Thio-sugars. Part 3.[1] 4-Thiotetrofuranose Nucleosides

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Nucleosides have been prepared for biological testing with 6-substituted purines, theophylline, and 5-substituted uracils as bases and 4-thio-DL-erythrofuranose and 4-thio-DL-threofuranose as sugars. 1-*O*-Acetyl-4-thioerythrofuranose 2,3-phenylboronate has again proved a valuable synthetic intermediate, yielding under mild conditions the purine nucleoside esters in the presence of toluene-*p*-sulphonic acid and the pyrimidine compounds from the silylated bases with tin(IV) chloride. The corresponding 2,3-dibenzoates of both sugars were also used, but in all cases the uracil N^3-nucleosides were obtained.

SUGARS with sulphur in the ring became available in 1961 and nucleosides with this modification soon afterwards.[2] The base–sugar bond in these analogues is more stable towards enzymic cleavage than in the naturally occurring compounds and the substitution of S for O markedly affects the conformation of the sugar ring; interesting biological differences have been observed.[3,4] We now describe the preparation of some nucleosides of 4-thio-DL-erythrofuranose and 4-thio-DL-threofuranose, with a view to assessing the influence of these sugar moieties on antitumour and antiviral properties. The absence of the 5′-hydroxy-group in tetrofuranose nucleosides[5] makes 5′-phosphorylation impossible and also alters the solubility, in addition to the effects arising from introduction of a sulphur atom. The work now outlined further[1] illustrates the synthetic value of the phenylboronate acetate (1a) obtained by Pummerer rearrangement.

Attention was first turned to 6-substituted purines. 6-Chloropurine nucleosides have intrinsic biological interest[3] and are also key chemical intermediates.[6] In addition, 6-chloropurine reacts more readily than many other bases with sugar derivatives. Although the phenylboronate group has not been used hitherto in nucleoside synthesis,[7] we found that the acetate (1a) afforded (51%) the ester (1c) when heated briefly in nitromethane with a little toluene-*p*-sulphonic acid. This product was predominantly the *trans*-anomer, showing a singlet for H_1' at τ 3.93. The small amount (*ca.* 20%) of *cis*-compound was eliminated during work-up of the deboronation product, giving the free nucleoside

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[4] M. Bobek, A. Bloch, R. Parthasarathy, and R. L. Whistler, *J. Medicin. Chem.*, 1975, **18**, 784.

[5] D. H. Murray, J. Prokop, and A. Bloch, *J. Pharm. Sci.*, 1969, **58**, 1275; L. M. Lerner, *J. Org. Chem.*, 1969, **34**, 101.

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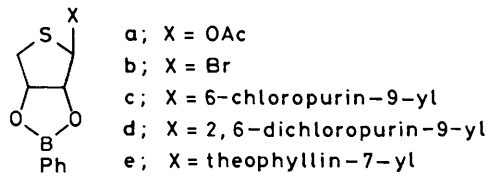
(2a). The $J_{1',2'}$ values for this (7 Hz) and the bicyclic derivative (1c) are quite different, as has sometimes been observed with other esters and acetals.[8] As in the case of *O*- and *S*-glycosides, the coupling constant for the anomeric proton in bicyclic derivatives is of great value in assigning configuration.[1]

Trifluoroacetic anhydride as Pummerer reagent provided convenient access to the bromide (1b).[1] It also proved useful here in the preparation of compound (1c) (45% overall from the sulphoxide phenylboronate;[9] short reaction times). In (2a), the 6-chlorine atom was readily displaced by various nucleophiles,[6] giving nucleosides (2b—e), while oxidation of the *vic*-diol function with periodate led to a dialdehyde which was isolated in the form of cyclic nitrogen derivatives.[1]

Oxidation of the inosine analogue (2f) would give a product corresponding closely to the so-called ' inosine dialdehyde ' which shows high activity against transplantable mouse tumours and is being assessed clinically.[10] It proved particularly difficult (see Experimental section) to convert the chloride (2a) into the hypoxanthine derivative (2f), but this was finally achieved indirectly by the action of sodium iodide in acetic acid on the benzyl ether (2d). A crystalline hydrazide adduct (8a) of the dialdehyde was obtained. The methyl ether (2e) was also oxidised to yield derivatives (8b, c).



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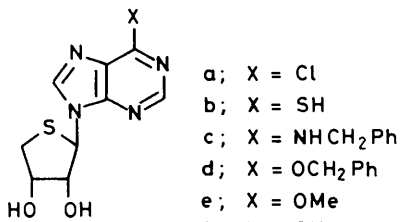

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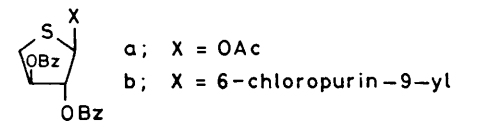

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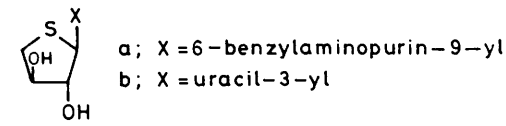

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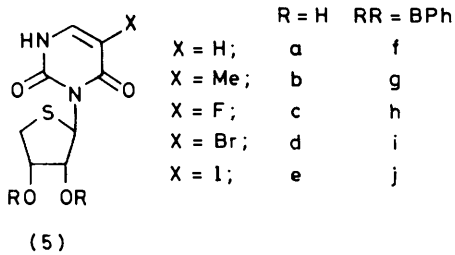

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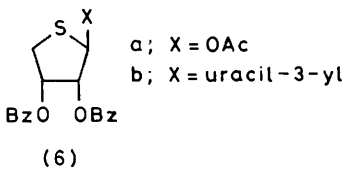

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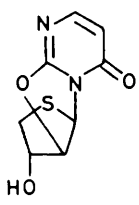

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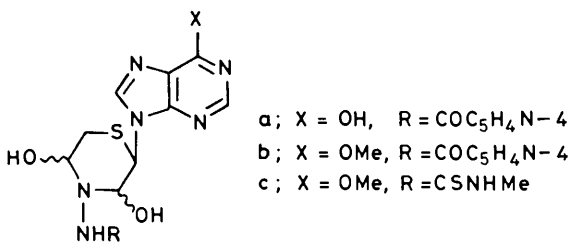

(8)

The mixture of 4-thiothreose dibenzoates (3a and anomer) gave the nucleoside ester (3b), but in lower yield (14%) than in the analogous reaction with the phenylboronate (1a). The compound isolated probably has the anomeric proton (singlet at τ 3.60) *trans* to H-2'. Again, the (unisolated) 1-trifluoroacetate corresponding to (3a) gave the dibenzoate (3b) in comparable yield. The isomer (4a) of the *N*-benzyladenine nucleoside (2c)

[8] E. H. Hamamura, K. Sato, and J. G. Moffatt, *J. Medicin. Chem.*, 1972, **15**, 1061; R. A. Sharma, M. Bobek, and A. Bloch, *ibid.*, 1975, **18**, 473.

[9] J. E. McCormick and R. S. McElhinney, *J.C.S. Perkin I*, 1976, 2533.

[10] R. L. Cysyk and R. H. Adamson, *Cancer Treatment Reports*, 1976, **60**, 555,563; S. K. Carter and M. Slavik, *Cancer Treatment Rev.*, 1976, **3**, 49.

was obtained by reaction of the dibenzoate (3b) with benzylamine in methanol; deacylation was accompanied by nucleophilic displacement in the purine ring.[11]

Nucleosides (5a—e) (Table 2) were prepared from uracil and some of its 5-substituted derivatives. From reaction of bis(trimethylsilyl)uracil with the phenylboronate (1a) in the presence of tin(IV) chloride was isolated (65%) a nucleoside ester with u.v. absorption maximum at 263 (pH 7) or 295 nm (pH 12; bathochromic shift characteristic of N^3-substituted uracil derivatives such as isouridine [12,13]). Under the conditions of the reaction, substitution at N-3 in uracils by sugar residues usually [13,14] occurs only in the presence of a bulky substituent at C-6.[15] However, the singlet for H-1′ at τ 3.75 indicates the anticipated *trans*-configuration (5f).

Minor amounts of other isomers (N^1-substituted and 1′,2′-*cis*) may be present in the crude product from uracil, and indeed the n.m.r. spectrum of the purified product from 5-bromouracil indicated a 3 : 1 mixture of N^3-*trans* (5i) and N^3-*cis*, while some of the later fractions from 5-iodouracil exhibited a much smaller bathochromic shift in the u.v. maximum than the main one. However, deboronation yielded (58%) a homogeneous 5-bromouracil nucleoside (5d) and the purified phenylboronate products (Table 1) from other analogues were homogeneous. The stereoselectivity of glycosidation using the phenylboronate (1a) is thus probably in the order O > N > S.[1]

As in the case of *O*-glycosides, the phenylboronate was a much better source than the dibenzoate (6a or anomer) of uracil nucleoside esters. Contrary to expectation,[14] the dibenzoate obtained also proved to be the N^3-compound (6b). The *trans*-dibenzoate mixture (3a and anomer) and bis(trimethylsilyl)uracil did not yield a crystalline ester but debenzoylation gave as a monohydrate the N^3-threoside (4b), whose configuration was deduced as follows.

The erythroside (5a) was converted by diphenyl carbonate [16] into the 2,2′-anhydro-compound (7), a cyclisation which involves inversion at C-2′. If in the threoside H-2′ were *cis* to H-1′, it would lead to the same anhydro-compound. In fact it gave, in poor yield, a different anhydro-compound (A), so H-1′ is *trans* to H-2′ (4b). The structure of (A) is under investigation. Where both H-2′ and H-3′ are *trans* to H-1′, 2,2′-anhydro-compounds are formed in preference to 2,3′,[17] but the precursor (4b) of (A) has H-3′ *cis* to H-1′, and in addition sulphur for oxygen in the furanose ring and the uracil moiety linked through N-3.

2,6-Dichloropurine was also converted readily, by the method used for 6-chloropurine, into a nucleoside phenylboronate, probably of configuration shown in (1d). The product similarly obtained from the less reactive theophylline consisted mainly of *trans*-compound (1e) (singlet for H-1′ at τ 3.75), although repeated recrystallisation concentrated the relatively insoluble *cis*-anomer (doublet for H-1′ at τ 3.98, $J_{1',2'}$ 7 Hz) to the extent of almost 50% of the analysis sample. However, deboronation directly after the initial purification gave in good yield the homogeneous *trans*-nucleoside [doublet for H-1′ at τ 3.92, $J_{1',2'}$ 7 Hz; spectrum very similar to that of the nucleoside (2a)] which, together with a number of other compounds now described, is undergoing biological evaluation.

EXPERIMENTAL

General conditions are given in Part 2.[1] Trimethylsilyl chloride and tin(IV) chloride were freshly distilled.

Nucleoside Esters (*Table* 1).—Purines were condensed directly with the sugar esters, pyrimidines as the silylated derivatives.

The phenylboronate (1d). The acetate (1a) (502 mg, 1.9 mmol) and 2,6-dichloropurine (359 mg, 1.9 mmol) in nitromethane (4.75 ml) containing toluene-*p*-sulphonic acid monohydrate ($TsOH,H_2O$) (19 mg) were stirred (10 min) at 100 °C. The mixture was evaporated and the residue dissolved in chloroform (20 ml), shaken with aqueous sodium hydrogen carbonate, and dried ($MgSO_4$; charcoal). Evaporation and trituration with methanol afforded the product (404 mg). When bis-(*p*-nitrophenyl) phosphate was used instead of $TsOH,H_2O$ as catalyst, the yield was 29%.

The phenylboronate (1c). This was obtained as for (1d), but with a reaction time of 1 h. It was also formed from the (unisolated) ester (1; X = O_2CCF_3),[1] in yields of 45, 34, and 0% for reaction times of 5, 15, and 60 min, respectively.

The phenylboronate (1e). The acetate (1a) (13.2 g, 50 mmol), theophylline (9.01 g), and $TsOH,H_2O$ (1.75 g) were stirred (100 °C; 1 h) in nitromethane (250 ml). Unchanged purine (1.88 g, 21%) was filtered after 2.5 h from the cooled mixture. The crude product (15.65 g) in acetonitrile (100 ml) was treated with charcoal and concentrated to 50 ml. The resulting crystals (6.54 g, then 226 mg) were triturated with hot water, yielding material (5.96 g) which was used for deboronation. Further recrystallisation from acetonitrile gave a sample of m.p. 230.5—233° (see Table 1), which was an isomeric mixture (*ca.* 1 : 1) showing τ[$(CD_3)_2SO$] 3.75 (s, H-1′ of *trans*-anomer), 3.98 (d, *J* 7 Hz, H-1′ of *cis*-anomer). The sample was partly insoluble in acetone and the signals at τ[$(CD_3)_2CO$] 3.65 and 3.85 represented a *trans* : *cis* ratio of >9 : 1.

The dibenzoate (3b). This was obtained from the acetate mixture (3a and anomer) under the conditions for the phenylboronates (reaction time 1.5 h). The unisolated

[11] H. M. Kissman and M. J. Weiss, *J. Org. Chem.*, 1956, **21**, 1053; L. Goldman, J. W. Marsico, and R. B. Angier, *J. Amer. Chem. Soc.*, 1956, **78**, 4173.

[12] (*a*) J. P. Scannell and F. W. Allen, *J. Org. Chem.*, 1960, **25**, 2143; (*b*) J. O. Polazzi, D. L. Leland, and M. P. Kotick, *ibid.*, 1974, **39**, 3114; (*c*) M. Prystaš and F. Šorm, *Coll. Czech. Chem. Comm.*, 1969, **34**, 2316.

[13] A. H. Haines, *Tetrahedron*, 1973, **29**, 2807.

[14] F. W. Lichtenthaler, A. Heerd, and K. Strobel, *Chem. Letters*, 1974, 449.

[15] U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, 1974, **39**, 3654, 3660; H. Vorbrüggen, K. Krolikiewicz, and U. Niedballa, *Ann. New York Acad. Sci.*, 1975, **255**, 82.

[16] J. P. H. Verheyden, D. Wagner, and J. G. Moffatt, *J. Org. Chem.*, 1971, **36**, 250.

[17] D. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 1958, 3028; J. A. Secrist III, *Carbohydrate Res.*, 1975, **42**, 379.

trifluoroacetate (3; X = O_2CCF_3) gave the same yield in 5 min.

The phenylboronates (5f—j). Uracil or its 5-substituted analogue (10 mmol) and trimethylsilyl chloride (15 ml) in dry benzene (50 ml) were treated quickly dropwise at room temperature with triethylamine (20 ml) in benzene (50 ml). Stirring was continued for 3.5 h and the mixture filtered (Celite) and evaporated. To the bis(trimethylsilyl) derivative were added methylene chloride (70 ml) and the acetate (5j), but attempts to isolate the N^1-isomer gave unsatisfactory results.

The dibenzoate (6b). In addition to the ester isolated (Table 1), a further amount (9%) was obtained as the diol after debenzoylation of the mother liquors as described in the synthesis of the *trans*-diol (4b).

Nucleosides (*Table* 2).—The purine and pyrimidine derivatives (2a) and (5a—e) were obtained by reactions [1] of the phenylboronates with propane-1,3-diol; the esters (1d and e) were also deboronated in this way. All were recrystallised from methanol. Other nucleosides were prepared as follows.

TABLE 1

Nucleoside esters

Compound	Yield (%)	Cryst. solvent	M.p. (°C)	τ[a](H–1′)	$\lambda_{max.}$ [b] nm	Formula	Found(%) C	H	N	S	Required(%) C	H	N	S
(1c)	51	MeCN	153—190 [c]	3.93(s) [d,e]	266	$C_{15}H_{12}BClN_4O_2S$ [f]	50.3	3.35	15.8	8.5	50.2	3.3	15.6	8.9
(1d)	54	MeOH	230—232.5		275	$C_{15}H_{11}BCl_2N_4O_2S$ [g]	46.2	2.9	14.4	8.1	45.8	2.8	14.25	8.1
(1e)	31	MeCN	230.5—233		276	$C_{17}H_{17}BN_4O_4S$	53.5	4.5	15.0	7.7	53.1	4.4	14.6	8.3
(3b)	14	MeCN	195—198	3.60(s) [d]	267	$C_{23}H_{17}ClN_4O_4S$ [h]	57.4	3.6	12.2	6.7	57.45	3.5	11.7	6.7
(5f)	65	MeOH [i]	242.5—244.5	3.75(s) [j]	263(295)	$C_{14}H_{13}BN_2O_4S$	53.4	4.2	9.0	10.2	53.2	4.1	8.9	10.1
(5g)	55	MeOH [k]	248—249.5	3.78(s)	268(301)	$C_{15}H_{15}BN_2O_4S$ [l]	54.0	4.7	8.2		54.55	4.5	8.5	
(5h)	40	MeOH [k]	248—250	3.82(bs) [m]	270(306)	$C_{14}H_{12}BFN_2O_4S$	50.3	3.7	8.0	9.6	50.3	3.6	8.4	9.6
(5i)	60	MeOH	238—240.5 [n]	3.75(s) [o]	279(309)	$C_{14}H_{12}BBrN_2O_4S$	42.1	3.1	6.7	8.1	42.5	3.0	7.1	8.1
(5j)	57	MeOH [k]	220 [n]	3.77(s) [p]	285(314)	$C_{14}H_{12}BIN_2O_4S$	38.2	2.9	6.0	6.8	38.0	2.7	6.3	7.2
(6b)	35	EtOAc	218—220.5		266(295)	$C_{22}H_{18}N_2O_6S$	59.9	4.2	6.3	7.1	60.3	4.1	6.4	7.3

[a] In $(CD_3)_2SO$ except as indicated. [b] At pH 7; in parentheses, at pH 12. [c] M.p. sharp, but variable in this range. [d] In $CDCl_3$. [e] Sample contains *ca.* 20% of *cis*-1′,2′-anomer: τ 3.65(d, *J* 4 Hz, N-1′). [f] Found: B, 3.2. Required: B, 3.1%. [g] Found: Cl, 18.1. Required: Cl, 18.1%. [h] Found: Cl, 7.3. Required: Cl, 7.4%. [i] Triturated first with MeOH. [j] τ 4.30 (d, *J* 8 Hz, H-5), 2.47 (d, *J* 8 Hz, H-6). [k] Triturated first with hot MeOH. [l] *m/e* 330. [m] τ 2.02 (s, H-6). [n] With decomp. [o] τ 2.00(s, H-6). Sample contains *ca.* 25% of *cis*-1′,2′-anomer: τ 3.73 (d, *J* 6 Hz, H-1′) and 2.07 (s, H-6). [p] τ 1.98 (s, H-6).

TABLE 2

Nucleosides

Compound	Yield (%)	M.p. (°C)	Formula	Found(%) C	H	N	S	Required(%) C	H	N	S
(2a)	88	152.5 [a]	$C_9H_9ClN_4O_2S$ [b]	39.7	3.3	20.5	11.6	39.6	3.3	20.5	11.7
From (1d)	74	165—165.5 [a]	$C_9H_8Cl_2N_4O_2S$ [c]	35.0	2.7	18.2	10.5	35.2	2.6	18.2	10.4
From (1c)	77 [f]	179—182.5	$C_{11}H_{14}N_4O_4S$ [g]	44.2	4.75	18.6	10.5	44.3	4.7	18.8	10.7
(2b)	81	231 [a]	$C_9H_{10}N_4O_2S_2$	40.2	3.4	21.1	23.7	40.0	3.7	20.7	23.7
(2c)	83	208—209.5	$C_{16}H_{17}N_5O_2S$	55.8	5.1	20.2	9.4	56.0	5.0	20.4	9.3
(2d)	83	162—164	$C_{16}H_{16}N_4O_3S$	55.7	4.8	16.3	9.1	55.8	4.65	16.3	9.3
(2e)	66	176—177.5	$C_{10}H_{12}N_4O_3S$	44.6	4.4	20.9	11.9	44.75	4.5	20.9	11.95
(2f)	90	228—230 [a]	$C_9H_{10}N_4O_3S$, ½MeOH	42.6	4.5	20.7	12.1	42.2	4.4	20.7	11.85
(4a)	70	228.5—231	$C_{16}H_{17}N_5O_2S$	55.8	4.8	20.0	9.2	56.0	5.0	20.4	9.3
(4b)	32	128—140 [d]	$C_8H_{10}N_2O_4S$, H_2O [e]	38.4	4.9	10.8	13.2	38.7	4.8	11.3	12.9
(5a)	70 [f]	206.5—208	$C_8H_{10}N_2O_4S$ [h]	41.4	4.4	12.0	13.9	41.75	4.35	12.2	13.9
(5b)	67 [f]	229—230 [a]	$C_9H_{12}N_2O_4S$	44.0	5.35	11.2	13.0	44.3	4.9	11.5	13.1
(5c)	66 [f]	208.5—209.5	$C_8H_9FN_2O_4S$	38.9	3.75	11.2	12.7	38.7	3.6	11.3	12.9
(5d)	58 [f]	198 [a]	$C_8H_9BrN_2O_4S$	31.4	3.0	9.0	10.1	31.1	2.9	9.1	10.35
(5e)	60 [f]	199.5 [a]	$C_8H_9IN_2O_4S$	27.1	2.8	7.5	8.7	27.0	2.5	7.9	9.0

[a] With decomp. [b] Found: Cl, 13.0. Required: Cl, 13.0%; τ[$(CD_3)_2SO$] 3.90 (d, *J* 7 Hz, H-1′). [c] Found: Cl, 22.9. Required: Cl, 23.1%. [d] With gas evolution. Sample air dried; more vigorous drying did not lead to a sharper m.p. [e] $\lambda_{max.}$ 262(pH 7) or 295 nm (pH 12). [f] Crude product triturated with methanol. [g] τ[$(CD_3)_2SO$] 3.92 (d, *J* 7 Hz, H-1′). [h] τ[$(CD_3)_2SO$] 3.78 (d, *J* 6.5 Hz, H-1′), 4.42 (d, *J* 7.5 Hz, H-5), and 2.57 (d, *J* 7.5 Hz, H-6).

(1a) (1 equiv.). The cooled (0 °C), stirred mixture was treated with tin(IV) chloride (1 ml) and the clear golden solution kept at room temperature; next day it was shaken carefully with aqueous sodium hydrogen carbonate (2 × 15 ml) and worked up in the usual manner.

Uracil was, alternatively, silylated by refluxing in hexamethyldisilazane (1.5 ml per mmol) for 8.5 h. Thymine however did not react under these conditions.

Some of the ester (5j) often separated in the reaction mixture from the acetate (1a) and 5-iodouracil and in the organic layer during treatment with sodium hydrogen carbonate. The remainder of the product appeared from u.v. data to be a mixture of N^3- and N^1-substituted isomers. Recrystallisation from methanol afforded more N^3-isomer

9-(4-*Thio*-DL-*erythrofuranosyl*)*purine*-6-*thiol* (2b). Hydrogen sulphide was passed during 1 h through an ice-cooled solution of sodium methoxide [from sodium (0.53 g)] in dry methanol (60 ml). The solution was treated with chloropurine (2a) (2.45 g, 9 mmol) in methanol (150 ml) at room temperature and passage of hydrogen sulphide was continued (4 h). The *thiol* (2b) (1.97 g) began to separate after 1.5 h and was crystallised from aqueous 15% dimethylformamide. It was also formed (36%) by refluxing (1 h) equimolar amounts of the chloropurine (2a) and thiourea in ethanol.

6-*Benzylamino*-9-(4-*thio*-DL-*erythrofuranosyl*)*purine* (2c). The chloropurine (2a) (1.09 g, 4 mmol) was stirred (2 h) with benzylamine (12 ml). Ether (80 ml) was added and the mixture filtered (Celite) and evaporated. This process was repeated and the excess of benzylamine distilled off (bath temp. 95—105 °C). The residual solid was triturated with methanol (3 ml) to give the *amine* (2c) (1.14 g) (from aqueous 40% dimethylformamide).

6-*Benzyloxy*-9-(4-*thio*-DL-*erythrofuranosyl*)*purine* (2d). After reaction (½ h; 100 °C) of the chloropurine (2a) (1.09 g, 4 mmol) with sodium (184 mg) in dry benzyl alcohol (24 ml), the cooled solution was treated, with shaking, with 2N-HCl (2.0 ml), and the organic layer diluted with ethyl acetate (75 ml) and separated. The aqueous layer was extracted twice further with ethyl acetate and the dried organic solutions were evaporated (finally at 0.15 mmHg). Addition of ether to the residue caused crystallisation of the *benzyl ether* (2d) (1.14 g), m.p. 159.5—160.5° (Found: C, 55.5; H, 4.75; N, 16.7; S, 9.3%) (from acetonitrile); $\nu_{max.}$ 935, 1 080, 1 130, and 1 270 cm^{-1}. Crystallisation from methanol afforded a solvated product which required heating at 65 °C *in vacuo* before showing m.p. 162—164° (see Table 2); $\lambda_{max.}$(MeOH) 251 nm; $\nu_{max.}$ 1 040 and 1 325 cm^{-1}, but none of the peaks indicated earlier; identical spectra before and after heating at 65 °C. The *diacetate* had m.p. 105—106.5° (from methanol) (Found: C, 54.9; H, 4.7; N, 12.8. $C_{20}H_{20}N_4O_5S,\frac{1}{2}H_2O$ requires C, 54.9; H, 4.8; N, 12.8%).

6-*Methoxy*-9-(4-*thio*-DL-*erythrofuranosyl*)*purine* (2e). A mixture of the chloropurine (2a) (818 mg), 2N-NaOH (3 ml), water (6 ml), and methanol (9 ml) was refluxed (½ h). The cooled, neutralised solution was evaporated, and extraction with boiling 1 : 4 methanol–acetonitrile (3 × 10 ml) yielded the *methyl ether* (2e) (from acetonitrile).

6-*Hydroxy*-9-(4-*thio*-DL-*erythrofuranosyl*)*purine* (2f). The benzyl ether (2d) (2.752 g, 8 mmol) dissolved during 45 min with swirling in a solution of sodium iodide [18] (1.80 g, 12 mmol) in acetic acid (9.6 ml). The mixture then slowly deposited a hygroscopic solid (1.812 g), containing iodine, which was isolated after 7 h, washed rapidly with acetic acid and light petroleum, and dried. A second fraction (377 mg) was collected after 45 h. Treatment of this material overnight with equal amounts (2.1 ml) of acetic anhydride and pyridine afforded the desired product as its 2,3-*diacetate* (1.65 g), m.p. 256—258° (from methanol) (Found: C, 45.7; H, 4.1; N, 16.5; S, 9.7. $C_{13}H_{14}N_4O_5S$ requires C, 46.15; H, 4.1; H, 16.6; S, 9.5%); $\nu_{max.}$ 1 670 cm^{-1} (CO).[19] The remaining mixture was evaporated and the residue, after trituration with ether, was also treated with acetic anhydride and pyridine to give a further amount of the diacetate (403 mg; total 76% from the benzyl ether). The *nucleoside* (2f) (550 mg) was obtained by mixing the diacetate (845 mg, 2.5 mmol) in dry methanol (85 ml) with a solution of sodium methoxide [from sodium (58 mg)] in methanol (10.6 ml). After 16 h, acetic acid (0.3 ml) was added, the mixture was evaporated, and the residue triturated with water.

The use of hydrogen bromide [18] instead of sodium iodide in the above reaction resulted in decomposition, even at 0 °C; when the reaction, starting with either of the ethers (2d and e), was moderated by dilution of the medium with methylene chloride, a pale yellow hygroscopic solid separated but this, in each case, failed to yield the diacetate described above. Acidic (0.1N-HCl) hydrolysis [20,21] of the nucleosides (2a and d), followed by acetylation of the products, led to materials, m.p. >300°, indicating cleavage of the glycosidic bond; *cf.* the lower yield of the thiol (2b) from thiourea. Attempts to hydrolyse the chloro-nucleoside (2a) using aqueous alkali [22] alone or with t-butyl alcohol were also unproductive, possibly because of the sensitivity of the imidazole ring.[20,23] Finally, the nucleoside (2a) was found to be inert at room temperature to dimethyl sulphoxide,[24] a reagent which converts certain chloro-substituted nitrogen heterocycles into the corresponding oxo-compounds; at 100 °C, decomposition occurred.

6-*Benzylamino*-9-(4-*thio*-DL-*threofuranosyl*)*purine* (4a). The dibenzoate (3b) (336 mg, 0.7 mmol) was refluxed (5 h) with benzylamine (1.2 ml) in methanol (24 ml) and the solvent evaporated off. Ether (14 ml) was added to the residue, insoluble material filtered off, and the filtrate evaporated. This process was repeated. Trituration with light petroleum (20 ml) and next day with hot acetonitrile (4 ml), gave the *amine* (4a) (169 mg) (from methanol).

3-(4-*Thio*-DL-*threofuranosyl*)*uracil* (4b). The dibenzoate (3a) (12 mmol) was condensed with bis(trimethylsilyl)uracil by the general method. Attempts to crystallise the crude product were unsuccessful so the gum was treated in dry methanol (150 ml) with a solution of sodium methoxide [from sodium (250 mg)] in methanol (50 ml). Next day, neutralisation with methanol-washed Amberlite IR 120 (H^+) resin, filtration and evaporation, removal of methyl benzoate by trituration with ether (3 × 50 ml), and addition of methanol (6 ml) gave a solution which slowly deposited the *nucleoside monohydrate* in two fractions. A third fraction after recrystallisation from methanol afforded more of the desired material (416 mg; total 960 mg).

2,2′-*Anhydro*-3-(4′-*thio*-DL-*threofuranosyl*)*uracil* (7).—3-(4′-Thio-DL-erythrofuranosyl)uracil (130 mg, 0.56 mmol), diphenyl carbonate (161 mg), and sodium hydrogen carbonate (3.6 mg) in hexamethylphosphoric triamide (HMPT) (0.56 ml) were heated at 150 °C during 20 min. Water (11 ml) was added and the mixture shaken with chloroform (2 × 2.25 ml). The filtered, aqueous layer was evaporated and the residue triturated with methanol (0.5 ml) to yield the *anhydro-derivative* (56 mg, 46%), m.p. 216—217.5° (from methanol) (Found: C, 44.9; H, 3.75; N, 12.9; S, 14.7. $C_8H_8N_2O_3S$ requires C, 45.3; H, 3.8; N, 13.2; S, 15.1%); $\lambda_{max.}$(MeOH) 273 nm, $\lambda_{min.}$ 236 nm, unchanged by addition of alkali. This is closely analogous to the spectra of other 2,2′-anhydro-N^3-nucleosides.[12b] The possible alternative 2′,4-anhydro-N^3-structure is unlikely as 3-methyluracil is *O*-alkylated exclusively on O-2.[25]

Anhydro-derivative (A) *from the Nucleoside* (4b).—The monohydrate (230 mg) of the nucleoside (4b) was similarly treated with diphenyl carbonate (285 mg) in HMPT (1 ml) containing sodium hydrogen carbonate (6.4 mg). Evaporation of the aqueous layer gave an oil which was triturated with ethyl acetate (1 ml). Insoluble material (38 mg) was discarded and the filtrate deposited the anhydro-derivative

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(24 mg, 11%), m.p. 189—191° (from ethyl acetate) (Found: C, 45.0; H, 3.8; N, 12.8. Calc. for $C_8H_8N_2O_3S$: C, 45.3; H, 3.8; N, 13.2%); $\lambda_{max.}$(MeOH) 275 nm, $\lambda_{min.}$ 236 nm, unchanged by addition of alkali. When larger proportions of diphenyl carbonate were used, none of the anhydro-compound was isolated.

Periodate Oxidation of the Nucleosides (2e *and* f).—A partial solution of the nucleoside (2f) (381 mg, 1.5 mmol) in water (20 ml) was oxidised at 4—6 °C during 10 min with aqueous sodium periodate (321 mg, 1.5 mmol; 6 ml). The resulting, clear solution was, after removal of iodate,[1] treated with aqueous isonicotinoylhydrazine (206 mg, 1.5 mmol; 3 ml) causing separation of the *adduct* (8a) (542 mg, 93%), m.p. 202—204° (decomp.) (from 30% aqueous dimethylformamide; bath temp. 70 °C) (Found: C, 45.2; H, 3.85; N, 24.7; S, 8.1. $C_{15}H_{15}N_7O_4S,\frac{1}{2}H_2O$ requires C, 45.2; H, 4.0; N, 24.6; S, 8.0%).

The nucleoside (2e) (381 mg, 1.42 mmol) in water (12.5 ml) was oxidised similarly and samples (≡0.47 mmol) of the resulting solution were treated, respectively, with aqueous solutions of isonicotinoylhydrazine (0.5 mmol) and 4-methylthiosemicarbazide (0.5 mmol) to give the *adducts* (8b) (174 mg, 92%), m.p. 159° (decomp.) (from dimethylformamide–methanol; bath temp. 70 °C) (Found: C, 47.1; H, 4.25; N, 23.6; S, 7.8. $C_{16}H_{17}N_7O_4S$ requires C, 47.65; H, 4.25; N, 24.3; S, 7.95%), and (8c) (125 mg, 72%), m.p. 166.5° (decomp.) (from dimethylformamide–water; bath temp. 70 °C) (Found: C, 38.6; H, 4.65; N, 25.8; S, 17.4. $C_{12}H_{17}N_7O_3S_2$ requires C, 38.8; H, 4.6; N, 26.4; S, 17.25%); $\lambda_{max.}$(MeOH) 248 nm; *m/e* 335 ($M - 2H_2O$). The product (8c) (72%) also resulted from 4-methylthiosemicarbazide (2 equiv.).

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