444. *Hydroxylation of Nitrobenzene.*

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The hydroxylation of nitrobenzene has been carried out at room temperature by the action of hydroxyl radicals produced by the hydrogen peroxide–ferrous salt reaction (Haber and Weiss, *Proc. Roy. Soc.*, 1934, *A*, **147**, 332). It has been found that under these conditions *o*-, *p*-, and *m*-nitrophenols are formed, the relative quantities of which have been determined. *mm'*-Dinitrodiphenyl has also been isolated as one of the by-products of the reaction. These results are in agreement with a free-radical mechanism of hydroxylation.

Many theoretical considerations have been published regarding the orientation of substituents in the aromatic nucleus, mainly on substitution by electrophilic, nucleophilic, and also by free-radical reagents (cf. Ingold, *Ann. Reports*, 1926, **23**, 112; 1927, **24**, 106; *Chem. Reviews*, 1934, **15**, 225; Hey, *Ann. Reports*, 1940, **37**, 282; Wheland, "The Theory of Resonance," New York and London, 1947).

However, very limited experimental evidence is available regarding substitution by free radicals in the monosubstituted aromatic nucleus, particularly quantitative data, with the exception of some recent work in which it was found that substitution by aryl radicals takes place at all three positions with respect to CO_2Et (Hey, *J.*, 1934, 1966) and Cl and Br (France, Heilbron, and Hey, *J.*, 1938, 1364).

It is known that the system hydrogen peroxide–ferrous salt produces hydroxyl radicals by the reaction $Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH$ (Haber and Weiss, *loc. cit.*; Baxendale, Evans, and Park, *Trans. Faraday Soc.*, 1946, **42**, 155).

It seemed to be of interest, therefore, to investigate the action of the hydroxyl radicals produced by this and by other means (Stein and Weiss, *Nature*, 1948, **161**, 650) on simple aromatic compounds. We have so far investigated the action on benzene, phenol, benzoic acid, and nitrobenzene. The case of nitrobenzene which offers a number of interesting points is now reported.

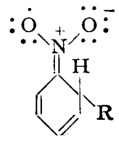
It is to be expected that the nitro-group removes electrons from the carbon atom to which it is attached and thus increases its electron affinity. As a result of this, substitution by the common electrophilic reagents takes place in the *m*-position, whereas nucleophilic reagents would be expected to attack the *o*- and *p*-positions although with greater difficulty. With regard to free radicals, it remained to be seen whether the strong directive influence of the nitro-group has some effect or whether substitution takes place in all three positions and to determine the relative abundance of the isomers formed.

We found that, in spite of the well-known comparative resistance of nitrobenzene to further oxidation, hydroxylation of nitrobenzene proceeded with great ease under suitable conditions even at room temperature, and that the products of the reaction are further attacked, leading to the formation of polyphenolic compounds. In order to restrict the attack to the first stages and thus to get some idea of the relative proportions of the monohydroxylated isomers, we had to work at low pH's and to use a large excess of nitrobenzene so that only a relatively small portion of it was converted and thus further attack on the primary reaction products was inhibited.

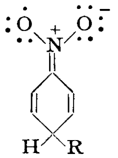
The reaction was carried out by allowing dilute solutions of ferrous sulphate and hydrogen peroxide to drop simultaneously into a well-stirred mixture of nitrobenzene and water. Under these conditions all three isomeric nitrophenols could be isolated from the reaction mixture in the approximate proportions *o*- 0·56, *p*- 1·0, *m*- 0·44.

It will be seen that, in spite of the fact that of the five available positions in which substitution can occur only one is *p*-, the amount of the *p*-isomer is considerably greater than that of the *o*- or the *m*-isomer. This cannot be due in this case to the ease of its isolation, as the *o*-isomer can be isolated at least as easily. The *m*-isomer is clearly not favoured in this case, as its proportion is about 20% of the total amount, this being only about half the amount to be expected on purely statistical grounds. Furthermore, steric hindrance does not seem to prevent the formation of the *o*-isomer, which is produced in larger quantity than the *m*-compound.

The result is in general agreement with those of earlier workers (*locc. cit.*) and with the theoretical considerations of Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900), *viz.*, that any radical reagent should attack preferentially the *o*- and *p*-positions on account of (i) the greater availability of an unpaired electron at the *o*- and *p*-positions, (ii) the fact that the quinonoid resonance structures for the *o*- and *p*-transition states (I, II) are more stable than the corresponding one for the *m*-substitution (III).



(I.)



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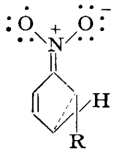

(III.)

It has been possible also to isolate a small quantity of *m*-dinitrodiphenyl from the reaction mixture, indicating that free nitrophenyl radicals are formed in the reaction. The fact that only this dimer has been isolated in a pure state does not exclude the possibility of other isomers also being formed in the reaction. We will discuss the mechanism of these reactions in subsequent papers, but the results reported above indicate that the hydroxylation of nitrobenzene by the ferrous–hydrogen peroxide reagent proceeds by a free-radical mechanism. It is somewhat remarkable and of some interest that the hydroxylation of the relatively inert nitrobenzene—which frequently requires extreme conditions and high temperatures to become reactive—proceeds in this case with ease at room temperature, as is often the case in free-radical reactions.

EXPERIMENTAL.

(All m. p.s are uncorrected.)

Freshly steam-distilled nitrobenzene (5 g.) was mixed with sulphuric acid (150 ml.; 2N.), and 4-vol. hydrogen peroxide (100 ml.) and ferrous sulphate solutions (100 ml., 2%) were added with stirring during 45 minutes. If the solution is neutral or less acid or the peroxide is added more rapidly, a dark mixture of polyphenolic nature results. However, if the process is carried out as above, a pale yellow liquid results, the nitrobenzene layer having only a slightly deeper orange colour. The total amount of nitrophenols formed is about 150 mg. The reaction mixture was extracted exhaustively with ether, the extracts of several runs united, washed with dilute acid and water, and extracted exhaustively with dilute sodium hydroxide, and the alkaline extracts acidified immediately. The acid solution was extracted with benzene, and the extract dried ($CaCl_2$), boiled for 1—2 minutes with charcoal, and filtered. For further separation Karrer and Nielsen's method of chromatography (*Zangger Festschrift*, 1934, 954) was tried but good results were obtained by the following simple procedure.

The benzene solution was once more extracted with dilute sodium hydroxide and the alkaline extract steam-distilled. When the distillate was free from organic material, the solution was acidified and further steam-distilled in the micro-steam-distilling apparatus. The *o*-nitrophenol crystallised from the distillate in yellow prisms, m. p. 44°, mixed m. p. 44°. The residual solution is extracted with ether, the ether extract was dried and evaporated, and a few drops of 10% sodium hydroxide were added to the residue. The sodium salt of *p*-nitrophenol, which is nearly insoluble in 10% sodium hydroxide, was precipitated and filtered off. The alkaline solution containing the *m*-isomer was acidified and extracted with ether, and the extract on evaporation yielded the *m*-nitrophenol.

The sodium salt of *p*-nitrophenol was dissolved in very little hot water and acidified; long colourless needles of *p*-nitrophenol crystallised overnight, giving m. p. and mixed m. p. 114°. The *m*-isomer, obtained as above, had m. p. *ca.* 84°. One recrystallisation from hot dilute hydrochloric acid gave crystals, m. p. and mixed m. p. 94°. The relative amounts of the isomers in several experiments were within the following limits: *o*-, 25—30; *p*-, 50—55; *m*-, 20—25%.

A part of the reaction products was neither volatile with steam nor soluble in dilute alkali, and yielded a dark precipitate when the reaction mixture was basified; this was filtered off, washed with water, dried, and then sublimed in a vacuum, forming yellow crystals, m. p. 170—180°, which on recrystallisation from absolute alcohol yielded colourless crystals, m. p. 198°, corresponding to the reported m. p. of *mm'*-dinitrodiphenyl (Found: C, 59·2; H, 3·0. Calc. for $C_{12}H_8O_4N_2$: C, 59·2; H, 3·3%). The mixed m. p. with an authentic specimen was 198°.

The yellow alcoholic mother-liquor from the recrystallisation, on slow dilution with water, gave a very small yield of pale yellow crystals, m. p. 100°, which is possibly another dinitrodiphenyl.

Part of the experimental work was carried out by one of us (H. L.) whilst at the Université Libre, Brussels, and our thanks are due to Professor Martin for his hospitality and interest. We also thank Professor G. R. Clemo for his interest in this work.

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