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SYNTHESIS OF A NEW PYRIMIDINE NUCLEOSIDE ANALOG RELATED TO URIDINE

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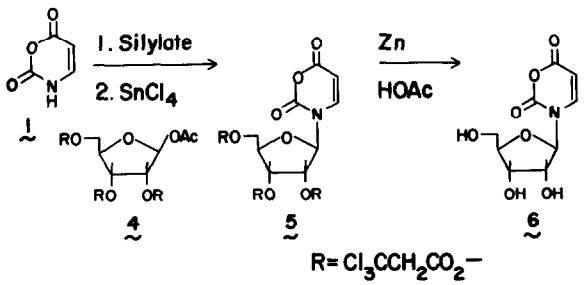
In this laboratory we have long been interested in the preparation of pyrimidine nucleoside analogs and their evaluation and development as potential tumor-inhibitory and antiviral drugs (1). As a continuation of this work we are concentrating on isosteric replacements of the nitrogen atoms in the pyrimidine ring. Some 3-deazapyrimidine nucleoside analogs have already been prepared (2,3). In 1970 (1), we also proposed to synthesize nucleosides of 3H-2,3-dihydro-1,3-oxazine-2,6-dione (1, "uracil anhydride"), which contains an oxygen isosteric replacement. These compounds, due to their size and shape, would be expected to go to the active sites of certain enzymes concerned with the metabolism of pyrimidine nucleotides and then, because of their anhydride function, would become an "active site-directed irreversible inhibitor" as defined by B. R. Baker (4). Compound 1 was synthesized in 1927 by Rinkes (5), and very recently by Washburne et al. (6) and Kuhar et al. (7). In view of recent reports of the moderate biological activities of 1 (7,8), we now wish to report the synthesis of its ribonucleoside, 3-(β-D-ribofuranosyl)-2,3-dihydro-1,3-oxazine-2,6-dione, 6, which represents a new class of pyrimidine nucleoside analogs.

Because of the lability of 1, particularly to base, it was necessary to select a protecting group for the sugar that could be removed by non-hydrolytic conditions. Such a group is the β,β,β-trichloroethoxycarbonyl, which can be removed by a β-elimination using zinc dust in acetic acid (9-11), and which has not hitherto been used in nucleoside syntheses.

Methyl β-D-ribofuranoside, 3, (12) was acylated (0°, 1.5 hr) by a slight excess of β,β,β-trichloroethoxycarbonyl chloride in DMF and anhydrous pyridine. Without extensive purification, the resulting product was treated (13) with excess acetic acid and acetic anhydride in the presence of concentrated sulfuric acid (room temperature, 16 hr) to afford the protected sugar, 4.



Compound 1 (6) was silylated with an equimolar mixture of trimethylchlorosilane and hexamethyldisilazane in tetrahydrofuran (room temp, 20 min). After evaporation, the residue was condensed (room temp, 24 hr) with the protected sugar, 4 (0.4 equiv to 1), in the presence of stannic chloride (2 equiv to 1) and 1,2-dichloroethane to give the blocked nucleoside, 5, in 90% yield, (110°d): nmr ($CDCl_3$, TMS) δ 4.81 (6H, bs), 5.75 (1H, d, J = 8Hz), 5.96 (1H, d, J = 4.3 Hz), 7.60 (1H, d, J = 8 Hz); uv (dioxane) λ_{max} 260 nm (log ε 3.78). Removal of the protecting groups with zinc dust in acetic acid gave, following purification on Amberlite IRC-50 and preparative TLC, the final product, 6, (hygroscopic solid) in 20% yield: ir (fluorolube) 1785 and 1720 cm^{-1}; nmr (DMSO-d_6) δ 5.72 (1H, d, J = 4 Hz), 5.92 (1H, d, J = 8 Hz), 8.35 (1H, d, J = 8 Hz); uv (H_2O) λ_{max} 265 nm (log ε 3.79).

It is generally recognized that condensation in the presence of a Lewis acid of silylated pyrimidines with sugars having a 2-acyloxy substituent leads almost exclusively to the β-anomer of nucleosides (14-16). The simplicity of the nmr spectrum, the relatively

small coupling constant of the doublet at 5.72 δ ($J_{1',2'}$ = 4 Hz), and the circular dichroism spectrum which shows a positive ellipticity effect centered at 270 nm, strongly suggest that 6 has the β-configuration. The similarities of ir (1785 and 1720 cm^{-1}, fluorolube) and uv (λ_{max} 265 nm, H_2O) spectra of 1 and 6 indicate that 6 is a N-nucleoside.

All new compounds gave satisfactory analyses, and the spectral data are in agreement with the structures assigned. Compounds 1 and 6 have approximately the same activities in inhibiting the growth of L5178Y cells in culture.

While this manuscript was in preparation, the synthesis of the deoxyribonucleoside of 1 was reported (17).

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