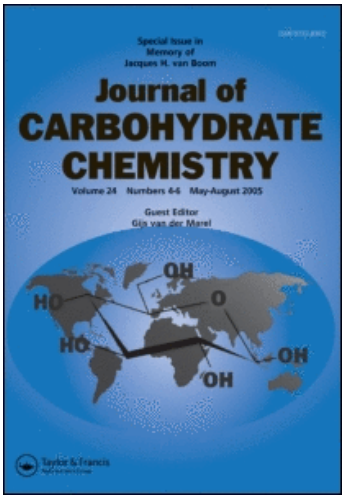

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STUDIES ON THE CONFORMATION OF POLYHYDROXYALKYLPYRAZOLO(3,4-b)QUINOXALINES

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ABSTRACT

^{1}H NMR spectral studies on polyhydroxyalkylpyrazolo-(3,4-b)-quinoxaline derivatives of sugars having five to seven carbon atoms have shown that the polyhydroxyalkyl chain exists in a conformation in which a hydrogen bond is formed between the 1'-hydroxyl group and N-2 of the pyrazolo(3,4-b)-quinoxaline base moiety. The polyhydroxyalkyl chain exists in the planar zigzag conformation, where no 1,3 syn axial interaction is present. Substitution in the base moiety did not change the extent of the population of the planar zigzag conformation.

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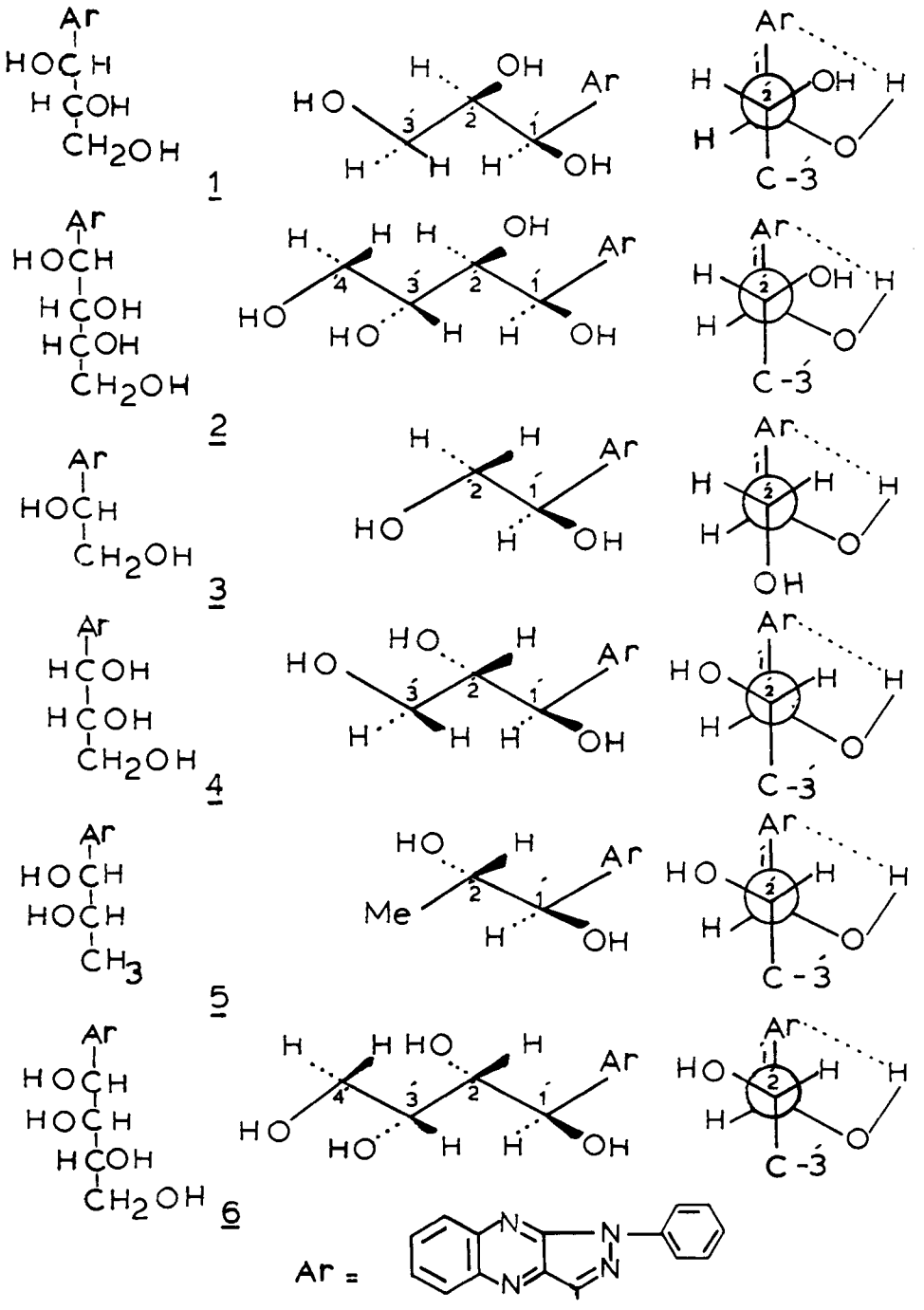
INTRODUCTION

There has been considerable interest recently in the conformation of straight chain derivatives of sugars in solution. The fully extended zigzag arrangement for the aliphatic hydrocarbon chain has generally been regarded as the favored conformation for acyclic sugar derivatives in solution.[1-3] Parallel 1,3 interactions between substituents decrease the stability of the zigzag form. In such a case rotation around one carbon-carbon bond occurs to give a bent (sickle) form as the favored conformation.[2] Various types of sugar derivatives have been examined by ^{1}H NMR spectroscopy and the coupling constants provide information on the conformation of the polyhydroxyalkyl chain. Saccharide heterocyclic derivatives of quinoxaline,[4,5] glyculose arylosotriazoles[6] and their acetylated derivatives,[7] and acetylated thiazoles[8] have been examined by ^{1}H NMR spectroscopy. The spin couplings of the protons of the acyclic sugar chain have been shown to be consistent with the planar zigzag conformation, except when this would lead to a parallel 1,3 interaction between oxygen atoms on the chain.

Saccharide pyrazolo(3,4-b)quinoxalines are compounds of biological interest.[9] A possible link of biological activity with the chain configuration and the resulting conformational disposition of acyclic carbohydrate derivatives, has been proposed.[10-12] In the present study a series of polyhydroxyalkylpyrazolo-(3,4-b)quinoxalines were studies by ^{1}H NMR spectroscopy, and the results were interpreted in terms of the favored conformation of the polyhydroxyalkyl side chains. The effect of substitution in the base moiety on the population of the planar zigzag conformation is discussed.

^{1}H NMR Spectra. The spectra of compounds (1-6) were first measured in dimethyl sulfoxide-d_6 to observe signals of the OH groups as well as the C-H protons. Acetic acid-d_4 was added to exchange the hydroxyl protons, which collapsed to a single line,



SCHEME 1

and the signals of the methine or methylene protons adjacent to hydroxyl groups also collapsed to simpler patters. The spectra were analyzed by first assigning signals in the acid-exchanged spectra. The hydroxyl proton signals in the original spectra were then assigned. The signals in the ^{1}H NMR spectra occur in two regions, the low field region δ 7.0-8.5, corresponding to the aromatic protons of the pyrazolo(3,4-b)quinoxaline base moiety, and the higher field region, δ 3.0-6.0, representing the sugar protons, the coupling constants of which give information on the configuration of the polyhydroxyalkyl chain. A sample spectrum for the protons of the side chain for compound 2 is shown in Figure 1. The chemical shifts and coupling constants for compounds 1-6 are shown in tables 1 and 2, respectively. The effect of substitution at the base moiety of compound 2 on the population of the planar zigzag conformation is shown in Table 3.

DISCUSSION

The chemical shift data listed in Table 1 for compounds 1-6 indicate that in each case the C-1' hydroxyl proton resonates at lower field than the rest of the sugar protons of the polyhydroxyalkyl chain, except that for compound 2, where the C-1' proton was the most downfield signal. This observation is characteristic for polyhydroxyalkylpyrazolo(3,4-b)quinoxalines having the D-arabino-configuration of the side chain. The C-1' proton likewise resonates at lower field than the rest of the sugar protons for compounds 1-6. Deshielding by the adjacent aromatic residue undoubtedly is the major factor in causing these signals to appear at low field. Additional deshielding might also arise from formation of an intramolecular hydrogen bond between the C-1' hydroxyl group and the pyrazolo(3,4-b)quinoxaline base moiety. Hydrogen bonding of this type was suggested in polyhydroxyalkyltriazole analogs.[6] For the pyrazolo(3,4-b)quinoxaline analogs 1-6, two types of hydrogen bonding between 1'-OH and the base moiety are possible (Fig. 2). The C-1' hydroxyl group can be hydrogen bonded at either N-2 of the pyrazole ring in five-

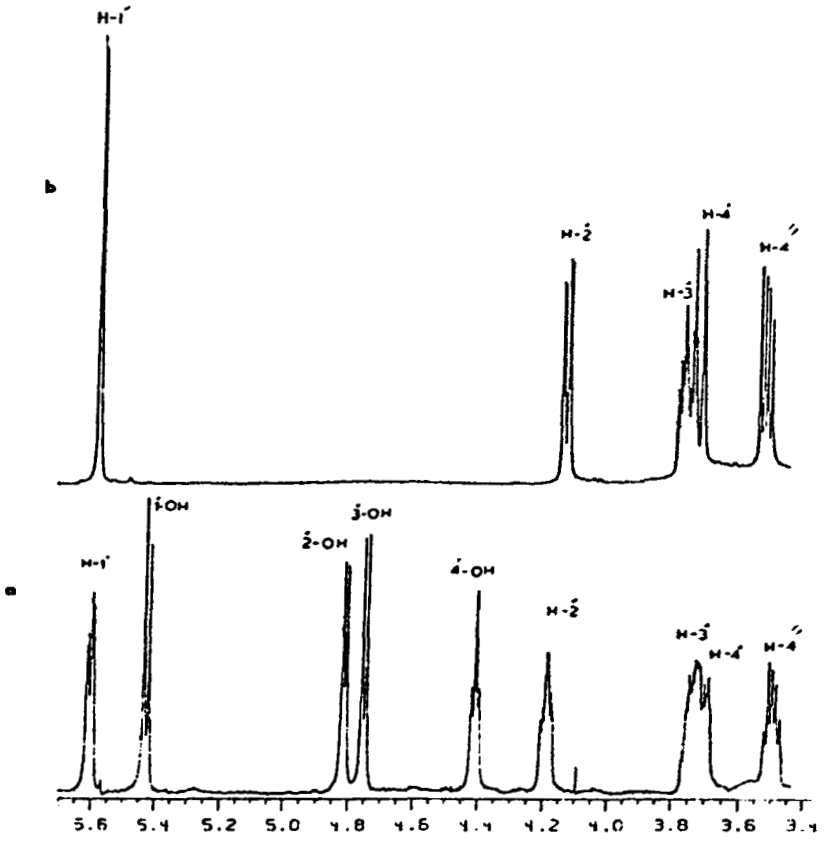


Fig. 1. The 470 MHz ^{1}H NMR spectrum of 1-phenyl-3-(D-arabino-tetritol-1-yl)pyrazolo(3,4-b)quinoxaline (2) in dimethyl sulfoxide-d_6; a, before addition of CD_3CO_2D and b, after addition.

membered ring (structure A), or to N-4 of the quinoxaline ring in a six-membered ring (structure B). Examination of models shows that structure B would be destabilized by the fused benzene ring, and in structure A, the interfering nonbonded interactions are at minimum.

The tendency of hydrogen bonding formation of C-1' hydroxyl group and the base moiety is greater than the hydrogen bonding formation of C-1' proton and the base moiety. This is attributed

TABLE 1

Chemical Shift Data for Pyrazolo(3,4-b)quinoxalines[a] 1-6 (δ P.P.M.).

Compd	confign	H-1'	H-2',H-2"	H-3',H-3"	H-4',H-4"	1'-OH	2'-OH	3'-OH	4'-OH
1	Threo	5.38d	4.43q	3.30-3.80m		5.58d	4.83d	4.61t	
2	arabino	5.62d	4.22dd	3.67-3.70m, 3.5q		5.40d	4.62bs	4.67d	4.33t
3	glycero	5.38t	4.43-4.43m			5.80d	4.90t		
4	erythro	5.13d	4.51m	3.29-3.81m		5.77d		4.32-4.60m	
5	erythro	4.94d	4.54m	(CH_3),1.40d		5.83d			
6	lyxo	5.37d	4.59d	4.15t	3.59-3.67 bd	5.80d	4.4d	4.4d	4.5t

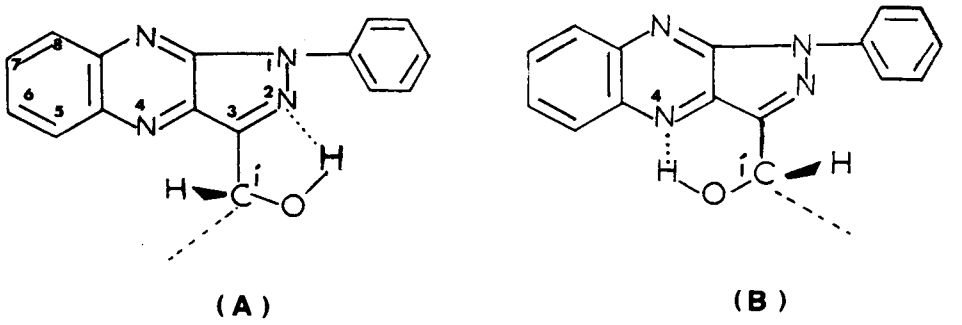
[a]values for methine and methylene protons of the polyhydroxyalkyl chain are taken from spectra after addition of CD_3CO_2D. The δ values recorded for the H-1' signal are within 0.05 ppm of the values observed in nonacidified methyl sulfoxide-d_6.

TABLE 2

First-order Coupling Constants (JHz) for Pyrazolo(3,4-b)quinoxalines 1-6.[a]

Compd	config	$J_{1',2'}$ ($J_{1',2''}$)	$J_{2',3'}$ ($J_{2',3''}$)	$J_{3',4'}$ ($J_{3',4''}$)	J_{gem}	$J_{1',OH}$	$J_{2',OH}$	$J_{3',OH}$	$J_{4',OH}$
1	threo	4.9	5.3 (b)		10.9	6.2	5.0	6.0	
2	arabino	2.7	7.7	6.07 (3.17)	11.1	6.0	4.6	4.0	6.0
3	glycero	6.5 (3.6)			11.0	5.1	6.0		
4	erythro	8.7	5.3 (3.1)		11.3	5.0	b	b	
5	erythro	7.5	6.0			5.0	b		
6	lyxo	9.3	(~0)	6.5 (~0)	10.4	5.0	6.9	7.5	b

[a]By direct measurement of peak spacings; no detectable differences in the $J_{1',2'}$ couplings were noted before and after adding CD_3CO_2D.
[b]Not determined.



(A) (B)

Fig. 2.

to the stronger hydrogen bonding formation between nitrogen and oxygen, rather than between nitrogen and carbon (C-1'). This was evident by the greater deshielding of the C-1' hydroxyl than C-1' proton. Only compound 2 showed greater deshielding of the C-1' proton than the C-1' hydroxyl.

The deshielding of the C-1' proton, in general, is explained by electronic deshielding by the adjacent aromatic base moiety beside the intramolecular hydrogen bonding. That deshielding of C-1' proton caused not only by hydrogen bonding was proved from the deshielding of the analogous proton in the acetyl derivatives of quinoxaline[4] and triazole[7] analogs. It was observed at lower field than the other protons on the side chain, in spite of the absence of intramolecular hydrogen bonding as a result of acetylation. However, the extent of deshielding of H-1' in polyhydroxyalkylpyrazolo(3,4-b)quinoxalines, relative to other methine protons on the chain, and the magnitude of deshielding of the 1'-OH proton, relative to other hydroxyl protons, suggests that intramolecular hydrogen bonding is, nevertheless, significant in polyhydroxyalkylpyrazolo(3,4-b)quinoxalines.

The hydrogen bonding between C-2' hydroxyl group and N-2 of the pyrazole ring through a six-membered ring is excluded, since the 2'-OH signal appears in the region δ 4.6-4.9, a region which is characteristic of nonanomeric hydroxyl protons (in di-

methyl sulfoxide) that are not intramolecularly hydrogen bonded.[6,13]

Inspection of the chemical shift data for H-1' and 1'-OH protons for the saccharide pyrazolo(3,4-b)quinoxalines 1-6 (Table 1) and their coupling constant values ($J_{1',2'}$, Table 2), reveals similarities between homomorphous derivatives. Compounds 1 and 2 having the threo configuration at C-1' and C-2', show higher field shift for 1'-OH (δ 5.40-5.58) and relatively low values for the coupling constant $J_{1',2'}$ (2.7-4.9 Hz). In contrast, compounds 4-6 having the erythro configuration at C-1' and C-2' show downfield shift for 1'-OH (δ 5.80) and higher $J_{1',2'}$ values (7.5-9.3 Hz). Compounds having the arabino and lyxo configuration show the extreme values in each group, indicating that the conformational population is affected by the chain length of the side chain. Compound 3 having the D-glycero configuration shows 1'-OH chemical shift and $J_{1',2'}$ value close to the group having the erythro configuration at C-1' and C-2'.

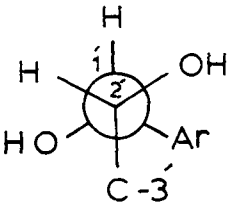
If the extent of deshielding is a measure of the stability of the hydrogen-bonded structure having the 1'-OH group coplanar with the pyrazolo(3,4-b)quinoxaline moiety, compounds 3-6 adopt the hydrogen bonded conformation to the greatest extent, and compounds 1 and 2 to the least extent. Compound 2 in particular, shows the 1'-OH signal at higher field (δ 5.40) indicating the least extent of hydrogen bonding. The inverse correlation is observed for the C-1' proton; it will statistically exist at lower field (δ 5.62). This is due to the existence of the C-1' proton, to a greater extent in the rotamer having H-1' coplanar with the aryl residue where deshielding is at a maximum.[14]

An explanation for the greater deshielding of the 1'-OH proton for compounds 3-6 than for compounds 1 and 2 can be reached from their Newman projection formula (Scheme 1). Compounds 3-6 have maximum staggering of large groups along C-1' and C-2'. In their planar conformations, the H-2' atom bisects the angle of the aryl residue and 1'-OH group. In compounds 1 and 2 where the 1'-OH signals are at higher field, the 2'-OH group is largely

constrained to bisect the angle of the aryl group and the 1'-OH group. In this orientation the 1'-OH•••N hydrogen bond may be weakened by gauche steric interference, by competitive hydrogen bonding of the 2'-OH group with O-1' or with the aryl nitrogen atom, or by a combination of these effects.

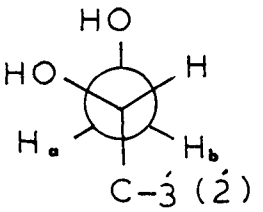
Conformation of the side chain. For sugars and their derivatives in the liquid state or in solution, at room temperature, there are rapid interconversions between rotamers because of the small free-energy difference between various conformers. The ^{1}H NMR data only give information for the average conformation. However, certain conformers are nevertheless, energetically favored. The range of coupling constants reflects the alterations in the dihedral angle which results from the differences in stereochemistry. If it can be assumed that vicinal, antiparallel protons show spin-spin coupling constant of 8-9 Hz, and that vicinal gauche protons show coupling of 2-3 Hz,[15] it is possible to make predictions of favored conformation in terms of the observed coupling constant.

The low coupling constant $J_{1',2'}$ (2.7 Hz) for compound 2, indicates a gauche arrangement between H-1' and H-2'. There is another possible C-1'-C-2' rotamer 2a (Fig. 3) which would give a small $J_{1',2'}$ value, but this rotamer can be excluded for compound 2, because it would generate a 1,3 interaction between parallel hydroxyl groups at C-1' and C-3' and produce a gauche interaction between C-3' and the aryl residue. The large coupling constant $J_{2',3'}$ value (7.70 Hz) for compound 2 indicates antiparallel arrangement between H-2' and H-3'. The fact that $J_{3',4'}$ and $J_{3',4''}$ values are different (6.07 and 3.17 Hz, respectively) indicates that one proton at C-4' is gauche to H-3' and the other one, although not exclusively antiparallel, is preponderantly so. This is compatible with the terminal group conformation 2b (Fig. 4), or with the rotamer 2c having antiparallel hydroxyl groups at C-3' and C-4'. The latter would, how-

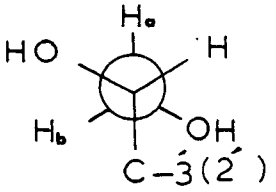


1 a
2 a

Fig. 3.



2 b
4 a



2 c
4 b

Fig. 4.

ever, have parallel interaction between the hydroxyl groups at C-2' and C-4' and is presumably less favored.

These data are consistent with the extended planar zigzag conformation 2 in which the terminal hydroxyl group is coplanar with the carbon chain. The resolution of the spectrum indicates a high degree of conformational purity, and in agreement with the extended planar zigzag conformation as the favored conformation with minimum nonbonded interactions between groups. Analogous results were found for the triazole[6,16] and quinoxaline[4] analogs having the D-arabino configuration of the side chain.

The observed coupling constant $J_{1',2'}$ (4.9 Hz) for compound 1, is, however, intermediate between that expected for antiparal-

lel and gauche arrangement of H-1' and H-2'. It indicates a major contribution from the conformer having H-1' and H-2' in gauche arrangement in the planar zigzag structure (1). The rotamer having antiparallel arrangement between H-1' and H-2' would be destabilized by 1,3 interaction between C-3' and the aryl residue. The fact that $J_{1',2'}$ is larger than the $J_{1',2'}$ value for compound 2, suggests that while preponderance of the planar zigzag conformation with gauche relationship of H-1' and H-2', a minor contribution of the rotamer having H-1' and H-2' antiparallel, is more favored in 1 than in 2. The other C-1'-C-2' rotamer 1a (fig. 3) having gauche arrangement between H-1' and H-2' is probably less favored as it would bring C-3' and the aryl residue into a gauche relationship.

The coupling constant value $J_{1',2'}$ (6.5 Hz) for compound 3 indicates that H-1' is preponderantly antiparallel with H-2', with a population factor[8] of about 70%. The $J_{1',2''}$ value (3.6 Hz) indicates that H-1' and H-2" are gauche to each other. These results are in accord with the extended planar zigzag conformation for compound 3. The other possible rotamer having gauche arrangement of H-1' and H-2', although having antiparallel arrangement of 1'-OH and 2'-OH groups, is destabilized by 1,3 interaction between the aryl residue and 2'-OH group.

The observed coupling constants for compound 4 are in accord with the planar zigzag conformation depicted for its enantiomorph. The large coupling constant $J_{1',2'}$ (8.7 Hz) indicates that H-1' and H-2' are exclusively antiparallel. Similarly, the different coupling constants $J_{2',3'}$ and $J_{2',3''}$ values (5.3 and 3.1 Hz) indicate that H-2' is gauche to one of the protons at C-3' and almost antiparallel to the other. It has the terminal group conformation 4a (Fig. 4). The terminal group rotamer 4b arising from C-2'-C-3' rotation is destabilized by the 1,3 interaction at C-1' and C-3'.

The large coupling constant $J_{1',2'}$ value (7.5 Hz) for compound 5, indicates antiparallel arrangement between H-1' and H-2'. This is in accord with the presence of the planar zigzag

conformation as the preponderant conformer. Replacement of the terminal hydroxymethyl group of compound 4 by the methyl group at compound 5, resulted in little change in the population of the planar zigzag conformation.

The observed coupling constant $J_{1',2'}$ value (9.3 Hz) for compound 6 indicates that H-1' and H-2' are exclusively antiparallel and this will also bring the 1'-OH and 2'-OH groups antiparallel to each other. The observed doublet corresponding to the H-2' signal ($J_{2',3'} \sim 0$), indicates gauche arrangement of H-2' and H-3'. These results are in accord with extended planar zigzag arrangement of the carbon atoms in the side chain which was found[6,16] for acyclic sugar derivatives having the lyxo configuration of the side chain.

The foregoing data are entirely consistent with those of saccharide heterocyclic analogs.[4,6,8] The polyhydroxyalkylpyrazolo(3,4-b)quinoxaline analogs having the arabino and lyxo configuration (2 and 6, respectively) exist almost exclusively in the extended planar zigzag conformation, and those of the erythro configuration (4 and 5) are preponderantly in this conformation. Those having the threo and glycero configuration (1 and 3, respectively) while adopting a planar zigzag conformation, minor contribution from the C-1'-C-2' rotamers are more favored than for compounds (4 and 5) having the erythro configuration.

Substitution in the base moiety in compound 2 having the arabino configuration of the side chain did not show appreciable change in the population of the planar zigzag conformation of the polyhydroxyalkyl chain. This was concluded from the close agreement of the coupling constant values (Table 3) of the substituted derivatives 7-11 (Fig. 5) with that for compound 2.

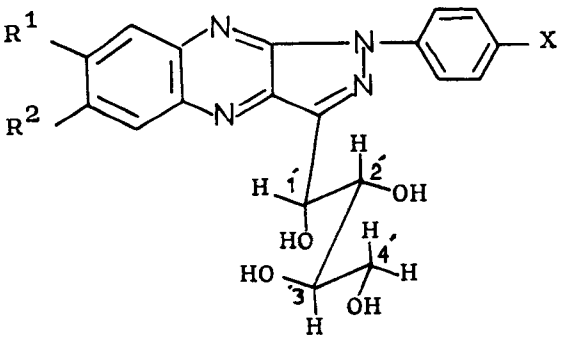
EXPERIMENTAL

The preparation of compounds 1-6 was effected by standard procedures.[19-21] 3-(3'-D-threo-Glycerol-1-yl)-1-phenylpyrazolo(3,4-b)-quinoxaline[20] (1) was obtained from D-galactose, 1-phyenyl-3-(D-arabino-tetritol-1-yl)-pyrazolo(3,4-b)quinoxaline[21]

TABLE 3

Coupling constants (Hz) for substituted (D-arabino-tetritol-1-yl)pyrazolo(3,4-b)quinoxaline analogs 7-11 in DMSO-d_6 at 470 MHz.

Compound	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{3',4''}$	Ref.
7	2.96	8.14	3.08	6.17	17
8	2.63	8.00	3.45	5.87	17
9	2.85	8.06	3.11	5.82	18
10	2.84	8.13	3.01	5.76	18
11	2.81	8.00	3.00	5.90	18



7, $R^1=R^2=H$, X=Me

8, $R^1=R^2=H$, X=F

9, $R^1=R^2=Me$, X=H

10, $R^1=R^2=X=Me$

11, $R^1=R^2=Me$, X=Cl

Fig. 5.

(2) was obtained from D-glycero-D-gulo-heptose, 3-(L-glycero-dihydroxyethyl)-1-phenylpyrazolo(3,4-b)-quinoxaline[20] (3) was obtained from L-arabinose, 3-(D-erythro-glycerol-1-yl)-1-phenylpyrazolo(3,4-b)quinoxaline[20] (4) was obtained from D-glucose, 3-(3'-Deoxy-L-erythro-glycerol-1-phenylpyrazolo(3,4-b)-quinoxaline[20] (5) was obtained from L-rhamnose, 1-phenyl-3-(D-lyxo-tetritol-1-yl)pyrazolo(3,4-b)quinoxaline[19] (6) was obtained from D-glycero-L-manno-heptose. Each product was recrystallized several times from propyl alcohol and all had melting points in good agreement with the literature values.[19-21] Compounds 7-11, were prepared by procedures described in the literature.[17,18] ^{1}H NMR spectra were recorded with Varian EM-390 (90-MHz), Varian FT-80 (80 MHz) and Nicolet 470 MHz (for compounds 2 and 6), using tetramethylsilane as a reference. Chemical shifts and coupling constants are first-order values, as measured directly from spectral spacings.

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