Novel *cine* Substitution in the Reaction of 2,3-Dinitrophenol with Secondary Amines

By ROGER E. MARKWELL†
(*Roche Products Limited, Welwyn Garden City, Hertfordshire* AL7 3AY)

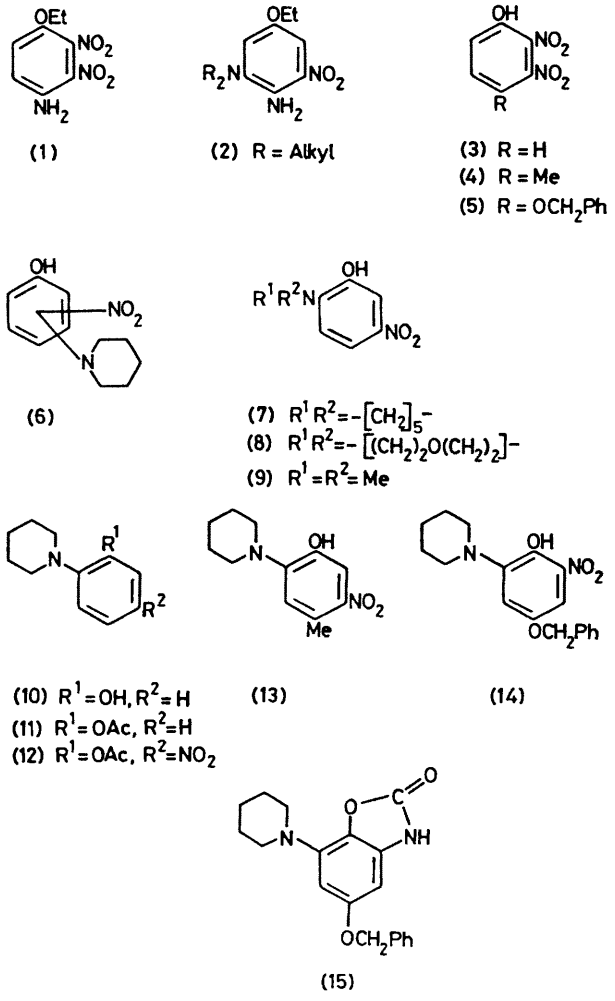
Summary A novel nucleophilic aromatic *cine* substitution has been discovered in the reactions of 2,3-dinitrophenol with secondary amines giving 2-(*NN*-dialkylamino)-5-nitrophenols.

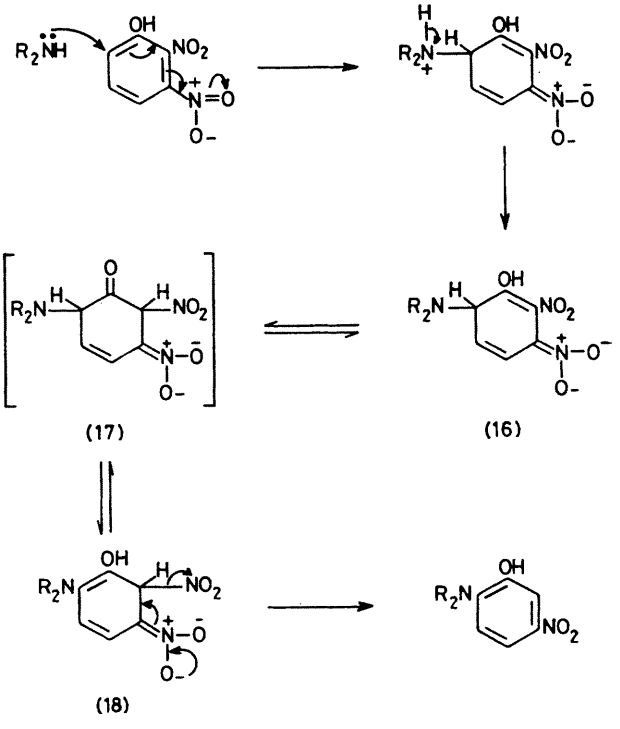
ALTHOUGH nucleophilic substitution reactions of aliphatic amines with 2,4- and 2,6-dinitro aromatic derivatives have been extensively studied,[1] there are few reports of reactions with 2,3-dinitro derivatives. As well as activating an

† *Present address:* Beecham Research Laboratories, Coldharbour Road, The Pinnacles, 4th Avenue, Harlow, Essex.

aromatic ring for nucleophilic substitution, a nitro group is itself an excellent nucleofuge. 1,2-Dinitrobenzene undergoes substitution reactions with a variety of nucleophiles with the loss of one of the nitro groups.[2] 4-Ethoxy-2,3-dinitroacetanilide undergoes nucleophilic substitution with secondary amines with direct displacement of the 3-nitro group,[3] but the corresponding aniline (**1**) undergoes *cine* substitution leading to nitroanilines with structure (**2**).[3] In this reaction the incoming amino group is situated *para* to the outgoing nitro group. We now report a novel *cine* substitution in the reactions of 2,3-dinitrophenol (**3**)[4] with secondary amines, in which the incoming amino group is situated *meta* to the outgoing nitro group.

When the phenol (**3**) was heated with an excess of piperidine, the product (58% yield after silica gel chromatography) was a nitropiperidinophenol (**6**). Its u.v. spectrum in 8 M H_2SO_4 [λ_{max} 228, 266, and 322 nm (ϵ 9200, 6650, and 2300, respectively)] indicated[5] that the phenolic hydroxy and nitro groups were *meta*-orientated, and structure (**7**) was considered the most likely on the basis of the n.m.r. spectrum [δ {$(CD_3)_2SO$} 6·74 (1H, d, J 10 Hz, 3-H), 7·42 (1H, d, J 2 Hz, 6-H), and 7·48 (1H, dd, J 10 and 2 Hz, 4-H)]. This structure was confirmed by synthesis. Acetylation of 2-piperidinophenol (**10**)[6] afforded the acetate (**11**) which was nitrated (fuming nitric acid in acetic acid at 15 °C) giving the nitro derivative (**12**) as the major product (75%). Hydrolysis of (**12**) (5% sodium hydroxide at 100 °C) gave the phenol (**7**) (80%), identical with the product from the reaction of (**3**) with piperidine.





SCHEME

The results of treating several 2,3-dinitrophenols with aliphatic amines are summarised in the Table. In contrast to secondary amines, primary amines were unreactive.

TABLE. Reactions of primary and secondary amines with 2,3-dinitrophenols.[a]

Dinitrophenol	Amine	Solvent	Time/h	Product	Yield[d]/%	M.p./°C
(3)	Piperidine	—	2	(7)	58	76—77
(3)	Morpholine	—	4	(8)	64	155—156
(3)	*NN*-Dimethylamine	MeOH	14	(9)	54	77—78[e]
(3)	Methylamine	EtOH–Pr^{i}OH	20	(3)[b]	94	163—165
(3)	Isopropylamine	Pr^{i}OH	15	(3)[c]	95	126—127
(4)	Piperidine	—	22	(13)	52	86—87
(5)	Piperidine	—	12	(14)	54	88—89

[a] Bath temperature 100—110 °C. [b] As methylamine salt. [c] As isopropylamine salt. [d] Yield of purified material after one crystallisation. [e] Lit. m.p. 79 °C (ref. 5).

A 4-methyl substituent [*viz.* compound (**4**)[7]] had little effect on the reaction, but a 4-benzyloxy substituent [*viz.* compound (**5**)‡] changed the course of the reaction giving the phenol (**14**) [δ ($CDCl_3$) 6·75 (1H, d, *J* 3 Hz, 5-H) and 7·10 (1H, d, *J* 3 Hz, 3-H)] on reaction with piperidine. Hydrogenation of (**14**) over Raney nickel, followed by reaction with phosgene in acetic acid furnished the benzoxazolinone (**15**) (ν_{max} 1798 cm^{-1}) thus proving that the nitro and phenolic hydroxy groups in (**14**) were *ortho*-orientated.

A possible mechanism for formation of the 2-(*NN*-dialkylamino)-5-nitrophenols is outlined in the Scheme. Attack of the amine at C-6 would give the stabilised intermediate (**16**), which could undergo a 1,3-proton transfer *via* the oxo-tautomer (**17**). Loss of the 2-nitro group (as NO_2^-) from (**18**) would give the observed products. Evidence for the intermediacy of an oxo-intermediate such as (**17**), comes from the observation that 2,3-dinitrophenyl ethers do not undergo analogous *cine*-substitution reactions with aliphatic amines. Primary amines cause direct displacement of the 2-nitro group giving high yields of the corresponding 2-alkylamino-3-nitrophenyl ethers,[8,9] whereas piperidine reacts to give 3-nitro-5-piperidinophenyl ethers.[9] Satisfactory spectral and analytical data have been obtained for all new compounds.

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