# Synthesis of Potential Anticancer Agents[1]

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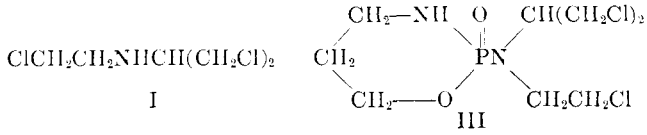
Two new secondary nitrogen mustards, 2-chloroethyl-1,3-dichloro-2-propylamine (I) and 1,3-dichloro-2-propylamine[2] (II), have been synthesized and tested in tumor-bearing animals.[3] Compound I exhibits greater anticancer activity and less toxicity than bis(2-chloroethyl)amine (nor-HN2) which has been widely employed in cancer chemotherapy research.

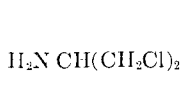
These secondary amines were phosphorylated and incorporated into compounds analogous to 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide (cytoxan), an anticancer drug that has been used with success in the treatment of human and animal tumors. *In vivo* cleavage of the phosphamide linkage would be expected to release these secondary nitrogen mustards that possess larger therapeutic indices than nor-HN2. In spite of these alterations, the oxazaphosphorines were inactive when tested in cancer-bearing animals.



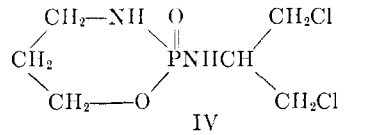
I



III



II



IV

## Experimental Section

**Materials.**—2-Amino-1,3-propanediol was obtained as a sample through the courtesy of Commercial Solvents Corp., New York, N. Y.

**2-Hydroxyethyl-1,3-dihydroxy-2-propylamine.**—2-Amino-1,3-propanediol (91.1 g, 1.00 mole) was dissolved in 75 ml of water. Ethylene oxide (14.7 g, 0.330 mole) was slowly bubbled through the rapidly stirred mixture over a period of 5 hr. The reaction temperature was maintained at 40–45°. After the addition was completed, the mixture was stirred for an additional hour and then distilled. A 30.5-g (67.7%) yield of the desired product was collected as a light yellow viscous oil, bp 211–212° (4 mm).

*Anal.* Calcd for $C_5H_{13}NO_3$: C, 44.4; H, 9.7; N, 10.4. Found: C, 44.4; H, 9.8; N, 10.7.

**2-Chloroethyl-1,3-dichloro-2-propylamine Hydrochloride (I).**—From a dropping funnel warmed with a heat lamp to afford free flow of liquid, 70.0 g (0.510 mole) of 2-hydroxyethyl-1,3-dihydroxy-2-propylamine was added dropwise to 550 ml of freshly distilled $SOCl_2$ over a period of 2 hr with external cooling at 45–55°. After the addition was completed, the reaction mixture was heated to reflux and 200 ml of $SOCl_2$ was removed by distillation. Benzene (350 ml) was added and reflux was continued for an additional 3 hr. The solvent was then removed by distillation at reduced pressure and 150 ml of benzene was added. The benzene solution was extracted (three 100-ml portions of water), and the combined extracts were made strongly alkaline with 10% aqueous NaOH. The aqueous solution was extracted (three 100-ml portions of $CHCl_3$), and the combined extracts were dried ($Na_2SO_4$). Upon the addition of HCl and cooling, the desired product separated as a light brown crystalline solid. Recrystallization from 2-butanone yielded 36.8 g (32%) of product as a white crystalline solid, mp 95.5–96.5°.

*Anal.* Calcd for $C_5H_{11}Cl_4N$: C, 26.5; H, 4.9; Cl, 62.5. Found: C, 26.7; H, 4.9; Cl, 62.1.

**N-(2-Chloroethyl-1,3-dichloro-2-propyl)phosphoramic Dichloride.**—2-Chloroethyl-1,3-dichloro-2-propylamine hydrochloride (22.7 g, 0.100 mole) was suspended in 250 ml of freshly distilled $POCl_3$. After stirring at reflux for 40 hr the excess $POCl_3$ was removed at reduced pressure. Distillation of the darkened residue yielded 22.0 g (71.4%) of colorless liquid, bp 126° (0.25 mm).

*Anal.* Calcd for $C_5H_9Cl_5NOP$: C, 19.5; H, 3.0; Cl, 57.7. Found: C, 19.5; H, 3.0; Cl, 57.6.

**2-(2-Chloroethyl-1,3-dichloro-2-propylamino)tetrahydro-2-oxo-2H-1,3,2-oxazaphosphorine (III).**—To N-(2-chloroethyl-1,3-dichloro-2-propyl)phosphoramic dichloride (40.1 g, 0.130 mole) dissolved in 100 ml of dioxane were added slowly a solution of 9.75 g (0.130 mole) of freshly distilled 3-amino-1-propanol and 26.3 g (0.260 mole) of triethylamine in 100 ml of dioxane while the stirred reaction mixture was maintained at 30–35°. After the addition was completed, the reaction mixture was allowed to remain at room temperature for 16 hr and filtered, and the solvent was removed at reduced pressure. The residue was dissolved in 150 ml of ethyl acetate and then washed (five 100-ml portions of 10% $Na_2CO_3$, then four 100-ml portions of 10% NaCl). After drying ($Na_2SO_4$) the solvent was removed under reduced pressure (ambient temperature). The remaining oil was dissolved in 150 ml of ether and the solution was cooled to approximately −50°. The product was then precipitated by the addition of cold petroleum ether (bp 30–60°). Upon warming, the suspended solid melted. The solvent was decanted and the remaining oil was dried for 40 hr at 25° (3 mm). A yield of 10 g (25%) of a viscous light yellow oil was obtained. It was insoluble in water, but absorbed 1 mole of water upon standing in a moist atmosphere.

*Anal.* Calcd for $C_8H_{16}Cl_3N_2O_2P$: C, 31.0; H, 5.2; N, 9.1. Found: C, 31.0; H, 5.3; N, 9.0

**1,3-Dichloro-2-propylamine Hydrochloride (II).**—2-Amino-1,3-propanediol (18.2 g, 0.200 mole) was added in small portions to 150 ml of refluxing $SOCl_2$. After refluxing and stirring for an additional 7 hr, the mixture was allowed to stand overnight and the excess $SOCl_2$ was removed under reduced pressure. The almost black residue was extracted (four 50-ml portions of water), and the combined extracts were made strongly alkaline with concentrated NaOH. The aqueous solution was extracted (four 50-ml portions of $CHCl_3$), and the combined extracts were dried ($Na_2SO_4$). Upon the addition of dry HCl to the chloroform solution, a white solid separated. This material was collected on a filter, washed ($CHCl_3$), and recrystallized from a mixture of ethyl acetate and acetone. A yield of 10.2 g (31.0%) of white needles, mp 165°, was obtained.

*Anal.* Calcd for $C_3H_8Cl_3N$: C, 21.9; H, 4.9; Cl, 64.7. Found: C, 22.1; H, 4.7; Cl, 64.3.

**N-(1,3-Dichloro-2-propyl)phosphoramic Dichloride.**—1,3-Dichloro-2-propylamine hydrochloride (32.9 g, 0.200 mole) was suspended in 300 ml of freshly distilled $POCl_3$. After stirring at reflux for 9 hr, the excess $POCl_3$ was removed under reduced pressure. Distillation of the darkened residue yielded 15.2 g (31.0%) of a clear yellow oil, bp 121° (0.6 mm), $n^{22}D$ 1.5163.

*Anal.* Calcd for $C_3H_6Cl_4NOP$: C, 14.7; H, 2.5; Cl, 57.9. Found: C, 14.9, H, 2.5; Cl, 57.9.

**2-(1,3-Dichloro-2-propylamino)tetrahydro-2-oxo-2H-1,3,2-oxazaphosphorine.**—N-(1,3-Dichloro-2-propyl)phosphoramic dichloride (14.65 g, 0.0598 mole) and triethylamine (12.14 g, 0.1200 mole) were dissolved in 65 ml of dioxane. 3-Amino-1-propanol (4.50 g, 0.0598 mole) was then added dropwise to the stirred mixture while the reaction temperature was maintained at 25–30°. After standing overnight at room temperature, the mixture was filtered and the solvent was removed from the filtrate at reduced pressure. Trituration of the residual brown oil with ether caused the crude product to solidify. Recrystallization from benzene yielded 4.5 g (30%) of white crystalline solid, mp 133–134°.

*Anal.* Calcd for $C_6H_{13}Cl_2N_2O_2P$: C, 29.2; H, 5.3; Cl, 28.7. Found: C, 29.3; H, 5.3; Cl, 28.8.

(1) Supported in part by the U. S. Army Edgewood Arsenal Research Laboratories In-House Laboratory Independent Research Program.

(2) R. Preussmann, *Arzneimittel-Forsch.*, **8**, 638 (1958).

(3) The compounds reported herein were submitted to the Cancer Chemotherapy National Service Center for Screening. This agency publishes its results in supplements to *Cancer Research*.