New Compounds

5-Substituted Pyrimidines. II. The Synthesis of 2-Amino-4-hydroxy-6-methyl-5-(2-hydroxy-3-amino)propylpyrimidines[1,2]

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We report the synthesis, by an essentially analogous procedure, of compounds related to ethyl N-[2-hydroxy-3-(2-amino-4-hydroxy-6-methyl-5-pyrimidyl)]propyl-*p*-aminobenzoate (I).[2] None of them showed significant biological activity.[3]

Experimental Section[4]

2-Amino-4-hydroxy-6-methyl-5-(2-hydroxy-3-anilino)propylpyrimidine (II).—Aniline and 1-chloro-2,3-epoxypropane were condensed according to the procedure of McKelvey, *et al.*,[5] to give N-2-hydroxy-3-chloropropylaniline (IIa) as an oil that solidified at −10°.

Anal. Calcd for $C_9H_{12}ClNO$: C, 58.24; H, 6.51; N, 7.55. Found: C, 58.09; H, 6.39; N, 7.49.

A solution of IIa (50 g, 0.27 mole) in ethanol (200 ml) was added to an ice-cold stirred solution of sodium (6.2 g, 0.27 g-atom) in ethanol (200 ml). The mixture was stirred for 60 min, then added to a solution of ethyl acetoacetate (35.1 g, 0.27 mole) in 300 ml of ethanolic $NaOC_2H_5$ (from 6.2 g of Na) stirred at 0°. Stirring was continued at room temperature for 12 hr. The resultant solution of keto ester (probably as the γ-lactone[2]) was not purified but was added to a solution of guanidine (from 25.7 g of guanidine hydrochloride and 6.2 g of Na) in ethanol (200 ml). The mixture was stirred at room temperature for 24 hr, then refluxed for a further 12 hr. The solvent was removed by evaporation under reduced pressure, and the residue was dissolved in 10% HCl and extracted with two 200-ml portions of ether, and the aqueous phase was basified with 5% NH_4OH to give a solid which was washed well with water and recrystallized from ethanol to give II (18.5%): mp 174–175°; $\lambda_{max}^{pH\ 1}$ 227 mμ (ε 6790), 265 mμ (ε 5730); $\lambda_{max}^{pH\ 10}$ 241 mμ (ε 13,420), 292 mμ (ε 4220).

Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.31; H, 6.61; N, 20.42. Found: C, 61.03; H, 6.64; N, 19.99.

2-Amino-4-hydroxy-6-methyl-5-[2-hydroxy-3-(N-2-hydroxyethyl)anilino]propylpyrimidine (III).—N-2-Hydroxyethylaniline and 1-chloro-2,3-epoxypropane were condensed[5] to give N-2-hydroxyethyl-N-(2-hydroxy-3-chloro)propylaniline (IIIa) in 80% yield as white plates from benzene with mp 59.5–60°.

Anal. Calcd for $C_{11}H_{16}ClNO_2$: C, 57.52; H, 7.02; Cl, 15.44; N, 6.2. Found: C, 57.22; H, 6.83; Cl, 15.24; N, 6.03.

By a method similar to that described under II, IIIa gave III in 21% yield; mp 144–146° (water); $\lambda_{max}^{pH\ 1}$ 228 mμ (ε 7355), 266 mμ (ε 7015); $\lambda_{max}^{pH\ 10}$ 258 mμ (ε 14,880), 296 mμ (ε 4450).

Anal. Calcd for $C_{16}H_{22}N_4O_3$: C, 60.38; H, 6.97; N, 17.60. Found: C, 60.40; H, 7.10; N, 17.20.

Ethyl N-2-Hydroxyethyl-N-[2-hydroxy-3-(2-amino-4-hydroxy-6-methyl-5-pyrimidyl)]propyl-*p*-aminobenzoate (IV).—Ethyl N-2-hydroxyethyl-*p*-aminobenzoate and 1-chloro-2,3-epoxypropane were condensed in ethanolic solution[2] to give ethyl N-2-hydroxyethyl-N-(2-hydroxy-3-chloro)propyl-*p*-aminobenzoate (IVa) in 58% yield, mp 85° (from benzene).

Anal. Calcd for $C_{14}H_{20}ClNO_4$: C, 55,73; H, 6.66; N, 4.85 Found: C, 55.32; H, 6.45; N, 5.09.

Condensation of IVa with ethyl acetoacetate and guanidine gave V in 18% yield; mp 186–187 (aqueous ethanol); $\lambda_{max}^{pH\ 1}$ 229 mμ (ε 21,060), 266 mμ (ε 8740); $\lambda_{max}^{pH\ 10}$ 226 mμ (ε 15,870), 309 mμ (ε 23,380).

Anal. Calcd for $C_{19}H_{26}N_4O_5 \cdot H_2O$: C, 57.11; H, 6.81; N, 14.04. Found: C, 56.96; H, 6.61; N, 14.25.

N-[2-Hydroxy-3-(2-amino-4-hydroxy-6-methyl-5-pyrimidyl)]propylphthalimide (V) was prepared from 2,3-epoxypropylphthalimide[6] and ethyl acetoacetate by the general method described under II. The yield was near-quantitative; mp 173–175° (water); $\lambda_{max}^{pH\ 1}$ 223 mμ (ε 39,700), 267 mμ (ε 8040), 306 mμ (ε 1754); $\lambda_{max}^{pH\ 10}$ 226 mμ (ε 20,650), 276 mμ (ε 5780).

Anal. Calcd for $C_{16}H_{16}N_4O_4 \cdot H_2O$: C, 55.51; H, 5.24; N, 16.18. Found: C, 55.30; H, 5.13; N, 16.46.

(6) M. Weizmann and S. Malkawa, *Compt. Rend.*, **190**, 495 (1930).

Synthesis of N-(2-Chloroethyl)amides of Amino Acids as Potential Cytotoxic Agents[1a]

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We reported the synthesis of both "two-armed" bis(2-chloroethyl)amides and "one-armed" 2-chloroethylamides of several amino acids as potential anticancer agents in a previous paper.[2] Preliminary biological studies of these compounds indicated that when tested for cytotoxicity against tissue cells growing in culture, "one-armed" derivatives were all significantly cytotoxic, whereas "two-armed" compounds were uniformly inactive. This interesting observation prompted us to prepare a series of "one-armed" mustard (2-chloroethylamides) derivatives of amino acids.

Experimental Section

The mixed carboxylic–carbonic acid anhydride[3] procedure, applied earlier[4] by us for the preparation of 2-chloroethylamides of acylated dipeptide derivatives, has now been developed as the method of choice for the synthesis of these amides in good yields with high degree of purity.

The melting points were determined in a Kofler block apparatus and not corrected. The infrared spectra were recorded in a Perkin-Elmer 137 spectrophotometer. The following experimental methods[5] represent in general the procedure for obtaining these amides as listed in Tables I and II.

(1) This work was supported by Grant CA-06645 from the National Cancer Institute, U. S. Public Health Service.

(2) Part I: A. M. Triggle and D. J. Triggle, *J. Pharm. Sci.*, **54**, 795 (1965).

(3) We are indebted to Dr. P. Hebborn and Miss J. Hampshire for this information.

(4) Melting points were recorded on a Thomas–Kofler hot stage and are corrected. Ultraviolet spectra were recorded with a Perkin-Elmer spectrophotometer, Model 202. Analyses are by Galbraith Laboratories, Knoxville, Tenn., and Dr. A. E. Bernhardt, Mülheim, W. Germany.

(5) J. B. McKelvey, B. H. Webre, and R. R. Benerito, *J. Org. Chem.*, **25**, 1424 (1960).

(1) (a) Supported by a research grant (CA-02130) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. (b) To whom correspondence should be addressed.

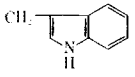
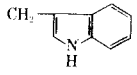
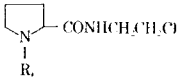
(2) H. Sommer, C. Scher, S. Bien, G. Olsen, J. K. Chakrabarti, and O. M. Friedman, *J. Med. Chem.*, **9**, 84 (1966).

(3) (a) J. R. Vaughan, *J. Am. Chem. Soc.*, **73**, 3547 (1951); (b) J. R. Vaughan and R. L. Osato, *ibid.*, **74**, 676 (1952); (c) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); (d) T. Wieland and H. Bernard, *Ann.*, **572**, 190 (1951).

(4) J. K. Chakrabarti and O. M. Friedman, *Chem. Ind.* (London), 898 (1965).

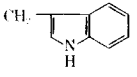
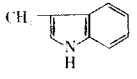
(5) The reactive side chain functions in N-carbobenzoxyamino acids were masked by suitable groups. The hydroxyl group in serine and second carboxyl group in aspartic acids were protected by benzylation, the phenolic group in tyrosine and ε-amino group in lysine by carbobenzoxylation, and the guanido group in arginine by percarbobenzoxylation. The anhydride underwent facile coupling with 2-chloroethylamine in the expected way to give the desired amide almost exclusively. Steric hindrance imposed by a β-branched chain as in valine and isoleucine did not present any complication, as would be evident from the high yields of product in such cases.

TABLE I: 2-CHLOROETHYLAMIDE DERIVATIVES (I) OF AMINO ACIDS $C_6H_5CH_2OCONHC(R)HCONHCH_2CH_2Cl$

No.	R	Original amino acid	Mixed anhydrides (C=O) ν_{max}, cm^{-1}	Yield, % I	Mp, °C	[α]D, deg (c, CHCl$_3$)	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % N	Found, % C	Found, % H	Found, % Cl	Found, % N
1	$CH(CH_3)_2$	DL-Val	1818, 1768	78	171–172	...	$C_{15}H_{21}ClN_2O_3$	57.50	6.77	11.35	8.96	57.46	6.68	11.49	8.85
2	$CH(CH_3)CH_2CH_3$	L-Heu	1830, 1778	81	173–174	−4.3 (1.26)	$C_{16}H_{23}ClN_2O_3$	58.80	7.09	10.85	8.57	58.74	6.99	10.77	8.42
3	$CH_2OCH_2C_6H_5$	DL-Ser	1822, 1768	60	86–88	...	$C_{20}H_{23}ClN_2O_4$	61.43	5.94	9.07	7.17	61.61	6.01	8.87	7.07
4	$CH_2C_6H_4OCOOCH_2C_6H_5$	DL-Tyr	1826, 1782	76	139–141	...	$C_{27}H_{27}ClN_2O_6$	63.60	5.33	6.91	5.49	63.45	5.40	6.74	5.57
5	$CH_2CH_2CH_2CH_2$ | $NHCOOCH_2C_6H_5$	L-Lys	1807, 1759	54	119–122	−11.3 (2.00)	$C_{34}H_{39}ClN_4O_5$	60.57	6.37	7.44	8.82	60.40	6.43	7.32	8.76
6	$CH_2CH_2CH_2$ | $N=C(NHCOOCH_2C_6H_5)_2$	L-Arg	1811, 1765	51	162–164	+24.5 (2.01)	$C_{39}H_{36}ClN_5O_7$	60.23	5.69	5.56	10.97	60.30	5.60	5.50	10.90
7		DL-Try	1818, 1768	80	138–139	...	$C_{21}H_{22}ClN_3O_3$	63.17	5.56	8.84	10.50	63.10	5.70	8.80	10.50
8		L-Try	1818, 1768	68	140–141	...	$C_{21}H_{22}ClN_3O_3$	63.17	5.56	8.84	10.50	63.70	5.60	8.50	10.10
9	$CH_2COOCH_2C_6H_5$	β-BZ-L-Asp	1811, 1759	82	120–121	+9.9 (2.90)	$C_{21}H_{23}ClN_2O_5$	60.21	5.54	8.46	6.69	60.18	5.62	8.45	6.59
10[a]	$R_1HNCHCOOCH_2C_6H_5$ | $CH_2CONHCH_2CH_2Cl$	α-BZ-L-Asp	1822, 1775	58	126–128	+8.4 (2.61)	$C_{21}H_{23}ClN_2O_5$	60.21	5.54	8.46	6.69	60.30	5.68	8.37	6.81
11[a]	NHR_1 | $CH_2CH_2CONHCH_2CH_2Cl$	β-Ala	1818, 1772	60	114–115	...	$C_{13}H_{17}ClN_2O_3$	54.83	6.02	12.46	9.84	54.93	5.87	12.42	10.03
12[a]		L-Pro	1804, 1751	75	62–64	−68.2 (2.20)	$C_{15}H_{18}ClN_2O_3$	57.97	6.18	11.41	9.01	57.87	6.44	11.33	8.94

[a] R_1 = $COOCH_2C_6H_5$.

TABLE II: 2-CHLOROETHYLAMIDE DERIVATIVES OF AMINO ACIDS $RCONH_2HCONHCH_2CH_2Cl$

R	Original amino acid	Yield, %	Mp, °C	Amide (C=O) ν_{KBr}, cm^{-1}	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Calcd, % N	Found, % C	Found, % H	Found, % Cl	Found, % N
$CH(CH_3)_2$	DL-Val	86	83–86	1667	$C_7H_{15}ClN_2O \cdot HCl$	39.11	7.51	32.82	13.05	39.32	7.75	32.60	13.20
$CH(CH_3)CH_2CH_3$	L-Heu	80	150–151	1660	$C_8H_{17}ClN_2O \cdot HCl$	41.95	7.92	30.95	12.23	41.79	7.90	30.89	12.11
CH_2OH	DL-Leu	70	109–111	1655	$C_5H_{11}ClN_2O_2 \cdot HCl$	29.57	5.96	34.91	13.80	29.41	5.82	35.12	13.65
$CH_2C_6H_4OH$	DL-Tyr	70	201–203 dec	1673	$C_{11}H_{13}ClN_2O_2 \cdot HCl$	47.32	5.78	25.40	10.02	47.52	5.93	25.20	9.94
	DL-Try	75		1660	$C_{13}H_{16}ClN_3O \cdot HCl \cdot 0.25H_2O$	50.88	5.80	23.21	...	50.70	6.30	23.30	...
	L-Try	80		1664	$C_{13}H_{16}ClN_3O \cdot HCl \cdot 0.25H_2O$	50.88	5.80	23.21	...	50.90	6.00	23.60	...
CH_2COOH	β-L-Asp	50	152–155 dec	1667	$C_6H_{11}ClN_2O_3$	37.02	5.69	18.12	14.39	36.86	5.82	17.80	14.33
$H_2NCHCOOH$ | $CH_2CONHCH_2CH_2Cl$	α-L-Asp	57	167–170 dec	1655	$C_6H_{11}ClN_2O_3$	37.02	5.69	18.12	14.39	36.96	5.60	18.05	14.28
$NH_2CH_2CH_2CONHCH_2CH_2Cl$	β-Ala	92	127–129	1660	$C_5H_{11}ClN_2O \cdot HCl$	32.10	6.47	37.90	14.97	32.03	6.32	37.74	14.80

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]

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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.