N-Carbobenzoxy-DL-valine N-2-Chloroethylamide.—A solution of 1.26 g (0.005 mole) of N-carbobenzoxy-DL-valine and triethylamine (0.75 ml, 0.005 mole) in 12 ml of absolute tetrahydrofuran (THF) was cooled in an ice–salt bath (0 to −5). To this cold well-stirred solution was added 0.5 ml (0.005 mole) of ethyl chlorocarbonate; the insoluble triethylamine hydrochloride separated, and the mixture was kept stirring for about 30 min at −5°. The anhydride formation (ν_{max} 1818, 1768 cm^{-1}) was checked by running an infrared spectrum of a sample in THF, drawn from the reaction flask, protected against atmospheric moisture. To this cold anhydride *in situ* was added 2-chloroethylamine, freshly prepared by neutralizing 0.87 g (0.0075 mole) of 2-chloroethylamine hydrochloride in ice-cold chloroform (15 ml) with 1.1 ml (0.0075 mole) of triethylamine. The mixture was stirred initially at ice-bath temperature for about 1 hr and then allowed to attain room temperature during a period of another hour; stirring was continued for additional 2 hr at room temperature. The solvents were removed under reduced pressure at room temperature, and the residue was taken up in sufficient chloroform and filtered. The $CHCl_3$ solution was washed successively (1 *N* HCl, H_2O, 5% $NaHCO_3$ solution, H_2O) and then dried (Na_2SO_4). The evaporation of the solvent left a residue, which was crystallized from chloroform; yield 1.22 g (78%), mp 171–172°.

DL-Valine N-(2-Chloroethyl)amide Hydrochloride.—To a solution of N-carbobenzoxy-DL-valine N-(2-chloroethyl)amide (0.63 g, 0.002 mole) in 75 ml of absolute ethanol was added 0.002 mole of ethanolic HCl. The mixture was hydrogenated in presence of 0.2 g of 10% Pd–C catalyst under stirring at 10–15°. After complete uptake of hydrogen, the catalyst was filtered off. The solution on evaporation in a rotary evaporator at room temperature gave a gummy residue, which afforded crystalline solid in acetone–ether; yield 0.37 g (86%), mp 83–86°.

Synthesis of New Alkylating Agents[1]

LISE NICOLE[2] AND LOUIS BERLINGUET

Department of Biochemistry, School of Medicine, Laval University, Quebec, Canada

Received August 15, 1966

In 1955 Ross, *et al.*,[3] reported the condensation of benzaldehyde nitrogen mustard with some aniline derivatives. During the past few years, Popp and his colleagues[4,5] have continued to enlarge the series by using a wide variety of amines and also several benzaldehyde mustards having various substituents on the benzene ring.[6] Since some of these compounds have antitumor activity as reported by the latter authors, we decided to make similar derivatives starting from other amines.

Among the primary amines, 1,5-dimethylhexylamine was transformed into a mustard. This compound has a therapeutic index[7] of 2 which is somewhat higher than the low therapeutic index of 1 which was found for the parent compound obtained from 1,4-cyclohexanebis(methylamine).

It has also recently been reported[8] that *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane dihydrochloride and N,N'-dibenzyl-1,4-cyclohexanebis(methylamine) are very potent cholesterol-lowering agents. We therefore decided to attach two alkylating groups at both ends of the parent molecule, 1,4-cyclohexanebis(methylamine).

Experimental Section

Condensation of Various Amines with *p*-[N,N-Bis(2-chloroethyl)amino] Aromatic Aldehydes.[9-11]—Amines and nitrogen mustards of aromatic aldehydes were condensed according to the method of Popp, *et al.*[4,5] In most cases, a pure compound was obtained without recrystallization (see Tables I and II).

N,N'-Dibenzylidene-1,4-cyclohexanebis(methylamine).[12]—1,4-Cyclohexanebis(methylamine)[13] (28.4 g, 0.2 mole) was added very slowly to a solution of benzaldehyde (42.4 g, 0.4 mole) in 60 ml of ethanol. The solution was stirred and kept at room temperature during 20 min to yield 43 g of product, mp 96–97°.

Anal. Calcd for $C_{22}H_{26}N_2$: N, 8.79. Found: 8.68.

Further evaporation of the filtrate gave an additional crop of yellow crystals (15 g) pure enough to be hydrogenated in the next step. The compound can be recrystallized from Skellysolve; total yield 92%.

N,N'-Dibenzyl-1,4-cyclohexanebis(methylamine).—N,N'-dibenzylidene-1,4-cyclohexanebis(methylamine) (20 g, 0.062 mole) in 300 ml of ethanol was reduced with $NaBH_4$ (10.2 g, 0.22 mole). The title product was recrystallized from ethanol and water giving a yield of 82% (16.5 g), mp 76–77°. The compound had been previously described as an oil.[12] Its dihydrochloride melts at 358°.

Anal. Calcd for $C_{22}H_{30}N_2$: N, 8.68. Found: N, 8.47.

1,4-Cyclohexane-N,N,N',N'-tetrakis(2-hydroxyethyl)bis(methylamine).—1,4-Cyclohexanebis(methylamine) (28.44 g, 0.2 mole) and ethylene oxide (42 ml, 0.8 mole) were mixed in cold benzene and placed in an hermetically closed tubular bomb.[14] The temperature was then raised to 80° for 16 hr. The solvent was removed *in vacuo* to yield the title compound as an oil. After 24 hr, the colorless product crystallized in 59% yield (37.5 g). It could be crystallized from acetone, mp 81°.

Anal. Calcd for $C_{16}H_{34}N_2O_4$: C, 60.34; H, 10.76; N, 8.79. Found: C, 60.28; H, 10.76; N, 8.61.

1,4-Cyclohexane-N,N,N',N'-tetrakis(2-chloroethyl)bis(methylamine) Dihydrochloride.—1,4-Cyclohexane-N,N,N',N'-tetrakis(2-hydroxyethyl)bis(methylamine) (15.9 g, 0.05 mole) was dissolved in a minimum of chloroform. Then, $SOCl_2$ (75 ml) was very slowly added to the cooled solution. A white gum was formed. The solution was evaporated to dryness and ethanol was added to the residue and then removed *in vacuo*. The product was crystallized from hot glacial acetic acid to give a 50% yield (12 g), mp 208–214°.

Anal. Calcd for $C_{16}H_{32}Cl_4N_2 \cdot 2HCl$: C, 41.31; H, 6.93; Cl, 45.73; N, 6.02. Found: C, 41.49; H, 6.76; Cl, 46.29; N, 6.16.

The reduction with $NaBH_4$ can be done directly on the oil, instead of on the crystals, saving the purification step and thus increasing the total yield from the amine to 64%.

1,4-Cyclohexane-N,N,N',N'-tetrakis(2-chloroethyl)bis(methylamine).—Upon treatment of the dihydrochloride (4.63 g, 0.01 mole) with Na_2CO_3 (1.06 g in 10 ml of H_2O), the free base precipitated and was extracted with chloroform. It was crystallized from 2-propanol; yield 77.6% (3.05 g), mp 65°.

Anal. Calcd for $C_{16}H_{30}Cl_4N_2$: C, 48.90; H, 7.70; Cl, 36.15; N, 7.19. Found: C, 48.96; H, 7.72; Cl, 37.16; N, 7.19.

N,N-Bis(2-chloroethyl)-1,5-dimethylhexylamine Hydrochloride.—1,5-Dimethylhexylamine (12.9 g, 0.1 mole) and ethylene oxide (10.5 ml, 0.2 mole) were combined as described previously for the 1,4-cyclohexanebis(methylamine). The resulting oil was dissolved in a minimum of chloroform and treated by $SOCl_2$ as usual. The dark solid obtained was crystallized from ethanol and ether. The yield was 30%, mp 77°.

Anal. Calcd for $C_{12}H_{25}Cl_2N \cdot HCl$: C, 49.58; H, 9.01; Cl, 36.58; N, 4.82. Found: C, 49.58; H, 8.85; Cl, 36.50; N, 5.13.

(1) (a) Presented in part before the Division of Organic Chemistry, ACFAS, Ottawa, Ontario, Canada, Nov 6–8, 1964. (b) This investigation was supported in part by Grant No. 312 from the National Research Council of Canada and by the National Cancer Institute of Canada.

(2) Holder of a Canadian Life Insurance Fellowship for Medical Research.

(3) W. C. J. Ross, G. P. Warwick, and J. J. Roberts, *J. Chem. Soc.*, 3110 (1955).

(4) F. D. Popp, *J. Org. Chem.*, **26**, 1566 (1961).

(5) F. D. Popp and W. Kirsh, *ibid.*, **26**, 3855 (1961).

(6) F. D. Popp, *J. Med. Chem.*, **7**, 210 (1964).

(7) See *Cancer Chemotherapy Rept.*, **25**, 1 (1962), for the meaning of the therapeutic index.

(8) C. Chappel, J. Dubuc, D. Dvornik, M. Givner, L. Humber, M. Kraml, K. Voith, and R. Gaudry, *Nature*, **201**, 497 (1964).

(9) All the compounds described in Tables I and II were prepared by a similar method.

(10) Infrared spectra were obtained employing KBr disks on a Beckman Model IR8, calibrated by polystyrene.

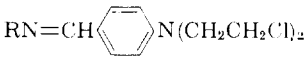
(11) Frinton Laboratories, South Vineland, N. J.

(12) M. Kraml, L. G. Humber, J. Dubuc, and R. Gaudry, *J. Med. Chem.*, **7**, 500 (1964).

(13) The 1,4-cyclohexanebis(methylamine) used was a commercial sample obtained from Eastman Chemical Products and contained a mixture of *cis* (40%) and *trans* (60%) isomers.

(14) From Parr Instruments.

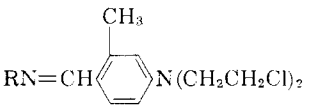
TABLE I
CONDENSATIONS OF AMINES WITH BENZALDEHYDE NITROGEN MUSTARD



Amine (RNH_2)	Mp, °C[a]	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found[b] C	% found[b] H	% found[b] N
Cyclohexanemethylamine	48	95	$C_{18}H_{26}Cl_2N_2$	64.49	6.01	8.35	63.58	7.79	8.69
3-Amino-9-ethylcarbazole	112–113	91	$C_{27}H_{29}Cl_2N_3$	69.52	6.26	9.00	68.21	5.43	9.29
1,2-Diaminopropane	125–126	93	$C_{25}H_{32}Cl_4N_4$	56.61	6.08	10.56	56.52	6.22	10.21
1,4-Diaminobutane	111–112	72	$C_{26}H_{34}Cl_4N_4$	57.36	6.47	10.29	57.43	6.47	10.21

[a] Melting points were determined on a Fisher-Johns apparatus and are uncorrected. [b] Organic microanalyses by Dr. C. Daessle, Montreal, Canada.

TABLE II
CONDENSATIONS OF AMINES WITH TOLUALDEHYDE NITROGEN MUSTARD



Amine (RNH_2)	Mp, °C	Yield, %	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N
Cyclohexanemethylamine	41–43	89	$C_{19}H_{28}Cl_2N_2$	65.33	6.46	8.02	64.76	7.98	7.98
3-Amino-9-ethylcarbazole	111	85	$C_{28}H_{27}Cl_2N_3$	69.02	6.01	9.28	68.16	6.20	9.16
Sulfanilamide	165	±90	$C_{18}H_{21}Cl_2N_3O_2S$	52.17	5.10	10.14	53.17	5.61	10.10
1,5-Dimethylhexylamine	34	77	$C_{26}H_{32}Cl_2N_2$	64.67	8.68	7.54	64.91	8.96	7.53
2-Methoxy-5-nitroaniline	133–135	47	$C_{19}H_{21}Cl_2N_3O_3$	55.61	5.15	10.24	55.82	5.63	10.06
Ethyl *p*-aminobenzoate	112–113	63	$C_{21}H_{21}Cl_2N_2O_2$	61.97	5.93	6.87	61.67	5.95	7.01
1,2-Diaminopropane	148–149	90	$C_{27}H_{36}Cl_4N_4$	58.07	6.49	10.03	58.01	6.54	9.69
1,4-Diaminobutane	132–133	94	$C_{28}H_{36}Cl_4N_4$	58.72	6.69	9.78	58.00	6.63	9.78
1,3-Diaminopropane	80	±90	$C_{27}H_{36}Cl_4N_4$	58.07	6.49	10.03	58.06	6.58	9.70

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1,3-Dimethyl-5-fluoro-6-azauracil and Some 5-Bromo-6-azauracil Derivatives[1]

G. J. DURR

Department of Chemistry, Le Moyne College, Syracuse, New York 13214

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The anticancer activity of 6-azauracil is well known.[2] The syntheses of the following 6-azauracil analogs are here described: 5-bromo-3-methyl 6-azauracil [6-bromo-4-methyl-*as*-triazine-3,5(2H,4H)-dione] (I), 1-acetyl-5-bromo-3-methyl-6-azauracil [2-acetyl-6-bromo-4-methyl-*as*-triazine-3,5(2H,4H)-dione] (II), 5-bromo-3-methyl-1-trifluoroacetyl-6-azauracil [6-bromo-4-methyl-2-trifluoroacetyl-*as*-triazine-3,5(2H,4H)-dione] (III), 5-bromo-1,3-dimethyl-6-azauracil [6-bromo-2,4-dimethyl-*as*-triazine-3,5-(2H,4H)-dione] (IV), 1,3-dimethyl-5-fluoro-6-azauracil [2,4-dimethyl-6-fluoro-*as*-triazine-3,5(2H,4H)-dione] (V), and 5-bromo-1,3-bis(diphenylmethyl)-6-azauracil [6-bromo-2,4-bis(diphenylmethyl)-*as*-triazine-3,5(2H,4H)-dione] (VI) (Table I). Attempts to prepare 5-fluoro-6-azauracil failed.

(1) Supported largely by the Research Grant CA 08095 from the National Cancer Institute, Public Health Service.

(2) J. Skoda, *Progr. Nucleic Acid Res.*, **3**, 197 (1963); G. B. Elion and G. H. Hitchings, *Advan. Chemotherapy*, **2**, 91 (1965).

Experimental Section[3]

5-Bromo-3-methyl-6-azauracil (I).—On stirring a mixture of 508 mg (4 mmoles) of 3-methyl-6-azauracil,[4] 10 ml of water, and 1.44 g (9 mmoles) of bromine over night, I crystallized from solution.

1-Acetyl-5-bromo-3-methyl-6-azauracil (II).—A mixture of 412 mg (2 mmoles) of I and 5 ml of acetic anhydride was refluxed for 30 min,[5] at which time it was filtered to remove a small amount of insoluble material. Evaporation of the filtrate, *in vacuo*, gave II as an oil. The crystallization solvent is recorded in Table I.

5-Bromo-3-methyl-1-trifluoroacetyl-6-azauracil (III).—A mixture of 550 mg (2.66 mmoles) of I and 5 ml of trifluoroacetic anhydride was refluxed overnight. On cooling in an ice bath III crystallized as needles.

5-Bromo-1,3-dimethyl-6-azauracil (IV).[6]—A mixture of 2.1 g (15 mmoles) of 1,3-dimethyl-6-azauracil,[4] 30 ml of water, and 2.0 ml (30 mmoles) of bromine was stirred overnight at room temperature and cooled, and the product (IV) was removed by filtration.

1,3-Dimethyl-5-fluoro-6-azauracil (V).—A mixture of 440 mg (2 mmoles) of IV, 440 mg of anhydrous KF, and 1 ml of dry dimethyl sulfoxide was stirred at 125° for 7 days. On cooling to −10°, 60 mg of V crystallized and was removed by filtration. The filtrate was diluted with 12 ml of water and extracted with chloroform. After drying, the chloroform layer was evaporated to dryness, yielding an additional 50 mg of V.

5-Bromo-1,3-bis(diphenylmethyl)-6-azauracil (VI).—A mixture of 1.8 g (9.4 mmoles) of 5-bromo-6-azauracil[7] in 20 ml of

(3) Melting points were determined using a Koller hot stage. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(4) K. Y. Zee-Cheng and C. C. Cheng, *J. Org. Chem.*, **27**, 976 (1962); J. Gut, M. Prystas, J. Jonas, and F. Šorm, *Collection Czech. Chem. Commun.*, **26**, 974 (1961).

(5) The acylation of 6-azauracil is described by A. Novacek, D. Hesoun, and J. Gut, *ibid.*, **30**, 1890 (1965).

(6) The synthesis of this compound by the methylation of 5-bromo-6-azauracil is given by M. Horak and J. Gut, *ibid.*, **28**, 3392 (1963).

(7) P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.*, **80**, 976 (1958).