# ANTINEOPLASTIC AGENTS

## XVII. N-(2-BROMOETHYL)-N-(2-CHLOROETHYL)AMINES[1,2]

GEORGE R. PETTIT[3] AND MAURICE R. CHAMBERLAND

*Department of Chemistry, University of Maine, Orono, Maine, and Department of Chemistry, Arizona State University, Tempe, Arizona*

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ABSTRACT

A convenient synthesis (I*a* → IV*a*) starting with N-bis(2-chloroethyl)amine has been devised for obtaining N-(2-bromoethyl)-N-(2-chloroethyl)amine. Several N-alkyl (IV*b* and VIII) and N-benzyl (VII) derivatives of the unsymmetrically halogenated amine (IV*a*) were prepared for cancer chemotherapeutic evaluation.

The majority of characterized N-bis(2-haloethyl)amines are those bearing symmetrically substituted chlorine atoms (1). With the exception of derivatives of N-(2-chloroethyl)-N-(2-fluoroethyl)amine (see e.g. ref. 2), only a few examples of unsymmetrically halogenated nitrogen mustards have been described. Of the five remaining analogous possibilities, only derivatives of N-(2-chloroethyl)-N-(2-iodoethyl)amine appear to have been reported (3). For example, Ross has isolated N-(2′-chloroethyl)-N-(2′-iodoethyl)-4-methoxybenzylamine among products obtained by treating the corresponding dichloro derivative with sodium iodide in aqueous acetone (3*a*). Continued interest in utilizing (for the design of nitrogen mustards with more desirable antineoplastic properties) differences in chemical reactivity based on variance of halogen substituents in N-bis(2-haloethyl)amines led us to evaluate N-(2-bromoethyl)-N-(2-chloroethyl)amines. Interesting biological properties discovered recently in the case of several bromine-containing amines (5), combined with the results of our prior study of N-bis(2-bromoethyl)amines (6), suggested that amine IV*a* and several selected derivatives should receive biological evaluation.

Although a number of synthetic methods were initially considered, the general route illustrated in Reaction Scheme 1 appeared to be the most promising from a practical standpoint, and emphasis was placed on this approach. Also, a useful procedure for obtaining amine III would provide, in principle, a method for obtaining the remaining unknown unsymmetrically halogenated nitrogen mustards. A sequence based on N-bis(2-chloroethyl)amine was first investigated. Preparation of amide I*a* and subsequent rearrangement in ethanol to ester II*a* was effected by a routine method previously developed in our laboratory (7). Ester II*a* was subjected to acid hydrolysis and 2-(2′-chloroethylamino)ethyl alcohol hydrochloride (III*a*) was isolated in essentially quantitative yield. Of several procedures explored for the bromination of alcohol III*a*, one based on phosphorus tribromide (providing 78% conversion into amine IV*a* hydrobromide) was found to be most satisfactory whereas another employing thionyl bromide (75% conversion of amine IV*a* hydrobromide) was considered to be less useful. An alternate reaction sequence starting with N-bis(2-bromoethyl)amine was also studied. Here amide I*b* was prepared and converted into ester II*b* as described earlier (6), and the ester was hydrolyzed with hydrobromic acid to yield alcohol III*b*. Although chlorination of alcohol III*b* with thionyl chloride readily gave amine IV*a* hydrochloride in good yield (98%), the overall method

[1] *For part XVI in this series, see G. R. Pettit and L. Garson, Can. J. Chem., 43, 2640 (1965).*

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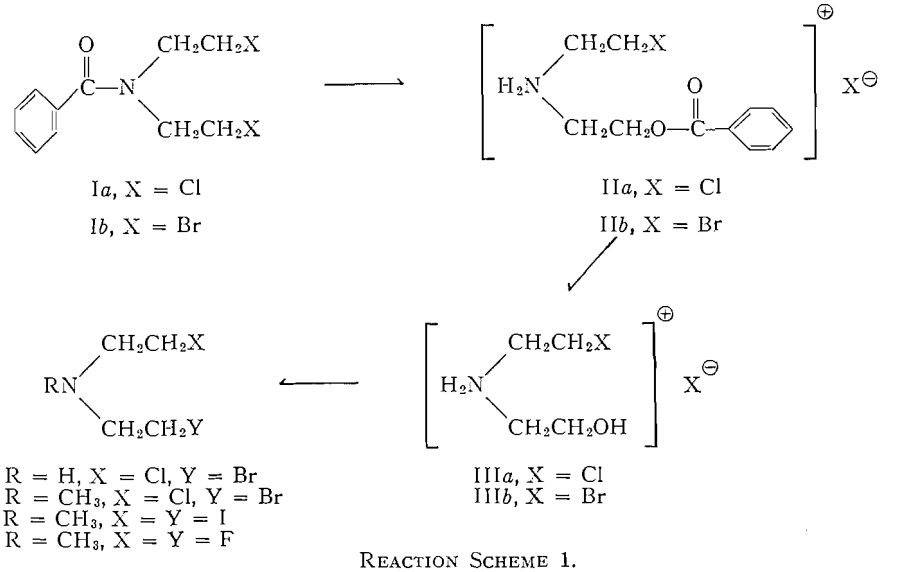
[3] *Present address: Department of Chemistry, Arizona State University, Tempe, Arizona.*



*Ia*, X = Cl
*Ib*, X = Br

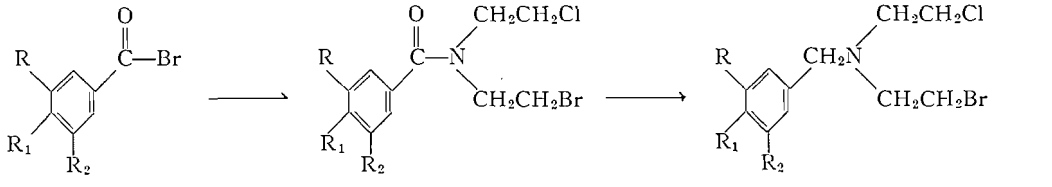
*IIa*, X = Cl
*IIb*, X = Br

*IVa*, R = H, X = Cl, Y = Br
*IVb*, R = $CH_3$, X = Cl, Y = Br
*IVc*, R = $CH_3$, X = Y = I
*IVd*, R = $CH_3$, X = Y = F

*IIIa*, X = Cl
*IIIb*, X = Br

REACTION SCHEME 1.

was less suitable, as N-bis(2-chloroethyl)amine is a more readily available starting material. To compare the antineoplastic activity of N-methylamine IV*b* with that of N-methyl-N-bis(2-chloroethyl)amine, nitrogen mustard IV*a* hydrobromide was methylated by a formaldehyde – formic acid technique (8). Methylation of N-bis(2-fluoroethyl)-amine and N-bis(2-iodoethyl)amine was performed for the same reason.



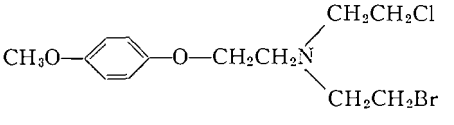
V

VI

*VIIa*, R = $R_1$ = $R_2$ = H
*VIIb*, R = $R_2$ = $OCH_2O$, $R_2$ = H
*VIIc*, R = $R_2$ = $OCH_3$, $R_1$ = H

REACTION SCHEME 2.

For biological studies four derivatives (VII*a*–VII*c*, VIII) of N-(2-bromoethyl)-N-(2-chloroethyl)amine were selected for preparation. Two of these substances, amines VII*b* and VII*c*, were chosen because of promising antitumor activity evidenced by the corresponding dichloro derivatives (7*a*). Synthesis of benzylamines VII*a*–VII*c* and aliphatic amine VIII proceeded as shown in Reaction Scheme 2.[4] The acyl bromide was



VIII

[4]*Previously (7a) a novel halogen exchange reaction provided the key step in a route believed to yield amine VIIb hydrochloride. However, the synthesis of amine VIIa described in the present contribution provides a more uniformly reliable synthetic approach to substances of this type.*

prepared with oxalyl bromide[5] or phosphorus tribromide. Reaction between the acyl bromide and 2 equivalents of amine IV*a* (in benzene solution) yielded the corresponding amide (VI), which was easily reduced with lithium aluminium hydride. In each case, the amine derivative was characterized as the hydrobromide salt. Structural assignments were confirmed by the results of infrared and proton magnetic resonance (p.m.r.) (e.g. see ref. 4*b*) spectral studies. Presently available results of biological studies[6] allow comparison of the effects of amine VII*a* and its dichloro (7*a*) and dibromo (6) analogues against Walker 256 (subcutaneous) in randomly bred albino rats. The N-(2-bromoethyl)-N-(2-chloroethyl)-amine VII*c* hydrobromide at a dose of 12.5 mg/kg caused 92% inhibition of tumor growth whereas the N-bis(2-chloroethyl)amine (at 4.8 mg/kg) and N-bis(2-bromoethyl)amine (at 12.5 mg/kg) counterparts showed, respectively, complete and 95% inhibition. The dose (in saline solution given intraperitoneally) regimen was begun on the first day of tumor transport and continued for 5 days. Tumor growth was measured on the 10th day.

## EXPERIMENTAL

The p.m.r. spectra were obtained in deuterium oxide solution and are reported relative to the peak response of HDO as internal reference. The p.m.r. equipment and general experimental techinques used below are described in introductions to the Experimental sections of refs. 4*b* and 6. All analytical samples were colorless, and infrared spectra were recorded in potassium bromide.

*2-(2′-Chloroethylamino)ethyl Benzoate Hydrochloride (IIa)*

First, preparation of N-bis(2-chloroethyl)benzamide (I*a*) was achieved by condensing (cf. ref. 7*a*) N-bis(2-chloroethyl)amine (from 100 g of the hydrochloride derivative) with benzoyl chloride (40 g) in benzene (250 ml) solution. After N-bis(2-chloroethyl)amine hydrochloride was collected, the filtrate was concentrated *in vacuo* to a pale yellow oil. A solution of the crude amide in 95% ethanol (300 ml) was heated at reflux for 2 h. Evaporation (*in vacuo*) of solvent yielded ester II*a* as pale yellow crystals weighing 58.6 g (79%). Recrystallization from acetone gave colorless needles melting at 134–135° (ref. 9 reports m.p. 135°).

*N-(2-Bromoethyl)-N-(2-chloroethyl)amine (IVa) Hydrobromide*

*Method A*

A solution of 2-(2′-chloroethylamino)ethyl benzoate hydrochloride (II*a*, 50.0 g) in 10% hydrochloric acid (200 ml) was heated at reflux for 3 h. After cooling, the solution was filtered to remove benzoic acid (22.6 g, corresponding to a 98% recovery) and washed with chloroform (2 × 100 ml). The hydrochloric acid solution was concen trated *in vacuo* to a clear viscous oil, which was further dried azeotropically with benzene. The oily sample of *2-(2′-chloroethylamino)ethyl alcohol hydrochloride (IIIa)* was obtained in a quantitative yield and resisted a number of attempts at crystallization. However, the viscous oil proved to be satisfactory for conversion into amine IV*a*.

A sample (18 g) of hydrochloride III*a* was slowly added with rapid stirring to warm (steam bath) phosphorus tribromide (43 ml). Heating at steam bath temperature and stirring were continued for an additional hour while a deep straw colored solid separated. The mixture was washed with benzene (3 × 100 ml); the residual solid was dissolved in water (150 ml), neutralized (with cooling) with 6 *N* sodium hydroxide (60 ml), and extracted with benzene (500 ml). The dry benzene solution was treated with anhydrous hydrogen bromide and diluted with diethyl ether to yield 23.4 g (78%) of colorless crystals melting at 190–194°. Two recrystallizations from methanol – diethyl ether gave needles[7] melting at 198–200°; $\nu_{max}$ 2 900, 2 750, 2 400, 1 580, 1 450, 1 430, 1 395, and 1 280 $cm^{-1}$.

Anal. Calcd. for $C_4H_{10}Br_2ClN$: C, 17.96; H, 3.77; Br, 59.77; Cl, 13.26; N, 5.27. Found: C, 17.85; H, 3.77; Br, 59.96; Cl, 13.14; N, 5.11.

The procedure described directly above for obtaining amine IV*a* hydrobromide gave consistently good results and was used routinely.

*Method B*

A sample (25 g) of hydrochloride III*a* was suspended in dry benzene (100 ml) and treated with thionyl bromide (63.0 g, freshly prepared as described in ref. 10 during a 45 h reaction period) in benzene (50 ml). The mixture was stirred at reflux for 1 h and at room temperature for an additional hour. During the reaction

[5]*A cursory examination of the reaction between benzoyl chloride and amine IVa indicated that concomitant halogen exchange as previously observed in the case of N-bis(2-bromoethyl)amine (7a) might generally preclude use of the acyl chloride approach.*

[6]*We are indebted to the Cancer Chemotherapy National Service Center, National Institutes of Health, U.S. Public Health Service, for this valuable information.*

[7]*Consult ref. 4b for the p.m.r. spectrum of this substance.*

period, a color change from golden yellow to reddish brown was noted, and a more dense and darker oily phase appeared. The upper layer was decanted and the residue was diluted with methanol. The methanol solution in turn was diluted with diethyl ether. Cooling the solution led to amine IV*a* hydrobromide as colorless needles weighing 30.9 g (75%), m.p. 197–199°.

*N-(2-Bromoethyl)-N-(2-chloroethyl)amine (IVa) Hydrochloride*

*Method A*

A 1.0 g specimen of amine IV*a* hydrobromide (prepared by method B in the preceding experiment) was neutralized with 3 *N* sodium hydroxide. The base was extracted with benzene and the dry organic phase was treated with ethereal hydrogen chloride. The resulting hydrochloride derivative was recrystallized (3 times) from methanol – diethyl ether to yield an analytical sample melting at 195–197°.

Anal. Calcd. for $C_4H_{10}BrCl_2N$: C, 21.55; H, 4.52; Br, 35.85; Cl, 31.80; N, 6.28. Found: C, 21.48; H, 4.34; Br, 36.21; Cl, 32.01; N, 6.01.

*Method B*

A mixture of 2-(2′-bromoethylamino)ethyl benzoate (II*b*, 23 g, prepared as described in ref. 6) and 10% hydrobromic acid (150 ml) was heated at reflux for 3 h. After cooling, filtration, and washing with chloroform, the hydrobromic acid solution was concentrated *in vacuo* to a pale yellow oil (15.8 g, nearly quantitative conversion into amine III*b*). The oil was suspended in chloroform (130 ml) and treated (dropwise) with thionyl chloride (25 ml) in chloroform (30 ml). The mixture was heated at reflux for 0.5 h. Cooling the solution led to separation of amine IV*a* hydrochloride as yellow crystals, yield 16.9 g (98%), m.p. 185–189°. Three recrystallizations from ethanol – diethyl ether gave pure colorless needles melting at 195–197°. An infrared spectral comparison of the product and that obtained by method A confirmed the mutual identity of both hydrochloride salts.

Anal. Found: C, 21.26; H, 4.40; Br, 36.70; Cl, 31.80; N, 6.30.

*N-Methyl-N-(2-bromoethyl)-N-(2-chloroethyl)amine (IVb) Hydrobromide*

A mixture of amine IV*a* hydrobromide (3.0 g), 37% formalin (2.5 ml), and 98% formic acid (2 ml) was heated on a steam bath for 2 h. The solution was concentrated (*in vacuo*) to dryness and the residue dissolved in water (20 ml). The solution was neutralized with 6 *N* sodium hydroxide (20 ml) and the aqueous mixture extracted with benzene. Treating the benzene solution with ethereal hydrogen bromide yielded 2.8 g (87%) of amine IV*b* hydrobromide as colorless crystals, m.p. 114–115°. Two recrystallizations from methanol – diethyl ether yielded an analytical sample as needles melting at 122–125°; $\nu_{max}$ 2 900, 2 650, 2 575, 2 500, 2 350, 1 470, 1 375, 1 320, 1 285, 1 290, 950, and 760 (broad) $cm^{-1}$; p.m.r. responses at 3.15 (three methyl protons) and 3.7–4.3 (complex, eight methylene protons, principal signal at 3.91) $\delta$.

Anal. Calcd. for $C_5H_{12}Br_2ClN$: C, 21.34; H, 4.30; Br, 56.79; Cl, 12.60; N, 4.98. Found: C, 21.36; H, 4.60; Br, 56.73; Cl, 12.65; N, 4.85.

*N-Methyl-N-bis(2-iodoethyl)amine (IVc) Hydroiodide*

Amine IV*c* hydroiodide was prepared from N-bis(2-iodoethyl)amine hydroiodide (4.5 g (6)), 37% formalin (3 ml), and 98% formic acid (2.0 g) as described in the preceding experiment (see IV*b*). The product weighed 4.1 g (88%) and melted at 165–167°. Three recrystallizations from methanol gave an analytical specimen as needles; m.p. 173–175° (11); $\nu_{max}$ 2 900, 2 700, 1 460, 1 450, 1 425, 1 365, 1 210, 1 190, 1 060, 1 010, 965, and 930 $cm^{-1}$.

Anal. Calcd. for $C_5H_{12}I_3N$: C, 12.86; H, 2.59; I, 81.56; N, 3.00. Found: C, 12.74; H, 2.74; I, 81.66; N, 3.13.

*N-Methyl-N-bis(2-fluoroethyl)amine (IVd) Hydrobromide*

The procedure used for converting N-bis(2-fluoroethyl)amine hydrobromide (2.3 g (4*a*)) into amine IV*d* hydrobromide (m.p. 96–98°, 1.4 g, 57% yield) with 37% formalin (2 ml) and 98% formic acid (1.0 g) was that illustrated in the case of amine IV*b* hydrobromide. Recrystallization (twice) from methanol – diethyl ether gave an analytical sample as needles melting at 102–104°; $\nu_{max}$ 2 900, 2 700, 2 650 (doublet with shoulder at 2 500), 1 460, 1 450, 1 435, 1 420, 1 240, 1 195, 1 170, 1 110, 1 090, 1 070, 1 045, 1 035, 1 010, 970, 900, 880, and 860 $cm^{-1}$.

Anal. Calcd. for $C_4H_{10}BrF_2N$: C, 29.43; H, 5.93; Br, 39.16; N, 6.86. Found: C, 29.64; H, 6.00; Br, 39.15; N, 6.68.

Childs (12) has summarized a route to amine IV*d*, and more recently Nemets and Epshtein (13) reported conversion of bromofluoroethane (with methylamine) into amine IV*d* hydrochloride.

*N-(2-Bromoethyl)-N-(2-chloroethyl)benzylamine (VIIa) Hydrobromide*

In a typical experiment, amine IV*a* hydrobromide (10.0 g) was dissolved in water (50 ml) – ice (20 g) and treated with 6 *N* sodium hydroxide (20 ml). The mixture was extracted with benzene, and the dry (magnesium sulfate) extract was treated (dropwise during 10 min) with benzoyl bromide (3.5 g, prepared from benzoic acid and phosphorus tribromide). Before the solution was cooled, stirring was continued at room temperature for 2 h. The solution was filtered to remove amine IV*a* hydrobromide (4.5 g, 89% recovery) and the filtrate was slowly added with stirring during 0.5 h to a mixture of lithium aluminium hydride (0.76 g)

and dry diethyl ether (100 ml). After a total reaction period at room temperature of 1 h, water (approximately 4 ml) was cautiously added to the mixture. The general procedure employed at this point has been described in a prior contribution (6). Next, the solution was filtered, dried, and treated with anhydrous hydrogen bromide. Further dilution with diethyl ether led to the separation of amine VII*a* hydrobromide as colorless crystals, yield 4.3 g (63%), m.p. 165–170°. Two recrystallizations from methanol – diethyl ether gave a pure sample as needles; m.p. 176–179°; $\nu_{max}$ 2 900, 2 650, 2 550, 2 350, 1 490, 1 450, 1 430, 1 375, 1 245, 1 210, 1 010, 960, 930, 765, 750, and 700 $cm^{-1}$; p.m.r. responses at 3.8–4.2 (complex, eight methylene protons, principal signal at 3.92), 4.70 (two benzyl protons), and 7.72 (five aromatic protons) $\delta$.

Anal. Calcd. for $C_{11}H_{16}Br_2ClN$: C, 36.95; H, 4.51; Br, 44.70; Cl, 9.92; N, 3.92. Found: C, 36.85; H, 4.46; Br, 44.97; Cl, 9.76; N, 3.92.

*N-(2′-Bromoethyl)-N-(2′-chloroethyl)-3,4-methylenedioxybenzylamine (VIIb) Hydrobromide*

The acid bromide prepared from piperonylic acid (2.5 g) and oxalyl bromide (6 g) was allowed to react with the base corresponding to amine IV*a* hydrobromide (10.7 g) as described in the preceding experiment (see VII*a*). The crude amide was reduced by the lithium aluminium hydride (0.6 g) procedure (compare VII*a*), and the resulting amine hydrobromide weighed 5.3 g (88%), m.p. 159–163°. After two recrystallizations from methanol – diethyl ether the analytical sample (needles) melted at 164–165°; $\nu_{max}$ 2 900, 2 625, 2 500, 2 350, 1 500, 1 490, 1 445, 1 385, 1 260, 1 245, 1 105, 1 045, 950, 930, 880, 820, 810, 780, and 765 $cm^{-1}$; p.m.r. responses at 3.4–4.2 (complex, eight methylene protons, principal signal at 3.78), 4.50 (two benzyl protons), 6.08 (two methylenedioxy protons), and 7.08 (three aromatic protons) $\delta$.

Anal. Calcd. for $C_{12}H_{16}Br_2ClNO_2$: C, 35.89; H, 4.02; Br, 39.80; Cl, 8.83; N, 3.49. Found: C, 35.76; H, 4.08; Br, 40.04; Cl, 8.75; N, 3.41.

*N-(2′-Bromoethyl)-N-(2′-chloroethyl)-3,5-dimethoxybenzylamine (VIIc) Hydrobromide*

A sample of 3,5-dimethoxybenzoyl bromide (3.7 g, prepared as noted in ref. 6) was allowed to react with the amine corresponding to 10.7 g of nitrogen mustard IV*a* hydrobromide. The resulting amide was reduced with lithium aluminium hydride (0.57 g). The hydrobromide derivative of the product weighed 4.8 g (80%) and melted at 160–163°. The general experimental technique and method used for purifying the product was that illustrated in the case of amine VII*a*. The analytical specimen was obtained as needles; m.p. 165–167°; $\nu_{max}$ 2 850, 2 800, 2 600, 2 575, 1 595, 1 480, 1 460, 1 430, 1 360, 1 305, 1 215, 1 170, 1 160, 1 070, 1 060, and 845 $cm^{-1}$; p.m.r. responses at 3.4–4.2 (complex, eight methylene protons and six methoxy protons, principal signals at 3.80–3.90), 4.50 (two benzyl protons), and 6.80 (three aromatic protons) $\delta$.

Anal. Calcd. for $C_{13}H_{20}Br_2ClNO_2$: C, 37.39; H, 4.83; Br, 38.28; Cl, 8.49; N, 3.35. Found: C, 37.41; H, 5.10; Br, 38.60; Cl, 8.35; N, 3.47.

*N-(2′-Bromoethyl)-N-(2′-chloroethyl)-4-methoxyphenoxyethylamine (VIII) Hydrobromide*

Oxalyl bromide (9 g) containing 4-methoxyphenoxyacetic acid (3.6 g) was heated at reflux for 2 h. After removal (*in vacuo*) of excess oxalyl bromide the acyl bromide was obtained as a light brown oil. Without further purification the acyl bromide was treated with the free amine corresponding to 11.8 g of amine IV*a* hydrobromide. Subsequent reduction and purification of the product was accomplished as described for the isolation of amine VII*a* hydrobromide. The hydrobromide derivative of amine VIII was obtained in 63% yield (5.3 g). A pure specimen melted at 143–145°; $\nu_{max}$ 2 900, 2 650, 2 550, 2 350, 1 510, 1 485, 1 465, 1 440, 1 230, 1 020, 830, and 735 $cm^{-1}$; p.m.r. responses at 3.7–4.2 (complex, ten methylene and three methoxy protons, principal signals at 3.75 and 3.82), 4.22–4.50 (two methylene protons), and 6.90 (four aromatic protons) $\delta$.

Anal. Calcd. for $C_{13}H_{20}Br_2ClNO_2$: C, 37.39; H, 4.83; Br, 38.28; Cl, 8.49; N, 3.35. Found: C, 37.09; H, 4.90; Br, 38.40; Cl, 8.35; N, 3.23.

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