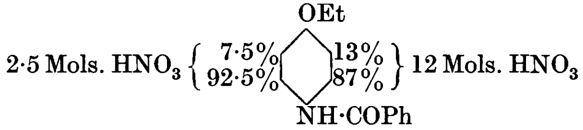
CCCXXII.—*The Relative Directive Powers of Groups of the Forms* RO *and* RR′N *in Aromatic Substitution. Part VII. The Nitration of Benzphenetidide and of* o-, m-, *and* p-*Nitrobenzphenetidides.*

By REGINALD C. FAWCETT and ROBERT ROBINSON.

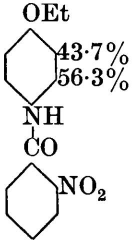
IN considering the factors governing the relative ease of occurrence of electronic changes, such as those involved in conjugated polarisation, originated or permitted by different atoms, Kermack and Robinson (J., 1922, **121**, 427) suggested two guiding principles: (*a*) that the free electrons in the outer shells are the less active the greater their number; and (*b*) that the activity of free electrons diminishes with increasing atomic weight of the element. Obviously such rules may apply only approximately, and there are alternative ways of stating them, but they serve to correlate experimental results in several fields and give such sequences as $NMe_2 > SMe > OMe > I > Cl > F$ for the proton avidity (strength of bases) in the compounds HX and for the effectiveness of the groups in crotenoid systems, and hence for their directive powers in aromatic substitutions of certain types (compare *Chem. and Ind.*, 1925, **44**, 684). The effects of charges, as in the phenoxide and phenylammonium ions, may reverse the order in the series, and this is also true of the effects of substituents which may induce displacements of electrons equivalent to charges. Thus, although the order $N > O$ in aromatic substitution (kationoid reagent, crotenoid system) is theoretically inevitable and justified by everyday laboratory experience so long as we compare neutral, tervalent nitrogen with neutral, bivalent oxygen, yet the application of theory becomes ambiguous when we pass to the comparison of such groups as ·NR·COR and ·OR. Experiment shows that the directive powers of the nitrogenous group can be regulated over a wide range; thus Reverdin (*Ber.*, 1896, **29**, 2595) and Hinsberg (*Annalen*, 1896, **292**, 249) found that the nitration of acet-*p*-anisidide gave acet-3-nitro-*p*-anisidide, establishing beyond question that the directive power of ·NHAc is much greater than that of OMe. Reverdin and Düring (*Ber.*, 1899, **32**, 164) further showed that acet-*o*-phenetidide is changed by nitric acid (41° Beaumé) into its 5-nitro-derivative, although 4-nitro-*o*-phenetidine is obtained by the nitration of *o*-phenetidine in sulphuric acid solution. Similarly the nitration of acet-*o*-anisidide was found to give chiefly the 5-nitro-derivative (Mühlhäuser, *Annalen*, 1881, **207**, 242; Meldola, Woolcott, and Wray, J., 1896, **69**, 1330;

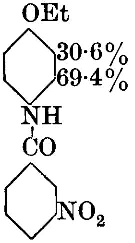
Vermeulen, *Rec. trav. chim.*, 1905, **25**, 12). This has been recently confirmed by Ingold and Ingold (J., 1926, 1310), whose work suggests that owing to the formation of small, undetermined amounts of by-products, the nitration of acet-*o*-anisidide is not a reaction that is suitable for exact quantitative study. On the other hand, Brady, Quick, and Welling (J., 1925, **127**, 2264) found that the nitration of succin-*p*-tolil gave as much as 84% of *N*-2-nitro-*p*-tolylsuccinimide, showing that the group $\cdot N(CO)_2(CH_2)_2$, although itself almost exclusively *p*-directive, is far weaker than methyl in directive power. An explanation, on an electronic basis, of the diminished directive power of nitrogen in such *neutralised* systems (N·CO, etc.) has been already advanced (Robinson, *Chem. and Ind.*, 1925, **44**, 18, 456; Rây and Robinson, J., 1925, **127**, 1618; Part IV, J., 1926, 404; Part V, *ibid.*, p. 411) and may be summarised in the statement that the carbonyl group competes with the aromatic nucleus for the free electrons of the nitrogen octet.

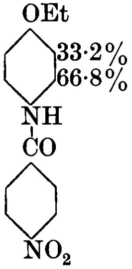
The present investigation is the first of a series in which it is hoped to study the effect of the substituents (R, R') on the directive power of the group R·CO·NR'. In the cases discussed below, R' is H and R is Ph or *o*-, *m*-, or *p*-$NO_2\cdot C_6H_4$. The circumstance that R' is H involves the possibility of incipient ionisation increasing the directive power or of actual removal of a proton in one of the later phases of the reaction, with the same apparent result. These occurrences should, however, be the more facile the stronger the acid $R\cdot CO_2H$, so they would not influence the directive powers in the sense actually observed, and if taken into account the effects would appear enhanced. The method adopted was to put the groups in turn in competition with ethoxyl, and the reaction examined has been the nitration of the benz-*p*-phenetidides in acetic acid solution at about 0°. Reverdin (*Ber.*, 1911, **44**, 2362) has already studied the nitration of benz-*p*-anisidide and of the isomeric nitrobenz-*p*-anisidides: in each case, the nitrobenzamido-groups were found to be much more powerfully directive than methoxyl, but nothing more than approximately quantitative results were sought. In the present series of experiments, the products were obtained in almost theoretical yield, and thermal analysis showed them to behave as binary mixtures that could contain only traces of other substances. In the case of benz-*p*-phenetidide, the nitration was carried out under two sets of conditions; in the first, nitric acid (2·5 mols.) was gradually added to the phenetidide in acetic acid, and in the second the phenetidide was added to nitric acid (12 mols.) and acetic acid. Thus not only was more acid used in the latter case, but also it was present from the beginning of the operation. The results are exhibited in the annexed scheme, in which the figures show the proportions in which the nitro-derivatives were formed.



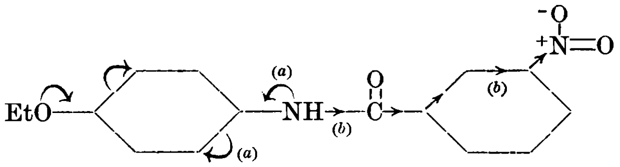
The stronger acid medium has the effect of depressing the directive power of the benzamido-group, and this is clearly due to salt formation and is in harmony with previous experience (compare, *e.g.*, Noelting and Collin, *Ber.*, 1884, **17**, 261; Hollemann, Hartogs, and van der Linden, *Ber.*, 1911, **44**, 704). The nitrobenz-*p*-phenetidides were nitrated under the second set of conditions (12 mols. HNO_3), and as all analogies indicate that these amides should be weaker bases than benz-*p*-phenetidide, the effect of the medium may be expected to be relatively small. The results are expressed graphically thus :



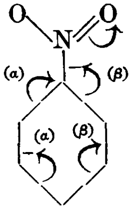




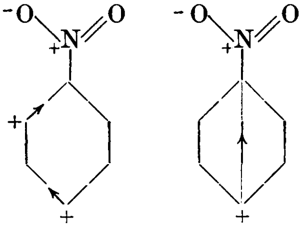
In all three cases, nitration could not be accomplished under the conditions (2·5 mols. HNO_3) that sufficed for the quantitative transformation of benz-*p*-phenetidide, and therefore the general electrical effect of the nitroxyl group makes itself felt over the whole molecule. The figures show, however, that the directive power of the benzamido-group has been diminished to the greater relative extent; the appropriate theory on an electronic basis is represented in the case of the *m*-nitrobenzamido-group by the scheme



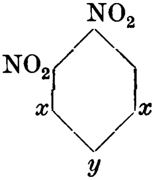
in which (*a*) is the directive process and (*b*) is the counteracting general electronic displacement. The effect (*b*) should be more powerful in the *o*- than in the *m*-nitrobenzoyl derivative, and it should be weakest in the *p*-isomeride. The former deduction is in agreement and the latter in disagreement with the results, which, therefore, suggest that a mechanism exists that enables the more distant group to be the more effective. Such a mechanism may be conjugative (A) or inductive (B) in Kekulé, Dewar, or Claus structures (the last two being regarded as highly improbable and included merely for the sake of completeness), and will also contribute to the enhancement of the effect of an *o*-situated nitroxyl group. In either case, *m*- and *p*-situated nitroxyls induce positive charges at *x* and *y*, respectively (C). In (A) (β), the conjugation is crotonoid and in (A) (α) it is butadienoid and initiated by the general effect of the nitroxyl; this process is almost indistinguishable from that shown in (B) (I). Oxford and Robinson (Part II, J., 1926, 383) found that the directive powers of the *m*- and *p*-nitrobenzyloxy-groups were identical, and the contrast with the results obtained in the present investigation is probably due to the fact that in the benzamido-compounds there is an unbroken sequence of unsaturated atoms, and the point (C of CO), where the effect can theoretically operate so as to influence the directive power of the group, is nearer to the nitrophenyl group than is the corresponding point (O of Ar·O·CH_2) in the nitrobenzyloxy-compounds. We have examined mathematically the question as to whether a *direct* general effect of the dipole, NO, could give the sequence $o>p>m$, on the theory that in its average position in space a line can be drawn through the centre of the hexagon (benzene ring) and the nitrogen and oxygen atoms. On this stereochemical basis, the disparity between the anticipated effects from the *m*- and *p*-positions is reduced by reason of the oblique orientation of the dipole couple in the *m*-position, but on every probable assumption in regard to the relative distances (nuclear C to N, N to O, nuclear C to a point X, where the effect is operative across the intervening space to the couple N—O) we find $o>m>p$ for the resultant field (at X in the direction of the centre of the nucleus) of the dipole. Taking dynamic conditions into consideration, *e.g.*, free revolution of the nitroxyl group and other



(A.)



(I.) (B.) (II.)



(C.)

ambiguities, it cannot yet be concluded, however, that an explanation of the order $o > p > m$ is impossible on purely stereochemical lines. It is proposed to extend the investigation with the help of an experimental model.

Finally, a point raised by Orton and Bradfield (this vol., p. 986) in connexion with the directive power of the benzamido-group may be mentioned. These authors have found that the velocity of chlorination of benzanilide exceeds that of acetanilide, which indicates that the directive power of benzamido- is greater than that of acetamido-. (In passing, it may be remarked that Brady, Quick, and Welling, *loc. cit.*, found that phthalimido- had a somewhat greater directive power than succinimido-, providing further evidence in the same direction.) The inconsistency of this result on our electronic basis with the fact that benzoic acid is stronger than acetic acid was commented on. Kermack and Robinson (*loc. cit.*) suggested, however, that the aromatic nucleus is a resonator, being either key-negative or key-positive, according to circumstances. It should be regarded as subservient, in a measure, to the needs of other groups, and ready in some phases to supply electrons, in others to accept them. A further generally applicable conception is that when phases leading to activation and phases leading to inhibition of some particular process or reaction alternate, then the activation phases assume by far the greater importance in producing the observed results. In benzoyl derivatives, there will be phases in which the electron density in the neighbourhood of the carbonyl group is increased (retardation of ionisation of benzoic acid, but acceleration of substitution in benzanilide), and other phases in which it is relatively decreased (acceleration of ionisation of benzoic acid, but retardation of substitution in benzanilide).

EXPERIMENTAL.

2-Nitro-4-aminophenetole sulphate was obtained in 50% yield by Reverdin's method (*Helv. Chim. Acta*, 1927, **10**, 3). 3-Nitro-4-aminophenetole was prepared from phenacetin (40 g.) by the method described in D.R.-PP. 99338 and 38322; the yield of product, m. p. 112·7—113·2°, was 37·5 g.

2-*Nitro*-4-*benzamidophenetole*, (A).—2-Nitro-4-aminophenetole sulphate (10 g.) was added to pyridine (200 c.c.), and benzoyl chloride (10 g.) gradually introduced with vigorous shaking. After 1 hour water was slowly added and the precipitated solid was collected; it crystallised from methyl alcohol (charcoal) in flat, yellow needles, m. p. 149—150° (Found : C, 62·8; H, 5·0. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9%).

3-*Nitro*-4-*benzamidophenetole*, (B).—3-Nitro-4-aminophenetole (10 g.) was similarly benzoylated by means of benzoyl chloride (15 g.) in pyridine (150 c.c.); the product crystallised from alcohol (charcoal) in tufts of slender, orange needles, m. p. 121·5—122° (Found : C, 63·0; H, 5·1%).

Mixtures of the Isomerides (A) *and* (B).—The freezing points were determined with the usual precautions, first approximately and then more accurately, the outer bath being kept at such a temperature as to maintain the tube containing the material at 1—2° below the freezing point. The mixture was then heated to 15—20° above the m. p. and allowed to cool after the tube was replaced in the air-jacket. Vigorous stirring was practised at 1—2° above the f. p., and slower but steady stirring in the neighbourhood of the f. p. Several concordant results were obtained for each mixture, and all values were rejected when the degree of supercooling exceeded 0·5—1°. All the graphs constructed were smooth, two-branched curves.

The following f. p.'s were determined :

By adding (A) *to* (B).

% (B)	100·0	95·1	89·8	84·3	78·1	72·4	64·8
F. p.	120·2°	118·2°	116·2°	114·2°	111·95°	109·6°	106·2°

By adding (B) *to* (A).

% (B)	41·7	35·4	33·6	26·5	20·5	13·5	6·4	0·0
F. p.	124·5°	128·1°	129·1°	134·2°	137·4°	141·1°	144·8°	147·75°

Nitration of Benz-p-*phenetidide.*—Benz-*p*-phenetidide, prepared by the Schotten–Baumann method, crystallised from alcohol in glistening, white laminæ, m. p. 174·5—175°.

(1) *Nitration with* 2·5 *mols. of nitric acid.* A mixture of boiled nitric acid (*d* 1·41; 5 c.c.) and pure acetic acid (12·5 c.c.) was added in the course of ½ hour to benz-*p*-phenetidide (5 g.) suspended in acetic acid (125 c.c.), the vessel being surrounded by melting ice. The highest temperature recorded was 3°. After 1·5 hours, the product was precipitated by water, collected, washed, and dried (5·85 g. or 98·7%) (Found : C, 62·6; H, 4·9. Calc. : C, 62·9; H, 4·9%). This material had f. p. 117·3°, corresponding, from the graph, with a mixture (*a*) containing 92·5% of the isomeride (B), or to a second composition excluded by the confirmatory tests. A mixture of the nitration product (0·8222 g.) and (A) (0·1315 g.) should therefore contain 79·75% of (B) : actually, it had f. p. 112·5°, corresponding with 79·8% of (B). The further addition of (A) (1·1502 g.) to this mixture gave a product of f. p. 128·0°, corresponding to 36·5% of (B) [Calc. from (*a*) : 36·1% of (B)].

(2) *Nitration with* 12 *mols. of nitric acid.* Benz-*p*-phenetidide (2 g.) was added to a mixture of boiled nitric acid (10 c.c., *d* 1·41) and

acetic acid (40 c.c.) cooled in melting ice; after 10 minutes' stirring, water (400 c.c.) was added, stirring continued for 15 minutes, and the product isolated (2·35 g., or 99·0%) (Found : C, 63·0; H, 5·0%). The following results were obtained on thermal analysis.

Mixture taken, g.	Isomeride added, g.	F. p.	Composition, % (B): From graph.	Composition, % (B): Calc. from (*b*).
1·1836	—	115·2°	87 (*b*)	—
1·1836	1·2481 (B)	117·7	93·2	93·3
0·3823	0·8056 (A)	132·6	28·5	28·0

2-*Nitro*-4-o-*nitrobenzamidophenetole*, (C), prepared by the pyridine method, crystallised from methyl alcohol (charcoal) in pale yellowish-green, nacreous plates, m. p. 165—166° (Found : C, 54·5; H, 4·1; N, 12·9. $C_{15}H_{13}O_6N_3$ requires C, 54·4; H, 3·9; N, 12·7%). On exposure to light the crystals become pink. 3-*Nitro*-4-o-*nitrobenzamidophenetole*, (D), obtained similarly in 70% yield, crystallised from methyl alcohol (charcoal) in colourless, prismatic needles, m. p. 131—131·5° (Found : C, 54·2; H, 4·0%).

Mixtures of the Isomerides (C) *and* (D).—

By adding (C) *to* (D).

% (D)	100·0	94·5	87·05	82·5	76·1	69·5	63·8
F. p.	129·7°	126·7°	122·6°	119·9°	116·1°	112·6°	112·6°

By adding (D) *to* (C).

% (D)	40·4	32·9	28·1	22·3	17·1	5·4	0·0
F. p.	138·2°	144·0°	146·9°	150·3°	153·8°	161·0°	164·3°

Nitration of o-*Nitrobenz*-p-*phenetidide*.—The phenetidide (11·8 g.) was derived from *p*-phenetidine (9 g.) and *o*-nitrobenzoyl chloride (12 g.) in pyridine (100 c.c.) solution; it crystallised from methyl alcohol (charcoal) in long, silky, white needles, m. p. 170—171° (Found : C, 62·9; H, 5·1. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9%).

o-Nitrobenz-*p*-phenetidide (2·25 g.) was added to a mixture of boiled nitric acid (10 c.c.; *d* 1·41) and acetic acid (40 c.c.), cooled in melting ice, and stirred for 1 hour; the temperature did not rise above 3°. The product was isolated (2·55 g., or 97·9%) (Found : C, 54·2; H, 4·0%). The f. p. of this material was in a neighbourhood in which the determinations of f. p. were somewhat unsatisfactory. The nitration product (0·8397 g.) mixed with (D) (0·8366 g.) had f. p. 117·2°, corresponding with 78% of (D), and hence the original product contained 56·1% of (D). The nitration product (0·3856 g.) mixed with (C) (0·3977 g.) had f. p. 147·2°, corresponding with 27·8% of (D), and hence had initially contained 56·5% of (D).

2-*Nitro*-4-m-*nitrobenzamidophenetole*, (E), obtained in the usual manner, crystallised from ethyl acetate in matted, hair-like, lemon-yellow needles, m. p. 202—203° (Found: C, 54·4; H, 4·3. $C_{15}H_{13}O_6N_3$ requires C, 54·4; H, 3·9%). The isomeric 3-*nitro*-4-m-*nitrobenzamidophenetole*, (F), crystallised from alcohol in long, silky, golden needles, m. p. 157·5—158° (Found: C, 54·3; H, 4·0%).

Mixtures of the Isomerides (E) *and* (F).—

By adding (E) *to* (F).

% (F)	100·0	93·0	89·2	82·2	80·8	73·0
F. p.	157·4°	153·7°	151·6°	147·9°	147·1°	143·0°

By adding (F) *to* (E).

% (F)	67·0	60·6	52·2	47·4	41·25	34·5	26·3	9·3	0·0
F. p.	152·5°	161·6°	168·9°	172·4°	177·2°	182·4°	187·0°	197·2°	201·6°

Nitration of m-*Nitrobenz*-p-*phenetidide*.—The *m*-nitrobenzoylation of *p*-phenetidine (5 g.) in pyridine solution gave the phenetidide, which crystallised from alcohol in pale yellow needles (7·2 g.), m. p. 163·5—164° (Found: C, 63·1; H, 4·7. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9%). The nitration (of 2 g.) was carried out like that of the *o*-nitrobenz-*p*-phenetidide and the yield was 2·30 g. (99·4%) (Found: C, 54·4; H, 4·0; N, 12·9. Calc.: C, 54·4; H, 3·9; N, 12·7%). This crude product was stirred at 18° for 3 hours with methyl alcohol (40 c.c.), then collected, washed with methyl alcohol (10 c.c.), and dried (loss in weight in the process, 0·05 g.). In order to determine whether this washing produced a change in composition, a mixture of (E) (1·0 g.) and (F) (1·0 g.) was treated in exactly the same manner; the recovered material (1·94 g.) had f. p. 170·5°, corresponding to 50% of (F), so the alcohol had dissolved 0·03 g. of each isomeride. The washed nitration product had f. p. 146·0°, corresponding with 78·7% or 70·5% of (F). The nitration product (0·9583 g.) mixed with (F) (1·2589 g.) had f. p. 150·4°, corresponding to 87·0% of (F), and hence the initial content of (F) was 70%. A mixture of the nitration product (0·6811 g.) and (E) (0·6904 g.) froze at 182·4°, corresponding to 34·5% of (F), and hence the original product contained 69·5% of (F). Taking the mean, 70·0% of (F), and correcting for the solubility in methyl alcohol, we find that the crude nitration product contained 69·4% of (F).

2-*Nitro*-4-p-*nitrobenzamidophenetole*, (G), crystallised from alcohol in yellow needles, m. p. 208·5—209·5° (Found: C, 54·4; H, 3·9. $C_{15}H_{13}O_6N_3$ requires C, 54·4; H, 3·9%). 3-*Nitro*-4-p-*nitrobenzamidophenetole*, (H), crystallised from alcohol in flat, glistening, orange needles, m. p. 183·5—184·5° (Found: C, 54·5; H, 4·1%).

Mixtures of the Isomerides (G) *and* (H).—

By adding (G) *to* (H).

% (H)	100·0	95·5	89·9	82·3	74·3	69·3	62·7	58·1
F. p.	183·4°	181·2°	178·8°	175·3°	171·4°	169·0°	165·2°	*ca.* 167°

By adding (H) *to* (G).

% (H)	35·8	28·9	23·1	18·9	11·9	9·4	5·5	0·0
F. p.	185·9°	190·4°	194·0°	196·0°	200·2°	201·6°	203·9°	207·2°

Nitration of p-*Nitrobenz*-p-*phenetidide*.—The phenetidide crystallised from methyl alcohol in flat, pale yellow needles, m. p. 189—190° (Found: C, 63·0; H, 4·9. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9%). *p*-Nitrobenz-*p*-phenetidide (4 g.) was nitrated at 0° during 1 hour by means of a mixture of boiled nitric acid (20 c.c.; *d* 1·41) and acetic acid (80 c.c.). The product (yield, 99·6%) (Found: C, 54·4; H, 3·9; N, 13·0. Calc.: C, 54·4; H, 3·9; N, 12·7%) was washed with methyl alcohol, exactly as described above for the *m*-nitrobenznitrophenetidides, and 2·31 g. gave 2·20 g. of the dried, washed material. A mixture of (G) (1·0 g.) and (H) (1·0 g.) was washed in the standard manner and gave 1·90 g. of material, f. p. 174·5°, corresponding to 49·0% of (H); hence the methyl alcohol dissolved 0·03 g. of (G) and 0·07 g. of (H). The following results were obtained on analysis of the washed nitration product.

Mixture taken, g.	Isomeride added, g.	F. p.	Composition, % (H): From graph.	Calc. from (*c*).
1·0005	—	168·3°	68·5 (*c*)	—
1·0005	0·1249 (H)	170·2	72·1	72·0
0·9310	0·8504 (G)	185·3	36·7	35·8

After correction for the methyl alcohol washing, the crude nitration product is found to have contained 66·8% of (H).

Attempts were made to carry out a series of nitrations of the nitrobenzphenetidides in 60% aqueous nitric acid, but, owing to the fact that the nitro-derivatives covered the surface of the crystals, quantitative mono-nitration could not be secured.

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