Synthesis and Biological Evaluation of Certain 4-Alkylamino and 4-Arylalkylamino Derivatives of the Imidazo[4,5-*d*]pyridazine and *v*-Triazolo[4,5-*d*]pyridazine Ring Systems (1a)

Shih-Fong Chen (1b) and Raymond P. Panzica*

Department of Medicinal Chemistry, University of Rhode Island
Kingston, Rhode Island 02881
and
Daniel L. Dexter, Ming-Yu Wang Chu, and Paul Calabresi
Department of Medicine, Roger Williams General Hospital,
Division of Biology and Medicine, Brown University
Providence, Rhode Island 02912

Received August 4, 1980

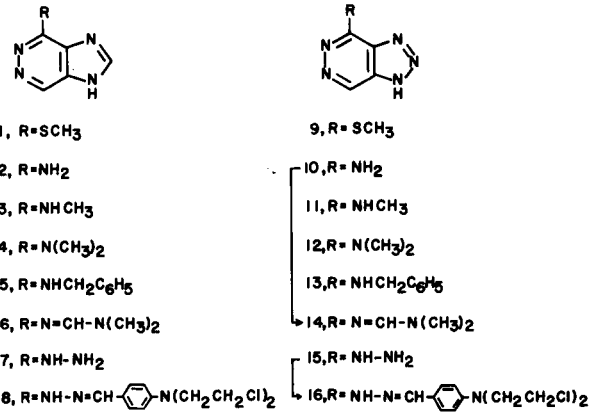
Revised January 15, 1982

Certain 4-alkylamino and 4-arylalkylamino derivatives of the imidazo- and *v*-triazolo[4,5-*d*]pyridazine ring systems were prepared and evaluated against two human colon carcinomas (DLD-1 and HCT-15) and one human lung carcinoma (LX-1), *in vitro*. 4-Methylthioimidazo[4,5-*d*]pyridazine (**1**) and 4-methylthio-*v*-triazolo-[4,5-*d*]pyridazine (**9**) served as precursors to the title compounds. Treatment of these heterocycles with the appropriate amine (ammonia, methylamine, dimethylamine, benzylamine and hydrazine) provided the desired derivatives of that ring system. 4-AIP (**2**) and 2-aza-4-AIP (**10**) served as precursors to the 4-dimethylaminomethyleneamino derivatives **6** and **14**, respectively. Likewise, the 4-hydrazino analogs (**7** and **15**) served as intermediates in the syntheses of benzaldehyde-*p*-[bis(2-chloroethyl)amino]imidazo[4,5-*d*]-pyridazin-4-yl-hydrazone (**8**) and benzaldehyde-*p*-[bis(2-chloroethyl)amino]-*v*-triazolo[4,5-*d*]pyridazin-4-yl-hydrazone (**16**), respectively.

J. Heterocyclic Chem., **19**, 285 (1982).

The ability of purine analogs to function as substrates for the salvage pathway enzymes continues to be an important factor in their development as chemotherapeutic agents. Those analogs which resemble adenine are potential candidates for adenine phosphoribosyltransferase (APRT), an enzyme which will convert them to their respective ribonucleotides. 4-Aminoimidazo[4,5-*d*]pyridazine (4-AIP, **2**), an analog which is modified in the six-membered ring portion of the purine ring, is a good substrate for APRT (2-5). When 4-AIP was incubated with human erythrocytes, formation of analog nucleotides was observed (5). This heterocycle also exhibited *in vitro* cytotoxicity against L1210 and L5178Y leukemias (6). In view of the biological activity demonstrated by 4-AIP (**2**), we initiated a synthetic program to prepare selected derivatives of this heterocycle as well as those of its 2-aza counterpart, *i.e.*, 4-amino-*v*-triazolo[4,5-*d*]pyridazine(2-aza-4-AIP, **10**).

The synthetic route we selected to prepare these analogs utilized 4-methylthioimidazo[4,5-*d*]pyridazine (**1**) and 4-methylthio-*v*-triazolo[4,5-*d*]pyridazine (**9**) as starting materials. 4-Methylthioimidazo[4,5-*d*]pyridazine (**1**) was synthesized according to the method of Martin and Castle (**7**) whereas **9** was prepared by a modification of the procedure of Yanai and coworkers (8). Heating either **1** or **9** with methanolic ammonia in a steel reaction vessel at 160° furnished 4-AIP (**2**) (9) and 2-aza-4-AIP (**10**) (7), respectively, in good yield. These two derivatives served as precursors to their corresponding 4-dimethylaminomethyleneamino derivatives **6** and **14**. Treatment of **2** with *N,N*-dimethylformamide dimethyl acetal and **10** with *N,N*-dimethylformamide dineopentyl acetyl in dry *N,N*-dimethylformamide at room temperature provided excellent yields



of **6** and **14**, respectively. These derivatives are considerably more water soluble than their parent amino analogs **2** and **10**, thus facilitating formulation and administration during biological evaluation. The 4-dimethylaminomethyleneamino derivative of 4-amino-pyrazolo[3,4-*d*]primidine (4-APP) (10) has been shown to slowly hydrolyze back to 4-APP in aqueous media. The activity exhibited by this analog against lymphoid leukemia L1210 supports the theory (11) that derivatives of this type

possibly function as pro-drugs of their parent amino analogs.

Reaction of **1** and **9** with either 40% aqueous methylamine, ethanolic dimethylamine, c ethanolic benzylamine using a similar set of conditions a described for the preparation of 4-AIP and 2-aza-4-AIP provided the corresponding 4-methylamino, 4-dimethylamino, and 4-benzylamino derivatives. It is interesting to note that when 40% aqueous dimethylamine replaced ethanolic dimethylamine in the reaction with **1**, imidazo[4,5-*d*]-pyridazine-4-one was formed exclusively rather than the desired **4**. This was not observed with 40% aqueous methylamine. A possible explanation for this occurrence could be a result of the dissociation constants of methylamine *verses* dimethylamine in aqueous solution where the equilibrium of the latter slightly favors the formation of hydroxide ions.

The synthesis of the mustards **8** and **16** were undertaken based on the noted anticancer activity (12) exhibited by benzaldehyde-*p*-[bis(2-chloroethyl)amino]purin-6-yl hydrazone (13). The preparation of the intermediary 4-hydrazino derivatives (**7** and **15**) from **1** and **9** were conducted according to Martin and Castle (7). Condensation of **7** and **15** with *p*-*N*,*N*-[bis(2-chloroethyl)amino]benzaldehyde in *N*,*N*-dimethylformamide furnished the hydrazones **8** and **16** in moderate yield.

Two human colon carcinoma cell lines (HCT-15(14) and DLD-1(14)) and one human lung carcinoma (LX-1(15)) cell line were used in the *in vitro* examination of compounds **2-7** and **10-15** for possible antineoplastic activity. All of the aforementioned heterocycles were examined against the DLD-1 cell line and their ID_{50} (16) values were greater than 10^{-4} *M*. Only 4-AIP (**2**) and 2-aza-4-AIP (**10**) were evaluated against the HCT-15 colon carcinoma cell line and both had ID_{50} values greater than 10^{-4} *M*. Compounds **2, 5, 6, 10, 13** and **14** were evaluated against the LX-1 lung carcinoma and with the exception of **6**, which exhibited low level activity, they were inactive.

Table 1

Ultraviolet Spectra Data [λ/nm (ε × 10^{-3})] for Certain 4-Alkylamino- and 4-Arylalkylamino Derivatives of the Imidazo- and *v*-Triazolo[4,5-*d*]pyridazine Ring Systems

Compound	λ max (*p*H 1)		λ min (*p*H 1)		λ max (water)		λ min (water)		λ max (*p*H 11)		λ min (*p*H 11)	
3	259	(8.91)	234.5	(3.63)	259.5	(7.25)	239	(3.99)	(a) sh 283.5	(3.60)	245	(3.59)
	sh 226.5	(8.27)							267.5	(5.38)		
									(a) sh 226.5	(15.36)		
4	265	(11.00)	239.0	(3.17)	270	(9.63)	245.5	(4.24)	276.5	(7.59)	251	(4.16)
	sh 230	(8.78)			218.5	(14.23)			228.5	(16.17)		
5	259.5	(13.06)	237.5	(6.98)	260	(10.63)	240	(6.04)	268.5	(8.29)	247	(5.95)
									226.5	(24.06)		
6	sh 319.5	(18.45)	253.5	(4.57)	306.5	(20.01)	261	(5.70)	290	(14.45)	260	(7.61)
	310.0	(20.58)			sh 255.5	(6.35)			239.5	(18.07)		
	230.5	(15.83)			227	(14.91)						
8	371	(24.72)	289.5	(6.44)	371	(26.14)	265	(6.67)	sh 407	(11.05)	263	(5.51)
	269	(9.81)	260	(9.48)	sh 317.5	(12.21)			361	(28.88)		
	sh 240.5	(18.35)							sh 317	(16.10)		
									235	(16.10)		
11	266	(8.00)	239	(3.76)	sh 291.5	(3.51)	242	(4.56)	287	(7.01)	247.5	(3.03)
					sh 279.5	(7.13)			226	(9.55)		
					266.5	(8.86)						
					222	(14.87)						
12	274	(8.21)	241	(2.53)	sh 297.5	(3.89)	246	(3.78)	297.5	(7.39)	252	(2.41)
					sh 285.5	(8.21)			227.5	(9.08)		
					275	(9.52)						
					225	(12.69)						
13	267.5	(9.28)	240.5	(4.30)	sh 291.5	(3.91)	244.5	(4.89)	286.5	(8.14)	247.5	(3.37)
					sh 281	(7.15)			226.5	(10.98)		
					268	(8.60)						
					sh 226	(14.16)						
14	sh 332.5	(18.52)	257	(4.22)	sh 330	(19.16)	268	(4.94)	306	(15.70)	258	(4.34)
	319.5	(23.42)			319	(26.76)			233	(10.86)		
	228	(14.08)			sh 238.5	(10.70)						
16	388	(24.60)	302	(7.43)	380	(21.40)	301	(6.61)	377	(34.92)	261	(4.66)
	sh 348	(19.15)	263.5	(7.36)	282.5	(7.43)	269	(7.13)	sh 362.5	(32.48)	222	(7.40)
	283.5	(9.01)			sh 247	(10.59)			234	(14.12)		
	sh 253	(9.20)										

(a) sh = shoulder.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The infrared spectra were determined in pressed potassium bromide disks with a Beckman IR-8 spectrophotometer. The ^{1}H nmr spectra were determined on a Varian A-60 or Varian EM-360A 60 MHz spectrometer using DMSO-d_6 as solvent. Chemical shifts are expressed in parts per million with respect to TMS: s, singlet; d, doublet; br s, broad singlet. The ultraviolet absorption spectra were recorded on a Beckman DB-GT Grating spectrophotometer. Thin layer chromatography was run on pre-coated (0.25 mm) Silica Gel 60 F-254 plates manufactured by EM Laboratories, Inc. and short wave ultraviolet light (254 nm) was used to detect the uv absorbing spots. Evaporations were performed with Buchi Rotovapor at 40° unless otherwise stated. Compressed gases (ammonia, methylamine and dimethylamine) were purchased from Matheson. *p-N,N*-[Bis(2-chloroethyl)amino]benzaldehyde was obtained from Chemicals Procurement Laboratories, Inc. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

4-Methylaminoimidazo[4,5-*d*]pyridazine (**3**).

4-Methylthioimidazo[4,5-*d*]pyridazine (**1**) (7) (466 mg, 2.1 mmoles) and 40% aqueous methylamine (20 ml) were heated at 160-165° (oil bath) in a glass-lined stainless steel reaction vessel for 24 hours. After cooling, the excess gases were vented off and the reaction mixture was filtered through a Celite bed. The filtrate was evaporated to dryness *in vacuo* and the residue crystallized from 95% ethanol furnish 242 mg of **3** (58%) as white crystals, mp > 300° (lit (17) 298-300° dec); ^{1}H nmr: δ 3.17 (s, 3, NCH_3), 8.40 (s, 1, H2), 9.11 (s, 1, H7).

Anal. Calcd. for $C_6H_7N_5$: N, 46.95. Found: N, 47.16.

4-Dimethylaminoimidazo[4,5-*d*]pyridazine (**4**).

To a suspension of **1** (166 mg, 1 mmole) in 15 ml of absolute ethanol was added anhydrous dimethylamine (5ml). This mixture was heated at 130° (oil bath) in a glass-lined stainless steel reaction vessel for 6 hours. After cooling, the excess gases were vented, and the reaction mixture was filtered through a Celite bed. The filter bed was washed (2 × 10 ml) with ethanol and the combined filtrate and wash was evaporated to dryness under diminished pressure. The solid residue was crystallized from 95% ethanol (Norit) to provide 107 mg of **4** (66%) as white needles. An analytical sample was obtained by recrystallization from 95% ethanol, mp 235-236.5°; ^{1}H nmr: δ 3.55 (s, 6, N(CH_3)$_2$), 8.52 (s, 1, H2), 9.13 (s, 1, H7).

Anal. Calcd. for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.92. Found: C, 51.40; H, 5.74; N, 43.19.

4-Benzylaminoimidazo[4,5-*d*]pyridazine (**5**).

A mixture of **1** (700 mg, 4.2 mmoles), absolute ethanol (20 ml), and benzylamine (5 ml) was heated in a glass-lined stainless steel reaction vessel at 160° (oil bath) for 24 hours. The reaction was worked up as described in the experimental of **4**. The resulting residue was triturated with AR chloroform (10 ml) to remove the last traces of benzylamine and filtered. The solid was washed twice (2 × 10 ml) with chloroform and then crystallized from 95% ethanol to afford 900 mg (95%) of **5** as white crystals. Recrystallization of **5** from 95% ethanol provided an analytical sample, mp 222-225°; ^{1}H nmr: δ 4.87 (s, 2, -CH_2C$_6$H$_5$), 7.2-7.6 (m, 5, -CH$_2$C$_6$H$_5$), 8.38 (s, 1, H2), 8.97 (s, 1, H7).

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.99; H, 4.92; N, 31.09. Found: C, 63.95; H, 4.89; N, 31.25.

4-Dimethylaminomethyleneaminoimidazo[4,5-*d*]pyridazine (**6**).

To a stirred suspension of **2** (9) (200 mg, 1.48 mmoles) in dry, *N,N*-dimethylformamide (6 ml) was added *N,N*-dimethylformamide dimethyl acetal (0.6 ml). The suspension was stirred at room temperature under anhydrous conditions. After 10 minutes solution was effected and stirring was continued for 15 hours. The solution was evaporated *in vacuo* to a light-yellow, microcrystalline solid. The solid was triturated with cold, absolute ethanol (2 ml), and air-dried to furnish 166 mg (59%) of **6**, mp 232-235°; ^{1}H nmr: δ 3.33 (s, 3, NCH_3), 3.43 (s, 3, NCH_3), 8.73 (s, 1, H2), 9.27 (s, 1, H7), 9.98 (s, 1, =CH).

Anal. Calcd. for $C_8H_{10}N_6$: C, 50.52; H, 5.30; N, 44.18. Found: C, 50.26; H, 5.38; N, 43.93.

Benzaldehyde-*p*-[bis(2-chloroethyl)amino]imidazo[4,5-*d*]pyridazin-4-yl Hydrazone (**8**).

To a solution of **7** (7) (200 mg, 1.3 mmoles) in 1.3 ml of distilled water 0.66 ml of concentrated hydrochloric acid was added a solution of *p-N,N*-[bis(2-chloroethyl)amino]benzaldehyde (500 mg, 2.0 mmoles) in *N,N*-dimethylformamide (5 ml). A yellow precipitate formed immediately and the reaction mixture was stirred at room temperature for 30 minutes. The solid was removed by filtration, washed with cold water (10 ml), and air-dried to provide 530 mg (70%) of **8**. Recrystallization from 95% ethanol furnished **8** as yellow crystals, mp 277-280° dec; ^{1}H nmr: δ 3.85 (s, 8, -CH_2CH_2-), 6.88 and 7.91 (ABq, 4, =CHC$_6$$H_4$N-, J_{AB} = 9 Hz), 8.50 (s, 1, =CH-), 8.82 (s, 1, H2), 9.05 (s, 1, H7).

Anal. Calcd. for $C_{16}H_{17}N_7Cl_2 \cdot 1.5\ H_2O$ (18): C, 47.41; H, 4.97; N, 24.19. Found: C, 47.84; H, 4.57; N, 24.54.

4-Methylthio-*v*-triazolo[4,5-*d*]pyridazine (**9**).

Into a three-necked round bottom flask (3 liter), fitted with a dropping funnel and a low temperature thermometer, was added 4,5-diamino-3-methylthiopyridazine (19) (9.5 g, 60.8 mmoles) and 10% aqueous acetic acid (660 ml). The resulting solution was mechanically stirred and cooled to 0° and then sodium nitrite (13.7 g, 198.5 mmoles) dissolved in water (139 ml) was added dropwise while maintaining the temperature at 0°. When one-half of the amount of sodium nitrite solution had been added, a crystalline, off-white solid began to precipitate. After the addition of the sodium nitrite solution was complete (*ca.* 2 hours), the reaction mixture was stirred an additional hour at 0°. The crystalline mass was then collected by filtration, washed with cold, distilled water (100 ml), and air-dried to furnish 9.14 g (89.9%) of **9**. Recrystallization from 95% ethanol provided pure **9** (8.13 g, 81%) as light-tan needles, mp 214-215° dec (lit. (7) 210.5-211.5°; (8) 224-225° dec); ^{1}H nmr: δ 2.83 (s, 3, SCH_3), 10.03 (s, 1, H7), 14.6 (br s, 1, N*H*); uv: ($\epsilon \times 10^{-3}$) λ max (*p*H 1) 310 nm (7.44), sh 280 (5.52), 237 (8.36); λ min (*p*H 1) 262.5 nm (4.53), 230 (8.16); λ max (water) 290 nm (6.85), sh 241 (7.52); λ min (water) 257 nm (4.61); λ max (*p*H 11) 290 nm (7.52), 232 (6.85); λ min (*p*H 11) 254 (2.27).

Anal. Calcd. for $C_5H_5N_5S$: N, 41.89. Found: N, 41.89.

4-Methylamino-*v*-triazolo[4,5-*d*]pyridazine (**11**).

A reaction between 4-methylthio-*v*-triazolo[4,5-*d*]pyridazine (**9**) (500 mg, 3 mmoles) and 40% aqueous methylamine (25 ml) was worked up in a similar manner as **3**. The residue was crystallized from ethanol-water (9:1, v/v) to afford 300 mg (67%) of **11** as white crystals. An analytical sample of **11** was recrystallized from the same solvent, mp > 300°; ^{1}H nmr: δ 3.18 (s, 3, NCH_3), 9.14 (s, 1, H7).

Anal. Calcd. for $C_6H_6N_6$: C, 40.00; H, 4.03; N, 55.97. Found: C, 40.24; H, 4.22; N, 55.88.

4-Dimethylamino-*v*-triazolo[4,5-*d*]pyridazine (**12**).

Into a glass-lined, stainless steel reaction vessel was placed **9** (500 mg, 3 mmoles) and methanolic dimethylamine (30 ml) (20). The reaction mixture was heated (oil bath) at 160° for 20 hours. After cooling, the excess gases were vented off and the solution was filtered through a Celite bed. The Celite bed was washed with methanol (2 × 10 ml) and the combined filtrate and wash was evaporated to dryness under diminished pressure. The residue was crystallized from 95% ethanol to give 480 mg (98%) of **12** as white crystals. Recrystallization from the same solvent provided an analytical sample, mp > 300°; ^{1}H nmr: δ 3.71 (s, 6, N(CH_3)$_2$), 9.11 (s, 1, H7).

Anal. Calcd. for $C_6H_8N_6$: C, 43.90; H, 4.91; N, 51.19. Found: C, 43.81; H, 5.25; N, 50.86.

4-Benzylamino-*v*-triazolo[4,5-d]pyridazine (**13**).

To a suspension of **9** (700 mg, 4.19 mmoles) on 25 ml of dry methanol was added 5 ml of benzylamine. This reaction mixture was worked up in

a similar manner as **5**. This procedure provided 730 mg (77%) of **13**. An analytical sample was prepared by recrystalization from 95% ethanol to furnish **13** as pale yellow crystals, mp 304-306° dec; ^{1}H nmr: δ 4.95 (s, 2, -C*H*$_2$C$_6$H$_5$), 7.20-7.52 (m, 5, -CH$_2$C$_6$*H*$_5$), 9.12 (s, 1, H7).

Anal. Calcd. for $C_{11}H_{10}N_6$: C, 58.40; H, 4.46; N, 37.15. Found: C, 57.92; H, 4.30; N, 37.45.

4-Dimethylaminomethyleneamino-*v*-triazolo[4,5-*d*]pyriazine (**14**).

N,N-Dimethylformamide dineopentyl acetal (1.2 ml) was added to a stirred suspension of **10** (7) (500 mg, 3.65 mmoles) in dry *N,N*-dimethylformamide (12 ml). The suspension was stirred at room temperature for 24 hours. The crystalline solid was collected by filtration, washed with methylene chloride (10 ml), and air-dried to provide 400 mg (54%) of **14** as white crystals, mp 284-285° dec; ^{1}H nmr: δ 3.27 (s, 3, NC*H*$_3$), 3.39 (s, 3, NC*H*$_3$), 9.13 (s, 1, H7), 9.80 (s, 1, =C*H*-).

Anal. Calcd. for $C_7H_9N_7$: C, 43.97; H, 4.74; N, 51.28. Found: C, 44.19; H, 4.78; N, 51.22.

Benzaldehyde-*p*-[bis(2-chloroethyl)amino]-*v*-triazolo[4,5-*d*]pyridazin-4-yl Hydrazone (**16**).

To a solution of **15** (7) (400 mg, 2.3 mmoles) in 2.6 ml of distilled water and 1.32 ml of concentrated hydrochloric acid was added a solution of *p-N,N*-[bis(2-chloroethyl)amino]benzaldehyde (1.0 g, 4.0 mmoles) in 10 ml of *N,N*-dimethylformamide. On addition of the *p-N,N*-[bis(2-chloroethyl)-amino]benzaldehyde a red precipitate formed and the resulting suspension was vigorously stirred for 2 hours at room temperature. At the end of this period, the precipitated solid was removed by filtration, washed with cold water (10 ml), and air-dried to provide 750 mg (75%) of **16**. Recrystallization from 95% ethanol and treatment with Norit afforded an analytical sample of **16** as yellow crystals, mp 240-241° dec; ^{1}H nmr: δ 3.80 (s, 8, -C*H*$_2$C*H*$_2$-), 6.80 and 7.85 (ABq, 4, =CHC$_6$*H*$_4$N-, J_{AB} = 9 Hz), 8.46 (s, 1, =C*H*-), 9.13 (s, 1, H7).

Anal. Calcd. for $C_{15}H_{16}N_8Cl_2$: C, 47.51; H, 4.25; N, 29.55. Found: C, 47.34; H, 4.16; N, 29.64.

Acknowledgments.

The authors wish to thank Professors Elie Abushanab and Charles I. Smith for many helpful discussions concerning this project and Ms. Sylvia Stoner for technical assistance. This work is a collaborative effort of the Roger Williams Cancer Center, CA 20892 and CA 13943.

REFERENCES AND NOTES

(1a) Presented in part at the 8th International Congress of Heterocyclic Chemistry, Graz, Austria, August, 1981, p 62; (b) Recipient of a University of Rhode Island Graduate Fellowship, 1979-1980.

(2) L. L. Bennett, Jr., M. H. Vail, S. Chumley, and J. A. Montgomery, *Biochem. Pharmacol.*, **15**, 1719 (1966).

(3a) L. L. Bennett, Jr., and J. A. Montgomery in "Methods of Cancer Research", Vol. 3, H. Busch, ed., Academic Press, New York, 1967, p 549; (b) J. A. Montgomery, *Progr. Med. Chem.*, **7**, 69 (1970).

(4) R. E. A. Gadd and J. F. Henderson, *Can. J. Chem.*, **48**, 295 (1970).

(5) S.-F. Chen, K. C. Agarwal, J. D. Stoeckler, B. S. Robison, R. E. Parks, Jr., and R. P. Panzica, Abstracts, Meeting of New England Pharmacologists, Boston, Massachusetts, February, 1981.

(6) S.-F. Chen and R. E. Parks, Jr., unpublished observations.

(7) S.-F. Martin and R. N. Castle, *J. Heterocyclic Chem.*, **6**, 93 (1969).

(8) M. Yanai, T. Kinoshita, S. Takeda, M. Mori, H. Sadaki, and H. Watanabe, *Chem. Pharm. Bull.*, **18**, 1685 (1970).

(9) R. N. Castle and W. S. Seese, *J. Org. Chem.*, **23**, 1534 (1958).

(10) R. P. Panzica and L. B. Townsend in "Nucleic Acid Chemistry: Improved and New Sythetic Procedures, Methods, and Techniques", Part 1, L. B. Townsend and R. S. Tipson, eds., Wiley-Interscience, New York, 1978, p 111.

(11) S. Hanessian, *J. Med. Chem.*, **16**, 290 (1973).

(12) M. H. Fleysher and A. Bloch, *J. Carbohyd. Nucleosides Nucleotides*, **4**, 121 (1977).

(13) R. C. Elderfield, R. N. Prasad, and T.-K. Liao, *J. Org. Chem.*, **27**, 573 (1962).

(14) D. L. Dexter, J. A. Barbosa, and P. Calabresi, *Cancer Res.*, **39**, 1020 (1979).

(15) M. Y. Chu, T. Takeuchi, K. S. Yeskey, H. Bogaars, and P. Calabresi, *Proc. Am. Assoc. Cancer Res.*, **20**, 151 (1979).

(16) The ID_{50} is the concentration required to reduce the growth rate of either DLD-1, HCT-15, or LX-1 cells in culture to half of the control rate.

(17) J. A. Carbon, *J. Am. Chem. Soc.*, **80**, 6083 (1958).

(18) The water of hydration was verified by ^{1}H nmr spectroscopy.

(19) S.-F. Chen and R. P. Panzica, *J. Heterocyclic Chem.*, **18**, 303 (1981).

(20) Dimethylamine gas was bubbled into cold (ice bath), AR methanol (23 ml) until the final volume was 30 ml.