

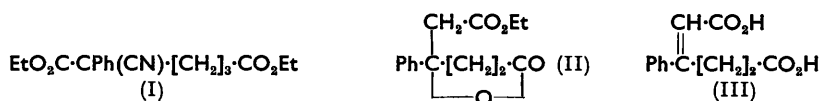
851. *The Synthesis of α - and β -Phenyladipic Acid.*

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Syntheses are described of α - and β -phenyladipic acid in yields which are greatly superior to those previously reported.

SEVERAL methods of preparing α - and β -phenyladipic acid have been described but where the yields are based on readily available materials they are below 10% overall. For example, Case ¹ obtained α -phenyladipic acid in about 6% yield from propane-1 : 3-diol and ethyl phenylmalonate. Baker and Jones ² synthesized this acid from ethyl α -cyano- α -phenylacetate and 3-chloropropyl cyanide in 39% yield, but as the chlorocyanide is prepared from propane-1 : 3-diol in 25% yield,³ the overall value from readily available compounds is 10%. It is impossible to estimate the yield in Kuhn and Michel's synthesis ⁴ because the essential information is not given for each of the six stages. Oxidation of 3-phenylcyclohexene with potassium permanganate to α -phenyladipic acid has been described ⁵ but the percentage conversion is not recorded.

The need for several hundred grams of each acid in these Laboratories stimulated a search for alternative and better syntheses. The following synthesis, from commercially available starting materials, proved satisfactory and gave consistently good yields of α -phenyladipic acid. Treatment of γ -butyrolactone with hydrogen bromide followed by thionyl chloride and ethanol gave ethyl γ -bromobutyrate.⁶ This was condensed with ethyl α -cyano- α -phenylacetate in the presence of sodium ethoxide to yield ethyl α -cyano- α -phenyladipate (I) which was simultaneously hydrolysed and decarboxylated to α -phenyladipic acid (cf. Baker and Jones ²). The overall yield from γ -butyrolactone was 61%. Ethyl α -cyano- α -phenylacetate was prepared by Wideqvist's method ⁷ since higher and more consistent yields were obtained than by Horning and Finelli's procedure.⁸



β -Phenyladipic acid was first synthesised (in 8% yield) by Manske ⁹ from ethyl phenylsuccinate. Von Braun and Weissbach's synthesis ¹⁰ from 4-hydroxydiphenyl followed in the same year, but yields are not given for all the steps. A more recent synthesis in 10% yield is that by Price and Karabinos ¹¹ from 2-hydroxydiphenyl by a series of reductions and oxidations. The synthesis of β -2-naphthyladipic acid by Bachmann and Morin ¹² furnished a method which, if it could be adapted to the benzene series, promised to be superior. Friedel-Crafts acylation of benzene with succinic anhydride ¹³ followed by esterification gave ethyl β -benzoylpropionate.¹⁴ The latter was treated with ethyl bromoacetate and zinc dust to produce the lactone (II). Ring opening and hydrolysis of this with aqueous-methanolic sodium hydroxide and hydrogenation of the resulting syrup gave β -phenyladipic acid. The overall yield from succinic anhydride was 42%. A lower yield

¹ Case, *J. Amer. Chem. Soc.*, 1933, **55**, 2927.

² Baker and Jones, *J.*, 1951, 787.

³ Allen, *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 156.

⁴ Kuhn and Michel, *Ber.*, 1938, **71**, 1119.

⁵ Berlande, *Bull. Soc. chim. France*, 1942, **9**, 641.

⁶ Avison and Morrison, *J.*, 1950, 1471.

⁷ Wideqvist, *Arkiv Kemi, Mineralog., Geol.*, 1947, **24**, B, No. 14.

⁸ Horning and Finelli, *Org. Synth.*, 1950, **30**, 43.

⁹ Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1104.

¹⁰ Von Braun and Weissbach, *Ber.*, 1931, **64**, 1785.

¹¹ Price and Karabinos, *J. Amer. Chem. Soc.*, 1940, **62**, 1159.

¹² Bachmann and Morin, *ibid.*, 1944, **66**, 553.

¹³ Somerville and Allen, *Org. Synth.*, Coll. Vol. II, p. 81.

¹⁴ Kugel, *Annalen*, 1897, **299**, 50; Adkins and Scanley, *J. Amer. Chem. Soc.*, 1951, **73**, 2854.

of β -phenyladipic acid was obtained when crystalline $\alpha\beta$ -dihydro- γ -phenylmuconic acid (III) was isolated from the syrup and subsequently hydrogenated to β -phenyladipic acid.¹⁵

EXPERIMENTAL

Ethyl γ -Bromobutyrate.— γ -Butyrolactone (64.5 g.) was dissolved in aqueous hydrobromic acid (d 1.47; 90 ml.), cooled to 0°, and saturated with hydrogen bromide. Saturation took much less time than if the lactone was dissolved in water.⁶ Ethyl γ -bromobutyrate (110.3 g., 75%) b. p. 77—80°/6 mm., n_D^{20} 1.4520, was isolated as described.⁶

Ethyl α -Cyano- α -phenylacetate.—This compound, b. p. 135°/3.5 mm., n_D^{20} 1.5040, was prepared as described by Wideqvist,⁷ in 86% yield.

Ethyl α -Cyano- α -phenyladipate ¹⁸ (I).—A solution of sodium (10.6 g.) in dry ethanol (170 ml.) was placed in a 1 l. flask fitted with a reflux condenser carrying a drying tube. Ethyl cyano-phenylacetate (92.8 g.) was added, followed by ethyl γ -bromobutyrate (87.3 g.). The mixture was refluxed for 6 hr. during which sodium bromide separated. Ethanol was distilled off and water (150 ml.) was added. Ether extracts of this solution were combined and dried and the solvent was removed. Distillation of the residue gave ethyl α -cyano- α -phenyladipate (116.0 g., 85%), b. p. 140—146°/0.02 mm., n_D^{20} 1.4948, as an almost colourless oil.

α -Phenyladipic Acid.—The above ester (120 g.) was refluxed for 27 hr. with concentrated hydrochloric acid (600 ml.). The crystals which separated on cooling were filtered off and washed with cold water. Recrystallisation from water gave α -phenyladipic acid (85.0 g., 96%), m. p. 137° (Found: C, 65.1; H, 6.5. Calc. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.3%). Baker and Jones³ give m. p. 137—138°.

γ -Oxo- γ -phenylbutyric Acid.—In order to minimise the tendency for the reactants to form a pasty mass, Somerville and Allen's method¹³ was modified in that succinic anhydride and aluminium chloride were added in small amounts to the stirred benzene during 1 hr. Isolation of the acid in 92% yield was carried out in the usual way.

Ethyl γ -Oxo- γ -phenylbutyrate.—The acid was esterified by refluxing ethanol and concentrated sulphuric acid for 6 hr. The excess of ethanol was distilled off and the residual oil was taken up in ether. Sulphuric acid was removed by washing with dilute sodium carbonate solution and with water, and the ethereal solution was dried ($MgSO_4$). Removal of the solvent and distillation of the residue gave an 89% yield of the ester, b. p. 120°/0.2 mm., n_D^{20} 1.5196.

γ -Ethoxycarbonylmethyl- γ -phenyl- γ -butyrolactone (II).—To purified zinc powder (8.2 g.), suspended in dry benzene (20 ml.), stirred and heated under reflux, was added dropwise during 5 min. a mixture of ethyl γ -oxo- γ -phenylbutyrate (21.4 g.) and ethyl bromoacetate (20.8 g.). Heating was discontinued where necessary to keep the reaction under control. The greenish-brown mixture was heated under reflux for 50 min., cooled, diluted with benzene, and poured into 20% sulphuric acid (100 ml.). The benzene layer was separated, then washed with aqueous sodium carbonate solution, and with water. After drying and removal of the solvent, distillation gave the lactone ester (20.7 g., 80%), b. p. 96—98°/0.1 mm., n_D^{20} 1.5144 (Found: C, 68.7; H, 6.8. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%).

$\alpha\beta$ -Dihydro- γ -phenylmuconic Acid.—The above lactone (15.3 g.) was heated under reflux for 4.5 hr. in methanol (200 ml.) and water (80 ml.) containing sodium hydroxide (4.8 g.). Methanol was then distilled off and the solution was acidified. The brown oil which separated was extracted with ether, and the solution dried ($MgSO_4$) and concentrated. Colourless crystals separated after 2 days. Recrystallisation from benzene gave $\alpha\beta$ -dihydro- γ -phenylmuconic acid (4.7 g., 35%), m. p. 144° (Found: C, 65.5; H, 5.7. $C_{12}H_{12}O_4$ requires C, 65.5; H, 5.5%).

β -Phenyladipic Acid.—(a) From γ -ethoxycarbonylmethyl- γ -phenyl- γ -butyrolactone. The lactone (27.4 g.) was heated under reflux for 4.5 hr. with N -sodium hydroxide (219 ml.) and methanol (285 ml.). After evaporation of the methanol and acidification, the mixture was extracted with ethyl acetate. The combined extracts were shaken in an atmosphere of hydrogen in the presence of 5% platinum-charcoal (1.5 g.) until the uptake of hydrogen ceased. After filtration the solvent was allowed to evaporate slowly, whereupon crystals of β -phenyladipic acid (17.0 g., 69%), m. p. 130—135°, were obtained. Recrystallisation from ethyl acetate-benzene gave crystals (16.0 g., 65%), m. p. 146—147° (Found: C, 64.4; H, 6.4. Calc. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.3%).

(b) From $\alpha\beta$ -dihydro- γ -phenylmuconic acid (III). A solution of $\alpha\beta$ -dihydro- γ -phenylmuconic

¹⁵ Cf. Dreiding and Tomasewski, *J. Amer. Chem. Soc.*, 1954, **76**, 540.

¹⁶ Wideqvist, *Arkiv Kemi*, 1951, **3**, No. 7, p. 59.

acid (5.0 g.) in ethyl acetate (100 ml.) was shaken with 10% platinum-charcoal (1 g.) in hydrogen. When hydrogen uptake ceased the catalyst was filtered off and the solvent allowed to evaporate slowly, yielding crystals of β -phenyladipic acid (4.6 g., 91%), m. p. 148°. Price and Karabinos¹¹ give m. p. 147—148°.

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