Synthesis of *N*-Alkyl-2-(4-nitrophenoxy)-ethanamines. Intermediates in Desulphonative Double Smiles' Rearrangement of *N*-Alkyl-*N*-(2-hydroxyethyl)-4-nitrobenzenesulphonamides

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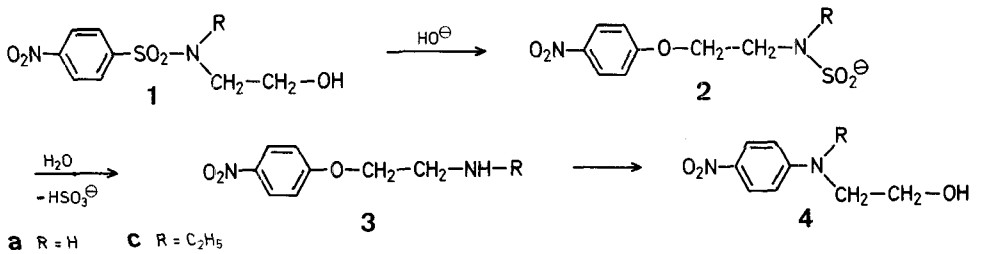
In 1968, Kleb suggested[1] that the desulphonation (**1**→**4**) of *N*-alkyl-*N*-(2-hydroxyethyl)-4-nitrobenzenesulphonamides (**1**), which occurs in aqueous alkali, proceeds via intermediate *N*-alkyl-2-(4-nitrophenoxy)-ethanamines (**3**). It was, however, realised that 2-phenoxyethanamines (**3**) could not be prepared from the corresponding sulphonamides (**1**) under these conditions since their subsequent rearrangement to yield 2-(*N*-alkyl-4-nitroanilino)-ethanols (**4**) occurs readily. The corresponding "double Smiles' rearrangement" sequence has been the topic of a recent kinetic investigation[2] and may be outlined as follows:

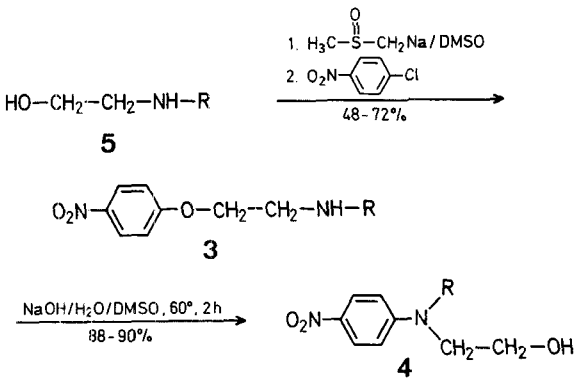


a R = H **c** R = C_2H_5
b R = CH_3 **d** R = *i*-C_3H_7

Kleb also pointed out that compounds synthesised by Weddige[3] and believed to be 2-(2- and 4-nitrophenoxy)-ethanamines are in fact the products of their subsequent Smiles' rearrangement; this is not surprising since the attempted synthesis of these reactive phenoxyamines involve heating the corresponding 2-bromoethyl ether with alcoholic ammonia at 100–120° for several hours. Smiles' rearrangements of 2-(nitrophenoxy)-alkanamines have also confounded the attempts of Caldwell and Schweiker[4] to obtain 2-hydroxy-1-(2- and 4-nitrophenoxy)-propanamines by hydrolysis of the corresponding 2-acetoxy-1-(2- and 4-nitrophenoxy)-3-phthalimidopropanes; 1-(2- and 4-nitroanilino)-2,3-propanediols were instead obtained.

N-Alkyl-2-(di- and tri-nitrophenoxy)-ethanamines have been synthesised[5], as their ammonium salts, by acidifying the corresponding Meisenheimer complexes which form readily in ethanol and in aqueous dimethyl sulphoxide. This procedure is, however, inapplicable to less activated mononitro systems.

In this paper, we report the first successful method of synthesis of *N*-alkyl-2-(4-nitrophenoxy)-ethanamines (**3a–d**) and also an effective method for their conversion to the corresponding aminoalcohols **4a–d**. Syntheses of **3a–d** have been achieved by a procedure whereby the corresponding 2-alkylaminoethanol is caused to react, as an oxygen nucleophile, with *p*-chloronitrobenzene under conditions which are relatively unconducive to subsequent Smiles' rearrangement (**3**→**4**). Thus, preferential nucleophilic attack by oxygen (rather than the amino group) is ensured by prior complete conversion of the aminoalcohol to its conjugate oxyanion base (by reaction with NaH/DMSO) while use of a dipolar aprotic solvent favours this intermolecular anionic reaction relative to subsequent intramolecular rearrangement of the product phenoxyethanamine (**2**).



Preparation of *N*-Alkyl-2-(4-nitrophenoxy)-ethanamines (3a–d); General Procedure:

Reaction of sodium hydride (0.01 mol) with dimethyl sulphoxide (5 ml) is effected during 30 min at 40° with stirring. The 2-alkylaminoethanol is added to the solution of DMSO anion at room temperature and *p*-chloronitrobenzene (0.01 mol) is added 10 min later, with stirring. Formation of **3** is monitored by U.V. spectroscopy. After 20 min, the reaction mixture is diluted with dichloromethane (100 ml), washed with water, and then extracted twice with 4 *M* hydrochloric acid (100 ml). The acid extracts are bulked and washed once with dichloromethane. Ethyl acetate (125 ml) is then added and the mixture is cooled to 6–8° before the aqueous layer is adjusted to pH 11 by gradual addition of 8 *M* aqueous sodium hydroxide, with vigorous stirring. The organic layer is

washed twice with water, dried with magnesium sulphate, and rotary-evaporated at 35°. The resultant oil is induced to crystallise at low temperature following removal of solvent traces under vacuum (Recrystallisation techniques were not perfected).

2-(4-Nitrophenoxy)-ethanamine (**3**, R = H); yield: 72%; m.p. 29–30°.

$C_8H_{10}N_2O_3$	calc.	C 52.84	H 5.53
(182.1)	found	53.14	5.73

U.V. (CH_2Cl_2): λ_{max} = 312 nm.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.20 (d, 2H, J = 9.3 Hz); 6.98 (d, 2H, J = 9.3 Hz); 4.1 (t, 2H, J = 5.3 Hz); 3.25 ppm (t, 2H, J = 5.3 Hz).

N-*Methyl-2-(4-nitrophenoxy)-ethanamine* (**3**, R = CH_3); yield: 48%; m.p. 33–34°.

$C_9H_{12}N_2O_3$	calc.	C 55.07	H 6.17
(196.1)	found	55.16	6.16

U.V. (CH_2Cl_2): λ_{max} = 312 nm.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.22 (d, 2H, J = 9.3 Hz); 7.00 (d, 2H, J = 9.3 Hz); 4.2 (t, 2H, J = 5.3 Hz); 3.16 ppm (t, 2H, J = 5.3 Hz).

N-*Ethyl-2-(4-nitrophenoxy)-ethanamine* (**3**, R = C_2H_5); yield: 53%; m.p. 13–14°.

$C_{10}H_{14}N_2O_3$	calc.	C 57.12	H 6.72
(210.0)	found	57.16	7.25

U.V. (CH_2Cl_2): λ_{max} = 313 nm.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.23 (d, 2H, J = 9.3 Hz); 7.00 (d, 2H, J = 9.3 Hz); 4.23 (t, 2H, J = 5.3 Hz); 3.28–2.58 (m, 4H); 1.18 ppm (t, 3H, J = 6.6 Hz).

N-*Isopropyl-2-(4-nitrophenoxy)-ethanamine* (**3**, R = *i*-C_3H_7); yield: 50%; m.p. 9–10°.

$C_{11}H_{16}N_2O_3$	calc.	C 58.91	H 7.20
(224.1)	found	59.05	7.07

U.V. (CH_2Cl_2): λ_{max} = 319 nm.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.10 (d, 2H, J = 9.3 Hz); 7.00 (d, 2H, J = 9.3 Hz); 4.13 (t, 2H, J = 5.3 Hz); 3.23–2.63 (m, 3H); 1.10 ppm (d, 6H, J = 6.6 Hz).

2-(*N*-Alkyl-4-nitroanilino)-ethanols (4) from *N*-Alkyl-2-(4-nitrophenoxy)-ethanamines (3):

The *N*-alkyl-2-(4-nitrophenoxy)-ethanamine (**3**) is heated with excess 1 *N* aqueous sodium hydroxide in 40% dimethyl sulphoxide at 60° for 2 h. Upon completion of the reaction, dichloromethane is added, the organic layer is washed with water, dried, and evaporated.

2-(4-Nitroanilino)-ethanol (**4**, R = H); yield: 90%, m.p. 109° (Ref.[1], m.p. 110°.

U.V. (CH_2Cl_2): λ_{max} = 395 nm.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.08 (d, 2H, J = 9.3 Hz); 6.58 (d, 2H, J = 9.3 Hz); 3.9–3.3 ppm (m, 4H).

2-(N-Methyl-4-nitroanilino)-ethanol (**4**, R = CH_3); yield: 88%; m.p. 104° (Ref.[1], m.p. 104°).

U.V. (CH_2Cl_2): λ_{max} = 405 nm.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.05 (d, 2H, J = 9.3 Hz); 6.68 (d, 2H, J = 9.3 Hz); 4.05–3.52 (m, 4H); 3.22 ppm (s, 3H).

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