2′-Deoxypseudouridine

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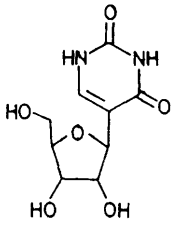
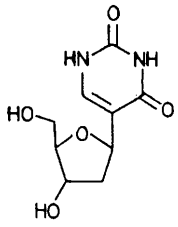
Summary The synthesis of 2′-deoxypseudouridine (**2**) is reported by condensation of 2,4-di-t-butoxy-5-lithiopyrimidine with 3,5-di-*O*-benzyl-2-deoxyribose and with 3,4-*O*-isopropylidene-2-deoxyribose (both giving the α-

anomer also), and stereospecifically from pseudouridine (**1**) *via* a 4,2′-anhydro-intermediate and the 2′-chloro-2′-deoxynucleoside (**4**).

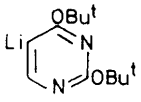
CONSIDERABLE interest is at present focussed on *C*-nucleosides and their synthesis.[1] Pseudouridine (**1**) is present in tRNA and in 5·8 S RNA[2] but there is no evidence for 2′-deoxypseudouridine (**2**) or any analogous *C*-nucleoside in DNA. Our interest in (**2**) arises from the fact that it and its *N*(1)-methyl derivative are analogues of 2′-deoxyuridine and thymidine, respectively and as such might be capable of incorporation into DNA. Moreover, depending on the *syn*- or *anti*-orientation of the pyrimidine ring of (**2**), two hydrogen-bonding systems are potentially available for base-pair formation and thus incorporated residues of (**2**) or the corresponding isocytosine derivative (the deoxycytidine analogue) could lead to a novel type of error-induction during replication.



(1)



(2)



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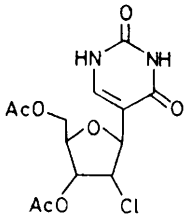

(4)

We have synthesised (**2**) and its α-anomer. The lithio-derivative[3] (**3**) reacted with 3,5-di-*O*-benzyl-2-deoxy-D-ribose[4] in tetrahydrofuran at −78 °C to give two epimeric substituted 5-pyrimidinyl polyols, whence cyclisation with methanol–hydrochloric acid (9 : 1) at room temperature for 90 min afforded a separable mixture of the 3′,5′-di-*O*-benzyl ether of (**2**) and its α-anomer (22 and 25%, respectively of crystalline products, based on starting sugar). Treatment of either anomer with BCl_3 quantitatively yielded (**2**), its α-anomer, and in small amount, one of the pyranose isomers (previously obtained by a corresponding synthesis using 3,4-*O*-isopropylidene-5-*O*-benzoyl-2-deoxyribose[5]). An alternative synthesis in which the sugar component was 3,4-*O*-isopropylidene-2-deoxyribose gave two polyols, which were deprotected and cyclised directly by acid to the deoxypseudouridine mixture. Although further work is necessary it is clear that acid-catalysed cyclisation to the furanosides and subsequent anomerisation are fast compared with the corresponding reactions in the pseudouridine series.[6]

Chromatographic separation of the deoxypseudouridine mixture on cellulose gave the crystalline β-anomer (**2**), m.p. 216—217·5 °C, followed by the α-anomer, m.p. 214—216 °C (decomp.). The presence of the furanose ring in each was established by observing the hydroxy ^1H n.m.r. signals in dry $(CD_3)_2SO$. Each showed both the expected doublet [δ 4·9 (3′-OH)] and triplet [δ 4·5 (5′-OH)]. The assignment of the anomeric configurations of (**2**) and its α-anomer followed from the close similarity of the n.m.r. signals of the C-2′ protons in D_2O with other anomeric pairs of pyrimidine deoxynucleosides[7] [δ (100 MHz, D_2O): β-anomer, 2·1—2·3 (2H, m); α-anomer, 1·8—2·3 (1H, m, H′); and 2·5—2·9 (1H, quintet, H″)].

Confirmation of the structure of β-deoxypseudouridine (**2**) was obtained by an alternative synthesis from (**1**). Following earlier work on uridine,[8] treatment of (**1**) with $SiCl_4$ in hot acetic acid stereospecifically gave the 2′-chloro-2′-deoxy derivative (**4**) *via* a 4,2′-anhydro-intermediate.[9] Reduction of (**4**) with tri-n-butyltin hydride, then mild deacetylation gave (**2**) alone, hence establishing its sugar ring size and the β-anomeric configuration.

We thank the S.R.C. for postgraduate studentships to S.D.B. and R.C.O. and Drs. I. S. Denniss and I. L. Batey for help with the n.m.r. spectroscopy and chromatography.

(*Received*, 20*th April* 1977; *Com.* 375.)

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