Tetrahedron Letters No.59, pp. 5197-5200, 1969. Pergamon Press. Printed In Great Britain.

ELUCIDATION OF ANHYDRONUCLEOSIDE STRUCTURES USING CARBON-13 MAGNETIC RESONANCE SPECTROSCOPY.

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(Received in USA 30 October 1969; received in UK for publication 24 November 1969)

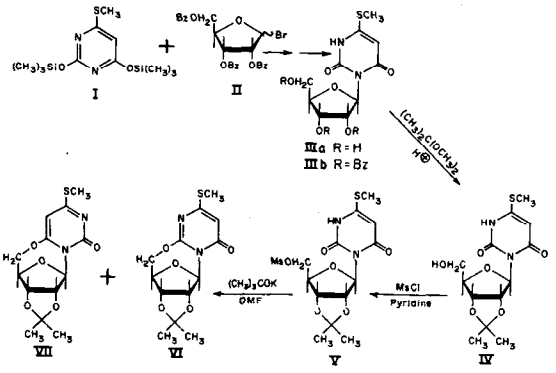
Recent studies[2,3] on the chemistry of 6,5'-anhydropyrimidine nucleosides have shown this class of compounds to be useful intermediates in the synthesis of 6-substituted pyrimidine nucleosides[4,6], which are of considerable chemical and biological interest.

We report herein the synthesis and structural elucidation of the isomeric pair of anhydronucleosides VI and VII.

Using standard silation and alkylation procedures outlined in the accompanying reaction scheme the synthesis of 4-methylthio-1-(β-D-ribofuranosyl)uracil (IIIa) has been described[5]. IIIa was converted into its crystalline 2',3'-O-isopropylidene derivative IV (yield 70%, m.p. 171-172°), which on treatment with methylsulfonyl chloride in pyridine gave the 5'-methylsulfonyl derivative (V, m.p. 155-157°), in almost quantitative yield.

Treatment of V with potassium tertiary butoxide in N,N-dimethylformamide yielded a crystalline mixture (m.p. 149-151°) of the cyclosides VI and VII. This mixture was resolved by chromatography on alumina into a major fraction [52%, m.p 170-171°; λ_{max}^{KBr} 1680 cm^{-1}] and a minor fraction [8%; m.p. 179-180°; λ_{max}^{KBr} 1680 cm^{-1}].

The pmr spectra of VI and VII exhibit only minor differences though the cycloside structure for each of these compounds is convincingly demonstrated. Completely resolved signals include a single vinylic proton for H-5 (δ = 6.04) and essentially an AB quartet (centered at δ 4.36, $J_{5',5'}$ = 13 Hz for the major component and centered at δ = 4.40, $J_{5',5'}$ = 13 Hz for the minor component) typical of that observed for the non-equivalent H-5' protons in anhydronucleosides



containing an oxygen bridge[3,7]. The chemical shift difference between the AB nuclei is greater in the minor component.

In order to resolve the structures of the isomers VI and VII we have determined the natural abundance carbon-13 spectra (15.1 MHz) using proton noise-decoupling techniques[8] in conjunction with a time averaging device for spectral accumulation. The spectra shown in Figure 1 for solutions in chloroform were obtained after 225 successive scans. The carbon-13 chemical shifts have been assigned from studies of a variety of related compounds and are reported relative to benzene. Thus, the high field lines (>100 ppm) may be attributed to methyl groups, those at 102.5 and 104.2 ppm, along with the line at 15.5 ppm, being characteristic of an isopropylidene group. This is shown by the absence of these lines in the spectrum of 4-methylthio-1-(β-D-ribofuranosyl)-pyrimidine-6-one (VIII) (in DMSO) also given in Figure 1. The line at ca. 115 ppm in all of these spectra has been assigned from independent

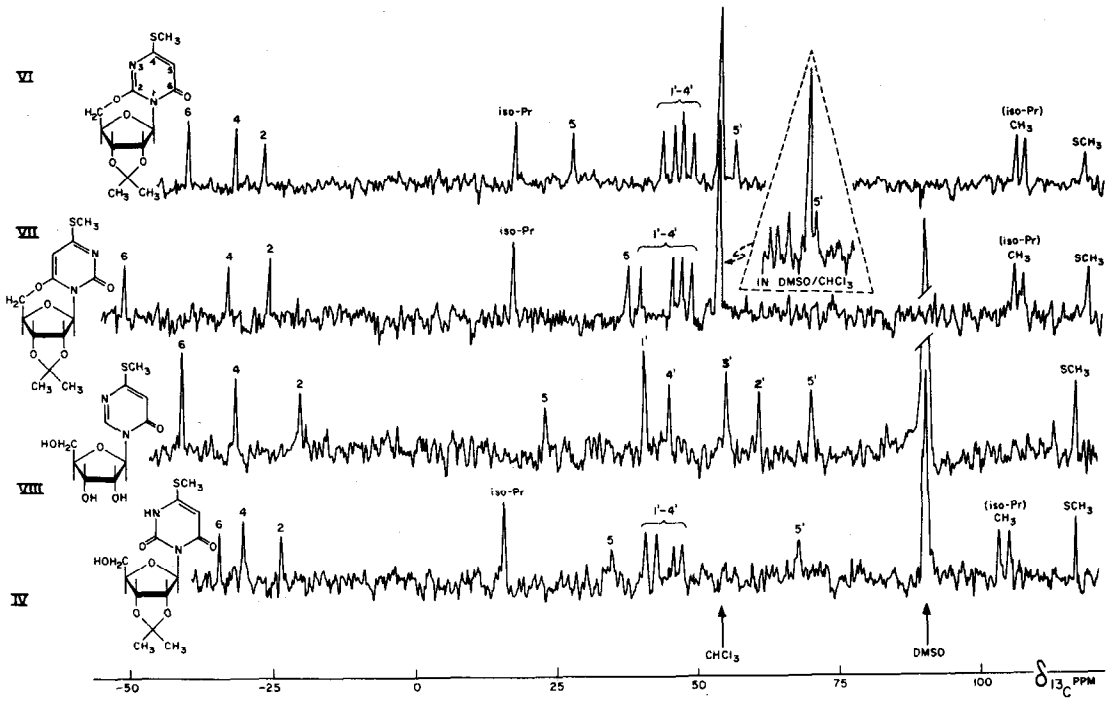


Figure 1

studies on unsubstituted compounds to the carbon in the methylthio-group.

The carbon-13 resonances attributable to the sugar-carbons in these systems exhibit characteristic chemical shifts over the range 37 to 67 ppm. The highest field line of this group is attributed to C-5' as evidenced by the low field shift (66 to ca. 53 ppm) on cyclisation at this position in the isomers VI and VII compared with the nucleoside VIII. In the isopropylidene derivatives it has not been possible to differentiate between C-1' to C-4', though the ordering shown for the nucleoside VIII has been shown to be generally characteristic in unsubstituted ribosides[9].

To further confirm the above assignments the spectrum of the precursor IV (in DMSO) of the isomers VI and VII is also included in Figure 1. Protonation of the pyrimidine ring in IV, however, limits the usefulness of this compound as a model in discussing structural effects on the chemical shifts in this ring. The order of shifts C-6, C-4, C-2 and C-5 for the pyrimidine peaks is well established from related compounds[9], and this order is used along with other supporting arguments to assign the corresponding peaks in VI, VII and VIII.

The highest field pyrimidine peak for each compound has been assigned to C-5 from observations of undecoupled spectra. Only broad multiplet structure for all lines above 16 ppm occurred, while the singlets due to the four quarternary carbon atoms (including the isopropylidene carbon) were clearly visible. The high-field position for C-5 is in keeping with the high electron density and electrophilic reactivity for this position expected in pyrimidine nucleosides. No definitive explanation is proposed for the significant changes observed in the shift of C-5 in this series of compounds, but it is noted that C-5 tends to move in opposite directions from C-6 in the two cyclic isomers suggesting a correlated polarization of charge at these adjacent positions. The similarity of chemical shifts at C-4 is expected from the identical structural environment found for this carbon in each compound. Likewise C-2 shifts are also quite similar except in VIII where an expected upfield shift was recorded. The almost identical observed shifts at C-6 in VI and VIII emphasize the similar electronic environment at this position in these compounds. Thus the approximately -10 ppm shift noted in C-6 in VII relative to both VI and VIII constitutes the principle basis upon which this structure is assigned to the minor isomer. Table I presents the shift values relative to benzene for the pyrimidine carbons.

This example of the use of carbon-13 chemical shifts is an indication of the superiority this method has over the more common pmr techniques and of the potential expected for this

valuable tool in structural studies of large biologically important molecules.

TABLE I

Compound	C-2	C-4	C-5	C-6
IV	-22.5_4	-29.0_1	$+33.7_3$	-32.9_8
VI	-26.7_7	-31.7_8	$+25.6_3$	-39.9_6
VII	-25.3_3	-32.4_2	$+35.6_4$	-50.4_5
VIII	-20.3_2	-31.4_4	$+21.5_8$	-40.7_4

Acknowledgments: The authors would like to express their sincere gratitude to Professor R. K. Robins for his encouragement throughout the course of this work, and to the National Institutes of Health for their support of this research under grants GM 08521-09 and CA 08109-04.

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