Approaches to the Synthesis of 2'-Thio Analogues of Pyrimidine Ribosides

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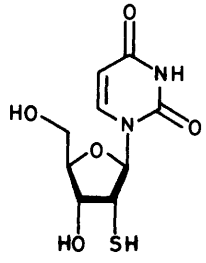
2'-Deoxy-2'-mercaptouridine (**1**) was obtained in 75% isolated yield by heating 2'-deoxy-2'-(4-methoxybenzylthio)uridine (**4a**) with phenol in trifluoroacetic acid solution. When triphenylmethanol or 9-phenylxanthen-9-ol (**5**) was added to the products before work-up, compound (**4c**) or (**4d**) was obtained. Compound (**4d**) was also obtained in satisfactory overall yield from crude (**1**), prepared in two steps from 2'-deoxy-2'-(t-butylthio)uridine (**4b**). Treatment of compound (**4d**) first with acetic anhydride in pyridine and then with phosphoryl trichloride, triethylamine, and 1,2,4-triazole in acetonitrile gave the triazolo compound (**10**) in 73% overall yield. Reaction between compound (**10**) and ammonia in dichloromethane [or dimethylamine in dioxane] followed by methanolic ammonia gave the cytidine derivative (**11a**) [or (**11b**)] in good yield. When compounds (**11a**) and (**11b**) were allowed to react with hydrochloric acid in 2-mercaptoethanol solution at room temperature, the hydrochloride salts of 2'-deoxy-2'-mercaptocytidine (**2a**) and its 4,4-di-*N*-methyl derivative (**2b**) were obtained in high isolated yields. The latter compounds readily underwent aerial oxidation in the presence of triethylamine in methanol solution to give the corresponding dimeric disulphides (**12a**) and (**12b**). The NMR spectra of the synthetic products are discussed.

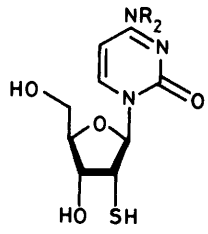
Although 2'-thio derivatives are relatively simple and rather obvious analogues of the common ribonucleosides, the only fully characterized member of this class of compounds described previously in the literature[1] is 2'-deoxy-2'-mercaptouridine (**1**). A synthesis of the corresponding cytidine derivative (**2a**) has also been reported[2] but it is not clear (see below) from the NMR spectroscopic evidence presented that compound (**2a**) was actually obtained. Several years ago, we showed[3] that 2,2'-anhydrouridine (**3**) reacted with a number of arene- and alkanethiolate ions (RS^-) to give the corresponding sulphides (**4**). We now report that two of the latter compounds [(**4a**) and (**4b**)] may be converted into 2'-deoxy-2'-mercaptouridine (**1**), and indirectly also into 2'-deoxy-2'-mercaptocytidine (**2a**) and its 4-*N*,4-*N*-dimethyl derivative (**2b**).

When 2'-deoxy-2'-(4-methoxybenzylthio)uridine[3] (**4a**) was heated, under reflux, in trifluoroacetic acid (TFA) solution in the presence of phenol, 2'-deoxy-2'-mercaptouridine (**1**) was obtained and was isolated from the products as a crystalline solid in 75% yield. The 4-methoxybenzyl [as in (**4a**)] group has been widely used[4] for the protection of the thiol functions of cysteine residues in peptide synthesis; it has been removed both under acidic (TFA[5] or hydrogen fluoride,[6] in the presence of anisole) and reductive (sodium/liquid ammonia[5]) conditions. We ruled out the latter reductive unblocking conditions in order to avoid the possibility of base-promoted disulphide formation occurring. When a slight excess of triphenylmethanol was added to the crude 2'-deoxy-2'-mercaptouridine (**1**) (see above) before removal of the TFA, 2'-deoxy-2'-(tritylthio)uridine (**4c**) was obtained and was isolated from the products as a crystalline solid in 80% yield. In the same way, 2'-deoxy-2'-(9-phenylxanthen-9-ylthio)uridine (**4d**) was obtained, also as a crystalline solid in 80% isolated yield, by addition of a slight excess of 9-phenylxanthen-9-ol[7] (PxOH) (**5**) before removal of the TFA. Unfortunately, attempts to prepare compounds (**4c**) and (**4d**) directly from 2,2'-anhydrouridine and the appropriate thiols [triphenylmethanethiol and 9-phenylxanthene-9-thiol (PxSH), respectively] were unsuccessful.[8]

The t-butyl group was removed from 2'-deoxy-2'-(t-butylthio)uridine (**4b**), which is somewhat more readily accessible[3] than compound (**4a**), by Pastuszak and Chimiak's two-step procedure.[9] When compound (**4b**) was allowed to react with a slight excess of 2-nitrobenzenesulphenyl chloride in glacial acetic acid solution for 16 h at room temperature, 2'-deoxy-2'-(2-nitrophenyldithio)uridine (**6**) was obtained and was isolated from the products as a yellow crystalline solid in 83% yield. Cleavage of the disulphide linkage occurred when compound (**6**) was treated with an excess of 2-mercaptoethanol and triethylamine in methanol solution at room temperature. Attempts to isolate pure 2'-deoxy-2'-mercaptouridine (**1**) from the crude products were unsuccessful. However, when the latter products were treated with an excess of 9-phenylxanthen-9-ol (**5**) in glacial acetic acid solution at room temperature, crystalline 2'-deoxy-2'-(9-phenylxanthen-9-ylthio)uridine (**4d**) was obtained in 76.5% isolated yield. When compound (**4d**) was heated in glacial acetic acid solution in the presence of redistilled pyrrole[10] for 2.5 h at 70 °C, the uridine derivative (**1**) was regenerated and was isolated as a pure crystalline solid in 78% yield. Acid-catalysed removal of the trityl protecting group from 2'-deoxy-2'-(tritylthio)uridine (**4c**) occurs less easily and apparently less efficiently. Thus, when compound (**4c**) was allowed to react with an excess of pyrrole in TFA solution at room temperature, no starting material remained after 10 min, but it was possible to isolate 2'-deoxy-2'-mercaptouridine (**1**) from the products in only 51% yield. However, compound (**4c**) was converted into the uridine derivative (**1**) in 86% isolated yield by treatment first with a very slight excess of silver nitrate[11] in pyridine–methanol solution and then by bubbling of hydrogen sulphide through a suspension of the resulting precipitate in methanol–acetic acid.

The previously reported[1] preparation of 2'-deoxy-2'-mercaptouridine (**1**) involved two steps, starting from 3',5'-di-*O*-acetyl-2,2'-anhydrouridine (**7**). When the latter compound was heated with a large excess of mercaptoacetic acid in dioxane solution at 110 °C for 6 h, the triacetate (**8**) was obtained in 65% yield. Saponification of compound (**8**) with potassium hydroxide in aqueous ethanol solution at 10 °C and neutralization of the products gave 2'-deoxy-2'-mercaptouridine (**1**) in 97% yield. Thiols (or rather their conjugate bases), including nucleoside thiols[12–14] show a marked tendency to undergo oxidative dimerization in basic solution. It was therefore rather surprising that the saponification product of triacetate (**8**) was obtained free from the dimeric disulphide (**9**).


(1)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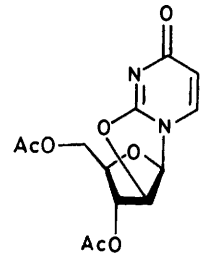
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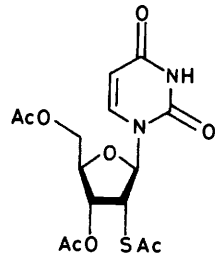
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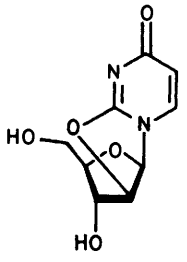
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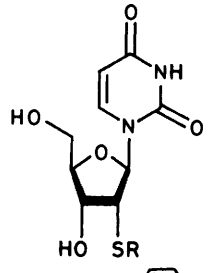
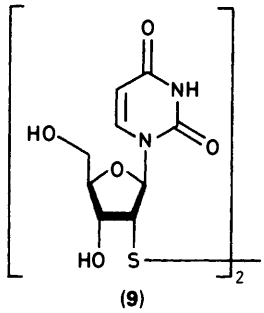

(4) a; R = MeO-C6H4-CH2
b; R = Me3C
c; R = Ph3C
d; R = Px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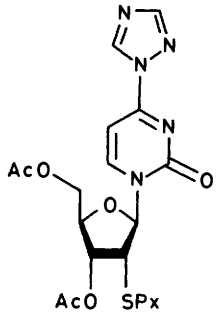
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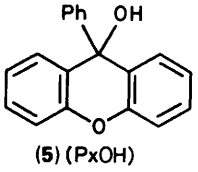
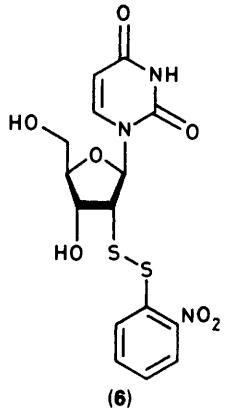

(5) (PxOH)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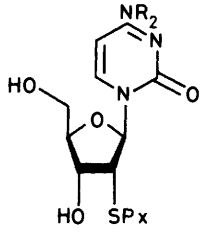
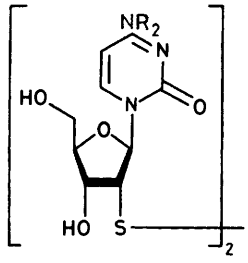

(11) a; R = H
b; R = Me


(12) a; R = H
b; R = Me

Despite this successful use of a base-labile protecting group, it seems that, if disulphide formation is to be avoided, it is generally advisable to use an acid-labile protecting group for the thiol function in the preparation of 2′-deoxy-2′-mercapto-ribonucleosides. For this reason, we decided to use the relatively easily removable 9-phenylxanthen-9-yl (Px) protecting group in the preparation of 2′-deoxy-2′-mercaptocytidine (**2a**) and its 4-*N*,4-*N*-dimethyl derivative (**2b**).

Following the procedure that we developed[15] originally for the conversion of 1-β-D-arabinofuranosyluracil into 1-β-D-arabinofuranosylcytosine and its 4-*N*-alkyl and -aryl derivatives, 2′-deoxy-2′-(9-phenylxanthen-9-ylthio)uridine (**4d**) was treated first with acetic anhydride in pyridine and the product was then allowed to react with phosphoryl trichloride, triethylamine, and 1,2,4-triazole in acetonitrile at room temperature to give the triazolo derivative (**10**) which was isolated as a pure crystalline solid in 73% overall yield. The latter compound was allowed to react with an excess of ammonia in dichloromethane solution at room temperature for 48 h, and the products were further treated with ammonia in methanol solution to give 2′-deoxy-2′-(9-phenylxanthen-9-ylthio)cytidine (**11a**) as a crystalline solid in 81% isolated yield. Similarly, when compound (**10**) was treated first with an excess of a 30% solution of dimethylamine in dioxane at room temperature overnight and then with methanolic ammonia, 2′-deoxy-4,4-di-*N*-methyl-2′-(9-phenylxanthen-9-ylthio)cytidine (**11b**) was obtained, and was isolated as a crystalline solid in 80% yield. The 9-phenylxanthen-9-yl (Px) protecting group was readily removed from compound (**11a**) by keeping it in 2-mercaptoethanol–conc. hydrochloric acid (50:1 v/v) solution overnight at room temperature. The desired 2′-deoxy-2′-mercaptocytidine (**2a**) was isolated from the products as its pure, crystalline hydrochloride salt in 88% yield. In the same way, compound (**11b**) was converted into the hydrochloride of 2′-deoxy-2′-mercapto-4,4-di-*N*-methylcytidine (**2b**) in 90% yield.

In order to establish that the synthetic 2′-thio analogues [(**1**), (**2a**), and (**2b**)] were free from the corresponding dimeric disulphides [(**9**), (**12a**), and (**12b**), respectively], it was decided to undertake the preparation of the latter compounds. The dimer (**9**) of the uridine analogue (**1**), which had already been obtained[1] by treatment of compound (**1**) with a stoicheiometric quantity of iodine in aqueous ethanol, was prepared from 2′-deoxy-2′-(4-methoxybenzylthio)uridine[3] (**4a**) in two steps [(i) phenol, TFA; reflux; 1 h; (ii) iodine, triethylamine, pyridine; room temperature; 5 h] in 64% overall yield. The dimers [(**12a**) and (**12b**), respectively] of the cytidine derivatives (**2a**) and (**2b**) were obtained when their hydrochlorides were stirred with an excess of triethylamine in methanol solution overnight at room temperature; these compounds were obtained in 90 and 96% isolated yields, respectively. The cytidine analogues [(**2a**) and (**2b**)] appeared to undergo

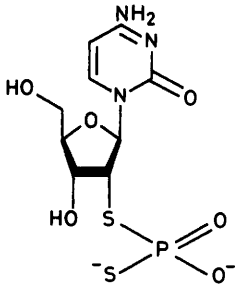
Table. NMR spectra[a] of 2′-deoxy-2′-mercapto ribonucleosides and their derivatives.

Entry	Compound	Base residue	1′-H (*J*/Hz)	2′-H (*J*/Hz)	3′-H (*J*/Hz)	4′-H	5′-H_2	C-2′
1	(**4c**)	Uracil	6.01 (9.9)	2.89 (4.4, 9.9)	3.06	3.80	3.30	52.22
2	(**4d**)	Uracil	5.91 (9.9)	3.12 (4.4, 9.9)	3.22	3.80	3.32	51.74
3	(**1**)	Uracil	5.89 (9.0)	3.49 (5.2, 9.0)	4.09	3.95	3.58	44.87
4	(**9**)	Uracil	6.17 (8.6)	3.63 (5.6, 8.6)	4.17	3.84	3.54	55.52
5	(**11a**)	Cytosine	6.03 (10.0)	3.03 (4.3, 10.0)	3.11	3.74	3.28	52.04
6	(**2a**)[b]	Cytosine	5.92 (7.7)[c]	3.56 (5.4, 7.6)	4.14 (2.4, 5.3)	4.02	3.63	45.95
7	(**12a**)	Cytosine	6.16 (8.1)[c]	3.66 (5.6, 8.1)	4.25	3.83	3.56	57.48
8	(**11b**)	4,4-Di-*N*-methylcytosine	6.04 (10.0)	3.16[d]	3.16[d]	3.75	3.29	53.79
9	(**2b**)[b]	4,4-Di-*N*-methylcytosine	5.95 (8.0)[c]	3.57[e]	4.14 (2.0, 5.1)	3.99	3.61[e]	45.72
10	(**12b**)	4,4-Di-*N*-methylcytosine	6.16 (8.1)[c]	3.64 (5.5, 8.1)	4.25	3.83	3.56	57.56

[a] ^{1}H and ^{13}C NMR spectra were measured in $(CD_3)_2SO$ solution with a Bruker WM 250 spectrometer. [b] As its hydrochloride salt. [c] The assignment of this resonance signal to 1′-H (rather than to 5-H) has not been established by spin-decoupling or from a COSY spectrum. [d] 2′-H and 3′-H give overlapping signals. [e] 2′-H and 5′-H give overlapping signals.

oxidative dimerization in basic solution in the presence of air with particular facility.

It can be seen from the Table that ^{13}C NMR spectroscopy is of considerable value in distinguishing between the 2′-deoxy-2′-mercapto ribonucleoside derivatives [(**1**), (**2a**), and (**2b**)] and the corresponding dimeric disulphides [(**9**), (**12a**), and (**12b**), respectively]. While the chemical shifts of the C-2′ resonance signals of compounds (**1**), (**2a**), and (**2b**) [entries nos. 3, 6, and 9] are 44.87, 45.95, and 45.72 ppm, respectively, those of disulphides (**9**), (**12a**), and (**12b**) (entries nos. 4, 7, and 10) are 55.52, 57.48, and 57.56 ppm, respectively. However, it can be seen under the same entries in the Table that the chemical shifts of the 2′-H resonance signals of thiols (**1**), (**2a**), and (**2b**) [3.49, 3.56, and 3.57 ppm] are only very marginally upfield from those of their disulphides (**9**), (**12a**), and (**12b**) (3.63, 3.66, and 3.64 ppm). It is also instructive to compare the chemical shifts of the 2′-H and 3′-H resonance signals of the 2′-deoxy-2′-mercapto ribonucleosides [(**1**), (**2a**), and (**2b**); entries nos. 3, 6, and 9] with those of their *S*-(9-phenylxanthen-9-yl) derivatives [(**4d**), (**11a**), and (**11b**), respectively; entries nos. 2, 5, and 8]. It is apparent that the introduction of a 2-*S*-(9-phenylxanthen-9-yl) group leads, on the average, to the shielding of 2′-H and 3′-H by 0.44 and 0.96 ppm, respectively.



(**13**)

As indicated above, an alternative synthesis of 2′-deoxy-2′-mercaptocytidine (**2a**) had been reported[2] previously. This synthesis, which was based on the acid phosphatase-promoted hydrolysis of the putative phosphorodithioate (**13**), itself prepared in essentially two steps from 2,2′-anhydrocytidine, is not unambiguous and, furthermore, it is not clear from the ^{1}H NMR spectroscopic data presented[2] [δ (D_2O) 4.05 (1 H, d, *J* 6.0 Hz, 2′-H), 4.25 (2 H, m, 5′-H_2), 4.53 (1 H, m, 4′-H), 4.85 (1 H, d, *J* 2.7 Hz, 3′-H), 6.50 (1 H, d, *J* 7.7 Hz, 5-H), 6.72 (1 H, d, *J* 8.5 Hz, 1′-H), and 8.15 (1 H, d, *J* 7.7 Hz, 6-H)] that compound (**2a**) was indeed obtained. Our ^{1}H NMR spectroscopic data for compound (**2a**) [Table, entry no. 6] relate to its hydrochloride salt and the spectrum was measured in $(CD_3)_2SO$ rather than in D_2O solution. However, the chemical shift differences between our spectrum and that reported[2] by Patel *et al.*, which are, on average, *ca.* 0.6 ppm per proton, would appear to be unduly large. It can be seen [entries nos. 3 and 6] that the chemical shifts of the resonance signals of the corresponding sugar protons in 2′-deoxy-2′-mercapto-uridine and -cytidine [(**1**) and (**2a**), respectively] are all within 0.1 ppm of each other. Although Imazawa *et al.* have reported[1] that the sugar protons in compound (**1**) resonate, on the average, *ca.* 0.2 ppm further downfield when the spectrum is measured in D_2O as compared with in $(CD_3)_2SO$ solution, this effect would hardly seem to be great enough to account for the data reported by Patel *et al.*[2] In any case, we believe that the fact that *S*-(9-phenylxanthen-9-yl) derivatives of 2′-deoxy-2′-mercapto ribonucleosides are fairly readily accessible crystalline compounds, which may be unblocked under relatively mild acidic conditions, recommends the approach to the synthesis of 2′-thio analogues of pyrimidine ribosides described in this paper.

Experimental

^{1}H and ^{13}C NMR spectra were measured with a Bruker WM 250 spectrometer; tetramethylsilane was used as internal standard. UV absorption spectra were measured with a Kontron Uvikon 820 recording spectrophotometer. Merck silica gel 60 F_{254} plates were used for TLC; Merck silica gel H was used for short-column chromatography.

2′-Deoxy-2′-(tritylthio)uridine (**4c**).—2′-Deoxy-2′-(4-methoxybenzylthio)uridine[3] (1.5 g, 3.94 mmol), phenol (0.56 g, 5.95 mmol), and anhydrous TFA (15 ml) were heated together, under reflux, with the exclusion of moisture. After 1 h, the products were allowed to cool to room temperature and triphenylmethanol (1.104 g, 4.24 mmol) was added. After a further period of 1 h, the products were concentrated under reduced pressure, then redissolved in chloroform (20 ml) and the solution was neutralized with triethylamine. The chloroform solution was washed successively with saturated aqueous sodium hydrogen carbonate (10 ml) and water (10 ml); it was then dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by short-column chromatography: the appropriate fractions, which were eluted with chloroform–methanol (9:1 v/v), were combined, evaporated under reduced pressure, and the residue was crystallized from ethyl acetate to give the *title compound* (1.59 g, 80%) (Found: C, 67.0; H, 5.1; N, 5.8; S, 6.4. $C_{28}H_{26}N_2O_5S$ requires C, 66.9; H, 5.2; N, 5.6; S, 6.4%) as crystals, m.p. 208–209 °C; δ_H[$(CD_3)_2SO$] 2.89 (1 H, dd, *J* 4.4, 9.9 Hz), 3.06 (1 H, m), 3.30 (2 H, m), 3.80 (1 H, m), 4.84 (1 H, m), 5.32 (1 H, d, *J* 4.7 Hz), 5.48 (1 H, d, *J* 8.1 Hz), 6.01 (1 H, d, *J* 9.9 Hz), 7.2–7.4 (16 H, m), and 11.36 (1 H, br s); δ_C[$(CD_3)_2SO$]

52.22, 61.78, 67.24, 71.87, 85.75, 87.12, 102.86, 126.94, 128.18, 129.22, 140.15, 144.53, 151.04, and 163.22.

2'-Deoxy-2'-(2-nitrophenyldithio)uridine (**6**).—2'-Deoxy-2'-(t-butylthio)uridine[3] (1.94 g, 6.13 mmol) and 2-nitrobenzenesulphenyl chloride (1.40 g, 7.4 mmol) were stirred together in glacial acetic acid (36 ml) solution at room temperature for 16 h. The products were then concentrated under reduced pressure and the residue obtained was purified by short-column chromatography: the appropriate fractions, which were eluted with chloroform–methanol (9:1 v/v), were combined, evaporated under reduced pressure, and the residue was crystallized from aqueous ethanol to give the *title compound* (2.12 g, 83%) (Found: C, 43.8; H, 3.8; N, 10.2. $C_{15}H_{15}N_3O_7S_2$ requires C, 43.6; H, 3.7; N, 10.2%) as yellow needles, m.p. 177 °C; $\delta_H[(CD_3)_2SO–D_2O]$ *inter alia* 3.67 (1 H, dd, *J* 5.3, 9.3 Hz), 3.93 (1 H, m), 4.37 (1 H, m), 5.44 (1 H, d, *J* 8.0 Hz), 6.24 (1 H, d, *J* 9.3 Hz), 7.51 (1 H, m), 7.62 (1 H, d, *J* 8.2 Hz), 7.80 (1 H, m), 8.13 (1 H, d, *J* 7.9 Hz), and 8.20 (1 H, d, *J* 8.2 Hz); $\delta_C[(CD_3)_2SO]$ 57.91, 61.18, 72.28, 86.45, 86.87, 102.21, 125.89, 126.96, 127.14, 134.73, 135.60, 139.83, 144.84, 150.59, and 162.36.

2'-Deoxy-2'-(9-phenylxanthen-9-ylthio)uridine (**4d**).—(*a*) 2'-Deoxy-2'-(4-methoxybenzylthio)uridine[3] (1.925 g, 5.06 mmol), phenol (0.71 g, 7.54 mmol), and anhydrous TFA (19 ml) were heated together, under reflux, with exclusion of moisture. After 1 h, the products were allowed to cool and were evaporated to dryness under reduced pressure. The residue was dissolved in glacial acetic acid (10 ml) and a solution of 9-phenylxanthen-9-ol[7] (2.06 g, 7.5 mmol) in glacial acetic acid (10 ml) was added to the stirred solution at room temperature. After 20 min, the products were concentrated under reduced pressure, the residue was redissolved in chloroform (50 ml), and the resulting solution was neutralized with triethylamine and then washed successively with saturated aqueous sodium hydrogen carbonate (25 ml) and water (25 ml). The dried ($MgSO_4$) chloroform solution was evaporated under reduced pressure and the residue was purified by short-column chromatography: the appropriate fractions, which were eluted with chloroform–methanol (9:1 v/v), were combined and evaporated under reduced pressure. Crystallization of the residue from aqueous ethanol gave the *title compound* (2.09 g, 80%) (Found: C, 62.7; H, 4.8; N, 5.2. $C_{28}H_{24}N_2O_6S·H_2O$ requires C, 62.9; H, 4.9; N, 5.2%) as crystals, m.p. 224 °C; $\delta_H[(CD_3)_2SO–D_2O]$ *inter alia* 3.12 (1 H, dd, *J* 4.4, 9.9 Hz), 3.22 (1 H, m), 3.32 (2 H, m), 5.22 (1 H, d, *J* 8.1 Hz), 5.91 (1 H, d, *J* 9.9 Hz), 6.82 (1 H, m), and 7.0–7.4 (13 H, m); $\delta_C[(CD_3)_2SO]$ 51.74, 55.67, 61.64, 71.79, 85.54, 86.87, 102.51, 115.95, 116.12, 123.31, 123.41, 124.57, 125.00, 127.03, 127.86, 128.28, 128.78, 128.93, 129.88, 130.90, 138.49, 146.24, 149.77, 149.96, 150.50, and 162.71.

(*b*) 2-Mercaptoethanol (0.14 ml, 2.00 mmol) was added to a stirred solution of 2'-deoxy-2'-(2-nitrophenyldithio)uridine (0.412 g, 1.00 mmol) and triethylamine (0.14 ml, 1.00 mmol) in methanol (8 ml) at room temperature. After 2 min, the products were neutralized with acetic acid and concentrated to dryness under reduced pressure. The residue was redissolved in glacial acetic acid (6 ml) at room temperature and 9-phenylxanthen-9-ol (0.52 g, 1.90 mmol) was added. After 20 min, the products were concentrated under reduced pressure, and the residue was dissolved in chloroform. The resulting solution was washed successively with saturated aqueous sodium hydrogen carbonate (20 ml) and water (20 ml); it was then dried ($MgSO_4$), evaporated under reduced pressure, and the residue was purified as above by short-column chromatography to give the title compound (0.394 g, 76.5%), identical with the material described under (*a*) above.

2'-Deoxy-2'-mercaptouridine (**1**).—(*a*) A stirred solution of 2'-deoxy-2'-(9-phenylxanthen-9-ylthio)uridine (0.208 g, 0.40 mmol) and redistilled pyrrole (0.071 ml, 1.0 mmol) in glacial acetic acid (4 ml) was heated at 70 °C for 2.5 h. The products were then concentrated under reduced pressure and the residue was purified by short-column chromatography: the appropriate fractions, which were eluted with chloroform–methanol (1:1 v/v), were combined and evaporated under reduced pressure. Crystallization of the residue from methanol gave the title compound (0.082 g, 78%) (Found: C, 41.3; H, 4.7; N, 10.8; S, 11.9. Calc. for $C_9H_{12}N_2O_5S$: C, 41.5; H, 4.65; N, 10.8; S, 12.3%) as crystals, m.p. 174–176 °C (lit.,[1] 171–174 °C); [FAB] *m/z* 261 $(M + 1)^+$; λ_{max}(95% EtOH) 260 nm (ε 10 000); λ_{min} 230 nm (ε 2 300); $\delta_H[(CD_3)_2SO–D_2O]$ *inter alia* 3.49 (1 H, dd, *J* 5.2, 9.0 Hz), 3.58 (2 H, m), 3.95 (1 H, m), 4.09 (1 H, dd, *J* 1.2, 5.1 Hz), 5.73 (1 H, d, *J* 8.0 Hz), 5.89 (1 H, d, *J* 9.0 Hz), and 7.81 (1 H, d, *J* 8.2 Hz); $\delta_C[(CD_3)_2SO]$ 44.87, 61.52, 71.93, 86.51, 88.90, 102.45, 140.47, 151.01, and 163.07.

(*b*) A solution of 2'-deoxy-2'-(4-methoxybenzylthio)uridine[3] (1.00 g, 2.63 mmol) and phenol (0.37 g, 3.93 mmol) in TFA (10 ml) was heated, under reflux, for 2 h. The cooled products were evaporated under reduced pressure, the residue was redissolved in ethanol, and the solution was evaporated again. The residue was triturated several times with ether and was then crystallized from 95% ethanol to give the title compound (0.516 g, 75%), identical with the material described under (*a*) above.

(*c*) 2'-Deoxy-2'-(tritylthio)uridine (0.15 g, 0.30 mmol) and pyrrole (0.039 ml, 0.56 mmol) were stirred together in TFA (1.5 ml) solution at room temperature. After 10 min, the products were concentrated under reduced pressure and the residue was purified by chromatography on silica gel as above to give the title compound (0.04 g, 51%), identical with the material described under (*a*) above.

(*d*) A solution of silver nitrate (0.071 g, 0.42 mmol) in methanol (2.9 ml) was added to 2'-deoxy-2'-(tritylthio)uridine (0.20 g, 0.40 mmol) and pyridine (0.033 ml). The resulting mixture was stirred at room temperature for 5 min and was then filtered. The colourless residue was washed with methanol and was then suspended in methanol (9 ml). Glacial acetic acid (1.0 ml) was added and hydrogen sulphide gas was bubbled through the stirred suspension for 20 min. The products were flushed with nitrogen and the black precipitate was then removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was crystallized from methanol to give the title compound (0.09 g, 86%) as a solid that was identical with the material described under (*a*) above.

Bis-(2'-deoxyuridin-2'-yl) Disulphide (**9**).—2'-Deoxy-2'-(4-methoxybenzylthio)uridine[3] (0.385 g, 1.01 mmol), phenol (0.142 g, 1.51 mmol), and anhydrous TFA (3.8 ml) were heated together, under reflux, for 1 h. The cooled products were concentrated under reduced pressure and the residue was dissolved in pyridine (2 ml). Triethylamine (0.3 ml, 2.15 mmol) and iodine (0.254 g, 1.00 mmol) were added and the solution obtained was stirred at room temperature. After 5 h, the products were evaporated under reduced pressure and the residue was purified by short-column chromatography: the appropriate fractions, which were eluted with chloroform–methanol (7:3 v/v), were combined and evaporated under reduced pressure, and the residue was crystallized from ethyl acetate to give the title compound (0.189 g, 64%) (Found: C, 41.9; H, 4.1; N, 10.7. Calc. for $C_{18}H_{22}N_4O_{10}S_2$: C, 41.7; H, 4.3; N, 10.8%) as crystals, m.p. 158 °C (lit.,[1] 161–164 °C); [FAB] *m/z* 519 $(M + 1)^+$; λ_{max}(95% EtOH) 260 nm (ε 16 900); λ_{min} 230 nm (ε 4 800); $\delta_H[(CD_3)_2SO]$ 3.54 (4 H, m), 3.63 (2 H, dd, *J* 5.6, 8.6 Hz), 3.84 (2 H, m), 4.17 (2 H, m), 5.11 (2 H, m), 5.69 (2 H, d, *J* 8.0 Hz), 5.81 (2 H, d, *J* 5.6 Hz), 6.17 (2 H, d, *J* 8.6 Hz), 7.78 (2 H, d, *J* 8.1 Hz), and 11.38 (2 H, br s); $\delta_C[(CD_3)_2SO]$ 55.52, 61.31, 72.16, 86.65, 87.83, 102.47, 140.66, 150.89, and 163.10.

1-[3',5'-*Di*-O-*acetyl*-2'-*deoxy*-2'-(9-*phenylxanthen*-9-*ylthio*)-β-D-*ribofuranosyl*]-4-(1,2,4-*triazol*-1-*yl*)*pyrimidin*-2-(1 H)-*one* (**10**).—Acetic anhydride (4.7 ml, 39.7 mmol) and 2'-deoxy-2'-(9-phenylxanthen-9-ylthio)uridine (5.40 g, 10.45 mmol) were stirred together in anhydrous pyridine (17 ml) at room temperature. After 5 h, methanol (18 ml) was added and after a further period of 5 min the products were concentrated under reduced pressure and purified by short-column chromatography: the appropriate fractions, which were eluted with chloroform–methanol (9:1 v/v), were combined and concentrated under reduced pressure to give a glass (5.04 g). Triethylamine (8.40 ml, 60.3 mmol) and phosphoryl trichloride (1.20 ml, 12.9 mmol) were added to a stirred solution of the latter glass (4.00 g) in acetonitrile (40 ml). 1,2,4-Triazole (4.14 g, 59.9 mmol) was then added and the reactants were stirred together at room temperature. After 17 h, triethylamine–water (6:1 v/v; 20 ml) followed by saturated aqueous sodium hydrogen carbonate (100 ml) were added to the products and the resulting mixture was extracted with chloroform (2 × 100 ml). The dried ($MgSO_4$) chloroform extracts were evaporated under reduced pressure and the residue was crystallized from ethanol to give the *title compound* [3.95 g, 73% overall yield for the two steps starting from compound (**4d**)] (Found: C, 62.6; H, 4.4; N, 10.8. $C_{34}H_{29}N_5O_7S$ requires C, 62.7; H, 4.5; N, 10.75%) as crystals, m.p. 132 °C; $\delta_H[(CD_3)_2SO]$ 2.12 (3 H, s), 2.14 (3 H, s), 3.15 (1 H, dd, *J* 5.7, 9.9 Hz), 3.91 (1 H, m), 4.00 (2 H, m), 4.24 (1 H, m), 6.20 (1 H, d, *J* 9.9 Hz), 6.47 (1 H, m), 6.74 (1 H, d, *J* 7.3 Hz), 6.9–7.4 (12 H, m), 7.74 (1 H, d, *J* 7.4 Hz), 8.49 (1 H, s), and 9.49 (1 H, s); $\delta_C[(CD_3)_2SO]$ 20.34, 20.48, 50.09, 55.79, 63.78, 73.09, 82.33, 86.99, 95.98, 115.95, 116.00, 123.52, 123.75, 123.86, 127.30, 128.56, 128.99, 129.47, 129.94, 130.91, 143.87, 145.68, 146.23, 149.43, 149.56, 153.42, 154.33, 158.67, 169.40, and 169.93.

2'-*Deoxy*-2'-(9-*phenylxanthen*-9-*ylthio*)*cytidine* (**11a**).—The above triazolo compound (**10**) (0.512 g, 0.79 mmol) was dissolved in a saturated solution of ammonia in dichloromethane (9 ml) and the solution was kept at room temperature for 48 h. The products were then concentrated under reduced pressure and the residue was redissolved in half-saturated methanolic ammonia (10 ml) at room temperature. After 24 h, the solution was evaporated to dryness and the residue was crystallized from methanol to give the *title compound* (0.328 g, 81%) (Found: C, 65.4; H, 4.8; N, 8.0; S, 6.3. $C_{28}H_{25}N_3O_5S$ requires C, 65.2; H, 4.9; N, 8.15; S, 6.2%) as crystals, m.p. 210 °C; $\delta_H[(CD_3)_2SO]$ *inter alia* 3.03 (1 H, dd, *J* 4.3, 10.0 Hz), 3.11 (1 H, m), 3.28 (2 H, m), 3.74 (1 H, m), 4.84 (1 H, m), 5.21 (1 H, d, *J* 4.4 Hz), 5.31 (1 H, d, *J* 7.4 Hz), 6.03 (1 H, d, *J* 10.0 Hz), 6.79 (1 H, m), and 6.95–7.5 (13 H, m); $\delta_C[(CD_3)_2SO]$ 52.04, 55.65, 61.78, 71.53, 85.49, 86.34, 95.03, 115.66, 115.99, 123.19, 123.43, 124.90, 126.96, 127.99, 128.18, 128.59, 128.81, 129.76, 130.84, 139.35, 145.85, 149.94, 155.29, and 165.22.

2'-*Deoxy*-2'-*mercaptocytidine* (**2a**).—Conc. hydrochloric acid (0.2 ml) was added to a stirred solution of 2'-deoxy-2'-(9-phenylxanthen-9-ylthio)cytidine (0.515 g, 1.00 mmol) in 2-mercaptoethanol (10 ml) at room temperature. After 17 h, absolute ethanol (5 ml) was added and the products were concentrated under reduced pressure to *ca.* 2 ml. The residual solution was added dropwise to stirred ether (150 ml). The resulting precipitate was collected by centrifugation, washed several times with ether, and crystallized from aqueous ethanol to give the *title compound* as its *hydrochloride salt* (0.262 g, 88%) (Found: C, 36.4; H, 5.0; N, 13.85. $C_9H_{14}ClN_3O_4S$ requires C, 36.55; H, 4.8; N, 14.2%) as crystals, m.p. 187 °C (decomp.); λ_{max} (95% EtOH) 282 nm (ε 7 400); λ_{min} 245 nm (ε 2 000); $\delta_H[(CD_3)_2SO–D_2O]$ *inter alia* 3.56 (1 H, dd, *J* 5.4, 7.6 Hz), 3.63 (2 H, m), 4.02 (1 H, m), 4.14 (1 H, dd, *J* 2.4, 5.3 Hz), 5.92 (1 H, d, *J* 7.7 Hz), 6.18 (1 H, d, *J* 7.8 Hz), and 8.18 (1 H, d, *J* 7.9 Hz); $\delta_C[(CD_3)_2SO]$ 45.95, 61.02, 71.24, 86.73, 90.32, 94.84, 143.97, 148.79, and 159.86.

Bis-(2'-*deoxycytidin*-2'-*yl*) *Disulphide* (**12a**).—Triethylamine (0.096 ml, 0.69 mmol) was added to a stirred suspension of 2'-deoxy-2'-mercaptocytidine hydrochloride (0.100 g, 0.34 mmol) in methanol (1 ml) at room temperature. After 17 h, the resulting homogeneous solution was evaporated under reduced pressure, redissolved in the minimum possible volume of methanol, and chloroform–light petroleum (b.p. range 40–60 °C) (1:1 v/v; 10 ml) was added. The title compound (0.07 g, 90%) was obtained as a precipitate and was isolated following centrifugation; [FAB] *m/z* 517 $(M + 1)^+$; $\delta_H[(CD_3)_2SO]$ 3.56 (4 H, m), 3.66 (2 H, dd, *J* 5.6, 8.1 Hz), 3.83 (2 H, m), 4.25 (2 H, m), 5.09 (2 H, m), 5.75 (2 H, d, *J* 5.3 Hz), 5.79 (2 H, d, *J* 7.6 Hz), 6.16 (2 H, d, *J* 8.1 Hz), 7.30 (2 H, br s), 7.40 (2 H, br s), and 7.76 (2 H, d, *J* 7.5 Hz); $\delta_C[(CD_3)_2SO]$ 57.48, 61.15, 71.53, 85.94, 87.69, 94.69, 141.35, 155.44, and 165.40.

2'-*Deoxy*-4,4-di-N-*methyl*-2'-(9-*phenylxanthen*-9-*ylthio*)*cytidine* (**11b**).—The above triazolo compound (**10**) (1.305 g, 2.00 mmol) was dissolved in a 30% solution of dimethylamine in dioxane (20 ml) at room temperature. After 17 h, the products were concentrated under reduced pressure and the residue was dissolved in methanolic ammonia (20 ml; prepared by saturating methanol with ammonia at 0 °C and diluting the solution with an equal volume of methanol) at room temperature. After a further period of 17 h, the products were evaporated under reduced pressure and the residue was crystallized from methanol to give the *title compound* (0.87 g, 80%) (Found: C, 66.5; H, 5.3; N, 7.6. $C_{30}H_{29}N_3O_5S$ requires C, 66.3; H, 5.4; N, 7.7%) as crystals, m.p. 213 °C; $\delta_H[(CD_3)_2SO]$ 3.07 (6 H, br s), 3.16 (2 H, m), 3.29 (2 H, m), 3.75 (1 H, m), 4.85 (1 H, m), 5.28 (1 H, d, *J* 4.5 Hz), 5.60 (1 H, d, *J* 7.8 Hz), 6.04 (1 H, d, *J* 10.0 Hz), 6.70 (1 H, m), and 6.95–7.45 (13 H, m); $\delta_C[(CD_3)_2SO–CD_3OD]$ 37.37, 38.13, 53.79, 57.08, 63.16, 73.23, 87.91, 94.44, 116.87, 117.23, 124.36, 124.50, 126.16, 126.25, 127.97, 129.12, 129.58, 129.84, 131.62, 132.32, 140.74, 148.01, 151.35, 151.50, 157.40, and 164.20.

2'-*Deoxy*-2'-*mercapto*-4,4-*di*-N-*methylcytidine* (**2b**).—Conc. hydrochloric acid (0.2 ml) was added to a stirred solution of 2'-deoxy-4,4-di-*N*-methyl-2'-(9-phenylxanthen-9-thio)cytidine (0.271 g, 0.50 mmol) in 2-mercaptoethanol (5 ml) at room temperature. After 48 h, absolute ethanol (2 ml) was added and the products were concentrated under reduced pressure to *ca.* 1 ml. The residual solution was added dropwise to stirred light petroleum (40–60 °C)–ether (1:1 v/v; 10 ml). The resulting precipitate was collected by centrifugation, washed several times with light petroleum (40–60 °C)–ether (1:1 v/v) and then dried to give the title compound (0.146 g, 90%); [FAB] *m/z* 288 $(M - Cl)^+$; $\delta_H[(CD_3)_2SO]$ *inter alia* 3.25 (6 H, s), 3.57 (1 H, m), 3.61 (2 H, m), 3.99 (1 H, m), 4.14 (1 H, dd, *J* 2.0, 5.1 Hz), 5.95 (1 H, d, *J* 8.0 Hz), 6.40 (1 H, d, *J* 8.2 Hz), and 8.09 (1 H, d, *J* 8.1 Hz); $\delta_C[(CD_3)_2SO]$ 39.61, 40.47, 45.72, 60.86, 71.28, 86.86, 90.07, 93.73, 142.48, 148.84, and 157.01.

Bis-(2'-*deoxy*-4,4-*di*-N-*methylcytidin*-2'-*yl*) *Disulphide* (**12b**).—Triethylamine (0.055 ml, 0.4 mmol) and 2'-deoxy-2'-mercapto-4,4-di-*N*-methylcytidine hydrochloride (0.086 g, 0.27 mmol) were dissolved in methanol (1 ml) at room temperature. After 16 h, the discoloured crystalline precipitate was collected by filtration and recrystallized from methanol to give the *title compound* (0.073 g, 96%) (Found: C, 46.0; H, 5.6; N, 14.4. $C_{22}H_{32}N_6O_8S_2$ requires C, 46.1; H, 5.6; N, 14.7%), m.p. 220 °C; $\delta_H[(CD_3)_2SO]$ 3.06 (12 H, s), 3.56 (4 H, m), 3.64 (2 H, dd, *J* 5.5, 8.1 Hz), 3.83 (2 H, m), 4.25 (2 H, m), 5.08 (2 H, m), 5.73 (2 H, d, *J* 4.9 Hz), 6.06 (2 H, d, *J* 7.9 Hz), 6.16 (2 H, d, *J* 8.1 Hz), and 7.82 (2

H, d, J 7.8 Hz); $\delta_C[(CD_3)_2SO]$ 36.55, 37.49, 57.56, 61.22, 71.60, 86.03, 87.86, 92.14, 141.59, 154.68, and 163.04.

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