(32). A mixture of 2.88 g (12 mmol) of the acid, 10 ml of $SOCl_2$, and 40 ml of benzene was heated at reflux for 4 hr. The solvent was then removed in vacuo. The oily residue was dissolved in 25 ml of THF and added to 50 ml of THF saturated with NH_3; NH_3 was bubbled through for an additional hour and the mixture taken to dryness. The residue was suspended in water, collected on a filter, and then recrystallized from aqueous methanol. There was obtained 2.30 g of the amide **31**, mp 173–177°.

A solution of the amide obtained above in 75 ml of THF was added to 1.0 g of $LiAlH_4$ in 10 ml of THF. The mixture was heated at reflux for 3 hr, cooled in ice, and treated in turn with 1 ml of H_2O, 1 ml of 15% NaOH, and 3 ml of H_2O. The gel was removed by filtration and the filtrate taken to dryness. The residue was dissolved in ether (30 ml) and treated with 10 ml of 3.7 *N* ethereal HCl. The precipitated solid was recrystallized from methanol to afford 1.82 g (57%) of product, mp 290–292°. Anal. ($C_{15}H_{22}ClNO$) C, H.

1-Methyl-4-[*p*-(bicyclo[2.2.2]oct-1-yloxy)phenyl]-4-hydroxypiperidine (33). Butyllithium (6.5 ml of 1.55 *N*) was added to a solution of 3.28 g (1.0 mmol) of the iodo compound in a Dry Ice–acetone bath. Following 2 hr of stirring in the cold there was added 1.2 g of 1-methyl-4-piperidone in 20 ml of THF. The mixture was allowed to stand at room temperature overnight. The solvent was removed in vacuo and the residue dissolved in ether and water. The organic layer was then extracted with four 40-ml portions of 2.5 *N* HCl. The last extracts were made strongly basic and extracted with ether. The ethereal extract was worked up in the usual way. The residue was recrystallized from ether–Skellysolve B to afford 0.20 g (6.3%) of product, mp 137–139°. Anal. ($C_{20}H_{29}NO_2$) C, H.

References and Notes

(1) D. S. Fredrickson and R. I. Levy in "The Metabolic Basis of Inherited Disease", 3rd ed, J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson, Ed., McGraw-Hill, New York, N.Y., 1972, p 545.
(2) C. J. Glueck, R. W. Fallat, F. Millett, W. V. Brown, and D. Puppione, *Circulation*, **50**, III-20 (1974).
(3) C. Alexander and C. E. Day, *Comp. Biochem. Physiol. B*, **46**, 295 (1973).
(4) C. E. Day, B. Barker, and W. W. Stafford, *Comp. Biochem. Physiol. B*, **49**, 501 (1974).
(5) W. A. Philipps and C. P. Berg, *J. Nutr.*, **53**, 481 (1954).
(6) W. B. Block, K. J. Jarrett, Jr., and J. B. Levine in "Automation in Analytical Chemistry", L. T. Skeggs, Jr., Ed., Mediad, New York, N.Y., 1965, p 345.
(7) P. E. Schurr and C. E. Day in "Atherosclerosis Drug Discovery", C. E. Day, Ed., Plenum Press, New York, N.Y., in press.
(8) P. E. Schurr, J. R. Schultz, and T. M. Parkinson, *Lipids*, **7**, 68 (1972).
(9) Z. Suzuki and K. I. Morita, *J. Org. Chem.*, **32**, 31 (1967).
(10) K. Bowden and P. N. Green, *J. Chem. Soc.*, 1795 (1954).
(11) L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, **33**, 1636 (1968).
(12) All melting points are uncorrected and recorded as obtained on a Thomas-Hoover capillary melting point apparatus. The authors are indebted to the Department of Physical and Analytical Chemistry Research of The Upjohn Co. for elemental analyses. Where analyses are indicated only by symbols for the elements, the analytical values were within 0.4% of theory.

Nucleic Acid Related Compounds. 17. 3-Deazauridine. Stannous Chloride Catalysis of *cis*-Diol vs. Phenolic Base Methylation with Diazomethane[1]

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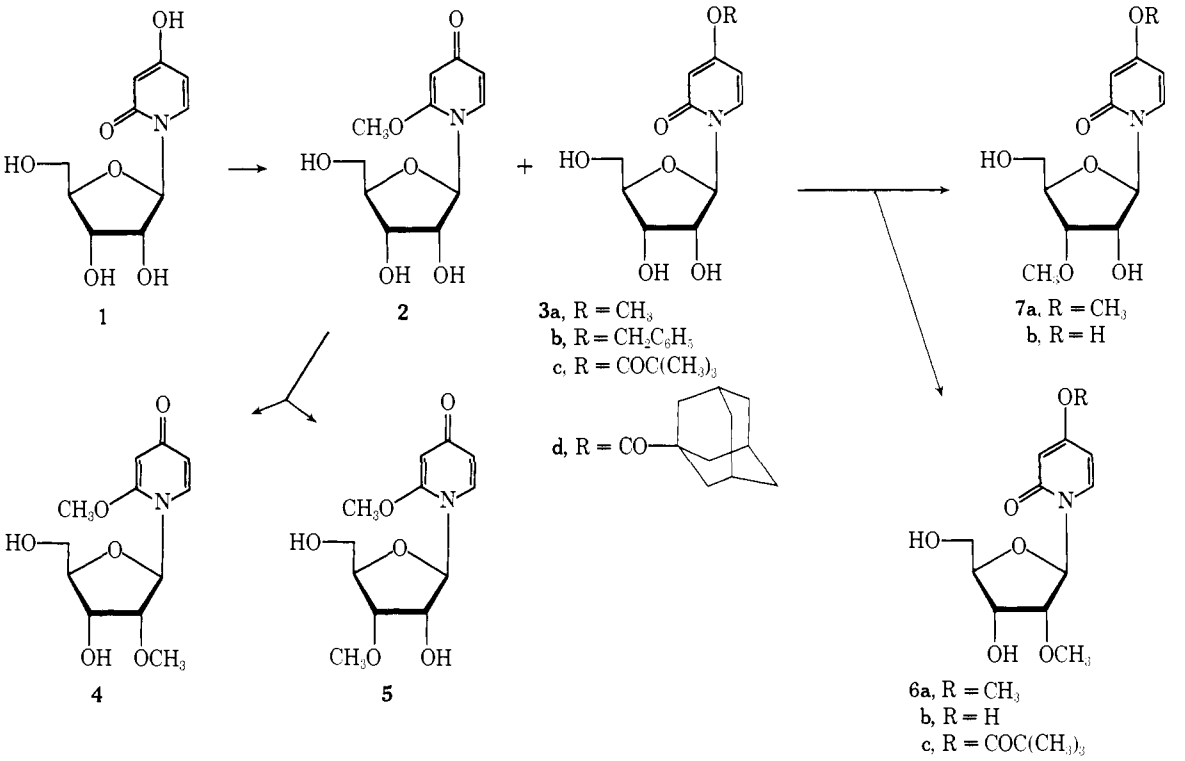
Treatment of a methanolic solution of 4-hydroxy-1-β-D-ribofuranosyl-2-pyridinone (3-deazauridine, 1) with diazomethane gave 2-methoxy-1-β-D-ribofuranosyl-4-pyridinone (**2**) and 4-methoxy-1-β-D-ribofuranosyl-2-pyridinone (**3a**) in an approximate ratio of 1:2. Analogous treatment of 1 with diazomethane in the presence of stannous chloride dihydrate gave eight detected products including **2**, 2-methoxy-1-(2-*O*-methyl-β-D-ribofuranosyl)-4-pyridinone (**4**), 2-methoxy-1-(3-*O*-methyl-β-D-ribofuranosyl)-4-pyridinone (**5**), **3a**, 4-methoxy-1-(2-*O*-methyl-β-D-ribofuranosyl)-2-pyridinone (**6a**), 4-methoxy-1-(3-*O*-methyl-β-D-ribofuranosyl)-2-pyridinone (**7a**), 2′-*O*-methyl-3-deazauridine (**6b**), and 3′-*O*-methyl-3-deazauridine (**7b**). For comparison, the 2′-*O*- and 3′-*O*-methyl derivatives of **2** (**4** and **5**) and of **3a** (**6a** and **7a**), respectively, were prepared in good overall yields by stannous chloride catalyzed methylation of **2** and **3a**. Treatment of 1 with benzyl bromide gave 4-benzyloxy-1-β-D-ribofuranosyl-2-pyridinone (**3b**). Stannous chloride catalyzed methylation of 4-pivaloxy-1-β-D-ribofuranosyl-2-pyridinone (**3c**) gave the corresponding 2′-*O*-methyl derivative **6c**. These compounds were tested in leukemia L1210 culture and against three bacterial strains and were found to be uniformly inactive. This provides a striking example of nucleoside structure specificity and also adds support to the depot storage-enzymic cleavage mode of antileukemic activity of 4-(adamantane-1-carbonyloxy)-1-β-D-ribofuranosyl-2-pyridinone (**3d**).

The pyridine nucleus analog of uridine, 4-hydroxy-1-β-D-ribofuranosyl-2-pyridinone (3-deazauridine, 1), was synthesized[2a] in order to examine the biological effects of such a formal replacement of –NHCO– by –CH=COH– at positions 3 and 4 in the pyrimidine system. Both 1 and the corresponding 3-deazacytidine[2b] (4-amino-1-β-D-ribofuranosyl-2-pyridinone) were found to exert marked inhibitory effects on the growth of neoplastic and bacterial cultures.[3] A number of other 3-deaza analogs of the pyrimidine 2′-deoxy nucleosides, arabinosides, orotic acid, etc., were subsequently prepared.[4] However, little activity was noted with these compounds.[5] Heidelberger and coworkers and Shone have recently extended this concept to the preparation of pyridine analogs of 5-fluorouracil and thymine bases, nucleosides, and 2′-deoxy nucleosides.[6] Again, unfortunately, biological activity was found to be lacking.[6a] The lone example of retained (and, indeed, enhanced) activity in a modified 3-deazauracil nucleoside involved esterification of the phenolic 4-oxygen of 3-deazauridine with adamantane-1-carboxylic acid.[5] However, evidence was presented which was compatible with enzymatic hydrolysis of the ester function, making this derivative (**3d**) a depot-storage form of 3-deazauridine (1) per se.

It has been found very recently[7] that 3-deazauridine has markedly enhanced activity in leukemia strains which have become resistant to 1-β-D-arabinofuranosylcytosine (ara-C). Toxicity levels appear manageable (Dr. A. Bloch, private communication) and clinical trials appear to be warranted. Bloch and coworkers[8] have now reported that 3-deazauridine 5′-triphosphate inhibits the mammalian enzyme cytidine triphosphate synthetase, and this may be the major site of action. This, coupled with the observed enzymatic phosphorylation of 1 to the triphosphate level but lack of incorporation into nucleic acids,[9] might rationalize

Scheme I



the inactivity of other nucleic acid component 3-deazauracil analogs. Since 3-deazauridine has spectrophotometrically determined pK_a values of 0.40 ± 0.08 and 6.33 ± 0.13, substitution on the pyridine ring could impose electronic effects (as well as steric) which might severely alter its hydrogen bonding or charge association with the enzyme (CTP synthetase) at physiological pH. Antiviral activity against RNA viruses by undetermined mechanism(s) has also been reported.[10] An interesting X-ray single-crystal study of 3-deazauridine indicated that the molecule is in the 4-hydroxy-2-pyridinone form with the "aromatic" heterocycle essentially planar.[11] A short C^4–O^4 bond was observed, which may correlate with the marked acidity, pK_{a_2} ~ 6.3 (pK_a = 6.2[12]). Watson–Crick hydrogen bonding analogous to that of cytidine was again[2] suggested and model schemes were illustrated.[11] Previous ^1H NMR results[2] demonstrating $^1H \rightleftarrows {}^2H$ exchange with D_2O at C^3 of 3-deazauridine are compatible with $-CH{=}C(OH)- \rightleftarrows -CH_2CO-$ tautomeric equilibrium, although the enolic form (cytosine H-bonding analog) is the only isomer present in concentrations which are visible spectroscopically. This is of interest since 3-deazauridine apparently blocks the action of an enzyme which catalyzes overall amination of UTP to CTP. Upon enzymic demand, the base of 3-deazauridine could resemble uracil or cytosine with a much more acidic hydrogen than cytosine (product of the conversion) for strong donative hydrogen bonding.[11] In view of these considerations, 3-deazauridine derivatives with specific oxygen alkylation, which would remove the acidic pK_a function, lock the base into a given tautomer, and which would be expected to resist facile enzymatic hydrolysis to the free nucleoside, were of interest. The enhanced activity[5] of the O^4-adamantane-1-carboxylic ester derivative **3d** made the preparation of 4-*O*-alkyl products of special concern. Sugar methylated nucleosides are also of current interest[13] due to altered enzymatic susceptibilities.[14]

Treatment of a methanolic solution of 1 with diazomethane in glyme[13a] (1,2-dimethoxyethane) gave the O^2 and O^4 methylated nucleosides **2** and **3a** (88% combined) in an approximate ratio of 1:2, respectively. A mixture of 1 and anhydrous sodium carbonate in dry *N,N*-dimethylformamide (DMF) was treated with benzyl bromide to give the O^4-benzyl product **3b**, which crystallized after chromatographic purification.

Stannous chloride[13a] and various other inorganic compounds[15] have been found to be potent catalysts for monomethylation of the *cis*-diol system of nucleosides (and other model diols) using diazomethane. Uridine and pseudouridine were selectively methylated at the 2′- and 3′-hydroxyl groups with stannous chloride present, whereas in its absence, the uracil ring (pK_a ~ 9.2) is readily N-methylated.[13a] However, 3-deazauridine (1) (pK_a ~ 6.3) is analogous to an electron-deficient phenol, and such phenols are known to be easily O-methylated by diazomethane[16] (Scheme I).

Dropwise treatment of a methanolic solution of 1 and 0.11 equiv of $SnCl_2{\cdot}2H_2O$ with diazomethane in glyme gave eight detected products (**2, 3a, 4, 5, 6a, b, 7a, b**). The sugar methylated (but base unsubstituted) **6b** and **7b** were produced in a combined isolated yield of 67% and in a ratio of ~5:1, respectively (NMR) (see the Experimental Section for the distribution of other products). From this mixture, a 40% yield of pure 2′-*O*-methyl-3-deazauridine (**6b**) was chromatographically separated. The presence of the 3′-*O*-methyl isomer **7b** was indicated spectroscopically. After chromatographic separation of pure **6b**, the remaining mixture (**6b** and **7b**) had uv spectra analogous to pure **6b** and the highest mass spectral ion had *m/e* 257. Two narrowly separated *O*-methyl peaks were present in the NMR spectrum. These isomers were not resolved cleanly by several TLC systems and the minor product, **7b**, was not investigated further.

For structure comparison purposes as well as to provide further substituted nucleosides for biological evaluation, the catalyzed methylation procedure was applied to **2** and **3a**. The 2-methoxy-4-pyridone nucleoside **2** gave the corresponding 2′- and 3′-*O*-methyl products 4 and 5 in a ratio of 1:1.2, respectively, which were easily resolved on the Dek-

Table I. NMR Data of 3-Deazauridine Derivatives[a]

Compd	H^3 (J_{3-5})	H^5(J_{5-6})[b]	H^{6c}	$H^{1'}$ ($J_{1'-2'}$)	2'-OCH_3[d]	3'-OCH_3[d]	2-OCH_3[d]	4-OCH_3[d]
2	5.61 (2.4)	5.91 (8.0)	7.91	5.80 (4.5)			3.84	
3a	5.76 (2.8)	5.90 (8.0)	7.85	5.98 (3.5)				3.73
3b[e]	5.85 (2.6)	6.01 (7.8)	7.86	5.98 (3.2)				
4	5.61 (2.5)	5.89 (8.0)	7.90	5.86 (5.0)	3.36		3.84	
5	5.60 (2.5)	5.87 (8.0)	7.82	5.73 (5.0)		3.33	3.82	
6a	5.73 (2.8)	5.95 (8.0)	7.89	6.05 (3.9)	3.37			3.71
7a	5.77 (2.6)	5.97 (7.9)	7.85	5.97 (4.2)		3.34		3.73
6b	5.55 (2.6)	5.88 (7.8)	7.83	6.05 (4.0)	3.37			
6c[f]	6.03–6.20 (m)	6.03–6.20 (m)	8.13 (J_{6-5} = 8.0)	6.03–6.20 (m)	3.42			

[a]Chemical shifts in δ (parts per million from Me_4Si), first-order coupling constants J in hertz. [b]Doublet of doublets $J_{5-3} = J_{3-5}$. [c]Doublet $J_{6-5} = J_{5-6}$. [d]Singlet. [e]δ 5.07 (s, 2, CH_2Ph), 7.40 (br s, 5, $-C_6H_5$). [f]δ 1.27 [s, 9, $COC(CH_3)_3$].

Table II. Selected Mass Spectral Ions,[a] *m/e* (% Relative Intensity)

Compd	M	M − 30	B + 58	B + 44	B + 30	B + 2H	B + H	*m/e* 146	*m/e* 87
4	271 (3.3)	241 (0.8)	182 (9.7)	168 (2.8)	154 (8.6)	126 (100)	125 (83)	43	42
5	271 (13)	241 (1.4)	182 (4.2)	168 (8.4)	154 (7.4)	126 (90)	125 (100)	1.8	45
6a	271 (4.4)	241 (1.7)	182 (13)	168 (2.4)	154 (11)	126 (100)	125 (51)	81	29
7a	271 (3.8)	241 (1.7)	182 (1.0)	168 (6.6)	154 (11)	126 (100)	125 (28)	1.3	7.5
6b	257 (4.3)	227 (1.3)	168 (13)	154 (2.1)	140 (10)	112 (100)	111 (46)	70	50
6c	341 (4.1)	311 (1.0)	252 (3.2)	238 (0.3)	224 (3.3)	196 (22)	195 (8.7)	100	28

[a]Ions named as illustrated in ref 13a.

ker column[17] [Dowex 1-X2 (OH^-)]. In contrast, analogous treatment of **3a** gave **6a** and **7a** in a ratio (NMR) of ~4.5:1, respectively. These isomers were not separated on the anion exchanger in water or in several alcohol–water mixtures. Fractional crystallization and absorption chromatography provided pure samples of these compounds.

Treatment of **1** with pivalic acid chloride in pyridine gave the 4-*O*-pivalyl product **3c** which was methylated directly with diazomethane in the presence of stannous chloride. The chromatographically isolated product (78%) was crystallized in 55% yield and found to be the 2'-*O*-methyl isomer **6c**.

The various isomeric structures were readily ascertained by spectroscopic techniques. Identification of O^2- vs. O^4-alkylation of the pyridine moiety follows from the uv spectral studies of den Hertog and Buurman.[2b,18] Dialkylation at N^1 (sugar) and O^2 leads to uv max ~252 nm whereas N^1-(sugar) and O^4-dialkyl products have uv max ~281 nm in neutral solution. Sugar 2'-O vs. 3'-O substitution has been shown to give characteristically consistent ^1H NMR shift and mass spectral fragmentation patterns in a representative series of 2'-*O*- and 3'-*O*-methyl nucleosides.[13a] The anomeric proton ($H^{1'}$) resonance is at lower field for 2'-*O*-methyl than 3' isomers in all examples studied[13a,19] and the methyl singlet is at lower field for 2'-*O*-methyl isomers in the pyrimidine (but not purine) series.[13a] As seen in Table I, these trends are consistently followed in the present examples, although only slight shift differences in the methyl singlets exist.

Table II contains mass spectral fragmentation data with selected ions as indicated previously (see ref 13a and 20 for structures and discussion). The enhanced intensity of the B + 58 ion relative to that of the B + 44 ion (heterocyclic base plus carbons 1' and 2' with the attached 2' function) is diagnostic for 2'-O-methylation as is the rearranged sugar fragment *m/e* 146 ion[13a,20] (see Table II). The ubiquitous presence of the *m/e* 87 ion[13a] in the sugar methylated products was again observed.

Biological. Compounds **2, 3a,b, 4–6c,** and **7a** were evaluated in leukemia L1210, *Streptococcus faecium*, *Escherichia coli* K_{12}, and *E. coli* B cultures as described previously.[5] No 50% growth inhibition was found at less than 10^{-3} *M* in the bacterial systems or at less than 10^{-4} *M* in L1210 culture (the maximum concentrations tested). It is interesting that the biological structure specificity for 3-deazauridine (**1**) is so pronounced. This provides further indirect support for the depot-storage function of **3d,** since even a 2'-*O*-methyl substituent (as in **6b**) is not tolerated.

The present study demonstrates that the 4-oxygen of the pyridine system of **1** is more susceptible to methylation by diazomethane under neutral conditions and markedly more prone to benzylation in the presence of a proton acceptor. The catalytic effectiveness of stannous chloride with *cis*-diols is demonstrated emphatically by the formation of ~67% of sugar alcohol monomethylation products with diazomethane in the presence of an acidic (pK_a = 6.33) phenolic system. The biological findings of this study combined with those involving other base changes[3,5,6a] would suggest that alteration of the chemical structure of 3-deazauridine (**1**) is futile, and future efforts would be more profitably expended in search of more effective transport and/or storage forms analogous to the active adamantane-1-carboxylate **3d**.[5] This rigid structure–activity specificity coupled with lack of incorporation of 3-deazauridine (or its 2'-deoxy nucleoside) triphosphate into nucleic acids[9] is compatible with a specific enzymic[8] target mechanism of action. Such specificity may be expected to be advantageous with respect to toxic side effects in the antileukemia drug use of 3-deazauridine.

Experimental Section

Melting points were determined on Reichert Micro Stage and

Mel-Temp apparatus and are uncorrected. Uv spectra were recorded on Cary 14 or 15 spectrometers. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter using a 10-cm 1-ml microcell. NMR spectra were recorded on Varian A-60 and HA-100 spectrometers. Mass spectra were determined by the mass spectroscopy laboratory of this department on AEI MS-2 and MS-9 instruments at 70 eV using a direct probe for sample introduction. Evaporations were effected using Büchler rotating evaporators under aspirator or mechanical oil pump vacuum at 40° or lower. Analytical TLC was run on Eastman silica gel sheets (13181 with 6060 indicator), thick-layer plates (~1 mm × 20 × 20 cm) were spread with Brinkmann PF 254 silica gel, and J. T. Baker (3405) silica gel was used for column chromatography. Elemental analyses were determined by the microanalytical laboratory of this department and Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Analytical results for C, H, and N agreed within ±0.4% of theory.

Diazomethane Solution. To an ice-cold mixture of 100 ml of 40% aqueous KOH and 150 ml of 1,2-dimethoxyethane (glyme) was slowly added 15 g of *N*-nitroso-*N*-methylurea with vigorous stirring. Stirring was continued for an additional 20 min at 0° and the phases were allowed to separate. The upper organic layer was decanted and dried over KOH pellets. The dried solution was filtered before use. Standardization of the diazomethane solution using 0.2 *N* benzoic acid in glyme and back titration with 0.1 *N* NaOH gave an average value of 0.43 *N* CH_2N_2 in glyme.

Methylation of 3-Deazauridine (1) without Catalyst. 2-Methoxy-1-β-D-ribofuranosyl-4-pyridinone (2) and 4-Methoxy-1-β-D-ribofuranosyl-2-pyridinone (3a). To a stirred solution of 123 mg (0.5 mmol) of 1 in 20 ml of MeOH at 0° was slowly added a total of 18 ml of diazomethane solution over a period of 4 hr. The solution was evaporated and the residue in MeOH was applied to a silica plate. The plate was developed using MeOAc–MeOH–concentrated NH_4OH (3:1:0.1) and the two major bands were removed from the plate and extracted with MeOH. Solvent was evaporated and the more rapidly migrating product was crystallized from MeOH–Me_2CO to give 72 mg (55%) of **3a**: mp 136–139°; $[\alpha]^{23}D$ 38.7° (*c* 0.34, H_2O); uv (H_2O) max 280 nm (ε 4500), min 251 nm (ε 1500); uv (0.1 *N* HCl) max 277 nm (ε 4300), min 250 nm (ε 1900); uv (0.1 *N* NaOH) max 280 nm (ε 4400), min 252 nm (ε 1700). Anal. ($C_{11}H_{15}NO_6$) C, H, N.

The more slowly migrating product was crystallized from EtOH–Skellysolve B to give 43 mg (33%) of **2**: mp 171–172 and 184–186° (two crystal forms); $[\alpha]^{23}D$ −9.7° (*c* 0.53, H_2O); uv (H_2O) max 254, 212 nm (ε 21,000, 18,000), min 226 nm (ε 2700); uv (0.1 *N* HCl) max 236 nm (ε 13,400), sh 260 nm (ε 8000), min 216 nm (ε 4500); uv (0.1 *N* NaOH) max 255 nm (ε 21,000), min 228 nm (ε 3700). Anal. ($C_{11}H_{15}NO_6$) C, H, N.

Methylation of 3-Deazauridine (1) Using Stannous Chloride Catalysis. 4-Hydroxy-1-(2-O-methyl-β-D-ribofuranosyl)-2-pyridinone (2′-O-Methyl-3-deazauridine, 6b). A solution of 256 mg (1.05 mmol) of 1 and 25 mg (0.11 mmol) of $SnCl_2 \cdot 2H_2O$ in 100 ml of MeOH was stirred and a total of 64 ml of diazomethane solution was added slowly over a period of 3 hr. TLC (MeOAc–MeOH–concentrated NH_4OH 3:1:0.1) showed three major components plus a trace of starting 1. The solution was evaporated and the residue in MeOH was applied to silica plates and developed in the same solvent system. Five bands were observed as follows: fastest band 37 mg (13%) of a mixture of **6a** and **7a** (31:7 by NMR); second band 10 mg (3.7%) of **3a**; third band 30 mg (10.5%) of a mixture of **4** and **5** (5:4 by NMR); fourth band 20 mg (7.4%) of **2**; and fifth band 180 mg (67%) of a mixture of **6b** and **7b** (5:1 by NMR) (total yield by weight, of bands extracted with MeOH followed by evaporation to dryness in vacuo, 101.6%). The evaporation residue from band 5 was dissolved in MeOH and 2 g of silica was added. The mixture was evaporated in vacuo and the impregnated powder was applied to a dry-packed column (1.4-cm diameter) of 20 g of the same silica. The column was developed with EtOAc–EtOH–H_2O (10:1:0.1). Fractions (5 ml) 4–10 contained pure (NMR) **6b** and were pooled and evaporated to give 140 mg (52%) of a colorless glass. This material was treated with ~2.5 ml of Me_2CO and after several days, 108 mg (40%) of colorless flakes of **6b** were filtered: mp 175–177°; $[\alpha]^{23}D$ 106.2° (*c* 0.61, H_2O); uv (H_2O) max 279 nm (ε 4800), min 248 nm (ε 2800); uv (0.1 *N* HCl) max 280 nm (ε 4400), min 251 nm (ε 2000); uv (0.1 *N* NaOH) max 255 nm (ε 8500), min 212 nm (ε 4000). Anal. ($C_{11}H_{15}NO_6$) C, H, N.

Fractions 11–20 were pooled and evaporated to give 36 mg (13%) of a mixture of 6b and 7b. No further resolution of this mixture was attempted.

2-Methoxy-1-(2-O-methyl-β-D-ribofuranosyl)-4-pyridinone (4) and 2-Methoxy-1-(3-O-methyl-β-D-ribofuranosyl)-4-pyridinone (5). A stirred solution of 120 mg (0.47 mmol) of **2** in 50 ml of 1 m*M* $SnCl_2 \cdot 2H_2O$ in MeOH was slowly treated with ~10 ml of diazomethane solution. When reaction was complete (TLC) the solution was evaporated and the residue was dissolved in a small volume of H_2O. This solution was applied to a column (1.8-cm diameter) of 100 ml of Dowex 1-X2 (OH^-) (200–400 mesh) resin packed in and developed with H_2O. Fractions (5 ml) 71–96 gave 65 mg of material which was crystallized from EtOH–EtOAc to give 50 mg (40%) of **4**: mp 197–199°; $[\alpha]^{23}D$ −14.5° (*c* 0.76, MeOH); uv analogous to that of **2**. Anal. ($C_{12}H_{17}NO_6$) C, H, N.

Fractions 123–152 contained 55 mg of material which was crystallized from EtOH–EtOAc to give 40 mg (32%) of **5**: mp 140–142 and 162–164° (two crystal forms); $[\alpha]^{23}D$ −21.3° (*c* 1, H_2O); uv analogous to that of **2**. Anal. ($C_{12}H_{17}NO_6$) C, H, N.

4-Methoxy-1-(2-O-methyl-β-D-ribofuranosyl)-2-pyridinone (6a) and 4-Methoxy-1-(3-O-methyl-β-D-ribofuranosyl)-2-pyridinone (7a). A 210-mg (0.82 mmol) portion of **3a** in 100 ml of 1 m*M* $SnCl_2 \cdot 2H_2O$ in MeOH was methylated with ~18 ml of diazomethane solution as described above for the conversion of **2** → **4** + **5**. The residue from evaporation of the reaction mixture was dissolved in EtOH–Me_2CO and allowed to stand at 0° for 24 hr. An analytically pure sample (30 mg, 13.5%) of **7a** crystallized with mp 188–190°; $[\alpha]^{23}D$ 74.3° (*c* 0.9, H_2O); uv analogous to that of **3a**. Anal. ($C_{12}H_{17}NO_6$) C, H, N.

The filtrate from this crystallization was evaporated and the residue was chromatographed on a column (1.4-cm diameter) of 12 g of silica using MeOAc as solvent. Fractions 5–25 were evaporated and the residue was crystallized from EtOH–Me_2CO to give 140 mg (63%) of **6a**: mp 136–138°; $[\alpha]^{23}D$ 105.9° (c 0.9, H_2O); uv analogous to that of **3a**. Anal. ($C_{12}H_{17}NO_6$) C, H, N.

Fractions 25–45 contained 20 mg (9%) of a mixture of **6a** and **7a**.

4-Pivaloxy-1-(2-O-methyl-β-D-ribofuranosyl)-2-pyridinone (6c). A stirred solution of 100 mg (0.41 mmol) of 1 in 4 ml of dry pyridine was treated with 0.25 ml of freshly distilled pivalyl chloride in 2.5 ml of dry $CHCl_3$ added dropwise over a period of 10 min. The colorless solution was stirred for 1.5 hr and 2 ml of saturated aqueous $NaHCO_3$ solution was added. This solution was stirred for 5 min and 2 ml of H_2O and 2 ml of $CHCl_3$ were added. The phases were separated and back extracted. The combined organic phase was washed with 2 ml of $NaHCO_3$ solution and 5 ml of H_2O, dried (Na_2SO_4), filtered, and evaporated. The oily **3c** did not crystallize readily and was dissolved in 32 ml of 1 m*M* $SnCl_2 \cdot 2H_2O$ in MeOH. This solution was slowly treated with ~15 ml of diazomethane solution until reaction was complete (TLC) and was then evaporated. The residue was chromatographed on a silica plate ($CHCl_3$–MeOH 9:1) and the major band was extracted with EtOH. Evaporation of solvent gave 110 mg (78%) of a colorless glass which was crystallized from a small volume of MeOH to give 77 mg (55%) of **6c**: decomposition begins at 175–180°, completely melted at 214°; $[\alpha]^{23}D$ 101.1° (*c* 0.75, H_2O); uv (H_2O) max 291 nm (ε 4500), min 245 nm (ε 450); uv (0.1 *N* HCl) max 291 nm (ε 4700), min 246 nm (ε 740); uv (0.1 *N* NaOH) max 255 nm (ε 6500), min 233 nm (ε 3300) (see ref 5 for uv data on the analogous **3d**). Anal. ($C_{16}H_{23}NO_7$) C, H, N.

4-Benzyloxy-1-β-D-ribofuranosyl-2-pyridinone (3b). A stirred mixture of 250 mg (1.03 mmol) of 1 and 100 mg of anhydrous Na_2CO_3 in 10 ml of dry DMF was treated with 0.15 ml of benzyl bromide. A second 0.2-ml portion of $C_6H_5CH_2Br$ was added after 16 hr and reaction was complete (TLC) after 30 hr. The residue after evaporation was dissolved in MeOH and 2 g of silica was added. The mixture was evaporated in vacuo and the impregnated powder was applied to a dry-packed column (1.4-cm diameter) of 15 g of the same silica. The column was developed with $CHCl_3$–MeOH (9:1). Evaporation of fractions (5 ml) 6–17 gave an oil which was crystallized from EtOH–EtOAc to give 110 mg (32%) of **3b**. The filtrate was evaporated and chromatographed on a silica plate using EtOAc–MeOH (9:1). An additional 100 mg (total yield 61%) of pure **3b** was obtained: mp 139–141°; $[\alpha]^{23}D$ 33.1° (*c* 1, MeOH); uv analogous to that of **3a**. Anal. ($C_{17}H_{19}NO_6$) C, H, N.

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References and Notes

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For the previous paper in this series, see M. J. Robins, G. Ramani, and M. MacCoss, *Can. J. Chem.*, **53**, 1302 (1975).
(2) (a) M. J. Robins and B. L. Currie, *Chem. Commun.*, 1547 (1968). (b) B. L. Currie, R. K. Robins, and M. J. Robins, *J. Heterocycl. Chem.*, **7**, 323 (1970).
(3) M. J. Robins, B. L. Currie, R. K. Robins, and A. Bloch, *Proc. Am. Assoc. Cancer Res.*, **10**, 73 (1969).
(4) B. L. Currie, M. J. Robins, and R. K. Robins, *J. Heterocycl. Chem.*, **8**, 221 (1971); M. J. Robins, B. L. Currie, R. K. Robins, and A. D. Broom, *Can. J. Chem.*, **49**, 3067 (1971).
(5) A. Bloch, G. Dutschman, B. L. Currie, R. K. Robins, and M. J. Robins, *J. Med. Chem.*, **16**, 294 (1973).
(6) (a) S. Nesnow, T. Miyazaki, T. Khwaja, R. B. Meyer, Jr., and C. Heidelberger, *J. Med. Chem.*, **16**, 524 (1973); (b) R. L. Shone, *Tetrahedron Lett.*, 3079 (1973).
(7) R. W. Brockman, S. C. Shaddix, M. Williams, and D. A. Nelson, *Ann. N.Y. Acad. Sci.*, in press (presented by Dr. Brockman at the Conference on the Chemistry, Biology, and Clinical Uses of Nucleoside Analogs, New York, N.Y., Sept 4–6, 1974.)
(8) R. P. McPartland, M. C. Wang, A. Bloch, and H. Weinfeld, *Cancer Res.*, **34**, 3107 (1974).
(9) M. C. Wang and A. Bloch, *Biochem. Pharmacol.*, **21**, 1063 (1972).
(10) W. M. Shannon, G. Arnett, and F. M. Schabel, Jr., *Antimicrob. Agents Chemother.*, **2**, 159 (1972); W. M. Shannon, R. W. Brockman, L. Westbrook, S. Shaddix, and F. M. Schabel, Jr., *J. Natl. Cancer Inst.*, **52**, 199 (1974); G. Khare, R. W. Sidwell, J. H. Hoffman, R. L. Tolman, and R. K. Robins, *Proc. Soc. Exp. Biol. Med.*, **40**, 880 (1972).
(11) C. H. Schwalbe, H. G. Gassen, and W. Saenger, *Nature (London), New Biol.*, **238**, 171 (1972).
(12) H. G. Gassen, H. Schetters, and H. Matthaei, *Biochim. Biophys. Acta*, **272**, 560 (1972).
(13) See for example (a) M. J. Robins, S. R. Naik, and A. S. K. Lee, *J. Org. Chem.*, **39**, 1891 (1974); (b) J. T. Kusmierek, J. Giziewicz, and D. Shugar, *Biochemistry*, **12**, 194 (1973), and references cited therein.
(14) See, for example, M. Honjo, Y. Kanai, Y. Furukawa, Y. Mizuno, and Y. Sanno, *Biochim. Biophys. Acta*, **87**, 696 (1964); Y. Furukawa, K. Kobayashi, Y. Kanai, and M. Honjo, *Chem. Pharm. Bull*, **13**, 1273 (1965); L. Hudson, M. Gray, and B. G. Lane, *Biochemistry*, **4**, 2009 (1965).
(15) M. J. Robins, A. S. K. Lee, and F. A. Norris, *Carbohydr. Res.*, **41**, 304 (1975).
(16) H. Zollinger, "Azo and Diazo Chemistry", Interscience, New York, N.Y., 1961, pp 69–70, 102–104.
(17) C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).
(18) H. J. den Hertog and D. J. Buurman, *Recl. Trav. Chim. Pays-Bas*, **75**, 257 (1956).
(19) D. M. G. Martin, C. B. Reese, and G. F. Stephenson, *Biochemistry*, **7**, 1406 (1968).
(20) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *J. Am. Chem. Soc.*, **92**, 2510 (1970).

Synthesis of Thebaine and Oripavine from Codeine and Morphine

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A practical synthesis of thebaine and oripavine has been developed from codeine and morphine, respectively. Attempts to use a codeinone intermediate gave poor yields; however, methylation of the potassium salt of codeine to give codeine methyl ether followed by oxidation with γ-MnO_2 gave thebaine in 67% yield from codeine. Similarly, the potassium salt of the di-O-anion of morphine was selectively alkylated to give morphine 6-methyl ether (heterocodeine) in better than 90% yield. Heterocodeine was then acetylated and oxidized to oripavine 3-acetate which was hydrolyzed to give oripavine in 73% yield from morphine.

Thebaine is the least abundant among the hydrophenanthrene alkaloids in *Papaver somniferum*, and it has no medicinal use in itself. Yet it is singularly important as the key intermediate in the synthesis of many useful opiate derivatives. This is uniquely the case for the naloxone family of opiate antagonists[1] and for the highly potent oripavine derivatives initiated from the Diels–Alder adducts of thebaine.[2]

The significant increase of opiate abuse in the United States, starting in the late 1960's, focused attention on the potential role of antagonists and raised the real danger of a thebaine shortage.[3] This danger was aggravated by the temporary cessation of opium cultivation in Turkey which stimulated the search for new sources of thebaine such as *P. bracteatum*.[4] With the ebb and flow of drug diplomacy[5] now resulting in the resumption of Turkish opium cultivation, *P. somniferum* appears to be restored as the most abundant and efficient source of the medicinal opiates.

We have sought to develop a practical and economic method for the synthesis of thebaine from the more available alkaloids of *P. somniferum*, morphine and codeine. Corollary to this is our objective of devising a ready source of oripavine, which is naturally occurring in very minor amounts in *P. bracteatum*.[4,6] Readily available oripavine is of interest since its use may obviate the final and difficult *O*-3-methyl ether cleavage in the synthesis of the Diels–Alder derived narcotics.[2]

The literature teaches three methods for the synthesis of thebaine (**2a**). The first[7] converts dihydrocodeinone to thebaine in four steps in 27% yield. Considering the preparation of dihydrocodeinone from codeine,[8] this leads to a 20% overall yield from codeine. Although this conversion could undoubtedly be improved, the improvement is limited and the process inconvenient since six steps are involved. The second process[9] involves direct methyl enol ether formation from codeinone and claims a 27% yield of thebaine; further comments on this process are given below.

The third process[10] is a total synthesis in which the key step is the oxidative coupling of a reticuline derivative to a salutaridine derivative. While the yields in this coupling step have been improved dramatically (by a factor of 1000), the overall yield of *dl*-thebaine remains in the 1–2% range, based on isovanillin.

Discussion

In considering the conversion of codeine (**1b**) to thebaine (**2a**), the two changes which must be effected, both in ring C, are oxidation (removal of two hydrogens) and methylation (formation of a methyl ether at O-6). Our first attempts followed the common pathway, namely, first oxidation to codeinone[11] and then formation of the methyl enol ether directly or via the dimethyl ketal and methanol elimination.[7] This is the same path as followed recently[9] and our