(17) J. A. Secrist III and M. W. Logue, *J. Org. Chem.*, **37**, 335 (1972).
(18) U. Reichman, D. H. Hollenberg, C. K. Chu, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **41**, 2042 (1976).
(19) G. Fodor and J. Kiss, *J. Chem. Soc.*, 1589 (1952).
(20) Alternatively, the ester groups of **9a** could be removed with ammonia–methanol to give the diacetamido diol, which could then be treated with hydrochloric acid to give **16a.** Benzoate **9c,** when subjected to the same treatment with hydrochloric acid, was hydrolyzed to a monoacetamide which retained the benzoyl blocking group on the primary hydroxyl. Thus, neighboring-group participation by the primary hydroxyl group does not account for the acid lability of one of the acetamido groups of **9a.**
(21) L. Goodman, *Adv. Carbohyd. Chem.*, **22**, 109 (1967), and references cited therein.
(22) F. W. Lichtenthaler and P. Emig in "Synthetic Procedures in Nulceic Acid Chemistry", Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N.Y., 1968, pp 232–235, and references cited therein.
(23) When the inversion of **28** was attempted with 2 equiv of tosyl chloride in pyridine at room temperature for 5 days, most of the **28** was recovered.
(24) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955).
(25) R. Vince and S. Daluge, manuscript in preparation.
(26) Repeated attempts to dry this solid in a vacuum desiccator for a few hours or overnight resulted in loss of the product. The solid turned from a white fluffy material to a shrunken tan mass no longer soluble in CCl_4. Although it was occasionally possible to dry samples of tosyl cyanide, especially in smaller runs, the unpredictability of this decomposition led to changing the workup. Another person in this lab reported an explosion of sufficient force to blow the top off a large vacuum desiccator when drying a 100-g sample of tosyl cyanide.
(27) Failure to adequately cool in one run resulted in generation of considerable heat; **1** was separated with difficulty in low yield (~30%) from black tarry material by column chromatography.
(28) Attempts to characterize the free amine were unsuccessful as it appears to decompose on contact with air. Solutions darkened rapidly and attempts to solidify the material gave only colloidal yellow solid that turned to gum on contact with the air. Immediately after opening the Parr shaker, TLC (20% MeOH–$CHCl_3$) showed one major spot and one minor lower R_f spot. However, after a few hours, numerous new spots started to appear.
(29) An attempt to carry out the acetylation with acetic anhydride–pyridine gave tar. Apparently the free amine is base sensitive.
(30) In order to confirm spectral assignments, a sample of (±)-9-[β-(3α-amino-2α-hydroxy)cyclopentyl]-6-dimethylaminopurine 2′,3′-carbamate[3a] was acetylated in acetic anhydride–pyridine and the *N*-acetyl derivative characterized: 74% (from ethyl acetate–hexanes); mp 142–143 °C; IR (KBr) 1790 (urethane C=O, appears at 1779 before acetylation), 1705 cm^{-1} ($AcNCO_2$); ^1H NMR (Me_2SO-d_6) δ 2.40 (s, CH_3CONCO_2–). Anal. C, H, N.
(31) Preparative TLC (15% MeOH–$CHCl_3$) of such mother liquor contents gave a pure sample of the greater R_f impurity as a pale yellow solid foam (3%). Elemental analysis, mass spectrum, and NMR agree for $C_{14}H_{18}N_8O_2Cl_2 \cdot CH_3CO_2Et$ (ethyl acetate used to obtain foam). Apparently, hydrolysis of **9a** results in a small amount of diamine which reacts with two molecules of 5-amino-4,6-dichloropyrimidine.
(32) The chloroform mother liquors contained, in addition to more **28,** a higher R_f product. Purification of a portion of such material by chromatography on preparative plates developed in 15% MeOH–$CHCl_3$ gave a colorless glass (~5%) which NMR ($CDCl_3$) showed to be a di-4-methoxytrityl derivative.
(33) The oxazoline intermediate formed in the epimerization of **23** is hydrolyzed completely to **24** by sodium acetate, but the same hydrolysis conditions here leave a considerable amount of unhydrolyzed oxazoline. When the hydrolysis of the crude reaction products was carried out for longer periods (2–3 days) at 65 °C or at reflux temperature overnight, the reaction mixture turned dark brown and the combined yield of **29** and **30** was lower, but the ratio of **29/30** was greater. In practice such mixtures of **29** and **30** were not separated, but converted by formic acid treatment to **32** (see below).
(34) TLC (20% MeOH–$CHCl_3$) of the mother liquor showed a mixture of unhydrolyzed **20** and **21.**
(35) An attempt was made to characterize the free base by neutralization of the acetic acid salt with Amberlite IRA-400 (OH^-) resin as for the synthesis of isomer **21.** The gummy material isolated could not be solidified and appeared to decompose slowly in air. This behavior has been noted with other *cis*-aminocyclopentanols, in contrast to the stable, solid trans isomers.[3g]

Convenient Synthesis of Some Purine 8,5′-Imino Cyclonucleosides

Tadashi Sasaki,* Katsumaro Minamoto, and Hidemi Itoh

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

Received November 10, 1977

Synthesis of some purine 8,5′-imino and aminimino cyclonucleosides was achieved starting from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-8-bromoadenosine (**1**) and anhydrous hydrazine. **1** with anhydrous hydrazine in ethanol gave 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2a**), which was oxidatively converted to the corresponding 8,5′-imino cyclonucleoside (**2b**). The *N*-amino group in **2a** was quantitatively protected with hot acetic acid and phthalic anhydride to afford the 8,5′-acetamidimino (**2c**) and 8,5′-phthalimidimino analogues (**8**), respectively. Acidic treatment of **2a** and **2b** gave the parent cyclonucleosides **4a–b.** On the other hand, treatment of **2a, 2c,** and **8** with nitrous acid gave the corresponding inosine analogues **5, 7,** and **9.** Dephthaloylation of **9** with methanolic hydrazine gave 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**10**) as a 1:1 complex with the released phthalazine-1,4-dione. Treatment of **5** and **10** with 90% trifluoroacetic acid gave the corresponding parent hypoxanthine analogues **6** and **11,** while the treatment of a mixture of **10** and **11** with methanol–concentrated hydrochloric acid (3:1) gave the derivative of 2,5′-aminimino-bridged AICA riboside (**12**).

In recent years a large number of cyclonucleosides have been synthesized as basic models for gaining insight into the relationship between conformation and biological activity[1] or physicochemical properties.[2] Limiting the viewpoint to the synthesis in the purine series, the accumulated data have demonstrated the possibility of bonding the 8 position of the base with $C_{2'}$, $C_{3'}$, and $C_{5'}$ of the sugar through a heteroatom (O, S, or limitedly N)[3] or directly with $C_{5'}$.[4] Although the synthesis of oxygen- and sulfur-bridged nucleosides has been and continues to be elaborated for various purine nucleosides,[3c,5] the recorded synthesis of nitrogen isostere is quite limited. The hitherto known four compounds of this class are all 8,2′-imino cyclonucleosides obtainable by heating 8-amino-2′-*O*-triisopropylbenzenesulfonyladenosine with base[3b] or of preformed 8-aminopurinenucleosides with diphenyl carbonate.[3c]

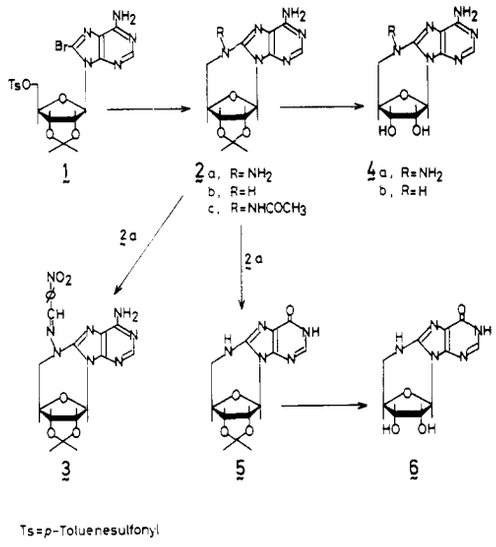
8-Aminoadenosine is known to exhibit significant inhibition of sarcoma 180 ascites cells and is resistant toward adenosine deaminase.[6] 8-Aminopurinenucleosides also attracted much interest because of their structural similarity to a paralytic marine toxin, saxitoxin.[7] These findings gave an impetus to the extensive synthesis of a variety of 8-aminopurinenucleosides and their analogues.[8]

In view of these facts, synthesis of purine 8,5′-iminonucleosides and analogues which are restricted in anti conformation seemed to be of primary importance, and we herein describe a simple and effective synthesis of this class of compounds from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-8-bromoadenosine (**1**)[9] and hydrazine as the nitrogen source.

To circumvent the formidable N^3,$C_{5'}$ cyclization of **1** (this excludes a priori the application of the methods used for the synthesis of 8,2′-imino purinenucleosides), **1** was treated with

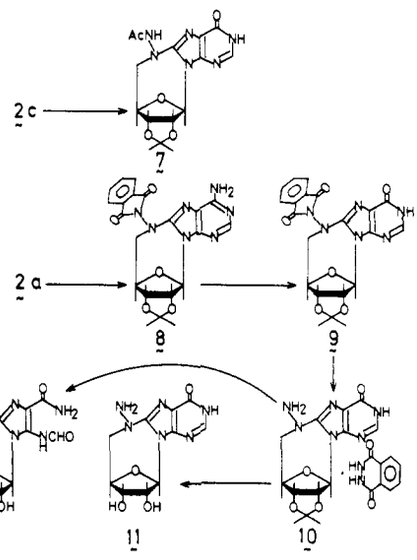
0022-3263/78/1943-2320$01.00/0

Scheme I



Ts=*p*-Toluenesulfonyl

Scheme II



a large excess of hydrazine at ambient temperature to afford 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2a**) as crystals in 90% yield (Scheme I). Its structure was easily deduced from the UV absorption at 272 nm comparable with those of 8-aminoadeninenucleosides[8b,c] and the ^{1}H NMR spectrum, in which two amino signals appeared at 4.92 and 6.81 ppm, the former being assigned to the hydrazino group. The other signals were also consistent with the proposed structure. The presence of a 1,1-disubstituted hydrazino structure was further confirmed by the preparation of its *p*-nitrobenzylidene derivative (**3**) (see Experimental Section). In this series of work, synthesis of parent 8,5′-aminimino-bridged compounds was also intended, since it was conceived that this type of compounds represents analogues of 8-aminopurinenucleosides retaining a "naked" amino group in the anti conformation and hence interesting substrates for biological survey. **2a** was quantitatively oxidized to 8,5′-imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2b**) with iodine pentoxide in 85% THF. The oxidative elimination of the *N*-amino group was tried in various ways. Thus, lead tetraacetate, mercuric oxide, potassium permanganate, and sodium metaperiodate also proved to be applicable using the standard procedures, giving the same compound in moderate to good yields, but the iodine pentoxide procedure seemed to be the most simple and time-saving. The structure of **2b** was fully confirmed by the spectroscopic data described in the Experimental Section. An attempt to deacetonate **2a** with hot 80% acetic acid failed, giving instead a good yield of 8,5′-acetamidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2c**). It was found afterward that **2a** could be quantitatively converted to **2c** using hot acetic acid and this compound appeared to be a hopeful intermediate for the transformation of the base moiety. Deprotection of **2a** and **2b** to 8,5′-aminimino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**4a**) and 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**4b**) was achieved by the use of more stronger acids. The general analysis and spectroscopic data confirmed their structures (see Experimental Section).

We next attempted to synthesize the hypoxanthine analogues of **4a,b** as the first step of base transformation starting from the same key intermediate (**2a**). Thus, the conventional diazotization converted **2a** into 8,5′-imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**5**) in 72% isolated yield in one step.[10] Deisopropylidenation of **5** with 90% trifluoroacetic acid proceeded smoothly to give the parent compound 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (**6**). We next challenged the synthesis of 8,5′-aminimino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (**11**) (Scheme II) starting from the above obtained protected nucleoside (**2c**). **2c** was treated with nitrous acid to give 8,5′-acetamidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**7**), deacetylation of which, however, met with difficulty when several kinds of acids and bases were applied. Selective deisopropylidenation using 90% trifluoroacetic acid seemed to have occurred in terms of TLC, but gave no isolable crystalline product.[11] We then selected phthalic anhydride as a protecting agent mainly from a consideration on crystallinity and stepwise deprotection. Thus, **2a** was converted to 8,5′-phthalimidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**8**) using the standard method and the latter diazotized to obtain 8,5′-phthalimidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**9**); both steps proceeded almost quantiatively. The location of the phthalimino group in both compounds was evident from the lack of an *N*-amino signal in the NMR spectra. Treatment of **9** with 0.2 M methanolic hydrazine at room temperature gave a 84% isolated yield of 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**10**) as a 1:1 complex with the released phthalazin-1,4-dione.[12] Several trials for removing the phthalazin from the complex were unsuccessful, especially because both components contain the similar lactam group, excluding the conventional separation method using aqueous base. Accordingly, the complex was directly submitted to acid treatment, after which **11** was fortunately isolated as crystalline hydrochloride hemi-methanolate. The pyrimidine part in such an 8-aminohypoxanthine system appeared to be particularly sensitive to acid as shown by an experiment using aqueous hydrochloric acid. Thus, the treatment of a mixture of **10** and **11** with a mixture of concentrated hydrochloric acid and methanol (1:3) at room temperature yielded 2,5′-aminimino-1-(5′-deoxy-β-D-ribofuranosyl)-5-*N*-formylamino-imidazole-4-carboxamide (**12**) as hydrochloride, which would, however, be another interesting substrate when compared with the recently exploited 2-substituted derivatives of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA riboside).[13] The ring-opened structure of **12** was supported by the extensive bathochromic shift of the major UV absorption as compared with the closed structure.[14]

At this point, some comments on the optical and mass spectroscopic behavior of these compounds are in order. CD spectra[15] of **4a,b, 6, 11,** and **12** (Figures 1 and 2) show strong positive Cotton effects in the 255–270-nm region and reinforce the typical anti conformation of these compounds. The

Table I. Principal Mass Spectral Peaks in the Spectra of Purine 8,5′-Aminimino and Imino Cyclonucleosides (4a, 4b, and 6)[a]

Compound	M	M − 29 (*b*)	M − 57 (*c*)	M − 87 (*d*)	M − 88 (*e*)	M − 88 − X (*f*)	M − 101 (*g*)	*a*	*a* + 1
4a	279	250	222	- - -	191	175	178	165	166
	(100)	(2.0)	(4.1)		(3.3)	(14.3)	(8.7)	(57)	(11.8)
4b	264	235	207	177	176	175	163[b]	150	151
	(100)	(6.7)	(17.9)	(3.9)	(8.0)	(21.7)	(30.6)	(72.4)	(50)
6	265	236	208	178	177	176	164	151	152
	(65.7)	(9.3)	(21.1)	(4.1)	(11.3)	(34.7)	(29.7)	(100)	(83)

[a] The upper number represents the *m/e* of a given ion; the lower is the intensity relative to the base peak. [b] The same ion also occurs in the spectrum of **4a** in a relative intensity of 35.1%.

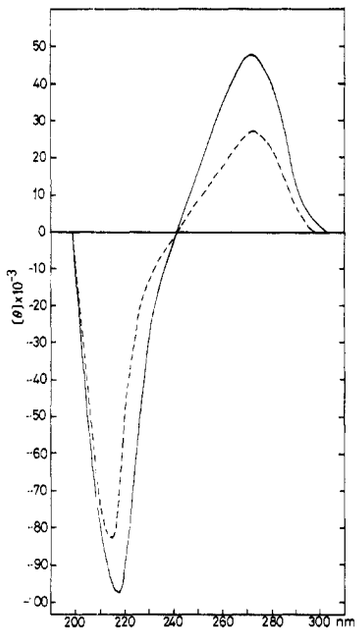


Figure 1. CD spectra of 8,5′-aminimino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**4a**) (—) and 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**4b**) (- - -) in methanol.

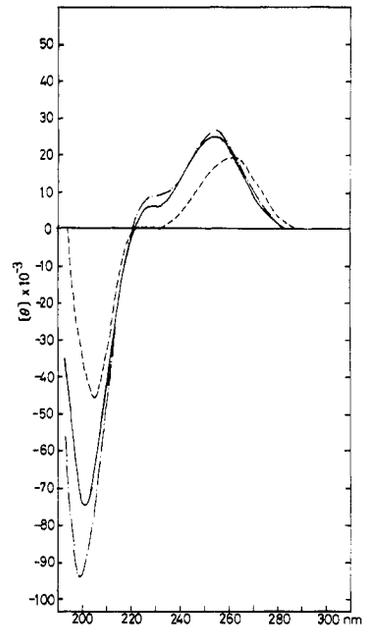
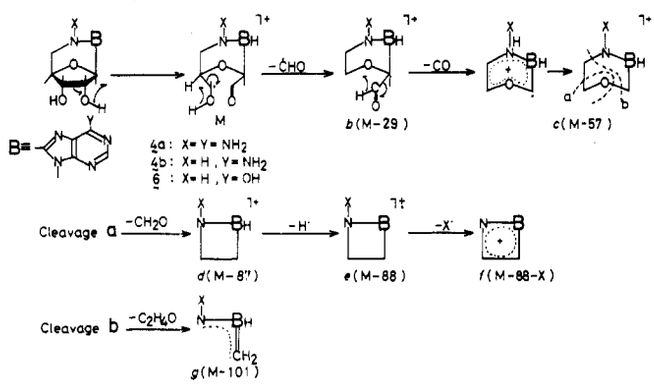
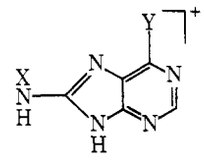


Figure 2. CD spectra of 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)-hypoxanthine (**6**) (- - -) in water, and 8,5′-aminimino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine hydrochloride (**11**) (—) and 2,5′-aminimino-1-(5′-deoxy-β-D-ribofuranosyl)-5-*N*-formylaminoimidazole-4-carboxamide hydrochloride (**12**) (· · · · ·) in methanol.

spectrum of **12** (this seems to be the first example recorded for a nucleoside with an opened base) suggests the applicability of the empirical rule of circular dichroism to nucleosides with such an opened base structure. The mass spectra of available samples, **4a,b** and **6** were also recorded[16] and compared with those of the other oxygen- and sulfur-bridged adenosine 8-cyclonucleosides.[17] Although high resolution measurements were not conducted, the marked spectral correlation between these compounds and the known fragmentation patterns of purine and pyrimidine cyclonucleosides[17-19] permit some crude generalizations of the principal cleavage processses. The plausible fragmentation pathways in the upper mass range and the relative peak intensities are given in Scheme III and Table I. As is generally observed with cyclonucleosides,[17-19] the three compounds show the high stability of the molecular ion radicals: in two (**4a** and **4b**) of the three the molecular ions appeared as base peaks. The observation of abundant 8-amino and 8-aminimino purine radicals is also in agreement with the previous observation.[17] These ions, which seem to have formed by mechanisms involving a double hydrogen transfer, are formulated as *a* according to the precedent literature[17] and given in the table with the one mass unit higher ions (*a* + 1). Notably, M − 29 and M − 57 ion peaks shown by our three compounds lack from the spectra of 8,5′-*O*- and *S*-cycloadenosines,[17] while M − 59 and M − 77

Scheme III. Mass Spectral Fragmentations of Purine 8,5′-*N*-Cyclonucleosides (4a, 4b, and 6)





a

X = Y = NH_2
X = H; Y = NH_2
X = H; Y = OH

ions observed for one of the latter were mostly absent or negligible in the spectra of our compounds. Appreciable amounts of M − 89 (corresponding to M − 88 − X in Table I) and M − 101 ions were found also in our case. The common apparition of M − 29 and M − 57 ions in the spectra of **4a,b** and **6** suggests a different start of fragmentation, and this could be rationalized by initial cleavage between $C_{2'}$ and $C_{3'}$ with the concurrent shift of a hydroxyl hydrogen to the base (probably triggered by favorable ionization at 8-imino nitrogen) (Scheme III). Subsequent ejections of an aldehyde radical and a ketone would give ion *c* (M − 57). Indeed, in the spectra of pyrimidine O^6,5′-cyclonucleosides,[18] somewhat similar seven-membered heterocyclic fragment (M − 59) and M − 29 ion were observed. Thus, the slight discrepancy of the fragmentations of our purine 8-*N*-cyclonucleosides from those of pyrimidine O^6,5′-cyclonucleosides and 8,5′-*O*- and *S*-cycloadenosines seems to be conditioned by the presence of a more ionizable 8-imino group.[20] Cleavage of ion *c* along the dotted line a and b would reasonably generate the fused imidazole cation *f* and *g* ions (or its closed alternative).

The above exemplified aminimino bridging synthetic method would provide a new and in principle versatile route to a variety of purine 8,5′- and as yet unknown 8,3′-imino cyclonucleosides, especially when the precursors with a leaving group at $C_{5'}$ or $C_{3'}$ are heat-sensitive.[21] Furthermore, the strong nucleophilicity and the oxidant-sensitive nature of the introduced *N*-amino group would permit its highly selective protection or its complete elimination to an imine with a wide variety of oxidants which can specifically transform the base or sugar moiety. Further studies along this line are under way.

Experimental Section

8,5′-Aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (2a). To a stirred suspension of **1** (6.02 g, 11.14 mmol) in ethanol (76 mL) was added 100% hydrazine monohydrate (24 mL). After 4 h, the resulting solution was left at room temperature for 2 days. The mixture was evaporated and the residue repeatedly co-evaporated with ethanol to remove excess hydrazine. The obtained pasty residue was partitioned between chloroform (300 mL) and water (30 mL). The separated chloroform layer was dried over sodium sulfate and evaporated to give a powder, which was recrystallized from a mixture of ethanol and chloroform to afford 3.024 g (90.10%) of fine needles (7–10 h reaction usually gave satisfactory yields of 80 to 85%): mp 232–234 °C; λ_{max}^{MeOH} (ε) 215 (27 100) and 272 nm (21 800); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 1.29 and 1.47 (each 3 H, s, isopropylidene methyls), 3.44–3.69 (2 H, m, 5′-methylene), 4.58 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.64 (1 H, d, J = 1 Hz, $H_{4'}$), 4.92 (2 H s, N–NH_2, D_2O exchangeable), 4.97 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.14 (1 H, s, $H_{1'}$), 6.81 (2 H, br s, 6-amino group, D_2O exchangeable) and 8.05 (1 H, s, H_2).

Anal. Calcd for $C_{13}H_{17}N_7O_3$: C, 48.89; H, 5.37; N, 30.71. Found: C, 48.94; H, 5.33; N, 30.70.

***p*-Nitrobenzylidene Derivative of 2a (3).** A mixture of **2a** (100 mg, 0.313 mmol), *p*-nitrobenzaldehyde (47.5 mg, 0.314 mmol), and granules of calcium chloride (50 mg) in ethanol (5 mL) was heated to reflux. After 1 h and 40 min, further *p*-nitrobenzaldehyde (47.5 mg) was added and the mixture heated for further 30 min. Then, further *p*-nitrobenzaldehyde (47.5 mg) and calcium chloride (20 mg) were added. After a total of 3.5 h, the mixture was cooled and adjusted to pH 8 with a mixture of methanol and concentrated ammonium hydroxide (3:1), and the yellow precipitate was collected by suction. Recrystallization from methanol gave 89 mg (63%) of yellow needles (**3**): mp 290–291 °C; λ_{max}^{MeOH} (ε) 211 (25 500) and 273 nm (24 900); ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 1.26 and 1.48 (each 3 H, s, isopropylidene), 3.60–3.82 (2 H, m, 5′-methylene), 4.46–4.88 (4 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$, and –N=CH–), 6.20 (1 H, s, $H_{1'}$), 7.23 (2 H, br s, D_2O exchangeable, 6-amino group), 7.85–8.39 (4 H, m, phenyl protons), and 8.82 (1 H, s, H_2).

Anal. Calcd for $C_{20}H_{20}O_5N_8$: C, 53.09; H, 4.46; N, 24.77. Found: C, 53.15; H, 4.55; N, 24.80.

8,5′-Imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (2b). To a stirred solution of **2a** (1 g, 3.13 mmol) in 85% THF (64 mL) was added at 0 °C iodine pentoxide (1.1 g, 3.3 mmol). After stirring at this temperature for 30 min and then at room temperature for another 30 min, the mixture was neutralized with a mixture of methanol and concentrated ammonium hydroxide (3:1) and evaporated. The residue was taken into water (40 mL) and repeatedly extracted with chloroform until the aqueous phase indicated no product on a TLC plate. The combined chloroform solution was decolorized with 10% sodium thiosulfate solution, dried over sodium sulfate, and evaporated to give homogeneous crystals. Recrystallization from ethanol gave 1 g (95%) of **2b** as an ethanolate of mp 184–186 °C. This product also solvates with chloroform or ethyl acetate. λ_{max}^{MeOH} (ε) 211 (31 300) and 272 nm (21 600); ^{1}H NMR (100 MHz, Me_2SO-d_6, solvent signals excluded) δ 1.28 and 1.47 (each 3 H, s, isopropylidene methyls), 3.08–3.51 (2 H, m, 5′-methylene), 4.56 (1 H d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.63 (1 H, m, $H_{4'}$), 4.87 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.11 (1 H, s, $H_{1'}$), 6.64 (2 H, br s, 6-amino group, D_2O exchangeable), 6.96 (1 H, br d, J = 4 Hz, –NH–, D_2O exchangeable), and 8.01 (1 H, s, H_2).

Anal. Calcd for $C_{13}H_{16}N_6O_3 \cdot C_2H_5OH$: C, 51.42; H, 6.33; N, 23.98. Found: C, 51.32; H, 6.44; N, 23.73.

8,5′-Acetamidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (2c). Compound **2a** (500 mg, 1.57 mmol) in acetic acid (20 mL) was heated at 95–100 °C for 3. 5 h. The solvent was evaporated and the crystalline residue repeatedly co-evaporated with ethanol to remove the residual acetic acid. Recrystallization from ethanol gave 565 mg (quantitative) of needles (**2c**), which did not melt below 290 °C: λ_{max}^{MeOH} (ε) 212 (28 300) and 270 nm (20 400); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 1.29 and 1.48 (each 3 H, s, isopropylidene methyls), 1.92 (3 H, s, acetyl), 3.44–3.78 (2 H, m, 5′-methylene), 4.62 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.67 (1 H, br s, $H_{4'}$), 5.21 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.18 (1 H, s, $H_{1'}$), 6.81 (2 H, br s, 6-amino group, D_2O exchangeable), 8.07 (1 H, s, H_2), and 10.34 (1 H, s, –N–NH–COMe, D_2O exchangeable).

Anal. Calcd for $C_{15}H_{19}O_4N_7$: C, 49.85; H, 5.31; N, 27.14. Found: C, 49.90; H, 5.34; N, 26.93.

8,5′-Aminimino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (4a). Compound **2a** (500 mg, 1.57 mmol) in a mixture of methanol (15 mL) and concentrated hydrochloric acid (7 mL) was warmed at 45–50 °C for 18 h. The mixture was evaporated and the residual solid repeatedly co-evaporated with warm methanol to remove excess hydrogen chloride. The finally obtained powder was dissolved in methanol (120 mL), neutralized with anion exchange resin, IRA-410 (OH form) (20 mL). The resin was filtered and eluted with methanol (200 mL). The methanol solution was once filtered with Norit and evaporated to give a practically homogeneous solid, which was recrystallized from methanol to colorless needles (**4a**): mp 243–245 °C; yield 230 mg (53%); λ_{max}^{MeOH} (ε) 213 (27 500) and 272 nm (20 800); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 3.20–3.63 (2 H, m, 5′-methylene), 4.03 (1 H, t, $J_{2',3'} = J_{2' \text{ or } 3',OH}$ = 6 Hz, $H_{2'}$ or $H_{3'}$, collapsed to a doublet with J = 6 Hz on D_2O addition), 4.34 (1 H, br t, $J_{2',3'} = J_{3' \text{ or } 2',OH}$ = 6 Hz, $H_{3'}$ or $H_{2'}$, collapsed to d with J = 6 Hz on D_2O addition), 4.47 (1 H, s, $H_{4'}$), 4.93 (2 H, br s, –N–NH_2, D_2O exchangeable), 5.24 (1 H, br d, J = 6 Hz, 2′- or 3′-OH, D_2O exchangeable), 5.44 (1 H, br d, J = 6 Hz, 3′- or 2′-OH, D_2O exchangeable), 6.07 (1 H, s, $H_{1'}$), 6.76 (2 H, br s, 6-amino group, D_2O exchangeable), and 8.05 (1 H, s, H_2).

Anal. Calcd for $C_{10}H_{13}O_3N_7$: C, 43.01; H, 4.69; N, 35.11. Found: C, 43.30; H, 4.67; N, 34.94.

8,5′-Imino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (4b) A solution of **2b** (200 mg, 0.66 mmol) in 90% CF_3CO_2H (8 mL) was left at room temperature for 5 h. The total was evaporated and the residue co-evaporated with methanol to remove the residual acid. The residual paste was taken into methanol (20 mL) and neutralized with anion-exchange resin, IRA-410 (8 mL). The subsequent workup as in the case of **4a** gave 50 to 60% yield of **4b** as colorless needles: mp 290–295 °C (dec); λ_{max}^{MeOH} (ε) 210 (25 200) and 272 nm (17 600); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 3.06–3.46 (2 H, m, 5′-CH_2), 3.99 (1 H, t, $J_{2',3'} = J_{2' \text{ or } 3',OH}$ = 6 Hz, $H_{2'}$ or $H_{3'}$, collapsed to d on D_2O addition), 4.27 (1 H, t, $J_{2',3'} = J_{3' \text{ or } 2',OH}$ = 6 Hz, $H_{3'}$ or $H_{2'}$, collapsed to d on D_2O addition), 5.22 (1 H, br d, J = 6 Hz, 2′- or 3′-OH, D_2O exchangeable), 5.44 (1 H, br d, J = 6 Hz, 3′- or 2′-OH, D_2O exchangeable), 6.06 (1 H, s, $H_{1'}$), 6.62 (2 H, br s, 6-amino group, D_2O exchangeable), 6.94 (1 H, br d, J = 4 Hz, NH bridge, D_2O exchangeable) and 8.03 (1 H, s, H_2).

Anal. Calcd for $C_{10}H_{12}O_3N_6$: C, 45.45; H, 4.58; N, 31.81. Found: C, 45.57; H, 4.79; N, 31.74.

8,5′-Imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (5). Sodium nitrite (324 mg, 4.7 mmol) was added at 0 °C to a solution of **2a** (300 mg, 0.94 mmol) in 80% acetic acid (19 mL). The mixture was left at 0 °C overnight and then at room temperature for another 5 h. After evaporating the solvent, the residue was digested with a small volume of ice–water and the insoluble part

collected by suction and air dried. Recrystallization from a large amount of methanol gave 207 mg (72.2%) of powder-like crystals (**5**): mp above 300 °C; λ_{max}^{MeOH} (ϵ) 261 (19 400) and 288 nm (9200, sh); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 1.28 and 1 46 (each 3 H, s, isopropylidene methyls), 3.00–3.46 (2 H, m, 5′-methylene), 4.59 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.65 (1 H, s, $H_{4'}$, overlapped on the signal at 4.59 ppm), 4.85 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.03 (1 H, s, $H_{1'}$), 6.97 (1 H, br d, J = 5 Hz, –NH– bridge, D_2O exchangeable), 7.87 (1 H, s, H_2), and 12.16 (1 H, br s, –NHCO– in the base).

Anal. Calcd for $C_{13}H_{15}O_4N_5$: C, 51.14; H, 4.95; N, 22.94. Found: C, 51.09; H, 4.92; N, 23.13.

8,5′-Imino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (6). A solution of **5** (65 mg, 0.213 mmol) in 90% trifluoroacetic acid (4 mL) was left at room temperature for 24 h, and then thoroughly evaporated. Co-evaporation with ethanol was also carried out. The residue was dissolved in methanol (25 mL), neutralized with Amberlite IRA-93 resin (OH form, weakly basic), and filtered. The resin was eluted with methanol (200 mL) and the combined methanol solution was evaporated to give a crystalline solid, which was recrystallized from aqueous methanol to afford 30 mg (53.1%) of powdery crystals (**6**): mp above 300 °C, λ_{max}^{MeOH} 261 nm (ϵ 20 600); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 3.02–3.42 (2 H, m, 5′-methylene), 4.00 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.24 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 4.47 (1 H, br s, $H_{4'}$), 5.30 (2 H, br s, D_2O exchangeable, hydroxyls), 5.98 (1 H, s, $H_{1'}$), 6.96 (1 H, br d, J = 4 Hz. D_2O exchangeable, NH bridge), and 7.88 (1 H, s, H_2). Low-field measurement was omitted.

Anal. Calcd for $C_{10}H_{11}O_4N_5$: C, 45.28; H, 4.18; N, 26.41. Found: C, 45.44; H, 4.37; N, 26.64.

8,5′-Acetamidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (7). Sodium nitrite (310 mg, 4.5 mmol) was added at 0 °C to a solution of **2c** (540 mg, 1.5 mmol) in 90% acetic acid (20 mL), and the mixture was left at 0 °C for 24 h. The solvent was evaporated, and the residue was washed with a small volume of water and extracted with hot acetone (5 × 30 mL). Evaporation of acetone and recrystallization of the residual solid from methanol gave 400 mg (74%) of colorless powdery crystals which did not melt below 300 °C: λ_{max}^{MeOH} 259 nm (ϵ 19 200).

Anal. Calcd for $C_{15}H_{13}O_5N_6$: C, 49.72; H, 5.01; N, 23.20. Found: C, 49.46; H, 5.04; N, 23.18.

8,5′-Phthalimidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (8). A mixture of **2a** (319 mg, 1 mmol) and phthalic anhydride (200 mg, 1.35 mmol) in chloroform (10 mL) was heated to reflux at 70 °C for 4 h. The mixture was evaporated and the residual solid filtered with a small volume of methanol. Recrystallization from a mixture of methanol and chloroform gave 420 mg (93.3%) of colorless prisms (**8**): mp above 300 °C; λ_{max}^{MeOH} (ϵ) 215 (63 900) and 269 nm (20 300); ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 1.33 and 1.50 (each 3 H, s, isopropylidene methyls), 4.13 (2 H, m, 5′-methylene), 4.71–4.80 (2 H, m, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$ and $H_{4'}$), 5.16 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.22 (1 H, s, $H_{1'}$), 6.88 (2 H, br s, 6-amino group, D_2O exchangeable), and 7.94–8.05 (5 H, m, H_2 and phthaloyl protons).

Anal. Calcd for $C_{21}H_{19}O_5N_7$: C, 56.12; H, 4.26; N, 21.82. Found: C, 56.07; H, 4.40; N, 22.01.

8,5′-Phthalimidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (9). A solution of **8** (700 mg, 1.56 mmol) in 80% acetic acid (33 mL) was treated with sodium nitrite (747 mg, 10.83 mmol) and the total was left at 0 °C for 2 days. The solvent was evaporated off and the residue repeatedly co-evaporated with ethanol. Digestion of the residue with a small amount of water gave a practically pure solid, which was collected and recrystallized from methanol to afford 665 mg (95%) of needles (**9**): mp above 300 °C; λ_{max}^{MeOH} (ϵ) 256 (21 400) and 279 nm (13 400, sh); ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 1.3 and 1.45 (each 3 H, s, isopropylidene methyls), 4.02 (2 H, m, 5′-methylene), 4.70–4.80 (2 H, $H_{2'}$ or $H_{3'}$ and $H_{4'}$), 5.07 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 6.12 (1 H, s, $H_{1'}$), 7.93 (5 H, s, phthaloyl and H_2) and 12.21 (1 H. br s, D_2O exchangeable, NH).

Anal. Calcd for $C_{21}H_{18}O_6N_6$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.68; H, 4.21; N, 18.71.

8,5′-Aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine–Phthalazin-1,4-dione Complex (10). Compound **9** (165 mg, 0.366 mmol) was dissolved in 0.2 M methanolic hydrazine by slight warming and the solution was left at room temperature overnight. The solvent and excess hydrazine were evaporated and the residue repeatedly co-evaporated with ethanol. Recrystallization from methanol gave 135 mg (76%) of homogeneous crystals of the complex (**10**): mp above 290 °C (dec at 280 °C); λ_{max}^{MeOH} (ϵ) 260 (19 100) and 283 nm (10 600, sh); ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 1.27 and 1.42 (each 3 H, s, isopropylidene methyls), 4.56–4.98 (5 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$ and –N–NH_2), 6.02 (1 H, s, $H_{1'}$), and 7.76–8.17 (5 H, m, phthalyl and H_2).

Anal. Calcd for $C_{13}H_{16}O_4N_6$ + $C_8H_6O_2N_2$: C, 52.28; H, 4.60; N, 23.23. Found: C, 52.47; H, 4.71; N, 23.34.

The homogeneity of this product was confirmed by TLC using silica gel and the solvent mixtures, chloroform/methanol, 9:1 and 92:8.

Hydrochloride of 8,5′-Aminimino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (11). A solution of **10** (300 mg, 0.62 mmol) in 90% trifluoroacetic acid (12 mL) was left at room temperature for 26 h and then at 0 °C overnight. The mixture was evaporated below 35 °C and repeatedly co-evaporated with ethanol and/or methanol. The residue was dissolved in methanol (70 mL), neutralized with anion-exchange resin, IRA-93, and filtered. The resin was thoroughly washed with methanol and the combined methanol solution was evaporated to give a powder, which was shown by TLC (silica gel, 8:2 mixture of chloroform and methanol) to be a mixture of two compounds, the faster moving of which seemed to be phthalazin-1,4-dione. The total was swirled with warm water (30 mL) and a small amount of the insoluble part was filtered off. The aqueous filtrate was concentrated in vacuo to ca. 10 mL and repeatedly extracted with ethyl acetate until the faster moving substance was removed. The aqueous layer was evaporated and co-evaporated with methanol to give a homogeneous gum, which resisted crystallization. Hence, the gum was again dissolved in dry methanol (ca. 100 mL), acidified with a saturated dioxane solution of hydrogen chloride, and evaporated. The semi-solid residue was repeatedly co-evaporated with methanol to give a powder, which was recrystallized from a small volume of methanol at room temperature (by spontaneous evaporation) to afford very gradually 65.5 mg (32%) of **11** as colorless powdery crystals, decomposition at 165 °C: λ_{max}^{MeOH} (ϵ) 260 (15 000) and 290 nm (inflection).

Anal. Calcd for $C_{10}H_{12}O_4N_6$·HCl·½MeOH: C, 37.90; H, 4.54; N, 25.26. Found: C, 37.65; H, 4.67; N, 25.38.

Hydrochloride of 2,5′-Aminimino-1-(5′-deoxy-β-D-ribofuranosyl)-5-*N*-formylaminoimidazole-4-carboxamide (12). A solution of **10** (62 mg, 0.194 mmol) in 90% trifluoroacetic acid (2 mL) was left at room temperature for 22 h. TLC with an aliquot of the reaction mixture using silica gel and 30% ethanol in benzene showed the presence of a single product corresponding to **11** with a tiny amount of the starting material. The mixture was worked up as in the case of **6**, involving treatment with IRA-93 resin. However, purification of the finally obtained powdery mixture proved to be difficult. Hence, the total was suspended in a mixture of concentrated hydrochloric acid and methanol (1:3) (10 mL) and stirred at room temperature overnight. TLC with an aliquot (after neutralization with IRA-93 resin) showed the conversion of the major part of **11** to another substance. The total was evaporated and repeatedly co-evaporated with methanol, and the residue was recrystallized from methanol to give 30 mg (46.3%) of **12** as colorless needles, decomposition at 260–270 °C. λ_{max}^{MeOH} (ϵ) 216 (21 100) and 277 nm (12 400).

Anal. Calcd for $C_{10}H_{14}O_5N_6$·HCl: C, 35.88; H, 4.52; N, 25.11. Found: C, 35.93; H, 4.54; N, 24.98.

Registry No.—**1**, 20789-78-0; **2a**, 65879-28-9; **2b**, 65879-29-0; **2c**, 65879-30-3; **3**, 65879-31-4; **4a**, 65879-32-5; **4b**, 65879-33-6; **5**, 65879-34-7; **6**, 65879-35-8; **7**, 65879-36-9; **8**, 65879-37-0; **9**, 65879-38-1; **10**, 65879-40-5; **11** HCl, 65879-41-6; **12** HCl, 65879-42-7; *p*-nitrobenzaldehyde, 555-16-8; phthalic anhydride, 85-44-9.

References and Notes

(1) (a) W. Saenger, *Angew. Chem.*, **85**, 680 (1973); (b) C-H. Lee, F. E. Evans, and R. H. Sarma, *J. Biol. Chem.*, **250**, 1290 (1975); (c) F. E. Evans and R. H. Sarma, *J. Am. Chem. Soc.*, **97**, 3215 (1975) (d) J. Zemlička, *ibid.*, **97**, 5896 (1975), and the literature cited therein.

(2) T. L. V. Ulbricht, "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 2, W. W. Zorbach and R. S. Tipson, Ed., Wiley-interscience, New York, N.Y., 1973, p 177, and the literature cited therein.

(3) (a) M. Ikehara, *Acc. Chem. Res.*, **2**, 47 (1969); (b) M. Kaneko, B. Shimizu, and M. Ikehara, *Tetrahedron Lett.*, 3113 (1971); (c) K. K. Ogilvie, L. A. Slotin, J. B. Westmore, and D. C. K. Lin, *J. Heterocycl. Chem.*, **9**, 1179 (1972).

(4) (a) K. N. V. Duong, A. Gaudemer, M. D. Johnson, R. Quillivic, and J. Zylber, *Tetrahedron Lett.*, 2997 (1975); (b) P. J. Harper and A. Hampton, *J. Org. Chem.*, **37**, 795 (1972); (c) A. Matsuda, M. Tezuka, and T. Ueda, *Nucleic Acids Res., Spec. Publ.*, **No. 2**, 13 (1976).

(5) (a) M. Ikehara and M. Kaneko, *Tetrahedron*, **26**, 4251 (1970); (b) M. Ikehara and T. Maruyama, *ibid.*, **31**, 1369 (1975).

(6) A. Bloch, E. Mihich, C. A. Nichol, R. K. Robins, and R. H. Whistler, *Proc. Am. Assoc. Cancer Res.*, **7**, 7 (1966).

(7) (a) H. Rapaport, *Science*, **151**, 860 (1966). (b) For a recent review on marine toxins including Saxitoxin, see P. Scheuer, *Acc. Chem. Res.*, **10**, 33 (1977).

(8) (a) R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 1772 (1965); (b) R. A. Long, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, **32**, 2751 (1967); (c) E. J. Reist, D. F. Calkins, L. V. Fisher, and L. Goodman, *ibid.*, **33**, 1600 (1968).

(9) M. Ikehara, M. Kaneko, and M. Sagai, *Chem. Pharm. Bull.*, **16**, 1151

(1968).
(10) One referee has called in question of the conversion of **2a** to **5** since, he believes, **2a** should rapidly react to give an *N*-diazonium hydroxide. Whatever intermediate may have formed (*N*-diazonium hydroxide or *N*-nitroso compound), the thermodynamic product obtained by us must be **5** on the basis of the combustion data, UV, CD (the positive Cotton effect), NMR, and mass spectral data (abudant M^+ ion etc.). The guanidin type structure seems to particularly stabilize the $C_{5'}$–N–C_8 bond of our compounds, in contrast to the oxidation or diazotization reactions of many *N*-amino alicyclic amines.
(11) The crystallization process was hampered by strong solvation with protic solvents to form a gelatine.
(12) Some spectral comparisons between **9** and **10: 9** absorbs at 256 (ε 21 400) and 279 nm (ε 13 400, sh), while **10** absorbs at 260 (ε 19 100) and 283 nm (ε 10 600, sh) (see Experimental Section). The ^{1}H NMR spectrum of **9** indicated the resonance of the lactam NH at 12.21 ppm and that of the phthaloyl group at 7.93 ppm (overlayed on the H_2 signal) as a sharp singlet (accidentally conditioned by steric and electronic factors in the nucleoside molecule). On the other hand, the spectrum of **10** exhibited the phthaloyl resonance at 7.76–8.17 ppm as a complex multiplet and no lactam resonances for both inosine base and phthalazin-1,4-dione under the same measurement conditions (60 MHz, Me_2SO-d_6). This latter finding seems to suggest complex formation by hydrogen bonding between the molecules.
(13) G. A. Ivanovics, R. J. Rousseau, M. Kawana, P. C. Strivastava, and R. K. Robins, *J. Org. Chem.*, **39**, 3651 (1974).
(14) This is also the case with adenine or adenine *N*-oxide base. For example, see M. A. Stevens and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2759 (1958).
(15) The CD spectra were recorded by the Japan Spectroscopic Co., Ltd., using a JASCO Model J-20 recording spectropolarimeter, for which we are grateful.
(16) The mass spectra were measured using a JMS-OISG2 mass spectrometer in the laboratory of the Daiichi Pharmaceutical Co., Ltd., to whom we are grateful. The ionization potential was 75 eV and ionizing current 200 μA for all the compounds; temperature 205 °C for **4a** and 230 °C for **4b** and **6**. The direct insertion probe was used.
(17) M. Ikeda, Y. Tamura, and M. Ikehara, *J. Heterocycl. Chem.*, **7**, 1377 (1970).
(18) E. G. Lovett and D. Lipkin, *J. Am. Chem. Soc.*, **95**, 2312 (1973).
(19) S. Tsuboyama and J. A. McCloskey, *J. Org. Chem.*, **37**, 166 (1972).
(20) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, pp 297, 382.
(21) For an example of intramolecular N^3,3′-cyclization see: (a) E. J. Reist, V. J. Bartuska, D. F. Calkins, and L. Goodman, *J. Org. Chem.*, **30**, 3401 (1965); (b) A. P. Matinez, W. W. Lee, and L. Goodman, *ibid.*, **31**, 3263 (1966); (c) E. J. Reist, D. F. Calkins, and L. Goodman, *ibid.*, **32**, 2538 (1967).

Purine *N*-Oxides. 67. Redox and Rearrangement Reactions of 1,7-Dimethylguanine 3-Oxide with Anhydrides[1]

James C. Parham,* Mary Agnes Templeton, and Morris N. Teller

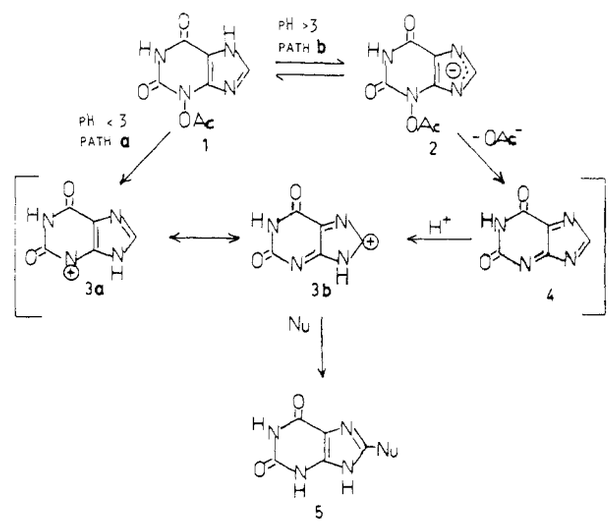
Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received October 26, 1977

Acetylation of 1,7-dimethylguanine 3-oxide in aqueous or methanolic solution produces an intermediate that undergoes an extremely rapid intermolecular reaction with the solvent under ambient conditions to yield 8-substitution products of 1,7-dimethylguanine. This reaction occurs despite the presence of an alkyl group at N-7 that prevents delocalization of a positive charge generated at N-3 to the C-8 position. Added nucleophiles, even at high concentrations, do not react to yield 8-substitution products. Iodide and bromide ions undergo a redox reaction with the intermediate to afford 1,7-dimethylguanine and iodine or bromine. The extent of 8 substitution with water and the reduction by bromide ion are inversely affected by variations in the concentrations of bromide ion, indicating that the two reactions are competitive and proceed from a single intermediate. A delocalized nitrenium ion is proposed as the common intermediate. Accompanying the 8-substitution reaction is a competitive, slower reaction that results in loss of UV absorption. This reaction can be enhanced at the expense of the 8-substitution reaction by the use of trifluoroacetic anhydride. Oncogenicity assays in rats show that 1,7-dimethylguanine 3-oxide does not induce tumors.

A number of *O*-acyl esters of purine 3-oxides[2-6] undergo a spontaneous N-3 elimination–C-8 substitution reaction that parallels those observed with some oncogenic *N,O*-diacyl aromatic hydroxylamines.[7-12] As part of studies to elucidate the mechanism of tumor induction by N-oxidized purines, the reactions of one ester, 3-acetoxyxanthine (**1**, Scheme I), were examined in detail. Those studies[13] indicated that the 8-substitution reaction of **1** can proceed by either of two routes (Scheme I) depending upon the pH of the medium. A relatively slow S_N1' reaction (path a) is observed in the pH range 0 to 3, while the faster path b, requiring ionization of the imidazole proton, predominates at pH's above 3. Interference with delocalization of the positive charge in the common intermediate **3** by a substituent at N-7 was found to inhibit the 8-substitution reaction by both routes.[3,13] A second spontaneous reaction of **1**, reduction to xanthine, was observed only in conjunction with the 8-substitution reaction via path b. The presence of iodide ion greatly enhanced the reduction of **1**, and the enhanced reduction was accompanied by oxidation of iodide to iodine. It was suggested[13] that the redox reaction with iodide ion was correlated with the spontaneous reduction of **1** and proceeded via the same intermediate. A radical anion, presumed to form by homolysis of the N–O bond of **2**, was suggested as the common intermediate. However, recent evidence[14] indicates that oxidation of iodide can also occur in conjunction with path a and thus cannot proceed solely via a radical from **2**.

Scheme I



One member of the purine *N*-oxide series, 1,7-dimethylguanine 3-oxide (**6**, Scheme II), appeared to react anoma-

0022-3263/78/1943-2325$01.00/0