The Extension of the Sugar Chain of Thymidine: a New Route to 5′-Deoxyhexose Nucleosides

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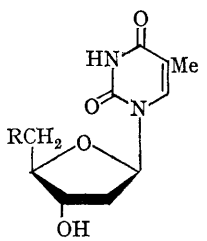
INCREASING interest is shown in hexofuranose homologues of naturally occurring nucleosides, *e.g.* purine homoribonucleosides.[1] Here we describe a new and simple route to 5′-deoxyhexofuranose nucleosides by direct prolongation of the sugar chain of pentofuranose nucleosides, *e.g.* thymidine (I). 5′-Deoxy-5′-iodothymidine (II), readily obtained from the 5′-*O*-toluene-*p*-sulphonate of (I) with NaI,[2] reacted with sodium cyanide in dimethyl sulphoxide at room temperature to give 5′-cyano-5′-deoxythymidine (III), which was isolated by chromatography on silica gel {44%, m.p. 224° (decomp.), $[\alpha]_D^{20}$ + 31° in dimethyl formamide}. Under similar conditions the 5′-*O*-toluene-*p*-sulphonate of (I) and NaCN produced only O(2),5′-cyclothymidine.



	R
(I)	OH
(II)	I
(III)	CN
(IV)	$CH_2 \cdot NH_2$
(V)	$CH_2 \cdot NHAc$
(VI)	$CH_2 \cdot OH$

Selective catalytic hydrogenation of the cyano-group of (III) with 5% palladium on barium sulphate[3] in ethanol under acidic conditions (HCl or Dowex H^+) at atmospheric pressure followed by adsorption on Dowex 50 (H^+) and elution with N-NH_4OH gave amorphous 1-(6′-amino-2′,5′,6′-trideoxy-β-D-*erythro*-hexofuranosyl)thymine (IV), which crystallized on trituration with acetone (80%, m.p. 175—177° (decomp.), $[\alpha]_D^{20}$ +20° in water). No formation of a secondary amine was observed. With palladium on charcoal no reduction of (III) took place. Attempts to interrupt the reduction of (III) at the aldimino-/aldehydo-stage by addition of carbonyl reagents, such as phenylhydrazine or semicarbazide, failed.[4] Compound (IV) was selectively acetylated at the amino-group by acetic anhydride in methanol to give (V), m.p. 208—209°, $[\alpha]_D^{20}$ +35° in water, ν_{max} (KBr) 1570 cm.$^{-1}$ ($CH_2 \cdot NH \cdot CO$). Treatment of the amino-sugar nucleoside (IV) with sodium nitrite in diluted acetic acid led to a mixture of products containing one major and three less polar nucleosides. The major component, separated chromatographically on Celite,[5] was shown to be the hitherto unknown 1-(2′,5′-dideoxy-β-D-*erythro*-hexofuranosyl)thymine (homothymidine) [(VI); 51% based on (IV), m.p. 170°, $[\alpha]_D^{20}$ +39° in water]. The yield of (VI) based on (III) could be increased if the acidified solution obtained after the hydrogenation of (III) was treated with sodium nitrite without isolation of (IV). The thymine nucleoside (VI) did not consume periodate and gave a diacetate with acetic anhydride in pyridine (amorphous, $[\alpha]_D^{20}$ +22·6° in ethanol). The presence of a terminal CH_2OH group in (VI) was confirmed by the ^1H n.m.r. spectrum (D_2O, 1% sodium 3-trimethylsilylpropane-1-sulphonate, 60 Mc./sec.) showing multiplets at: τ 2·52 (H-6, d), 3·78 (H-1′, t), 5·41 (H-2′ and H-3′), multiplet at 5·6—6·0 (H-3′ and H-4′), 6·24 (H-6′, t), 7·65 (H-2′, q), 8·09 (H-5′, q), 8·10 (5-Me, d).

The spectrum of (VI) is very similar to that reported for purine homoribonucleosides;[1] it shows no signal above τ 8·4. In contrast, the spectra of related 6-deoxy-sugars[1a] show a doublet around τ 8·8 due to the three protons at C-6′. All new compounds had the requisite spectral and analytical properties.

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