Registry No.—**3**, 67938-72-1; **5**, 67938-73-2; **6**, 67938-74-3; **9**, 67938-75-4; **10**, 67938-76-5; **12**, 67938-77-6; methyl hippurate, 1205-08-9; 2,5-dichloropyridine, 16110-09-1; diethyl acetamidomalonate, 1068-90-2; 2-chloro-5-nitropyridine, 4548-45-2; benzylideneglycine ethyl ester, 40682-54-0; isoamyl nitrite, 110-46-3; cupric chloride, 7447-39-4; nitric oxide, 10102-43-9; hog renal acylase I, 9012-37-7; *tert*-butoxycarbonyl azide, 1070-19-5.

References and Notes

(1) (a) Contribution 60 in the series Antineoplastic Agents. For part 59, see J. Polonsky, Z. Varon, H. Jacquemin, and G. R. Pettit, *Experientia*, **34**, 1122 (1978). (b) Abstracted in part from the Ph.D. Dissertation of Mark T. Edgar, Arizona State University, 1977.
(2) G. R. Pettit, R. B. Von Dreele, D. L. Herald, M. T. Edgar, and H. B. Wood, Jr., *J. Am. Chem. Soc.*, **98**, 6743 (1976).
(3) (a) B. H. Arison and J. L. Beck, *Tetrahedron*, **29**, 2743 (1973); (b) F. A. Schmid and D. J. Hutchison, *Cancer Res.*, **32**, 808 (1972); (c) P. N. Rao, S. Mahagaokar, E. J. Freireich, T. L. Loo, and J. A. Gottlieb, *ibid.*, **35**, 2996 (1975); (d) J. A. Gottlieb, E. J. Freireich, G. P. Bodey, V. Rodriguez, K. B. McCredie, and J. U. Gutterman, *Proc. Am. Assoc. Cancer Res.*, **16**, 86 (1975); (e) R. W. Brockman, S. C. Shaddix, D. J. Adamson, and R. F. Struck, *ibid.*, **16**, 35 (1975); (f) S. E. Jones, W. G. Tucker, A. Haut, B. L. Tranum, C. Vaughn, E. M. Chase, and B. G. M. Durie, *Cancer Treat. Rep.*, **61**, No. 9 (1977).
(4) M. Viscontini and H. Raschig, *Helv. Chim. Acta*, **42**, 570 (1959).
(5) W. Gruber, *Can. J. Chem.*, **31**, 1181 (1953).
(6) (a) J. De Graw and L. Goodman, *J. Org. Chem.*, **27**, 1395 (1962); (b) R. K. Barclay, M. A. Phillips, G. C. Perri, and K. Sugiura, *Cancer Res.*, **24**, 1324 (1964).
(7) A. P. Krapcho and E. A. Dundulis, *Tetrahedron Lett.*, 2205 (1976).
(8) (a) H. L. Yale, "Pyridine and its Derivatives", Supplement Part 2, R. A. Abramovitch, Ed., Wiley, New York, N.Y., 1974, Chapter 7; (b) R. A. Abramovitch, R. T. Coutts, and E. M. Smith, *J. Org. Chem.*, **37**, 3585 (1972).
(9) G. Stork, A. Y. W. Leong, and A. M. Touzin, *J. Org. Chem.*, **41**, 3491 (1976).
(10) T. Moriya, K. Hagio, and N. Yoneda, *Bull. Chem. Soc. Jpn.*, **48**, 2217 (1975).
(11) W. Brackman and P. J. Smit, *Recl. Trav. Chim. Pays-Bas*, **85**, 857 (1966).
(12) J. I. G. Cadogan, D. A. Roy, and D. M. Smith, *J. Chem. Soc. C*, 1249 (1966).
(13) A. Berger, M. Smolarsky, N. Kurn, and H. R. Bosshard, *J. Org. Chem.*, **38**, 457 (1973).
(14) J. B. Gin and C. A. Dekker, *Biochemistry*, **7**, 1413 (1968).
(15) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Vol. 3, Wiley, New York, N.Y., 1961, p 1831.
(16) G. R. Pettit, S. K. Gupta, and R. H. Ode, *J. Chem. Soc., Perkin Trans. 1*, 950 (1973); G. R. Pettit, "Synthetic Peptides", Vol. 4, Elsevier Scientific Publishing Co., New York, N.Y., 1976.
(17) E. Taschner and C. Wasielewski, *Justus Liebigs Ann. Chem.*, **646**, 134 (1961).
(18) J. F. Biernat, B. Rzeszotarska, and E. Taschner, *Justus Liebigs Ann. Chem.*, **646**, 125 (1961).
(19) "Esterification", Bulletin 721C, Supelco, Inc., Bellefonte, Pa., 1975.
(20) S. M. Hecht and J. W. Kozarich, *Tetrahedron Lett.*, 1397 (1973).
(21) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 1209.
(22) J. C. Sheehan and V. J. Grenda, *J. Am. Chem. Soc.*, **84**, 2417 (1962).
(23) Several attempts to trap the carboxylate anion with methyl iodide or methyl sulfate prior to decarboxylation failed.
(24) N. Yoshino and T. Yoshino, *Bull. Chem. Soc. Jpn.*, **46**, 2899 (1973).
(25) P. Rosenmund and K. Kaiser, *Angew. Chem., Int. Ed. Engl.*, **9**, 162 (1970).
(26) A. L. Davis, C. G. Skinner, and W. Shive, *Arch. Biochem. Biophys.*, **87**, 88 (1960).
(27) M. Hatanaka and T. Ishimaru, *Bull. Chem. Soc. Jpn.*, **46**, 3600 (1973).
(28) G. R. Pettit, C. L. Herald, G. F. Judd, G. Bolliger, and P. S. Thayer, *J. Pharm. Sci.*, **64**, 2023 (1975).
(29) G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972).

Halo Sugar Nucleosides. 6. Synthesis of Some 5′-Deoxy-5′-iodo and 4′,5′-Unsaturated Purine Nucleosides[1]

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Reactions of the 5′-hydroxyl groups of suitably substituted purine nucleosides with methyltriphenoxyphosphonium iodide (1) in nonpolar solvents such as tetrahydrofuran and dichloromethane give the corresponding 5′-deoxy-5′-iodo nucleosides in high yield. Previously, N^3,5′-cyclonucleosides were the major products of these reactions when DMF was used as solvent. Efficient syntheses of 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)purine nucleosides are described via dehydrohalogenation of various 5′-deoxy-5′-iodoinosine, -guanosine, and -adenosine derivatives with either silver fluoride in pyridine or 1,5-diazabicyclo[4.3.0]non-5-ene in DMF or pyridine.

In previous papers in this series,[1,3] we have described the synthesis of various 5′-deoxy-4′,5′-unsaturated nucleosides by dehydrohalogenation of the corresponding 5′-deoxy-5′-iodo derivatives. These halogenated nucleosides[4] were obtained by reaction of the 5′-hydroxyl group of suitably substituted pyrimidine nucleosides with methyltriphenoxyphosphonium iodide[5] (1) in dimethylformamide. However, the reaction of 2′,3′-*O*-isopropylidene derivatives of purine nucleosides **3**, **10**, and **25a** with 1 gave mainly the corresponding N^3,5′-cyclonucleosides.[4] Previous work by Jahn[6] has shown that acylation of the 6-amino function in the adenosine series decreases the tendency toward formation of N^3,5′-cyclonucleosides via reduction of the electronegativity of N^3. Along these lines we have reported that reaction of N^6,N^6,$O^{2'}$,$O^{3'}$-tetrabenzoyladenosine with 1 leads to the corresponding 5′-deoxy-5′-iodonucleoside in high yield.[1]

While the above method has been of great synthetic value, the incorporation of *N*-acyl substituents is sometimes not desirable. In this paper, we describe an alternate method for minimizing the formation of N^3,5′-cyclonucleosides, thus permitting the synthesis, in good yield, of 5′-deoxy-5′-iodopurine nucleosides. The latter compounds can then be transformed into the corresponding 5′-deoxy-4′,5′-unsaturated derivatives by dehydrohalogenation using previously developed methods.

During the reaction of a purine nucleoside derivative with **1**, a common oxyphosphonium intermediate, **2**, is considered to be the precursor of both the desired 5′-deoxy-5′-iodo compound (via path b) and the undesired N^3,5′-cyclonucleoside (via path a). Rather than seek new methods to reduce the nucleophilicity of N^3 through heterocyclic derivatization, we have attempted to control the relative rates of paths a and b via changes in solvent and temperature.

It has been demonstrated that triphenylphosphine dihalides exist largely in a dissociated form [e.g., $(C_6H_5)_3P^+$–X X^-] in polar solvents and in a pentacovalent form [e.g., $(C_6H_5)_3PX_2$] in nonpolar media.[7] A similar situation probably exists with the related reagent **1**. It is therefore likely that in solvents such as dimethylformamide[8] electrostatic attraction between the 5′-oxygen of the nucleoside and the positive

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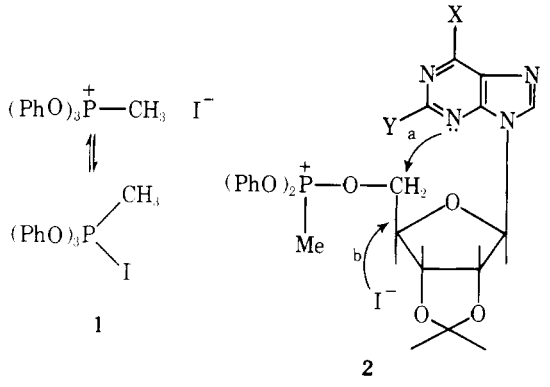
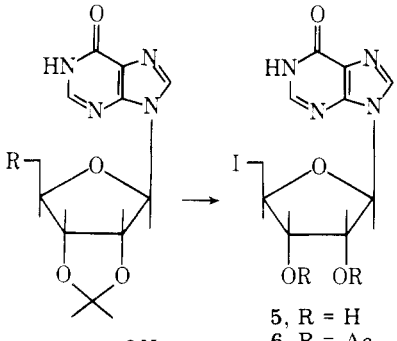


1 2

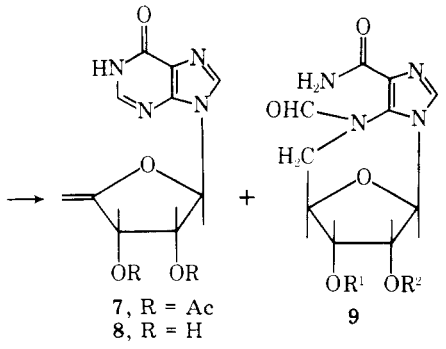
phosphorus in 1 will lead rather rapidly to generation of the intermediate 2 as compared to the similar reaction in a nonpolar solvent. In dimethylformamide, cation solvation would be expected to largely disrupt the ion pair in 2 leading to decreased proximity of the iodide ion to $C_{5'}$. The ring nitrogen, N^3, remains, however, within bonding distance and preferential intramolecular cyclization occurs. In addition, the known solvation of polarizable anions, particularly iodide, by dimethylformamide will tend to decrease the nucleophilicity of iodide relative to that of the ring nitrogen.[8] The differences in rate between paths a and b must be substantial since, as will be seen later, there is no increase in the low isolated yield (14%) of N^6-benzoyl-5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneadenosine obtained from **25b** and 1 in dimethylformamide upon addition of 10 molar equiv of lithium iodide.

We have previously emphasized the advantages, in terms of both rate and yield, of using dimethylformamide as the solvent during iodinations of various pyrimidine nucleosides.[4] The considerations above, however, led us to believe that the use of nonpolar solvents would be advantageous for the preparation of 5′-deoxy-5′-iodo derivatives of purine nucleosides. This hypothesis was confirmed when 2′,3′-*O*-isopropylideneinosine (3) was treated with a small excess of 1 in tetrahydrofuran or in dichloromethane and the corresponding crystalline 5′-deoxy-5′-iodonucleoside **4**[4,9] was isolated in 87% yield. Tetrahydrofuran is the preferred solvent in this case because it increases the rate of the reaction substantially and gives slightly better yields. In general, however, these solvents



3, R = OH
4, R = I

5, R = H
6, R = Ac



7, R = Ac
8, R = H

9

are interchangeable. The reactions were advantageously run by allowing a mixture of the reactants at −70 °C to warm to room temperature. Previously,[4] using dimethylformamide as solvent, **4** was obtained in only 15% yield, the major product of the reaction being the ring-opened cyclonucleoside **9** [R^1, R^2 = $C(Me)_2$].[10] Removal of the isopropylidene group from **4** via acid hydrolysis with 90% formic acid, followed by acetylation, gave crystalline 2′,3′-di-*O*-acetyl-5′-deoxy-5′-iodoinosine (**6**) in almost quantitative yield. Treatment of **6** with silver fluoride in pyridine at room temperature for 4 days[3,11] gave the unsaturated nucleoside 9-(2,3-di-*O*-acetyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)hypoxanthine (**7**) in 81% yield by direct crystallization. In this way **7** was obtained in an overall yield of 70% from **3** without need of chromatography. Hydrolysis of the acetyl group with methanolic triethylamine gave the desired crystalline, unsaturated nucleoside (**8**) in 54% yield after removal of a trace of ring-opened cyclonucleoside (**9**, R^1 = R^2 = H) by preparative thin-layer chromatography. The cyclonucleoside **9** was characterized by its UV spectrum, which was identical to that of the known 2′,3′-*O*-isopropylidene derivative,[4,10] elemental analyses, and ^{1}H-NMR spectrum. The latter showed the same very high field position (2.80 ppm) for one of the $C_{5'}$ protons previously reported for the corresponding 2′,3′-acetonide.[4,10] The successful synthesis of **8** and its protected precursor, **7**, in high overall yields from **3** makes these compounds readily available for further transformations and encouraged us to proceed with the more demanding guanosine series.

Treatment of 2′,3′-*O*-isopropylideneguanosine (**10**) with 1 in tetrahydrofuran as described above gave the corresponding 5′-deoxy-5′-iodonucleoside (**13**) in 58% yield after purification by chromatography. Some 2′,3′-*O*-isopropylidene-N^3,5′-cycloguanosine (**23**)[4,12] was also produced during this reaction. An attempt to facilitate purification of the products via acetylation of the crude mixture with formation of more soluble materials met with failure. Following such treatment the desired N^2-acetyl-5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneguanosine (**16**) was only obtained in 27% yield, while N^2-acetyl-2′,3′-*O*-isopropylidene-N^3,5′-cycloguanosine (**24**) was also isolated in 30% yield. The formation of **24** occurred, at least in part, during the acetylation since similar treatment of pure **13** with acetic anhydride and pyridine gave **16** and **24** in yields of 73 and 15%, respectively. As expected, the ultraviolet spectrum of **16** was essentially the same as those of other N^2-acetylguanosine derivatives (e.g., **14**, **15**, **17**, and **18**), while that of **24** is quite different in both acid and base. Typical of a number of other N^3,5′-cyclonucleosides,[4] the 5′ protons of **24** were highly nonequivalent in the ^{1}H NMR spectrum and appeared as ABX patterns at 3.72 and 5.26 ppm. Since elemental analyses were in agreement with structure **24**, the formation of an ionic cyclonucleoside or a heterocyclic ring-opened product (analogous to **9**) seems to be precluded. Hydrolysis of the isopropylidene group in **13** with 90% formic acid gave poor results due to the low solubility of both the starting material and the final product in this solvent. However, using 50% aqueous formic acid for a longer period of time, crystalline 5′-deoxy-5′-iodoguanosine (**19**) was obtained in 75% yield. The latter compound can also be obtained by treatment of the *N*-acetyl derivative (**17**, see below) with methanolic ammonia. While **19** was crystalline and gave a well-resolved ^{1}H-NMR spectrum, it decomposed over a considerable temperature range, presumably as a consequence of thermal cyclonucleoside formation.

In view of the low solubility of the above nucleosides containing a free amino group on the guanine ring, it was decided to approach the synthesis of the 4′,5′-olefin, **22**, via N^2-acetylguanosine derivatives. This approach has the added advantage of further reducing the tendency toward formation of N^3,5′-cyclonucleosides. In a preliminary experiment, it was

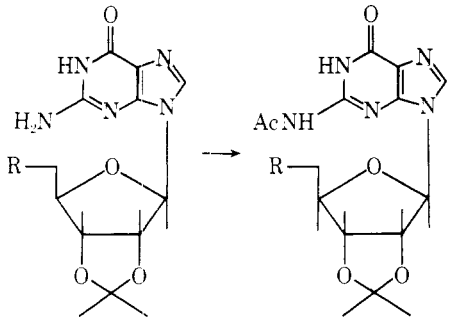
discovered that selective 5′-*O*-acetylation of **10** is possible when the reaction is conducted in acetic anhydride containing a catalytic amount of 4-dimethylaminopyridine,[13] 5′-*O*-acetyl-2′,3′-*O*-isopropylideneguanosine (**11**) being obtained in 82% yield. Using a similar approach, the $C_{5'}$-hydroxyl was selectively formylated using formic–acetic anhydride, and this intermediate (**12**) was directly acetylated at N^2 in the presence of acetic anhydride and pyridine to give **14**, which was crystalline and stable enough to be fully characterized. For preparative purposes, **14** was treated directly with dilute methanolic ammonium hydroxide in order to selectively hydrolyze the formyl group, giving crystalline **15** in an overall yield of 82%. The iodination of **15** was carried out in dichloromethane as described for **10** and the corresponding 5′-deoxy-5′-iodo derivative **16** was isolated by direct crystallization and shown to be identical to the compound obtained in lower yield by acetylation of **13**. Removal of the isopropylidene group from **16** with 90% formic acid gave crystalline N^2-acetyl-5′-deoxy-5′-iodoguanosine (**17**) in 94% yield. Dehydrohalogenation of **19** using 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) and pyridine followed by direct acetylation gave the acetylated 4′,5′-olefin, **21**, in 64% overall yield. This compound could also be obtained in a somewhat improved overall yield (77%) by initial acetylation of **19** followed by treatment of the resulting **18** with silver fluoride and pyridine. The ^{1}H-NMR spectrum of **21** showed the expected pattern for the $C_{5'}$ protons, which appeared as a pair of slightly broadened doublets exhibiting small (2.5 Hz) geminal coupling.[1,3] The allylic $C_{3'}$ proton appeared as a non-first-order pattern at low field (6.36 ppm). Since allylic 3′,5′ coupling is very small (<0.5 Hz), the $C_{3'}$ proton pattern appears to be the consequence of virtual coupling to $C_{1'}$H, which is superimposed upon $C_{2'}$H.

Deacetylation of **21** was accomplished with dilute methanolic ammonia giving the desired 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)guanine (**22**) as a crystalline monohydrate in 49% overall yield from 2′,3′-*O*-isopropylideneguanosine (**10**).

Appropriately blocked 4′,5′-unsaturated adenosine derivatives have proved to be useful starting materials for the synthesis of various 4′-substituted nucleosides[14] including the antibiotic nucleocidin.[15] Accordingly, we have further investigated the iodination of 2′,3′-*O*-isopropylideneadenosine (**25a**) using **1** in dichloromethane. In this case, it was important not to quench the reaction with methanol since this treatment led to the formation of substantial amounts of N^3,5′-cyclonucleoside. Without any purification the crude reaction product, **26a**, was hydrolyzed with 90% formic acid giving crystalline 5′-deoxy-5′-iodoadenosine, **27a**, in 53% yield. This halogenated adenosine derivative had been obtained previously by Jahn[6] by displacement of the 5′-*O*-tosyl derivative of **25a** with sodium iodide in acetic anhydride followed by removal of the isopropylidene group with sulfuric and acetic acids.

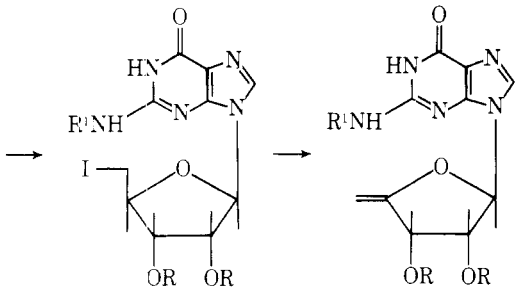
A similar approach was used starting from N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine (**25b**), the corresponding 5′-deoxy-5′-iodo derivative (**26b**) being obtained in 84% yield after purification by chromatography. It is important to note that the crude product of the iodination reaction must be purified immediately, since storage of the crude product overnight at −18 °C before chromatography reduced the yield from 84 to 60%. Removal of the isopropylidene group with 90% formic acid followed by dehydrohalogenation of **27b** with 1,5-diazabicyclo[4.3.0]non-5-ene in dimethylformamide then gave the desired N^6-benzoyl-9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine (**28**) in 71% yield. The latter compound was readily identified by its ^{1}H-NMR spectrum, which was typical of other 4′,5′-unsaturated nucleosides.[1,3] Preparation of the debenzoylated analogue of **28** has previously been described via different routes by our group[1,14] and by McCarthy et al.[16]

The above results on the iodination of **25b** in dichloromethane are to be contrasted with previous results obtained in this laboratory by Dr. I. D. Jenkins during work on the synthesis of nucleocidin. In this work, treatment of **25b** with **1** in dimethylformamide at room temperature led to the isolation of two compounds of widely different solubilities. The major, chloroform insoluble product could be crystallized in 60% yield and proved to be N^6-benzoyl-2′,3′-*O*-isopropylidene-N^3,5′-cycloadenosine iodide (**29**) on the basis of spectroscopic and analytical data. The minor product, isolated in crystalline form in 8% yield, proved to be 5′,N^5-anhydro-4-(*N*-benzoylcarbamimidoyl)-5-formamido-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole (**30**), the product of hydrolytic ring opening of **29**. The *N*-acetyl analogues of both **29** and **30** have previously been described via acetylation of 2′,3′-*O*-isopropylidene-N^3,5′-cycloadenosine iodide[15] and the ^{1}H-NMR spectra for both series show the expected similarities, especially the appearance of the formyl proton at 8.49 ppm and the high field position of one of the $C_{5'}$ protons in **30** (cf. **9**). It is interesting to note that treatment of 2′,3′-*O*-isopropylidene-N^3,5′-cycloadenosine iodide with benzoyl chlo-



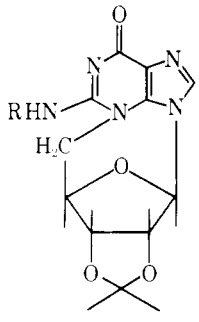
10, R = OH
11, R = OAc
12, R = OCHO
13, R = I

14, R = OCHO
15, R = OH
16, R = I



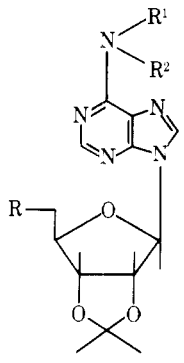
17, R = H; R′ = Ac
18, R = R′ = Ac
19, R = R′ = H

20, R = H; R′ = Ac
21, R = R′ = Ac
22, R = R′ = H

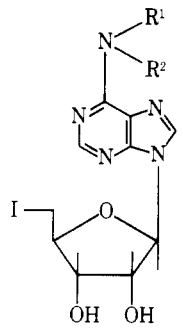


23

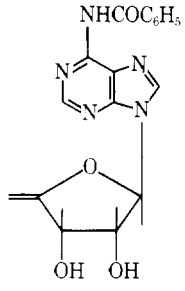
23, R = H
24, R = Ac



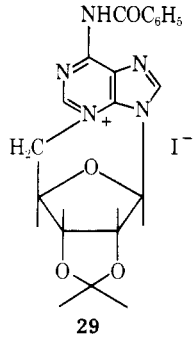
25a, R = OH; $R^1 = R^2 = H$
b, R = OH; $R^1 = H$; $R^2 = COC_6H_5$
26a, R = I; $R^1 = R^2 = H$
b, R = I; $R^1 = H$; $R^2 = COC_6H_5$



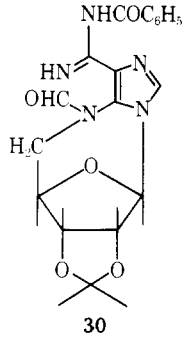
27a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = COC_6H_5$



28



29



30

ride in pyridine at room temperature leads predominantly to formation of the chloride equivalent of the ionic cyclonucleoside (**29**) on the basis of TLC, paper electrophoresis, and UV spectroscopy. Addition of aqueous sodium bicarbonate to a solution of **29** in Me_2SO leads to rapid hydrolysis giving crystalline **30.** It should be noted that Hampton et al.[17] have described the isolation of the neutral form of **29** via treatment of 2′,3′-*O*-isopropylidene-N^3,5′-cycloadenosine tosylate with benzoic anhydride in pyridine at 50 °C. The material was, however, reported to be a crystalline hydrate and its UV spectrum closely matches that of **30.** In the absence of electrophoretic or NMR data we must conclude that the compound isolated by Hampton et al. is indeed the hydrolysis product **30,** once again pointing out the destabilizing effect of *N*-acylation upon purine N^3,5′-cyclonucleosides.[15]

From the work described in this paper, it is clear that the Rydon reagent **1** used in nonpolar solvents gives access to 5′-deoxy-5′-iodopurine nucleosides in good yield. Dehydrohalogenation of these nucleosides using either DBN or silver fluoride leads to previously undescribed 4′,5′-unsaturated purine nucleosides which are useful starting materials for elaboration of variously 4′-substituted nucleosides.[14,15] It should be noted that the method described in this paper has been communicated to Dr. P. C. Srivastava, who has used it in an efficient preparation of 5-amino-1-(5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide.[18]

Experimental Section

General Methods. Proton magnetic resonance (^{1}H-NMR) spectra were obtained using a Varian HA-100 spectrometer. Spectra are recorded in parts per million downfield of an internal standard of tetramethylsilane and are presented in Tables I and II. Mass spectra were obtained using an Atlas CH-4 instrument with a direct inlet system and optical rotatory dispersion (ORD) spectra, using a Jasco ORD/UV-5 instrument. Preparative thin-layer chromatography (preparative TLC) and column chromatography were conducted on silica gels GF 254 and 60, respectively, from E. M. Laboratories, Elmsford, N.Y. Melting points are corrected. Some elemental analyses were obtained from Dr. A. Bernhardt, Elbach über Engelskirchen, Germany, and other instrumental analyses were done by the staff of the Analytical Laboratories of Syntex Research, to whom we extend our thanks. We are especially grateful to Dr. M. Maddox, Mrs. J. Nelson, and Dr. L. Tökés for their help with NMR and mass spectra.

5′-Deoxy-2′,3′-*O*-isopropylidene-5′-iodoinosine (4). Methyltriphenoxyphosphonium iodide (**1,** 6.8 g, 15 mmol)[4] was added to a cooled (−70 °C), stirred suspension of **3** (3.08 g, 10 mmol) in dry tetrahydrofuran (50 mL) and the mixture was allowed to warm to room temperature. After 3 h the solvent was evaporated and a solution of the brown residue in chloroform (500 mL) was quickly washed with aqueous sodium thiosulfate and water, then dried ($MgSO_4$) and evaporated to dryness. The crystalline residue was suspended in a mixture of hexane and chloroform (95:5) and then filtered giving 3.65 g (87%) of pure **4** with mp 195–196.5 °C (lit. mp 195–197,[4] 203–204 °C[9]). This material gave a ^{1}H-NMR spectrum identical to that described previously.[4]

5′-Deoxy-5′-iodoinosine (5). A solution of **4** (3.2 g, 7.65 mmol) in 90% formic acid (30 mL) was kept at room temperature for 21 h and then evaporated to dryness. A solution of the residue in methanol was made slightly basic by addition of a few drops of concentrated ammonium hydroxide and again evaporated to dryness. The white crystalline residue was recrystallized from ethyl acetate–methanol giving 2.8 g (97%) of **5.** An analytical sample was recrystallized from aqueous methanol with mp 196–204 °C dec: λ_{max} (MeOH) 245 nm (ε 12 000), 250 (12 100), 268 (sh, 5400).

Anal. Calcd for $C_{10}H_{11}IN_4O_4$ (378.13): C, 31.76; H, 2.93; N, 14.82. Found: C, 31.74; H, 2.88; N, 14.97.

2′,3′-Di-*O*-acetyl-5′-deoxy-5′-iodoinosine (6). A solution of **5** (2.5 g, 6.6 mmol) and acetic anhydride (2.0 mL, 20 mmol) in dry pyridine (25 mL) was reacted for 20 h at room temperature and then evaporated to dryness after addition of methanol. A solution of the residue in chloroform was washed with water several times, then dried ($MgSO_4$) and evaporated to dryness. Crystallization of the residue from chloroform–hexane gave 3 g (98%) of **6** with mp 162.5–163.5 °C dec: λ_{max} (MeOH) 244 nm (ε 10 400), 249 (10 225), 268 (sh, 4500); λ_{max} (0.01 N NaOH–MeOH) 254 nm (ε 13 500); mass spectrum (70 eV) *m/e* 462 (M^+), 402 (M^+ − AcOH), 327 (sugar), 267 and 207 (sugar − AcOH and − 2AcOH), 136 (base + H).

Anal. Calcd for $C_{14}H_{15}IN_4O_6$ (462.2): C, 36.38; H, 3.27; N, 12.12. Found: C, 36.27; H, 3.23; N, 11.96.

9-(2,3-Di-*O*-acetyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)hypoxanthine (7). Silver fluoride (1.9 g, 15 mmol) was added to a solution of **6** (2.8 g, 6 mmol) in pyridine (20 mL) and the mixture was stirred in the dark for 4 days at room temperature. After filtration of the mixture through Celite the filtrate was evaporated and a solution of the residue in chloroform (200 mL) was washed with saturated aqueous sodium bicarbonate, aqueous sodium thiosulfate, and water. The dried ($MgSO_4$) organic layer was evaporated to dryness and the residue crystallized from chloroform–hexane giving 1.2 g of **7.** The mother liquors were purified by preparative TLC (chloroform–methanol, 9:1) giving a further 0.42 g (total yield 81%) of **7**: mp 222–225 °C; λ_{max} (MeOH) 243 nm (ε 11 100), 248 (10 800), 268 (sh, 4900); λ_{max} (0.01 N NaOH–MeOH) 254 nm (ε 11 000); mass spectrum (70 eV) *m/e* 335, 334 (M^+ + 1, M^+), 274 (M^+ − AcOH), 232 (M^+ − AcOH − CH_2CO), 199 (sugar), 139 (sugar − AcOH), 136, 137 (base + H, +2H), 97 (sugar − AcOH − CH_2CO).

Anal. Calcd for $C_{14}H_{14}N_4O_6$ (334.28): C, 50.29; H, 4.22; N, 16.76. Found: C, 50.13; H, 4.37; N, 16.71.

9-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)hypoxanthine (8). A solution of **7** (1.236 g, 3.7 mmol) in a mixture of methanol (15 mL), water (5 mL), and triethylamine (1.1 mL) was stirred overnight at room temperature and then evaporated to dryness. After several coevaporations with aqueous ethanol, a suspension of the residue in warm methanol was filtered giving 50 mg (5%) of **9** ($R^1 = R^2 = H$): λ_{max} (H_2O) 253 nm (ε 6700).

Anal. Calcd for $C_{10}H_{12}N_4O_5$ (268.23): C, 44.78; H, 4.51; N, 20.89. Found: C, 44.26; H, 5.04; N, 21.22.

Table I. 100 MHz NMR Chemical Shifts (ppm)

	registry no.	solvent[a]	C_1'H	C_2'H	C_3'H	C_4'H	C_5'H_a	C_5'H_b	C_2, C_8	other
5	18945-36-3	D	5.87 (d)	4.66 (dd)	4.11 (dd)	3.96 (ddd)	3.59 (dd)	3.41 (dd)	8.04, 8.29 (s)	
6	68200-58-8	D	6.17 (d)	5.96 (dd)	5.47 (dd)	4.26 (ddd)	3.66 (dd)	3.49 (dd)	8.07, 8.32 (s)	1.98, 209 (s, 3, OAc)
7	68200-59-9	D	6.49 (d)	6.00 (dd)	6.10 (br d)		4.56 (dd)	4.49 (br d)	8.03, 8.31 (s)	2.02, 2.11 (s, 3, OAc)
8	68200-60-2	D	6.15 (d)	4.75 (dd)	4.65 (d)		4.34 (d)	4.24 (d)	8.10, 8.34 (s)	
9	68200-61-3	D	5.92 (d)	3.91 (d)	4.25 (d)	4.39 (br s)	4.64 (dd)	2.80 (dd)	7.92 (s)	8.29 (s, CHO)
11	52417-04-6	D	5.97 (d)	5.24 (dd)	5.10 (dd)	4.27 (ddd)	4.26 (dd)	4.12 (dd)	7.81 (s)	1.31, 1.50 (s, 3, CMe_2), 1.97 (s, 3, OAc)
13	68200-62-4	D	5.99 (d)	5.30 (dd)	5.03 (dd)	4.24 (ddd)	3.30 (dd)	3.36 (dd)	7.86 (s)	1.31, 1.50 (s, 3, CMe_2), 6.52 (bs, 2, NH_2)
14	68200-63-5	D	6.09 (d)	5.29 (dd)	5.17 (dd)	4.25 (m)	4.25 (m)	4.25 (m)	8.14 or 8.12 (s)	1.31, 1.51 (s, 3, CMe_2), 2.18 (s, 3, NAc), 8.14 or 8.12 (s, 1, OCHO)
15	68200-64-6	D	5.99 (d)	5.21 (dd)	4.99 (dd)	4.14 (ddd)	3.60 (dd)	3.46 (dd)	8.19 (s)	1.32, 1.51 (s, 3, CMe_2), 2.17 (s, 3, NAc)
16	68200-65-7	D	6.09 (d)	5.35 (dd)	5.07 (dd)	4.22 (ddd)	3.41 (dd)	3.28 (dd)	8.17 (s)	1.33, 1.52 (s, 3, CMe_2), 2.19 (s, 3, NAc)
17	68200-66-8	D	5.77 (d)	4.63 (dd)	4.08 (dd)	3.95 (ddd)	3.55 (dd)	3.36 (dd)	8.19 (s)	2.14 (s, 3, NAc)
18	68200-67-9	D	6.07 (d)	5.97[b]	5.43 (dd)	4.30 (ddd)	3.70 (dd)	3.51 (dd)	8.25 (s)	2.17, 2.11, 1.98 (s, 3, NAc and OAc)
19	68200-68-0	D*	5.70 (d)	4.61 (dd)	4.07 (dd)	3.88 (ddd)	3.58 (dd)	3.33 (dd)	7.88 (s)	
21	68200-69-1	D	5.99 (m)	5.99 (m)	6.36 (dd)		4.59 (br d)	4.45 (br d)	8.26 (s)	2.17, 2.11, 2.01 (s, 3, NAc and OAc)
22	68200-70-4	D	5.93 (d)	4.60 (m)	4.60 (m)		4.27 (br d)	4.17 (br d)	7.88 (s)	
24	68200-71-5	D	6.46 (d)	4.84 (d)	4.46 (d)	4.87 (dd)	5.26 (dd)	3.72 (dd)	8.01 (s)	1.22, 1.43 (s, 3, CMe_2), 2.12 (s, 3 NAc)
26b	68200-72-6	C	6.17 (d)	5.49 (dd)	5.07 (dd)	4.42 (ddd)	3.44 (dd)	3.26 (dd)	8.17, 8.76 (s)	1.41, 1.62 (s, 3, CMe_2)
27a	4099-81-4	P	6.61 (d)	5.40 (dd)	4.99 (dd)	4.69 (ddd)	4.26 (dd)	4.06 (dd)	8.53, 8.62 (s)	
27b	6044-47-9	D	6.04 (d)	4.84 (dd)	4.20 (dd)	4.00 (dd)	3.63 (dd)	3.42 (d)	8.68, 8.73 (s)	
28	68200-73-7	P	6.90 (dd)	5.35 (m)	5.35 (m)		4.72 (dd)	4.61 (dd)	8.85, 8.85 (s)	
29	68200-74-8	D	6.86 (s)	5.08 (d)	4.65 (d)	5.17 (br s)	5.36 (dd)	4.81 (dd)	8.80, 9.24 (s)	1.22, 1.48 (s, 3, CMe_2), 7.75–8.2 (m, 5, Ar)
30	39947-06-3	D	6.27 (s)	5.07 (d)	4.61 (d)	4.80 (br s)	4.93 (dd)	3.07 (dd)	8.14 (s)	1.25, 1.44 (s, 3, CMe_2), 8.49 (s, CHO), 7.3–8.2 (m, 5, Ar)

[a] Solvents are designated as D (Me_2SO-d_6), D* (Me_2SO-d_6 + D_2O), C ($CDCl_3$), and P (pyridine-d_5). [b] AB of ABM.

Table II. First-Order Coupling Constants (Hz)

	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	other
5	5.5	5.5	4.5	7	5	10	
6	6	5.5	4	5	7	10.5	
7	4.5	5				2.5	$J_{3',5'a} \sim 1$ Hz, $J_{3',5'b} \sim 0$
8	5	5				1	$J_{3',5'a} = J_{3',5'b} \sim 0$
9	0	6	0	2.5	1	14	
11	2	6	3	4	3.5	12	
13	2	6	3	7	7	14	
14	2	6.5	2.5	*a*	*a*	*a*	
15	2.5	6	3	5	4	14	
16	2	6	3.5	7	7	10 or 14	
17	5.5	5	3	6	6	10.5	
18	6.5	5	3	6	7	10.5	
19	6	5	3	5.5	4	10.5	
21	*a*	4				2.5	$J_{1',3'} \sim 1$ Hz (virtual coupling), $J_{3',5'a} = J_{3',5'b} \sim 0$
22	4.5	m				1.5	$J_{3',5'a} = J_{3',5'b} \sim 0$
24	0	5.5	0	3	2	14.5	
26b	2	6	3	7.5	5	10	
27a	6	5.5	3.5	2.5	2.5	12	
27b	6	5.5	3.5	6	0	10	
28	1.5	*a*				1	$J_{1',3'} = 1.5$ Hz (virtual coupling), $J_{3',5'a} = J_{3',5'b} = 1$ Hz
29	0	5.5	0	2	4	14	
30	0	5.5	0	2.5	1.5	14	

[a] Unresolved.

The filtrate was evaporated and the residue (796 mg) purified by preparative TLC ($CHCl_3$–MeOH–Et_3N, 80:20:0.1) to remove the last traces of **9** ($R^1 = R^2 = H$). Elution of the major UV absorbing band with methanol, followed by slow crystallization (1 week) from methanol, gave pure **8** (500 mg, 54%) in two crops: mp 132.5–134.5 °C; λ_{max} (MeOH) 244 nm (ϵ 10 900), 250 (10 800), 267 (sh, 4700); λ_{max} (0.01 N NaOH–MeOH) 254 nm (ϵ 11 500); $[\alpha]_D$ −67.9° (*c* 1.0, MeOH).

Anal. Calcd for $C_{10}H_{10}N_4O_4$ (250.21): C, 48.00; H, 4.02; N, 22.39. Found: C, 47.69; H, 4.37; N, 22.32.

5'-*O*-Acetyl-2',3'-*O*-isopropylideneguanosine (11). 4-Dimethylaminopyridine (40 mg) was added to a suspension of **10** (646 mg, 2 mmol) in acetic anhydride (10 mL). The resulting mixture was stirred at room temperature for 36 h and then evaporated to dryness. The residue was recrystallized from a mixture of acetone, methanol, and water giving 600 mg (82%) of **11** with mp 290–293 °C:[19] λ_{max} (0.01 N NaOH–MeOH) 212 nm (ϵ 23 300), 259 (12 000), 267 (12 100); λ_{max} (0.01 N HCl–MeOH) 260 nm (ϵ 13 600), 278 (sh, 9500); mass spectrum (70 eV) *m/e* 365 (M^+), 350 ($M^+ - CH_3$), 215 (sugar), 157 (sugar −

$(CH_3)_2CO$), 151, 152 (base + H, +2H).

Anal. Calcd for $C_{15}H_{19}N_5O_6$ (365.3): C, 49.31; H, 5.24; N, 19.17. Found: C, 49.06; H, 5.16; N, 19.32.

5'-Deoxy-5'-iodo-2',3'-*O*-isopropylideneguanosine (13). Methyltriphenoxyphosphonium iodide (6.8 g, 15 mmol) was added to a cooled (−78 °C) suspension of **10** (3.23 g, 10 mmol) in tetrahydrofuran (100 mL) and the mixture was allowed to warm to room temperature. After 4 h the excess I was destroyed by addition of methanol (0.3 mL) and the solvents were removed by evaporation. The residue was suspended in a mixture of ether and hexane (1:1) and the solid was filtered and thoroughly washed. The resulting crude **13** was sufficiently pure to be used in further reactions. An analytical sample was purified by chromatography over silica gel. Elution with chloroform–methanol (9:1) gave 2.5 g (58%) of **13** which decomposed slowly from 180–250 °C without melting: λ_{max} (0.1 N NaOH–MeOH) 265 nm (ϵ 12 600); λ_{max} (0.1 N HCl–MeOH) 261 nm (ϵ 13 700); mass spectrum (70 eV) *m/e* 305 ($M^+ - I$), 254 (I_2^+).

Anal. Calcd for $C_{13}H_{16}IN_5O_4$ (433.2): C, 36.04; H, 3.72; N, 16.17. Found: C, 36.13; H, 3.64; N, 16.13.

N^2-Acetyl-5'-*O*-formyl-2',3'-*O*-isopropylideneguanosine (14). 4-Dimethylaminopyridine (200 mg) was added to a solution of **10** (6.47 g, 20 mmol) in acetic–formic anhydride[20] (100 mL). After 24 h at room temperature the mixture was evaporated to dryness and the white residue was suspended in dry pyridine (100 mL). Acetic anhydride (6 mL, 63.5 mmol) was added and the mixture was stirred at room temperature for 26 h. Methanol was then added with cooling and the solvents were removed in vacuo. The brown residue crystallized upon addition of methanol and recrystallization from methanol gave 6.05 g (79%) of **14** in two crops. An analytical sample melted at 237–237.5 °C: λ_{max} (0.01 N HCl–MeOH) 264 nm (ϵ 17 200); mass spectrum (70 eV) *m/e* 393 (M^+), 378 ($M^+ - CH_3$), 194 (base + 2H).

Anal. Calcd for $C_{16}H_{19}N_5O_7$ (393.4): C, 48.85; H, 4.87; N, 17.81. Found: C, 48.94; H, 4.93; N, 18.04.

N^2-Acetyl-2',3'-*O*-isopropylideneguanosine (15). 2',3'-*O*-Isopropylideneguanosine (**10**, 646 mg, 2 mmol) was treated as described above for the preparation of **14** except that **14** was not isolated but directly treated with methanol (15 mL) containing concentrated ammonium hydroxide (3 mL) for 15 min at room temperature. The mixture was then evaporated to dryness and the residue was purified either by preparative TLC ($CHCl_3$–MeOH, 9:1, two passes) or on a column of silica gel using a gradient of 5–20% methanol in chloroform. Crystallization from chloroform–methanol gave 650 mg (88%) of **15** with mp 153–154.5 °C: λ_{max} (0.01 N HCl–MeOH) 264 nm (ϵ 16 500); λ_{max} (0.01 N NaOH–MeOH) 267 nm (ϵ 13 200); mass spectrum (70 eV) *m/e* 365 (M^+), 350 ($M^+ - CH_3$), 193 (base + H), 151 (base + H − CH_2CO).

Anal. Calcd for $C_{15}H_{19}N_5O_6$ (365.3): C, 49.31; H, 5.24; N, 19.17. Found: C, 49.08; H, 5.35; N, 19.51.

N^2-Acetyl-5'-deoxy-5'-iodo-2',3'-*O*-isopropylideneguanosine (16). (a) From 15. Methyltriphenoxyphosphonium iodide (2 g, 4.5 mmol) was added under dry nitrogen to a cooled (−70 °C) suspension of **15** (1.1 g, 3 mmol) in dry dichloromethane (20 mL). The mixture was allowed to warm to room temperature and stirred for 1.5 h before addition of methanol (1 mL) and then chloroform (200 mL). The resulting solution was washed with aqueous sodium thiosulfate and water, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized from chloroform–hexane (9:1) giving 1.2 g (84%) of **16.** An analytical sample from methanol had mp 196–197 °C: λ_{max} (0.01 N HCl–MeOH) 266 nm (ϵ 18 900); λ_{max} (0.01 N NaOH–MeOH) 267 nm (ϵ 14 300); mass spectrum (70 eV) *m/e* 475 (M^+), 460 ($M^+ - CH_3$), 347 ($M^+ - HI$), 332 ($M^+ - HI - CH_3$), 305 ($M^+ - HI - CH_2CO$), 295 ($M^+ - HI - CH_2CO - CH_3$), 283 (sugar).

Anal. Calcd for $C_{15}H_{18}IN_5O_5$ (475.2): C, 37.91; H, 3.82; N, 14.74. Found: C, 37.89; H, 3.82; N, 14.54.

(b) From 13 with Formation of N^2-Acetyl-2',3'-*O*-isopropylidene-N^3,5'-cycloguanosine (24). Acetic anhydride (10 mL, 106 mmol) was added to a suspension of crude **13** (4.3 g, ~10 mmol) in dry pyridine (40 mL) and the mixture was stirred at room temperature overnight. Ice and water were then added, the solvents were removed by evaporation, and the residue was dried by coevaporation with toluene leaving a semicrystalline mass. Addition of toluene and chloroform precipitated a red solid which was removed by filtration. The filtrate was evaporated and separated into two major components by preparative TLC ($CHCl_3$–MeOH, 95:5, three passes). The more polar band was eluted with methanol giving 1.3 g (27% from **10**) of **16** identical to that from (a). Elution of the less polar band gave 1.03 g (30% from **10**) of N^2-acetyl-2',3'-*O*-isopropylidene-N^3,5'-cycloguanosine (**24**) with mp 273.5–282 °C dec: λ_{max} (0.01 N HCl–MeOH) 273 nm (ϵ 13 900); λ_{max} (0.01 N NaOH–MeOH) 223 nm (ϵ 13 500), 245 (16 800), 280 (13 400); ORD (MeOH) $[\Phi]^{tr}_{309}$ −4100°, $[\Phi]_{299}$ 0°, $[\Phi]^{pk}_{282}$ 16 400°, $[\Phi]_{269}$ 0°, $[\Phi]^{tr}_{255}$ −13 000°, $[\Phi]^{pk}_{240}$ −9900°, $[\Phi]^{tr}_{227}$ −13 700°, $[\Phi]_{219}$ 0°; mass spectrum (70 eV) *m/e* 347 (M^+), 332 ($M^+ - CH_3$), 305 ($M^+ - CH_2CO$).

Anal. Calcd for $C_{15}H_{17}O_5N_5$ (347.3): C, 51.86; H, 4.93; N, 20.17. Found: C, 51.99; H, 4.79; N, 20.59.

N^2-Acetyl-5'-deoxy-5'-iodoguanosine (17). A solution of **16** (3.96 g, 8.36 mmol) in 90% formic acid (50 mL) was kept at 37 °C for 36 h and then evaporated to dryness. A solution of the residue in methanol (50 mL) was made slightly basic with concentrated ammonium hydroxide and evaporated to dryness. The residue was coevaporated with methanol several times and crystallized from aqueous methanol to give 3.43 g (94%) of **17.** An analytical sample from a large volume of acetone had mp 188–191 °C: λ_{max} (0.01 N HCl–MeOH) 264 nm (ϵ 16 600); λ_{max} (0.01 N NaOH–MeOH) 267 nm (ϵ 13 800).

Anal. Calcd for $C_{12}H_{14}IN_5O_5$ (435.2): C, 33.12; H, 3.24; N, 16.09. Found: C, 33.03; H, 3.28; N, 16.03.

N^2,O^2',O^3'-Triacetyl-5'-deoxy-5'-iodoguanosine (18). (a) From 17. A solution of **17** (3.675 g, 8.44 mmol) in a mixture of pyridine (125 mL) and acetic anhydride (17 mL, 180 mmol) was stirred at room temperature overnight, cooled to 0 °C, and quenched with methanol (25 mL). After 15 min, the solvents were removed by evaporation and the residue was recrystallized from warm chloroform giving 3.7 g (85%) of **18** in three crops. An analytical sample from ethyl acetate–hexane had mp 126.5–130 °C: λ_{max} (0.01 N HCl–MeOH) 261 nm (ϵ 18 700), 275 (sh, 16 800); λ_{max} (0.01 N NaOH–MeOH) 265 nm (ϵ 13 700); mass spectrum (70 eV) *m/e* 519 (M^+), 327 (sugar), 254 (I_2^+), 193 (base + H).

Anal. Calcd for $C_{16}H_{18}IN_5O_7$ (519.2): C, 37.01; H, 3.49; N, 13.49. Found: C, 36.72; H, 3.55; N, 13.28.

(b) From 19. Acetic anhydride (6 mL, 63 mmol) was added in three portions at 24-h intervals to a solution of **19** (320 mg, 0.8 mmol) in pyridine (15 mL). Two days after the last addition, the reaction was worked up as above and the product purified by preparative TLC ($CHCl_3$–MeOH, 9:1) to give 610 mg (58%) of **18** which was identical to that from (a) above.

5'-Deoxy-5'-iodoguanosine (19). (a) From 13. A suspension of **13** (217 mg, 0.5 mmol) in 50% aqueous formic acid (10 mL) was stirred for 2 days at room temperature and then evaporated. A methanolic solution (10 mL) of the residue was made slightly basic with ammonium hydroxide and coevaporated several times with methanol. The residue crystallized from aqueous methanol giving 147 mg (75%) of **19** with mp 192–216 °C dec: λ_{max} (0.01 N NaOH–MeOH) 265 nm (ϵ 13 300); λ_{max} (0.01 N HCl–MeOH) 260 nm (ϵ 14 000), 273 (sh, 6200).

Anal. Calcd for $C_{10}H_{12}IN_5O_4$ (395.2): C, 30.54; H, 3.08; N, 17.81. Found: C, 30.74; H, 3.21; N, 17.79.

(b) From 17. A suspension of **17** (1 g, 2.3 mmol) in methanolic ammonia (¼ saturated at 0 °C, 20 mL) was stirred at room temperature for 24 h. Water was then added until dissolution occurred and after 48 h the solvents were removed in vacuo. The crystalline residue was treated with charcoal and recrystallized from boiling water to give 0.6 g (66%) of **19,** identical to that obtained in (a).

N^2-Acetyl-9-(2,3-di-*O*-acetyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)guanine (21). (a) From 18 Using Silver Fluoride. Finely powdered silver fluoride (950 mg, 7.5 mmol) was added to a solution of **18** (1.5 g, 2.9 mmol) in dry pyridine (30 mL) and the suspension was stirred in the dark for 4 days at room temperature. The dark green mixture was then evaporated to a syrup which was diluted with chloroform and filtered through Celite. The filtrate was washed with saturated aqueous sodium chloride and water, dried ($MgSO_4$), and evaporated to dryness giving 1 g (90%) of **21** as a foam which was essentially homogeneous by TLC (chloroform–methanol, 9:1) and NMR analysis but which did not give acceptable elemental analyses. It was, however, suitable for direct use in the next step.

(b) From 19 Using DBN. A solution of **19** and 1,5-diazabicyclo[4.3.0]non-5-ene (150 μL, 1.2 mmol) in pyridine (5 mL) was stirred in the dark at room temperature for 12 h. Acetic anhydride (2 mL, 21 mmol) was then added and the mixture was stirred for 24 h. The solvents were removed by evaporation and the residue purified by preparative TLC ($CHCl_3$–MeOH, 9:1, three passes). The major UV absorbing band was eluted to give 250 mg (64%) of **21** as a colorless foam having identical properties (TLC, NMR) to that from (a).

9-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)guanine (22). A solution of **21** (800 mg, 2 mmol) in methanolic ammonia (half-saturated at 0 °C) was stirred at room temperature for 24 h. The reaction mixture was evaporated and the crystalline residue was recrystallized from methanol–water giving 500 mg (92%) of homogeneous **22.** An analytical sample from water showed only slow decomposition above 184 °C: λ_{max} (0.1 N NaOH–MeOH) 267 nm (ϵ 11 100); mass spectrum (70 eV) *m/e* 151 (base + H), 114 (sugar − H).

Anal. Calcd for $C_{10}H_{11}N_5O_4 \cdot H_2O$ (283.2): C, 42.40; H, 4.62; N, 24.73. Found: C, 42.34; H, 4.25; N, 24.41.

N^6-Benzoyl-5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneadenosine (26b). Solid **1** (6.8 g, 15 mmol) was added, under nitrogen in a drybox, to a cooled (−70 °C) solution of **25b** (4.1 g, 10 mmol) in dry dichloromethane and the mixture was allowed to warm to room temperature. After 2 h the reaction was quenched with methanol (0.5 mL) and diluted with chloroform (250 mL). The resulting solution was washed with sodium thiosulfate (10% aqueous) and water, dried ($MgSO_4$) and evaporated in vacuo. The residual syrup was immediately purified by chromatography on silica gel, elution with chloroform–methanol (9:1) giving 4.4 g (84%) of **26b** as a homogeneous syrup: λ_{max} (MeOH) 230 nm (ϵ 13 100), 266 (sh, 12 300), 280 (14 500); ORD (MeOH) $[\Phi]^{tr}_{296}$ −2600°, $[\Phi]_{276}$ 0°, $[\Phi]^{pk}_{270}$ 1000°, $[\Phi]^{tr}_{268}$ 1000°, $[\Phi]^{pk}_{242}$ 5300°; mass spectrum (70 eV) *m/e* 521 (M^+), 520 ($M^+ - H$), 506 ($M^+ - CH_3$), 393 ($M^+ - HI$), 239 (base + H).

Anal. Calcd for $C_{20}H_{20}IN_5O_4$ (521.3): C, 46.07; H, 3.87; N, 13.44. Found: C, 45.86; H, 3.92; N, 13.19.

5′-Deoxy-5′-iodoadenosine (27a). Solid **1** (678 mg, 1.5 mmol) was added in a drybox to a cooled (−70 °C) suspension of 2′,3′-*O*-isopropylideneadenosine (**25a**) (307 mg, 1 mmol) in dry dichloromethane (20 mL) and the mixture was allowed to warm to room temperature. After 2 h the solution was diluted with chloroform (50 mL), washed with aqueous sodium thiosulfate and water, dried ($MgSO_4$), and evaporated to dryness. The residue was hydrolyzed in 90% formic acid for 18 h at room temperature and then evaporated to dryness. A methanol solution of the residue was made slightly basic with ammonium hydroxide and then evaporated to dryness. Purification of the residue by preparative TLC ($CHCl_3$–MeOH–HCOOH, 85:15:0.1) gave a major UV absorbing band that was eluted with a mixture of acetone and methanol (1:1) giving 200 mg (53%) of crystalline **27a:** mp 171–172 °C (lit.[6] mp 170 °C).

N^6-Benzoyl-5′-deoxy-5′-iodoadenosine (27b). A solution of **26b** (4 g, 7.7 mmol) in 90% formic acid (50 mL) was kept at 30 °C for 36 h and then evaporated to dryness. A solution of the residue in methanol (50 mL) was made slightly basic with concentrated ammonium hydroxide and then evaporated to dryness. After a few coevaporations with methanol the residue crystallized giving 3.0 g (81%) of **27b** in two crops. An analytical sample from aqueous acetone had mp 188–190 °C: λ_{max} (MeOH) 231 nm (ϵ 13 900), 260 (sh, 12 900), 280 (20 800).

Anal. Calcd for $C_{17}H_{16}O_4N_5I$ (481.2): C, 42.43; H, 3.35; N, 14.55. Found: C, 42.57; H, 3.39; N, 14.64.

N^6-Benzoyl-9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)-adenine (28). 1,5-Diazabicyclo[4.3.0]non-5-ene (75 μL, 0.6 mmol) was added to a solution of **27b** (240 mg, 0.5 mmol) in DMF (5 mL) and stirred in the dark at room temperature for 10 h. The mixture was then evaporated to dryness and the residue purified by preparative TLC ($CHCl_3$–MeOH, 9:1, two passes). Elution of the major UV absorbing band with methanol gave 200 mg (71%) of **28** with mp 198.5–200 °C dec from aqueous acetone: λ_{max} (MeOH) 229 nm (ϵ 14 100), 279 (21 300); mass spectrum (70 eV) *m/e* 353 (M^+), 352 ($M^+ - H$), 324 ($M^+ - H_2O$), 282, 240 (base + 2H), 239 (base + H).

Anal. Calcd for $C_{17}H_{15}N_5O_4$ (353.3): C, 57.76; H, 4.28; N, 19.82. Found: C, 57.61; H, 4.10; N, 19.92.

Reaction of 25b and 1 in Dimethylformamide (by Dr. I. D. Jenkins). A solution of **25b** (7.6 g, 18.5 mmol) and **1** (9.76 g, 21.6 mmol) in dimethylformamide (100 mL) was stirred at room temperature for 30 min. After addition of methanol (1 mL) the solvent was evaporated and the residue was partitioned between chloroform and aqueous sodium thiosulfate giving a yellow precipitate which was collected by filtration. This material was crystallized from dimethylformamide–methanol giving 5.8 g (60%) of pure **29** with mp 257–259 °C: λ_{max} (MeOH) 220 nm (ϵ 26 700), 306 (16 100), 333 (sh, 10 400).

Anal. Calcd for $C_{20}H_{20}N_5O_4I$ (521.31): C, 46.08; H, 3.87; N, 13.43. Found: C, 46.05; H, 3.91; N, 13.21.

The chloroform solution from the above partitioning was washed with water, dried ($MgSO_4$) and evaporated. Crystallization of the residue from benzene gave 0.63 g (8%) of **30** which melted with gas evolution at 236 °C: λ_{max} (MeOH) 264 nm (ϵ 15 000), 306 (16 100). The putative neutral tautomer of **29** was reported[17] to have mp 245–246 °C: λ_{max} (MeOH) 266 nm (ϵ 12 500), 308 (12 600).

Anal. Calcd for $C_{20}H_{21}N_5O_5$ (411.41): C, 58.38; H, 5.15; N, 17.02. Found: C, 58.06; H, 5.09; N, 17.13.

As expected, upon paper electrophoresis in 1 M acetic acid **29** behaved as a cation with a mobility of 0.75 relative to 2′,3′-*O*-isopropylidene-N^3,5′-cycloadenosine while **30** was neutral.

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Registry No.—**1** charged form, 18631-95-3; **1** uncharged form, 4167-91-3; **3,** 2140-11-6; **4,** 22413-28-1; **10,** 362-76-5; **12,** 68200-75-9; **25a,** 362-75-4; **25b,** 39947-04-1; **26a,** 30685-66-6.

References and Notes

(1) For Part 5, see E. J. Prisbe, J. Smejkal, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **41,** 1836 (1976).
(2) Syntex Postdoctoral Fellow, 1971–1973.
(3) (a) J. P. H. Verheyden and J. G. Moffatt, *J. Am. Chem. Soc.*, **88,** 5684 (1966); (b) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **39,** 3573 (1974).
(4) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35,** 2319, 2868 (1970).
(5) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).
(6) W. Jahn, *Chem. Ber.*, **98,** 1705 (1965).
(7) G. A. Wiley and W. R. Stine, *Tetrahedron Lett.*, 2321 (1967); G. S. Harris and M. F. Ali, *ibid.*, 37 (1968).
(8) For reviews, see, e.g., (a) A. J. Parker, *Q. Rev., Chem. Soc.*, **16,** 163 (1962); (b) J. F. Bunnett, *Annu. Rev. Phys. Chem.*, **14,** 271 (1963).
(9) A. Hampton, M. Bayer, V. S. Gupta, and S. Y. Chu, *J. Med. Chem.*, **11,** 1229 (1968).
(10) J. T. Witkowski, G. P. Kreishman, M. P. Schweizer, and R. K. Robins, *J. Org. Chem.*, **38,** 180 (1973).
(11) B. Helferich and E. Himmen, *Chem. Ber.*, **61,** 1825 (1928); L. Hough and B. Otter, *Chem. Commun.*, 173 (1966).
(12) R. E. Holmes and R. K. Robins, *J. Org. Chem.*, **28,** 3483 (1963).
(13) W. Steglich and G. Hofle, *Angew. Chem., Int. Ed. Engl.*, **8,** 981 (1969).
(14) I. D. Jenkins, G. R. Owen, S. D. Dimitrijevich, C. M. Richards, P. C. Srivastava, N. Le-Hong, J. P. H. Verheyden, and J. G. Moffatt, *Ann. N.Y. Acad. Sci.*, **255,** 151 (1975).
(15) I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, *J. Am. Chem. Soc.*, **98,** 3346 (1976).
(16) J. R. McCarthy, R. K. Robins, and M. J. Robins, *J. Am. Chem. Soc.*, **90,** 4993 (1968).
(17) A. Hampton, T. Sasaki, and B. Paul, *J. Am. Chem. Soc.*, **95,** 4404 (1973).
(18) P. C. Srivastava, A. R. Newman, T. R. Matthews, and R. K. Robins, *J. Med. Chem.*, **18,** 1239 (1975).
(19) This compound was first obtained in these laboratories by Dr. A. F. Russell as a byproduct during preparation of N^2,$O^{5'}$-diacetyl-2′,3′-*O*-isopropylideneguanosine. Unpublished results.
(20) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1968, p 4.