1625, 1590 cm^{-1}; ^1H NMR (T-60) δ 1.25 (3 H, t, J = 6.5 Hz, OCH_2CH_3), 4.17 (2 H, q, J = 6.5 Hz, OCH_2CH_3), 7.00–7.67 (4 H, m, aromatic), 12.25 (2 H, br, NH).

8(7*H*,9*H*)-(Carbethoxycyanomethylene)theophylline (26). $FeCl_3 \cdot 6H_2O$ (1.9 g, 7.2 mmol) was added to a suspension of **4b** (1 g, 3.6 mmol) in 100 mL of water, and the mixture was heated on a water bath for 1 h. Crystals were filtered off and washed with water and EtOH to give an almost pure sample of **26** in 60% yield, which was recrystallized from water: mp 246–247 °C; mass analysis, m/e 291.0967 (M^+, calcd 291.0967), 245.0523 (M^+ – EtOH, calcd 245.0548); IR (KBr) 2220, 1715, 1680, 1605 cm^{-1}; ^1H NMR δ 1.23 (3 H, t, J = 6.5 Hz, OCH_2CH_3), 3.20 (3 H, s, NCH_3-1), 3.53 (3 H, s, NCH_3-3), 4.12 (2 H, q, J = 6.5 Hz, OCH_2CH_3), 6.47 (2 H, br, NH).

8-(Cyanomethyl)theophylline (27). A solution of 0.1 g of **26** in 10 mL of DMF was refluxed at 180 °C for 2 h. The solution was evaporated to dryness and the residue was washed with DMF and hot ethanol to give a powder of pure **27** in 90% yield: mp 260–261 °C; mass analysis, m/e 219 (M^+); IR (KBr) 2260, 1710, 1642 cm^{-1}; ^1H NMR (T-60) δ 3.22 (3 H, s, NCH_3-1), 3.42 (3 H, s, NCH_3-3), 4.20 (2 H, s, CH_2).

Registry No. **1a**, 21025-49-0; **1b**, 21025-47-8; **3a**, 87984-97-2; **3b**, 42510-47-4; **4a**, 21025-59-2; **4b**, 21025-58-1; **4c**, 87970-39-6; **12a**, 59495-67-9; **12b**, 59495-66-8; **15**, 6726-48-3; **16**, 61165-09-1; **19a**, 61165-10-4; **19b**, 61165-11-5; **19d**, 61165-12-6; **19e**, 61165-13-7; **21a**, 61165-14-8; **21b**, 61165-15-9; **21c**, 61165-16-0; **22a**, 4933-40-8; **22b**, 59591-86-5; **26**, 87970-38-5; **27**, 37941-31-4.

A Ring Expansion Approach to 1,3-Diazepin-2-one Nucleosides

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A ring expansion approach toward the still unreported riboside of 4-methoxy-1,3,4,5-tetrahydro-2*H*-1,3-diazepin-2-one (**15**) was developed. To that effect, the easily accessible 1-β-D-ribofuranosyl-1,2-dihydropyrimidin-2-one was converted to the corresponding cyclopropa[4,5]pyrimido ring system in two steps by taking advantage of the nucleoside's tendency to exist completely in its cyclic form **11a** when suitably protected by the 2',3'-isopropylidene moiety. This property permitted an easy access to the required bicyclic system through a dihalocarbene insertion reaction on the olefinic bond of **11a–d** with $C_6H_5HgCX_2Br$ (X = Cl or Br). These two steps were found to be completely stereospecific, giving in each case a single isomer with the absolute stereochemistry as depicted in structures **12a–e** and **14a,b**. Definite confirmation of these assignments was corroborated by single-crystal X-ray analysis of **12a** (Figure 1). The conversion of **12d** to **14b** was sequentially performed with n-Bu_3SnH and with NaOMe/MeOH (stoichiometric) in order to remove the halogen atoms and the protective *N*-benzoyl group. Adjustment of the final methanolic reaction mixture to pH 4 induced a rapid and quantitative ring expansion of **14b** to **15**, which was obtained as a mixture of C(4)-OMe epimers. This reaction represents the final step of a very efficient ring expansion method which afforded 26% yield of **15** from **11a** after five steps.

Coformycin (**4b**) and isocoformycin (**5b**), both powerful inhibitors of the enzyme adenosine deaminase,[2,3] have been isolated after the base-catalyzed ring expansion of the mesylated methanol photoadduct **1b** of 9-β-ribo-D-furanosylpurine (nebularine).[4,5] The course of this reaction appears very complex, and variable amounts of both compounds, plus other minor products, could be obtained by altering the conditions of the reaction.[4] Although no mechanism was provided to explain the formation of isocoformycin, both **4a** and **5a** can be visualized as resulting from two different pathways (a and b) as shown in Scheme I.

As a result of our continued interest in 1,3-diazepin-2-one nucleosides, which behave as potent inhibitors of a similar aminohydrolase, cytidine deaminase,[6,7] we decided to explore whether a similar mechanism of ring expansion was applicable to the pyrimidine series.

Synthetic Strategy

Retrosynthetic analysis of the desired targets, when analyzed in light of the mechanisms depicted in Scheme I, suggested structures **7** and **9** as probable precursors for the desired 1,3-diazepin-2-one nucleotides **6** and **8**.

Since we had already achieved the synthesis of compound **6** by other means,[8] it was decided to investigate the ring expansion approach for the construction of the 1,3-diazepin-2-one nucleoside of structure **8**. Precursor **9**, however, did not appear very practical in view of the expected instability of the glycosidic linkage caused by the positively charged nitrogen. Therefore, synthon **10**, with a potential leaving group X expected to be ejected during the course of the ring expansion, was considered. Such qualifications were met by the cyclonucleoside **14b** where the leaving group X is an oxygen atom that forms part of the sugar moiety itself. This key compound was prepared in two steps from **11a** as shown in Scheme II. The synthesis of **11a** was performed, as described previously, from 1-β-D-ribofuranosyl-1,2-dihydropyrimidin-2-one in 65% yield.[7,9] yield.[7,9]

(1) (a) Drug Design and Chemistry Section, LMCP, DTP, DCT, NCI, NIH. (b) Laboratory of Chemistry, NHLBI, NIH.
(2) Cha, S.; Agarwal, R. P.; Parks, R. E., Jr. *Biochem. Pharmacol.* **1975**, *24*, 2187.
(3) Shimazaki, M.; Kumada, Y.; Takeuchi, T.; Umezawa, H.; Watanbe, K. *J. Antibiot.* **1979**, *32*, 654.
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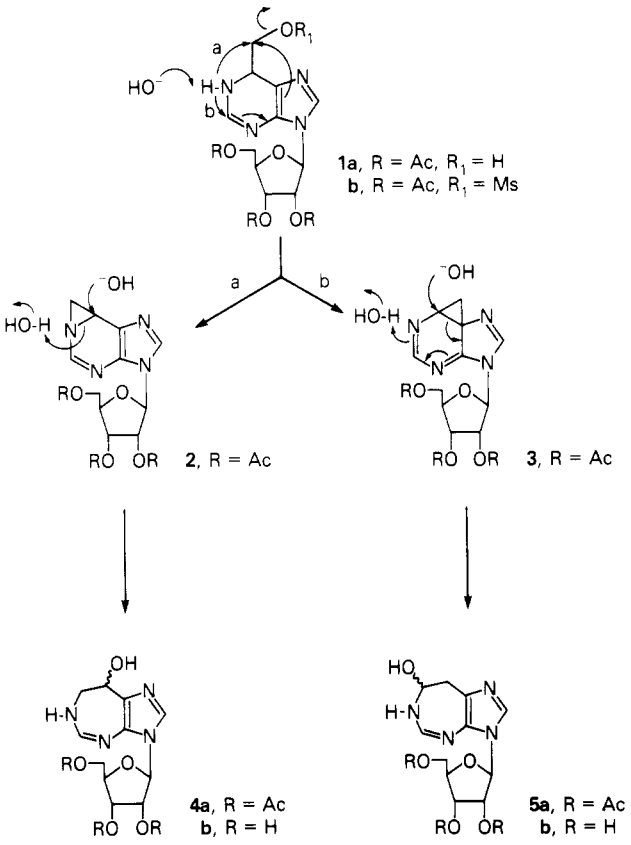
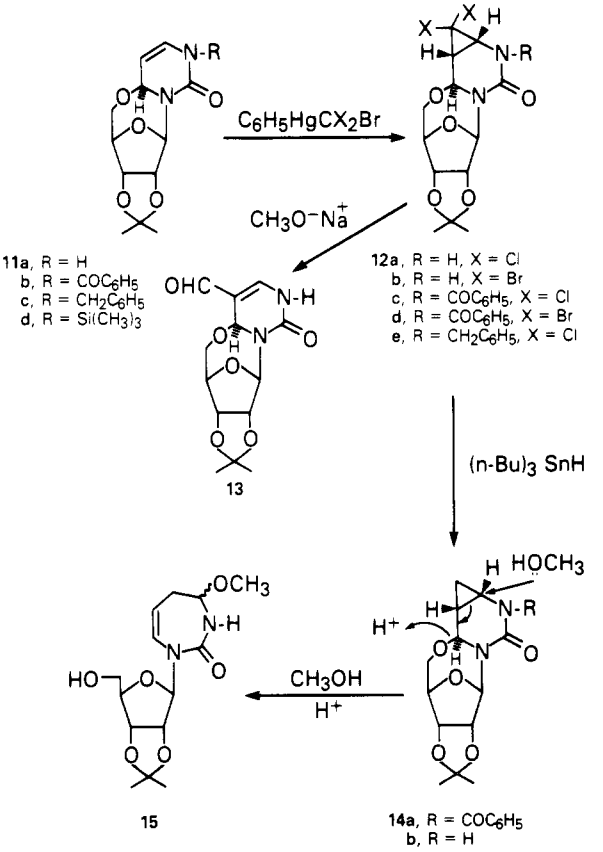
(8) Liu, P. S., Marquez, V. E.; Kelley, J. A.; Driscoll, J. S. *J. Org. Chem.* **1980**, *45*, 5225.
(9) Rao, K. V. B.; Marquez, V. E.; Kelley, J. A.; Corcoran, M. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 127.

0022-3263/84/1949-0912$01.50/0

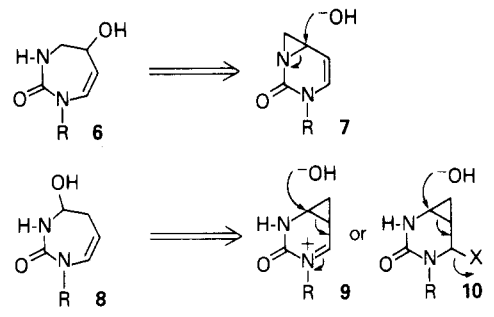
Scheme I



Scheme II



Compound **11a**, when suitably protected with benzoyl, benzyl, or trimethylsilyl groups at N-3 (**11b–d**), underwent a smooth dihalocarbene insertion reaction with the $:CX_2$ precursor $C_6H_5HgCX_2Br$ (X = Cl or Br)[10,11] to give good to excellent yields of the corresponding cyclopropa[4,5]-pyrimido ring system **12a–e**.[12] Reactions of this type with uridine derivatives have been reported previously by Pandit and co-workers,[13,14] and similar cyclopropa[5,6]-pyrimido ring systems have also been prepared by Kunieda and Witkop through the reaction of dimethyloxosulfonium methylide with protected uridine.[15] The use of the trimethylsilyl group permitted the synthesis of **12a** directly from **11a** in a single operation. Unfortunately, the same procedure did not work well for the preparation of the dibromocarbene adduct **12b**. A more general method for the synthesis of **12a** and **12b** was provided by deblocking the N-benzoylated intermediates **12c** and **12d**, which yielded the desired products after treatment with equimolar amounts of sodium methoxide. If excess of sodium methoxide was used, a base-catalyzed reaction ensued to give the aldehyde **13** (vide infra). The *N*-benzyl compound **12e**, however, was extremely stable toward debenzylation. Catalytic hydrogenation (40 psi) with PtO_2 at room temperature in methanol only caused the reduction of the benzene ring to cyclohexane. Kunieda and Witkop also noted a similar reduction of an *N*-benzyl protecting group when attempting to deblock dibenzylcyclothymine.[15]



R = β-D-Ribofuranosyl

The dihalocarbene insertion reaction with compounds **11b–d** was found to be very stereospecific and only one isomer was isolated in each case. These results were in contrast with carbene insertion reactions performed previously with uridine derivatives, which produced diastereoisomeric mixtures of adducts.[13] Confirmation of the basic skeleton of these molecules was obtained by observing the changes in the NMR spectra of these cyclonucleosides before and after the carbene reaction (Table I). In all these compounds the anomeric proton appeared as a singlet, indicating that in these rigid-caged structures the dihedral angle between C(1′)-H and C(2′)-H is close to 90°. The C(6)-H signal, which was situated very low (δ 4.81–5.53), was very informative and suggested that the configuration at this carbon was such that the hydrogen was down in the vicinity of the furanose oxygen. This situation was unequivocally confirmed later by X-ray crystallographic analysis of one of the dihalocarbene ad-

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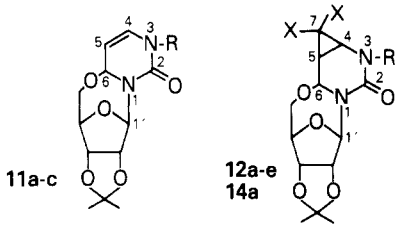
(11) Seyferth, D.; Mui, Y. P.; Damraner, D. *J. Am. Chem. Soc.* **1968**, *90*, 6182.
(12) While a more appropriate nomenclature for these bycyclic systems would be 2,4-diazabicyclo[4.1.0]heptane, we have chosen to name them as cyclopropa[4,5]pyrimido ring systems in order to preserve an analogous numbering sequence to the pyrimidine nucleosides.
(13) Thiellier, H. P. M; van der Burg, A. M.; Koomen, G. J.; Pandit, U. K. *Heterocycles* **1974**, *4*, 467.
(14) Thiellier, H. P. M; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1977**, *33*, 1493.
(15) Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3478.

Table I. NMR Spectra Data of Cyclonucleoside Derivatives[a]



compound	H-1′	H-4	H-5	H-6
11a (R = H)	5.80 (s)	6.25 (dd), $J_{4,5}$ = 8, $J_{4,NH}$ = 5	under 4.60 (m)	5.50 (d), $J_{6,5}$ = 3
11b (R = COC_6H_5)	5.76 (s)	7.10 (d), $J_{4,5}$ = 8	5.21 (dd), $J_{5,4}$ = 8, $J_{5,6}$ = 3	5.53 (d), $J_{6,5}$ = 3
11c (R = $CH_2C_6H_5$)	5.85 (s)	6.20 (d), $J_{4,5}$ = 8	under 4.75 (m)	5.50 (d), $J_{6,5}$ = 3
12a (R = H, X = Cl)	5.95 (s)	3.32 (m), 3.32 (d) (D_2O exchange), $J_{4,5}$ = 11	2.23 (d), $J_{5,4}$ = 11	5.07 (s)
12b (R = H, X = Br)	5.75 (s)	3.25 (m), 3.25 (d) (D_2O exchange), $J_{4,5}$ = 10	2.24 (d), $J_{5,4}$ = 10	4.83 (s)
12c (R = COC_6H_5, X = Cl)	5.98 (s)	under 4.09 (m)	2.49 (dd), $J_{5,4}$ = 10, $J_{5,6}$ = 3.5	4.98 (d), $J_{6,5}$ = 3.5
12d (R = COC_6H_5, X = Br)	5.84 (s)	3.78 (d), $J_{4,5}$ = 12.5	2.46 (dd), $J_{5,4}$ = 12.5, $J_{5,6}$ = 3.5	4.81 (d), $J_{6,5}$ = 3.5
12e (R = $CH_2C_6H_5$, X = Cl)	6.00 (s)	3.10 (d), $J_{4,5}$ = 11	2.15 (dd), $J_{5,4}$ = 11, $J_{5,6}$ = 1	5.02 (d), $J_{6,5}$ = 1
14a (R = COC_6H_5, X = H)	5.96 (s)	3.45 (m)	under 1.88 (m)	under 4.73 (m)

[a] Values are given in δ, J values in hertz.

ducts (vide infra). The coupling constants for these C(6)-H protons were small (1–3.5 Hz) in either the olefinic precursors or carbene adducts, except for the free N-H analogues **12a** and **12b**, where the coupling constants vanished to zero. The most diagnostic signals corresponded to those of the C(4)-H and C(5)-H protons, which displayed the expected upfield shift in the products **12a–e**. In addition, the coupling constants of 10–12.5 Hz were typical of cyclopropyl bridgehead protons for this class of compounds.[14] The assignment of the C(5)-H signal was facilitated by its further coupling to the C(6)-H proton and was also confirmed by double-resonance experiments. Irradiation of the C(5)-H signal at δ 2.15 in **12e**, for example, caused both the C(6)-H and C(4)-H doublets to coalesce to single resonances.

After this point had been reached in the synthesis, three new asymmetric centers had been generated in structures **12a–e**: one originating from the stereoselective formation of **11a** and two more simultaneously created by the carbene addition reaction. Although according to the synthetic strategy (Scheme II) two of these centers (C(5) and C(6)) were destined to disappear during the ring expansion leading to **15** and the third one was supposed to generate an epimeric mixture of 4-methoxydiazepinones, the determination of the stereochemistry of these products was of interest in view of the surprising stereoselectivity of these reactions both in the formation of **11a** and **12a–e**. Suitable crystals for X-ray analysis were obtained for compound **12a**, and the complete stereochemistry was resolved (Figure 1). The configuration of C(6) is α (down) as inferred previously from the NMR data (Table I) and consequently the O(5′) oxygen is up very close to the C(4)–C(5) bond of the pyrimidine ring. Since this situation must be the same in the precursor olefins **11a–d**, the O(5′) oxygen atom could efficiently block preferentially one face of the C(4)–C(5) double bond and, hence, direct the halocarbene addition from the opposite side, resulting in the formation of a single isomer. The reason as to why the cyclization of 1-β-D-ribofuranosyl-1,2-dihydropyrimidin-2-one leads exclusively to **11a** is not entirely clear; however, it probably has to do with the fact that formation of **11a** is an equilibrium process and therefore both the O(5′) and furanose oxygen (O(1′)) would tend to be as far as possible from each other in a configuration similar to that depicted in Figure 1 for structure **12a**.

Crystallographic Analysis of 12a

In order to facilitate the discussion the numbering system chosen is that commonly employed in pyrimidine nucleosides. In the structure of **12a** there are seven asymmetric centers; C(1′), C(2′), C(3′), C(4′), C(4), C(5), and C(6), and their absolute configurations are *R*, *R*, *R*, *R*, *R*, and *S*, respectively. Both five-membered rings have enveloped conformations, the first being an O(1′) envelope and the second a C(8) envelope. The seven-membered ring is in the twist-chair conformation, which, according to Bucourt,[16] is the most stable form for cycloheptane. There are some distortions form ideality, particularly in the decrease of the torsion angle of the N(1)–C(1′) bond from 41° to 25.1° and the increase in the torsion angle of the O(1′)–C(4′) bond to 92° from 76°. In principle, given the cyclopropane fusion and the carbonyl function, the six-membered ring might be expected to be fairly flat, although the planar form of cyclohexane itself has an increase in energy of 9.3 kcal over the nonplanar form.[17] The torsion angles in the ring are small; the largest being that at the N(1)–C(6) bond (−11.4°). While the ring is not flat, the deviations from the least-squares plane

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(17) Bucourt, R.; Hainaut, D. *Bull. Soc. Chim. Fr.* **1967**, 4562.

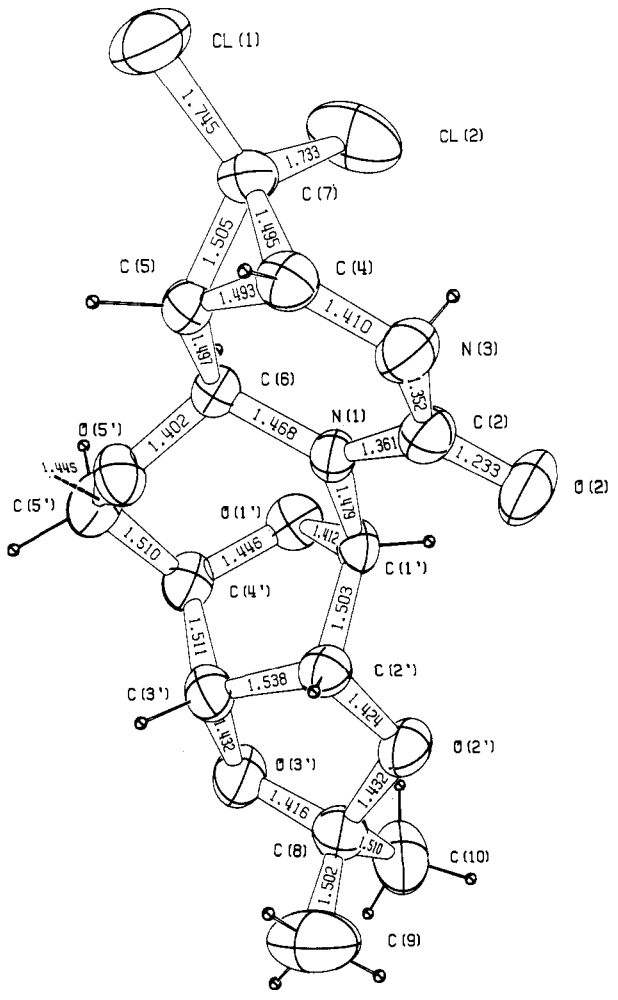
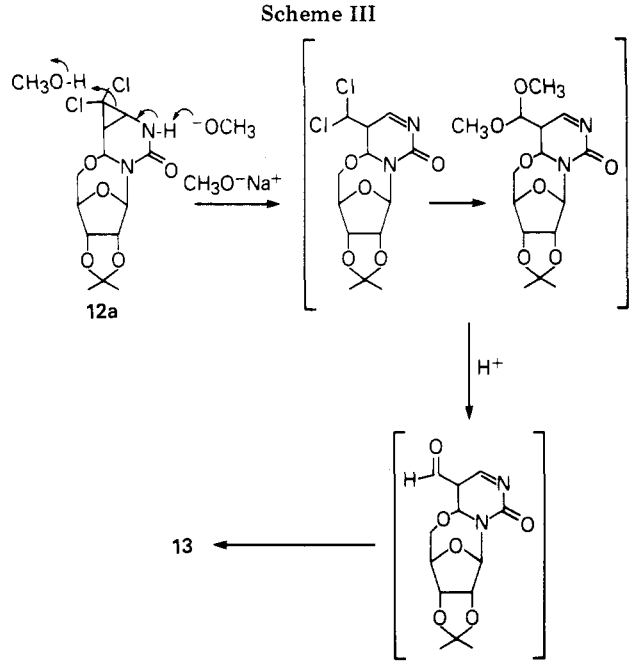


Figure 1. Three-dimensional structure of **12a** as determined from X-ray analysis.

through atoms N(1), C(2), N(3), C(4), C(5), and C(6) are small; the largest being that of C(6), which is 0.054 Å from the plane. O(2) is 0.034 Å out of the plane. While the groups N(3), C(4), C(5), and C(6) and N(1), C(2), O(2), and N(3) are not rigorously planar on the basis of the χ^2 test, maximum deviations from the appropriate least-squares planes are 0.004 and 0.005 Å, respectively. The last group has a very slight distortion toward tetrahedral bonding at C(2), which is 0.006 Å from the plane of the other three atoms. The two planar groups of atoms make an angle of 3.9° with each other. The bond lengths and crystal conformation are shown in Figure 1. Overall, the bond lengths are as might be expected although there are significant differences in the lengths of formally similar C–O bonds. There are some H atom interatomic contacts that are slightly shorter than the van der Waals distance (2.40 Å as given by Bondi).[18] The distances H-2′···H-3′, H-4···H-5, H-6···H-5′, and H-4′···H-5′ are 2.179, 2.358, 2.280, 2.305 Å, respectively. The only one of these that does not involve H atoms on adjacent heavy atoms is H-6···H-5′, and this contact is indicative of the deviation from the ideal minimum energy conformation for a seven-membered ring. Many H–C–C–H torsion angles deviate greatly from the normal multiples of 60° required by gauche conformations.

There do not appear to be many strong intermolecular interactions. However, there may be a hydrogen bond between N(3) and O(2′) in a molecule related by the *b* screw axis (N(3)···O(2′); 2.962 Å; H···O(2′); 2.647 Å; N-(3)-H···O(2′); 107.7°). The angle is rather far from 180°, but the H atom appears to form a bifurcated bond. N(3) is also close to Cl(2) in the same molecule (N(3)···Cl(2); 3.055 Å; H···Cl(2); 2.670 Å; N(3)-H···Cl(2); 114.3°). Although the relevant interatomic distances are not very short, they are less than the van der Waals distance of Bondi (N···O; 3.07 Å; N···Cl; 3.50 Å, H···O; 2.72 Å, and H···Cl; 2.95 Å).[18] There is also a short contact between Cl(2) and O(5′) in a molecule related by the *a* screw axis, 3.080 Å, which is significantly less than the van der Waals contact (3.27 Å)[18] and may be caused by dipolar interactions.

Scheme III



Ring Expansion

Initial attempts to induce compounds **12a–e** to undergo ring expansion by thermolysis[19] or electrophilic attack with Ag^+ salts[20] failed. Either unchanged starting material was recovered or numerous decomposition products were obtained under more drastic conditions. These results contrast with those of Pandit et al. who reported obtaining variable yields (unspecified) of diazepinone derivatives after the thermal ring expansion of dihalocyclopropauracil adducts.[19] These thermal ring openings appear to proceed by a concerted disrotatory motion that may be forbidden in the case of **12a–e** due to the rigidity of the molecular structure of these compounds, which would present a stiff opposition to the required bond rotation.

An attempted base-catalyzed ring opening of the cyclopropane ring also failed to produce a diazepinone ring system; instead, high yields of the aldehyde **13** were obtained. The most likely pathway for this ring opening is shown in Scheme III. Bond cleavage of the external C–CCl_2 bond should produce an intermediate that in the presence of excess methoxide is likely to give the dimethyl acetal derivative. This dimethyl acetal could then be readily converted to the conjugated aldehyde during the acidic workup.

Compounds **12a–e** likewise resisted acid-catalyzed methanolysis at room temperature, probably due to the

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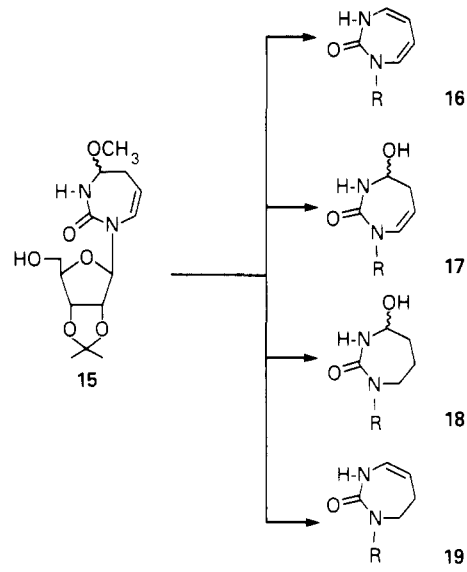
(20) Skell, P. S.; Sandler, S. R. *J. Am. Chem. Soc.* **1958**, *80*, 2024.

steric hindrance afforded by the halogen atoms. Consequently, removal of the halogen atoms in **12d** was performed with n-Bu_3SnH to give **14a** in 94% yield. Following the removal of the N-benzoyl group in **14a** with an equivalent amount of sodium methoxide, the deblocked compound **14b** solvolyzed rapidly to the desired diazepinone derivative **15** in methanol at 0 °C after the pH of the mixture was lowered to 4. Compound **15** was formed in nearly quantitative yields, showing this reaction to be a highly efficient ring expansion. As expected, this material was obtained as a mixture of C-4 epimers. Confirmation of its structure was provided by NMR, MS, and elemental analysis. The NMR spectrum of **15**, shown in Figure 2, contains two different methoxy group resonances (δ 3.41 and 3.42) integrating for three protons and two different anomeric signals at δ 5.28 and 5.37, respectively, which integrate for a total of one proton. The coupling constant observed for each signal was small (J = 2.4 Hz) as expected for an isopropylidene-protected nucleoside derivative.[21] Irradiation of the δ 5.00 multiplet which contained the C(6)-H olefin and the C(2')-H and C(3')-H sugar protons, reduced the C(7)-H signal (δ 5.95) to a singlet and converted both anomeric proton signals into two sharp singlets. Analysis of underivatized **15** by direct-probe electron ionization mass spectrometry did not give a spectrum containing the expected molecular ion at m/z 314. Instead, the apparent molecular ion and all the expected fragments from the nucleoside aglycon were shifted 32 units lower (loss of CH_3OH) to give a spectrum indicative of the isopropylidene derivative of **16**. In-beam volatilization of underivatized **15**, however, was successful in producing an electron ionization mass spectrum with a molecular ion at m/z 314 and the appropriate fragments from the aglycon, but this spectrum likewise showed extensive loss of CH_3OH. The mass spectrum of the *N,O*-bis(trimethylsilyl) derivative of **15** also exhibited the expected molecular ion at m/z 458, but peaks at m/z 426 and 354 again corresponded to loss of CH_3OH or its trimethylsilylated derivative. Apparently the 4-methoxy substituent is both chemically and thermally labile, so that CH_3OH is lost during heating to volatile the sample for conventional mass spectral analysis. A positive ion FAB mass spectrum finally confirmed the identity of **15**, since the MH^+ peak at m/z 315 was now the base peak and only a small peak corresponding to loss of CH_3OH was observed at m/z 283. This spectrum also showed a characteristic (MH + glycerol)$^+$ adduct and a M_2H^+ dimer at m/z 629.

Compound **15** has been efficiently obtained in 26% yield from the easily accessible 2-β-D-ribofuranosyl-1,2-dihydropyrimidin-2-one after five steps. This riboside represents a very useful and versatile precursor for the preparation of other diazepinone nucleosides. Its conversion to a series of potentially useful cytidine deaminase inhibitors, such as compounds **16–19**, is already in progress in our laboratory. Preliminary biological results indicate that some of these compounds are indeed powerful inhibitors of cytidine deaminase with K_i values ranging from 10^{-7} to 10^{-8} M. The complete characterization and biological activity of these new diazepinone nucleosides will be the subject of a forthcoming report.



R = β-D-Ribofuranosyl

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Specific rotations were measured in 1-dm cell with a Perkin-Elmer Model 141 polarimeter. ^1H NMR spectra were determined on Varian T-60 or XL-200 instruments. Chemical shifts are given as δ values with reference to $SiMe_4$. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tn. Low-resolution electron ionization mass spectra (70 or 75 eV) were obtained on either a VG 7070E or DuPont 21-492B gas chromatograph–mass spectrometer (GC/MS) system. Both instruments were interfaced to a VG 2040 data system for on-line data acquisition and processing. Samples were introduced either by direct probe or via a GC (trimethylsilyl derivatives) coupled to the mass spectrometer by a single-stage glass jet separator. Typical mass spectrometer operating conditions were transfer line and jet separator, 240 °C; ion source, 250 °C; accelerating voltage, 1.6 kV (DuPont 21-492B) or 6.0 kV (VG 7070E); ionizing current, 200–250 μA; scan speed, 2 s/decade. Positive-ion fast atom bombardment (FAB) mass spectra were obtained on the VG 7070E mass spectrometer which was equipped with a FAB ion source. The sample was dissolved in a glycerol matrix, and ionization was effected by a beam of xenon atoms derived by neutralizing xenon ions accelerated through 8.6 kV. Columns for chromatography were packed with silica gel (Bio-Sil A, 200–400 mesh, Bio-Rad Laboratories) and eluted with the solvents indicated in the individual experiments. Preparative HPLC was performed on a Waters instrument prep LC/system 500A.

Crystal data (12a): molecular formula $C_{15}H_{18}N_2O_5Cl_2$; molecular weight 377.22 daltons; habit prismatic; radiation Cu Kα (graphite monochromator); wavelength 1.5418 Å, space group $P2_12_12_1$ (No. 19); cell dimensions (from least-square reflections of $\pm\theta$ data) a = 7.1547 (6) Å, b = 10.8571 (9) Å, c = 20.4126 (13) Å; V = 1585.64 Å^3, Z = 4, D_x = 1.580 g cm^{-3}, crystal size ca. 0.3 × 0.25 × 0.25 mm^3; reflections; 1861 ($534 < I\sigma$); maximum sin θ/γ; 0.6229 Å^{-1}; diffractometer, Nonius CAD-4; function minimized; $\sum wd^2$; anisotropic temperature factor $\exp(-2\pi^2(\sum_i\sum_j U_{ij}a_i^*a_j^*h_ih_j))$; final R factor (observed reflections only), 5.1%.

The x-ray intensity data were collected by standard techniques. A linear decay of 5% in the intensities of standard reflections was observed during the 44-h X-ray exposure time. The phase problem was solved by using MULTAN78,[22] and all heavier atoms were visible in the best E map. The strucuture was refined by standard techniques using the programs of XRAY 72.[23] All H atoms were visible in a difference map, and the structure was refined to an R factor of 5.3% by using anisotropic thermal parameters for the heavier atoms and isotropic parameters for H atoms. At

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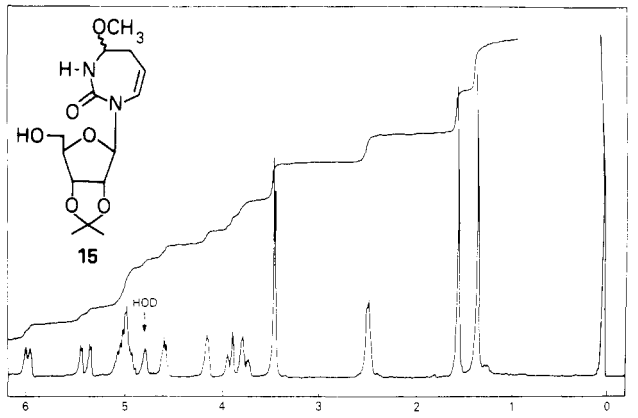

Figure 2. ^1H NMR spectrum (200 MHz) of **15** in $CDCl_3$ after D_2O exchange.

Table II. Atomic Parameters for the Heavier Atoms. The *U* Values Given are the Geometric Means of the Diagonal Terms of the Vibration Tensors

atom	*x*	*y*	*z*	*U*
Cl(1)	−975 (3)	8413 (2)	9280 (1)	101 (1)
Cl(2)	−2773 (3)	6013 (2)	9246 (1)	100 (1)
N(1)	810 (6)	4134 (3)	8648 (2)	42 (1)
C(1′)	1310 (7)	2818 (4)	8715 (3)	44 (2)
O(1′)	1542 (5)	2507 (3)	9381 (2)	53 (1)
C(2)	−195 (8)	4424 (5)	8103 (3)	53 (2)
O(2)	−747 (7)	3616 (4)	7726 (2)	81 (2)
O(2′)	3004 (6)	1276 (3)	8130 (2)	64 (1)
C(2′)	3119 (7)	2497 (4)	8382 (3)	47 (2)
N(3)	−546 (7)	5627 (5)	7986 (3)	61 (2)
O(3′)	5119 (6)	1147 (4)	8937 (2)	71 (1)
C(3′)	4578 (8)	2417 (5)	8934 (3)	53 (2)
C(4)	45 (8)	6630 (5)	8373 (3)	49 (2)
C(4′)	3484 (8)	2696 (5)	9550 (3)	53 (2)
C(5)	1059 (7)	6298 (4)	8987 (3)	47 (2)
O(5′)	3295 (5)	4861 (3)	9298 (2)	50 (1)
C(5′)	3730 (10)	3988 (5)	9810 (3)	58 (2)
C(6)	1378 (7)	4981 (4)	9172 (2)	41 (2)
C(7)	−845 (8)	6883 (5)	9022 (3)	53 (2)
C(8)	4647 (8)	617 (5)	8325 (3)	62 (2)
C(9)	6193 (15)	805 (9)	7838 (5)	109 (4)
C(10)	4135 (12)	−714 (6)	8439 (5)	80 (3)

this point anomalous dispersion corrections were introduced for Cl, O and N,[24] and parallel refinements were conducted for the original and opposite enantiomorphs. The difference between the two *R* factors (5.1% and 6.0%) is significant.[25] The enantiomorph of lower *R* factor is shown as an ORTEP[26] diagram in Figure 1. Table II gives atomic parameters. The listing of observed and calculated structure factors was submitted to the referees and may be obtained from J.V.S.

1-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyl)-*O*^{6},5′-cyclo-1,2,3,6-tetrahydropyrimidin-2-one (11a). This compound was obtained in 65% yield from 1-β-D-ribofuranosyl-1,2-dihydropyrimidin-2-one as reported previously by us.[7,9]

3-Benzoyl-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-*O*^{6},5′-cyclo-1,2,3,6-tetrahydropyrimidin-2-one (11b). Freshly distilled benzoyl chloride (3.96 mL, 34.11 mmol) was added dropwise to an ice-cold solution of **11a** (3.294 g, 12.28 mmol) in dry pyridine (120 mL) with continuous stirring. Stirring was continued for 1 h at this temperature and overnight at 25 °C. A second addition of an identical amount of benzoyl chloride under the same conditions was performed. The mixture was then poured into an ice-cold saturated solution of $NaHCO_3$ (1.12 L) and extracted with chloroform. The chloroform extract was washed successively with 5% H_2SO_4 and water, dried (Na_2SO_4), and reduced to dryness under vacuum. The resulting residue was dissolved in chloroform and purified by flash chromatography over silica gel using hexane–ethyl acetate (7:3) as eluant. The fractions containing the product were combined and the solvent was evaporated to give 4.04 g (88%) of **11b** as a white solid: mp 166–167 °C (hexane–ethyl acetate); $[\alpha]^{26}_D$ + 112.41° (*c* 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.45 (m, 5, aromatic), 7.10 (d, 1, *J* = 8 Hz, H-4), 5.76 (s, 1, H-1′), 5.53 (d, 1, *J* = 3 Hz, H-6), 5.21 (dd, 1, *J* = 8 Hz, *J′* = 3 Hz, H-5), 4.52 (m, 3, H-2′, H-3′, H-4′), 3.79 (m, 2, H-5′, H-5$_a$′), 1.44 (s, 3, CH_3), 1.28 (s, 3, CH_3); mass spectrum, *m/z* (relative intensity) 372 (M^+·; 0.7), 357 (M − CH_3, 2), 342 (1), 314 (M − CH_3COCH_3, 5), 267 (M − COC_6H_5, 0.8), 258 (1), 237 (12), 201 (9), 172 (20), 105 (100), 77 (57), 68 (23), 59 (19), 43 (40). Anal. Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.40; H, 5.51; N, 7.43.

Dichlorocarbene Adduct of 11b (12c). A mixture of **11b** (1.12 g, 3 mmol) and phenyl(bromodichloromethyl)mercury (3.96 g, 9 mmol) in dry benzene (30 mL) was refluxed under nitrogen with continuous stirring for 25 h. After being cooled to 25 °C, the reaction mixture was filtered and the filtrate concentrated at reduced pressure (ca 6 mL) and purified by flash chromatography over silica gel using hexane–ethyl acetate (7:3) as eluant. Fractions containing the product were combined and concentrated in vacuo to give **12c** (1.12 g, 82%) as a white fluffy solid: mp 182–183 °C (ethyl acetate–hexane); $[\alpha]^{26}_D$ − 105.06° (*c* 0.104, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.41 (m, 5, aromatic), 5.98 (s, 1, H-1′), 4.98 (d, 1, *J* = 3.5 Hz, H-6), 4.59 (m, 3, H-2′, H-3′, H-4′), 4.09 (m, 3, H-5; H-5$_a$′, H-4), 2.49 (dd, 1, *J* = 10 Hz, *J′* = 3.5 Hz, H-5), 1.47 (s, 3, CH_3), 1.27 (s, 3, CH_3); mass spectrum, *m/z* (relative intensity) 454 (M^+; 6.4; a 9:6:1 peak cluster indicative of two Cl was observed), 439 (M − CH_3, 2.5), 150 (5.0), 105 (100), 77 (93), 43 (48). Anal. Calcd for $C_{20}H_{20}Cl_2N_2O_6$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.78; H, 4.54; N, 5.90.

Dibromocarbene Adduct of 11b (12d). A mixture of **11b** (2.59 g, 7.0 mmol) and phenyl(tribromomethyl)mercury (11.04 g, 22.8 mmol) in dry benzene (130 mL) was refluxed under nitrogen with continuous stirring for 28 h. In order to drive the reaction to completion an additional amount of phenyl(tribromomethyl)mercury (7.36 g, 15.2 mmol) was added and the solution was refluxed further for 24 h. The reaction mixture was cooled to 25 °C and filtered. The filtrate was reduced to dryness and reextracted with benzene. The benzene extract was purified by flash chromatography over silica gel using hexane–ethyl acetate (3:1) as eluant. Fractions containing the product were combined and concentrated in vacuo to yield **12d** (1.86 g, 49%) as a white foamy solid: mp 173–174 °C (ethyl acetate–hexane); $[\alpha]^{26}_D$ −106.54° (*c* 0.096, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.18–7.39 (m, 5, aromatic), 5.84 (s, 1, H-1′), 4.81 (d, 1, *J* = 3.5 Hz, H-6), 4.60 (m, 2, H-2′, H-3′), 4.41 (s, 1, H-4′), 4.00 (m, 2, H-5′, H-5$_a$′), 3.78 (d, 1, *J* = 12.5 Hz, H-4), 2.46 (dd, 1, *J* = 12.5 Hz, *J′* = 3.5 Hz, H-5), 1.40 (s, 3, CH_3), 1.24 (s, 3, CH_3); mass spectrum, *m/z* 542 (M^+·, a 1:2:1 peak cluster indicative of two Br was seen), 527 (M − CH_3). Anal. Calcd for $C_{20}H_{20}Br_2N_2O_6$: C, 44.14; H, 3.70; N, 5.15. Found: C, 43.95; H, 3.69; N, 5.03.

3-Benzyl-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-*O*^{6},5′-cyclo-1,2,3,6-tetrahydropyrimidin-2-one (11c). To a solution of **11a** (1.10 g, 4.1 mmol) in dry Me_2SO (30 mL) was added 0.27 g (6.8 mmol) of powdered NaOH followed by 0.78 mL (6.6 mmol) of benzyl chloride. The entire mixture was stirred for 1 h at room temperature after which time it was treated with cold water (150 mL) and extracted with chloroform (5 × 20 mL). The chloroform extract was reduced to dryness and excess Me_2SO was eliminated by vacuum distillation at 0.1 μm of Hg. The residue was purified by dry column chromatography over silica gel using hexane–ethyl acetate (1:1) as eluant. the segment containing the product as visualized by UV light was extracted with ethyl acetate and evaporated to give **11c** (0.73 g, 50%) as a yellow oil: ^1H NMR δ 7.30 (s, 5, aromatic), 6.20 (d, l, *J* = 8 Hz, H-4), 5.85 (s, 1, H-1′), 5.50 (d, 1, *J* = 3 Hz, H-6), 4.40–5.00 (m, 6, H-5, H-2′; H-3′; H-4′; H-5′; H-5$_a$′), 3.75 (m, 2, $CH_2C_6H_5$), 1.50 (s, 3, CH_3), 1.30 (s, 3, CH_3); mass spectrum, *m/z* 358 (M^+·), 343 (M − CH_3). This compound was used without further purification for the synthesis of **12e**.

Dichlorocarbene Adduct of 11c (12e). A mixture of **11c** (0.29 g, 0.8 mmol) and phenyl(bromodichloromethyl)mercury (1.11 g,

(24) "International Tables for X-ray Crystallography"; International Union of Crystallography, Kynoch Press: Birmingham, England, 1968; Vol. III.
(25) Hamilton, W. C. "Statistics in Physical Science", Ronal Press: New York, 1964; p 159.
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2.5 mmol) in dry benzene (10 mL) was refluxed for 6 h under nitrogen with continuous stirring. After the reaction mixture was cooled to room temperature, it was filtered. The filtrate was reduced to dryness and purified by preparative TLC (silica gel, 2000 μm) using hexane–ethyl acetate (4:1) as a developing solvent. The desired band was isolated and extracted with ethyl acetate. After removing the solvent at reduced pressure, **12e** (0.23 g, 63%) was obtained as a white solid: mp 149–150 °C dec; $[\alpha]^{26}_D$ −62.03° (*c* 0.113, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36 (s, 5, aromatic), 6.00 (s, 1, H-1′), 5.20 (d, 1, *J* = 7.5 Hz, H-2′), 5.02 (d, 1, *J* = 1 Hz, H-6), 4.65 (s, 2, $CH_2C_6H_5$), 4.45 (d, 1, *J* = 2 Hz, H-4′), 4.25 (d, 1, *J* = 15 Hz, H-3′), 3.85 (m, 2, H-5′, H-5_a′), 3.10 (d, 1, *J* = 11 Hz, H-4), 2.15 (dd, 1, *J* = 11 Hz, *J*′ = 1 Hz, H-5), 1.50 (s, 3, CH_3), 1.35 (s, 3, CH_3); mass spectrum, *m*/*z* 440 (M^+·), 425 (M − CH_3), 405 (M − Cl). Anal. Calcd for $C_{20}H_{22}Cl_2N_2O_5$: C, 54.43; H, 5.03; N, 6.35. Found: C, 54.16; H, 5.21; N, 6.21.

Dichlorocarbene Adduct of 11a (12a). Method A. A solution of **12c** (1.10 g, 2.42 mmol) in 1 N methanolic sodium methoxide (2.42 mL, 2.42 mmol) was kept at 4 °C for 13 h with occasional stirring. The reaction mixture was then diluted with more absolute methanol and treated with prewashed cation exchange resin (AG 50W-X8, H^+, 3.4 mequiv) for 1 min. After removal of the resin the filtrate was reduced to dryness under reduced pressure; the residue obtained was dissolved in methylene chloride and purified by flash chromatography over silica gel using hexane-ethyl acetate (3:2) as eluant. Fractions containing a single product were pooled together and evaporated under vacuum to give 0.82 g (97%) of **12a** as a white solid: mp 167–168 °C dec (ethyl acetate-hexane); $[\alpha]^{26}_D$ −123.05° (*c* 0.089, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.95 (s, 1, H-1′), 5.63 (br s, 1, NH, D_2O exchanged), 5.07 (s, 1, H-6), 4.68 (s, 2, H-2′, H-3′), 4.51 (m, 1, H-4′), 3.90 (m, 2, H-5′, H-5_a′), 3.32 (m, 1, transformed into d, *J* = 11 Hz, after D_2O exchange, H-4), 2.23 (d, 1, *J* = 11 Hz, H-5), 1.54 (s, 3, CH_3), 1.34 (s, 3, CH_3); mass spectrum, *m*/*z* (relative intensity) 350 (M^+, ·4.8; a 9:6:1 peak cluster indicative of two Cl was observed), 335 (M − CH_3, 3.9), 314 (M − HCl, 2.6), 299 (5.6), 272 (3.7), 179 (base + H, 4.1), 152 (17), 143 (14), 126 (30), 69 (46), 59 (48), 43 (100). Anal. Calcd for $C_{13}H_{16}Cl_2N_2O_5$: C, 44.46; H, 4.59; N, 7.98. Found: C, 44.25; H, 4.57, N, 7.85.

Method B. A solution of **11a** (1.47 g, 5.48 mmol) in dry acetonitrile (42 mL) was treated with bis(trimethylsilyl)trifluoroacetamide (BSTFA) (14 mL, 52.7 mmol) and stirred under nitrogen at room temperature for 45 min. The solution was concentrated in vacuo at 25 °C and the oily residue dissolved in 70 mL of dry benzene. To this solution was added phenyl(bromodichloromethyl)mercury (7.28 g, 16.5 mmol) and the mixture was refluxed under nitrogen for 3 h. The solution was immediately cooled in an ice-water bath and filtered quickly. The filtrate was concentrated under vacuum (25 °C) and the residue triturated with methanol (70 mL) for 15 min and filtered. The new filtrate was again reduced to dryness in vacuo, dissolved in methylene chloride, and purified by flash chromatography, as in method A, to give 1.08 g (56%) of **12a** identical in every respect with that obtained by method A.

Dibromocarbene Adduct of 11a (12b). A suspension of **12d** (0.54 g, 1.0 mmol) in 0.17 N methanolic sodium methoxide (6 mL, 1.0 mmol) was stirred for 1 min at room temperature. During this time the starting material was gradually dissolved and was followed by the immediate precipitation of a crystalline product. The mixture was made homogenous by the addition of more methanol, and the solution was neutralized at 0 °C with an equivalent amount of prewashed cation exchange resin (AG 50W-X8, H^+). The mixture was filtered and the filtrate concentrated under vacuum. The residue was recrystallized from ethyl acetate-hexane to give 0.39 g (89%) of **12b**: mp 153–154 °C; $[\alpha]^{26}_D$ −51.58° (*c* 0.136, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.10 (br s, 1, NH, D_2O exchanged), 5.75 (s, 1, H-1′), 4.83 (s, 1, H-6), 4.52 (s, 2, H-2′; H-3′), 4.37 (m, 1, H-4′), 3.77 (m, 2, H-5′, H-5_a′), 3.25 (m, 1, transformed into d, *J* = 10 Hz, after D_2O exchange, H-4), 2.24 (d, 1, *J* = 10 Hz, H-5), 5.37 (s, 3, CH_3), 1.28 (s, 3, CH_3); mass spectrum, *m*/*z* 438 (M^+·, a 1:2:1 peak cluster indicative of two Br was observed), 423 (M − CH_3). Anal. Calcd for $C_{13}H_{16}Br_2N_2O_5$: C, 35.47; H, 3.66; N, 6.37. Found: C, 35.27; H, 3.82; N, 6.24.

5-Formyl-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-*O*^{6},5′-cyclo-1,2,3,6-tetrahydropyrimidin-2-one (13). A mixture of **12a** (1.18 g, 3.4 mmol) and 1 N methanolic sodium methoxide (13 mL) was stirred for 48 h at room temperature. The flask was cooled to 0 °C and the pH of the solution adjusted to 4 with the aid of glacial acetic acid. The solution was then reduced to dryness under vacuum at 25 °C, and the resulting solid was triturated twice with benzene. The benzene extract was reduced to dryness in vacuo and the residue purified by flash chromatography using ethyl acetate-hexane (9:1) and methylene chloride-methanol (19:1) as successive eluants. Fractions containing the product were combined and reduced to dryness to yield 0.80 g (80%) of **13** as a white solid: mp 218 °C; $[\alpha]^{26}_D$ −207.93° (*c* 0.103, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.38 (s, 1, CHO), 8.07 (br s, 1, NH, D_2O exchanged), 7.23 (d, 1, *J* = 6 Hz, transformed into a singlet after D_2O, H-4), 5.86 (s, 1, H-1′), 5.68 (s, 1, H-6), 4.71 (m, 3, H-2′, H-3′, H-4′), 3.93 (m, 3, H-5′, H-5_a′), 1.55 (s, 3, CH_3), 1.35 (s, 3, CH_3); mass spectrum as a trimethylsilyl derivative, *m*/*z* (relative intensity) 368 (M^+·, 1.2), 353 (M − CH_3, 2.3), 338 (5.7), 323 (1.2), 265 (323 −CH_3COCH_3, 16), 197 (11), 196 (base, 30), 181 (base − CH_3, 67), 154 (35), 100 (73), 85 (17), 59 (47), 43 (100), 29 (30). Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.71; H, 5.60; N, 9.29.

Carbene Adduct of 11b (14a). To a solution of **12d** (0.98 g, 1.8 mmol) in dry dioxane kept under nitrogen was added tri-*n*-butyltin hydride (2.2 mL, 8.2 mmol), and the reaction mixture was stirred under nitrogen at 25 °C for 41 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography over silica gel using hexane–ethyl acetate (3:2) as eluant. The fractions containing a single product were pooled and reduced to dryness to give 0.66 g (94%) of **14a** as a white solid: mp 174–175 °C; $[\alpha]^{26}_D$ −45.412° (*c* 0.108, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.34 (m, 5, aromatic), 5.96 (s, 1, H-1′), 4.73 (m, 3, H-6, H-2′, H-3′), 4.45 (m, 1, H-4′), 4.00 (s, 1, H-5′), 3.82 (d, 1, *J* = 4 Hz, H-5_a′), 3.45 (m, 1, H-4), 1.88 (m, 3, H-5, H-7′, H-7_a′), 1.43 (s, 3, CH_3), 1.28 (s, 3, CH_3); mass spectrum, *m*/*z* (relative intensity) 386 (M^+·; 5.3), 371 (M − CH_3, 4.8), 328 (M − CH_3COCH_3, 7.8), 281 (23), 171 (16), 105 ($C_6H_5CO^+$, 100), 77 ($C_6H_5^+$; 45), 43 (15). Anal. Calcd for $C_{20}H_{22}N_2O_6$: C 62.16; H, 5.22; N, 7.25. Found: C, 61.97; H, 5.36; N, 7.13.

1-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyl)-4-methoxy-1,3,4,5-tetrahydro-2*H*-1,3-diazepin-2-one (15). A suspension of **14a** (0.50 g, 1.3 mmol) in a 0.17 N solution of methanolic sodium methoxide (7.8 mL, 1.3 mmol) was stirred at room temperature. Within 1 min the insoluble material went into solution and the solution was rapidly chilled to 0 °C in an ice bath. The solution was acidified to pH 4 with the aid of acid cation exchange resin (AG 50W-X8, H^+). The mixture was filtered and the filtrate neutralized with methanolic ammonia at 0 °C. The resulting solution was concentrated under reduced pressure, and the residue obtained was purified twice by flash chromatography over silica gel using ethyl acetate and chloroform-methanol (19:1) as successive eluants to yield 0.40g (98%) of **15** as a foam; $[\alpha]^{29}_D$ −12.76° (*c* 0.109, $CHCl_3$); ^1H NMR δ 6.04 (br s, l, NH, D_2O exchanged), 5.95 (d, 1, *J* = 10 Hz, H-7), 5.28 and 5.37 (doublets, 1, *J* = 2.5 Hz, two distinct anomeric H-1′ protons from each diasteroisomer), 4.94 (m, 3, H-6, H-2′, 407 (MH 4.54 (m, 1, H-4), 4.12 (m, 1, H-4′), 3.79 (m, 2, H-5′, H-5_a′), 3.41 and 3.42 (singlets, 3, two distinct OCH_3 signals from each diastereoisomer), 3.19 (m, 1, OH, D_2O exchanged), 2.45 (m, 2, C-5 protons), 1.53 (s, 1, CH_3), 1.34 (s, 3, CH_3); in-beam electron ionization mass spectrum, *m*/*z* (relative intensity) 314 (M^+·; 1.6), 299 (M −CH_3, 1.3), 282 (M −CH_3OH, 1.3), 267 (M − CH_3 − CH_3OH, 4.5), 251 (1.2), 239 (2.4), 224 (2.7), 142 (base + H, 16), 110 (base + H− CH_3OH, 100), 59 (53), 43 (56); FAB mass spectrum, *m*/*z* (relative intensity) 629 (M_2H^+, 2.7), 407 (MH + + glycerol, 3.5) 315 (MH^+, 100) 283 (11), 143 (base + 2 H, 31), 111 (143 − CH_3OH, 84). Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.06; N, 8.91. Found: C, 53.25; H, 7.00; N, 8.77.

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Registry No. **11a**, 88494-20-6; **11b**, 88425-58-5; **11c**, 88425-59-6; **11d**, 88425-69-8; **12a**, 88425-63-2; **12b**, 88425-64-3; **12c**, 88425-60-9;

12d, 88425-61-0; 12e, 88425-62-1; 13, 88425-65-4; 14a, 88425-66-5; 14b, 88425-70-1; α-15, 88425-67-6; β-15, 88425-68-7; phenyl(bromodichloromethyl)mercury, 3294-58-4; phenyl(tribromomethyl)mercury, 3294-60-8.

Supplementary Material Available: A table listing all the bond angles from the crystallographic study of compound 12a (1 page). Ordering information is given on any current masthead page.

Trifluoroacetonitrile Oxide

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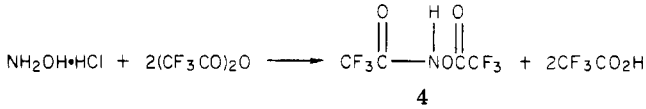
Trifluoroacetonitrile oxide (1) is a reactive intermediate that can be generated by the dehydrochlorination of trifluoroacetohydroximoyl chloride (2) with base. It reacts with mercaptans and amines in a stereospecific manner to give *Z* oximes 3 and 15 and forms a cycloadduct (10) with benzonitrile. In the absence of trapping agents, it dimerizes to give either the expected furoxan dimer 7 or the unusual dioxadiazine dimer 8, depending upon conditions. A convenient synthesis for 2 based on hydroxylamine hydrochloride, trifluoroacetic anhydride, and PCl_5 was developed to make 1 easily accessible.

Del'tsova, Ananyan, and Gambaryan[2] reported that trifluoroacetonitrile oxide (1) can be generated as a reactive intermediate by the dehydrochlorination of trifluoroacetohydroximoyl chloride (2) with triethylamine and trapped with electron-rich dipolariphiles such as vinyl ethers and vinyl amines. These investigators also report that in marked contrast to all other known nitrile oxides, 1 did not form a dimer.

We wished to investigate the reactions of thiols with 1 as a possible route to *N*-hydroxythioimidates 3, which are intermediates we needed to prepare fluorinated analogues of the insecticide methomyl.[3] However, the only literature methods for the preparation of the intermediate 2 are the reaction of capriciously explosive trifluorodiazoethane with nitrosyl chloride[4] and the low yield reaction of 1-nitro-2,2,2-trifluoroethane with benzoyl chloride and triethylamine.[5] Neither method is amenable to large-scale preparation.

In order to make the intermediate 2 more readily available, we developed a convenient, inexpensive method for its preparation. First, hydroxylamine hydrochloride was stirred at room temperature with 2 equiv of trifluoroacetic anhydride to give a nearly quantitative yield



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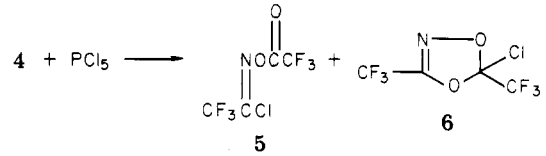
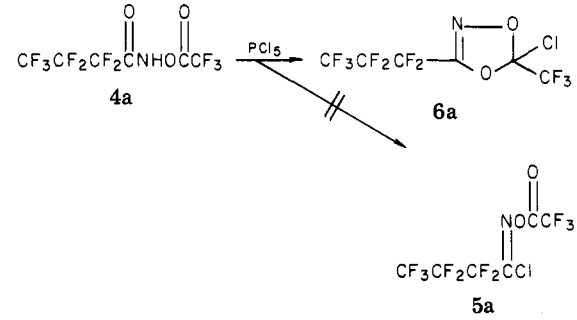


5 6

2

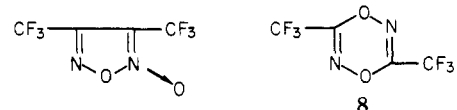
of *O,N*-bis(trifluoroacetyl)hydroxylamine[5] (4). Second, 4, in the form of a dry powder, was mixed with phosphorus pentachloride, and the resulting mixture was distilled to give the (trifluoroacetyl)hydroximoyl chloride 5 along with smaller amounts of the isomeric dioxazole 6. Mixing 5 with an equivalent amount of methanol gave 2 in 91% yield. Since none of these reactions required solvent, large-scale (2 mol or more) laboratory preparations of 2 were possible.

An attempt to prepare perfluorobutyrohydroximoyl chloride (2a) by a similar procedure was not successful. When *O*-(trifluoroacetyl)-*N*-(perfluorobutyryl)hydroxylamine (4a) was treated with PCl_5, only the dioxazole 6a was formed, to the exclusion of the hydroximoyl chloride 5a.



4a 6a 5a

Contrary to the previous report,[2] we found that trifluoroacetonitrile oxide (1), when generated from 2 by treatment with triethylamine in ether, gives a dimer if no trapping agent is present. The same dimer was also formed, along with some polymeric material, when other bases (NaH, CsF) and other solvents were utilized. This dimer has the dioxadiazine structure 8 and is probably



7 8

formed by the reaction of 2 or its anion with 1. A different dimer, having the furoxan structure 7, was formed when 1 was generated in the absence of excess 2 by a vapor-phase dechlorination of 2 over Ascarite (NaOH on asbestos). Both the dioxadiazine[6] and the furoxan[7] dimers of other

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(3) Middleton, W. J. U.S. Patent 4 323 757, 1982.
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(6) (a) Brandi, A.; De Sarlo, F; Guara, A. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1827. (b) De Sarlo, F. *Ibid.* **1974**, 1951.

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