CH_2CH_3), 1.77 (d, 3, J_{PH} = 16 Hz, PCH_3), 3.68 (d, 3, J_{PH} = 12 Hz, OCH_3), 4.42 (q, 2, J_{HH} = 7 Hz, CH_2CH_3), 7.16 (d, 1, J_{PH} = 1 Hz, pyrazole H); mass spectrum (90 eV), *m/e* 232 ($M^{+\cdot}$), 217 ($M^{+\cdot} - CH_3$), 202 ($M^{+\cdot} - OCH_3$), 187 ($M^{+\cdot} - OCH_2CH_3$).

Anal. Calcd for $C_8H_{13}N_2O_4P$: C, 41.38; H, 5.65; N, 12.07. Found: C, 41.32; H, 5.66; N, 12.10.

Triazoles 8a and 8b. *tert*-Butyl azidoacetate[5] (5.86 g, 37.3 mmol) and 1 (4.4 g, 37.3 mmol) were heated in refluxing benzene (25 mL) for 36 h. Removal of the solvent gave a mixture (by NMR) of triazoles **8a** (ca. 75%) and **8b** (ca. 25%). The mixture was chromatographed on silica gel (95:5 cyclohexane ethyl acetate). Fraction 1, **8b**: 2.20 g (7.99 mmol, 21.43%); mp 81-83 °C; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9, $C(CH_3)_3$), 1.78 (d, 3, J_{PH} = 16 Hz, PCH_3), 3.67 (d, 3, J_{PH} = 12 Hz, OCH_3), 5.42 (s, 2, NCH_2), 7.88 (s, 1, triazole H); mass spectrum (FI), *m/e* 276 ($M^{+\cdot}$ + H), 202 ($M^{+\cdot} - (CH_3)_3CO$, major).

Anal. Calcd for $C_{10}H_{18}N_3O_4P$: C, 43.63; H, 6.60; N, 15.27. Found: C, 43.36; H, 6.50; N, 15.54.

Fraction 2, **8a**: 7.04 g (25.57 mmol, 68.56%); mp 113-114 °C; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9, $C(CH_3)_3$), 1.83 (d, 3, J_{PH} = 15 Hz, PCH_3), 3.68 (d, 3, J_{PH} = 12 Hz, OCH_3), 5.17 (s, 2, NCH_2), 8.24 (s, 1, triazole H); mass spectrum (FI), *m/e* 276 ($M^{+\cdot}$ + H), 202 ($M^{+\cdot} - (CH_3)_3SO$, trace).

Anal. Calcd for $C_{10}H_{18}N_3O_4P$: C, 43.63; H, 6.60; N, 15.27. Found: C, 43.70; H, 6.60; N, 15.22.

Registry No. 1, 72275-56-0; 2, 1066-52-0; 3, 72283-20-6; 4, 72275-57-1; 5, 72275-58-2; 6, 72275-59-3; 7, 72275-60-6; 8a, 72275-61-7; 8b, 72275-62-8; dimethyl methylphosphonate, 756-79-6; benzhydroximic acid chloride, 698-16-8; 4-chlorobenzhydroximic acid chloride, 28123-63-9; diethylamine, 109-89-7; 4-fluorobenzhydroximic acid chloride, 42202-95-9; ethyl diazoacetate, 623-73-4; *tert*-butyl azidoacetate, 6367-36-8; methyl chloride, 74-87-3.

(5) A. T. Moore and H. N. Rydon, *Org. Synth.*, 45, 47 (1965).

Facile Synthesis of Carbocyclic Lyxo- and Ribonucleosides

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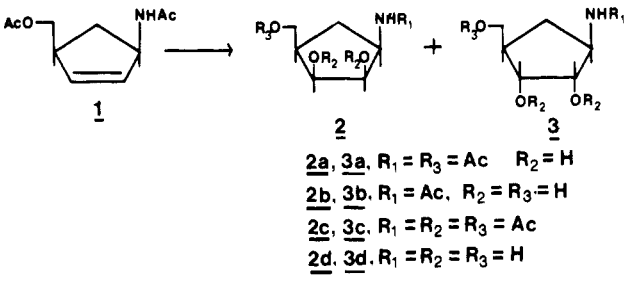
The lengthy, low-yield routes to carbocyclic adenosines which have been described[1] offer extremely limited approaches to the synthesis of new carbocyclic nucleosides, especially those requiring stereochemical modifications or substitutions in the cyclopentane ring. A recent description of an unequivocal route to (*cis*-4-acetamidocyclopent-2-ene)methyl acetate (1)[2] offers a unique starting point for the synthesis of carbocyclic nucleosides of known geometric configuration. For example, we have recently reported the conversion of **1** to a variety of carbocyclic arabinosylpurine nucleosides[2,3] and aminonucleosides[2] via the corresponding epoxide.

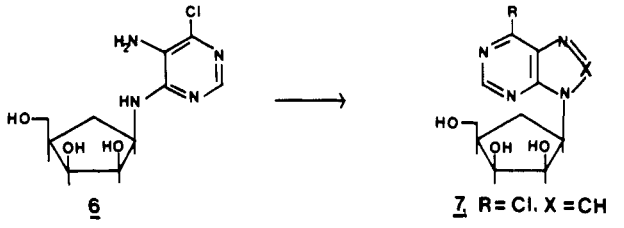
The present report provides an account of a facile route to the carbocyclic ribofuranosylpurines and the previously unattainable lyxofuranosylpurines. Thus, a catalytic osmium tetraoxide cis dihydroxylation of olefin (1) was employed using *N*-methylmorpholine *N*-oxide to regenerate OsO_4 during glycolization.[4] The initial glycolization products **2a** and **3a** (not isolated) were formed in a 2:1 ratio (Scheme I). A convenient separation of products from this mixture was based on the behavior of amides **2a** and **3a** in dilute hydrochloric acid. It is well-known that acid-catalyzed hydrolysis of an amide is remarkably facilitated by the presence of an adjacent cis-hydroxyl group because of acyl migration.[5] Mild acidic hydrolysis of the reaction mixture resulted in formation of the amino alcohol **2d** and the amide **3b** which were separated on a cation exchange resin.

Scheme I



2a, **3a**, $R_1 = R_3 = Ac$ $R_2 = H$
2b, **3b**, $R_1 = Ac$, $R_2 = R_3 = H$
2c, **3c**, $R_1 = R_2 = R_3 = Ac$
2d, **3d**, $R_1 = R_2 = R_3 = H$

Scheme II



7, R = Cl, X = CH
8, R = NH_2, X = CH
9, R = Cl, X = N
10, R = NH_2, X = N

In a separate experiment the product mixture obtained from the oxidation of **1** (before acid treatment) was acetylated and gave a mixture of **2c** and **3c** as a syrup (89%). Such mixtures exhibited two NH resonances (^1H NMR) but could not be separated on TLC or by crystallization. In a third experiment, the product mixture from oxidation of **1** was treated with methanolic ammonia, and the resulting mixture of triols **2b** and **3b** was separated on silica gel eluted with 5-15% methanol-methylene chloride. The **2b** was eluted from the column first as a glass which could not be crystallized. We concluded that the mild acidic hydrolysis followed by resin separation of the lyxo and ribo isomers was the method of choice. The amide triol **3b** (mp 117-117.5 °C) was identical with an authentic sample supplied by Y. F. Shealy.[6] Acid hydrolysis of **3b** gave the aminetriol **3d**, which is easily converted to carbocyclic adenosine as previously described.[6]

Amine **2d** was condensed with 5-amino-4,6-dichloropyrimidine and gave the pyrimidine **6** (90%) (Scheme II), a key intermediate for the synthesis of carbocyclic lyxofuranosylpurines. Ring closure with diethoxymethyl acetate converted **6** to the 6-chloropurine **7** (not isolated). Reaction of the chloropurine with ammonia gave (±)-9-[2α,3α-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-adenine (carbocyclic lyxofuranosyladenine) (**7**) in good yield (71%) as a crystalline solid after brief treatment with

(1) (a) Y. F. Shealy, J. D. Clayton, and C. A. O'Dell, *J. Heterocycl. Chem.*, **10**, 601 (1973), and references cited therein; (b) A. Holy, *Collect. Czech. Chem. Commun.*, **41**, 647, 2096 (1976); (c) R. Marumoto, Y. Yoshioka, Y. Furukawa, and M. Honjo, *Chem. Pharm. Bull.*, **24**, 2624 (1976); (d) Y. F. Shealy and C. A. O'Dell, *J. Heterocycl. Chem.*, **13**, 1015, 1041, 1353 (1976).

(2) (a) S. Daluge and R. Vince, *Tetrahedron Lett.*, 3005 (1976); (b) S. Daluge and R. Vince, *J. Org. Chem.*, **43**, 2311 (1978).

(3) H. J. Lee and R. Vince, *J. Pharm. Sci.*, in press.

(4) V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, 1973 (1976).

(5) G. Fodor and J. Kiss, *J. Chem. Soc.*, 1589 (1952).

(6) Y. F. Shealy and J. D. Clayton, *J. Am. Chem. Soc.*, **91**, 3075 (1969).

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dilute acid to remove ethoxymethylidenes and acetates formed during the ring-closure reaction.

The 8-azapurine analogue was obtained by ring closure of **6** with sodium nitrite and hydrochloric acid. The corresponding intermediate (**9**) was converted in good yield (73%) to (±)-7-amino-3-[2α,3α-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-*vic*-triazolo[4,5-*d*]pyrimidine (**10**).

Experimental Section

Thin-layer chromatography (TLC) was done using 0.25-mm layers of Merck silica gel 60F-254, and column chromatography on Merck silica gel 60. Melting points were determined with a Mel-Temp apparatus and are uncorrected. UV spectra were taken with a Beckman 25 spectrophotometer, IR spectra with a Perkin-Elmer 237B spectrophotometer, NMR spectra with a Varian A-60D or a Varian T-60 spectrometer using an internal standard of tetramethylsilane, and mass spectra with an AEI-Scientific Apparatus Limited MS-30 mass spectrometer. Low-resolution mass spectra were obtained for all compounds, and the molecular ion and fragmentation patterns were reasonable. Samples were dried at 56 °C (0.1 mm) before analysis.

Catalytic Osmium Tetraoxide Oxidation of 1. Isolation of (±)-4α-Amino-2α,3α-dihydroxy-1α-cyclopentanemethanol (2d) and (±)-4β-Acetamido-2α,3α-dihydroxy-1β-cyclopentanemethanol (3b). The method used is a modification of the procedure described in ref 4. To a stirred solution of *N*-methylmorpholine *N*-oxide[7] (15.32 g, 100 mmol as dihydrate) and 0.02 M OsO_4 in *tert*-butyl alcohol[8] (50 mL, 1 mmol) in water (50 mL) under N_2 atmosphere was added a solution of **1** (19.72 g, 100 mmol) in *tert*-butyl alcohol (50 mL). The resulting black mixture (no exothermicity noted on rapid addition of **1**) was quickly brought to 85–90 °C (oil bath), at which time the black color (indicating osmate ester) was replaced by a clear yellow solution (indicating rapid reoxidation of osmate ester to osmium tetraoxide by *N*-methylmorpholine *N*-oxide).[9] After 30 min at 85–90 °C, the black color suddenly reappeared (indicating that all of the *N*-oxide had been consumed). The reaction mixture was evaporated to a black[10] syrup from which portions of toluene (3 × 200 mL) were evaporated to remove *N*-methylmorpholine. The residue was dissolved in 2 N HCl (1 L) and maintained at 70 °C for 1 h. This solution was evaporated to dryness, and the residual black syrup redissolved in H_2O (250 mL) and passed slowly through a column of Dowex 1-X8-50 (OH^- form) resin (500 mL). The black osmium-containing material remained on the column. The colorless basic aqueous eluent (2 L) was passed slowly through a column of Dowex 50W-X4 cation exchange resin. The aqueous eluent (3 L) was evaporated, leaving **3b** as a chromatographically homogeneous colorless glass (6.52 g, 35%) which crystallized to white granules from absolute EtOH: mp 117–117.5 °C; mmp (with authentic sample from Y. F. Shealy having having mp 116–117 °C) 116–117.5 °C; IR (KBr) identical with that of the authentic sample. In an identical run the yield of **3b** was 38%.

Elution of the resin column with 2 N NH_4OH (1 L) and evaporation in vacuo gave crude **2d** as a pale yellow syrup (7.65 g, 52%)[11] which was sufficiently pure for use. In an identical run the yield of crude **2d** was 45%. Attempts to solidify **2d** were unsuccessful.

A small sample of **2d** (200 mg) was acetylated in acetic anhydride (5 mL) and pyridine (5 mL) at room temperature overnight and gave 4α-acetamido-2α,3α-diacetoxy-1α-cyclopentanemethyl acetate (**2c**, 198 mg), mp 116–116.5 °C. The IR and NMR spectra of **2c** were identical with those of an authentic sample;[2b] mmp with authentic sample 115–116 °C.

(±)-5-Amino-4-[[2α,3α-dihydroxy-4α-(hydroxymethyl)-cyclopent-1α-yl]amino]-6-chloropyrimidine (6). A freshly prepared sample of **2d** (11.3 g, ca. 76.8 mmol), 5-amino-4,6-dichloropyrimidine (25.2 g, 153 mmol), triethylamine (53 mL), and 1-butanol (350 mL) were refluxed under N_2 for 24 h. The solution was evaporated to dryness, and the residue was partitioned between H_2O (500 mL) and $CHCl_3$ (250 mL). The aqueous layer was separated and extracted with additional $CHCl_3$ (3 × 70 mL). The combined $CHCl_3$ layers showed only 5-amino-4,6-dichloropyrimidine on TLC. The aqueous layer was stirred briefly with IRA-400 (OH^-) resin (125 mL). The H_2O was then evaporated, leaving a yellow solid foam which could not be crystallized. The crude product was purified by passing quickly through a silica gel column (150 g) eluted with 10–15% MeOH–CH_2Cl_2 (2 L), giving **6** as a pale yellow solid foam (18.9 g, 90%), sufficiently pure for use. A portion of such a sample was further purified by chromatography on preparative silica gel plates developed with 15% MeOH–CH_2Cl_2. Extraction of the major band (several minor bands of greater R_f were discarded) with 20% MeOH–CH_2Cl_2 gave an analytical sample of **6** as white solid foam (84% recovery from plates): IR (KBr) 3300 (br, OH, NH), 1650 (sh, NH), 1580 (br, C=C, C=N) cm^{-1}.

Anal. Calcd for $C_{10}H_{15}ClN_4O_3$: C, 43.72; H, 5.50; Cl, 12.91; N, 20.40. Found: C, 43.55; H, 5.29; Cl, 12.80; N, 20.68.

(±)-9-[2α,3α-Dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (8). A solution of **6** (8.80 g, 32.0 mmol) in diethoxymethyl acetate (100 mL) was stirred at room temperature overnight and then at 100 °C for 1 h. The solution was evaporated to dryness, and the residue shaken with NH_3 (200 mL) in a stainless steel bomb at room temperature overnight.[12] The NH_3 was allowed to evaporate, and the residue was dissolved in 1 N HCl (300 mL) and stirred at 60 °C for 45 min. The solution was evaporated to dryness, redissolved in H_2O (250 mL), and stirred with Dowex 1-X8-50 resin (OH^-, 250 mL). The resin was removed by filtration and washed with H_2O (3 × 250 mL). The combined aqueous fractions were evaporated to a residual gum. The crude product was triturated with absolute EtOH and gave 6.00 g (71%) of **8** as a chromatographically homogeneous white powder, mp 226–228 °C dec. Crystallization from H_2O gave **8** as fine white needles (46%): mp 248–257 °C dec; IR (KBr) 3410, 3310, 3160 (OH, NH_2), 1665, 1608, 1570 cm^{-1} (adenine); ^1H NMR (Me_2SO-d_6) δ 8.15, 8.10 (both s, 2.0, 2 purine CH), 7.13 (br s, 2.0, NH_2), 5.3–4.7 (m, 3.1, 2 OH, CHO), 4.48 (br t, J = 10 Hz, 1.1, CH_2OH), 4.2–4.0 (m, 1.9, CHO, CHN), 4.8–3.3 (m, 2.3, CH_2OH, H_2O in solvent), 2.5–1.5 (m, 3.0, CH, CH_2).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.71; H, 5.66; N, 26.66.

(±)-7-Amino-3-[2α,3α-dihydroxy-4α-(hydroxymethyl)-cyclopent-1α-yl]-*vic*-triazolo[4,5-*d*]pyrimidine (10). To a cooled (ice bath) solution of **6** (3.06 g, 11.1 mmol) in 1 N HCl (25 mL) was added solid $NaNO_2$ (923 mg, 13.4 mmol). The ice bath was removed after 20 min. After a total of 1 h, concentrated NH_4OH (40 mL) was added, and the solution refluxed gently for 40 min.[12,13] The solution was concentrated to 45 mL and cooled. The solid which formed was filtered off and washed with additional H_2O (10 mL), giving a tan powder (3.3 g). The powder was redissolved in boiling H_2O (70 mL), and the solution was decolorized with charcoal and cooled overnight in the refrigerator to give **10** as a white powder (2.156 g, 73%): TLC (silica gel, 20% MeOH–CH_2Cl_2) showed one spot; mp 244–246 °C dec; IR (KBr) 3200 (br, OH, NH_2), 1697, 1665 (sh, 1620, 1578 (C=C, C=N) N=N) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.17 (s) overlapped by 8.12 (br s, 3.0, purine CH, NH_2), 5.6–3.0 (m, 8.1, 3 OH, 2 CHO, 2CHO, CHN, CH_2O), 3.0–2.0 (m, overlaps Me_2SO-d_5, CH_2, CH).

Anal. Calcd for $C_{10}H_{14}N_6O_3$: C, 45.11; H, 5.30; N, 31.56. Found: C, 44.82; H, 5.19; N, 31.76.

(7) Prepared as in ref 4, except that an equivalent amount of 30% H_2O_2 was used instead of 50%. It was assumed that the product was a dihydrate.

(8) K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, 98, 1986 (1976).

(9) When an attempt was made to carry out this reaction at room temperature, as described in ref 4, there was no reaction after 1 h and very low conversion after 18 h. At room temperature the initially formed black color remains throughout the reaction period. This indicates that osmate ester forms but is very slow to reoxidize and cleave under these conditions.

(10) Repeated attempts to remove osmium as described in ref 4 and 8 or by chromatography on silica gel were incomplete and time-consuming on a large scale.

(11) The ratio of **2d**:**3b** was lower (ca. 1:1) when the oxidation was carried out at room temperature. However, appreciable olefin remained even after 18 h at room temperature.

(12) Earlier attempts to use liquid ammonia for this step resulted in mixtures (indicated by TLC) which contained **10**. The product was sufficiently contaminated to prevent solidification.

(13) An attempt to isolate and purify the chloropurine **9** by chromatography was unsuccessful; the compound appeared to be decomposing on the column.

Acknowledgment. This investigation was supported by Grants CA13592 and CA23263 from the National Cancer Institute, Department of Health, Education, and Welfare.

Registry No. 1, 61865-50-7; **2c**, 65941-40-4; **2d**, 72301-31-6; **3b**, 72345-98-3; **3c**, 24587-83-5; **6**, 72345-99-4; **8**, 72346-00-0; **10**, 72346-01-1.

Aralkylation of Guanosine by the Carcinogen *N*-Nitroso-*N*-benzylurea

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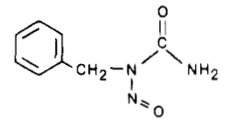
Our recent investigations[1] of the solvent effects on sites of reaction on adenosine and guanosine with benzyl bromide, benzyl chloride, and benzyl tosylate led us to suggest that alkylation and aralkylation of exocyclic sites on nucleoside purine residues (i.e., N^6 of adenosine as well as N^2 and O^6 of guanosine) are favored by changes in substrate structure or reaction medium which advance carbon-leaving group bond breakage and thus reduce the sensitivity of the substrate to the nucleophilicity of ring nitrogen sites (e.g., N-1 of adenosine and N-7 of guanosine). In addition, the positive charge density or "hardness"[2] of the reaction center determines the ratio of reaction at the O^6 and N^2 sites on guanosine: when the center is "soft", reaction with the exocyclic amino group is favored. Higher charge density, creating a "harder" center, directs a greater portion of the total reaction to exocyclic oxygen.

N-Nitroso-*N*-benzylurea (1) has recently been shown to be a potent, locally acting carcinogen.[3] As an aralkyl nitrosourea its reaction with nucleosides would be expected to result in the transfer of a benzyl moiety through an intermediate benzyldiazonium ion.[4] This should render this benzylating agent less susceptible to the nucleophilicity of ring nitrogen sites than the agents examined previously[1] and should, in addition, impose the highest positive charge density on the benzylic carbon reaction center. Consequently, under similar solvent conditions, we would expect that, of the four benzylating agents, the reactions of **1** with guanosine and adenosine would yield the highest ratio of exocyclic-substituted/ring-substituted products and the highest ratio of O^6/N^2 substitution with guanosine. The data we present here demonstrate that these expectations are met. Furthermore, the type and distribution of nucleoside adducts resulting from reaction with **1** should be common to reactions of other carcinogens (e.g., the unsymmetrical alkylbenzylnitrosamines)[5] whose interactions with nucleic acid components could proceed through a benzyldiazonium ion intermediate.



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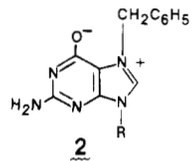

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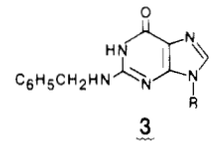

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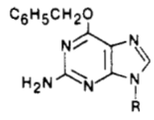

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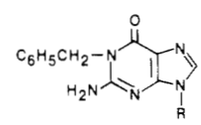

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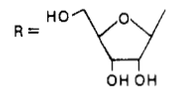

Reactions of guanosine with **1** yielded four products, 7-benzylguanosine (**2**), N^2-benzylguanosine (**3**), O^6-benzylguanosine (**4**), and 1-benzylguanosine (**5**). Product distributions as a function of solvent composition are presented in Table I. These data, presented as percentage of radioactive guanosine converted to benzylated product, were collected after 24-h reaction incubations. Since the half-life of *N*-nitroso-*N*-benzylurea is far less than 24 h under all solvent conditions employed here, these percentages (Table I) represent the extent of nucleoside benzylation at reaction completion. Most of **1** reacts with the solvent under these conditions.

The data of Table I show that for the reaction of *N*-nitroso-*N*-benzylurea with guanosine in 99% aqueous solution, the major sites of reaction are N-7 and *both* the exocyclic amino and oxo group of the purine residue, i.e., the N^2 and O^6 positions. Furthermore, reaction at these exocyclic sites is significantly more extensive than reaction at ring nitrogen. Changes in solvent composition from 1% *N*,*N*-dimethylformamide (DMF) in water to either 60% DMF or 60% ethanol (EtOH) in water caused a decrease in the yield of benzylated products, but these same solvent changes had little effect on product ratios presumably because the neutral leaving group in this case, N_2, is little affected by the electrophilic (anionic solvating) properties of the solvent. These results differ significantly from those obtained previously with benzylating agents bearing anionic leaving groups.[1] With these latter agents, increases in the water content of the solvent mixtures dramatically increased the exocyclic-substitution/ring-substitution ratios.

Reactions of guanosine with **1** in the four least aqueous solvents afforded substantially different product distributions. In either 80% DMF or 80% EtOH in water as well as absolute DMF and EtOH, benzylation at the N-1 position of guanosine was observed and reaction at this site was accompanied by an increased extent of reaction at the O^6 position. Indeed, the greatest amounts of **4** and **5** were obtained in dry DMF solution. Substitution at the exocyclic amino group was not observed in DMF, and, although it was detectable in EtOH, the yield of **3** in this solvent was the lowest observed in the EtOH–water series. The observation that reaction at O^6 is accompanied by reaction at N-1 in the least aqueous solutions points to the involvement of guanosine anion under these conditions while reaction at O^6 in the more aqueous solvents (where it is not accompanied by N-1 substitution) probably results

(1) R. C. Moschel, W. R. Hudgins, and A. Dipple, *J. Org. Chem.*, **44**, 3324 (1979).
(2) R. G. Pearson in "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Eds., Plenum Press, London, 1972, p 281.
(3) S. Ivankovic, *Z. Krebsforsch.*, **91**, 63 (1978).
(4) Reaction of **1** with 2-aminopyridine in aqueous solution has been examined: P. L. Skipper, S. R. Tannenbaum, J. E. Baldwin, and A. Scott, *Tetrahedron Lett.*, 4269 (1977).
(5) H. Druckrey, R. Preussmann, S. Ivankovic, and D. Schamal, *Z. Krebsforsch.*, **69**, 103 (1967).

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