The Synthesis of Imidazole-2-thione Nucleosides (1)

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Ribosylation of the trimethylsilyl derivative (**1b**) of imidazole-2-thione (**1a**) using either stannic chloride or silver perchlorate as catalyst resulted in the formation of the acylated derivatives of 1-(β-D-ribofuranosyl)imidazole-2-thione (**3c**) and 1,3-di-(β-D-ribofuranosyl)imidazole-2-thione (**4c**) with the latter predominating (**4c**:**3c**, *ca.* 2:1). The diribosylated nucleoside **4c** was shown to be the *N,N*-disubstituted product rather than the *N,S*-disubstituted product by ^{1}H nmr and ^{13}C nmr spectroscopy. Employment of the iodine-catalyzed fusion procedure reversed the aforementioned product ratios and provided the monoriboside **3c** in excellent yield. When the trimethylsilyl derivative (**5b**) of 2-methylthioimidazole (**5a**) was reacted with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**2d**) in acetonitrile, the major product was 1,3-di-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazole-2-thione (**4b**). The formation of **4b** in this reaction is thought to arise *via* the Hilbert-Johnson mechanism.

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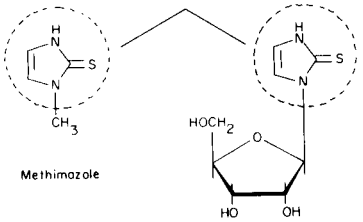
Heterocycles containing the thioureylene group constitute the majority of known effective antithyroid agents (2). Methimazole (1-methylimidazole-2-thione, Tapazole ®), one of the drugs currently employed in the treatment of hyperthyroidism, possesses this characteristic structural feature. With this in mind, we focused our attention on the synthesis of imidazole nucleosides possessing the thioureylene grouping, *i.e.*, the imidazole-2-thione moiety, with expectations that such nucleosides might possess similar chemotherapeutic properties as methimazole, even anticancer activity.



Our initial attempt at synthesizing **3c** (Scheme 1) involved a reaction of the silyl derivative of imidazole-2-thione (**1b**) (3) and 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl chloride (**2a**) (4) in acetonitrile at room temperature for three days. This reaction afforded only a small amount of nucleoside material (tlc) and thus we abandoned this approach and selected another glycosylation procedure. A recent report (5) showed that silylated 2-thiouracils react with acylated 1-halosugars in the presence of silver perchlorate in benzene to provide acylated 2-thiopyrimidine nucleosides in excellent yield. Employing this method with our reactants, *i.e.*, **1b** and **2b**, we obtained a near-quantitative yield of crystalline nucleoside product which we tentatively assigned as **3b**. However, we soon discovered that our initial assignment was incorrect as the elemental analysis of this material indicated that it was the diriboside. Thus, we were faced with two tasks, one to establish the sites of ribosylation, *i.e.*, whether we had the *N,N*- or *N,S*-diribosylated product, and two, to determine the anomeric configurations of the ribosyl moieties.

In order to determine the sites of ribosylation, the nucleoside was first debenzoylated using methanolic ammonia and then a thorough spectral anaysis was made on the deblocked material. A comparison of the uv spectral data of this compound with that of 1-methyl-2-methylthioimidazole (6), (**6** Table 1) immediately suggested that the nucleoside was not the *N,S*-diribosylated product, but rather the symmetrical *N,N*-diribosylated product. This preliminary finding was further supported by the ^{1}H nmr and ^{13}C nmr spectra. In the pmr spectrum, the H4 and H5 imidazole protons appeared as a sharp singlet at δ 7.42 (Table 2), an unlikely spectral feature (7) if the molecule was unsymmetrical. For example, the signals of the H4, H5 protons of **6** were observed as a broad, unresolved doublet at δ 7.09. Also, the anomeric protons of the nucleoside appeared as a single doublet centered at δ 6.12. The symmetry of this nucleoside was illustrated again by the ^{13}C nmr spectrum which exhibited only seven

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Scheme I

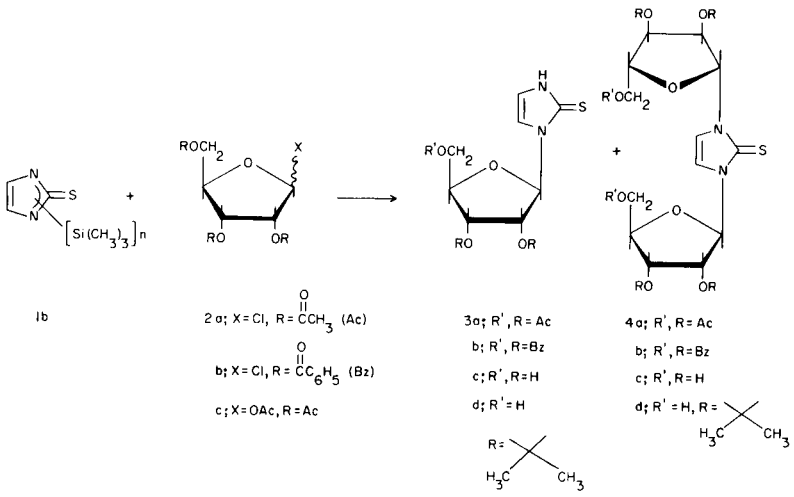


Table 1

Ultraviolet Spectral Data [λ/nm (ε × 10^{-3})] for Certain 2-Mercaptoimidazoles (a)

Compound	λ Max (*p*H 1)	λ Min (*p*H 1)	λ Max (Water)	λ Min (Water)	λ Max (Methanol)	λ Min (Methanol)	λ Max (*p*H 11)	λ Min (*p*H 11)
1a (b)	252	222.5	252	223.5	257.5		251	
	(15.39)	(5.54)	(15.28)	(6.18)	(14.19)		(13.55)	
Methimazole	251		251		257.5		250.5	
	(16.19)		(15.30)		(15.71)		(15.16)	
5a	250	233.5	245.5	238.5	248.5	238	245	238.0
	(6.53)	(5.0)	(5.04)	(4.91)	(4.45)	(3.88)	(4.97)	(4.82)
6	251	239	246	241	248.5	240.5	245.5	241
	(5.49)	(5.02)	(4.78)	(4.72)	(4.47)	(4.22)	(5.03)	(4.99)
			223		222.5			
			(6.57)		(6.48)			
3c					259			
					(15.70)			
4c	268.5	241	268.5	241	268.5	236	268	239
	(13.56)	(6.05)	(12.72)	(4.66)	(13.37)	(3.57)	(13.01)	(4.92)
			228.0		226			
			(5.39)		(3.90)			

(a) Each compound was dissolved in water (10 mg./100 ml.) and from this stock solution the final dilution was made with the appropriate solvent. The spectra were obtained on a Beckman Acta C III spectrophotometer. (b) Hemihydrate.

signals, two for the imidazole aglycone and five for the carbohydrate moieties (Table 3).

Having established the sites of ribosylation as N1 and N3, we turned our attention to the determination of the anomeric configurations. The anomeric configurations were assigned using pmr spectral data obtained on the 2′,3′-*O*-isopropylidene derivative. The observed difference in the chemical shifts (Δδ) of the isopropylidene methyl groups (each signal integrated for six protons) was 0.21 which is consistent with established criteria (8) for β-D-ribofuranosyl nucleosides. Therefore, on the basis of the aforementioned information, the structure of the deblocked nucleoside is 1,3-di-(β-D-ribofuranosyl)imidazole-2-thione (**4c**) with the initial benzoylated compound being **4b** and the isopropylidene derivative **4d**.

Next we concentrated on establishing conditions that would give, predominately, the desired monoribosylated nucleoside, 1-(β-D-ribofuranosyl)imidazole-2-thione (**3c**). A silyl alkylation was tried using **1b** and **2a** in acetonitrile in the presence of 3 Å sieves, but this method furnished only a meager amount of **3a** (12%) and gave rise to several unidentified products (9). Thus, we abandoned the non-catalytic approach and examined a catalytic route using anhydrous stannic chloride. Recent work reported (10) from one of our laboratories (J.-L.I.) demonstrated that the effect of stannic chloride on glycosylation reactions is

Table 2

Pertinent Proton Chemical Shifts (a) of Certain Imidazole-2-thione Nucleosides and Heterocycles

Compound	Solvent	H4/H5	H1′	NH	NCH_3	SCH_3	$-C(=O)-CH_3$	
1a (b)	DMSO-d_6	6.80 s		11.80 vbs				
5a (b)	DMSO-d_6	7.00 s		11.92 vbs		2.52 s		
3a (c)	Deuteriochloroform	6.94/6.78	6.48 d ($J_{1',2'}$ = 5.25 Hz)	11.62 vbs			2.08 2.10 2.12	
	DMSO-d_6	7.25/6.98	6.38 d ($J_{1',2'}$ = 6.0 Hz)	12.35 vbs			2.04 2.08 2.11	
3c (c)	DMSO-d_6	7.30/6.91 ($J_{4,5}$ = 2.5 Hz)	6.04 d ($J_{1',2'}$ = 4.25 Hz)	12.12 vbs				
3d (d)	DMSO-d_6							1.53 1.30 $\Delta\delta$ = 0.23
4a (c)	Deuteriochloroform	7.00 s	6.54 d ($J_{1',2'}$ = 5.25 Hz)				2.08 2.10 2.12	
	DMSO-d_6	7.48 s	6.43 d ($J_{1',2'}$ = 6.0 Hz)				2.03 2.06 2.10	
4c (b,c)	DMSO-d_6	7.42 s	6.12 d ($J_{1',2'}$ = 4.25 Hz)					
4d (d)	DMSO-d_6							1.53 1.32 $\Delta\delta$ = 0.21
6 (b)	DMSO-d_6	7.20-6.98 vbd			3.58 s	2.52 s		

(a) Chemical shifts are in parts per million with respect to TMS; s = singlet, d = doublet, vbs = very broad singlet. (b) Spectra obtained on a Jeol C60h or Varian EM-390 spectrometer. (c) Spectra obtained on a Varian HA 100 or Brucker 80 spectrometer. (d) Spectra obtained on unpurified material with a Varian T60.

Table 3

Carbon-13 Chemical Shifts (a) of 1,3-Di-(β-D-ribofuranosyl)imidazole-2-thione

		Aglycone (b)		Ribose (c)				
Solvent	Concentration *M*	C2	C4/C5	C1′	C2′	C3′	C4′	C5′
DMSO-d_6	0.65	162.9$_7$	115.1$_9$	88.8$_9$	74.4$_0$	69.8$_6$	84.5$_9$	61.0$_0$

(a) Chemical shifts are in parts per million with respect to TMS. (b) Assignments confirmed by a single frequency off-resonance decoupling (SFORD) experiment. (c) Assigned according to H. H. Mantsch and I. C. P. Smith, *Biochem. Biophys. Res. Commun.*, **46**, 808 (1972) and verified by a SFORD experiment.

highly dependent on the amount used and the specific reaction conditions employed. As shown in Table 4, when less than one equivalent of stannic chloride per **1a** was used, the yields were quite poor with only a small amount of **3a**, being formed in each case. When the ratio of stannic chloride to **1a** was equal or greater than one, while keeping the **2c/1a** ratio constant, the glycosylation reaction worked very well. However, in each case **4a** predominated (*ca.* 2:1). Increasing the equivalents of **2c** only favored the formation of **4a**.

The iodine-catalyzed fusion reaction was attempted next and this glycosylation method (Scheme 2) was more fruitful (Table 5). Fusion of **2c** (1.1 equivalents) with **1a** at 183° under 12 mm Hg diminished pressure with a catalytic amount of iodine for 20 minutes furnished an excellent yield of **3a**. Treatment of **3a** with methanolic ammonia provided the desired **3c**. A comparison of the uv absorption data of **3c** with that of methimazole confirmed the site of ribosylation as N1 and a ^1H nmr spectral examination of **3d**, *i.e.*, similar to that described for **4d**, established the anomeric configuration of **3c** as β.

During our initial attempts at synthesizing **3b** we decided to circumvent the problem of diribosylation by using 2-methylthioimidazole (**5a**) as our starting heterocycle. We had originally intended to functionalize the C2 position of **3a** by methylation of the thione group and subsequent

Scheme 2

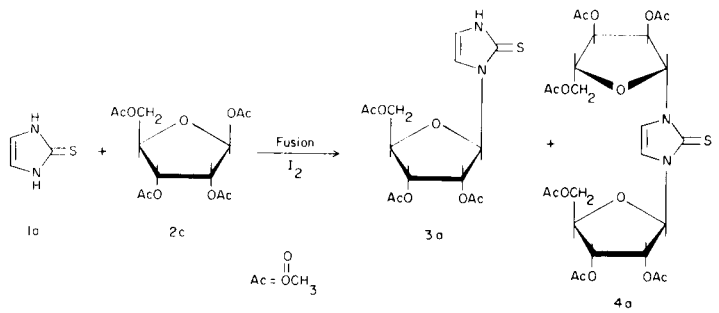


Table 4

Conditions Governing Product Distribution from the Ribosylation of **1b** using Anhydrous Stannic Chloride as Catalyst

Amount of Stannic Chloride (Equivalents/**1a**)(b)	Amount of Sugar (Equivalents **2c**/**1a**)(b)	Solvent	Temperature °C	Reaction Time	% Products (a) Monoribioside (**3a**)	Diriboside (**4a**)	Total
0.3	0.95	1,2-Dichloroethane	R.T.	8 Days	3	0	3
1.0	0.95	1,2-Dichloroethane	R.T.	8 Days	34	64	98
1.5	0.95	1,2-Dichloroethane	R.T.	8 Days	34	64	98
1.0	0.95	Acetonitrile	R.T.	8 Days	28	66	94
1.4	0.8(c)	Acetonitrile	R.T.	20 Hours	0	14 (d)	14 (d)
0.3	0.95	1,2-Dichloroethane	Reflux	3/4 Hour	3	0	3
1.5	0.95	1,2-Dichloroethane	Reflux	3/4 Hour	42	52	94
1.5	2.00	1,2-Dichloroethane	R.T.	8 Days	14	77	91

(a) Yields were determined by ^{1}H nmr examination of the crude reaction mixture in deuteriochloroform. The percentages were calculated from the integration of the H4, H5 signals of the ribosides minus the contribution of the integral from the H1 signal of unreacted **2c**. (b) The equivalents of stannic chloride or **2c** were calculated on the amount of **1a** prior to its silylation. (c) The sugar used in this experiment was 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose. (d) Isolated cyrstalline yield.

Table 5

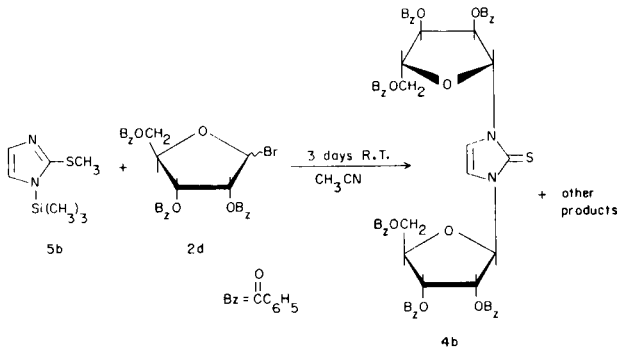
Conditions Governing Product Distribution from the Fusion of **1a** with **2c** Using Iodine as Catalyst (a)

Amount of Iodine (% moles/mole **1a**)	Amount of Sugar (Equivalents **2c**/**1a**)	Temperature °C	% Products (b) Monoriboside (**3a**)	Diriboside (**4a**)	Total
0.7	1.1	160	17	trace	17
5.2	1.1	160	70	9.5	79.5
0.7	1.1	183	68	5.0	73
5.2	1.1	183	75	11.0	86
0.7	1.1	205	58	5.0	63
5.2	1.1	205	71	9.0	80
5.2	2.00	183	29	54.0	83

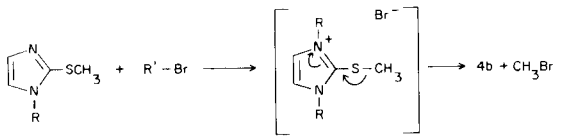
(a) Reactions run for 20 minutes using a diminished pressure of 12 mm Hg. (b) Yields were determined by ^{1}H nmr examination of the crude reaction mixture in deuteriochloroform. The percentages were calculated from the integration of H4, H5 signals of the ribosides minus the contribution from the H1 signal of unreacted **2c**.

displacement of the resulting methylthio function by a variety of nucleophiles. Thus, ribosylation of **5a** provided an attractive route to these 2-substituted imidazole nucleosides and offered a means of eliminating the problem of diribosylation. Reaction of the silyl derivative (**5b**) of **5a** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**2d**, Scheme 3) in dry acetonitrile at room temperature for 3 days provided, after work up, a crystalline nucleoside. To our surprise, it wasn't the expected nucleoside 2-methylthio-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazole, but rather the diriboside **4b**. The formation of **4b** in this reaction is reminiscent of the Hilbert-Johnson reaction (11) and probably occurs as depicted in Scheme 4.

Scheme 3



Scheme 4



R' = 2,3,5-tri-O-benzoyl-D-ribofuranosyl

R = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl

We could increase the formation of **4b**, *via* this pathway by doubling the amount of **2d** (**2d:5a** = 2:1) employed. Two other components were detected (tlc, lower Rf's), however, their separation and subsequent isolation eluded our efforts (9).

We found the ultraviolet absorption maxima of the heterocycles and nucleosides described herein to be highly sensitive to solvent effects. This spectroscopic phenomenon has been observed earlier (12) with heterocycles possessing the thioureylene group and was attributed to the predominance of either the thiol or thione tautomer in solution. The tautomeric populations were suggested to be influenced by the polarity of the solvent employed. Solvents that can form strong hydrogen bonds, *e.g.*, water, favor the thiol tautomer ($\geq$C-SH) whereas in those solvents that do not, *e.g.*, chloroform, the thione form ($\rangle$C=S) is preferred. Although an attractive explanation, we feel that other factors should be considered, especially the effect of solvent on the $n\rightarrow\pi^*$ transition; the transition responsible for the absorption maxima in question. In hydroxylic solvents, the lone pair of electrons on the (thione) sulfur atom serve as an electron donor to the hydrogen of the solvent to form a hydrogen bond (13). This results in lowering the energy of the n orbital and is approximately equal to the energy of the hydrogen bond formed. When one of the electrons is removed from the n orbital and promoted to the π^* orbital the hydrogen bond is weakened and breaks. The hypsochromic shift of the wavelength maxima (Table 6) as the solvent is changed from chloroform to water can be considered as a measure of the strength of the hydrogen bond. For example, in methimazole the $n\rightarrow\pi^*$ transition occurs at 251 nm in water and at 267 nm in chloroform. This shift of 16 nm corresponds to an energy change of 6.9 kcal/mole and is in agreement with the known energy associated with a hydrogen bond (14).

EXPERIMENTAL

Melting points were determined with either a Thomas-Hoover or a Gallenkamp apparatus and are uncorrected. The methods used to obtain the ultraviolet absorption spectra and ^{1}H nmr spectra are described in

Table 6

The Effects of Solvent on the $n\rightarrow\pi^*$ Transition of Certain Imidazole-2-thione Nucleosides and Heterocycles

Compound	λ Max (nm)	(ε × 10^{-3})	Solvent (a)
4(5)-Methylimidazole-2-thione	257	(15.0)	water (b)
	263	(14.7)	ethanol (b)
	271	(13.7)	chloroform (b)
Methimiazole	251	(15.3)	water
	257.5	(15.7)	methanol
	260	(13.6)	ethanol (b)
	267	(17.0)	chloroform (b)
1-(β-D-Ribofuranosyl)imidazole-2-thione (**3c**)	259	(15.7)	methanol
	265	(15.7)	95% ethanol (c)
1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-2-thione (**3a**)	266	(15.6)	95% ethanol (c)
	276	(11.8)	chloroform (c)
1,3-Di-(β-D-ribofuranosyl)imidazole-2-thione (**4c**)	268.5	(12.7)	water
	268.5	(13.4)	methanol
1,3-Di-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-2-thione (**4a**)	271	(15.5)	95% ethanol (c)
	277	(13.7)	chloroform (c)

(a) The hydrogen bonding ability of solvents follow this order: water > methanol > ethanol > chloroform (12). (b) Reference 11. (c) Compounds were dissolved and run in the solvent indicated. The spectra were obtained on a Optica Model 10.

Table 1 and Table 2, respectively. The ^{13}C nmr spectra were recorded on a Varian CFT-20 spectrometer at ambient temperature. A pulse delay of 1.023s and a flip angle (α) of 42.5° was employed. The infrared spectra were determined in pressed potassium bromide disks with a Beckman IR-8 spectrophotometer. The optical rotations were obtained with either a Perkin-Elmer Model 141 or Model 241 polarimeter. Thin layer chromatography was run on glass plates coated (250-μ) with SilicAR 7 GF (Mallinckrodt) or Merck GF 254 and short-wave ultraviolet light (254 nm) was used to detect the uv absorbing spots. All solvent proportions are by volume unless otherwise stated. The trimethylsilyl derivatives **1b** and **5b** were prepared using either hexamethyldisilazane/ammonium sulfate or bis(trimethylsilyl)acetamide/acetonitrile and were used in the glycosylation reactions without purification. Elemental analyses were performed either by the Microanalysis Service of the CNRS (Division of Montpellier) or MHW Corporation, Garden City, Michigan.

General Procedure for the Fusion of 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose (**2c**) with Imidazole-2-thione (**1a**) (Table 5).

A dry, finely powdered mixture of imidazole-2-thione (**1a**), 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2c**, 10% excess), and twice-sublimed iodine (0.7% or 5.2% mole per mole of **1a**) were fused in a pear-shaped flask for 20 minutes with a vacuum of 12 mm Hg. The fusions were performed at the following temperatures: 160°, 183°, and 205° (Table 5). The presence of nucleoside material(s) was detected by tlc (toluene-acetonitrile, 7:3 or chloroform-acetone, 9:1) and percent composition was determined by ^1H nmr spectroscopy in deuteriochloroform. In a typical reaction the crude reaction mixture was dissolved in the minimal amount of chloroform, applied to a silica gel column (6.3 × 20 cm, Merck 70-230 mesh ASTM), and eluted with chloroform-acetone (95:5). The first uv absorbing material off the column was 1,3-di-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-2-thione (**4a**), foam; ms: (Jeol JMS D 100): M^+ 616.

Anal. Calcd. for $C_{25}H_{32}N_2O_{14}S$: C, 48.70; H, 5.23; N, 4.54. Found: C, 49.07; H, 5.37; N, 4.37.

The second uv absorbing material off of the column was 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-2-thione (**3a**), which was isolated as an oil.

Anal. Calcd. for $C_{14}H_{18}O_7N_2S$: C, 46.92; H, 5.06; N, 7.8. Found: C, 47.20; H, 5.12; N, 7.3.

1-β-D-Ribofuranosylimidazole-2-thione (**3c**).

A suspension of **3a** (1.0 g., 2.79 mmoles) in methanolic ammonia (60 ml., saturated at -5°) was kept at room temperature for 24 hours in a sealed pressure bottle. The resulting solution was filtered and the solvent was removed under diminished pressure to furnish a syrup. The syrup was coevaporated twice with methanol (20 ml.) and the material was crystallized from absolute ethanol to provide **3c** (0.58 g., 89.5%), m.p. 187-188°; $[\alpha]_D^{25}$ -4 (c 1.0 DMSO).

General Procedure for the Stannic Chloride Catalyzed Ribosylation of Silylated Imidazole-2-thione (**1b**) (Table 4).

A solution of **1b** in dry dichloroethane or acetonitrile was added to a solution of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2c**, 0.95 equivalents per **1a**) in the same solvent. To this combined solution was added anhydrous stannic chloride [0.3, 1, or 1.5 equivalents per **1a** (Table 4)] and the mixture was either heated at reflux for 45 minutes or let stir at room temperature for 8 days. The crude reaction mixture was then diluted with dichloroethane [when acetonitrile was the solvent, the reaction mixture was evaporated *in vacuo* (40° waterbath) and the residue extracted with dichloroethane] and neutralized by the addition to a cold, saturated sodium bicarbonate solution (in excess). The resulting emulsion was filtered through a Celite pad and the organic phase separated from the aqueous layer. The aqueous layer was extracted with a small portion of dichloroethane, the dichloroethane combined with the organic phase, and the combined layer dried over anhydrous sodium sulfate. Tlc (toluene-acetonitrile, 7:3 or chloroform-acetone, 9:1) indicated the presence of **3a**, **4a**, and unreacted **1a** and **2c**. Concentration of the dried dichloroethane layer and subsequent column chromatography (as described for the fusion reaction) afforded the pure, acetylated nucleosides **3a** and **4a**, identical in all respects to those isolated and characterized from the fusion procedure.

1,3-Di-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-2-thione (**4b**).

Method A.

A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (**2b**), prepared from 1.33 g. (2.63 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, in dry benzene (20 ml.) was added to the crystalline trimethylsilyl derivative (**1b**), prepared from 2.65 mg. (2.63 mmoles) of dry imidazole-2-thione (**1a**). To this solution was added anhydrous silver perchlorate (543 mg., 2.63 mmoles) suspended in benzene (10 ml.). The reaction mixture was then stirred for 24 hours at room temperature in a sealed vessel. Absolute ethanol (2 ml.) and chloroform (10 ml.) were added to the reaction mixture, stirred for 15 minutes, and then filtered through Celite. The Celite pad was washed with chloroform (3 × 10 ml.) and the combined filtrate and washings were concentrated under diminished pressure (40°, waterbath). The residual syrup was dissolved in chloroform (50 ml.), washed with cold, saturated sodium bicarbonate solution (2 × 20 ml.), water (2 × 20 ml.), dried over anhydrous magnesium sulfate and evaporated under diminished pressure to afford a colorless syrup. The syrup was dissolved in hot ethyl acetate, methanol added to the cloud point, and then let stand at room temperature. The white crystalline material was filtered off, washed with cold methanol (20 ml.), and air-dried to furnish 1.10 g. (41.6%) of **4b**, m.p. 195-196.5°.

Anal. Calcd. for $C_{55}H_{44}N_2O_{14}S \cdot H_2O$: C, 65.60; H, 4.60; N, 2.78. Found: C, 65.68; H, 4.36; N, 3.01. The water of hydration was verified by ^1H nmr spectroscopy.

A second reaction was conducted to maximize the yield of **4b**. In this reaction, the trimethylsilyl derivative **1b**, prepared from 1.0 g. (10 mmoles) of **1a**, was reacted with **2b**, prepared from 10.08 g. (20 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, in benzene (110 ml.) in the presence of silver perchlorate (4.17 g., 20 mmoles). Upon work up (see Method A), 4.89 g. of crystalline **4b** was obtained. Column chromatography [Mallinckrodt CC7 (3.5 × 23 cm); eluent, chloroform-methanol (32:1)] of the mother liquor furnished an additional 0.46 g. of **4b** [5.35 g., 53.1% (based on monohydrate)]. The remaining material (syrup) contained two slower moving spots (tlc, chloroform-methanol, 49:1) which were not purified or identified.

Method B.

To the oily trimethylsilyl derivative **5b** [from 228 mg. (2 mmoles) of 2-methylthioimidazole (15) (**5a**)] was added a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**2d**) [from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1.02 g., 2 mmoles)] in dry acetonitrile (25 ml.). The reaction mixture was protected from moisture and stirred for 3 days at room temperature. To the brown solution was added an ethanol-water mixture (10:1, 20 ml.) and stirring continued for 10 minutes. The solvent was removed *in vacuo* (45° waterbath) and the residual syrup dissolved in chloroform (50 ml.). The chloroform layer was washed with cold, saturated sodium bicarbonate solution (2 × 40 ml.), water (2 × 40 ml.), dried (magnesium sulfate) and then evaporated to a hard foam. The foam was dissolved in a minimal amount of hot ethyl acetate, methanol added to the cloud-point, and then let stand at room temperature. The precipitate was collected by filtration, air-dried, and recrystallized from ethyl acetate-methanol to afford **4b** (391 mg., 19.7%), m.p. 194-195°. The pmr (deuteriochloroform, ir (potassium bromide) and chromatographic mobilities of the nucleoside were identical to **4b** isolated in the preceding method.

A second reaction was run to maximize the amount of **4b**. In this experiment, the trimethylsilyl derivative **5b** [from **5a** (684 mg., 6 mmoles)] was reacted with **2d** [from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (6.05 g., 12 mmoles)] in dry acetonitrile (50 ml.) for 4 days at room temperature. The above described work-up afforded 3.25 g. of crude nucleoside material. Recrystallization from ethyl acetate-methanol fur-

nished pure **4b** (16) (2.98 g., 50.3%). The mother liquor was concentrated to a syrup [contained **4b**, two slower moving spots, and unreacted starting materials (tlc, chloroform)], dissolved in chloroform, applied to a silica gel column [4.5 × 30 cm, Woelm (0.05-0.20 mm)], and eluted with chloroform. This made possible the separation of unreacted materials and certain impurities from the two slower moving spots (*ca.* 2.3 g.), but failed to separate the latter from one another (9).

1,3-Di-(β-D-ribofuranosyl)imidazole-2-thione (**4c**).

Method A.

A suspension of **4b** (3.02 g., 3 mmoles) in methanolic ammonia (100 ml., saturated at -5°) was kept at room temperature in a sealed pressure bottle. After 3 days solution was effected and the solution was let stand an additional 2 days. The solvent was removed under diminished pressure, the syrup was triturated with carbon tetrachloride (2 × 30 ml.), and the carbon tetrachloride was decanted. The residual solid was dissolved in methanol and evaporated, *in vacuo*, to a crystalline mass. The material was recrystallized from ethanol-water (6:1) to provide **4c** (1.02 g., 93%) as heavy, colorless needles, m.p. 185-186°; $[\alpha]_D^{25}$ - 12.6 (c, 1.055, water), $[\alpha]_D^{25}$ -14 (c, 1.0, DMSO); ms: (17) (70 eV, **4c**, 6 TMS) M^+ 796.

Anal. Calcd. for $C_{13}H_{20}N_2O_8S$: C, 42.85; H, 5.53; N, 7.68. Found: C, 42.62; H, 5.44; N, 7.44.

Method B.

A suspension of **4a** (1.0 g., 1.62 mmoles) in methanolic ammonia (60 ml., saturated at -5°) was kept at room temperature for 24 hours in a sealed pressure bottle. The resulting solution was filtered and the solvent was removed under diminished pressure to afford a syrup. The syrup was co-evaporated twice with methanol (20 ml.) and the material was crystallized from 95%-ethanol to furnish 0.54 g. (91.4%) of **4c**. This compound was identical to nucleoside **4c** isolated in Method A.

Formation of the Isopropylidene Derivatives **3d** and **4d**.

The nucleoside **3c** (100 mg.) was dissolved in a solution of dry acetone (3 ml.) and 2,2-dimethoxypropane (1 ml.) which contained *p*-toluenesulfonic acid (*ca.* 4 mg.) and stirred at room temperature for 3 hours. A saturated sodium carbonate solution (0.5 ml.) was added to the reaction mixture. The mixture was dried over anhydrous sodium sulfate and then filtered through Celite. The filtrate was evaporated under diminished pressure to an oil, which was co-evaporated twice with carbon tetrachloride (2 ml.) The residual syrup which contained **3d** was analyzed directly by ^1H nmr without further purification (see Table 2).

The nucleoside **4d** was synthesized in a similar manner from 100 mg. of **4c**, but the amounts of each reagent were doubled.

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(9) We believe the major product from the silyl alkylation reaction **1b** with **2a**), is a *S*-ribosylated product (λ max ethanol 238.5 mm). This product was found to be quite unstable and complete characterization was impossible. A similar situation was encountered with the two components isolated (but not separated) from the reaction of **5b** with **2d**. The syrup containing these materials possessed a faint odor of methanethiol and tlc indicated some breakdown. Attempted separation of these two components by column chromatography failed as silica gel apparently promotes the breakdown (strong smell of methanethiol) of one or both of these components.

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(16) Because of the apparent breakdown of the slower moving components (see reference 9) and to corroborate the proposed pathway (Scheme 4) leading to **4b**, a sulfur analysis was conducted on the deblocked nucleoside **4c** (arising from **4b** in this reaction). *Anal.* Calcd. for $C_{13}H_{20}N_2O_8S$: S, 8.80. Found: S, 8.80.

(17) The authors wish to thank Professor James A. McCloskey and his staff (University of Utah) for running the mass spectra of trimethylsilylated **4c**.