THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 4

FEBRUARY 17, 1978

Introduction of a New 1,3-Electrophilic C–N–C Annulation Reagent in the Synthesis of 2,2′-Anhydrodihydro-5-azathymidine[1]

Wendell Wierenga* and John A. Woltersom

Experimental Chemistry Research, The Upjohn Company, Kalamazoo, Michigan 49001

Received June 28, 1977

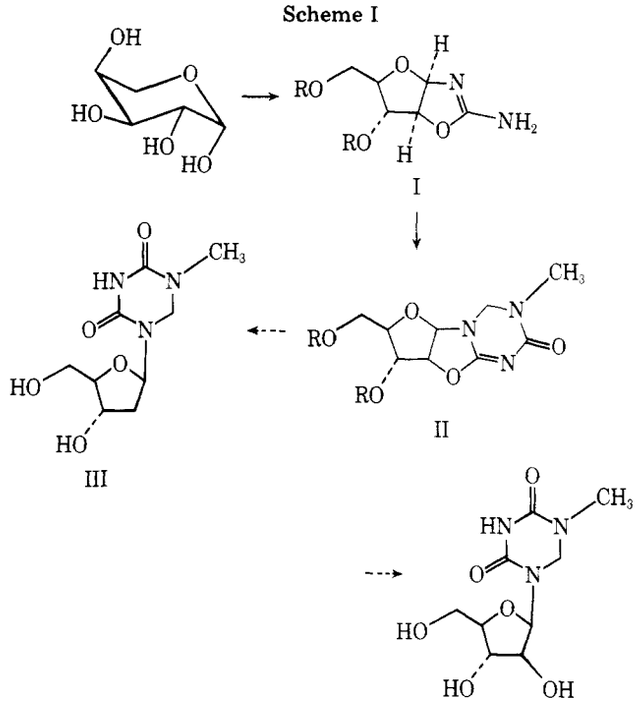
Dihydro-5-azathymidine [1-(2-deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione], isolated from *Streptomyces platensis*, exhibits interesting antibacterial and antiviral properties. As a means of preparing several analogues of this new nucleoside, a synthetic route to the 2,2′-anhydronucleoside analogue was accomplished. The aminooxazoline of arabinose was exploited in a preparation of both possible isomeric triazine anhydronucleosides, II and VI, by direct annulation and a stepwise route, respectively. The conversion to the arabinose analogue is also described.

Recently an unusual nucleoside, III, was isolated from *Streptomyces platensis* (var. clarensis).[2] Besides the antibiotic activity exhibited by this deoxynucleoside, which was the reason for its isolation, interesting antiviral activity was also uncovered. Dihydro-5-azathymidine (1-(2-deoxy-β-D-ribofuranosyl)-5,6-dihydro-5-methyl-*s*-triazine-2,4(1*H*,3*H*)-dione) demonstrated activity against DNA viruses, particularly against Herpes-type viral infection in vivo, both prophylactically and therapeutically, but was inactive against RNA viruses.[3]

Although no toxicity was noted in rats or mice, aplastic anemia developed in dogs and marrow suppression in cats and rabbits.[4] We initiated efforts to synthesize the 2,2′-anhydronucleoside II in an attempt both to minimize toxicity and maintain antiviral activity as well as to entertain the possibility of also securing the scarce, fermentation-derived nucleoside itself (III).[5] Anhydronucleosides have previously been exploited as key synthons for useful analogues such as ribo-, arabino-, and deoxynucleosides.[6]

As outlined in Scheme I, we envisioned a synthetic route which would exploit the ready availability of the aminooxazoline of arabinose, I. Several of the relevant key features of I are (1) it is prepared in a one-step, base-catalyzed condensation of the inexpensive sugar D-arabinose with cyanamide,[7] (2) it incorporates the prerequisite asymmetric centers for the planned synthesis, and (3) it has latent functionality for the desired triazine ring of II. We wish to report herein the successful utilization of I to prepare, via direct annulation, the anhydronucleoside, II, prefaced by an alternate approach which introduces the requisite three atoms of the isomeric triazine-ring system in a stepwise manner.

Scheme I



Results and Discussion

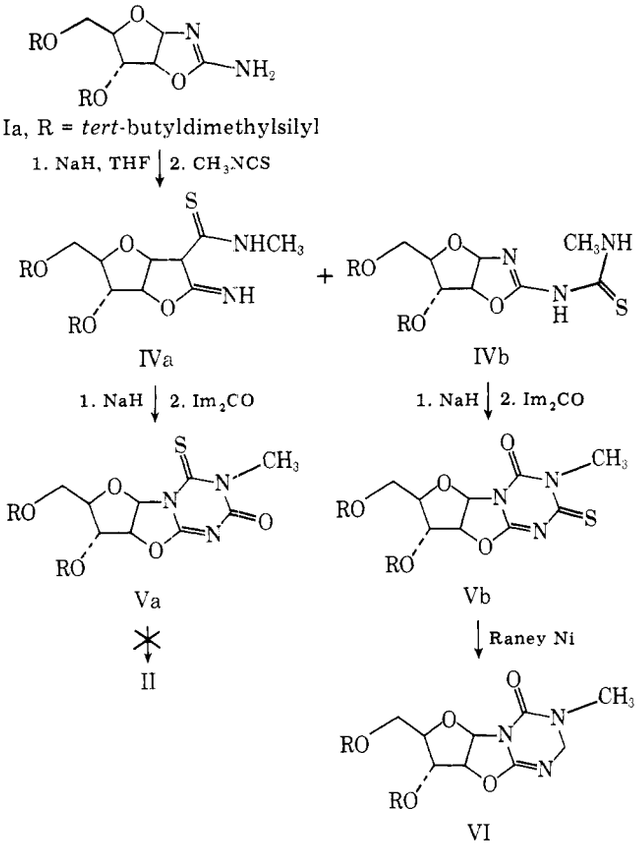
Our initial endeavors evolved from the concept of a stepwise buildup of the required triazine ring system of II. However, this chemistry required protection of the diol group in I. The primary requirements for acceptable protecting groups were (1) base stability, (2) inability to employ acid removal due to the rapid protonic decomposition of II or III,[8] (3) enhanced lipophilicity for chemical and analytical manipulatability, and (4) the obvious regioselectivity for the 3′,5′-diol. We were pleased to find that the *tert*-butyldimethylsilyl group[9] fulfilled these criteria. The excellent adaptability of this group to nucleosides was concurrently reported by Ogilvie and coworkers.[10]

Treatment of the DMF-insoluble I with *tert*-butyldimethylsilyl chloride under standard conditions afforded the

bis(silyl) ether Ia in 85–90% yields recrystallized from hexane. The silyl ether protection allowed a wide range of solvent choices in subsequent chemistry as well as in ready GC and GC–MS analyses.

The aminooxazoline moiety, because of its unsymmetrical, ambident amidine function, has the inherent problem of regioselectivity, both in predicting which nitrogen will be the initial reaction site and then in the structural determination after the fact.[11] When Ia was treated with sodium hydride (NaH) followed by methyl isocyanate, only one product (90%) was produced (Scheme II).[12] However, when methyl isothiocyanate was employed, both isomers (IVa and IVb) were produced in similarly high yield in a 50:50 mixture. Simply heating in THF without base afforded primarily the desired IVa.

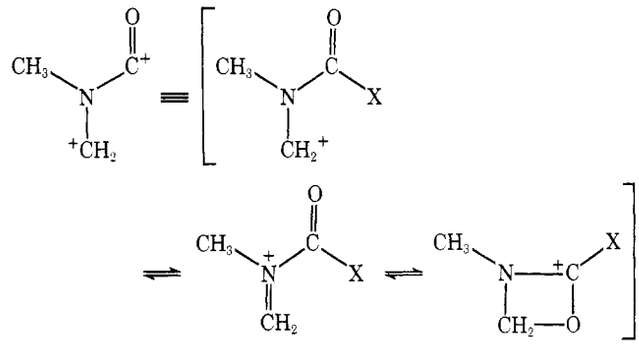
Scheme II



Ring closure with 1,1′-carbonyldiimidazole of either IVa or IVb individually or as a mixture yielded the triazine thiones, Va and Vb, in 95% yield, separable by HPLC (silica gel). Indeed, the conversion of Ia to Va and Vb could be accomplished more efficiently with comparable yields utilizing 1 equiv of base followed by sequential methyl isothiocyanate–carbonyldiimidazole treatment. Unfortunately, we were unable to reductively desulfurize Va to the desired anhydronucleoside II, even though this was readily accomplished with the undesired isomer Vb to yield VI in 65% yield using Raney nickel.[13] Exploring other reduction procedures such as phosphites or borohydrides proved fruitless.

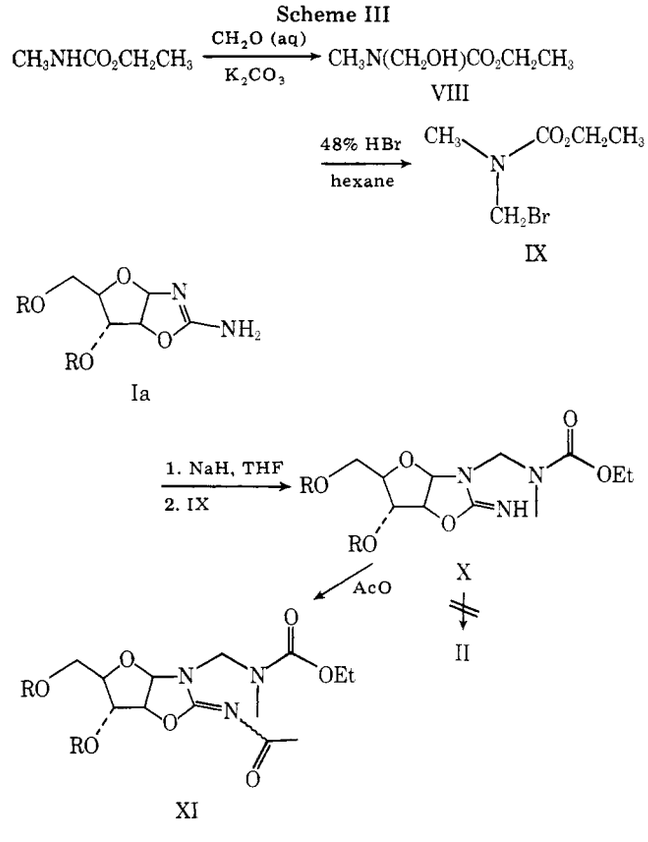
The structure assignments are based on IR, NMR, and UV data with particular emphasis on ^{13}C NMR and lanthanide-shift studies (vide infra) in conjunction with the interrelating chemistry of the isomeric series.

The utility of an approach to nucleoside synthesis based on a three-atom annulation of the aminooxazoline of arabinose has several precedents. These have all involved the three-carbon propriolonitrile (ester) or a functional equivalent to generate the desired regiochemical pyrimidine-ring isomer.[14] As a means of circumventing the problems encountered with the stepwise approach, we initiated efforts to devise an annulation reagent that exhibited the selective alkylation required of the unsymmetrical amidine grouping of the aminooxazoline, that had the desired oxidation state, and that was readily available. Such a species is depicted by VII, wherein X is an appropriate leaving group.



We initially attempted to generate an *N*-carbethoxy-*N*-methyl iminium species via hydride abstraction on ethyl-*N*,*N*-dimethylcarbamate with trityl fluoroborate[15] in chloroform. Even though a high yield of triphenylmethane was realized, the presumed iminium species proved too reactive to utilize directly. A more stable equivalent appeared to be a Mannich-type base such as IX (Scheme III). This was prepared by formaldehyde condensation with methylurethane to yield the hydroxymethylcarbamate, VIII. After a variety of unsuccessful attempts to convert the hydroxyl to a chloro or mesylate group, we found that a two-phase hydrobromic acid system afforded the bromomethylurethane, IX, in 75–80% yield. The reagent is isolated simply by decantation and concentration of the organic phase. It is characterized by a

Scheme III



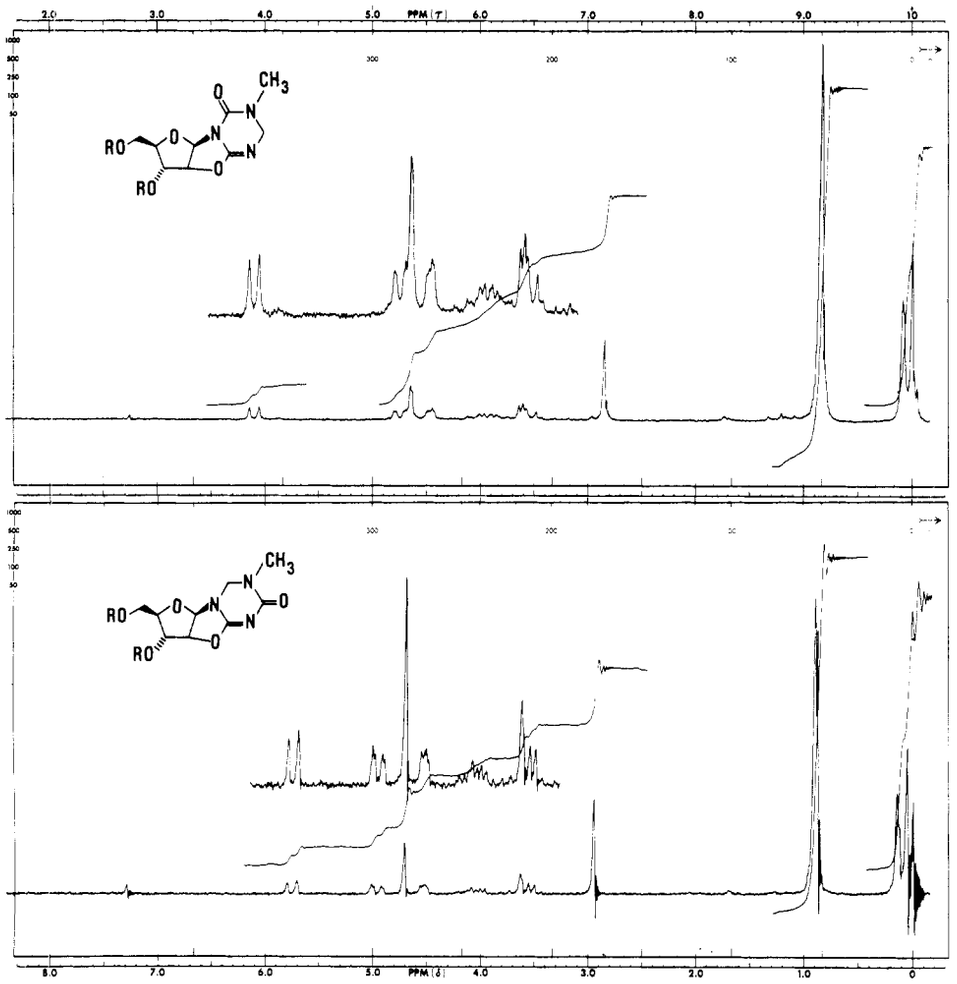


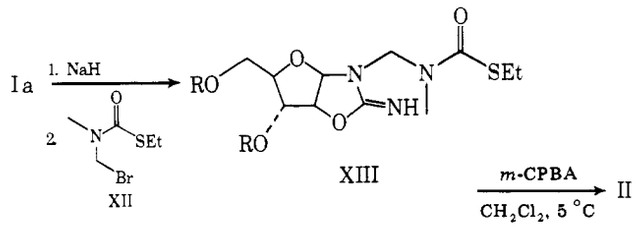
Figure 1. ^{1}H NMR spectra of compounds VI (top) and II (bottom).

shift in the methylene ^{1}H NMR resonance from δ 4.88 to 5.35. Even though it is unstable to standard TLC or column chromatography (silica gel), it can be stored for several weeks in benzene at 0 °C with little decomposition.

Generation of the sodium salt of aminooxazoline Ia followed by addition of the annulation reagent yielded primarily the ring-alkylated derivative X (75% yield). No ring-closed material was detected. That the structure of X is correctly assigned is based not only on spectral characterization and subsequent chemistry but also by acylation with acetic anhydride to XI. The ^{1}H NMR spectrum of XI exhibited two equivalent CH_3CO singlets at δ 2.04 and 2.15, as well as a λ_{max} of 232 nm (ε 9500) in the UV spectrum. If initial alkylation with IX had occurred at the amino nitrogen, the two possible products of acylation would not exhibit these UV characteristics.

Although the annulation reagent, IX, is a potential 1,3 electrophile, the carbamoyl carbonyl proved resistant to intramolecular nucleophilic attack in this system to effect ring closure to the desired 2,2′-anhydronucleoside, II. A variety of conditions (acid, base, neutral, and thermal[16a]) and several leaving groups (OCH_3, OCH_2CH_3, and OCH_2Ph) were tried without success. In attempting to employ better leaving groups, such as phenoxy, we were unable to prepare the annulation reagent under the described conditions.[17a]

To enhance the electrophilicity of the carbamoyl group and still preserve the excellent regioselectivity of IX, we turned to the thiocarbamate system with the idea of modifying the valence of sulfur after alkylation to improve its leaving group capacity with concomitant cyclization. The thiocarbamate reagent, XII,[17b] was prepared analogously to IX, and alkylation proceeded smoothly to XIII (50% yield). Again acylation yielded two isomeric acylimides with a λ_{max} of 233 nm (ε 17 500). Treatment of XIII with 2 equiv of *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded the desired II in 75% yield.



It is presumed that the oxidative cyclization proceeds through the carbamoyl sulfone as an intermediate since 2 equiv of peracid are required.[16b,18] Activation of thioesters to intermolecular nucleophilic substitution by oxidation at sulfur was first reported by Kumamoto and Mukaiyama[19a] and later utilized in an intramolecular application by Masamune and co-workers.[19b]

Now in hand were the two possible anhydronucleoside isomers, VI and II, as indicated by elemental composition and mass spectrometry [characteristic *m/e* 414 (M^+ − *tert*-butyl)]. IR and UV spectra strongly supported the assigned structures with VI exhibiting a C=O at 1750 cm^{-1} and a λ_{max} of 217 nm, whereas II exhibited a C=O at 1665 cm^{-1} and a λ_{max} of 238 nm (ε 4050) in ethanol, with a bathochromic shift to 227 nm (ε 3950) in ether.

Since the ^{1}H NMR spectrum was not definitive in confirming the structural assignments (Figure 1), we investigated

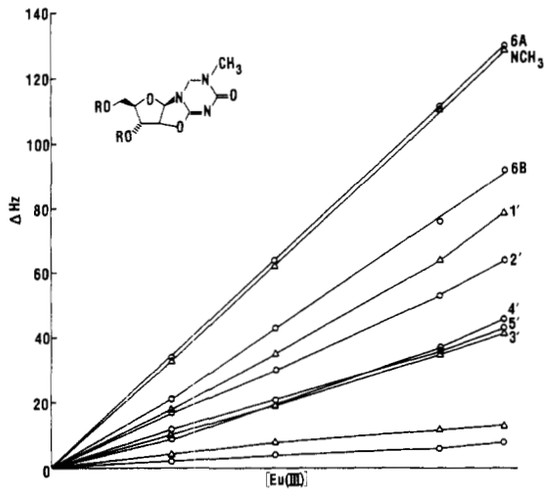


Figure 2. Lanthanide-induced-shift study of compound II using $Eu(dmp)_3$.

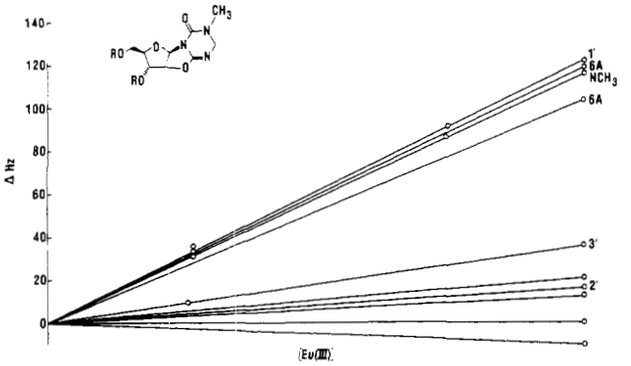


Figure 3. Lanthanide-induced-shift study of compound VI using $Eu(dmp)_3$.

the possible use of a lanthanide-induced-shift study. Although this technique has seen limited application in nucleoside structure determinations due to solubility difficulties in noncomplexing solvents, competing sites for complexation, and often rapid glycosidic bond rotation, we anticipated a possible use since these problems were minimized or nonexistent in II and VI. Indeed, the use of $Eu(dmp)_3$ afforded linear shifts (Figures 2 and 3), suggesting predominate carbonyl complexation over the concentration range investigated. Eu(III) complexation of the C-4 carbonyl isomer (II, Figure 2) exhibited maximal effects on the more proximate N–CH_3 and C-6 hydrogens, whereas the C-6 carbonyl isomer (VI, Figure 3) showed a more pronounced effect on the C-1′ hydrogen relative to the N–CH_3 and C-4 hydrogens.

The calculated values arising from an LISC program generator[20] utilizing x-ray coordinates from dihydro-5-azathymidine (III)[21] allowed for an acceptable fit of the experimental shift data. The results of the computer simulation are summarized in Table I.

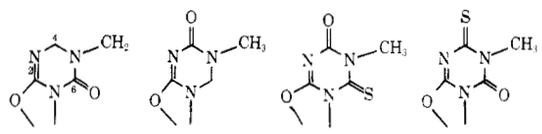
Table II denotes the pertinent ^{13}C NMR data for the isomeric series VI, II, Va, and Vb. The assignments are based primarily on the data obtained for similar compounds as detailed in Tables III and IV. Of interest is the trend delineated in Table II, where the carbonyl resonance is shifted downfield 13 ppm when conjugated with the C=N (VI to II) and the thiocarbonyl is shifted 13.8 ppm downfield (Va to Vb). Similarly, the β effect on C-2 is a downfield shift of 0.2–4.4 ppm in proceeding from VI to II, Va, or Vb. Although this phenomenon is opposite to that generally seen with α,β-C=C conjugated carbonyls, it is consistent with other anhydropyrimidine nucleosides.[23–25]

Table I

	II	VI
Computed positional parameter for Eu(III)	2.5 Å	2.3 Å
	107°	90°
	145°	140°
R factors[a]		
Correct	0.079	0.072
Incorrect	0.244	0.222
R-factor ratio	3.09	3.08

[a] Based on use of six protons in the calculations.

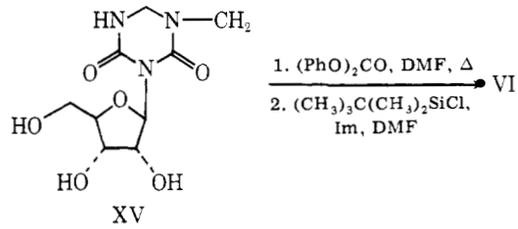
Table II[a]



	VI	II	Va	Vb
C-2	152.8	157.2	153.0	155.9
C-4	64.8	162.8	159.3	187.9
C-6	149.8	59.4	174.1	145.8
N–CH_3	31.0	33.1	34.9	34.9

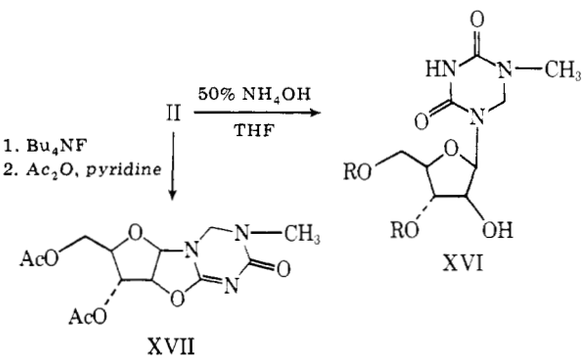
[a] The assignments are given in ppm in $CDCl_3$ (0.1–0.4 M) with a 0.5-s acquisition time. Only the triazine-ring structure is shown, as the bis(silyl)-protected furanose was deleted for simplification.

As an ultimate confirmation for the anhydronucleoside VI, we were able to prepare it by independent chemistry employing the diphenyl carbonate mediated[27] dehydration of riboside XV.[25] This was shown to be identical to VI by TLC, GC, NMR, and mass spectral comparison.



The 2,2′-anhydrodihydro-5-azathymidine (II) exhibited the usual property of facile base hydrolysis to afford the arabinose[6] XVI (Scheme IV), as indicated by the loss of the

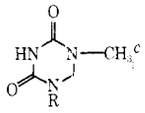
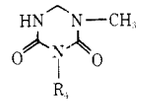
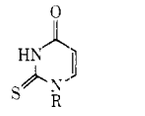
Scheme IV



UV-absorbing chomophore at 233 nm and confirmed by the characteristic upfield shift of the C-2′ hydrogen in the ^1H NMR spectrum.[27] Employing conventional procedures,[6] we were unable to convert II to the parent deoxynucleoside, III.

Removal of the *tert*-butyldimethylsilyl protecting groups

Table III[a]

	R	Registry no.	C-2	C-4	C-6	N–CH_3
	H	64332-47-4	153.3[b]	153.6[b]	56.0	31.2
	R_1	57350-36-4	154.6[b]	155.0[b]	57.0	32.7
	R_2	64332-48-5	152.2[b]	152.5[b]	56.7	32.3
	R_3	64332-49-6	153.9[b]	158.8[b]	57.0	35.1
	R_4[25]	64332-50-9	153.7[b]	55.7	152.0[b]	33.0
	H	141-90-2	175.5	160.5		

[a] The assignments are given in ppm in $CDCl_3$ (0.15–0.2 M), unless otherwise noted, with a 0.5-s acquisition time. R_1 = 2′-deoxy-β-D-ribofuranose, R_2 = triacetyl-β-D-arabinofuranose, R_3 = 3′,5′-bis(*tert*-butyldimethylsilyl)-β-D-arabinofuranose, and R_4 = β-D-ribofuranose. [b] Values may be interchanged. [c] In Me_2SO-d_6. [d] In D_2O.[22]

was readily effected with tetra-*n*-butylammonium fluoride in THF, affording XVII in 84% yield after acetylation. This chemistry worked equally well with VI.

Experimental Section

General. All solvents employed were reagent grade. Tetrahydrofuran was distilled from sodium/benzophenone under N_2 prior to use. All reagents were used as received, and moisture-sensitive materials were stored over indicating calcium sulfate.

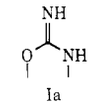
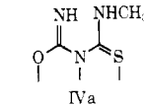
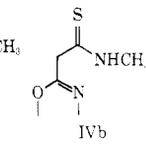
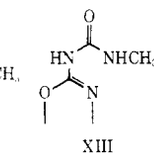
^1H NMR spectra were recorded on either Varian A-60-A or T-60 spectrometers in $CDCl_3$ with internal Me_4Si unless otherwise noted. GC–MS data were recorded on either LKB 9000 or Varian Mat CH-7 instruments. ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer with all values referenced to internal Me_4Si. GC was performed on a Hewlett-Packard 402 instrument with glass columns and He carrier gas.

2-Amino-3′,5′-bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran[1′,2′:4,5]-2-oxazoline (Ia). To 3.48 g (0.02 mol) of 2-amino-β-D-arabinofuran[1′,2′:4,5]-2-oxazoline[14e] in 50 mL of dry DMF (dimethylformamide, distilled from CaH_2 and stored over activated 4-A molecular sieves) under N_2 in an ice bath was added 3.40 g (0.05 mol) of imidazole, followed by 7.5 g (0.05 mol) of *tert*-butyldimethylsilyl chloride. After 15 min, the now homogeneous solution was allowed to come to room temperature and was stirred for another 2 h. The solution was poured into a stirred, cold 2% sodium carbonate solution (300 mL), filtered after 10 min, washed with 50 mL of cold water, and then allowed to partially dry at room temperature for several hours. The off-white solid was azeotroped once with benzene and then dissolved in hexane (250 mL) with heating, allowed to crystallize, and then filtered and dried at room temperature. Final recovery from the mother liquor yielded a total of 7.0 g (87% yield). An analytical sample recrystallized from hexane had mp 172–173 °C (the product will sublime in vacuo); IR (CCl_4) 1705 cm^{-1} (C=N); NMR δ 5.88 (1 H, d, J = 5.5 Hz, C-1′), 4.50 (1 H, dd, J = 5.5 Hz, C-2′), 4.37 (1 H, m, C-3), 4.3 (2 H, br, NH_2), 3.83 (1 H, m, C-4), 3.62 (2 H, m, C-5), 0.90 (18 H, s, *tert*-butyl), 0.13 and 0.08 (9 H, s, CH_3); TLC, R_f 0.22 (85% EtOAc/hexane); GC, 1.9 min (270 °C, 6 ft, 3.8% UCW-98); GC–MS 402 (no M^+), 387 (2, M − CH_3), 345 (12, M − *tert*-butyl), 261 (29), 97 (35), 89 (100).

Anal. Calcd for $C_{18}H_{38}N_2O_4Si_2$: C, 53.69; H, 9.51; N, 6.96. Found: C, 53.24; H, 9.38; N, 6.78.

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran-[1′,2′:4,5]oxazolo-5-methyl-4-thiono-1,3,5-triazin-6-one (Vb). To 51 mg (1.0 mmol) of 45% NaH (washed twice with hexane) in 10 mL of dry THF at room temperature under N_2 was added 402 mg (1 mmol) of the aminooxazoline Ia in several portions. After 30 min of stirring, the reaction was cooled in an ice bath and 75 μL of CH_3NCS in 125 μL of THF was added dropwise over 10 min. Stirring was continued for 1 h at 5 °C and then for 30 min while warming to room temperature. The solution was taken up in EtOAc, washed with water and brine, and dried over Na_2SO_4. After concentration, the solution was dissolved in 50% EtOAc/hexane and rapidly passed through a 15-g silica gel column with the same solvent. The UV-absorbing material was collected and concentrated, yielding 410 mg (86% yield) of a yellow oil. Separation of the isomers can be achieved by careful column chromatography to ~80% of a single component. NMR (approximately an equal mixture of the two isomers) δ 6.93 and 6.00 (d, J = 5.5 Hz, C-1′), 4.80 and 4.70 (d, J = 5.5 Hz, C-2′), 3.18 and 3.10 (d, J = 5 Hz, N–CH_3); TLC, R_f 0.55 (25% EtOAc/hexane), 0.37 (both UV-active); LC, t_R = 5.0 and 15 min with 2.5% EtOAc/hexane at 1.5 mL/min on a 12-in Lichrosorb SI-60 column.

Table IV[a]

	 Ia	 IVa	 IVb	 XIII
C-2	162.9	155.3	163.2	158.5
C-4			189.8	169.9
C-6		170.8		56.2
N–CH_3		32.1	31.9	34.6

[a] The assignments are given in ppm in $CDCl_3$ (0.1–0.4 M) with 0.5-s acquisition time. Only the triazine-ring structure is shown, as the bis(silyl)-protected furanose was deleted for simplification.

A 410-mg amount of the isomers was treated with 43 mg of hexane-washed NaH (45% oil dispersion) in 5 mL of dry THF at room temperature under N_2 with stirring. After gas evolution ceased, 275 mg of carbonyldiimidazole (1.7 mmol) was added, and the reaction was stirred for 24 h. The heterogeneous solution was worked up as above, including the rapid chromatography, to yield 415 mg (83%) of a yellow solid: IR ($CHCl_3$) 1730 and 1645 cm^{-1} (C=N, C=O) 1100 (C=S); NMR, isomer Va, δ 6.65 (1 H, d, J = 5.5 Hz, C-1′), 5.15 (1 H, d, J = 5.5 Hz, C-2′), 3.66 (3 H, s, N–CH_3); NMR, isomer Vb, δ 6.43 (1 H, d, J = 5.5 Hz, C-1′), 5.23 (1 H, dd, J = 5.5 Hz, C-2′), 3.66 (3 H, s, N–CH_3); TLC, one spot, R_f 0.43 (25% EtOAc/hexane); GC, Va, 7.4 min (55%), Vb, 8.7 min (45%) (265 °C, 4 ft, 3.8% UCW-98); LC, isomer A, t_R = 18 min, isomer B, 21 min (5% EtOAc/hexane at 1.5 mL/min on a 12-in Lichrosorb SI-60 column); (repeated crystallization from ethanol yielded pure isomer Vb with mp 160–161 °C) GC–MS, Va, 501 (no M^+), 444 (23, M^+ − *tert*-butyl), 298 (26), 261 (62), 231 (31), 89 (100); GC–MS, Vb (no M^+), 444 (M^+ − *tert*-butyl), 261 (65), 231 (33), 184 (46), 89 (100).

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran-[1′,2′:4,5]oxazolo-5-methyl-1,3,5-triazin(4,4*H*)-6-one (VI). A 415-mg amount (0.83 mmol) of the ca. 1:1 Va and b isomer mixture was dissolved in absolute ethanol (10 mL) and stirred with 1 mL of Raney nickel (active No. 28, Grace), which had been washed with distilled water extensively and then ethanol likewise. After 1 h at room

temperature, the solution was filtered and concentrated on the rotovapor. GLPC analysis indicated a new peak (6.2 min) with concomitant disappearance of isomer Vb (15.5 min at 250 °C, 4 ft, 3.8% UCW-98; isomer Va still substantially present). The resultant oil was chromatographed employing 60% EtOAc/hexane on a Merck B silica gel column with a 2.0 mL/min flow rate. A 120-mg amount (32% yield) of a colorless oil, which is an overall yield of 20% from Ia, was recovered: IR (CCl_4) 1750 cm^{-1} (C=O), 1720 (C=N); NMR δ 6.18 (1 H, d, J = 5.5 Hz, C-1′), 4.82 (1 H, dd, J = 5.5 Hz, C-2′), 4.72 (2 H, "d" or AB, J < 1 Hz, C-4), 4.55 (1 H, m, C-3′), 3.95 (1 H, m, C-4′), 3.65 (2 H, m, C-5′), 2.90 (3 H, s, N-CH_3), 0.88 (18 H, s, *tert*-butyl), 0.13 and 0.05 (9 H, s, CH_3-Si); UV (EtOH) λ_{min} 265 nm sh (ϵ 350); UV λ_{max} 215–220 nm (ϵ 2000); MS M^+ 471.2560 (calcd for $C_{21}H_{41}N_3O_5Si_2$), 471.2584 (found); GC–MS 471 (no M^+), 456 (2, $M^+ - CH_3$), 414 (14, M^+ – *tert*-butyl), 261 (32), 231 (16), 89 (100); $[\alpha]_D$ −140 ± 14° (EtOH); ORD, $[\phi]_{229}$ −12 400 (trough); CD, $[\theta]_{218}$ −7300 (shoulder); TLC, R_f 0.57 (85% EtOAc/hexane).

3′,5′-Bis(*O*-acetyl)-β-D-arabinofuran[1′,2′:4,5]oxazolo-5-methyl-1,3,5-triazin(4,4*H*)-6-one. To 680 mg (1.45 mmol) of the bis(silyl)-2,2′-anhydro-VI in 20 mL of dry THF under N_2 at room temperature was added with stirring 4.9 mL of tetra-*n*-butylammonium fluoride solution in THF (prepared by the procedure of Pless[28] to a concentration of 0.65 mmol/mL in THF and stored under N_2 over activated 4-Å molecular sieves at 5 °C). After 2 h, the solution was concentrated and placed under 0.01 Torr for 1 h. The resultant gum was taken up in 10 mL of dry pyridine, to which was added, under N_2 with stirring, 3 mL of distilled acetic anhydride. After 4 h at room temperature, the solution was concentrated under high vacuum, taken up in EtOAc, and added to a 100-g silica gel column prepared in the same solvent. After elution with 200 mL of EtOAc, the solvent was changed to 5% MeOH in EtOAc. A 380-mg (80% yield) amount of product was recovered: NMR δ 6.30 (1 H, d, J = 5.5 Hz, C-1′), 5.30 (1 H, m, C-3′), 5.08 (1 H, d, J = 5.5 Hz, C-2′), 4.77 (2 H, J_{AB} = −11 Hz, C-4), 4.0–4.6 (3 H, m, C-4′,5′), 2.91 (3 H, s, N-CH_3), 2.13 and 2.10 (6 H, s, CH_3CO); TLC, R_f 0.49 (10% MeOH/EtOAc); GC, 2.6 min (240 °C, 3.8% UCW-98, 4 ft); GC–MS 327 (3, M^+), 284 (3, $M^+ - CH_3CO$), 225 (12, $M^+ - CH_3 - 2\ CH_3CO$), 183 (22), 128 (100).

Cyclization of 3-β-D-Ribofuranosyl-5-methyl-1,3,5-triazin(4,4*H*)-6-one to the 2,2′-Anhydroarabinofuranosyl. To 300 mg (1.1 mmol) of the riboside XV in 5 mL of dry DMF under N_2 was added 490 mg (2.3 mmol) of diphenyl carbonate and 20 mg of sodium bicarbonate. The stirred solution was heated to 145 °C for 30 min. The resulting brown solution was cooled and poured into 200 mL of ether with stirring. The brown solid was collected by decantation and washed with another 50 mL of ether. It was then taken up in 20 mL of dry DMF, to which was added, under N_2 with stirring, 375 mg (2.5 mmol) of *tert*-butyldimethylsilyl chloride and 173 mg of imidazole. After 3 h at room temperature, the solution was taken up in 100 mL of EtOAc and washed with 50 mL of water, followed by brine. The initial aqueous phase was back-extracted with EtOAc, and this was combined, dried over Na_2SO_4, and concentrated. Chromatography on a Merck silica gel A column employing 40% EtOAc/hexane yielded 20 mg (4% yield) of the anhydro-2,2′-nucleoside. This was identical with VI by TLC (85 and 50% EtOAc/hexane), GC (265 °C, 3.8% UCW-98, 6 ft, 6.0 min), ^1H NMR, and GC–MS.

***S*-Ethyl *N*-Methylthiocarbamate.** To 20 mL of dry ether under N_2 was added 6.0 mL (7.14 g, 0.115 mol) of ethanethiol. The solution was cooled in an ice bath, and 5 mg of a 45% NaH/oil dispersion was added, followed by the rapid dropwise addition of 3.0 mL (4.0 g, 0.07 mol) of methyl isocyanate. Approximately 15 min after the addition was completed, the reaction was taken up in 100 mL of ether, washed with a 50% saturated brine solution (25 mL), dried over $MgSO_4$, and concentrated at reduced pressure to yield 6.3 g (75%): bp 62–68 °C (0.3 mm); NMR δ 6.0 (1 H, brd s, NH), 2.92 (2 H, q, J = 7 Hz, SCH_2), 2.87 (3 H, d, J = 4 Hz, NCH_3), 1.27 (3 H, t, J = 7 Hz, CH_3).

Anal. Calcd for C_4H_9NOS: C, 40.31; H, 7.61; N, 11.75. Found: C, 40.40; H, 7.66; N, 12.64.

S-Ethyl *N*-Hydroxymethyl-*N*-methylthiocarbamate. To 6.3 g (0.053 mol) of the *N*-methylthiocarbamate in 20 mL of water were added 5 mL of 37% formaldehyde, 50 mg of potassium carbamate, and 3 mL of MeOH. The reaction solution was stirred for 2 h at room temperature. Approximately 20 mL of saturated NaCl (aqueous) was added, and the mixture was extracted with 2 × 75 mL of methylene chloride. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. TLC analysis indicated the usual mixture of starting material and desired product. The mixture was resolved by a 200-g silica gel column employing 40% EtOAc/hexane eluant. The product was obtained in 49% yield (3.85 g). The recovered starting material can be recycled. IR (neat) 3400 cm^{-1} (OH), 1650 (C=O); ^1H NMR δ 4.88 (2 H, s, CH_2OH), 4.6 (1 H, brd s, OH), 3.03 (3 H, s, N-CH_3), 2.90 and 1.27 (SCH_2CH_3); ^{13}C NMR 170.05 ppm (C=O), 72.57 (NCH_2O), 33.71 (NCH_3), 24.67 (SCH_2), 15.18 (CH_3); TLC, R_f 0.41 (50% EtOAc/hexane).

Anal. Calcd for $C_5H_{11}NO_2S$: C, 40.24; H, 7.43; N, 9.39. Found: C, 40.01; H, 7.97; N, 9.37. Ethyl *N*-hydroxymethyl-*N*-methylcarbamate is prepared analogously.

***S*-Ethyl *N*-Bromomethyl-*N*-methylthiocarbamate (XII).** To 300 mg (2.0 mmol) of the hydroxymethylthiocarbamate in 15 mL of hexane/1 mL of benzene were added 87 mg (1 mmol) of lithium bromide (anhydrous) and 2.0 mL of 48% hydrobromic acid. The solution was stirred vigorously under N_2 for 2.5 h, following which the organic phase was decanted off. The aqueous phase was washed once with 10 mL of hexane and then combined with the hexane/benzene mixture and concentrated (rotovapor), followed by the addition of 10 mL of benzene and reconcentrating to give 400 mg of a slightly yellow oil. The NMR spectrum ($CDCl_3$) indicated ca. 75–80% bromide (δ 5.38 singlet for CH_2Br and NCH_3 singlet at δ 3.32) and 20–25% starting material. The starting material was also noted by TLC. However, the bromide product appeared to decompose on silica gel TLC. The bromide product was usually utilized immediately after preparation but could be stored in benzene at <0 °C for several months. The yield (NMR-based) was ca. 70%.

1-(*S*-Ethyl *N*-Methyl-*N*-methylenethiocarbamoyl)-3′,5′-bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran[1′,2′:4,5]-2-oxazolimine (XIII). To 51 mg (1 mmol) of 45% NaH/oil dispersion (washed twice with hexane) in 10 mL of dry THF under N_2 at room temperature was added 402 mg (1 mmol) of the bis(TBDMS)aminooxazoline Ia in several portions. After gas evolution ceased, 400 mg (ca. 1.4 mmol, 75% purity) of the bromomethylthiourethane (XII) was added dropwise (in ca. 1 mL of THF via a glass pipette) with stirring over a 5-min period. After stirring for 1 h, the heterogeneous solution was taken up in EtOAc, washed once with 50% saturated saline, dried over Na_2SO_4, and concentrated. Column chromatography (Merck silica gel B, 5 EtOAc/hexane) afforded 255 mg (48% yield) of the monoalkylated product (usually a smaller amount of slightly higher R_f bis(alkylated)oxazolimine was seen by TLC, depending on how much starting material remained): IR (neat) 3350 cm^{-1} (NH), 1700 (C=N), 1665 (C=O); NMR δ 5.82 (1 H, d, J = 5.5 Hz, C-1′), 5.00 (2 H, dd, J_{AB} = −15 Hz, no collapse with MeOH-d_4 and D_2O, C-6), 4.95 (1 H, s, NH), 4.67 (1 H, d, J = 5.5 Hz, C-2′), 4.48 (1 H, m, C-3′), 4.0 (1 H, m, C-4′), 3.62 (2 H, m, C-5′), 3.13 (3 H, s, N-CH_3), 2.99 (2 H, q, J = 7 Hz, S-CH_2), 1.35 (3 H, t, J = 7 Hz, CH_3), 0.91 (18 H, s, *tert*-butyl), 0.15 and 0.07 (9 H, s, CH_3-Si); TLC, R_f 0.50 (50% EtOAc/hexane); GC, 5.8 min (4 ft, 3.8% UCW-98, 260 °C); GC–MS for *S*-methyl ester, 519 (M^+), 504 ($M^+ - CH_3$), 462 (M^+ – *tert*-butyl), 444 ($M^+ - CO_2Et$), 415 (M^+ – *tert*-butyl – OEt), 261 (100).

3-(*S*-Ethyl *N*-Methyl-*N*-methylenethiocarbamoyl)-1-*N*-acetyl-3′,5′-bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran-[1′,2′:4,5]-2-oxazolimine. To 53 mg (0.1 mmol) of XIII in 2 mL of distilled acetic anhydride at room temperature under N_2 was added 20 mg of anhydrous sodium acetate. After stirring for 30 min, the reaction solution was concentrated. The resulting oil was taken up in EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated to yield 57 mg (100%): IR ($CHCl_3$) 1610–1670 cm^{-1} [broad C=O (C=N)]; UV (EtOH) λ_{max} 233 nm (ϵ 17 500), OEt analogue – λ_{max} = 232 nm (ϵ 9500); NMR ($CDCl_3$) two equivalent CH_3CO singlets at δ 2.04 and 2.15; TLC, R_f 0.61 (50% EtOAc/hexane).

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-β-D-arabinofuran-[1′,2′:4,5]oxazolo-5-methyl-1,3,5-triazin(6,6*H*)-4-one (II). To 25 mL of dichloromethane was added 530 mg (1 mmol) of the thiocarbamoyloxazoline XIII, followed by cooling to 5 °C under N_2. With stirring, 500 mg (2.2 mmol, 81% pure) of *m*-chloroperbenzoic acid was added followed by 130 mg (1 mmol) of sodium carbonate. After 1 h at 5 °C followed by 1 h at room temperature, the solution was taken up in EtOAc, washed with saturated sodium bicarbonate and then brine, dried over Na_2SO_4, and concentrated. Chromatography on a Merck A silica gel column employing 90% EtOAc/hexane afforded 370 mg of a white solid (77% yield). Recrystallization from hexane gave mp 145–147 °C (sublimation noted); IR (CCl_4) 1665 cm^{-1} (C=O, C=N); NMR δ 5.82 (1 H, d, J = 5.5 Hz, C-1′), 4.99 (1 H, d, J = 5.5 Hz, C-2′), 4.72 (2 H, s, C-6), 4.52 (1 H, m, C-3′), 4.07 (1 H, m, C-4′), 3.60 (2 H, m, C-5′), 2.93 (3 H, s, N-CH_3), 0.90 and 0.87 (18 H, s, *tert*-butyl), 0.15 and 0.06 (9 H, s, CH_3Si); UV (EtOH) λ_{max} 238 nm (ϵ 4050); UV (EtO_2) λ_{max} 227 nm (3950); MS 471 (no M^+), 456 ($M^+ - CH_3$), 414 (M^+ – *tert*-butyl); $[\alpha]_D$ −130 ± 16°; ORD, $[\phi]_{258}$ −20 300 (0 at 239 mμ) $[\phi]_{218}$ +17 800; CD, $[\theta]_{241}$ −28 400; TLC, R_f 0.12 (85% EtOAc/hexane).

Anal. Calcd for $C_{21}H_{41}N_3O_5Si_2$: C, 53.47; H, 8.76; N, 8.90. Found: C, 53.54; H, 8.55, N, 8.92.

3′,5′-Di-*O*-acetyl-β-D-arabinofuran[1′,2′:4,5]oxazolo-5-me-

thyl-1,3,5-triazin(6,6*H*)-4-one (XVII). To 155 mg (0.3 mmol) of II in 5 mL of dry THF under N_2 at room temperature was added 1.1 mL of tetra-*n*-butylammonium fluoride/THF solution. After 2 h of stirring, the solution was concentrated and stored at 0.1 Torr for 1 h, subsequent to which it was dissolved in 3 mL of dry pyridine and 1 mL of distilled acetic anhydride. After 4 h of stirring at room temperature, the solution was concentrated in vacuo, applied to two 20 × 20 cm, 2000 μ silica gel plates, and eluted with 3 MeOH/EtOAc. The recovered UV band (R_f 0.23 on TLC, same solvent) yielded 82 mg (84% yield): NMR δ 5.99 (1 H, d, J = 5.5 Hz, C-1′), 5.3 (2 H, m, C-2′,3′), 4.78 (2 H, dd, $J_{AB} = -7$ Hz, C-6), 3.9–4.6 (3 H, m, C-4′,5′), 2.95 (3 H, s, NCH_3), 2.13 and 2.08 (6 H, s, CH_3CO).

3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-1-β-D-arabinofuranosyl-5-methyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (XVI). To 100 mg (0.2 mmol) of II in 2 mL of THF was added 100 μL of 50% ammonium hydroxide, and the mixture was stirred for 48 h. The solution was concentrated and azeotroped in vacuo twice with benzene. After preparative TLC (four 20 × 20 cm, 250 μ silica gel plates) in EtOAc, the product was isolated in 50% yield (50 mg): R_f 0.37 in 85% EtOAc/hexane; no UV; NMR ($CDCl_3$) δ 5.80 (1 H, d, J = 6 Hz, C-1′), 5.2 (2 H, brd s, NH and OH), 4.81 (2 H, dd, $J_{AB} \simeq -10$–12 Hz, C-6), 4.68 (1 H, d, $J \simeq 6$ Hz, C-2′), 3.02 (3 H, s, $N-CH_3$), remainder unchanged from III; GC, 3.6 min (240 °C, 6 ft, 3.8% UCW-98), 2.6 min for II at 255 °C; MS (no M^+) 474 ($M^+ - CH_3$), 433, 432 (M^+ – *tert*-butyl), 261.

Acknowledgment. The authors thank Mr. S. A. Mizsak for performing the LISC calculations and some of the NMR-shift studies, Drs. G. Slomp and B. V. Cheney for the use of their LISC program, and Dr. J. C. Babcock for helpful discussions.

Registry No.—VI, 64332-43-0; II, 64332-44-1; Va, 64332-45-2; Vb, 64332-46-3; Ia, 64332-51-0; IVa, 64332-52-1; IVb, 64332-53-2; XIII, 64332-54-3; I (R = H), 27963-98-0; VIII, 53774-80-4; IX, 64332-55-4; XII, 64332-56-5; 3-*N*-acetyl XIII, 64345-59-1; XVII, 64332-57-6; methylurethane, 105-40-8; *tert*-butyldimethylsilyl chloride, 18162-48-6; 3′,5′-di-*O*-acetyl-β-D-arabinofuran[1′,2′:4,5]oxazolo-5-methyl-1,3,5-triazin(4,4*H*)-6-one, 64332-58-7; *S*-ethyl *N*-methylthiocarbamate, 14128-44-0; ethanethiol, 76-08-1; methyl isocyanate, 624-83-9; *S*-ethyl *N*-hydroxymethyl-*N*-methylthiocarbamate, 64332-59-8.

References and Notes

(1) Presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., 1976, Abstracts, No. CARB 44.
(2) C. DeBoer and B. Bannister, U.S. Patent 3 907 643 and 3 907 779 (1975).
(3) H. E. Renis, B. A. Court, and E. F. Edison, Abstracts, the ASM Meeting, Atlantic City, N.J., 1976.
(4) Unpublished results, Dr. J. Gray, Pathology and Toxicology, The Upjohn Co.
(5) H. I. Skulnick, unplublished results.
(6) L. Goodman, *Basic Prin. Nucleic Acid. Chem.*, **1**, 180–186 (1974).
(7) R. A. Sanchez and L. E. Orgel, *J. Mol. Biol.*, **47**, 531 (1971).
(8) Standard conditions (acetic acid) for trityl or THP removal decomposed the nucleoside, III,[5] presumably due to ring opening at the aminal carbon (C_6).
(9) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(10) K. K. Ogilvie, E. Thompson, M. A. Quilliam, and J. B. Westmore, *Tetrahedron Lett.*, 2865 (1974); K. K. Ogilvie, S. L. Beaucage, D. W. Entwistle, E. A. Thompson, M. A. Quilliam and J. B. Westmore, *J. Carbohydr., Nucleosides, Nucleotides*, **3**, 197 (1976).
(11) See, for examples, H. Reimlinger, *Chem. Ber.*, **104**, 2232 (1971); M. Nagano, J. Tobitsuka, T. Matsui, and K. Oyamada, *Chem. Pharm. Bull.*, **20**, 2619 (1972); D. L. Klayman and T. S. Woods, *J. Org. Chem.*, **39**, 1819 (1974).
(12) Unpublished results. This and related work will be published elsewhere.
(13) W. R. Boon, H. C. Carrington, N. Greenhalgh, and C. H. Vasey, *J. Chem. Soc.*, 3263 (1954).
(14) (a) D. T. Gish, G. L. Neil, and W. J. Wechter, *J. Med. Chem.*, **14**, 882 (1971); (b) C. M. Hall, G. Slomp, S. A. Miszak, and A. J. Taylor, *J. Org. Chem.*, **37**, 3290 (1972); (c) D. H. Shannahoff and R. A. Sanchez, *ibid.*, **38**, 593 (1973); (d) A. Holy, *Collect. Czech. Chem. Commun.*, **39**, 3177 (1974), and references therein; (e) E. J. Hessler, *J. Org. Chem.*, **41**, 1828 (1976).
(15) H. Volz and H. H. Klitz, *Tetrahedron Lett.*, 1917 (1970), reported trityl cation mediated-hydride abstraction of several dialkyl (aryl) methylamines.
(16) (a) We have accomplished ring closure in a model study utilizing the 2-aminopyridine system. Several examples of reports on ring closure of other carbamates include W. Standbauer and T. Keppe, *Chem. Ber.*, **109**, 3661 (1976), S. Y.-K. Tam, J-S. Hwang, F. G. DeLas Heras, R. S. Klein, and J. J. Fox, *J. Heterocycl. Chem.*, **13**, 1305 (1976), and R. Esmail and F. Kurzer, *Synthesis*, 301–314 (1975), and references cited therein. (b) We have found in a model system that 1 equiv of peracid was sufficient for cyclization, implicating the sulfoxide oxidation state as the penultimate intermediate.
(17) (a) There are several examples of a much more reactive system where chloride is the leaving group; however, the problem of regioselectivity is magnified due to competition for initial condensation with the carbonyl as well. Uses and preparations of (1-chloroalkyl)carbamoyl chlorides include J. P. Chupp, *J. Heterocycl. Chem.*, **8**, 677 (1971), H. Kieffer, *Synthesis*, 39 (1972), and K. Koyano and C. R. McArthur, *Can. J. Chem.*, **51**, 333 (1973). (b) G. Jaeger, C. Metzer, W. Ritter, and R. Wegler, German Patent 2 119 278 (1972); *Chem. Abstr.*, **78**, 58109u (1973), reports the preparation of *N*-(chloromethyl)carbamates and thiocarbamates.
(18) D. H. R. Barton, D. P. Manly, and D. A. Widdowson, *J. Chem. Soc., Perkin Trans.* 1, 1568 (1975).
(19) (a) T. Kumamoto and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **41**, 2111 (1968); (b) S. Masamusne, S. Kumata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975).
(20) Derived from the LISC program compiled by G. Slomp and B. V. Cheney, based on M. R. Willcott III, R. E/ Lenkinski, and R. F. David, *J. Am. Chem. Soc.*, **94**, 1749 (1972).
(21) D. J. Duchamp, unpublished results.
(22) We thank B. Bannister, S. A. Mizsak, and G. Slomp for the unpublished data.
(23) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Am. Chem. Soc.*, **92**, 4079 (1970); *J. Phys. Chem.*, **74**, 2684 (1970).
(24) D. E. Dorman and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, **65**, 19 (1970).
(25) The suggested assignments of C-2 and C-6 in structure VI were derived from the best-shift correlations with structures II, IV, V, XIII, and the 6-oxo analogue of II (not shown),[12] which exhibits C-2 (155.5 ppm), C-4 (161.2), and C-6 (147.4).
(26) We thank H. I. Skulnick for this compound.
(27) T. Kanai, M. Ichino, A. Hoshi, F. Kanzawa, and K. Kuretani, *J. Med. Chem.*, **15**, 1218 (1972).
(28) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).
(29) J. Pless, *J. Org. Chem.*, **39**, 2645 (1974).