Rotatory Dispersion Studies. VI.[1a] Phenylosotriazole Derivatives of the Aldo Sugar Family[1b-d]

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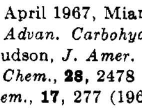
A study of the ORD and CD curves of osotriazole derivatives of sugars having four to six carbon atoms has shown that the phenylosotriazole chromophore is optically anisotropic, producing Cotton effect curves which result in the following rule: a positive Cotton effect at 265 nm will be produced if the C-3 hydroxyl group (α to the aromatic ring) is at the right in a standard Fischer projection [(*R*) configuration] of the phenylosotriazole derivative. The optical rotatory power of the osotriazoles in four solvents showed a correlation between the dielectric constant and the magnitude of rotation indicating the probability of intramolecular hydrogen bonding. The nmr spectra were consistent with a conformation (B) of the osotriazole in which a hydrogen bond is formed between the 3-hydroxyl group and a nitrogen of the osotriazole ring while the tetraacetyl derivatives appeared to have the usual zigzag conformation. A sector rule has been devised correlating the Cotton effects of the phenylosotriazole chromophoric system with the configuration of the sugar residue in a hydrogen-bonded conformation. The signs and amplitudes of the Cotton effects of all of these compounds were consistent with the sector rule.

The correlation of the absolute configuration of a molecule and its optical rotatory power has been sought in many systems of organic compounds, but it has been successful in relatively few cases. The carbohydrates have been especially attractive for such studies because of the multiplicity of structurally similar chiral centers. The challenge of the carbohydrates led to early considerations of three-dimensional structures, and the correlation of optical rotations with stereochemical assignments resulted in several useful rules, especially those of Hudson.[2] One of the Hudson rules states that the sign of the D-line rotation reflects the absolute configuration of the hydroxyl group on the carbon α to the benzimidazole ring in these derivatives of sugars, thus permitting the configurational assignment at the 2 position of the original sugar.[2b]

An extension of this rule to another cyclic derivative, the phenylosotriazole structure, has been suggested by Khadem[3] and Mills.[4] By the conversion of a sugar into this derivative the configuration at C-3 of the original sugar may be established on the basis of the osotriazole rule. Khadem and El-Shafei[5] have also suggested the general applicability of the rule to all aromatic systems declaring that "the sign of rotation of a heterocyclic or aromatic compound having more than one asymmetric carbon depends only on the configuration of the asymmetric carbon atom attached to the heterocyclic or benzene ring provided no other ring is present in the molecule." The sign of rotation at the D line is correlated with the configuration, below, giving a positive rotation.



benzene or aromatic heterocycle

Where R is a sugar moiety and the aromatic group is the osotriazole ring, the configurational designation is *R*.[6]

In view of the availability of spectropolarimeters for measurements below 300 nm, it seemed desirable to investigate this correlation, which was based on D-line rotations, with attention to the variation of rotation with the wavelength of the incident polarized light. If the aromatic ring produced a Cotton effect curve whose sign was consistent with the D-line rotation, this would indicate the dominance of the ORD curve by this aromatic chromophore and, perhaps, the possibility of designing a sector rule for this chromophore (*vide infra*). By examining a series of derivatives (**1**–**6**) of simple sugars (four to six carbons per sugar molecule) that possess almost all possible combinations of the stereorelationships of adjacent hydroxyl groups, it should also be possible to determine the conformation of the sugar residue from nmr spectral analysis.[7]

Assuming that the aromatic nucleus substituted on the asymmetric carbon atom represented the parent structure, the synthesis of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-triazole (**1**) was carried out. Potato starch was converted into potato oxystarch and thence to a mixture of phenylosazones.[8] A portion of this mixture of osazones was purified by column chromatography to yield D-erythrose phenylosazone free of glyoxal phenylosazone and β-acetylphenylhydrazine which were also isolated and characterized. Either pure erythrose osazone or the osazone mixture was converted into the phenylosotriazole **1** by cyclization with copper(II) sulfate. The crystalline osotriazole **1** was the only derivative which had not been previously reported in this family. The properties are described in the Experimental Section.

The preparation of the phenylosazones of the five-

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[1] (a) Part V: G. G. Lyle and W. Gaffield, *Tetrahedron*, **23**, 51 (1967). (b) This study was supported in part by a grant GM-07239 and continuation grants from the National Institutes of Health. (c) Taken in part from the thesis of M. J. P. submitted to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements of the Ph.D. Degree. (d) Presented before the Carbohydrate Division of the American Chemical Society at the 153rd Meeting, April 1967, Miami, Fla., Abstracts, p C10.

[2] (a) N. K. Richtmyer, *Advan. Carbohyd. Chem.*, **6**, 175 (1951); (b) N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, **64**, 1612 (1942).

[3] H. El Khadem, *J. Org. Chem.*, **28**, 2478 (1963).

[4] J. A. Mills, *Aust. J. Chem.*, **17**, 277 (1964).

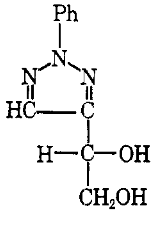
[5] H. El Khadem and Z. M. El-Shafei, *Tetrahedron Lett.*, 1887 (1963).

[6] R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966).

[7] After this manuscript was submitted to the editor, a paper appeared [W. S. Chilton and R. C. Krahn, *J. Amer. Chem. Soc.*, **89**, 4129 (1967)] describing the results of an ORD study of aryl derivatives of carbohydrates. The authors concluded that the aryl substituent would give a Cotton effect whose sign was consistent with the configuration of the chiral group attached to the aromatic ring, and they included one example of a phenylosotriazole derivative. Note Added in Proof.—Two recent publications have described some ORD results [W. S. Chilton and R. C. Krahn, *ibid.*, **90**, 1318 (1968)] and nmr studies in methyl sulfoxide-d_6 [H. S. El Khadem, D. Horton, and T. F. Page, Jr., *J. Org. Chem.*, **33**, 734 (1968)] on which conformational preferences have been suggested.

[8] V. C. Barry and P. W. D. Mitchell, *J. Chem. Soc.*, 4020 (1954).

and six-carbon sugars was effected by standard procedures, and they were converted into the cyclic osotriazoles (2–6) by heating with $CuSO_4$. The osotriazoles prepared in this study are listed in the Experimental Section. All possible isomers except D-*ribo*-hexose phenylosotriazole were prepared and subjected to spectropolarimetric study.



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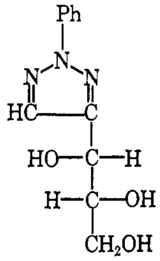

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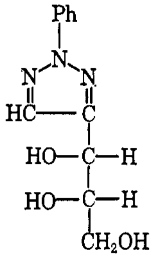

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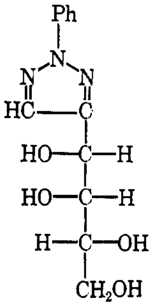

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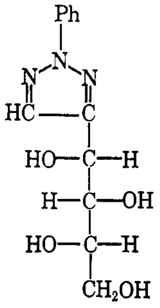

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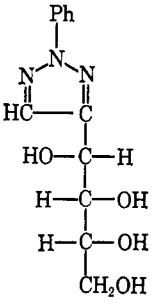

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A comparison of the rotatory power in four solvents between 600 and 300 nm was carried out, and the data were subjected to analysis by a one-term Drude equation using the procedure previously described.[9] The Drude constants showed little similarity indicating that the data were not amenable to a simple Drude plot. This is probably because of the strong, relatively long wavelength absorption band of the osotriazole ring which is optically anisotropic and dominates the ORD curve in the visible region.

The results showed that the optical rotatory power was generally the lowest in water and the highest in pyridine. The curves for L-*xylo*-hexose phenylosotriazole (5) in four solvents are shown in Figure 1. The ORD curves in methanol and acetic acid were quite similar except in the case of the osotriazole 3 derived from arabinose. In this case the ORD curve in methanol showed stronger rotation than in any of the other three solvents. There seems to be no simple explanation for the solvent effects except to assume a change in conformation depending on the solvent. The decreasing rotatory power with increasing dielectric constant suggests that in pyridine the molecules can assume the maximum amount of intramolecular hydrogen bonding, the relative conformational rigidity thus resulting in the larger rotatory power. This is consistent with the pattern which has been observed in which cyclic structures generally show larger D-line rotations than acyclic analogs.[10] In water, however, the solvation of the osotriazole nitrogens as well as the hydroxyl groups would increase the random structure and produce a decrease in the rotatory power.

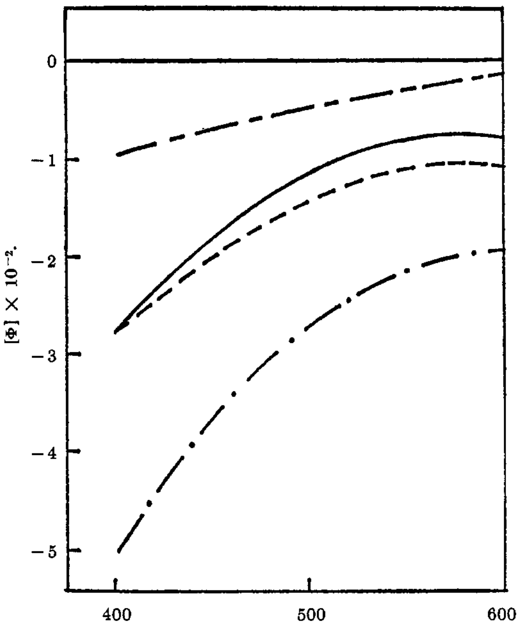

Figure 1.—ORD curves of 4-(L-*xylo*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (5). The curves were obtained from the Rudolph instrument using pyridine (—·—), methanol (——), acetic acid (— — — —), and water (— — —) as the solvents.

The ORD curves of the phenylosotriazole derivatives below 400 nm[11] were generally characterized by having the same sign of rotation at 400 nm as the D line and a strong Cotton effect between 250 and 300 nm of the same sign. The midpoints of the Cotton effects occurred at 259–266 nm, in excellent agreement with the maximal ultraviolet absorption at 265–267 nm (ϵ 19,000–24,000) of all six compounds. An experimental complication was noted with these derivatives and should be mentioned. They showed considerable fluorescence above 300 nm which can lead to erroneous readings of the amplitudes of the Cotton effects similar to the errors introduced in measuring uv data of fluorescing species. When the absorbance was kept below 2, however, the fluorescence gave no problems but, in some low-rotating derivatives, the quantitative values of the amplitudes may be of diminished reliability. The Cotton effects shown by the two pentose phenylosotriazoles (2 and 3) have the same sign, thus reflecting the configurations at the α carbon rather than the β carbon where the configurations are opposite (Figure 2). The amplitude of the single Cotton effect of the *threo* isomer 2 was considerably larger than the combined Cotton effects in the same region shown by 3. In the curves of 5 and 6 as well as 3 the extremum at about 240 nm was split into two peaks (Figure 3). That this indicated more than one Cotton effect was verified by examination of the circular dichroism (CD) spectra[12] of 1 and 6. The curve of 6 showed three negative maxima and a shoulder between 280 and 240 nm (Figure 4). The uv spectra gave no indication of fine structure in methanol solution, while the ORD suggested and the CD proved the oc-

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(9) G. G. Lyle, *J. Org. Chem.*, **25**, 1779 (1960).

(10) W. J. Kauzmann, J. E. Walter, and H. Eyring, *Chem. Rev.*, **26**, 339 (1940).

(11) The generosity of Dr. W. Gaffield of the Western Regional Research Laboratory of the Department of Agriculture, Albany, Calif., and of Professor W. Klyne, Westfield College, University of London, England, for measuring the low-wavelength ORD curves is gratefully acknowledged.

(12) We are grateful to Mr. W. Ungerer of the Jouan Co. for arranging for these curves to be obtained on the Jouan Dichrograph. More recently, Mr. N. Mitchell of Cary Instruments has furnished additional curves which duplicate those reported in this paper.

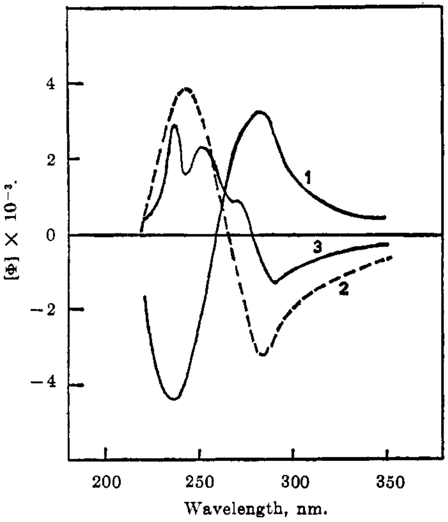


Figure 2.—ORD curves of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (1), 4-(D-*threo*-trihydroxypropyl)-2-phenyl-1,2,3-osotriazole (2), and 4-(L-*erythro*-trihydroxypropyl)-2-phenyl-1,2,3-osotriazole (3).

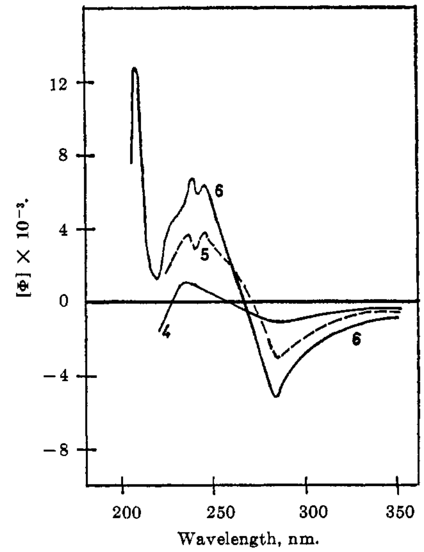


Figure 3.—ORD curves in methanol of 4-(D-*lyxo*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (4), 4-(L-*xylo*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (5), and 4-(D-*arabino*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (6).

currence of more than a single electronic transition in this region. The CD curve also showed a positive Cotton effect at lower wavelength which had been suggested by the appearance of a peak at 207 nm in the ORD curve of 6. The CD curve of 1 was enantiomeric to that of 6 above 215 nm except for the difference in intensity. A similar difference was noted in the ORD curves. Below 215 nm, both compounds gave a negative direction to the curves which suggests that there is an electronic transition below 200 nm which may have the same sign.

Since the signs of the long-wavelength Cotton effects are the same as the D-line rotations, there is possible a restatement of the osotriazole rule: *The sign of the Cotton effect at 265 nm is positive if the hydroxyl group α to the phenylosotriazole ring is to the right (R configuration) in a standard Fischer projection.* The narrow range of values for the amplitudes of these Cotton effects indicates the dominance of this asymmetric carbon atom.

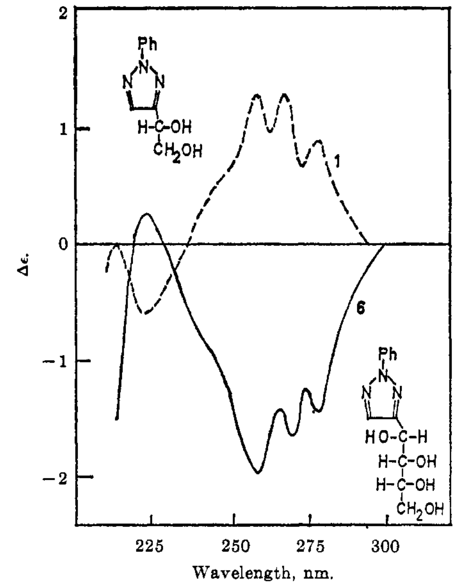
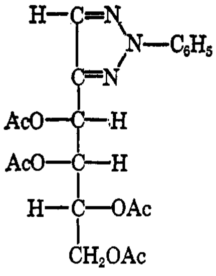


Figure 4.—CD curves in methanol of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (1) and 4-(D-*arabino*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (6).

The ORD curve of D-*lyxo*-hexose phenylosotriazole tetraacetate (7) showed a Cotton effect centered at 278 nm which appeared on the side of a larger Cotton effect at lower wavelength. The second Cotton effect probably resulted from the ester bands of the acetate groups but the entire Cotton effect was not visible. The sign of the long-wavelength Cotton effect is the same as that of the osotriazole 4 from which 7 was prepared.



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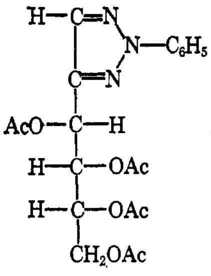

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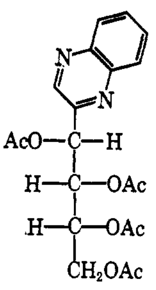

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A comparison of the nmr spectra of D-*arabino*-hexose phenylosotriazole (6) and its tetraacetate derivative 8 with the analogous quinoxaline derivative 9 indicated that 8 possessed the zigzag conformation (A, Figure 5) similar with that assigned[13] to 9. The coupling constant of the proton α to the aromatic ring in 8 was 3.9 Hz, close to that in 9. In view of the correspondence of the remainder of the aliphatic proton parts of the spectra of 8 and 9 in both chemical shift and coupling constant, the zigzag conformation may be assigned to 8. Examination of the nmr of 7 showed that the coupling constants for the C-3 and C-4 hydrogens corresponded to those anticipated for a zigzag conformation. It is possible for a large number of conformations to exist, but these data suggest that the zigzag conformation is of significance. A comparison of the spectral data for these tetraacetate derivatives is given in the Experimental Section.

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

TABLE I

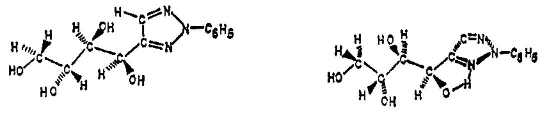
APPROXIMATE DIHEDRAL ANGLES OF α- AND β-CH BONDS IN SUGAR PHENYLOSOTRIAZOLES IN VARIOUS CONFORMATIONS[a]

	Dihedral angle and predicted coupling constant							
	Conformation A		Conformation B[b]		Conformation C[b]			
Compd	Angle, deg	J^c	Angle, deg	J^c	Angle, deg	J^c	α-Proton chemical shift, τ	J^c
1	*d*		*d*		*d*		4.42	5.6
Pentoses								
2	60	1.8	60	1.8	30	6.1	4.17	3.6
3	180	9.2	150	6.8	150	6.8	4.23	5.9
Hexoses								
4	180	9.2	150	6.8	150	6.8	4.15	7.3
5	60	1.8	40	4.7	20	8.7	4.12	5.1
6	60	1.8	60	1.8	50	3.2	3.85	<2[e]
Tetraacetates								
7	180	9.2					3.30	7.5
8	60	1.8					3.58[f]	3.9
9	60	1.8					3.55[f,g]	3.0[g]

[a] The solvent used was pyridine-d_5. [b] In both hydrogen-bonded conformations the remainder of the sugar chain was assumed to be in conformations which would allow the maximum amount of intramolecular hydrogen bonding and with the minimum of nonbonded interactions. [c] Coupling constants are given in hertz. [d] Two coupling constants and two angles are possible for each conformation. The observed J represents the time-averaged spectrum which prohibits any selection of preferential conformation where the methylene protons are equivalent. [e] Half-band width. [f] The solvent used was $CDCl_3$. [g] Reference 13.

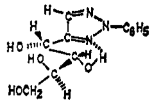
Three conformations of the hexose phenylosotriazole molecules appeared the most plausible. The zigzag conformation (A, Figure 5) would show no intramolecular hydrogen bonding and is the most probable conformation for the tetraacetate molecules **7**, **8**, and **9**. Although the monocyclic sugars may have little or no intramolecular hydrogen bonding in polar solvents,[14] the osotriazoles should show such bonding because of the possibility of O—H···N bonds, these being strong compared to the weaker O—H···O bonds possible in the sugars. Such bonding could occur between the C-3 hydroxyl group and nitrogen to form a five-membered ring (B, Figure 5) or between the C-4 hydroxyl and nitrogen resulting in a six-membered ring (C, Figure 5). Examination of space-filling models shows that the six-membered, hydrogen-bonded ring would be destabilized by the interference of the phenyl group. It apparently becomes impossible for the hydrogen bonding to remain in effect when the phenyl is coplanar with the triazole ring. If a five-membered ring is formed, however, the interfering nonbonded interactions are at a minimum. A decision as to the conformational preference of the hexose osotriazoles was sought *via* analysis of the nmr spectra.

The spectrum of **1** in pyridine-d_5 showed the signal for the C-3 proton as a triplet at τ 4.4 (J = 5.6 Hz). The methylene protons appeared as a doublet at τ 5.56 (J = 5.6 Hz). For the glucose derivative **6**, the C-3 proton was a broad singlet at τ 3.83 with a half-band width of less than 2 Hz, while in pyridine as solvent and on another instrument this single peak was resolved as a doublet (J = 1.5 Hz). The same proton in **5** appeared as a doublet at τ 4.10 (J = 5.1 Hz), whereas in **4** this proton resonated at 4.14 (J = 7.3 Hz). The data for the pentose derivatives are recorded in Table I. The fact that the J values represent time averages of a number of conformations must be emphasized. The dihedral angle of the α and β protons was estimated from Dreiding models of the osotriazoles for each conformer consistent with the spatial requirements estimated from Fisher–Hirschfelder models. Exact measurement was impossible for these flexible hydrogen-bonded models.



zig zag, A

C-3 OH hydrogen bonded, B



C-4 OH hydrogen bonded, C

Figure 5.—Possible conformations of 4-(D-*arabino*-tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (**6**). The hydroxyl groups not hydrogen bonded to nitrogen in B and C may be hydrogen bonded to each other or in a zigzag conformation. The data calculated for Table I assumed conformations approximating the ones drawn based on a minimization of nonbonded interactions as judged from space-filling models.

Using the Karplus correlation[15] the coupling constant was calculated for the angle between the α-CH and β-CH for each conformation (Table I). The correspondence of the values for $J_{\alpha\beta}$ to those for conformation B in preference to A or C is evident in all three hexose phenylosotriazoles. The resolution of the nmr spectra indicates reasonable conformational homogeneity. This, of course, does not exclude other possible conformers but supports a hydrogen-bonded conformation over the zigzag conformation on the nmr time scale for the structures having free hydroxyl groups.

The remainder of the nmr spectra was consistent with the structural assignments for these systems. The proton attached to the osotriazole ring was shifted to low field, τ 1.5–1.6 (1 H), as expected. The phenyl protons appeared as two multiplets, two doublets centered at τ 1.8 (2 H) and a split quartet at 2.7 (3 H). The hydroxyl protons appeared as a broad band at τ 3.4–3.5. The methylene protons generally appeared as a doublet but in **5** they gave only a broad singlet at τ 5.56. Only in the case of **2** was the signal split further and to such an extent that the nonequivalence

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(14) A. B. Foster, R. Harrison, J. Lehman, and J. M. Webber, *J. Chem. Soc.*, 4471 (1963).

(15) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

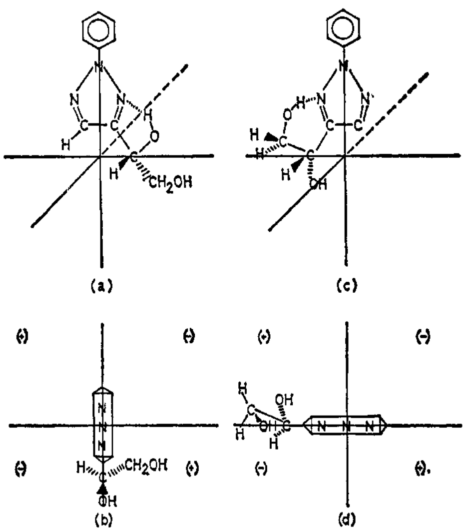

Figure 6.—Orientation of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (1) on an eight-sector diagram. In part a this structure assumes a conformation similar to B in Figure 5, whereas the conformation in part c is analogous to C in Figure 5. The diagrams in parts b and d represent views from the *para* position of the benzene ring bisecting the triazole ring. These views maintain the signs of the four pertinent rear sectors and orient the molecules consistent with the experimentally observed positive Cotton effect for 1.

of the methylene protons was apparent. The remaining β and γ protons showed multiplets at τ 5.1–5.4.

The coupling constants of the α protons in the osotriazoles were smaller (2–5 Hz) for the *threo* α,β hydrogens than those for the *erythro* series (6–7 Hz). The range of coupling constants reflects the alterations in dihedral angle imposed by the variety of conformations in the remainder of the molecule which results from the differences in stereochemistry. The zigzag conformation for **3** would require the dihedral angle of α- and β-CH bonds to be 180° with $J = 9.2$ Hz, whereas in **2** the dihedral angle should be 60° ($J = 1.8$ Hz) for the same idealized conformation. The hydrogen-bonded conformations for **2** would be relatively similar to those for **5** or **6**, whereas **3** should be similar to **4** (Table I). The values observed indicated that **2** may have any of the three possible conformations, preferably A or B. The conformation of **3**, however, is more probably the hydrogen-bonded (B or C) rather than the zigzag structure. The data for the pentose derivatives are somewhat more equivocal than for the hexose phenylosotriazoles.

In view of the evidence from the ORD and nmr spectra as to the probable conformations of these sugar derivatives, it should be possible to construct a reasonable model by which one may predict the sign of the Cotton effect. Such a design would be analogous to the octant rule established for the carbonyl function.[16] The phenyl and triazole rings may be assumed to be coplanar for maximum π orbital overlap. The symmetry of the phenylosotriazole rings directs one symmetry axis through the *para* position of the phenyl ring, the central nitrogen atom, and between the two carbons of the triazole ring (Figure 6a). A second nodal plane is in the plane of the paper. The exact locations of any other nodal planes are less certain, but the sector diagrams shown in Figure 6 seem most plausible. It is possible that the symmetry may be of the C_{2v} type and a four-sector diagram may provide a satisfactory model. It has been suggested that the monosubstituted benzene would best fit a C_{2v} model,[17] and the triazole ring is, fortunately, of similar symmetry.

In designing a sector rule for the aromatic chromophore attached to an acyclic side chain, the conformational possibilities seem almost limitless. The number of possible conformations of the substituents attached to the asymmetric carbon atom bearing the osotriazole ring must be reduced to a single conformation of substantial probability before such a design is feasible. If the aromatic ring is placed on a three-coordinate axis, the α carbon will have the usual six basic conformations with each substituent either eclipsed by or perpendicular to the aromatic ring. If there is reasonably stabilized hydrogen bonding of the C-3 hydroxyl group to a nitrogen of the osotriazole ring as postulated from the nmr evidence above, the predominant conformation may be assigned to that where the groups which appear in the sectors are the C-3 hydrogen and the $-(CHOH)_n-CH_2OH$ substituents (Figure 5). This situation then requires only the decision as to whether the aromatic moiety be horizontal or vertical on the three-coordinate diagram. Kuriyama, *et al.*,[18] designed an octant rule for the 1,2,4,5-tetrasubstituted aromatic chromophore in alkaloids placing the aromatic ring horizontally. This rule is not applicable to the five-membered, hydrogen-bonded ring of the phenylosotriazole derivatives since the experimental observations do not agree with the predicted signs of the Cotton effects. In view of the difference in the chromophoric system, this is not surprising and it would be very fortuitous if all compounds containing an aromatic chromophore could be correlated by a single sector rule.

The rule proposed herein is, therefore, based on the experimental observation that the configuration of the C-3 carbon determines the sign of the Cotton effect group centered at about 265 nm. The symmetry of the phenylosotriazole chromophore requires that one plane pass vertically through the *para* position of the aromatic ring bisecting the C-1–C-2 bond of the osotriazole ring. This means that the C-3 chiral center does *not* lie at the origin but has one finite coordinate (Figure 6a). Viewing the substituents from the *para* position of the benzene ring, the schematic sector diagram of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (1) may be represented as in Figure 6b. The striped area represents the phenylosotriazole chromophore and the C-3 carbon and hydroxyl are in the same nodal plane. If the signs of the sectors are the same as those designated by the octant rule,[16] conformation a (Figure 6) for **1** would be expected to show a positive Cotton effect since the CH_2OH substituent will be in the lower right rear, a positive sector, outweighing the C-3 hydrogen opposite it. The remainder of the molecule will lie in a nodal plane.

It is apparent that the sector diagram having the horizontal aromatic chromophore would be applicable to the phenylosotriazole system provided an alternate conformation were used. The six-membered, hydro-

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[16] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

[17] J. A. Schellman, *J. Chem. Phys.*, **44**, 55 (1966).

[18] K. Kuriyama, T. Iwata, M. Moriyama, K. Kotera, Y. Hamada, R. Mitsui, and K. Takeda, *J. Chem. Soc., Sect. B*, 46 (1967).

gen-bonded ring would fit such a rule and cannot be discarded. The representation is shown in Figure 6c. Since the nmr evidence appeared to support the five-membered hydrogen-bonded ring, it has been used as the primary model. It seems, therefore, that conformation B (Figure 5) drawn on the sector rule of Figure 6a,b is plausible based on the experimental observations of the osotriazole rule. In addition, this conformation is consistent with the data obtained from the nmr study. It represents, therefore, a useful model of this system for study of a sector rule for an aromatic chromophore.

Experimental Section[19]

Potato Oxystarch.—A colloidal suspension of 4.5 g of potato starch and 6.18 g of sodium metaperiodate was kept stirring in the dark for 48 hr. At the end of this time the insoluble oxystarch was separated by filtration and washed with water until free from periodate and iodate. The gelatinous solid was washed with absolute alcohol until a white powder was obtained. The powder was washed with ether and dried by passing air through the filter cake. The yield was quantitative.

Phenylosazone of Potato Oxystarch.—A mixture of 2.3 g of potato oxystarch in 100 ml of water was heated under reflux in 200 ml of ethanol, 25 ml of phenylhydrazine and 30 ml of glacial acetic acid. Solution of the oxystarch took place in about 10 min after which the ethanol was removed under reduced pressure. To the remaining solution was added with rapid stirring 500 ml of cold water producing a golden yellow precipitate. The precipitate was collected by filtration and washed with 50-ml portions of 10% acetic acid followed by two 50-ml portions of cold water, yielding 3.5 g of the phenylosazone which was used without further purification in the following experiment.

D-Erythrose Phenylosazone.—A solution of 2 g of the crude potato oxystarch osazone was dissolved in 100 ml of benzene and absorbed on a 150-g neutral alumina column. The column was eluted with 1 l. of ether or until the initial wide yellow band came off the column. The ether eluted the glyoxal osazone and β-acetyl phenylhydrazine as one band. The column was washed free of the remaining solid with 95% ethanol. The ethanol solution was concentrated under reduced pressure and the erythrose phenylosazone was precipitated by the addition of water to the rapidly stirring solution. The yellow precipitate was collected by filtration and was recrystallized from 60% ethanol–water yielding 0.42 g of D-erythrose phenylosazone, mp 175–177° (lit.[20] mp 175–177°).

4-(D-*glycero*-Dihydroxyethyl)-2-phenyl-1,2,3-triazole (1).—A suspension of 20 g of the crude potato starch phenylosazone and 1800 ml of water was heated to boiling and a solution of 16.7 g of copper sulfate pentahydrate in 100 ml of boiling water was added. After 30 min of heating under reflux, the solution was allowed to cool to room temperature and freed of decomposition products by filtration. Hydrogen sulfide was bubbled through the solution as long as a black precipitate continued to form. The black precipitate was separated by filtration leaving a yellow solution which was boiled with 20 g of barium carbonate until the solution was slightly basic to litmus. After cooling, the mixture was separated by filtration and the filtrate was concentrated to a syrup under reduced pressure. The syrup was extracted with two 250-ml portions of carbon tetrachloride. The combined extracts of carbon tetrachloride were concentrated under reduced pressure and cooled for 2 hr under refrigeration. The white, voluminous precipitate was dried and dissolved in hot isopropyl ether and *n*-hexane was added until the first sign of turbidity appeared. The solution was allowed to cool to room temperature and then refrigerated overnight. The white precipitate was separated by filtration and washed with two 25-ml portions of *n*-hexane yielding 2.5 g of 4-(D-*glycero*-dihydroxyethyl)-2-phenyl-1,2,3-triazole (1): mp 64–65°; λ_{max} 265 nm (ϵ 20,147), 208 (14,117); nmr gave τ 1.63 (1 H) for osotriazole proton, 1.75 (two doublets, 2 H) and 2.6 (multiplet, 3 H) for the phenyl protons, a triplet at 4.42 (1 H, J = 5.6 Hz), and a doublet at 5.55 (2 H, J = 5.6 Hz).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 59.10; H, 5.23; N, 19.83.

Preparation of Osazones.—A mixture of 10 g of the sugar, 20 g of phenylhydrazone hydrochloride, 25 ml of a saturated solution of sodium bisulfite, 30 g of crystalline sodium acetate, and 200 ml of distilled water was heated with stirring on a steam bath for 0.5 hr. The precipitate was separated by filtration, washed with water and combined with a second crop obtained after heating the filtrate for several hours. Recrystallization yielded 56–75% of the phenylosazone whose physical constants agreed with those recorded in the literature.

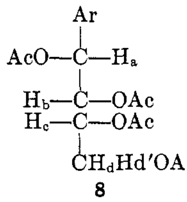
The osazone of arabinose was prepared in methyl cellosolve and precipitated on contact with water. The work-up was comparable with that above, yielding 60% of product, mp 170–171° (lit.[21] mp 172–172°).

Preparation of Phenylosotriazoles.—A mixture of 20 g of the phenylosazone, 16.7 g of $CuSO_4 \cdot 5H_2O$, and 1200 ml of water was heated under reflux for 30–60 min. The color changed from a red to green to yellow green. A red precipitate was removed, hydrogen sulfide was bubbled through the solution, and the CuS was separated by filtration. The filtrate was boiled for 15 min with 10 g of barium carbonate or until the solution was neutral to pH paper. Insoluble material was removed and the filtrate was concentrated to a syrup under reduced pressure. The syrup either deposited crystals or was extracted with ethyl acetate (for **5**) or chloroform (for **4**) which yielded the crystalline product. Recrystallization from ether or ether–hexane gave 40–70% of the phenylosotriazoles which agreed in melting point with literature values and are listed with ORD and CD data below.

4-(D-*arabino*-Tetrahydroxybutyl)-2-phenyl-1,2,3-triazole (6).—The insolubility of the osazone from glucose required modification of the above procedure. A mixture of 180 ml of water, 10 ml of 0.5 *N* sulfuric acid, 2 g of the osazone, 6 g of copper sulfate pentahydrate, and 120 ml of isopropyl alcohol was heated under reflux for 1 hr and separated by filtration, and the liquid was concentrated to 50 ml. The tan precipitate was dissolved in water and decolorized with Norit. After being freed from Norit, the crystalline osotriazole (6), 300 mg (20%), melted at 193–193.5° (lit.[20] mp 195–196°).

Preparation of Tetraacetoxy Derivatives of Phenylosotriazoles.—The phenylosotriazoles **4** and **6** were treated with acetic anhydride in pyridine at 20° for 48 hr. The product in each case was extracted into chloroform, dried, and crystallized from dioxane–water to yield (90%) the tetraacetoxy derivatives **7**, mp 104–105° (lit.[22] mp 105–106°), and **8**, mp 81–82° (lit.[20] mp 81–82°).

The nmr of **8** in $CDCl_3$ showed a singlet at τ 2.13 (1 H, osotriazole ring proton), a multiplet at 2.82 (5 H, phenyl), C(=O)-CH_3 at 7.82, 7.87, 7.89, 7.97 (3 H each), and five aliphatic protons of chemical shift and apparent coupling constant as listed under compound **8**. Second-order coupling was disregarded for H_b.



$$\begin{array}{c} \mathrm{Ar} \\ | \\ \mathrm{AcO{-}C{-}H_a} \\ | \\ \mathrm{H_b{-}C{-}OAc} \\ \mathrm{H_c{-}C{-}OAc} \\ | \\ \mathrm{CH_dHd'OAc} \end{array}$$

8

H_a, τ 3.55 (d) (J_{ab} = 3.9 Hz)
H_b, τ 4.18 (q) (J_{ab} = 3.9 Hz, J_{bc} = 7.9 Hz)
H_c, τ 4.58 (m)
H_d, τ 5.72 (m)

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[19] The ultraviolet absorption spectra were recorded on a Cary 15 instrument using 95% ethanol as solvent. The ORD curves were obtained on a Rudolph recording spectropolarimeter (λ 600–350 nm), a Cary 60 or Bellingham and Stanley Bendix-Ericsson instrument (λ <350 nm) in 10-, 5-, or 1-mm cells, adjusting concentration and path length for maximum signal. The nmr data were recorded on a Varian A-60 (purchased with the assistance of a National Science Foundation Equipment Grant G22718 to the University of New Hampshire) and on a Perkin-Elmer instrument using pyridine-d_5 as the solvent. Grateful acknowledgment is accorded to Mrs. E. Richards and Mr. P. Cherry of Dyson-Perrins Laboratory, Oxford, England, for determining many of these spectra. Microanalyses were by Schwartzkopf Laboratory, Woodside, N. Y.

[20] R. M. Hann and C. S. Hudson, *J. Amer. Chem. Soc.*, **66**, 735 (1944).

[21] W. T. Haskins, R. M. Hann, and C. S. Hudson, *ibid.*, **68**, 1766 (1946).

[22] W. T. Haskins, R. M. Hann, and C. S. Hudson, *ibid.*, **67**, 939 (1945).

The data were compared with those obtained from the analogous quinoxaline derivative **9** analyzed previously[13] and which showed J_{ab} = 3.0 Hz and J_{bc} = 8.5 Hz. The Karplus equation[15] predicts dihedral angles of 45° for two protons coupled by 3.9 Hz and 51° for those where J = 3.0 Hz. The coupling constants for J_{bc} in **8** and **9** correspond, respectively, to dihedral angles of 158 and 164°. These data suggest that there may be slightly more deviation from the ideal staggered conformation in the triazole **8** than in the quinoxaline **9**. The difference between the two seems relatively minor as compared with the deviation from ideal. The data, of course, merely reflect an average of a large number of conformations and suggest only that of the extremes possible the staggered conformation predominates.

The nmr data for the tetraacetate derivative **7** which has the *lyxo* stereochemistry (H_{ab} *erythro*) instead of the *arabino* stereochemistry of **8** and **9** (H_{ab} *threo*) showed in pyridine-d_5 τ 1.72 (1 H, osotriazole proton), a complex aromatic region centered approximately at 2.24 (5 H), and four acetyl groups at 7.88 (3 H), 7.92 (3 H), and 7.98 (6 H). The five aliphatic protons showed signals for H_a at τ 3.30 (d) (J_{ab} = 7.5 Hz); H_b at 3.76 (q) (J_{ab} = 7.5 Hz, J_{bc} = 3.5 Hz); H_c at about 4.0 (m); and H_d at 5.40 (q). The quartet for H_d shows the nonequivalence of these methylene protons ($J_{dd'}$ = 13 Hz, J_{cd} = 7 Hz). The dihedral angles for the H_{ab} and H_{bc} bonds are calculated to be approximately 155 and 48°, respectively, which suggests the staggered conformation very similar to that shown by the osotriazole **7** and reflecting the enantiomeric configuration at C-4.

Optical rotatory dispersion data were recorded on a Cary 60 spectropolarimeter in methanol solution.

4-(D-*glycero*-Dihydroxyethyl)-2-phenyl-1,2,3-osotriazole (**1**), mp 64–65°, *c* 0.07, had the following ORD values: $[\Phi]_{350}$ +435, $[\Phi]_{282.5}$ +3280, $[\Phi]_{235}$ −4550, $[\Phi]_{222}$ −1640.

4-(D-*threo*-Trihydroxypropyl)-2-phenyl-1,2,3-osotriazole (**2**), mp 87–88.5° (lit.[22] mp 88–89°), *c* 0.043, had the following ORD values: $[\Phi]_{350}$ −670, $[\Phi]_{285}$ −3240, $[\Phi]_{241}$ +3880, $[\Phi]_{220}$ 0.

4-(L-*erythro*-Trihydroxypropyl)-2-phenyl-1,2,3-osotriazole (**3**), mp 65–68.5° (lit.[20] 69–70°), *c* 0.084, had the following ORD values: $[\Phi]_{350}$ −296, $[\Phi]_{289}$ −1340, $[\Phi]_{270-265}$ +894, $[\Phi]_{250}$ +2350, $[\Phi]_{242.5}$ +1670. $[\Phi]_{237}$ +2900, $[\Phi]_{220}$ +190.

4-(D-*lyxo*-Tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (**4**) mp 108–109° (lit.[22] 110–111°), *c* 0.045, had the following ORD values: $[\Phi]_{350}$ −284, $[\Phi]_{284}$ −1154, $[\Phi]_{234}$ +1036, $[\Phi]_{220}$ −1508.

4-(D-*lyxo*-Tetraacetoxybutyl)-2-phenyl-1,2,3-osotriazole (**7**), *c* 0.085, had the following ORD values: $[\Phi]_{350}$ −589, $[\Phi]_{285}$ −2117, $[\Phi]_{270}$ +1650, $[\Phi]_{264}$ +1303, $[\Phi]_{236}$ +5781, $[\Phi]_{221}$ 0.

4-(L-*xylo*-Tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (**5**), mp 151–152° (lit.[22] mp 158–159°), *c* 0.0045, had the following ORD values: $[\Phi]_{350}$ −559, $[\Phi]_{285}$ −3108, $[\Phi]_{245}$ +3768, $[\Phi]_{240}$ +2828, $[\Phi]_{235}$ +3676, $[\Phi]_{225}$ +1884.

4-(D-*arabino*-Tetrahydroxybutyl)-2-phenyl-1,2,3-osotriazole (**6**), *c* 0.131, had the following ORD values: $[\Phi]_{350}$ −910, $[\Phi]_{283}$ −5250, $[\Phi]_{245}$ +6410, $[\Phi]_{241}$ +5830, $[\Phi]_{239}$ +6700, $[\Phi]_{217}$ 0, $[\Phi]_{207}$ +12,800, $[\Phi]_{205}$ +7860.

Circular dichroism data were recorded in methanol on a Jouan Dichrograph Model 185. The following values were recorded: for compound **6**, 300 nm ($\Delta\epsilon$ 0), 277 (−1.43), 274 (−1.24), 270 (−1.84), 265 (−1.42), 258 (−1.93), 244 [−0.90 (sh)], 227 (0), 223 (+0.27), 219 (0), 213 (−1.52); for **1**, 295 nm ($\Delta\epsilon$ 0), 277 (+0.90), 273 (+0.66), 265 (+1.28), 262 (+0.96), 258 (+1.26), 248 [+0.60 (sh)], 236 (0), 222 (−0.58), 213 (0), 210 (0.24).

Ultraviolet absorption spectra were recorded in 95% ethanol on the Cary 15 or Perkin-Elmer 4000 instrument. The λ_{max} (ϵ) values for the osotriazole derivatives follow: **1**, 265 nm (20,150); **2**, 267 (20,240); **3**, 266 (19,830); **4**, 266 (19,550); **5**, 266 (18,810); **6**, 267 (24,450); **7**, 264 (22,070).

Registry No.—**1**, 16336-37-1; **2**, 15476-33-2; **3**, 15476-35-4; **4**, 15476-32-1; **5**, 15476-34-3; **6**, 16346-56-8; **7**, 6341-06-6; **8**, 7770-63-0; **9**, 4710-99-0.

The Conformation of α-D-Idopyranose Pentaacetate[1,2]

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The proton nmr spectrum of α-D-idopyranose pentaacetate (**1**) at 220 MHz in acetone-d_6 or chloroform-*d* is completely first order and shows that the *C1* chair conformation, having the acetoxymethyl group equatorial and the four acetoxy groups axial, is the favored conformation. In addition to the normal spin couplings of vicinal protons, long-range ^4J couplings are observed between the equatorial protons H-1 and H-3, and similarly between H-2 and H-4. A ^5J coupling between H-1 and H-4 is also observed. The alternative chair (*1C*) conformation, having all groups equatorial except the acetoxymethyl group, is considerably less stable than the *C1* form.

Conformational analysis of polysubstituted chains and ring systems may be studied conveniently by use of various types of carbohydrate derivative. Such compounds offer the advantage that several stereoisomers, and frequently complete sets of stereoisomers, are available in a given system. A program in this laboratory has been concerned with determination of favored conformation and conformational populations at equilibrium, in highly substituted tetrahydropyran ring systems, as provided by pyranoid sugar derivatives,[1] and in the open-chain structures of acyclic derivatives of sugars.[6]

Polysubstituted tetrahydropyran derivatives may be formulated in two energetically nonequivalent chairlike conformations and in a flexible cycle of skew forms interconvertible through the boat forms.[7,8] Conformers in the flexible cycle are generally considered to be of higher energy than the favored chairlike conformer, except perhaps for certain fused-ring derivatives.[9] A rationale for predicting the favored chair conformation for pyranose sugars and their derivatives

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(1) This paper is part of a series "Application of 220-MHz Nmr to the Solution of Stereochemical Problems." For previous papers from this laboratory concerned with conformations of pyranoid sugar derivatives, see (a) D. Horton and W. N. Turner, *J. Org. Chem.*, **30**, 3387 (1965); (b) C. V. Holland, D. Horton, and J. S. Jewell, *ibid.*, **32**, 1818 (1967); (c) N. S. Bhacca and D. Horton, *Chem. Commun.*, 867 (1967); (d) C. V. Holland, D. Horton, M. J. Miller, and N. S. Bhacca, *J. Org. Chem.*, **32**, 3077 (1967); (e) N. S. Bhacca and D. Horton, *J. Amer. Chem. Soc.*, **89**, 5993 (1967).

(2) A preliminary report of part of this work has been given: P. L. Durette, D. Horton, and N. S. Bhacca, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, p C22.

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