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Note

High-pressure approach to the synthesis of "C–O–N" analogues of nucleosides

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We have described a new class of monosaccharide derivatives, *O*-phthalimidohexoses, readily available *via* the Mitsunobu reaction[1], and have been interested in the synthesis of *N*-(glycosyloxy)phthalimides as model compounds for the study of "C–O–N" analogues of nucleosides. *N*-Hydroxyphthalimide, *N*-hydroxytriazoles, and *N*-hydroxyimidazoles have been used in these studies[2]. When the sugar components were protected by acyl groups, the Mitsunobu reaction failed, and a direct method involving the reaction between sodium salts of *N*-hydroxy compounds and monosaccharide halides was applied[3].

We now report on the synthesis of *N*-(D-ribofuranosyloxy)uracil (**2**), a new "C–O–N" analogue of uridine (**1**) where C–O–N connotes C-1 and O-1 of the sugar and N-1 of the uracil.

2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl chloride (**3**) was chosen as the starting material for this synthesis since it is readily available and easily debenzoylated without destruction of the C–O–N bonds. Moreover, it is well known that acylated sugars react with nitrogenous bases to form mainly β-nucleosides[4].

The reaction of **3** with *N*-hydroxyuracil (**4**) in boiling acetonitrile in the presence of triethylamine gave only 10% of an αβ-mixture (**5** and **6**) in the ratio 1:9, which was fractionated by preparative t.l.c. to give crystalline **5** and **6**. The removal of the protecting groups of the chromatographically pure **5** afforded *N*-(β-D-ribofuranosyloxy)uracil (**2**) in 79% yield.

Attempts to increase the efficiency of the above reaction by variation of the reaction parameters and using the trimethylsilylated base[5] were unsuccessful. However, when **3** was condensed with **4** in acetonitrile in the presence of triethylamine at 50° and 10 kbar, using the previously described high-pressure technique[6], 46% of the 1:9 αβ-mixture (**5** and **6**) was obtained. Elevation of the pressure to 15 kbar gave a slightly higher yield (51%) so that optimisation of pressure and temperature

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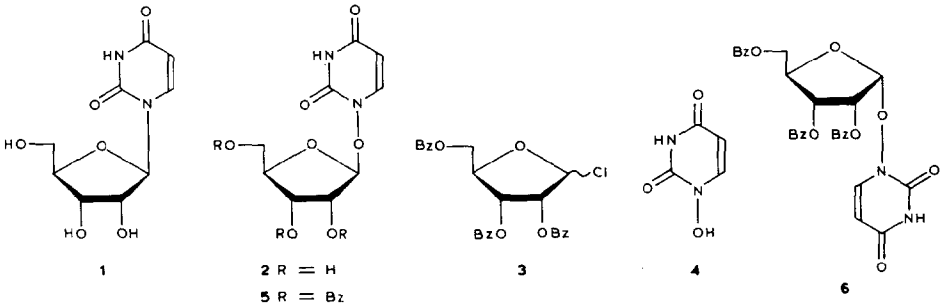

may not have been achieved. Extension of the high-pressure approach to the synthesis of other nucleosides and their "C–O–N" analogues is under investigation.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot-stage and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter. ^{1}H-N.m.r. spectra were recorded with Jeol JNM-4H-100 and Bruker SM-100 (100 MHz) spectrometers on solutions in $(CD_3)_2SO$ (internal Me_4Si). All reactions were monitored by t.l.c. on Silica Gel 60 (Merck), which was also used for preparative t.l.c. Column chromatography was performed with Kieselgel 60 (230–400 mesh, Merck). 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl chloride[7] (**3**) and *N*-hydroxyuracil[8] (**4**) were prepared by the reported methods.

N-*(2,3,5-Tri*-O-*benzoyl-β-* (**5**) *and -α-*D-*ribofuranosyloxy)uracil* (**6**). — *N*-Hydroxyuracil (**4**; 320 mg, 2.5 mmol) was added to a stirred solution of sodium ethoxide prepared from sodium (58 mg, 2.5 mmol) and ethanol (10 mL), and stirring was continued for 30 min at ambient temperature. The mixture was then concentrated to dryness, and to a suspension of the residue in acetonitrile (20 mL) was added **3** (1.2 g, 2.5 mmol). The mixture was boiled under reflux for 3 h and then kept for 12 h at room temperature. The precipitated unreacted **4** was collected and washed with acetonitrile, and the combined filtrate and washings were concentrated. Column chromatography (benzene–ether, 7:3) of the semi-solid residue followed by preparative t.l.c. (hexane–ethyl acetate, 3:2) afforded **5** (132 mg, 9.2%) and **6** (14 mg, 1%).

Compound **5** had m.p. 185–187° (from aqueous ethanol), $[\alpha]_D^{25}$ −13° (*c* 1.2, methyl sulfoxide). ^{1}H-N.m.r. data (100 MHz): δ 11.6 (s, 1 H, NH), 8.2–7.3 (m, 15 H, 3 Ph), 7.7 (d, $J_{5,6}$ 8 Hz, 1 H, H-6), 5.96 (s, 1 H, H-1′), 5.9 (d, $J_{2',3'}$ 5 Hz, 1 H, H-2′), 5.56 (d, 1 H, H-5), 4.99 (d, 1 H, H-3′), 4.75 (m, 1 H, H-4′), 3.86 (m, 2 H, H-5′,5′).

Compound **6** had m.p. 164–166° (from aqueous ethanol), $[\alpha]_D^{25}$ +40.5° (*c* 2, methyl sulfoxide). ^{1}H-N.m.r. data (100 MHz): δ 11.5 (s, 1 H, NH), 8.55 (d, $J_{5,6}$ 8 Hz, 1 H, H-6), 8.2–7.3 (m, 15 H, 3 Ph), 6.22 (dd, $J_{1',2'}$ 9, $J_{1',3'}$ 3 Hz, 1 H, H-1′), 5.8 (m, 2 H, H-2′,3′), 5.28 (d, 1 H, H-5), 4.6 (m, 3 H, H-4′,5′,5′).

Anal. Calc. for $C_{30}H_{24}N_2O_{10}$: C, 62.9; H, 4.2; N, 4.9. Found: for **5**, C, 63.2; H, 4.4; N, 4.5. Found: for **6**, C, 62.5; H, 4.5; N, 4.5.

High-pressure reaction of **3** *with* **4**. — A solution of **3** (130 mg, 0.27 mmol), **4** (34 mg, 0.27 mmol), and triethylamine (0.08 mL) in acetonitrile (2.5 mL) was charged into a Teflon ampoule[9], placed in a high-pressure vessel filled with ligroin as the transmission medium, and compressed (10 kbar) for 19 h at 50°. After cooling and decompression, the mixture was worked-up as described above, to afford 46% of a mixture of **5** and **6** in the ratio of 9:1.

N-*(β-*D-*Ribofuranosyloxy)uracil* (**2**). — To a stirred solution of **5** (114 mg, 0.2 mmol) in anhydrous methanol was added a solution of sodium methoxide prepared from sodium (46 mg, 2 mmol) and methanol (5 mL), and stirring was continued for 16 h at ambient temperature. The mixture was then treated with Dowex 50 (H^+) until the solution was no longer basic. After removal of Dowex, the filtrate was evaporated to dryness and the residue was crystallised from ethanol to give **2** (41 mg, 79%), m.p. 236° (dec.), $[\alpha]_D^{25}$ −7.5° (*c* 2.4, methyl sulfoxide). ^{1}H-N.m.r. data (100 MHz): δ 11.3 (s, 1 H, NH), 7.8 (d, $J_{5,6}$ 8 Hz, 1 H, H-6), 5.82 (s, 1 H, H-1′), 5.4 (d, 1 H, H-5), 5.3 (m, 2 H, H-2′,3′), 4.1 (m, 1 H, H-4′), 3.9 (m, 2 H, H-5′,5′).

Anal. Calc. for $C_9H_{12}N_2O_7$: C, 41.5; H, 4.6; N, 10.8. Found: C, 41.2; H, 4.7; N, 10.4.

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