# **711.** *β-Aroylpropionic Acids. Part I. The Mechanism of Interaction between Phenol and Succinic Anhydride in Presence of Aluminium Chloride. The Nature of the Fries Reaction.*

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The action of aluminium chloride on a mixture of succinic anhydride and phenol gives a mixture of *β-o-* and *β-p*-hydroxybenzoylpropionic acid. The reaction proceeds through the intermediate formation of phenyl hydrogen succinate. When the latter compound is heated with aluminium chloride in toluene, the product contains *β-o*-hydroxybenzoyl- and *β-p*-toluoylpropionic acid, and a trace of *β-p*-hydroxybenzoylpropionic acid. This result indicates that the Fries reaction is partly intermolecular.

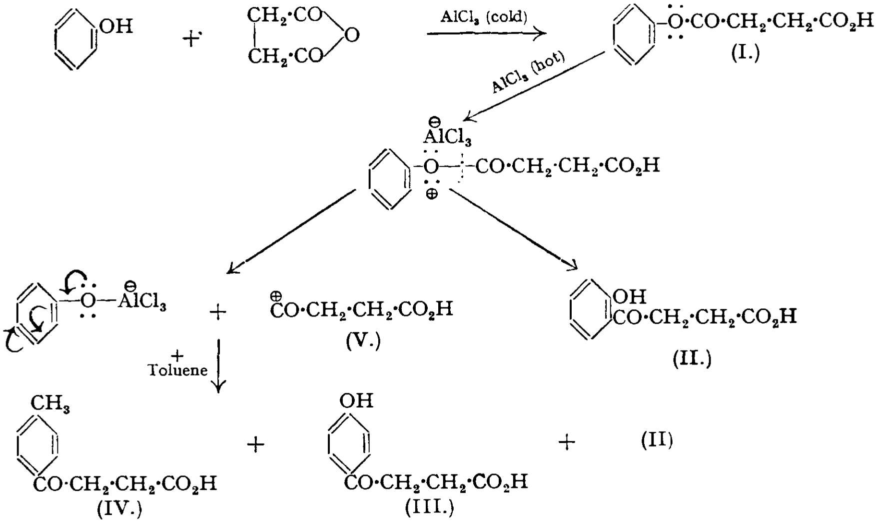
Mitter and Shyamakanta De (*J. Indian Chem. Soc.*, 1939, **16**, 35) stated that the action of aluminium chloride on a mixture of succinic anhydride and phenol gave only β-*o*-hydroxybenzoylpropionic acid. The experiment was repeated but the indefinite m. p. of the crude product indicated that it was a mixture. Its constituents were shown to be β-*o*- and β-*p*-hydroxybenzoylpropionic acid, the former being predominant.

The fact that the action of aluminium chloride on a mixture of succinic anhydride and anisole gives only β-*p*-anisoylpropionic acid (cf. Mitter and Shyamakanta De, *loc. cit.*; Haworth and Sheldrick, *J.*, 1934, 1951) indicates that the two reactions must proceed by different mechanisms. Thus, whereas the latter reaction is one of direct substitution, the former proceeds by a Fries reaction mechanism (cf. Fries and Finck, *Ber.*, 1908, **41**, 4271; Blatt, *Chem. Reviews*, 1940, **27**, 429), *i.e.*, it proceeds through the intermediate formation of phenyl hydrogen succinate (I), which by the action of aluminium chloride gives rise to a mixture of β-*o*- and β-*p*-hydroxybenzoylpropionic acid (II and III, respectively). This assumption is supported by the isolation of phenyl hydrogen succinate as an intermediate product in the above reaction. However, the fact that the percentage of the *p*-hydroxy-acid obtained by the action of aluminium chloride on a mixture of succinic anhydride and phenol is slightly higher than that obtained by the action of aluminium chloride on phenyl hydrogen succinate suggests that the former reaction most probably proceeds both by direct substitution, which gives mainly the *p*-hydroxy-acid, and by the Fries reaction which gives rise to a mixture of the *o*- and *p*-hydroxy-acids.

When solvent acetylene tetrachloride was replaced by toluene, the product from the action of aluminium chloride on phenyl hydrogen succinate contained β-*o*-hydroxybenzoylpropionic acid, β-*p*-toluoylpropionic acid (IV), and a trace of the *p*-hydroxy-acid. This showed that the Fries reaction in this particular case is partly of an intermolecular nature.

The fact that the formation of β-*p*-toluoylpropionic acid occurred mainly at the expense of β-*p*-hydroxybenzoylpropionic acid could be taken as an indication that the Fries reaction is of both the intramolecular and the intermolecular type (cf. Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56; Ralston *et al.*, *J. Org. Chem.*, 1940, **5**, 645; Gershzon, *J. Gen. Chem. U.S.S.R.*, 1943, **13**, 68). However, the validity of this assumption is now under investigation.

The formation of β-*p*-toluoylpropionic acid in the above reaction can be explained by assuming that the co-ordination of aluminium chloride with phenyl hydrogen succinate facilitates its heterolytic fission to the cation (V). This cation then undergoes an electrophilic substitution on the phenoxide ion or the toluene molecule to give β-*o*- and β-*p*-hydroxybenzoylpropionic acid (II and III), or β-*p*-toluoylpropionic acid (IV), respectively.



## EXPERIMENTAL.

(M. p.s are not corrected. Microanalyses were carried out by Drs. Weiler and Strauss of Oxford.)

*β-o- and β-p-Hydroxybenzoylpropionic Acid.*—A mixture of phenol (20 g., 1 mol.), succinic anhydride (20 g., 1 mol.), and acetylene tetrachloride (150 c.c.) was thoroughly stirred, and treated portionwise with powdered aluminium chloride (60 g., 2·1 mols.). The mixture was kept at room temperature for 4 hours, then the reaction was completed as stated by Mitter and Shyamakanta De (*loc. cit.*). The product (20—22 g.; m. p. 110—125°) was separated into its components by either of two methods.

(i) It was crystallised from water (700—750 c.c.), and the acid which separated on cooling was recrystallised from water (*ca.* 450 c.c.) to give β-*o*-hydroxybenzoylpropionic acid in crystals, m. p. 145—146° [Found: C, 61·9; H, 5·3%; *M* (Rast), 182. Calc. for $C_{10}H_{10}O_4$: C, 61·9; H, 5·2%; *M*, 194]; yield, 10—11 g. Mitter and Shyamakanta De (*loc. cit.*) give m. p. 145°.

The combined mother-liquors from the above crystallisations were concentrated (*ca.* 40—50 c.c.), and allowed to crystallise. On recrystallisation from water *β-p-hydroxybenzoylpropionic acid* was obtained in lustrous needles, m. p. 160—161° [Found: C, 62·1; H, 5·0; active H, 0·90%; *M* (Rast), 200. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2; active H, 1·03%; *M*, 194]; yield *ca.* 4·5 g.

(ii) The mixture (4 g.) was treated with an ethereal solution of diazomethane (from 12 g. of nitrosomethylurea), and left overnight at 0°. The solution was washed with sodium carbonate solution to remove any unesterified acids, then with sodium hydroxide solution to extract phenolic esters. Acidification of the carbonate solution precipitated β-*o*-hydroxybenzoylpropionic acid (*ca.* 2·2 g.). The neutral product was hydrolysed with alcoholic potassium hydroxide solution, and the acid (*ca.* 1·1 g.) was crystallised from dilute alcohol to give β-*p*-anisoylpropionic acid as plates, m. p. 150—151°, undepressed on admixture with an authentic specimen (Found: C, 63·5; H, 5·8; OMe, 14·4%; *M*, 212. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·8; OMe, 14·9%; *M*, 208). Mitter and Shyamakanta De (*loc. cit.*) and Haworth and Sheldrick (*loc. cit.*) give m. p.s 146° and 147—148°, respectively.

*Phenyl Hydrogen Succinate.*—(i) A mixture of phenol (10 g., 1 mol.) and succinic anhydride (10 g., 1 mol.) was heated at 140—150° for 3 hours. The product was treated with ether and filtered from the insoluble succinic anhydride (*ca.* 2 g.). The ethereal solution was extracted with ice-cold sodium carbonate solution, which on acidification gave a crystalline acid. When this was crystallised from benzene–light petroleum (b. p. 60—70°), it gave phenyl hydrogen succinate, m. p. 97—98° (Found: C, 62·1; H, 5·4. Calc. for $C_{10}H_{10}O_4$: C, 61·9; H, 5·2%) (*ca.* 10 g.). Determination of the molecular weight by Rast's method gave a low value, indicating that the substance dissociated when heated into succinic anhydride and phenol. This was found to be the case when a sample of phenyl hydrogen succinate was heated at 170° for about 5 minutes. The ester was easily hydrolysed when heated with sodium carbonate solution, or boiled with water.

The ethereal mother-liquor was extracted with sodium hydroxide solution to remove unchanged phenol. Evaporation of the ether left a neutral substance, which on crystallisation from benzene–light petroleum (b. p. 40—60°) gave diphenyl succinate as needles, m. p. 120—121° (cf. Rheinische

Kampfer Fabrik, *Centr.*, 1933, **104**, I, 1686; D.R.-P. 565,969; Schering-Kahlbaum A.G., E.P. 397,505; *Centr.*, 1934, **105**, I, 129) (Found : C, 71·3; H, 5·3%; *M*, 288. Calc. for $C_{16}H_{14}O_4$ : C, 71·1; H, 5·2%; *M*, 270) (*ca.* 1 g.). When the reaction was carried out at 100° or at 190—200°, a poorer yield of phenyl hydrogen succinate was obtained.

(ii) A stirred mixture of phenol (10 g.), succinic anhydride (10 g.), and acetylene tetrachloride (100 c.c.) was cooled in water, and treated with powdered aluminium chloride (30 g.) at such a rate that the temperature did not exceed 30°. The stirring was continued for about 4 hours, and the reaction mixture decomposed with ice and hydrochloric acid. The product was extracted with ether, and the ethereal solution shaken with sodium carbonate solution. The precipitated acid was crystallised from benzene–light petroleum (b. p. 40—60°), giving phenyl hydrogen succinate, m. p. 97—98° (10 g.), undepressed on admixture with the above ester (Found : C, 61·7; H, 4·9%).

*Action of Aluminium Chloride on Phenyl Hydrogen Succinate.*—A solution of the ester (15 g., 1 mol.) in acetylene tetrachloride (100 c.c.) was treated at 20—25° with powdered aluminium chloride (20 g., 2 mols.), and the mixture heated in an oil-bath at 120—130°, or at 130—140° for 2 hours. The reaction mixture was worked up as in the first experiment, and the constituents of the product were separated by fractional crystallisation from water (see first experiment) into β-*o*-hydroxybenzoylpropionic acid, m. p. 146—147° (*ca.* 4·8 g.), and the *p*-isomer, m. p. 160—161°; both m. p.s were undepressed on admixture with authentic specimens.

*Action of Aluminium Chloride on Phenyl Hydrogen Succinate in Presence of Toluene.*—A solution of phenyl hydrogen succinate (10 g., 1 mol.) in toluene (50 c.c.) was treated with powdered anhydrous aluminium chloride (15 g., 2 mols.), and the mixture heated at 120—130° for 2 hours, decomposed with water, and worked up as usual. The precipitated acids (*ca.* 6 g.) were esterified with methyl alcohol and hydrogen chloride. Alcohol was removed, and the product extracted with ether, and washed with sodium carbonate solution to remove unesterified acids, then with sodium hydroxide solution to extract phenolic esters. The precipitated phenolic acids (*ca.* 3·4 g.) were treated with ethereal diazomethane solution and worked up as before. The product consisted mainly of β-*o*-hydroxybenzoylpropionic acid (*ca.* 2·9 g.), with only traces of the *p*-hydroxy-acid. The neutral product was hydrolysed with alcoholic alkali, and the resulting acid (*ca.* 1·2 g.) was crystallised from benzene–light petroleum (b. p. 40—60°), giving β-*p*-toluoylpropionic acid in shining flakes, m. p. and mixed m. p. 128—129° (Found : C, 69·1; H, 6·2%; *M*, 184. Calc. for $C_{11}H_{12}O_3$ : C, 68·8; H, 6·3%; *M*, 192) (cf. Barnett and Sanders, *J.*, 1933, 434).

β-o-*Anisoylpropionic Acid.*—A mixture of β-*o*-hydroxybenzoylpropionic acid (6 g.), methyl iodide (15 g.), potassium carbonate (15 g.), and dry acetone (50 c.c.) was refluxed for 8 hours. The product was worked up as usual, then distilled in a vacuum to give methyl β-*o*-anisoylpropionate as a colourless viscous oil, b. p. 176—178°/8 mm. (*ca.* 5·2 g.). The acid obtained on hydrolysis of the ester was crystallised from benzene–light petroleum (b. p. 40—60°) to give β-o-*anisoylpropionic acid* in colourless crystalline aggregates, m. p. 100—101° (Found : C, 63·3; H, 5·8; OMe, 15·8%; *M*, 198. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8; OMe, 14·9%; *M*, 208) (yield 70%).

γ-o-*Methoxyphenylbutyric Acid.*—(i) γ-*o*-Hydroxyphenylbutyric acid (cf. Mitter and Shyamakanta De, *loc. cit.*) (9 g.) was methylated with methyl iodide (12 g.), potassium carbonate (15 g.), and acetone (80 c.c.) as stated above. The resulting ether ester was distilled in a vacuum, and the fraction, b. p. 122—124°/3 mm. (7·7 g.), was hydrolysed with alcoholic alkali to give γ-*o*-methoxyphenylbutyric acid. Crystallised from light petroleum (b. p. 40—60°) it had m. p. 41—42° (Found : C, 68·3; H, 7·2; OMe, 15·7%; *M*, 206. Calc. for $C_{11}H_{14}O_3$ : C, 68·0; H, 7·2; OMe, 16·0%; *M*, 194). Lockett and Short (*J.*, 1939, 789) give m. p. 39—39·5°. If the acid fails to solidify, it can be further purified by vacuum distillation; b. p. 165—168°/2 mm.

(ii) β-*o*-Anisoylpropionic acid (3 g.) was reduced with zinc amalgam (30 g.), and concentrated hydrochloric acid (60 c.c.) by Clemmensen's modified method (cf. Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438). The acid was extracted from the toluene layer with sodium hydroxide solution, precipitated, and crystallised from light petroleum (b. p. 40—60°) to give γ-*o*-methoxyphenylbutyric acid, m. p. 41—42°, undepressed on admixture with a specimen from (i) (yield *ca.* 85%).

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