CCLIV.—*The Influence of Nitro-groups on the Reactivity of Substituents in the Benzene Nucleus.*

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ALTHOUGH the enhanced reactivity of substituents in the ortho- or para-position relatively to a nitro-group has been a familiar fact since it was first observed by Pisani in the case of picryl chloride (*Annalen*, 1854, **92**, 326), little insight appears to have been gained into the nature of the processes which result in the displacement of such substituents by others.

The "activating" influence of the nitro-group is in direct contrast with its retarding, and at times inhibitive, effect on other reactions. Whilst, however, the nitro-group shares its power of steric hindrance with other substituents of large molecular volume, quite irrespective of whether they are meta- or ortho- and para-directive, this is not the case where the opposite effect is concerned. In general, only meta-directive groupings can render substituents in the ortho-position mobile; for instance, Schöpf and his pupils showed that the carboxy-, aldehydo-, sulphonic, and cyano-groups each conferred mobility on a bromine atom in the ortho- or para-position (*Ber.*, 1889, **22**, 900, 3281; 1890, **23**, 3440, 3445, 3450; 1891, **24**, 3771, 3785, 3808). The presence of a nitro-group was not essential, but its influence was much more powerful than that of the other groups named, and at least two of these, as compared with a single nitro-group in the ortho- or para-position (compare Lobry de Bruyn, *Rec. trav. chim.*, 1894, **13**, 101), were required to render a substituent mobile. Ortho-para-directive substituents appear, however, to increase the mobility of substituents in the meta-position in some cases. Thus Laubenheimer showed that, whilst the conversion of *o*-dinitrobenzene into *o*-nitroaniline by means of alcoholic ammonia requires ten weeks at the ordinary temperature for its completion, the corresponding reaction in the case of 5-chloro-1:2-dinitrobenzene is complete within five days, and leads to the formation of 5-chloro-2-nitroaniline (*Ber.*, 1876, **9**, 1826; 1878, **11**, 1156).

Similarly, Tiemann found that *o*-chloro-*p*-nitrobenzaldehyde is easily converted into *o*-chloro-*p*-anisaldehyde by the action of sodium methoxide, *p*-nitrobenzaldehyde being stable in these circumstances (*Ber.*, 1891, **24**, 709). Attention has apparently not been previously directed to this phase of the problem, and it is therefore at present not possible to indicate how far this influence of the chlorine atom is general, or shared by other ortho-para-directive substituents.

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The evidence as it stands, however, suggests a close connexion between the phenomena at present under discussion and those of directive substitution; and, indeed, the various facts just enumerated find a ready explanation in terms of the views advocated by Flürscheim (*J. pr. Chem.*, 1902, [ii], **66**, 321; 1905, **71**, 497; 1907, **76**, 165, 185; T., 1909, **95**, 718; 1910, **97**, 84). Thus it is clear from the diagram that a nitro-group in the ortho- or para-position, and a chlorine atom in the meta-position, each weaken the attachment of the substituent X to the nucleus, rendering it more mobile:

and that their influence is cumulative. Conversely, it may be expected that the effect of, for instance, a nitro-group in the meta-position, or a chlorine atom in the ortho- or para-position, would be a detrimental one. Quantitative experiments on the velocities of such reactions are therefore desirable, in order to discover whether these influences exist, and, if so, whether they are parallel with those observed, for example, by Staudinger and Kon (*Annalen*, 1912, **384**, 38), which are also capable of interpretation in the light of Flürscheim's views.

It must be remarked, however, that the attachment of the nitro-group to the benzene nucleus has been frequently assumed to be a comparatively strong one. Thus Kaufmann ("Die Auxochrome," Stuttgart, 1909, p. 76) refers to the aliphatic nature of the nitro-compounds, as illustrated by the reactivity of the chloro-nitro-compounds, and later (p. 93) attributes the formula I to nitrobenzene:

The adoption of this formula, preceded as it is (pp. 80, 85) by the formulæ II and III for benzene with the "ideal auxochrome" as a substituent, and for aniline, involves certain difficulties. Thus Kaufmann is at once driven to attribute something in the nature of an amphoteric character to the phenyl residue, and to assume "dass die Absättigung der Partialvalenzen bei Antiauxochromen polar zu der bei Auxochromen statthat." Further, it is probable

that the presence of residual affinity on the ortho- and para-carbon atoms, as represented by Kaufmann, would tend to promote the substitution in the ortho- and para-positions which actually takes place. If, then, Kaufmann's formula for nitrobenzene be accepted, substitution might be expected to take the same course in this case, but this is not so. The strongest evidence in favour of Kaufmann's view is probably supplied by the work of Meisenheimer (*Annalen*, 1902, **323**, 222; 1907, **355**, 249), who examined very thoroughly the action of potassium methoxide on various nitro-compounds, and explained his results in terms of Thiele's theory of partial valencies, making the same assumption in regard to the nitro-group as that made by Kaufmann. It will, however, be suggested that these results are not irreconcilable with the opposite point of view. Nor is Kaufmann's formula, in the author's opinion, a necessary consequence of Thiele's theory, which is based on a conception of the nature of the double bond uniting two atoms of the same element. Where a double bond connects two different elements, it is conceivable that one of these, that of greater residual affinity, may claim the whole of the available affinity of the other. This is especially so as regards the nitro-group, where the single nitrogen atom is attached to two oxygen atoms, and if such were actually the case, Flürscheim's formula would represent nitrobenzene more accurately. Further, Werner's explanation of the activity and inertia of the respective halogen atoms in triphenylmethyl bromide and tribenzoyl-bromomethane (*Ber.*, 1906, **39**, 1282), symbolised by the formulæ:

appears to lend support to the following formula for bromotrinitromethane, the bromine atom of which is also inert (Meisenheimer and Schwarz, (*Ber.*, 1906, **39**, 2544):

The evidence supplied by these considerations is therefore also in favour of Flürscheim's views.

The following instance appears to show that the activating influence of nitro-groups may act through a chain of atoms, which do not all form part of an aromatic nucleus. Whilst *o*-hydrazinobenzoic acid only passes over into 3-keto-1:3-dihydroindazole when it is heated alone to 220–230° or with boiling phosphoryl chloride (E. Fischer, *Ber.*, 1880, **13**, 681; E. Fischer and Seuffert, *ibid.*, 1901, **34**, 795), methyl 3:5-dinitro-2-hydrazinobenzoate cannot be isolated as a product of the interaction of methyl 1-chloro-3:5-dinitrobenzoate and hydrazine hydrate, but is immediately converted into 5:7-dinitro-3-keto-1:3-dihydroindazole. The following scheme shows that this reaction is also in accordance with the views just discussed:

It might, however, be objected that, whereas Flürscheim has applied his views to explain the replacement of a hydrogen atom in the meta-position with respect to a nitro-group, they are here employed to explain the replacement of substituents in the ortho- or para-positions. This consideration is of great importance because it shows that, whatever the nature of the substitutive processes involved in the two cases may be, they must be essentially different in character. Such a conclusion is supported by the facts that the steric hindrance of the negative groups in the ortho-position is to a large extent, although not completely, overcome, and that the nitro-group, which is the substituent most effective in exerting this hindrance, is also the most effective in promoting the condensations of the type under consideration. It seems clear that the activating group is itself concerned in the reaction. In view of the increasing favour with which the addition theory of chemical reaction is now received, and of the fact that the nitro-group is especially prone to take part in the production of molecular compounds, it seems natural to assume that the formation of such a compound is the first step in the process at present under discussion: and, indeed, when an aromatic amine, for example, reacts with an active chloronitro-compound in alcoholic solution, an intense coloration is at once produced which differs from that imparted to alcohol by the final condensation product, and is probably to be attributed to the formation of an additive compound. This suggestion is not a novel one, and appears to have been originally made by Bamberger (*Ber.*, 1900, **33**, 102), who, however, expressed no opinion as to the nature of the process by which the intermediate product passed over into the final condensation product. Bamberger actually isolated a molecular compound of picryl chloride and α -naphthylamine, from which picryl- α -naphthylamine was easily formed; whilst Sudborough and Picton isolated similar additive compounds of 4:6-dichloro-1:3-dinitrobenzene and of 2:4-dichloro-1:3:5-trinitrobenzene, each with one molecular proportion of α - or β -naphthylamine (*T.*, 1906, **89**, 583). Sudborough and Picton

suggested the following scheme to explain the mechanism of the reaction (compare also Richter, *Ber.*, 1875, **8**, 1419):

whilst Borsche has recently (*Annalen*, 1911, **386**, 356; 1913, **402**, 81; compare also Meisenheimer, *ibid.*, 1902, **323**, 218) advocated the following expression of the reaction between 4-chloro-1:3-dinitrobenzene and ethyl sodiomalonate*:

Lapworth (P., 1903, **19**, 123; compare Meisenheimer and Patzig, *Ber.*, 1906, **39**, 253; Lobry de Bruyn, *Rec. trav. chim.*, 1904, **23**, 60) suggested the formation of the same type of intermediate product, as a result of the passage of the substituting radicle from an α - to a γ -position (T., 1898, **73**, 445):

It is obvious that the whole question depends on that of the constitution of the molecular compounds first formed. The fact that

* 4:6-Dichloro-1:3-dinitrobenzene furnishes first ethyl 5-chloro-2:4-dinitrophenylmalonate, only reacting with a further molecular proportion of ethyl sodiomalonate with much greater difficulty, and this unequal reactivity is considered to be "an experimental proof" of Kekulé's benzene formula, as against Thiele's or the centric formula. It appears exceedingly doubtful whether this evidence is as valuable as that afforded by the work of Marckwald (*Annalen*, 1894, **279**, 5), for it is hardly convincing that evidence, which is interpreted with the assistance of Thiele's theory of partial valencies, should be used to disprove a formula which follows from an application of this theory to Kekulé's formula.

Further, it may be remarked that the formula of ethyl sodiomalonate used by Borsche is not the one generally adopted, and to this extent his choice of an illustration for his theory is not a happy one.

Also, according to Borsche, the chlorine atom in the compound under discussion is not loosely held. In this case it is difficult to account for the fact that Ullmann's synthesis of diphenyl derivatives by heating the haloid benzenes with copper powder is only applicable to chloro-compounds when they contain nitro-groups in the ortho- or para-position to the halogen atom (Ullmann and Bielecki, *Ber.*, 1907, **34**, 2177).

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tetranitromethane and other aliphatic nitro-derivatives may form such compounds (Werner, *Ber.*, 1909, **42**, 4328) appears to be decisive evidence against a formula of the type postulated by Sudborough and Picton, and by Borsche, whilst Lapworth's formula supplies no explanation of the intense colour phenomena observed. The formula (IV) suggested by Werner (*loc. cit.*) is seen to be

(IV.)

(V.)

closely related to that (V) adopted by Hantzsch for the nitro-anilines (*Ber.*, 1910, **43**, 1669), and is in harmony with the observations of Sudborough and Beard (*T.*, 1910, **97**, 779), that substituents which tend to increase the auxochromic effect of the amino-group always tend to increase the depth of colour of the additive compounds of trinitrobenzene with amines (compare also Green and Rowe, *T.*, 1912, **101**, 2446; Meldola and Hewitt, *T.*, 1913, **103**, 884; Meldola and Hollely, this vol., p. 413). No attempt appears to have been made to institute a quantitative comparison by an examination of the absorption spectra of the two series of compounds, but it seems to the present author that this point needs attention before the alternative formula (VI), hinted at by Pfeiffer (*Annalen*, 1914, **404**, 13), is accepted:

(VI.)

Meanwhile, Werner's formula has been retained in the following attempt to depict in outline the course of the reaction by which an arylamino-radicle displaces a mobile substituent X:

As a consequence of the formation of the molecular compound, a certain amount of unsatisfied valency may be expected momentarily to exist, as shown, on the carbon atom to which X is attached, and

may either be absorbed by X or engage a portion of the residual affinity of the spatially proximate nitrogen atom. Of the two alternatives, the latter, represented by the third formula in the scheme, seems the more probable because it enables the system, by a subsequent rearrangement in the manner indicated, to attain a condition of smaller potential energy.

The process by which the nitro-group facilitates the condensation is thus considered to consist in rendering it intra- rather than inter-molecular by bringing the amine molecule into a position favourable to the formation of a five-membered ring (or, if Pfeiffer's formula were adopted, of a six-membered ring). It is this feature that differentiates the views now put forward from those of Lapworth; whilst, in the author's opinion, the supporters of the remaining theory are confronted with the dilemma that the steric hindrance of groups is probably explicable in a manner substantially similar to that by which they seek to explain the opposite effect. Thus Henry's theory, that esterification depends on the formation of the intermediate compound (VII), has been extended

by Wegscheider to the case of the phenols, it being assumed that the sterically active group X prevents the formation of the intermediate additive compound (VIII) (*Monatsh.*, 1895, **16**, 140; compare also Davies, T., 1900, **77**, 33). The theory, that this is the usual mode of formation of substitution derivatives of phenol, has been current for a considerable time, and is strongly supported by experimental evidence recently adduced (Meyer and Lenhardt, *Annalen*, 1913, **398**, 51; Meyer, Irschich and Schlösser, *Ber.*, 1914, **47**, 1741; compare Auwers and Michaelis, *ibid.*, p. 1275).

In this connexion attention may be drawn to the behaviour of picramide. This amine furnishes a reddish-brown explosive potassium salt (Green and Rowe, T., 1913, **103**, 513), but is attacked by acetic anhydride only in the presence of sulphuric acid* (Witt and Witte, *Ber.*, 1908, **41**, 3092; compare Paal and Benker, *Ber.*, 1899, **32**, 1251; Paal and Härtel, *ibid.*, p. 2051; Meldola and Hollely, this vol., p. 410). Similarly, 5:7-dinitro-3-keto-1:3-dihydroindazole

* It is noteworthy that sulphuric acid has also been found to be effective in facilitating the esterification of acids which remain unaffected under the usual conditions (Wegscheider, *Ber.*, 1895, **28**, 3128; Kenner and Mathews, this vol., p. 2474).

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furnished a *monoacetyl* derivative (IX), and a deep brown explosive *disodium* salt (X), whereas its 2-phenyl derivative could not be acetylated, and only yielded a *monosodium* salt* (XI). It thus appears that the hydrogen atom in position (1) cannot be acetylated under ordinary conditions, but can take part in salt-formation. Since a diacetyl derivative and a monosodium salt are obtained from 3-keto-1:3-dihydroindazole itself, it is clear that its relationship in these respects to its dinitro-derivative corresponds exactly with that of aniline to picramide:

These examples illustrate the fact that a nitro-group can protect an amino-group by steric hindrance, and yet render its hydrogen atoms active towards alkali. In other words, the two processes involved, of which one is a particular example of those with which this paper is concerned, are fundamentally different.

A group of large molecular volume occupying the second ortho-position to the substituent X may, of course, be expected to exercise the steric hindrance usually observed in such cases of ring-formation, and we therefore find that 2-chloro-1:3-dinitrobenzene reacts much less rapidly than 4-chloro-1:3-dinitrobenzene (Borsche and Rantscheff, *Annalen*, 1911, **379**, 152). Steric influences must further be considered in regard to their effect on the formation of the primary additive compound. Thus Sudborough and Picton (*loc. cit.*) showed that the introduction of three methyl or two methoxyl groups, or three bromine atoms into the molecule of trinitrobenzene completely inhibited the formation of molecular compounds with α - or β -naphthylamine, whilst Hofmann and Kirmreuther found that alcoholic solutions of trinitromesitylene and of trinitro-*m*-xylene, in contrast with trinitrobenzene, developed no colour when hydrazine hydrate was added (*Ber.*, 1910, **33**, 1765). Similarly, Jackson and Boos showed that di- and tri-nitromesitylenes did not give coloured additive products with metallic alkyl-oxides (*Amer. Chem. J.*, 1898, **20**, 444). The importance of this factor is illustrated by the case of 4:6-dibromo-1:2-dinitrobenzene, from which the 1-nitro-group is displaced by the amino-group (Blanksma, *Rec. trav. chim.*, 1908, **27**, 50):

* The formulæ given to these salts in the text are of course alternative to paraquinonoid ones, or to Hantzsch's *aci*-formulæ.

A comparison with the behaviour, already quoted, of 4-chloro- (or bromo)-1:2-dinitrobenzene at once suggests that the nitro-group in position 2 would be the more easily displaced were it not that the other nitro-group is sterically prevented from forming the necessary additive compound.

The above considerations are applicable in other cases. Thus, the reaction between potassium methoxide and trinitrophenetole (Meisenheimer, *loc. cit.*) may be represented in the following manner :

The formation of coloured salts of nitrophenols, to which Hantzsch has assigned the formula (XII) (*Ber.*, 1912, **45**, 90), can be expressed in the same manner :

and it is no longer remarkable that "echte Nitrokörper mit einer zweiten negativen Gruppe isomerisieren sich als Pseudosäuren (durch Wasser oder Alkalien) niemals nur zur ersten Stufe der einfachen

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aci-Nitrokörper, sondern stets sofort zu der zweiten Stufe der konjugierten *aci*-Nitrokörper, so dass in dem folgenden Umwandlungsschema das Mittelglied nicht existiert" (Hantzsch, *loc. cit.*):

The course of the condensation of 2:4-dinitrotoluene with benzaldehyde in presence of secondary bases (Thiele and Escales, *Ber.*, 1901, **34**, 2842) may perhaps be considered to take place in a similar manner. This suggestion at once accounts for certain observations made by Borsche (*Annalen*, 1911, **386**, 351), which he was unable to explain. Whilst 4:6-dinitro-(XIII)- and 2:4:6-trinitro-(XIV)-*m*-xylenes respectively give yields of 35 and 43 per cent. of the corresponding distyrylbenzenes when condensed with benzaldehyde, 2:4-dinitro-(XV) and 2:4:6-trinitro-(XVI)-mesitylenes are unchanged.

In the last two cases the nitro-groups are sterically prevented from forming the required additive compound, but in the first two cases both the 4- and the 6-nitro-groups are free to do so. If, however, the condensation took place by direct interaction of the methyl groups with the aldehydes, trinitro-*m*-xylene should be unchanged, as trinitromesitylene is, whilst dinitromesitylene should react with ease. Also, a comparison of the behaviour of the two reactive compounds is interesting as illustrating the resultant influence of, on

the one hand the activating influence, and on the other the steric hindrance to the later stages of the reaction, of the 2-nitro-group. Further, it may be observed that Hope and Robinson, when considering the mechanism of the condensation of nitromeconine with cotarnine (shown on p. 2726), attributed two functions to the imino-group: "first, in attracting the nitro-compound and in forming a loose combination of the type of the compounds obtained from amines and trinitrobenzene, and secondly, in effecting the condensation between the aldehyde and methylene groups" (T., 1911, **99**, 1153, 2114). The views thus expressed approximate very closely to those advocated above.

The reactivity induced by other meta-directive groups may possibly be explained in a similar manner. Thus there is abundant evidence that the carbonyl group is able to take part in the formation of molecular compounds (compare, for example, Pfeiffer, *Annalen*, 1910, **376**, 285; 1911, **383**, 92; *Ber.*, 1914, **47**, 1580), and it is probable that the same will be found to be true of the sulphonyl and the cyanogen groups.

It is possible that similar considerations might lead to an explanation of the activity of the chlorine atom and the methyl group in 2-chloro- and 2-methyl-pyridines. At any rate, these examples serve to expose the inaccuracy of Vorländer's statement (*Annalen*, 1910, **320**, 66), according to which the "reactive" unsaturated group, $\cdot X:Y \cdot$, causes mobility of the hydrogen atom in system XVII, but not in XVIII or XIX:

Whilst, however, the views just developed suffice to explain a number of observed facts, they do not embrace another reaction, which was observed during the course of the experiments about to be described. Thus it was found that 3-chloro-5:7-dinitroindazole (XX), formed when 5:7-dinitro-3-keto-1:3-dihydroindazole is heated under pressure with phosphoryl chloride at 140°, is converted into 3:5:7-trichloroindazole (XXI) if the reaction is carried out at 180°; and the 2-phenyl derivative showed a similar behaviour:

Analogous observations have been made by Lobry de Bruyn (*Rec. trav. chim.*, 1896, **15**, 84), who found that, among others,

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s-trinitrobenzene and the three dinitrobenzenes were converted into the corresponding chloro-derivatives when heated with saturated hydrogen chloride solution at 200—300°. Similarly Zincke and Kuchenbecker (*Annalen*, 1904, **330**, 50) showed that 2:2'-dinitroazobenzene-4:4'-disulphonic acid, when heated with concentrated hydrochloric acid at 160°, furnished tetrachloroazobenzene:

The facts that all the nitro-groups are displaced, and that in the cases of the dinitrobenzenes the reaction is independent of their orientation, would appear to indicate that the cause of the reaction is to be sought in the relationship of the nitro-groups to the benzene nucleus rather than in any direct mutual influence of these groups. Since, however, nitrobenzene itself does not undergo this reaction (Lobry de Bruyn and van Leent, *loc. cit.*), it is evident that the second nitro-group does play some part, probably by suitably modifying the condition of the benzene nucleus. This surmise receives some measure of support from the fact that the displacement of nitro-groups by chlorine atoms takes place much more readily in the case of naphthalene derivatives (Atterberg, *Ber.*, 1876, **9**, 1187, 1732; 1877, **10**, 1843), in which the condition of the nuclei is generally acknowledged to be somewhat different from that of the ordinary benzene nucleus. This idea is not novel, for it is implied in the term "negativity," by which the chapter of organic chemistry dealing with such cases of mobility is sometimes designated. It is therefore also probable that this effect of nitro-groups on the benzene nucleus must be taken into account in connexion with the reactions to which the main part of the present discussion has been devoted. Similarly, the nature of the substituent to be replaced also requires consideration. Thus Sudborough and Picton were unable to prepare picryl- α -naphthylamine from picrylaniline, although the necessary additive compound was isolated (*loc. cit.*, p. 587). The fact that *s*-trinitrobenzene is converted into 3:5-dinitroanisole by the action of sodium methoxide, but is not affected by ammonia (Lobry de Bruyn, *Rec. trav. chim.*, 1890, **9**, 214, 218; 1894, **13**, 148), shows that the nature of the entrant group is also of importance. It must, however, be observed that these factors operate by predisposing the system to reaction rather than by playing any active part in the change.

Still other influences are noticeable in certain cases. Thus the displacement of a nitro-group in the course of the synthesis of 3:5-dinitro-oxazine from 2:4:6-trinitro-2'-hydroxydiphenylamine,

observed by Turpin (T., 1891, **59**, 722; see also Kehrman, *Ber.*, 1899, **32**, 2605):

is comparable with the conversion, just cited, of *s*-trinitrobenzene into 3:5-dinitroanisole, and is probably a result of the negativity of the benzene nucleus. This, however, affords no explanation of the fact, observed by Ullmann, that whilst Turpin's reaction is applicable to 2:6-dinitro-2'-hydroxydiphenylamine, it fails in the case of the 2:4-isomeride (*Annalen*, 1909, **366**, 79).

Further, the result of the action of potassium cyanide on alcoholic solutions of the bromonitrobenzenes and similar compounds at 180°, first studied by Richter, is remarkable. Para- and meta-bromonitrobenzenes are respectively converted into meta- and ortho-bromobenzoic acids, but the ortho-isomeride is recovered unchanged (*Ber.*, 1871, **4**, 21, 461, 553; 1874, **7**, 1145; 1875, **8**, 1418; compare Zincke, *Ber.*, 1874, **7**, 1503). Whilst these reactions are normal in the sense that the hydrogen atom in the ortho-position to the nitro-group is attacked in each case, they disclose a strong tendency, not observed in any of the cases previously referred to, on the part of the substituting group (in this case cyanogen, which is subsequently hydrolysed), to enter the nucleus as close to the other negative group as possible. So strong is this tendency that it prevents the conversion of *o*-bromonitrobenzene into *m*-bromobenzoic acid, although both the bromine atom and the nitro-group in this case conduce to the mobility of the meta-hydrogen atom; whilst in the second case quoted above the reaction takes place irrespective of considerations of steric hindrance, which would suggest the para-hydrogen atom as more likely to be attacked.* If due allowance is made for this factor, the action of potassium cyanide on various nitro-compounds, apparently so bewildering in the variety of results observed (collated by Lobry de Bruyn, *Rec. trav. chim.*, 1904, **23**, 47), affords an excellent illustration of the effect of the influences previously discussed, namely:

- (a) the loosening influence of meta-directive groupings on ortho- and para-substituents;
- (b) the corresponding effect of ortho-para-directive groups on meta-substituents;

* Probably bromonitrobenzonitriles are first produced in this reaction. For evidence of the mobility of the nitro-group in such compounds, compare the cases of *o*-nitrobenzonitrile, *m*-dinitrobenzene, and other compounds referred to later.

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(c) steric hindrance to the formation of the initial additive compound and to the attack of otherwise mobile groups;

(d) the negative condition of the benzene nucleus:

(e) the nature of the substituent to be replaced and of the entrant group. It will be observed that, in the following instances, nitro-groups attached to a negative nucleus and hydrogen atoms alone suffer displacement. Halogen atoms are not affected by potassium cyanide.

The following table shows the more notable of the results obtained in this direction, accompanied by references to the above summary:

Nitro-compound.	Conditions employed.	Product.	Influences.	References to literature.
<i>o</i> -Dinitro-benzene.	Alcoholic solution at 170°.	No change.	?	Bruyn and van Geuns, <i>Rec. trav. chim.</i> , 1904, 23 , 32.
<i>p</i> -Dinitro-benzene.	Boiling alcoholic solution.	<i>p</i> -Nitroanisole.	(a) + (d).	Bruyn and van Geuns, <i>loc. cit.</i>
<i>m</i> -Dinitro-benzene.	Boiling alcoholic solution.	[2·6-Dinitro-benzonitrile] → 6-nitro-2-methoxybenzonitrile.*	(a) + (d).	Bruyn and van Geuns, <i>loc. cit.</i> ; other references in this paper.
Dinitrated 6·nitro-2-ethoxybenzonitrile.	Warm alcoholic solution.	A dinitrile, the 6-nitro-group being displaced.	(a) + (b) + (d).	van Geuns, quoted by Bruyn, <i>Rec. trav. chim.</i> , 1904, 23 , 52.
1:2:4-Tri-nitrobenzene.	Boiling alcoholic solution.	2:4-Dinitroanisole.	(a) + (d).†	Bruyn, <i>Rec. trav. chim.</i> , 1890, 9 , 193.
4-Chloro-1:3-dinitrobenzene.	Boiling alcoholic solution.	5-Chloro-6-nitro-2-methoxybenzonitrile.	(a) + (b) + (d) + (e).	van Heteren, <i>Rec. trav. chim.</i> , 1901, 20 , 107; Blanksma, <i>ibid.</i> , 1902, 21 , 424.

* The cyanogen group renders a nitro-group in the ortho-position mobile (influences (a) + (d)). Thus *o*- and *p*-nitrobenzonitriles, when boiled with a solution of sodium methoxide, are converted into *o*- and *p*-methoxybenzonitriles (Ringer, *Rec. trav. chim.*, 1899, **18**, 330; Reinders and Ringer, *ibid.*, 326). Lulofs showed that some *o*-nitroanisole is also produced in the former case (*Rec. trav. chim.*, 1901, **20**, 321). Further, Lobry de Bruyn showed that 2-methoxy-6-nitrobenzonitrile was converted into 2:6-dimethoxybenzonitrile by methyl-alcoholic potassium hydroxide (*Rec. trav. chim.*, 1883, **2**, 205).

† The 1-nitro-group diminishes the mobility of the 3-hydrogen atom, and thus prevents the reaction from following a similar course to that observed in the case of *m*-dinitrobenzene. The influence of the chlorine atom and the amino-group in the cases next quoted is, however, in favour of such a result. This influence of the chlorine atom is clearly responsible for the partial conversion of 5-chloro-

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Nitro-compound.	Conditions employed.	Product.	Influences.	References to literature.
2:4-Dinitro-aniline.	Alcoholic solution at 60°.	2:6-Dinitro-3-aminophenol.	(a) + (b) + (d) + (c).	Lippmann and Fleissner, <i>Monatsh.</i> , 1885, 6 , 807; 1886, 7 , 95.
2:4:6-Tri-nitrophenol.	Aqueous solution at 35° (Nietzki and Petri).	Potassium <i>isopurpurate</i> .*	(a) + (b) + (c) + (e).	Nietzki and Petri, <i>Ber.</i> , 1900, 33 , 1788; Borsche, <i>Ber.</i> , 1900, 33 , 2718, 2995; Borsche and Locatelli, <i>Ber.</i> , 1902, 35 , 569; Borsche and Böcker, <i>Ber.</i> , 1903, 36 , 4357; Bruyn, <i>Rec. trav. chim.</i> , 1904, 23 , 56.
Di- and tri-nitromesitylenes.	—	No change.	(c).	Blanksma, <i>Rec. trav. chim.</i> , 1901, 20 , 411, 423.

1:3-dinitrobenzene into 3-chloro-5-nitroanisole by the action of sodium methoxide, whilst 1:3-dinitrobenzene is simply reduced (Kock, *Rec. trav. chim.*, 1901, **20**, 111; Steger, *ibid.*, 1899, **18**, 13).

* The authorities quoted agree that *isopurpuric* acid contains cyanogen groups in the 3- and 5-positions, but differ in regard to the fate of the 2- and 6-nitro-groups. According to Nietzki and Petri, one of them is converted into an amino-group, whilst Borsche suggests that the reduction only reaches the stage of a hydroxylamino-group. Lobry de Bruyn considers that the colour of the compound would be better explained by the presence of a nitroso- and a hydroxylamino-group in place of the two nitro-groups. The question as to the extent to which the nitro-groups suffer reduction has, however, no bearing on the present discussion.

Two points in connexion with the above table call for explanation. No attempt is made to explain the introduction at one time of a cyanogen group, at another of an alkyloxy-group, as a result of the action of potassium cyanide. This problem, which lies outside the scope of the present discussion, was considered by Lobry de Bruyn, who, however, was unable to arrive at any very definite conclusion (*Rec. trav. chim.*, 1904, **23**, 47). Also, the term "influences" at the head of one column of the table is only meant to comprehend those which would appear to play a decisive part in determining the final result.

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EXPERIMENTAL.

[With RAYMOND CURTIS.]

5:7-Dinitro-3-keto-1:3-dihydroindazole,

An alcoholic solution of hydrazine hydrate (6 grams) was cautiously added to a solution of methyl 2-chloro-3:5-dinitrobenzoate (10 grams) in warm alcohol (100 c.c.). Each addition caused a vigorous reaction, which became violent if the initial temperature was too high, and a dark red hydrazine salt was immediately precipitated. After dilute hydrochloric acid had been added to the mixture, the free indazole derivative was collected, and purified by crystallisation from glacial acetic acid. It separated from the solution in yellow, hexagonal plates, melting and decomposing at about 300°:

0.1900 gave 0.2596 CO₂ and 0.0368 H₂O. C=37.26; H=2.15.

0.1736 „ 38.2 c.c. N₂ at 17° and 734 mm. N=25.06.

C₇H₄O₅N₄ requires C=37.50; H=1.78; N=25.00 per cent.

The compound was not appreciably soluble in cold alcohol, water, benzene, or chloroform; it was fairly soluble in boiling alcohol, and readily so in glacial acetic acid or acetic anhydride.

The *disodium* salt was prepared by triturating 5:7-dinitro-3-keto-1:3-dihydroindazole (2 grams) with 5*N*-sodium hydroxide solution (7 c.c.). After the addition of absolute alcohol (5—10 c.c.) to the resulting deep brown paste, the salt was collected and washed with absolute alcohol until the washings were free from alkali. For analysis two different specimens were prepared, the second by the use of a considerable excess of sodium hydroxide solution; although the products were dried at 130°, the salt still retained two molecular proportions of water:

0.1288 gave 0.0603 Na₂SO₄. Na=15.17.

0.2938 „ 0.1380 Na₂SO₄. Na=15.22.

0.134 required 9.2 c.c. *N*/10-H₂SO₄. M.W.=291.*

C₇H₂O₅N₃Na₂·2H₂O requires Na=15.13 per cent.; M.W.=304.

The salt exploded when heated, and this prevented determinations of its other elements being made. It was readily soluble in

* The salt itself served as indicator in the titration. Owing to the difficulty in determining the exact end-point, no claim can be made for great accuracy in the result.

water, soluble in alcohol or acetone, but insoluble in benzene or chloroform. By treating its aqueous solution with suitable reagents, a reddish *ferric* salt, an insoluble dark brown *silver* salt, and a moderately soluble dark brown *copper* salt were obtained.

The *monoacetyl* derivative separated in greenish-yellow crystals on cooling the solution obtained by boiling the compound (2 grams) with acetic anhydride (5 grams) for eight hours. It crystallised from glacial acetic acid in rectangular prisms, melting at 195—200°:

0.1701 gave 0.2548 CO₂ and 0.0340 H₂O. C=40.85; H=2.22.

0.1548 „ 28.6 c.c. N₂ at 18° and 741 mm. N=21.2.

C₉H₆O₆N₄ requires C=40.60; H=2.25; N=21.05 per cent.

The solubility relationships of the acetyl derivative corresponded with those of the parent substance. It was soluble in alkali, forming a deep red solution.

All attempts to prepare a diacetyl derivative were fruitless, the monoacetyl derivative being produced in every case.

5: 7-Diamino-3-keto-1: 3-dihydroindazole.

The dinitro-derivative (4 grams) was added to a solution of stannous chloride in glacial acetic acid (80 grams), saturated with hydrogen chloride. After twelve hours, the reduction product was isolated from the precipitate by treatment with hydrogen sulphide in the usual manner. It was analysed in the form of its *oxalate*, which was precipitated when ammonium oxalate was added to an aqueous solution of the hydrochloride of the base:

0.1062 gave 20.8 c.c. N₂ at 18° and 740 mm. N=21.95.

C₇H₈ON₄, C₂H₂O₄ requires N=22.20 per cent.

5: 7-Dinitro-3-keto-2-phenyl-1: 3-dihydroindazole,

An alcoholic solution of phenylhydrazine (12 grams) was slowly added to a warm solution of methyl 2-chloro-3: 5-dinitrobenzoate (10 grams) in alcohol (100 c.c.). After the mixture had been heated on the water-bath for fifteen minutes, it was worked up as

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in the previous case. The product consisted of two compounds, one of which was extracted by boiling alcohol. The residue (90—95 per cent. of the yield) crystallised from glacial acetic acid in flat needles, which melted and decomposed between 220° and 250°:

0.1814 gave 0.3464 CO₂ and 0.0477 H₂O. C=52.08; H=2.91.

0.1552 „ 25.2 c.c. N₂ at 16.5° and 740 mm. N=18.72.

C₁₃H₈O₅N₄ requires C=52.00; H=2.66; N=18.66 per cent.

The compound was therefore either the 1- or the 2-phenyl derivative of 5:7-dinitro-3-keto-1:3-dihydroindazole. It was only sparingly soluble in boiling alcohol, benzene, or chloroform. It was moderately soluble in glacial acetic acid and in epichlorohydrin.

The *monosodium* salt was obtained as an amorphous powder in the manner already described in the case of dinitroketodihydroindazole, and exhibited a similar tendency to explode when heated. It was readily soluble in water, soluble in alcohol or acetone, but insoluble in chloroform or benzene:

0.2162 gave 0.0491 Na₂SO₄. Na=7.35.

0.1610 required 5.0 c.c. N/10-H₂SO₄. M.W.=322.

C₁₃H₇O₅N₄Na requires Na=7.1 per cent.; M.W.=322.

By double decomposition with its aqueous solution, an insoluble, deep red *silver* salt, and a moderately soluble, brown *copper* salt were obtained. The compound is insufficiently acidic to permit of the formation of a ferric salt.

Attempts to prepare an acetyl derivative by various methods were unsuccessful, the original compound being recovered in each case. A colourless substance separated from the solution obtained by adding sulphuric acid to a mixture of the compound with acetic anhydride, but it decomposed and turned yellow immediately it came in contact with the moisture of the atmosphere.

As explained in the introduction, these reactions agree with the behaviour of picramide, and it is therefore considered that the compound is a 2-phenyl derivative. This conclusion is in harmony with the results of E. Fischer (*Annalen*, 1878, **190**, 67), who showed that the condensation of picryl chloride with phenylhydrazine results in the formation of trinitrohydrazobenzene. It appears that other products may result under slightly different conditions (Willgerodt and Ferko, *J. pr. Chem.*, 1888, [ii], **37**, 346; Fischer, *Annalen*, 1889, **253**, 1), and Fischer himself showed that a mixture of symmetrical and unsymmetrical derivatives is produced by the action of alkyl bromides on phenylhydrazine (compare also Michaelis and Schmidt, *Ber.*, 1887, **20**, 43). These facts may throw some light on the formation in the present case of a

second compound, which was deposited from the above-mentioned alcoholic solution in yellow, rhomboidal plates. After repeated crystallisation from alcohol, the compound melted at 175° :

0.1420 gave 0.2897 CO_2 and 0.0502 H_2O . $\text{C}=55.64$; $\text{H}=3.93$.

0.1450 ,, 25.6 c.c. N_2 at 16° and 737 mm. $\text{N}=20.51$.

$\text{C}_{19}\text{H}_{18}\text{O}_5\text{N}_6$ requires $\text{C}=55.89$; $\text{H}=3.92$; $\text{N}=20.60$ per cent.

The compound therefore resulted from the condensation of one molecular proportion of the ester with two of phenylhydrazine:

We were unable to oxidise it with mercuric oxide, to condense it with aldehydes, to convert it into the indazole derivative produced simultaneously with it, or to prepare it from 2:4-dinitro-6-carbomethoxyhydrazobenzene. Unless steric influences be assumed, this evidence is at variance with the possible formulæ XXII and XXIII, whilst formula XXIV, representing the product of the semidine inversion of XXIII, is rendered improbable by the fact that the compound in question may be isolated without the aid of acid by removing the phenylhydrazine salt of dinitroketophenyl-dihydroindazole by solution in cold alcohol:

2:4-Dinitro-6-carbomethoxyhydrazobenzene,

After phenylhydrazine (8 grams) had been added to a solution of methyl 2-chloro-3:5-dinitrobenzoate (10 grams) in alcohol (100 c.c.), the mixture was heated to the boiling point, and then cooled. The precipitate thus obtained was warmed with alcohol, and, after filtration, the solution deposited orange crystals of the hydrazo-derivative. After further crystallisation from warm alcohol, it melted at $144\text{--}145^{\circ}$:

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0.1634 gave 0.3016 CO_2 and 0.0523 H_2O . $\text{C}=50.45$; $\text{H}=3.55$.

0.1430 „ 21.7 c.c. N_2 at 20° and 732 mm. $\text{N}=17.11$.

$\text{C}_{14}\text{H}_{13}\text{O}_6\text{N}_4$ requires $\text{C}=50.60$; $\text{H}=3.61$; $\text{N}=16.87$ per cent.

When its alcoholic solution was boiled for a few minutes, internal condensation took place, and the corresponding dihydroindazole derivative was precipitated. The same product was obtained when attempts were made to condense the hydrazo-derivative with phenylhydrazine or benzaldehyde.

s-2:4:2':4'-Tetranitro-6:6'-dicarbomethoxytetraphenyl-

An alcoholic solution of hydrazobenzene (2 grams) was heated with a solution of methyl 2-chloro-3:5-dinitrobenzoate (6 grams) in alcohol (60 c.c.) on the water-bath for one hour. The brick-red precipitate, after filtration and crystallisation from nitrobenzene, melted at above 340° :

0.1777 gave 0.3480 CO_2 and 0.0526 H_2O . $\text{C}=53.40$; $\text{H}=3.29$.

0.1918 „ 21.6 c.c. N_2 at 20° and 747 mm. $\text{N}=12.94$.

$\text{C}_{28}\text{H}_{20}\text{O}_{12}\text{N}_6$ requires $\text{C}=53.16$; $\text{H}=3.16$; $\text{N}=13.29$ per cent.

It was insoluble in alkalis, and in most organic solvents except nitrobenzene and epichlorohydrin. Attempts to hydrolyse the compound with acid or with alkali were unsuccessful.

If the constitution assigned to the phenylindazole derivative, already described, is accepted, it is remarkable that the second phenylamino-group of hydrazobenzene reacts with a second molecule of ester rather than with the carbomethoxyl group of the first molecule, and it might be suggested that this is evidence in favour of the alternative constitution. On the other hand, however, it may be argued that the velocity of reaction in the present case is much slower than when phenylhydrazine is used, and that this is due to the greater facility with which the ester condenses with the amino-group of phenylhydrazine.

5:7-Dinitro-3-keto-1:3-dihydroindazole (5 grams) was heated with phosphoryl chloride (35 grams) for four hours under pressure at 120 — 140° . After the excess of phosphoryl chloride had been removed by warming the product under diminished pressure, the

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residue was stirred with water, collected, and repeatedly crystallised from glacial acetic acid. In this way, yellow needles (3 grams) were obtained, which melted at $179-180^{\circ}$:

0.1994 gave 0.2508 CO_2 and 0.0197 H_2O . $\text{C}=34.30$; $\text{H}=1.09$.

0.2020 ,, 40.6 c.c. N_2 at 18° and 752 mm. $\text{N}=23.39$.

0.3615 ,, 0.2112 AgCl . $\text{Cl}=14.46$.

$\text{C}_7\text{H}_3\text{O}_4\text{N}_4\text{Cl}$ requires $\text{C}=34.66$; $\text{H}=1.19$; $\text{N}=23.09$; $\text{Cl}=14.64$.
per cent.

5 : 7-Dinitro-3-keto-1 : 3-dihydroindazole was heated under pressure with 10 parts by weight of phosphoryl chloride for ten hours at $160-180^{\circ}$. The product was isolated in the same manner as in the previous preparation, and separated from glacial acetic acid in microscopic, white twinned needles, which melted at $190-190.5^{\circ}$:

0.1085 gave 11.8 c.c. N_2 at 18° and 740 mm. $\text{N}=12.47$.

$\text{C}_7\text{H}_3\text{N}_2\text{Cl}_3$ requires $\text{N}=12.64$ per cent.

After a sealed tube containing a mixture of 5 : 7-dinitro-3-keto-2-phenyl-1 : 3-dihydroindazole (3 grams) and phosphoryl chloride (24 grams) had been heated for four hours at $120-140^{\circ}$, and cooled, it was found that the above chloroindazole derivative had crystallised. After separation from the liquor, and recrystallisation from glacial acetic acid, somewhat indefinite small, greenish-yellow needles were obtained:

0.2000 gave 30.7 c.c. N_2 at 17° and 725 mm. $\text{N}=17.3$.

$\text{C}_{13}\text{H}_7\text{O}_4\text{N}_4\text{Cl}$ requires $\text{N}=17.6$ per cent.

5 : 7-Dinitro-3-keto-1-phenyl-1 : 3-dihydroindazole (5 grams) was heated with phosphoryl chloride (40 grams) for fourteen hours

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under pressure at 160—170°. The product, isolated in the same manner as in the previous cases, separated from glacial acetic acid in silky, yellow needles, which melted at 208—210°:

0.1779 gave 13.8 c.c. N_2 at 18.5° and 754 mm. $N=9.06$.

0.3783 „ 0.5429 AgCl. $Cl=35.53$.

$C_{13}H_7N_2Cl_3$ requires $N=9.41$; $Cl=35.79$ per cent.

Action of Phosphoryl Chloride on s-2:4:2':4'-Tetranitro-6:6'-dicarbomethoxytetraphenylhydrazine.

A mixture of the hydrazine derivative (3 grams) with phosphoryl chloride (40 grams) was heated for ten hours under pressure at 170—180°. The product of the reaction could not be crystallised from the ordinary solvents, and was therefore purified by digestion with sodium hydroxide solution and reprecipitation from the filtered solution:

0.1815 gave 0.3572 CO_2 and 0.0436 H_2O . $C=53.67$; $H=2.66$.

0.1672 „ 11.0 c.c. N_2 at 20° and 731 mm. $N=7.4$.

$C_{26}H_{16}O_8N_4Cl_2$ requires $C=53.51$; $H=2.74$; $N=9.90$ per cent.

$C_{26}H_{16}O_4N_2Cl_4$ „ $C=55.51$; $H=2.84$; $N=4.99$ „ „

The product was therefore a mixture of two acids, derived from the original ester by hydrolysis and replacement of respectively two and four of its nitro-groups by chlorine. The incomplete nature of the reaction was probably due to the high molecular weight and sparing solubility of the hydrazine derivative.

This result is of value, since it shows that the pyrazole ring was not the predisposing cause of the mobility of the nitro-groups in the previous instances, although this mobility is specially noticeable in the naphthalene series (see the introduction), and Fries has shown (*Annalen*, 1912, **389**, 313) that 6-hydroxyindazole is comparable in its reactions with β -naphthol.

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