268. *A Re-examination of the Reported* m-*Nitration of Phenols and Phenolic Ethers.*

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The products of mononitration of phenol and anisole have been analysed by several independent methods for the presence of *m*-isomerides. The conclusion has been reached that, contrary to the views of earlier investigators, the proportions in which *m*-isomerides are formed in these reactions are less than 0·1%.

Arnall claimed (*J.*, 1924, **125**, 911) that 2·1—3·3% of *m*-nitrophenol is formed when phenol is mononitrated, as it can be, smoothly, by nitric acid in acetic acid. This conclusion is supported by the claim of Griffiths, Walkey, and Watson (*J.*, 1934, 631) that 1·4—2·2% of *m*-nitroanisole is formed in the mononitration of anisole by nitric acid of *d* 1·42, by nitric acid in sulphuric acid, nitric acid in acetic acid, nitric acid in acetic anhydride, and by benzoyl nitrate.

It seems improbable that strongly *op*-orienting groups like $^-$OH and $^-$OR could lead to appreciable *m*-nitration, when the weakly *op*-orienting halogens do not do so. This conclusion is reinforced by the consideration that the *op*-orienting property of $^-$OR groups, as of halogens, in aromatic substitution, is a tautomeric effect, and, unlike the inductive effect, is almost wholly a polarisability, therefore leading exclusively to *op*-substitution (Ingold and Shaw, *J.*, 1927, 2918).

Being engaged in a kinetic study of some of the special features of the mono-nitration of phenol and its derivatives we investigated these outstanding points concerning the orientation of nitration in these compounds.

Arnall and Griffiths, Walkey, and Watson based their conclusions on thermal analyses of the isolated nitration products; such methods may be unreliable unless by-products of mononitration can be removed more completely than can sometimes be established by ordinary analysis, however satisfactory apparently.

We have used three methods, applying one to phenol, one to anisole, and a third to both. These three methods give consistent results, disagreeing with those of the previous workers.

The first method, that of chromatographic adsorption, was applied to the product of the mononitration of phenol by nitric acid in acetic acid. It is possible to resolve mixtures of *o*-, *m*-, and *p*-nitrophenol by this method (cf. Strain, " Chromatographic Adsorption Analysis ", Interscience Publishers, Inc., New York, 1942, p. 94); but, in application to the mononitration product of phenol, it was found that repeated adsorption of the various bands failed to reveal any trace of *m*-nitrophenol. This result, by itself, is not conclusive, as the method is difficult to standardise for small quantities of the *m*-compound, especially as the chromatogram is complicated by the presence of small amounts of derivatives of dihydroxydiphenylnitrogen oxide, which are formed during nitration of phenols.

The other method applied to phenol was an extension of Albert and Large's specific test for *m*-diamines (*Nature*, 1938, **142**, 435; Albert, *J.*, 1939, 920). They observed that *m*-diamines react with glycerol and oxalic acid in the presence of zinc or calcium chloride to give the fluorescent 2 : 8-diaminoacridine. By addition of stannous chloride to their reagent they extended the test to *m*-nitroamines and *m*-dinitro-compounds.

Our further extension of this test was to convert *m*-nitrophenol into *m*-nitroaniline by heating with amminozinc chloride and ammonium chloride. As the fluorescence of 2 : 8-diaminoacridine is quenched by phenols, any unconverted phenols were removed by extraction of the product from alkaline solution. No fluorescence was observed when this test was applied to the products of nitration of phenol by nitric acid in acetic acid, although when a trace of *m*-nitrophenol was first added to the nitration product a strong fluorescence was observed. Control experiments by this method established that the proportion of *m*-nitration under our conditions was less than 0·1%.

The first method to be applied to the nitration product of anisole was that of thermal analysis; but the fractionating column used in the removal of the non-isomeric by-products of mononitration was probably much more efficient than any at the disposal of earlier workers. We investigated this mononitration under several of the conditions used by Griffiths, Walkey, and Watson, *viz.*, nitration by nitric acid of *d* 1·42, by nitric acid in sulphuric acid, and by nitric acid in acetic acid. Two methods of thermal analysis were applied to each isolated product. One was a determination of the eutectic temperature, as the second arrest-point of the cooling curve. This temperature was always that of the binary mixture of *o*- and *p*-nitroanisoles to within our experimental error (about $\pm$ 0·1°). The other method involved

a determination of the clearing point, followed by similar determinations after additions of pure *o*-nitroanisole sufficient, first, to lower the clearing temperature in stages to the eutectic point, and then to raise it beyond that point. In each case, the composition–temperature curve thus traced coincided (to within the accuracy of the clearing point measurements : usually ± 0·3°), with the curve for binary mixtures of *o*- and *p*-nitroanisoles. This curve was first traced by Griffiths, Walkey, and Watson (*loc. cit.*), whose measurements we confirm. These determinations showed that the proportions of *m*-isomeride in our mononitration products could not have been more than a small fraction of 1%.

The second method applied to the mononitration products of anisole was the fluorescence test as described for the nitrophenols. Like *m*-nitrophenol, *m*-nitroanisole is converted into *m*-nitroaniline by heating with amminozinc chloride and ammonium chloride, and the product can be converted into 2 : 8-diaminoacridine by the method of Albert and Large. This test gave no detectable fluorescence when applied to the nitration products of anisole, although, as with phenol, a readily detectable fluorescence was obtained on the addition of small amounts of *m*-nitroanisole to the nitration product. Control experiments on these lines give an upper limit of 0·1% of *m*-nitration in the mononitration of anisole.

Thus it is proved by three independent methods that the proportions of *m*-isomeride formed in the mononitration of phenol and anisole are lower than we could detect, and very much lower than the proportions previously reported.

Experimental.

Materials.—Phenol was dried and distilled under reduced pressure in an all-glass apparatus. Anisole, alkali-washed and distilled, had b. p. 154—154·5°. The nitrophenols, from British Drug Houses, Ltd., were not further purified. The *m*- and *p*-nitroanisole, after crystallisation from aqueous alcohol, and the *o*-nitroanisole, prepared from steam-distilled *o*-nitrophenol and distilled, had m.p.s agreeing with those of Griffiths, Walkey, and Watson (here given in parentheses); *o*-, 10·4° (10·45°); *m*-, 35·7° (35·5°); *p*-, 52·1° (52·0°). Acetic acid was purified with chromium trioxide and fractionated. Nitric acid (95%) was distilled successively from 100% sulphuric acid and barium nitrate.

Miscellaneous Methods.—The initial content of the lower oxides of nitrogen in the nitrating mixtures was determined by the chloramine-T method (von Eck, *Pharm. Weekblad*, 1926, **63**, 1117; see also Minkoff, Thesis, London, 1945). The nitration of phenol by nitric acid in acetic acid was carried out with excess of phenol at 20°. The nitration products were poured into excess of alkali, and unchanged phenol was removed by treatment with carbon dioxide and ether. The mixture was just acidified with acetic acid, extracted with ether, and washed. The ether was removed, and the product dried in a vacuum desiccator. The nitrations of anisole by nitric acid (*d* 1·42), by nitric acid in sulphuric acid, and by nitric acid in acetic acid, were carried out essentially as described by Griffiths, Walkey, and Watson (*loc. cit.*). The products were extracted by ether from excess of alkali. Activated alumina was used for chromatographic adsorption; mixtures of ether and benzene were used as solvent, and in order to develop the chromatogram. Nitrophenols and nitroanisoles, either reference specimens or nitration products, were converted into nitroanilines by heating with amminozinc chloride (4 parts) and ammonium chloride (1 part) at 330° for 30 hours (cf. Menz and Muller, *Ber.*, 1886, **19**, 2916). The nitroanilines were then treated by the method of Albert and Large (*loc. cit.*). Cooling curves were determined in double-walled tubes, with stirring. Clearing points were determined in narrow, thin-walled tubes with stirring by a fine glass rod.

Examples of Thermal Analyses for the Nitration of Anisole.—(*a*) Anisole (0·95 g.-mol.) was treated with nitric acid (*d* 1·42; 1 g.-mol.) at 45° for 5 hours with continuous stirring. The product yielded the following data : Eutectic temperature from cooling curve, − 7·0°. Clearing point, + 23·3°. Deduced composition *o*-/(*o*- + *p*-) = 43·1% (Found : C, 55·9; H, 4·7; N, 9·1. Calc. for $C_7H_7O_3N$: C, 55·0; H, 4·8; N, 9·1%. Purity by $TiCl_3$ equivalent, 99·8%). Mixtures of the product with *o*-nitroanisole gave the following results :

Calc. % *o*- after addn.	43·1	65·0	69·8	80·0	84·5
Clearing point, calc.	(+23·3°)	+0·6°	−6·3°	−0·6°	+2·6°
,, ,, obs.	+23·3°	+0·9°	−6·1°	−0·4°	+2·3°

(*b*) Anisole (0·45 g.-mol.) was treated with a mixture of nitric acid (*d* 1·42; 0·5 g.-mol.) and sulphuric acid (0·5 g.-mol.) at 45° for 4 hours with continuous stirring. The product yielded the following data : Eutectic temperature from cooling curve, − 7·3°. Clearing point, + 26·2°. Deduced composition, *o*-/(*o*- + *p*-) = 39·8% (Found : C, 55·4; H, 4·5; N, 9·9%. Purity by $TiCl_3$ equivalent, 99·9%).

Calc. % *o*- after addn.	39·8	66·6	68·1	72·8	77·1
Clearing point, calc.	(+26·2°)	−1·9°	−4·0°	−5·4°	−2·4°
,, ,, obs.	+26·2°	−1·9°	−4·3°	−5·5°	−2·1°

(*c*) Anisole (0·05 g.-mol.) was treated with 200 c.c. of nitric acid (3M) in acetic acid at 20° for 12 hours, the initial concentration of nitrous acid being 0·03M. The product yielded the following data : Eutectic temperature from cooling curve, − 7·2°. Clearing point, + 33·0°. Deduced composition, *o*-/(*o*- + *p*-) = 30·5% (Found : C, 56·0; H, 4·8; N, 9·0%. Purity by $TiCl_3$ equivalent, 100·1%).

Calc. % *o*- after addn.	30·5	47·4	64·6	71·3	75·1	84·5
Clearing point, calc.	(+33·0°)	+20·2°	+1·5°	−6·4°	−3·8°	+2·0°
,, ,, obs.	+33·0°	+20·4°	+2·0°	−6·1°	−3·7°	+2·5°

(*d*) Anisole (0·05 g.-mol.) was treated with 200 c.c. of nitric acid (6·3M) in acetic acid at 20° for 15 hours, the initial concentration of nitrous acid being 0·12M. The product yielded the following data: Eutectic temperature from cooling curve, − 7·0°. Clearing point, + 30·4°. Deduced composition, *o*-/(*o*- + *p*-) = 34·0% (Found: C, 55·1; H, 4·7; N, 10·0%. Purity by $TiCl_3$ equivalent, 99·8%).

Calc. % *o*- after addn.	34·0	44·4	59·6	74·0	87·5
Clearing point, calc.	(+30·4°)	+22·7°	+7·6°	−4·5°	+3·8°
,, ,, obs.	+30·4°	+23·0°	+7·5°	−4·4°	+3·6°

Synthetic mixtures. (i) A mixture of *o*- and *p*-nitroanisole of composition *o*-/(*o*- + *p*-) = 69·3% gave the following results: Eutectic temperature, − 7·2° (Griffiths *et al.* give the same value). Clearing point, − 5·8° (interpolated from accepted values, − 5·7°). Clearing point after addition of 2·0% of *m*-nitroanisole, − 6·7°.

(ii) A mixture of *o*- and *p*-nitroanisole of composition *o*-/(*o*- + *p*-) = 81·8% gave the following results: Clearing point, + 0·9° (interpolated from accepted values, + 0·7°). Clearing point after addition of 1·5% of *m*-nitroanisole, + 0·6°.

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