A Novel *cine* Substitution in the Reaction of 4-Alkoxy-2,3-dinitroanilines with Secondary Amines

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Summary A novel nucleophilic aromatic *cine* substitution has been discovered in the reactions of 4-alkoxy-2,3-dinitroanilines with secondary amines.

In 1908 Blanksma[1] reported the reaction of 4-ethoxy-2,3-dinitroacetanilide with alcoholic ammonia under pressure to give 3-amino-4-ethoxy-2-nitroacetanilide; the work was later repeated by Reverdin and Roethlisberger[2] who concluded that the product was, in fact, 2-amino-4-ethoxy-3-nitroacetanilide. However, Bogert and Taylor[3] subsequently found that the 3-NO$_2$ group in 4-ethoxy-2,3-dinitroacetanilide was more susceptible to displacement by nucleophilic amines than that in the 2-position.

In the present work, 4-ethoxy-2,3-dinitroacetanilide was subjected to nucleophilic displacement reactions with various cyclic secondary amines. Thus, *e.g.*, when the substrate was heated under reflux for 4·5 h with piperidine and the reaction mixture poured into methanol–water (1 : 1), a solid was obtained which was recrystallised from light petroleum (b.p. 60—80 °C). Analysis and spectral data indicated that the product was an ethoxynitropiperidinoacetanilide (**1**).

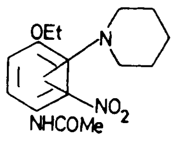
The aromatic proton signals in the ^{1}H n.m.r. spectrum were present as two separate doublets with a *J* value of 9 Hz, consistent with *ortho* coupling; this indicated that a normal substitution reaction had taken place.

In order to determine which of the nitro-groups had been displaced, the product was subjected to a catalytic hydrogenation, thus reducing NO$_2$ to NH$_2$. Subsequent treatment of the amino-derivative with acid (in this case 98% formic acid) under reflux for 3 h yielded a benzimidazole derivative, thus proving that the NH$_2$ group (and hence the NO$_2$ group in the displacement product) was *ortho* to the NHCOMe group. Hence the substitution product was (**2**). Similar displacement reactions on 4-ethoxy-2,3-nitroacetanilide with pyrrolidine, hexahydroazepine, morpholine, and *N*-methylpiperazine and on 4-methoxy-2,3-dinitroacetanilide with piperidine gave analogous products.

The intermediate involved for substitution at the 3-position could be stabilised by hydrogen bonding between the *ortho* NO$_2$ group and the NHCOMe, as shown in (**3**), whereas the corresponding intermediate for attack at the 2-position could not be stabilised in this way [see (**4**)] by hydrogen bonding.

When, however, such displacement reactions with secondary amines were carried out on the corresponding amine, *e.g.* (**5**; R = Et), they took an entirely different course. Thus, treatment of (**5**; R = Et) with morpholine at reflux temperature yielded a product which crystallised from light petroleum (b.p. 80—100 °C) as yellow-red needles, m.p. 85 °C (compound A) and whose i.r. spectrum indicated the presence of an NH$_2$ group (ν 3450 and 3360 cm^{-1}) and an NO$_2$ group (1510 and 1335 cm^{-1}). Analysis indicated that a nitro-group had been displaced and a morpholino group had been introduced into the molecule.

However, close investigation of the ^{1}H n.m.r. spectrum of A revealed that the aromatic protons had a splitting pattern whose *J* value was 3 Hz; this is consistent with *meta* interaction and not *ortho* interaction which leads to *J* values ranging from 7—10 Hz. Thus, simple displacement and products such as (**6**) and (**7**) are ruled out and this leaves (**8**) and (**9**) as possible structures for compound A.



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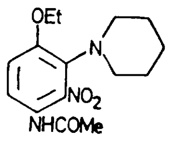

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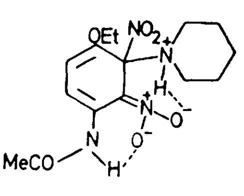

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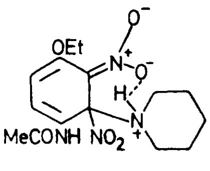

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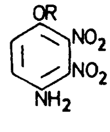

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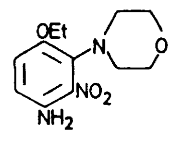

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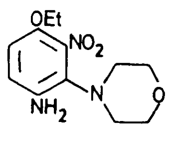

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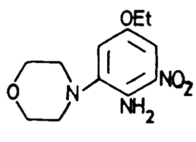

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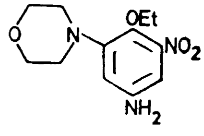

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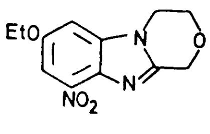

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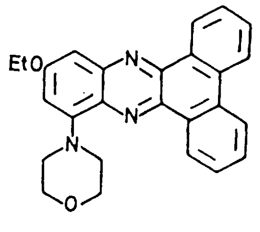

(11)

Treatment of A with performic acid, following the method of Meth-Cohn and Suschitzky,[4] led to the formation of a cyclised product, a morpholino [1,2-*a*]benzimidazole [in fact (**10**)], proving that the NH$_2$ group is *ortho* to the morpholino-substituent as in (**8**).

Conclusive proof that (**8**) is the structure was obtained by catalytically reducing the NO$_2$ group in A and treating the intermediate with 9,10-phenanthraquinone; this gave rise to a phenazine derivative [in fact (**11**)], showing that the NO$_2$ group in A is *ortho* to the NH$_2$ group.

Similar *cine* substitutions have been observed when (**5**; R = Me or Et) has been treated with other secondary amines such as piperidine and *N*-methylpiperazine. Satisfactory spectral and analytical data have been obtained for all new compounds.

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