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SYNTHESIS OF 4-THIO-*C*-NUCLEOSIDE ANALOGUES BY DEHYDRATION OF 4-THIOPOLYHYDROXYALKYL HETEROCYCLES

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ABSTRACT

The thio-*C*-nucleoside analogues 1,3-dihydro-3-methyl-4-(4-thio-α- and -β-D-erythrofuranosyl)-1-*p*-tolyl-2*H*-imidazole-2-thiones (**8** and **9**) were obtained by acid-catalysed dehydration of 1,3-dihydro-3-methyl-4-(4-thio-D-*arabino*-tetritol-1-yl)-1-*p*-tolyl-2*H*-imidazole-2-thione. The thiol group was introduced in position 4′ of 1,3-dihydro-3-methyl-4-(D-*arabino*-tetritol-1-yl)-1-*p*-tolyl-2*H*-imidazole-2-thione by selective tosylation, followed by acetylation, displacement of the tosyloxy group with potassium thiolacetate, and deacetylation. The conformation of **8** in the solid state and the preponderant conformer in solution were the same.

INTRODUCTION

Few natural and synthetic 4-thio-*N*-nucleosides[1–7] with sulphur replacing the ring oxygen are known in spite of their potential as antibiotics[4–7]. Although the synthesis of *C*-nucleosides[8] has received considerable attention due to their significant antitumour and antiviral activities[9], little effort has been devoted to the synthesis of 4-thio-*C*-nucleosides. (4-Thio-β-D-erythrofuranosyl)furan has been described[10], and the corresponding α anomer was detected spectroscopically in a non-resolved mixture.

We now report on the preparation of 4-thio-α- (**8**) and -β-D-erythrofuranosyl (**9**) *C*-nucleoside analogues from the (4-thio-D-*arabino*-tetritol-1-yl)dihydroimidazole derivative **5** based on the acid-catalysed dehydration of (alditol-1-yl)-heterocycles[11–14].

RESULTS AND DISCUSSION

Treatment of 1,3-dihydro-3-methyl-4-(D-*arabino*-tetritol-1-yl)-1-*p*-tolyl-2*H*-imidazole-2-thione[15] **1** with 2 mol. equiv. of tosyl chloride in pyridine followed by acetic anhydride gave the 4′-tosylate **2** contaminated with the tetra-acetate **3**[15] (^{1}H-

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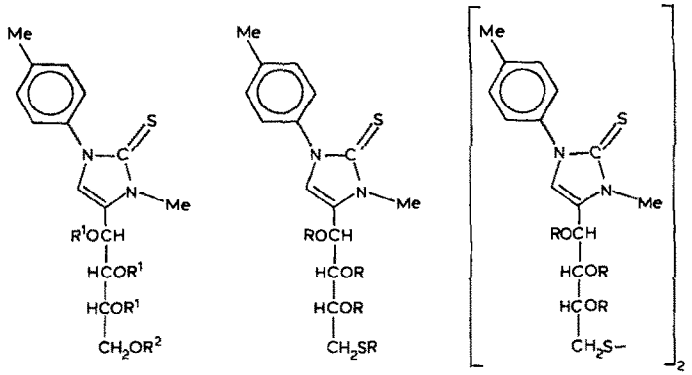
n.m.r. data). Crude **2** reacted with potassium thiolacetate to give the crystalline 4-thiotetra-acetate **4** (73% from **1**), which showed a strong i.r. absorption at 1686 cm^{-1} for S–C=O. The δ values of H-4′ and H-4″ (Table I) were in agreement with *S* substitution. Treatment of **4** briefly with methanolic sodium methoxide gave the (4-thio-D-*arabino*-tetritol-1-yl)dihydroimidazole derivative **5** together with a small amount of the disulphide **6**. When **4** was treated with methanolic sodium methoxide for 24 h, a quantitative yield of **6** was obtained due to the ready autoxidation[16] of the thiol at high pH. The structure of **6** was based on analytical and spectroscopic data (Table I) together with those of the corresponding hexa-acetate **7**. The resonances for H-4′ and H-4″ in **7** were shifted up-field compared with those for **4**.



1 $R^1 = R^2 = H$
2 $R^1 = Ac$, $R^2 = Ts$
3 $R^1 = R^2 = Ac$

4 R = Ac
5 R = H

6 R = H
7 R = Ac

The conformations of the acetylated compounds **3, 4,** and **7** in chloroform were different from those of **1** and **6** in methyl sulphoxide, as indicated by the $J_{1',2'}$ values (Table I), namely, 6.7–7.8 Hz for the former and 0–1.2 Hz for the latter. The disulphide **6** adopted mainly the **P** conformation[17] **15**, whereas, for the hexa-acetate **7** and the thioacetate **4**, there was an equilibrium between the ${}_1G^+$ (**16**) and ${}_1G^+{}_2G^+$ (**17**) conformations according to the $J_{2',3'}$ values (4.9–5.2 Hz). The parallel interaction between the heterocycle and the AcO-3′ in **16** is avoided in the sickle conformation **17**. The 4′-thio derivatives **4, 6,** and **7** do not have the chain-end flexibility of the oxygen analogues[17–19]. The conformational equilibrium of the tetra-acetate **3** comprises mainly the ${}_1G^+$ form **16**, with contributions from the **P** and ${}_1G^+{}_2G^+$ (**17**) conformations and the forms ${}_1G^+{}_3G^+$ and ${}_3G^+$ (not shown) associated with chain-end flexibility. Complex conformational equilibria have been described for (tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)dihydroimidazole[20].

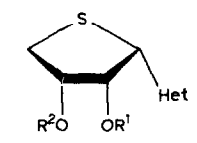
Dehydration of the (4-thio-D-*arabino*-tetritol-1-yl)dihydroimidazole derivative **5** with refluxing methanol–water–trifluoroacetic acid gave a 3:2 mixture (^{1}H-n.m.r. data) of the α- (**8**) and β-4-thiofuranoid (**9**) compounds which were isolated by fractional crystallisation in yields of 32% and 15%, respectively. Compounds **8**

TABLE I

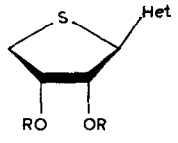
^{1}H-N.M.R. DATA (δ SCALE, J IN Hz) FOR COMPOUNDS **1**, **3**, **4**, **6**, AND **7**

Compound	*Carbohydrate moiety*								*Heterocycle*			
	H-1'	*H-2'*	*H-3'*	*H-4'*	*H-4''*	*OH*($J_{H,OH}$)	*OAc*	*SAc*	*H-5*	*N-Me*	*Me*	*Ar*
1[a,c]	4.88d $J_{1',2'}$ ~0	←		3.7–3.5m	→	5.21d (7.6) 4.89d (6.7) 4.75d (4.9) 4.65t (5.5)			7.15s	3.62s	2.35s	7.25–7.50m
3[b,d]	6.12d $J_{1',2'}$ 6.7	5.63t $J_{2',3'}$ 6.5	5.20m	4.36dd $J_{4',3'}$ 3.2	4.13dd $J_{4'',3'}$ 5.7 $J_{4'',4'}$ 12.3		2.09s (6 H) 2.05s (6 H)		6.97s	3.78s	2.39s	7.20–7.47m
4[b,d]	6.16dd $J_{1',2'}$ 7.6	5.63dd $J_{2',3'}$ 5.2	5.02m	3.39dd $J_{4',3'}$ 3.2	2.99dd $J_{4'',3'}$ 7.8 $J_{4'',4'}$ 14.4		2.12s 2.10s 2.01s	2.32s	7.05s	3.81s	2.40s	7.21–7.51m
6[a,c]	4.85dd $J_{1',2'}$ 1.2	3.54m $J_{2',3'}$ 8.1	3.80m	3.23dd $J_{4',3'}$ 2.5	2.80dd $J_{4'',3'}$ 8.6 $J_{4'',4'}$ 13.3	5.27d (7.5) 5.05d (7.6) 5.15d (6.6)			7.14d $J_{5,1'}$ 1.2	3.59s	2.34s	7.23–7.45m
7[b,c]	6.07d $J_{1',2'}$ 7.8	5.63dd $J_{2',3'}$ 4.9	5.20m	2.93dd $J_{4',3'}$ 4.4	2.79dd $J_{4'',3'}$ 7.8 $J_{4'',4'}$ 14.6		2.09s 2.08s 2.02s		7.04s	3.76s	2.39s	7.18–7.36m

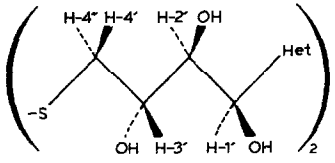
[a]In $(CD_3)_2SO$. [b]In $CDCl_3$. [c]At 200 MHz (20°). [d]At 90 MHz (35°).



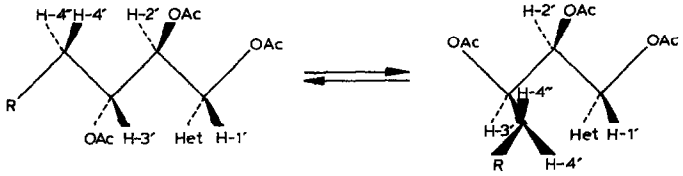
8 $R^1 = R^2 = H$
10 $R^1, R^2 = CMe_2$
12 $R^1 = R^2 = Ts$
14 $R^1 = H, R^2 = Ts$



9 R = H
11 R = CMe_2
13 R = Ts



15 (P)

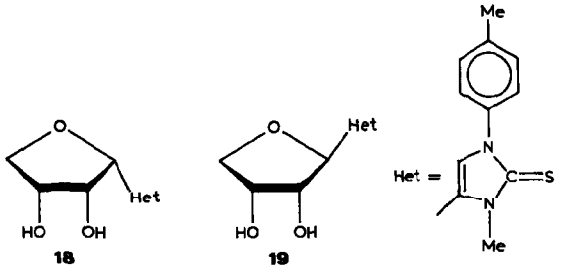


16 ($_1G^+$) **17** ($_1G^+$ $_2G^+$)

and **9** were also formed in the same ratio by treating **5** with anhydrous trifluoroacetic acid.

The steric course of the acid-catalysed dehydration of polyhydroxyalkylfurans and -pyrroles has been explained by a mechanism involving a resonance-stabilised C-1′ carbocation[21,22] as has that of (4-thio-D-erythrofuranosyl)furans from [4-*S*-(*tert*-butyl)-4-thio-D-*arabino*-tetritol-1-yl]furans[10]. However, this mechanism does not explain the preponderant formation of the sterically less-stable α-anomer **8**, since the transition state leading to **25** from the C-1′ carbocation **21** should be more stable than that leading to **24**. It is possible that the α anomer is formed *via* the 1′,2′-epoxide **22** generated by displacement of protonated HO-1′ by HO-2′. The formation of the β-anomer **9** by the attack of the thiol group on C-1′ in **20** or in the epoxide **23** is also a possibility. Not only can the heterocycle stabilise the C-1′ carbocation but it can also stabilise[23] the S_N2 transition state at C-1. Displacement of protonated HO-1′ by HO-4′ has been proposed for the dehydration of (pentitol-1-yl)uracils[24]. The S_N2 mechanism can be predominant in the intramolecular dehydration of (ω-thioalditolyl)-heterocycles due to the high nucleophilicity of the sulphur[25].

The dehydration of **1** with anhydrous trifluoroacetic acid at room temperature yielded[13] a 1:1 $\alpha\beta$-mixture (**18** and **19**) and the β anomer preponderated when refluxing dilute acid was used, probably because of the reversible ring opening of


Het
HO OH
18
Het
HO OH
19
Me
Het =
N
C=S
N
Me

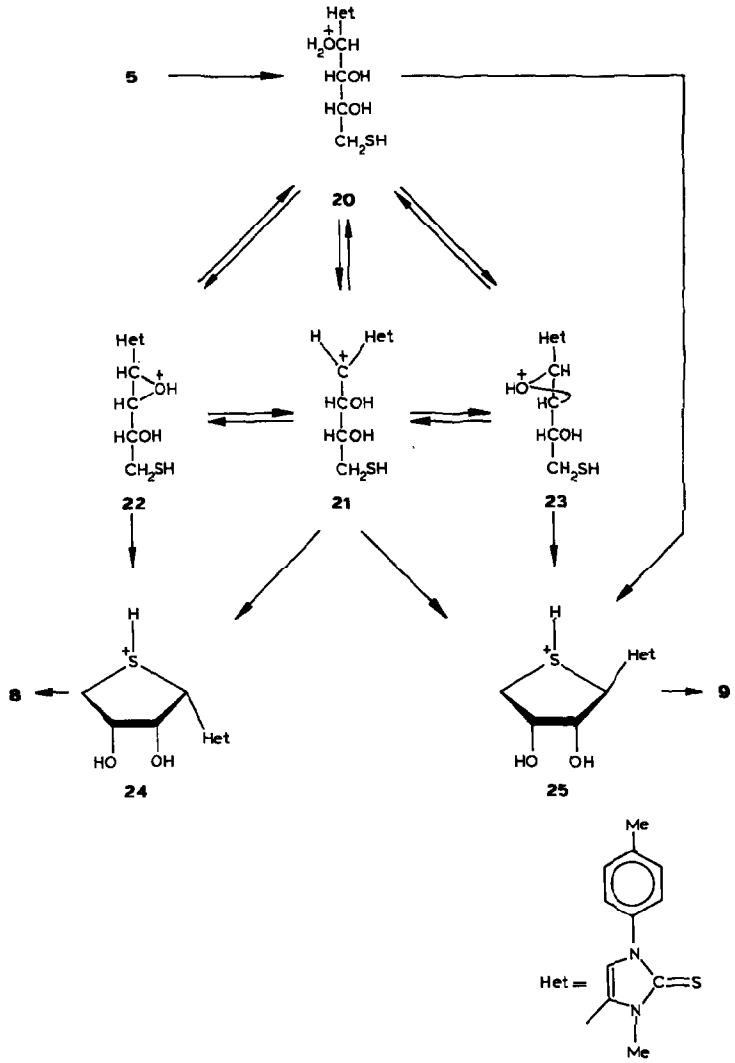

5
Het
H2OCH
HCOH
HCOH
CH2SH
20
Het
HC
OH
HCOH
CH2SH
22
H
Het
HCOH
HCOH
CH2SH
21
Het
CH
HO
HC
HCOH
CH2SH
23
8
H
S
Het
HO OH
24
9
H
S
Het
HO OH
25
Me
Het =
N
C=S
N
Me

TABLE II

^{1}H-N.M.R. DATA (δ SCALE, J IN Hz) FOR COMPOUNDS **8–14**

Compound	*Carbohydrate moiety*							*Heterocycle*			
	H-1'	*H-2'*	*H-3'*	*H-4'*	*H-4''*	*OH* ($J_{H,OH}$)	*CMe*$_2$	*H-5*	*N-Me*	*Me*	*Ar*
8[a,c]	4.67dd $J_{1',2'}$ 3.4	⟵ 4.21m ⟶		⟵ 2.90m ⟶		5.27d (3.3) 5.21d (5.2)		7.08d $J_{5,1'}$ 1.0	3.58s	2.35s	7.48–7.26m (4 H)
9[a,c]	4.35d $J_{1',2'}$ 7.3	4.16m $J_{2',3'}$ 3.2	4.26m	3.12dd $J_{4',3'}$ 4.4	2.74dd $J_{4'',3'}$ 3.2 $J_{4'',4'}$ 10.9	5.40d (6.1) 5.24d (4.3)		7.23s	3.58s	2.36s	7.50–7.27m (4 H)
10[b,d]	4.11dd $J_{1',2'}$ 3.8	4.85dd $J_{2',3'}$ 5.6	4.95m	3.05d 1/2($J_{4',3'}$ +	3.05d $J_{4'',3'}$) 2.3		1.50s 1.33s	7.04d $J_{5,1'}$ 0.9	3.74s	2.40s	7.50–7.22m (4 H)
11[b,d]	4.27dd $J_{1',2'}$ 2.1	4.81dd $J_{2',3'}$ 5.8	4.98m	3.05d 1/2($J_{4',3'}$ +	3.05d $J_{4'',3'}$) 3.2		1.57s 1.33s	6.62d $J_{5,1'}$ 1.2	3.71s	2.39s	7.46–7.18m (4 H)
12[b,c]	4.57dd $J_{1',2'}$ 4.6	5.26dd $J_{2',3'}$ 3.4	5.09m	3.18dd $J_{4',3'}$ 8.8	2.99dd $J_{4'',3'}$ 6.6 $J_{4'',4'}$ 10.5			6.92d $J_{5,1'}$ 0.9	3.55s	2.46s 2.39s 2.39s	7.73–7.22m (12 H)
13[b,c]	4.59m $J_{1',2'}$ 7.0	4.62m $J_{2',3'}$ 2.5	5.19m	3.28dd $J_{4',3'}$ 4.6	3.20dd $J_{4'',3'}$ 4.6 $J_{4'',4'}$ 12.4			6.66s	3.54s	2.47s 2.40s 2.35s	7.80–7.60m (12 H)
14[b,c]	4.48dd $J_{1',2'}$ 4.6	4.54dd $J_{2',3'}$ 3.1	4.98m	3.24dd $J_{4',3'}$ 8.3	2.97dd $J_{4'',3'}$ 6.4 $J_{4'',4'}$ 10.6			7.05d $J_{5,1'}$ 1.0	3.65s	2.46s 2.39s	7.84–7.24m (8 H)

[a]In $(CD_3)_2SO$. [b]In $CDCl_3$. [c]At 200 MHz (20°). [d]At 90 MHz (35°).

TABLE III

^{13}C-N.M.R. CHEMICAL SHIFTS[a] FOR COMPOUNDS **8** AND **9**

Compound	*Sugar moiety*				*Heterocycle*				p-*Tolyl*				
	C-1'	*C-2'*	*C-3'*	*C-4'*	*C-2*	*C-4*	*C-5*	*N-Me*	*C-1*	*C-2,C-6*	*C-3,C-5*	*C-4*	*Me*
8	38.9	73.3[b]	70.2[b]	29.9	159.3	125.8	115.2	29.7	133.1	122.9	126.7	134.6	18.0
9	39.2	75.4	70.3	30.7	159.5	127.7	113.0	29.7	132.8	122.9	126.7	135.0	17.9

[a]In $(CD_3)_2SO$. [b]Assignments may have to be reversed.

the α anomer. However, the stability of the thiofuranoside rings[25] is such that dehydration of **5** under strong or mild conditions yielded a 3:2 $\alpha\beta$-mixture.

The anomeric configuration of **8** and **9** was assigned as follows. The β anomer **9** was strongly levorotatory and the α anomer **8** was dextrorotatory, in agreement with the data reported for the analogues **18** and **19**[13] and other pairs of erythrofuranosyl-*C*-nucleosides[13,21,26]. The resonance of H-1′α (Table II) was at lower field than that of H-1′β as in D-*ribo*-*N* and *C*-nucleosides[27,28]. The value of $J_{1',2'}$ was smaller for the α anomer (3.4 Hz) than for the β anomer (7.3 Hz). Similar $J_{1',2'}$ values have been reported for their analogues **18** and **19**[13], suggesting that the preferred conformation of the sugar ring does not change markedly on replacement of the ring oxygen by sulphur.

The resonances of C-1′ and C-4′ of **8** and **9** (Table III) were at lower field than those for C-2′ and C-3′, reflecting the presence of the ring sulphur. In the ^{1}H-coupled-^{13}C-n.m.r. spectrum, C-3′ of **9** was coupled only with H-3′ and with one H-4′ in agreement[29] with the conformation ^2_3T calculated from $J_{H,H}$ values.

Conventional acetonation of **8** and **9** yielded the 2,3-*O*-isopropylidene derivatives **10** and **11**, respectively, the ^{1}H-n.m.r. spectra (Table II) of which confirmed the assigned anomeric configurations; $J_{1',2'}$ was larger for the α anomer **10** than for the β anomer **11**, as described for related compounds[30]. Also, H-1′α resonated at higher field than H-1′β as reported[13] for the isopropylidene derivatives of the analogues **18** and **19**, but opposite to that described for 2,3-*O*-isopropylidene-D-ribofuranosyl-*C*-nucleosides[27]. The $\Delta\delta$ values (0.17 for **10** and 0.23 for **11**) for the isopropylidene moiety accord with the Imbach rule[31].

Tosylation of **8** and **9** by phase-transfer catalysis[32] yielded the 2,3-ditosylates **12** and **13**, respectively, which are useful as transformation intermediates[33,34]. Conventional treatment of **8** with 2.2 mol. equiv. of tosyl chloride in pyridine gave a 3:7 mixture of **12** and the 3-tosylate **14**; the 2-tosylate was not detected (^{1}H-n.m.r.). The bulky substituent on C-1′ is responsible for the high stereoselectivity of the tosylation on HO-3′. The position of the tosyloxy groups was indicated by the fact that the chemical shift of the H-2′ resonance in **14** (4.54 p.p.m.) was at higher field than that of **12** (5.26 p.p.m.) (Table II). The i.r. bands associated with H-5 were at higher frequencies for the α-anomers **8, 10,** and **12** (3155, 3125, 3140 cm^{-1}) than for the β-anomers **9, 11,** and **13** (3120, 3080, 3115 cm^{-1}). Similar relations have been observed for the analogues with oxygen in the ring[13].

Numerous communications[35–39] have dealt with the conformational analysis of the furanosyl ring of nucleosides. The torsion angles ($\Phi_{H,H}$) between the vicinal protons of **9** (Table IV), calculated from the observed ^3J values using the equation proposed by Coxon[40], were very similar to those for the solid state, except that for $\Phi_{3,4trans}$. The $\Phi_{H,H}$ values for the solid state were calculated from the endocyclic torsion angles τ_i, obtained from the X-ray diffraction data of crystalline **9**[41], and a trigonal projection symmetry was assumed (120° symmetry). The use of the empirical correlation between τ_i and $\Phi_{H,H}$ deduced by Altona[39] for β-D-ribofuranosyl nucleosides gave values of $\Phi_{1',2'}$ (159.3°) and $\Phi_{2',3'}$ (52.2°) higher than the mean

value $\Phi_{H,H}$ deduced from the different non-proton angles ($\Phi_{1',2'}$ 154.2°, $\Phi_{2',3'}$ 48.8°). From the endocyclic torsion angles τ_i, the phase angles of pseudorotation (P 186.6°) and the puckering amplitude (Φ_m 48.4) defined by Altona and Sundaralingam[42] were calculated. This P value corresponds to a conformation intermediate between twist ${}^2_3T$ and envelope E_3. Similar results were obtained[40] using the ring puckering co-ordinates defined by Cremer and Pople[43]. From the similarities between $\Phi_{H,H}$ values in the solid state and $\Phi_{H,H}$ values deduced from the ${}^3J_{H,H}$ values (Table IV), it appears that the thio sugar exists in solution preferentially in a conformation close to ${}^2_3T$ (**29**) or, at least, that there is a strong preference for S conformers, which occupy the southern part of the pseudorotational circle (P = 180 ±90°).

It is generally assumed that the furanose ring in solution exists in equilibrium between N and S conformers[35–39]. Using the Karplus equation with the parameters A 10.2 and B −1.2 used in the conformational analysis of *C*-nucleosides[37] and assuming an equilibrium between conformations ${}^3_2T$ (P 0°) (**28**) and ${}^2_3T$ (P 180°) (**29**) with the ring puckering found in the solid state (Φ_m 48.4), it was calculated from the values of $J_{1',2'}$ (7.3 Hz) and $J_{3',4'trans}$ (3.2 Hz) that the sugar ring of **9** in solution in methyl sulphoxide existed as the conformers **28** (N) and **29** (S) in the ratio 29:71 (mean deviation, 2%). In the same way, the ditosylate **13** in solution in chloroform showed an equilibrium between conformers N and S in the ratio 38:62 (mean deviation, 8%).

On the other hand, the 4-thiofuranosyl ring of the α-anomers **12** (2,3-ditosylate) and **14** (3-tosylate) exhibited a preference for conformations N, as deduced from the high values (8.3–8.8 Hz) of $J_{3',4'trans}$. Using the method of Tran-Dinh *et al.*[37] for the conformational analysis of α-*C*-nucleosides, the pseudorotational parameters P_N, P_S, and Φ_m were deduced from the values of $J_{1',2'}$ and $J_{2',3'}$ and the N/S ratio was calculated from that of $J_{3',4'trans}$. Thus the conformational behaviour of **12** can be described by P_N −4°, P_S 176°, Φ_m 50, and N/S 88:12 and that of **14** by P_N −1°, P_S −179°, Φ_m 52, and N/S 80:20. The calculated values of P indicated the sugar ring to be in equilibrium between conformers close to ${}^3_2T$ (**26**) and ${}^2_3T$ (**27**), as assumed for the β anomers. The Φ_m values (50–52) calculated for the α anomers are close to that (48.4) found for **9** in the solid state. The contribution of the ${}^2_3T$

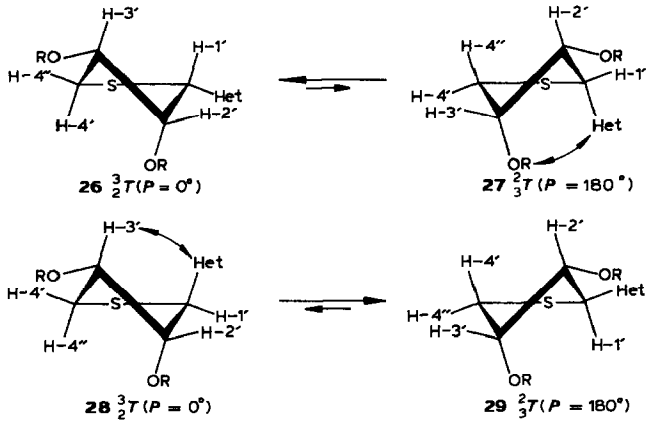
TABLE IV

VICINAL-PROTON TORSION ANGLES (Φ, DEGREES) FOR **9** IN THE SOLID STATE AND DEDUCED FROM THE ^{1}H-N.M.R. DATA

H,H	$J_{H,H}$	$\Phi_{H,H}$ *(in solution)*[a]	$\Phi_{H,H}$ *(in solid state)*[b]
1',2'	7.3	152.9 (18.9)[c]	152.6
2',3'	3.2	49.4 (126.5)	−48.0
$3',4'_{cis}$	4.4	41.5 (133.9)	40.2
$3',4''_{trans}$	3.2	126.5 (49.4)	−79.8

[a]Calculated by using the expression proposed by Coxon[40]. [b]Deduced from endocyclic torsion angles[41] τ_1 = 32.6, τ_2 = −48.0, τ_3 = 40.2. [c]Values in parentheses are not compatible with the structure.

conformer **27** in the equilibrium is low for the α anomers, due to the steric interaction between the heterocycle and the substituent on C-3′. The contribution of the $^{3}_{2}T$ conformer **28** is not so low for the β anomers, because the interaction is between the heterocycle and H-3′.



EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. I.r. spectra (KBr discs) were recorded with a Perkin–Elmer 299 spectrophotometer. ^{1}H-N.m.r. spectra were recorded with Perkin–Elmer R-32 (90 MHz) and Varian XL-200 (200 MHz, F.t.) spectrometers. Assignments were confirmed by double-resonance experiments and H/D exchange. ^{13}C-N.m.r. spectra (50.2 MHz) were recorded with a Varian XL-200 spectrometer. Proton-decoupled APT[44] (Attached Proton Test) and proton-coupled spectra were obtained to assist in signal assignments. T.l.c. was performed on Silica Gel HF_{254} (Merck), with detection by u.v. light or iodine vapour.

*1,3-Dihydro-3-methyl-1-*p*-tolyl-(1,2,3-tri-*O*-acetyl-4-*S*-acetyl-4-thio-*D*-arabino-tetritol-1-yl)-2*H*-imidazole-2-thione* (**4**). — To a solution of **1**[15] (10 g, 30.8 mmol) in pyridine (25 mL) at −15° was added a cooled solution of *p*-toluenesulphonyl chloride (11.75 g, 61.6 mmol) in pyridine (25 mL) followed, after 1 h, by acetic anhydride (50 mL). The mixture was stored for 12 h at ~0° and then poured into ice–water, and the product was collected and dried (P_2O_5) to give **2** (18 g) contaminated with 1,3-dihydro-3-methyl-1-*p*-tolyl-4-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-2*H*-imidazole-2-thione[15] (**3**) (^{1}H-n.m.r. data). A solution of crude **2** and potassium thiolacetate (4.2 g, 36.7 mmol) in butanone (180 mL) was boiled under reflux for 4 h. Insoluble material was collected and washed with acetone (20 mL), the combined filtrate and washings were concentrated to dryness, and a solution of the residue in dichloromethane (50 mL) was washed with water (3 × 50 mL), dried ($MgSO_4$), and concentrated. The residue was crystallised from

ethanol (25 mL) to give **4** (11.42 g, 73% from **1**), m.p. 137–138°, $[\alpha]_D^{29}$ −67° (*c* 1, pyridine), R_F 0.28 (dichloromethane); λ_{max}^{EtOH} 218 and 262 nm (ε_{mM} 20.7 and 10.0); ν_{max} 3120 (HC= heterocycle), 1745, 1735 (C=O ester), 1686 (thioester), 1615, 1604 (C=C heterocycle and aromatic), 1575, 1510 (C=C aromatic), 1225, 1215, 1208 (ester and thioester), 826 and 810 cm^{-1} (aromatic). The ^1H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{23}H_{28}N_2O_7S_2$: C, 54.31; H, 5.54; N, 5.51; S, 12.61. Found: C, 54.28; H, 5.54; N, 5.40; S, 12.57.

4,4'-Dithiobis[*4-(4-deoxy*-D-arabino-*tetritol-1-yl)-1,3-dihydro-3-methyl-1*-p-*tolyl-2*H-*imidazole-2-thione*] (**6**). — To a suspension of **4** (0.5 g, 0.98 mmol) in methanol (2.5 mL) was added a solution of sodium methoxide (3.92 mmol) in methanol (2.5 mL). After 24 h at room temperature, the solution was neutralised with Amberlite IR-120 (H^+) resin and filtered, the resin was washed with methanol (10 mL), and the combined filtrate and washings were concentrated to dryness. The residue was crystallised from ethanol to give **6** (0.32 g, 97%), m.p. 144–145°, $[\alpha]_D^{29}$ −58° (*c* 1, pyridine), R_F 0.12 (ether–ethanol, 40:1); λ_{max}^{EtOH} 216 and 276 nm (ε_{mM} 35.6 and 15.4); ν_{max} 3350 (OH), 3140 (HC= heterocycle), 1605 (C=C heterocycle and aromatic), 1575, 1510 (C=C aromatic), and 820 cm^{-1} (aromatic). The ^1H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{30}H_{38}N_4O_6S_4$: C, 53.07; H, 5.64; N, 8.25; S, 18.89. Found: C, 52.96; H, 5.66; N, 7.98; S, 19.09.

4,4'-Dithiobis[*1,3-dihydro-3-methyl-1*-p-*tolyl-4-(1,2,3-tri*-O-*acetyl-4-deoxy*-D-arabino-*tetritol-1-yl)-2*H-*imidazole-2-thione*] (**7**). — Conventional treatment of **6** (0.35 g, 0.37 mmol) with pyridine (1 mL) and acetic anhydride (1 mL) gave **7** (0.44 g, 92%), m.p. 102–120° (from ethanol–water), $[\alpha]_D^{29}$ −79° (*c* 1, pyridine), R_F 0.10 (dichloromethane); λ_{max}^{EtOH} 216 and 262 nm (ε_{mM} 38.4 and 21.1); ν_{max} 3120 (HC= heterocycle), 1745 (C=O ester), and 1604 (C=C heterocycle and aromatic). The ^1H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{42}H_{50}N_4O_{12}S_4$: C, 54.17; H, 5.41; N, 6.02; S, 13.77. Found: C, 54.32; H, 5.55; N, 5.73; S, 13.36.

*1,3-Dihydro-3-methyl-4-(4-thio-α- and -β-*D-*erythrofuranosyl)-1*-p-*tolyl-2*H-*imidazole-2-thione* (**8** *and* **9**). — To a suspension of **4** (8 g, 15.7 mmol) in methanol (50 mL) was added sodium methoxide (62.8 mmol) in methanol (30 mL). After storage for 5 min at room temperature, the solution was neutralised as for **6**. T.l.c. (ether–ethanol, 40:1) of the syrupy product (5.36 g) revealed a main component with R_F 0.56 contaminated by **6** (R_F 0.12). The main compound was identified as 1,3-dihydro-3-methyl-4-(4-thio-D-*arabino*-tetritol-1-yl)-1-*p*-tolyl-2*H*-imidazole-2-thione (**5**) by the ^1H-n.m.r. spectrum of the mixture in Me_2SO (δ 2.06, dd, $J_{SH,4'}$ 9.0, $J_{SH,4'}$ 7.0 Hz, SH interchangeable with D_2O).

(*a*) A solution of the crude mixture (2.68 g) in ethanol–water 1:1 (25 mL) containing trifluoroacetic acid (0.5 mL, 6.5 mmol) was boiled under reflux for 3 h and then neutralised with Amberlite IRA-400 (HO^-) resin. The resin was collected and washed with methanol (25 mL), and the combined filtrate and washings were

concentrated to dryness. T.l.c. (ether–ethanol, 40:1) of the residue revealed **8** and **9** (R_F 0.34 and 0.45) in the ratio 3:2 (^{1}H-n.m.r. data). The mixture was crystallised from ethanol (7 mL) to give **8** (0.83 g, 32% from **4**), m.p. 194–195° (dec.), $[\alpha]_D^{29}$ +20° (*c* 1, pyridine); λ_{max}^{EtOH} 217 and 272 nm (ε_{mM} 26.2 and 11.2); ν_{max} 3360, 3300 (OH), 3155 (HC= heterocycle), 1619, 1600 (C=C heterocycle and aromatic), 1574, 1510 (C=C aromatic), and 820 cm^{-1} (aromatic). The ^{1}H- and ^{13}C-n.m.r. data are given in Tables II and III, respectively.

Anal. Calc. for $C_{15}H_{18}N_2O_2S_2$: C, 55.87; H, 5.63; N, 8.69; S, 19.89. Found: C, 56.21; H, 5.71; N, 8.87; S, 20.23.

The mother liquor was concentrated to dryness and the residue was recrystallised twice from water to give **9** (0.38 g, 15% from **4**), m.p. 180–181° (dec.), $[\alpha]_D^{29}$ −208° (*c* 1, pyridine); λ_{max}^{EtOH} 215, 248, and 272 nm (ε_{mM} 17.1, 9.4, and 8.5); ν_{max} 3390, 3230 (OH), 3120 (HC= heterocycle), 1608 (C=C heterocycle and aromatic), 1575, 1508 (C=C aromatic), 812 and 800 cm^{-1} (aromatic). The ^{1}H- and ^{13}C-n.m.r. data are given in Tables II and III, respectively.

Anal. Found: C, 55.96; H, 5.73; N, 8.79; S, 20.06.

(*b*) A solution of the above crude mixture (2.68 g) in trifluoroacetic acid (6.7 mL, 8.7 mmol) was left for 24 h at room temperature and then co-concentrated with ethanol (4 × 5 mL). The residue (2.5 g) contained **8** and **9** in the ratio 3:2 (^{1}H-n.m.r. data). The mixture was crystallised from ethanol (5 mL) to give **8** (0.72 g, 28% from **4**). The mother liquor was concentrated to dryness and column chromatography (silica gel, ether) of the residue and crystallisation of the product from water gave **9** (0.24 g, 9% from **4**).

A solution of **8** or **9** (0.05 g, 0.15 mmol) in ethanol–water (1:1, 1 mL) containing trifluoroacetic acid (0.02 mL, 0.26 mmol) was boiled under reflux for 3 h. T.l.c. then revealed that no anomerisation had occurred.

*1,3-Dihydro-4-(2,3-*O*-isopropylidene-4-thio-α-*D*-erythrofuranosyl)-3-methyl-1-*p*-tolyl-2*H*-imidazole-2-thione* (**10**). — A solution of **8** (0.1 g, 0.31 mmol) in acetone (15 mL) containing *p*-toluenesulphonic acid (0.15 g, 0.87 mmol) was left for 24 h at room temperature and then poured into saturated aqueous sodium hydrogencarbonate (80 mL) at 0°. Chromatographically pure **10** (0.093 g, 82%) was precipitated and crystallisation from ethanol gave a sample with m.p. 156–157°, $[\alpha]_D^{29}$ −55° (*c* 1, pyridine), R_F 0.45 (ether); λ_{max}^{EtOH} 215, 255, and 270 nm (ε_{mM} 19.9, 11.2, and 10.8); ν_{max} 3125 (HC= heterocycle), 1615 (C=C heterocycle and aromatic), 1575, 1510 (C=C aromatic), and 820 cm^{-1} (aromatic). The ^{1}H-n.m.r. data are given in Table II.

Anal. Calc. for $C_{18}H_{22}N_2O_2S_2$: C, 59.64; H, 6.12; N, 7.73; S, 17.69. Found: C, 59.80; H, 6.33; N, 8.08; S, 17.87.

*1,3-Dihydro-4-(2,3-*O*-isopropylidene-4-thio-β-*D*-erythrofuranosyl)-3-methyl-1-*p*-tolyl-2*H*-imidazole-2-thione* (**11**). — Acetonation of **9** (0.25 g, 0.77 mmol) was performed as described for **10**. Column chromatography (ether) of the crude product (0.21 g, 76%) gave **11** (0.185 g, 66%) as a syrup, $[\alpha]_D^{29}$ −199° (*c* 1.1, pyridine), R_F 0.87 (ether); λ_{max}^{EtOH} 215 and 262 nm (ε_{mM} 20.7 and 11.2); ν_{max} 3080 (HC=

heterocycle), 1600 (C=C heterocycle and aromatic), and 817 cm^{-1} (aromatic). The ^{1}H-n.m.r. data are given in Table II.

Anal. Calc. for $C_{18}H_{22}N_2O_2S_2$: C, 59.64; H, 6.12; N, 7.73; S, 17.69. Found: C, 59.73; H, 6.44; N, 7.77; S, 17.76.

*1,3-Dihydro-3-methyl-4-(4-thio-2,3-di-*O-p-*tolylsulphonyl-α-*D-*erythrofuranosyl)-1-*p-*tolyl-2*H-*imidazole-2-thione* (**12**). — To a solution of **8** (0.05 g, 0.15 mmol), tetrabutylammonium hydrogensulphate (0.01 g, 0.031 mmol), and *p*-toluenesulphonyl chloride (0.065 g, 0.34 mmol) in dichloromethane (5 mL) was added aqueous 5% sodium hydroxide (0.5 mL, 0.62 mmol). The mixture was shaken for 2 h at room temperature, and the organic layer was separated, washed with water (3 × 5 mL), dried ($MgSO_4$), and concentrated. Crystallisation of the residue (0.08 g) from ethanol gave **12** (0.052 g, 53%), m.p. 100–101°, $[\alpha]_D^{29}$ −1° (*c* 1, pyridine), R_F 0.48 (ether–hexane, 5:1); λ_{max}^{EtOH} 223, 259, and 271 nm (ε_{mM} 43.8, 12.1, and 11.4); ν_{max} 3140 (HC= heterocycle), 1590, 1510 (C=C aromatic), 1190, 1175 (SO_2), and 812 cm^{-1} (aromatic and C–O–S). The ^{1}H-n.m.r. data are given in Table II.

Anal. Calc. for $C_{29}H_{30}N_2O_6S_4$: C, 55.21; H, 4.79; N, 4.44; S, 20.33. Found: C, 55.18; H, 4.90; N, 4.16; S, 20.11.

*1,3-Dihydro-3-methyl-4-(4-thio-2,3-di-*O-p-*tolylsulphonyl-β-*D-*erythrofuranosyl)-1-*p-*tolyl-2*H-*imidazole-2-thione* (**13**). — Ditosylation of **9** (0.16 g, 0.49 mmol) was carried out as described above. Crystallisation of the crude product (0.28 g) from ethanol gave **12** (0.23 g, 74%), m.p. 181–182° (dec.), $[\alpha]_D^{29}$ −128° (*c* 1, pyridine), R_F 0.73 (ether–hexane, 5:1); λ_{max}^{EtOH} 223, 261, and 271 nm (ε_{mM} 43.8, 11.9, and 11.3); ν_{max} 3115 (HC= heterocycle), 1590, 1510 (C=C aromatic), 1190, 1175 (SO_2), 838 and 815 cm^{-1} (aromatic and C–O–S). The ^{1}H-n.m.r. data are given in Table II.

Anal. Calc. for $C_{29}H_{30}N_2O_6S_4$: C, 55.21; H, 4.79; N, 4.44; S, 20.33. Found: C, 55.19; H, 4.90; N, 4.16; S, 20.11.

*1,3-Dihydro-3-methyl-4-(4-thio-3-*O-p-*tolylsulphonyl-α-*D-*erythrofuranosyl)-1-*p-*tolyl-2*H-*imidazole-2-thione* (**14**). — To a solution of **8** (0.20 g, 0.62 mmol) in pyridine (1 mL) at 0° was added *p*-toluenesulphonyl chloride (0.26 g, 1.36 mmol). The mixture was stored for 24 h at 0°, water (1 mL) was added, and the mixture was left for 1 h at 0°. Conventional work-up gave a 3:7 mixture (0.35 g) of **12** and **14** (^{1}H-n.m.r. data). Column chromatography (dichloromethane) gave **12** (0.096 g, 24%), m.p. 100–101° (from ethanol), and **14** (0.184 g, 62%) as a syrup. Compound **14** had $[\alpha]_D^{29}$ +60° (*c* 1, pyridine), R_F 0.39 (ether–hexane); λ_{max}^{EtOH} 221, 250, and 271 nm (ε_{mM} 30.0, 11.0, and 10.0); ν_{max} 3480, 3280 (OH), 3140 (HC= heterocycle), 1590, 1510 (C=C aromatic), 1187, 1170 (SO_2), and 815 cm^{-1} (aromatic and C–O–S). The ^{1}H-n.m.r. data are given in Table II.

Anal. Calc. for $C_{22}H_{24}N_2O_4S_3$: C, 55.43; H, 5.07; N, 5.88; S, 20.18. Found: C, 55.40; H, 5.34; N, 5.81; S, 19.91.

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