17199-29-0; (*R*)-laudanosine (+)-mandelate, 54677-48-4; (*R*)-laudanosine, 85-63-2; *dl*-armepavine, 5884-67-3; (*S*)-armepavine (−)-mandelate, 54677-49-5; (*S*)-armepavine, 14400-96-5; (*R*)-armepavine (+)-mandelate, 54677-50-8; (*R*)-armepavine, 524-20-9; phenol, 108-95-2; cupric oxide, 1317-38-0; pentafluorophenylcopper, 18206-43-4.

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Synthesis of the Potentially Cytotoxic Compound 5-[Bis(2-chloroethyl)amino]-1,3-phenylene Biscarbamate

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Received February 6, 1975

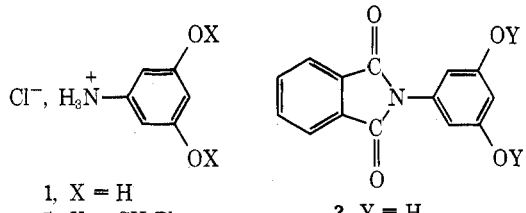
5-Aminoresorcinol hydrochloride (**1**) reacted with ethylene oxide to give **2**, which could not be converted to its bis(2-chloroethyl)amino derivative in the presence of standard reagents. Compound **1** was therefore converted to **3** by treatment with phthalic anhydride and thence to **4** by reaction with benzyl bromide under alkaline conditions. Removal of the phthalimido group with hydrazine, followed by treatment with hydrochloric acid, gave the hydrochloride **5**, which reacted with ethylene oxide to produce **6**. Bistosylation to **7**, followed by treatment with lithium chloride in acetone, afforded the mustard **8** in high yield. Removal of the blocking groups to give **9** was accomplished with refluxing trifluoroacetic acid in the presence of anisole as a benzyl cation scavenger, the product being isolated and characterized as its trifluoroacetic acid solvate. Treatment of **9** with cyanogen bromide gave the dicyanate **10** as a crude powder which underwent addition of water to give the dicarbamate **11** upon treatment with hydrochloric acid. Compounds **8**–**11** are potentially cytotoxic nitrogen mustards.

The presence of the *O*-carbamate group as a structural feature of a number of antitumor compounds[1] suggests that this group might be incorporated in concert with other structural moieties of known antitumor propensities. The synthetic objective undertaken in the present work was to incorporate two *O*-carbamate functions into the structure of an aromatic nitrogen mustard, the latter being a structural class having established antitumor activity.[2] Furthermore, it has been demonstrated in certain instances that more favorable antitumor activity was obtained with meta-substituted aromatic nitrogen mustards than with the corresponding ortho or para derivatives.[3]

Phenolic derivatives of aniline mustard have been prepared by Artico and Ross[4] and more recently by Edwards et al.[5] In addition, two nitrogen mustards of the pyrocatechol series have been described by Vasil'eva and Berlin.[6]

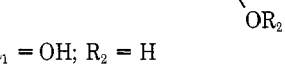
Synthetic strategy directed toward the synthesis of **11** was focused at first on schemes originating with demethylation of the known compound 1-[bis(2-chloroethyl)amino]-3,5-dimethoxybenzene.[7] Conventional reagents and conditions for demethylation of phenolic ethers, such as hot hydrochloric acid, gave consistently unsatisfactory results. Attention was next given to the synthesis of **2** as a possible substrate for mustard synthesis. The diol **2** was prepared by treating 5-aminoresorcinol hydrochloride (**1**)[8] with ethylene oxide. It was found, however, that **2** underwent extensive decomposition when attempts were made to replace the aliphatic hydroxyl groups by chloro groups using a variety of methods.

Protection of the aromatic hydroxyl groups was therefore a necessity before attempting further structural modification of **1**. This required that the amino function itself be protected at the outset. This was accomplished by phthalimidation according to a modification of the general method of Wanag,[9] using phthalic anhydride in acetic acid to provide **3**. Subsequent formation of the bisbenzyl ether **4** was undertaken with the expectation that eventual removal



1, X = H
5, X = CH_2Ph

3, Y = H
4, Y = CH_2Ph



2, R_1 = OH; R_2 = H
6, R_1 = OH; R_2 = CH_2Ph
7, R_1 = OTs; R_2 = CH_2Ph
8, R_1 = Cl; R_2 = CH_2Ph
9, R_1 = Cl; R_2 = H; CF_3COOH solvate
10, R_1 = Cl; R_2 = CN
11, R_1 = Cl; R_2 = $CONH_2$

Ph = phenyl
Ts = *p*-toluenesulfonyl

could be accomplished without difficulty,[5] a prediction which fortunately proved to be correct. Synthesis of **4** proceeded in a satisfactory manner by treatment of **3** with benzyl bromide in dimethylformamide in the presence of sodium methoxide as a proton acceptor. The phthalimido group was next removed with hydrazine in aqueous ethanol and the product was isolated as the hydrochloride **5.** Conventional treatment of **5** with ethylene oxide in aqueous acetic acid gave the diol **6,** now ready for the crucial and sensitive construction of the bis(2-chloroethyl)amino moiety. Among the possible conditions explored were tosyl chloride–pyridine,[10] phosphorus oxychloride–chloroform (or benzene),[4,11] and thionyl chloride–pyridine.[12] Each of these attempts at direct conversion gave intractable gums or oils whose NMR spectra suggested the presence of degraded starting material. Mesyl chloride–pyridine[13] resulted in the formation of crude bis(methanesulfonate). Use of the system triphenylphosphine–carbon tetrachloride[14] provided some encouragement as the NMR spectrum of the reaction product showed the presence of the desired mustard. However, a number of attempts to separate the desired compound from the by-products and unchanged starting material were not successful.

Synthesis of the protected mustard **8** was performed in two steps via displacement of the bistosylate **7** according to a modification of the method of Werner,[15] in which the system lithium chloride–acetone[16] was used. Consistently high (>90%) yields were realized in the displacement step. Conditions used for debenzylation of **8** to **9** were generally those described by Marsh and Goodman,[17] with the inclusion of anisole as a benzyl cation scavenger as described by Sakakibara et al.[18] Use of the reagent trifluoroacetic acid proved to be a fortunate choice here, in view of the fact that purification proceeded in a facile manner to provide the stabilized trifluoroacetic acid solvate of the product. Subsequent experiments showed that when the trifluoroacetic acid was removed [Amberlite IR-45 (OH^-); methanol solution] the resultant desolvated **9** was obtained as an unstable oil.[19] Conversion of **9** to **11** proceeded in two stages via the dicyanate **10** using the cyanogen halide method, developed by Grigat and Pütter.[20] Preliminary experiments in which the model compound resorcinol was converted to its dicarbamate showed commercial cyanogen bromide to be an effective reagent.[21] Furthermore, it was established with the model system that prior neutralization of the trifluoroacetic acid of solvation with triethylamine permits the reaction with cyanogen bromide to proceed without difficulty. Application of this method to the conversion of **9** to **11** was seen to proceed in a facile manner. The dicyanate **10** was isolated during a probe preparation as a reasonably pure solid having a correct infrared spectrum. A satisfactory purification method was not found for **10,** and it was usually not isolated during the preparation of **11.**

It is planned to have the new compounds described herein screened for antitumor activity by the Drug Research and Development Branch, National Institutes of Health.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt using open capillary tubes and are uncorrected. An atmosphere of nitrogen was maintained above each of the reaction mixtures. Evaporations were performed at diminished pressure on a rotary evaporator. Petroleum ether refers to that fraction boiling at 30–60°. Analyses indicated in the table only by the symbols of the elements were within ±0.3% of the theoretical values. The ir spectra were obtained on a Perkin-Elmer Model 137 recording spectrophotometer and the uv spectra by G. B. Smith and staff using a Cary Model 118 spectrophotometer. Varian Associates A-60A and JEOL C-60HL instruments were used by A. W. Douglas and staff for recording NMR spectra. In each case where the preparation of a new compound is described it was found to have ir (Nujol), NMR (DMSO-d_6), and uv spectra which were in accord with expectation. The authors are grateful to R. N. Boos (and J. L. Gilbert) and associates for microanalyses. Assistance in the preparation of intermediates was provided by J. J. Seman and M. A. Ryder.

5-Aminoresorcinol Hydrochloride (1). Concentrated ammonium hydroxide (3 l.) was added over a 3-min period to 500 g (3.1 mol) of solid phloroglucinol dihydrate, while stirring and cooling. Upon completion of the addition a stream of ammonia was bubbled through the reaction mixture for 30 min. The cooling bath was removed and stirring was continued at room temperature for 46 hr. Vacuum concentration (bath, 50°) of the clear brown solution gave a solid, to which was added 1 l. of 5 *N* HCl, and the mixture was concentrated under vacuum (nitrogen was no longer required) to a yellow solid. Crystallization from 1.5 l. of warm acetone (Darco G-60) gave 419 g (84%) of **1.** A sample of the product decomposed without melting when heated to 260°, consistent with melting point behavior described in the literature.[8] A high level of purity was substantiated by examination of spectra (ir and NMR) and elemental determinations.

5-Phthalimidoresorcinol (3). A mixture was prepared from 200 g (1.24 mol) of **1,** 276 g (1.87 mol) of phthalic anhydride, and 2.6 l. of glacial acetic acid. This was stirred and to it was added all at once 112 g (1.36 mol) of anhydrous sodium acetate. The mixture was heated under reflux for 75 min, then poured, with stirring, into 6 l. of hot water. This was boiled for 5 min, and the solid was collected by filtration and washed with 700 ml of hot water. The light tan product amounted to 268 g (85%) of pure **3;** when heated the compound decomposed above 300° without prior melting.

5-Phthalimidoresorcinol Dibenzyl Ether (4). A clear solution was prepared by dissolving 616 g (2.42 mol) of **3** in 3.45 l. of DMF. This was cooled in an ice bath and to it was added 279 g (5.16 mol) of sodium methoxide at a rate such that the temperature did not exceed 25°. A suspension was obtained to which was added cautiously 616 ml (887 g, 5.2 mol) of benzyl bromide, again keeping the temperature close to 25°. Stirring was continued for 24 hr, whereupon the turbid mixture was poured into 10.3 l. of vigorously agitated water. A gum was obtained which was separated and vacuum dried at room temperature. Trituration of this with 6 l. of hot ethanol caused solidification. The mixture was cooled, and the solid was collected and washed with 1 l. of ethanol, then dried to give 854 g (81%) of nearly pure product. A sample prepared in a separate run using the same procedure was crystallized from acetone to give white crystals of **4,** mp 137–139°.

5-Aminoresorcinol Dibenzyl Ether Hydrochloride (5). To a stirred suspension of 28 g (0.064 mol) of **4** in 179 ml of ethanol was added 9.3 g (0.16 mol of $N_2H_4 \cdot H_2O$) of an 85% aqueous solution of hydrazine hydrate. The reaction mixture was heated under reflux for 2 hr (thickening of the reaction mixture required the addition of 100 ml of ethanol during this period). Concentration under vacuum (room temperature) gave a white paste which was slurried with 156 ml of ether and the mixture was combined with 156 ml of 40% aqueous KOH. The layers were separated, the aqueous layer was extracted with four 150-ml portions of ether, and the combined ether solutions were dried (K_2CO_3), decolorized (Norit A), and filtered through a pad of Celite 545. The filtrate was reduced in volume to 175 ml, cooled, and treated with a stream of gaseous HCl (30 min). The precipitated solid was washed with ether and dried to give a first crop of 12.8 g, mp 188–189°. Concentration of the ethereal mother liquors to a volume of 75 ml gave an additional 4.4 g (same melting point), bringing the total crude yield to 17.2 g (79%).[22] These crops were combined and crystallized twice from ethanol (Darco G-60) to give 10.7 g (49%) of pure **5,** mp 191–193°.

5-[Bis(2-hydroxyethyl)amino]resorcinol Dibenzyl Ether (6). In a flask protected from moisture and equipped with a cold-finger condenser containing a Dry Ice–acetone mixture were placed 250 g (0.73 mol) of **5** and 1.61 l. of 50% aqueous acetic acid. The mixture was stirred and cooled to 0°, then to it was added all at once 242 ml (4.86 mol) of ethylene oxide. Stirring was continued for 19 hr while the flask and its surrounding bath came to room temperature. Residual ethylene oxide was removed with a stream of nitrogen (1.5 hr) causing a solid to separate. This was collected by filtration, washed with water, and dried to yield 231 g (80%) of **6,** mp 94–95°. A sample for analyses was recrystallized from ethanol, mp 93–96°.

5-[Bis(2-tosyloxyethyl)amino]resorcinol Dibenzyl Ether (7). A solution was prepared from 5.0 g (0.013 mol) of **6** and 21 ml of pyridine (dried over KOH). This was cooled to −5° and to it was added in one portion 5.3 g (0.028 mol) of *p*-toluenesulfonyl chlo-

ride. Following 30 min of stirring at 0 to −5° the reaction mixture was kept overnight in the refrigerator. It was next cooled to 0° and 62 ml of water was added in small portions while keeping the temperature below 5°. An orange oil separated. To the mixture was added 50 ml of $CHCl_3$, and after being stirred for 30 min the layers were separated and the aqueous layer was back-extracted with two 50-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4), treated with Darco G-60, and concentrated to dryness (bath, 50°). The resultant oil was evaporated successively with two 50-ml portions each of ethanol, acetone, and petroleum ether. It was next covered with 50 ml of ethanol and warmed to 50°, with stirring, for 30 min. Light orange crystals were obtained which were washed successively with cold 10-ml portions of ethanol, petroleum ether, and ether. When dried the product amounted to 6.7 g (75%) of pure **7**, mp 86–89°.

5-[Bis(2-chloroethyl)amino]resorcinol Dibenzyl Ether (8). A glass-lined reaction vessel was charged with 60.0 g (0.085 mol) of **7**, 14.5 g (0.34 mol) of dry lithium chloride, and 600 ml of dry acetone. The vessel was sealed and heated at 80° for 8 hr with agitation. Upon cooling a solid was seen to have separated. This was removed by filtration and washed with acetone, the combined filtrate and wash liquors then being concentrated to dryness. This solid residue was stirred thoroughly with 250 ml of $CHCl_3$, leaving behind a granular solid (mp >275°) which was separated by filtration. The filtrate was next washed with 250 ml of water and the aqueous layer was back-extracted with 250 ml of $CHCl_3$. The combined $CHCl_3$ layers were dried ($MgSO_4$), filtered, and concentrated to dryness.

A total of 178 g (0.254 mol) of **7** was processed in this manner in three separate runs. The combined crude solids were crystallized from hot ethanol (600 ml) and the crystalline product was washed successively with 100-ml portions of cold ethanol and petroleum ether to yield 104 g (95%) of **8**, mp 88–89°.

5-[Bis(2-chloroethyl)amino]resorcinol Solvate with Trifluoroacetic Acid (9). A solution was prepared from 98.7 g (0.23 mol) of **8**, 987 ml of trifluoroacetic acid, and 31.6 ml (31.5 g, 0.29 mol) of anisole. The reaction mixture was stirred and heated under reflux for 5 hr, then cooled and concentrated to an oil (bath 50°). This was evaporated with three 1-l. portions of C_6H_6 and triturated with 1 l. of $CHCl_3$. Overnight storage under $CHCl_3$ in the refrigerator gave a crystalline solid which was washed with cold $CHCl_3$ and vacuum dried at room temperature to provide 70.2 g (84%) of **9**, mp 138–143°. Differential thermal analysis (20 deg/min) showed a melting point endotherm at 144° followed immediately by a decomposition exotherm.

The description of compound **9** as a solvate (rather than a salt) is based on the following experimental observations. Firstly, potentiometric titration ($HClO_4$–HOAc solvent) showed equiv wt 371 (calcd for $C_{10}H_{13}Cl_2NO_2 \cdot C_2HF_3O_2$, equiv wt 364), without first generating the free amine as is necessary with amine hydrochlorides [using excess $Hg(OAc)_2$]. This substantiated the availability of the electron pair on nitrogen under these conditions. Furthermore, the NMR spectra of the solvate **9** and the desolvated compound showed identical methylene proton signals. The only difference was in the position and integration of the active envelope, an expected result of the difference in acidity. This indicated an absence of protonation on nitrogen by trifluoroacetic acid, which would be expected to produce a chemical shift difference and splitting of the absorption. Also, the infrared spectrum of **9** showed a distinct carbonyl band at 5.7 μ, characteristic of molecular trifluoroacetic acid, in contrast to the known shift of this absorption to longer wavelengths which accompanies salt formation. Finally, thermogravimetric analysis showed a weight loss of 21% at 100° (browning), which is well below the observed melting point, indicating the release of solvent as opposed to the dissociation of a salt.

5-[Bis(2-chloroethyl)amino]-1,3-phenylene Biscarbamate (11). To a stirred solution (at 3°) of **9** (10 g, 28 mmol) in acetone (100 ml) containing 4.0 ml (28 mmol) of triethylamine was added in one portion a solution of cyanogen bromide (10 g, 97 mmol) in 100 ml of acetone, causing a temperature increase to 8°. The temperature was lowered to −5° and 8.0 ml (56 mmol) of additional triethylamine was added over a 6-min period (temperature about 0°). The reaction mixture was stirred at 0° for 0.5 hr and then poured with stirring into 750 ml of cold water, giving a solid which was collected and washed with water. In a separate preparation this solid was washed with ether to give the crude dicyanate **10**, mp 73–75°, ir ν_{CN} 4.4 μ. The combined filtrate and wash liquors were extracted with an equal volume of $CHCl_3$, which on concentration gave a brown oil. This was combined with the solid dicyanate from above, dissolved in 75 ml of acetone, cooled to 0°, and treated with 28 ml of 20% HCl at such a rate that the temperature did not rise above 5°. The temperature was maintained at 0° for 15 min, then allowed to come to room temperature (30 min), and the solution was finally concentrated to dryness (bath, 50°) giving a brown glass. This became crystalline when triturated with 50 ml of ethanol and left at room temperature for 64 hr. The product was washed lightly with ethanol and then with ether, giving 5.7 g (61%) of white crystalline **11**, mp 187–188° dec. If necessary, it could be recrystallized from acetone.

5-[Bis(2-hydroxyethyl)amino]resorcinol (2). A solution of **1** (10 g, 0.062 mol) in ethanol (100 ml) containing 230 mg of *p*-toluenesulfonic acid monohydrate was treated with ethylene oxide (61.6 ml, 1.24 mol) in the usual way (see preparation of **6**). Concentration (bath, 50°) gave a syrup which solidified when triturated with 15 ml of acetone to give 4.8 g (36%) of yellow crystals, mp 157–159° dec. A sample for analysis was obtained by crystallization from ethanol, mp 161–162° dec.

Acknowledgment. This investigation was supported by Contract NIH-72-2002 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

Registry No.—**1**, 6318-56-5; **2**, 54845-06-6; **3**, 54845-07-7; **4**, 54845-08-8; **5**, 54845-09-9; **6**, 54845-10-2; **7**, 54845-11-3; **8**, 54845-12-4; **9**, 54845-13-5; **10**, 54845-14-6; **11**, 54845-15-7; ammonium hydroxide, 1336-21-6; phloroglucinol, 108-73-6; phthalic anhydride, 85-44-9; ethylene oxide, 75-21-8; *p*-toluenesulfonyl chloride, 98-59-9; cyanogen bromide, 506-68-3.

Supplementary Material Available. Spectral and analytical data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1556.

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(22) In a repeat preparation using this procedure a crude yield of 97% was realized.