102 mg (94%): λ_{max}^{film} 2.89 (OH), 3.05 (C≡CH), 4.73 (C≡C), 7.23 μm (CMe_2); nmr (chloroform-*d*), τ 5.55–6.05 (four-proton multiplet, H-3,4,5,5′), 6.60 (broad singlet, disappears on deuteration, OH), 7.45 (one-proton doublet, $J_{1,2}$ = 1.7 Hz, H-1), 8.51, 8.60 (three-proton singlets, CMe_2).

3-*O*-(3,5-Dinitrobenzoyl)-4,5-*O*-isopropylidene-1-pentyne-D-*erythro*-3,4,5-triol (17).—To a solution of compound **2** (63 mg) in dry pyridine (3 ml) was added 3,5-dinitrobenzoyl chloride (100 mg), and the mixture was stirred for 8 hr at room temperature. Ice and water (50 ml) were then added, and after 45 min the crystalline product was filtered, washed with water, and dried, yield 78 mg (56%). The product was recrystallized twice from absolute methanol to give **17** as small white needles: mp 133–133.5°; $[\alpha]^{23}D$ +50 ± 1° (*c* 2, chloroform); λ_{max}^{KBr} 3.05 (C≡CH), 4.70 (C≡C), 5.78 (C=O), 6.12, 6.48, 6.83, 13.72 (aryl), 7.41 μm (CMe_2); nmr (chloroform-*d*), τ 1.80 (three-proton singlet, aryl protons), 4.16 (one-proton quartet, $J_{1,3}$ = 2.4 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 5.4–6.1 (three-proton multiplet, H-4,5,5′), 7.29 (one-proton doublet, H-1), 8.58 (six-proton singlet, CMe_2); X-ray powder diffraction data, 11.48 m, 8.04 m, 6.71 m, 5.79 w, 5.54 w, 5.18 w, 4.93 w, 4.67 m, 4.40 m, 4.04 s (1), 3.78 w, 3.44 vw, 3.33 w, 3.01 w, 2.92 w, 2.76 w.

Anal. Calcd for $C_{15}H_{14}N_2O_8$: C, 51.43; H, 4.03; N, 8.00. Found: C, 51.52; H, 4.29; N, 8.17.

3-*O*-(3,5-Dinitrobenzoyl)-4,5-*O*-isopropylidene-1-pentyne-D-*threo*-3,4,5-triol (18).—Compound **7** (110 mg) was acylated with 3,5-dinitrobenzoyl chloride (200 mg) in pyridine (3 ml) by the procedure used for preparation of **17**. The crude product was recrystallized from methanol, yield 179 mg (75%), mp 128–129°. Further recrystallization gave **18** as long, colorless needles: mp 133.5–134.5°; $[\alpha]^{24}D$ −31.5 ± 1° (*c* 1.5, chloroform); λ_{max}^{KBr} 3.03 (C≡CH), 4.67 (C≡C), 5.71 (C=O), 6.09, 6.41, 6.83, 13.70 (aryl), 7.39 μm (CMe_2); nmr (chloroform-*d*), τ 1.7 (three-proton singlet, aryl protons), 4.16 (one-proton quartet, $J_{1,3}$ = 2.2 Hz, $J_{3,4}$ = 7.3 Hz, H-3), 5.4–6.1 (three-proton multiplet, H-4,5,5′), 7.29 (one-proton doublet, H-1), 8.58 (six-proton singlet, CMe_2); X-ray powder diffraction data, 13.00 vs (1), 8.34 m, 7.38 m, 6.81 w, 6.24 w, 5.40 s, 4.85 vs (2), 4.67 w, 4.48 w, 4.23 s, 4.00 w, 3.74 m, 3.62 w, 3.45 m, 3.28 w, 3.15 w.

Anal. Calcd for $C_{15}H_{14}N_2O_8$: C, 51.43; H, 4.03; N, 8.00. Found: C, 51.38; H, 4.09; N, 8.36.

A mixture of the epimers **17** and **18** melted over the range 93–124°.

Registry No.—**1,** 15186-48-8; **2,** 4688-33-4; **3,** 4978-99-8; **4,** 15215-76-6; **7,** 4 957-71-5; **8,** 4688-51-1; **9,** 15215-80-2; **17,** 15215-78-8; **18,** 15215-79-9; erythritol tetrakis (*p*-nitrobenzoate), 15275-61-3.

The Structure of Osotriazoles of the Sugars. Conformational and Configurational Correlations of the Polyhydroxyalkyl Chain

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Received October 10, 1967

The phenylosotriazoles of the five-carbon sugars having the L-*erythro* and D-*threo* configurations, the six-carbon sugars having the D-*arabino*, D-*lyxo*, and L-*xylo* configurations, and their 6-deoxy analogs having the L-*lyxo* and L-*arabino* configurations have been correlated by nmr spectroscopy in methyl sulfoxide-d_6. In each example, the methine proton at C-1 of the side chain (C-3 of the original sugar) and the hydroxyl-group proton at the same position are deshielded relative to corresponding protons on the remainder of the side chain. Differences in chemical shift and vicinal proton–proton spin couplings between members of the series studied are interpreted in terms of conformational influence on the strength of intramolecular hydrogen bonding and the favored rotamer states of the side chain. The planar, zigzag arrangement of carbon atoms appears to be the favored conformation except where such an arrangement would lead to an eclipsed, 1,3 interaction of hydroxyl groups.

The favored conformation of unsubstituted, straight-chain hydrocarbons is considered to be that in which the carbon atoms adopt a planar, zigzag arrangement, in which the largest groups along each carbon–carbon bond are antiparallel.[3] The introduction of substituents along such a chain necessitates the steric and electronic requirements of these substituents to be taken into account in predicting the favored conformation. The polyhydroxyalkyl chains of acyclic sugar derivatives provide a system in which the conformational effect of oxygen atoms at adjacent carbon atoms on a chain can be studied as configurational relationships are varied. In the crystalline state it has been shown that a conformation in which the carbon atoms are essentially in the planar, zigzag arrangement is adopted in the D-gluconate ion,[4] the D-arabinonate ion,[5] and in galactitol.[6] The conformations of acyclic sugar chains in solution have not been studied extensively by physical methods. In an earlier report from this laboratory,[7] an analysis of the nmr spectrum of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline was presented. The spin couplings of the protons of the acyclic sugar chain were shown to be consistent with a planar, zigzag arrangement of the carbon chain, corresponding to attainment of minimum nonbonded interactions between the small–medium–large sets of groups at the ends of each carbon–carbon bond, as the most highly populated rotamer state.

It is not known to what extent the conformational model that accords with results on a limited number of configurational examples may be applicable to the full range of configurational possibilities. Steric effects

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(3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, Chapter 1.

(4) C. D. Littleton, *Acta Cryst.*, **6**, 775 (1953).

(5) S. Furberg and S. Helland, *Acta Chem. Scand.*, **16**, 2373 (1962).

(6) H. M. Berman and G. A. Jeffrey, *Acta Cryst.*, in press; *cf.* D. Horton in "Handbook of Biochemistry and Biophysics," H. C. Damm, Ed., World Publishing Co., Cleveland, Ohio, 1966, pp 128–129.

(7) D. Horton and M. J. Miller, *J. Org. Chem.*, **30**, 2457 (1965).

TABLE I

CHEMICAL-SHIFT DATA FOR PHENYLOSOTRIAZOLES[a]

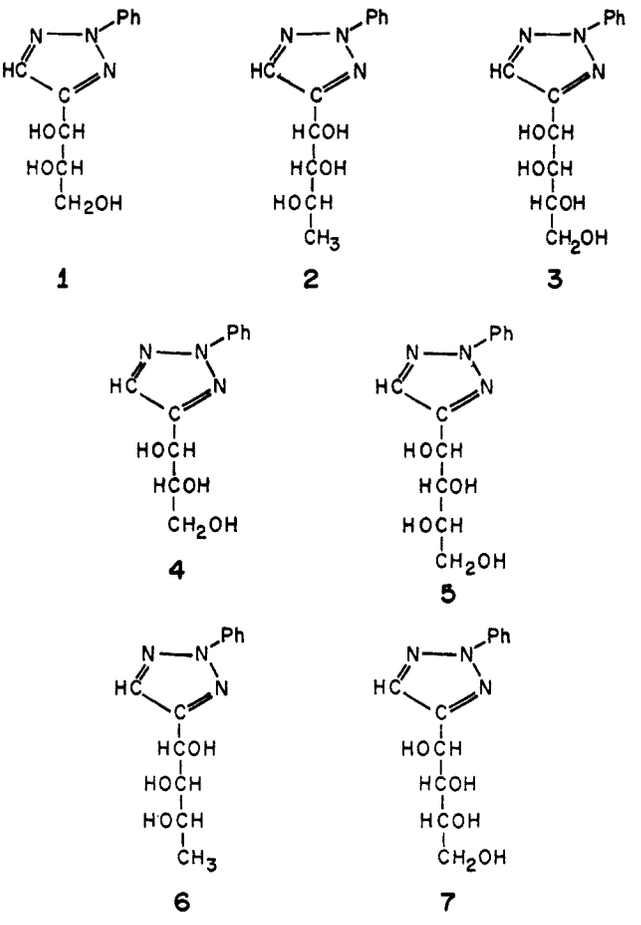
		Chemical shifts (τ) in methyl sulfoxide-d_6										
Compd	Confign	H-1	H-2	H-3	H-3′	H-4	H-4′	1-OH	2-OH	3-OH	4-OH	5′-H[b]
1	*erythro*	5.20	6.18	6.37	6.58			4.48	5.22	5.37		2.03
2	*lyxo*	5.20	6.50	6.18		8.84		4.51	5.52	5.72		2.04
3	*lyxo*	5.19	6.06–6.87					4.51	5.45–5.82			2.05
4	*threo*	5.08	6.10–6.64					4.67	5.28	5.40		2.02
5	*xylo*	5.08	6.20–6.69					4.63	~5.54			2.04
6	*arabino*	4.90	6.66	6.28		8.82		4.78	~5.39			2.03
7	*arabino*	4.88	6.23–6.60					4.72	5.30–5.47		5.62	2.03

[a] Values for methine and methylene protons of the polyhydroxyalkyl chain are taken from spectra after acidification. The τ values recorded for the H-1 signal are within 0.02 ppm of the values observed in nonacidified methyl sulfoxide-d_6. [b] The H-5 proton of the 1,2,3-triazole ring.

beyond vicinal interactions must be considered, especially parallel 1,3 interactions between oxygen atoms, which are analogous to 1,3-diaxial interactions in cyclohexane systems.[8] Polar factors may also exert a strong influence in determining favored conformation,[9,10] and intramolecular hydrogen bonding[11] may also be involved.[12]

The present report describes a detailed analysis by nmr spectroscopy of seven 4-substituted 2-phenyl-1,2,3-triazoles (osotriazoles) having the following groups at C-4: L-*erythro*-1,2,3-trihydroxypropyl (**1**), D-*threo*-1,2,3-trihydroxypropyl (**4**), D-*arabino*-1,2,3,4-tetrahydroxybutyl (**7**), D-*lyxo*-1,2,3,4-tetrahydrobutyl (**3**), L-*xylo*-1,2,3,4-tetrahydroxybutyl (**5**), L-*arabino*-1,2,3-trihydroxybutyl (**6**), and L-*lyxo*-1,2,3-trihydroxybutyl (**2**) (Chart I).[13] The results are interpreted in terms of the favored conformation of the polyhydroxyalkyl side chains.

CHART I



Spectral Measurements

The nmr spectrum of each osotriazole (**1**–**7**) was first measured in pure methyl sulfoxide-d_6 to observe signals for the OH protons, as well as the C–H protons.[14] Hydroxyl resonances are observable individually since exchange of hydroxyl-group protons is very slow in this solvent.[15] Thus, fine structure due to spin coupling between hydroxyl-group protons and the adjacent methine (or methylene) protons is also observed. A trace of hydrogen chloride gas (~0.0005 wt %) was then added to catalyze rapid exchange of hydroxyl protons. With rapid exchange, all of the hydroxyl-proton resonances collapse to a single line. At the same time the signals of methine (or methylene) protons adjacent to hydroxyl groups also collapse to simpler patterns, because of removal of observable spin coupling of these protons with the hydroxyl-group protons.

Spectra were analyzed by first assigning signals in the acid-exchanged spectrum. The hydroxyl-proton signals in the original spectrum were then assigned, where possible, to specific hydroxyl groups in the molecule. This was done by correlating the splitting of each hydroxyl-proton signal with splittings, observed in the methine-proton signals, that collapsed when acid was added to the solution.

The measured chemical shifts are recorded in Table I and Table II gives the observed first-order coupling constants. Signals of the 2-phenyl-1,2,3-triazole ring system are unexceptional. The H-5 signal of the triazole ring is observed as a singlet at about τ 2.04, within the two-proton multiplet (τ ~2.00) of the protons in

(8) The authors acknowledge discussions on this point with Dr. J. C. P. Schwarz, University of Edinburgh, Scotland, in July 1964; compare F. C. Hartman and R. Barker, *Biochemistry*, **4**, 1068 (1965); G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, **30**, 2020 (1965). It has recently been shown by X-ray crystallography [N. Tanaka, T. Ashida, Y. Sasada, and M. Kakudo, *Bull. Chem. Soc. Japan*, **40**, 1737 (1967)] that, in riboflavin hydrobromide monohydrate, the ribitol chain adopts a conformation having C-1 and C-4 disposed *gauche* along the C-2–C-3 bond. A planar, zigzag arrangement of the carbon chain would have led to a parallel interaction of hydroxyl groups at C-2 and C-4.

(9) A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, **84**, 743 (1962).

(10) C. V. Holland, D. Horton, and J. S. Jewell, *J. Org. Chem.*, **32**, 1818 (1967); L. D. Hall and J. F. Manville, *Carbohydrate Res.*, **4**, 512 (1967).

(11) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, Chapter 5.

(12) O. L. Chapman, R. W. King, W. J. Welstead, Jr., and T. J. Murphy, *J. Am. Chem. Soc.*, **86**, 4968 (1964).

(13) These compounds are named more simply as phenylosotriazoles of the appropriate ketose sugars. In this paper the position numbers used refer, unless otherwise stated, to the positions on the polyhydroxyalkyl side chain.

(14) H. S. El Khadem, M. L. Wolfrom, and D. Horton, *J. Org. Chem.*, **30**, 838 (1965).

(15) O. L Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

TABLE II

FIRST-ORDER COUPLING CONSTANTS FOR PHENYLOSOTRIAZOLES[a]

Compd	Confign	Coupling constants, Hz								
		$J_{1,2}$	$J_{2,3}$	$J_{2,3'}$	$J_{3,3'}$	$J_{3,4}$	$J_{1,OH}$	$J_{2,OH}$	$J_{3,OH}$	$J_{4,OH}$
1	*erythro*	5.8	3.7	6.3	10.8		5.1	*b*	*b*	
2	*lyxo*	7.6	3.0			6.3	5.5	7.0	6.0	
3	*lyxo*	8.4	*b*			*b*	5.6	*b*	*b*	*b*
4	*threo*	3.4	*b*	*b*	*b*		6.4	5.0	5.0	
5	*xylo*	5.6	*b*			*b*	4.9	*b*	*b*	*b*
6	*arabino*	2.5	7.8			6.0	7.0	5.7	5.7	
7	*arabino*	<2	*b*			*b*	6.7	*b*	*b*	5.1

[a] By direct measurement of peak spacings. Spectra determined in acidified methyl sulfoxide-d_6 were used for the HCCH couplings recorded; no detectable differences in the $J_{1,2}$ couplings were noted before acidification. [b] Not determined because first-order analysis was not possible.

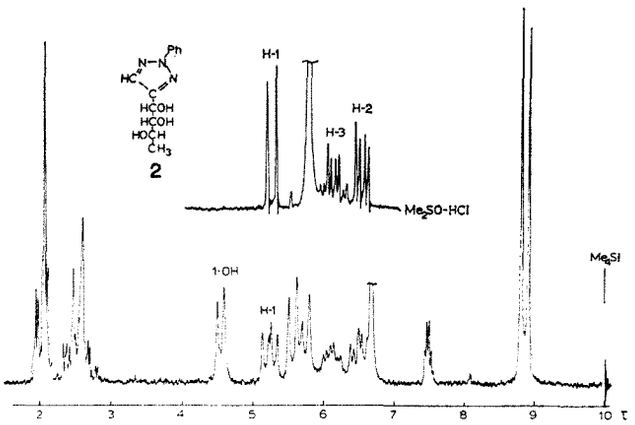


Figure 1.—The 60-MHz nmr spectrum of 6-deoxy-L-*lyxo*-hexulose phenylosotriazole (2) in methyl sulfoxide-d_6, before and after addition of a trace of hydrogen chloride.

the *ortho* position of the phenyl ring. A three-proton multiplet at about τ 2.56 can be assigned to protons in the *meta* and *para* positions of the phenyl ring. Signals of the protons on the side chain show wide variation with structure and configuration, and analysis of this portion of the spectrum is presented for each of the seven compounds individually.

6-Deoxy-L-*lyxo*-hexulose Phenylosotriazole (2).—The spectrum of this compound (Figure 1) was analyzed completely. A sharp, three-proton doublet at high field is assigned to the methyl group at C-4 of the side chain (C-6 of the parent sugar) and its spacing gives the $J_{3,4}$ coupling constant. In the spectrum of the acidified sample, the sharp doublet at τ 5.20 is assigned to H-1 of the side chain and its splitting gives the $J_{1,2}$ coupling constant. The quartet at τ 6.50 also has this spacing, indicating that this signal is that of H-2, and the small spacing in this signal gives the $J_{2,3}$ coupling constant. Between these signals is an eight-peak multiplet assigned to H-3. The measured width of this signal (21.9 Hz) agrees with that predicted ($3 \times J_{3,4} + J_{2,3} = 21.9$ Hz) and spin decoupling by irradiation of the C-4 methyl-group signal caused the anticipated collapse of the H-3 multiplet to a simpler pattern.

In the spectrum before acidification, a signal for one of the hydroxyl groups is observed at τ 4.51 as a doublet having a spacing of 5.5 Hz. The H-1 signal now appears as a quartet through coupling with H-2 and also with the proton of the 1-hydroxyl group. Since the additional spacing in the H-1 signal is 5.5 Hz, the doublet at τ 4.51 may be assigned to the 1-OH group, because each of the two remaining hydroxyl-proton signals shows a splitting larger than 5.5 Hz.

One of the remaining hydroxyl-proton signals is observed at τ 5.52 as a doublet having a splitting of 7.0 Hz and this same spacing is observed in the H-2 signal, indicating that the signal at τ 5.52 is that of the 2-hydroxyl proton. The lower portion of the H-2 signal, anticipated to be a triplet of narrow doublets, can be observed, but the signal of the water obscures part of the H-2 signal. The other hydroxyl-group signal, at τ 5.72, is assigned to the 3-hydroxyl proton; this proton has $J_{3,OH} = 6.0$ Hz and gives rise to additional splitting in the signal of the C-3 proton.

The coupling constants given are first-order values, but since the spectrum showed little indication of substantial second-order effects, these values should be close to the absolute $|J|$ values.[16]

L-*erythro*-Pentulose Phenylosotriazole (1).—The spectrum of this compound in acidified methyl sulfoxide-d_6 shows the H-1 signal as a wide doublet at low field. The proton on C-2 and the methylene group at C-3 give rise to an ABX pattern of signals[17] and the X pattern (H-2) shows additional splitting because of the $J_{1,2}$ coupling. First-order $J_{2,3}$, $J_{2,3'}$, and $J_{3,3'}$ values recorded in Table II may be less than the absolute J values because the multiplets of the A and B signals (H-3 and H-3′) overlap.[16] Nevertheless, the width of the H-2 multiplet (15.5 Hz) agrees closely with the sum of the measured splittings $J_{1,2} + J_{2,3} + J_{2,3'}$ (15.5 Hz).

In nonacidified methyl sulfoxide-d_6, the three hydroxyl-proton signals are observed as doublets at τ 4.48 and 5.22 and as a broad, poorly resolved multiplet at τ 5.37. The latter signal was assigned to the 3-OH proton. The resonance at τ 5.22 partially obscures the H-1 signal, so it was difficult to assign the 1-OH signal by recognizing the $J_{1,OH}$ coupling in the H-1 signal. However, the signals at $\tau \sim 5.2$ appear as simple overlap of the H-1 signal with a hydroxyl-group signal and the latter was thus assignable to the 2-OH proton. Had the signal at τ 5.22 been that of the 1-OH proton, the $J_{1,OH}$ coupling and the small difference in chemical shift would have given rise to a more complex pattern, such as the AB portion of an ABX system (or the A_2 portion of an A_2X system). The remaining hydroxyl-pro-

(16) See C. V. Holland, D. Horton, M. J. Miller, and N. S. Bhacca, *J. Org. Chem.*, **32**, 3077 (1967), for comparisons of first-order chemical shifts and coupling constants with the calculated values in various sugar derivatives.

(17) For details of the ABX notation, see J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 132.

ton resonance, at τ 4.48, was assigned, therefore, to the 1-OH group.

D-*lyxo*-**Hexulose Phenylosotriazole (3).**—The spectrum in acidified methyl sulfoxide-d_6 shows the H-1 signal as a wide doublet. Although detailed analysis of the higher field multiplet for the H-2, 3, 4, and 4′ protons was not made, the sharpness of the H-1 signal indicates that the difference in chemical shift of the higher field signals was sufficient that no significant virtual coupling[18] of H-1 with H-3 was involved.

In nonacidified methyl sulfoxide-d_6, the 1-OH resonance is observed as a low-field (τ 4.51) doublet and the H-1 signal is observed as a quartet. Signals of the 2-OH, 3-OH, and 4-OH protons appear as a multiple series of peaks in the range τ 5.45–5.82 and were not individually assigned.

D-*threo*-**Pentulose Phenylosotriazole (4).**—In acidified methyl sulfoxide-d_6 the H-1 signal is observed as a narrow doublet, slightly perturbed by second-order effects, and the signals of H-2, H-3, and H-3′ appear as a complex pattern (ABC system) not amenable to first-order analysis. The spectrum prior to acidification shows a hydroxyl resonance at τ 4.67 clearly assignable to the 1-OH proton because its splitting ($J_{1,OH}$ = 6.4 Hz) is also observed in the H-1 quartet. The remaining hydroxyl-proton signals could be recognized as a doublet at τ 5.28, assigned to the 2-OH proton ($J_{2,OH}$ = 5.0 Hz), and the upper two peaks of a 1:2:1 triplet centered at τ 5.40, with the lower peak coincident with the upper peak of the 2-OH doublet. The triplet was assigned to the 3-OH proton and its spacing gave $J_{3,OH}$ = 5.0 Hz.

L-*xylo*-**Hexulose Phenylosotriazole (5).**—In acidified methyl sulfoxide-d_6, the H-1 signal is a slightly perturbed, sharp doublet, $J_{1,2}$ = 5.6 Hz; analysis of the H-2,3,4,4′ multiplet was not attempted. Before acidification the H-1 signal showed additional multiplicity from which the $J_{1,OH}$ coupling was determined and a hydroxyl-proton doublet at τ 4.63 that showed this coupling was, therefore, assigned to the 1-OH group. The remaining hydroxyl groups give an overlapping series of resonances at higher field.

6-Deoxy-L-*arabino*-hexulose Phenylosotriazole (6).—The spectrum in acidified methyl sulfoxide-d_6 shows the H-1 signal as a narrow doublet and the H-4 methyl-group protons as a three-proton doublet. A doublet of narrow doublets at τ 6.66 was readily assigned to H-2 and the larger spacing of this signal gave $J_{2,3}$ = 7.8 Hz. The remaining multiplet, at τ 6.28, assigned to H-3, has a width of 25.9 Hz, in good agreement with that predicted as $3 \times J_{3,4} + J_{2,3}$ (25.8 Hz). Because of the proximity of the H-2 signal, some deviation from first-order appearance is observed in the H-3 signal.

In nonacidified methyl sulfoxide-d_6 a two-proton multiplet is observed near the position of the H-1 signal, indicating that one hydroxyl proton and H-1 have similar chemical shifts. That this signal was that of the 1-OH group was indicated by the fact that there was spin interaction of H-1 and this hydroxyl proton, giving rise to a second-order pattern of the AB type with B (H-1) further coupled with H-2. Analysis of the multiplet indicated that the 1-OH group had τ 4.78, with $J_{1,OH}$ = 7.0 Hz. Signals of the two remaining hydroxyl groups coincide at τ 5.39, and show $J_{2,OH} = J_{3,OH}$ = 5.7 Hz.

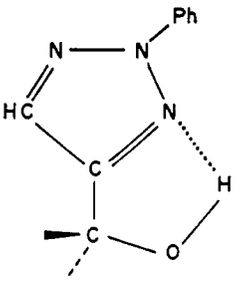


Figure 2.—Intramolecular hydrogen bonding between the C-1 hydroxyl group and the N-3 atom of the 1,2,3-triazole ring.

D-*arabino*-**Hexulose Phenylosotriazole (7).**—The H-1 signal is observed in acidified methyl sulfoxide-d_6 as a broadened singlet whose width indicates that $J_{1,2}$ is $\leqslant$ 2 Hz. Virtual coupling may contribute to the lack of resolution of this signal, because the H-2, 3, 4, and 4′ resonances appear as a closely spaced, complex multiplet.

In nonacidified methyl sulfoxide-d_6 the 1-OH signal is readily recognized at τ 4.85, as a doublet due to spin coupling with H-1. A hydroxyl-proton resonance at τ 5.62 is observed as a triplet, indicating that it is the 4-OH signal.

Discussion

Chemical Shifts of Protons on the Side Chain.—The chemical shift data listed in Table I indicate that, in each case, the C-1 proton resonates at lower field (τ ~5.0) than the other protons on the side chain. The C-1 hydroxyl proton likewise resonates at lower field (τ ~4.6) than the other hydroxyl protons. Electronic deshielding by the adjacent aromatic residue undoubtedly is a major factor in causing these signals to appear at low field. Additional deshielding might also arise by formation of an intramolecular hydrogen bond between the C-1 hydroxyl group and the N-3 atom of the 1,2,3-triazole ring (Figure 2).[19] That the deshielding of H-1 is not caused by hydrogen bonding alone is evident from the fact that the analogous proton in the quinoxaline derivative[7] **8** is observed ~0.6 ppm to lower field than the other protons on the side chain, in spite of the fact that the hydroxyl groups are acetylated and are unable to engage in hydrogen bonding. However, the extent of deshielding of H-1 in the osotriazoles, relative to other methine protons on the chain (~1 ppm), and the magnitude of the deshielding of the 1-OH proton, relative to the other hydroxyl protons (0.6–1.2 ppm), suggests that intramolecular hydrogen bonding is, nevertheless, significant in the osotriazoles. That this bonding is through the C-1 hydroxyl group in a five-membered ring structure and not through the C-2 hydroxyl group in a six-membered ring is evident since the 2-OH signal appears in the τ 5.2–5.8 region. This region is characteristic[20] of nonanomeric hydroxyl protons (in methyl sulfoxide) that are not intramolecularly hydrogen bonded.

(18) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1961).

(19) The possibility of hydrogen bonding of this type has also been suggested by G. G. Lyle and M. J. Piazza, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, Abstract C10.

(20) B. Casu, M. Reggiani, G. G. Gallo, and A. Vigevani, *Tetrahedron*, **22**, 3061 (1966).

Inspection of the chemical shift data for the H-1 and 1-OH protons of the seven phenylosotriazoles **1–7** (Table III) reveals similarities between homomorphous derivatives. The three derivatives having the *erythro* configuration at C-1 and C-2 (**1**, **2**, and **3**, first group) show the H-1 signal at τ ~5.2 and the 1-OH signal at τ ~4.5. Those having the *threo* configuration at C-1 and C-2 (**4–7**) show the H-1 signal at lower field and the 1-OH signal at higher field than derivatives having the *erythro* configuration. The *threo* series can be further subdivided into the pair **4** and **5** (second group), in which H-1 resonates at τ ~5.1 and the 1-OH group at τ ~4.65, and the pair **6** and **7** (third group) in which H-1 resonates at lowest field (τ ~4.9) and the 1-OH proton at the highest field (τ ~4.75) of the group. The third group has the *arabino* configuration at C-3, C-2, and C-1.

TABLE III
CORRELATION OF SIDE-CHAIN CONFIGURATION WITH CHEMICAL SHIFT AND COUPLING OF C-1 METHINE AND HYDROXYL PROTONS

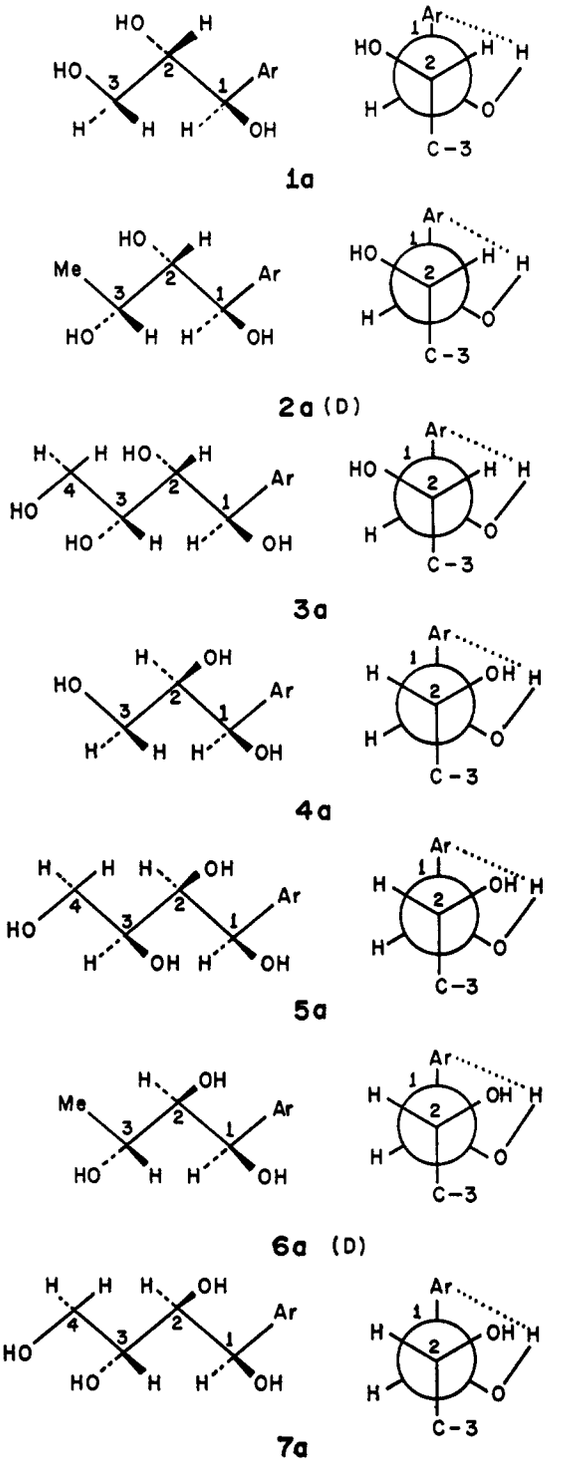
Compd	Structure of side chain	Chemical shifts, τ 1-OH	Chemical shifts, τ H-1	Coupling constants, Hz $J_{1,OH}$	Coupling constants, Hz $J_{1,2}$
	First Group				
1	HOCH$_2$C(OH)H—C(OH)H—	4.48	5.20	5.1	5.8
2	CH$_3$C(OH)H—C(H)OH—C(OH)H—	4.51	5.20	5.5	7.6
3	HOCH$_2$C(OH)H—C(H)OH—C(OH)H—	4.51	5.19	5.6	8.4
	Second Group				
4	HOCH$_2$C(H)OH—C(OH)H—	4.67	5.08	6.4	3.4
5	HOCH$_2$C(OH)H—C(H)OH—C(OH)H—	4.63	5.08	4.9	5.6
	Third Group				
6	CH$_3$C(OH)H—C(OH)H—C(H)OH—	4.78	4.90	7.0	2.5
7	HOCH$_2$C(H)OH—C(H)OH—C(OH)H—	4.72	4.88	6.7	<2

If the extent of deshielding of the 1-OH signal is a measure of the stability of the hydrogen-bonded structure having the 1-OH group coplanar with the 1,2,3-triazole ring, the compounds in the first group (**1–3**) adopt the hydrogen-bonded conformation to the greatest extent and the compounds of the third group (**6** and **7**) to the least extent of the examples studied. The inverse correlation of the H-1 chemical shift with the shift of the 1-OH signal may be rationalized on the basis that, in the structures having the least contribution from the hydrogen-bonded structure, the C-1 proton will, statistically, exist to a greater extent in the rotomers having H-1 coplanar with the aryl system, where deshielding is at a maximum.[21] In the more strongly hydrogen-bonded structures, H-1 will be constrained out of the plane of the 1,2,3-triazole ring, where it will experience less deshielding.[21]

Conformation of the Polyhydroxyalkyl Chain.—The torsional barrier to rotation along each bond in the side chain and the energy required to break a hydrogen-bonded structure are presumed to be sufficiently low

(21) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

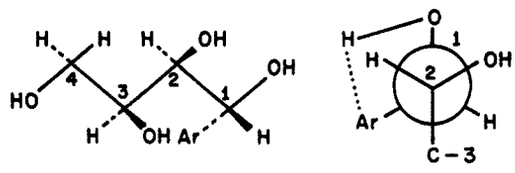
CHART II



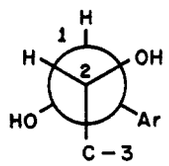
that it can be assumed that rapid interconversion between rotamers and between all possible hydrogen-bonded and nonbonded structures is taking place at room temperature. Certain conformations are, nevertheless, energetically favored and a statistical picture of the molecules would give a distribution with heavy proportional weighting of the form or forms of lowest energy, according to the classical thermodynamic distribution. If it can be assumed that vicinal, antiparallel protons show spin–spin coupling of 8–9 Hz and that vicinal, *gauche* protons show coupling of 3–4 Hz,[22] it is

(22) M. Karplus, *ibid.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963); L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, 51 (1964).

CHART III



5b



4b, 6b (D), 7b

possible to make predictions of favored conformation in terms of the observed couplings.

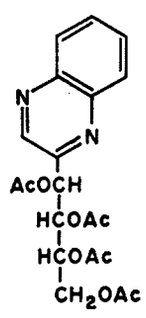
In all seven examples it was possible to measure the $J_{1,2}$ coupling. The $J_{2,3}$ couplings could also be determined in the case of substances **1**, and **2**, and **6**. If each of the derivatives **1**–**7** is formulated in the conformation having a planar, zigzag arrangement of carbon atoms in the side chain, the series can be represented as shown in the corresponding formulas **1a**–**7a** (Chart II).[23] The planar, zigzag conformation (**2a**) shown for the enantiomorph of substance **2** accords well with the observed coupling data. The $J_{1,2}$ coupling (7.6 Hz) indicates that the preponderant conformer has H-1 and H-2 antiparallel. The small $J_{2,3}$ coupling is consistent with two possible *gauche* arrangements of H-2 and H-3, the one depicted (**2a**) and one in which H-3 bisects the dihedral angle of the H-2 and 2-OH groups. The latter would give rise to the unfavorable parallel interaction of hydroxyl groups at C-3 and C-1 and would also bring C-2 and C-4 into a *gauche* relationship. The planar, zigzag arrangement (**2a**) undoubtedly has fewer nonbonded interactions. Similar arguments presumably apply in the case of **3**. The observed $J_{1,2}$ coupling (8.4 Hz) indicates that H-1 and H-2 are antiparallel and excludes the other two staggered rotamers at C-1–C-2 as significant contributors to the conformational population. It was not possible to measure $J_{2,3}$ in the case of **3**, but there is probably little difference between **3** and its 4-deoxy analog with respect to favored conformation.

The coupling data observed for **1** also accord with the planar, zigzag conformation (**1a**) as the preponderant conformer. The fact that $J_{2,3}$ and $J_{2,3'}$ are different indicates that the preponderant C-2–C-3 rotamer has one pair of antiparallel protons. This is compatible with conformation **1a** or with the rotamer having antiparallel hydroxyl groups at C-2 and C-3. The latter would, however, have a parallel interaction between the hydroxyl groups at C-3 and C-1 and is presumably less favored. The value of $J_{1,2}$ (5.8 Hz) indicates a major contribution from the conformer having H-1 and H-2 antiparallel, in the planar, zigzag structure (**1a**). The fact that this value is smaller than the $J_{1,2}$ values observed for **2** and **3** suggests that the C-3 hydroxymethyl substituent is accommodated more easily in the other C-1–C-2 rotamers than is the larger C-3 group in **2** or **3**. Thus, while the planar zigzag structure preponderates, minor contributions from the alternative C-1–C-2 rotamers are more favored in **1** than in **2** or **3**.

Substance **4**, a diastereoisomer of **1**, gives a $J_{1,2}$ coupling (3.4 Hz) consistent with the planar, zigzag form depicted. Another C-1–C-2 rotomer (**4b**, Chart III) is also possible, likewise having a *gauche* relationship of H-1 and H-2, and may contribute to the conformational population. The latter is probably less favored because it would bring C-3 and the aryl residue into a *gauche* arrangement.

The coupling data for the *xylo* isomer **5** are of interest because of the large $J_{1,2}$ value (5.6 Hz) observed. This value is not compatible with the principal conformer being either the planar, zigzag conformation depicted (**5a**) or the other C-1–C-2 rotamer having H-1 and H-2 in *gauche* relationship, because these structures would give small $J_{1,2}$ values. The observed $J_{1,2}$ value suggests that there is a major contribution from the C-1–C-2 rotamer (**5b**) having H-1 and H-2 antiparallel. Such an arrangement would not have the aryl group and the C-3 substituent in the antiparallel arrangement, but would lead to greater net staggering of large groups along this bond. Probably more important, however, is the fact that conformation **5b** would eliminate the parallel 1,3 interaction of hydroxyl groups that is present in conformation **5a**.

The coupling-constant data for **6** support the planar, zigzag structure (depicted for the enantiomorph as **6a**) as the favored conformation. Such a structure is analogous to that reported[7] for the side chain of the quinoxaline derivative **8**. The large $J_{2,3}$ value (7.8 Hz) for **6** indicates that H-2 and H-3 are antiparallel, the $J_{1,2}$ value indicates the *gauche* relationship of H-1 and H-2. The same is probably true of the analog **7** and although the $J_{2,3}$ value was not measured, it may be expected that **7** would favor the planar, zigzag conformation **7a**. In the case of **6**, **7** (and **8**), it is possible to formulate another C-1–C-2 rotamer (**6b**, **7b**) that would give a small $J_{1,2}$ value, but such a rotomer can almost certainly be excluded because it would generate a 1,3 interaction between parallel hydroxyl groups and also give rise to a *gauche* interaction between C-3 and the aryl residue.



8

If the chemical shift of the 1-OH proton is related to the strength of its hydrogen bonding to an aryl nitrogen atom, a correlation can be made between the posi-

(23) In the case of substances **2** and **6**, the conformational representations **2a** and **6a** are those of the enantiomorphs. This modification emphasizes conformational relationships with the other structures in the series, which would be less readily apparent if the mirror-image forms were represented.

tion of the C-2 hydroxyl group in the favored conformation and the extent of such bonding. The first group of derivatives (**1**, **2**, and **3**), which show the 1-OH signal at low field (τ 4.5), have in their planar conformations (**1a**, **2a**, and **3a**) the H-2 atom bisecting the dihedral angle of the aryl residue and the 1-hydroxyl group and have the 2-hydroxyl group *trans* to the 1-hydroxyl group. Interaction between the C-1 and C-2 hydroxyl groups in this conformation is not possible. Maximum staggering of large groups along C-1–C-2 is achieved. In the third group of derivatives (**6** and **7**), where the 1-OH signals are at higher field (τ ~4.75), the 2-hydroxyl group is largely constrained to bisect the angle of the aryl group and the 1-hydroxyl group. In this orientation the 1-OH–N hydrogen bond may be weakened by *gauche* steric interference, by competitive hydrogen bonding of the 2-hydroxyl group with O-1 or with the aryl nitrogen atom, or by a combination of these effects.[24] In substance **4** the same situation exists as noted with **6** and **7** and the somewhat lower chemical shift (τ 4.67) of the 1-OH group may be due to greater conformational freedom because of the smaller side chain. In the case of **5**, the 1-OH proton is further deshielded (τ 4.63), probably reflecting the fact that there is less steric interference with hydrogen bonding in the rotamer **5b** which apparently makes a major contribution to the conformational population.

Further studies in this laboratory are in progress to furnish additional data on related systems.

(24) The unusually small $J_{1,2}$ values observed with **6** and **7** may result from distortion of the favored C-1–C-2 rotamer to give an H-1–H-2 dihedral angle larger than 60°.

Experimental Section

Preparation of Phenylosotriazoles.—Each of the derivatives **1–7** was prepared by standard methods[25] by way of the appropriate phenylosazones. L-*erythro*-Pentulose phenylosotriazole[26] (**1**) was obtained from L-arabinose, 6-deoxy-L-*lyxo*-hexulose phenylosotriazole[27] (**2**) was obtained from L-fucose, D-*lyxo*-hexulose phenylosotriazole[28] (**3**) was obtained from D-galactose, D-*threo*-pentulose phenylosotriazole[28] (**4**) was obtained from D-xylose, L-*xylo*-hexulose phenylosotriazole[28] (**5**) was obtained from L-sorbose, 6-deoxy-L-*arabino*-hexulose phenylosotriazole[27] (**6**) was obtained from L-rhamnose, and D-*arabino*-hexulose phenylosotriazole[29] (**7**) was obtained from D-glucose. Each product was recrystallized several times and all had melting points and specific rotations in good agreement with literature values.

Nmr Measurements.—Spectra were measured with a Varian HR-60 nmr spectrometer, at a temperature of approximately 32°. Tetramethylsilane (τ 10.00) was used as the internal standard and spectra were calibrated by the side-band technique. Chemical shifts and coupling constants are first-order values, as measured directly from spectral spacings. The measured spacings are believed to be accurate to ±0.15 Hz or better.

Samples were used as ~10% solutions in methyl sulfoxide-d_6. After each spectrum had been recorded, a trace of hydrogen chloride gas was introduced and the spectrum was recorded again. The addition of hydrogen chloride gas was effected by filling a fine-tipped capillary pipet with the vapor from the top of a bottle of concentrated hydrochloric acid and then bubbling this vapor through the prepared sample. The resulting concentration of hydrogen chloride was of the order of 0.0005 wt %.

Registry No.—**1**, 15476-35-4; **2**, 15476-31-0; **3**, 15476-32-1; **4**, 15476-33-2; **5**, 15476-34-3; **6**, 15476-07-0; **7**, 6341-06-6.

(25) N. K. Richtmyer, *Methods Carbohydrate Chem.*, **2**, 132 (1963).
(26) W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **68**, 1766 (1946).
(27) W. T. Haskins, R. M. Hann, and C. S. Hudson, *ibid.*, **69**, 1461 (1947).
(28) W. T. Haskins, R. M. Hann, and C. S. Hudson, *ibid.*, **67**, 939 (1945).
(29) R. M. Hann and C. S. Hudson, *ibid.*, **66**, 735 (1944).

An Investigation of the Role of Dimethyl Acetals in the Formation of Methyl Glycosides[1]

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Received August 9, 1967

The effect of configuration on the rates of glycosidation of the pentoses has been studied and found to be similar to that observed in the acid-catalyzed dehydration of the pentitols, indicating that an acyclic intermediate may be involved in the glycosidation. The hypothesis that the dimethyl acetals are intermediates in the glycosidation reaction has been disproved and the possibility that the acyclic methyl hemiacetals are intermediates in the glycosidation process cannot be tested readily. Partial glycosidations of D-arabinose-1-C^{14} and D-galactose-1-C^{14} have been carried out and the respective dimethyl acetals isolated by chromatographic and by dilution techniques. An investigation of the kinetics of the glycosidations of D-arabinose, D-galactose, and their dimethyl acetals has permitted an estimation of the role of acetals as intermediates in glycosidation. A comparison of this theoretical variation of acetal concentration with time with that obtained experimentally has disproved Fischer's proposal that the dimethyl acetals of sugars are obligatory intermediates in the formation of glycosides.

The acyclic dimethyl acetals of sugars were proposed as intermediates in the formation of methyl glycosides by Fischer in one of his first papers on the preparation of methyl glycosides.[2a] Later Campbell and Link[2b] and Wolfrom and Waisbrot[3] examined the behavior of the dimethyl acetals of galactose and glucose under glycoside-forming conditions and showed that the acetals were rapidly converted to glycosides. The initial rapid reaction appeared to be the formation of furanosides which were slowly converted to pyranosides. The over-all process of glycoside formation also involves the initial formation of furanosides. This fact was clearly demonstrated by Bishop and Cooper,[4] who confirmed the earlier observations of Levene, *et al.*[5]

The effect of configuration on the rate of methyl glycoside formation was examined by Levene, *et al.*,[5] and

(1) Supported in part by a Public Health Service Grant (GM 11,963) and a Public Health Service Research Career Program Award (GM 24,808 to R. B.) from the Institute of General Medical Sciences.
(2) (a) E. Fischer, *Ber.*, **28**, 1145 (1895); (b) H. A. Campbell and K. P. Link, *J. Biol. Chem.*, **122**, 635 (1938).
(3) M. L. Wolfrom and S. W. Waisbrot, *J. Am. Chem. Soc.*, **61**, 1409 (1939).
(4) C. T. Bishop and F. P. Cooper, *Can. J. Chem.*, **41**, 2743 (1963).
(5) P. A. Levene, A. L. Raymond, and R. T. Dillon, *J. Biol. Chem.*, **95**, 969 (1952).