794. *The Direct Introduction of the Diazonium Group into Aromatic Nuclei. Part I. The Basic Reaction, yielding Diazonium Salts from Polyalkylbenzenes, Phenol Ethers, Phenols, and Aromatic Tertiary Amines.*

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A general reaction involving the action of excess of nitrous acid on aromatic compounds to yield diazonium salts is demonstrated:

$$\mathrm{ArH} + 2\mathrm{HNO_2} + \mathrm{HX} \longrightarrow \mathrm{Ar{\cdot}N_2^+X^-} + 2\mathrm{H_2O} + 2[\mathrm{O}]$$

With aromatic compounds containing activating groups the yields of diazonium salt are sufficient to give the reaction preparative value.

Diazonium salts are usually prepared by diazotisation of amines with nitrous acid. Conversion of an aromatic hydrocarbon into a diazonium salt by this method involves three steps: nitration, reduction to the amine, and diazotisation. The work described in the present series of papers is concerned with the development of methods whereby this conversion can be carried out in one step. Previously two reactions which lead to the formation of some diazonium salt directly from aromatic hydrocarbon derivatives have been reported. The first of these is a side-reaction occurring during the normal preparation of nitrosophenols by direct nitrosation. If phenols are treated with excess of nitrous acid for long periods, the nitroso-derivatives first formed react further to yield diazonium salts.[1] That this is a general reaction of preparative value does not seem to have been appreciated. The second reaction by which a diazonium group is directly introduced into an aromatic nucleus involves treating a reactive aromatic compound with a solution of an alkyl nitrite in trifluoroacetic anhydride.[2] Only moderate yields of diazonium salt were obtained by this method from mesitylene and anisole, while very expensive trifluoroacetic anhydride was required, and considerable by-products were formed. There are a few other reactions [3] in which diazonium salts occur as minor by-products.

This first paper gives an account of work aimed at establishing the existence of a quite general reaction of which the above were specific examples. The general reaction involves initial nitrosation of the aromatic nucleus by a solution containing nitrous acid or a nitrosyl derivative. The nitroso-derivative so formed reacts with more nitrous acid to yield the diazonium salt. In all cases, except tertiary amines and phenols where the nitroso-derivative is stabilised in the quinone monoxime structure, the second reaction occurs so rapidly that no nitroso-derivative can be isolated.

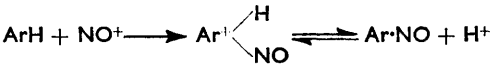
$$\mathrm{ArH} \xrightarrow[\mathrm{-HX}]{\mathrm{HNO_2}} [\mathrm{ArNO}] \xrightarrow[\mathrm{-HX}]{\mathrm{HNO_2}} \mathrm{Ar{\cdot}N_2^+X^-}$$

Phenols can be readily nitrosated by cold dilute aqueous solutions of sodium nitrite in hydrochloric acid, or by solutions of ethyl nitrite and hydrogen chloride in aqueous ethanol. By use of excess of nitrosating solution good yields of diazonium salt have been obtained from *p*-cresol (56%) by the former method, and from phenol (80%) by the latter. The ethanolic system is likely to be particularly valuable for insoluble phenols.

Tertiary amines are also nitrosated in either of these media and as is well known, in the presence of excess acid, the *p*-nitroso-derivative can be obtained in very high yield. However, even under these conditions traces of diazonium salt (*ca.* 1%) are present in the mother-liquors. Undoubtedly, in the presence of excess of acid the nitroso-derivative is converted into the salt with a quinone imine oxime structure which is unaffected by further nitrous acid. In the case of *NN*-dimethyl-*p*-nitrosoaniline, the hydrochloride is relatively insoluble in water, inhibiting the second stage of the reaction still further. However, by treating these compounds with excess of nitrous acid, but no excess of mineral acid, diazonium salts can be prepared and moderate yields have been obtained from *NN*-dimethyl- (55%) and *NN*-diethyl-aniline (70%).

The success or failure of the general reaction with less reactive compounds depends to a large extent on the initial nitrosation reaction. With phenols and tertiary amines this step possibly involves electrophilic attack on the aromatic nucleus by molecular nitrosyl chloride. Less reactive compounds are unaffected by this reagent and more acidic media are necessary. Ingold and his co-workers have postulated and provided strong evidence for nitrosation as an intermediate step in nitrous acid-catalysed nitrations in nitric acid.[4] The reaction is believed to proceed through electrophilic attack by the nitrosonium ion:

$$\mathrm{HNO_2 + HX \rightleftharpoons H_2NO_2^+ + X^- \rightleftharpoons NO^+ + H_2O + X^-}$$



$$\mathrm{ArH + NO^+ \longrightarrow Ar^+\!\!<^{H}_{NO} \rightleftharpoons Ar{\cdot}NO + H^+}$$

In nitration, HX is nitric acid and the nitroso-compound is oxidised to the nitro-derivative. Nitric acid is therefore an unsuitable solvent for the formation of diazonium salts, but sulphuric acid is both more acidic and less likely to oxidise the intermediate nitroso-derivatives. Further, sodium nitrite is known to dissolve in concentrated sulphuric acid

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[1] Weselsky, *Ber.*, 1871, **4**, 613; 1875, **8**, 98; Morel and Sisley, *Bull. Soc. chim. France*, 1927, **41**, 1223; Hodgson, *J.*, 1931, 1494; 1932, 866; Philpot and Small, *Biochem. J.*, 1938, **32**, 534.

[2] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1952, 1695.

[3] Horner and Hubenett, *Chem. Ber.*, 1952, **85**, 804; Horner and Betzel, *Annalen*, 1953, **579**, 193.

[4] Bunton, Hughes, Ingold, Jacobs, Jones, Minkoff, and Reed, *J.*, 1950, 2628.

to form ionised nitrosylsulphuric acid, thus providing a strongly acidic medium in which nitrosonium ions are likely to be particularly abundant:

$$NaNO_2 + 3H_2SO_4 \longrightarrow NO^+ + H_3O^+ + 2HSO_4^- + NaHSO_4$$

This system was indeed found to be very effective in the formation of diazonium salts directly from aromatic hydrocarbons. However, this mixture alone, although giving small yields of diazonium salt from phenol ethers, alkylbenzenes, and even benzene itself, failed to give good yields (*i.e.*, better than 20%) even with reactive compounds such as mesitylene; and, what is more important, the diazonium salts isolated as the β-naphthol coupling compounds proved to be largely nitro-derivatives. Thus diazonium salt formation was accompanied by various side-reactions in which nitration predominated. The explanation of these side reactions can probably be found in the second stage of the basic reaction, namely, the conversion of the nitroso-compound into a diazonium salt.

The conversion of nitrosobenzene into benzenediazonium nitrate was first studied by Bamberger who treated a chloroform solution of nitrosobenzene with nitric oxide.[5] Later he obtained a better yield by using sodium nitrite in acetic acid solution, and also found pentyl nitrite to be effective.[6] Several empirical schemes can be written for these reactions:

$$PhNO + 4HNO_2 \longrightarrow PhN_2^+ + NO_3^- + 2H_2O + 2NO_2$$

$$PhNO + 3HNO_2 \longrightarrow PhN_2^+ + NO_3^- + H_2O + HNO_3$$

$$PhNO + HNO_2 \longrightarrow PhN_2^+ + OH^- + 2[O]$$

The first reaction would be consistent with the intermediate formation of nitric oxide which then reacted with nitrosobenzene as Bamberger first demonstrated, but his later work is more consistent with the second reaction. However, both Bamberger's " equations " contain the third, which is the simplest possible form and probably expresses the initial reaction. The two atoms of oxygen would be expected to react with excess of nitrous acid, giving an overall balance consistent with either of the former equations. So far it has not been possible to establish the stoicheiometry of the reaction unequivocally.

The formation of nitro-derivatives as by-products in the preparation of diazonium salts is readily explained by these equations, which also suggest methods by which they may be avoided. By carrying out the reaction in 67% sulphuric acid, a poor yield (5·5%) of diazonium salt was obtained from mesitylene, but the product, unlike that from concentrated or 75% sulphuric acid, proved to be mesitylenediazonium sulphate uncontaminated by nitro-products. Although nitration of the diazonium salt was avoided in this medium, nitration of the free mesitylene occurred and the yield of diazonium salt was very low. However, concurrent sulphonation and nitration was almost completely avoided by carrying out the reaction in an inert atmosphere in nitrobenzene solution. Reasonable yields of diazonium salt were obtained from anisole, mesitylene, and *m*-xylene in this medium. The most reactive compound of these three, anisole, was treated in nitrobenzene with crystalline nitrosylsulphuric acid (prepared separately from nitric acid and sulphur dioxide) at 0°. Nitrosylsulphuric acid is only slightly soluble in nitrobenzene, but carbon dioxide bubbled through the mixture provided sufficient agitation to promote complete reaction. The stream of carbon dioxide was intended to remove any oxygen or higher oxides of nitrogen formed during the reaction, but more recent work suggests this was unnecessary. A 48% yield of diazonium salt was obtained from anisole by this method. Mesitylene and *m*-xylene were treated in nitrobenzene with excess of nitrosylsulphuric acid in concentrated sulphuric acid (prepared *in situ* by dissolving sodium nitrite in excess of sulphuric acid, before addition to the nitrobenzene and the hydrocarbon). The mixture separated into two layers, but as before agitation by an inert gas was sufficient to promote the reactions which were carried out at room temperature. Yields of 78% and 43% were

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[5] Bamberger, *Ber.*, 1897, **30**, 506.
[6] *Idem*, *Ber.*, 1918, **51**, 634.

obtained from mesitylene and *m*-xylene respectively. In similar nitrobenzene solutions a negligible yield of diazonium salt was obtained from toluene, and benzene was unaffected.

No attempt has yet been made to achieve maximum yields or find optimum conditions, but the results described above provide evidence for a general reaction of a wide range of aromatic compounds, in which a diazonium group is introduced directly into the aromatic nucleus. A more detailed study of the reaction with phenols and tertiary amines is in progress.

EXPERIMENTAL

p-*Hydroxyphenylazo*-β-*naphthol*.—Phenol (0·51 g.) was dissolved in aqueous ethanol (5 c.c.). Ethyl nitrite (10 c.c.) followed by a saturated solution of hydrogen chloride in ethanol (5 c.c.) were then added. The mixture was kept below 10° for 36 hr., then poured into ice–water (300 c.c.). The aqueous solution was exhaustively extracted with ether (to remove unchanged phenol or quinone monoxime) before being neutralised with solid sodium hydrogen carbonate and treated with excess of alkaline β-naphthol solution. The azo-dye was extracted with chloroform, and the extract washed with 0·01N-sodium hydroxide and dried (Na_2SO_4). Evaporation of the chloroform left a bright red solid (1·22 g.), m. p. 189—190°. Recrystallisation from acetone gave red needles,[7] m. p. 194° (Found: C, 72·7; H, 5·1. Calc. for $C_{16}H_{12}O_2N_2$: C, 72·7; H, 4·6%).

2 : 2′ : 4′-*Trihydroxy*-5-*methylazobenzene*.—*p*-Cresol (1·07 g.) was dissolved in ice-water (100 c.c.) and acetone (50 c.c.). Sodium nitrite (5 g.) was added, followed by 2N-hydrochloric acid (25 c.c.). The solution was left for 14 hr. at +2° to −2°. A small precipitate was then filtered off, and the solution extracted with ether. The aqueous residue was neutralised with sodium hydrogen carbonate and treated with excess of resorcinol. The solution was then made more alkaline (pH 12), becoming very intensely red. After 0·5 hr. the whole was acidified with dilute hydrochloric acid, and the precipitated azo-dye extracted with chloroform. The extract was washed repeatedly with water to remove excess of resorcinol, dried (Na_2SO_4), and evaporated. The crude azo-dye (1·21 g.), m. p. 209—211°, was recrystallised from acetone. The pure *dye*, m. p. 214°, gave a bright orange colour in concentrated sulphuric acid and a deep crimson-red in alkaline solution (Found: C, 63·9; H, 5·0; N, 11·3. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 4·9; N, 11·5%).

p-NN-*Dimethylaminophenylazo*-β-*naphthol*.—Dimethylaniline (1·0 c.c.) was dissolved in ice-water (100 c.c.) and acetone (50 c.c.). Sodium nitrite (5·0 g.) was added, followed by 2N-hydrochloric acid (25 c.c.) at 0°. After 14 hr. at 0° a small precipitate was removed, and the solution neutralised with sodium hydrogen carbonate. The neutral solution was exhaustively extracted with chloroform and the aqueous residue treated with a slight excess of alkaline β-naphthol solution. After ½ hr. the dye was extracted with chloroform. The extract was washed twice with dilute sodium hydroxide solution and once with 2N-hydrochloric acid, dried (Na_2SO_4), and evaporated, to leave a black crystalline residue (1·41 g.), m. p. 170—175° (decomp.). The dye recrystallised from acetone as blue-black needles, m. p. 180—182° (decomp.), dissolving in chloroform to a very deep crimson solution, and in acetone or alcohol to an intense red brown one; the colour in sulphuric acid is magenta (Found: C, 74·1; H, 6·3; N, 14·0. Calc. for $C_{18}H_{17}ON_3$: C, 74·2; H, 5·8; N, 14·4%).

p-NN-*Diethylaminophenylazo*-β-*naphthol*.—A solution of diethylaniline (1·0 c.c.) in acetone (100 c.c.) and water (50 c.c.) was treated with sodium nitrite (5·0 g.) and 2N-hydrochloric acid (25 c.c.). The reactants were kept below 2° for 14 hr. and then worked up as in the previous experiment. The crude azo-dye (1·42 g.), m. p. 115—118°, recrystallised from acetone as blue-black needles, m. p. 119—120°. The appearance and properties of this *compound* were identical with those of the dye from dimethylaniline (Found: C, 75·4; H, 6·9; N, 13·2. $C_{20}H_{21}ON_3$ requires C, 75·3; H, 6·6; N, 13·2%).

Reaction between Mesitylene and Nitrosylsulphuric Acid.—(a) *In concentrated sulphuric acid*. Mesitylene (1·0 c.c.) was added to a solution of sodium nitrite (4 g.) in concentrated sulphuric acid (15 c.c.) through which carbon dioxide had been bubbled for 20 min. before the reaction started. The mixture was stirred for 3 hr. at 8° and then poured on crushed ice. The aqueous mixture was extracted with ether, and the extract discarded. The lower layer was neutralised with sodium carbonate, and a copious brown precipitate was formed (possibly an indazole

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[7] Niementowski, *Anz. Akad. Wiss. Krakau*, 1902, 413 (*Chem. Zentr.*, 1902, II, 938).

derivative). The whole mixture was filtered and the filtrate was coupled with alkaline β-naphthol. The azo-dye was extracted with chloroform, washed with alkali, and dried (Na_2SO_4), and the chloroform evaporated, to leave an amorphous red powder, m. p. 160—168° (0·14 g.). The dye gave an intense purple colour in sulphuric acid.

(b) *In* 75% *sulphuric acid.* Sodium nitrite (4·0 g.) was dissolved in a mixture of sulphuric acid (12·0 c.c.) and water (7·0 c.c.). The solution was cooled and mesitylene (1·0 c.c.) was added. The mixture was stirred at room temperature for 3·5 hr. and the azo-dye prepared as before. The crude dye (0·24 g.) after one recrystallisation from acetone had m. p. 178—179° and was further purified to give an amorphous red powder, m. p. 181—182°, dissolving in concentrated sulphuric acid with an intense purple colour (Found: C, 73·9; H, 5·6; N, 9·3%). The identity of the compound has not been definitely established.

(c) *In* 67% *sulphuric acid.* Under similar conditions mesitylene (1·0 c.c.) was stirred with a solution of sodium nitrite (4·0 g.) in sulphuric acid (10·0 c.c.) and water (8·7 c.c.). The crude dye [2] (0·12 g.) after one recrystallisation from acetone had m. p. 131—132°, undepressed on admixture with 2 : 4 : 6-trimethylphenylazo-β-naphthol, and gave a bright crimson colour in concentrated sulphuric acid. The ether extract contained nitro-compounds.

Reaction between Toluene and Sodium Nitrite in Concentrated Sulphuric Acid.—Toluene (1 c.c.) was added to sodium nitrite (4 g.) in concentrated sulphuric acid (15 c.c.). The system, which was not homogeneous, was stirred under carbon dioxide for 16 hr. at 20—22°, then poured on ice, and the aqueous mixture was extracted with ether. The aqueous layer was neutralised with sodium carbonate and filtered. The filtrate was treated with excess of β-naphthol, and the azo-dye isolated in the usual way. The crude dye (0·13 g.) gave a purple colour in concentrated sulphuric acid. Recrystallisation gave a small yield of dark red needles, m. p. 254—256° (Found: C, 65·7; H, 4·2. Nitrotolylazo-β-naphthol, $C_{17}H_{13}O_3N_3$, requires C, 66·2; H, 4·6%). The identity of this compound was not established, but it was probably 2-nitro-4-tolylazo-β-naphthol. The other likely isomer 4-nitro-2-tolylazo-β-naphthol is known and has somewhat different properties.[8]

Reaction Between Benzene and Sodium Nitrite in Concentrated Sulphuric Acid.—In a series of experiments aliquot portions of benzene (1 c.c.) were added to sodium nitrite (4 g.) in concentrated sulphuric acid (10 c.c.). Reaction times of 6—36 hr. and temperatures from 20° to 45° were employed. The diazonium salt formed was estimated by coupling with β-naphthol exactly as in the preceding experiment. Traces of azo-dye were obtained, but in no case more than 2%. All the dyes gave purple colours in sulphuric acid and m. p.s *ca.* 180—190°. They were not investigated in detail but are believed to have been crude nitrophenylazo-β-naphthols.

p-*Methoxyphenylazo*-β-*naphthol.*—Anisole (1·0 c.c.) was added to a mixture of nitrosylsulphuric acid (3·18 g.) (prepared separately from fuming nitric acid and sulphur dioxide) and nitrobenzene (10 c.c.) at 0°. The mixture darkened instantly. A stream of carbon dioxide was bubbled through the mixture at 0° for 4 hr. The mixture was poured on iced water and extracted with ether. The ether layer was washed with dilute sodium hydroxide solution, and the ether discarded. The washings were re-acidified and extracted with fresh ether. This second extract was dried (Na_2SO_4) and evaporated, to leave a phenolic residue (0·22 g.). The main aqueous solution was neutralised with sodium carbonate and then treated with a slight excess of sodium β-naphthoxide. The resulting dye was extracted with chloroform, washed with dilute sodium hydroxide and then water, and dried (Na_2SO_4). The chloroform was evaporated, to leave a bright red solid (0·73 g.). A single recrystallisation from acetone gave red needles,[9] m. p. 140° (Found: C, 72·8; H, 5·1. Calc. for $C_{17}H_{14}O_2N_2$: C, 73·4; H, 5·0%).

2 : 4 : 6-*Trimethylphenylazo*-β-*naphthol.*—Sodium nitrite (4·2 g.) was dissolved in concentrated sulphuric acid (10 c.c.). The mixture became warm, all the sodium nitrite dissolved, then a paste was formed. Nitrobenzene (10 c.c.) was added to the mixture and the paste stirred. Hydrogen was bubbled slowly through the system and after 20 min. mesitylene (1·0 c.c.) was injected into the mixture. Every hour a glass rod was inserted into the system and the solid was broken up. The glass rod on withdrawal was washed with sodium hydrogen carbonate solution and these washings tested with alkaline β-naphthol solution; in each test a red precipitate was obtained. After 4 hr., the mixture was poured on crushed ice, and the aqueous solution filtered. The nitrobenzene being solid was recovered and was dissolved in chloroform and extracted with aqueous sodium hydrogen carbonate solution, the aqueous

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[8] Leonard and Browne, *Sci. Proc. Roy. Dublin Soc.*, 1920, **16**, 105.

[9] Koch, Milligan, and Zuckerman, *Ind. Eng. Chem. Analyt.*, 1944, **16**, 755.

extract being retained while the chloroform solution was discarded. The main aqueous solution was extracted with chloroform to remove traces of nitrobenzene, and then neutralised with solid sodium hydrogen carbonate; this solution was then combined with the washings from the nitrobenzene. The azo-dye was prepared by adding an excess of a solution of β-naphthol in aqueous sodium carbonate. After 2 hr. the azo-dye was extracted with chloroform and the combined extracts were washed twice with 0·01N-sodium hydroxide to remove co-precipitated β-naphthol. The chloroform solution was dried (Na_2SO_4) and evaporated under reduced pressure to leave a semi-crystalline red solid, m. p. 130—131° (1·60 g.). (Mesityl-azo-β-naphthol[2] has m. p. 132°.) Recrystallisation from acetone yielded bright red needles, m. p. 133—134° (Found: C, 78·2; H, 6·3. Calc. for $C_{19}H_{18}ON_2$: C, 78·6; H, 6·2%).

2 : 4-*Dimethylphenylazo*-β-*naphthol*.—Sodium nitrite (4·1 g.) was dissolved in concentrated sulphuric acid (10 c.c.), and nitrobenzene (10 c.c.) was added. A stream of carbon dioxide was bubbled through the mixture for 20 min. before *m*-xylene (1·0 c.c.) was added. The mixture which separated into two layers was agitated by carbon dioxide and the reaction was allowed to continue for 6 hr., during which the solid was broken up occasionally. Then the mixture was poured on ice and extracted with chloroform, the chloroform extract being discarded. The dye was prepared and isolated as in the previous experiments. The crude product (1·12 g.) melted at 158—159° and a single recrystallisation from acetone gave red needles,[7] m. p. 159—160° (Found: C, 77·8; H, 5·6. Calc. for $C_{18}H_{16}O_2N_2$: C, 78·3; H, 5·8%).

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