

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 Blanksma¹ 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 Roethlisberger² who concluded that the product was, in fact, 2-amino-4-ethoxy-3-nitroacetanilide. However, Bogert and Taylor³ subsequently found that the 3-NO₂ 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).

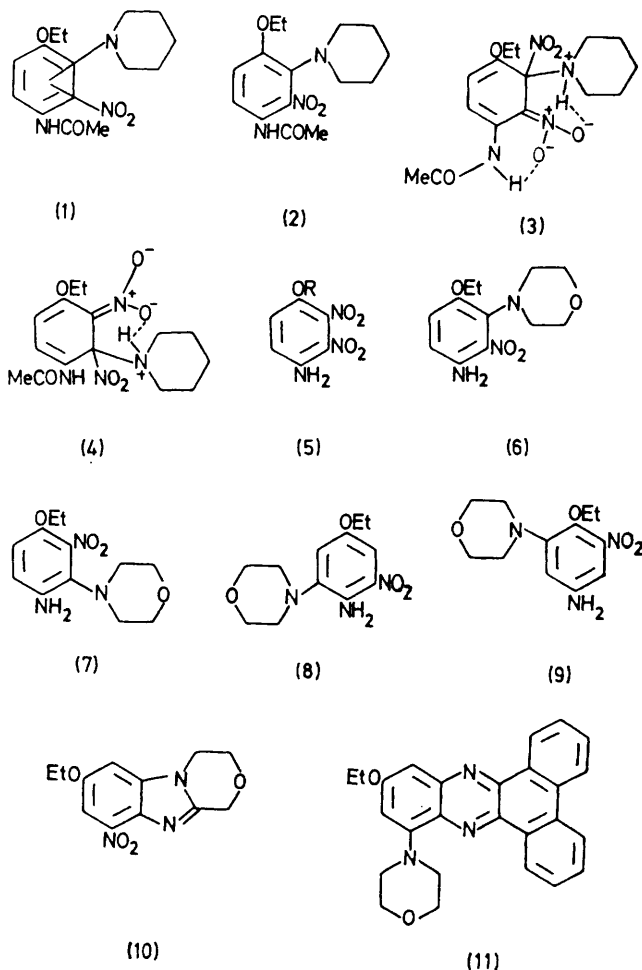
The aromatic proton signals in the ¹H n.m.r. spectrum were present as two separate doublets with a *J* value of 9 Hz, consistent with *ortho* coupling; this indicated that a normal substitution reaction had taken place.

In order to determine which of the nitro-groups had been displaced, the product was subjected to a catalytic hydrogenation, thus reducing NO₂ to NH₂. 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 NH₂ group (and hence the NO₂ 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* NO₂ 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 NH₂ group (ν 3450 and 3360 cm⁻¹) and an NO₂ 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 ¹H 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.



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 NH₂ group is *ortho* to the morpholino-substituent as in (8).

Conclusive proof that (8) is the structure was obtained by catalytically reducing the NO₂ group in A and treating the intermediate with 9,10-phenanthraquinone; this gave rise to a phenazine derivative [in fact (11)], showing that the NO₂ group in A is *ortho* to the NH₂ 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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³ M. T. Bogert and W. H. Taylor, *J. Amer. Chem. Soc.*, 1927, **49**, 1578.

⁴ O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, 1963, 4666.