Tetrahedron Letters No. 22, pp 1951 - 1954, 1973. Pergamon Press. Printed in Great Britain.

NUCLEOSIDES LXXXI. AN APPROACH TO THE SYNTHESIS OF C-C LINKED β-D-RIBOFURANOSYL NUCLEOSIDES FROM 2,3-O-ISOPROPYLIDENE-5-O-TRITYL-β-D-RIBOFURANOSYL CHLORIDE [1]

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(Received in USA 29 March 1973; received in UK for publication 17 April 1973)

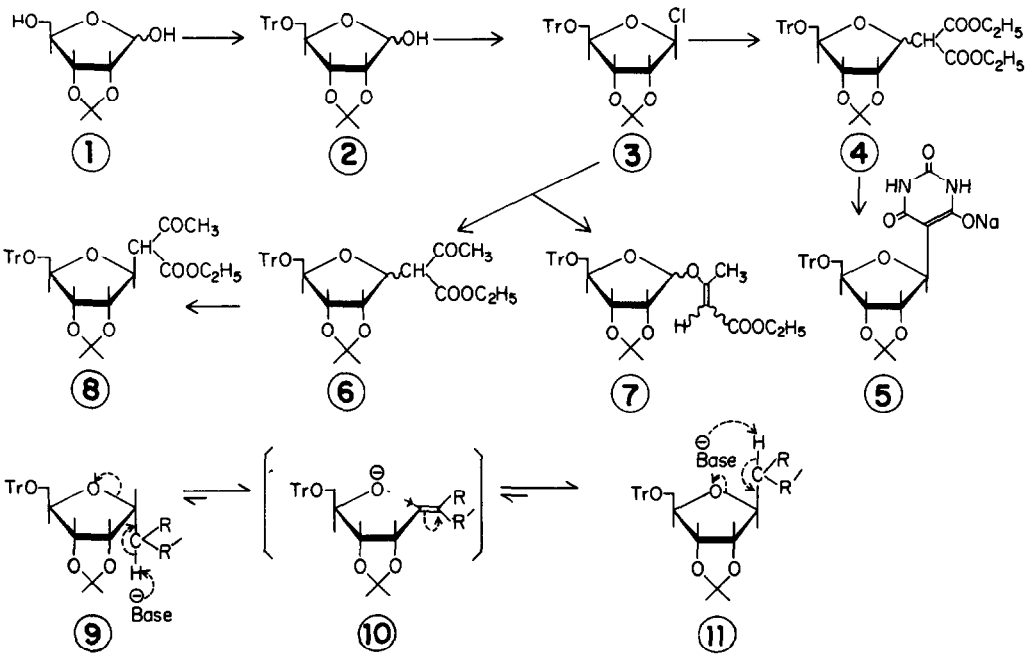
In recent years a new class of naturally-occurring nucleosides containing the unusual C-ribosyl linkage ("C-nucleosides") has been discovered [2,3]. Several synthetic routes directed to C-nucleosides have been reported [3-8]. Recently, Hanessian and Pernet [9] reported the successful condensation of tetra-O-acetyl-α-D-glucopyranosyl bromide with sodio diethyl or dibenzyl-malonate and, further, suggested the possibility of formation of C-C bonds at the anomeric position of D-ribofuranose by condensation of a suitably-protected ribofuranosyl halide with carbanions [10].

A halogenose for starting material which would lend itself to the synthesis of a C-nucleoside should meet the following requirements: a) neighboring-group participation by the 2-substituent must be avoided (as shown by Hanessian) [9] which precludes the use of acyl substituents; b) the condensation reaction with carbanions should give (either from steric considerations and/or by subsequent equilibration) predominantly or exclusively the β-anomer; and c) the protecting groups on the sugar should be stable to the conditions to be used in subsequent cyclization reaction and such groups should be removable under mild conditions. In this communication we report the synthesis of a suitably-protected ribofuranosyl halide (3) which meets these qualifications and its conversion to a C-nucleoside derivative (5) in good overall yields.

Treatment of 2,3-O-isopropylidene-D-ribofuranose (1) [11] with trityl chloride in pyridine gave the 5'-trityl derivative (2) as a syrup in good yield which, without purification, was treated with triphenylphosphine and CCl_4 in DMF [12] at room temperature to afford an excellent yield (quantitative by tlc) of 2,3-O-isopropylidene-5-O-trityl-β-D-ribosyl chloride (3), mp 114-115°, δ ($CDCl_3$); 6.10 (1H, sharp s, H-1). Condensation of 3 with sodio diethylmalonate in the presence of sodium iodide in 1,2-dimethoxyethane under reflux for 4 hr yielded (almost quantitatively) an anomeric mixture of the C-glycoside, diethyl 2,3-O-isopropylidene-5-O-trityl-D-ribofuranosyl malonate (4), λ_{max}^{film} 1600 (trityl), 1730, 1750 cm^{-1} (ester); δ ($CDCl_3$):

1.25 and 1.45 (6H, 2s, IP methyls), 1.30 (6H, m, ester methyls), 7.30 (15H, m, trityl). The α/β ratio of this anomeric mixture (R_f = 0.75 and 0.80 in benzene-ether 10:1) was altered by prolongation of the reflux time. Thus after 24 hr under reflux, the faster moving isomer (considered to be the β-anomer, vide infra) was the main product.

Treatment of 4 with urea and sodium ethoxide in ethanol under reflux for 8 hr gave the sodium salt of 5-(2',3'-O-isopropylidene-5'-O-trityl-β-D-ribofuranosyl)barbituric acid in 65% yield (recrystallized from pyridine), mp 215-127° dec, δ (DMSO-d_6): 1.23 and 1.46 (6H, 2s, IP group), 3.10 (2H, m, H-5'), 3.80 (1H, m, H-4'), 4.50 (1H, m, H-3'), 5.08 (1H, m, H-2'), 5.05 (1H, sharp s, H-1' indicating a β-nucleoside), 7.30 (15H, m, trityl), 9.08 (2H, s, NH);



$\lambda_{max}^{pH\ 7}$ (H_2O) = 263 nm (ϵ, 24,260). In N HCl selective absorption at 263 nm is essentially absent as shown previously [13] for barbituric acids.

A plausible mechanism for the conversion of anomeric mixture (4) to predominantly β is shown on the flow chart (9-11). It is noteworthy that the active proton is essential for this mechanism. The isopropylidene group would favor formation of the more thermodynamically stable β ("trans") isomer in the equilibrium process and would prevent polymerization (e.g. from 10) by favoring the tetrahydrofuran ring structure [14].

A similar epimerization phenomenon was observed with the ethyl acetoacetate analog (6) of 4. Treatment of 3 with sodio ethyl acetoacetate under similar conditions used for the synthesis of 4 afforded (quantitatively) a 1:1 mixture (by nmr) of the C-glycosyl derivative (6) and the O-glycoside (7) which were separated by column chromatography (silica gel G with benzene-ether 30:1 as eluant). Spectral data supporting structures 6 and 7 are as follows: for 6: δ ($CDCl_3$); 1.30 (3H, m, ester methyl), 1.25 and 1.50 (6H, 2s, IP methyls), 2.30 (1H, s, 1/3 $\underline{CH_3}\overset{O}{\overset{\|}{C}}$-), 2.35 (2H, s, 2/3 $\underline{CH_3}\overset{O}{\overset{\|}{C}}$-), 3.20 (2H, m, H-5), 4.16 (2H, m, ester methylene, 3.90-5.10 (5H for H-1, H-2, H-3, H-4 and methine proton of the ethylacetoacetate moiety), 7.32 (15H, m, trityl); λ_{max}^{film} 1600 (trityl), 1720, 1750 (ester and ketone) cm^{-1}: for O-glycoside (7): δ ($CDCl_3$); 2.02 (1.5H, s, 1/2 $CH_3\overset{O-}{\overset{|}{C}}=$), 2.15 (1.5H, s, 1/2 $CH_3\overset{O-}{\overset{|}{C}}=$), 5.02 (1/2H, broad s, H-1 of β-anomer), 5.85 (1/2H, d, $J_{1,2}$ = 4 cps, H-1 of α-anomer); λ_{max}^{film} 1660 ($\rangle C{=}C\overset{O}{\overset{\diagup}{\diagdown}}$). Theoretically, there are four possible isomers in 6, however only two methyl signals ($\underline{CH_3}\overset{O}{\overset{\|}{C}}$-) are detected by nmr. These signals are considered to be those of the α and β anomers because under similar conditions the α,β mixture (4) was obtained. Treatment of 6 with sodium ethoxide in ethanol under reflux gave one compound exclusively which exhibited its methyl signal at δ 2.30. These results are consistent with the epimerization discussed above. Compound 8 is considered to be the β-anomer by analogy with the conversion of 4 to 5.

The application of the halogenose (3) to the synthesis of other C-nucleosides and to other type reactions is underway in our laboratory.

Proper elemental analyses have been obtained for compounds 3-6.

Acknowledgement

The authors are grateful to Mr. Marvin J. Olsen for the nmr spectra.

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1. This investigation was supported in part by funds from the National Cancer Institute, N.I.H., U.S.P.H.S. Grant No. 08748.
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