# Synthesis of Mustards from Putrescine, Cadaverine, and 1,3-Diaminopropane[1]

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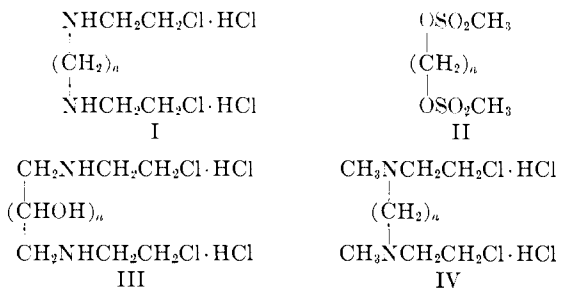
Three α,ω-bis(2-chloroethylamino)alkanes (I, $n$ = 3–5) were synthesized for antitumor screening. In the preparation of I ($n$ = 4 and 5) from the starting α,ω-diaminoalkanes, benzyl blocking groups were necessary to control the amount of hydroxyethylation. The N,N′-bis(2-hydroxyethyl)-N-N′-dibenzyl-α,ω-diaminoalkanes were chlorinated and the benzyl groups were catalytically removed with hydrogen to give the mustards (I, $n$ = 4, 5). The order of these two steps could be reversed, but the former sequence was preferred. All three mustards (I, $n$ = 3–5) showed confirmed activity against Leukemia L1210 and negligible activity against Sarcoma 180 and Walker 256.

Putrescine mustard (I, $n$ = 4) has some structural similarity to the known antitumor agents 1,4-dimethanesulfonyloxybutane (Myleran[2]) (II, $n$ = 4), 1,4-bis-(2-chloroethylamino)-1,4-dideoxyerythritol dihydrochloride[3] (III, $n$ = 2), and 1,6-bis(2-chloroethylamino)-1,6-deoxy-D-mannitol dihydrochloride[4] (III, $n$ = 4). It was therefore of interest to prepare putrescine mustard for tumor screening.

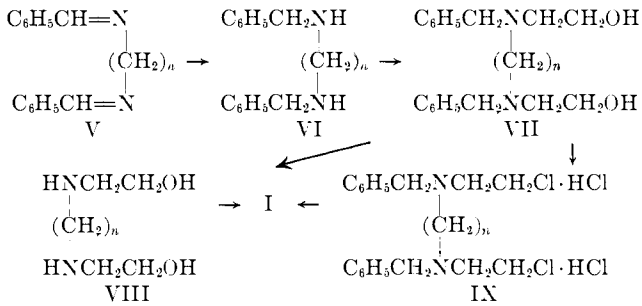
Two other mustards of structure I ($n$ = 2 and 6) have already been prepared and found to have no inhibitory action on a number of animal tumors.[4] However, the change of chain length in I from $n$ = 2 and 6 to $n$ = 4 may have some effect on biological activity. In the case of the dimethanesulfonates (II, $n$ = 2–10), maximum activity[2] occurred at $n$ = 4. The other two homologs I ($n$ = 3, 5) became of interest when inhibitory action against Leukemia L1210 was observed initially with putrescine mustard (I, $n$ = 4).

A series of mustards related to I bearing tertiary amine groups (IV, $n$ = 2–6, 9) has been prepared by Ishidate and co-workers.[5] They concluded that IV ($n$ = 6, 9) had the most promising chemotherapeutic indices against Yoshida sarcoma.

This paper reports the synthesis of putrescine mustard (I, $n$ = 4), cadaverine mustard (I, $n$ = 5), and the trimethylenediamine mustard (I, $n$ = 3).




Direct reaction of ethanolamine with the required α,ω-dibromoalkane[4] was not suitable for preparing the hydroxyethyl precursors of I ($n$ = 4, 5). In both cases, facile cyclization to a pyrrolidine or piperidine could be anticipated and, in fact, little or none of the desired VIII could be obtained by this route.




In the alternative approach starting from the α,ω-diaminoalkanes, it was necessary to block the amino groups in order to introduce only one hydroxyethyl

Table I

Screening Data Summary[a] for I ($n$ = 3–5) Against Leukemia L1210 in the Mouse

| $n$ | Dose, mg./kg. | Wt. difference, $T/C$[b] | % $T/C$[c] |
|---|---|---|---|
| 5 | 100 | −2.8 | 129 |
| | 100 | −2.9 | 138 |
| | 100 | −3.7 | 136 |
| | 65 | −1.2 | 118 |
| | 40 | −0.6 | 112 |
| 4 | 56 | −3.1 | 147 |
| | 56 | −3.4 | 108 |
| | 84 | −4.1 | 93 |
| | 56 | −4.7 | 97 |
| | 37 | −3.2 | 163 |
| | 25 | −2.3 | 142 |
| 3 | 48 | −5.1 | 76 |
| | 24 | −2.7 | 164 |
| | 24 | −0.5 | 103 |
| | 36 | −1.0 | 176 |
| | 24 | −1.2 | 128 |
| | 16 | 0.1 | 130 |
| | 10 | 0.8 | 101 |

[a] Screening was performed under the auspices of the Cancer Chemotherapy National Service Center according to its protocol outlined in "Protocols for Screening Chemical Agents and Natural Products Against Animal Tumors and Other Biological Systems" in Cancer Chemotherapy Reports (25), December, 1962, p. 1. [b] Weight difference (g.) of treated ($T$) minus control ($C$). The greater the weight difference, the more toxic the dose of drug. [c] Effect of treatment on survival is given in per cent $T/C$; that is, in per cent of ratio of survival (days) of treated ($T$)/control ($C$). A value of $T/C \leq 85\%$ is considered a toxic test. A value of $T/C \leq 125\%$ is considered a positive result.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center.

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TABLE II
SUBSTITUTED $\alpha,\omega$-DIAMINOALKANES

| Compound | $n$ | % yield[a] | M.p., °C.[b] | Formula | Analysis,[c] % C | H | Cl | N |
|---|---|---|---|---|---|---|---|---|
| VI·2HCl[d] | 5 | (50) | *ca.* 300 dec.[e] | $C_{19}H_{28}Cl_2N$ | 64.3 | 7.94 | | 7.89 |
| | | | | | 64.2 | 8.15 | | 7.53 |
| VI·2HCl[f] | 4 | (59) | >300[f] | $C_{18}H_{26}Cl_2N$ | 63.5 | 7.66 | 20.8 | 8.24 |
| | | | | | 63.6 | 7.30 | 20.7 | 8.23 |
| VII | 5 | (69) | Sirup | $C_{23}H_{34}N_2O_2$ | 74.6 | 9.25 | | 7.56 |
| | | | | | 74.3 | 9.03 | | 7.53 |
| VII·2HCl | 4 | 38 | 206–208[g] | $C_{22}H_{34}Cl_2N_2O_2$ | 61.5 | 8.00 | 16.5 | 6.53 |
| | | | | | 61.0 | 7.98 | 16.3 | 6.17 |
| IX·2HCl[h] | 5 | 88 | 180–181.5[i] | $C_{23}H_{34}Cl_4N_2$ | 57.5 | 7.14 | 29.5 | 5.84 |
| | | | | | 57.7 | 7.23 | 29.3 | 5.85 |
| IX·2HCl | 4 | 61(32) | 230–232[e] | $C_{22}H_{32}Cl_4N_2$ | 56.7 | 6.91 | 30.4 | 6.02 |
| | | | | | 57.0 | 6.56 | 30.4 | 5.99 |
| I[j] | 5 | 79 | 234–237[g] | $C_9H_{22}Cl_4N_2$ | 36.0 | 7.40 | 47.3 | 9.34 |
| | | | | | 36.0 | 7.29 | 47.1 | 9.28 |
| I | 4 | 74 | 249–251[g] | $C_8H_{20}Cl_4N_2$ | 33.6 | 7.00 | 49.5 | 9.79 |
| | | | | | 33.5 | 7.09 | 49.3 | 9.46 |
| I[k] | 3 | 53(25) | 240–248 dec.[g] | $C_7H_{18}Cl_4N_2$ | 30.9 | 6.68 | 52.2 | 10.3 |
| | | | | | 30.9 | 6.85 | 52.4 | 10.0 |
| VIII·2HCl | 5 | 80 | 216–217[l] | $C_9H_{24}Cl_2N_2O_2$ | 41.1 | 9.18 | 27.0 | 10.6 |
| | | | | | 41.1 | 9.28 | 26.7 | 10.6 |
| VIII·2HCl | 4 | 87 | 156–158[e] | $C_8H_{22}Cl_2N_2O_2$ | 38.6 | 8.88 | 28.4 | 11.2 |
| | | | | | 38.6 | 8.36 | 28.5 | 11.3 |
| VIII·2HCl[m] | 3 | (50) | 155–157[n] | $C_7H_{20}Cl_2N_2O_2$ | 35.8 | 8.57 | 30.2 | 11.9 |
| | | | | | 35.3 | 8.74 | 29.8 | 11.6 |

[a] Yields are for compounds of sufficient purity for use in the next step. Yields for analytical samples are in parentheses. [b] Of analytical samples. [c] For each compound, analytical values are given in two rows: the calculated values are on the top row; the results found on the bottom. [d] The yield of free base, sufficiently pure for the next step, was 99% for VI ($n$ = 5) and 74% for VI ($n$ = 4). The latter never crystallized (lit.[6] m.p. 65°). [e] Crystallized from 90% ethanol (VI·2HCl); 95% ethanol (IX·2HCl); absolute ethanol (VIII·2HCl). [f] Crystallized from 3 *N* hydrochloric acid. [g] Crystallized from methanol. Compounds I ($n$ = 4, 5), required thorough drying for 16–24 hr. (0.1 mm.) and toluene reflux temperature to remove solvent completely. [h] Reaction medium was thionyl chloride–chloroform (3:1). [i] Crystallized from ethanol–Skellysolve B. [j] Twice the amount of catalyst was used. [k] Prepared like IX by reaction with thionyl chloride. Acetonitrile (or sometimes a large excess of thionyl chloride) was used as solvent. The dihydrochloride of VIII ($n$ = 3), was formed *in situ* before the slow addition of thionyl chloride. Heating at reflux for 3 hr. was necessary for complete solution and complete reaction. [l] Crystallized from methanol–ethanol: softened at 208°. Hydrogenolysis of VII·2HCl ($n$ = 5) was performed at room temperature. [m] Obtained 62% of the free base (VIII), b.p. 138–150° (0.05 mm.), m.p. 20–30°, very hygroscopic, suitable for the next step, from the reaction of 1,3-dibromopropane and ethanolamine by a standard literature procedure.[3] [n] Crystallized from methanol–ether.

group per amino nitrogen. The anils (V, $n$ = 4,[6] 5) were reduced with sodium borohydride[7] to the dibenzylamines (VI, $n$ = 4,[6] 5). These were converted by ethylene oxide to the N,N′-bis(2-hydroxyethyl)-amines (VII, $n$ = 4, 5). Debenzylation with hydrogen and palladium–charcoal to VIII followed by chlorination with thionyl chloride gave the desired mustards (I, $n$ = 4, 5). The least satisfactory step was the last; chlorination of VIII ($n$ = 4, 5) under a variety of conditions inevitably gave low yields of dark, impure I ($n$ = 4, 5).

A marked improvement in the synthesis was possible by reversing the order of the last two steps. The debenzylation of IX proceeded smoothly without any dehalogenation of the mustard. Similar catalytic hydrogenolyses to remove benzyl groups from mustard molecules have been employed by Friedman and Seligman with an N-phosphorylated nitrogen mustard[8] and by Benn, *et al.*,[9] in an improved synthesis of phenol mustard.

The synthesis of the mustard I ($n$ = 3) proceeded by the standard method.[4] The reaction of 1,3-dibromobutane and ethanolamine gave VIII ($n$ = 3). Chlorination of this proceeded best in excess thionyl chloride as solvent or in acetonitrile. In other solvents, complete chlorination was difficult because the insoluble dihydrochloride of VIII ($n$ = 3) precipitated.

The mustards I ($n$ = 3–5) exhibited confirmed activity[10] against Leukemia L1210 in the mouse, and no activity against Sarcoma 180 in the mouse and Walker 256 (subcutaneous) in the rat. Against Adenocarcinoma 755 in the mouse, I ($n$ = 5) was inactive, while I ($n$ = 3, 4) were somewhat effective in inhibiting tumor growth but had such toxicity that their utility against Adenocarcinoma 755 is doubtful.

The Leukemia L1210 data are summarized in Table I. The results show that the activity increases for I in the order $n$ = 5, 4, 3. However, the toxicity also increases in the same order, as shown by the weight difference data and by toxicity data in other animal systems. For example, in the Walker 256 tests, the $LD_{10}$[11] were about 14, 12.5, and 2 for I ($n$ = 5, 4, 3), respectively. The results for I ($n$ = 3 to 5) are not comparable with those obtained by Vargha, *et al.*, for I ($n$ = 2, 6[4]) because different tumor systems were used. The results on hand, however, do not suggest a sharp peak of

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(7) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957); see J. H. Billman and J. W. McDowell, *ibid.*, **26**, 1437 (1961), for references to other methods of reducing Schiff bases.

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(9) M. H. Benn, A. M. Creighton, L. N. Owen, and G. R. White, *J. Chem. Soc.*, 2365 (1961).

(10) Confirmed active as defined by the Cancer Chemotherapy National Service Center protocol. See footnote *a*, Table I.

(11) The highest dose (mg./kg.) killing no more than 10% of the animals is defined as the $LD_{10}$.

activity for the series I as was found with the dimethanesulfonates II at $n = 4$.[2]

The activity against Leukemia L1210 shown by I ($n$ = 3 to 5) suggests that similar mustards from other diamines or polyamines, such as spermine and spermidine, may be interesting candidates for antitumor study.

## Experimental[12]

**1,5-Di(benzylideneamino)pentane (V, $n = 5$).**—A 10-g. portion (0.098 mole) of 1,5-diaminopentane was added slowly to a solution of 20.8 g. (0.196 mole) of benzaldehyde in 30 ml. of absolute ethanol. The solution was kept at room temperature for 20 min., at reflux temperature for 25 min., and was evaporated *in vacuo* to a sirup which crystallized on cooling to give 26.8 g. (99%) of V ($n = 5$), m.p. 30–31.5. This was sufficiently pure for the next step. Three recrystallizations from Skellysolve B gave the analytical sample of V ($n = 5$), with unchanged melting point; $\lambda_{max}^{Nujol}$ 3.28, 3.32 (C–H of N=CH— and phenyl), 6.05 (C=N) $\mu$.

*Anal.* Calcd. for $C_{19}H_{22}N_2$: C, 82.0; H, 7.97; N, 10.1. Found: C, 81.7; H, 7.82; N, 9.93.

**1,5-Di(benzylamino)pentane (VI, $n = 5$) Dihydrochloride.**—Excess sodium borohydride (14.0 g., 0.37 mole) was added in small portions over a period of 1 hr. to a stirred solution of 23.8 g. (0.0856 mole) of V ($n = 5$) in 230 ml. of methanol cooled in an ice bath. The solution was stirred for 40 min. more at room temperature, heated at reflux on a steam bath for 15 min., then evaporated *in vacuo* at 50° to leave a semisolid. This was taken up in 360 ml. of water, and the oil which separated was extracted with two 200-ml. portions of methylene chloride. The dried extract was evaporated to leave 23.9 g. (99%) of VI ($n = 5$), as a yellow oil sufficiently pure for the next step.

A portion of the oil in ethanol was converted to the dihydrochloride with gaseous hydrogen chloride. The precipitated salt was crystallized twice from 90% aqueous ethanol to give the dihydrochloride salt of VI (see Table II).

**N,N′-Bis(2-hydroxyethyl)-N,N′-dibenzyl-1,5-diaminopentane (VII, $n = 5$).**—An ice-cooled solution of 10.0 g. (0.035 mole) of the dibenzylamine VI ($n = 5$) in 130 ml. of methanol was treated with 35.2 ml. (0.71 mole) of freshly distilled ethylene oxide. The flask was capped and the mixture was stirred overnight with the temperature allowed to rise gradually to about 25°. The solution was evaporated *in vacuo* (bath, 35°) to leave 14.8 g. of sirup. This was taken up in 30 ml. of methylene chloride; the solution was washed with four 30-ml. portions of water, dried, filtered, and evaporated *in vacuo*, finally at 55° (0.1 mm.), to give 9.07 g. (69%) of analytically pure light yellow, sirupy VII ($n = 5$).

**N,N′-Bis(2-chloroethyl)-N,N′-dibenzyl-1,4-diaminobutane Dihydrochloride (IX, $n = 4$).**—A solution of 61.5 g. (0.143 mole) of the bishydroxyethylamine VII ($n = 4$) in 200 ml. (2.78 moles) of thionyl chloride was heated at reflux for 1 hr., then poured into 2 l. of petroleum ether (b.p. 30–60°). The precipitate was collected, washed with petroleum ether, then benzene, and dried to give 65 g. (98%) of crude product. Recrystallization from 95% ethanol (1 g./50 ml.) gave 40.4 g. (60.6%) of product, m.p. 206–219° dec., of sufficient purity for the hydrogenolysis step.

**N,N′-Bis(2-chloroethyl)-1,4-diaminobutane Dihydrochloride (I, $n = 4$).**—A mixture of 15.0 g. (0.032 mole) of the dibenzyl mustard IX ($n = 4$) and 1.88 g. of 5% palladium-on-carbon in 250 ml. of 95% acetic acid was hydrogenated in a Parr apparatus at room temperature (initial pressure 3.5 kg./cm.²). The theoretical amount of hydrogen was taken up in 30–40 min.; no further uptake was noted after a total of 4.5 hr. The reaction mixture was filtered through a Celite pad, the catalyst was washed well with methanol, and the combined filtrate and washes were evaporated *in vacuo* at 60° to leave 9.1 g. (99%) of product, m.p. 235–241° dec. Recrystallization from methanol gave 6.8 g. (74%) of I ($n = 4$), m.p. *ca.* 240–245° dec. (varies with heating rate).

**N,N′-Bis(2-hydroxyethyl)-1,4-diaminobutane (VIII, $n = 4$) Dihydrochloride.**—A mixture of 1.00 g. (2.4 mmoles) of the dibenzylamine dihydrochloride VII·2HCl ($n = 4$) and 100 mg. of 5% palladium-on-charcoal in 50 ml. of 2-methoxyethanol (or 35 ml. of 6 *N* hydrochloric acid), was hydrogenated 75–80° and 3.15 kg./cm.² (initial) to give 0.50 g. (87%) of product, m.p. 128–133°.

(12) Melting points were obtained with the Fisher–Johns apparatus and are corrected. The solvent Skellysolve B is essentially hexane (b.p. 60–68°). The general experimental procedures are illustrated by one example each. The physical data and analyses for all the compounds are listed in Table II. The infrared spectra of all the compounds were compatible with their structures.

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# Transformation of Codeine to an Analog of the Potent Analgesic Phenazocine

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Codeine has been transformed to an analog IX of phenazocine incorporating the 4,5-oxygen bridge originally present in the parent alkaloid. The analgesic activity of IX was found to be approximately twice that of morphine.

The high analgesic effectiveness of phenazocine [(±)-2′-hydroxy-2-phenethyl-5,9-dimethyl-6,7-benzomorphan] (X) has been well demonstrated.[1] One may view this substance as being related to the morphine system in which the 4,5-oxygen bridge has been abolished and ring "III" opened and partially degraded. Although the pronounced analgesic properties of the morphinans[2] demonstrate that the oxygen bridge apparently is not essential for activity, it nevertheless was a matter of theoretical interest to prepare an analog of phenazocine incorporating the oxygen bridge to determine its effect on pharmacological activity. It was evident at the outset of this investigation that the most promising way to the system envisaged (IX) would be through degradation of an appropriate morphine derivative utilizing reactions that would reasonably ensure the integrity of the 4,5-oxygen system.

The feasibility of oxidative cleavage of ring III in the morphine series was first demonstrated in this Laboratory some years ago in degradation studies with dihydrothebaine.[3] In essence this involved osmic acid hydroxylation of an unsaturated center followed by lead tetraacetate oxidation of the resulting glycol.

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