Experimental Section

TLC was routinely performed on Eastman 13181 silica or 13254 cellulose as detailed in Table I. Melting points were determined on a Mel-Temp apparatus in sealed, Pyrex capillaries and are corrected. The spectrometers used were as follows: Cary 15 (UV), Perkin-Elmer 241MC (polarimetry) with a Lauda RC-3B refrigerated circulator, Varian T-60 (NMR).

3′,5′-Dichloromethotrexate (DCM). Methotrexate disodium salt (Lederle) (5.00 g, 11.0 mmol) was dissolved in 100 mL of glacial HOAc at 25 °C. Slow addition of 2.3 equiv of *t*-BuOCl (Frinton) in 10 mL of HOAc followed by 1 h of reaction gave complete formation of DCM uncontaminated by MTX or monochloromethotrexate (MCM) by TLC. The solution was evaporated to dryness and redissolved in aqueous NaOH. The pH was lowered to 4 with concentrated HCl. The solid was filtered to give DCM (4.63 g, 80%) identical with authentic DCM (Lederle) by TLC, NMR, and UV.

Similarly, 1.1 equiv of *t*-BuOCl afforded 98% (MCM).

3-Chloro-4-(dimethylamino)benzoic Acid. To 3.3 g (20 mmol) of 4-(dimethylamino)benzoic acid (Aldrich) in 100 mL of 10% HOAc–CH_2Cl_2 was added slowly 2.3 g (21 mmol) of *t*-BuOCl in 18 mL of 20% HOAc–CH_2Cl_2 at 25 °C. After 3 h, a second addition of 0.2 mL of *t*-BuOCl in 7 mL of CH_2Cl_2 completely converted the starting material into a single product by TLC (silica). The solution was extracted twice with H_2O (150 mL), dried ($MgSO_4$), and evaporated to dryness. Recrystallization from EtOAc–hexane in two crops afforded 3-chloro-4-(dimethylamino)benzoic acid (2.66 g, 67%).

Acknowledgment. This work was supported by Research Grant No. CA 17718, awarded to Michael Chaykovsky by the National Cancer Institute, Department of Health, Eduation, and Welfare.

Registry No. Dichloromethotrexate, 528-74-5; monochloromethotrexate, 5472-96-8; methotrexate, 59-05-2; dichlorofolic acid, 47748-46-9; folic acid, 59-30-3; dimethyl *N*-(3,5-dichloro-4-aminobenzoyl)-L-glutamate, 72244-64-5; dimethyl *N*-(4-aminobenzoyl-L-glutamate, 52407-60-0; 3,5-dichloro-4-(methylamino)benzoic acid, 51928-43-9; 3-chloro-4-(methylamino)benzoic acid, 72228-73-0; 4-(methylamino)benzoic acid, 10541-83-0; 3,5-dichloro-4-(dimethylamino)benzoic acid, 72228-74-1; 3-chloro-4-(dimethylamino)benzoic acid, 72228-75-2; 4-(dimethylamino)benzoic acid, 619-84-1.

Dipolar Cycloadditions of an Acetylenic Phosphinate

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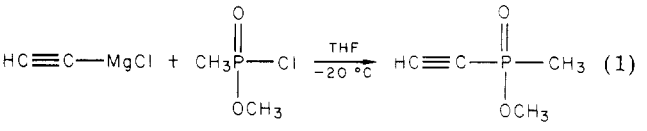
The literature abounds with methods of forming carbon–phosphorus bonds to prepare organophosphinates.[1] Although these transformations allow entry into a variety of chemical architecture, severe limitations are also encountered. For example, the Arbuzov reaction is restricted to a rather narrow range of halide types (primary, benzyl), and often stressing conditions are necessary. These problems are most acute when the carbon–phosphorus bond is formed late in a synthesis (substrates are usually multifunctional). An alternative to late incorporation of a phosphinate group is use of a small organophosphinate, with a reactive organic moiety, as an intermediate. The carbon–phosphorus bond, once formed, is quite stable and surprisingly inert to an array of conditions for carbon transformations.[1] This note describes the synthesis of such a reactive organophosphinate, acetylene **1**, and its use in the preparation of heterocyclic phosphinates.

Results

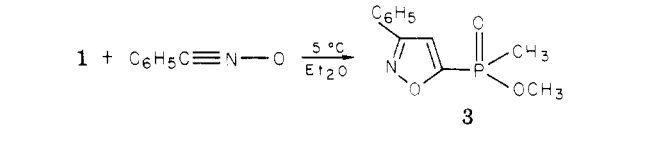
Equation 1 outlines a successful synthesis of **1**. Addition of the acetylenic Grignard at −20 °C to acid chloride **2** and workup give a 50% isolated yield of **1**. Use of lithium



2 1

acetylide significantly decreases the yield of **1**. Acetylene **1** is a water-clear, distillable liquid, stable to storage at 0 °C. The ^1H NMR spectrum of **1** is characterized by doublets at δ 1.70 and 3.88 for the methyl groups and a doublet (J_{PH} = 10 Hz) at δ 3.14 for the acetylenic proton. This material is completely miscible with water, and the water used in the workup must be continuously extracted with CH_2Cl_2 to obtain the product in good yield.

Acetylene **1** has been found to be an excellent 1,3-dipolarophile. Reaction of **1** with benzonitrile oxide and 4-chlorobenzonitrile oxide proceeds to give good yields of 5-phosphinylisoxazoles (**3**, 81%; **4**, 53%). The isoxazole



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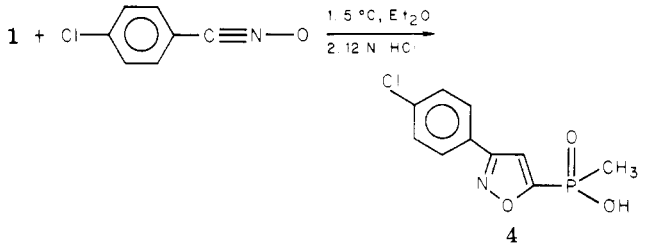

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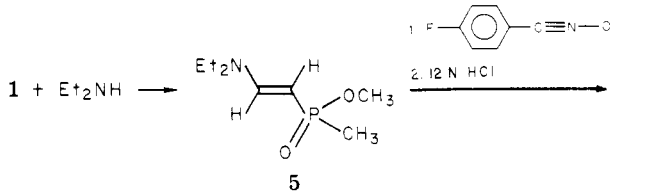

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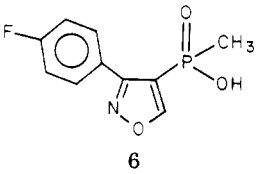

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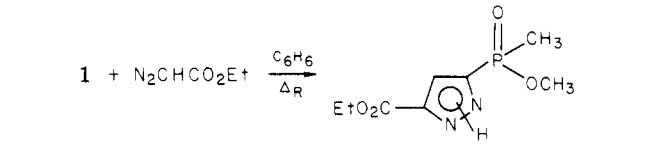

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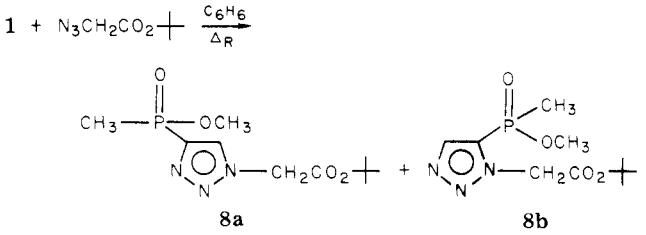

8a 8b

(1) G. M. Kosolapoff and L. Maier, Eds., "Organic Phosphorus Compounds", Vol. 6, Wiley-Interscience, New York, 1973, Chapter 14, and references therein.

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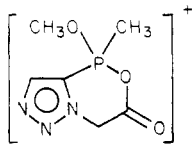
protons of **3** and **4** are observed at δ 7.41 and 7.02 in the ^{1}H NMR spectra, confirming the substitution patterns as assigned.[2] None of the 4-phosphinyl regioisomers could be detected in the crude reaction mixture or on chromatography of a sample. This substitution pattern is available via enamine phosphinate **5**. Slow addition of diethylamine to a benzene solution of **1** gives **5** as the only product. Reaction of this enamine with 4-fluorobenzonitrile oxide followed by acid hydrolysis gives isoxazole **6** in 50% yield. In contrast to **3** and **4**, the isoxazole proton of **6** appears downfield at δ 9.4 in the ^{1}H NMR spectrum.

At ambient temperature in ether, ethyl diazoacetate cycloadds to **1** to give 5-phosphinylpyrazole **7** in 80% yield. The pyrazole proton appears at δ 7.16 (doublet, J_{PH} = 1 Hz) in the ^{1}H NMR spectrum.[2] None of the 4-phosphinyl isomer is found. Unlike 4-fluorobenzonitrile oxide, ethyl diazoacetate does not cycloadd with enamine phosphinate **5**.

tert-Butyl azidoacetate also cycloadds to **1**, but with reduced regioselectivity. At 80 °C in benzene, triazoles **8a** and **8b** are formed in ca. 3:1 ratio. Structural assignments for **8a** and **8b** are based on ^{1}H NMR and mass spectral data. The triazole proton of **8a** is 0.36 ppm downfield relative to the triazole proton in **8b**, probably because of the deshielding effect of the ester carbonyl. The closer proximity of the electron-withdrawing phosphinate group causes the methylene protons of **8b** to be downfield relative to these protons in **8a**. The field ionization mass spectra of both regioisomers show a strong $M^{+\cdot}$ + H peak. The spectrum of **8b** also shows a peak of nearly equal intensity at m/e 202 resulting from loss of $(CH_3)_3COH$ from the protonated parent ion. Only the slightest indication of a peak at m/e 202 is found for **8a**. Formation of a phosphonium species such as **9** is probably the driving force for fragmentation of **8b**. Such a structure is, of course, not available for **8a**.



9

We have shown that acetylene **1** is a useful intermediate for the preparation of heterocyclic phosphinates via dipolar cycloadditions. Further studies of this compound continue.

Experimental Section

General Procedures. Melting points were determined on a Laboratory Devices Mel-temp apparatus and are uncorrected. NMR spectra were obtained on Varian T-60 and JEOLCO FX-100 spectrometers. Results are reported on the δ scale, parts per million (ppm) downfield from tetramethylsilane internal standard. Mass spectra were obtained on a Varian CH-7 mass spectrometer. Analyses were performed by the Atlantic Microlab Inc.

Acid Chloride (2). Dimethyl methylphosphonate (80 mL, 184.6 mmol) in benzene (160 mL) was cooled to 0 °C (ice–salt bath), and PCl_5 (153.7 g, 184.6 mmol) was added so that the temperature did not exceed 10 °C. After 1 h of stirring, the solvent and $POCl_3$ were removed under high vacuum. The residue was distilled to give 75 g of **2**, bp 64 °C (15 mm) [lit.[3] bp 73 °C (22 mm)].

Methyl Ethynylmethylphosphinate (1). Acetylene was passed through a trap at −78 °C (to remove acetone) and into dry THF (300 mL) cooled to −10 °C (N_2 atmosphere). Methylmagnesium chloride (100 mL of a 3.2 M solution in THF) was added to the stirred solution at a rate so that the temperature remained below −5 °C. After addition, the solution was stirred for 15 min more and then transferred under N_2 to an addition funnel. The Grignard reaction was slowly added to a cold solution of methyl methylphosphonyl chloride (**2**; 41.12 g, 0.32 mol) in dry THF (300 mL) (temperature ≤ −15 °C). After complete addition, saturated aqueous NH_4Cl was added slowly and the THF separated. Removal of the solvent gave 4.8 g of product. The water–NH_4Cl mixture was continuously extracted with CH_2Cl_2 for 48 h. Removal of the solvent gave a brown liquid. Distillation gave 18.97 g (0.161 mol, 50.2%) of acetylene **1**: bp 70 °C (0.4 mm); ^{1}H NMR δ 1.70 (d, 3, J_{PH} = 16 Hz, PCH_3), 3.14 (d, 1, J_{PH} = 10 Hz, C≡CH), 3.88 (d, 3, J_{PH} = 13 Hz, OCH_3); mass spectrum (90 eV) m/e 118 ($M^{+\cdot}$), 103 ($M^{+\cdot} - CH_3$), 88 ($M^{+\cdot} - CH_2O$), 87 ($M^{+\cdot} - OCH_3$).

Anal. Calcd for $C_4H_7O_2P$: C, 40.68; H, 5.99. Found: C, 40.49; H, 6.01.

5-(Methylmethoxyphosphinyl)-3-phenylisoxazole (3). To a cold (5 °C), stirred ether (70 mL) solution of **1** (1.0 g, 8.47 mmol) and benzhydroximic acid chloride[4] (1.32 g, 8.47 mmol) was added triethylamine (1.18 mL, 8.47 mmol). After 1 h of stirring, the mixture was filtered and the solvent removed to give an oil. Chromatography on silica gel (9:1 cyclohexane/ethyl acetate) gave 1.64 g (6.89 mmol, 81.4%) of **3** as a light yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 1.88 (d, 3, J_{PH} = 16 Hz, PCH_3), 3.80 (d, 3, J_{PH} = 12 Hz, OCH_3), 7.41 (d, 1, J_{PH} = 1 Hz, isoxazole H), 7.57 (m, 3), 7.93 (m, 2); mass spectrum (90 eV) m/e 237 ($M^{+\cdot}$), 144 [$M^{+\cdot} - PO(CH_3)(OCH_3)$].

Anal. Calcd for $C_{11}H_{12}NO_3P$: C, 55.69; H, 5.11; N, 5.91. Found: C, 55.75; H, 5.27; N, 6.13.

3-(4-Chlorophenyl)-5-(hydroxymethylphosphinyl)isoxazole (4). To a stirred, cold (5 °C) ether (200 mL) solution of **1** (4.77 g, 40.41 mmol) and 4-chlorobenzhydroximic acid chloride[4] (7.68 g, 40.41 mmol) was added triethylamine (4.09 g, 40.41 mmol). After 1 h of stirring, the solution was filtered and the solvent removed. The residue was heated in 12 N HCl (125 mL) for 12 h. A white solid that formed on cooling was collected and recrystallized from CH_2Cl_2/EtOAc to give 5.52 g (21.4 mmol, 53.02%) of **4**: mp 166–168 °C; ^{1}H NMR ($CDCl_3$) δ 1.82 (d, 3, J_{PH} = 15 Hz, PCH_3), 7.02 (d, 1, J_{PH} = 1 Hz, isoxazole *H*), 7.35 (d, 2), 7.63 (d, 2), 10.92 (broad s, 1); mass spectrum (90 eV), m/e 257 ($M^{+\cdot}$), 111 ($C_6H_4Cl^{+\cdot}$).

Anal. Calcd for $C_{10}H_9ClNO_3P$: C, 46.62; H, 3.53; N, 5.44. Found: C, 46.45; H, 3.54; N, 5.37.

3-(4-Fluorophenyl)-4-(hydroxymethylphosphinyl)isoxazole (6). To a stirred, cold (5 °C) ether (100 mL) solution of acetylene **1** (5.0 g, 42.34 mmol) was slowly added diethylamine (3.41 g, 46.57 mmol). After an initial exotherm, the solution was stirred 10 min and the solvent removed to give enamine **5** as the only product: ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 6, J_{HH} = 7.5 Hz, CH_2CH_3), 1.38 (d, 3, J_{PH} = 14 Hz, PCH_3), 3.14 (q, 4, J_{HH} = 7.5 Hz, CH_2CH_3), 3.53 (d, 3, J_{PH} = 12 Hz, OCH_3), 3.75 (dd, 1, J_{PH} = 19 Hz, J_{HH} = 14.7 Hz, H gem to P), 6.92 (t, 1, J_{PH} = J_{HH} = 14.7 Hz).

Enamine **5** was added to a cold (5 °C) ether (200 mL) solution of 4-fluorobenzhydroximic acid chloride[4] (8.08 g 40.41 mmol). Triethylamine (5.63 mL, 40.41 mmol) was added and the mixture stirred for 1 h. After filtration and solvent removal, the residue was hydrolyzed in refluxing 12 N HCl to give 4.93 g (20.44 mmol, 50.59%) of isoxazole **6**: mp 142–148 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.50 (d, 3, J_{PH} = 15 Hz, PCH_3), 7.45 (m, 2), 8.0 (m, 2), 9.4 (d, J_{PH} = 1 Hz, isoxazole H); mass spectrum (90 eV), m/e 241 ($M^{+\cdot}$), 95 ($C_6H_4F^{+\cdot}$).

Anal. Calcd for $C_{10}H_9FNO_3P$: C, 49.80; H, 3.76. Found: C, 49.80; H, 3.65.

Ethyl 3-(Methylmethoxyphosphinyl)pyrazole-2-carboxylate (7). Ethyl diazoacetate (3.87 g, 33.88 mmol) and **1** (4.0 g, 33.88 mmol) were stirred in benzene at ambient temperature for 48 h. Removal of the solvent gave a tacky solid. Recrystallization from ether gave 6.31 g (27.16 mmol, 80.2%) of **7**: mp 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3, J_{HH} = 7 Hz,

(2) For an analysis of chemical shift correlations for isoxazoles and pyrazoles see: A. Battaglia, A. Dondoni, and F. Taddei, *J. Heterocycl. Chem.*, **7**, 721 (1970); J. Elguero, R. Jacquier, and H. C. N. Tien Duc, *Bull. Soc. Chim. Fr.*, 3727 (1970); L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

(3) Z. Pelchowicz, *J. Chem. Soc.*, 238 (1961).

(4) N. A. Genco, R. A. Partis, and H. Alper, *J. Org. Chem.*, **38**, 4365 (1973).

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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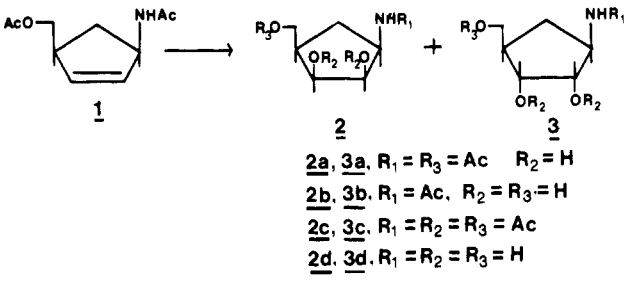
Received July 20, 1979

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.

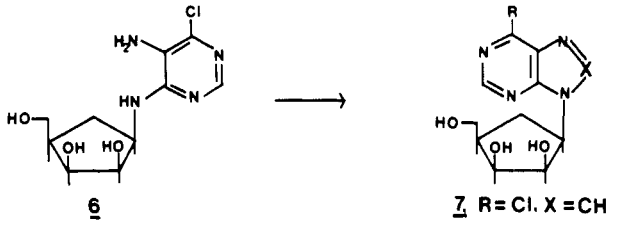
The present report provides an account of a facile route to the carbocyclic ribofuranosylpurines and the previously unattainable lyxofuranosylpurines. Thus, a catalytic osmium tetraoxide cis dihydroxylation of olefin (1) was employed using *N*-methylmorpholine *N*-oxide to regenerate OsO_4 during glycolization.[4] 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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