infrared spectrum and melting point (270–272°). Reported melting points for the compound are 252–254,[13a] 276–278,[13b] 269–270,[13c] 273–275,[13d] 267–268.5,[13e] and 273°.[13f]

2-Ethoxyethyldimethylphosphine Oxide (VI).—Methylmagnesium iodide was prepared from 10.2 g of Mg and 60 g of methyl iodide in 250 ml of ether. 2-Bromoethylphosphonic dichloride[14] (43 g) in 50 ml of ether was added dropwise with stirring at room temperature over a period of 1.5 hr, and the mixture was stirred overnight at room temperature. Ethanolic KOH (60 g in 2000 ml of ethanol) was added with vigorous stirring, and $Mg(OH)_2$ was removed by filtration. The basic filtrate was refluxed 1 hr, neutralized with concentrated HCl, and filtered, and the filtrate was concentrated *in vacuo*. Distillation *in vacuo* gave 2-ethoxyethyldimethylphosphine oxide (VI), yield 15.3 g (54%), bp 98–101° (0.5 mm). An analytical sample was obtained by redistillation *in vacuo* through a Vigreux column; yield 9.6 g, bp 104–105° (1.5 mm).

Anal. Calcd for $C_6H_{15}O_2P$: C, 47.99; H, 10.07; P, 20.63. Found: C, 47.99; H, 10.05; P, 20.74.

2-Bromoethyldimethylphosphine Oxide (V).—2-Ethoxyethyldimethylphosphine oxide (VI) (5.1 g) was refluxed with stirring for 4 hr with 20 ml of 48% HBr. The solution was concentrated by distillation at atmospheric pressure, and the last traces of water were removed by evaporation *in vacuo*. The residue in chloroform solution was treated with anhydrous HBr (passed rapidly into the solution) for 4 hr at reflux. After cooling, the lower layer was separated and distilled *in vacuo;* the fraction that boiled in the range 101–122° (0.07–0.5 mm) was collected. The distillate (crystallized in the receiver) was sublimed *in vacuo*, and the sublimate was crystallized three times from $CHCl_3$ (3, 1, and 1 ml); yield 450 mg (7%), mp 89–90°.

Anal. Calcd for $C_4H_{10}BrOP$: C, 25.96; H, 5.41; Br, 43.20; P, 16.73. Found: C, 25.76; H, 5.58; Br, 43.37; P, 16.53.

Dimethylvinylphosphine Oxide (VII).—Treatment of methylmagnesium iodide (0.18 mole) with 2-bromoethylphosphonic dichloride[14] (0.09 mole) as described for VI followed by decomposition of the cold (0°) reaction mixture with alcoholic KOH, filtration, neutralization of the filtrate with concentrated HCl, filtration, and concentration of the filtrate *in vacuo* gave a syrupy residue that was distilled *in vacuo*. A fraction was collected with bp 68–69° (1.6 mm); yield 1.83 g (20%); $\bar{\nu}_{max}$ (in cm^{-1}) 3080, 3030, 2990, 2970, 2905 (CH including $CH{=}CH_2$), 1615, 1400 ($-CH{=}CH_2$), 1295 (PCH_3), 1165 (P=O); positive test for unsaturation with $KMnO_4$.

Anal. Calcd for C_4H_9OP: P, 29.74. Found: P, 29.99.

Acknowledgment.—The authors express their appreciation to Dr. J. A. Montgomery for encouragement in this work and to Drs. W. J. Barrett, W. C. Coburn, Jr., P. D. Sternglanz, and members of the Analytical Section of Southern Research Institute who performed the spectral and microanalytical determinations reported. Some of the microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Tumor and tissue culture test data were obtained by the Chemotherapy Division of Southern Research Institute under the direction of Drs. F. M. Schabel, Jr., W. R. Laster, Jr., and G. J. Dixon.

(14) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **70**, 1971 (1948); P. A. Rossiiskaya and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 389 (1947).

Glycerol 1,3- and 1,2,4-Butanetriol 1,4-Bismethanesulfonates

PETER W. FEIT AND OLE TVAERMOSE NIELSEN

Leo Pharmaceutical Products, Ballerup, Denmark

Received December 15, 1965

The title compounds were prepared for antitumor screening. Especially 1,2,4-butanetriol 1,4-bismethanesulfonate is closely related to both busulfan and L-threitol 1,4-bismethanesulfonate;[1] the latter compound possesses antineoplastic activity[2] and has recently been clinically compared[3] with busulfan. The (*S*)-1,2,4-butanetriol derivative was prepared from diethyl L-maleate. After protection of the hydroxy group the synthesis was based on the principle described[1b] for L-threitol 1,4-bismethanesulfonate from diethyl 2,3-*O*-isopropylidene-L-tartrate.

Screening of these bismethanesulfonates by the Cancer Chemotherapy National Service Center, National Institutes of Health, has revealed no significant inhibition of cell growth in the KB cell culture system. For DL- and (*S*)-butanetriol bismethanesulfonate a summary of the test data in the Walker carcinoma system is presented in Table I. The glycerol derivative was completely inactive in this system.

TABLE I

SCREENING DATA IN THE WALKER CARCINOSARCOMA 256 (SUBCUTANEOUS) SYSTEM FOR DL- AND (*S*)-1,2,4-BUTANETRIOL 1,4-BISMETHANESULFONATE

Config	Daily dose, mg/kg[a]	Survivors	Mean tumor weight (test/control), %[b]	ED_{90},[c] mg/kg/day
DL	200	6/6	0	
	100	6/6	0	
	50	5/6	14	57
	25	6/6	93	
(*S*)	200	6/6	0	
	100	5/6	8	
	50	4/6	78	96
	25	2/6	----	

[a] Administered intraperitoneally once daily, days 1 through 5 postinoculation. [b] Sacrificed and evaluated 10 days postinoculation. [c] The dose that inhibits growth to 10% of control growth.

Experimental Section[4]

Glycerol 1,3-Bismethanesulfonate.—A mixture of 1,3-dibromo-2-propanol (21.6 g), silver methanesulfonate (42 g), and acetonitrile (100 ml) was refluxed for 18 hr. After filtration from silver bromide (33 g) and evaporation *in vacuo*, the residue was extracted with acetone leaving unreacted silver methanesulfonate. Addition of 10 *N* ethanolic HCl (0.1 ml), filtration (decolorizing carbon), evaporation, and recrystallization from ethanol (120 ml, 99.9%) yielded the crude material (7 g), mp 66–67°. Several recrystallizations from ethanol (99.9%) gave the colorless analytically pure compound, mp 66–67°.

Anal. Calcd for $C_5H_{12}O_7S_2$: C, 24.19; H, 4.87; S, 25.83. Found: C, 24.29; H, 4.95; S, 25.85.

DL-1,2,4-Butanetriol 1,4-Bismethanesulfonate.—To a solution of 1,4-dibromo-2-butanone[5] (40 g) in diethyl ether (250 ml), a solution of $NaBH_4$ (2.2 g) in cold water (40 ml) was added dropwise while stirring at 5–8°. The reaction mixture was stirred for an additional 2 hr to attain room temperature. The organic layer was washed with water, dried ($MgSO_4$), and fractionated *in vacuo*, resulting in slightly impure 1,4-dibromo-2-butanol (24.5 g), bp 110–116° (10 mm). This product (23 g) was treated with silver methanesulfonate for 4 hr as described for 1,3-dibromo-2-propanol. After evaporation of the acetone solution crystallization was effected by treatment with a mixture of diethyl ether–acetone (9:1); yield 7.2 g, mp 72.5–73.5° (ethanol, 99.9%).

(1) (a) P. W. Feit, *Tetrahedron Letters*, 716 (1961); (b) *J. Med. Chem.*, **7**, 14 (1964).

(2) (a) R. Jones, W. B. Kessler, H. E. Lessner, and L. Rane, *Cancer Chemotherapy Rept.*, **10**, 90 (1960); (b) F. R. White, *ibid.*, **24**, 95 (1962).

(3) V. Loeb, Jr., *ibid.*, **42**, 39 (1964).

(4) Analyses by G. Cornali and W. Egger of these laboratories. Melting points were rounded off to half degrees, using a Hershberg apparatus with thermometers subdivided in 0.1°.

(5) J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 278 (1948).

Anal. Calcd for $C_6H_{14}O_7S_2$: C, 27.48; H, 5.38; S, 24.45. Found: C, 27.64; H, 5.41; S, 24.49.

Diethyl 2-*O*-(2-Tetrahydropyranyl)-L-maleate.—To a mixture of diethyl maleate (95 g) and purified dihydropyran (46 g), concentrated HCl (0.2 ml) was added. The reaction mixture was allowed to warm and kept for 28 hr at room temperature. Neutralization of the HCl with excess of Ag_2O[6] and distillation *in vacuo*, leaving some undistilled material in the distillation flask in order to avoid any risk caused by peroxide formation, yielded 49 g of the ester, bp 118.5–119° (0.4 mm), $[\alpha]^{20}D$ −59° (*c* 6, acetone).

Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.64; H, 8.14.

2-*O*-(2-Tetrahydropyranyl)-(*S*)-1,2,4-butanetriol.—A suspension of $LiAlH_4$ (20 g) in diethyl ether (500 ml) was refluxed for 1 hr. A solution of diethyl 2-*O*-(2-tetrahydropyranyl)-L-maleate (46 g) in diethyl ether (50 ml) was added dropwise with stirring, the heat of reaction causing a gentle refluxing. After additional heating for 2 hr ethyl acetate (70 ml) was carefully added, and the reaction mixture was cooled. After successive cautious additions of water (20 ml) and 4 *N* NaOH (20 ml), the inorganic precipitate was removed by filtration, washed several times with diethyl ether (500 ml), and extracted with hot chloroform (200 ml). The combined organic solutions were dried ($MgSO_4$) and evaporated *in vacuo*. Distillation of the residue yielded 13.9 g, bp 115–123° (0.2 mm), $[\alpha]^{20}D$ −47.1° (*c* 6, acetone).

Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 57.16; H, 9.42.

(*S*)-1,2,4-Butanetriol 1,4-Bismethanesulfonate.—To a solution of 2-*O*-(2-tetrahydropyranyl)-(*S*)-1,2,4-butanetriol (5.2 g) in pyridine (15 ml), methanesulfonyl chloride (6 ml) was added dropwise while stirring at −20 to −15° over a period of 30 min, and the reaction mixture was then kept at −15 to −5° for an additional 40 min. After standing for 20 hr at about 5° the mixture was poured into ice–water (300 ml). The separated heavy oil was washed with water by repeated decantation, and dissolved in chloroform. After drying ($MgSO_4$) and evaporation *in vacuo*, the resulting crude 2-*O*-(2-tetrahydropyranyl)-(*S*)-1,2,4-butanetriol 1,4-bismethanesulfonate was refluxed in ethanol (35 ml) for 20 min after addition of methanesulfonic acid (0.3 ml). After standing at about −5° for 20 hr (*S*)-1,2,4-butanetriol 1,4-bismethanesulfonate (2.2 g) separated, mp 68–70°. Additional material (1.6 g) with the same melting point could be isolated from the mother liquor. Recrystallization from ethanol raised the melting point to 68.5–70°, $[\alpha]^{20}D$ −16.5° (*c* 6, acetone).

Anal. Calcd for $C_6H_{14}S_2O_7$: C, 27.48; H, 5.38; S, 24.45. Found: C, 27.41; H, 5.35; S, 24.36.

Acknowledgment.—The authors are indebted to the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md., for the screening of the compounds and for making the results available.

(6) Work-up by treating with $NaHCO_3$ solution resulted in a product with decreased optical rotation.

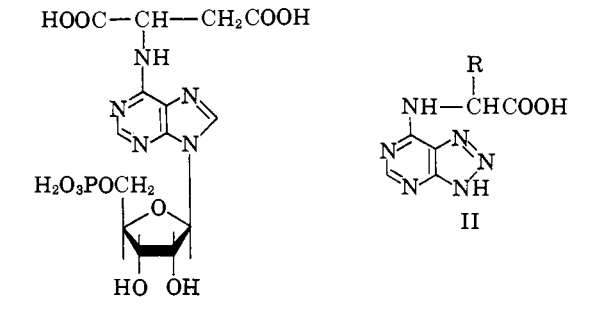
v-Triazolo[4,5-*d*]pyrimidines. III. N-(3-Alkyl-5-amino-3H-*v*-triazolo[4,5-*d*]pyrimidin-7-yl)-amino Acids[1]

Y. FULMER SHEALY, C. ALLEN O'DELL, AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

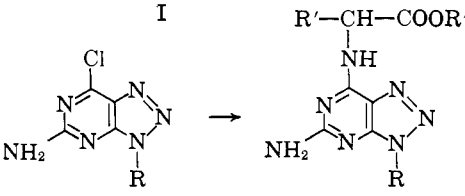
Received January 22, 1966

N-[9-(β-D-Ribofuranosyl)purin-6-yl]aspartic acid 5′-phosphate (I) is an intermediate in the biochemical interconversion of inosinic and adenylic acids and is, therefore, an intermediate in the biosynthesis of nucleic acids.[2] A number of other N-(purin-6-yl)amino acids have been prepared as analogs of the aspartic acid derivative.[3] In addition, Ballweg[4] has synthesized a few N-(*v*-triazolo[4,5-*d*]pyrimidin-7-yl)amino acids (II). We report here the synthesis and antitumor evaluation of several N-(5-amino-*v*-triazolo[4,5-*d*]pyrimidin-7-yl)amino acids that have an alkyl substituent at the position corresponding to that occupied by the ribofuranosyl group in I.



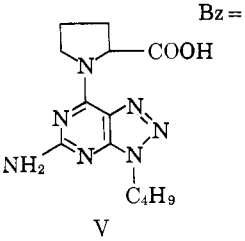
I

II



III, R = C_2H_5
IV, R = C_4H_9

VI, R = C_2H_5; R′ = R″ = H
VII, R = C_4H_9; R′ = $C_6H_5CH_2$; R″ = H
VIII, R = C_4H_9; R′ = $BzOOCCH_2$; R″ = Bz
IX, R = C_4H_9; R′ = $HOOCCH_2$; R″ = H
X, R = C_2H_5; R′ = $BzOOCCH_2$; R″ = Bz
XI, R = C_2H_5; R′ = $HOOCCH_2$; R″ = H
Bz = benzyl



V

The *v*-triazolo[4,5-*d*]pyrimidin-7-ylamino acids were prepared from 5-amino-7-chloro-3-ethyl-3H-*v*-triazolo-[4,5-*d*]pyrimidine[5] (III) or the 3-butyl derivative (IV). Equivalent amounts of free amino acid and triethylamine in anhydrous alcohol were employed for the preparation of the monobasic amino acid derivatives. The aspartic acid derivatives (IX and XI) were obtained by displacing the 7-chloro group of III and IV with dibenzyl aspartate and hydrogenating the resulting ester derivatives (VIII and X).

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740, and by the C. F. Kettering Foundation.

(2) C. E. Carter and L. H. Cohen, *J. Am. Chem. Soc.*, **77**, 499 (1955); R. Abrams and M. Bentley, *ibid.*, **77**, 4179 (1955); I. Lieberman, *ibid.*, **78**, 251 (1956); J. M. Buchanan and S. C. Hartman, *Advan. Enzymol.*, **21**, 199 (1959).

(3) See, for example, H. Lettré and H. Ballweg, *Ann.*, **633**, 171 (1960); **656**, 158 (1962); A. Ballio and V. DiVittorio, *Gazz. Chim. Ital.*, **90**, 501 (1960); D. N. Ward, J. Wade, E. F. Walborg, Jr., and T. S. Osdene, *J. Org. Chem.*, **26**, 5000 (1961).

(4) H. Ballweg, *Ann.*, **657**, 141 (1962).

(5) Y. F. Shealy, R. F. Struck, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **26**, 4433 (1961).