599. 4-*Hydroxy*iso*phthalic Acid.*

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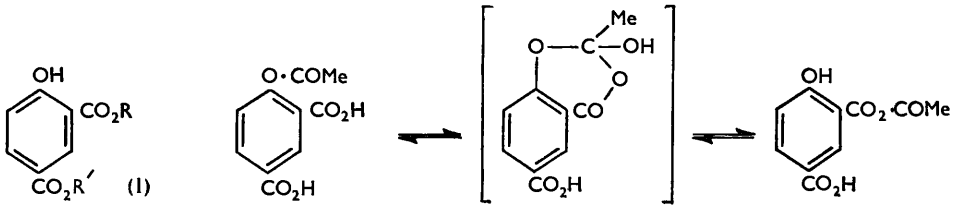
Some aspects of the chemistry of 4-hydroxy*iso*phthalic acid, a by-product of the carboxylation of phenol by the Kolbe–Schmitt reaction, have been explored. A number of mono- and di-esters is described. The acetylated derivative, in some of its reactions, behaves as a mixed anhydride. Some 5-substituted derivatives of the acid and its dimethyl ester have been prepared and their ultraviolet absorption spectra are reported and discussed.

4-Hydroxy*iso*phthalic acid is formed to the extent of 3—5% in the commercial synthesis of salicylic acid from sodium phenoxide and becomes the major constituent of the " brown dust " residue from the sublimation process for purification of salicylic acid.[1,2] These residues, hitherto considered an industrial waste, were found to consist of 4-hydroxy-*iso*phthalic acid (80—83%), 2-hydroxy*iso*phthalic acid (2—3%), unsublimed salicylic acid (10—12%), and inorganic material (2—4%) and were the source of the 4-hydroxy-*iso*phthalic acid used in the present work. The origin of the acid as a by-product of the Kolbe–Schmitt reaction will be discussed later. Methods were developed for the extraction of the acid from the " brown dust "; of these, esterification, followed by separation and purification of the ester and subsequent hydrolysis, proved to be the most convenient. The dimethyl ester sublimes readily and is thus easily purified. The interesting pharmacological results obtained with 4-hydroxy*iso*phthalic acid [3] led the authors to study some of its reactions and prepare several new derivatives.



By Fischer–Speier esterification diesters are obtained, together with small amounts of the mono-esters which are easily removed by treatment with dilute alkali solution. As reported below, the orientation of the monomethyl ester has been established as (I; R = H, R′ = Me). The same ester is obtained by partial hydrolysis of the dimethyl ester

[1] Whittaker and Smith in Thorpe's " Dictionary of Applied Chemistry," 4th edn., Longmans & Co., London, 1950, Vol. X, p. 664.
[2] Hunt, Jones, and Lindsey, *Chem. and Ind.*, 1955, 417.
[3] Chesher, Collier, Robinson, Taylor, Hunt, Jones, and Lindsey, *Nature*, 1955, **175**, 206.

with potassium hydroxide in aqueous methanol. The monoethyl ester (I; R = H, R′ = Et) obtained by direct esterification is identical with that obtained by Hähle [4] by carboxylation of the sodium derivative of ethyl *p*-hydroxybenzoate. Other esters are described in the Experimental section.

Acetylation of the dimethyl and the diethyl ester with acetic anhydride in the conventional manner gave the 4-acetoxy-derivatives. However, attempts to acetylate the free acid by the standard methods or by using trifluoroacetic anhydride failed. This is now ascribed to hydrolysis of the acetate resulting from use of aqueous solutions in the working-up process. In the presence of a cation-exchange resin as catalyst, and by working up the product under anhydrous conditions, treatment with acetic anhydride gave the acetate, as well as much polymeric material. However, good yields of the acetate could be obtained, in the absence of catalyst, merely by allowing a suspension of the acid in ether to stand with excess of acetic anhydride at room temperature. The acetate is readily hydrolysed in cold water and, like aspirin,[5] it displays marked acid anhydride character, arising from the reversible rearrangement shown. This is reflected in the ease with which it is hydrolysed, its ability to acetylate β-naphthol quantitatively, its liberation of carbon monoxide and dioxide from anhydrous oxalic acid in pyridine, and its positive reaction in Davidson's colour test for anhydrides.[6] By the same procedure, the acetyl derivative of the monomethyl ester (I; R = H, R′ = Me) was also prepared; this, too, behaves as a mixed anhydride, providing additional confirmation of the orientation of the monoester. An earlier lack of success in acetylating γ-resorcylic acid [7,8] is similarly ascribed to the ready hydrolysis of the resulting acetate, and acetylation has now been successfully accomplished by a similar procedure (see Experimental).

When kept in pyridine solution the acetyl derivatives of the acid and the monomethyl ester give products of m. p. 285° and 145° respectively. These are thought to be condensation products formed in a manner analogous to the formation of acetyldiplosal from aspirin.[9] This observation accounts for the failure to obtain the simple acetyl derivative when the acetylation was carried out in pyridine solution. Condensation polymers of aromatic acetoxy-carboxylic acids have been described recently by Hasegawa.[10] Acetylation of 4-hydroxy*iso*phthalic acid under reflux conditions with acetic anhydride and an acid catalyst leads to extensive polymer formation, the polymers presumably being of the type described by Hasegawa.

Treatment of 4-hydroxy*iso*phthalic acid with aqueous bromine led to electrophilic displacement of the carboxyl groups with formation of tribromophenol. Barth and Schreder [11] reported that 2 : 4 : 4 : 6-tetrabromo*cyclo*hexa-2 : 5-dienone was formed initially but was converted into 2 : 4 : 6-tribromophenol during recrystallisation. Similar displacement of carboxyl groups during bromination has also been observed with salicylic and *p*-hydroxybenzoic acid.[12] Similarly, treatment of 4-hydroxy*iso*phthalic acid with the usual nitrating mixtures gave picric acid quantitatively. The method given in the patent literature [13] for the preparation of 4-hydroxy-5-nitro*iso*phthalic acid (no yield is quoted) was also unsatisfactory in our hands, giving yields of less than 10% of the 5-nitro-compound.

In contrast to the free 4-hydroxy*iso*phthalic acid the diesters were amenable to chemical reaction, and were readily isolated, together with the monoester, after esterification of the brown-dust residues. Treatment of the monomethyl ester with aqueous bromine gave methyl 3 : 5-dibromo-4-hydroxybenzoate and confirmed that the carboxyl group *para* to the hydroxy-group was esterified. The esterification of the *o*-carboxyl group is undoubtedly sterically hindered by the hydroxy-group.[14]

[4] Hähle, *J. prakt. Chem.*, 1891, **44**, 12.
[5] Davidson and Auerbach, *J. Amer. Chem. Soc.*, 1953, **75**, 5984.
[6] Davidson, *Analyt. Chem.*, 1954, **26**, 576.
[7] Cartwright, Jones, and Marmion, *J.*, 1952, 3499.
[8] Watson, *J.*, 1952, 2940, and personal communication.
[9] G.P. 236,196, 237,211; *Friedländer*, 1903, **10**, 1115, 1117.
[10] Hasegawa, *Bull. Chem. Soc. Japan*, 1954, **27**, 327.
[11] Barth and Schreder, *Monatsh.*, 1882, **3**, 805.
[12] Robertson, *J.*, 1902, **81**, 1475.
[13] G.P. 555,410/1932.
[14] Cf. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell, London, 1953, p. 777.

Dimethyl 4-hydroxy*iso*phthalate was readily brominated in the 5-position by aqueous bromine, its orientation being established by conversion into 6-bromo-2 : 4-dinitrophenol, which was directly compared with an authentic specimen. Chlorination of dimethyl 4-hydroxy*iso*phthalate in glacial acetic acid gave the corresponding 5-chloro-derivative. Treatment of the 5-bromo-derivative with aqueous potassium hydroxide and copper powder led to nucleophilic replacement of bromine by hydroxyl, to give 4 : 5-dihydroxy*iso*phthalic acid. The product was isolated by esterification and sublimation as the monomethyl and the dimethyl esters, which were readily hydrolysed to the free acid. Freudenberg and Klink [15] prepared 4 : 5-dihydroxy*iso*phthalic acid from *iso*hemipinic acid, which they obtained by methylation and hydrolysis of lignin.

Nitration of dimethyl 4-hydroxy*iso*phthalate with nitric–sulphuric acid gave the 5-nitro-derivative, together with smaller amounts of picric acid and methyl 3 : 5-dinitrosalicylate, separable by chromatography. By using a large excess of nitric acid the product was substantially methyl 3 : 5-dinitrosalicylate. Milder nitrating conditions were attained by using glacial acetic acid as solvent, and good yields of dimethyl 4-hydroxy-5-nitro*iso*phthalate were then obtained. Diethyl 4-hydroxy-5-nitro*iso*phthalate was prepared similarly.

Reduction of the 5-nitro-derivatives with aqueous sodium dithionite afforded the corresponding 5-amino-compounds. Diazotisation of dimethyl 5-amino-4-hydroxy*iso*phthalate led initially to precipitation of the yellow diazonium sulphate, which when warmed in aqueous suspension was converted into the brilliant red diazo-oxide. Hydrolysis of the *para*-ester group also occurred and the compound was isolated as 1-methyl 3-hydrogen *iso*phthalate 5 : 6-diazo-oxide, stable towards hot sulphuric acid but decomposing explosively when heated.

An alternative route to 4 : 5-dihydroxy*iso*phthalic acid was studied, starting with dimethyl 4-methoxy*iso*phthalate. This was readily nitrated to give the 5-nitro-derivative. Reduction to the 5-amino-compound by aqueous sodium dithionite was unsatisfactory and the preferred method was hydrogenation in methanol over platinum black. A number of experiments involving preparation of the diazonium sulphate followed by treatment with boiling copper sulphate solution, however, failed to convert this into the expected dimethyl 5-hydroxy-4-methoxy*iso*phthalate. When the diazonium chloride was used the product was essentially dimethyl 5-chloro-4-methoxy*iso*phthalate.

Schwenk *et al.*[16] have shown that, on treatment of *o*- and *p*-methoxybenzoic acid with Raney nickel and aqueous sodium hydroxide, hydrogenolysis occurs with formation of benzoic acid; *m*-methoxybenzoic acid, however, is unaffected by this treatment. Application of this method to 4-methoxy*iso*phthalic acid afforded *iso*phthalic acid in over 80% yield.

An examination of the ultraviolet absorption spectra of the compounds listed in the Table shows that in general the three main absorption peaks characteristic of benzene carrying conjugated chromophoric groups are present. The 4-methoxy-5-nitro-compounds, however, appear exceptional in this respect. Braude [17] has termed these component bands *E*, *K*, and *B*, and these correspond respectively to the second and the first primary and secondary bands quoted for *para*-disubstituted benzene derivatives by Doub and Vandenbelt.[18]

The spectra of 4-methoxy- and 4-hydroxy-*iso*phthalic acid and of their dimethyl esters are similar, only the secondary bands showing any marked shifts. 2-Hydroxy*iso*phthalic acid shows shifts of both primary and secondary bands. With substitution in the 5-position in both 4-hydroxy*iso*phthalic acid and its dimethyl ester an increasing shift of the first primary band towards the visible region occurs in the sense $NH_2 > OH > Br > Cl$, *i.e.*, in a parallel sense to their electromeric effect as shown by the polarising forces of the substituents calculated by Price.[19] Substitution of a $-E$ group, as in the

[15] Freudenberg and Klink, *Ber.*, 1940, **73**, 1369.
[16] Schwenk, Papa, Whitman, and Ginsburg, *J. Org. Chem.*, 1944, **9**, 1.
[17] Braude, *Ann. Reports*, 1945, **42**, 105.
[18] Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714; 1949, **71**, 2414.
[19] Price, "Mechanism of Reactions at Carbon–Carbon Double Bonds," Interscience Publ., Inc., New York, 1946, p. 27.

Maxima of ultraviolet absorption bands (*in* EtOH).

	Substituted *iso*phthalic acids				Substituted dimethyl *iso*phthalates			
	$\lambda_{max.}$ (mμ)	log ε	λ (prim. −218)	λ (sec.)/ λ (prim.)	$\lambda_{max.}$ (mμ)	log ε	λ (prim. −221)	λ (sec.)/ λ (prim.)
Unsubst.	208	4·60	—	—	—	—	—	—
	225	4·07						
	280	2·93						
	288	2·92						
4-Hydroxy	218	4·45	0	1·38	221·2	4·58	0	1·37
	255	4·05			253·5	4·02		
	301	3·50			303	3·49		
5-Chloro-4-hydroxy	223	4·51	+ 5	1·38	225	4·58	+ 4	1·38
	258·5	3·91			245 (sh)	3·94		
	307	3·55			309·5	3·62		
5-Bromo-4-hydroxy	225·6	4·55	+ 7·6	1·38	228	4·56	+ 7	1·36
	252 (sh)	3·86			246 (sh)	3·98		
	310	3·58			309·5	3·66		
4 : 5-Dihydroxy	226·5	4·49	+ 8·5	1·37	230	4·54	+ 9	1·40
	315	3·49			321	3·59		
5-Amino-4-hydroxy	234	4·44	+16	—	237	4·46	+16	1·45
	275 (sh)	3·59			285·5	3·51		
					344	3·58		
4-Hydroxy-5-nitro ...	217·6	4·47	− 0·4	1·52	221·6	4·47	+ 0·4	1·44
	330	3·49			289	3·77		
					318 (sh)	3·48		
							λ (prim. −219)	
4-Methoxy-	217·6	4·59	0	1·41	219	4·48	0	1·34
	253	4·23			255	4·15		
	293	3·51			294	3·43		
5-Chloro-4-methoxy	—	—			215·5	4·56	− 3·5	1·36
	—	—			293	3·24		
5-Amino 4-methoxy	210	4·25	+10	1·48	—	—		
	228	4·42			229	4·45	+10	1·46
	326	3·60			335	3·55		
4-Methoxy-5-nitro ...	206—207	4·47	−12	—	206	4·58	−13	—
2-Hydroxy-	212·8	4·51	—	1·50	—	—	—	—
	319	3·70						

5-nitro-derivatives, however, caused very little shift of the first primary band. Similar remarks apply to the few spectra of 5-substituted 4-methoxy*iso*phthalic acids and esters which are recorded in the Table. There the 5-nitro-derivatives are again anomalous, since only the high-intensity first primary band appears between 200 and 350 mμ, and represents a marked shift away from the visible region.

The surprising regularity of the shifts of both the first primary and secondary absorption peaks was noted for mono- and *para*-di-substituted benzene derivatives by Doub and Vandenbelt,[18] and also occurs in the present series of compounds as shown by the very small variation in the value of the secondary : primary ratio. By plotting the shift of the first primary band in the 5-substituted compounds (compared with the first primary band of the unsubstituted compound) against λ primary, straight-line plots were obtained having slopes almost identical with those obtained similarly from the mono-substituted benzenes.[18] Similarly, plots of the shifts of the secondary band against λ secondary gave straight lines. These results support the views of Doub and Vandenbelt.

Survey of the literature shows that only a few isolated studies of the pharmacological activity of derivatives of 4-hydroxy*iso*phthalic acid have been reported. Fosdick and Fancher [20] found that the alkyl and aminoalkyl esters of 4-methoxy*iso*phthalic acid were less toxic than the procaine series and had an anæsthetic efficiency of somewhat the same magnitude. Antitubercular activity in 6-amino-4-hydroxy*iso*phthalic acid has also been

[20] Fosdick and Fancher, *J. Amer. Chem. Soc.*, 1941, **63**, 1277.

claimed,[21] but other investigators have found the activity to be low.[22] Diethyl 5-amino-4-hydroxy*iso*phthalate prepared in the present work has been tested for antibacterial activity, in dextrose–peptone-water, with *Myco. phlei* NCTC 525 as test organism. However, even at the highest level of solubility in the medium, 25 μg./ml., the compound was inactive.[23] Details of pharmacological tests on the analgesic and antipyretic activities of 4-hydroxy*iso*phthalic acid and some related compounds have been published elsewhere.[24]

Experimental

General.—Microanalyses were carried out by Miss M. Corner and her staff of this Laboratory. Ultraviolet absorption spectra were measured in EtOH with a Unicam SP500 spectrophotometer which had been calibrated against an alkaline solution of potassium chromate.[25]

Ferric chloride colorations were obtained by dissolving approx. 1 mg. of compound in 2 ml. of redistilled ethanol and adding one drop of ferric chloride solution (1% neutral solution in ethanol). Colours recorded lasted at least 1 minute.

Preparation of 4-*Hydroxy*iso*phthalic Acid from Brown Dust Residues.*—4-Hydroxy*iso*phthalic acid was extracted from commercial " Brown Dust Residues " from the Kolbe–Schmitt salicylic acid synthesis, from which the bulk of the salicylic acid had been removed either by sublimation or other processes. Typical extraction experiments are given below.

(i) *Solvent extraction.* Brown-dust residues (20 g.) were continuously extracted first with carbon tetrachloride at room temperature in a modified Soxhlet apparatus to give salicylic acid (2·2 g.), then with chloroform at room temperature to give 2-hydroxy*iso*phthalic acid (0·6 g.), and finally with dry methanol to separate the residual 4-hydroxy*iso*phthalic acid (16·5 g.) from the inorganic material (0·5 g.). The 4-hydroxy*iso*phthalic acid, recrystallised from aqueous methanol, had m. p. 309—310° (decomp.).

(ii) *Steam-distillation.* Brown-dust residues (60 g.) suspended in water (500 ml.) were steam-distilled until the distillate no longer contained salicylic acid (3·1 g. recovered). The suspension of solids was treated with slight excess of solid barium carbonate (approx. 80 g.) whilst hot and with continuous stirring. Filtration removed insoluble barium salts, excess of barium carbonate, and much of the coloured impurities. Acidification of the filtrate gave moderately pure 4-hydroxy*iso*phthalic acid (36 g.), which recrystallised from aqueous methanol as pale buff needles, m. p. 296—300° (decomp.). Further crystallisation gave a pure specimen, m. p. 310° (decomp.).

(iii) *Esterification.* The diesters being more useful starting materials for substitution experiments, this method of separating 4-hydroxy*iso*phthalic acid was preferred.

Brown-dust residues (100 g.), dissolved in dry methanol (1 l.) and filtered to remove inorganic material (4 g.), were esterified by refluxing for 24 hr. in the presence of concentrated sulphuric acid (10 ml.). Much of the methanol (approx. 700 ml.) was distilled off and the residue added to a solution of sodium carbonate (50 g.) in water (1 l.). The precipitated dimethyl *iso*phthalate (51 g.) was filtered off and dried, and finally crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 97·5° (Found : C, 57·1; H, 4·8. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·8%). Ether-extraction of the alkaline filtrate gave methyl salicylate and a little dimethyl 4-hydroxy*iso*phthalate which was added to the main product. The rest of the methyl salicylate was recovered from the light petroleum mother-liquors; the bulked material amounted to 12·7 g.

Acidification of the alkaline filtrate by hydrochloric acid gave the crude monomethyl 4-hydroxy*iso*phthalate (32 g.) (I; R = H, R′ = Me). Crystallisation (charcoal) from aqueous methanol and light petroleum (b. p. 60—80°) gave the monoester as platelets, m. p. 200° (Found : C, 55·2; H, 4·2. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%). Treatment of an aqueous suspension of the monomethyl ester with bromine gave methyl 3 : 5-dibromo-4-hydroxybenzoate, m. p. 125° after crystallisation from light petroleum (b. p. 80—100°) (Found : C, 31·0; H, 1·9; Br, 51·4. Calc. for $C_8H_6O_3Br_2$: C, 31·0; H, 1·9; Br, 51·6%).

By use of ethanol as solvent, diethyl 4-hydroxy*iso*phthalate, m. p. 54·5° (Found : C, 60·5; H, 5·8. Calc. for $C_{12}H_{14}O_5$: C, 60·5; H, 6·0%), and 1-*ethyl* 3-*hydrogen* 4-*hydroxy*iso*phthalate*,

[21] Bavin, Drain, Seiler, and Seymour, *J. Pharm. Pharmacol.*, 1952, **4**, 844.
[22] Cf. Beyerman and Alberda, *Rec. Trav. chim.*, 1950, **69**, 1021; Checcacci, Logemann, Pistoia, and Lauria, *Nature*, 1954, **173**, 588.
[23] The authors are indebted to Dr. H. O. J. Collier for permission to publish this result.
[24] Collier and Chesher, *Brit. J. Pharmacol.*, 1956, **11**, 20.
[25] Haupt, *J. Res. Nat. Bur. Stand.*, 1952, **48**, 414.

m. p. 195·6° (I; R = H, R′ = Et) (Found : C, 57·1; H, 4·8. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·7%), were prepared in the same way.

Alkaline hydrolysis of either the mono- or the di-ester and recrystallisation of the free acid from aqueous methanol gave 4-hydroxy*iso*phthalic acid as needles, m. p. 312—313° (decomp.) (Found : C, 52·7; H, 3·2. Calc. for $C_8H_6O_5$: C, 52·7; H, 3·3%), giving a claret ferric chloride colour. Infrared absorption spectrum (as mull in Nujol) (Nujol bands omitted) : 3155 (w; sh), 2967 (s), 2653 (w), 2545 (w), 1704 (s; sh), 1669 (s), 1653 (s; sh), 1590 (m), 1468 (s; sh), 1418 (m), 1311 (m; sh), 1289 (m; b), 1233 (m), 1212 (m), 1198 (m), 1155 (w), 1117 (w), 1083 (w), 935 (w), 920 (w), 851 (w), 800 (w), 773 (w), 691 (m) $cm.^{-1}$ (w = weak, m = medium, s = strong, sh = shoulder, b = broad).

*Mono- and Di-*n*-propyl, Di-*n*-butyl, and Di-*n*-pentyl Esters of* 4-*Hydroxy*iso*phthalic Acid.*—Esterification of 4-hydroxy*iso*phthalic acid with *n*-propyl, *n*-butyl, and *n*-pentyl alcohol respectively in the presence of sulphuric acid gave good yields of *di*-n-*propyl* (from light petroleum, b. p. 40—60°), m. p. 23·5°, b. p. 142—145°/0·15 mm. (Found : C, 63·4; H, 6·7. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%), *mono*-n-*propyl*, m. p. 171—172° (from methanol) (Found : C, 58·85; H, 5·3. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·3%), *di*-n-*butyl*, purified by distillation, m. p. −3° to −1°, b. p. 159°/0·1 mm., n_D^{20} 1·5048 (Found : C, 65·3; H, 7·35. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%), and *di*-n-*pentyl* 4-*hydroxy*iso*phthalate*, b. p. 188—192°/0·1 mm., n_D^{20} 1·5012 (Found : C, 67·6; H, 7·8. $C_{18}H_{26}O_5$ requires C, 67·1; H, 8·1%).

Partial Hydrolysis of Dimethyl 4-*Hydroxy*iso*phthalate.*—To a solution of the dimethyl ester (1·0 g.) in 3% methanolic potassium hydroxide (10 ml.) was added water (10 ml.), and the solution refluxed for 3 hr. Ether-extraction removed non-hydrolysed ester (~50 mg.) and acidification gave the monomethyl ester (800 mg.). It recrystallised as almost colourless flakes, m. p. and mixed m. p. 196—197° (Found : C, 54·9; H, 4·1. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%), from aqueous methanol.

Acetylation of Dimethyl and Diethyl 4-*Hydroxy*iso*phthalate.*—The dimethyl ester (500 mg.) in dry pyridine (20 ml.) with acetic anhydride (2 ml.) overnight gave dimethyl 4-acetoxy-*iso*phthalate which on recrystallisation from methanol had m. p. 92° (Found : C, 57·3; H, 4·7. Calc. for $C_{12}H_{12}O_6$: C, 57·15; H, 4·8%) and depressed the m. p. of the starting material on admixture.

Acetylation of diethyl 4-hydroxy*iso*phthalate similarly gave the *acetate*, b. p. 205—219°/0·9 mm., n_D^{25} 1·5043 (Found : C, 60·1; H, 5·8. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·75%).

Acetylation of 4-*Hydroxy*iso*phthalic Acid.*—Attempts to acetylate the acid by pyridine–acetyl chloride, pyridine–acetic anhydride, acetic anhydride–sulphuric acid, acetic anhydride–perchloric acid, acetic anhydride–sodium acetate, and trifluoroacetic anhydride failed and in most cases the acid was recovered. Refluxing 4-hydroxy*iso*phthalic acid (10 g.) with acetic anhydride (75 ml.) in the presence of sulphonated polystyrene resin beads (Amberlite 112) for 5 hr., filtering off the resin and removing the excess of acetic anhydride and acid azeotropically with dry benzene (reduced pressure) led to a gum. Extraction of this with ethyl acetate furnished 4-*acetoxy*iso*phthalic acid* (1 g.), which after recrystallisation from light petroleum (b. p. 80—100°)–ethyl acetate had m. p. 192—193° (decomp.) (Found : C, 53·7; H, 3·6. $C_{10}H_8O_6$ requires C, 53·6; H, 3·6%). With ethanolic ferric chloride it gave no colour but on standing in water it was hydrolysed readily to the parent acid, which then gave a claret colour with ferric chloride. The non-crystalline residue separated from acetone–benzene as an amorphous powder, m. p. 285—290° (Found : C, 55·1; H, 3·4%), which gave no colour with alcoholic ferric chloride.

Acetylation was effected more readily without the use of a catalyst. 4-Hydroxy*iso*phthalic acid (10 g.) with acetic anhydride (30 g.) in ether (100 ml.) was kept at room temperature for 3 days. After 24 hr. the acid was completely in solution. Removal of the ether and addition of benzene gave 4-acetoxy*iso*phthalic acid (10·8 g.), m. p. 192° (decomp.) (Found : C, 53·5; H, 3·8%). From the benzene solution a small amount of resin was obtained.

Reactions of 4-*Acetoxy*iso*phthalic Acid.*—(*a*) The acid (2·5 g.) was heated for 15 min. on the steam-bath with β-naphthol (1·4 g.) in pyridine (5 ml.). Adding water precipitated β-naphthyl acetate (1·6 g.), m. p. 71° (from methanol–water).

(*b*) Addition of the acid to a pyridine solution of anhydrous oxalic acid led to vigorous evolution of carbon dioxide and monoxide.

(*c*) *With* (±)-α-p-*nitrobenzamido*-α-*phenylacetic acid*[26] (*Davidson's reagent*). Addition of the acid (30 mg.) to a 3% solution (1 ml.) of the reagent in pyridine gave an intense blue colour. This gradually faded but the colour was restored on warming or on addition of dilute sodium hydroxide solution.

[26] Ingersoll and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 2930.

(*d*) A solution of the acid (3 g.) in pyridine (10 ml.) was kept at room temperature for 24 hr. Addition of water did not cause precipitation but with dilute hydrochloric acid a white precipitate separated. This was extracted with ether and furnished material (2·7 g.), m. p. 285° (decomp.) (Found: C, 55·7; H, 3·8. Calc. for $C_{18}H_{12}O_{10}$: C, 55·7; H, 3·1%) after recrystallisation from benzene–acetone. Further purification failed to give closer agreement in the analytical results.

Acetylation of 1-*Methyl* 3-*Hydrogen* 4-*Hydroxy*iso*phthalate.*—The ester (1 g.) was kept for 3 days with acetic anhydride (2 g.) in ether (10 ml.). Removal of solvent and crystallisation of the residue from light petroleum (b. p. 60—80°)–chloroform gave the *acetate*, m. p. 143° (1·1 g.) (Found: C, 55·5; H, 4·2. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%). This derivative gave a blue colour with Davidson's reagent. A solution of the ester (0·5 g.) in pyridine (5 ml.) deposited in 24 hr. needles, m. p. 145° [from light petroleum (b. p. 60—80°)–chloroform] which depressed the m. p. of the original ester. It contained nitrogen and was presumably a pyridine salt of an unidentified condensation product.

Acetylation of γ-Resorcylic Acid.—γ-Resorcylic acid (2 g.) was refluxed in acetic anhydride (50 g.) in the presence of a sulphonated polystyrene resin (Amberlite 112) for 3 hr. After removal of the resin and distillation of the solvent under reduced pressure 2 : 6-*diacetoxybenzoic acid*, m. p. 113—114° (from benzene) (Found: C, 55·5; H, 4·4. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%), was obtained in quantitative yield. It gave no colour with alcoholic ferric chloride.

Bromination of 4-*Hydroxy*iso*phthalic Acid.*—Aqueous bromine was added to a solution of 4-hydroxy*iso*phthalic acid (500 mg.) in aqueous ethanol until the yellow colour persisted. The precipitated bromo-compound was washed and recrystallised from aqueous ethanol. The dried material (350 mg.; m. p. 90—91°) sublimed as needles, m. p. 93—94° alone or mixed with 2 : 4 : 6-tribromophenol (Found: C, 21·5; H, 0·9; Br, 72·9. Calc. for $C_6H_3OBr_3$: C, 21·75; H, 0·9; Br, 72·5%).

Dimethyl 5-*Bromo*-4-*hydroxy*iso*phthalate.*—Aqueous bromine was added to a methanolic solution of dimethyl 4-hydroxy*iso*phthalate (0·5 g.) with stirring and warming until the yellow colour persisted. The precipitate, recrystallised from methanol (charcoal), gave *dimethyl* 5-*bromo*-4-*hydroxy*iso*phthalate* as needles, m. p. 146—147° (Found: C, 41·5; H, 3·05; Br, 27·3. $C_{10}H_9O_5Br$ requires C, 41·5; H, 3·1; Br, 27·7%), giving a red ferric chloride colour. Alkaline hydrolysis of this ester gave 5-*bromo*-4-*hydroxy*iso*phthalic acid*, needles, m. p. 298° (decomp.) (from water) (Found: C, 37·1; H, 1·9; Br, 30·7. $C_8H_5O_5Br$ requires C, 36·8; H, 1·9; Br, 30·7%), giving a claret-coloured ferric chloride reaction.

Confirmation of the Orientation of 5-*Bromo*-4-*hydroxy*iso*phthalic Acid.*—5-Bromo-4-hydroxy-*iso*phthalic acid (0·5 g.) was added gradually to concentrated sulphuric acid (4·5 ml.), fuming nitric acid (3·5 ml.), and water (1·0 ml.) at room temperature. When evolution of carbon dioxide had ceased and all the material was in solution, the mixture was poured immediately into an equal volume of water. Overnight, bright yellow crystals (250 mg.) separated which on crystallisation from ethanol had m. p. 118—119° alone or mixed with 6-bromo-2 : 4-dinitrophenol.

Dimethyl 5-*Chloro*-4-*hydroxy*iso*phthalate.*—A slow stream of chlorine was passed for 1·5 hr. through a solution of dimethyl 4-hydroxy*iso*phthalate (1·00 g.) in glacial acetic acid (15 ml.), which was then set aside overnight. The prisms (900 mg.) which had separated were filtered off and recrystallised from methanol, to give *dimethyl* 5-*chloro*-4-*hydroxy*iso*phthalate* as prisms, m. p. 139—140° (Found: C, 48·8; H, 3·7; Cl, 14·1. $C_{10}H_9O_5Cl$ requires C, 49·1; H, 3·7; Cl, 14·5%), giving a red ferric chloride colour.

Alkaline hydrolysis gave 5-*chloro*-4-*hydroxy*iso*phthalic acid*, needles, m. p. 292—293° (decomp.) (from water) (Found: Cl, 16·6. $C_8H_5O_5Cl$ requires Cl, 16·4%) (claret-coloured ferric chloride reaction).

Conversion of Dimethyl 5-*Bromo*-4-*hydroxy*iso*phthalate into* 4 : 5-*Dihydroxy*iso*phthalic Acid.*—Dimethyl 5-bromo-4-hydroxy*iso*phthalate (3·0 g.) was refluxed with 20% aqueous potassium hydroxide (20 ml.) and copper powder (0·1 g.) for 18 hr. under nitrogen. After filtration and addition of an equal volume of water, concentrated hydrochloric acid gave a precipitate containing silica. The product [2·5 g.; m. p. 265° (decomp.)] was recovered by ether-extraction. Preliminary experiments had shown that this product, consisting of 4 : 5-dihydroxy- with a small amount of 4-hydroxy-*iso*phthalic acid, was not readily purified by recrystallisation or chromatography. It was esterified by methanol–sulphuric acid and separated in the usual way into dimethyl 4 : 5-dihydroxy*iso*phthalate, needles (1·45 g.), m. p. 140—141° (Found: C, 53·1; H, 4·5. Calc. for $C_{10}H_{10}O_6$: C, 53·1; H, 4·45%) (pale blue ferric chloride colour), and methyl hydrogen 4 : 5-dihydroxy*iso*phthalate (0·7 g.), needles, m. p. 218—219° (after sublimation at

185°/20 mm.) (Found: C, 50·8; H, 3·8. Calc. for $C_9H_8O_6$: C, 50·95; H, 3·8%) (royal-blue ferric chloride colour).

Alkaline hydrolysis of the dimethyl ester gave the dicarboxylic acid which recrystallised from water as needles, m. p. 296° (decomp.) (Found: C, 48·6; H, 3·15. Calc. for $C_8H_6O_6$: C, 48·5; H, 3·0%) (royal-blue ferric chloride colour).

Nitration of 4-*Hydroxy*iso*phthalic Acid.*—(i) 4-Hydroxy*iso*phthalic acid (1·0 g.) was added slowly to fuming nitric acid (9 ml.), sulphuric acid (9 ml.), and water (2 ml.) at 0°. After the solid had dissolved (with some effervescence) the solution was left overnight at room temperature, then poured into water (150 ml.). The product, crystallised from chloroform, had m. p. 120—122°, alone or mixed with picric acid, m. p. 122°.

(ii) (Cf. G.P. 555,410/1952.) To 4-hydroxy*iso*phthalic acid (2 g.), dissolved in concentrated sulphuric acid (2·4 ml.; *d* 1·84) and cooled to 0°, was added dropwise ice-cold sulphuric acid (1·6 ml.)–nitric acid (1·6 ml.; *d* 1·38). Some effervescence occurred and, after the mixture had attained room temperature, it was heated for 2 hr. on the steam-bath and poured into a small volume of ice-cold water (10 ml.). 4-Hydroxy-5-nitro*iso*phthalic acid (0·2 g.) separated which on crystallisation from chloroform had m. p. 235—236° alone or mixed with the 5-nitro-diacid prepared by hydrolysis (see below).

Nitration of Dimethyl 4-*Hydroxy*iso*phthalate.*—To a solution of dimethyl 4-hydroxy*iso*phthalate (11·8 g.) in concentrated sulphuric acid (12 ml.) at 0° was added an ice-cold mixture of sulphuric acid (4 ml.) and nitric acid (3·9 ml.; *d* 1·42) dropwise with stirring. After being left overnight at room temperature the mixture was poured into ice-water (100 ml.). Crystallisation of the crude product (9 g.), which also contained small amounts of picric acid and methyl 3 : 5-dinitrosalicylate, did not effect purification. Part of the crude product (2 g.) was therefore chromatographed in benzene on silica gel, giving (fractions 7—17; benzene) dimethyl 4-hydroxy-5-nitro*iso*phthalate (0·8 g.), m. p. 105·5° (from methanol) (Found: C, 47·05; H, 3·6; N, 5·4. Calc. for $C_{10}H_9O_7N$: C, 47·1; H, 3·5; N, 5·5%), giving an orange ferric chloride colour.

Alkaline hydrolysis of the diester gave 4-hydroxy-5-nitro*iso*phthalic acid, needles, m. p. 237—238° (from water) (Found: C, 42·6; H, 1·8; N, 6·1. Calc. for $C_8H_5O_7N$: C, 42·3; H, 2·2; N, 6·2%) (orange ferric chloride colour).

A similar nitration experiment but with a large excess of nitric acid gave substantially methyl 3 : 5-dinitrosalicylate, m. p. 129·5° (Found: C, 40·0; H, 2·6; N, 11·0. Calc. for $C_8H_6O_7N$: C, 39·8; H, 2·5; N, 11·3%), hydrolysed to 3 : 5-dinitrosalicylic acid, m. p. 171·5—172° (from water) (Found: C, 36·7; H, 1·9; N, 12·35. Calc. for $C_7H_4O_7N_2$: C, 36·85; H, 1·75; N, 12·3%).

Nitration of Diethyl 4-*Hydroxy*iso*phthalate.*—To an ice-cold solution of diethyl 4-hydroxy*iso*phthalate (20 g.) in sulphuric acid (40 ml.; *d* 1·84) and acetic acid (40 ml.) was added dropwise ice-cold sulphuric acid (12 ml.)–nitric acid (12 ml.; *d* 1·50). After 30 min. the product crystallised and was completely precipitated by water. *Diethyl* 4-*hydroxy*-5-*nitro*iso*phthalate* (21 g.), recrystallised from ethanol, had m. p. 92—93° (Found: C, 50·9; H, 4·65; N, 4·8. $C_{12}H_{13}O_7N$ requires C, 50·9; H, 4·6; N, 4·95%).

Dimethyl 5-*Amino*-4-*hydroxy*iso*phthalate.*—To a stirred suspension of dimethyl 4-hydroxy-5-nitro*iso*phthalate (3·2 g.) in water (30 ml.) was added portionwise sodium dithionite dihydrate (12 g.) at <30°. After 4 hours' stirring, the mixture was made alkaline by sodium carbonate and extracted with ether, and the amine removed from the ethereal solution by 50% hydrochloric acid. Treatment with sodium carbonate liberated *dimethyl* 5-*amino*-4-*hydroxy*iso*phthalate* (1·7 g.), m. p. 170° (Found: C, 53·4; H, 5·05; N, 6·3. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 5·0; N, 6·2%) (pale green-blue ferric chloride colour).

Diethyl 5-*Amino*-4-*hydroxy*iso*phthalate.*—To a stirred suspension of diethyl 4-hydroxy-5-nitro*iso*phthalate (8 g.) in water (80 ml.) and ethanol (30 ml.) was added sodium dithionite (35 g.) portionwise, at <30°. Next morning, basification and ether-extraction removed the free amine and unchanged material. Washing the ether extract with 17% hydrochloric acid and liberating the product with aqueous ammonia gave *diethyl* 5-*amino*-4-*hydroxy*iso*phthalate* (5·8 g.), needles (from methanol), m. p. 127° (Found: C, 57·0; H, 6·3; N, 5·25. $C_{12}H_{15}O_5N$ requires C, 57·0; H, 5·9; N, 5·5%).

5-*Amino*-4-*hydroxy*iso*phthalic Acid.*—Dimethyl 5-amino-4-hydroxy*iso*phthalate (225 mg.) was hydrolysed with 0·1N-sodium hydroxide (35·2 ml.). From the acidified solution 5-*amino*-4-*hydroxy*iso*phthalic acid* crystallised as needles (185 mg.) which, recrystallised from water, had m. p. 297° (decomp.) (Found: C, 48·8; H, 3·5; N, 7·35. $C_8H_7O_5N$ requires C, 48·7; H, 3·6; N, 7·1%) (orange ferric chloride colour).

Diazotisation of Dimethyl 5-*Amino*-4-*hydroxy*iso*phthalate.*—To a solution of dimethyl

5-amino-4-hydroxy*iso*phthalate (2 g.) in 50% sulphuric acid (15 ml.) at 0° was added an ice-cold solution of sodium nitrite (0·6 g.) in water (5 ml.). An immediate yellow colour developed and, gradually, a yellow precipitate. Water (20 ml.) was added, excess of nitrite removed with urea, and the mixture warmed on the steam-bath for 2 hr. The red precipitate (1·5 g.), repeatedly crystallised from acetone, gave *3-methoxycarbonylbenzoic acid 5 : 4-diazo-oxide* as dark red crystals, m. p. 154° (explode) (Found : C, 48·9; H, 2·8; N, 12·6. $C_9H_6O_5N_2$ requires C, 48·65; H, 2·7; N, 12·6%).

After treatment of the diazo-oxide with concentrated sulphuric acid and hot copper sulphate solution it was recovered unchanged.

Dimethyl 4-*Methoxy*iso*phthalate.*—4-Hydroxy*iso*phthalic acid (21 g.) with aqueous sodium hydroxide and dimethyl sulphate gave a mixture of mono- and di-methyl esters. Esterification was completed by refluxing methanol–sulphuric acid. The non-acidic fraction gave dimethyl 4-methoxy*iso*phthalate (10 g.), m. p. 95° (from methanol) (Found : C, 58·8; H, 5·4. Calc. for $C_{11}H_{12}O_5$: C, 58·85; H, 5·4%).

*4-Methoxy*iso*phthalic Acid by Oxidation of 2 : 4-Dimethylanisole.*—4-Methoxy*iso*phthalic acid (56·5 g.) was obtained by oxidation of 2 : 4-dimethylanisole (67 g.) with potassium permanganate.[20] Crystallised from water, it had m. p. 276° (decomp.).

*Hydrogenolysis of Dimethyl 4-Methoxy*iso*phthalate.*—Dimethyl 4-methoxy*iso*phthalate (200 mg.) was warmed with 10% aqueous sodium hydroxide (10 ml.) until dissolved, the temperature then raised to 90°, and Raney nickel (1·0 g.) added portionwise. After a further hour at 90°, the filtered solution was poured into concentrated hydrochloric acid. The precipitate, washed with water, dried, crystallised from methanol, and sublimed, gave *iso*phthalic acid (120 mg.), m. p. 310—320° (sublimes) (Found : C, 57·75; H, 3·55. Calc. for $C_8H_6O_4$: C, 57·8; H, 3·6%), giving no colour with aqueous ferric chloride. Ultraviolet absorption max. (in EtOH) : 207, 225, 280, 288 mμ (log ε 4·57, 4·08, 2·98, 2·98 respectively) [Morton and Stubbs [27] give $\lambda_{max.}$ 227, 280, 288 mμ (log ε 4·16, 3·11, 3·05 respectively)].

*Nitration of Dimethyl 4-Methoxy*iso*phthalate.*—To an ice-cold solution of the ester (5 g.) in sulphuric acid (10 ml.) and glacial acetic acid (10 ml.) was added dropwise an ice-cold mixture of sulphuric acid (3 ml. ; *d* 1·84) and nitric acid (3 ml. ; *d* 1·50). The reaction mixture was kept at room temperature for 2·5 hr., then poured on ice (100 g. approx.). *Dimethyl 4-methoxy-5-nitro*iso*phthalate* (4 g.), recovered by filtration, recrystallised from methanol and then light petroleum (b. p. 60—80°) as needles, m. p. 85° (Found : C, 49·1; H, 4·3; N, 5·25. $C_{11}H_{11}O_7N$ requires C, 49·1; H, 4·1; N, 5·2%). Alkaline hydrolysis gave *4-methoxy-5-nitro*iso*phthalic acid*, needles, m. p. 225—256° (from water) (Found : C, 44·7; H, 2·9; N, 6·0. $C_9H_7O_7N$ requires C, 44·8; H, 2·9; N, 5·8%).

*Dimethyl 5-Amino-4-methoxy*iso*phthalate.*—Dimethyl 4-methoxy-5-nitro*iso*phthalate (1·0 g.) in anhydrous methanol (25 ml.) containing Adams catalyst (0·1 g.) was shaken in hydrogen. Absorption was rapid until the theoretical amount had been taken up. Filtration and evaporation under reduced pressure gave an orange oil which crystallised from methanol (low temperature) or benzene–light petroleum (b. p. 80—100°) (room temperature), to give *dimethyl 5-amino-4-methoxy*iso*phthalate* (0·7 g.), m. p. 63—64° (Found : C, 55·4; H, 5·6; N, 6·0. $C_6H_{13}O_5N$ requires C, 55·2; H, 5·5; N, 5·85%).

*Diazotisation of Dimethyl 5-Amino-4-methoxy*iso*phthalate.*—To this ester (2·3 g.) in 50% hydrochloric acid (20 ml.) at 0° was added an ice-cold solution of sodium nitrite (0·69 g.) in water (5 ml.). Urea was added and the solution run slowly into a boiling solution of copper sulphate (100 g.) in water (120 ml.), covered with toluene (20 ml.), which was continuously stirred. After 10 minutes' heating, the solution was cooled, the toluene layer separated, and the copper sulphate solution washed with toluene (10 ml.) which was added to the main bulk. Removal of toluene under reduced pressure gave a solid (2 g.), m. p. 70—75°, which on chromatography in light petroleum (b. p. 40—60°) over alumina, elution with light petroleum (b. p. 40—60°)–benzene, and crystallisation from light petroleum (b. p. 60—80°) gave *dimethyl 5-chloro-4-methoxy*iso*phthalate* as needles, m. p. 77—78° (Found : C, 51·1; H, 4·3; Cl, 13·9. $C_{11}H_{11}O_5Cl$ requires C, 51·1; H, 4·2; Cl, 13·7%).

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[27] Morton and Stubbs, *J.*, 1940, 1348.