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Uracil- and Thymine-Substituted Thymidine and Uridine Derivatives

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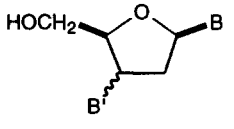
Abstract: The four possible 3'-uracil-1-yl and 3'-thymin-1-yl derivatives of 3'-deoxythymidine and the four analogous derivatives of 2'-deoxyuridine have been synthesised from thymidine and uridine, respectively. Advantages of the 2-(methoxycarbonyl)vinyl group to prevent the formation of anhydronucleosides and of $SnCl_2$/PhSH/Et_3N in relation to H_2/Pd for the reduction of most azido groups are disclosed.

Preparation of 2',3'-dideoxynucleosides has become a subject of great interest, in relation with the AIDS chemotherapy.[1] 2'/3'-Deoxynucleosides with the nucleobase at C3' or C2' ("isonucleosides") have drawn much attention as well.[2] In this context, it occurred to us that pentofuranoses with two nucleobases, such as **1** and **2**, deserved to be investigated not only as they may be viewed as a special subclass of C3'- or C2'-substituted deoxynucleosides or might be converted to "isonucleosides" by hydrolysis, but also because some of them could give rise to a novel type of antisense oligonucleotides,[3] while some others —in principle, those with two *cis* pyrimidine rings— could serve as models in studies related with the effect of the UV light on DNA.[4,5] In this communication we report on syntheses of the hitherto unknown eight members of the series that follows: **1**, B = thymin-1-yl, B' = uracil-1-yl or thymin-1-yl; and **2**, B = uracil-1-yl, B' = uracil-1-yl or thymin-1-yl).



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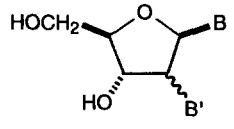

2

Conversion of 5'-*O*-tritylthymidine to tritylated AZT by a standard procedure,[6] followed by reduction with $SnCl_2$/PhSH/Et_3N,[7] afforded the desired 3'-aminothymidine derivative, which by treatment either with 3-ethoxypropenoyl isocyanate or 3-methoxy-2-methylpropenoyl isocyanate and cyclisation under acidic conditions[8] afforded **1a** and **1b**,[9,10] respectively (Scheme 1). On the other hand, blocking of N3 of 5'-*O*-tritylthymidine with the 2-(methoxycarbonyl)vinyl group[11] (Mocvinyl) to avoid the participation of the pyrimidine ring in the next step, substitution of the azido by hydroxy group through a Mitsunobu-like reaction,[12] removal of the Mocvinyl group with pyrrolidine at room temperature,[11] and reduction of the azide as above afforded the alternative amino derivative (3'β, or "up"), also in good overall yields; again, the method of Shaw and Warrener[8] was successfully utilised to build up the uracil and thymine rings of **1c** and **1d**,[10,13] respectively.

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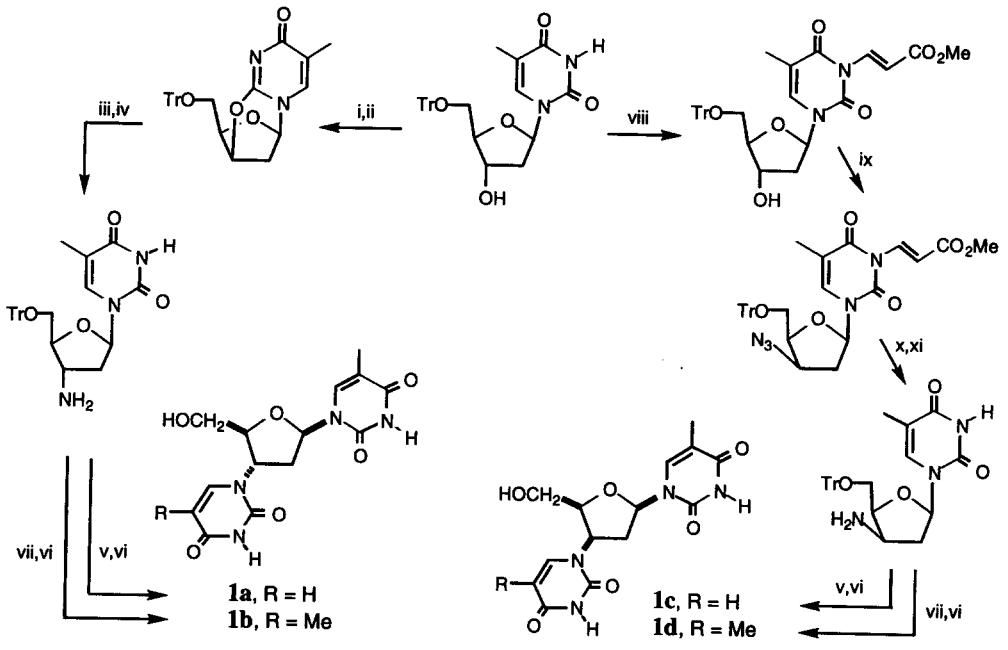
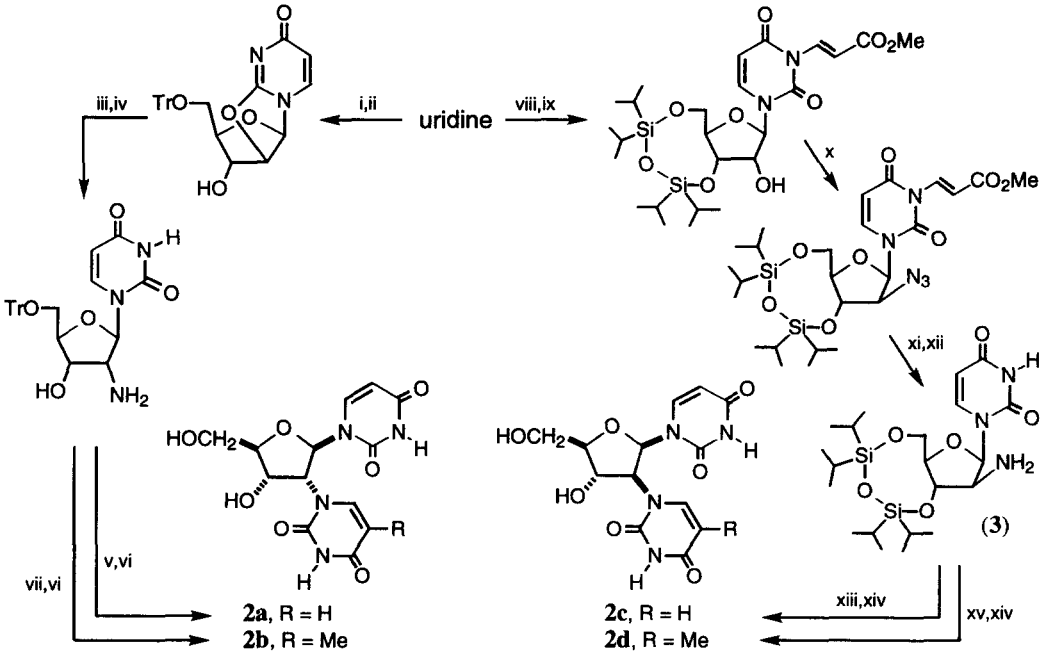


Scheme 1. i, $MeSO_2Cl$, py, 0 °C, 15 h, 95%; ii, K^+ phthalimide$^-$, DMF/H_2O, 90 °C, 3 h, 85%; iii, NaN_3, DMF/H_2O, Δ, 15 h, 80%; iv, $SnCl_2$/PhSH/Et_3N (1.5:4.5:4.5), CH_3CN, rt, 30 min, 85%; v, EtO-CH=CH-CO-N=C=O (2.0), C_6H_6/DMF, rt, 2 h, ≈90%; vi, 1 M H_2SO_4/dioxan, Δ, 4 h, 80–85%; vii, MeO-CH=CMeCO-N=C=O (2.0), C_6H_6/DMF, rt, 2 h, 85%; viii, HC≡C-COOMe (1.0), DMAP (0.3), CH_3CN/CH_2Cl_2, rt, 40 min, 83%; ix, Ph_3P/DEAD/$(PhO)_2PON_3$ (3.0), THF, 0–20 °C, 5 h, 97%; x, $SnCl_2$/PhSH/Et_3N, CH_3CN, rt, 5 h, 75%; xi, pyrrolidine (exc.), CH_3CN, rt, 4 h, 94%.

Some practical details related to Scheme 1 are worthy of mention. First, introduction of the blocking group at N3 (Mocvinyl group, step viii) is so chemoselective and substitution of azido for hydroxy group (step ix) so stereoselective that only the desired 3'ß azido derivative is obtained (its 3'α epimer is not detected). Secondly, reduction of the sterically crowded azido group to the amine (step x) with our $[Et_3NH][Sn(SPh)_3]$ complex[7] is advantageous in relation to other standard reducing agents, even as compared to H_2/Pd(C), which also reduces the double bond of the Mocvinyl group (the resulting CH_2CH_2COOMe substituent at N3 being afterwards not so easily eliminated); catalytic hydrogenation can be employed, however, if steps x and xi are reversed, ie if Mocvinyl is first removed and then the azide is reduced (H_2, Pd/C, MeOH, rt, 5 h, 66%). Thirdly, as step vi indicates, cyclisation of the intermediate *N*-3-ethoxyacryloylureas (EtO-CH=CH-CO-NHCONH-R) and *N*-3-methoxymethacryloylureas (MeO-CH=CMe-NHCONH-R) is accomplished in excellent yields by heating in dioxan with dilute acid for only 4 h —the glycosidic bond is not hydrolised under these conditions—, whereas other attempted conditions (such as heating with ammonia, ammonia in pyridine, or some Lewis acids) have appeared to be inefficient to promote these cyclisations.

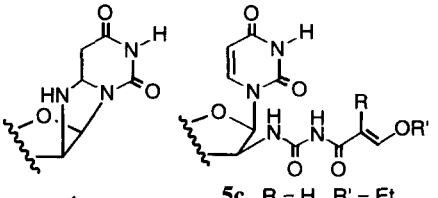
Scheme 2 summarises synthetic routes to 2'α- and 2'ß-substituted uridine-related derivatives **2a–d**.[10] Most steps are identical or similar to those of the preceding Scheme.[14] Nevertheless, regarding the preparation of **2c** and **2d** via the corresponding azide (see step x of Scheme 2), the tendency of uridine derivatives to afford O^2,2'-anhydronucleosides (cyclonucleosides) could have posed a problem greater than in the case of **1c** and **1d**. Fortunately, the same protocol as above has turned out to be feasible;[12] in other words, the N3-blocking Mocvinyl group is very appropriate in all cases.

Another problem that worried us from the beginning, concerning the synthesis of **2c** and **2d**, is the *cis*-1,2 relationship between the nucleobases. In practice, reduction of the 2'ß azido group in this case was slower than



Scheme 2. i, TrCl, py, 120 °C, 2 h, 95%; ii, $Im_2C{=}S$, toluene, 110 °C, 30 min, 80%; iii, Me_3SiN_3, LiF, DMF/TMEDA, 110 °C, 48 h, 60%; iv, $SnCl_2$/PhSH/Et_3N, CH_3CN, rt, 30 min, 95%, or H_2, Pd/C, MeOH, rt, 1 h, 95%; v, EtOCH=CH-CO-N=C=O (1.2), C_6H_6/DMF 1:1, rt, 3 h, 85%; vi, 1 M H_2SO_4/dioxan, Δ, overnight, 80–90%; vii, MeOCH=CMe-CO-N=C=O (1.2), C_6H_6/DMF, rt, 3 h, 85%; viii, $ClSiPr^i_2OSiPr^i_2Cl$ (1.05), py, rt, overn., 95%; ix, HC≡C-COOMe (1.0), DMAP (0.3), CH_3CN/CH_2Cl_2 4:1, rt, 40 min, 88%; x, Ph_3P/DEAD/$(PhO)_2PON_3$ (3.0), THF, 0–20 °C, overnight, 68%; xi, pyrrolidine, CH_3CN, rt, 3 h, 98%; xii, H_2, Pd/C, MeOH, rt, 3 h, then MeOH, 40 °C, 12 h, 65%; xiii, EtOCH=CHCO-NCO (2.0), C_6H_6/DMF, rt, 5 h, 72%; xiv, 1 M H_2SO_4/dioxan, Δ, 5 h, 70–75%; xv, MeOCH=CMeCO-NCO (2.0), C_6H_6/DMF, rt, 5 h, 70%.

in previous substrates. Moreover, when the reduction was effected with $SnCl_2$/PhSH/Et_3N, a mixture of **3** and **4** was obtained, in which the last compound —the isomer arising from a conjugate addition of the amino group— predominated. Hydrogenation of the same azide over Pd/C (step xii of Scheme 2) afforded a different mixture, but on warming in MeOH most of the crude was converted to the desired amine (**3**). Thus, as an exception, catalytic hydrogenation was the method of choice in this particular case. Reaction of **3** with acryloyl isocyanate derivatives, although slower than in previous instances, gave *N*-acryloylureas **5c** and **5d** in yields around 70%. More readily than expected at first sight, these ureas cyclised under acidic conditions to **2c** and **2d**, respectively, with concomitant deprotection of the hydroxy groups.



4

5c, R = H, R' = Et
5d, R = R' = Me

In summary, the stereoselective introduction of an azido group at position 3'β of the thymidine parent system and, even more remarkably, at position 2'β of the uridine system without participation of the nucleobase (i.e. without formation of anhydronucleosides as intermediates) has been achieved by blocking N3 with a Mocvinyl group. All the amino nucleosides described in this work can be readily converted into the title compounds (**1a–d**, **2a–d**) by the method of Shaw and Warrener[8] (via cyclisation under acidic conditions, but not through other attempted procedures); even in the cases of sterically crowded compounds **2c** and **2d**, the intramolecular cyclisation could be performed in good yield.[15] Photochemical studies with some of these substrates,[16] incorporation into oligonucleotide sequences, and base-pairing studies are in course.

Acknowledgments

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9. 3'-Deoxy-3'-(uracil-1-yl)thymidine (**1a**): dec. 198 °C (softens at 144 °C); R_f (CH_2Cl_2/MeOH 80:20) 0.32; ^1H NMR (CD_3OD) δ 1.99 (d, J =1.2, 3 H), 2.53 (ddd, 14.3, 10.1, 6.2, 1 H), 2.84 (ddd, 14.3, 7.1, 5.5, 1 H), 3.81 (dd, 12.2, 3.5, 1 H), 3.94 (dd, 12.2, 3.3, 1 H), 4.37 (ddd, 6.4, 3.5, 3.3, 1 H), 4.57 (ddd, 10.1, 6.4, 5.5, 1 H), 5.79 (d, 8.0, 1 H), 6.54 (dd, 7.1, 6.2, 1 H), 7.75 (d, 8.0, 1 H), 7.89 (q, 1.2, 1 H); ^{13}C NMR (DMSO-d_6) δ 12.4 (CH_3), 35.6 (CH_2), 57.4 (CH), 61.2 (CH_2), 82.2 (CH), 84.0 (CH), 101.9 (CH), 109.8 (C), 136.7 (CH), 144.3 (CH), 150.6 (C), 151.0 (C), 163.5 (C), 163.9 (C).
3'-Deoxy-3'-(thymin-1-yl)thymidine (**1b**): dec. 223 °C (softens at ≥ 115 °C); R_f (CH_2Cl_2/MeOH 90:10) 0.43; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.77 (d, J = 1.2, 3 H), 1.78 (d, 1.2, 3 H), 2.31 (ddd, 14.5, 10.5, 6.0, 1 H), 2.52 (ddd, 14.5, 7.0, 6.0, 1 H), 3.5–3.6 (m, 2 H), 4.07 (dt, 7.0, 3.8, 1 H), 4.92 (dt, 10.5, 7.0, 6.0, 1 H), 5.04 (t, 4.8, OH), 6.36 (dd, 7.0, 6.0, 1 H), 7.66 (q, 1.2, 1 H, H6 of thymine at 3'), 7.72 (q, 1.2, 1 H), 11.27 (br s, 2 H); ^{13}C NMR (DMSO-d_6) δ 12.2, 12.4, 35.6, 56.4 (C3'), 61.2, 82.3 (C1'), 83.9 (C4'), 109.7 (C5 of thym. at 3'), 109.9, 136.7, 139.6 (C6 of thym. at 3'), 150.6, 151.0 (C2 of thym. at 3'), 164.0, 164.1. Assignments established by ^1H-^{13}C COSY and HMBC. FABMS m/z 351 $[M+1]^+$.
10. Satisfactory microanalytical data have been obtained for the final products (**1a–d** and **2a–d**).
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13. 1-[2',3'-Dideoxy-3'-(uracil-1-yl)-ß-D-*threo*-pentofuranosyl]thymine (**1c**): dec. 197 °C (softens at 139 °C); R_f (CH_2Cl_2/MeOH 90:10) 0.25; ^1H NMR (CD_3OD) δ 1.90 (d, J = 1.2, 3 H), 2.5–2.7 (m, 2 H), 3.45 (dd, 12.2, 2.6, 1 H), 3.71 (dd, 12.2, 3.1, 1 H), 4.36 (m, 1 H), 5.14 (m, 1 H), 5.67 (d, 8.1, 1 H), 6.18 (dd, 8.8, 5.4, 1 H), 7.78 (d, 8.1, 1 H), 8.05 (q, 1.2, 1 H); ^{13}C NMR (CD_3OD) δ 12.5, 34.2, 58.0, 61.7, 79.4, 84.2, 101.5, 111.8, 138.4, 145.1, 152.4, 153.2, 154.9, 166.3.
1-[2',3'-Dideoxy-3'-(thymin-1-yl)-ß-D-*threo*-pentofuranosyl]thymine (**1d**): dec. ≥ 159 °C (softens at 150 °C); R_f (CH_2Cl_2/MeOH 90:10) 0.36; ^1H NMR (CD_3OD, 300 MHz) δ 1.88 (d, J = 1.2, 3 H), 1.90 (d, 1.2, 3 H), 2.54 (ddd, 11.8, 7.8, 5.5, 1 H), 2.75 (ddd, 11.8, 11.5, 9.0, 1 H), 3.50 (dd, J = 12.2, 3.1, 1 H), 3.73 (dd, 12.2, 3.4, 1 H), 4.37 (ddd, 7.8, 3.4, 3.1, 1 H), 5.14 (dt, 11.5, 7.8, 1 H), 6.19 (dd, 9.0, 5.5, 1 H), 7.64 (q, 1.2, 1 H), 8.11 (q, 1.2, 1 H); ^{13}C NMR (DMSO-d_6) δ 12.4, 12.6, 37.2, 55.8, 60.3, 77.9, 82.2, 108.1, 109.7, 136.5, 139.2, 150.7, 151.6, 163.9, 164.1; FABMS m/z 351 $[M+1]^+$.
14. For the use of 1,1'-thiocarbonyldiimidazole, step ii, see: Fox, J. J.; Wempen, I. *Tetrahedron Lett.* **1965**, 643. Ruyle, W. V.; Shen, T. Y.; Patchett, A. A. *J. Org. Chem.* **1965**, *30*, 4353. For step iii, see: Kirschenheuter, G. P.; Zhai, Y.; Pieken, W. A. *Tetrahedron Lett.* **1994**, *35*, 8517.
15. Samples of **1a–d** and **2a–d** (**1b** and **1c** as 5'-*O*-acetyl derivatives) were submitted to the National Cancer Institute, NIH, Bethesda, USA. The results, just received, show that none of them are sufficiently active against NCI standard cell lines.
16. For instance, whereas irradiation of **1d** (with two thymine rings in a 1,3-*cis* relationship) in acetone/water affords a mixture of five products, that of **2c** (with the uracil and thymine rings in a 1,2-*cis* relationship) gives one major [2+2]-cycloadduct (the expected cis-syn-cis, CONH-exo stereoisomer, as established by ^1H–^{13}C COSY and NOESY experiments).