

218. β -Aroylpropionic Acids. Part XIX.* Further Observation on the Fries Rearrangement.

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Phenol and *p*-cresol, when heated with phenylsuccinic anhydride, give the corresponding aryl hydrogen phenylsuccinates, but *m*-cresol does not undergo this reaction.

When the two phenyl hydrogen phenylsuccinates are heated with aluminium chloride they give *p*-hydroxy-keto-acids, whereas the *p*-tolyl esters under similar conditions give *o*-hydroxy-keto-acids.

IN continuation of our previous investigation,¹ the half-esters (I) obtained by the fusion of phenol and *p*-cresol with phenylsuccinic anhydride at 130–140° were subjected to the Fries rearrangement, so as to establish their structure and obtain more information about the mechanism of this reaction.

When phenol was fused with phenylsuccinic anhydride it gave a mixture of the isomeric phenyl hydrogen phenylsuccinate (Ia and b; Ar = Ph) in the ratio 2 : 3, respectively. The same mixture [poorer yield and higher percentage of acid (Ia)] was obtained when the reactants were treated with aluminium chloride in carbon disulphide.

When both half-esters (I; Ar = Ph) were heated with aluminium chloride in acetylene tetrachloride or in nitrobenzene at 117–120°, they gave β -*p*-hydroxybenzoyl- α - (VIa; X = C₆H₄) and β -phenylpropionic acid (VIb; X = C₆H₄), respectively. The structure of these acids (VI; X = C₆H₄) was established by converting them into the corresponding methoxy-acids (VIc and d; X = C₆H₄) which were identical with authentic specimens.² Replacement of acetylene tetrachloride by toluene gave rise to α - and β -phenyl- β -*p*-toluoylpropionic acids (VII) as the main product, together with traces of acids (VIa and b; X = C₆H₄).

p-Cresol and phenylsuccinic anhydride were similarly treated; they gave a mixture of the *p*-tolyl hydrogen esters (Ia and b; Ar = *p*-Me·C₆H₄) in 16 and 45% yield, respectively. When these half-esters were heated with aluminium chloride at 117–120° in acetylene tetrachloride or in nitrobenzene, they gave β -(2-hydroxy-5-methylbenzoyl)- α - (IIIa; R''O·X = 2,5-HO·C₆H₃Me) and - β -phenylpropionic acid (IIIb; R''O·X = 2,5-HO·C₆H₃Me), respectively. The structure of the former of these products (III) was established by converting it into its methyl ether methyl ester, which was identical with an authentic specimen prepared according to scheme B. 2'-Methoxy-5'-methylchalcone (VIIIa) with hydrogen cyanide gave the nitrile (IXa), which was hydrolysed with aqueous potassium hydroxide to the acid (IIIc; R''O·X = 2,5-MeO·C₆H₃Me), then methylated to the corresponding methyl ester. The structure of the isomer (IIIb; R''O·X = 2,5-HO·C₆H₃Me) was inferred from its analytical data and from the fact that its methyl ether methyl ester was different from the above authentic specimen.

When the *p*-tolyl half-esters (Ia and b) were heated with aluminium chloride in toluene, they gave a mixture of β -(2-hydroxy-5-methylbenzoyl)- α - and - β -phenylpropionic acid (IIIa and b; R''O·X = 2,5-HO·C₆H₃Me, respectively) and phenylsuccinic acid. No phenyl- β -*p*-toluoylpropionic acid was obtained. The isolation of phenylsuccinic acid indicates that part of the tolyl ester (Ia or b) remained unchanged at the end of the reaction.

Condensation of m-Cresol and its Methyl Ether with Phenylsuccinic Anhydride.—Attempts to prepare the *m*-tolyl hydrogen phenylsuccinates (Ia and b; Ar = *p*-Me·C₆H₄) by fusing

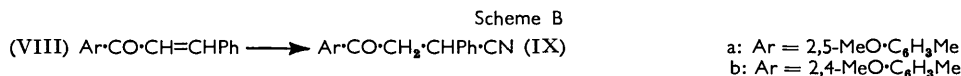
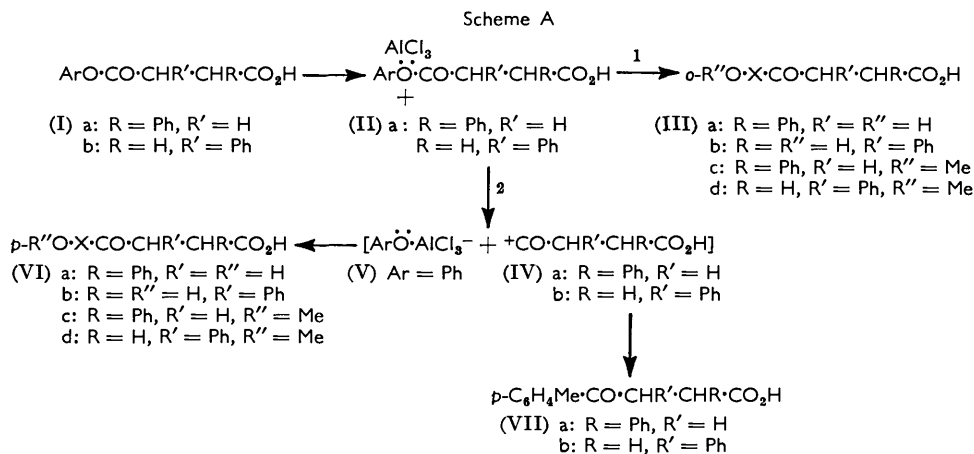
* Part XVIII, *J.*, 1961, 707.

¹ Awad, Baddar, and Marei, *J.*, 1954, 4538.

² Wali, Khalil, Bhatia, and Ahmed, *Proc. Indian Acad. Sci.*, 1941, **144**, 139.

m-cresol with phenylsuccinic anhydride or treating their ice-cold mixture in carbon disulphide or in acetylene tetrachloride with aluminium chloride, were unsuccessful. However, when the mixture of *m*-cresol and phenylsuccinic anhydride was left with aluminium chloride for 24 hr. at room temperature or at 170° for 2 hr., it was converted into β -(2-hydroxy-4-methylbenzoyl)- α -phenylpropionic acid (IIIa; R''O·X = 2,4-HO·C₆H₃Me); the latter method gave a better yield. The position of succinylation was established by methylating the product and oxidising the resulting methyl ether to a methoxyterephthalic acid. The exact structure of the methyl ether was confirmed by its identity with an authentic specimen prepared from the chalcone (VIIIb) according to scheme B.

When methyl *m*-tolyl ether was allowed to stand with aluminium chloride and phenylsuccinic anhydride at room temperature for 3 days, it gave β -(4-methoxy-2-methylbenzoyl)- α - or - β -phenylpropionic acid (VIc or d; R''O·X = 4,2-MeO·C₆H₃Me). Its structure was established by oxidation to 4-methoxyphthalic acid.



The rearrangement of phenyl hydrogen phenylsuccinates appears to take place exclusively by an intermolecular mechanism according to scheme A (step 2). In presence of a solvent which is not susceptible to electrophilic attack, such as acetylene tetrachloride or nitrobenzene, the oxo-carbonium ion (IVa or b) attacks the *para*-position of the phenoxy-aluminium chloride complex (V) to give acids (VIa and b; R''O·X = HO·C₆H₄). The intermolecular nature of the reaction was inferred from the facts that (i) no β -*o*-hydroxybenzoyl- α - or - β -phenylpropionic acid was formed, and (ii) the reaction in toluene gives nearly exclusively β -*p*-toluoyl- α - and - β -phenylpropionic acid, respectively.

That the *p*-tolyl esters (I) failed to give β -*p*-toluoyl- α - and - β -phenylpropionic acid when heated with aluminium chloride in toluene indicates that this rearrangement takes place intramolecularly, involving a π -complex³ (cf. scheme A, step 1).

The reaction of phenylsuccinic anhydride with *m*-cresol appears to be a Fries rearrangement and not a Friedel-Crafts reaction, since the product is not the same as that from methyl *m*-tolyl ether. The reaction appears to proceed by the intermediate formation

³ Dewar, "Electronic Theory of Organic Chemistry," Oxford, 1949, p. 229; Baddar and El-Assal, *J.*, 1950, 3606; Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56; Ralston, McCorkle, and Bauer, *J. Org. Chem.*, 1940, **5**, 645; Gershzon, *J. Gen. Chem. (U.S.S.R.)*, 1943, **13**, 68; Cocker and Fateen, *J.*, 1951, 2632.

of *β-m*-tolyl hydrogen phenylsuccinate. A similar reaction took place with succinic anhydride.^{1,4}

EXPERIMENTAL

β-(2-Methoxy-5-methylbenzoyl)-*α*-phenylpropionitrile (IXa).—A mixture of 2-methoxy-5-methylchalcone⁵ (25 g.), 95% ethanol (5 ml.) and glacial acetic acid (6 g.) was warmed with stirring to 35°, and a 35% aqueous solution of potassium cyanide (37 ml.) was added during about 15 min. Stirring and warming were continued for 3 hr. After cooling, the precipitated nitrile was filtered off, and washed with cold 50% ethanol (8 ml.) and water until free from cyanide. The light yellow nitrile (26 g., 90%), crystallised from ethanol, had m. p. 103—104° (Found: C, 77.6; H, 6.1; N, 5.3. C₁₈H₁₇O₂N requires C, 77.4; H, 6.1; N, 5.0%).

β-(2-Methoxy-5-methylbenzoyl)-*α*-phenylpropionic Acid (IIIc).—The solution of the nitrile (10 g.) in 60% alcoholic potassium hydroxide solution (20 ml.) was refluxed for 10 hr. The alcohol was evaporated under reduced pressure, then water was added. The obtained aqueous alkaline solution was extracted with ether, cooled in ice, then acidified with concentrated hydrochloric acid. *β*-(2-Methoxy-5-methylbenzoyl)-*α*-phenylpropionic acid (9 g., 80%), crystallised from benzene, had m. p. 173—174° (Found: C, 72.4; H, 6.1. C₁₈H₁₈O₄ requires C, 72.5; H, 6.1%).

The methyl ester, prepared in 75% yield by refluxing the acid (5 g.) with methyl sulphate (17 g.) and potassium carbonate (30 g.) in acetone (15 ml.) for 12 hr., had m. p. 67—68° [from benzene-light petroleum (b. p. 60—80°)] (Found: C, 72.7; H, 6.7. C₁₉H₂₀O₄ requires C, 73.1; H, 6.45%).

β-(2-Methoxy-4-methylbenzoyl)-*α*-phenylpropionic Acid.—Benzaldehyde (5.3 g., 0.05 mole) was added with stirring to a mixture of 2-methoxy-4-methylacetophenone⁷ (8.2 g., 0.05 mole), ethanol (13 ml.), and 10% sodium hydroxide solution (20 ml.). The temperature was kept at 25—30° for 3 hr., then the whole was cooled in ice. The separated oil was extracted, washed,

TABLE I.

Half-ester	M. p.	Solvent ¹	Yield (%) by method		Formula	Found (%)		Required (%)	
			(a)	(b)		C	H	C	H
Ia; Ar = Ph	104—105°	C ₆ H ₆ -Pet.	19	11	C ₁₆ H ₁₄ O ₄	70.5	5.2	71.1	5.2
Ib; Ar = Ph	130—131	C ₆ H ₆	30	14		70.4	5.3		
Ia; Ar = <i>p</i> -Me·C ₆ H ₄ ...	95—96	C ₆ H ₆ -Pet.	16	14	C ₁₇ H ₁₆ O ₄	72.2	6.0	71.8	5.7
Ib; Ar = <i>p</i> -Me·C ₆ H ₄ ...	128—129	C ₆ H ₆	45	37		71.6	5.7		

¹ Pet. = light petroleum (b. p. 60—80°).

dried, and distilled to give 2-methoxy-4-methylchalcone (IXb) as a yellow liquid, b. p. 180—182°/1 mm. (10 g., 80% yield). It gave a deep red 2,4-dinitrophenylhydrazone, m. p. 204—205° (from acetic acid) (Found: C, 63.3; H, 4.6; N, 12.4; OMe, 7.8. C₂₃H₂₀N₄O₅ requires C, 63.9; H, 4.7; N, 12.9; OMe, 7.2%).

Glacial acetic acid (1 ml.) was added to a mixture of the chalcone (4 g.), ethanol (100 ml.), potassium cyanide (6 g.), and water (*ca.* 5 ml.). The mixture was kept at 70—80° for 50 hr. cooled, filtered, and evaporated under reduced pressure. The crude nitrile, a brown oil, was hydrolysed by refluxing concentrated hydrochloric acid (60 ml.) for 10 hr. The solid product was filtered off, dissolved in ether, washed, and extracted with concentrated sodium carbonate. Acidification of the alkaline solution gave *β*-(2-methoxy-4-methylbenzoyl)-*α*-phenylpropionic acid which, crystallised from benzene-light petroleum (b. p. 60—80°), had m. p. 148—149° (3.5 g., 80% yield) (Found: C, 72.5; H, 6.1. C₁₈H₁₈O₄ requires C, 72.5; H, 6.1%).

Preparation of Aryl Hydrogen Phenylsuccinates (I).—(a) The phenol (0.1 mole) and phenylsuccinic anhydride (0.1 mole) were heated at 130—140° for 3 hr. The product was treated

⁴ Raval, Bokil, and Nargund, *J. Univ. Bombay*, 1938, **7**, 184.

⁵ Simonis and Lear, *Ber.*, 1926, **59**, 2908.

⁷ Dilthey, Frode, and Koenen, *J. prakt. Chem.*, 1926, **114**, 153; Auwers, Lechner, and Bundesmann, *Ber.*, 1925, **58**, 36.

with ether, and the ethereal solution was extracted with ice-cold 5% sodium carbonate solution. (b) To a stirred, cooled mixture of the phenol (0.05 mole) and phenylsuccinic anhydride (0.05 mole) in carbon disulphide (75 ml.), anhydrous aluminium chloride (0.12 mole) was gradually added. Stirring was continued for a further 3 hr. The sticky brown mass was hydrolysed with ice and concentrated hydrochloric acid. Ether was then added and the ether-carbon disulphide layer was separated, washed with cold water, and extracted with cold concentrated sodium carbonate solution.

The ice-cold alkaline extract from (a) or (b) was acidified (at once, to avoid hydrolysis) and the oil was extracted with ether. Evaporation of the solvent gave a residue, which was extracted with hot benzene to remove any of the insoluble phenylsuccinic acid. Concentration of the filtrate precipitated the corresponding α -phenyl β -acid (Ib). Addition of light petroleum (b. p. 60–80°) to the mother liquor precipitated the β -phenyl α -acid (Ia). The results are summarised in Table 1.

Fries Rearrangement.—A stirred mixture of aryl hydrogen phenylsuccinate (0.011 mole) and solvent (0.115 mole) was treated gradually with aluminium chloride (0.022 mole) (Prolabo-Produite pour Laboratoires, Rhône Poulenc) at room temperature during 30 min. The temperature was kept thereat for another 30 min., then raised to 117° (boiling butan-1-ol bath) for a further 1.5 hr. The sticky dark brown mass obtained was hydrolysed with ice and dilute hydrochloric acid. The mixture was worked up by one of two procedures: (i) The solvent was removed in steam, and the precipitated dark solid residue was digested with the least possible amount of concentrated sodium carbonate solution. (ii) Ether was added and the ether solution was washed with water and extracted with sodium carbonate solution. The alkaline extract from (i) or (ii) was boiled to hydrolyse any unchanged ester (charcoal), filtered, and acidified with concentrated hydrochloric acid. In the case of *s*-tetrachloroethane or nitrobenzene, the precipitated acids were separated as recorded in Table 2. For the other solvent (toluene) the phenolic acids were separated from the non-phenolic acids by esterification with hydrogen chloride and ethanol. The alcohol was removed, and the product was extracted with ether and washed with sodium carbonate solution to remove unesterified acids, followed by sodium hydroxide solution to remove the phenolic esters (these were usually hydrolysed during extraction). Acidification of the sodium hydroxide solution precipitated the phenolic acid. The ester of the non-phenolic acid was hydrolysed with boiling 8% potassium hydroxide solution (3 hr.), and the acid (VII) was crystallised and identified by m. p. and mixed m. p. (cf. Table 2).

TABLE 2. Yields (g.).

Solvent	(Ia); Ar = Ph		(Ib); Ar = Ph		(Ia); Ar = <i>p</i> -C ₆ H ₄ Me		(Ib); Ar = <i>p</i> -C ₆ H ₄ Me	
	VIIa	VIa	VIIb	VIb	VIIa	IIIa	VIIb	IIIb
C ₆ H ₂ Cl ₄	—	1.1 *	—	1.0 *	—	1.5 *	—	1.8 *
PhNO ₂	—	0.75	—	0.70	—	1.1	—	1.2
PhMe	1.0 *	Traces	0.9 *	Traces	—	0.4 †	—	0.5 †

* See text. † Together with phenylsuccinic acid (0.8 g.).

β -(*p*-Hydroxybenzoyl)- α -phenylpropionic acid, crystallised from benzene-light petroleum (b. p. 60–80°), m. p. 204–205°, gave no colour with ferric chloride (Found: C, 71.1; H, 5.3. C₁₆H₁₄O₄ requires C, 71.1; H, 5.2%). This was methylated by methyl sulphate and potassium carbonate in acetone and the resulting methyl ether methyl ester was hydrolysed with 3% alcoholic potassium hydroxide to β -*p*-anisoyl- α -phenylpropionic acid, m. p. 149–150°, undepressed on admixture with an authentic specimen.⁸

β -(*p*-Hydroxybenzoyl)- β -phenylpropionic acid, crystallised from benzene, had m. p. 165–166° and gave no colour with ferric chloride (Found: C, 70.5; H, 5.3%). It gave β -*p*-anisoyl- β -phenylpropionic acid, m. p. 147–148°, undepressed on admixture with an authentic specimen.⁸

α -Phenyl- β -*p*-toluoylpropionic acid (from ether) had m. p. and mixed m. p. 153–154°.⁹

β -Phenyl- α -*p*-toluoylpropionic acid (from ether) had m. p. and mixed m. p. 156–157°.⁹

β -(2-Hydroxy-5-methylbenzoyl)- α -phenylpropionic acid (from benzene) had m. p. 130–131° and gave a violet colour with ferric chloride (Found: C, 71.9; H, 5.6. C₁₇H₁₆O₄ requires C, 71.8; H, 5.7%). Methyl β -(2-methoxy-5-methylbenzoyl)- α -phenylpropionate, prepared by

⁸ Heller, *Ber.*, 1912, **45**, 418.

⁹ Baddar, Fleifel, and Sherif, *J. Chem. (U.A.R.)*, 1960, **3**, No. 1, 47.

using methyl sulphate and potassium carbonate in acetone, had m. p. 167—168° [from benzene-light petroleum (b. p. 60—80°)], undepressed on admixture with an authentic specimen (see above). With toluene as solvent a considerable amount of phenylsuccinic acid was also obtained.

β-(2-Hydroxy-5-methylbenzoyl)-*β*-phenylpropionic acid (crystallised from benzene), m. p. 167—168°, gave a violet colour with ferric chloride (Found: C, 71.15; H, 5.8. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.7%). Methyl *β*-(2-methoxy-5-methylbenzoyl)-*β*-phenylpropionate, prepared as above, m. p. 59—60° [from light petroleum (b. p. <40°)], depressed on admixture with methyl *β*-(2-methoxy-5-methylbenzoyl)-*α*-phenylpropionate (above) (Found: C, 72.9; H, 6.2. $C_{19}H_{20}O_4$ requires C, 73.1; H, 6.45%). When toluene was the solvent a considerable amount of phenylsuccinic acid was also isolated.

Action of Aluminium Chloride on m-Cresol and Phenylsuccinic Anhydride in s-Tetrachloroethane.—(i) *At low temperature.* To an ice-cold mixture of *m*-cresol (9.2 g.) and phenylsuccinic anhydride (15 g.) in *s*-tetrachloroethane (130 g.), aluminium chloride (21 g.) was added in 3 lots. Stirring was continued for 4 hr. in ice, then the mixture was left overnight at room temperature. The product was worked up as usual, then treated with hot benzene to remove the insoluble phenylsuccinic acid (10.5 g.). On cooling, *β*-(2-hydroxy-4-methylbenzoyl)-*α*-phenylpropionic acid separated (9 g., 37%), having m. p. 172—173° (Found: C, 71.7; H, 5.65. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.7%). It gave a violet colour with alcoholic ferric chloride solution. (ii) *At high temperature.* The above experiment was repeated except that after addition of the 3 lots of aluminium chloride in the cold, the mixture was left for 0.5 hr. in ice and 1 hr. at room temperature, then heated for 2 hr. at 170—180°. *β*-(2-Hydroxy-4-methylbenzoyl)-*α*-phenylpropionic acid was obtained in 82% yield (20 g.).

The methyl ether methyl ester, prepared in quantitative yield by use of methyl sulphate and potassium carbonate in acetone (15 ml.), had m. p. 112—113° [from light petroleum (b. p. 60—80°)] (Found: C, 72.9; H, 6.2; OMe, 19.8. $C_{19}H_{20}O_4$ requires C, 73.0; H, 6.4; OMe, 19.9%).

β-(2-Methoxy-4-methylbenzoyl)-*α*-phenylpropionic acid was obtained quantitatively by refluxing this ester (5 g.) in 3% alcoholic potassium hydroxide solution (100 ml.) for 2 hr., having m. p. and mixed m. p. 152—153° (from benzene).

Oxidation of the last acid (1 g.) by potassium permanganate (3 g.) in boiling 3% potassium hydroxide solution (40 ml.) for 2 hr. produced methoxyterephthalic acid (0.5 g.), m. p. 286—288° (from water, undepressed on admixture with an authentic specimen).¹⁰

Friedel-Crafts Reaction of Methyl m-Tolyl Ether with Phenylsuccinic Anhydride.—To a stirred ice-cold mixture of methyl *m*-tolyl ether (10.5 g.), phenylsuccinic anhydride (15 g.) and *s*-tetrachloroethane (130 g.), aluminium chloride (21 g.) was added in 3 lots. Stirring was continued for 4 hr. with ice-cooling, then the mixture was left at room temperature for 3 days with occasional stirring. The product was worked up as usual, then crystallised from benzene-light petroleum (b. p. 60—80°), to give *β*-(4-methoxy-2-methylbenzoyl)-*α*- or *β*-phenylpropionic acid (18 g., 75%) m. p. 120—121° (Found: C, 72.2; H, 6.0. $C_{18}H_{18}O_4$ requires C, 72.5; H, 6.0%). Oxidation of the acid as above gave 4-methoxyphthalic acid, m. p. 170° (from water).

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¹⁰ Duff, *J.*, 1941, 547.