Synthesis of 3′,5′-dithiothymidine and related compounds

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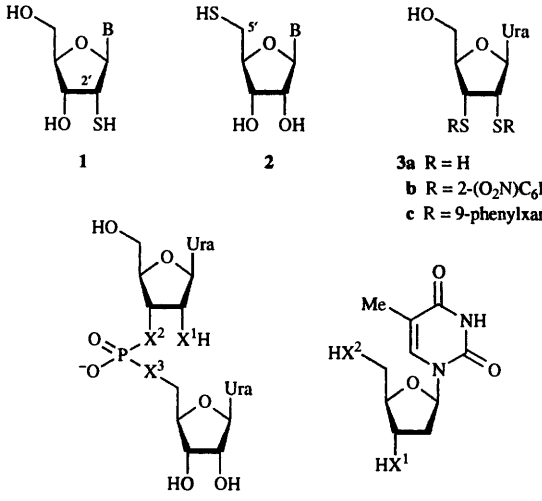
When 3′,5′-di-*O*-mesylthymidine 7 is heated first with triethylamine in ethanol solution and then with the sodium salt of 4-methoxyphenylmethanethiol 9 in *N*,*N*-dimethylacetamide (DMA) solution, the bis-(sulfide) 11a is obtained in high yield; when the dimesyl ester 7 is treated with the same thiolate salt in hexamethylphosphoric triamide (HMPA) solution at room temperature, the *threo*-bis(sulfide) 12a is obtained stereospecifically. Treatment of the two bis(sulfides) 11a and 12a first with 2-nitrobenzene-sulfenyl chloride 10 in acetic acid–dichloromethane (1 : 9 v/v) at 0 °C and then with zinc in hot acetic acid gives 3′,5′-dithiothymidine 5a and the cyclic disulfide 16, respectively, as crystalline solids in good overall yields. Although attempts to isolate the pure *threo*-dithio compound 12b lead to the formation of the cyclic disulfide 16, when the crude material is treated with 2,2-dimethoxypropane in the presence of acid, its 3′,5′-*S*-isopropylidene derivative 17 is obtained and isolated as a crystalline solid in good overall yield.

Introduction

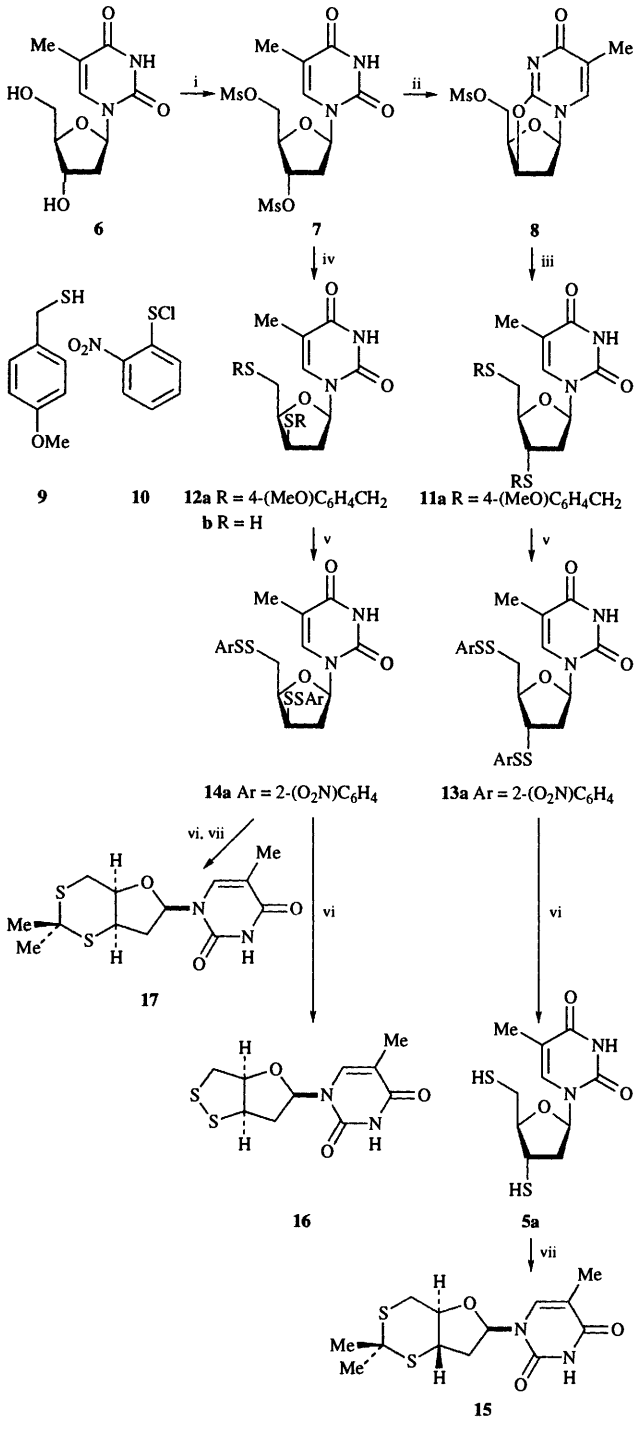
The potential value of nucleoside analogues as antitumour and antiviral agents has stimulated much interest in their synthesis. In the past decade or so, this area of study has been considerably activated by the search for compounds with anti-human immunodeficiency virus (anti-HIV) activity.[1,2] In connection with our interest in nucleoside chemistry, we have directed our attention towards one of the simplest possible nucleoside modifications, that is, the replacement of one or more of the sugar hydroxy functions by thiol groups. In earlier studies, we concerned ourselves with ribonucleoside derivatives and developed methods for the synthesis of 2′-thioribonucleosides[3,4] **1**, their 5′-isomers[5] **2** and 2′,3′-dithiouridine[6] **3a**. In what we considered to be a fundamental study in RNA chemistry, we also synthesized[7–9] three isomeric sulfur-containing uridylyl-(3′→5′)-uridine analogues **4a–c**, and examined their reactions with acids, bases and phosphorolytic enzymes. Very recently, we have turned our attention towards thio analogues of 2′-deoxyribonucleosides and now report the synthesis of 3′,5′-dithiothymidine **5a** and related compounds. While there are a number of reports in the literature relating to the synthesis both of 2′-deoxy-3′-thio- and 2′-deoxy-5′-thio-nucleosides, such as 3′-thiothymidine[10] **5b** and 5′-thiothymidine[11] **5c**, we are unaware of any previous reports relating to the synthesis of 2′-deoxy-3′,5′-dithionucleosides.



Results and discussion

Unless considerable care is taken to exclude atmospheric oxygen, we have found[3] that it is advisable to generate free thionucleosides under acidic conditions. We have developed a convenient procedure for converting *S*-(4-methoxybenzyl) derivatives of thiols into the free thiols in good yields, and have used a modification of our published procedure[6] in the preparation of 3′,5′-dithiothymidine **5a** (Scheme 1). Thymidine **6** was first converted into its 3′,5′-di-*O*-mesyl derivative **7** by treatment with methanesulfonyl chloride in pyridine solution. When the crude product **7** was heated, under reflux, with an excess of triethylamine in ethanol solution, the 5′-*O*-mesyl-2,3′-anhydronucleoside **8** was obtained and isolated as a crystalline solid in 84.5% overall yield for the two steps starting from thymidine. The derived bis-*S*-(4-methoxybenzyl) derivative **11a** was obtained as a glass in ~90% yield when the anhydro-nucleoside derivative **8** was heated with the sodium salt of 4-methoxyphenylmethanethiol **9** in DMA solution at 100 °C. Not surprisingly, this reaction was stereospecific and none of the 3′-*threo* diastereoisomer **12a** was obtained. However, it was particularly interesting to find that the sodium salt of 4-methoxyphenylmethanethiol **9** also reacted stereospecifically with 3′,5′-di-*O*-mesylthymidine **7** in HMPA solution at room temperature to give exclusively the 3′-*threo* diastereoisomer **12a** in 80% overall yield for the two steps starting from thymidine **6**. Such complete control of stereochemistry was not observed when the dimesyl derivative **7** was heated with the conjugate base of the thiol **9** in DMA solution. Most probably, under the latter conditions, formation of the 2,3′-anhydronucleoside derivative **8** competed to some extent with the direct attack of thiolate ions on C-3′ of the dimesyl compound **7**.

In an earlier approach to thionucleoside synthesis, we found[3] that *S*-(*tert*-butyl) derivatives of thionucleosides reacted relatively slowly with 2-nitrobenzenesulfenyl chloride **10** in glacial acetic acid solution at room temperature to give the corresponding *S*-(2-nitrophenylsulfanyl) derivatives which may readily be converted (see below) into free thionucleosides. We have since found[12] that *S*-(4-methoxybenzyl) derivatives of thionucleosides, which may be converted directly[3] into free thionucleosides under rather drastic acidic conditions, react



Scheme 1 *Reagents and conditions:* i, $MeSO_2Cl$, C_5H_5N, 0 °C, 15 h; ii, Et_3N, EtOH, reflux, 18 h; iii, **9**, NaH, DMA, 100 °C, 30 min; iv, **9**, NaH, HMPA, argon, room temp., 24 h; v, **10**, AcOH–CH_2Cl_2 (1:9 v/v), 0 °C, 1 h; vi, Zn dust, AcOH–water (4:1 v/v), 75 °C, 2 h; vii, $Me_2C(OMe)_2$, CSA, MeCN, room temp., 18 h

with 2-nitrobenzenesulfenyl chloride **10** much more readily[6,8] than do *S*-(*tert*-butyl) derivatives.[3,12] Thus, when the bis-*S*-(4-methoxybenzyl) derivative **11a** was treated with ~3 mol equiv. of 2-nitrobenzenesulfenyl chloride **10** in acetic acid–dichloromethane (1:9 v/v) solution at 0 °C for 1 h, the desired bis-disulfide **13a** was obtained and isolated as a yellow solid in 94% yield. Under the same conditions, the isomeric *threo*-bis-*S*-(4-methoxybenzyl) compound **12a** was converted into the corresponding bis-*S*-(2-nitrophenylsulfanyl) derivative **14a**, which was also isolated as a yellow solid and in comparable (95%) yield.

We have already described two procedures for the conversion of 2-nitrophenylsulfanyl derivatives into free thionucleosides. The first procedure[3] involved treatment with 2-mercaptoethanol and triethylamine in methanol solution and, unless considerable precautions were taken to exclude atmospheric oxygen, there was a serious risk that the product would undergo oxidative dimerization. A much safer procedure was used[6] in the preparation of 2′,3′-dithiouridine **3a**. This involved treating the intermediate 2-nitrophenylsulfanyl derivative (*i.e.*, **3b**) with triphenylphosphine[4,5,13] and 9-phenylxanthen-9-ol in acetic acid–water (99:1 v/v) at 60 °C for 30 min to give the corresponding bis(9-phenylxanthen-9-yl) derivative (*i.e.*, **3c**). The 9-phenylxanthen-9-yl protecting groups were then removed by treatment with pyrrole[14] in glacial acetic acid solution at 70 °C. We now describe a much simpler and equally safe procedure. When the bis-*S*-(2-nitrophenylsulfanyl) derivative **13a** was treated with a large excess of zinc dust in acetic acid–water (4:1 v/v) solution at 75 °C for 2 h, 3′,5′-dithiothymidine **5a** was obtained and readily isolated as a crystalline solid in 92% yield. Presumably, under these reaction conditions, reduction of the nitro group occurred as well as reductive cleavage of the sulfur–sulfur bond. However, no attempt was made to confirm the putative presence of 2-amino(thiophenol) in the products. The characterization of 3′,5′-dithiothymidine **5a** is based on ^1H and ^{13}C NMR spectroscopic evidence and on microanalytical data. The resonance signals assigned to the 3′- and 5′-SH protons overlap with the 5′-H resonance signals at δ ~2.8 in the ^1H NMR spectrum of compound **5a**. However, the structural assignment is well supported[5,6,10] by the C-5′ and C-3′ resonance signals at δ_C 25.5 and 37.2, respectively, in the ^{13}C NMR spectrum of **5a**. In further confirmation of the assigned structure, when 3′,5′-dithiothymidine was treated with 2,2-dimethoxypropane in the presence of a catalytic amount of (±)-camphor-10-sulfonic acid (CSA) in acetonitrile solution, its 3′,5′-*S*-isopropylidene derivative **15** was obtained and isolated as a solid in 94% yield. 3′,5′-*O*-Isopropylidene derivatives of simple 2′-deoxyribonucleosides (*e.g.*, thymidine **6**) and ribonucleosides are to the best of our knowledge unknown, presumably because the resulting *trans*-fused six- and five-membered ring systems would be particularly strained. Due to the larger size of the 3′- and 5′-sulfur atoms, the *trans*-fused ring system in 3′,5′-*S*-isopropylidene derivatives of 3′,5′-dithionucleosides (*e.g.*, compound **15**) would be expected to be much less strained.

When the *threo*-bis(2-nitrophenylsulfanyl) derivative **14a** was heated with zinc dust in acetic acid–water (4:1 v/v) at 75 °C, free 1-(2-deoxy-3,5-dithio-β-D-*threo*-pentofuranosyl)-thymine **12b** was obtained. However, all attempts to purify the latter compound by chromatography on silica gel led to the isolation of the known cyclic disulfide[15] **16** which was obtained as a crystalline solid in 91% yield. The fact that the free *threo*-dithionucleoside **12b** was indeed obtained was demonstrated by trapping it as its 3′,5′-*S*-isopropylidene derivative **17**. Thus, following the reduction of bis(disulfide) **14a** with zinc dust in acetic acid–water (4:1 v/v), the products were worked up and treated directly with 2,2-dimethoxypropane and CSA in acetonitrile solution, in an atmosphere of argon, without prior chromatographic purification. In this way, the 3′,5′-*S*-isopropylidene derivative **17** was obtained and isolated as a crystalline solid in 87% overall yield, based on the bis(2-nitrophenylsulfanyl) derivative **14a**.

In conclusion, we believe that the methods that we have described in this article should find more general application in the preparation of other nucleoside thiols, and in the conversion of other relatively sensitive alcohols into the corresponding thiols.

Experimental

Mps were measured with a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra, unless otherwise stated, were measured at 360 MHz with a Bruker AM 360

spectrometer; ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Tetramethylsilane was used as the internal standard, and J values are given in Hz. Merck silica gel 60 F_{254} plates were developed in solvent systems A [chloroform–methanol (19:1 v/v)] and B [chloroform–methanol (4:1 v/v)]. Merck silica gel H was used for short-column chromatography. Pyridine and triethylamine were dried by heating, under reflux, over calcium hydride and were then distilled; DMA and HMPA were dried by distillation over calcium hydride under reduced pressure.

1-(2,3′-Anhydro-5′-*O*-methylsulfonyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine 8

Methanesulfonyl chloride (9.3 cm^3, 0.12 mol) was added dropwise over a period of 15 min to a cooled (ice–water-bath) solution of thymidine (13.26 g, 54.7 mmol) in dry pyridine (180 cm^3). The cooled reactants were then stirred at ~0 °C for 15 h. The products were then poured into a vigorously stirred ice–water mixture (~1500 g). The precipitated solid, which was assumed to be 3′,5′-di-*O*-(methylsulfonyl)thymidine **7**, was collected by filtration, washed with water (4 × 100 cm^3) and dried *in vacuo* over P_2O_5 at 60 °C; yield 20.29 g; R_f 0.31 (system A).

The above material (6.12 g), triethylamine (15.3 cm^3, 0.11 mol) and ethanol (153 cm^3) were heated together, under reflux, for 18 h. The products were cooled, and the precipitate was collected by filtration and washed with cold ethanol (3 × 10 cm^3) to give the *title compound* **8** (4.22 g, 84.5% overall yield based on thymidine **6**) (Found, in material crystallized from acetonitrile: C, 44.0; H, 4.6; N, 9.1. $C_{11}H_{14}N_2O_6S$ requires C, 43.7; H, 4.7; N, 9.3%), mp 186–188 °C; R_f 0.26 (system B); $\delta_H[(CD_3)_2SO]$ 1.77 (3 H, s), 2.54 (1 H, m), 2.62 (1 H, d, J 12.8), 3.21 (3 H, s), 4.22 (1 H, dd, J 8.1 and 12.2), 4.49 (2 H, m), 5.36 (1 H, s), 5.91 (1 H, d, J 3.7) and 7.60 (1 H, s); $\delta_C[(CD_3)SO]$ 13.1, 32.7, 36.7, 68.2, 77.0, 81.9, 87.9, 116.2, 136.7, 153.2 and 170.9.

3′,5′-Bis-*S*-(4-methoxybenzyl)-3′,5′-dithiothymidine 11a

4-Methoxyphenylmethanethiol **9** (4.85 cm^3, 34.8 mmol) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil; 1.10 g, 27.5 mmol) in dry DMA (20 cm^3) at 0 °C (ice–water-bath) under nitrogen. The reactants were stirred at room temperature for *ca.* 1 h after which a clear solution was obtained. The latter solution was added to a stirred suspension of 1-(2,3′-anhydro-5′-*O*-methylsulfonyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine **8** (2.73 g, 9.0 mmol) in dry DMA (15 cm^3). The reaction mixture was then heated at 100 °C. After 30 min, ethyl acetate (300 cm^3) was added to the cooled products and the resulting mixture was washed first with water (3 × 150 cm^3) and then with brine (5 × 100 cm^3). The organic layer was separated, dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with ethyl acetate–light petroleum (distillation range 40–60 °C) (30:70 to 50:50 v/v) were evaporated under reduced pressure to give the *title compound* **11a** as a glass (4.23 g, ~90%) (Found: M^+, 514.1536; $^{12}C_{26}{}^{1}H_{30}{}^{14}N_2{}^{16}O_5{}^{32}S_2$ requires M, 514.1596); R_f 0.53 (system A); $\delta_H[(CD_3)_2SO]$ 1.79 (3 H, s), 2.26 (1 H, m), 2.41 (1 H, m), 2.62 (1 H, dd, J 6.2 and 14.1), 2.76 (1 H, dd, J 4.3 and 14.1), 3.29 (1 H, m), 3.67 (2 H, s), 3.72 (6 H, s), 3.79 (2 H, s), 3.89 (1 H, m), 6.11 (1 H, m), 6.86 (4 H, m), 7.19 (2 H, d, J 8.4), 7.26 (2 H, d, J 8.4), 7.47 (1 H, s) and 11.37 (1 H, s); $\delta_C[(CD_3)_2SO]$ 12.2, 33.2, 34.1, 35.3, 37.4, 44.4, 55.0, 83.3, 83.5, 109.8, 113.7, 113.8, 129.9, 130.0, 136.1, 150.4, 158.2, 158.3 and 163.7.

1-[3′,5′-Bis-*S*-(4-methoxybenzyl)-2-deoxy-3,5-dithio-β-D-*threo*-pentofuranosyl]thymine 12a

4-Methoxyphenylmethanethiol **9** (5.55 cm^3, 40 mmol) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil; 1.20 g, 30 mmol) in dry HMPA (40 cm^3) at 0 °C (ice–water-bath) under argon. The reactants were stirred at room temperature for *ca.* 1 h after which a clear solution was obtained. Putative 3′,5′-bis-*O*-(methylsulfonyl)-thymidine **7** (see above under the preparation of compound **8**; 3.98 g, ~10 mmol) was added to the latter solution and the reactants were stirred at room temperature. After 24 h, ethyl acetate (400 cm^3) was added and the resulting mixture was washed with water (3 × 200 cm^3). The organic layer was separated, dried, and evaporated under reduced pressure. The residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with ethyl acetate–light petroleum (40–60 °C) (1:1 v/v), were evaporated under reduced pressure to give the *title compound* **12a** as a solid (4.43 g, 80% overall yield based on thymidine **6**) [Found, in material crystallized from ethyl acetate–light petroleum (40–60 °C): C, 60.6; H, 5.85; N, 5.4. $C_{26}H_{30}N_2O_5S_2$ requires C, 60.7; H, 5.9; N, 5.4%], mp 120–122 °C; R_f 0.46 (system A); $\delta_H[(CD_3)_2SO]$ 1.78 (3 H, d, J 0.9), 2.03 (1 H, m), 2.60 (1 H, m), 2.70 (2 H, m), 3.47 (1 H, dd, J 6.3 and 12.8), 3.73 (10 H, m), 4.16 (1 H, m), 5.98 (1 H, t, J 6.5), 6.87 (4 H, m), 7.21 (4 H, m), 7.61 (1 H, m) and 11.34 (1 H, s); $\delta_C[(CD_3)_2SO]$ 12.3, 32.4, 34.9, 35.1, 37.3, 44.6, 55.0, 80.2, 83.1, 109.3, 113.8, 129.8, 130.0, 130.2, 136.1, 150.5, 158.2, 158.3 and 163.7.

3′,5′-Bis-*S*-(2-nitrophenylsulfanyl)-3′,5′-dithiothymidine 13a

2-Nitrobenzenesulfenyl chloride **10** (4.69 g, 24.7 mmol) and 3′,5′-bis-*S*-(4-methoxybenzyl)-3′,5′-dithiothymidine **11a** (4.14 g, 8.04 mmol) were stirred together in acetic acid–dichloromethane (1:9 v/v; 50 cm^3) solution at 0 °C (ice–water-bath). After 1 h, the products were evaporated under reduced pressure. The residue was triturated with diethyl ether (50 cm^3) to give the *title compound* **13a** as a yellow solid (4.04 g, 94%) [Found, in material crystallized from tetrahydrofuran (THF)–methanol: C, 45.2; H, 3.4; N, 9.3. $C_{22}H_{20}N_4O_7S_4$ requires C, 45.5; H, 3.5; N, 9.65%], mp 186–189 °C; R_f 0.49 (system A); $\delta_H[(CD_3)_2SO]$ 1.76 (3 H, d, J 0.6), 2.39 (1 H, m), 2.55 (1 H, m), 3.19 (1 H, dd, J 7.7 and 14.0), 3.29 (1 H, dd, J 4.2 and 14.0), 3.81 (1 H, m), 4.07 (1 H, m), 6.10 (1 H, dd, J 5.5 and 7.3), 7.51 (3 H, m), 7.83 (2 H, m), 8.24 (4 H, m) and 11.35 (1 H, s); $\delta_C[(CD_3)_2SO]$ 12.1, 35.8, 40.9, 49.2, 81.7, 83.7, 109.9, 126.1, 126.2, 127.1, 127.2, 127.3, 134.8, 134.9, 135.5, 135.9, 136.3, 145.0, 150.3 and 163.6.

1-[3′,5′-Bis-*S*-(2-nitrophenylsulfanyl)-2-deoxy-3,5-dithio-β-D-*threo*-pentofuranosyl]thymine 14a

2-Nitrobenzenesulfenyl chloride **10** (4.54 g, 23.9 mmol) and 1-[3′,5′-bis-*S*-(4-methoxybenzyl)-2-deoxy-3,5-dithio-β-D-*threo*-pentofuranosyl]thymine **12a** (4.12 g, 8.0 mmol) were stirred together in acetic acid–dichloromethane (1:9 v/v, 50 cm^3) solution at 0 °C (ice–water-bath). After 1 h, the products were evaporated under reduced pressure. The residue was triturated with diethyl ether (100 cm^3) to give the *title compound* **14a** as a yellow solid (4.45 g, 95%) (Found, in material crystallized from THF–methanol: C, 45.6; H, 3.4; N, 9.4. $C_{22}H_{20}N_4O_7S_4$ requires C, 45.5; H, 3.5; N, 9.65%), mp 190–192 °C; R_f 0.49 (system A); $\delta_H[(CD_3)_2SO]$ 1.79 (3 H, d, J 0.9), 2.24 (1 H, m), 2.73 (1 H, m), 3.39 (2 H, m), 3.90 (1 H, dd, J 6.3 and 13.3), 4.39 (1 H, m), 5.91 (1 H, t, J 6.5), 7.52 (3 H, m), 7.85 (2 H, m), 8.17 (1 H, dd, J 1.1 and 8.2), 8.29 (3 H, m) and 11.37 (1 H, s); $\delta_C[(CD_3)_2SO]$ 12.2, 36.7, 40.1, 50.6, 78.7, 83.2, 109.6, 126.1, 126.3, 127.2, 127.3, 127.4, 134.9, 135.0, 135.2, 135.6, 136.0, 145.0, 145.3, 150.3 and 163.6.

3′,5′-Dithiothymidine 5a

Zinc dust (4.18 g, 0.064 g atom), 3′,5′-bis-*S*-(2-nitrophenylsulfanyl)-3′,5′-dithiothymidine **13a** (2.32 g, 4.0 mmol) and acetic acid–water (4:1 v/v; 50 cm^3) were stirred and heated together at 75 °C. After 2 h, the products were cooled, and evaporated under reduced pressure. The residue was partitioned between dichloromethane (50 cm^3) and hydrochloric acid (~3 mol dm^{-3}; 150 cm^3). The aqueous layer was back-extracted with dichloromethane (5 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), and concentrated under

reduced pressure. The residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with chloroform–acetic acid (99.9:0.1 to 99.5:0.5 v/v), were evaporated under reduced pressure to give the *title compound* **5a** as a solid (1.01 g, 92%) [Found, in material crystallized from ethanol–acetic acid (99.9:0.1 v/v): C, 43.65; H, 5.1; N, 10.0. $C_{10}H_{14}N_2O_3S_2$ requires C, 43.8; H, 5.1; N, 10.2%], mp 163–166 °C; R_f 0.10 (system A); δ_H[$(CD_3)_2SO$–D_2O] 1.80 (3 H, d, *J* 0.9), 2.29 (1 H, m), 2.50 (1 H, m), 2.80 (1 H, dd, *J* 6.1 and 14.1), 2.94 (1 H, dd, *J* 3.9 and 14.1), 3.41 (1 H, m), 3.78 (1 H, m), 6.13 (1 H, dd, *J* 4.2 and 7.8) and 7.54 (1 H, m); δ_C[$(CD_3)_2SO$] 12.3, 25.5, 37.2, 40.6, 82.9, 87.6, 110.0, 136.5, 150.5 and 163.9.

3′,5′-*S*-Isopropylidene-3′,5′-dithiothymidine 15

2,2-Dimethoxypropane (0.49 cm^3, 4.0 mmol), 3′,5′-dithiothymidine **5a** (0.549 g, 2.0 mmol), CSA (0.093 g, 0.4 mmol) and dry acetonitrile (10 cm^3) were stirred together at room temperature. After 18 h, the products were concentrated under reduced pressure and the residue was partitioned between chloroform (50 cm^3) and saturated aq. sodium hydrogen carbonate (50 cm^3). The aqueous layer was back-extracted with chloroform (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$), and evaporated under reduced pressure. The residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with chloroform, were evaporated under reduced pressure to give the *title compound* **15** as a solid (0.595 g, 94%) (Found, in material crystallized from aq. methanol: C, 49.7; H, 5.7; N, 8.7. $C_{13}H_{18}N_2O_3S_2$ requires C, 49.7; H, 5.8; N, 8.9%), mp 191–192.5 °C; R_f 0.43 (system A); δ_H[$(CD_3)_2SO$] 1.54 (3 H, s), 1.84 (3 H, s), 1.94 (3 H, s), 2.16 (2 H, m), 2.93 (1 H, dd, *J* 3.3 and 12.9), 3.30 (1 H, dd, *J* 11.1 and 12.8), 3.45 (1 H, m), 3.73 (1 H, m), 6.10 (1 H, dd, *J* 3.2 and 7.9), 7.53 (1 H, m) and 11.21 (1 H, s); δ_C[$(CD_3)_2SO$] 12.0, 29.1, 29.4, 32.5, 35.2, 40.1, 49.8, 80.8, 81.6, 110.0, 136.3, 150.4 and 163.7.

1-(3,5-Epidithio-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl)-thymine 16

Zinc dust (2.09 g, 0.032 g-atom), 1-[3′,5′-bis-*S*-(2-nitrophenylsulfanyl)-2-deoxy-3,5-dithio-β-D-*threo*-pentofuranosyl]-thymine **14a** (1.16 g, 2.0 mmol) and acetic acid–water (4:1 v/v, 25 cm^3) were stirred and heated together at 75 °C. After 2 h, the products were worked-up as in the above preparation of 3′,5′-dithiothymidine **5a** and fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with chloroform–methanol (99:1 v/v), were evaporated under reduced pressure to give the title compound **16** (0.50 g, 91%) [Found, in material crystallized from dimethyl sulfoxide–water (1:1 v/v), washed with water and dried *in vacuo* over P_2O_5: C, 43.8; H, 4.4; N, 10.1. Calc. for $C_{10}H_{12}N_2O_3S_2$: C, 44.1; H, 4.4; N, 10.3%], mp 252 °C (decomp.) [lit.,[15] 259–263 °C (decomp.)]; R_f 0.42 (system A); δ_H[$(CD_3)_2SO$] 1.78 (3 H, s), 1.91 (1 H, m), 2.80 (1 H, m), 2.95 (1 H, dd, *J* 3.6 and 12.8), 3.52 (1 H, d, *J* 12.9), 4.38 (1 H, m), 4.97 (1 H, m), 5.97 (1 H, m), 7.51 (1 H, m) and 11.39 (1 H, br s); δ_C[$(CD_3)_2SO$] 12.4, 38.7, 48.7, 55.2, 82.2, 86.0, 110.0, 135.0, 150.2 and 163.6.

1-(3′,5′-*S*-Isopropylidene-2-deoxy-3,5-dithio-β-D-*threo*-pentofuranosyl)thymine 17

Zinc dust (5.23 g, 0.080 g-atom), 1-[3′,5′-bis-*S*-(2-nitrophenylsulfanyl)-2-deoxy-3,5-dithio-β-D-*threo*-pentofuranosyl]thymine **14a** (2.90 g, 5.0 mmol) and acetic acid–water (4:1 v/v; 65 cm^3) were stirred and heated together at 75 °C. After 2 h, the products were worked up as in the above preparation of 3′,5′-dithiothymidine **5a**. The residue obtained was not chromatographed but was co-evaporated with toluene (2 × 25 cm^3) under argon. The residue was dissolved in dry acetonitrile (50 cm^3), also under argon, and 2,2-dimethoxypropane (3.06 cm^3, 24.9 mmol) and CSA (0.232 g, 1.0 mmol) were added. The resulting solution was stirred at room temperature. After 18 h, the products were evaporated under reduced pressure and the residue was partitioned between chloroform (150 cm^3) and saturated aq. sodium hydrogen carbonate (150 cm^3). The aqueous layer was separated and back-extracted with chloroform (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), and evaporated under reduced pressure. The residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with dichloromethane–methanol (99:1 v/v), were evaporated under reduced pressure to give the *title compound* **17** (1.38 g, 87%) [Found, in material crystallized from ethyl acetate–light petroleum (40–60 °C): C, 49.85; H, 5.9; N, 9.0. $C_{13}H_{18}N_2O_3S_2$ requires: C, 49.7; H, 5.8; N, 8.9%], mp 171–173 °C; R_f 0.46 (system A); δ_H[$(CD_3)_2SO$] 1.55 (3 H, s), 1.68 (3 H, s), 1.72 (1 H, m), 1.79 (3 H, s), 2.82 (1 H, m), 3.12 (1 H, dd, *J* 6.1 and 14.8), 3.29 (1 H, dd, *J* 3.9 and 14.9), 3.77 (1 H, m), 4.19 (1 H, m), 5.95 (1 H, dd, *J* 3.7 and 7.3), 7.93 (1 H, m) and 11.29 (1 H, br s); δ_C[$(CD_3)_2SO$] 12.3, 28.5, 31.2, 31.5, 37.6, 38.7, 48.3, 71.5, 83.3, 107.8, 136.8, 150.3 and 163.8.

Acknowledgements

We thank the Medical Research Council AIDS Directed Programme for generous support of this research.

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Paper 6/02558G
Received 12*th April* 1996
Accepted 21*st May* 1996