Some Reactions of (5*R*)-2-Methylene-5-(thymin-1-yl)-2,5-dihydrofuran

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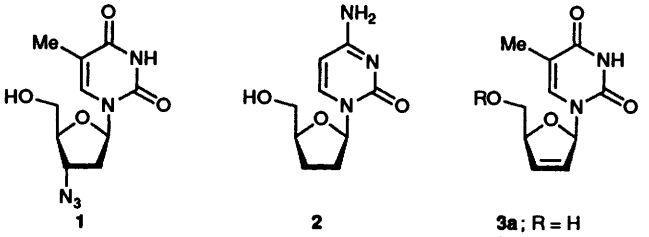
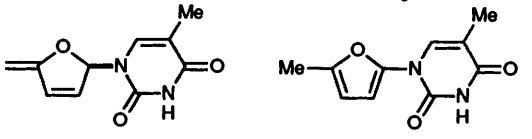
The title compound **4** was quantitatively converted into the isomeric furan derivative **5** under relatively mild acidic conditions; when compound **4** was treated with 3-chloroperbenzoic acid in dichloromethane and sodium hypochlorite in aqueous dioxane, compounds **9** and **11**, respectively, were obtained. Both compounds were isolated in 48% yield.

The fact that 2',3'-dideoxynucleosides, such as 3'-azido-3'-deoxythymidine (AZT, **1**), 2',3'-dideoxycytidine (ddC, **2**), and 2',3'-didehydro-3'-deoxythymidine (D4T, **3a**) display considerable anti-HIV activity[1,2] has recently led to a big surge in interest in the synthesis of deoxygenated nucleoside analogues. In the course of a study directed towards the modification of the base residue of D4T **3a**, we found a convenient route for the preparation of the previously reported (5*R*)-2-methylene-5-(thymin-1-yl)-2,5-dihydrofuran[3,4] **4** and have examined some of its reactions. We now report the results of our experiments.

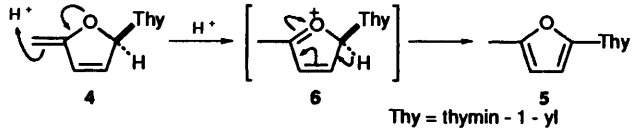


1 **2** **3a**; R = H **3b**; R = SO_2Me



4 **5**

Treatment of D4T[5] **3a** with methanesulfonyl chloride and triethylamine in dichloromethane solution at 0 °C gave its 5'-*O*-mesyl derivative **3b**, which was isolated as a crystalline solid in over 80% yield. When the latter compound **3b** was heated, under reflux, with an excess of sodium methoxide in methanol solution, (5*R*)-2-methylene-5-(thymin-1-yl)-2,5-dihydrofuran **4** was obtained and isolated in over 90% yield. Although compound **4** is a tautomer of the aromatic furan derivative **5**,[4] it displays little tendency to undergo base-catalysed isomerization except under very strongly basic conditions. Thus, we confirmed that when compound **4** was treated with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) solution at room temperature,[3,4] compound **5** was obtained as a crystalline solid in 83% isolated yield. Wang and Hogenkamp[4] have attempted to rationalize the comparative stability of compound **4** to base by arguing that the ionization of 1'-H is made more difficult by the fact that, in alkaline solution, compound **4** is present as its conjugate base due to the ionization of 3-H.

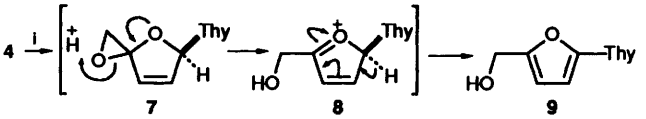


4 **6** **5**

Thy = thymin - 1 - yl

Scheme 1

It is well known[6] that the removal of the 2'- and 3'-hydroxy functions from ribonucleosides facilitates the acid-catalysed hydrolysis of their glycosidic linkages. We therefore examined the effect of aqueous acid on compound **4** and were most interested to observe that the acid-catalysed conversion of **4** ⟶ **5** (Scheme 1) proceeded with much greater facility than the above base-catalysed conversion. Thus, when compound **4** was treated with 0.3 mol dm^{-3} hydrogen chloride in tetrahydrofuran (THF)–water (9:1 v/v) at room temperature, it was quantitatively converted into its isomer **5** within 10 min. On a preparative (1.0 mmolar) scale, compound **4** was converted under the latter conditions into its isomer **5** in 75% isolated yield. No thymine could be detected in the products. In glacial acetic acid solution at room temperature, the same transformation was complete in 20 min. Acid-catalysed nucleoside hydrolysis is believed to proceed[7] by protonation of the base residue followed by, in the rate-determining step, cleavage of the glycosidic bond. It must be assumed that in the case of compound **4**, protonation on C-5' to give the intermediate cation **6** (Scheme 1) followed by ionization of 1'-H is a more favourable process.



7 **8** **9**

Thy = thymin - 1 - yl

Scheme 2 *Reagents:* i, 3-chloroperbenzoic acid, magnesium oxide, dichloromethane

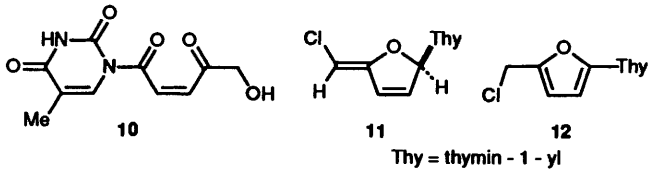
We then examined the effect of two other electrophilic agents on compound **4** in the expectation of obtaining 5-(thymin-1-yl)furan derivatives, functionalized on C-5'. First, treatment of compound **4** with 3-chloroperbenzoic acid (MCPBA) in dichloromethane in the presence of magnesium oxide did indeed lead to the expected 1-hydroxymethyl-5-(thymin-1-yl)furan **9**, albeit in only 48% yield. In addition, thymine was isolated from the products in 12% yield. A possible mechanism for the conversion of **4** into **9** *via* intermediates **7** and **8** is indicated in Scheme 2. It has very recently been reported[8] that 2,5-disubstituted furans are oxidized by MCPBA to the corresponding enediones. A possible explanation for the formation of thymine is that compound **9** could undergo further oxidation by MCPBA to give keto amide **10** which, like all 1-acyl derivatives of thymine, would be expected[9] to be very sensitive to hydrolysis. In the case of compound **10**, hydrolytic cleavage of the 1-acyl group could be further facilitated by the neighbouring group participation of the alcoholic hydroxy function.

Treatment of compound **4** with an excess of sodium hypochlorite in aq. 1,4-dioxane surprisingly gave the direct substitution product **11** in 48% isolated yield. None of the

Table 1 ^{1}H NMR spectroscopic data[a] relating to compounds **4** and **11**

Compound	1'-H	2'-H	3'-H	5'-H	5'-H' (5"-H)	6-H	5-Me
4	7.13 m	6.41 m[b]	6.77 dd[b]	4.26 m	4.41 m	6.97 m	1.76 d
11	7.22 m	6.45 dd	6.80 dd	5.78 m		7.07 m	1.76 d

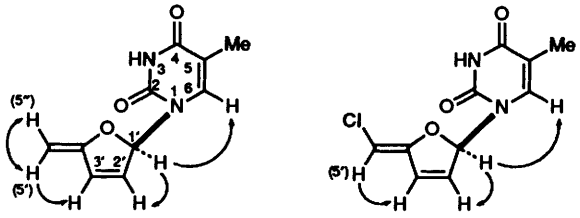
[a] See Experimental section for details relating to the measurement of the NMR spectra and, where appropriate, the magnitude of the coupling constants. [b] In a previous report,[4] these assignments were interchanged.



10 **11** **12**

Thy = thymin - 1 - yl

isomeric furan derivative **12** was detected in the products. Furthermore, while compound **11** was found to be unstable both in acidic and basic media, we have not so far been successful in characterizing any of the products thereby obtained. It is noteworthy that only one geometrical isomer, which on the basis of NMR spectroscopic data (see Table 1 and below) appears to be the *Z*-isomer **11**, was isolated from the products of this chlorination reaction. We are at present unable to explain this apparent stereoselectivity.



13 **14**

The assignments of the proton resonance signals of compounds **4** and **11** (Table 1) were made on the basis of COSY and NOE experiments. In the case of compound **4** (see formula **13**), irradiation at δ 4.26 (5'-H) led to a large positive NOE at δ 4.41 (5"-H) and a medium positive NOE at δ 6.77 (3'-H), while irradiation at δ 4.41 (5"-H) led to a large positive NOE at δ 4.26 (5'-H) and a very small *negative* NOE at δ 6.77 (3'-H). Irradiation at δ 7.13 (1'-H) led to a medium positive NOE at δ 6.41 (2'-H), and a small positive NOE at δ 6.97 (6-H). In the case of compound **11** (see formula **14**), irradiation at δ 5.78 (5'-H) led to a medium positive NOE at δ 6.80 (3'-H), and irradiation at δ 7.22 (1'-H) led to a medium positive NOE at δ 6.45 (2'-H) and a small positive NOE at δ 7.07 (6-H).

Experimental

M.p.s were measured on a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 360 MHz on a Bruker AM 360 spectrometer; ^{13}C NMR spectra were measured at 90.6 MHz on the same spectrometer. Tetramethylsilane was used as internal standard, and *J* values are given in Hz. Merck silica gel 60 F_{254} TLC plates were developed in solvent system A [chloroform–ethanol (98:2 v/v)]. Merck silica gel H was used for short-column chromatography. THF and 1,4-dioxane were dried by heating, under reflux, over calcium hydride and were then distilled; DMSO was dried by heating over calcium hydride at 60 °C and was then distilled under reduced (water-pump) pressure; dichloromethane was dried over phosphorus pentaoxide and then distilled. All dried solvents were stored over 4 Å molecular sieves.

2',3'-Didehydro-3'-deoxy-5'-O-(methylsulfonyl)thymidine **3b**.—Methanesulfonyl chloride (1.15 cm^3, 14.9 mmol) was added to a stirred solution of 2',3'-didehydro-3'-deoxythymidine[4] **3a** (2.24 g, 10.0 mmol) and triethylamine (3.03 cm^3, 21.7 mmol) in dry dichloromethane (15 cm^3) at 0 °C. After the reactants had been stirred at room temperature for a further 30 min, saturated aq. sodium hydrogen carbonate (2 cm^3) was added and the products were concentrated under reduced pressure. Water (5 cm^3) was added to the residual syrup and the solid obtained was collected by filtration, washed with water, and then dried. Crystallization from ethyl acetate–light petroleum (b.p. range 60–80 °C) gave the *title compound* (2.44 g, 80.8%) (Found: C, 43.7; H, 4.6; N, 9.0. $C_{11}H_{14}N_2O_6S$ requires C, 43.7; H, 4.7; N, 9.3%), m.p. 115 °C; R_f 0.22 (system A); δ_H [$(CD_3)_2SO$] 1.75 (3 H, d, *J* 0.7), 3.17 (3 H, s), 4.42 (2 H, m), 5.04 (1 H, m), 6.04 (1 H, m), 6.44 (1 H, m), 6.86 (1 H, m), 7.27 (1 H, m) and 11.37 (1 H, br s); δ_C[$(CD_3)_2SO$] 11.78, 36.48, 70.16, 83.26, 88.94, 109.62, 127.18, 132.90, 135.85, 150.69 and 163.70.

(5R)-2-Methylene-5-(thymin-1-yl)-2,5-dihydrofuran **4**.—A solution of 2',3'-didehydro-3'-deoxy-5'-*O*-(methylsulfonyl)-thymidine **3b** (1.51 g, 5.0 mmol) and 30% methanolic sodium methoxide (1.73 cm^3, ~9 mmol) in methanol (5 cm^3) was heated under reflux. After 15 min, additional 30% methanolic sodium methoxide (1.73 cm^3, ~9 mmol) was added and the reactants were heated for a further 25 min. Saturated methanolic ammonium chloride (10 cm^3) was added to the cooled products, and the resulting mixture was stirred for 30 min and then concentated under reduced pressure. The residue was extracted with chloroform (3 × 25 cm^3), and the combined extracts were washed successively with aq. ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was fractionated by chromatography on silica gel: the appropriate fractions, which were eluted with chloroform–ethanol (98:2 v/v), were combined, and evaporated under reduced pressure, and the residue was crystallized from ethanol to give compound **4** (0.937 g, 91%) (Found: C, 58.1; H, 4.9; N, 13.6. Calc. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.9; N, 13.6%), m.p. 158 °C (lit.,[3] 163–165 °C); $[\alpha]_D^{25}$ +212° (*c* 0.2, EtOH); R_f 0.30 (system A); δ_H [$(CD_3)_2SO$] 1.76 (3 H, d, *J* 1.2), 4.26 (1 H, m), 4.41 (1 H, m), 6.41 (1 H, m), 6.77 (1 H, dd, *J* 1.7 and 5.75), 6.97 (1 H, m), 7.13 (1 H, m) and 11.48 (1 H, br s); δ_C [$(CD_3)_2SO$] 11.94, 84.26, 89.02, 110.52, 130.62, 130.75, 134.87, 150.44, 161.93 and 163.57.

2-Methyl-5-(thymin-1-yl)furan **5**.—(*a*) A solution of (5*R*)-2-methylene-5-(thymin-1-yl)-2,5-dihydrofuran **4** (0.206 g, 1.0 mmol) and potassium *tert*-butoxide (0.168 g, 1.5 mmol) in DMSO (3 cm^3) was stirred at room temperature. After 15 min, an excess of solid carbon dioxide was added and the neutralized products were partitioned between chloroform (50 cm^3) and water (3 × 25 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the residue was fractionated on silica gel: the appropriate fractions, which were eluted with chloroform, were combined, and evaporated under reduced pressure, and the residue was crystallized from benzene to give compound **5** (0.175 g, 83%) (Found: C, 58.0; H, 4.8; N, 13.6. Calc. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.9; N, 13.6%), m.p. 174 °C (lit.,[5] 165–166.5 °C), R_f 0.30 (system A); δ_H[$(CD_3)_2SO$] 1.79 (3 H, d, *J* 1.2), 2.27 (3 H, d, *J* 0.8), 6.18 (1 H, m), 6.35 (1 H, d,

J 3.2), 7.56 (1 H, d, *J* 1.3) and 1.57 (1 H, br); δ_C[$(CD_3)_2SO$] 11.60, 13.18, 104.91, 107.33, 109.84, 139.68, 141.89, 149.32, 149.62 and 163.85.

(*b*) Compound **4** (0.206 g, 1.0 mmol) was added to a stirred solution of 3.0 mol dm^{-3} hydrochloric acid (0.5 cm^3) in THF (4.5 cm^3) at room temperature. After 10 min, the products were neutralized with 1 mol dm^{-3} aq. sodium hydroxide and the mixture was then evaporated to dryness under reduced pressure. The residue was extracted with hot acetone (2 × 25 cm^3), and the combined extracts were evaporated under reduced pressure and then fractionated on silica gel to give crystalline compound **5** (0.156 g, 75%), identical (m.p., TLC, NMR) with the material obtained in (*a*) above.

(*c*) A solution of compound **4** (0.103 g, 0.5 mmol) in glacial acetic acid (0.5 cm^3) was kept at room temperature for 20 min. Chloroform (20 cm^3) was then added and the resulting solution was extracted with saturated aq. sodium hydrogen carbonate (3 × 10 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the residue was crystallized from benzene to give compound **5** (0.078 g, 76%), identical with the material obtained in (*a*) and (*b*) above.

2-*Hydroxymethyl*-5-(*thymin*-1-yl)*furan* **9**.—Magnesium oxide (0.05 g, 1.2 mmol) and MCPBA (85%; 0.172 g, ~0.85 mmol) were added to a stirred solution of compound **4** (0.206 g, 1.00 mmol) in dichloromethane (5 cm^3) at room temperature. After 10 min, saturated aq. sodium hydrogen carbonate (2 cm^3) was added and the mixture was evaporated to dryness under reduced pressure. The residue was extracted with hot acetone (3 × 25 cm^3), and the combined extracts were concentrated under reduced pressure and then fractionated on silica gel: the appropriate fractions, which were eluted with chloroform–ethanol (95:5 v/v), were combined, and evaporated under reduced pressure, and the residue was crystallized from ethyl acetate to give the *title compound* (0.107 g, 48%) (Found: C, 53.9; H, 4.5; N, 12.0. $C_{10}H_{10}N_2O_4$ requires C, 54.05; H, 4.5; N, 12.6%), m.p. 143 °C; R_f 0.23 (system A); δ_H [$(CD_3)_2SO$] 1.80 (3 H, d, *J* 1.1), 4.38 (2 H, d, *J* 5.7), 5.32 (1 H, t, *J* 5.8), 6.39 (1 H, d, *J* 3.3), 6.42 (1 H, d, *J* 3.3), 7.61 (1 H, m) and 11.61 (1 H, s); δ_C [$(CD_3)_2SO$] 11.68, 55.61, 104.51, 108.40, 110.07, 139.36, 142.73, 149.53, 152.92 and 163.85.

Later fractions, eluted from the column with chloroform–ethanol (75:25 v/v), were combined, and then evaporated under reduced pressure to give thymine (0.015 g, 12%), identical (TLC, UV, NMR) with authentic material.

(5R)-2-*Chloromethylene*-5-(*thymin*-1-yl)-2,5-*dihydrofuran* **11**.—Aq. sodium hypochlorite (~2 mol dm^{-3}; 3.5 cm^3, ~7 mmol) was added in small (0.5 cm^3) portions at 5 min intervals to a solution of compound **4** (0.206 g, 1.0 mmol) in 1,4-dioxane (5 cm^3) at room temperature. After a further period of 10 min, the products were concentrated under reduced pressure to small volume and were then partitioned between chloroform (50 cm^3) and water (10 cm^3). The chloroform layer was washed with saturated aq. ammonium chloride (15 cm^3) and water (15 cm^3); it was then dried ($MgSO_4$), and evaporated under reduced pressure. The residue was fractionated on silica gel to give starting material **4** (0.055 g) and the *title compound* (0.084 g after crystallization from ethyl acetate, 48% based on starting material **4** consumed) (Found: C, 50.1; H, 3.6; N, 11.3. $C_{10}H_9ClN_2O_3$ requires C, 49.9; H, 3.8; N, 11.6%), m.p. 132 °C (decomp.); $[\alpha]_D^{25}$ +331° (*c* 0.08, EtOH); R_f 0.29 (system A); δ_H [$(CD_3)_2SO$] 1.76 (3 H, d, *J* 0.9), 5.78 (1 H, m), 6.45 (1 H, dd, *J* 1.8 and 5.8), 6.80 (1 H, dd, *J* 1.8 and 5.8), 7.07 (1 H, m), 7.22 (1H, m) and 11.52 (1 H, br s); δ_C [$(CD_3)_2SO$] 11.94, 90.09, 90.31, 110.86, 128.65, 130.46, 135.13, 150.51, 157.32 and 163.63.

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