Cytotoxic Compounds. Part 21.[1] Chloro-, Methoxy-, and Methoxycarbonyl-derivatives of (Bis-2-chloroethylamino)-phenols and -anilines

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New or improved syntheses are described of some *NN*-bis-2-chloroethylanilines carrying both a free phenolic group and a methoxycarbonyl ring substituent.

A study has been made of the hydroxyethylation, with ethylene oxide, of a variety of chloro-, methoxy-, and methoxycarbonyl-nitroanilines, and of methoxy- and methoxycarbonyl-*N*-acylphenylenediamines. Bishydroxyethylation was inhibited by an *o*-methoxycarbonyl group and by an *o*- or *p*-nitro-group, but otherwise the *NN*-bis-2-hydroxyethyl derivatives were obtained and subsequently converted into the *NN*-bis-2-chloroethyl compounds. Reduction of the nitro-group, or hydrolysis of the acylamino-group, in these dichlorides led to *NN*-bis-2-chloroethylanilines carrying both a free amino-group and also a methoxycarbonyl-, methoxy-, or chloro-group as ring substituents.

The ring-substituted (bis-2-chloroethylamino)-phenols or -anilines are precursors of mustard urethanes having potential importance as anti-tumour agents.

In Part 17 [2] attention was drawn to the particular chemotherapeutic advantage shown by aromatic nitrogen mustards of types (1) and (2), the most favourable antitumour activity (chemotherapeutic indices in the range 50—150) being shown [3] by those carbamates in which the substituent in the non-mustard ring is chloro, methoxy, or methoxycarbonyl.† No mustard carbamates are known in which an additional substituent is present in the *mustard* aryl ring, and our objective was to synthesise suitably functionalised aryl mustards from which such urethanes could be prepared. Many *NN*-bis-2-chloroethylanilines, carrying two additional ring substituents, have been described,‡ but very few include a phenolic [6-8] or amino-group [9,10] through which, by reaction with an isocyanate or a chloroformate respectively, the carbamate function could be generated.

In the original synthesis [2,6] of the phenolic mustard (4) the yield from the corresponding triol (3), by selective reaction of the hydroxyethyl group with thionyl chloride, was poor. Reinvestigation of this stage has now shown that a major by-product is the benzoxazine (27), which evidently arises by an intramolecular cyclisation of the type previously studied by Knorr.[11] Recently, catalysis by zinc chloride has been reported to be very effective for the conversion of alcohols into chlorides by thionyl chloride,[12] and by the use of this method a much improved yield (58%) of the mustard (4) was obtained. Reaction of the triol (5) (prepared by hydroxyethylation of methyl 5-aminosalicylate) with this reagent likewise gave an acceptable yield (52%) of the mustard (6).

In their synthesis of the mustard (8), Baker and his associates [7] failed to achieve selective reaction of the hydroxyethyl groups in the triol (7) and they found it necessary to effect temporary protection of the phenolic group; the overall yield of the phenolic mustard was very low. In view of our successful reactions with thionyl chloride–zinc chloride on the triols (3) and (5) we therefore treated the triol (7) in the same way. The product, however, had a high chlorine content and the ^{1}H n.m.r. spectrum (which included resonances for phenolic hydroxy-groups at τ −1.55 and −0.72) indicated that it consisted essentially of the chlorinated compounds (28) and (29) in equal proportions. Reports of nuclear halogenation by thionyl chloride are rare,[13] but the orientation of the substituents in the triol (7) is more favourable for electrophilic substitution than in the isomers (3) and (5). Selective formation of the desired mustard (8) was eventually achieved in 65% yield by use of the pyridine–methanesulphonyl chloride reagent.[14]

Substituted nitroanilines are potential starting materials for the synthesis of amino-mustards by eventual reduction of the nitro-group, but the susceptibility of the aniline to bishydroxyethylation is very dependent on its base strength and therefore on the nature and orientation of the substituents.[15,16] The weakly basic methyl 5-amino-2-nitrobenzoate, when treated at ambient temperature with ethylene oxide in

† Simple nitrogen mustards show very low values because of their high toxicity, and even the clinically useful Chlorambucil has an index of only 12 when measured under the same conditions.[4]

‡ A comprehensive list has been compiled.[5]

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[3] T. J. Bardos, Z. F. Chmielewicz, and P. Hebborn, *Ann. New York Acad. Sci.*, 1969, **163**, 1006; personal communication.

[4] T. J. Bardos, N. Datta-Gupta, P. Hebborn, and D. J. Triggle, *J. Medicin. Chem.*, 1965, **8**, 167.

[5] A. J. Abela Medici, Ph.D. Thesis, University of London, 1976.

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[7] B. R. Baker, W. W. Lee, A. P. Martinez, L. O. Ross, and L. Goodman, *J. Org. Chem.*, 1962, **27**, 3283.

[8] M. Artico and W. C. J. Ross, *Biochem. Pharmacol.*, 1968, **17**, 883.

[9] W. C. J. Ross, G. P. Warwick, and J. J. Roberts, *J. Chem. Soc.*, 1955, 3110.

[10] P. Kristian, A. Hulka, K. Antos, P. Nemec, and L. Drobnica, *Chem. Zvesti*, 1959, **13**, 103; V. Bieksa, D. Burduliene, and J. Degutis, *Liet. T.S.R. Mokslu Acad. Darb., Ser. B*, 1971, **64**(1), 133; 1973, **77**(4), 55, 67; O. Barauskaite, V. Bieksa, and J. Degutis, *ibid.*, 1971, **66**(3), 139; J. Degutis and V. Bieksa, *Liet. T.S.R. Acad. Darb., Ser. B*, 1965, **42**(3), 71.

[11] L. Knorr, *Ber.*, 1889, **22**, 2081.

[12] T. G. Squires, W. W. Schmidt, and C. S. McCandlish, *J. Org. Chem.*, 1975, **40**, 134.

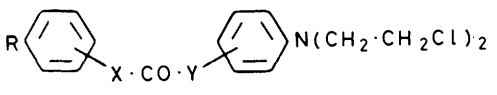
[13] H. Meyer, *Monatsh.*, 1915, **36**, 723; H. S. Mosher and M. Look, *J. Org. Chem.*, 1955, **20**, 283; *cf.* S. D. Saraf, *Canad. J. Chem.*, 1969, **47**, 2803.

[14] M. Szekerke, R. Wade, and F. Bergel, *J. Chem. Soc.*, 1965, 1907.

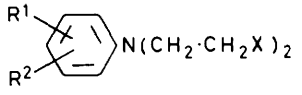
[15] W. C. J. Ross, *J. Chem. Soc.*, 1949, 183.

[16] M. Freifelder and K. R. Stone, *J. Org. Chem.*, 1961, **26**, 1477.

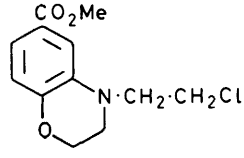
aqueous acetic acid, gave only a low yield of the diol (9), the main product being the *N*-monohydroxyethyl derivative. When the latter was treated with ethylene oxide at 140 °C, a small amount of the diol was formed,



(1) X = O, Y = NH
(2) X = NH, Y = O



	R^1	R^2	X
(3)	2-OH	5-CO_2Me	OH
(4)	2-OH	5-CO_2Me	Cl
(5)	4-OH	3-CO_2Me	OH
(6)	4-OH	3-CO_2Me	Cl
(7)	3-OH	4-CO_2Me	OH
(8)	3-OH	4-CO_2Me	Cl
(9)	4-NO_2	3-CO_2Me	OH
(10)	4-NO_2	3-CO_2Me	Cl
(11)	3-NHAc	4-CO_2Me	OH
(12)	3-NHAc	4-CO_2Me	Cl
(13)	3-NH_2	4-CO_2Me	Cl
(14)	2-NO_2	4-OMe	OH
(15)	5-NO_2	2-OMe	OH
(16)	5-NO_2	2-OMe	Cl
(17)	5-NH_2	2-OMe	Cl
(18)	3-NHAc	4-OMe	OH
(19)	3-NHAc	4-OMe	Cl
(20)	3-NH_2	4-OMe	Cl
(21)	5-NO_2	2-Cl	OH
(22)	5-NO_2	2-Cl	Cl
(23)	5-NH_2	2-Cl	Cl
(24)	3-NO_2	4-Cl	OH
(25)	3-NO_2	4-Cl	Cl
(26)	3-NH_2	4-Cl	Cl



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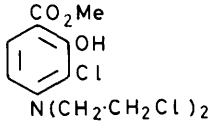

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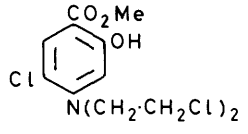

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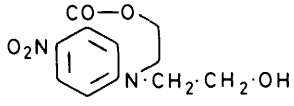

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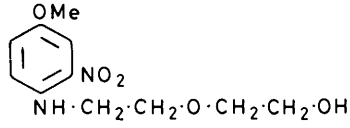

(31)

together with the lactone (30), identified analytically and by ^1H n.m.r. and mass spectra. Reaction of the diol with phosphoryl chloride gave the mustard (10) but the overall yield was so low that the final reduction was not practicable.

Hydroxyethylation of methyl 2-amino-4-nitrobenzoate under various conditions gave small yields of the *N*-hydroxyethyl derivative but no diol; methyl 2-amino-4-phthalimidobenzoate (prepared by selective acylation of methyl 2,4-diaminobenzoate) likewise gave only the mono-*N*-substituted product. Similar low reactivity has been reported [17] for methyl 2-aminobenzoate, though its basic strength (pK_a 2.23) is close to that of *m*-nitroaniline (pK_a 2.47), which forms a bishydroxyethyl derivative without difficulty.[18] The difference in behaviour of these anthranilate compounds may therefore be due to steric hindrance,[16] possibly in conjunction with hydrogen bonding between an amine proton and the neighbouring carbonyl group. In contrast, when methyl 2-acetamido-4-nitrobenzoate was reduced to the 4-amino-compound, no difficulty was found in preparing the diol (11), from which the mustard (12) was obtained. Solvolysis with methanolic hydrogen chloride then afforded the amino-mustard (13), characterised as the 2-chlorophenyl carbamate.

The basic strength of *o*-anisidine (pK_a 4.52) is only slightly less than that of aniline, whilst that of *p*-anisidine (pK_a 5.30) is greater, but the dominating deactivation by an *o*- or *p*-nitro-group was evident in the hydroxyethylation of 2-methoxy-4-nitroaniline and 4-methoxy-2-nitroaniline. In aqueous acetic acid, only the *N*-2-hydroxyethyl derivative was found in each case, though under more drastic conditions the 4-methoxy-compound gave a 3% yield of the diol (14) together with 5% of the isomeric *N*-2-(2-hydroxyethoxy)ethyl derivative (31), separated by t.l.c. and distinguished by their ^1H n.m.r. spectra. 2-Methoxy-5-nitroaniline, however, gave the diol (15) in good yield; conversion into the mustard (16) followed by hydrogenation over palladium gave the amino-mustard (17). Similarly, a high yield of the diol (18) was obtained from 3-acetamido-4-methoxyaniline; conversion into the mustard (19) was best effected with the pyridine–methanesulphonyl chloride reagent [14] and subsequent hydrolysis with hydrochloric acid gave the amino-mustard (20). Both amines (17) and (20) rapidly deteriorated, and therefore were immediately treated with phenyl chloroformate to give the stable phenyl carbamates.

The behaviour of four chloronitroanilines on hydroxyethylation followed what had now become a familiar pattern. Diols could not be prepared from 2-chloro-4-nitroaniline or from 4-chloro-2-nitroaniline, only mono-*N*-substitution being achieved, but the diols (21) and (24) were obtained from 2-chloro-5-nitroaniline and 4-chloro-3-nitroaniline, respectively, and were subsequently converted into the mustards (22) and (25); catalytic hydrogenation then afforded the amino-mustards (23) and (26).

Hydroxyethylation of arylamines with ethylene oxide in aqueous acetic acid has never been investigated in detail. From the results which we have accumulated it is clear that the course of the reaction is very dependent on the nature and orientation of the substituents, but, even when a good yield of the bishydroxyethyl derivative is obtained, t.l.c. shows that a complex mixture is formed. ^1H N.m.r. evidence [5] indicates that acetates

[17] J. L. Everett, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 1953, 2386.
[18] P. D. Edwards, Ph.D. Thesis, University of London, 1972.

and chain-extension products such as (31) are frequently present. When for electronic or steric reasons bis-hydroxyethylation is slow, the predominance of by-products makes the isolation of the required diol extremely difficult.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded for solutions in deuteriochloroform (Varian T-60 instrument), and hydroxy- or amino-functions were identified by deuterium exchange; resonances for aromatic protons are omitted. I.r. spectra were recorded for all products, and were used to assist in identifications and comparisons, but the absorptions were unexceptional and are not reported. Kieselgel GF_{254} (Merck) was used for t.l.c., and grade 3 neutral alumina (prepared from B.D.H. grade 1 alumina) for column chromatography. Extracts were dried over magnesium sulphate, and solvents were removed under reduced pressure below 50 °C. Petroleum refers to the fraction of b.p. 40—60°.

General Procedure for Hydroxyethylation in Acetic Acid.—The amine, acetic acid, water (or dioxan), and freshly distilled ethylene oxide were mixed at 0 °C and stirred in a sealed flask at ambient temperature for the time specified. The solution was then concentrated under reduced pressure and the residue was taken up in ether, dichloromethane, or ethyl acetate, and washed with aqueous sodium hydrogen carbonate. Evaporation of the dried extract then gave the crude product, which was examined as individually described.

Methyl 3-(*Bis*-2-*chloroethylamino*)-4-*hydroxybenzoate* (4).—(*a*) Thionyl chloride (12 ml) was added to a solution of methyl 3-(bis-2-hydroxyethylamino)-4-hydroxybenzoate [2] (3.4 g) in dry benzene (25 ml). The mixture was boiled under reflux for 20 min and then cooled. A precipitate was formed; this was collected and partitioned between chloroform and aqueous ammonia to give (from the washed and dried organic layer) the dichloride (4) (0.9 g), which after t.l.c. (chloroform) and recrystallisation from acetone–petroleum had m.p. 75—78° (lit.,[2] 76°), τ 2.22br (1 H, OH), 6.10 (3 H, s, CO_2Me), and 6.57 (8 H, t, 4 × CH_2). Evaporation of the benzene solution and purification of the residue by t.l.c. ($CHCl_3$) gave *methyl* 4-(2-*chloroethyl*)-3,4-*dihydro*-2H-1,4-*benzoxazine*-6-*carboxylate* (27), m.p. 74—75°, $\nu_{max.}$ 1 702 cm^{-1}, τ 5.7 (2 H, t, O·CH_2), 6.10 (3 H, s, CO_2Me), 6.27 (4 H, s, N·CH_2·CH_2Cl), and 6.50 (2 H, t, ring CH_2·N) (Found: C, 56.3; H, 5.5; Cl, 14.1; N, 5.5. $C_{12}H_{14}ClNO_4$ requires C, 56.4; H, 5.5; Cl, 13.9; N, 5.5%). The m.p. of a mixture with the mustard (4) was 50—69°. Other, unidentified fractions were also isolated by t.l.c.

(*b*) Thionyl chloride (12 ml) in benzene (10 ml) was slowly added (30 min) to a boiling solution of the same triol (3.4 g) in benzene (25 ml) containing powdered anhydrous zinc chloride (*ca.* 0.25 g). After being heated for a further 20 min, the mixture (a precipitate had formed) was cooled and filtered. The solid was dissolved in dichloromethane, and washed with aqueous ammonia and with water, and this solution was then concentrated; purification of the residue by t.l.c. gave the mustard (4) (2.24 g), m.p. 72—75°, identified by the characteristic n.m.r. spectrum. Reaction with phenyl isocyanate in the presence of triethylamine, for 48 h at 66—68°, gave 2-(*bis*-2-*chloroethylamino*)-4-*methoxycarbonylphenyl* N-*phenylcarbamate*, m.p. 89—90° (from ether–petroleum) (Found: C, 55.55; H, 4.8; Cl, 17.0; N, 6.8. $C_{19}H_{20}Cl_2N_2O_4$ requires C, 55.5; H, 4.9; Cl, 17.2; N, 6.8%).

Methyl 5-(*Bis*-2-*hydroxyethylamino*)-2-*hydroxybenzoate* (5).—Methyl 5-amino-2-hydroxybenzoate [19] (3.35 g), water (15 ml), acetic acid (50 ml), and ethylene oxide (24 ml) after 24 h gave a solid (4.7 g) which on recrystallisation from chloroform–petroleum (b.p. 60—80 °C) afforded the *triol*, m.p. 113—115°, τ −0.28 (1 H, s, phenolic OH), 6.05 (3 H, s, CO_2Me), 6.20 (4 H, t, O·CH_2), 6.55 (4 H, t, N·CH_2), and 6.87br (2 H, aliphatic OH) (Found: C, 56.3; H, 6.7; N, 5.3. $C_{12}H_{17}NO_5$ requires C, 56.5; H, 6.7; N, 5.5%).

Methyl 5-(*Bis*-2-*chloroethylamino*)-2-*hydroxybenzoate* (6).—Thionyl chloride (3.6 ml) in chloroform (3 ml) was slowly added (45 min) to a stirred solution of the triol (5) (1.0 g) in chloroform (12 ml) containing zinc chloride (*ca.* 0.1 g). The mixture was boiled under reflux for 15 min, and was then concentrated, neutralised with aqueous ammonia, and extracted with dichloromethane to give an oil. T.l.c. gave the *dichloride* (0.6 g), m.p. 83—84° (from acetone–petroleum), τ −0.28 (1 H, s, OH), 6.07 (3 H, s, CO_2Me), and 6.12 (8 H, s, 4 × CH_2) (Found: C, 49.2; H, 5.2; Cl, 24.2; N, 4.6. $C_{12}H_{15}Cl_2NO_3$ requires C, 49.3; H, 5.2; Cl, 24.3; N, 4.8%).

Methyl 4-(*Bis*-2-*hydroxyethylamino*)-2-*hydroxybenzoate* (7).—Methyl 4-amino-2-hydroxybenzoate [20] (18.9 g), water (50 ml), acetic acid (200 ml), and ethylene oxide (25 ml), after 48 h gave, after recrystallisation from benzene, the triol (15.3 g), m.p. 97—100° (raised by further recrystallisation to 101—103°; lit.,[7] 97—98°), τ −0.94 (1 H, s, phenolic OH), 6.10 (3 H, s, CO_2Me), 6.12 (4 H, t, O·CH_2), 6.39 (4 H, t, N·CH_2), and 6.57br (2 H, aliphatic OH); *tribenzoate*, m.p. 115—116° (Found: C, 69.9; H, 5.1; N, 2.25. $C_{33}H_{29}NO_8$ requires C, 69.8; H, 5.15; N, 2.5%).

On reaction with thionyl chloride and zinc chloride in benzene, as described for the preparation of the dichloride (4), the triol (1.2 g) gave an oil, which by t.l.c. (dichloromethane) furnished as a main fraction (0.53 g) a 1 : 1 mixture of methyl 3- and 5-chloro-4-(bis-2-chloroethylamino)-2-hydroxybenzoates (28) and (29), τ −1.55 (0.5 H, s, OH), −0.72 (0.5 H, s, OH), 6.05 (3 H, s, CO_2Me), and 6.37 (8 H, s, 4 × CH_2) (Found: C, 44.0; H, 4.3; Cl, 30.7; N, 4.5. Calc. for $C_{12}H_{14}Cl_3NO_3$: C, 44.0; H, 4.3; Cl, 32.6; N, 4.3%).

Methyl 4-(*Bis*-2-*chloroethylamino*)-2-*hydroxybenzoate* (8).—Methanesulphonyl chloride (5.3 ml) in pyridine (5 ml) was added to a solution of the triol (7) (4 g) in pyridine (25 ml). When the exothermic reaction had subsided the mixture was heated on a steam-bath for 20 min, then cooled, and filtered to remove pyridine methanesulphonate (5.8 g), m.p. 174°, which was washed with dichloromethane and with petroleum. The combined filtrate and washings were washed successively with dilute hydrochloric acid, aqueous sodium carbonate, and water; evaporation of the dried solution then gave an oil, which by t.l.c. gave the dichloride (8) (2.95 g), m.p. 61—62° (from ether–petroleum) (lit.,[7] 60.5—61°), τ −0.98 (1 H, s, OH), 6.10 (3 H, s, CO_2Me), and 6.28 (8 H, s, 4 × CH_2).

Methyl 5-*Amino*-2-*nitrobenzoate*.—Commercial 5-amino-2-nitrobenzoic acid (30.4 g) was dissolved in dry methanol (200 ml) saturated with hydrogen chloride. The solution was boiled under reflux for 40 h, then evaporated to dry-

[19] L. Gattermann, *Ber.*, 1894, **27**, 1927.

[20] D. J. Drain, D. D. Martin, B. W. Mitchell, D. E. Seymour, and F. S. Spring, *J. Chem. Soc.*, 1949, 1498; J. A. McCubbin, R. Y. Moir, and G. A. Neville, *Canad. J. Chem.*, 1970, **48**, 942.

ness. The residue was partitioned between ether and aqueous sodium carbonate to give the crude ester (27 g), m.p. 86—94°. This was dissolved in hot methanol and water was gradually added to precipitate a red oil, which was removed; more water was added, in small portions, to precipitate further small amounts of red oil, until the colour of the solution had changed from orange to bright yellow. When the yellow solution was cooled in ice the required *methyl ester* was obtained, m.p. 98—100° (Found: C, 49.0; H, 4.3; N, 14.2. $C_8H_8N_2O_4$ requires C, 49.0; H, 4.1; N, 14.3%); *N*-acetyl derivative had m.p. 109° (lit.,[21] 111—112°).

The red oil crystallised, and after purification by t.l.c. gave an isomeric ester, m.p. 194—195° (from methanol) (Found: C, 49.3; H, 4.2; N, 14.4%) evidently derived from an impurity in the original acid. The m.p. (significantly different from those of the known methyl aminonitrobenzoates) suggests that it is one of the three isomers not yet described.[5]

Hydroxyethylation of Methyl 5-Amino-2-nitrobenzoate.—The amine (2.0 g), water (10 ml), acetic acid (30 ml), and ethylene oxide (4 ml), after 48 h gave an oil, which by column chromatography (ether) gave (i) unchanged amine (0.8 g); (ii) *methyl 5-(2-hydroxyethylamino)-2-nitrobenzoate* (1.1 g), an oil, τ 4.5br (1 H, NH), 6.07 (3 H, s, CO_2Me), 6.22 (2 H, t, O·CH_2), 6.63 (2 H, t, N·CH_2), and 7.35br (1 H, OH) (Found: C, 49.8; H, 5.2; N, 11.4. $C_{10}H_{12}N_2O_5$ requires C, 50.0; H, 5.0; N, 11.7%); and (iii) methyl 5-(bis-2-hydroxyethylamino)-2-nitrobenzoate (9) (0.1 g), an oil, τ 6.4br (2 H, OH), 6.10 (3 H, s, CO_2Me), and 6.2 (8 H, m, 4 × CH_2).

Fraction (ii) (1.0 g), ethylene oxide (3 ml), and dioxan (3 ml) were heated in a sealed tube for 16 h at 140 °C to give (t.l.c. in ether) starting material (0.3 g), the diol (9) (0.1 g), and the *lactone* (30) of *5-(bis-2-hydroxyethylamino)-2-nitrobenzoic acid* (0.1 g), m.p. 143—144° (from dichloromethane–petroleum), τ 5.03 (2 H, s, ring O·CH_2), 5.73 (2 H, t, aliphatic O·CH_2), 6.03 (2 H, s, ring N·CH_2), 6.08br (1 H, OH), and 6.47 (2 H, t, aliphatic N·CH_2), M^+ 252 (Found: C, 52.7; H, 4.7; N, 11.1. $C_{11}H_{12}N_2O_5$ requires C, 52.4; H, 4.8; N, 11.1%; *M*, 252). When this oxazocine was treated for 1 h with boiling methanol saturated with hydrogen chloride, it gave the diol (9), identified by the n.m.r. spectrum.

Methyl 5-(Bis-2-chloroethylamino)-2-nitrobenzoate (10).—Phosphoryl chloride (1.0 g) in benzene (3 ml) was added to a solution of the diol (9) (0.5 g) in benzene (3 ml). The mixture was boiled under reflux for 6 h, then cooled, washed with aqueous ammonia, dried, and concentrated to an oil, which by t.l.c. (dichloromethane) gave the *dichloride*, m.p. 89—91° (from dichloromethane–petroleum), τ 6.06 (3 H, s, CO_2Me) and 6.22 (8 H, q, 4 × CH_2) (Found: C, 44.8; H, 4.5; N, 8.45. $C_{12}H_{14}Cl_2N_2O_4$ requires C, 44.9; H, 4.4; N, 8.7%).

Hydroxyethylation of Methyl 2-Amino-4-nitrobenzoate.—The amine (2.0 g), water (25 ml), acetic acid (50 ml), and ethylene oxide (25 ml) after 48 h gave a solid, which was separated by column chromatography (ether) into unchanged amine (1.0 g) and *methyl 2-(2-hydroxyethylamino)-4-nitrobenzoate* (0.6 g), m.p. 112—113°, τ 1.87br (1 H, NH), 6.07 (2 H, m, O·CH_2), 6.10 (3 H, s, CO_2Me), 6.57 (2 H, t, N·CH_2), and 7.73br (1 H, OH) (Found: C, 50.2; H, 5.3; N, 11.6. $C_{10}H_{12}N_2O_5$ requires C, 50.0; H, 5.0; N, 11.7%). Similar results were obtained when water was replaced by dioxan, and also when the amine (2.0 g), dioxan (5 ml), and ethylene oxide (2 ml) were heated in a sealed tube for 16 h at 150 °C.

Hydroxyethylation of Methyl 2-Amino-4-phthalimidobenzoate.—A mixture of methyl 2,4-diaminobenzoate (1.7 g), phthalic anhydride (1.5 g), toluene (20 ml), and triethylamine (0.5 ml) was boiled in a Dean and Stark apparatus for 2 h. When cooled, the solution deposited the *4-phthalimido-derivative* (2.05 g), m.p. 207—208° (from chloroform–petroleum) (Found: C, 64.65; H, 4.2; N, 9.4. $C_{16}H_{12}N_2O_4$ requires C, 64.9; H, 4.1; N, 9.5%). This product (0.5 g), dioxan (10 ml), acetic acid (10 ml), and ethylene oxide (2 ml) after 48 h gave a solid; recrystallisation from dichloromethane–petroleum gave *methyl 2-(2-hydroxyethylamino)-4-phthalimidobenzoate*, m.p. 185—186°, τ 6.09 (3 H, s, CO_2Me), 6.13 (2 H, t, O·CH_2), 6.57 (2 H, t, N·CH_2), and 8.27br (2 H, NH, OH) (Found: C, 63.4; H, 4.6; N, 8.1. $C_{18}H_{16}N_2O_5$ requires C, 63.5; H, 4.7; N, 8.2%).

Methyl 2-Acetamido-4-(bis-2-hydroxyethylamino)benzoate (11).—A solution of methyl 2-acetamido-4-nitrobenzoate [22] (12 g) in methanol (300 ml), with 10% palladium–charcoal (1.2 g), was hydrogenated for 18 h at 50 °C and 25 atm to give *methyl 2-acetamido-4-aminobenzoate* (9.3 g), m.p. 215—216° (from chloroform) (Found: C, 57.5; H, 5.6; N, 13.5. $C_{10}H_{12}N_2O_3$ requires C, 57.7; H, 5.8; N, 13.45%). This amine (1.0 g), dioxan (15 ml), acetic acid (15 ml), and ethylene oxide (4 ml), after 100 h gave an oil, which by t.l.c. (ethyl acetate) gave two main fractions: (i) *methyl 2-acetamido-4-(2-hydroxyethylamino)benzoate* (0.4 g), m.p. 130—131° (from dichloromethane–petroleum), τ −1.38br (1 H, NH), 6.12 (3 H, s, CO_2Me), 6.0—7.6 (7 H, m), and 7.77 (3 H, s, Ac) (Found: C, 55.3; H, 6.4; N, 10.4. $C_{12}H_{16}N_2O_4$,0.5H_2O requires C, 55.15; H, 6.55; N, 10.7%); and (ii) the *diol* (11) (0.85 g), m.p. 118—120° (from dichloromethane–petroleum), τ −1.3br (1 H, NH), 5.9br (2 H, OH), 6.14 (3 H, s, CO_2Me), 6.3 (8 H, m, 4 × CH_2), and 7.83 (3 H, s, Ac) (Found: C, 56.9; H, 6.6; N, 9.4. $C_{14}H_{20}N_2O_5$ requires C, 56.75; H, 6.8; N, 9.45%).

Methyl 2-Acetamido-4-(bis-2-chloroethylamino)benzoate (12).—Methanesulphonyl chloride (1.2 ml) was added to a solution of the diol (11) (1.6 g) in pyridine (12 ml). The mixture was heated at 100 °C for 20 min, then poured on ice and extracted with dichloromethane. Concentration of the washed and dried extract and purification of the product by t.l.c. gave the *dichloride* (12) (0.8 g), m.p. 73—75° (from petroleum), τ −1.28br (1 H, NH), 6.12 (3 H, s, CO_2Me), 6.22 (8 H, t, 4 × CH_2), and 7.78 (3 H, s, Ac) (Found: C, 50.5; H, 5.35; Cl, 21.6; N, 8.25. $C_{14}H_{18}Cl_2N_2O_3$ requires C, 50.5; H, 5.4; Cl, 21.3; N, 8.4%). A slightly lower yield of the same product was obtained by the use of thionyl chloride in benzene.

Methyl 2-Amino-4-(bis-2-chloroethylamino)benzoate (13).—A solution of the acetamido-compound (12) (0.53 g) in methanolic 50% hydrogen chloride (50 ml) was boiled under reflux for 1 h, the end of the condenser being fitted with a balloon to prevent loss of hydrogen chloride. Evaporation then gave the crude amine hydrochloride (0.52 g), m.p. 135—137°. This appeared to be unstable and it was dissolved in pyridine (1 ml) and benzene (10 ml) and

[21] J. F. Bunnett and M. M. Rauhut, *J. Org. Chem.*, 1956, **21**, 944.

[22] J. J. Blanksma and D. Hoegen, *Rec. Trav. chim.*, 1946, **65**, 333.

treated with 2-chlorophenyl chloroformate (0.4 g) to give *2-chlorophenyl N-[2-methoxycarbonyl-5-(bis-2-chloroethylamino)phenyl]carbamate* (0.5 g), m.p. 111—112° (from ether–petroleum), τ −0.98br (1 H, NH), 6.13 (3 H, s, CO_2Me), and 6.27 (8 H, t, 4 × CH_2) (Found: C, 51.4; H, 4.3; Cl, 24.2; N, 6.0. $C_{19}H_{19}Cl_3N_2O_4$ requires C, 51.2; H, 4.3; Cl, 23.9; N, 6.3%).

Hydroxyethylation of 2-Methoxy-4-nitroaniline.—(*a*) Reaction of the amine (2.0 g) with ethylene oxide (4 ml) in water (8 ml) and acetic acid (26 ml) for 52 h gave a brown solid, which was dissolved in dichloromethane. The solution was diluted with petroleum until no more dark oil was precipitated. From the decanted solution, *4-(2-hydroxyethylamino)-3-methoxynitrobenzene* (0.5 g) crystallised; m.p. 87—88°, τ 4.6br (1 H, NH), 6.06 (3 H, s, OMe), 6.09 (2 H, t, O·CH_2), 6.57 (2 H, t, N·CH_2), and 7.9br (1 H, OH) (Found: C, 50.9; H, 5.8; N, 13.2. $C_9H_{12}N_2O_4$ requires C, 50.9; H, 5.7; N, 13.2%). A similar result was obtained in dioxan–acetic acid, and (at 150 °C) in dioxan alone. Starting material (*ca.* 60%) was recovered in all experiments.

Hydroxyethylation of 4-Methoxy-2-nitroaniline.—The amine (2.0 g), water (8 ml), acetic acid (26 ml), and ethylene oxide (2 ml) after 60 h gave a solid, which on recrystallisation from dichloromethane–petroleum gave *1-(2-hydroxyethylamino)-4-methoxy-2-nitrobenzene* (2.25 g), m.p. 90—92°, τ 1.8br (1 H, NH), 6.03 (2 H, t, O·CH_2), 6.20 (3 H, s, OMe), 6.43 (2 H, t, N·CH_2), and 7.95br (1 H, OH) (Found: C, 51.0; H, 5.9; N, 13.1. $C_9H_{12}N_2O_4$ requires C, 50.9; H, 5.7; N, 13.2%).

(*b*) The amine (5.0 g), ethylene oxide (5 ml), and dioxan (5 ml) were heated in a sealed tube at 160 °C for 16 h. Column chromatography (ether) of the product gave (i) unchanged amine (0.8 g); (ii) the *N*-2-hydroxyethyl derivative (1.2 g), m.p. 88—91°, spectroscopically identical with that previously described; (iii) *2-[2-(2-hydroxyethoxy)-ethylamino]-5-methoxynitrobenzene* (31) (0.4 g), an oil, τ 1.87br (1 H, NH), 6.20 (3 H, s, OMe), 6.1—6.7 (8 H, m, 4 × CH_2), and 7.5br (1 H, OH) (Found: C, 51.4; H, 6.3; N, 11.0. $C_{11}H_{16}N_2O_5$ requires C, 51.55; H, 6.3; N, 10.9%); and (iv) *2-(bis-2-hydroxyethylamino)-5-methoxynitrobenzene* (14) (0.2 g), an oil, τ 6.13 (3 H, s, OMe), 6.38 (4 H, t, O·CH_2), 6.77 (4 H, t, N·CH_2), and 7.10br (2 H, OH) (Found: C, 51.2; H, 5.95; N, 10.5. $C_{11}H_{16}N_2O_5$ requires C, 51.55; H, 6.3; N, 10.9%).

3-(Bis-2-hydroxyethylamino)-4-methoxynitrobenzene (15).—2-Methoxy-5-nitroaniline (20 g), water (80 ml), acetic acid (380 ml), and ethylene oxide (30 ml) after 120 h gave the *diol* (24.5 g), m.p. 74° (from dichloromethane–petroleum), τ 6.05 (3 H, s, OMe), 6.35 (4 H, t, O·CH_2), 6.65 (4 H, t, N·CH_2), and 7.5br (2 H, OH) (Found: C, 51.4; H, 6.2; N, 10.9. $C_{11}H_{16}N_2O_5$ requires C, 51.55; H, 6.3; N, 10.9%).

3-(Bis-2-chloroethylamino)-4-methoxy-1-nitrobenzene (16).—The diol (15) (0.51 g) was treated with phosphoryl chloride (1 ml) in boiling benzene (3 ml) for 2 h. The cooled solution was diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate and with water, dried, and evaporated to give the *dichloride* (0.48 g), m.p. 55° (from ether–petroleum), τ 6.0 (3 H, s, OMe) and 6.4 (8 H, s, 4 × CH_2) (Found: C, 45.2; H, 5.1; Cl, 23.8; N, 9.4. $C_{11}H_{14}Cl_2N_2O_3$ requires C, 45.1; H, 4.8; Cl, 24.2; N, 9.6%).

[23] F. H. Bergeim, K. Losee, and W. A. Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 583.

3-(Bis-2-chloroethylamino)-4-methoxyaniline (17).—A solution of the nitro-compound (16) (2.9 g) in methanol (70 ml), containing 10% palladium–charcoal (0.3 g) was hydrogenated at ambient temperature and atmospheric pressure for 6 h. The solution was then filtered into methanolic 50% hydrogen chloride (60 ml), and on evaporation the crude amine hydrochloride was obtained as a solid (2.9 g) which soon became brown. It was immediately treated with benzene (80 ml), pyridine (2 g), and phenyl chloroformate (2.0 g); purification of the oily product by t.l.c. (dichloromethane), followed by crystallisation from ether–petroleum, gave *phenyl N-[3-(bis-2-chloroethylamino)-4-methoxyphenyl]-carbamate* (1.0 g), m.p. 63—66° (Found: C, 56.45; H, 5.3; Cl, 18.3; N, 7.25. $C_{18}H_{20}Cl_2N_2O_3$ requires C, 56.4; H, 5.3; Cl, 18.5; N, 7.3%).

5-(Bis-2-hydroxyethylamino)-2-methoxyacetanilide (18).—5-Amino-2-methoxyacetanilide [23] (18.0 g) treated with ethylene oxide (55 ml) in water (100 ml) and acetic acid (100 ml) for 44 h, gave (by extraction of the neutralised solution with ethyl acetate) the *diol* (18) (18.0 g), m.p. 90° (from ether), τ 2.20br (1 H, NH), 6.15 (3 H, s, OMe), 6.19 (4 H, t, O·CH_2), 6.50 (4 H, t, N·CH_2), and 7.85 (3 H, s, Ac) (Found: C, 58.3; H, 7.6; N, 10.5. $C_{13}H_{20}N_2O_4$ requires C, 58.2; H, 7.5; N, 10.4%).

5-(Bis-2-chloroethylamino)-2-methoxyaniline (20).—Methanesulphonyl chloride (0.7 ml) was added to a solution of the diol (18) (0.5 g) in pyridine (3 ml) and the mixture was set aside for 5 h. The precipitate (pyridine methanesulphonate) was filtered off and the filtrate was concentrated to remove most of the pyridine. The residue was dissolved in dichloromethane and the solution was washed, dried, and evaporated to give *5-(bis-2-chloroethylamino)-2-methoxyacetanilide* (19), an oil (0.33 g), purified by t.l.c. (ether), τ 2.16br (1 H, NH), 6.17 (3 H, s, OMe), 6.32 (8 H, s, 4 × CH_2), and 7.81 (3 H, s, Ac) (Found: C, 51.15; H, 6.1; Cl, 23.2; N, 9.0. $C_{13}H_{18}Cl_2N_2O_2$ requires C, 51.2; H, 5.9; Cl, 23.2; N, 9.2%). This was dissolved in 50% hydrogen chloride in methanol (10 ml), and the solution was boiled under reflux for 2 h, then evaporated to give the hydrochloride (0.23 g) of the amine (20). Treatment in the usual way with phenyl chloroformate in pyridine–benzene gave *phenyl N-[5-(bis-2-chloroethylamino)-2-methoxyphenyl]-carbamate*, m.p. 118—120° (from dichloromethane–petroleum) (Found: C, 56.65; H, 5.4; N, 7.2. $C_{18}H_{20}Cl_2N_2O_3$ requires C, 56.4; H, 5.3; N, 7.3%).

Hydroxyethylation of 2-Chloro-4-nitroaniline.—The amine (2.0 g), water (25 ml), acetic acid (35 ml), and ethylene oxide (10 ml) after 100 h gave a solid, which on fractional crystallisation from dichloromethane–petroleum gave unchanged amine (1.0 g) and 3-chloro-4-(2-hydroxyethylamino)-1-nitrobenzene (0.45 g), m.p. 115—117° (lit.,[24] 120°) (Found: C, 44.5; H, 4.4; N, 12.7. Calc. for $C_8H_9ClN_2O_3$: C, 44.4; H, 4.2; N, 12.9%). A similar result was obtained by heating the amine (5 g), dioxan (5 ml), and ethylene oxide (5 ml) at 140 °C for 16 h.

Hydroxyethylation of 4-Chloro-2-nitroaniline.—Reaction of the amine (1.0 g) with ethylene oxide (5 ml) in acetic acid (20 ml) and water (10 ml) for 120 h gave a solid (1.1 g). A sample of this by t.l.c. was separated into unchanged amine (74%) and 4-chloro-1-(2-hydroxyethylamino)-2-nitrobenzene (23%), m.p. 107—108° (lit.,[24] 107.5°), τ 1.87br (1 H, NH), 6.10 (2 H, t, O·CH_2), 6.47 (2 H, t, N·CH_2), and 8.05br (1 H, OH).

[24] C. B. Kremer and A. Bendich, *J. Amer. Chem. Soc.*, 1939, **61**, 2658.

3-(*Bis*-2-*hydroxyethylamino*)-4-*chloro*-1-*nitrobenzene* (21).—Reaction of 2-chloro-5-nitroaniline (20 g) with ethylene oxide (90 ml) in water (80 ml) and acetic acid (380 ml) for 100 h, followed by 70 h at 50 °C, gave an oil (43 g) which was subjected to column chromatography (dichloromethane, followed by ether). The slow-running fraction which contained the required product (n.m.r. spectrum) was further purified by t.l.c. (ether) to give the *diol* (21) (2.6 g), m.p. 93—95° (from dichloromethane–petroleum), τ 6.30 (4 H, t, O·CH_2), 6.60 (4 H, t, N·CH_2), and 6.85br (2 H, OH) (Found: C, 46.3; H, 4.75; N, 10.6. $C_{10}H_{13}ClN_2O_4$ requires C, 46.1; H, 5.0; N, 10.75%).

3-(*Bis*-2-*chloroethylamino*)-4-*chloroaniline* (23).—Reaction of the diol (21) (2.6 g) with phosphoryl chloride (5 ml) in boiling benzene (15 ml) for 5 h gave, after t.l.c., 3-(*bis*-2-*chloroethylamino*)-4-*chloro*-1-*nitrobenzene* (22) (2.6 g), m.p. 61—62° (from ether–petroleum) (Found: C, 40.5; H, 3.75; Cl, 35.7; N, 9.5. $C_{10}H_{11}Cl_3N_2O_2$ requires C, 40.4; H, 3.7; Cl, 35.7; N, 9.4%). Hydrogenation of this compound (1.5 g) in methanol (35 ml) containing 10% palladium–charcoal (0.15 g) for 3 h, followed by filtration into methanolic 15% hydrogen chloride (90 ml) and evaporation, gave the crude hydrochloride (1.5 g) of the amine (23). This was immediately treated, as previously described, with phenyl chloroformate in pyridine–benzene; purification of the urethane by t.l.c. (dichloromethane–petroleum, 1 : 1) gave *phenyl* N-[3-(*bis*-2-*chloroethylamino*)-4-*chlorophenyl*]*carbamate* (1.05 g), m.p. 64—66° (from dichloromethane–petroleum) (Found: C, 52.95; H, 4.7; Cl, 27.2; N, 7.0. $C_{17}H_{17}Cl_3N_2O_2$ requires C, 52.7; H, 4.4; Cl, 27.4; N, 7.2%).

4-(*Bis*-2-*hydroxyethylamino*)-1-*chloro*-2-*nitrobenzene* (24).—4-Chloro-3-nitroaniline (2.0 g), water (10 ml), acetic acid (20 ml), and ethylene oxide (4 ml) after 120 h gave an oil which crystallised from dichloromethane. Recrystallisation from acetone–petroleum gave the *diol* (24) (1.3 g), m.p. 108°, τ [$(CD_3)_2CO$] 5.9—6.6 (2 H, OH) and 6.40 (8 H, t, 4 × CH_2) (Found: C, 45.9; H, 4.9; N, 10.8. $C_{10}H_{13}ClN_2O_4$ requires C, 46.1; H, 5.0; N, 10.75%). A further quantity of the diol (0.4 g) was obtained from the mother liquor by t.l.c., which also furnished 4-(2-*acetoxyethylamino*)-1-*chloro*-2-*nitrobenzene* (77 mg), an oil, $\nu_{max.}$ 1 732 cm^{-1} (OAc), τ 5.67 (2 H, t, O·CH_2), 5.90br (1 H, NH), 6.57 (2 H, t, N·CH_2), and 7.90 (3 H, s, Ac) (Found: C, 46.6; H, 4.2; N, 10.7. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3; N, 10.8%).

When 4-chloro-3-nitroaniline (1.0 g) was heated with ethylene oxide (2 ml) in dioxan (3 ml) at 100 °C for 16 h, the products, separated by t.l.c. (dichloromethane), were (i) unchanged amine (0.45 g); (ii) 1-*chloro*-4-(2-*hydroxyethylamino*)-2-*nitrobenzene* (0.48 g), m.p. 74°, τ 5.3br (1 H, NH), 6.13 (2 H, t, O·CH_2), 6.70 (2 H, t, N·CH_2), and 7.1br (1 H, OH) (Found: C, 44.3; H, 4.2; Cl, 16.7; N, 12.8. $C_8H_9ClN_2O_3$ requires C, 44.4; H, 4.2; Cl, 16.4; N, 12.9%); and (iii) the diol (24) (0.26 g), m.p. 106—108°, spectroscopically identical with the authentic specimen.

5-(*Bis*-2-*chloroethylamino*)-2-*chloroaniline* (26).—Treatment of the diol (24) (5.75 g) with phosphoryl chloride (10 ml) in boiling benzene (30 ml) in the usual way afforded 4-(*bis*-2-*chloroethylamino*)-1-*chloro*-2-*nitrobenzene* (25) (4.0 g), m.p. 144° (from methanol) (Found: C, 40.3; H, 3.75; Cl, 36.0; N, 9.6. $C_{10}H_{11}Cl_3N_2O_2$ requires C, 40.4; H, 3.7; Cl, 35.7; N, 9.4%). A suspension of this nitro-compound (1.0 g) in methanol (60 ml) containing 10% palladium–charcoal (0.1 g) was hydrogenated under ambient conditions for 5 h, then filtered into methanolic 50% hydrogen chloride (30 ml). The crude hydrochloride, obtained on evaporation, reverted to the free *amïno-compound* (26), m.p. 176—178°, on recrystallisation from methanol–ether (Found: C, 44.7; H, 5.0; Cl, 40.0; N, 10.3. $C_{10}H_{13}Cl_3N_2$ requires C, 44.9; H, 4.9; Cl, 39.8; N, 10.5%).

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