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Note

Synthesis of 2[1], 6-anhydro-(perhydro-6-hydroxy-4-β-D-threofuranosylpyrimidine) derivatives*

F. J. LOPEZ APARICIO, J. A. LOPEZ SASTRE, AND J. MOLINA MOLINA
Department of Organic Chemistry, University of Granada, Granada (Spain)
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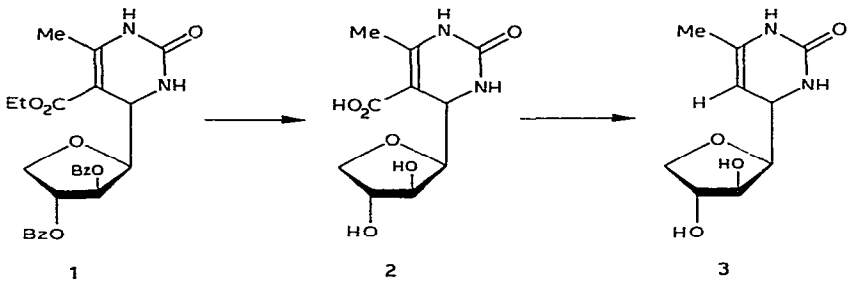
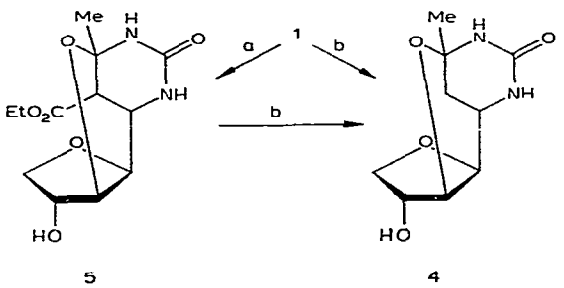
We have synthesised[1] *C*-nucleoside analogues by the reaction[2] of aldehydosugars with urea and ethyl acetoacetate. Following the use of 2,3-*O*-isopropylidene-D-glyceraldehyde[3], the reaction was extended to 2,5-anhydropentoses, yielding true *C*-nucleosides[4]. We now report on the hydrolysis of 4-(2,3-di-*O*-benzoyl-β-D-threofuranosyl)-5-ethoxycarbonyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine (**1**), obtained[2] from 2,5-anhydro-2,3-di-*O*-benzoyl-D-xylose[4].





a: methanolic sodium methoxide

b: aqueous , ethanolic sodium hydroxide

*C-Glycosyl Compounds, Part IX. For Part VIII, see ref. 1.

Hydrolysis[5] of **1** with aqueous, ethanolic sodium hydroxide gave a solid product (**4**), the analytical and spectroscopic data of which were not those expected for structure **2**. Thus, the singlet (3 H) at δ 1.23 in the n.m.r. spectrum did not correspond to any group in structure **2**, and the signal expected[6] at $\delta \sim 2$ for the allylic methyl group at C-6 was absent. Also, the signals at δ 1.45–2.15 (2 H) did not correspond to any of the groups in structure **2**, neither did that of the sole hydroxyl group. Moreover, the product did not give a specific glycol-reaction.

The behaviour of **1** contrasts with that of 5-ethoxycarbonyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine[9], which was converted into the 5-carboxy derivative on treatment with base.

Methanolysis of **1** with a trace of sodium methoxide gave **5** as a white solid which showed an i.r. carbonyl absorption at 1670 cm^{-1}. The analytical and spectroscopic data accorded with a structure having a single hydroxyl group and no ethylenic double-bond. Treatment of **5** with aqueous, ethanolic sodium hydroxide gave **4**.

The elemental analysis of **4** accorded with $C_9H_{14}N_2O_4$ and indicated decarboxylation in its formation and possibly structure **3**. However, this structure is not compatible with the n.m.r. data noted above. Loss of the 5,6 double-bond from the pyrimidine ring would accord with the absorption at δ 1.25, corresponding to a methyl group attached to a saturated ring, and also account for the shift of the NH-1 absorption. The absence of a signal for an acidic proton, together with the disappearance of the double bond, confirms the occurrence of decarboxylation and accounts for the ABX signals at δ 1.45–2.15 which can be assigned to a methylene group. The foregoing data and argument accord with the assigned structures **4** and **5**.

Compounds **4** and **5** are anhydro-*C*-nucleoside analogues. The formation of the oxygen bridge may be explained by an attack on the pyrimidine double-bond by HO-2′, probably in a manner analogous to that of intramolecular addition reactions[8].

The configuration of the anomeric centre (C-1′) in **1** has been assumed[9,10] to be *S*. A new chiral centre, C-4, is present in **4** and **5**, but the cyclisation of **1** to yield **5** and **4** appears to be stereospecific, as only one isomer of each was formed.

The absence of epimerisation at C-2 in the anhydro sugar during the synthesis of **1** fixes the configuration of C-1′ as *S*, and molecular models indicate that cyclisation to produce the oxygen bridge requires that both asymmetric centres, C-4 and C-6, be either *R* or *S*.

EXPERIMENTAL

Solvents were evaporated under diminished pressure at $<50°$. Melting points are uncorrected and were obtained with a Kofler apparatus. I.r. spectra were recorded with a Pye-Unicam spectrophotometer. ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded with a Hitachi–Perkin–Elmer R20-B spectrometer; chemical shifts are expressed in δ values and the coupling constants in Hz. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at 20°. Elemental analyses were per-

formed in our Department by Mr. J. A. Ruiz Caballero with a Carlo Erba elemental analyzer Model 1106.

Hydrolysis of 4-(2,3-di-O-benzoyl-β-D-threofuranosyl)-5-ethoxycarbonyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine (**1**). — (*a*) *With aqueous, ethanolic sodium hydroxide.* A solution of **1** (1.05 g) in 50% aqueous alcohol (16 ml) was stirred with M sodium hydroxide (6.3 ml) and boiled under reflux for 20 min. The cooled mixture was neutralised with acetic acid and concentrated, and a solution of the residue in water was treated with Amberlite IR-120 (H^+) resin, filtered, and extracted three times with chloroform. The aqueous layer was concentrated, and the residue was crystallised from ethanol to yield 2′,6-anhydro-(perhydro-6-hydroxy-6-methyl-2-oxo-4-β-D-threofuranosylpyrimidine) (**4**, 0.44 g) as a white solid, m.p. 295° (dec.; sublimation at 240°), $[\alpha]_D$ +25° (*c* 1, water); ν_{max}^{KBr} 3430, 3320, 2940, 1675, 1500, 1385, and 1080 cm^{-1}. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.25 (3 H, Me-6), 1.4–2.2 (2 H, H-5,5), 3.4–4.2 (6 H, H-1′,2′,3′,4,4′,4′), 5.0–5.2 (1 H, HO-3′, exchangeable with D_2O), 6.65–6.95 (1 H, NH-3, exchangeable with D_2O), and 6.95–7.25 (1 H, NH-1, exchangeable with D_2O).

Anal. Calc. for $C_9H_{14}N_2O_4$: C, 50.47; H, 6.54; N, 13.08. Found: C, 50.55; H, 6.51; N, 12.94.

(*b*) *With methanolic sodium methoxide.* Very dilute, methanolic sodium methoxide (3 drops) was added to a solution of **1** (0.2 g) in methanol (5 ml). The mixture was kept at room temperature for 30 min, treated with Amberlite IR-120 (H^+) resin, filtered, and concentrated. The residue was eluted from a column of silica gel by using acetone–ether mixtures. Methyl benzoate was eluted first and then 2′,6-anhydro-(5-ethoxycarbonylperhydro-6-hydroxy-6-methyl-2-oxo-4-β-D-threofuranosylpyrimidine) (**6**, 0.07 g), m.p. 195–200°; ν_{max}^{KBr} 3370, 3300, 1755, 1745, 1670, 1500, and 1100 cm^{-1}. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 1.05 (3 H, CH_3CH_2), 1.25 (3 H, Me-6), 2.4 (1 H, H-5), 3.35–4.15 (8 H, CH_3CH_2 and H-1′,2′,3′,4,4′,4′), 5.15 (1 H, OH, exchangeable with D_2O), and 6.10–7.25 (2 H, NH-1,3, exchangeable with D_2O).

Anal. Calc. for $C_{12}H_{18}N_2O_6$: C, 50.32; H, 6.34; N, 9.78. Found: C, 50.66; H, 6.14; N, 9.74.

Treatment of **5** with aqueous, ethanolic sodium hydroxide, as described for **1** in (*a*), gave **4**.

Hydrolysis of 5-ethoxycarbonyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine. — A solution of the title compound (1 g) in 50% aqueous alcohol (29 ml) was stirred with M sodium hydroxide (11.5 ml) and boiled under reflux for 1 h, and then filtered, neutralised with acetic acid, and concentrated. A solution of the residue in water was treated with Amberlite IR-120 (H^+) resin, and then concentrated to yield 5-carboxy-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine[7] as a yellow solid. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 2.25 (3 H, allylic Me), 5.05–5.25 (1 H, H-4), 7.0–7.5 (6 H, acidic and aromatic H), 7.55–7.75 (1 H, NH-3, exchangeable with D_2O), and 8.9–9.15 (1 H, NH-1, exchangeable with D_2O).

Treatment with methanolic sodium methoxide, as described in (*b*), caused no reaction.

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