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.

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(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.