H. Huffman, G. P. Khare, L. B. Allen, J. T. Witkowski, and R. K. Robins, *Science*, **177**, 705 (1972). Ribavirin, 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, is the name approved by the U.S. Adopted Names Council for this drug; Virazole is the ICN Pharmaceuticals, Inc., trademark.
(12) F. F. Snyder, J. F. Henderson, and D. A. Cook, *Biochem. Pharmacol.*, **21**, 2351 (1972); J. F. Henderson, C. M. Smith, F. F. Snyder, and G. Zombor, *Ann. N.Y. Acad. Sci.*, **255**, 489 (1975).
(13) (a) D. G. Streeter, J. T. Witkowski, G. P. Khare, R. W. Sidwell, R. J. Bauer, R. K. Robins, and L. N. Simon, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 1174 (1973); (b) D. G. Streeter, J. P. Miller, R. K. Robins, and L. N. Simon, *Ann. N.Y. Acad. Sci.*, **284**, 201 (1977); (c) J. P. Miller, L. J. Kigwana, D. G. Streeter, R. K. Robins, L. N. Simon, and J. Roboz, *ibid.*, **284**, 211 (1977).
(14) C. M. Smith, L. J. Fontenelle, H. Muzik, A. R. Paterson, H. Unger, L. W. Brox, and J. F. Henderson, *Biochem. Pharmacol.*, **23**, 2727 (1974).
(15) G. R. Revanker, T. R. Matthews, and R. K. Robins, *J. Med. Chem.*, **18**, 1253 (1975).
(16) (a) F. B. Rudolph and H. J. Fromm, *J. Biol. Chem.*, **244**, 3832 (1969); (b) J. G. Flaks, M. J. Erwin, and J. M. Buchanan, *ibid.*, **229**, 603 (1957).
(17) J. T. Witkowski, D. G. Streeter, and R. K. Robins, *J. Med. Chem.*, in press.
(18) S. C. Hartman in "Metabolic Pathways", Vol. IV, 3rd ed., D. M. Greenberg, Ed., Academic Press, New York, N.Y., 1970, p 1.
(19) L. N. Lukens and J. Flaks, *Methods Enzymol.*, **6**, 696 (1963).
(20) Merck high-performance thin-layer chromatography plates (HP-TLC silica gel 10 F-254) which detect ca. nanogram quantities via UV were employed. One microliter of a millimole solution of **19**, **20**, **22**, and **21** was used as standard.

Prodrugs of 9-β-D-Arabinofuranosyladenine. 1. Synthesis and Evaluation of Some 5′-(*O*-Acyl) Derivatives[1]

David C. Baker,* Theodore H. Haskell, and Sterling R. Putt

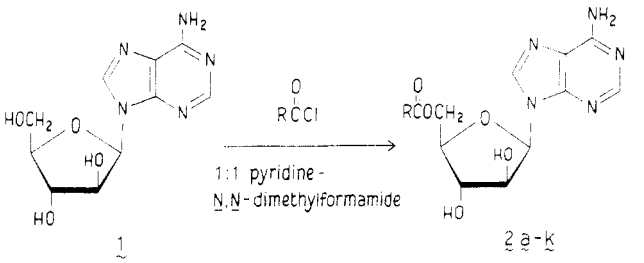
Chemistry Department, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan 48106.
Received April 3, 1978

A number of 5′-(*O*-acyl) derivatives of 9-β-D-arabinofuranosyladenine (*ara*-A, VIRA-A) (**2a–k**) were prepared by direct acylation of the parent nucleoside **1** in pyridine–*N*,*N*-dimethylformamide. These compounds, designed as prodrugs for **1**, offer a range of solubilities and lipophilicities indicating for several examples improved solubility and the potential for improved membrane transport over **1**. All are resistant to deactivation by adenosine deaminase. Of special interest is the 5′-(*O*-valeryl) derivative **2d** that shows a marked increase in antiviral activity over **1**.

The potent antiviral nucleoside 9-β-D-arabinofuranosyladenine (**1**) (*ara*-A, vidarabine, VIRA-A) has shown activity[2] against certain DNA viruses such as herpes, varicella, and cytomegaloviruses and has demonstrated clinical utility as a topical agent for herpes keratitis of the eye.[3] Most dramatically, however, the drug has been shown useful as a highly effective, relatively nontoxic, systemic agent to treat the usually fatal herpes encephalitis.[4] In an impressive, placebo-controlled study of biopsy-proven cases of the illness, the mortality rate was lowered[4] from 70 to 28%. Despite its proven efficacy, **1** does suffer from a number of limitations: (1) a low aqueous solubility[5] of ca. 0.4 mg/mL at 25 °C that poses a severe restraint to parenteral administration of the drug; (2) a ready deamination by adenosine deaminase to give 9-β-D-arabinofuranosylhypoxanthine (*ara*-Hx), the chief metabolite which possesses low-level antiviral activity;[6] and (3) a low lipophilicity that precludes the use of **1** as a topical agent for treating genital, oral, and other cutaneous herpes infections.

In an attempt to overcome these problems which manifest themselves as difficulties with formulation, delivery, and topical application, as well as with a lack of resistance to enzymic deactivation in vivo, a series of 5′-monoesters of **1** (**2a–k**) was synthesized. It was anticipated that such acyl derivatives would serve to counteract the various intra- and/or intermolecular hydrogen-bonding forces that are presumably responsible for rendering the arabino nucleoside far less soluble than adenosine, its ribo counterpart.[7] Compounds **2a–k** would be predicted to have a less compact crystal structure and thereby show lower melting points. The result is an increase in free energy within the crystalline matrix that would give rise to an expected increase in solubility that is desired for a parenteral drug. The gains in lipophilicity would be of an advantage in obtaining compounds that would be more prone to traverse biological membranes and skin layers, and thereby one might possibly gain insight into designing drugs that would be suited for topical application for treatment of cutaneous herpes infections. Such rationale has been followed in prodrug design for a variety of pharmaceuticals,[8,9] and this concept has been applied to prodrugs for the nucleoside antileukemic 3-β-D-arabinofuranosylcytosine (*ara*-C)[10,11] and, albeit with limited success, to **1**, as shown in certain 5′-esters,[12,13] as well as with tri-*O*-acyl derivatives[14] of **1**.

Scheme I



Chemistry. Direct acylation of the free nucleoside **1** was effected by adding 1.1 equiv of the appropriate acyl chloride to a suspension of the nucleoside in 1:1 pyridine–*N*,*N*-dimethylformamide (see Scheme I). It is to be pointed out that the solvent–base combination was found to greatly facilitate the selectivity of the acylation of the primary hydroxyl group over either of the secondary alcoholic groups. This result is apparently a consequence of having as the acylating reagent a charged species (i.e., *N*-acylpyridinium chloride) in an aprotic, nonpolar solvent such as *N*,*N*-dimethylformamide.[15,16] By maintaining ice-bath temperatures, the 5′-acylated nucleosides **2a–k**

* Address correspondence to this author at the Department of Chemistry, The University of Alabama, University, Ala. 35486.

0022-2623/78/1821-1218$01.00/0

Table I. Physical Data for 5′-(O-Acyl) Derivatives of 9-β-D-Arabinofuranosyladenine

no.	O ‖ RC-	yield,[a] %	mp, °C	λ_{max}^{MeOH}, nm (log ε)	$[\alpha]^{23}D$, deg (c 1, methanol)	formula (analyses)[b]	solubility, mg/mL	log P (1-pentanol/water)[c]
2a	$CH_3C(=O)$-	82	197.5-198.5	258 (4.18)	+23.6	$C_{12}H_{15}N_5O_5 \cdot 0.25H_2O$ (C, H, N)	6.6	0.12
2b	$CH_3CH_2C(=O)$-	61	201-203 (dec >190)	258 (4.17)	+22.8	$C_{13}H_{17}N_5O_5 \cdot 0.3EtOH$ (C, H, N)	9.2	0.58
2c	$CH_3(CH_2)_2C(=O)$-	64	184 (sinters) (dec 187-189)	259 (4.18)	+23.0	$C_{14}H_{19}N_5O_5$ (C, H, N)	16.1	0.90
2d	$CH_3(CH_2)_3C(=O)$-	47	glass	259 (4.18)		$C_{15}H_{21}N_5O_5 \cdot 0.2H_2O$ (C, H, N)	8.4	1.33
2e	$(CH_3)_2CHCH_2C(=O)$-	65	glass	258 (4.17)	+32.6	$C_{15}H_{21}N_5O_5 \cdot 1.25H_2O$ (C, H, N)	19.8	1.39
2f	$(CH_3)_3CC(=O)$-	30	glass	259 (4.17)	+35	$C_{15}H_{21}N_5O_6 \cdot 0.2H_4$furan (C, H, N)	7.0	1.63
2g	$CH_3(CH_2)_4C(=O)$-	35	glass	259 (4.16)		$C_{16}H_{23}N_5O_5 \cdot 0.2H_2O$ (C, H, N)	2.5	1.78
2h	$(CH_3)_3CCH_2C(=O)$-	42	glass	259 (4.17)	+31.2	$C_{16}H_{23}N_5O_5 \cdot 0.25H_2O$ (C, H, N)	7.8	1.70
2i	$CH_3(CH_2)_6C(=O)$-	45	glass	259 (4.16)	+29.4	$C_{18}H_{27}N_5O_5$[f] (C, H)	~0.1	≥2.00
2j	$C_6H_5(CH_2)_2C(=O)$-	39	glass	259 (4.17)	+28.8	$C_{19}H_{21}N_5O_5 \cdot 0.25H_2O$ (C, H, N)	1.5	1.73
2k[d]	$C_6H_5C(=O)$-	38	222-224[e]	259 (4.20), 230 (4.31)	+42		0.08	1.34

[a] Yields are based on pure components isolated after chromatography and, in general, are based on single experiments. [b] All solvates were verified by NMR spectroscopy. [c] For methodology see the Experimental Section; log P (vidarabine) = −0.47. [d] See ref 12. [e] Lit.[12] mp 223-224 °C. [f] N: calcd, 17.80; found, 17.12.

were obtained in yields of 30–80% after chromatography over silica gel to separate minor, peracylated contaminants and unreacted 1. The low-yielding reactions invariably contained much unreacted 1 (as revealed by TLC) that was not recovered and not accounted for in yield calculations; yields increased significantly, for example with **2a**, with a minimum of experimental development. The structures of the compounds were confirmed by their NMR spectra[17] in deuterated methyl sulfoxide that typically showed an expected downfield shift for the 5′-methylene function that was consonant with 5′-O-acylation of 1. The methinyl protons at C-2′ and C-3′ both appeared as overlapping complex multiplets that simplified somewhat upon exchange of the hydroxyl protons with deuterium oxide. That the amino group on the adenine ring remained unacylated was demonstrated by the UV spectra (λ_{max}^{MeOH} 258–259 nm; see Table I) that were indicative of a nonacylated adenine, as well as a broad singlet in the NMR spectrum at δ 7.26 that integrated for two protons ($-NH_2$). All new structures gave correct elemental analyses for C, H, and N.

Results and Discussion

As expected, the aqueous solubilities for the short-chain esters showed dramatic increases over that of **1**. Among the crystalline examples **2a–c**, 15-, 20-, and 34-fold increases in solubility, respectively, based on hydrated **1**, were obtained. The melting points were observed to drop by ca. 55–60 °C from that of **1** [mp (of 1) 257–275.5 °C].[18] The lipophilicities measured via a pentanol–water distribution show increases commensurate with increasing chain length. While no quantitative comparisons can be accurately made with the glassy examples **2d–j** due to the lack of an ordered, crystalline state, it is noted that for **2d–j** the solubilities are quite high for the glassy, five-carbon esters **2d–f** and the highly branched, *tert*-butylacetyl derivative **2h**. Comparison of the 5′-(*O*-valeryl) compound **2d** with the isomeric, 5′-(*O*-isovaleryl) ester shows an increased solubility of the latter, with an approximately equivalent partition ratio. As the hydrocarbon chains were lengthened to C-6 and C-8, the hydrophobic character imparted to the molecules, as revealed by log *P* values that approach ca. 2.0, resulted in a general decrease in aqueous solubility. The 5′-(*O*-octanoyl) derivative **2i** fell below that of **1** in equivalent solubility. The aryl ester **2k**[12] and the aralkyl analogue **2j** were both quite insoluble, with no apparent increase in lipophilicity over the lower alkyl derivatives **2d–h**.

When assayed[19] against calf mucosal adenosine deaminase in vitro, these esters exhibit complete resistance to deamination. This finding is not surprising, as it is in accord with the structure–activity relationships[20] established with studies on various adenine nucleosides that show a profound dependence on an available 5′-hydroxyl group for necessary auxillary binding to the enzyme. Furthermore, in studies carried out by Higuchi et al.,[21a] the 5′-(*O*-valeryl) derivative **2d** is shown in a culture of KB cells to give rise to unexpectedly high intracellular levels of the free-hydroxy parent nucloside **1** in relation to the metabolite, *ara*-Hx. Such results indicate that some deaminase protection mechanism, other than a simple lack of substrate activity for the enzyme, is operative. In vitro studies with calf mucosal adenosine deaminase showed that the intact ester functioned as a weak inhibitor of the enzyme ($K_i = 1.1 \times 10^{-5}$ M).[21b] While this inhibition is in no way as pronounced as that realized with the potent inhibitors such as pentostatin (covidarabine)[22–24] or coformycin,[25] the effect is dramatic in that the process occurs at the cellular level with impressive results.[21a] The possible biological implications are noteworthy as **2d** is a prodrug of 1 that is soluble, lipophilic, and not only resistant to adenosine deaminase but also apparently capable of inhibiting the enzyme and thus protecting 1 from enzymic deactivation as it is liberated. These interesting results have spawned similar studies with other ester analogues.[26]

Detailed aqueous stability studies were carried out on the 5′-(*O*-valeryl) ester **2d**. Ester hydrolysis rates were measured for **2d** at pH 6.56 (an arbitrary value) for temperatures of 60, 80, and 100 °C, and the pseudo-first-order rates were calculated. An Arrhenius plot of the log of these rates vs. reciprocal temperatures (K) gave a straight line that, when extrapolated to 25 °C, gave a rate

Table II. Antiviral Plaque-Reduction Assays[a]

no.	compound concn, M × 10^5 [c]	compound concn, μg/mL	compound % plaque redn	control (*ara*-A),[b] % plaque redn
2a	5.50	17	86	100
2b	1.78	6	83	88
2c	1.78	6	67	63
2d	1.69	6	100	54
	0.169	0.6	90	0
2e	1.87	7	53	87
2f	5.50	20	11	69
2g	1.76	6.5	25	87
2h	1.76	6.5	10	63
2i	0.51	2	45	64
2j	1.73	7	29	63
2k	1.75	6.5	71	87

[a] According to the published procedure (see ref 27) using herpes simplex type 1 virus. [b] The control experiment was conducted alongside the test sample, at the same molarity as the test drug, using an identical virus challenge. [c] Formula weights used were those calculated from NMR and elemental analyses data to include any molecules of solvation.

of 5.40×10^{-6} h^{-1}, corresponding to a $t_{1/10} = 2.25$ yr (i.e., the time required for 10% decomposition), a value considered suitable for aqueous formulation. This contrasts the aqueous stability reported[13] for the 5′-(*O*-formyl) analogue which showed $t_{1/2} = 10$ days in the zone of its maximum stability, pH 4.2–4.5.

Antiviral Assays. When assayed against herpes simplex type 1 virus by an in vitro plaque-reduction procedure,[27] the esters in general showed (see Table II) 40–80% reduction in plaques at a level of ca. $(1.8 \pm 0.1) \times 10^{-5}$ M, where **1** at a comparable level typically reduces plaques on an order of 60–90%. Thus, under in vitro conditions, most of the esters do function as effective antivirals. The most highly branched chain esters, i.e., the 5′-(*O*-pivaloyl) and 5′-(*O*-*tert*-butylacetyl) compounds **2f** and **2h**, respectively, show very low levels of plaque reduction, perhaps reflecting a tendency for these hindered esters to remain intact and fail to liberate **1** at the intracellular level. Although no proof is available, it might be speculated that these esters, **2a**–**e**,**g**, do act as true prodrugs and must liberate **1** which is the active agent. Supporting evidence for this theory comes from the fact that the 5′-(*O*-methyl ether),[28] a stable, nonhydrolyzable derivative, has been shown to be inactive toward a variety of DNA viruses.[29] Also, from studies at the molecular biological level, **1** must be converted to the 5′-triphosphate, the presumed bioactive component.[30]

Most noteworthy among these results is the activity of the 5′-(*O*-valeryl) derivative **2d** that has shown in duplicate assays (see Table II) 100% plaque reduction at the 1.69×10^{-5} M level (compare **1**, showing 54%) and 90% plaque reduction at 0.169×10^{-5} M, a level where **1** is inactive. This increased activity over **1** might be attributable to a combination of increased aqueous solubility, favorable lipophilicity, and mild inhibitory action toward adenosine deaminase that has been noted in the foregoing discussion.

Summary

Compounds **2a**–**k** represent a class of derivatives of **1** that offer varied solubilities and lipophilicities, with resistance to enzymic deactivation by adenosine deaminase. In vitro activity apparently depends upon a complex set of factors including the rate of hydrolysis to yield **1**, solubility, lipophilicity, and resistance to adenosine deaminase. In view of the low activity for **2f**, a true prodrug function seems indicated for the active compounds. How these results will translate to in vivo activities remains to be studied. Clearly a number of possible candidates for both topical and parenteral drugs are presented. Of special interest is the 5′-(*O*-valeryl) derivative **2d** that is ~15 times as soluble as **1** on a mole for mole basis, with increased lipophilicity and far more activity in the plaque-reduction screen, indicating the potential for a good parenteral or topical drug.

Experimental Section

Vidarabine (crystalline monohydrate; Parke, Davis & Co.) was dried at 100 °C (0.10 torr) for 12 h prior to use. All reagents were commercial, reagent-grade materials and were used directly. Thin-layer chromatography was conducted using E. Merck 0.25-mm silica gel GF plates; column chromatography was carried out with E. Merck silica gel 60 (70–200-μm particle size). Melting points are uncorrected values obtained on a Thomas-Hoover capillary melting point device. The NMR spectra were obtained using a Brüker WH-90 spectrometer; chemical shifts are on the δ scale, measured downfield in parts per million from tetramethylsilane. UV spectra were recorded on a Cary 11 unit.

General Procedure for Acylation. To a stirred suspension of 2.67 g (10.0 mmol) of dry 9-β-D-arabinofuranosyladenine in 100 mL of 1:1 pyridine-*N*,*N*-dimethylformamide cooled to 0 °C in an ice bath was added, dropwise, 10.1 mmol of the appropriate acyl chloride. The mixture became homogeneous and was stirred at 0 °C for 12–24 h at the end of which time ~10 mL of water was added, and the solvents were evaporated in vacuo at 50 °C. The residue was dissolved in methanol and adsorbed onto ~10 g of silica gel, and the excess solvent was evaporated off. Toluene was three-times evaporated from the solid mass, and the whole was loaded onto a 3 × 40 cm slurry-packed column of silica gel in chloroform and eluted with a linear gradient of chloroform (500 mL) to 20:80 methanol–chloroform (500 mL). The appropriate fractions, as determined by TLC, were combined, and the solvents were evaporated to yield the desired product that was either recrystallized (see Table II) or dried in vacuo to a glass. The noncrystalline compounds **2d**–**j** could be rendered free of contaminating ash by equilibrating between ethyl acetate and water, separating the organic phase, drying (magnesium sulfate), and evaporating to give an analytically pure glass. For yields and physical data see Table I.

Determination of the Aqueous Stability of 9-[5′-(*O*-Valeryl)-β-D-arabinofuranosyl]adenine (2d). A 0.1% solution (100 mL) of **2d** (pH 6.56) was prepared in distilled water, and, without delay, 2-mL aliquots were transferred to 36, 2-mL ampules. One dozen each of the ampules were kept at 60, 80, and 100 °C in constant temperature baths, respectively, and samples were periodically withdrawn and diluted with an equal volume of an internal standard, caffeine (0.6 mg/mL). The mixture was analyzed by high-pressure liquid chromatography using a reverse-phase system (5-μL sample, Reeve-Angel Partisil ODS, 0.45 × 25 cm, 40:60 methanol–water, 40 mL h^{-1}, 254-nm detection), and first-order rates were calculated from a plot of log [**2d**] vs. time: $k_{60} = 1.61 \times 10^{-4}$ h^{-1}, $k_{80} = 7.80 \times 10^{-4}$ h^{-1}, and $k_{100} = 3.36 \times 10^{-3}$ h^{-1}.

Determination of Solubility for Compounds 2a–k. An excess of each compound (10 mg) was agitated for 16 h in 25-mL volumetric flasks with 5 mL of 0.1 M phosphate buffer. The solutions were filtered from undissolved solids through 4–5.5-mesh (ASTM), sintered glass funnels, and concentrations of solute were determined from UV absorbance values previously determined in buffer.

Determination of Partition Coefficients for Compounds 2a–k. A solution (10 mL) of the compound in 0.1 M phosphate buffer having an absorbance of $A = 2$–2.5 at the λ_{max} was shaken with 10 mL of pentanol in a 125-mL separatory funnel for 1 h. The layers were separated, the concentration was determined by UV, and the partition coefficients were calculated as $P = [S]_{pentanol}/[S]_{water}$.

Acknowledgment. The authors thank Carola Spurlock for the solubility and partition coefficient data, Drs. D. Szulczewski and W. H. Hong for the stability data on compound **2d**, Dr. B. J. Sloan and associates for antiviral

screens, and Dr. W. I. Higuchi and co-workers at the College of Pharmacy, The University of Michigan, for their continuing collaborative work with these compounds.

References and Notes

(1) For a preliminary account see D. C. Baker, T. H. Haskell, and S. R. Putt, "Abstracts of Papers", 174th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1977, MEDI 27. The compounds are described in a patent: D. C. Baker and T. H. Haskell, U.S. Patent 4069382 (1978). Other names for 9-β-D-arabinofuranosyladenine include *ara*-A, adenine arabinoside, vidarabine (generic), and VIRA-A (Parke-Davis & Co.).
(2) W. M. Shannon in "Adenine Arabinoside, an Antiviral Agent", D. Pavan-Langston, R. A. Buchanan, and C. A. Alford, Eds., Raven Press, New York, N.Y., 1975, pp 1–44.
(3) A. J. Dresner and M. L. Seamans in ref 2, pp 381–392.
(4) R. J. Whitey, S. Soong, R. Dolin, G. J. Galasso, R. T. Ch'ien, and C. A. Alford, *N. Engl. J. Med.*, **297**, 289 (1977).
(5) Various solubilities have been reported, ranging generally from 0.4 to 0.5 mg/mL; compare A. J. Repta in "Pro-Drugs as Novel Drug Delivery Systems", T. Higuchi and V. Stella, Eds., American Chemical Society, Washington, D.C., 1975, p 202.
(6) J. D. Connor, L. Sweetman, S. Carey, M. S. Stuckey, and R. Buchanan in ref 2, pp 177–196.
(7) By our procedure (see the Experimental Section) adenosine has a solubility of 4.8 mg/mL at pH 7; see also ref 5.
(8) T. Higuchi and V. Stella, Eds., "Pro-Drugs as Novel Drug Delivery Systems", American Chemical Society, Washington, D.C., 1975.
(9) E. B. Roche, Ed., "Design of Biopharmaceutical Properties through Prodrugs and Analogs", American Pharmaceutical Association, Washington, D.C., 1977.
(10) W. J. Wechter, D. T. Gish, M. E. Greig, G. D. Gray, T. E. Moxley, S. L. Kuentzel, L. G. Gray, A. J. Gibbons, and G. L. Neil, *J. Med. Chem.*, **19**, 1013 (1976), and references cited therein.
(11) E. K. Hamamura, M. Prystasz, J. P. H. Verheyden, J. G. Moffatt, K. Yamaguchi, N. Uchida, K. Sato, A. Nomura, O. Shiratori, S. Takase, and K. Katagiri, *J. Med. Chem.*, **19**, 667 (1976).
(12) H. E. Renis, D. T. Gish, B. A. Court, E. E. Eidson, and W. J. Wechter, *J. Med. Chem.*, **16**, 755 (1973).
(13) A. J. Repta, B. J. Rawson, R. D. Shaffer, K. B. Sloan, N. Bodor, and T. Higuchi, *J. Pharm. Sci.*, **64**, 392 (1975).
(14) T. H. Haskell and S. Hanessian, U.S. Patent 3651045 (1972); T. H. Haskell, *Ann. N.Y. Acad. Sci.*, **284**, 81 (1977).
(15) A. H. Haines, *Adv. Carbohydr. Chem. Biochem.*, **33**, 11–109 (1976).
(16) J. M. Knoblich, J. M. Sugihara, and T. Yamazaki, *J. Org. Chem.*, **36**, 3407 (1971).
(17) A typical NMR spectrum is that for **2a** (90 MHz, Me_2SO-d_6): δ 2.03 (s, 3, Ac), 3.99 (m, 1, H-4′), 4.15 (m, 2, H-5′,5′a), 4.24–4.32 (m, 2, H-2′,3′), 5.66* (d, 1, OH), 5.75* (d, 1, OH), 6.26 (d, 1, H-1′, $J_{1,2}$ = 4.5 Hz), 7.26* (br s, 2, NH_2), 8.13, 8.14 (s, 1, 1, H-2, H-8); an asterisk indicates disappearance of the signal upon D_2O exchange.
(18) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 2648 (1960).
(19) H. M. Kalckar, *J. Biol. Chem.*, **167**, 461 (1947).
(20) A. Bloch, M. J. Robins, and J. R. McCarthy, Jr., *J. Med. Chem.*, **10**, 908 (1967).
(21) (a) R. A. Lipper, S. M. Machkovech, W. I. Higuchi, J. C. Drach, and C. Shipman, *Abstr. Pap. Acad. Pharm. Sci.*, **22**, abstract 66 (1977); (b) R. A. Lipper, S. M. Machkovech, J. C. Drach, and W. I. Higuchi, *Mol. Pharmacol.*, **14**, 366 (1978).
(22) P. W. K. Woo, H. W. Dion, S. M. Lange, L. F. Dahl, and L. J. Durham, *J. Heterocycl. Chem.*, **11**, 641 (1974).
(23) H. W. Dion, P. W. K. Woo, and A. Ryder, *Ann. N.Y. Acad. Sci.*, **284**, 21 (1977).
(24) B. J. Sloan, J. K. Kielty, and F. A. Miller, *Ann. N.Y. Acad. Sci.*, **284**, 60 (1977).
(25) H. Nakamura, G. Koyama, Y. Iitaka, M. Ohno, N. Yagisawa, S. Kondo, K. Maeda, and H. Umezawa, *J. Am. Chem. Soc.*, **96**, 4327 (1974).
(26) S. M. Machkovech, R. A. Lipper, W. I. Higuchi, J. C. Drach, and D. C. Baker, *Abstr. Pap. Acad. Pharm. Sci.*, **125**, P-69 (1978).
(27) G. D. Hsiung and J. L. Melnick, *Virology*, **1**, 533 (1955).
(28) E. Darzynkiewicz, F. Kazimierczuk, and D. Shugar, *Cancer Biochem. Biophys.*, **1**, 203 (1976).
(29) E. de Clercq, J. Descamps, E. Krajeswka, and D. Shugar, *Biochem. Pharmacol.*, **26**, 794 (1977).
(30) L. L. Bennett, Jr., W. M. Shannon, P. W. Allan, and G. Arnett, *Ann. N.Y. Acad. Sci.*, **255**, 342 (1975).