of pyridine at 0 °C (ice bath) *p*-toluenesulfonyl chloride (4.7 g, 24.4 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h and then let stand in the refrigerator (3 °C) for another 22 h. Pyridine was removed under diminished pressure at room temperature. The syrup was extracted with ether (5 × 50 mL) and water (5 × 100 mL), and the residue was then dissolved in 100 mL of chloroform. To the chloroform solution 100 mL of petroleum ether (35–60 °C) was added slowly with stirring. The product precipitated out as a white solid which was collected by filtration and washed thoroughly with ether and petroleum ether. The product was recrystallized from ethanol–petroleum ether to give 7.01 g (86%).

5-Fluoro-5′-azido-2′,5′-dideoxyuridine (3b). A mixture of **2b** (8.0 g, 20.0 mmol) and lithium azide (1.57 g, 32.0 mmol) in DMF (30 mL) was heated at 70–75 °C with stirring for 2 h. The mixture was cooled to room temperature and filtered. The solvent was removed in vacuo at 50–60 °C. The residue was dissolved in 200 mL of 50% aqueous ethanol, stirred for 30 min with 15 g of AG50W-X8 (H^+) resin to remove Li^+, and then filtered. The solvent was evaporated to dryness in vacuo. The residue was dissolved in a minimum volume of ethanol–ether and kept at −20 °C for a few days. The crystals were collected by filtration and dried to yield 2.82 g (52%) of product: IR (KBr) ν_{max} 4.76 μ (azido).

5-Iodo-5′-amino-2′,5′-dideoxyuridine (4e). Compound **3e**[4] (5.10 g, 13.5 mmol) and triphenylphosphine (5.79 g, 22.1 mmol) were dissolved in 35 mL of pyridine and kept at room temperature with stirring for 1 h. Concentrated ammonium hydroxide (5 mL) was then added and the solution was allowed to stand for an additional 2 h with stirring. The solvent was evaporated to dryness under reduced pressure at room temperature to give a syrup which was washed thoroughly with ether (3 × 100 mL). The residue was then extracted with 1 N ammonium hydroxide solution (2 × 150 mL), and the excess triphenylphosphine and triphenylphosphine oxide were removed by filtration. The filtrate was extracted with benzene (3 × 100 mL) and with ether (3 × 150 mL) to remove residual triphenylphosphine and then evaporated to dryness in vacuo at 50 °C to yield 4.43 g (93%) of solid which was extracted twice with 150-mL portions of boiling ethanol. The insoluble material was collected by filtration, washed with ethanol and ether, and dried to afford 2.51 g (53%) of an analytically pure product: UV λ_{max} (0.01 N HCl) 285 nm (ϵ 7420); UV λ_{min} (0.01 N HCl) 247 nm; UV λ_{max} (0.01 N NaOH) 279 nm (ϵ 5530); UV λ_{min} (0.01 N NaOH) 252 nm.

Compounds **4b–d** were synthesized from the corresponding 5′-azido derivatives, **3b**, **3c**,[4] and **3d**,[4] in the same manner as described in the preparation of 4e except that water was used as extracting solvent instead of 1 N ammonium hydroxide solution.

Acknowledgment. The authors wish to express their appreciation to Ms. Jung Ja Lee and Mrs. C. Chai for their excellent technical assistance. This research was supported by U.S. Public Health Service Research Grant CA-05262 from the National Cancer Institute and by the National Institutes of Health Research Grant No. 1-PO7-PR00798 from the Division of Research Resources.

References and Notes

(1) A. Bloch, Ed., "Chemistry, Biology and Chemical Use of Nucleoside Analogs", *Ann. N.Y. Acad. Sci.*, **255** (1975).
(2) W. H. Prusoff and D. C. Ward, *Biochem. Pharmacol.*, **25**, 1233 (1976).
(3) E. C. Herrmann, Jr., Ed., "Third Conference on Antiviral Substances", *Ann. N.Y. Acad Sci.*, **284** (1977).
(4) T. S. Lin, J. P. Neenan, Y. C. Cheng, W. H. Prusoff, and D. C. Ward, *J. Med. Chem.*, **19**, 495 (1976).
(5) T. S. Lin, C. Chai, and W. H. Prusoff, *J. Med. Chem.*, **19**, 915 (1976).
(6) Y. C. Cheng, B. Goz, J. P. Neenan, D. C. Ward, and W. H. Prusoff, *J. Virol.*, **15**, 1284 (1975).
(7) D. M. Albert, M. Lakov, P. N. Bhatt, T. W. Reid, R. E. Ward, R. C. Cykiert, T. S. Lin, D. C. Ward, and W. H. Prusoff, *J. Invest. Opthalmol.*, **15**, 470 (1976).
(8) D. M. Albert, D. H. Percy, C. A. Puliafito, E. Fritsch, T. S. Lin, D. C. Ward, and W. H. Prusoff, *Proc. Soc. Exp. Biol. Med.*, in press.
(9) M. S. Chen, D. C. Ward, and W. H. Prusoff, *J. Biol. Chem.*, **251**, 4833 (1976).
(10) W. H. Prusoff, D. C. Ward, T. S. Lin, M. S. Chen, G. T. Shaiu, C. Chai, E. Lentz, R. Capizzi, J. Idriss, N. H. Ruddle, F. L. Black, H. L. Kumari, D. Albert, P. N. Bhatt, G. D. Hsiung, S. Strickland, and Y. C. Cheng, *Ann. N.Y. Acad. Sci.*, **284**, 335 (1977).
(11) T. S. Lin and W. H. Prusoff, *J. Carbohydr., Nucleosides, Nucleotides*, **2**, 185 (1975).
(12) W. S. Mungall, G. L. Greene, G. A. Heavner, and R. Letsinger, *J. Org. Chem.*, **40**, 1695 (1975).
(13) R. M. K. Dale, D. C. Ward, D. C. Livingston, and E. Martin, *Nucleic Acid Res.*, **2**, 915 (1975).
(14) I. Schildkraut, G. M. Cooper, and S. Greer, *Mol. Pharmacol.*, 11, 153 (1975).
(15) P. K. Chang and A. D. Welch, *Biochem. Pharmacol.*, **8**, 327 (1961).

Synthesis and Biological Activity of Several Amino Analogues of Thymidine

Tai-Shun Lin* and William H. Prusoff

Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510. *Received May 23, 1977*

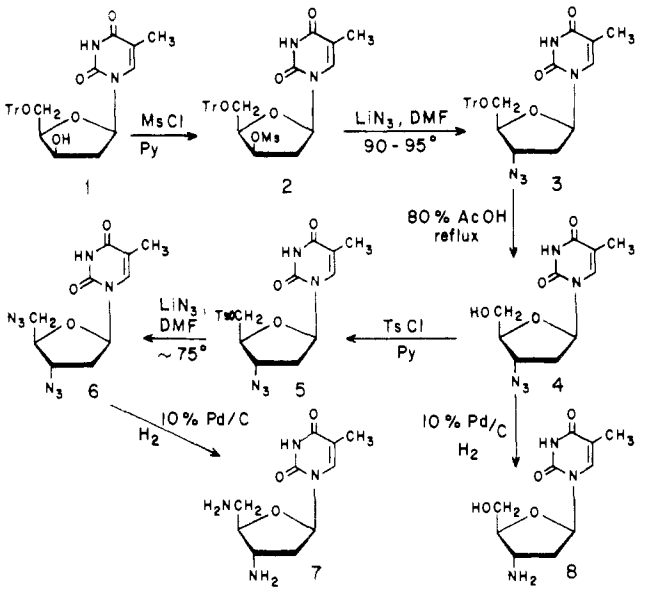
3′,5′-Diamino-3′,5′-dideoxythymidine (**7**) was synthesized via a nine-step synthesis from thymidine in good overall yield. 3′-Amino-3′-deoxythymidine (**8**) and 5′-amino-5′-deoxythymidine (**12**) were prepared with a minor modification of the procedure reported by Horwitz and co-workers. Although the 5′-amino analogue **12** had potent antiviral activity relative to the 3′-amino analogue **8**, the latter is a potent inhibitor of the replication of both murine sarcoma 180 cells (ED_{50} = 5 μM) and of murine L1210 cells (ED_{50} = 1 μM) in vitro. Most unexpectedly, however, was the finding of complete lack of either antiviral or antineoplastic activity by the 3′,5′-diamino analogue **7** which appears to have acquired the undesirable qualities of both the 3′-amino and 5′-amino analogues of thymidine.

Although the 3′- and the 5′-amino analogues of thymidine had been synthesized previously, their biological potential has not been explored.[1–3] The 5′-amino analogue of thymidine is a good competitive inhibitor of the phosphorylation of thymidine by thymidine kinase[4,5] and a modest inhibitor of thymidylate kinase.[6] Interest in amino analogues of nucleosides in general was stimulated by the findings that the 5′-amino analogues of thymidine and 5-iodo-2′-deoxyuridine have significant antiviral activity.[7–10]

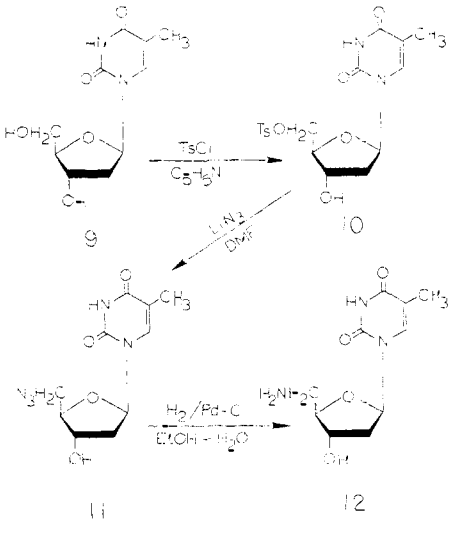
The 5′-amino analogue of 5-iodo-2′-deoxyuridine (AIdUrd, AIU) has demonstrated potent antiviral activity in the complete absence of toxicity to cells in culture or to day-old or adult mice.[7–11] Therapy of experimental Herpes simplex keratitis in rabbits indicated[12] that AIdUrd when in aqueous solution (8 mg/mL) is almost as effective as

0022-2623/78/1821-0109$01.00/0

Scheme I



Scheme II



idoxuridine (IdUrd, IUdR) (1 mg/mL) and is significantly indistinguishable when a 10% ointment preparation of AIdUrd is compared to IdUrd in 0.5% ointment.[13] The complete lack of toxicity of AIU to normal tissues is due to the lack of the Herpes simplex virus induced thymidine kinase which is required for activation.[14]

The present report describes the synthesis of the 3′-, the 5′-, and the 3′,5′-amino analogues of thymidine and the relationship of the location of the amino group on the thymidine molecule to biological activity.

Chemistry. The synthesis of amino analogues of thymidine (**7**, **8**, and **12**) is outlined in Schemes I and II. Treatment of 1-(2′-deoxy-5′-*O*-trityl-β-D-lyxosyl)-thymine[15,16] (**1**) with methylsulfonyl chloride in pyridine at 0 °C afforded the sulfonate **2**. Displacement of the 3′-methylsulfonyl group in **2** with lithium azide in *N*,*N*-dimethylformamide at 90–95 °C gave the corresponding 3′-azido derivative **3**. Detritylation of **3** with 80% aqueous acetic acid at refluxing temperature yielded 3′-azido-3′-deoxythymidine[2] (**4**) which was tosylated with *p*-tolylsulfonyl chloride in pyridine at 0 °C to give **5**. Compound **5** was converted to the corresponding 3′,5′-diazido analogue **6** by treatment with lithium azide in *N*,*N*-dimethylformamide at 75–80 °C. Hydrogenation of **6** in ethanol at 50 psi of hydrogen pressure in the presence of 10% palladium on charcoal afforded the final product, 3′,5′-diamino-3′,5′-dideoxythymidine (**7**).

Table I. Effect of 3′-, 5′-, and 3′,5′-Amino Analogues of Thymidine on the Replication of Sarcoma 180 Cells, L1210 Cells, and Herpes Simplex Virus in Vitro

Compd	Concn, μM	Percent inhibn S-180	L1210	HSV-1
5′-AmdThd (**12**)	400	None	None	98
3′, 5′-diAmdThd (**7**)	400	None	None	None
3′-AmdThd (**8**)	500		95	
	400			62
	250	73	93	
	50	66	92	
	25	68	88	
	15		91	
	5	55		
	3		87	
	1	37	58	
	0.5		43	

3′-Amino-3′-deoxythymidine[1,2] (**8**) and 5′-amino-5′-deoxythymidine[3] (**12**) were synthesized according to the procedure reported by Horwitz and co-workers with minor modification. Compound **8** was isolated as a free amino compound instead of the hydrochloride salt.[2] Thymidine (**9**) was converted directly to the corresponding 5′-*O*-*p*-tolylsulfonyl derivative **10** selectively by reacting with *p*-toluenesulfonyl chloride in pyridine at 0 °C for 24 h without blocking and then deblocking of the 3′-hydroxyl group.

Biological. The biological test methods used here have been described previously.[9] The 5′-amino analogue of thymidine had been shown previously to be a good inhibitor of the replication of Herpes simplex virus (HSV) in cell culture.[8] The 3′-amino analogue of thymidine, however, exerted a modest 62% inhibition of viral replication, and the 3′,5′-diamino analogue exerted no antiviral activity by HSV (Table I). The failure of the 3′,5′-diamino analogue to have antiviral activity was unexpected in view of the good activity of 5′-aminothymidine. Thus the presence of the 3′-amino moiety in the diamino analogue appears to decrease its potential for antiviral activity. The relative abilities of these three amino analogues of thymidine to be substrates for either the mammalian cell thymidine kinase or the HSV-induced thymidine kinase are under investigation.

Although the 5′-amino analogue has potent antiviral activity relative to the 3′-amino analogue, the latter is a potent inhibitor of the replication of both murine sarcoma 180 cells and of murine leukemia L1210 cells in vitro (Table I). The 5′-amino analogue is a good antiviral agent but a poor antineoplastic agent, whereas the 3′-amino analogue is an excellent antineoplastic agent but a poor antiviral agent. Most unexpectedly, however, was the finding of complete lack of either antiviral or antineoplastic activity by the 3′,5′-diamino-3′,5′-dideoxythymidine (Table I). Thus the 3′,5′-diamino analogue of thymidine appears to have acquired the undesirable qualities of both the 3′-amino and the 5′-amino analogues of thymidine.

A study of the effect of various nucleosides to prevent the inhibition by 3′-amino-3′-deoxythymidine of L1210 cells in vitro is presented in Table II. Of the various nucleosides evaluated only the pyrimidine deoxyribonucleosides appeared to be effective. Deoxyadenosine, deoxyguanosine, and the two pyrimidine ribonucleosides, uridine and cytidine, were all inactive in preventing the inhibitory activity of the 3′-amino-3′-deoxythymidine. When thymidine was present at a concentration which is equal to the molar concentration of the inhibitor (3 μM), the magnitude of inhibition was decreased almost in half.

Table II. Effect of Various Nucleosides on the Inhibition of the Replication of L1210 Cells in Vitro by 3′-Amino-3′-deoxythymidine (3′-AmdThd)

3′-AmdThd[a]	Nucleoside	Concn, μM	Percent inhibn[b]
+		3	100
+	Thymidine	1	75.2
+	Thymidine	3	55.2
+	Thymidine	9	38.1
+	Thymidine	27	22.4
−	Thymidine	30	0
+	Deoxyuridine	1	88
+	Deoxyuridine	5	74
+	Deoxyuridine	25	48
−	Deoxyuridine	25	4.0
+	Deoxycytidine	1	80
+	Deoxycytidine	5	61
+	Deoxycytidine	25	28
−	Deoxycytidine	25	2.0
+	Deoxyadenosine	1	89
+	Deoxyadenosine	5	89
+	Deoxyadenosine	25	93
−	Deoxyadenosine	25	1.5
+	Deoxyguanosine	1	87
+	Deoxyguanosine	5	86
+	Deoxyguanosine	25	102
−	Deoxyguanosine	25	1.2
+	Uridine	1	100
+	Uridine	5	99
+	Uridine	25	95
−	Uridine	25	23
+	Cytidine	1	100
+	Cytidine	5	100
+	Cytidine	25	99
−	Cytidine	25	21

[a] The concentration of 3′-amino-3′-deoxythymidine where present (+) is 3 μM. [b] Percent inhibition by 3′-AmdThd was normalized to 100. The average inhibition of five experiments was 83%.

Thymidine was slightly more effective than deoxycytidine in preventing inhibition, and deoxyuridine was least effective.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt apparatus and are not corrected. The UV spectra were recorded on a Beckman-25 spectrophotometer and the NMR spectra were taken on a Bruker 270 HX spectrometer. The elemental analyses were carried out by Baron Consulting Co., Analytical Services, Orange, Conn.

3′-Azido-5′-*O*-*p*-tolylsulfonyl-3′-deoxythymidine (5). To an ice-cooled solution of 3′-azido-3′-deoxythymidine[2] (4, 5.20 g, 19.63 mmol) in 30 mL of pyridine was added *p*-toluenesulfonyl chloride (4.49 g, 23.56 mmol). The reaction mixture was kept at 0 °C for 48 h. The solvent was removed under reduced pressure and the residue crystallized from ethanol. The tan color crystals were collected by filtration, washed with cooled ethanol and ether, and dried to yield 5.13 g of product (62%): mp 126–128 °C. Anal. ($C_{17}H_{19}N_5O_6S$) C, H, N.

3′,5′-Diazido-3′,5′-dideoxythymidine (6). A mixture of 5 (2.86 g, 6.79 mol) and lithium azide (0.67 g, 13.58 mmol) in 15 mL of *N*,*N*-dimethylformamide was heated at 70–75 °C for 2 h. The reaction mixture was cooled to room temperature and then added slowly to 200 mL of ice–water with vigorous stirring. The aqueous solution was extracted with chloroform (2 × 200 mL) and the organic phase was evaporated to dryness in vacuo to give a glassy residue which was used for the next preparation (hydrogenation) without further purification.

3′,5′-Diamino-3′,5′-dideoxythymidine (7). A solution of 6 in 60 mL of ethanol was hydrogenated at room temperature and 50 psi of hydrogen pressure in the presence of 10% palladium on charcoal (0.35 g) for 3 h. Norit was added to the mixture and stirred for 30 min. The mixture was then filtered through a Celite pad. The filtrate was concentrated to a small volume and during the process crystals started to come out. The solution was kept at 0 °C for 3 h and the crystals were isolated by filtration, washed with cooled ethanol and ether, and dried to afford 0.78 g (48%, based on 5). Compound 7 gave a positive ninhydrin test: mp 169–170 °C dec; NMR (Me_2SO-d_6) δ 7.69 (s, 1 H, C-6 H), 6.07 (t, 1 H, C-1′ H), 3.75–3.08 (br m, 6 H, C-3′ NH_2, C-5′ NH_2, D_2O exchangeable; C-3′ H, C-4′H), 2.16–1.89 (br m, 2 H, C-2′ CH_2), 1.78 (s, 3 H, C-5′ CH_3). Anal. ($C_{10}H_{16}N_4O_3 \cdot 0.5H_2O$) C, H, N.

3′-Amino-3′-deoxythymidine (8). A solution of 3′-azido-3′-deoxythymidine[2] (6.10 g, 22.83 mmol) in 100 mL of ethanol was hydrogenated under 50 psi of hydrogen pressure at room temperature for 5 h in the presence of 10% palladium on charcoal (0.7 g). The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in a minimum amount of water and the pH of the aqueous solution was adjusted to 3 with hydrochloric acid. The solution was then applied directly to a column (2 × 24 cm) of AG50W-X8 (H^+) ion-exchange resin and washed thoroughly with water (2 L), and the adsorbed product was eluted with 200 mL of 1 N NH_4OH solution. The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol to afford 3.69 g (67%) of product: mp 160–161 °C; UV λ_{max} (0.1 N HCl) 266 nm (ε 9190); UV λ_{min} (0.1 N HCl) 234 nm (ε 2250); UV λ_{max} (0.1 N NaOH) 268 nm (ε 7170); UV λ_{min} (0.1 N NaOH) 246 nm (ε 4240) [lit.[1] UV λ_{max} (0.1 N HCl) 265 nm (ε 9400); UV λ_{min} (0.1 N HCl) 233 nm (ε 2300); UV λ_{max} (0.1 N NaOH) 266.5 nm (ε 7400); UV λ_{min} (0.1 N NaOH) 244 nm (ε 4400)]; NMR (Me_2SO-d_6) δ 7.77 (s, 1 H, C-6 H), 6.08 (s, 1 H, C-1′ H), 4.97 (br s, 1 H, C-5′ OH, D_2O exchangeable), 3.70–3.46 (br m, 3 H, C-3′ H, C-5′ CH_2), 3.46–3.14 (br m, 3 H, C-3′ NH_2, D_2O exchangeable; C-4′ H), 2.18–1.90 (br m, 2 H, C-2′ CH_2), 1.77 (s, 3 H, C-5 CH_3).

5′-Amino-5′-deoxythymidine (12). The title compound was synthesized according to the procedure reported by Horwitz and co-workers[3] with minor modification. Thymidine (9) was converted directly to the corresponding 5′-*O*-*p*-tolysulfonyl derivative 10 selectively by reacting with *p*-toluenesulfonyl chloride in pyridine at 0 °C for 24 h without blocking and then deblocking of the 3′-hydroxyl group.

Acknowledgment. The authors wish to express their appreciation to Ms. Jung Ja Lee and Mrs. C. Chai for their excellent technical assistance. We also wish to thank Dr. G. T. Shiau for preparing the starting material, 5′-*O*-tritylthymidine. This research was supported by U.S. Public Health Service Research Grant CA-05262 from the National Cancer Institute, the U.S. Energy Research and Development Administration Research Contract E(11-1)-2468, and by the National Institutes of Health Research Grant No. 1-PO7-PR00798 from the Division of Research Resources.

References and Notes

(1) N. Miller and J. J. Fox, *J. Org. Chem.*, **29**, 1772 (1964).
(2) J. P. Horwitz, J. Chua, and M. Noel, *J. Org. Chem.*, **29**, 2076 (1964).
(3) J. P. Horwitz, A. J. Tomson, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3045 (1962).
(4) J. P. Neenan and W. Rohde, *J. Med. Chem.*, **16**, 580 (1973).
(5) Y. C. Cheng and W. H. Prusoff, *Biochemistry*, **13**, 1179 (1974).
(6) Y. C. Cheng and W. H. Prusoff, *Biochemistry*, **12**, 2612 (1973).
(7) Y. C. Cheng, J. P. Neenan, B. Goz, D. C. Ward, and W. H. Prusoff, *J. Virol.*, **15**, 1284 (1975).
(8) Y. C. Cheng, J. P. Neenan, B. Goz, D. C. Ward, and W. H. Prusoff, *Ann. N.Y. Acad. Sci.*, **255**, 332 (1975).
(9) T. S. Lin, J. P. Neenan, Y. C. Cheng, W. H. Prusoff, and D. C. Ward, *J. Med. Chem.*, **19**, 495 (1976).
(10) W. H. Prusoff, D. C. Ward, T. S. Lin, M. S. Chen, G. T. Shiau, C. Chai, E. Lentz, R. Capizzi, J. Idriss, N. H. Ruddle, F. L. Black, D. M. Albert, P. N. Ghatt, G. C. Hsiung, S. Strictland, and Y. C. Cheng, *Ann. N.Y. Acad. Sci.*, **284**, 355 (1977).
(11) W. H. Prusoff and D. C. Ward, *Biochem. Pharmacol.*, **25**, 1233 (1976).
(12) D. M. Albert, M. Lahav, P. M. Bhatt, T. W. Reid, R. E.

Ward, R. C. Cykiert, T. S. Lin, D. C. Ward, and W. H. Prusoff, *J. Invest. Opthalmol.*, **15**, 470 (1976).
(13) C. A. Puliafito, N. L. Robinson, D. M. Albert, T. S. Lin, D. C. Ward, and W. H. Prusoff, *Proc. Soc. Exp. Biol. Med.*, in press.
(14) M. S. Chen, D. C. Ward, and W. H. Prusoff, *J. Biol. Chem.*, **251**, 4833 (1976).
(15) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).
(16) J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *J. Org. Chem.*, **28**, 942 (1963).

Synthesis of 1-Deaza-6-thioguanosine and 1-Deaza-6-(methylthio)guanosine

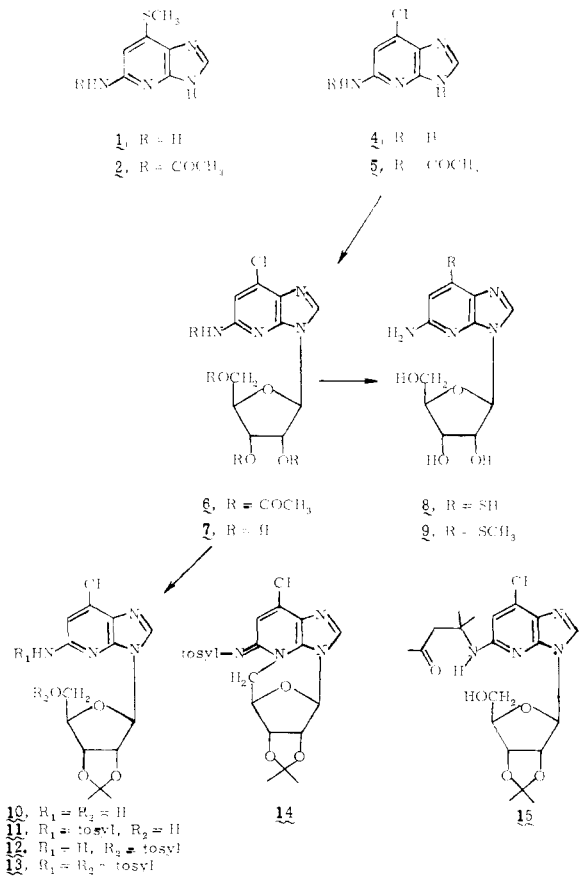
Robert D. Elliott* and John A. Montgomery

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205. *Received August 22, 1977*

A synthesis of 1-deaza-6-thioguanosine (**8**) and 1-deaza-6-(methylthio)guanosine (**9**) from 2-amino-6-chloro-1-deazapurine (**4**) is described. The reaction of the N^2-acetyl derivative of **4** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride in the presence of Linde 4A molecular sieve gave the blocked nucleoside **6**. Deacetylation of **6** gave the chloro nucleoside **7** which was treated at high temperature with hydrogen sulfide and methyl mercaptan to give **8** and **9**, respectively. The structure of **7** was confirmed by ^{1}H NMR and by conversion to the cyclonucleoside **14**. Compound **4** gave a 79% increase in life span in the L1210 mouse leukemia screen.

The reported antitumor activity of 6-thioguanine[1] and the nucleosides 6-thio-[2,3] and 6-(methylthio)guanosine[4] prompted our invesigation of synthetic routes to 5-amino-3,4-dihydro-3-β-D-ribofuranosyl-7*H*-imidazo[4,5-*b*]pyridine-7-thione (1-deaza-6-thioguanosine, **8**) and 7-(methylthio)-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]-pyridin-5-amine [1-deaza-6-(methylthio)guanosine, **9**].

An initial attempt was made to prepare **9** by a nucleoside coupling reaction between *N*-acetyl-7-(methylthio)-1*H*-imidazo[4,5-*b*]pyridin-5-amine (**2**) and 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride[5] (**3**). Acetylation of 7-(methylthio)-1*H*-imidazo[4,5-*b*]pyridin-5-amine[6] (**1**) in refluxing acetic anhydride gave **2** which was heated with **3** in 1,2-dichloroethane at 75 °C in the presence of Linde 4A molecular sieve for 6 days. Thin-layer chromatography indicated negligible nucleoside formation.



The successful route to **8** and **9** involved nucleophilic displacement of the chlorine from 7-chloro-3-β-D-ribofuranosyl-3*H*-imidazo[4,5-*b*]pyridin-5-amine (**7**). 7-Chloro-1*H*-imidazo[4,5-*b*]pyridin-5-amine[7] (**4**) was treated with acetic anhydride to give a diacetylation product which was partially hydrolyzed to give the monoacetyl derivative **5**. This compound was identified by comparison of physical properties (melting point, ^{1}H NMR, IR) with those described for **5** prepared by a different route.[8] Condensation of **5** with **3** in 1,2-dichloroethane containing Linde 4A molecular sieve gave the tetraacetyl nucleoside **6** which was deblocked with sodium methoxide in methanol to give **7**.

The proton-coupled ^{13}C NMR spectrum of **7** indicates that the ribose must be attached at N_1 or N_3. The C_2 absorption shows two spin–spin couplings: $^1J_{C_2H_2} = 211.5 \pm 0.6$ Hz and $^3J_{C_2H_{1'}} = 3.4 \pm 0.6$ Hz. The latter coupling would not be present if the attachment were at N_4 or the 5-amino group.

The site of ribosylation and anomeric configuration of **7** was confirmed[9] by conversion to the cyclonucleoside **14**. Treatment of **7** with acetone, 2,2-dimethoxypropane, and perchloric acid gave the isopropylidene derivative **10**. Tosylation of **10** in pyridine with 1 equiv of tosyl chloride gave the tosylamide **11** rather than the expected tosylate ester **12**. Tosylation of guanosine under the same conditions gives the 5′-*O*-tosyl ester.[10] The difference is apparently due to the increased basicity of the amino group of **10**. Evidence for structure **11** is based on NMR data, a mass ion of *m/e* 494 (M^+), and a UV spectrum different from **10** and similar to **5** at pH 1. Treatment of **11** with additional tosyl chloride in pyridine gave the crude ditosyl derivative **13** which was identified by ^{1}H NMR, a mass ion of *m/e* 648 (M^+), and a UV spectrum similar to **11**. The cyclonucleoside **14** was readily formed by heating a solution of **13** with triethylamine in benzene at 50 °C. The structure of the product is based on elemental analysis, a mass ion of *m/e* 476 (M^+), a UV spectrum different from **10** or **11**, and NMR data. There is a large (1.47 ppm) difference in the chemical shifts of the $H_{5'}$ bridge protons due to the difference in magnetic environments in which they are held by the cyclic structure. In the related guanosine cyclonucleoside the remote possibility that cyclization of $C_{5'}$ with the 2-amino group may occur has been considered by Reist et al.[10] and Chambers et al.;[11] however, Dreiding stereomodels strongly favor the 3–5′ ring structure for cycloguanosine and **14** (purine numbering).

The chlorine of the deazapurine **4** has been reported to

0022-2623/78/1821-0112$01.00/0