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PYRIMIDINE HOMONUCLEOSIDE ANALOGUES FROM 2,5-ANHYDROALDOSE DERIVATIVES*†

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ABSTRACT

3,4-Di-*O*-acetyl-2,5-anhydro-D-xylose diisobutyl dithioacetal (**1**) reacts with bromine to give a monobromo derivative which, on condensation with 2,4-diethoxypyrimidine or its 5-methyl analogue, affords the protected nucleoside derivatives **4** and **11**, respectively; ammonolysis of **4** gave the cytosine "homonucleoside" **7**, and hydrolysis of **11** gave the thymine "homonucleoside" **12**. The same type of "homonucleoside" may be produced by cyclization of the sugar chain in a suitable acyclic-sugar nucleoside, as in the conversion of 1-*S*-ethyl-1-thio-1-(uracil-1-yl)-D-xylitol (**16**, obtained from tetra-*O*-acetyl-D-xylose diethyl dithioacetal, **9**), by the action of one molar equivalent of *p*-toluenesulfonyl chloride, into a homonucleoside isolated as its diacetate **17**; acyclic-sugar derivatives not susceptible to such cyclization afford instead the 5-*p*-toluenesulfonates, as exemplified by the conversion of the D-*arabino* analogue (**13**) of **16** into the 5′-ester **14**. When cyclohexene is used to remove the excess of bromine in the preparation of nucleoside analogues from dithioacetals, the alkylsulfenyl bromide produced may react, by way of its cyclohexene adduct, with the heterocyclic base to give cyclohexane–base adducts, for example, compounds **6** and **10**.

INTRODUCTION

The work described here developed out of an interest, in the Grenoble laboratories[1,6], in the synthesis from anhydro sugar precursors of "homonucleosides" having a carbon atom interposed between a furanosyl group and a residue of a nucleic acid base, together with a program in the Columbus laboratories[3,7] for the preparation and evaluation of acyclic-sugar nucleosides in which the heterocyclic base

*Part X in the series "Homoanalogues of Aldofuranosyl Nucleosides", for Part IX, see ref. 1; and Part XVI of the series "2,5-Anhydrides of Sugars", for Part XV, see ref. 2; see also, ref. 3 for previous, related work.

†For preliminary reports, see refs. 4 and 5.

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is attached to a non-cyclized sugar chain. Reactions leading to oxolane rings in the former laboratory[8], and studies on acyclic-chain conformations in the latter[9], have provided the basis for joint studies[10] on the influence of conformational and configurational factors on the cyclization of sugar chains. The present investigation describes the synthesis of cytosine and thymine homonucleosides from a 2,5-anhydroaldose precursor, and also illustrates stereochemical control in the formation of a uracil homonucleoside from a pre-formed, acyclic-sugar nucleoside by subsequent cyclization of the sugar chain.

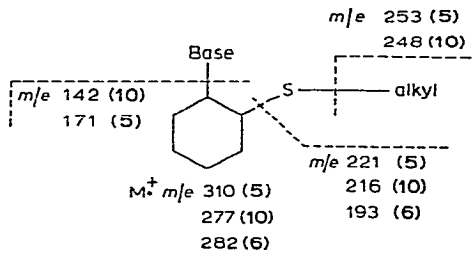
DISCUSSION

The synthetic procedure[3,11] used for base–sugar coupling to give acyclic-sugar nucleosides involves halogenation of an acylated aldose dialkyl dithioacetal to give an unstable, monohalo monothio derivative[12] which is at once coupled to a suitable derivative of a heterocyclic base[13]. Essentially the same route has been applied[2] with acylated 2,5-anhydroaldose dialkyl dithioacetals to give homonucleosides. In general, the route gives good yields of coupled product[2,3,7], although variable and unexplained low yields have on occasion been encountered in certain preparations for which high yields have been demonstrated. The cause of this difficulty is now shown to arise from the use of cyclohexene[2,3] as the scavenging agent for the excess of bromine in the first step of the reaction sequence, as illustrated in the two examples that follow; the difficulty is readily circumvented by use of a slightly modified experimental procedure.

3,4-Di-*O*-acetyl-2,5-anhydro-D-xylose diisobutyl dithioacetal[2] (**1**) in carbon tetrachloride was treated with an excess of bromine at room temperature; the resultant, unstable, monobromo derivative **3** was immediately treated, without isolation, with 2,4-diethoxypyrimidine, and then cyclohexene was added to trap the residual bromine. The reaction product was found to be a mixture containing the anticipated, coupled derivative **4** as the major product (whose characterization is described later), together with a minor product migrating more rapidly than **4** on silica gel.

The minor product was crystalline, optically inactive, had the empirical formula $C_{16}H_{26}N_2O_2S$, and gave u.v.- and n.m.r.-spectral data indicative of the presence of an aromatic ring (monoethoxypyrimidinone), an isobutyl group, and methylene groups of a cyclohexane ring. From these data, the mass spectrum (see Scheme I and Experimental section), and the properties of the product of acid hydrolysis, this compound was assigned the structure **5**, namely, a disubstituted cyclohexane having adjacent isobutylthio and uracil-1-yl substituents. Evidently, the cyclohexene used in the procedure reacts with isobutylsulfenyl bromide (**2**, formed in equimolar proportion to the bromide **3**), and the resultant adduct, presumably 2-(isobutylthio)cyclohexyl bromide, then reacts with 2,4-diethoxypyrimidine to give compound **5** through replacement of the bromine by the base. By analogy with observed reactions[13] of 2,4-diethoxypyrimidine with glycosyl halides, and from the

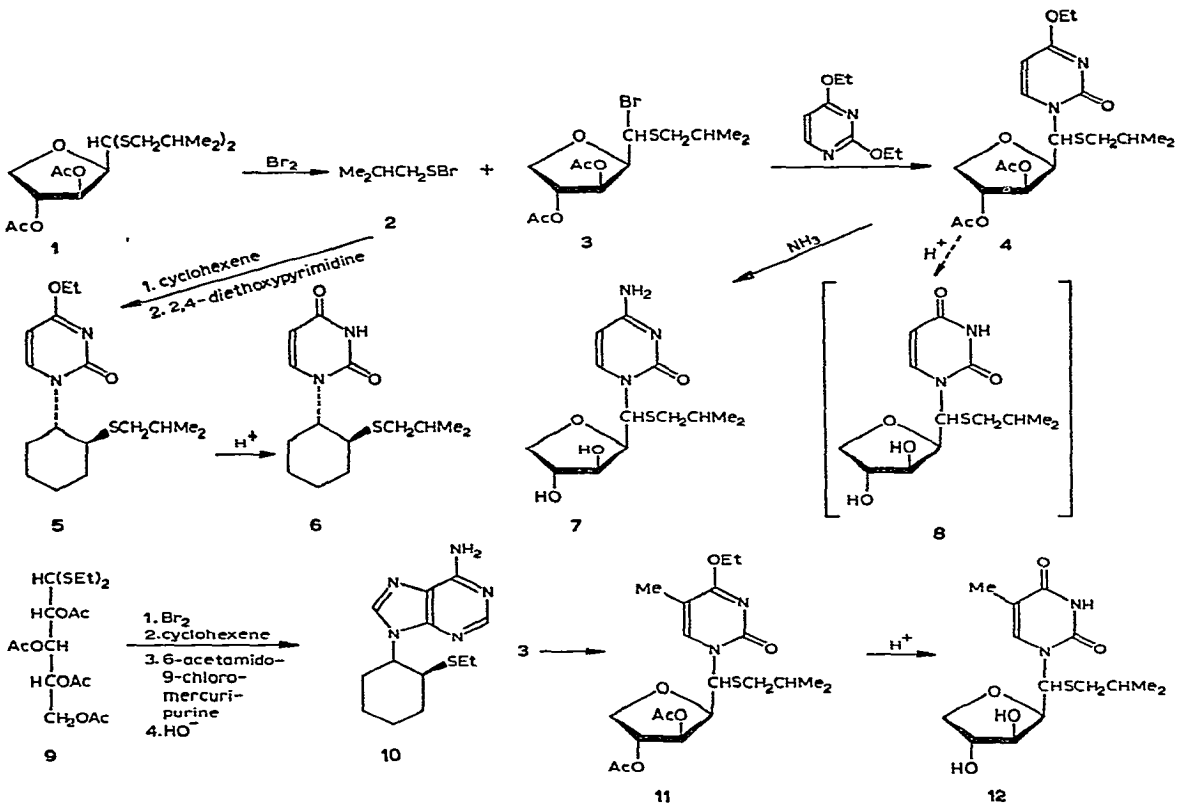
observed u.v.-spectral behavior, the product of attachment through N-1 was anticipated, with loss of the ethoxyl group at C-2, and the *trans*-disposition of the 1,2-substituents was expected through the operation of episulfonium-ion intermediates; the latter possibility was not rigorously established. Methanolic hydrogen chloride removed the ethyl substituent from **5** to give the uracil derivative **6**, whose microanalysis and u.v.-, n.m.r.-, and mass-spectral data (see Experimental section) were in accord with the structural assignment made for this compound, and further supported the structure proposed for the precursor **5**.



Scheme I. Major mass-spectral fragmentation modes of compounds **5**, **6**, and **10**.

A similar result was observed when cyclohexene was used in the attempted synthesis of an acyclic-sugar nucleoside from adenine and D-xylose. The acetylated diethyl dithioacetal (**9**) of D-xylose was treated with bromine to generate the desired 1-bromo-1-ethylthio intermediate, and cyclohexene was added to remove the excess of bromine before the addition of 6-acetamido-9-chloromercuripurine for the desired reaction with the bromide. After isolation by a scheme intended to give the acyclic-sugar nucleoside in its *N,O*-deacetylated form, the only product isolated, in low yield, proved to be a crystalline, oxygen-free, optically inactive compound, $C_{13}H_{19}N_5S$, that was formulated as (±)-*trans*-2-(adenin-9-yl)-1-(ethylthio)cyclohexane (**10**). The structure assigned is supported by spectral data (see Experimental section); in particular the n.m.r. spectrum was consonant with the presence of 9-substituted adenine, an ethylthio group, four contiguous methylene groups, and two vicinal, *trans*-related protons on the cyclohexane moiety. The mass spectrum also accorded well with the assigned structure (see Scheme I). As in the reaction leading to the cyclohexane–uracil derivative **6**, the reaction leading to **10** evidently results from the attack of alkanesulfenyl (ethanesulfenyl) bromide on cyclohexene, and favored reaction of the resultant adduct with the activated purine derivative instead of with the bromo sugar derivative.

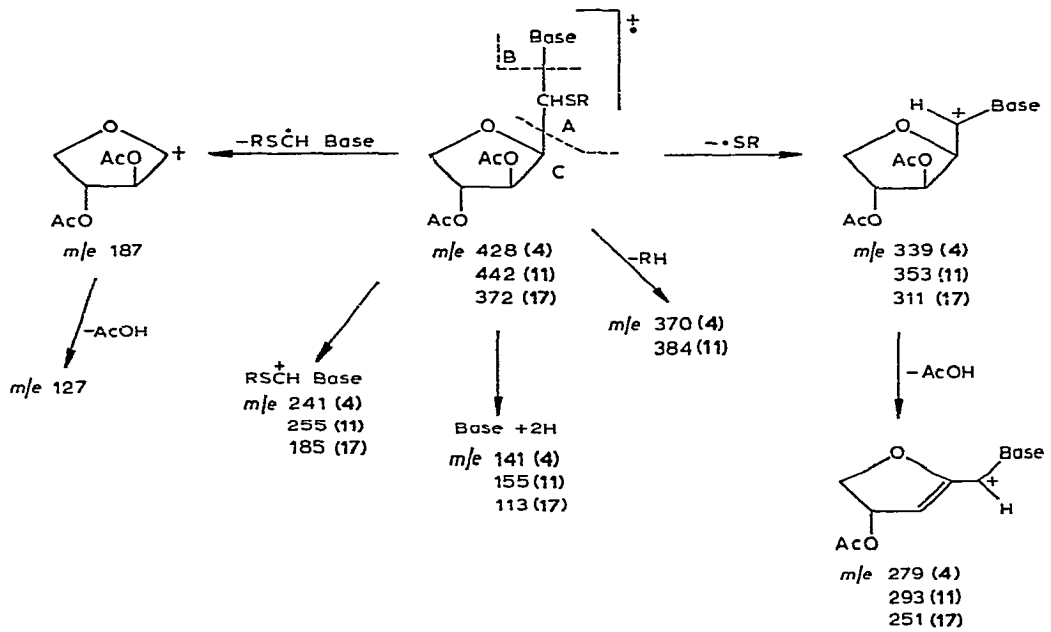
As a result of these observations, the use of cyclohexene in such syntheses is not recommended. After the initial reaction with bromine, which is normally rapid, the most advantageous procedure involves rapid removal of all volatile materials without elevation of the temperature and with evaporation of additional batches of carbon tetrachloride from the residue in order to remove residual bromine and



alkanesulfenyl bromide. By this procedure, an acyclic-sugar adenine nucleoside was obtained[3] in 63% yield from **9**.

The protected homonucleoside derivative **4** was obtained in 70% yield as a levorotatory gum showing the anticipated u.v.-spectral absorption at 285 nm. Although two products differing in stereochemistry at C-1 are theoretically possible, the n.m.r. spectrum clearly showed that the product was a single C-1 epimer, as only one H-1 doublet was evident and no additional multiplicity of signals was observed beyond that expected for a single isomer having the structure **4**. The major, mass-spectral fragmentation-modes exhibited by this compound are noted in Scheme II; these appear to be characteristic of homonucleosides having this general type of structure. The specific chirality at C-1 in **4** has not yet been assigned.

The use of 2,4-diethoxy-5-methylpyrimidine in the procedure used for preparing **4** gave, again, a mixture of a fast-migrating, minor product (presumably the 5-methyl analogue of **5**) and a slower-migrating, major product isolated in 62% yield as a levorotatory oil formulated as the 5-methyl analogue (**11**) of **4**. Compound **11** showed u.v.-, n.m.r.-, and mass-spectral data in very close accord with those given by **4** (see Experimental section, Table I, and Scheme II), with only the anticipated differences



Scheme II. Major mass-spectral fragmentation-modes of compounds **4**, **11**, and **17**.

arising from the 5-methyl group being evident. The product was again a single C-1 epimer, of the same chirality as compound **4**.

The protected homonucleoside **11** was treated with cold, methanolic hydrogen chloride to cleave the *O*-ethyl and the *O*-acetyl groups, and the crystalline, levorotatory thymine homonucleoside **12** was isolated. It showed the anticipated[13] u.v.

TABLE I

COMPARISON OF PHYSICAL DATA FOR THE HOMONUCLEOSIDE DIACETATES **4**, **11**, AND **17**

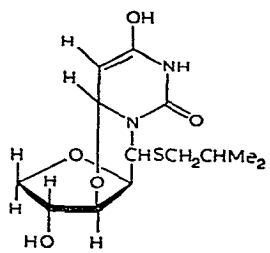
Compound	*Chemical shifts in δ (coupling constants in Hz)*[a]								$[\alpha]_D$ *(degrees, in* $CHCl_3$*)*
	H-1 ($J_{1,2}$)	*H-2*[b] ($J_{2,3}$)	*H-3* ($J_{3,4}$)	*H-4* ($J_{4,5b}$)	*H-5*[b] ($J_{5a,5b}$)	*H-5a* ($J_{4,5a}$)	*Acetate (δ)*		
4	6.29 (6.5)	4.31 (3.5)	5.34 (1.5)	5.26 (5)	4.41 (10.5)	3.96 (2.5)	2.22	2.12	−59
11	6.28 (6.5)	4.30 (3.5)	5.28 (1.5)	5.20 (5)	4.42 (10.5)	3.86 (2.5)	2.20	2.10	−78
17	6.06 (7.0)	4.18 (3.5)	5.40 (~1)	5.25 (5)	4.18 (10.5)	3.83 (2.5)	2.14	2.08	−74

[a]At 100 MHz in chloroform-*d*. [b]These 2,5-anhydrides are clearly differentiated from their non-cyclized analogues by the high-field (δ ~4.3) location of the H-2 signal in the 2,5-anhydrides; derivatives having an acetoxyl group at C-2 show the H-2 resonance about 1 p.p.m. to lower field. The H-2 resonance of compound **18** is part of a multiplet (H-2,3,4) at δ 5.30–5.62 ($CDCl_3$, 100 MHz).

absorption at 269 nm, not significantly shifted in alkaline solution. The n.m.r.- and mass-spectral data were in agreement with the assigned structure.

Treatment of the protected homonucleoside derivative **4** with methanolic ammonia for 12 h at 90° gave in 57% yield the expected cytosine homonucleoside, isolated as its crystalline hydrochloride **7**. It showed u.v. absorption at 273 nm and the anticipated n.m.r.- and mass-spectral behavior (see Experimental section).

In sharp contrast to the behavior observed when compound **11** was converted by methanolic hydrogen chloride into the thymine derivative **12**, similar treatment of compound **4** gave an 82% yield of a feebly dextrorotatory, crystalline product that did *not* show u.v. absorption between 240 and 300 nm in aqueous solution, indicating that the anticipated uracil homonucleoside **8** had not been formed. The product gave a satisfactory elemental analysis for $C_{13}H_{20}N_2O_5S$, and is probably a tautomeric form of the anticipated product **8**, formed by attack of O-2 of the sugar on C-6 of the heterocycle to generate structure **8a**. The n.m.r. data observed at 250 MHz in methyl sulfoxide-d_6 support this formulation; inspection of molecular models of compound **8a** reveals a dihedral angle of about 90° between H-6 and the proton at C-5, which would explain the observed lack of splitting of the H-6 signal. In alkaline solution, the compound shows u.v. absorption at 265 nm typical of a uracil derivative, suggesting that compound **8** is formed from **8a** in alkaline solution. These postulated structures await further, independent confirmation.



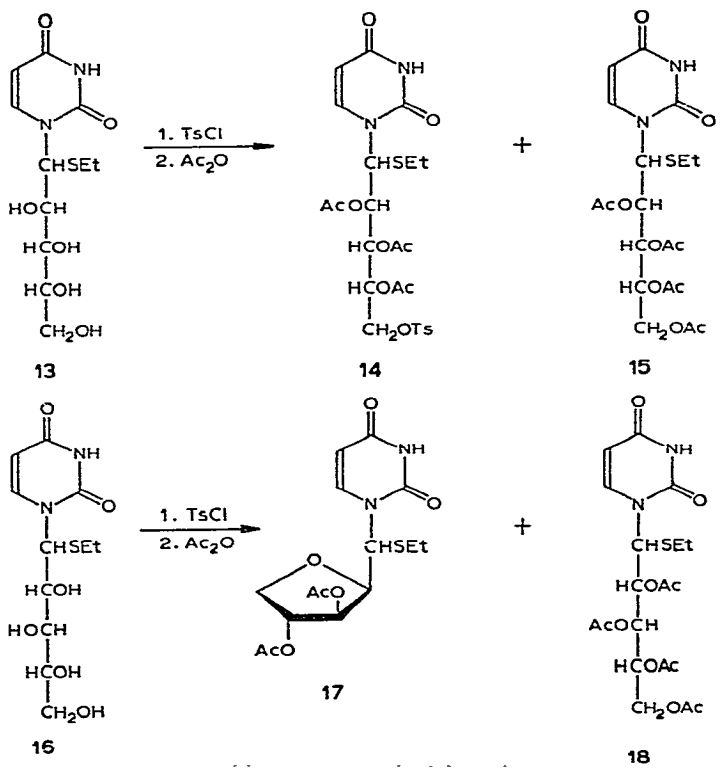
8a

The course of reaction of compound **4** with methanolic hydrogen chloride was unexpected in view of the straightforward conversion of the closely related compound **11** into the thymine homonucleoside **12**. From inspection of space-filling models, the 2′,6-cyclized form (**8a**) of **8** appears equally feasible for the thymine derivative **12**. In alkaline solution, the n.m. resonances for H-5 and H-6 typical of a uracil residue were observed for compound **8**. Intramolecular attack by O-2′ on C-6 is well documented[14] in β-D-*arabino* nucleosides and is favored by electron-withdrawing 5-substituents; the fact that **12** contains an electron-donating 5-substituent may thus be a factor suppressing the 2′,6-cyclization observed with **8**.

The conversion of acyclic-sugar derivatives into anhydro derivatives of the oxolane type is markedly influenced by the stereochemistry of the acyclic sugar chain[10].

For example, the pentose dialkyl dithioacetals having the *arabino* configuration react with one molar proportion of *p*-toluenesulfonyl chloride in pyridine to give the corresponding 5-*p*-toluenesulfonate, whereas the analogues having the *ribo*, *lyxo*, and *xylo* configurations give the respective 2,5-anhydropentose dialkyl dithioacetals instead, evidently as a result of a stereochemically favored, irreversible ring-closure through attack of O-2 on C-5 of an intermediate 5-*p*-toluenesulfonate. For the *arabino* derivatives, this behavior has been interpreted[10] in terms of stabilization of the fully extended ground-state, and steric compression in the transition state for cyclization. As such a differential behavior might be utilized as an independent route to homonucleosides by side-chain cyclization subsequent to the attachment of an acyclic sugar-chain to the base, the reaction with *p*-toluenesulfonyl chloride of two acyclic-sugar nucleosides differing only in stereochemistry was investigated.

Thus, 1-*S*-ethyl-1-thio-1-(uracil-1-yl)-D-arabinitol[3] (**13**) and its D-*xylo* analogue[3] (**16**) (both of which are single, C-1 epimers of as-yet-undetermined stereochemistry at C-1) were each treated in the cold with slightly more than one molar equiv. of *p*-toluenesulfonyl chloride in pyridine. The D-*arabino* derivative **13** gave a major product identified as the 5-mono-*p*-toluenesulfonate from the properties (see Experimental section) of its derived triacetate **14**, accompanied by a small proportion of unreacted starting-material **13**, identified as its crystalline tetraacetate[3] **15**.



In contrast, the *xylo* analogue **16** gave a major product containing no *p*-tolylsulfonyl group, together with a smaller proportion of unreacted starting-material **16** (identified as its tetraacetate[3] **18**). The major product gave a diacetate **17** as a levorotatory oil whose n.m.r. and mass spectra were in full accord with the homonucleoside structure indicated. The n.m.r. spectrum indicated that **17** is a single epimer, as there was no additional multiplicity observed in the signals beyond that anticipated for a single epimeric form. The chemical shifts and spin couplings for protons on the sugar residue were in close accord with those observed for compounds **4** and **11**, already described (see Table I), and the principal, mass-spectral fragmentations (see Scheme II) also showed close parallels with those of the homonucleoside derivatives **4** and **11**. It is, therefore, evident that the side-chain cyclization of the acyclic-sugar nucleosides to generate homonucleosides can be effectively realized along the lines of reactivity observed for simple acyclic-sugar derivatives.

EXPERIMENTAL

General methods. — Solutions were evaporated *in vacuo* at temperatures below 50°. Melting points were determined with a Leitz heated-block apparatus (compounds **4–8**, **11**, and **12**) or an oil-bath apparatus (Thomas–Hoover; other compounds described here). T.l.c. was performed with silica gel G (Merck) activated at 110°, with 3:1 dichloromethane–ether as the eluant (unless otherwise indicated), to monitor reactions, and demonstrate homogeneity of the acetylated products. Silica gel No. 7734 (Merck) was used for column chromatography. U.v. spectra were recorded with a Cary Model 14 spectrophotometer, and a Perkin–Elmer Model 137 spectrophotometer was used for recording i.r. spectra. Mass spectra were recorded with an AEI MS-9 spectrometer at an ionizing potential of 70 eV and a direct-introduction source operating at 250°, by C. R. Weisenberger (O.S.U.) or by M. Bouhet and M. Ulrich (Centre d'Études Nucléaires de Grenoble). N.m.r. spectra at 100 MHz were recorded with a Varian HA-100 spectrometer operating in the frequency-swept mode, with 5% of tetramethylsilane as the lock signal and internal standard; spectra at 250 MHz were recorded by M. Reutenauer with a Cameca-250 spectrometer at the Groupe Grenoblais de Resonance Magnétique Nucléaire à Haute Résolution, Centre d'Études Nucléaires de Grenoble. Microanalyses were made by W. N. Rond (O.S.U.) or by the Laboratoire Central de Microanalyse du C.N.R.S. (Thiais, France). X-Ray powder diffraction data give interplanar spacings in Å for CuKα radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

(±)-trans-(*Adenin-9-yl*)-*1*-(*ethylthio*)*cyclohexane* (**10**). — To a solution of tetra-*O*-acetyl-D-xylose diethyl dithioacetal[15] (**9**; 4.24 g, 10 mmoles) in dry ether (50 ml) was added bromine (1.6 g, 10 mmoles). After 15 min at ~25°, several drops of cyclohexene were added (to decompose any slight excess of bromine), and the solvent was evaporated off at ~25° to give a colorless syrup. The syrup was added

to a suspension of 6-acetamido-9-chloromercuripurine (4.1 g, 10 mmoles), cadmium carbonate (3.4 g), and Celite (1 g) that had been azeotropically dried, in toluene (100 ml). The mixture was stirred and boiled for 4 h under reflux. The hot suspension was filtered, and the filtrate evaporated. Both the residue and the filter cake were extracted with hot chloroform (250 ml), and the extract was washed twice with 30% aqueous potassium iodide and 3 times with water. The dried (sodium sulfate) extract was evaporated, and the resultant syrup, in ethanol (35 ml), was boiled for 5 min with a solution of picric acid (2.3 g, 10 mmoles) in ethanol (25 ml). The yellow precipitate that formed on cooling was filtered off, washed with ethanol, and suspended in warm 1:1 acetone–water (200 ml). An excess of Bio-Rad AG-1 X-2 (CO_3^{2-}) ion-exchange resin was then added, and the suspension was stirred for 10–15 min, whereupon the supernatant solution became practically colorless. The mixture was passed through a short column of the same resin, and the effluent was concentrated to ~100 ml and extracted with two 100-ml portions of chloroform; the dried (magnesium sulfate) extract was evaporated to give crystalline **10**; yield 100 mg (8%, based on **9**). It was recrystallized from ethanol–petroleum ether (b.p. 65–100°) to give pure **10**, m.p. 168–170°, $[\alpha]_D$ 0° (chloroform); R_F 0.8 (9:1 ether–methanol); λ_{max}^{MeOH} 264 nm (ε 12,600); λ_{max}^{KBr} 3.0, 3.14 (NH), 3.4 (CH), 5.9, 6.18, 6.25, 6.8 (purine), 7.03, 7.25, 7.58, 7.63, 8.0, 8.25, 9.25, 9.85, 10.2, 12.15, 12.9, and 13.8 μm; n.m.r. (100 MHz, $CDCl_3$): δ 8.34, 7.80 (singlets, H-2 and H-8 of purine), 6.91 (broad singlet, NH_2), 4.18 (apparent six-line pattern M of ABMX system, $J_{1',2'}$ 11.2, $J_{1',6'trans}$ 11.2, $J_{1',6'cis}$ 5.0 Hz, H-1 of cyclohexane residue), 3.36 (broadened, apparent 6-line pattern X of ABMX system, H-2 of cyclohexane residue), 2.12 (quartet, *J* 7.5 Hz, CH_2 of SEt), 2.60–1.56 (complex multiplet, H-3,4,5,6 of cyclohexane moiety), and 0.94 (triplet, CH_3 of Et); *m/e* 277 (8.6, M^+), 249 (0.5), 248 (4.13, $M^+ - \cdot C_2H_5$), 2.18 (4.3), 217 (37.1), 216 (6, $M^+ - \cdot SEt$), 188 (1.3), 174 (0.8), 168 (1.1), 162 (0.9), 148 (10), 144 (3), 143 (18.8), 142 (52.9, M^+ – adenine), 141 (1.5), 137 (6.5), 136 (100, adenine H^+), 135 (61.4, adenine), 121 (0.3), 119 (2.4), 114 (4.2), 113 (7.6), 109 (0.8), 108 (6.4), 101 (0.8), 92 (0.7), 86 (2.8), 85 (1.7), 81 (50.5), and 43 (2); X-ray powder diffraction data: 8.25 w, 7.36 vs (1), 6.92 m, 5.68 w, 4.84 vw, 4.29 s, 4.08 s (2,2), 3.77 vw, 3.50 w, and 3.26 s (2,2).

Anal. Calc. for $C_{13}H_{19}N_5S$: C, 56.27; H, 6.90; N, 25.25; S, 11.55. Found: C, 56.29; H, 6.90; N, 25.05; S, 11.76.

When the foregoing experiment was conducted by a modified procedure wherein the addition of cyclohexene was omitted, an acyclic-sugar nucleoside derivative[3] was obtained in 63% yield. The yield of **10** was increased when more cyclohexene was used.

*3,4-Di-*O*-acetyl-2,5-anhydro-1-(4-ethoxy-2-pyrimidinone-1-yl)-1-*S*-isobutyl-1-thio-*D*-xylitol* (**4**) *and 2-(4-ethoxy-2-pyrimidinone-1-yl)-1-(isobutylthio)cyclohexane* (**5**). — A solution of 3,4-di-*O*-acetyl-2,5-anhydro-D-xylose diisobutyl dithioacetal[2] (**1**; 5 g, 3.9 mmoles) in dry carbon tetrachloride (30 ml) was magnetically stirred at ~20°, and a solution of bromine (0.2 ml, 4 mmoles) in carbon tetrachloride (20 ml) was added dropwise. As soon as the addition was complete, a solution of 2,4-di-

ethoxypyrimidine (3 g, 17.8 mmoles) in carbon tetrachloride (5 ml) was added, and stirring was continued for another 10 min; several drops of cyclohexene were then added until the solution was decolorized, and the solution was evaporated at $<30°$. The resultant oil was dissolved in acetonitrile (30 ml), and the solution kept for 48 h at $\sim 20°$. Solvent and unreacted 2,4-diethoxypyrimidine were removed under high vacuum, and the resultant oil was dissolved in chloroform (25 ml). The solution slowly deposited a white powder (90 mg), which was filtered off, and identified as uracil (t.l.c. on cellulose, 1:1 ethanol–water). Evaporation of the filtrate gave an oil (3.4 g) containing two components (t.l.c. on silica gel, 3:1 dichloromethane–ether) which were separated on a column (3 × 50 cm) of silica gel with the t.l.c. solvent as the eluant. The first 210 ml of eluate gave an oil (1.11 g, 60% on the basis of **1** used) that crystallized from 3:2 methanol–water to give **5**, m.p. 96–98°, $[\alpha]_D$ 0° (chloroform); λ_{max}^{EtOH} 281 nm (ε 8,250); n.m.r. (100 MHz, $CDCl_3$): δ 7.38 (doublet, $J_{5,6}$ 7 Hz, H-6), 5.90 (doublet, H-5), 4.50 (quartet, CH_2 of Et), ~ 4.5 and ~ 2.9 (1-proton multiplets, H-1,2 of cyclohexane group), 2.50–1.06 (multiplets, 11 protons, H-3,4,5,6 of cyclohexane and $-CH_2CH-$ of isobutyl groups), 1.38 (triplet, CH_3 of Et), 0.96 and 0.90 (singlets, CH_3 of isobutyl); *m/e* 310 (2, $M^{\ddagger}$), 281 (5, $M^{\ddagger} - \cdot C_2H_5$), 267 (5, $M^{\ddagger} - 43$), 253 (13, $M^{\ddagger} - 57$), 222 (17), 221 (14, $M^{\ddagger} -$ · Sisobutyl), 193 (8), 191 (6), 172 (37), 171 (90, $\overset{+}{C}_6H_{10}SCH_2CHMe_2$), 170 (100), 142 (43), 141 (100, B+2H), 127 (37), 116 (42), 115 (84), 114 (100), and 113 (100).

Anal. Calc. for $C_{16}H_{26}N_2O_2S$: C, 61.90; H, 8.44; N, 9.02; O, 10.31; S, 10.32. Found: C, 61.92; H, 8.45; N, 9.01; O, 10.24; S, 10.56.

The next 330 ml of solvent eluted the nucleoside derivative **4** as a gum; yield 1.2 g (70%), $[\alpha]_2^{22}$ −58.9° (*c* 1.2, chloroform); λ_{max}^{EtOH} 285 nm (ε 6,250); n.m.r. (100 MHz, $CDCl_3$): δ 8.04 and 6.02 (doublets, $J_{5,6}$ 7.5 Hz, H-5,6 of pyrimidine), 6.29 (doublet, $J_{1,2}$ 6.5 Hz, H-1), 5.34 (doublet of doublets, $J_{2,3}$ 3.5, $J_{3,4}$ 1.5 Hz, H-3), 5.26 (6-line pattern, 9 Hz wide, H-4), 4.52 (quartet, CH_2 of Et), 4.41 (quartet, $J_{4,5b}$ 5, $J_{5a,5b}$ 10.5 Hz, H-5b), 4.31 (doublet of doublets, H-2), 3.96 (quartet, $J_{4,5a}$ 2.5 Hz, H-5a), 2.48 (octet, CH_2 of isobutyl), 2.22 and 2.12 (singlets, OAc), 1.76 (multiplet, CH of isobutyl), 1.42 (triplet, CH_3 of Et), 1.03 and 0.96 (narrow doublets, $J \sim 1$ Hz, CH_3 of isobutyl); *m/e* 428 (4, $M^{\ddagger}$), 385 (1, $M^{\ddagger} - 43$), 370 (46, $M^{\ddagger} - Me_2CHCH_2$, H), 339 (41, $M^{\ddagger} -$ · Sisobutyl), 329 (1), 325 (2, $M^{\ddagger} - 43 - 60$), 311 (34, $M^{\ddagger} - 58 - 59$), 297 (10), 279 (31, $M^{\ddagger} -$ · Sisobutyl − 60), 269 (7), 255 (7), 253 (36), 251 (16), 241 (50), 237 (21, $M^{\ddagger} -$ · Sisobutyl − 60 − 42), 228 (15), 221 (16), 209 (13), 194 (16), 191 (9), 189 (5), 187 (9, anhydro ring), 186 (12), 185 (10), 183 (9), 172 (12), 165 (67), 157 (20), 148 (25), 141 (100), 127 (12, anhydro ring − 60), 115 (33), 113 (44), 112 (16), 101 (11), 98 (20), 97 (41), 96 (28), and 87 (15).

Anal. Calc. for $C_{19}H_{28}N_2O_7S$: C, 53.24; H, 6.57; N, 6.53; S, 7.48. Found: C, 53.25; H, 6.78; N, 6.79; S, 7.65.

1-(Isobutylthio)-2-(uracil-1-yl)cyclohexane (**6**). — The ethoxy derivative **5** (1.38 g) in dichloromethane (60 ml) was treated with a 1:4 (w/w) solution of hydrogen chloride in methanol (15 ml), and the mixture was kept for 24 h at $\sim 20°$. The solution was evaporated at $\sim 25°$, and ethanol (3 × 15 ml) was added to, and evaporated from,

the residue. The crystalline residue was dissolved in anhydrous ethanol (15 ml), and petroleum ether was added, to afford crystalline **6**; yield 0.8 g (88%), m.p. 185–187°; λ_{max}^{EtOH} 267 nm (ε 9,360) unchanged on addition of 0.1M sodium hydroxide; n.m.r. (100 MHz, $CDCl_3$): δ 7.1 (doublet, $J_{5,6}$ 8 Hz, H-6 of uracil), 5.73 (doublet, H-5 of uracil), 4.2 and 2.8 (1-proton multiplets, H-1 and H-2 of cyclohexane), 2.36 (wide doublet, J 7 Hz, CH_2 of isobutyl), 2.2–1.1 (9-proton multiplet, CH_2 of cyclohexane and CH of isobutyl), 0.96 and 0.86 (broadened singlets, CH_3 of isobutyl); *m/e* 282 (2, $M^{\ddagger}$), 193 (4, $M^{\ddagger}$ – ·Sisobutyl), 170 (80, $M^{\ddagger}$ – BH), 114 (100, B+5H), 113 (25, B+2H), and 81 (55).

Anal. Calc. for $C_{14}H_{22}N_2O_2S$: C, 59.53; H, 7.85; N, 9.91; O, 11.33; S, 11.35. Found: C, 59.56; H, 7.86; N, 9.91; O, 11.20; S, 11.50.

3,4-Di-O-acetyl-2,5-anhydro-1-(4-ethoxy-5-methyl-2-pyrimidinone-1-yl)-1-S-isobutyl-1-thio-D-xylitol (**11**). — A solution of the dithioacetal **1** (2.3 g, 6 mmoles) in dry carbon tetrachloride (40 ml) was stirred at ~20°, and a solution of bromine (0.3 g, 6 mmoles) in carbon tetrachloride (25 ml) was added dropwise. A solution of 2,4-diethoxy-5-methylpyrimidine (4.5 g, 25 mmoles) in carbon tetrachloride (8 ml) was then added, and the mixture was stirred for 10 min, decolorized by addition of a few drops of cyclohexene, and evaporated below 30°. The resultant oil was dissolved in acetonitrile, the solution kept for 48 h at 25–30°, evaporated under high vacuum, and the resultant oil freed of the excess of 2,4-diethoxy-5-methylpyrimidine by extraction with petroleum ether (15 ml). The residual oil contained two components (t.l.c., silica gel, 3:1 dichloromethane–ether) that were separated on a column (100 × 3 cm) of silica gel with the t.l.c. solvent as the eluant. The first 660 ml of eluate gave 0.8 g of a component that was not further investigated, and the next 540 ml of eluate gave the desired product **11** as a colorless oil; yield 1.6 g (62%), $[\alpha]_D^{22}$ −78° (*c* 0.77, chloroform); λ_{max}^{EtOH} 285 nm (ε 6,450); n.m.r. (100 MHz, $CDCl_3$): δ 7.74 (narrow doublet, H-6 of thymine), 6.28 (doublet, $J_{1,2}$ 6.5 Hz, H-1), 5.28 (doublet of doublets, $J_{2,3}$ 3.5, $J_{3,4}$ 1.5 Hz, H-3), 5.20 (multiplet, 10 Hz wide, H-4), 4.50 (quartet, CH_2 of Et), 4.42 (quartet, $J_{5a,5b}$ 10.5, $J_{4,5b}$ 5 Hz, H-5b), 4.30 (doublet of doublets, H-2), 3.86 (quartet, $J_{4,5a}$ 2.5 Hz, H-5a), 2.46 (octet, CH_2 of isobutyl), 2.20 and 2.10 (singlets, OAc), 2.02 (narrow doublet, J ~1 Hz, CH_3 of thymine), 1.75 (m, CH of isobutyl), 1.10 (triplet, CH_3 of Et), and 1.00 and 0.94 (doublets, J ~1 Hz, CH_3 of isobutyl); *m/e* 442 (4, $M^{\ddagger}$), 427 (0.5, $M^{\ddagger}$ – 15), 413 (0.5, $M^{\ddagger}$ – 29), 399 (1, $M^{\ddagger}$ – 43), 384 (41, $M^{\ddagger}$ – Me_2CHCH_2, H), 370 (4, $M^{\ddagger}$ – 43 – 29), 353 (51, $M^{\ddagger}$ – ·Sisobutyl), 339 (5, $M^{\ddagger}$ – 43 – 60), 325 (26, $M^{\ddagger}$ – 58 – 59), 311 (12), 307 (20), 293 (38, $M^{\ddagger}$ – ·Sisobutyl – 60), 267 (31), 265 (19), 255 (60), 251 (24, $M^{\ddagger}$ – ·Sisobutyl – 60 – 42), 235 (20), 228 (24), 223 (15), 209 (16), 199 (15), 187 (14, anhydro ring), 186 (12), 179 (86), 170 (53), 162 (19), 157 (15), 155 (100), 141 (13), 139 (13), 127 (52, anhydro ring – 60), 114 (90), 110 (17), 103 (13), 101 (16), 97 (39), 85 (30, anhydro ring – 60 – 42), and 81 (43).

Anal. Calc. for $C_{20}H_{30}N_2O_7S$: C, 54.31; H, 6.82; N, 6.33; S, 7.24. Found: C, 54.06; H, 6.76; N, 6.31; S, 6.92.

Attempts to prepare **4** and **11** from the bromide **3** by fusion with 2,4-bis(tri-

methylsiloxy)pyrimidine or its 5-methyl analogue, as successfully realized[3] with acyclic-sugar analogues of **3**, failed to give the desired coupling-products, presumably because of the high thermal lability of **3**.

*2,5-Anhydro-1-*S*-isobutyl-1-thio-1-(uracil-1-yl)-*D*-xylitol* (**8**). — To a solution of diacetate **4** (1.2 g) in dichloromethane (80 ml) was added a 1:4 (w/w) solution of hydrogen chloride in methanol (20 ml). The solution was kept for 24 h at ~20°, and evaporated; ethanol (3 × 20 ml) was added to, and evaporated from, the residue, and the residual oil was dissolved in abs. ethanol (30 ml) and treated with ether (15 ml), to give a crystalline product tentatively formulated as the tautomer **8a**; yield 0.72 g (82%), m.p. 198–201°, $[\alpha]_D^{22}$ +1.7° (*c* 1.15, ethanol); $\lambda_{max}^{H_2O}$ none between 240 and 300 nm (*c* 1.4 mg/ml), $\lambda_{max}^{0.1M\ NaOH}$ 265 nm (ε 10,050); n.m.r. (250 MHz, Me_2SO-d_6): δ 10.64 (singlet, HO-4 of pyrimidine), 5.80 (singlet, $J_{1,2}$ ~0 Hz, H-1), 5.35 (doublet, *J* 3.5 Hz), 5.30 (dd, *J* 1.8 and 6 Hz), 4.14 (broadened singlet), 4.03 (broadened doublet, *J* 3.5 Hz), 3.95 (dd, *J* 4.5 and 9 Hz), 3.77 (narrow multiplet), 3.52 (doublet, *J* 9 Hz), 3.29 (doublet, *J* 6 Hz), 3.20 (doublet, *J* 6 Hz), 3.13 (doublet, *J* 6 Hz) (H-5 and 6 of pyrimidine and H-2,3,4,5a,5b and HO-3 of sugar), ~2.5 (CH_2 of isobutyl, obscured by solvent resonance), 1.80 (multiplet, CH of isobutyl), and 0.97 and 0.94 (doublets, CH_3 of isobutyl); *m/e* 316 (3, $M^{\ddagger}$), 260 (4, $M^{\ddagger} - Me_2CCH_2$, H), 256 (11), 255 (23), 228 (17), 227 (100, $M^{\ddagger}$ – ·Sisobutyl), 213 (7), 209 (2, $M^{\ddagger}$ – ·Sisobutyl – H_2O), 204 (2), 199 (1), 191 (1, $M^{\ddagger}$ – ·Sisobutyl – $2H_2O$), 184 (7, $M^{\ddagger}$ – ·Sisobutyl – 43), 167 (6), 155 (3), 142 (23), 125 (2), 113 (13, B+2H), and 97 (6).

Anal. Calc. for $C_{13}H_{20}N_2O_5S$: C, 49.33; H, 6.35; N, 8.82; S, 11.11. Found: C, 49.48; H, 6.25; N, 8.98; S, 11.00.

Addition of a few drops of a solution of NaOD in deuterium oxide to the solution in methyl sulfoxide-d_6 gave an n.m.r. spectrum (100 MHz) showing three 1-proton signals below δ 4.1: δ 7.59 (doublet, $J_{5,6}$ 7 Hz, H-6 of pyrimidine), 5.75 (multiplet, H-1, second-order, because of proximity of H-2,3,4 signals), and 5.54 (doublet, H-5 of pyrimidine). The data suggested that the compound exists as **8** after treatment with alkali, but that a tautomeric form, such as **8a**, is the form initially isolated.

*2,5-Anhydro-1-*S*-isobutyl-1-thio-1-(thymin-1-yl)-*D*-xylitol* (**12**). — The diacetate **11** (1.5 g) in dichloromethane (120 ml) was treated with 1:4 (w/w) methanolic hydrogen chloride (30 ml) according to the procedure of the preceding experiment, to give the thymine derivative **12** as crystals from chloroform–petroleum ether; yield 0.78 g (70%), m.p. 157–159°, $[\alpha]_D^{22}$ −90.7° (*c* 1.3, chloroform); λ_{max}^{EtOH} 207 (ε 8,210) and 269 nm (8,370), $\lambda_{max}^{0.1M\ NaOH}$ 266 nm (ε 6,270); n.m.r. (100 MHz, CD_3OH): δ 7.72 (narrow doublet, H-6 of thymine), 5.92 (perturbed doublet, $J_{1,2}$ ~7 Hz, H-1), 4.37–4.15, 3.95, and 3.73 (multiplets, H-2,3,4,5a,5b), 2.5 (octet, CH_2 of isobutyl), 1.92 (narrow doublet, *J* ~1 Hz, CH_3 of thymine), 1.75 (m, CH of isobutyl), and 1.00 and 0.92 (narrow doublets, *J* ~1 Hz, CH_3 of isobutyl); *m/e* 330 (17, $M^{\ddagger}$), 312 (2, $M^{\ddagger} - H_2O$), 270 (5), 241 (44), 228 (20, B+A+H), 227 (100, B+A^+), 223 (25),

205 (66, A+C$^+$), 181 (35), 180 (25), 171 (22), 169 (20), 127 (45, B+2H), 126 (25, B+H), and 103 (32, C$^+$).

Anal. Calc. for $C_{14}H_{22}N_2O_5S$: C, 50.88; H, 6.71; N, 8.48; S, 9.70. Found: C, 50.78; H, 6.79; N, 8.69; S, 9.55.

2,5-Anhydro-1-(cytosin-1-yl)-1-S-isobutyl-1-thio-D-xylitol hydrochloride (**7**). — The 4-ethoxy derivative **4** (0.6 g), in anhydrous methanol (30 ml) saturated at 0° with ammonia, was heated in a sealed tube for 12 h at 90°. The mixture was cooled, filtered to remove the precipitate of ammonium chloride, and the filtrate evaporated *in vacuo*. The residue was dissolved in chloroform (60 ml), and the pH of the solution brought to 5 by dropwise addition of methanolic hydrogen chloride (1:4, w/w). The resultant precipitate was filtered off, and recrystallized from 3:1 ethanol–ether; yield 280 mg (57%), m.p. 174–176°, $[\alpha]_D^{22}$ −111° (*c* 0.8, methanol); $\lambda_{max}^{H_2O}$ 273 nm (ε 12,700); n.m.r. (250 MHz, CD_3OD): δ 8.19 (doublet, *J* 7 Hz, H-6 of pyrimidine), 6.24 (doublet, H-5 of pyrimidine), 5.92 (multiplet, H-1), 4.36 (broad), ~4.2 (2-proton multiplet), 3.98 (broadened doublet, *J* 3 Hz), 3.70 (doublet, *J* 8 Hz; H-2,3,4,5a,5b), 2.61 and 2.43 (AB portion of ABX system, CH_2 of isobutyl), 1.83 (multiplet, CH of isobutyl), and 1.01 and 0.98 (narrow doublets, CH_3 of isobutyl); *m/e* 315 [1, M$^+$ (free base)], 304 (2), 294 (2.5), 283 (1), 266 (1), 265 (4), 264 (6), 258 (24, M$^+$ − Me_2CHCH_2, H), 241 (2, M$^+$ − 58 − 17), 227 (33, M$^+$ − ·Sisobutyl), 226 (11), 213 (27), 210 (7, M$^+$ − ·Sisobutyl − 17), 205 (10, fragmentation B, with charge retention on A), 204 (22), 193 (34), 192 (9, M$^+$ − ·Sisobutyl − 17 − 18), 186 (16), 178 (16), 170 (17), 169 (58), 167 (21), 148 (5, 205 − isobutyl), 142 (8), 136 (7), 130 (8), 122 (12), 116 (4, 205 − ·Sisobutyl), 114 (11), 113 (34), 112 (42, B+2H), 111 (82, B+H), 103 (22), and 97 (100).

Anal. Calc. for $C_{13}H_{22}ClN_2O_4S$: C, 44.36; H, 6.30; Cl, 10.08; N, 11.94; S, 9.14. Found: C, 44.48; H, 6.38; Cl, 9.93; N, 11.79; S, 8.89.

Reaction of 1-S-ethyl-1-thio-1-(uracil-1-yl)-D-arabinitol (**13**) *with p-toluenesulfonyl chloride.* — The nucleoside derivative[3] **13** (450 mg, 1.5 mmoles) was dried for 2 h at 40°/10 mtorr, and then dissolved in anhydrous pyridine (2 ml). The solution was cooled to −10°, and a solution of *p*-toluenesulfonyl chloride (315 mg, 1.65 mmoles) in anhydrous pyridine (2 ml) was added. The mixture was kept for 2 h at −10°, and then for 18 h at ~25°, and evaporated to a thin syrup, and pyridine was removed by successive addition and evaporation of toluene (3 × 30 ml) and carbon tetrachloride (3 × 30 ml). The residue was extracted with three 100-ml portions of acetone, and the extracts were combined, and evaporated to a thick syrup which, by t.l.c. (silica gel, 10:1 chloroform–methanol), showed 3 components, one minor (R_F 0.08), one major (R_F 0.35), and the third, a trace (R_F 0.45).

The foregoing syrup was resolved by preparative, loose-layer chromatography on 4 chromatoplates. Each plate was first developed with 10:1 chloroform–methanol and then with 4:1 chloroform–methanol. U.v. light was used as the indicator, and the band containing the major component was extracted with 9:1 chloroform–methanol (300 ml). Evaporation of the solution gave the major component as chromatographically homogeneous, amorphous product (yield 250 mg); it was dissolved in a

mixture of anhydrous pyridine (2 ml) and acetic anhydride (1 ml) precooled to 0°, and the mixture was kept for 16 h at ~25°. Ethanol (2 ml) was then added, and the solution was evaporated to a thin syrup, from which pyridine was removed by adding and evaporating several portions of 50% aqueous ethanol. The residue was extracted with chloroform, and evaporation of the extract gave 2,3,4-tri-*O*-acetyl-1-*S*-ethyl-1-thio-5-*O*-*p*-tolylsulfonyl-1-(uracil-1-yl)-D-arabinitol (**14**) as a chromatographically homogeneous glass; yield 300 mg (88%); $[\alpha]_D^{21}$ +96° (*c* 0.9, chloroform); R_F 0.45 (10:1 chloroform–methanol); λ_{max}^{MeOH} 263 nm (ε 8,900); λ_{max}^{film} 2.84–3.14 (NH), 5.75 (OAc), 5.95, 6.85 (uracil), 7.05, 7.25, 7.95, 8.25, 8.55, 8.95, 9.35, 9.7, 9.95, 10.9, 11.6, 12.2, 13.1, 14.1, and 14.6 μm; n.m.r. (100 MHz, $CDCl_3$): δ 7.52 (A_2B_2, aromatic protons of Ts), 7.51 (doublet, $J_{5,6}$ 8.0 Hz, H-6 of pyrimidine), 5.81 (doublet H-5 of pyrimidine), 5.92 (doublet, $J_{1,2}$ 7.5 Hz, H-1), 5.45–5.23 (multiplet, H-2,3), 5.18–4.08 (multiplet, H-4) 4.22 (quartet, $J_{4,5b}$ 3.0 Hz, $J_{5a,5b}$ 11.5 Hz, H-5b), 4.02 (quartet, $J_{4,5a}$ 5.5 Hz, H-5a), 2.47 (quartet, *J* 7.5 Hz, CH_2 of Et), 2.31 (singlet, CH_3 of Ts), 2.08 (2) and 1.99 (singlets, OAc), and 1.33 (triplet, CH_3 of Et).

Anal. Calc. for $C_{24}H_{30}N_2O_{11}S_2$: C, 49.19; H, 5.16; N, 4.77; S, 10.93. Found: C, 49.59; H, 5.40; N, 5.00; S, 10.92.

Similar extraction of the band containing the minor component gave an amorphous product, R_F 0.08 (10:1 chloroform–methanol) that was acetylated, and the product crystallized from ether, to give the tetraacetate (**15**) of **13** (yield 150 mg) which was identified by its X-ray powder diffraction pattern as the known[3] 2,3,4,5-tetra-*O*-acetyl-1-*S*-ethyl-1-thio-1-(uracil-1-yl)-D-arabinitol (**15**).

The net yield of the 5-*p*-toluenesulfonate **14** from **13** was 38%, and 21% of the starting material was recovered as its tetraacetate **15**.

Reaction of 1-S-ethyl-1-thio-1-(uracil-1-yl)-D-xylitol (**16**) *with p-toluenesulfonyl chloride.* — The nucleoside derivative[3] **16** (900 mg, 3.0 mmoles) was dried for 2 h at 40°/10 mtorr, and then dissolved in anhydrous pyridine (4 ml). The solution was cooled to −10°, and a solution of *p*-toluenesulfonyl chloride (630 mg, 3.3 mmoles) in anhydrous pyridine was added. The mixture was kept for 2 h at −10° and then for 18 h at ~25°, and evaporated to an oil; toluene (3 × 30 ml) and carbon tetrachloride (3 × 30 ml) were successively added and evaporated, and the residue was extracted with three 100-ml protions of acetone. The extracts were combined, and evaporated to a thick syrup that, by t.l.c. with 97:3 ethyl acetate–methanol, contained a minor (R_F 0.09), a major (R_F 0.34), and a trace component (R_F 0.79). The mixture was resolved by preparative-layer chromatography on 6 chromatoplates (200 × 200 × 1.2 mm), each plate being developed 3 times with 19:1 ethyl acetate–methanol. The band containing the major component was excised (by use of u.v. light as the indicator), and the product was extracted with 4:1 ethyl acetate–ethanol. Evaporation of the extract gave the major component as a thick glass that was converted by trituration with ether into an amorphous powder of 2,5-anhydro-1-*S*-ethyl-1-thio-1-(uracil-1-yl)-D-xylitol; yield 450 mg (53%), $[\alpha]_D^{25}$ −17° (*c* 0.5, methanol); λ_{max}^{KBr} 3.0 (NH, OH), 5.95, 6.85, 7.05, 7.30, 8.05, 8.55, 9.25, 9.35, 9.70, 10.35, 10.75, 11.35,

12.30, 13.10, and 13.90 μm. T.l.c. indicated that the product still contained a trace of the slower-moving component present in the original reaction-product.

Acetylation of the foregoing product (400 mg) by the procedure described for **14** gave 3,4-di-*O*-acetyl-2,5-anhydro-1-*S*-ethyl-1-thio-1-(uracil-1-yl)-D-xylitol (**17**) as a chromatographically homogeneous glass (a small quantity of chloroform-insoluble material that resulted was discarded); yield 330 mg (62%), $[\alpha]_D^{21}$ −74° (*c* 2.0, chloroform); R_F 0.32 (ether); λ_{max}^{MeOH} 264 nm (ε 5,600); λ_{max}^{film} 3.10 (NH), 5.70 (OAc), 5.9, 6.9 (uracil), 7.3, 8.05–8.20 (ester), 8.5, 9.25, 9.6, 9.8, 10.1, 10.6, 12.25, 13.15, and 13.65 μm; n.m.r. (100 MHz, $CDCl_3$): δ 7.73 (doublet, $J_{5,6}$ 8.0 Hz, H-6 of pyrimidine), 5.82 (doublets, H-5 of pyrimidine), 6.06 (doublet, $J_{1,2}$ 7.0 Hz, H-1), 5.40 (dd, $J_{3,4}$ ~1 Hz, H-3), 5.25 (multiplet, H-4), 4.38 (quartet, $J_{5a,5b}$ 10.5 Hz, $J_{4,5b}$ 5 Hz, H-5b), 4.18 (doublet of doublets, $J_{2,3}$ 3.5 Hz, H-2), 3.83 (quartet, $J_{4,5a}$ 2.5 Hz, H-5a), 2.55 (quartet, *J* 7.5 Hz, CH_2 of Et), 2.14 and 2.08 (singlets, OAc), and 1.26 (triplet, CH_3 of Et); *m/e* 372 (1.2, M^+), 343 (0.2, $M^+ - \cdot C_2H_5$), 311 (4.1, $M^+ - \cdot SEt$), 283 (1.4), 269 (1.6, $M^+ - \cdot SEt - CH_2{=}CO$), 261 ($M^+ - B$), 251 (1.6, $M^+ - \cdot SEt - AcOH$), 241 (1.4), 187 (8.8, anhydro ring), 185, (14.5, $B{-}C^+HSEt$), 167 (1.5), 127 (1.3, anhydro ring − AcOH), 113 (5.3, B^+H_2), 112 (4.7, B^+H), and 111 (1.8, B^+). The overall yield of **17** from **16** was 34%.

Anal. Calc. for $C_{15}H_{20}N_2O_7S$: C, 48.43; H, 5.41; N, 7.52; S, 8.61. Found: C, 48.41; H, 5.68; N, 7.22; S, 8.58.

The band containing the minor component (R_F 0.09) was extracted, and the product was acetylated to afford the tetraacetate (**18**) of **16**; yield 150 mg (12%), identified by comparison with an authentic specimen[3] of **18** by t.l.c. and by i.r. and n.m.r. spectroscopy.

The procedure was repeated with the following changes. The acyclic nucleoside **16** (410 mg, 1.14 mmoles) was dried, and dissolved in anhydrous pyridine (2 ml). The solution was cooled to −10°, and a solution of *p*-toluenesulfonyl chloride (253 mg, 1.3 mmoles) in anhydrous pyridine was added. The mixture was kept for 1 h at −10° and 18 h at 25°, and then processed by the procedure already described, to afford **17** as a chromatographically homogeneous glass; yield 250 mg (51%, based on **16**).

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