cedure has been used by (a) R. Grice and L. N. Owen, *J. Chem. Soc.*, 1947 (1963); (b) H. Bohme and G. Lerche, *Chem. Ber.*, **100**, 2125 (1967).

(8) (a) We are deeply indebted to Dr. Alan J. Rein of these laboratories for the Raman experiments and the interpretation of their significance. (b) We thank Dr. J. McCauley for this information.

(9) Complexes of thioanisole with (a) $AlCl_3$ and (b) $SnCl_4$ have recently been reported; see (a) G. H. Smith and F. J. Hamilton, *J. Phys. Chem.*, **72**, 3567 (1967); (b) I. P. Goldshtein, E. N. Kharlamova, and E. N. Guryanova, *Zh. Obshch. Khim.*, **38**, 1925 (1968).

(10) (a) A referee has suggested that if the aluminum chloride–methylal complex is very bulky, steric hindrance may account for the predominant product. We had discounted this possibility since the Sn, Ti, and Fe complexes should be bulkier than the one with aluminum, and should thus give even higher selectivity. Olah[11] has recently relegated steric factors to eighth in a list of eight influences on reactivity and selectivity in Friedel–Crafts chemistry. (b) The same referee has, in questioning the proposed mechanism, pointed out that a good case can be made that the thioanisole–aluminum chloride complex might be meta directing, and that it certainly should be deactivating. His first point probably rests on the well-known predominant meta direction of sulfoxides and sulfonium ions. We agree with the latter point concerning deactivation, and cite it as further evidence for complexation. The reaction is certainly slower (Table II) than would be expected for an aromatic substrate which has been reported to react 2.5 times as fast as mesitylene in electrophilic reaction.[3]

(11) G. A. Olah in "Friedel-Crafts Chemistry", Wiley, New York, N.Y., 1973, p 393.

(12) G. A. Olah and W. S. Tolgyesi in "Friedel-Crafts and Related Reactions", Vol. 2, G. A. Olah, Ed., Wiley, New York, N.Y., 1964, Part 2, Chapter XXI. See also "Aromatic Haloalkylations", Ph.D. Dissertation of D. A. Beal, Case Western Reserve University, 1973.

(13) G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

(14) After our work was completed, we happened upon a reference to the influence of, inter alia, the amount of aluminum chloride used in the chloromethylation of 2-acetyl- and 2-formylthiophene with chloromethyl methyl ether or bis(chloromethyl) ether. Variable orientation was obtained in that case also. The authors ascribed the effect to the influence of complexation with the carbonyl moiety. See L. I. Belen'kii, I. B. Karmanova, and Ya. L. Gol'dfarb, *J. Org. Chem. USSR*, **7**, 1809 (1971).

(15) R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 3610 (1961).

(16) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(17) Further evidence for a complex comes from the NMR spectrum of 1:1 aluminum chloride–thioanisole solutions. The aromatic protons are shifted selectively downfield, relative to thioanisole alone. The methyl proton singlet is also shifted downfield. The NMR spectrum of a 2:1 mole ratio of thioanisole and aluminum chloride shows chemical shifts intermediate between thioanisole and 1:1 thioanisole–aluminum chloride.

(18) V. A. Topchii and S. V. Zavgorodnii, *Zh. Org. Khim.*, **5**, 130 (1969).

(19) Commercially available reagents and solvents were used as purchased. NMR spectra were obtained on $CDCl_3$ solutions of the compounds with a Varian A-60A or Jeolco C-60HL spectrometer. The Raman spectra were obtained with a Carey Model 82 spectrometer excited with a Spectra-Physics Model 165-03 argon ion laser.

(20) We have been unable to detect the presence of either chloromethyl methyl ether or bis(chloromethyl) ether during reaction or work-up. Nevertheless, in view of the carcinogenicity of these two compounds,[4] considerable care should be exercised in experiments of this type.

(21) Some experiments were quenched *into* a large amount of water, and up to 3–5% hydrolysis of the product to the corresponding carbinol occurred. Rapid quench onto ca. 250 g of ice and water gave satisfactory results.

(22) GC analyses were run on a 6 ft × 0.125 in. S. S. column packed with 10% SP-2401 on 100/120 mesh Supelcoport, programmed from 110 to 170° at 4°/min. Thermal conductivity detection was used. The identity of the individual components was secured not only by mixed chromatograms with the pure substances, but also by GC–mass spectral methods. Quantitation of the thioanisole and **1** was by the internal standard method (tetradecane). The minor components are reported on an area percent rather than weight percent basis. We thank Mr. W. E. Tait for assay support.

Isonucleosides. I. Preparation of Methyl 2-Deoxy-2-(purin-9-yl)arabinofuranosides and Methyl 3-Deoxy-3-(purin-9-yl)xylofuranosides

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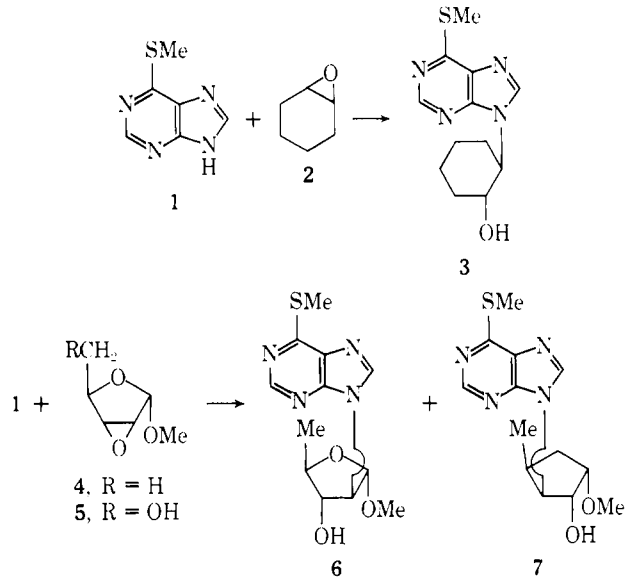
Since the reaction of 6-(methylthio)purine with methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside in the presence of base gave two products, the desired methyl 2,5-dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**6**) and methyl 3,5-dideoxy-3-[6-(methylthio)-9-purinyl]-α-D-xylofuranoside (**7**), resulting from attack by the purine anion on both C-2 and C-3 of the sugar, an alternative route to **6** and related structures was developed. The best procedure appeared to consist of reaction of 5-amino-4,6-dichloropyrimidine with **4** or **5** followed by ring closure of the resultant diaminopyrimidines to the corresponding purines. Replacement of the chloro group of **22** then gave the desired isonucleosides **23** and **24**.

In naturally occurring nucleosides and nucleotides, the purine ring is attached to C-1 of ribose or 2-deoxyribose, this linkage being part of an aminal structure, which is quite susceptive to both hydrolytic and enzymatic cleavage. The reasons for our interest in analogs of the naturally occuring nucleosides have been adequately discussed.[1] Available data indicate that if N-9 of the purine ring is attached to C-2 rather than C-1 of a pentofuranose, with the hydroxyl group at C-3 trans to the purine ring and the hydroxymethyl group at C-4 cis (see **23**), the resulting sugar derivative, which we have named isonucleoside, is likely to be a substrate for the anabolic enzyme adenosine kinase.[2] If the nucleotide is formed intracellularly by this enzyme, it may be capable of interfering with vital cellular metabolism (e.g., the biosynthesis or function of nucleic acids), and this type of structure would be of great potential interest.

Since one approach to the synthesis of such compounds is the reaction of a purine anion with the appropriate sugar epoxide, the reaction of 6-(methylthio)purine (**1**) with cyclohexene oxide (**2**) in the presence of pyridine was investigated and found to proceed satisfactorily (although the yield was low, no attempt was made to optimize it). That attack occurred as expected at N-9 of **1** to give the desired 9-(*trans*-2-hydroxycyclohexyl)-6-(methylthio)purine (**3**) (Scheme I) was demonstrated by comparing the uv spectrum of **3** with that of 7- and 9-benzyl-6-benzylthiopurine.[3] Since it is well known that epoxides open by rearward nucleophilic attack to give trans products, that aspect of the structural assignment was not open to question.

The success of the reaction of **1** with **2** caused us to study the reaction of **1** with methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside[4] (**4**), since it had been reported that attack by ammonia on **4** occurred exclusively at C-2 to give the arabino sugar derivate (**9**).[5,6] Attack by the anion of 6-(methylthio)purine on **4** was expected to give the desired arabino sugar **6** with the purine attached at C-2 and the hydroxyl at C-3 trans. The reaction of **1** with **4** proved sluggish, and more drastic conditions had to be employed than in the case with **2**. Less than half of **1** reacted and two sugar-containing products were formed (TLC). Although we original-

Scheme I

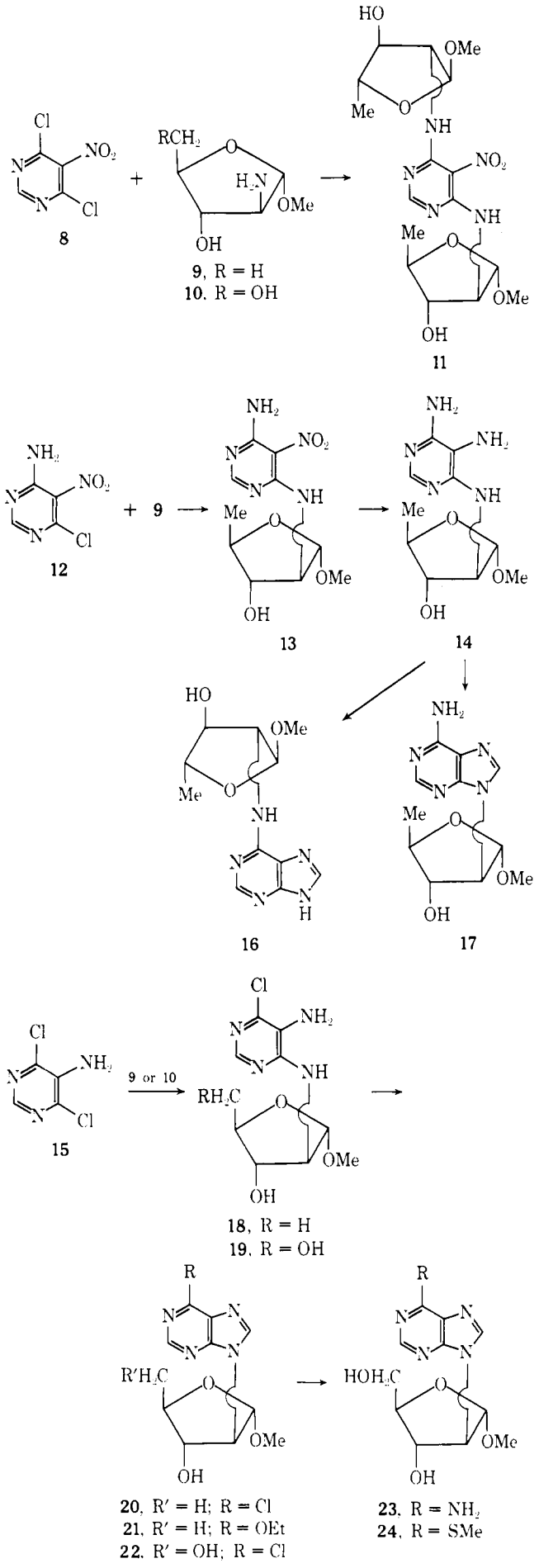


ly attributed the formation of two products to the conditions necessarily employed, further work established that, in fact, the reaction of **4** with ammonia gives almost equal amounts of **9** and **25** resulting from attack at both C-2 and C-3.[7] The identities of the two products obtained from the reaction of **1** with **4** were established by their ^{1}H NMR spectra (see Experimental Section) as methyl 2,5-dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**6**) and methyl 3,5-dideoxy-3-[6-(methylthio)-9-purinyl]-α-D-xylofuranoside (**7**); the ratio of isolated products was about three **6** to one **7**. Later, because of the difficulties encountered with alternative routes, we also investigated the reaction of **1** with **5**,[7] but this reaction proved even more difficult—after 20 hr much decomposition had occurred and a complex mixture of at least six components (TLC) resulted. Reaction of **1** with the 5-*O*-benzyl derivative[8] of **5** was not significantly better, so an alternative approach was finally adopted.

The alternative approach was based on a synthesis of 9-substituted purines developed in our laboratories some time ago.[9,10] At least three variations of this synthesis are possible and, because of the low yield obtained in the reaction of 5-amino-4,6-dichloropyrimidine (**15**) with **9**, they were all investigated. The low yield in the conversion of **15** to **18** resulted from side reactions encountered using conditions necessary to cause the relatively unreactive **15** to react with **9**. Among these side reactions were sugar decomposition, anomerization (^{1}H NMR), and displacement of the methoxy group of **9** (or **18**) by the solvent, 1-butanol (MS).

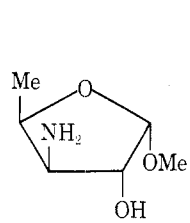
The much more reactive 5-nitro-4,6-dichloropyrimidine was next allowed to react with **9** using conditions that in other cases prevent disubstitution.[11,12] In this case, little or no monosubstituted pyrimidine formed, and only the bis compound, bis[methyl 2,5-dideoxy-2,2′-[(5-nitro-4,6-pyrimidinediyl)diimino]-α-D-arabinofuranoside] (**11**), could be isolated (Scheme II). This problem could be avoided by the use of 4-amino-6-chloro-5-nitropyrimidine (**12**), which is quite reactive despite the presence of the amino group. Methyl 2-(6-amino-5-nitro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**13**), obtained in high yield from **12**, was readily reduced with Raney nickel and hydrogen to the 5-aminopyrimidine **14**. Ring closure of **14** with formamide at 100° gave a mixture of the desired compound, methyl 2-(6-amino-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (**17**), and the isomeric methyl 2,5-dideoxy-

Scheme II

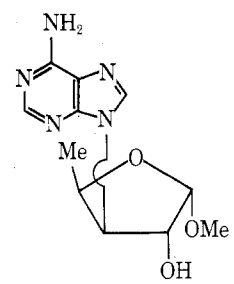


2-(6-purinylamino)-α-D-arabinofuranoside (**16**).[13] At 150° only **17** was detected (indicating that rearrangement of **16** to **17** may be possible), but the harsher conditions of this reaction caused much decomposition and only a low yield of **17** could be obtained. The much milder ring closure of **14** with diethoxymethyl acetate give, not unexpectedly, only methyl 2,5-dideoxy-2-(6-purinylamino)-α-D-arabinofuranoside (**16**).[14]

Because the separation of **9** and **25** is difficult and wasteful, the mixture was carried through the reaction sequence described above (**12** → **13** → **14** → **17**) for pure **9** in the hope that the separation of **17** from **26** would be easier than that of **9** from **25**. Although the former separation is probably somewhat better, this overall approach does not appear to be a significant improvement.



25



26

Thus, none of the obvious variations of the alternative pathway were entirely satisfactory, but the route via **18** was finally chosen because of its greater versatility. Ring closure of **18** with triethyl orthoformate and concentrated HCl was preferable to closure with diethoxymethyl acetate, in keeping with published results,[15] but still only a 54% yield was obtained. When an attempt was made to raise the yield by the addition of more acid and a longer reaction period, only methyl 2,5-dideoxy-2-(6-ethoxy-9-purinyl)-α-D-arabinofuranoside (**21**), resulting from displacement of the chloro group of **20**, was isolated.

We now turned our attention to the potentially more interesting sugar **10** (whose derivatives may be enzymatically phosphorylated), and converted it to methyl 2-(5-amino-6-chloro-4-pyrimidinylamino)-2-deoxy-α-D-arabinofuranoside (**19**) by reaction with 5-amino-4,6-dichloropyrimidine (**15**). Ring closure with triethyl orthoformate and concentrated HCl gave methyl 2-(6-chloro-9-purinyl)-2-deoxy-α-D-arabinofuranoside (**22**), which was converted by standard nucleophilic displacement reactions to the adenosine analog methyl 2-(6-amino-9-purinyl)-2-deoxy-α-D-arabinofuranoside (**23**) and the 6-(methylthio)purine ribonucleoside analog methyl 2-deoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**24**).

None of these isonucleosides so far evaluated for cytotoxicity or activity against leukemia L1210 have been found to be active.

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 100° for 2–4 hr. Brinkman 8-in., 2-mm silica gel plates were used for preparative chromatographic separations and Analtech precoated (250 μ) silica gel G(F) plates for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated $(NH_4)_2SO_4$. 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 Model 17 spectrophotometer; the uv maxima are reported in nanometers ($\epsilon \times 10^{-3}$). The ^1H NMR spectra were obtained with a Varian XL-100-15 spectrometer in the solvents indicated with tetramethylsilane as an internal reference. Chemical shifts (δ in parts per million) quoted in the case of multiplets are measured from the approximate center. Mass spectral data were taken from low-resolution spectra determined with a Hitachi Perkin-Elmer RMU-7 double-focusing instrument (70 eV) (M = molecular ion).

9-(*trans*-2-Hydroxycyclohexyl)-6-(methylthio)purine (3). A solution of 6-(methylthio)purine (**1**, 166 mg, 1 mmol) and cyclohexene oxide (**2**, 117 mg, 1.2 mmol) in ethanol (15 ml) containing pyridine (1 ml) was allowed to reflux for 26 hr with two additions of cyclohexene oxide (0.2 ml). Evaporation of the solution gave a dark residue that crystallized on the addition of absolute ethanol. This material (140 mg), shown by TLC to contain two purines, was chromatographed on a silica gel plate using 19 $CHCl_3$:1 MeOH as the developer. Elution of the heavier band gave 82 mg of homogeneous material that was recrystallized from ethanol: yield 50 mg (19%); mp 202–204°; uv (pH 1) 295 nm (17.7); uv (pH 7 and 13) 286 nm (19.1), 293 (19.1).

Anal. Calcd for $C_{12}H_{16}N_4OS$: C, 54.52; H, 6.10; N, 21.19. Found: C, 54.38; H, 5.86; N, 21.08.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-tosyl-β-D-arabinofuranoside. A mixture of 1,2-*O*-isopropylidene-3,5-*O*-ditosyl-β-D-arabinofuranoside[16] (254.7 g, 0.51 mol) and lithium aluminum hydride (80 g) in tetrahydrofuran (2 l.) was refluxed overnight (TLC for complete reaction) before it was treated successively with H_2O (80 ml), 15% NaOH (80 ml), and H_2O (240 ml). The gelatinous solid was removed by filtration and washed with ether. The combined filtrates (ether and tetrahydrofuran) were evaporated to dryness; a solution of the residue in $CHCl_3$ was washed with 1 *N* NaOH and then water and dried over $MgSO_4$ before evaporation to dryness, yield of chromatographically pure product 137.9 g (82%), MS 313 $[(M - CH_3)^+]$. This material, identical with that prepared by the tosylation of 5-deoxy-1,2-*O*-isopropylidene-α-D-arabinofuranoside,[17] was used in the next step[6] without further purification.

Methyl 2,5-Dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (6) and Its Xylo Isomer (7). A mixture of 6-(methylthio)purine (**1**, 332 mg, 2.00 mmol), methyl 2,3-anhydro-5-deoxy-α-D-ribofuranoside[6] (**4**, 260 mg, 2.00 mmol), and K_2CO_3 (276 mg, 2.00 mmol) in dry DMA (15 ml) was refluxed with stirring for 3 hr before it was filtered, and the filtrate was evaporated to dryness. The residue, when chromatographed on silica gel plates using 99 $CHCl_3$:1 MeOH as developer, gave two principal bands. About 180 mg (54%) of 6-(methylthio)purine was recovered from the slower traveling band. The second band proved to be a mixture of two purine-containing sugars (uv, char), which was resolved into two bands by chromatography on another plate using 6 BuOH:1 H_2O as the developer. Elution of the faster traveling band gave 102 mg (19%) of methyl 2,5-dideoxy-2-[6-(methylthio)-9-purinyl]-α-D-arabinofuranoside (**6**): mp 133–134°; uv (pH 1) 223 nm (11.8), 294 (17.2); uv (pH 7 and 13) 222 nm (12.2), 288 (19.1); ^1H NMR (DMSO-d_6) δ 1.35 (d, 3 H_5'), 2.7 (s, SMe), 3.3 (s, OMe), 4.0 (m, H_4'), 4.3 (m, H_3'), 4.8 (m, H_2'), 5.24 (d, $J_{1'2'}$ = 4 Hz, H_1'), 5.75 (broad d, OH), 8.62 and 8.76 (2 s, purine H).

Anal. Calcd for $C_{12}H_{16}N_4O_3S \cdot 0.2C_4H_9OH$: C, 49.41; H, 5.83; N, 18.00. Found: C, 49.31; H, 5.45; N, 18.04.

The identity of this purinyl sugar was confirmed by an NOE experiment. Irradiation of the methyl group at C_4 of the sugar gave a 15–20% enhancement of the signal from the proton at C_3 whereas irradiation 200 Hz upfield from the methyl group signal caused no change, indicating that the proton at C_3 must be on the same side of the ring as the methyl group and, therefore, that the purine must be attached at C_2.

Elution of the slower traveling band gave 42 mg (7%) of the second purinyl sugar, which could not be induced to crystallize. It was identified as methyl 3,5-dideoxy-3-[6-(methylthio)-9-purinyl]-α-D-xylofuranoside (**7**): ^1H NMR (DMSO-d_6) δ 0.75 (d, 3 H_5'), 2.7 (s, SMe), 3.4 (s, OMe), 4.6 (m, H_4'), 5.0 (m, H_3', H_2', H_1'), 5.55 (broad, OH), 8.62 and 8.75 (2 s, purine H).

The extremely high-field chemical shift of the signal due to the three protons at C_5 is a result of the anisotropic effect of the purine ring. There is essentially no effect on this signal when the purine is attached at C_2 (see above) rather than C_3 in keeping with the observed effects of the purine ring on the methyl signal of a *cis*-acetoxy group at C_2 and C_3 of acetylated purine nucleosides.[18]

Bis[methyl 2,5-dideoxy-2,2′-[(5-nitro-4,6-pyrimidinediyl)diimino]-α-D-arabinofuranoside] (11). A $CHCl_3$ (8 ml) solution of methyl 2-amino-2,5-dideoxy-α-D-arabinofuranoside[7] (**9**, 149 mg, 1 mmol) was added slowly to a vigorously stirred mixture of 4,6-dichloro-5-nitropyrimidine (**8**, 194 mg, 1 mmol) and $NaHCO_3$ (84 mg, 1 mmol) in $CHCl_3$ (15 ml). Vigorous stirring was continued overnight and then the $CHCl_3$ solution was washed with water and dried over $MgSO_4$ before evaporation to dryness. Trituration with

ether removed 4,6-dichloro-5-nitropyrimidine, leaving the product, a light yellow solid: mp 202–204°; ^{1}H NMR ($CDCl_3$) δ 1.36 and 1.12 (2 s, 2-C-Me), 3.44 (s, 2-OMe), 3.65 (m, 2 H_3'), 4.17 (m, 2 H_4'), 4.4 (m, 2 H_2' and 2 O_3' H), 4.97 (d, $J_{1'2'}$ = 2 Hz, 2 H_1'), 8.15 (s, H_2), 9.45 (broad, 2 NH).

Anal. Calcd for $C_{16}H_{25}N_5O_8$: C, 46.26; H, 6.07; N, 16.86. Found: C, 46.00; H, 5.92; N, 16.85.

When the reaction was carried out in the presence of acetic acid, a lower conversion to the bis compound resulted.

Methyl 2-(6-Amino-5-nitro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (13). A mixture of methyl 2-amino-2,5-dideoxy-α-D-arabinofuranoside[7] (**9**, 1.21 g, 8.24 mmol), 4-amino-6-chloro-5-nitropyrimidine (**12**, 2.88 g, 16.5 mmol), and triethylamine (1.67 g, 16.48 mmol) in 1-butanol was refluxed for 1.3 hr. More pyrimidine (1.44 g, 8.24 mmol) and triethylamine (0.84 g, 8.24 mmol) were added and the mixture was refluxed for 1 hr. After filtration, the solution was evaporated to dryness. Treatment of the residue with MeOH caused it to gel: yield 1.91 g (78%); mp 153–155°; uv (pH 1) 242, 296 sh, 339 nm (23.4, 4.22, 6.94); uv (pH 7 and 13) 342 nm (10.1).

Anal. Calcd for $C_{10}H_{15}N_5O_5 \cdot 0.2C_4H_9OH$: C, 43.23; H, 5.71; N, 23.34. Found: C, 43.37; H, 5.72; N, 23.52.

Methyl 2-(5,6-Diamino-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (14). Methyl 2-(6-amino-5-nitro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**13**, 428 mg) in EtOH (150 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel catalyst (75 mg wet) for 20 hr. The catalyst was removed by filtration before the solution was evaporated to dryness. The residual chromatographically homogeneous syrup (264 mg, 69%) was used in the next step without further purification: uv (pH 1) 225, 292 nm (15.8, 8.95); uv (pH 7 and 13) 222, 279 nm (22.7, 8.34).

Methyl 2,5-Dideoxy-2-(6-purinylamino)-α-D-arabinofuranoside (16). A solution of methyl 2-(5,6-diamino-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**14**, 200 mg) in diethoxymethyl acetate (10 ml) was allowed to stand at room temperature for 3 days before it was evaporated to dryness. A solution of the yellow syrupy residue in MeOH (22 ml) containing NaOMe (108 mg) was refluxed for 0.5 hr, neutralized with HOAc, and evaporated to dryness. The orange syrupy residue was chromatographed on silica gel plates using 17 $CHCl_3$:1 MeOH as the developer. Elution with MeOH gave 172 mg (65%) of a solid that was recrystallized from EtOH: mp 212–214°; uv (pH 1) 279 nm (19.8); uv (pH 7) 267 nm (18.5); uv (pH 13) 274 nm (17.5); ^{1}H NMR (DMSO-d_6) δ 1.28 (d, 3 H_5'), 3.26 (s, OMe), 3.8 (m, H_3' and H_4'), 4.6 (m, H_2'), 4.84 (d, $J_{1'2'}$ = 3.5 Hz, H_1'), 7.9 (broad d, NH), 8.13 and 8.2 (2 s, purine H).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.59; H, 5.50; N, 26.18.

Methyl 2-(6-Amino-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (17). A solution of methyl 2-(5,6-diamino-6-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**14**, 216 mg) in formamide (10 ml) was heated at 150° for 3 hr before it was evaporated to dryness. The residue was chromatographed on a silica gel plate using 17 $CHCl_3$:1 MeOH once and then 9 $CHCl_3$:1 MeOH twice as developers, yield 52 mg (23%). This material was recrystallized from EtOH: mp 211–212°; uv (pH 1) 258 nm (15.2); uv (pH 7 and 13) 261 nm (15.3); ^{1}H NMR (DMSO-d_6) δ 1.32 (d, 3 H_5'), 3.27 (s, OMe), 3.95 (m, H_4'), 4.2 (m, H_3'), 4.7 (m, H_2'), 5.19 (d, $J_{1'2'}$ = 4 Hz, H_1'), 5.68 (d, O_3' H), 7.2 (s, NH_2), 8.15 and 8.24 (2 s, purine H).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.91; H, 5.65; N, 26.45.

Methyl 2-(6-Amino-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (17) and Methyl 3-(6-Amino-9-purinyl)-2,5-dideoxy-α-D-xylofuranoside (26). Reaction of a mixture[7] of methyl 2-amino-2,5-dideoxy-α-D-arabinofuranoside (**9**) and methyl 3-amino-3,5-dideoxy-α-D-xylofuranoside (**25**, 0.982 g, 6.68 mmol) with **12** (2.33 g, 13.4 mmol) as described above for pure **9** gave 1.62 g (85%) of the pyrimidinylamino sugars (**13** and its xylo isomer). Hydrogenation of half of this material with Raney nickel catalyst as described above for **13** gave 646 mg (88%) of a mixture of **14** and its xylo isomer. A solution of this mixture in formamide (30 ml) was heated at 150° for 2 hr before it was evaporated to dryness. The residue was resolved by repeated chromatography on silica gel plates using first 9 $CHCl_3$:1 MeOH and then 43 BuOH:7 H_2O as developers. The isomers were both eluted with and recrystallized from MeOH. The faster traveling material (81 mg) was essentially identical with **17** obtained as described above. The slower traveling material (**26**, 15 mg) melted at 208–210°: uv (pH 1) 258 nm (14.2); uv (pH 7 and 13) 260 nm (15.6); ^{1}H NMR (DMSO-d_6) δ 0.73 (d, 3 H_5'), 3.4 (s, OMe), 4.5 (m, H_4'), 4.95 (m, H_1', H_2', and H_3'), 5.4 (m, O_2'H), 7.2 (broad s, NH), 8.14 and 8.25 (2 s, purine H). The unusually high-field signal (0.73 ppm) due to the three protons at C_5 is a result of the anisotropic effect of the purine ring attached at C_3 of **26** (see above, ^{1}H NMR spectrum of **7**).

Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 50.02; H, 5.49; N, 26.68.

Methyl 2-(5-Amino-6-chloro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (18). A solution of methyl 2-amino-2,5-dideoxy-α-D-arabinofuranoside[7] (**9**, 2.64 g, 18 mmol), 5-amino-4,6-dichloropyrimidine (**15**, 5.91 g, 36 mmol), and triethylamine (5.04 ml, 36 mmol) in 1-butanol (300 ml) was refluxed for 18 hr before it was evaporated to dryness. The residue was purified by chromatography on a silica gel column using a gradient elution with $CHCl_3$ → 97 $CHCl_3$:3 MeOH. In this manner the 5-amino-4,6-dichloropyrimidine was separated from the product, yield 1.38 g (27%). This material, which was chromatographically homogeneous, was used in the next step without further purification: uv (pH 1) 305 nm (12.8); uv (pH 7 and 13) 261, 292 nm (8.20, 9.35).

Methyl 2-(5-Amino-6-chloro-4-pyrimidinylamino)-2-deoxy-α-D-arabinofuranoside (19). A solution of methyl 2-amino-2-deoxy-α-D-arabinofuranoside[7] (**10**, 0.864 g, 5.3 mmol), 5-amino-4,6-dichloropyrimidine (**15**, 1.74 g, 10.6 mmol), and triethylamine (1.48 ml, 10.6 mmol) in 1-butanol (120 ml) was refluxed for 18 hr before it was evaporated to dryness. The residue was chromatographed on silica gel plates (9 $CHCl_3$:1 MeOH). The major band was eluted with MeOH: yield 1.18 g (46%); mp indefinite; uv (pH 1) 304 nm (11.8); uv (pH 7 and 13) 261, 291 nm (7.60, 8.65). This chromatographically homogeneous material was used in the next step without further purification. Unchanged **10** was also recovered from the silica gel plates.

Methyl 2-(6-Chloro-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (20). The addition of concentrated HCl (0.13 ml) to a suspension of methyl 2-(5-amino-6-chloro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**18**, 338 mg) in ethyl orthoformate (4 ml) caused solution. After standing at room temperature for 18 hr, the solution deposited a white solid, which was removed by filtration, washed with ethyl orthoformate, and dried: yield 187 mg (54%); mp 195°; uv (pH 1 and 7) 265 nm (9.21); uv (pH 13) 263 nm (8.22).

Anal. Calcd for $C_{11}H_{13}ClN_4O_3$: C, 46.41; H, 4.60; N, 19.62. Found: C, 46.27; H, 4.43; N, 19.63.

Methyl 2-(6-Ethoxy-9-purinyl)-2,5-dideoxy-α-D-arabinofuranoside (21). A solution of methyl 2-(5-amino-6-chloro-4-pyrimidinylamino)-2,5-dideoxy-α-D-arabinofuranoside (**18**, 338 mg) in triethyl orthoformate containing 0.26 ml of concentrated HCl was allowed to stand for 3 days at room temperature before it was neutralized with aqueous Na_2CO_3. Evaporation of the solution gave a residue which was purified by chromatography on silica gel plates using 97 $CHCl_3$:3 MeOH as the developer. Elution with MeOH gave a white solid which was recrystallized from MeOH: yield 192 mg (56%); mp 195–197°; uv (pH 1, 7, and 13) 252 nm (11.1).

Anal. Calcd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04. Found: C, 53.00; H, 5.97; N, 19.14.

Methyl 2-(6-Amino-9-purinyl)-2-deoxy-α-D-arabinofuranoside (23). The addition of concentrated HCl (0.11 ml) to a suspension of methyl 2-(5-amino-6-chloro-4-pyrimidinylamino)-2-deoxy-α-D-arabinofuranoside (**19**, 291 mg) in triethyl orthoformate (33 ml) caused immediate solution. After standing for 18 hr at room temperature, the solution was evaporated to dryness (no heat). A solution of the residue (**22**) in ethanolic ammonia (10 ml, saturated at 0°) was heated at 80° for 18 hr before it was evaporated to dryness. The residue was chromatographed on silica gel plates (9 $CHCl_3$:1 MeOH). After elution the product was converted to its picrate salt in MeOH. The picrate was converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}) in MeOH, yield 105 mg. Recrystallization of this material from EtOH gave 40 mg (14%) of pure product: mp 175–177°; uv (pH 1) 258 nm (14.4); uv (pH 7 and 13) 260 nm (14.8); ^{1}H NMR (DMSO-d_6) δ 3.28 (s, OMe), 3.66 (m, 2 H_5'), 3.9 (m, H_4'), 4.46 (m, H_3'), 4.75 (m, H_2'), 4.94 (m, O_5'H), 5.18 (d, $J_{1'2'}$ = 4 Hz, H_1'), 5.7 (d, O_3'H), 7.24 (broad s, NH_2), 8.16 and 8.23 (2 s, purine H).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 47.25; H, 5.27; N, 24.88.

Methyl 2-[6-(Methylthio)-9-purinyl]-2-deoxy-α-D-arabinofuranoside (24). Conversion of **19** (1.18 g) to **22** was effected as described above. A solution of the residue (**22**) from this procedure in 8.2 ml of 1 *N* NaSMe in MeOH was refluxed for 0.5 hr before it was filtered, neutralized with HOAc, and evaporated to dryness. The residue was chromatographed on silica gel plates (9 $CHCl_3$:1

MeOH). The major band was eluted and the material was rechromatographed using 9 $CHCl_3$:1 MeOH and again using ethyl acetate. The major band was eluted with MeOH and the solution was evaporated to a white glass that could not be induced to crystallize from EtOH: yield 255 mg (20%); uv (pH 1) 287 sh, 294 nm (14.0, 16.4); uv (pH 7 and 13) 287, 293 nm (18.0, 17.8); ^1H NMR (DMSO-d_6) δ 2.68 (s, SMe), 3.3 (s, OMe), 3.7 (m, 2 H_5'), 3.9 (m, H_4'), 4.5 (m, H_3'), 4.9 (H_2'), ca. 5 (broad, OH), 5.24 (d, $J_{1'2'}$ = 4 Hz, H_1'), 5.85 (broad, OH), 8.58 and 8.75 (2 s, purine H).

Anal. Calcd for $C_{12}H_{16}N_4O_4S \cdot 0.25C_2H_5OH$: C, 46.36; H, 5.45; N, 17.30. Found: C, 46.32; H, 5.31; N, 17.08.

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Registry No.—**1**, 50-66-8; **2**, 286-20-4; **3**, 55073-67-1; **4**, 55073-68-2; **6**, 55073-69-3; **7**, 55073-70-6; **8**, 4316-93-2; **9**, 52630-74-7; **10**, 52706-45-3; **11**, 55073-71-7; **12**, 4316-94-3; **13**, 55073-72-8; **14**, 55073-73-9; **15**, 5413-85-4; **16**, 55073-74-0; **17**, 55073-75-1; **18**, 55073-76-2; **19**, 55073-77-3; **20**, 55073-78-4; **21**, 55073-79-5; **22**, 55073-80-8; **23**, 55073-81-9; **24**, 55073-82-0; **25**, 52630-73-6; **26**, 55073-83-1; 5-deoxy-1,2-*O*-isopropylidene-3-*O*-tosyl-β-D-arabinofuranoside, 55073-84-2; 1,2-*O*-isopropylidene-3,5-*O*-ditosyl-β-D-arabinofuranoside, 55073-85-3.

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Naturally Occurring Lactones and Lactams. VIII.[1] Lactonization of Unsaturated β-Keto Esters. Total Synthesis of Carlic Acid, Carlosic Acid, and Viridicatic Acid

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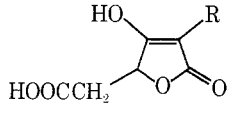
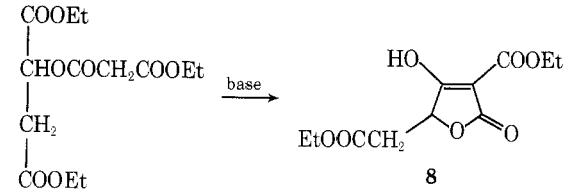
Treatment of diethyl *trans*-2-ethoxycarbonyl-3-oxo-4-hexenedioate (**11**) with concentrated sulfuric acid and subsequent hydrolysis gave the tetronic acid synthon **4**. In contrast diethyl cinnamoyl malonate (**19**) and diethyl crotonoyl malonate (**20**) were lactonized to δ-lactones. Extension of the synthetic principle to α-fumaroyl-β-keto esters provided a total synthesis of the naturally occurring tetronic acids carlosic acid (**2**) and viridicatic acid (**3**). Synthesis of carlic acid (**1**) along this route has been unsuccessful so far, whereas acylation of 5-methoxycarbonylmethyltetronic acid (**15**) with 4-chlorobutanoyl chloride and subsequent hydrolysis afforded the desired natural product.

As part of our attempts to develop general methods for the synthesis of the mold tetronic acids carlic acid (**1**, cf. **1a**), carlosic acid (**2**), and viridicatic acid (**3**), we have considered using the parent acid **4** as a synthon, since it has been demonstrated that Friedel–Crafts acylation of the tetronic acid nucleus may lead to natural products.[2-4]



1, R = $COCH_2CH_2CH_2OH$
2, R = $COCH_2CH_2CH_3$
3, R = $COCH_2CH_2CH_2CH_2CH_3$
4, R = H
5, R = $COCH_3$
6, R = Br

The synthon **4** has already been obtained in a minor quantity from a hydrogenation product of dimethyl ketipinate (dimethyl 3,4-dioxomuconate, **13**)[5] and from cyclization of the acetoacetyl derivative of dimethyl malate with potassium *tert*-butoxide in *tert*-butyl alcohol acting as condensing agent.[4] We therefore turned our interest to the ethoxycarbonylacetyl derivative of diethyl malate (**7**), since this compound on cyclization might give **8** from which the 3-ethoxycarbonyl group could easily be removed.



7 **8**

It proved, however, to be very difficult to find an appropriate reagent for the Dieckmann cyclization of **7**. Earlier reactions of this type have been carried out successfully with metallic sodium[6] and especially with diisopropylmagnesium bromide in ether[7] as bases. These reagents, as well as sodium hydride in various solvents, e.g., ether, benzene, toluene, or hexamethylphosphoric triamide, induced no cyclization.