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CONFORMATIONAL ANALYSIS OF NUCLEOSIDE ANALOGS OF SIX-MEMBERED HETEROCYCLES CONTAINING OXYGEN AND/OR SULFUR

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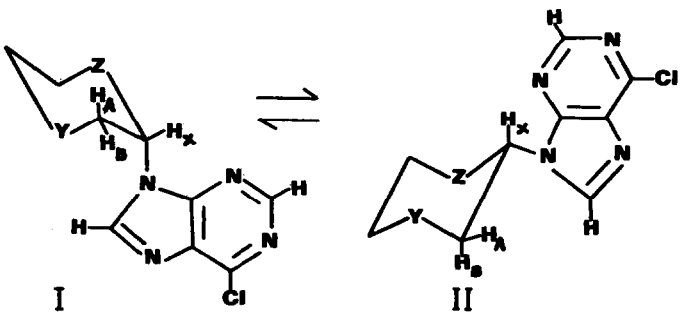
A project in this laboratory is concerned with the synthesis and biological examination of nucleoside analogs of five- and six-membered heterocycles such as compounds 1-6.[2] Some of these compounds exhibit antitumor activity.[3] Moreover, they are of further significance because of their interesting stereochemical properties; for example, it has been found[4] that the conformational equilibrium, in chloroform-d at ambient temperature, of the 3-substituted 1,4-oxathiane 6 contains ~90% of the conformer having the purine moiety in an axial orientation, whereas in the case of the regioisomer 5, there is a preponderance of the equatorial form. The high proportion of the axial conformer I in the case of compound 6 is highly



I ⇌ II

1 Z=O, Y=CH_2
2 Z=S, Y=CH_2
3 Z=O, Y=O
4 Z=S, Y=S
5 Z=O, Y=S
6 Z=S, Y=O

remarkable in view of the observations that, although some N-(glycopyranosyl)imidazoles,[5] in chloroform, and 2-azido- and 2-isocyanato-tetrahydropyrans,[6] in carbon tetrachloride or acetonitrile, exist preponderantly in the conformation having the nitrogen substituent in the axial orientation, in the case of several pyranosyl nucleosides of bulky heterocyclic bases such as 6-benzamidopurine,[7] indole,[8] and benzotriazole,[9] there is a preponderance of the equatorial form. Of relevance to the present work are the studies on 2-substituted 1,4-oxathianes by Foster and coworkers,[10] who discussed the conformational behavior in terms of the anomeric effect and steric factors, and by Zefirov and coworkers,[11] who also postulated a repulsive interaction referred to as the "hockey-stick" effect. The conformational peculiarities observed in compounds 5 and 6 promoted a systematic investigation of nucleoside analogs of

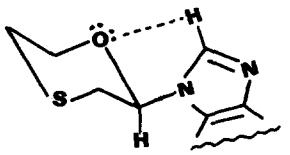
saturated six-membered rings containing one or two hetero atoms. Here we report preliminary results with compounds 1—6.

In Table I are summarized data on the conformational equilibrium of compounds 1–6 obtained by pmr spectroscopy; the proportion of the axial conformer I was estimated using the equation[11] cited in the footnote to the Table. A limitation of the method in the present work arises from the choice of appropriate values for J_{aa}, J_{ee}, J_{ae}, and J_{ea}; moreover, the spectroscopic data have been analyzed on the assumption that the six-membered heterocycles adopt the chair conformation (compare Refs. 11 and 15), although it is recognized that the hetero atoms can cause a puckering or flattening distortion.[16]

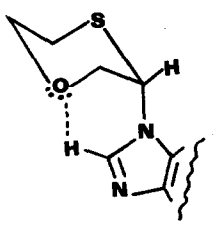
The first noteworthy feature is the observation of a preponderance of the equatorial form in the case of the tetrahydropyran and thiane derivatives 1 and 2. The results indicate that for these compounds, in the axial conformer I, the interaction of the purine moiety with the syn-axial hydrogens overcomes the anomeric effect;[17] the significantly smaller proportion of the axial conformer in the case of the thiane 2 is attributable to a difference between the interactions[17,18] in the O–C–N and S–C–N fragments of 1 and 2, respectively. Interestingly, replacement of the C-4 methylene group in 1 and 2 by oxygen and sulfur to give the 1,4-dioxane 3 and 1,4-dithiane 4, respectively, leads, in each case, to an increase in the proportion of the axial conformer; this phenomenon may be viewed, at least partially, as a manifestation of the gauche effect[18] in the O(S)–C–C–N fragments.

Probably the most puzzling conformational behavior of the present series of compounds is that exhibited by the pair of 1,4-oxathiane regioisomers 5 and 6. A relevant factor in a possible rationalization of the preponderance of the equatorial and axial forms for 5 and 6, respectively, is the geometry of the 1,4-oxathiane ring. On the basis of a smaller C–S–C bond angle (compared with C–O–C) and a longer C–S bond length (compared with C–O), the ring can adopt a distorted chair conformation in which the axial substituents on C-2 and C-6 are inward-pointing, and those on C-3 and C-5 are outward-pointing (compare Ref. 10); thus, in the axial conformers, the interaction of the purine moiety with the syn-axial hydrogen would be expected to be greater in 5 than in 6. Another suggestion to account for the observed results invokes the possible formation of a hydrogen bond between H-8 of the purine moiety and the oxygen of the 1,4-oxathiane ring as a stabilizing effect; accordingly, in the case of 5, the equatorial conformer would be stabilized (see 5a), whereas, in the case of 6, the axial conformer would be stabilized (see 6a). The very high proportion of the axial conformer in

the case of 6 compared with that in 2 is particularly spectacular.

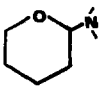
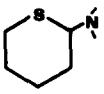
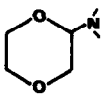
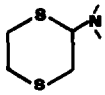
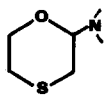
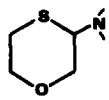


5a



6a

TABLE I. Conformational Equilibrium Data* of Compounds 1-6

Compound		Chemical shift of $H_x(\tau)$	Solvent	$J_{AX}+J_{BX}$ (Hz)	"Optimal set" of coupling constants (Hz)		% axial conformer I
	1	4.17	$CDCl_3$	11.5	J_{aa}=12, J_{ee}=2,	(Ref. 6)	35
		4.22	CD_3CN	12.4	J_{ae}=J_{ea}=3		26
	2	4.23	$CDCl_3$	13.0	J_{ae}=J_{ee}=J_{ea}=2.5,	(Ref. 12)	6
		4.23	CD_3CN	13.2	J_{aa}=11		4
	3	3.92	$CDCl_3$	8.5	J_{aa}=9.44, J_{ea}=0.9,	(Ref. 13)	44
		3.98	CD_3CN	8.4	J_{ee}=J_{ae}=2.78		45
	4	4.06	$CBCl_3$	10.0	J_{ea}=J_{ee}=3,	(Ref. 14)	62
		–	CD_3CN†	–	J_{aa}=10.6, J_{ae}=5.8		–
	5	3.95	$CDCl_3$	11.5	J_{ae}=J_{ee}=J_{ea}=2.5,	(Ref. 11)	24
		4.00	CD_3CN	12.2	J_{aa}=11		15
	6	4.43	$CDCl_3$	6.0	J_{ae}=J_{ee}=J_{ea}=2.5,	(Ref. 11)	88
		4.40	CD_3CN	5.2	J_{aa}=11		98

*The pmr spectra were recorded on a Bruker HX-60 spectrometer with TMS as the internal standard. The position of the conformational equilibrium was determined using the equation[11] $|J_{AX}+J_{BX}|=N_I(J_{ea}+J_{ee})+(1-N_I)(J_{aa}+J_{ae})$; the width or half-height width of the signal H_X was taken as the sum of coupling constants $|J_{AX}+J_{BX}|$.

†Compound 4 was insufficiently soluble in CD_3CN.

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