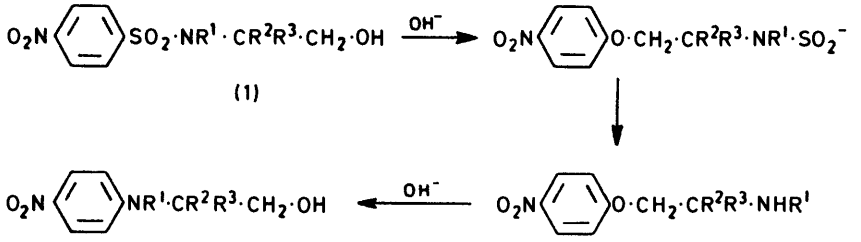
Synthesis of 2-(*p*-Nitrophenoxy)ethylamine and its *N*-Alkyl, *N*-Aryl, and 1,1-Dimethyl Derivatives

By **Anthony C. Knipe,* Narayan Sridhar,** and **Joseph Lound-Keast,** School of Physical Sciences, The New University of Ulster, Coleraine, Northern Ireland BT52 1SA

2-(*p*-Nitrophenoxy)ethylamines have been prepared by reactions of 2-aminoethanols (as oxygen nucleophiles) with *p*-chloronitrobenzene and by base-catalysed Smiles rearrangement of *N*-(2-hydroxyethyl)-*p*-nitrobenzenesulphonamides in aqueous acetone or in methylene chloride containing 18-crown-6-complexed potassium hydroxide.

It has been suggested [1] that the conversion of a series of *N*-(2-hydroxyethyl)-*p*-nitrobenzenesulphonamides (1) into the corresponding 2-(*N*-alkyl-*p*-nitroanilino)ethanols (3) proceeds in refluxing aqueous sodium hydroxide by a double Smiles rearrangement sequence (Scheme) *via* an intermediate 2-(nitrophenoxy)ethylamine (2). The conditions employed are however particularly conducive to rearrangement of the intermediate (2), which therefore cannot be isolated.

There have been several other unsuccessful attempts to isolate 2-(nitrophenoxy)ethylamines: thus, Kleb has pointed out that compounds which Weddige [2] claimed to be *o*- and *p*-nitrophenoxy-ethylamines had, in fact, also undergone rearrangement to 2-(*o*- and *p*-nitroanilino)-ethanols, respectively; this is not surprising since the preparative method involved heating the corresponding



R^N = H unless otherwise stated

b; R^1 = Me d; R^1 = Pr^i f; R^1 = Ph h; R^1 = *p*-MeO·C_6H_4 j; R^1 = *p*-Cl_6H_4
c; R^1 = Et e; R^2 = R^3 = Me g; R^1 = *p*-MeC_6H_4 i; R^1 = *m*-MeO·C_6H_4 k; R^1 = *m*-ClC_6H_4

[1] K. G. Kleb, *Angew. Chem. Internat. Edn.*, 1968, **7**, 251.
[2] A. Weddige, *J. prakt. Chem.*, 1881, **24**, 247, 254.

2-bromoethyl ether with alcoholic ammonia for several hours. Furthermore, attempts by Caldwell and Schweiker [3] to prepare 1-(*o*- and *p*-nitrophenoxy)-2-hydroxypropylamines by hydrolysis of the corresponding 1-(*o*- and *p*-nitrophenoxy)-2-acetoxy-3-phthalimidopropanes also failed because the amino-ethers rearranged to give 1-(*o*- and *p*-nitroanilino)propane-2,3-diols.

More recently hydrochloride salts of *N*-methyl-2-(di- and tri-nitrophenoxy)ethylamines were synthesised [4] under kinetically controlled conditions; this was achieved by rapid acidification of the cyclic Meisenheimer complexes formed upon reaction of *N*-methyl-*N*-2-hydroxyethyl-nitroarylamines with potassium hydroxide in ethanol, but the method is applicable only to di- and tri-nitro systems.

In this paper, we report the first successful syntheses of 2-(*p*-nitrophenoxy)ethylamines (2a—k) and confirm their intermediacy in the corresponding double Smiles rearrangements (1) ⟶ (3); an appropriate choice amongst the three alternative synthetic procedures is dependent upon the nature of the *N*-substituent (R^1).

RESULTS AND DISCUSSION

Method a. Kinetic studies of the desulphonative double Smiles rearrangement of *N*-alkyl-*N*-(2-hydroxyethyl)-*p*-nitrobenzenesulphonamides [5] have revealed that the intermediates (2a—e) are moderately stable at room temperature in dipolar aprotic solvents, even in the presence of strong base. This observation has been used to advantage in syntheses of (2a—e) whereby the appropriate 2-alkylaminoethanol reacts, as an oxygen nucleophile, with *p*-chloronitrobenzene in dimethyl sulphoxide; the aryl halide is added once the amino-alcohol has been converted into the active conjugate oxyanion base upon dissolution in dimethyl sulphoxide containing 1 equiv. of sodium methylsulphinylmethanide.

Under the same conditions 2-anilinoethanol gives 2-(*N*-phenyl-*p*-nitroanilino)ethanol (3f). This could occur either by formation and subsequent rearrangement of the phenoxyethylamine (2f) or by direct intermolecular reaction of the amino-alcohol as a nitrogen (rather than an oxygen) nucleophile. The former interpretation is supported by the failure of 2-phenylethylamine to react with *p*-chloronitrobenzene under the same conditions; furthermore, our kinetic studies [5] have revealed that the arylamino-ethers (2f—k) are unstable, relative to their *N*-alkyl counterparts, in dimethyl sulphoxide–base systems.

Method b. Our kinetic investigations [6] have established that the desulphonative double Smiles rearrangement of *N*-arylsulphonamides (1f—k), which occurs in aqueous alkali at 60 °C, proceeds by two distinct steps; thus, the sulphonamides (1f—k) are completely converted into the amines (2f—k) before much subsequent rearrangement to (3f—k) has occurred. Effective synthesis of the intermediates (2f—k) was therefore facilitated by a knowledge of the optimum reaction times for their formation in high yield. Furthermore, during reactions conducted at 60 °C in aqueous alkali containing 30% (v/v) acetone,* the amino-ethers separate as yellow oils which crystallise on cooling. Application of the above technique to the preparation of the phenoxy-amines (2a—e) (R^1 = H or alkyl) is, however, precluded by their greater solubility and their tendency to rearrange more rapidly than they form under the reaction conditions.

Method c. Since the work of Pederson,[7] crown ethers have been extensively used to form complexes with alkali metal cations and thereby to enhance both the reactivity of the anion and the solubility of the alkali metal salts in organic solvents. It was therefore expected that the first Smiles rearrangement (1) ⟶ (2) of the *N*-alkylsulphonamides (1b, c, and f) could be effected in methylene chloride containing 18-crown-6-complexed potassium hydroxide. This anionic rearrangement is expected to proceed by the formation of a spiro-Meisenheimer intermediate; formation of the transition state during the rate-determining cyclisation should involve dispersal of the charge of the oxyanion nucleophile and the reaction should therefore be facilitated by change to a weakly polar solvent. In contrast, the change from water to a less polar solvent should retard formation of the dipolar spiro-bicyclic transition state during subsequent Smiles rearrangement of the un-ionised amino-ether (2) to the amino-alcohol (3). This procedure has been used successfully to synthesise the amino-ethers (2b, c, and f) but is inapplicable to ionisable substrates (1) where R^1 = H; thus, the limited solubility of (1a) or of its potassium salt apparently precluded its rearrangement under the reaction conditions.

EXPERIMENTAL

A Perkin-Elmer R12A (60 MHz) instrument was used to record n.m.r. spectra (Me_4Si as internal standard). Perkin-Elmer 402 and Unicam SP 1700 spectrophotometers were used to record u.v.–visible spectra.

N-Substituted *N*-(2-hydroxyethyl)-*p*-nitrobenzenesulphonamides (1a—f) were prepared by a general procedure described elsewhere.[6] Dimethyl sulphoxide was stirred with calcium hydride at room temperature and then distilled under reduced pressure. 18-Crown-6 was prepared by the procedure of Gokel *et al.*[8] Commercial samples of *N*-substituted aminoethanols were distilled immediately before use.

Method a.—Sodium hydride (0.5 g of 50% suspension; 0.01 mol) was stirred with dimethyl sulphoxide (5 cm^3) at 40 °C until a homogeneous solution was obtained (15—20 min). The solution was cooled to room temperature and the appropriate amino-alcohol (0.01 mol) was added.

* Acetone was added in order to increase the solubility of the sulphonamide.

[3] W. T. Caldwell and G. C. Schweiker, *J. Amer. Chem. Soc.*, 1952, **74**, 5187.

[4] C. F. Bernasconi, R. H. De Rossi, and C. L. Gehriger, *J. Org. Chem.*, 1973, **38**, 2838.

[5] A. C. Knipe and J. Lound-Keast, unpublished results.

[6] A. C. Knipe, *Tetrahedron Letters*, 1975, 3563; *J.C.S. Perkin II*, 1976, 1471.

[7] C. J. Pederson, *J. Amer. Chem. Soc.*, 1967, **89**, 2495.

[8] G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, 1974, **39**, 2445.

After *ca.* 10 min *p*-chloronitrobenzene (1.58 g, 0.01 mol) was added and the formation of the amine (2) ($\lambda_{max.}$ *ca.* 310 nm) was periodically monitored by u.v. spectrophotometry. Methylene chloride (125 cm^3) was added on completion of the reaction, and the solution was washed with water; the amino-ether was then extracted into a layer of hydrochloric acid (4N; 100 cm^3), which was subsequently washed once with methylene chloride. Ethyl acetate (125 cm^3) was added to the acidic extract, and the mixture was cooled to 6—8 °C and gradually basified with sodium hydroxide (8N), with stirring. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated at 35 °C. Solvent traces were removed under vacuum, and the resultant oil was cooled in ice to induce crystallisation. Attempted recrystallisations were unsatisfactory. The following compounds were synthesised by the above procedure: 2-(p-*nitrophenoxy)ethylamine* (2a) (1.31 g, 72%), m.p. 29—30 °C (Found: C, 53.1; H, 5.7. $C_8H_{10}N_2O_3$ requires C, 52.8; H, 5.5%), δ ($CDCl_3$) 8.20 (2 H, d, *J* 9.3 Hz), 6.98 (2 H, d, *J* 9.3 Hz), 4.1 (2 H, t, *J* 5.3 Hz), and 3.25 (2 H, t, *J* 5.3 Hz); $\lambda_{max.}$ (CH_2Cl_2) 312 nm; N-*methyl*-2-(p-*nitrophenoxy)ethylamine* (2b) (0.94 g, 48%), m.p. 33—34 °C (Found: C, 55.2; H, 6.2. $C_9H_{12}N_2O_3$ requires C, 55.1; H, 6.2%); δ ($CDCl_3$) 8.22 (2 H, d, *J* 9.3 Hz), 7.00 (2 H, d, *J* 9.3 Hz), 4.2 (2 H, t, *J* 5.3 Hz), 3.16 (2 H, t, *J* 5.3 Hz), and 2.56 (3 H, s); $\lambda_{max.}$ (CH_2Cl_2) 312 nm; N-*ethyl*-2-(p-*nitrophenoxy)ethylamine* (2c) (1.11 g, 53%), m.p. 13—14 °C (Found: C, 57.2; H, 7.25. $C_{10}H_{14}N_2O_3$ requires C, 57.1; H, 6.7%); δ ($CDCl_3$) 8.23 (2 H, d, *J* 9.3 Hz), 7.00 (2 H, d, *J* 9.3 Hz), 4.23 (2 H, t, *J* 5.3 Hz), 3.28—2.58 (4 H, m), and 1.18 (3 H, t, *J* 6.6 Hz); $\lambda_{max.}$ (CH_2Cl_2) 313 nm; N-*isopropyl*-2-(p-*nitrophenoxy)ethylamine* (2d) (0.90 g, 40%), m.p. 9—10 °C (Found: C, 59.05; H, 7.05. $C_{11}H_{16}N_2O_3$ requires C, 58.9; H, 7.2%); δ ($CDCl_3$) 8.10 (2 H, d, *J* 9.3 Hz), 7.00 (2 H, d, *J* 9.3 H), 4.13 (2 H, t, *J* 5.3 Hz), 3.23—2.63 (3 H, m), and 1.10 (6 H, d, *J* 6.6 Hz); $\lambda_{max.}$ (CH_2Cl_2) 319 nm (log ε 4.13); * 1,1-*dimethyl*-2-(p-*nitrophenoxy)ethylamine* (2e) (1.15 g, 55%), m.p. 22.5—23.5 °C (Found: C, 57.0; H, 7.0. $C_{10}H_{14}N_2O_3$ requires C, 57.1; H, 6.7%); δ ($CDCl_3$) 7.97 (2 H, d, *J* 9.3 Hz), 6.84 (2 H, d, *J* 9.3 Hz), 3.68 (2 H, s), and 1.18 (6 H, s); $\lambda_{max.}$ (CH_2Cl_2) 314 nm.

Method b.—A solution of *N*-aryl-(2-hydroxyethyl)-*p*-nitrobenzenesulphonamide (0.004 mol) in aqueous sodium hydroxide (0.5N; 200 cm^3) containing 30% acetone (v/v) was refluxed for 3 h. The *N*-arylphenoxyethylamine, which separated as an orange oil, was recrystallised from benzene. The following compounds were obtained by this procedure: N-*phenyl*-2-(p-*nitrophenoxy)ethylamine* (2f) (0.38 g, 37%), m.p. 107 °C (Found: C, 65.0; H, 5.5. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.5%); δ ($CDCl_3$) 8.12 (2 H, d, *J* 9.0 Hz),7.40—6.50 (5 H, m), 6.67 (2 H, d, *J* 9.0 Hz), 4.25 (2 H, t, *J* 5.0 Hz), and 3.60 (2 H, t, *J* 9.0 Hz); $\lambda_{max.}$ (CH_2Cl_2) 315 nm (log ε 4.16); * N-p-*tolyl*-2-(p-*nitrophenoxy)ethyl*-p-*toluidine* (2 g) (0.68 g, 62%), m.p. 129 °C (Found: C, 65.7; H, 5.8. $C_{15}H_{16}N_2O_3$ requires C, 66.2; H, 5.9%); δ ($CDCl_3$) 8.16 (2 H, d, *J* 9.0 Hz), 7.01 (2 H, d, *J* 9.0 Hz), 6.94 (2 H, d, *J* 9.0 Hz), 6.59 (2 H, d, *J* 9.0 Hz), 4.23 (2 H, t, *J* 6.0 Hz), 3.58 (2 H, t, *J* 6.0 Hz), and 2.26 (3 H, s); $\lambda_{max.}$ (CH_2Cl_2) 310 nm; N-p-*methoxyphenyl*-2-(p-*nitrophenoxy)ethylamine* (2h) (0.56 g, 49%), m.p. 104 °C (Found: C, 62.3; H, 5.8. $C_{15}H_{16}N_2O_4$ requires C, 62.5; H, 5.6%); δ ($CDCl_3$) 8.10 (2 H, d, *J* 9.0 Hz), 7.20 (2 H, d, *J* 9.0 Hz), 7.20—6.40 (6 H, m), 4.13 (2 H, t, *J* 5.0 Hz), and 3.6 (5 H, m); $\lambda_{max.}$ (CH_2Cl_2) 315 nm; N-m-*methoxyphenyl*-2-(p-*nitrophenoxy)ethylamine* (2i) (0.84 g, 73%), m.p. 95 °C (Found: C, 62.4; H, 5.65. $C_{15}H_{16}N_2O_4$ requires C, 62.5; H, 5.6%); δ ($CDCl_3$) 8.12 (2 H, d, *J* 9.0 Hz), 7.20—6.10 (6 H, m), 4.10 (2 H, t, *J* 5.0 Hz), and 3.60 (5 H, m); $\lambda_{max.}$ (CH_2Cl_2) 305 nm: N-p-*chlorophenyl*-2-(p-*nitrophenoxy)ethylamine* (2j) (0.64 g, 55%), m.p. 100 °C (Found: C, 57.6; H, 4.7. $C_{14}H_{13}ClN_2O_3$ requires C, 57.4; H, 4.5%); δ ($CDCl_3$) 8.13 (2 H, d, *J* 9.0 Hz), 7.30—6.40 (6 H, m), 4.22 (2 H, t, *J* 5.0 Hz), and 3.60 (2 H, t, *J* 5.0 Hz); $\lambda_{max.}$ (CH_2Cl_2) 308 nm; N-m-*chlorophenyl*-2-(p-*nitrophenoxy)-ethylamine* (2k) (0.92 g, 79%), m.p. 101 °C (Found: C, 56.95; H, 4.6. $C_{14}H_{13}ClN_2O_3$ requires C, 57.4; H, 4.5%); ($CDCl_3$) 8.17 (2 H, d, *J* 9.0 Hz), 7.40—6.40 (6 H, m), 4.27 (2 H, t, *J* 5.0 Hz), and 3.65 (2 H, t, *J* 5.0 Hz); $\lambda_{max.}$ (CH_2Cl_2) 310 nm.

Method c.—The *N*-substituted *N*-(2-hydroxyethyl)-*p*-nitrobenzenesulphonamide (0.1 g) and the macrocyclic polyether 18-crown-6 (0.1 g) were dissolved in methylene chloride (2 cm^3), and a pellet of potassium hydroxide was added. The mixture was stirred continuously and the formation of the amine (2) ($\lambda_{max.}$ *ca.* 310 nm) was monitored periodically by u.v. spectrophotometry. Once the maximum concentration of (2) had been attained, the pellet of potassium hydroxide was removed; the solution was diluted with methylene chloride and extracted with hydrochloric acid (4N; 20 cm^3). *N*-Methyl (2b) (0.049 g, 70%) and *N*-ethyl-2-(*p*-nitrophenoxy)ethylamine (2c) (0.061 g, 80%) were prepared by this procedure and subsequently obtained from the corresponding acidic extracts as described for method a. The weak basicity of *N*-phenyl-2-(*p*-nitrophenoxy)ethylamine (2f) precluded its effective extraction into 4N-hydrochloric acid; the reaction mixture was alternatively diluted with methylene chloride, washed with water, dried ($MgSO_4$), and evaporated; 18-crown-6 was then removed by trituration with a 50 vol % solution of light petroleum in carbon tetrachloride to yield (2f) (0.023 g, 28%).

This work was supported by the S.R.C.

[6/1636 *Received, 23rd August,* 1976]

* Although log ε values have been determined only for (2d) (*N*-alkyl) and (2f) (*N*-aryl), it is clear that for the series of phenoxyethylamines (2a—k) log ε is *ca.* 4.14 and 310 nm.