94. β-*Aroylpropionic Acids. Part II. The Action of* o- *and* p-*Methoxyphenylmagnesium Bromide on Succinic Anhydride.*

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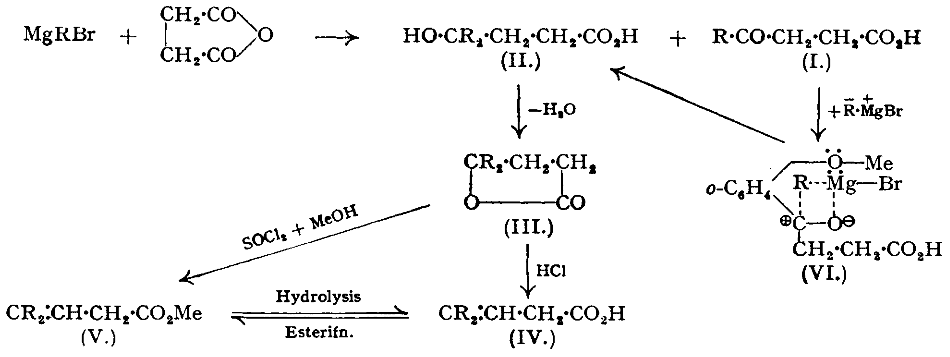
o-Methoxyphenylmagnesium bromide and succinic anhydride give a mixture of β-*o*-methoxybenzoylpropionic acid and γ-hydroxy-γγ-di-*o*-methoxyphenylbutyric acid; the latter acid is converted into its lactone when refluxed with alcohol. The lactone gives, when refluxed with concentrated hydrochloric acid, 3 : 3-di-*o*-methoxyphenylprop-2-ene-1-carboxylic acid (IV) which on oxidation with potassium permanganate gives 2 : 2′-dimethoxybenzophenone. When the lactone is treated with thionyl chloride followed by methyl alcohol, it gives the methyl ester of the acid (IV).

p-Methoxyphenylmagnesium bromide and succinic anhydride give mainly β-*p*-methoxybenzoylpropionic acid.

IN an attempt to prepare β-*o*-methoxybenzoylpropionic acid by the action of *o*-methoxyphenylmagnesium bromide on succinic anhydride (cf. Hill *et al.*, *J.*, 1937, 1621; Lockett and Short, *J.*, 1939, 789), a product was obtained, which was proved to be a mixture of β-*o*-methoxybenzoylpropionic acid (I) and chiefly γ-hydroxy-γγ-di-*o*-methoxyphenylbutyric acid (II) (cf. Weizmann, E. Bergmann, and F. Bergmann, *J.*, 1935, 1367; Weizmann, Blum-Bergmann, and F. Bergmann, *ibid.*, p. 1370). The acid (II) was converted into its lactone (III) when refluxed with alcohol. The structure of (III) was elucidated from the following facts: (i) It was identical with the product obtained by the action of *o*-methoxyphenylmagnesium bromide on β-*o*-methoxybenzoylpropionic acid. (ii) When the lactone was refluxed with concentrated hydrochloric acid for an hour, it was converted into 3 : 3-di-*o*-methoxyphenylprop-2-ene-1-carboxylic acid (IV), which was oxidised by cold alkaline potassium permangante to 2 : 2′-dimethoxybenzophenone. Esterification of the lactone (III) with thionyl chloride and methyl alcohol gave the methyl ester of the acid (IV).



(R = *o*-MeO·C_6H_4·)

The formation of the propene acid (IV) from the lactone (III) by boiling hydrochloric acid is similar to the isomerisation of γ-phenylbutyrolactone to 3-phenylprop-2-ene-1-carboxylic acid (cf. Fittig and Hadorff, *Annalen*, 1904, **334**, 119). Similarly, the formation of the unsaturated ester (V) from the lactone (III) by the action of thionyl chloride and methyl alcohol could be explained by assuming first the formation of the acid chloride of (IV), which readily reacts with methyl alcohol to give the unsaturated ester (V).

However, when *p*-methoxyphenylmagnesium bromide was similarly treated with succinic anhydride, it gave β-*p*-methoxybenzoylpropionic acid as the main product. Similarly, when the latter acid was treated with *p*-methoxyphenylmagnesium bromide, it was mainly recovered unchanged. The abnormal reactivity of the *o*-methoxy-acid compared with the *p*-methoxy-acid may be due to the co-ordination of a molecule of the Grignard reagent with the ethereal oxygen atom of the methoxyl group in (I), leading to a complex in a transition state (VI) which gives rise to the acid (II). The formation of such a transition state is impossible with β-*p*-methoxybenzoylpropionic acid. The validity of this assumption is under investigation.

EXPERIMENTAL.

(M. p.s are uncorrected. Microanalyses were carried out by Drs. Weiler and Strauss, Oxford.)

*γγ-Di-*o*-methoxyphenylbutyrolactone* (III).—(i) An ethereal solution of *o*-methoxyphenylmagnesium bromide [from freshly distilled *o*-bromoanisole (24·0 g., 1 mol.) and magnesium (3·1 g., 1 mol.) in dry ether (80 c.c.)] was added dropwise to a boiling solution of succinic anhydride (12·5 g., 1 mol.) in dry, thiophen-free benzene (200 c.c.), and the whole boiled under reflux for 2·5—3 hours, and left overnight at room temperature. The product was worked up as usual, and the benzene–ether layer was extracted with sodium hydroxide solution (charcoal). The acid precipitated on acidification (10 g.) was refluxed with absolute alcohol for 1—1·5 hours, the alcohol evaporated, and the residue extracted with cold sodium carbonate solution. The insoluble product was filtered off (*ca.* 5 g.), and crystallised from alcohol to give the *lactone* in colourless shining crystals, m. p. 177—178° [Found: C, 72·4; H, 6·0; OMe, 21·1%; *M* (Rast), 288. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0; OMe, 20·8%; *M*, 298].

The sodium carbonate solution gave on acidification an acid (*ca.* 3 g.) which, when crystallised from benzene–light petroleum (b. p. 40—60°), gave β-*o*-methoxybenzoylpropionic acid (I) in colourless crystals, m. p. 100—101°, undepressed on admixture with an authentic specimen (see Part I; *J.*, 1950, 3606) (Found: C, 63·6; H, 5·5; OMe, 16·3%; *M*, 198. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·8; OMe, 14·9%; *M*, 208). Dauben and Tanabe (*J. Amer. Chem. Soc.*, 1949, **71**, 2878) and Dauben and Tiller *J. Org. Chem.*, 1950, **15**, 788) give m.p. 95·6—96·6° and 93·5—95°, respectively.

The lactone was insoluble in cold 20% sodium hydroxide solution, and dissolved with difficulty on refluxing for 2—2·5 hours. It resisted the action of hot alkaline potassium permanganate solution.

(ii) *o*-Methoxyphenylmagnesium bromide [from *o*-bromoanisole (4·1 g., 2·1 mols.), magnesium (0·54 g., 2·2 mols.), ether (50 c.c.)] was added dropwise during 20 minutes to a boiling solution of *β*-*o*-methoxybenzoylpropionic acid (2·1 g., 1 mol.) in dry, thiophen-free benzene (50 c.c.), and worked up as above. The product insoluble in sodium carbonate solution was filtered off (*ca.* 1 g.), and crystallised from alcohol to give the same lactone as in (i), m. p. and mixed m. p. 177—178° (Found : C, 72·1; H, 6·2; OMe, 20·3%; *M*, 310).

3 : 3-*Di*-o-*methoxyphenylprop*-2-*ene*-1-*carboxylic Acid* (IV).—The lactone (III) (1 g.) was refluxed with concentrated hydrochloric acid (20 c.c.) for 1 hour. The product was extracted with sodium carbonate solution, and the extract gave on acidification a crystalline precipitate. On crystallisation from benzene–light petroleum (b. p. 40—60°), the *acid* (IV) was obtained in colourless crystalline aggregates (*ca.* 0·8 g.), m. p. 134—135° (Found : C, 72·2; H, 6·0; OMe, 20·5%; *M*, 280. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0; OMe, 20·8%; *M*, 298). The alkaline solution of this acid discharged the colour of potassium permanganate solution.

Methyl ester (V). (i) The above acid was esterified by use of thionyl chloride and methyl alcohol. The product, crystallised from light petroleum (b. p. 40—60°), gave the *methyl* ester, m. p. 64—65° (Found : C, 72·7; H, 6·2; OMe, 30·6%; *M*, 327. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4; OMe, 29·8%; *M*, 312), which, on hydrolysis with alcoholic potassium hydroxide solution, regenerated the original acid.

(ii) A solution of the lactone (3 g.) in benzene (10 c.c.) was refluxed for 30 minutes with thionyl chloride (3 c.c.). The benzene and excess of thionyl chloride were distilled off, and the residue refluxed with methyl alcohol for 2 hours. The alcohol was evaporated, and the product extracted with ether, washed with dilute sodium carbonate solution, and dried (Na_2SO_4). Removal of the ether left a residue which crystallised from light petroleum (b. p. 40—60°) to give the same methyl ester (2·4 g.) as was obtained in (i); m. p. and mixed m. p. 64—65° (Found C, 73·1; H, 6·2; OMe, 29·6%; *M*, 307).

Oxidation of the Acid (IV).—Potassium permanganate (1·8 g., 4 mols.) was added portionwise at room temperature (20—30°) to a solution of 3 : 3-di-*o*-methoxyphenylprop-2-ene-1-carboxylic acid (0·5 g., 1 mol.) in potassium carbonate solution, and the mixture left for 3—4 days with occasional shaking. Excess of permanganate was destroyed with hydrogen peroxide, and the precipitated manganese dioxide was filtered off and dried. Both the precipitate and the mother-liquor were thoroughly extracted with ether, and the ethereal solution was washed with dilute sodium hydroxide solution and dried. The product from the ether crystallised from methyl alcohol to give colourless crystals of 2 : 2′-dimethoxybenzophenone, m. p. and mixed m. p. 104—105° [Found : C, 74·4; H, 5·6; OMe, 24·1%; *M*(Rast), 224. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8; OMe, 25·6%; *M*, 242]. If the product failed to crystallise, it was purified by vacuum distillation. 2 : 2′-Dimethoxybenzophenone, prepared for comparison by methylation of 2 : 2′-dihydroxybenzophenone (see Graebe and Feer, *Ber.*, 1886, **19**, 2609) with methyl iodide and anhydrous potassium carbonate in dry acetone (see methylation of *β*-*o*-hydroxybenzoylpropionic acid, Part I, *J.*, 1950, 3606), crystallised from methyl alcohol in colourless crystals, m. p. 104—105° (Found : C, 74·3; H, 5·6; OMe, 25·6%; *M*, 222).

Action of p-*Methoxyphenylmagnesium Bromide on Succinic Anhydride.*—By essentially the same procedure as for the *o*-compound, this Grignard reagent (from *p*-bromoanisole, 8·8 g., 1 mol.) was caused to react with succinic anhydride (4·7 g., 1·1 mols.), and the mixture was worked up as above, yielding ultimately *β*-*p*-methoxybenzoylpropionic acid (*ca.* 4 g.), m. p. and mixed m. p. 151—152° (Found : C, 63·5; H, 5·9; OMe, 14·2%; *M*, 215).

Action of p-*Methoxyphenylmagnesium Bromide on β*-p-*Methoxybenzoylpropionic Acid.*—The bromide [from *p*-bromoanisole (9·5 g., 2·1 mols.), magnesium (1·3 g., 2·2 mols.), ether (60 c.c.)] was added dropwise during 20 minutes to a boiling solution of *β*-*p*-methoxybenzoylpropionic acid (4·6 g., 1 mol.) in dry, thiophen-free benzene (100 c.c.), and worked up as above. The acid product (*ca.* 3·2 g.) was unchanged *β*-*p*-methoxybenzoylpropionic acid (m. p. and mixed m. p.). The remaining ether–benzene solution was evaporated to dryness and the viscous oily residue was cooled and extracted with cold alcohol. The residual solid (*ca.* 1·2 g.), well washed with alcohol, had m. p. 196—197°. This crystallised from benzene–light petroleum (b. p. 40—60°) in lemon-yellow crystals, m. p. 198—199°; it was recovered unchanged when refluxed for 3 hours with concentrated hydrochloric acid or 20% sodium hydroxide solution, showing that it could not be a lactone; also it was not 4 : 4′-dimethoxydiphenyl. Its constitution is under investigation.

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