cine and *tele* Substitutions in the Reaction of 2,3-Dinitroaniline with Secondary Amines†

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Summary Nucleophilic aromatic *cine* and *tele* substitutions taking place simultaneously, have been discovered in the reactions of 2,3-dinitroaniline with secondary amines; the *cine* substitution is novel.

In an earlier communication[1] we reported a novel *tele* substitution in the reaction of 4-alkoxy-2,3-dinitroanilines with secondary amines, the incoming amino group entering *para* to the position vacated by the outgoing nitro group. Recently Markwell[2] has discovered a *tele* substitution in the reactions of 2,3-dinitrophenol with secondary amines in which the incoming amino group enters *meta* with respect to the leaving nitro group. This latter communication prompts us to report our results from the reactions of 2,3-dinitroaniline with secondary amines.

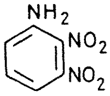
2,3-Dinitroaniline (**1**) was heated under reflux for 15 min with piperidine and, after chromatography on basic alumina, three isomeric nitropiperidinoanilines were obtained: a purple oil (compound '*A*') (29%), a purple solid of m.p. 102 °C (compound '*B*') (23%), and a scarlet solid of m.p. 92 °C (compound '*C*') (12%). Products '*A*' and '*C*' were shown by n.m.r. spectroscopy to be 1,2,3-trisubstituted benzene derivatives and hence must correspond to two of the following compounds: 2-nitro-3-*N*-piperidinoaniline (**2**), 2-nitro-6-*N*-piperidinoaniline (**3**), or 3-nitro-2-*N*-piperidinoaniline (**4**).

Diazotisation of '*A*' followed by reduction with 50% hypophosphorous acid gave 2-*N*-piperidinonitrobenzene, identical with an authentic sample[3] obtained by treatment of 1-chloro-2-nitrobenzene with piperidine; hence '*A*' must be either 2-nitro-3-*N*-piperidinoaniline or 3-nitro-2-*N*-piperidinoanaline. However, an authentic sample of the previously reported[4] 3-nitro-2-*N*-piperidinoaniline was prepared as an orange–brown oil (*cf.* compound '*A*') and was shown to possess completely different spectral properties (i.r., u.v. and n.m.r. spectra) from '*A*'; hence product '*A*' must be 2-nitro-3-*N*-piperidinoaniline (**2**).

Oxidation of compound '*C*' with peroxyformic acid, following the method of Meth-Cohn and Suschitzky[5] led to the formation of a cyclised product, a piperidino[1,2-*a*]-benzimidazole [in fact (**5**)], proving that the $-NH_2$ group is *ortho* to the piperidino substituent as in 2-nitro-6-*N*-piperidino aniline (**3**).

The ^1H n.m.r. spectrum of compound '*B*' clearly showed 1,2,4-coupling of aromatic hydrogens, hence this nitropiperidinoaniline is itself a 1,2,4-trisubstituted benzene derivative. Acid hydrolysis of the previously reported[6] 2-nitro-4-*N*-piperidinoacetanilide gave a compound identical with '*B*' (i.r. spectrum, mixed m.p.); hence compound '*B*' is 2-nitro-4-*N*-piperidinoaniline (**6**).

Whilst 2-nitro-3-*N*-piperidinoaniline (**2**) arises from 'normal' nucleophilic displacement of an activated $-NO_2$ group by piperidine and 2-nitro-6-*N*-piperidinoaniline (**3**) results from a *tele* substitution of the type previously observed,[1] 2-nitro-4-*N*-piperidinoaniline (**6**) is obtained by a novel *cine* displacement where the incoming piperidino group enters *ortho* with respect to the leaving nitro group. Similar results were obtained with the secondary amines, morpholine and *N*-methylpiperazine.



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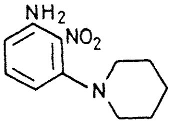

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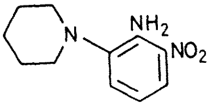

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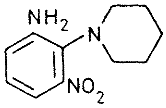

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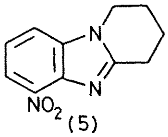

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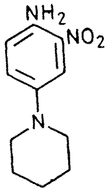

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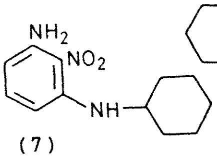

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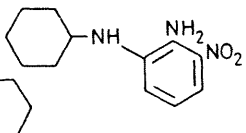

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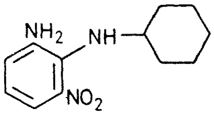

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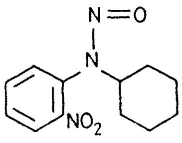

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When, however, 2,3-dinitroaniline (**1**) was treated in a similar manner with the primary amine cyclohexylamine only two isomeric cyclohexylnitroanilines [compounds '*D*' (4%) and '*E*' (67%)] were isolated after chromatography on basic alumina. These products were shown by n.m.r. spectroscopy to be 1,2,3-trisubstituted benzene derivatives

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† The term '*tele* substitution' is used in accordance with recent I.U.P.A.C. recommendations (Glossary of Terms used in Physical Organic Chemistry, ed. V. Gold, *Pure Appl. Chem.*, 1979, **51**, 1725) to denote reactions in which the entering group takes up a position more than one atom away from the atom to which the leaving group was attached. This term has also been used in the past to denote reactions in which the entering group takes up a position in a different substituent or different ring from that from which the leaving group has been displaced (see *e.g.* M. Novi, F. Sancassan, G. Guanti, and C. Dell'Erba, *J.C.S. Chem. Comm.*, 1979, 303).

and hence must correspond to two of the following compounds: 3-*N*-cyclohexylamino-2-nitroaniline (**7**), 2-*N*-cyclohexylamino-6-nitroaniline (**8**), or 2-*N*-cyclohexylamino-3-nitroaniline (**9**).

Compound '*D*' was found to be identical with an authentic sample of 2-*N*-cyclohexylamino-3-nitroaniline, prepared by the action of cyclohexylamine on 2,6-dinitrochlorobenzene, followed by partial reduction using the transfer-hydrogenation method of Entwistle *et al.*[7] Treatment of compound '*E*' with sodium nitrite in glacial acetic acid containing a trace of concentrated hydrochloric acid, followed by reduction with 50% hypophosphorous acid, gave the nitrosamine (**10**) identical with an authentic sample, prepared by the action of cyclohexylamine on 2-nitrochlorobenzene, followed by treatment with nitrous acid; hence '*E*' (different from '*D*') must be 3-*N*-cyclohexylamino-2-nitroaniline (**7**).

Thus treatment of 2,3-dinitroaniline (**1**) with cyclohexylamine (a primary amine) leads to the formation of the two possible 'normal' substitution products, the major one resulting from displacement of the 3-nitro substituent, the minor one affording the first known example of the displacement of a nitro group *ortho* to an amino group in a 2,3-dinitroaniline derivative; no *cine* or *tele* substitution products were observed. Similar results were obtained when aniline was used as the nucleophile.

When 2,3-dinitroaniline (**1**) was treated with the cyclic secondary amine, pyrrolidine, only the 'normal' (from displacement of the 3-nitro group) and the *cine* substitution products were formed; no product arising from a *tele* substitution could be detected by t.l.c. This anomalous behaviour of pyrrolidine has been noted by other workers,[8] this cyclic amine being intermediate in character between primary and 'true' secondary amines.

Satisfactory spectral and analytical data have been obtained for all new compounds.

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[1] K. G. Barnett, J. P. Dickens, and D. E. West, *J.C.S. Chem. Comm.*, 1976, 849.
[2] R. E. Markwell, *J.C.S. Chem. Comm.*, 1979, 428.
[3] J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051.
[4] K. H. Saunders, *J. Chem. Soc.*, 1955, 3275.
[5] O. Meth-Cohn and H. Suschitzky, *J. Chem Soc.*, 1963, 4666.
[6] D. P. Ainsworth and H. Suschitzky, *J. Chem. Soc.* (*C*), 1966, 111.
[7] I. D. Entwistle, R. A. W. Johnstone, and T. J. Povall, *J.C.S. Perkin I*, 1975, 1300.
[8] A. Heaton and M. Hunt, *J.C.S. Perkin I*, 1978, 1204.