

CLXIX.—*The Nature of the Alternating Effect in Carbon Chains. Part V. A Discussion of Aromatic Substitution with Special Reference to the Respective Rôles of Polar and Non-polar Dissociation ; and a further Study of the Relative Directive Efficiencies of Oxygen and Nitrogen.*

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THE preceding parts of this series describe a partial examination of the theories of the alternating polarisation of atoms (A), and of the alternating affinity content of valencies (B), as applied to aromatic substitution :



The criterion adopted was that, according to the first view, the more electronegative atoms of the series N, O, F, should produce the larger effects ($F > O > N$), whilst, according to the second, the reverse should hold, the most "unsaturated" atom being the most potent ($N > O > F$).

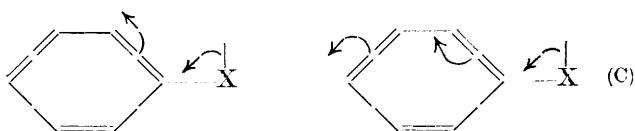
In Part III, a comparison of benzylamines and benzyl ethers was recorded, from which it was concluded that nitrogen is more effective than oxygen, which appeared to agree with theory (B). Observations have since been made, however, which show that even this theory is not adequate without extension, and that special factors must enter into the problem of the orientation of substances in which the "key-atom" is separated from the nucleus by a chain of one or more carbon atoms. It is therefore necessary to examine the application of other considerations. Nevertheless, the general conclusion previously reached with regard to the directive efficiencies of oxygen and nitrogen accords with that to which the present experiments on the nitration of derivatives of *o*-aminophenol have led.*

The results of these experiments are represented in the following

* The case of O versus F is dealt with in the following paper.

The low value found by Sugden (J., 1924, **125**, 1185) for the parachor of the group CO_2 in carboxylic esters would then be attributed to shrinkage arising from electrostatic attraction.

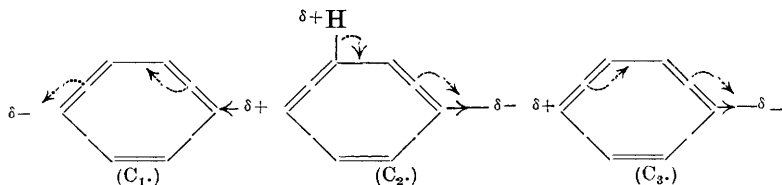
The above results, whilst they appear inconsistent with the idea of alternating polar charges (A), agree either with Flürscheim's theory of alternating affinity content (B), or with Robinson's theory (*Chem. and Ind.*, 1925, **44**, 456) of *op*-substitution by electronic displacement in conjugated systems (C).^{*} This theory leads to much the same key-efficiency series as Flürscheim's, if residual affinity be interpreted as an indication of the presence of loosely held, active electrons. The arrows represent the assumed electron displacements originating in a latent valency :



It will be obvious that the distribution of forces here involved is qualitatively the same as that in Flürscheim's theory, the completed change (C) corresponding with his figure for *op*-substitution :



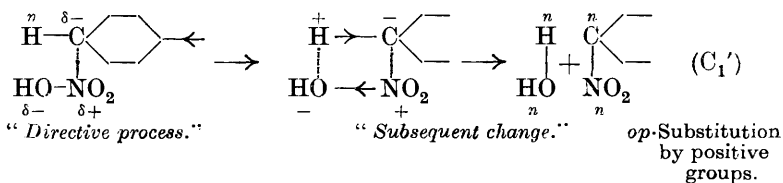
In applying these suggestive ideas to the cases of substitution previously described, we would regard the above formulæ as expressing only the direction of imaginary gross changes which actually do not at any time proceed to more than a limited (in some cases an exceedingly small) extent. This interpretation is placed upon the formulæ partly to cover the case of direction by methyl, which, we assume, has not electrons available for a complete co-valency change (even a momentary one), and is expressed by a slight change of symbolism (C_1),[†] the dotted arrows representing electronic strain :



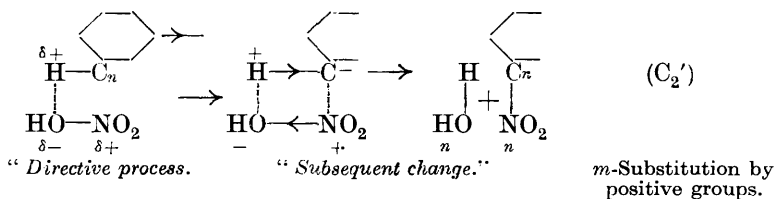
^{*} Since the above was written, a fuller statement has become available (this vol., p. 401).

[†] In this formula, and those which follow, $\delta+$ and $\delta-$ are used to signify small fractions of a unit charge; n represents neutrality, and the signs + and - connote unit charges.

It may then be supposed that the *incipient* negative polarisation of the *o*- and *p*-carbon atoms (in different electromeric phases) would be sufficient to attract the positive end of an *incipiently* ionised molecule (*e.g.*, nitric acid or chlorine).* This corresponds with Flürscheim's theory of molecular addition at a point by *residual* (not real) valencies, and may be termed the "directive process." This having occurred, the tendency for hydrogen to unite *as a positive ion* (compare Part IV) with, for instance, hydroxyl or chlorine acting as a negative one, would lead to reaction in a four-cycle † (the "subsequent change") with the unit electron displacements shown, and without the necessity for any further electronic displacement in the benzene system itself :



The case of *m*-substitution is regarded as an effect produced by groups which tend to withdraw electrons from the nucleus (*loc. cit.*). Combining this suggestion with the evidence, discussed in Part IV, of incipiently ionised hydrogen in combination with carbon, and of its extraction in the form of a true ion by the hydroxyl ion, the view may be expressed (formula C₂) that the meta-hydrogen atom in these cases reaches a state of incipient ionisation, owing to a pull on the electrons involved in its linking with the nucleus. The meta-carbon remains approximately neutral, and the attack of an incipiently ionised reagent therefore begins at the positively polarised hydrogen atom : ‡



* Since *ortho*- versus *para*-substitution is not now under consideration, the operation of direct exchange with the *p*-position is disregarded to abbreviate description.

† Or, a third molecule might enter into the reaction, giving a six-cycle.

‡ The assumption of a less direct type of activation preceding *m*-substitution is consistent with the generally smaller velocities of these reactions as compared with *op*-substitutions.

Formula C_3 corresponds with the direction of negative ions to the *op*-positions (Robinson, *loc. cit.*) and need not be expanded, since the "subsequent change" may pursue different paths (leading to the same goal) according as the ionisation of the reagent is incipient, or actual* (hydrolysis of *p*-chloronitrobenzene).†

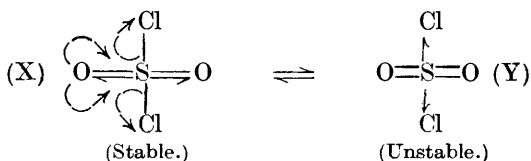
In applying these three principal directive effects, we bear in mind that they can determine only the (reversible) *initial attraction* of the reagent, and that the substitution cannot ensue unless the conditions necessary for the "subsequent change" are present. An essential condition in cases C_1 and C_2 is that the displaced atom should be one (*e.g.*, hydrogen) which tends to function as a *positive* ion, and can be extracted from the molecule as a positive ion under the conditions employed. Similarly, in C_3 the "subsequent change" can occur only if the expelled atom is one (*e.g.*, chlorine) which tends to function as a *negative* ion and is capable of being removed in this form by the reagent used. The importance of these auxiliary conditions may be illustrated by the fact that, neglecting them, C_3 necessitates that nitrobenzene and nitric acid should yield *p*-nitrophenol and nitrous acid, and many similar absurdities.

Taking count of "general" electronic restraint, subsidiary directive effects may be perceived which need not be stated. It has also to be remembered that the dissociation of a reagent into *neutral* atoms, or radicals, may lead to substitution in positions determined by the consideration that those neutral atoms (*e.g.*, Cl) which have to *gain* electrons to form their stable ions will seek out negative centres, and in this respect simulate a *positive* group, and *vice versa*. This may well be the mechanism of chlorination by phosphorus pentachloride, iodine trichloride and aryl iodide di-

* In this case there can be no reaction in a cycle, and the "subsequent change" may involve a complete reversible conversion into the quinonoid condition.

† Whether a particular group will act as an "electron-source" or "electron sink" (this vol., p. 1307) towards the benzene ring is, in general, determined by the fact that electronic strain can in each case operate only in one way if all octets are to be preserved. Thus -OMe is necessarily a source, and -CH:O necessarily a sink so far as principal directive effects are concerned. Also, a fluorine atom directly attached to the ring can only act as a source by the mechanism considered, although in saturated chains it should act as a sink, tending towards separation as a negative ion (general polarity). For this reason, when directly joined to the nucleus, it acts as a source only with reluctance, *i.e.*, is only feebly *op*-directing (compare following paper). Direction by methyl and vinyl are special cases which do not appear to be capable of determination *a priori* by generally recognised electronic principles, although *experiment* indicates that each functions as a source in aromatic substitution.

1925, **44**, 172, 427; Robinson, *ibid.*, p. 259); it is another instance of attack by a neutral radical :



Thus, in conformity with the two known kinds of dissociation of co-valency compounds, it is suggested that both polar and non-polar dissociation may be concerned in aromatic substitution, the main determining condition being the electronic constitution of the reagent. This view, we think, interprets the data more consistently than is possible by means either of a purely ionic or of a purely non-ionic conception; it is advanced, however, mainly to facilitate discussion, for it is clear that the main principles, even if true, must be held as subject to possible modifications arising from other influences.

EXPERIMENTAL.

(I) Nitration of Aceto-*o*-anisidide.

Mulhauser (*Annalen*, 1899, **207**, 242) nitrated aceto-*o*-anisidide and obtained a mononitro-derivative, m. p. 143°. Meldola, Woolcott, and Wray (J., 1896, **69**, 1330) found m. p. 145—146°, and suggested that it was the 5-nitro-derivative (for numbering, see Formula I, p. 1311) but did not prove this orientation. The Fabrik de Produits Chimique de Thann et de Mulhause (D.R.-P. 98637) stated that the substance was in reality a mixture of two isomerides, m. p. 153° and 131—132° respectively. We find that, whilst the first of these is a pure compound, identical with 5-nitroaceto-*o*-anisidide synthesised by Vermeulen (*Rec. trav. chim.*, 1905, **25**, 12), the second is a mixture containing, besides the 5-nitro-compound, its 4-nitro-isomeride, m. p. 174—175°. Small quantities of the 3-nitro-compound, m. p. 158—159°, and, probably, of the 6-nitro-compound, m. p. 103—104°, are also produced in the nitration. The 4-nitro-compound was synthesised by Meldola, Woolcott, and Wray (*loc. cit.*) and by Vermeulen (*loc. cit.*). The properties of the 3- and 6-nitro-derivatives and their orientation are described below.

Qualitative Separations.—(I) A well-cooled solution of 1.5 c.c. of nitric acid (*d* 1.5) in 5 c.c. of acetic anhydride was added to the paste obtained by cooling a solution of 5 g. of acetanisidide in 10 c.c. of acetic anhydride to 0°. Heat was generated, but the temperature was not allowed to rise above 45°. The mixture was kept at the ordinary temperature for 24 hours and, after addition of water,

shaken to destroy acetic anhydride. The solid product (6.0 g.) was subjected to about 20 fractional crystallisations from absolute alcohol, which yielded the following apparently pure substances, here named in the order of their appearance: (a) large, stout, prisms, m. p. 153—154° (2.0 g.); (b) long, silky needles, m. p. 173.5—175° (0.1 g.); (c) rosettes of small needles, m. p. 129—131° (0.5 g.). By direct comparison (a) was shown to be 5-nitroaceto-*o*-anisidide, and (b) 4-nitroaceto-*o*-anisidide. The crystals (c) we assume to be identical with the product, m. p. 131—132°, described in D.R.-P. 98637, but direct comparison showed that it was neither 3-, 4-, 5-, nor 6-nitroaceto-*o*-anisidide. It had the correct composition (Found: C, 51.7; H, 4.9. $C_9H_{10}O_4N_2$ requires C, 51.4; H, 4.8%), and, since its m. p. was depressed by the addition of the 3- and 6-nitro-compounds and raised by the addition of either the 4- or the 5-derivative, we regard it as a difficultly separable mixture of the last two isomerides. After hydrolysis of the acetyl group, the corresponding free bases can be separated in the pure condition, the 5-derivative being isolated in larger quantity than the 4-isomeride.

(II) Another experiment using 40 g. of aceto-*o*-anisidide was carried out in the same way, excepting that the most soluble fractions obtained after a rough separation were combined with the product isolated by neutralising the dilute acetic acid solution and extraction with ether, and fractionally crystallised as completely as possible. Fractions identical with (a) and (c) were obtained, and also a very small amount of a substance, m. p. 99—103°, which did not depress the m. p. (103—104°) of synthetic 6-nitroaceto-*o*-anisidide, but was insufficient for analysis.

Further experiments did not lead to the isolation of the 3-isomeride, although the presence of this was proved indirectly.

*3-Nitroaceto-*o*-anisidide.*—3-Nitro-*ON*-diacetyl-*o*-aminophenol (see below) (0.5 g.) was treated at 30—40° with 2 c.c. of cold 2*N*-sodium hydroxide and the deep red solution was shaken with successive small quantities of methyl sulphate, additional alkali being added as it became necessary. When the red colour had given place to lemon-yellow, the precipitate was collected and crystallised from alcohol; pale yellow needles, m. p. 158—159°, were then obtained (Found: C, 51.7; H, 4.8. $C_9H_{10}O_4N_2$ requires C, 51.4; H, 4.8%). The m. p. of this substance was depressed 20° to 60° by the addition of its isomerides, 4-, 5-, and 6-nitroaceto-*o*-anisidide. Since the 4-, 5-, and 6-compounds were all synthesised by methods which showed their constitutions, the orientation of the 3-derivative follows. It was confirmed by conversion of the substance into 3-nitroguaiacol by boiling for 36 hours with 2*N*-sodium hydroxide

and acidifying the resulting solution. This guaiacol was not synthesised for comparison, but the specimen obtained had the m. p. (60—61°) and properties recorded in the literature, and had the large volatility with steam characteristic of *o*-nitrophenols (see below). The base, *3-nitro-o-anisidine*, was obtained by heating the acetyl derivative for 30 minutes with 20% hydrochloric acid on the steam-bath and extracting the product with ether from the solution basified with ammonia. The same base was obtained along with 3-nitroguaiacol when the acetyl compound was boiled for 6 hours with 2*N*-aqueous sodium hydroxide. It separated from alcohol in bright scarlet needles, m. p. 75—76° (Found: C, 50.0; H, 4.8. $C_7H_8O_3N_2$ requires C, 50.0; H, 4.8%).

4-Nitroaceto-o-anisidide.—This was prepared by Meldola, Woolcott, and Wray's method (*loc. cit.*). It had m. p. 174—175°, and the corresponding free base, m. p. 117—118°. On boiling either the base or its acetyl derivative for 30 hours with 2*N*-aqueous sodium hydroxide under the conditions in which the 3- and 5-isomerides yield nitroguaiacols, deep-seated decomposition took place, although some unchanged base was recovered. A specimen of 4-nitroguaiacol, m. p. 103—104°, was prepared by the direct nitration of acetylguaiacol (Reverdin and Crepieux, *Ber.*, 1903, **36**, 2258; 1906, **39**, 4232; Paul, *Ber.*, 1906, **39**, 2779) but, even on seeding with a crystal of this, the same compound could not be obtained from the small quantity of acidic tar isolated from the product of hydrolysis. A few crystals, m. p. 80—90°, were obtained, but the amount was insufficient for purification.

5-Nitroaceto-o-anisidide.—Vermeulen's method (*loc. cit.*) was used for the preparation of this substance, which was obtained in large, pale yellow, nearly cubical prisms, m. p. 153—154°. On cooling a solution of it in warm concentrated hydrochloric acid, a sandy precipitate was obtained, which on treatment with water turned yellow. Its solution in much boiling water was rendered alkaline with sodium carbonate and cooled; the free base then separated as golden-yellow, flattened needles, m. p. 139—140°. On boiling for 36 hours with 2*N*-aqueous sodium hydroxide, either the acetyl derivative or the base is converted fairly smoothly into 5-nitroguaiacol, which is precipitated on acidification, the filtrate containing a further quantity isolable by extraction with ether. This nitroguaiacol had m. p. 99—100° and depressed the m. p. of 4-nitroguaiacol.

6-Nitroaceto-o-anisidide was synthesised from 2 : 6-dinitroanisole by partial reduction and acetylation of the nitro-base. An alcoholic solution of 2 : 6-dinitroanisole was treated for 30 minutes with a rapid stream of hydrogen sulphide. During the first 10 minutes

much heat was developed. Water was added, and the base extracted from the precipitate by digestion with 20% hydrochloric acid, from which it was reprecipitated on addition of ammonia. Having been dried as rapidly as possible, the crude base was repeatedly extracted with boiling ligroin until the extracts failed to crystallise on cooling. 6-Nitro-*o*-anisidine was thus obtained as bright yellow, flattened needles, m. p. 65—66°, a further quantity being recoverable from the ligroin solution. An additional crystallisation from ligroin raised the m. p. to 67° (Found : C, 50.0; H, 4.7. $C_7H_8O_2N_2$ requires C, 50.0; H, 4.8%). The *acetyl* derivative was obtained by boiling the base for 2 hours with acetic anhydride, and crystallised from methyl alcohol or dilute acetic acid in pale yellow prisms, m. p. 103—104° (Found : C, 51.5; H, 4.8. $C_9H_{10}O_4N_2$ requires C, 51.4; H, 4.8%). Attempts to convert either of these substances into 6-nitroguaiacol by the method used for the corresponding reaction in the 5-series led to deep-seated decomposition and products from which no crystalline substance could be isolated.

Attempted Estimation of the Proportions of the Isomerides.—(i) The nitration of 40 g. of aceto-*o*-anisidine was carried out in acetic anhydride as described above and the product allowed to crystallise over-night, when 9.1 g. of the 5-nitro-compound separated. The acetic anhydride was then removed by desiccation at a low pressure over potassium hydroxide. The residue was fractionally crystallised from alcohol, and a further quantity of 5-nitro-compound (1.5 g.) and some 4-nitro-compound (1.0 g.) were obtained. The weights are those of the fully purified isomerides. The unseparated residue was hydrolysed with hydrochloric acid and the bases were fractionated from alcohol, the 5-nitro-base (3.7 g.) and the 4-nitro-base (0.65 g.) being isolated. The unseparated portions were reacylated and by further crystallisation the 5-nitro-*acetyl* derivative (2.1 g.) and its 4-isomeride (1.4 g.) were obtained. About 1 g. of a mixture remained which was not resolved. The total pure substances isolated corresponded with 68% of 5-nitro-compound and 13% of 4-nitro-compound.

(ii) In a similar experiment to the above, 37% of 5-nitroaceto-*o*-anisidine separated from the acetic anhydride. The residue obtained on complete evaporation was boiled for 36 hours with 10 times its weight of 2*N*-sodium hydroxide, and the resulting solution diluted to dissolve the red, rather sparingly soluble sodium salt of 5-nitroguaiacol, and extracted with ether. The bases thus recovered (2.8 g., and in another similar experiment 3.5 g.) were contaminated with products of deep-seated decomposition, but yielded some crystalline 4-nitroanisidine. On acidification of the alkaline solution 5-nitroguaiacol (11.2 g.), m. p. 96—99°, was obtained, and the

mother-liquors yielded a mixture of guaiacols, which were recovered by extraction with ether and purified and partly separated by distillation in steam. Experiments with artificial mixtures of 3-nitroguaiacol and 5-nitroguaiacol showed that the former passed over completely in the early stages of distillation, but that a small quantity of the latter was present in all fractions. Further experiments to determine the volatility of 5-nitroguaiacol in steam indicated that, under the usual conditions of distillation, the steam reaching the condenser is not quite saturated; but by working under uniform conditions as regards apparatus and rate of distillation a fairly consistent figure of 1.20 g. per litre was obtained and this was regarded as sufficiently accurate in experiments carried out under like conditions. In the distillation of the mixed guaiacols described above, the first 500 c.c. of distillate yielded 1.26 g., m. p. 60—80°, whilst the succeeding 500 c.c. fractions each gave 0.6 g., m. p. 97—100°, so that 0.66 g. of the more volatile 3-nitroguaiacol was assumed to be present in the original mixture. This corresponded with a yield of 1.5%, whilst the total quantity of 5-nitroguaiacol was equivalent to 37% of the theoretical, a further 37% of 5-nitroaceto-*o*-anisidine having been also obtained as described above.

Combining these results, it follows that in the original nitrations the 5-nitro-derivative was formed to the extent of at least 74%, the 4-nitro-compound to the extent of at least 13% and the 3-isomeride to the extent of about 1.5%, a small quantity of the 6-compound probably also being produced. The total yield was 88.5%.

(II) Nitration of *ON*-Diacetyl-*o*-aminophenol.

The nitration of *ON*-diacetyl-*o*-aminophenol was carried out by Meldola, Woolcott, and Wray (*loc. cit.*), who isolated the 5-nitro-derivative, m. p. 189°, which they definitely oriented. They did not notice the formation of a second isomeride. Our attempts to follow their method yielded either dinitro-compound, or mixtures of unchanged material with mono- and di-nitro-derivatives. On the other hand, treatment with the theoretical quantity of nitric acid in warm acetic anhydride led to smooth mononitration.

Dinitration.—A solution of the diacetyl compound (10 g.) in a mixture of 40 c.c. of ordinary concentrated nitric acid and 20 c.c. of fuming acid at -5° was kept for 2 hours at $2-4^{\circ}$, and ice then added. The precipitate, which was collected on the next day, crystallised from boiling water in long, yellow needles, m. p. 202°. Since analysis (Found: C, 40.2; H, 3.2; N, 17.8. $C_8H_7O_6N_3$ requires C, 39.8; H, 2.9; N, 17.5%) indicated that one acetyl group had been eliminated, and the substance gave an immediate

precipitate of the red potassium salt when treated in alcoholic suspension with cold dilute potassium hydroxide solution, we regard it as 3:5-dinitro-*N*-acetyl-*o*-aminophenol. The compound was not definitely oriented, but the positions of the nitro-groups are inferred from the study of the mononitration of diacetylaminophenol described below.

Mononitration. Qualitative Separation of Isomerides.—The paste obtained by cooling a solution of diacetyl-*o*-aminophenol (20 g.) in acetic anhydride (40 g.) to 15° was treated gradually with an ice-cold mixture of 5 c.c. of nitric acid (*d* 1.5) and 20 c.c. of acetic anhydride. The crystals dissolved and the temperature rose rapidly, but was kept from exceeding 35° by external cooling. When self-heating had ceased, the mixture was allowed to cool to the ordinary temperature; a stiff paste of yellow crystals then formed. Several hours later, the acetic anhydride was destroyed by shaking with water, and the solid product, m. p. 140—160°, collected. This was fractionally extracted with boiling alcohol; the less soluble product, m. p. 165—180°, thus obtained, after four crystallisations from alcohol, yielded very characteristic, long, pale yellow needles, resembling glass wool, the m. p., 189°, of which was not further changed by crystallisation. The more soluble fractions were subjected to a prolonged series of fractional crystallisations from alcohol, when stout, pale yellow tablets, m. p. 183°, were obtained. The isolation of these was facilitated by the observation that, after slow crystallisation, they could be partly separated from the filamental needles by shaking and rapidly decanting the mother-liquor, but the process was slow, and after about 40 crystallisations, only 6.0 g. of the needles, m. p. 189°, and 3.1 g. of the tablets, m. p. 183°, had been obtained. Needles, m. p. about 160°, were also obtained, but these appeared to be a difficultly separable mixture of which the needles, m. p. 189°, formed one constituent.

*3-Nitro-ON-diacetyl-*o*-aminophenol.*—This constitution is assigned to the tablets, m. p. 183° (Found: C, 50.3; H, 4.1. $C_{10}H_{10}O_5N_2$ requires C, 50.4; H, 4.2%), since the corresponding free phenol is converted by methylation into 3-nitroaceto-*o*-anisidide, the orientation of which is described above. 3-Nitro-*o*-acetylaminophenol was formed as its sodium salt when the acetyl compound (0.5 g.) was treated with 2 c.c. of 2*N*-aqueous sodium hydroxide. The temperature rose to 40° and the solid dissolved, but the deep red solution did not crystallise. The phenol was precipitated on acidification and crystallised from hot water in orange-yellow needles, m. p. 169°.

*4-Nitro-ON-diacetyl-*o*-aminophenol.*—4-Nitro-*o*-aminophenol (3 g., obtained by reduction of 2:4-dinitrophenol with hydrogen sulphide)

was boiled with acetic anhydride (4.5 g.) and acetic acid (2 g.) for 2 hours. The excess of acetic acid was removed over potassium hydroxide in an evacuated desiccator, and the solid product drained on porous porcelain and crystallised twice from ethyl alcohol, when needles, m. p. 183—184°, were obtained (Found : C, 50.2; H, 4.2. $C_{10}H_{10}O_5N_2$ requires C, 50.4; H, 4.2%). 4-Nitro-*o*-acetylaminophenol was prepared as in the preceding series, but it yielded an orange sodium salt which separated from the alkaline solution in rosettes of needles. The free phenol crystallised from alcohol in colourless prisms, m. p. 278° (decomp.) (Found : C, 48.8; H, 4.1. $C_8H_8O_4N_2$ requires C, 49.0; H, 4.1%).

5-Nitro-ON-diacetyl-*o*-aminophenol.—This structure is assigned to the filamental needles, m. p. 189°, obtained by nitration, since the corresponding phenol on methylation gave 5-nitroaceto-*o*-anisidide. 5-Nitro-*o*-acetylaminophenol was prepared as in the last case. Crimson needles separated from the alkaline solution, which, on addition of water and acid, yielded the phenol. After crystallisation from ethyl alcohol, this was obtained in small, yellow prisms, m. p. 269° (decomp.) (Found : C, 48.8; H, 4.1. $C_8H_8O_4N_2$ requires C, 49.0; H, 4.0%).

Attempted Estimation of the Proportions of 3- and 5-Nitro-derivatives.—The nitration of diacetylaminophenol (40 g.) was carried out as described above, and the acetic anhydride removed in a vacuum, without separation of the part of the nitration product which crystallised spontaneously, since this was a mixture of isomerides. The solid residue was mixed with 120 c.c. of water and 180 c.c. of 4*N*-aqueous potassium hydroxide, the temperature being kept below 35°. When the decomposition (elimination of the *O*-acetyl group) was completed, the deep red liquid was acidified and the precipitated phenols were collected; a small additional quantity of solid was obtained by extracting the mother-liquor with ether. The whole solid was then mixed with 100 c.c. of 2*N*-potassium hydroxide and shaken at 25—35° with 10 c.c. of methyl sulphate. The methylation was almost complete in an hour, and was finished with the aid of small additional amounts of methyl sulphate and alkali. The precipitated solid was washed with water, boiled for 36 hours with 400 c.c. of 2*N*-aqueous potassium hydroxide (ammonia ceased to be evolved after the first 24 hours), and the cooled product extracted with ether to remove unchanged bases, and basic tars (7.0 g.). After the dissolved ether had been removed in a current of air, the solution was acidified. The mixed guaiacols thus precipitated were kept in contact with the mother-liquor for 24 hours to become thoroughly crystalline, and then collected, the dissolved portions being isolated by extraction with ether (total 25 g.). They

were separated and estimated by steam distillation, as described in the previous example. In this case, owing to the relatively large proportion in which it was present, the *O*-compound crystallised (5.8 g.) in a pure form (orange needles, m. p. 60—61°) from the first 2 l. of distillate. A further 2.2 g. was estimated to be present in solution in the first 3 l. of distillate, by extracting it with pure ether and correcting for the volatility in steam of the *p*-compound with which it was contaminated. Of this 2.2 g., about 1.1 g. were separated in the pure condition by fractional crystallisation from water. The distillate following the first 3 l. contained only the *p*-compound which, without crystallisation, melted at 96—99° and, after crystallisation, at 99—100°. These yields correspond with 23% of 3-nitrodiaetylaminophenol and 48% of the 5-nitro-compound. No solid product could be isolated from the tarry basic fraction, so the quantity of 4- and 6-derivatives formed is left undetermined.

(III) Nitration of *N*-Methylaceto-*o*-Anisidide.

N-Methyl-*o*-anisidine was prepared by methylating the formyl derivative of *o*-anisidine and, after hydrolysis of the formyl group, was isolated by means of the nitrosoamine, which was reduced to the secondary base as described by Diepolder (*Ber.*, 1899, **32**, 3515).

N-Methylaceto-*o*-anisidide was prepared by boiling the base for 2 hours with a slight excess of acetic anhydride and distilling the product. The fraction, b. p. 158—160°, set on cooling to a mass of large, inclined prisms, m. p. 46—50°, which, after crystallisation from ether-ligroin, melted at 51—53° (Found: C, 67.4; H, 7.3. $C_{10}H_{13}O_2N$ requires C, 67.0; H, 7.3%).

Mononitration: Isolation of 5-Nitro-, 4-Nitro-, and 3- or 6-Nitro-derivatives.—A cooled mixture of fuming nitric acid (2.5 c.c.) and acetic anhydride (12 c.c.) was added to *N*-methylaceto-*o*-anisidide (10 g.) dissolved in acetic anhydride (24 c.c.), the temperature being kept below 35°. Two methods of isolating the crude nitration product were employed. (i) The solution was poured into water, shaken to decompose the acetic anhydride, and made alkaline with sodium carbonate. Any solid which separated was collected, and the filtrate extracted with ether. The extract was dried with calcium chloride and reduced by evaporation to a small bulk, the crystals being separated fractionally. (ii) The acetic anhydride was removed by evaporation in a vacuum over potassium hydroxide.

Methylaceto-*o*-anisidide (20 g.) on nitration, followed by treatment in accordance with method (i), yielded 12.5 g. of a crystalline solid, m. p. 117—119°, which on crystallisation from ether formed

pale yellow prisms, m. p. 119—120.5°. This was shown to be 5-nitro-*N*-methylaceto-*o*-anisidide by direct comparison with a specimen synthesised as described below (Found : C, 53.8; H, 5.4. $C_{10}H_{12}O_4N_2$ requires C, 53.6; H, 5.4%).

On evaporating the ethereal extract to small bulk, very pale yellow prisms, m. p. 120—125°, which depressed the m. p. of the 5-nitro-compound, separated (0.9 g.). On crystallisation from benzene-ligroin the m. p. was raised to 126.5—127.5°. This substance was identified as 4-nitro-*N*-methylaceto-*o*-anisidide by comparison with a specimen synthesised as described below (Found : C, 53.8; H, 5.4; N, 12.7. $C_{10}H_{12}O_4N_2$ requires C, 53.6; H, 5.4; N, 12.5%).

The ethereal solution from which this had separated, on cooling to -15°, deposited crystals (1.6 g.), m. p. 98—99°, from which 0.65 g. of pure 5-nitro-compound was separated by fractional crystallisation. The second substance present in this fraction could not be definitely identified.

On long standing, the residual ethereal solution deposited large, colourless prisms, m. p. 103—105°, which after crystallisation from ether melted at 105—106° (0.08 g.). This m. p. was not changed by further crystallisation (Found : C, 53.6; H, 5.3. $C_{10}H_{12}O_4N_2$ requires C, 53.6; H, 5.4%). We believe this substance to be 3-nitro-*N*-methylaceto-*o*-anisidide, which is certainly formed in the nitration (see below), but there is no definite proof that it is not the 6-nitro-isomeride. A further quantity of these crystals (0.16 g.) separated after a few weeks, but the remainder of the nitration product refused to crystallise. The compound, m. p. 105—106°, yielded on hydrolysis a *base* melting at about the ordinary temperature, but the quantity obtained was too small for purification. In another nitration carried out as far as possible under similar conditions, none of the above nitro-compound was isolated, only the 4-derivative, m. p. 126.5—127.5°, being obtained on cooling the ethereal solution to -20°.

Preliminary experiments having shown that 5-nitro-*N*-methylaceto-*o*-anisidide only slowly evolves methylamine on boiling with 2*N*-alkali, but that this reaction occurs at 120° in sealed tubes (although not so smoothly as the analogous reaction described previously), the presence of 3-nitro-*N*-methylaceto-*o*-anisidide was proved by the following experiment. *N*-Methylaceto-*o*-anisidide (7.3 g.) was nitrated in the usual way, and the product treated in accordance with method (ii). The crude product (8.7 g.; theory 9.0 g.) having partly crystallised (4.3 g. of the 5-nitro-derivative), a portion (3.4 g.) of the mechanically separated oil was heated with 30 c.c. of 2*N*-aqueous potassium hydroxide for 12.5 hours at 120°.

After extraction of the basic portion * (1.0 g.) with ether, the solution was acidified and the guaiacols (1.8 g.) were extracted. Fractional distillation in steam indicated the presence of 0.29 g. of 3-nitroguaiacol, and a small portion of this was obtained from the early fractions of the steam distillate; after crystallisation from water, it was identified by comparison and a mixed m. p. determination with the specimen obtained as described previously.

5-Nitro-N-methyl-o-anisidine.—The acetyl derivative (above) (0.9 g.) was heated with concentrated hydrochloric acid for 1.5 hours on the steam-bath, and the reaction completed by boiling for 45 minutes. Neutralisation with ammonia precipitated the base, which separated from methyl alcohol or light petroleum in long, bright yellow, flattened needles, m. p. 101—102°. It was identified as 5-nitro-*N*-methyl-*o*-anisidine by comparison with a specimen prepared by synthesis (below) (Found : C, 52.6; H, 5.4. $C_8H_{10}O_3N$ requires C, 52.7; H, 5.5%).

4-Nitro-N-methyl-o-anisidine.—Prepared in the same way from its acetyl derivative (above), this base separated from light petroleum in orange, hair-like crystals, m. p. 87°, which were identified by comparison with a synthesised specimen (below) (Found : C, 52.6; H, 5.5. $C_8H_{10}O_3N_2$ requires C, 52.7; H, 5.5%).

Synthesis of 5-Nitro-N-methyl-o-anisidine.—5-Nitroanisidine (1 g.), methyl iodide (0.9 g.), and methyl alcohol (2 c.c.) were heated together for 1.5 hours at 100° in a sealed tube. The alcohol was then evaporated, and dilute potassium hydroxide was added to precipitate the bases which, after partial purification with chloroform, yielded the secondary base on crystallisation from dilute methyl alcohol and from light petroleum.

Synthesis of 4-Nitro-N-methylaceto-o-anisidine and 4-Nitro-NN-dimethyl-o-anisidine, 4-Nitro-N-methyl-o-anisidine, and 4-Nitro-3(or 5)-methylaceto-o-anisidine.—4-Nitroanisidine (6 g.), methyl iodide (5.4 g.), and methyl alcohol (12 c.c.) were heated for 2 hours at 100°, and the mixture of bases was isolated, as in the previous preparation. Many attempts were made to separate these by fractional crystallisation, but without success, and the mixture was therefore heated with acetic anhydride for 45 hours. After the excess of this reagent had been evaporated, water was added and the mixture made alkaline with sodium carbonate and extracted with ether, the extract

* As in the two cases previously described, the bases recovered after alkali treatment contained products of some more complex change than the mere elimination of an acetyl group from the 4- or 6-nitro-derivative. In this experiment, the basic fraction, even after distillation and attempted acetylation, yielded liquids which could not be crystallised and the nature of which was not revealed by analysis.

being washed with 15% hydrochloric acid. This was intended to remove the tertiary base from the mixture of acetyl compounds of the primary and secondary bases, and in the earlier experiments by this method 4-nitro-*NN-dimethyl-o-anisidine* was isolated in this way, the material obtained by basifying the hydrochloric acid solution and extraction with ether setting to a solid mass, which, on crystallisation from ligroin, yielded bright yellow, short needles, m. p. 38—39.5° (Found : C, 54.7; H, 6.0. $C_9H_{12}O_3N_2$ requires C, 55.1; H, 6.1%).

In certain subsequent experiments, carried out as far as possible under the same conditions, the bases obtained from the hydrochloric acid extract did not solidify immediately, but on keeping for several weeks in an evacuated desiccator, partly crystallised. The crystals thus obtained separated from benzene-ligroin in very pale yellow prisms, m. p. 127—128°, which did not depress the m. p. of the specimen of 4-nitro-*N-methylaceto-o-anisidide* obtained by nitration. On hydrolysis with hydrochloric acid, the substance yielded 4-nitro-*N-methyl-o-anisidine*, m. p. 87°, which was similarly identified with the base prepared from the 4-nitration product. As an isomeric base, in which the methyl group has apparently migrated to the ring, was also isolated in the course of these experiments (see below), the secondary character of this base, m. p. 87°, was confirmed by the preparation of its *nitrosoamine*, which was precipitated at once when sodium nitrite was added to a solution of the hydrochloride. Crystallised from benzene-ligroin, this compound formed very pale yellow needles, m. p. 119—120° (Found : N, 20.3. $C_8H_9O_4N_3$ requires N, 19.9%). From these experiments, it must be concluded that 4-nitro-*N-methylaceto-o-anisidide* is fairly easily soluble in hydrochloric acid of the strength used. The oil from which the crystals of this compound were obtained set, some weeks later, to a solid mass consisting principally of the tertiary base described above.

The ethereal solution from which the above-mentioned substances were extracted by hydrochloric acid, on evaporation, yielded a solid residue which examination with a lens showed to contain at least two compounds. One of these was easily separated by fractional crystallisation and proved to be the acetyl derivative of the original primary base. The second compound was separated partly by crystallisation and partly mechanically, and, after a final crystallisation from benzene-ligroin, was obtained as pearly plates, m. p. 127—128°. It therefore had the same m. p. as 4-nitro-*N-methylaceto-o-anisidide*, but its crystalline form was entirely different, and a mixture of the two compounds melted at about 100°. Analysis showed the new compound to be an isomeride (Found : C, 53.2; H, 5.1; N, 12.2. $C_{10}H_{12}O_4N_2$ requires C, 53.6; H, 5.4; N, 12.5%),

and it must therefore be 4-nitro-3(or 5)-methylaceto-*o*-anisidide, a methyl group having wandered to the ring. To confirm this, the compound was boiled with hydrochloric acid for 0.5 hour to eliminate the acetyl group, and the hydrochloride of the base diazotised in the usual way. No precipitate separated, indicating that secondary bases were absent, but on pouring the product into alkaline β -naphthol solution, a deep crimson dye was immediately precipitated.

*Action of Methyl Iodide on 6-Nitro-*o*-anisidine.*—The base (2.2 g.), methyl iodide (2.0 g.), and methyl alcohol (4.5 c.c.) were heated together, and the products treated as in the methylation of 4-nitro-anisidine. The mixture of acetyl compounds only partly solidified after long keeping. After several crystallisations from ether, colourless prisms were obtained, m. p. 106—107°, which depressed the m. p., 103—104°, of 6-nitroaceto-*o*-anisidide (Found: C, 52.7; H, 5.2. $C_8H_{10}O_3N_2$ requires C, 52.7; H, 5.5%). These analytical figures agree moderately well with those required for a nitromethyl-anisidine, but as the crystals were colourless, whilst the nitromethyl-anisidines described above are orange or yellow, it seems unlikely that this compound is a nitro-base of the series. Owing to the limited quantity of 6-nitro-*o*-anisidine available, we were not able to make a more detailed study of its methylation products, or to carry out further experiments with the substance described.

Attempted Estimation of the Proportions of the Nitration Products.—

(a) *N*-Methylaceto-*o*-anisidide (20 g.), nitrated as described above and treated by method (ii), gave 11.8 g. of crystalline 5-nitro-derivative and 12.0 g. of an oily mixture (total 23.8 g.; theory 25.0 g.). A part of the oil (9.3 g.) gave guaiacols consisting, as estimated from fractional distillation in steam, of 3.3 g. of 5-nitro- and 1.0 g. of 3-nitro-guaiacol. A basic oil (2.7 g.) and a neutral tar (1.0 g.) were also obtained.

(b) In another experiment, 20 g. of *N*-methylaceto-*o*-anisidide yielded 14.0 g. of the 5-nitro-derivative and 0.9 g. of the 4-nitro-derivative, both isolated as such in the pure condition. In another experiment, in which the material was treated by method (i), similar quantities of the 5- and 4-nitro-compounds were isolated, and also 0.24 g. of an isomeride believed to be the 3-nitro-derivative.

Combining these results, 73% of the material is accounted for as follows: 5-nitro-derivative, 64%; 4-nitro-derivative, 4%; 3-nitro-derivative, 5%.

Addendum. ON-Diacetyl-*N*-methyl-*o*-aminophenol.—*N*-Methyl-*o*-aminophenol, which we found to melt at 88° instead of 80° as recorded in the literature, (44 g.) was boiled for 1 hour with acetic anhydride (70 c.c.), and the product distilled. The fraction, b. p. 160—170°/2 mm., at once solidified to crystals (61 g., m. p. 58—60°) which, after

crystallisation from ether-ligroin, had m. p. 63—64° (Found : C, 64.0; H, 6.2. $C_{11}H_{13}O_3N$ requires C, 63.8; H, 6.3%).

Originally it was intended to include a study of the nitration of this substance in this investigation, but this project was abandoned when it was found that a considerable amount of oxidation took place under the conditions which had been used for the mononitration of the other three substances.

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