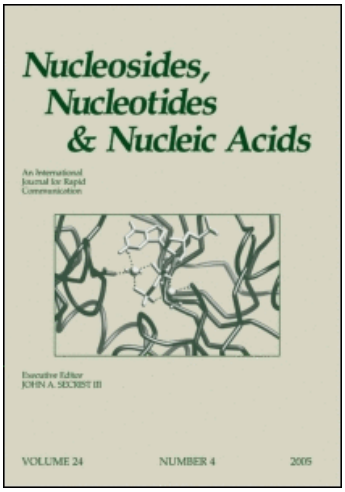

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A Short Syhthesis of 3'-(Methylsulfinyl)-3'-Deoxythymidine and Related Analogues

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A SHORT SYHTHESIS OF 3'-(METHYLSULFINYL)-3'-DEOXYTHYMIDINE AND RELATED ANALOGUES

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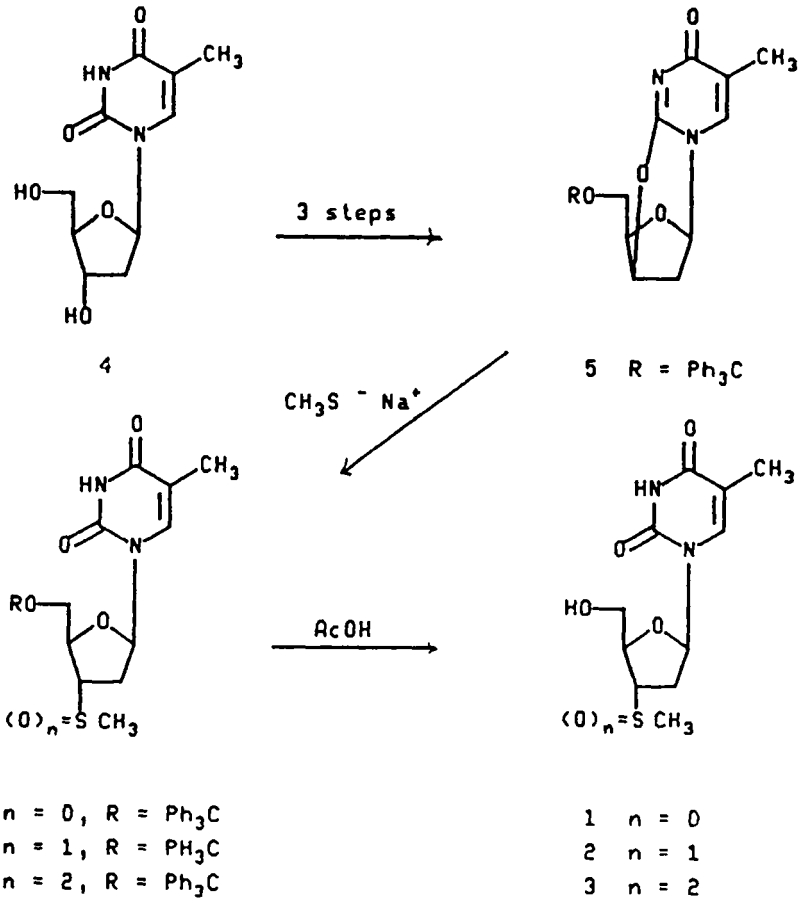
Abstract: The ring opening of the O-2,3'-anhydrothymidine **5** with the anion of methyl mercaptan gave the 3'-methylthio derivaative **6**. Subsequent oxidation and deprotection afforded 3'-(methylsulfinyl)-3'-deoxythymidine **2** and its sulfone analogue **3**.

3'-Azido-3'-deoxythymidine (AZT), a thymidine analogue in which the 3'-OH has been replaced by an azido group, is currently the only drug licensed for the treatment of AIDS.[1,2] In cells, AZT is metabolized to the triphosphate, AZT-TP, and this triphosphate can act as an inhibitor of the unique viral enzyme reverse transcriptase (RT), and thus in vivo replication.[3] The success of AZT has led to an interest in other purine and pyrimidine analogues as possible agents active against human immunodeficiency virus (HIV). 3'-Fluoro-3'-deoxythymidine (FddT)[4] and 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (d4T)[5] are other 3'-deoxythymidine analogues which have shown potent anti-HIV activity. The replacement of the 3'-OH by another substituent, however, does not guarantee biological activity. For example 3'-cyano-3'-deoxythymidine (CNT), is reported to be inactive.[6]

We have recently prepared three novel sulfur containing thymidine analogues, **1** - **3**, as potential anti-HIV agents. These analogues are especially interesting because they allow the study of the effect of polarity of the 3'-substituent within the same series of derivatives.

5'-O-Trityl-O-2,3'-anhydrothymidine (**5**) was chosen as the key intermediate to this series of compounds since direct nucleophilic S_N2 opening of the O-2,3'-anhydro bond guarantees the correct α stereochemistry for the incoming 3'-substituent. The anhydro compound **5** was readily prepared by a published procedure in 3 steps from thymidine (**4**) in 75 % overall yield without chromatography.[7] Reaction of **5** with a large excess of sodium methyl mercaptide at 100 °C for 16 h in DMF,[8] gave **6** in 45 % yield after chromatographic purification. 5'-O-Trityl-3'-epithymidine, which resulted from hydrolysis of the C-2,O-2-bond in **5** was the major side product. The ^{1}H NMR of the desired product clearly showed the upfield shift of the 3'-proton absorption from 5.27 ppm in **5** to 3.5 ppm in **6**, indicating that the sulfur was at the 3'-position. The absorption of the thiomethyl group in **6** appeared as a singlet slightly downfield from the methyl group on the thymine base. The 3'-proton resonance of **6** appeared as a quartet. Irradiation of the 4'-proton signal collapses the 3'-proton absorption to a apparent triplet.

Selective oxidation of **6** to either **7** or **8** was achieved by using the correct stoichiometric amount of m-chloroperoxybenzoic acid in methylene chloride at room temperature.[9a] The yields of **7** and **8** were greater than 80 % and no oxidation of the base moiety was seen.[9b] The ^{1}H NMR of these compounds showed downfield shifts of the thiomethyl group by 0.36 ppm for the sulfoxide **7** and 0.77 ppm for the sulfone **8** relative to the parent derivative **6**. The ^{13}C NMR also exhibited large downfield shifts of the C-3' absorption from 42.29 ppm in **6** to 53.55 ppm and 61.55 ppm for **7** and **8**, respectively. Both **7** and **8** proved easy to isolate by flash column chromatography. The sulfone **8** was less polar than the sulfoxide **7**; both were more polar than **6**. The sulfoxide was shown to be a 1:1 mixture of diastereomers by ^{1}H NMR which co-eluted during the chromatographic purification.



Scheme 1

Deprotection of 6, 7, and 8 with AcOH/H_2O gave 1, 2 and 3 in 50, 67, and 80 % yields, respectively. The compounds were isolated as the free nucleosides after removal of the solvent, trituration with diethyl ether to remove trityl alcohol, and recrystallization. The diastereomeric mixture of the sulfoxides was not enriched after deprotection and recrystallization.

The compounds 1, 2 and 3, which represent a new series of 3'-substituted thymidine analogues, were found to have no activity when tested in vitro against HIV (LAV strain) infected CEM cells.

EXPERIMENTAL

Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. TLC was performed on silica gel 60 F-254 plates purchased from E. Merck Co., and column chromatography was performed on flash silica gel (40-μM particle size, Baker Co.). Elemental analysis were performed by the Analytical Research Department, Bristol-Myers, Wallingford, CT. Mass spectra were recorded on a Finnegan 4500, and the high resolution measurements were recorded on a Kratos MS 25. NMR spectra were recorded on a 300 Bruker NMR and were provided by the Analytical Research Department, Bristol-Myers Co., Wallingford, CT. Chemical shifts are reported in parts per million downfield from tetramethylsilane.

3'-(Thiomethyl)-5'-O-trityl-3'-deoxythymidine (6)

5'-O-Trityl-O-2,3'-anhydrothymidine (5)[7] (2 g, 4.29 mmol) was added in one portion to a solution of sodium ethoxide (2.7 g, 40.29 mmol), ethanol (10 mL), and methyl mercaptan (10 mL) in DMF (15 mL). The solution was heated at 100 °C for 16 h under argon. The solvents were then removed in vacuo and water (20 mL) was added. The product was extracted into methylene chloride and the organic layer was dried (Na_2SO_4). After filtration, the solution was concentrated to leave a yellow oil, which was purified by flash column chromatography on silica gel, ethyl acetate/hexane (4:1). The desired product was isolated as a white solid (1.02 g, 45 %); mp >215 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) 8.16 (br s, 1 H, NH), 7.71 (s, 1 H, H-6), 7.42 - 7.23 (m, 15 H, trityl), 6.15 (dd, 1 H, J = 6.5 Hz, J = 4.4 Hz, H-1'), 3.94 (m, 1 H, H-4'), 3.62 (dd, 1 H, J = 10.6 Hz, J = 2.2 Hz, H-5'a), 3.50 (q, 1 H, J = 8.1 Hz, H-3'), 3.34 (dd, 1 H, J = 10.7 Hz, J = 2.9 Hz, H-5'b), 2.46 (m, 2 H, H-2'), 2.00 (s, 3 H, SCH_3), 1.41 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 163.38 (C-4), 143.21 (C-2), 135.47 (C-6), 128.67, 127.99, 127.42 (3 C, trityl), 110.69 (C-5), 87.28 (trityl), 85.24 (C-4'), 84.75 (C-1'), 62.5 (C-5'), 42.29 (C-3'), 39.79 (C-2'), 14.46 (SCH_3), 11.94 (CH_3); mass spectrum m/e = 514.

3'-(Methylsulfinyl)-5'-O-trityl-3'-deoxythymidine (7)

The thioether **6** (100 mg, 0.195 mmol) was suspended in methylene chloride (2 mL) and the mixture was stirred until homogeneous. m-Chloroperoxybenzoic acid (37 mg, 0.214 mmol) was added and the reaction mixture stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue purified by flash column chromatography on silica gel using methylene chloride/methanol (10:1) as the eluent. The desired compound **7** was isolated as a white solid (95 mg, 84%); mp > 215 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) (diastereomers) 7.53 (s, 1 H, H-6), 7.42 - 7.24 (m, 15 H, trityl), 6.08 (m, 1 H, H-1'), 4.5, 4.16 (m, 1 H, H-3), 3.59 (m, 1 H, H-4'), 3.32 (m, 2 H, H-5'), 2.81, 2.51, 2.36 (m, 5 H, H-2' and $S(O)CH_3$), 1.55, 1.50 (2 s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 163.62 (C-4), 150.31 (C-2), 135.98, 135.67 (2 s, C-6), 128.30, 128.16, 128.13, 127.99, 127.89, 127.26, 127.20 (trityl), 109.79, 109.64 (2 s,C-5), 86.54, 85.49 (trityl), 84.56, 83.92 (2 s,C-4'), 78.84, 77.15 (2 s, C-1'), 65.71, 64.18 (2 s, C-5'), 59.01, 58.55 (2 s, C-3'), 39.59 (under d_6-DMSO) 36.57 (2 s, C-2'), 33.18, 27.22 (2 s, $S(O)CH_3$), 11.99, 11.87 (2 s, CH_3); mass spectrum m/e MH^+ = 531.

3'-(Methylsulfonyl)-5'-O-trityl-3'-deoxythymidine (8).

The thioether **6** (200 mg, 0.398 mmol) was suspended in methylene chloride (2 mL) and the mixture was stirred until homogeneous. m-Chloroperoxybenzoic acid (137 mg, 0.796 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was added to saturated sodium bicarbonate solution (10 mL) and the organic layer partitioned. The aqueous layer was back-extracted with ethyl acetate (5 mL). The organic layers were combined, dried ($MgSO_4$), and the solvents removed in vacuo. The residue was purified by flash column chromatography on silica gel using ethyl acetate as the eluent. The sulfone **8** was isolated as a white solid (0.180 g, 85 %); mp > 215 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) 8.03 (br s, 1 H, NH), 7.56 (s, 1 H, H-6), 7.45 - 7.20 (m, 15 H, trityl), 6.23 (t, 1 H, H-1'), 4.56 (m, 1 H, H-4'), 3.83 (m, 1 H, H-3'), 3.75 (dd, 1 H, J = 11.0 Hz, J = 2.6 Hz, H-5'a),

3.38 (dd, 1 H, J = 11.0 Hz, J = 2.9 Hz, H-5'b), 2.9 (m, 1 H, H-2'a), 2.77 (s, 3 H, $S(O)_2CH_3$), 2.45 (m, 1 H, H-2'b), 1.54 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 162.9 (C-4), 142.87 (C-2), 135.04 (C-6), 128.48, 128.07, 127.57 (trityl), 111.42 (C-5), 87.62 (trityl), 85.08 (C-4'), 77.89 (C-1'), 63.57 (C-5'), 61.66 (C-3'), 39.77 (C-2'), 33.50 ($S(O)_2CH_3$), 11.85 (CH_3), mass spectrum m/e = 548.

3'-(Thiomethyl)-3'-deoxythymidine (1)

The thioether **6** (200 mg, 0.388 mmol) was dissolved in 80% AcOH/H_2O (5 mL) and warmed over a steam bath for 0.5 h. The solvent was removed in vacuo and the resulting white residue triturated with diethyl ether (3 x 30 mL) to remove trityl alcohol. The product was recrystallized from diethyl ether/ethanol to give a white solid (50 mg, 50 %); mp 152 - 154 °C; ^1H NMR (300 MHz, CD_3OD) 7.94 (s, 1 H, H-6), 6.12 (dd, 1 H, J = 9.6 Hz, J = 4.4 Hz, H-1'), 3.90 (m, 1 H, H-4') 3.86 (m, 1 H, OH), 3.75 (dd, 1 H, J = 12.21 Hz, J = 2.6 Hz, H-5'a), 3.39 (q, 1 H, J = 8 Hz, H-3'), 3.3 (m, 1 H, H-5'b), 2.40 (m, 2 H, H-2'), 2.16 (s, 3 H, SCH_3), 1.87 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, CD_3OD/d_6-DMSO) 166.3 (C-4), 152.37 (C-2), 138.32 (C-6), 111.23 (C-5), 87.46 (C-4'), 86.04 (C-1'), 62.36 (C-5'), 43.45 (C-3'), 40.0 (C-2'), 14.44 (SCH_3), 13.02 (CH_3). Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.88; N, 10.29. Found C, 48.62; H, 5.91; N, 10.19.

3'-(Methylsulfinyl)-3'-deoxythymidine (2)

The sulfoxide **7** (95 mg, 0.179 mmol) was dissolved in 80% AcOH/H_2O (5 mL) and heated on a steam bath for 1 h. The solvents were removed in vacuo and the residue purified by flash column chromatography on silica gel using ethyl acetate/methylene chloride (10:1) as the eluent. The resulting solid was recrystallized from methanol/ethyl acetate (35 mg, 67 %); mp 252 - 254 °C (dec); ^1H NMR (300 MHz, d_6-DMSO) (diastereomers) 11.4 (s, 1H, NH), 7.8 (2s, 1H, H-6), 6.0 (t, 1H, H-1'), 5.3 (t, 1H, OH), 4.4 (m, 1H, H-4'), 3.8 (m, 1H, H-5'), 3.6 (m, 2H, H-5' and H-3'), 2.6 (2s, 3H, $S(O)CH_3$), 2.45 (m, 2H, H-2'), 1.8 (2s, 3H, CH_3); ^{13}C NMR (75.5 MHz, d_6-DMSO) 163.73 (C-4), 150.40 (C-2), 136.21, 136.06 (C-6), 109.49 (C-5), 84.26, 83.73 (2 s,

C-4'), 80.71, 78.80 (2 s, C-1'), 62.78, 61.28 (2 s, C-5'), 58.85, 58.23 (2 s, C-3'), 39.56 (under d_6-DMSO), 36.76 (2 s, C-2'), 33.39, 27.75 (2 s, $S(O)CH_3$), 12.24 (CH_3); mass spectrum m/e = 289; Anal. Calc. for $C_{11}H_{16}N_2O_5S.0.33H_2O$: C, 44.89; H, 5.66; N, 9.52. Found C, 44.93; H, 5.62; N, 9.41; high resolution mass spectrum: Calcd for $C_{11}H_{16}N_2O_5S$ = 288.0780. Found 288.0784.

3'-(Methylsulfonyl)-3'-deoxythymidine (3)

The sulfone **8** (160 mg, 0.292 mmol) was treated with 80% AcOH/H_2O (5 mL) on a steam bath. After 1 h the solvent was removed and the residue purified by flash column chromatography on silica gel using ethyl acetate as the eluent. The resulting white solid was recrystallized from ethanol to give white needles (70 mg, 79%); mp 234 -236 °C; ^1H NMR (300 MHz, d_6-DMSO) 10.75 (br s, 1 H, NH), 7.85 (s, 1 H, H-6), 6.24 (m, 1 H, H-1'), 5.42 (br s, 1 H, OH), 4.47 (m, 1 H, H-4'), 4.15 (m, 1 H, H-3'), 3.84 (m, 1 H, H-5'a), 3.72 (m, 1 H, H-5'b), 3.22 (s, 3 H, $S(O)_2CH_3$), 2.76 (m, 1 H, H-2'), 2.5 (m, 1 H, H-2'), 1.89 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, d_6-DMSO) 163.56 (C-4), 150.26 (C-2), 135.85 (C-6), 109.51 (C-5), 83.73 (C-4'), 78.21 (C-1'), 62.19 (C-5'), 61.11 (C-3'), 40.39 (C-2'), 31.98 ($S(O)_2CH_3$), 12.20 (CH_3). Anal. Calcd for $C_{11}H_{16}N_2O_6S$: C, 43.42; H, 5.26; N, 9.21. Found C, 43.15; H, 5.07;, N, 8.89.

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