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HETEROCYCLIC COMPOUNDS FROM SUGARS

PART VI*. THE CONFORMATIONS OF 2-(POLYHYDROXYALKYL)- AND 2-(POLYACETOXYALKYL)BENZOTHIAZOLES. A NUCLEAR MAGNETIC RESONANCE STUDY†

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ABSTRACT

The conformation of several 2-(polyhydroxyalkyl)- and 2-(polyacetoxyalkyl)-benzothiazoles has been studied by n.m.r. spectroscopy at 100 MHz in dimethyl sulfoxide-d_6 and chloroform-*d* solutions, respectively. Compounds having the D-*arabino*, D-*galacto*, and D-*manno* configuration adopt an extended planar conformation in both series. On the other hand, coupling constant data for the D-*xylo*, D-*ribo*, and D-*gluco* configuration indicate that, in these cases, a bent conformation is preferred in which the unfavorable 1,3-dipolar interaction is relieved through rotation at either the C-1–C-2 or C-3–C-4 bond.

INTRODUCTION

Numerous studies have been made recently of the conformations of acyclic sugar derivatives in solution. Since the first report[2] on the conformations of 2-(D-arabinit-1-yl)quinoxaline and its tetraacetate, a great number of other open chain derivatives, including osotriazoles[3,4], acetylated aldose diethyl dithioacetals[5], fully acetylated aldonic acid thioamides[6], 2-(polyacetoxyalkyl) thiazoles[6], unsaturated open chain derivatives[7], sugar diphenyl dithioacetals[8], *aldehydo*-aldose acetates[9], ketose derivatives[10], acetylated pentononitriles[11], hexitol derivatives[12], and acetylated aldose dimethyl acetals[13] have been investigated and their conformations discussed on the basis of their n.m.r. spectra. Recently, prediction of the favored conformation based on the n.m.r. study of some acyclic sugar derivatives proved to be useful in interpreting the course of ring-forming reactions[14,15].

The application of n.m.r. to the conformational analysis of such systems has been described elsewhere[3,5,6] so that we only point out that all analyses use the Karplus equation (in a suitably modified form), and it is assumed[3,5,9] that 1,3-dipolar interactions play a decisive role in determining the preferred conformation and therefore the conformer ratio at the equilibrium[6].

*For Part V, see Ref. 1.
†Dedicated to Professor V. Deulofeu, in honor of his 70th birthday.

As it is known, vicinal coupling constants depend not only on dihedral angles[16] but also on C–C bond distances, H–C–C angles, electronegativities[17] and configurations[18–20] of electronegative substituents on the CH–CH fragment. Conclusions based solely on dihedral angle dependence are therefore subject to rather severe limitations. Such an approach has, nevertheless, been adopted in several studies[2–15] mainly because data that take into account the effects of the above factors are not available with similar systems.

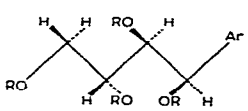
In this work we report on the n.m.r. study of several synthesized[21] 2-(polyhydroxyalkyl)- and 2-(polyacetoxyalkyl)benzothiazoles. Analysis of the spin-spin coupling data allows the study of the influence of the side-chain configuration on the conformational behavior of these compounds in solution.

RESULTS AND DISCUSSION

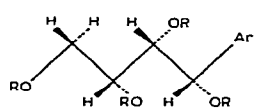
2-(Polyacetoxyalkyl)benzothiazoles. — The chemical shift and coupling constant data are reported in Table I. Assignments were based on analogies[3,6] and, when needed, verified by spin-decoupling experiments. Coupling constants were obtained on a first order basis.

The following compounds have been investigated: 2-(2,3,4,5-tetra-*O*-acetyl-D-arabinit-1-yl)benzothiazole (**1**) 2-(2,3,4,5-tetra-*O*-acetyl-D-xylit-1-yl)benzothiazole (**2**), 2-(2,3,4,5-tetra-*O*-acetyl-D-ribit-1-yl)benzothiazole (**5**), 2-(2,3,4,5-tetra-*O*-acetyl-D-glucit-1-yl)benzothiazole (**7**), 5-chloro-2-(2,3,4,5,6-penta-*O*-acetyl-D-glucit-1-yl)benzothiazole (**13**), 2-(2,3,4,5,6-penta-*O*-acetyl-D-galactit-1-yl)benzothiazole (**9**), 5-chloro-2-(2,3,4,5,6-penta-*O*-acetyl-D-galactit-1-yl)benzothiazole (**14**), and 2-(2,3,4,5,6-penta-*O*-acetyl-D-mannit-1-yl)benzothiazole (**11**).

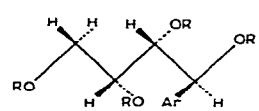
In each spectrum the H-1 signal appears as a doublet, well-separated from other signals at lowest field. The H-2 proton gives a quadruplet which could be easily identified in the case of **1**, **2**, and **5** since H-3 is expected to give rise to a more complicated pattern due to its coupling to three other protons (H-2, H-4, and H-4'). In the case of the hexose derivatives **7**, **13**, **9**, and **14**, two quadruplets, which considerably overlap in compound **11**, appear in the same region. Through spin decoupling it was possible to allocate the signals to H-2 and H-3, respectively, invariably the



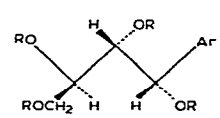
1a R = Ac
3a R = H



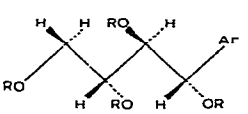
2a R = Ac
4a R = H



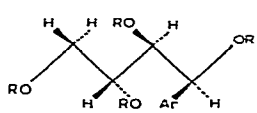
2b R = Ac
4b R = H



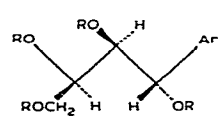
2c R = Ac
4c R = H



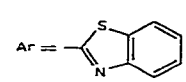
5a R = Ac
6a R = H

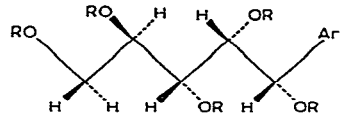


5b R = Ac
6b R = H

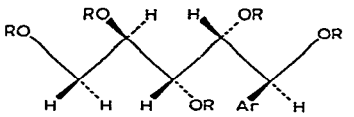


5c R = Ac
6c R = H

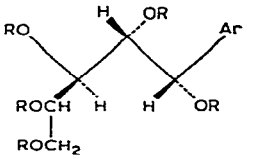




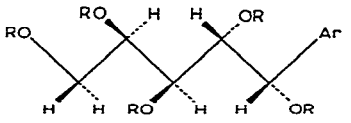
7a R = Ac
8a R = H
13 R = Ac; Ar'



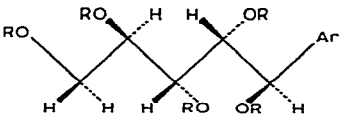
7b R = Ac
8b R = H



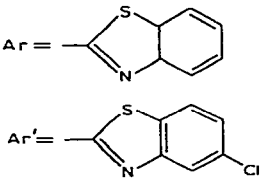
7c R = Ac
8c R = H



9a R = Ac
10a R = H
14 R = Ac; Ar'

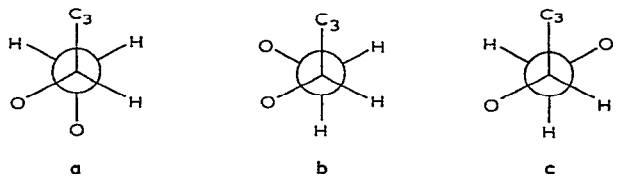


11a R = Ac
12a R = H



lower-field quadruplet was assigned to H-2. The H-3 of pentoses and the H-4 of hexoses give a complicated pattern, as just mentioned, so that $J_{3,4}$ and $J_{3,4'}$ on one hand, and $J_{3,4}$, $J_{4,5}$ and $J_{4,5'}$ on the other hand, were measured from the splittings of the H-4, H-4′ and from that of the H-3, H-5, and H-5′ signals, respectively. The terminal CH_2 group always constitutes the AB part of an ABX system and, thus, gives a characteristic eight line pattern, as it generally is the case in open-chain sugar derivatives[22,23].

*2-(2,3,4,5-Tetra-*O*-acetyl-*D*-arabinit-1-yl)benzothiazole* (**1**). — The coupling constants (Table I) are in good agreement with the planar zig-zag arrangement of the side-chain carbon atoms (**1a**). Since the coupling constant values are practically identical with those reported[6] for 4-(*p*-bromophenyl)-2-(2,3,4,5-tetra-*O*-acetyl-D-arabinit-1-yl)-1,3-thiazole, it is to be assumed that compound **1** adopts the same conformation. The possible staggered rotamers for the terminal CH_2OAc group are represented in



a b c

SCHEME I

Scheme 1. From these, rotamer **a** represents the energetically most favored situation[6]. The intermediate value of $J_{3,4'}$ (5 Hz) indicates, however, a fairly important contribution of rotamer **b**, so that the percentage of **b** may be higher than that calculated by Lee and Scanlon[6] who predicted $J_{3,4'}$ value of 7.6 Hz.

*2-(2,3,4,5-Tetra-*O*-acetyl-*D*-xylit-1-yl)benzothiazole* (**2**). — Both $J_{1,2}$ (6.2 Hz) and $J_{2,3}$ (4.3 Hz) are inconsistent with the planar zigzag conformation **2a** which

TABLE I

CHEMICAL SHIFT (δ) AND COUPLING CONSTANT (J) VALUES OF 2-(POLYACETOXYALKYL)BENZOTHIAZOLES[a]

Compound	*Configuration*	*Chemical shifts (p.p.m.)*							*Coupling constants (Hz)*							
		H-1	*H-2*	*H-3*	*H-4*	*H-4'*	*H-5*	*H-5'*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{3,4'}$	$J_{4,4'}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
1	D-*arabino*	6.48	5.85	5.33	4.34	4.15			3.0	8.9	2.4	5.0	12.4			
2	D-*xylo*	6.39	5.82	5.24	4.37	4.06			6.2	4.3	5.2	6.0	11.6			
5	D-*ribo*	6.37	5.73	5.25	4.28	4.12			4.3	7.1	3.1	4.8	12.2			
7	D-*gluco*	6.37	5.89	5.39	5.13		4.31	4.07	6.4	4.0	7.0			3.8	5.9	12.5
13	D-*gluco*	6.35	5.88	5.41	5.16		4.31	4.07	6.4	3.9	7.0			3.9	5.8	12.0
9	D-*galacto*	6.34	5.81	5.59	5.34		4.32	4.08	2.1	9.8	1.9			5.2	7.3	11.5
14	D-*galacto*	6.31	5.76	5.54	5.34		4.33	3.89	2.1	9.6	1.8			5.0	7.3	11.3
11	D-*manno*	6.13	5.76	5.67	5.17		4.28	4.10	8.7	2.1	8.7			2.8	4.8	12.4

[a]100-MHz n.m.r. spectra in chloroform-*d* solution.

would require both values to be about 2 Hz, *i.e. gauche* arrangement for both H-1–H-2 and H-2–H-3. Conformation **2a** represents indeed a highly unfavorable situation as a consequence of 1,3-dipolar interaction between the C-1 and C-3 acetoxy groups. Conformers **2b** and **2c** are free from such interaction so that they can be regarded as the main components of the equilibrium mixture, **2b** being in a slight excess over **2c** ($J_{2,3} < J_{1,2}$). Similar observations have been made on other open-chain derivatives having the *xylo* configuration[5,6,9].

*2-(2,3,4,5-Tetra-*O*-acetyl-*D*-ribit-1-yl)benzothiazole* (**5**). — The extended planar conformation **5a** is unfavorable for the same reason as it is in the case of compound **2**. This is shown by the $J_{1,2}$ value (4.3 Hz) which is very different from the value of 9.5 Hz expected for conformer **5a**. On the basis of the values of $J_{1,2}$ and $J_{2,3}$ (7.1 Hz), conformer **5b** seems to be the major component in the conformer equilibrium, but contributions from **5a** and **5c** cannot be completely ruled out. Although **5c** does not show an unfavorable 1,3-interaction, its contribution is likely to be very small because of the large $J_{2,3}$ value observed (7.1 Hz), instead of the expected value of 2 Hz for **5c**. The *gauche* interaction between C-2 (OAc) and C-3 (CH_2OAc) groups may be a reason, however, for the instability of conformer **5c**. On the other hand, the 4.3 Hz value for $J_{1,2}$ indicates a small but nonnegligible population for conformer **5a**. Thus, in this instance the *gauche* OAc–CH_2OAc and the 1,3-OAc–OAc interactions seem to provide destabilization factors of similar importance. An alternative explanation for the relatively large $J_{1,2}$ values (expected $J_{1,2} = 2$Hz for **5b**) may be the distortion of conformer **5b** from the perfect staggered arrangement.

*2-(2,3,4,5,6-Penta-*O*-acetyl-*D*-glucit-1-yl)benzothiazole* (**7**) *and 5-chloro-2-(2,3,4,5,6-penta-*O*-acetyl-*D*-glucit-1-yl)benzothiazole* (**13**). — The spectra of both compounds show almost exactly the same splittings, so that their conformations should be the same. Furthermore, as the D-*gluco* configuration is homomorphous with respect to C-1, C-2, and C-3 with the D-*xylo* configuration, a similar conformational behavior is to be expected in both series. A 1,3-dipolar interaction between C-1 (OAc) and C-3 (OAc), as with the D-*xylo* rotamer **2a**, causes conformation **7a** to be unfavorable. The large (6.4 Hz) $J_{1,2}$ coupling constant suggests a major contribution from conformer **7b** in which this interaction is relieved by rotation about the C-1–C-2 bond. A smaller contribution from conformer **7c** cannot be excluded, because the $J_{2,3}$ value (4.0 Hz) is greater than that predicted (2 Hz) for conformer **7b**.

*2-(2,3,4,5,6-Penta-*O*-acetyl-*D*-galactit-1-yl)benzothiazole* (**9**), *5-chloro-2-(2,3,4,5,6-penta-*O*-acetyl-*D*-galactit-1-yl)benzothiazole* (**14**), *and 2-(2,3,4,5,6-penta-*O*-acetyl-*D*-mannit-1-yl)benzothiazole* (**11**). — For the *galacto* and *manno* configuration the extended planar zig-zag conformations (**9a** and **11a**) do not present any unfavorable nonbonded interactions. The coupling constant data for these compounds (Table I) are almost identical with the predicted values (either 2 or 9.5 Hz). They are, therefore, fully consistent with the expectation that all these compounds exist practically entirely in the favored extended, planar conformations in chloroform-*d* solution.

2-(Polyhydroxyalkyl)benzothiazoles. — We have examined the following compounds: 2-(D-arabinit-1-yl)benzothiazole (**3**), 2-(D-xylit-1-yl)benzothiazole (**4**), 2-(D-

TABLE II

CHEMICAL SHIFT (δ) AND COUPLING CONSTANT (J) VALUES OF 2-(POLYHYDROXYALKYL)BENZOTHIAZOLES[a]

Compound	*Configuration*	*Chemical shift (p.p.m.)*					*Coupling constant (Hz)*				
		OH-1	*OH-2*	*OH-3*	*H-1*	*H-2*	*OH-1–H-1*	*OH-2–H-2*	*OH-3–H-3*	$J_{1,2}$	$J_{2,3}$
3	D-*arabino*	6.02	4.50		5.17	3.82	6.5			1.5	8.0
4	D-*xylo*	6.02			5.00	3.91	5.1			4.0	3.8
6	D-*ribo*	6.18	4.91	4.53	5.19		5.7	5.0	5.0	4.1	6.4
8	D-*gluco*	6.06	4.62	4.28	5.03	4.06	4.6	6.5		5.0	~2[b]
10	D-*galacto*	5.84			5.11	4.40	6.4			1.4	9.2
12	D-*manno*	6.26			4.86	3.93	5.5			~8.0	2.0

[a]100-MHz n.m.r. spectra in dimethyl sulfoxide-d_6 solution. [b]Calculated from the width at half height.

ribit-1-yl)benzothiazole (**6**), 2-(D-glucit-1-yl)benzothiazole (**8**), 2-(D-galactit-1-yl)benzothiazole (**10**), and 2-(D-mannit-1-yl)benzothiazole (**12**). The 100-MHz n.m.r. spectra of these compounds have been recorded in dimethyl sulfoxide-d_6 solution. The chemical shift and coupling constant data are reported in Table II.

At first the spectra were determined on dimethyl sulphoxide-d_6 solutions. Since the proton exchange of the hydroxyl group is very slow in this solvent[24], the OH-protons give well-separated and sharp lines and show spin-spin splittings due to the coupling with the adjacent methine protons. Upon treatment with deuterium oxide, only incomplete deuteration could be achieved. Complete deuteration *vs* fast proton exchange can be obtained by catalytic amounts of hydrogen chloride as described by El-Khadem, Horton, and Page[3]. The spectrum of **3** showed unusually broad signals for the protons OH-1 (δ 6.02), H-1 (δ 5.17), and (probably) OH-2 (δ 4.50). Upon addition of deuterium oxide, partial deuteration took place and the residual OH-1, OH-2, and H-1 signals showed clean splittings. Addition of hydrogen chloride removed the residual OH-signals and additional splitting from the H-1 signal.

After elimination of the OH-signals by exchange, spin decoupling was used in order to obtain more information. The side-chain methine (and methylene) protons generally gave strongly coupled spectra which were not amenable to first order analysis. However, the H-1 signal was in each case well separated from other low-field resonances (δ 4.8–5.3) in the deuterated spectra. Double-resonance experiments, with this line being irradiated, allowed identification of the H-2 resonance to obtain $J_{2,3}$. The H-2 signal occurs generally next to that of H-1, at higher field in the deuterium oxide-exchanged spectra. The lowest-field signal in the original spectra could be unequivocally assigned to OH-1. The deshielding of this proton may be explained in a manner similar to that of the osotriazoles[3].

Conformational significance of the coupling constants. — In each case it was possible to measure $J_{1,2}$ and $J_{2,3}$. In the case of the pentose derivatives **3**, **4**, and **6**, these couplings provided sufficient information to deduce the preferred side-chain conformations in these compounds. In compound **3** the values of $J_{1,2}$ (1.5 Hz) and $J_{2,3}$ (8.0 Hz) are reasonably close to the corresponding J values of the tetraacetate **1** and, thus, are entirely consistent with the planar zig-zag conformation **3a**. El Khadem, Horton, and Page[3] arrived at the same conclusion after examination of D-*arabino*-hexulose phenylosotriazole. Similarly, the $J_{1,2}$ (4.1 Hz) and $J_{2,3}$ (6.4 Hz) values of the D-*ribo* compound **6** are close to that found for the acetylated derivative **5**. Therefore, it can be safely assumed that both compounds possess similar conformations, *i.e.* the equilibrium mixture for **6** consists mainly of the "sickle" conformer **6b** with small contributions of conformer **6a** (which contains an unfavorable 1,3-dipolar interaction between OH-1 and OH-3) or of the other "sickle" conformer (**6c**) or of both. It can be equally assumed, as it was done in the case of compound **5**, that the deviation of the $J_{1,2}$ value from the predicted 2 Hz may be accounted for by a distortion of the chain from the perfect staggered arrangement. This explanation avoids the rather unconventional assumption that an energetically unfavorable structure (**6a**) could

contribute to the conformational equilibrium. In the case of the *xylo* derivative **4** the value of $J_{2,3}$ (3.8 Hz) is essentially the same as that of the corresponding acetate 2, but the value of $J_{1,2}$ (4.0 Hz) is considerably smaller. These values are compatible with a conformer equilibrium consisting of approximately equal amounts of the "sickle" conformer **4b** and **4c**. El Khadem, Horton, and Page[3] also emphasized, for 2-D-*xylo*-hexulose phenylosotriazole, the importance of the conformer similar to **4b**. The $J_{1,2} = 5.0$ Hz value for the D-*gluco* derivative **8** is inconsistent with the extended planar conformation **8a** which would require a coupling of ~ 2 Hz for $J_{1,2}$. On the other hand, the $J_{2,3} = 2$ Hz value is fully compatible with either **8a** or the bent-chain conformer **8b**, but incompatible with the other bent conformer **8c**. The 1,3-dipolar interaction between OH-1 and OH-3 in **8a** makes this conformation energetically unfavored. Its contribution cannot, however, be excluded, because the $J_{1,2}$ value is considerably smaller than that required by **8b** (9.5 Hz). This situation is likely to be the same as that of the *ribo* isomer **6**, so that the dominant conformer for the *gluco* derivative can be assumed to be **8b**, the C-1H–C-2H dihedral angle being somewhat different from the ideal 180° value.

In the case of the *galacto* (**10**) and *manno* (**12**) derivatives, the observed values for $J_{1,2}$ and $J_{2,3}$ (see Table II) are fully compatible with the preferred planar zig-zag conformations **10a** and **12a**, respectively.

It can be seen from the foregoing that, for a given configuration, there is no significant conformational difference between a poly(hydroxyalkyl) compound in dimethyl sulfoxide-d_6 and its corresponding acetate in chloroform-*d*. Therefore, it can be concluded that the solvent has no substantial influence on the conformation of these compounds and that intramolecular forces, especially 1,3-dipolar interactions, are the most important factors in determining the preferred conformations in solution. It seems probable that the same factors determine the conformations in the crystalline state as well[25].

EXPERIMENTAL

N.m.r. spectra at 100 MHz were recorded with Varian HA-100 and Jeol MH-100 instruments with hexamethyldisiloxane and tetramethylsilane as internal standards. Spin-decoupling experiments were performed with frequency-sweep or "synchro-track" decoupling methods, respectively. Experimental procedures for obtaining the compounds used in this study were reported elsewhere[21].

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