(10) J. A. Barltrop, A. J. Johnson, and G. D. Meakins, *J. Chem. Soc.*, 181 (1951); S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, *J. Org. Chem.*, **31**, 3446 (1966).
(11) S. F. Mason, *Q. Rev. Chem. Soc.*, **15**, 287 (1961).
(12) J. P. Freeman, *Chem. Ind. (London)*, 1624 (1960); *J. Org. Chem.*, **26**, 4190 (1961).
(13) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
(14) Y. L. Chow, S. C. Chen, K. S. Pillay, and R. A. Perry, *Can. J. Chem.*, **50**, 1051 (1972).
(15) See L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, p 20, for a good model.
(16) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4430 (1955).
(17) Francesconi and Cusmano[2] reported a much lower melting point for their β isomer; however, it contained methanol on crystallization, which our product did not.
(18) Ramart-Lucas and M. M. Grunfeld, *Bull. Soc. Chim. Fr.*, **4 (5)**, 478 (1937); A. Hantszch, *Ber.*, **64**, 661 (1931); J. T. Edward and S. C. R. Meacock, *Chem. Ind. (London)*, 536 (1955).
(19) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2009 (1957).
(20) We are grateful to a referee for suggesting this possible route.
(21) L. A. Flexser, L. P. Hammett, and A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2103 (1935).
(22) B. H. Pierson, A. N., Fletcher, and E. St. Clair Gantz, *Anal. Chem.*, **28**, 1218 (1956).

Isonucleosides. 2. Purine and Pyrimidine Derivatives of 1,4-Anhydro-2-deoxy-D-arabinitol

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1,4-Anhydro-D-xylitol (1), prepared from sorbose by three steps, was converted into 1,2:3,4-dianhydro-D-ribitol (7) by a sequence of six high-yield reactions. Reaction of 7 with concentrated ammonium hydroxide resulted in exclusive attack at C-2 to give 2-amino-1,4-anhydro-D-arabinitol (8), which was converted in three steps to the adenosine analogue 2-(6-amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (11). It was also converted to the uridine analogue 15.

The naturally occurring nucleosides and nucleotides are those in which the purine or pyrimidine base is attached to C-1 of ribose or 2-deoxyribose. This linkage is part of an aminal structure that is quite susceptive to both hydrolytic and enzymatic cleavage. For many years, the design of congeners of these compounds was based on the assumption that only analogues with bases attached in the β configuration to C-1 of D-furanoses were likely to fit the active sites of the anabolic enzymes necessary for activation of the enzymes whose inhibition by the resultant nucleotides results in cell death. The same requirements were assumed to apply also to the incorporation of analogues into cofactors or macromolecules. However, the discovery of the biologic activity of α-2′-deoxythioguanosine,[1] of the *α-arabino* nucleosides,[2] and of the carbocyclic analogues of nucleosides[3] has made it necessary to revise these concepts about structural requirements. Thus, it seemed worthwhile to investigate the biologic potential of isonucleosides—compounds in which the base is attached to the sugar at positions other than the normal C-1 position.

Previous work in this laboratory resulted in the preparation of purine isonucleosides by the reaction of methyl 2,3-anhydro-α-D-arabinofuranoside with ammonium hydroxide to give a mixture of methyl 2-amino-2-deoxy-α-D-arabinofuranoside and methyl 3-amino-3-deoxy-α-D-xylofuranoside.[4] The reaction of each of these compounds with 2,6-dichloro-5-aminopyrimidine followed by ring closure gave the isonucleosides, methyl 2-(6-chloro-9-purinyl)-2-deoxy-α-D-arabinofuranoside and methyl 3-(6-chloro-9-purinyl)-3-deoxy-α-D-xylofuranoside. In this manner, a number of purine isonucleosides were prepared by nucleophilic displacement of the 6-chloro group.[5,6]

We have now extended this work by the synthesis of compounds lacking the 1-*O*-methyl group of the sugar moiety in the hope that such compounds might be substrates for the anabolic enzymes such as adenosine kinase, and that they might therefore be activated to forms capable of interfering with vital cellular metabolism, such as the biosynthesis or function of nucleic acids.

The success of the reaction of methyl 2,3-anhydro-α-D-arabinofuranoside with ammonium hydroxide[4] led us to undertake the preparation of 1,2:3,4-dianhydro-D-ribitol (7). Preparation of 7 was initially attempted by reaction of 1,2-di-*O*-acetyl-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylofuranose[7] with ethereal HCl (saturated at 0 °C) to give 2-*O*-acetyl-3-*O*-mesyl-5-*O*-methoxycarbonyl-β-D-xylofuranosyl chloride.[8] Reduction of this chloride followed by ring closure should give the corresponding epoxide; however, all attempts to reduce the glycosyl chloride, either catalytically or chemically, were unsuccessful, giving in most cases unchanged starting material. Attempts were made to displace the 1-chloro group with sodium ethylmercaptide[9] and at the same time effect ring closure to the epoxide to give ethyl 2,3-anhydro-1-deoxy-1-thio-β-D-ribofuranose, which could then be reduced to give **7.** The reaction to prepare the thio sugar was unsuccessful, giving an intractable mixture.

An alternative approach to **7** involved the anhydridizing of sorbitol with sulfuric acid catalyst to give arlitan (1,4-sorbitan).[10] When the reaction was carried out as described in the literature (i.e., 135–145 °C for 30 min), we obtained, in addition to the product, a large amount of a by-product tentatively identified as isosorbide, since it is known that further treatment of arlitan with sulfuric acid results in the formation of isosorbide in high yield.[11] When the reaction was carried out at a lower temperature, 130 °C for 45 min, a cleaner product was obtained free of isosorbide. The method of Kjølberg for shortening the chain length of glycosides was used for the synthesis of 1,4-anhydro-D-xylitol (1).[12] Cleavage of the C^5–C^6 bond of arlitan with periodate gave the aldehyde, which was reduced with sodium borohydride to **1.**[13] (For the syntheses of compounds **2–16,** see Scheme I.) The 1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (**2**), a white crystalline solid, was prepared by the reaction of **1** with acetone containing 2,2-dimethoxypropane and 60% perchloric acid. Acetylation of **2** with pyridine–acetic anhydride furnished 2-*O*-acetyl-1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (**3**), a crystalline solid. By deacetonation of **3** in 1 N ethanolic HCl, 2-*O*-acetyl-1,4-

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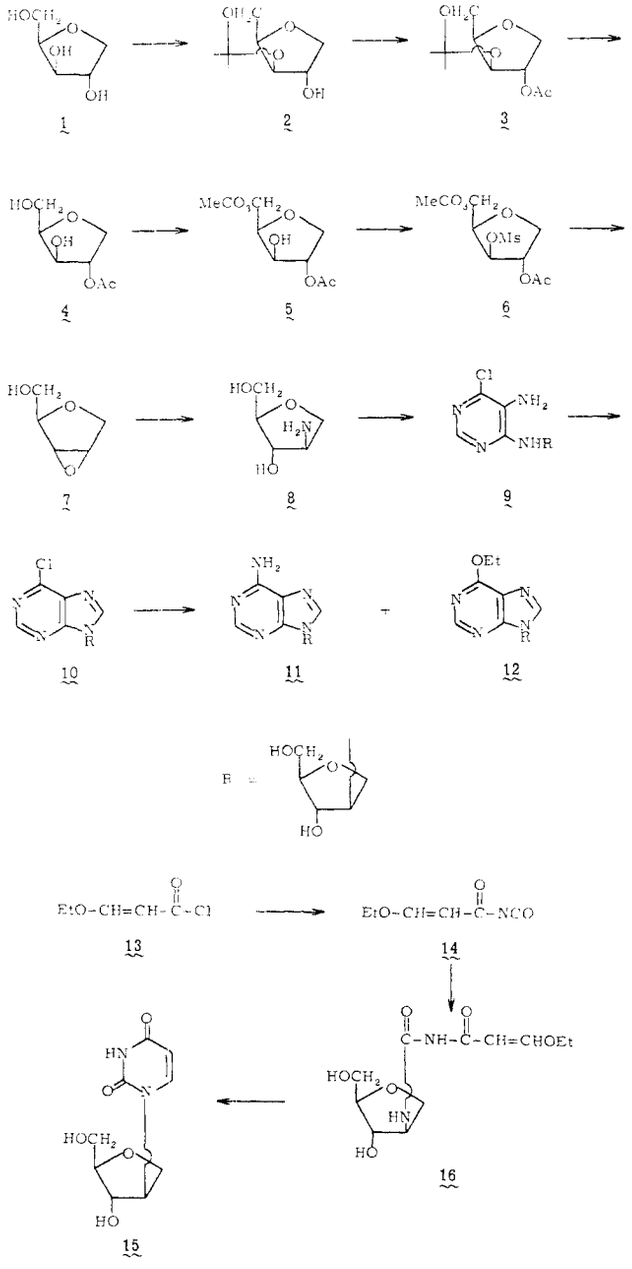
Scheme I



anhydro-D-xylitol (4) was obtained and subsequently acylated with an excess of methyl chloroformate in pyridine to 2-*O*-acetyl-1,4-anhydro-5-*O*-methoxycarbonyl-D-xylitol (5). Because of the large difference in the rate of acylation of the two hydroxyl groups, only a very small amount of the 3,5-di-*O*-methoxycarbonyl derivative was observed (TLC). The reaction of 5 with methanesulfonyl chloride in pyridine gave 1-*O*-acetyl-1,4-anhydro-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylitol (6), which was cyclized with cold 1 N sodium methoxide in methanol to the epoxide 7. The reaction of 7 with concentrated ammonium hydroxide at 100 °C took place exclusively at C-2 to give 2-amino-1,4-anhydro-2-deoxy-D-arabinitol (8) (the overall yield of 8 from 1, a seven-step sequence, was 33%). This is in contrast to the similar reaction with the methyl 2,3-anhydro-α-D-ribofuranose in which attack occurs at both C-2 and C-3 to give an almost equal mixture of arabino and xylo compounds,[4] indicating the electron-releasing properties of the glycosidic methoxy group; methyl 2,3-anhydro-β-D-ribofuranose is attacked exclusively at C-3,[14,15] a result of both steric and electronic effects. The structures of compounds 1–7 were confirmed by NMR spectral data. The structure of 8 as the arabino rather than the xylo isomer (resulting from attack at C-2 rather than C-3) could not be established from its NMR spectra alone, because the ^1H NMR peaks were largely unresolved, even in trifluoroacetic acid, and the ^{13}C spectrum was not stereochemically definitive, although it did establish that 8 was a single entity. The spectrum of the purine (11) prepared from 8 (see below), however, was well resolved and its arabino structure could be established unequivocally by spin-decoupling experiments.

The reaction of 8 with 5-amino-4,6-dichloropyrimidine in refluxing 1-butanol gave 2-(5-amino-6-chloro-4-pyrimidinylamino)-1,4-anhydro-2-deoxy-D-arabinitol (9), which was obtained pure in 45% yield by silica gel column chromatography. Ring closure in triethylorthoformate–concentrated HCl furnished 2-(6-chloro-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (10), which reacted with ethanolic ammonia to give a mixture that was resolved by silica gel chromatography providing a 67% yield of 2-(6-amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (11) and an 11% yield of 2-(6-ethoxy-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (12). The structures of 9–11 were confirmed by elemental analyses and UV and NMR spectral data. The structure of 12 was confirmed by elemental analysis and UV spectral data.

β-Ethoxyacryloyl chloride (13), prepared from the sodium salt of β-ethoxyacrylic acid by the method of Shaw and Warrener,[16] was allowed to react with silver cyanate in benzene under anhydrous conditions to give β-ethoxyacryloyl isocyanate (14). Reaction of 14 with the arabinitol 8, carried out in cold *N,N*-dimethylformamide solution,[17] provided the urea 16, which cyclized in concentrated ammonium hydroxide to give 1,4-anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-D-arabinitol (15), purified via its lead salt, in an overall yield of 18% from 8. The structure of 15 was verified by UV and NMR spectroscopy as well as elemental analysis.

None of these isonucleosides have been found to be cytotoxic, and the ones so far evaluated have shown no activity against leukemia L1210.

Experimental Section

All evaporations were carried out in vacuo with a rotary evaporator. Analytical samples were normally dried in vacuo over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated $(NH_4)_2SO_4$. Compounds containing amino groups were also detected with ninhydrin spray. All analytical samples were essentially TLC homogeneous. Melting points were determined with a Mel-Temp apparatus and are not corrected. The UV absorption spectra were determined in 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH with a Cary 17 spectrophotometer: the maxima are reported in nm ($\epsilon \times 10^{-3}$). The NMR spectra were determined with a Varian XL-100-15 spectrometer in the solvent indicated with tetramethylsilane as an internal reference: chemical shifts (δ in ppm) quoted in the case of multiplets are measured from the approximate center. The ^{13}C spectra were measured at 25.2 MHz in the pulsed, Fourier transform mode with a Digilab Model 400-2 pulser and NMR-3 data system.

1,4-Anhydro-3,5-*O*-isopropylidene-D-xylitol (2). A solution of anhydrous acetone (1.22 L) and 2,2-dimethoxypropane (32.9 mL) was stirred for 2 min before 60% perchloric acid (44 mL) was added. The resulting solution was stirred for 5 min and then poured into a flask containing 1,4-anhydro-D-xylitol[13] (12.8 g, 9.5 mmol). Vigorous stirring produced a complete solution within 5 min. After 50 min of additional stirring, the solution was chilled in an ice bath, neutralized with solid $NaHCO_3$, and evaporated to dryness in vacuo at ambient temperature. The residue was partitioned between H_2O and $CHCl_3$ (100 mL each). Further extraction of the aqueous layer was carried out seven times with $CHCl_3$ (100 mL each time). The $CHCl_3$ extracts were combined, dried over $MgSO_4$, and evaporated to dryness in vacuo to yield a white crystalline solid: yield 12 g (80%). Recrystallization from ether–petroleum ether gave the analytical sample (TLC, 9:1 $CHCl_3$–MeOH); ^1H NMR ($CDCl_3$) δ 1.35 (s, CH_3), 1.43 (s, CH_3), 2.88 (d, O_2H), 3.8, 4.0, and 4.2 (br m's, 2-H_1, H_2, H_3, H_4, 2-H_5); ^{13}C NMR

($CDCl_3$) δ 19.55 and 28.53 (CH_3 of IP), 60.70 (C-5), 72.20 (C-1), 74.43 (C-3), 75.59 and 76.61 (C-2 and C-4), 97.52 (C of IP).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.99; H, 7.84.

2-*O*-Acetyl-1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (3). To a cold (0 °C) solution of 1,4-anhydro-2,3-*O*-isopropylidene-D-xylitol (2.68 g, 15.3 mmol) in pyridine (10 mL) was added acetic anhydride (2.9 mL, 30.6 mmol). The resulting solution was allowed to warm up to ambient temperature and kept there for 20 h before it was poured into ice-saturated $NaHCO_3$ (100 mL). The resulting mixture was extracted with $CHCl_3$ (100 mL), which was washed with saturated $NaHCO_3$ (100 mL) and then H_2O (5 × 100 mL), dried over $MgSO_4$, and evaporated to dryness in vacuo at 70 °C (until there was no longer an odor of pyridine in the residue). A white crystalline solid was obtained: yield 2.91 g (88%) (TLC, 99:1 $CHCl_3$–MeOH); ^1H NMR ($CDCl_3$) δ 1.36 (s, CH_3), 1.43 (s, CH_3), 2.05 (s, CH_3 of Ac), 3.94 (br m, 2-H_1, 2-H_5), 4.34 (br m, H_2, H_4), 5.12 (d, H_3); ^{13}C NMR ($CDCl_3$) δ 19.48 and 28.46 (2 CH_3 of IP), 20.91 (CH_3 of Ac), 60.48 (C-5), 72.17 (C-1), 72.61 and 73.51 (C_3 and C_4), 78.92 (C_2), 97.74 (C of IP), 169.89 (C of C=O).

2-*O*-Acetyl-1,4-anhydro-D-xylitol (4). To a cold solution of 2-*O*-acetyl-1,4-anhydro-3,5-*O*-isopropylidene-D-xylitol (7.5 g, 34.7 mmol) in ethanol (175 mL) was added 1 N HCl (34.7 mL). The resulting solution was allowed to warm up to ambient temperature and kept there until the hydrolysis was complete as determined by hourly examinations by TLC (95:5 $CHCl_3$–MeOH). After 3 h, the solution was evaporated to dryness in vacuo. A solution of the residue in $CHCl_3$ (100 mL) was neutralized with solid Na_2CO_3, filtered, dried over $MgSO_4$, and evaporated to dryness in vacuo. A yellow syrup was obtained: yield 5.2 g (86%); ^1H NMR (Me_2SO-d_6) δ 2.0 (s, CH_3), 3.5 (m, H_4 and 2 H_5), 3.8 and 4.0 (m's, 2 H_1 and H_3), 4.5 (t, C_5OH), 4.9 (m, H_2), 5.3 (d, C_4OH); ^{13}C NMR (Me_2SO-d_6) δ 20.67 (CH_3 of Ac), 59.07 (C-5), 70.11 (C-1), 73.26, 79.52, and 81.49 (C-3, C-2, and C-4).

2-*O*-Acetyl-1,4-anhydro-5-*O*-methoxycarbonyl-D-xylitol (5). A solution of 2-*O*-acetyl-1,4-anhydro-D-xylitol (546 mg, 3.1 mmol) in pyridine (20 mL) and $CHCl_3$ (10 mL) was stirred and chilled in an ice bath while methyl chloroformate (0.48 mL, 6.2 mmol) was slowly added. After complete solution was attained, the reaction was kept at 3–5 °C. After 48 h another 6.2 mmol of methyl chloroformate was added and the resulting solution was kept at 3–5 °C for another 48 h. The solution was then poured into ice water (200 mL) and $CHCl_3$ (200 mL) was added. The $CHCl_3$ layer was washed with cold dilute H_2SO_4 until the aqueous layer remained acidic and then cold H_2O, dried over $MgSO_4$, and evaporated to dryness in vacuo. A yellow syrup was obtained: yield 570 mg (79%) (TLC, 95:5 $CHCl_3$–MeOH). This material, on TLC examination, contained a small amount of a faster moving material, possibly the disubstituted compound. It was, however, used in the next step without further purification.

2-*O*-Acetyl-1,4-anhydro-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylitol (6). To a cold (0–3 °C) solution of 2-*O*-acetyl-1,4-anhydro-5-*O*-methoxycarbonyl-D-xylitol (570 mg, 2.34 mmol) in pyridine (10 mL) was added mesyl chloride (0.46 mL, 4.68 mmol). After 4 h at ambient temperature, the solution was poured over ice and extracted with $CHCl_3$ (100 mL). The $CHCl_3$ solution was washed with saturated $NaHCO_3$ (100 mL), then H_2O (100 mL), ice-cold dilute H_2SO_4 until the aqueous layer remained acidic, and then H_2O, dried over $MgSO_4$, and evaporated to dryness in vacuo. A nearly colorless syrup was obtained: yield 671 mg (91%) (TLC, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.10 (s, CH_3 of Ac), 3.14 (s, CH_3 of mesyl), 3.78 (s, OCH_3), 3.82 (br m, sugar CH), 4.30 (br m, sugar CH), 5.22 (br m, sugar CH); ^{13}C NMR ($CDCl_3$) δ 20.72 (CH_3 of Ac), 38.45 (CH_3 of mesyl), 55.09 (CH_3 of MeOCO), 64.72 (C-5), 71.37 (C-1), 77.24 and 77.39 (C-3 and C-4), 81.49 (C-2), and 169.89 (C of C=O).

1,2:3,4-Dianhydro-D-ribitol (7). A solution of 2-*O*-acetyl-1,4-anhydro-3-*O*-mesyl-5-*O*-methoxycarbonyl-D-xylitol (6.6 g, 21.1 mmol) in 1 N NaOMe in MeOH (73 mL) with glacial acetic acid, and evaporated to dryness in vacuo. A $CHCl_3$ extract (100 mL) of the residue was dried over $MgSO_4$ and evaporated to dryness in vacuo. A thin syrup was obtained: yield 2.1 g (86%) (TLC, 95:5 $CHCl_3$–MeOH). This material was used in the next step without further purification.

2-Amino-1,4-anhydro-2-deoxy-D-arabinitol (8). A solution of 1,2:3,4-dianhydro-D-ribitol (1.32 g, 11.3 mmol) in concentrated NH_4OH (50 mL) was heated in a stainless-steel bomb at 100 °C for 8 h and evaporated to dryness in vacuo. A solution of the residue in EtOH (50 mL) was filtered to remove an insoluble solid and evaporated to dryness, giving an orange syrup: yield 1.32 g (87%) (TLC, MeOH); ^{13}C NMR (Me_2SO-d_6) δ 58.71 (C-2), 61.67 (C-5), 72.27 (C-1), 78.24 and 86.41 (C-3 and C-4).

2-(5-Amino-6-chloro-4-pyrimidinylamino)-1,4-anhydro-2-deoxy-D-arabinitol (9). A solution of 2-amino-1,4-anhydro-2-deoxy-D-arabinitol (2.26 g, 17 mmol), 5-amino-4,6-dichloropyrimidine (2.79 g, 17 mmol), and triethylamine (2.38 mL, 17 mmol) in 1-butanol (300 mL) was refluxed for 6 days and evaporated to dryness in vacuo. A solid weighing 5.44 g was obtained. A solution of the solid in MeOH (15 mL) was applied to a column of Biosil A (250 g). Elution of the column with 9:1 $CHCl_3$–MeOH gave the product as a white crystalline solid, yield 2.76 g (61%).

The analytical sample was obtained by recrystallization from MeOH–$CHCl_3$: yield 2.06 g (45%); mp 199–201 °C; UV; λ_{max} (pH 1) 305 (13.1), (pH 7, 13) 262, 292, (8.52, 9.70) nm; TLC, 9:1 $CHCl_3$–MeOH; ^1H NMR (Me_2SO-d_6) δ 3.6 (m, H_1', H_4', and H_5'), 4.1 (m, H_1' and H_3'), 4.3 (m, H_2'), 4.8 (t, $C_5'OH$), 5.1 (s, NH_2), 5.35 (d, $C_3'OH$), 6.9 (d, NH), 7.8 (s, H_2); ^{13}C NMR (Me_2SO-d_6) δ 59.63 (C_2'), 61.42 (C_5'), 70.74 (C_1'), 75.88 (C_3'), 85.68 (C_4'), 123.60 (C_5), 137.16 (C_6), 145.65 (C_2), 151.64 (C_4).

Anal. Calcd for $C_9H_{13}ClN_4O_3$: C, 41.47; H, 5.03; N, 21.49. Found: C, 41.24; H, 4.81; N, 21.68.

2-(6-Chloro-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (10). A suspension of 2-(5-amino-6-chloro-4-pyrimidinylamino)-1,4-anhydro-2-deoxy-D-arabinitol (920 mg, 3.52 mmol) in triethylorthoformate (17 mL) containing concentrated HCl (0.4 mL) was stirred for 16 h at ambient temperature. Another 0.6 mL of concentrated HCl was added, and stirring was continued for 1 h before the solid was collected by filtration to give 836 mg of white solid. Evaporation of the filtrate and trituration of the residue with ether gave a second crop of 156 mg: total yield 992 mg (84%). The analytical sample was obtained by recrystallization from EtOH: mp 192–194 °C, UV, λ_{max} (pH 1, 7) 265 (935), (pH 13) 257 (8.55) nm; TLC 9:1 $CHCl_3$–MeOH; ^1H NMR (Me_2SO-d_6) δ 3.7 (m, H_4' and H_5'), 4.2 (d, 2 H_1'), 4.5 (m, H_3'), 5.1 (q, H_2'), 5.8 (m, C_3'-OH), 8.75 and 8.8 (H_2 and H_8).

Anal. Calcd for $C_{10}H_{11}ClN_4O_3$: C, 44.37; H, 4.10; N, 20.70. Found: C, 44.69; H, 4.47; N, 20.74.

2-(6-Amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (11) and 2-(6-Ethoxy-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (12). A solution of 2-(6-chloro-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol (651 mg, 2.4 mmol) in 125 mL of EtOH–NH_3 (saturated at 0 °C) was heated in a stainless-steel bomb at 80 °C for 20 h and then evaporated to dryness in vacuo, giving 784 mg of a white solid. The solid was purified by chromatography on silica gel plates using 9:1 $CHCl_3$–MeOH as the developing solvent. Elution of the slower moving band with MeOH gave 2-(6-amino-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol as a white crystalline solid: yield 406 mg (67%); mp 220–221 °C. The analytical sample was obtained by recrystallization from MeOH; mp 221–222 °C; UV, λ_{max} (pH 1) 258 (14.2), (pH 7, 13) 260 (14.4) nm; ^1H NMR (Me_2SO-d_6) δ 3.7 (m, H_4' and 2 H_5'), 4.2 (m, 2 H_1'), 4.5 (m, H_3'), 5.0 (m, H_2' and $C_5'OH$), 5.9 (d, $C_3'OH$), 7.4 (s, NH_2), 8.24 and 8.28 (2 s, H_2 and H_8).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.22; N, 27.87. Found: C, 47.67; H, 5.52; N, 28.19.

Elution of the faster moving band with MeOH gave 2-(6-ethoxy-9-purinyl)-1,4-anhydro-2-deoxy-D-arabinitol as a white crystalline solid, yield 72 mg (11%). Recrystallization from ethanol gave the analytical sample: mp 183–184 °C; UV, λ_{max} (pH 1, 7, 13) 252 (11.7) nm.

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.05; H, 5.82; N, 20.10.

1,4-Anhydro-2-deoxy-2-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-D-arabinitol (15). A solution of the urea 16 (427 mg, 1.56 mmol) in concentrated NH_4OH (40 mL) was heated at 100 °C for 30 min and evaporated to dryness in vacuo. An aqueous solution of the residue was neutralized with 0.3 N HCl before an aqueous solution of $Pb(OAc)_3$·$3H_2O$ (4.68 mmol) was added. The resulting cloudy solution was filtered and the filtrate treated with an excess of concentrated NH_4OH. The precipitate that formed was collected by filtration, washed with H_2O, and dissolved in 20% aqueous acetic acid (25 mL). The solution was treated with H_2S, and the black precipitate of PbS was removed by filtration. Evaporation of the filtrate gave 145 mg of a white glass that was chromatographed on silica gel plates (9:1 $CHCl_3$–MeOH). The major band was eluted with MeOH and the solution deionized with Amberlite IR-120 (H^+) ion-exchange resin before evaporation to yield a white glass: yield 124 mg (40%); UV, λ_{max} (pH 1, 7) 267 (9.82), (pH 13) 266 (7.34) nm; ^1H NMR (Me_2SO-d_6) δ 3.5 (m, H_4' and 2 H_5'), 3.9 (m, 2 H_1'), 4.1 (m, H_3'), 4.8 (m, H_2' and $C_5'OH$), 5.6 (m, $C_3'OH$ and H_5), 7.6 (d, $J_{5,6}$ = 8 Hz, H_6). After addition of D_2O, the multiplet at 5.6 became a doublet ($J_{5,6}$ = 8 Hz).

Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.36; H, 5.30; N, 12.28. Found: C, 47.68; H, 5.56; N, 11.98.

1,4-Anhydro-2-deoxy-2-[3-(3-ethoxyacryloyl)ureido]-D-arabinitol (16). To a cold (−14 °C) solution of 2-amino-1,4-anhy-

dro-2-deoxy-D-arabinitol (666 mg, 5 mmol) in DMF (50 mL) was slowly added 24 mL of a benzene solution containing 5 mmol of β-ethoxyacryloyl isocyanate[16] at such a rate as to keep the temperature of the reaction solution below −10 °C. The resulting solution was kept for 1 h at −10 °C and then 18 h at ambient temperature before it was evaporated to dryness. The residue was purified by silica gel plates using 9:1 $CHCl_3$–MeOH as the developer. The product was obtained as a glass by elution with MeOH: yield 692 mg (44%).

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Registry No.—1, 53448-53-6; 2, 64332-64-5; 3, 64345-58-0; 4, 64332-65-6; 5, 64332-66-7; 6, 64332-67-8; 7, 64332-68-9; 8, 64332-69-0; 9, 64332-70-3; 10, 64332-71-4; 11, 64395-31-9; 12, 64332-72-5; 14, 57796-78-8; 15, 64332-73-6; 16, 64332-74-7; mesyl chloride, 124-63-0; 5-amino-4,6-dichloropyrimidine, 5413-85-4.

References and Notes

(1) Y. Nakai and G. A. LePage, *Cancer Res.*, **32**, 2445 (1972).
(2) L. L. Bennett, Jr., and D. L. Hill, *Mol. Pharmacol.*, **11**, 803 (1975).
(3) Y. F. Shealy, J. D. Clayton, and C. A. O'Dell, *J. Heterocycl. Chem.*, **10**, 601 (1973).
(4) J. A. Montgomery, M. C. Thorpe, S. D. Clayton, and H. J. Thomas, *Carbohydr. Res.*, **32**, 404 (1974).
(5) J. A. Montgomery, S. D. Clayton, and H. J. Thomas, *J. Org. Chem.*, **40**, 1923 (1975).
(6) J. A. Montgomery and H. J. Thomas, Abstr. SERACS Meeting, Charleston, S.C., Nov. 1973.
(7) C. V. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5247 (1958).
(8) J. A. Montgomery and S. D. Clayton, *J. Carbohydr., Nucleosides, Nucleotides*, **2**, 147 (1975).
(9) H. J. Jennings, *Can. J. Chem.*, **49**, 1355 (1971).
(10) S. Soltzberg, R. M. Goepp, Jr., and W. Freudenberg, *J. Am. Chem. Soc.*, **68**, 919 (1946).
(11) R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, and R. M. Goepp, Jr., *J. Am. Chem. Soc.*, **68**, 927 (1946).
(12) O. Kjølberg, *Acta Chem. Scand.*, **14**, 1118 (1960).
(13) E. J. Hedgley and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **86**, 1576 (1964).
(14) R. E. Schaub and M. J. Weiss, *J. Am. Chem. Soc.*, **80**, 4683 (1958).
(15) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5247 (1958).
(16) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 157 (1958).
(17) Y. F. Shealy and C. A. O'Dell, *J. Heterocycl. Chem.*, **13**, 1015 (1976).

Purine *N*-Oxides. 65. On the Mechanisms of the Reactions of 3-Acetoxyxanthine[1]

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The redox chemistry of 3-acetoxyxanthine, a model "activated ester" for the proximate form of the oncogen 3-hydroxyxanthine, has been explored. The results indicate that the oxidizing reactivity of the ester, previously attributed to the participation of a radical intermediate, is instead due to reactions at the electron-deficient nitrogen of an intermediate of the S_N1' 8-substitution reaction. A two-step reaction sequence is proposed for the reduction of the nitrenium ion in the presence of iodide and thiourea. 8-Iodoxanthine is shown not to be an intermediate in the reduction by iodide ion. Studies with formate, acetate, and phosphate buffers at pH's 4.0, 5.0, and 7.0, respectively, show that changes in the concentration of each buffer system elicit different responses in the reactions of 3-acetoxyxanthine. The combined studies provide support for a unifying mechanism for competitive redox and C-substitution reactions from a single ambident electrophile. It is proposed that redox reactions are frontier orbital controlled and result from soft–soft interactions at the nitrenium ion, while C-substitution reactions are charge controlled and occur via hard–hard interactions at the carbonium ion. The proposal accommodates the observations that in the presence of 3-acetoxyxanthine certain nucleophiles undergo oxidation only, other nucleophiles lead only to C-8 substitution, while some may participate in both types of reaction.

3-Hydroxyxanthine (**5**) (Scheme I) and certain related purine *N*-oxides are potent oncogens.[2-6] Studies to elucidate the mechanism of cancer induction by **5** have shown that while 3-hydroxyxanthine itself is relatively inert chemically its esters are extremely reactive.[7-11] Esterification in vivo is apparently a prerequisite for the initiation of oncogenesis.[6,12,13] 3-Acetoxyxanthine (**1**) was selected as a model ester for in vitro studies of the presumed "activated" or "proximate" form of 3-hydroxyxanthine.[10,11] Those studies demonstrated the diversity of spontaneous reactions that **1** can undergo, the high reactivity of **1** with nucleophiles,[10] and the strong influence that pH, temperature, and dielectric constant of the medium can exert on the course of these reactions.[11] The reaction with nucleophiles, designated the "3-acyloxypurine 8-substitution reaction",[11] can proceed by either of two routes, paths a and b (Scheme I), depending upon the pH of the medium. A second reaction of **1**, reduction to xanthine (**4**), was observed to be a characteristic only of path b. A radical anion (**3**) was proposed as an intermediate in this reduction, based in part on the quantitative oxidation of iodide ion but not of other halide ions. We now present evidence on the mechanisms of the reactions of 3-acetoxyxanthine that indicates the nitrenium ion (**6a**) rather than the radical anion (**3**) is the agent responsible for the oxidation of iodide ion, and possibly other species as well, and propose an integrated mechanism that accounts for the predominance of redox reactions with certain nucleophiles and of 8-substitution with others.

Results

Syntheses. 3-Acetoxyxanthine (1). The reported preparation of **1**,[14] utilizing equal volumes of acetic acid and acetic anhydride, was found to give incomplete acetylation. Extended reaction times and mild heating did not improve the conversion of **5** to **1**. The addition of acetyl chloride to the reaction medium, however, induced the conversion of almost all of **5** to **1**, which was isolated in 78% yield as the hydrochloride.

8-Iodoxanthine. Attempts to prepare 8-iodoxanthine by

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