the stereochemistry of compounds of the type of di-*o*-xylylene (I) in which two benzene rings are fused symmetrically to an 8-membered ring. It is possible that such molecules (in which any or all of the methylene groups may be replaced by suitable bivalent atoms or groups) might be isolable in two stereoisomeric forms, a rigid (in some cases centrosymmetrical) *trans*-form (chair), and a mobile, folded, *cis*-form (trough). Interconversion of the *cis*- and the *trans*-form without bond breaking necessitates passage through a very highly strained configuration. The *cis*-form can pass without strain into a second *cis*-form folded in the opposite way, and these two would be identical, *e.g.*, in the case of di-*o*-xylylene, or optical enantiomorphs, *e.g.*, in the case of disalicylide (II); intermediate between the two *cis*-forms is a skew form which, like the folded *cis*-forms, has no centre of symmetry.

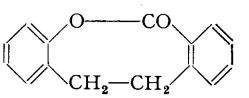
The possibility of stereoisomerism of this type was first suggested by Höhn (see Richter-Anschütz, "Chemie der Kohlenstoff-Verbindungen," 1935, Vol. II, 2, 392) to account for the existence of two supposed stereoisomerides of disalicylide, and it was discussed in some detail by Baker, Banks, Lyon, and Mann (*J.*, 1945, 27). It has been shown, however (Part II, Baker, Ollis, and Zealley, *J.*, 1951, 202) that one of the supposed disalicylides was trisalicylide, and the disalicylide has been proved by dipole-moment measurement to possess the folded *cis*-configuration (Edgerley and Sutton, *J.*, 1951, 1069). Contrary to previous claims, it has also been shown that only one stereoisomeride exists of di-*o*-, di-*m*-, and di-*p*-cresotide (Part III, Baker, Gilbert, Ollis, and Zealley, *J.*, 1951, 210) and of dithymotide (Part VI, Baker, Gilbert, and Ollis, preceding paper), and that these all have the *cis*-configuration (Edgerley and Sutton, *loc. cit.*; Saxby and Sutton, forthcoming publication). On the other hand, Davidson (quoted in *J.*, 1945, 30) has shown by *X*-ray methods that di-*o*-xylylene (dibenzo*cyclo*octa-1 : 5-diene) (I) has a centre of symmetry, and is, therefore, the *trans*-isomeride; and it may be presumed that molecules of this kind will exist in the *trans*-form unless they possess some constraining feature; for example, in disalicylide, resonance in the lactone groupings causes the molecule to take up the *cis*-form as this is the only form in which the lactone group can be planar (see discussion in Part II, *loc. cit.*).



(I) *Trans*



(II) *Cis*



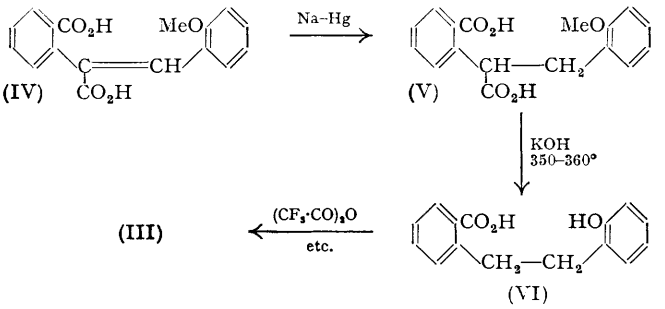
(III)

In considering which molecules of the type under discussion are most likely to exist in stereoisomeric forms, we have thought it worth while to synthesise the lactone of 2′-hydroxydibenzyl-2-carboxylic acid (III), in which the dimethylene group would favour the *trans*- and the lactone group the *cis*-configuration. Synthesis of the lactone was finally achieved, but only of one form, and this has been shown, by its high dipole moment (4·09 D), to possess the extreme folded configuration (Saxby and Sutton, forthcoming publication).

* Part VI, preceding paper.

Clearly the resonance energy requirements of the lactone grouping control the stereochemistry of the molecule.

The synthesis of the lactone (III) was carried out as follows. Reaction of either homophthalic acid or its anhydride with *o*-methoxybenzaldehyde in presence of acetic anhydride and sodium acetate gave a mixture of the *cis*- and the *trans*-isomer of *o*-methoxybenzylidenehomophthalic acid (IV). Reduction of each stereoisomer with sodium amalgam gave the same saturated acid (V), so that for preparative purposes they need not be separated. The acid (V) when fused for a few minutes with potassium hydroxide at 350—360° underwent simultaneous decarboxylation and demethylation, giving the acid (VI) in 57% yield; the structure of (VI) is proved by oxidation to phthalic acid and by formation of an acetyl derivative.

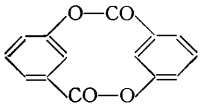


The dehydration of the acid (VI) to give the 8-membered lactone (III) presents several points of interest, and is a reaction involving the rigid-group principle in large-ring formation which was discussed in Part I of this series (Baker, McOmie, and Ollis, *J.*, 1951, 200). When heated with acetic anhydride and anhydrous sodium acetate the acid yielded simply the *O*-acetyl derivative, in contrast with the formation of a seven-membered lactone when 2-carboxy-2′-hydroxydiphenylmethane is treated with acetic anhydride (see following paper). When this acetyl derivative was heated at atmospheric pressure it lost acetic acid, and the sublimed product yielded some 10% of the lactone (III); this method is analogous to one of those employed in preparing di- and tri-salicylides and -cresotides from the *O*-acetyl-salicylic and -cresotic acids. Yields of the lactone (III) of 40—60% were obtained by dehydration of the acid (VI) with phosphoric anhydride in benzene, with phosphorus oxychloride in benzene, or with thionyl chloride followed by diethylaniline (cf. formation of salicylides and cresotides). By far the best reagent is trifluoroacetic anhydride (Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2977), which when employed in benzene solution gave the lactone in 95% yield. The lactones (III) prepared by all these methods were identical, and no indication could be obtained of the formation of a stereoisomer. The lactone (III) is readily hydrolysed by alkali, being much less stable in this respect than the closely related disalicylide, but, whereas disalicylide is rapidly hydrolysed by boiling with dilute acetic acid, the lactone (III) is almost unaffected by this treatment.

In an attempt to prepare the 8-membered cyclic ether corresponding to (III), having CH_2 in place of CO, the acid (VI) was reduced with lithium aluminium hydride to 2-hydroxy-2′-hydroxymethyldibenzyl, but the replacement of the aliphatic hydroxyl group by chlorine and subsequent cyclisation have not been successfully carried out.

In view of the successful synthesis of di-*m*-xylylene and of tri-*p*-xylylene by the Wurtz–Fittig reaction (Part IV, Baker, McOmie, and Norman, *J.*, 1951, 1114) we have investigated the dehydration of *m*- and *p*-hydroxybenzoic acids by the various methods which have been used for the preparation of cyclic di- and higher-anhydro-derivatives of *o*-hydroxybenzoic acids (see Parts II and III, *loc. cit.*). In no case, however, was anything but material of high molecular weight obtained, and the failure in the *m*-series to form the 10-membered lactide (VII) is probably due to the fact that the ester bridges are some 0·2 Å shorter than the dimethylene bridges of di-*m*-xylylene, so that steric interaction

between the two internal CH groups would be greater even than in di-*m*-xylylene (see Part IV, *loc. cit.*, p. 1115).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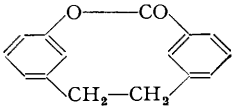
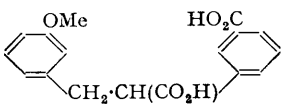

(VIII)


(IX)

The synthesis of the analogous lactone (VIII), which is more likely to be capable of formation than the lactide (VII), was therefore attempted by a series of reactions parallel to those used for the preparation of the lactone (III). *m*-Methoxybenzaldehyde was condensed with *iso*homophthalic acid and the product reduced by sodium amalgam to the acid (IX), but alkaline decarboxylation and demethylation could not be effected as with the isomeride (V), and only the demethylated dicarboxylic acid was isolated. Decarboxylation of (IX) with copper chromite was not successful.

Experimental

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and by Mr. W. M. Eno, Bristol.

cis- *and* trans-o-*Methoxybenzylidenehomophthalic Acids* (α-o′-*Carboxyphenyl*-2-*methoxycinnamic Acids*) (IV) —A mixture of homophthalic acid (2·2 g.) (Whitmore and Cooney, *J. Amer. Chem. Soc.*, 1944, **66**, 1239) or homophthalic anhydride (see Price, Lewis, and Meister, *ibid.*, 1939, **61**, 2762) (2·0 g.), *o*-methoxybenzaldehyde (2·01 g.), fused sodium acetate (1·01 g.), and redistilled acetic anhydride (5·04 g.) was heated at 160° for 3·5 hours, cooled, and poured into 2N-sodium hydroxide (100 c.c.). After being shaken at 100° for 15 minutes, the mixture was filtered, giving a filtrate *A* and a yellow solid (0·9 g.). This solid was heated with more 2N-sodium hydroxide until it dissolved (solution *B*).

Filtrate (*A*) was washed with ether, acidified, and extracted with ether. The extract, after drying ($MgSO_4$), yielded a gum, which was crystallised from benzene, and the solid (2·4 g., 65%), m. p. 195°, was recrystallised from ethyl acetate or aqueous ethanol, giving an *acid* (*isomer A*) (2·05 g.) as colourless rhombs, m. p. 210—211° (rapid heating) [Found : C, 68·1; H, 4·8; OMe, 10·9%; equiv., 149. $C_{14}H_9(OMe)(CO_2H)_2$ requires C, 68·4; H, 4·7; OMe, 10·4%; equiv., 149].

Solution *B* similarly gave a solid (0·36 g., 10%), m. p. 208—210°, which after three recrystallisations from methanol gave *isomer B* (0·21 g.) as colourless prisms, m. p. 218—221° (dependent on rate of heating) (Found : C, 68·3; H, 5·2; OMe, 10·0%; equiv., 162). These isomeric acids gave different ultra-violet light extinction curves in ethanol, but after irradiation for 12 hours with ultra-violet light the two solutions gave identical curves.

In some experiments conducted at 180°, isomer *B* was not isolated, and when the benzene mother-liquors of the first crystallisation of isomer *A* were concentrated, a crystalline solid (0·26 g.), m. p. 270—275°, separated which, after recrystallisation from ethanol or *n*-amyl acetate, gave a *substance* (0·14 g.) as colourless needles, m. p. 275—277° (decomp.) (Found : C, 75·5; H, 4·8; OMe, 8·0%; equiv., 410. $C_{25}H_{18}O_5$ requires C, 75·3; H, 4·6; OMe, 7·8%; equiv., 398). This compound was not further investigated.

α-o-*Methoxybenzylhomophthalic Acid* (α-o-*Carboxyphenyl*-β-o′-*methoxyphenylpropionic Acid*) (V).—(*a*) *o*-Methoxybenzylidenehomophthalic acid (isomer *A*) (2·66 g.), 2% sodium amalgam (250 g.), and water (100 c.c.) were left at room temperature for 24 hours with occasional shaking. Acidification gave a precipitate of the *acid* (V) (2·33 g., 88%), m. p. 165—166°, which, after recrystallisation from aqueous ethanol, formed colourless needles, m. p. 166° (Found : C, 68·1; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%).

(*b*) Similarly reduction of the isomer *B* gave the acid (V) (yield 86%), m. p. and mixed m. p. 166°.

(*c*) Homophthalic acid (11·1 g.), *o*-methoxybenzaldehyde (10 g.), anhydrous sodium acetate (6 g.), and acetic anhydride (24 c.c.) were heated at 160—170° for 2·25 hours, and the product boiled for 1 hour with 30% aqueous sodium hydroxide (150 c.c.) and poured into water (1 l.). Acidification and cooling to 0° gave the mixed acids (IV) (17·4 g., 95%) which were reduced with 2·5% sodium amalgam and water (500 c.c.), giving finally the acid (V) (15·9 g., 91%), m. p. 165—166°.

2'-Hydroxydibenzyl-2-carboxylic Acid (VI).—Many experiments showed that the following method was the most satisfactory.

α-*o*-Methoxybenzylhomophthalic acid (V) (5·0 g.) was added to fused potassium hydroxide (30 g.) in a nickel crucible in a metal-bath at 350—360° and the mixture stirred continuously with a nickel rod. The initial effervescence ceased after 3·25 minutes and 15 seconds later the melt was cooled and dissolved in water (250 c.c.) (the success of this reaction is markedly dependent upon the precise conditions under which it is carried out). The alkaline solution was filtered and acidified, giving crystalline material (2·8 g., 70%), m. p. 133—137°. Recrystallisation from carbon tetrachloride (50 c.c.) or benzene gave *2'-hydroxydibenzyl-2-carboxylic acid* (VI) (2·3 g., 57%) as colourless needles, m. p. 140—141° (Found: C, 74·4; H, 6·1%; equiv., 255. $C_{14}H_{13}O{\cdot}CO_2H$ requires C, 74·3; H, 5·8%; equiv., 242). This acid sublimed unchanged at 180—200°/16 mm.

Oxidation of this acid (46 mg.) with a hot saturated solution of potassium permanganate in acetone gave phthalic acid (23 mg.).

2'-Acetoxydibenzyl-2-carboxylic Acid.—2'-Hydroxydibenzyl-2-carboxylic acid (VI) (1 g.), acetic anhydride (10 c.c.), and fused sodium acetate (0·25 g.) were boiled for 2 hours, cooled, and poured into water. The solid (0·985 g., 87%), m. p. 95—102°, was recrystallised from benzene–light petroleum (b. p. 60—80°), giving *2'-acetoxydibenzyl-2-carboxylic acid* as colourless needles, m. p. 123° (Found: C, 71·8; H, 5·6%; equiv., 298. $C_{16}H_{15}O_2{\cdot}CO_2H$ requires C, 71·8; H, 5·7%; equiv., 284). This acid sublimed unchanged at 180—190°/1 mm.

Lactone of 2'-Hydroxydibenzyl-2-carboxylic Acid (III).—(a) *Action of thionyl chloride and diethylaniline on 2'-hydroxydibenzyl-2-carboxylic acid* (VI). A mixture of 2'-hydroxydibenzyl-2-carboxylic acid (0·25 g.), anhydrous benzene (20 c.c.), and purified thionyl chloride (0·16 g.) was kept at 45—50° for 1 hour and boiled under reflux for ½ hour. Diethylaniline (0·3 g.) was then added and after a further 2 hours' boiling the solvents were removed and the residue was shaken with ether and 2N-hydrochloric acid. The ethereal layer was washed with 2N-sodium hydroxide, dried ($MgSO_4$), and evaporated, yielding a dark residue (196 mg.) which gave a colourless sublimate (78 mg., 35%) at 160—170°/16 mm. Crystallisation from light petroleum (b. p. 100—120°) then gave the *lactone* (III) as colourless rhombs, m. p. 115—116° [Found: C, 80·6; H, 5·4%; *M*(Rast), 208; *M* (ebullioscopic in benzene), 228. $C_{15}H_{12}O_2$ requires C, 80·3; H, 5·4%; *M*, 224]. The yield fell to 22% after 12 hours' heating.

(b) *Action of trifluoroacetic anhydride on 2'-hydroxydibenzyl-2-carboxylic acid* (VI). Trifluoroacetic anhydride (6 c.c.) was added to a solution of the acid (4·55 g.) in anhydrous benzene (300 c.c.) at 35°, and after 1 hour at room temperature the solution was heated under reflux for a further hour, then washed with aqueous sodium carbonate and with water, and dried ($MgSO_4$), and the benzene removed under diminished pressure. The residue was dissolved in hot ether (100 c.c.), and this solution, after concentration, was left in a refrigerator overnight, giving the lactone (III) (4·0 g.; 95%), m. p. and mixed m. p. 115—116°.

The yield was not so good in the absence of a solvent; *e.g.*, the acid (VI) (0·5 g.) and trifluoroacetic anhydride (1·5 g.), after 30 minutes' heating under reflux, gave the lactone in 65% yield.

(c) *Action of heat on 2'-acetoxydibenzyl-2-carboxylic acid.* The acetoxy-acid was heated at 250—260° at atmospheric pressure, acetic acid being evolved. The residue was then sublimed at 250°/3 mm., and the sublimate, after being washed with 2N-sodium hydroxide, gave the lactone (III) (yield, *ca.* 10%), m. p. and mixed m. p. 114°.

(d) *Reaction of 2'-hydroxydibenzyl-2-carboxylic acid* (VI) *with phosphorus oxychloride in benzene.* The acid (1·5 g.), redistilled phosphorus oxychloride (1·0 g.), and anhydrous benzene (25 c.c.) were heated under reflux for 3 days. The decanted benzene solution, after being washed with 10% aqueous sodium carbonate and dried ($MgSO_4$), gave a crystalline residue (1·02 g., 63%) of the lactone (III), m. p. and mixed m. p. 115° after recrystallisation from ether.

(e) *Reaction of 2'-hydroxydibenzyl-2-carboxylic acid* (VI) *with phosphoric anhydride.* The acid (1·0 g.), phosphoric anhydride (4·0 g.), and anhydrous benzene (200 c.c.) were heated under reflux for 4 hours, cooled, and filtered. After being washed with 10% aqueous sodium carbonate and dried ($MgSO_4$), the benzene solution gave a solid residue (0·52 g., m. p. 95—110°) which, after crystallisation from ether, gave the lactone (III) (0·5 g.), m. p. and mixed m. p. 115°.

Alkaline Hydrolysis of the Lactone of 2'-Hydroxydibenzyl-2-carboxylic Acid (III).—The lactone (III) (115 mg.) and 2N-aqueous sodium hydroxide (10 c.c.) were boiled until a clear solution was obtained (5 minutes). Acidification then gave 2'-hydroxydibenzyl-2-carboxylic acid (VI) (115 mg., 93%), m. p. and mixed m. p. 140—141°. At room temperature a solution of the

lactone in ethanol was hydrolysed in ½ hour to the extent of 19% with 10% aqueous sodium carbonate, and 70% with 10% aqueous sodium hydroxide.

2-Hydroxy-2'-hydroxymethyldibenzyl.—2'-Hydroxydibenzyl-2-carboxylic acid (VI) (2 g.) in anhydrous ether (70 c.c.) was added dropwise to a stirred boiling solution of lithium aluminium hydride (1 g.) in anhydrous ether (100 c.c.) in an atmosphere of nitrogen. Water and dilute hydrochloric acid were added, and the dried ($MgSO_4$) ethereal layer and extracts gave a residue which was crystallised from aqueous ethanol. *2-Hydroxy-2'-hydroxymethyldibenzyl* separated as fine needles (1·44 g., 76%), m. p. 109·5° (Found: C, 78·9; H, 7·2. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·0%).

m-*Methoxybenzylidenehomo*iso*phthalic Acid* (α-m'-*Carboxyphenyl-3-methoxycinnamic Acid*).—A mixture of homo*iso*phthalic acid (3·2 g.) [prepared from *m*-cyanobenzyl cyanide (Reinglas, *Ber.*, 1891, **24**, 2416) by hydrolysis with dilute sulphuric acid (Kommpa and Hirn, *Ber.*, 1903, **36**, 3611)], *m*-methoxybenzaldehyde (2·86 g.), fused potassium acetate (1·77 g.), and acetic anhydride (7·45 g.) was heated under reflux (oil-bath at 170°) for 4 hours, cooled, diluted with water, and extracted with ether. The extract gave a product which was then dissolved in aqueous sodium carbonate, shaken with ethyl acetate and ether, and acidified. The solid (4·8 g., 90%) was recrystallised from aqueous acetic acid giving the *acid* (3 g.) as yellow rhombs, m. p. 216° (Found: C, 68·5; H, 4·8. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%).

α-m-*Methoxybenzylhomo*iso*phthalic Acid* (α-m-*Carboxyphenyl*-β-m-*methoxyphenylpropionic Acid*) (IX).—The foregoing acid (2·37 g.), 2% sodium amalgam (230 g.), and water (90 c.c.) were left for 6 days. Acidification precipitated the *acid* (IX) (2·28 g., 95%), m. p. 158—160°; after recrystallisation from aqueous acetic acid it was obtained as colourless microscopic crystals, m. p. 162—163° (Found: C, 68·3; H, 5·5. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). This acid was not decarboxylated when heated in quinoline with or without copper chromite. Attempted decarboxylation by fusion with alkali gave the following result.

α-m-*Hydroxybenzylhomo*iso*phthalic Acid* (α-m-*Carboxyphenyl*-β-m-*hydroxyphenylpropionic Acid*).—The acid (IX) (0·5 g.) was added to stirred, fused potassium hydroxide (3 g.) in a nickel crucible heated in a metal bath at 290°, and after 95 seconds it was rapidly cooled. The reaction mixture was dissolved in water, filtered, acidified, and extracted with ether (45 c.c.). The extract yielded the *hydroxy-acid* which crystallised from dilute hydrochloric acid as white rhombs (0·176 g., 37%), m. p. 170° [Found: C, 66·5; H, 4·9; OMe, 0·0%; equiv., 151. $C_{14}H_{12}O(CO_2H)_2$ requires C, 67·0; H, 4·9%; equiv., 143].

3 : 3-*Dibenzylphthalide.*—An ethereal solution (100 c.c.) of benzylmagnesium bromide prepared from benzyl bromide (13·6 g.) and magnesium (1·35 g.) was added (½ hour) to a boiling, stirred solution of phthalic anhydride (7·5 g.) in anhydrous benzene (150 c.c.) in an atmosphere of nitrogen. After a further 2·5 hours' heating, the mixture was poured on ice and 2N-hydrochloric acid (200 c.c.), the benzene layer separated, and the aqueous layer extracted with ether. The combined extracts were washed with 2N-sodium carbonate (acidification of which gave phthalic acid, 5·5 g.), dried ($MgSO_4$), and evaporated, leaving a residue (6·0 g.) which was crystallised from benzene. 3 : 3-*Dibenzylphthalide* forms needles, m. p. 205° (Found: C, 84·3; H, 5·7. $C_{22}H_{18}O_2$ requires C, 84·1; H, 5·8%).

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