2, CH_2OH), 9.08, 9.12, 9.18, 9.25 ($CHCH_3$'s); mass spectrum parent ion m/e 224.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.3; H, 12.5.

Registry No.—**3,** 34289-89-9; **5,** 4154-60-3; **6,** 17142-58-4; **7,** 33454-43-2; **8,** 26496-79-7; **10,** 34288-62-5; **11,** 34288-63-6; **13,** 34289-91-3; **14,** 5673-98-3; **15,** 17142-57-3; **16,** 34288-66-9; **17,** 26496-78-6; **19,** 26496-80-0; **20,** 26133-24-4; **21,** 34289-93-5; **22,** 34288-69-2; **25,** 34288-70-5; **31,** 34288-71-6.

Acknowledgment.—The authors acknowledge the helpful suggestions of Professor E. Wenkert and Professor E. C. Taylor and the technical assistance of Mr. Kerry Fitzpatrick.

Conformations of Acetylated Glyculose Phenylosotriazoles and Para-Substituted Phenylosotriazoles[1-3] in Solution

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Phenylosotriazoles and some para-substituted phenylosotriazoles of D-*erythro*- and L-*threo*-pentulose, D-*arabino*-, D-*lyxo*-, and L-*xylo*-hexulose, and 6-deoxy-L-*arabino*-hexulose have been examined as their peracetates by nmr spectroscopy at 100 MHz in chloroform-*d* solution. In each example, shielding of the protons along the side chain increases with distance from the heterocycle. From the spin–spin coupling data it can be inferred that the carbohydrate chain adopts a planar, zigzag arrangement of carbon atoms unless an eclipsed, 1,3 interaction between polar groups would thereby be generated or unless the polar substituent at C-2 (of the side chain) would thereby bisect the angle between the substituents on C-1, namely, the heterocycle and an acetoxyl group. Except for the arabino derivatives, which appear to be stabilized by stereochemical factors further along the chain, the favored conformations adopted when either or both of the aforementioned features would be present in the planar, zigzag arrangement are derived from the planar form by rotation about one or more of the carbon–carbon bonds along the chain. The variations of conformational preference displayed by the various acetylated, acyclic sugar derivatives examined to date are not presently amenable to more than superficial rationalization on the basis of apparent "size" of the chain-terminal group.

Conformational analysis of acyclic molecules can be traced back to van't Hoff[5] and to a casual observation by Rosanoff.[6] The statements of these authors were as general as they were fundamental, and the validity of their interpretations has not declined in the intervening years. Later interpretations of phenomena related to conformational properties of acyclic sugar molecules[7] drew specific conclusions that have been refuted.[8,9]

Recent work[2,9-20] has employed nmr spectroscopy to determine the conformational preferences of a variety of acyclic carbohydrate derivatives. In the initial paper of this series[10] the planar, zigzag arrangement of the carbon atoms in the side chain of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline and its tetraacetate was inferred to be the favored conformation by consideration of vicinal, proton–proton spin couplings as they relate to approximate angular dependences.[21] Implicit, qualitative corrections for the effects of substituent electronegativity[22] were made by assuming couplings of 2–4 Hz for gauche, vicinal protons and 8–9 Hz for vicinal, antiparallel protons, by analogy with data for acetylated, cyclic, carbohydrate systems.[23-25] Similarly, for a series of nonacetylated phenylosotriazole derivatives, the planar, zigzag arrangement of the carbohydrate chain was shown[11] to be favored, except when this would lead to a parallel, 1,3 interaction between oxygen atoms on the chain; such an interaction, as arising in L-*xylo*-hexulose phenylosotriazole, is alleviated by the molecule's adopting a different rotameric form about one or more of the carbon–carbon bonds of the chain.

Examination of a configurationally complete series of acetylated diethyl dithioacetals confirmed[12] the influence of parallel, 1,3 interactions in determining favored conformations of acyclic molecules. Coupling data for members having the ribo and xylo configurations indicate that, by rotation about C-3–C-4 or C-2–C-3, respectively, stabilization is achieved by the generation of "sickle" conformers free of 1,3 interactions. The corresponding acetylated diphenyl dithioacetals[13,14] show essentially identical behavior, except for

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a diminution in the magnitude of $J_{1,2}$, and a downfield shift of the H-1 signal. The variation in $J_{1,2}$ might reflect a sterically induced change of rotamer populations about C-1–C-2, but the attendant, large change of field position of the H-1 resonances suggested[13] that differences in electronic character[21,26] between the C-1 substituents influence the value of $J_{1,2}$. A series of acetylated dimethyl acetals showed[2] conformational behavior entirely analogous to that of the diethyl dithioacetals.

Although the steric size of the aldehyde group might be expected to be less than that of the bis(ethylthio)-methyl group, no substantial changes of chemical shifts or couplings were observed[14] between members of a configurational series of *aldehydo*-aldose peracetates and the corresponding dithioacetals, except for a shift of the H-1 signal to below τ 0.5 and a decrease in $J_{1,2}$ to near zero. The $J_{1,2}$ coupling was considered in terms of the Karplus relationship,[21] with reservations expressed about the effect of the electronegative O-1 and the trigonal hybridization at C-1; the conformations thus indicated were consistent with those deduced by various methods for simpler carbonyl derivatives.[27] For the xylo derivative there was indication that two sickle forms were contributing significantly to the conformational equilibrium.[25,28] As noted by Chilton and Krahn[15] in a conformational study of some acetylated quinoxaline derivatives having acyclic, carbohydrate side chains, coupling data can be accommodated by more than one conformer. However, an equilibrium between forms having eclipsed 1,3 interactions is not considered probable when an equilibrium between forms free of such interactions can accommodate the observed couplings.

In analyzing the nmr spectra of several 3,4,5,6-tetra-acetoxy-*trans*-1-nitro-1-hexenes, Williams[16] displayed cautious reserve in assigning rotamer states about the C-2–C-3 bond, because of shortage of available reference information; however, the conformational behavior of the chain of tetrahedrally hybridized carbon atoms was shown to accord with previous[10-12] and contemporary[9,13-15,17] reports.

The elegance and simplicity of the Karplus expression provides an extreme temptation for incautious overinterpretation of the significance of coupling data. The interdependence of vicinal couplings, dihedral angles, and substituent electronegativity has been demonstrated in cyclic carbohydrate derivatives,[22,24] but a definitive treatment of this relationship in acyclic molecules is currently lacking. Extraction of exact dihedral bond angles in acyclic molecules[17] is certainly an overapplication of the Karplus equation, and the deduction of quantitative values for the distributions of rotameric states about each carbon–carbon bond along the acyclic chain[18] requires perspicacious consideration of the limits of its precision, as it is predicated upon the implied conditions (1) that ideal bond geometry prevails, (2) that only the three fully staggered rotameric forms around each bond are represented, (3) that there is angular independence of the effect of acetoxyl substituents upon vicinal couplings, and (4) that the couplings between antiparallel and gauche pairs of protons invariably adopt those values assumed by analogy with cyclic derivatives.

X-Ray crystallographic studies on alditols[29,30] suggest that ideal bond geometry in these molecules is the exception rather than the rule, and the observed vicinal, dihedral angles in crystalline ribitol range[30] from 46.6 to 77.9°. In solution, rapid time averaging presumably takes place among all possible rotameric states along each carbon–carbon bond; positional time averaging between minimum-energy rotamers is an approximation to this condition. It is well documented that vicinal couplings for a given orientation are dependent upon substituent electronegativity;[22,24] furthermore, the report[9] that the *field positions* of signals in the nmr spectra of the methyl 2,3,4,6-tetra-*O*-acetyl-5-hexulosonates are dependent upon the orientation of the corresponding protons (with respect to the adjacent acetoxyl group) suggests that the *couplings* of such protons will be affected simultaneously. This implies that the coupling constants for the two different rotamers having vicinal, gauche protons will normally be different. Finally, the model couping values used[18] (9.5 Hz antiparallel, 2.0 Hz gauche) are inadequate for uncritical generalization; for example, 2,3,4,5-tetra-*O*-acetyl-6-deoxy-*aldehydo*-L-galactose shows[14] couplings more extreme ($J_{2,3}$ = 1.5 Hz, $J_{3,4}$ = 9.8 Hz) than these estimates.

Conformational equilibria of pyranoid sugar derivatives have been measured quantitatively[25,28] by performing nmr studies at a temperature low enough for interconversion to be slow on the nmr time scale, so that spectra of individual conformers can be observed ("conformational freeze-out"), and also by "averaging of spin couplings" by use of model compounds of demonstrated conformational homogeneity.[25,31] Because of the greater mobility of acyclic systems, a similar low-temperature study has not yet been applied successfully to acyclic sugar derivatives, nor have true, limiting values for couplings been established. At present, it seems, therefore, excessively speculative to attempt quantitative description of conformational equilibria in these acyclic systems. A qualitative identification of conformers as major or minor is a conservative, but more realistic, application of existing methods and information and can be expected to generate fewer errors of concept than a detailed quantitative treatment based on unsound foundations. An error limit of the order of 10%, as implied in the level of differentiation attributed to the analytical method of Lee and Scanlon[18] and applied with other systems,[9] is clearly unrealistic. Likewise, attempts[18] to calculate conformational behavior, from interaction energies between substituents

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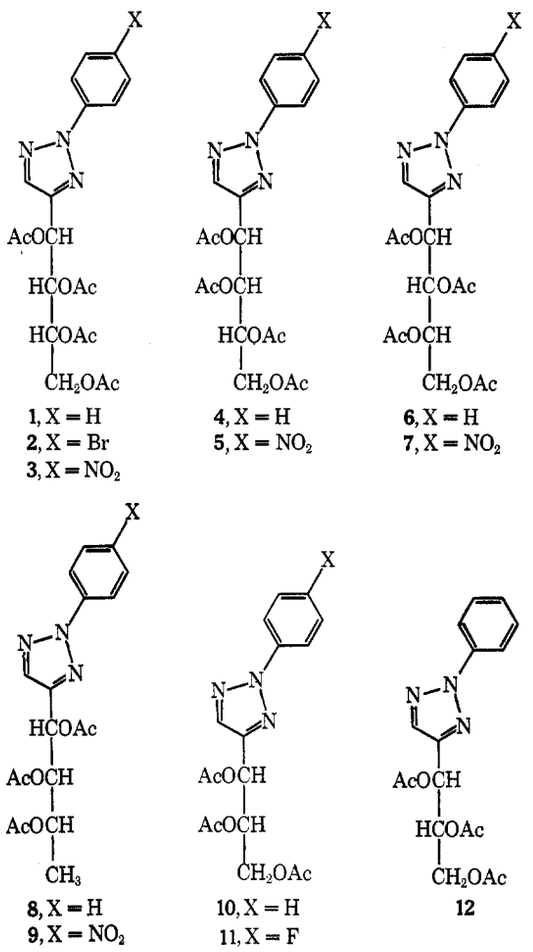
TABLE I
CHEMICAL SHIFT DATA FOR OSOTRIAZOLE PERACETATES

		Chemical shifts, τ, in chloroform-*d*								
Compd	Confign	Triazole proton	H-1	H-2	H-3[a]	H-3′	H-4[a]	H-4′	Acetyl groups	Aromatic[b]
1	Arabino	2.23	3.60	4.24	4.65		5.64	5.82	7.94, 7.92, 7.90, 7.84	2.57, 1.96
2	Arabino	2.25	3.65	4.28	4.69		5.66	5.85	7.94 (2), 7.91, 7.85	2.42, 2.08
3	Arabino	2.24	3.64	4.28	4.68		5.67	5.86	7.97, 7.95, 7.93, 7.87	1.84, 1.58
4	Lyxo	2.21	3.80	4.19	4.48		5.67	5.96	8.04, 7.97 (2), 7.94	2.63, 1.96
5	Lyxo	2.09	3.79	4.19	4.45		5.64	5.93	7.98, 7.92, 7.90, 7.87	1.77, 1.61
6	Xylo	2.26	3.76	4.25	4.81		5.69	5.99	7.99, 7.92, 7.91, 7.88	2.65, 1.98
7	Xylo	2.18	3.84	4.28	4.63		5.66	5.86	7.97, 7.95, 7.92, 7.85	1.83, 1.66
8	Arabino	2.23	3.63	4.37	4.88		8.75		8.00, 7.96, 7.91	2.63, 1.95
9	Arabino	2.08	3.76	4.35	4.66		8.71		7.96, 7.94, 7.90	1.75, 1.61
10	Erythro	2.23	3.71	4.33	5.56	5.73			7.97 (2), 7.90	2.63, 1.94
11	Erythro	2.25	3.75	4.35	5.57	5.75			7.95 (2), 7.87	2.81, 1.97
12	Threo	2.19	3.66	4.29	5.53	5.90			7.93, 7.89, 7.86	2.57, 1.92

[a] When two protons are present on the same carbon atom, the one whose signal resonates at higher field is designated by a prime, *e.g.*, H-3′. [b] Of the substituent on N-2 of the 1,2,3-triazole ring.

CHART I



originally defined for cyclic systems, appear premature at this stage.

The present report enumerates the favored conformations in solution, as determined by nmr spectroscopy, of tetra-*O*-acetyl-D-*arabino*-hexulose phenylosotriazole[32] (**1**) and its *p*-bromophenyl[33] (**2**) and *p*-nitrophenyl[34] (**3**) analogs, of tetra-*O*-acetyl-D-*lyxo*-hexulose phenylosotriazole[35] (**4**) and its *p*-nitrophenyl derivative[36] (**5**), of tetra-*O*-acetyl-L-*xylo*-hexulose phenylosotriazole[35] (**6**) and its *p*-nitrophenyl analog[36] (**7**), of tri-*O*-acetyl-6-deoxy-L-*arabino*-hexulose phenylosotriazole[37,38] (**8**) and its *p*-nitrophenyl analog[36] (**9**), of tri-*O*-acetyl-L-*erythro*-pentulose phenylosotriazole[38] (**10**) and its *p*-fluorophenyl analog[39] (**11**), and of tri-*O*-acetyl-D-*threo*-pentulose phenylosotriazole[35] (**12**) (Chart I).

TABLE II
FIRST-ORDER COUPLING CONSTANTS FOR OSOTRIAZOLE PERACETATES

		Coupling constants, Hz						
Compd	Confign	$J_{1,2}$	$J_{2,3}$[a]	$J_{2,3'}$[a]	$J_{3,3'}$[a]	$J_{3,4}$[a]	$J_{3,4'}$[a]	$J_{4,4'}$[a]
1	Arabino	3.8	8.2			3.4	4.5	12.2
2	Arabino	3.6	8.0			3.6	5.5	12.2
3	Arabino	3.6	7.9			3.1	6.0	12.3
4	Lyxo	7.8	3.1			4.7	7.0	12.0
5	Lyxo	7.7	3.3			5.0	6.8	12.0
6	Xylo	7.5	3.8			5.4	6.4	11.8
7	Xylo	3.6	8.0			3.4	5.5	12.2
8	Arabino	5.4	6.2			6.2		
9	Arabino	7.8	3.4			6.2		
10	Erythro	5.4	4.0	6.0	12.4			
11	Erythro	5.6	4.0	6.1	12.1			
12	Threo	6.4	4.4	5.6	12.0			

[a] See footnote *a* of Table I.

Spectral Measurements and Analysis.—The 100-MHz nmr spectrum of each compound (**1**–**12**) was measured at ~24° in chloroform-*d* containing 5% (v/v) of tetramethylsilane as an internal standard. Coupling patterns that could not be interpreted by inspection were resolved by double irradiation, and double irradiation was also used to verify assignments made by inspection. The chemical shifts and coupling constants measured for **1**–**12** are recorded in Tables I and II, respectively. The acetoxyl methyl groups resonated as a series of sharp singlets between τ 7.84 and 8.04. Aryl-proton resonances were observed near τ 2.0 as an AA′BB′ system in the spectra of **2**, **3**, **5**, **7**, and **9**, or near τ 2.2 as a pair of complex multiplets in the seven unsubstituted examples. A singlet at about τ 2.23 was caused by H-5 of the triazole ring (H-1 of

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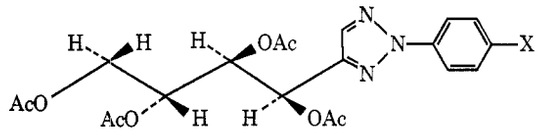
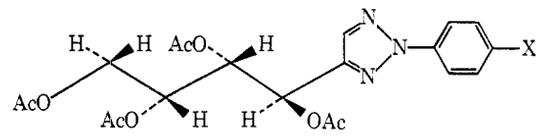
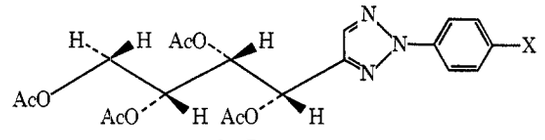
CHART II



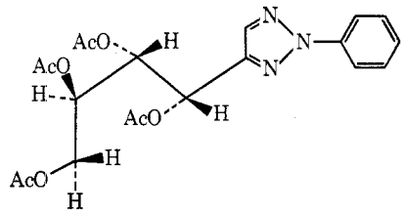
1a, 2a, 3a



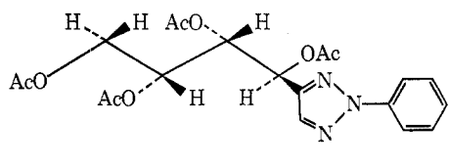
4a, 5a



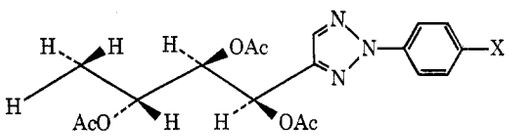
6a, 7a



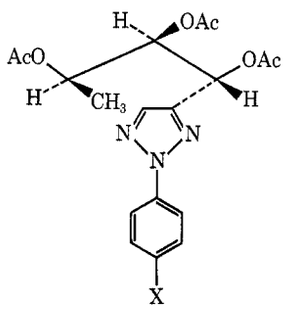
6b, 7b



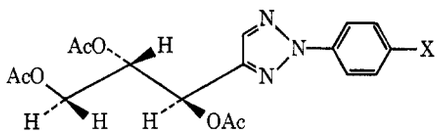
6c



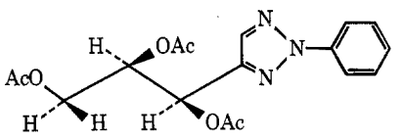
8a, 9a



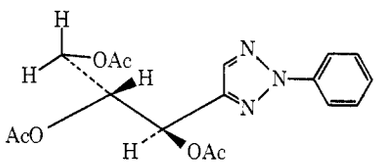
8b, 9b



10a, 11a



12a



12b

the original sugar); it was shifted slightly downfield in the nitro-substituted derivatives.

The C-1 proton of the polyacetoxyalkyl side chain (H-3 of the original sugar) gave rise to a sharp doublet near τ 3.7 whose spacing gave $J_{1,2}$ directly. The signal next upfield of H-1 was assigned to H-2; it appeared as a complex multiplet in **10–12** but as a well-defined quartet yielding $J_{1,2}$ and $J_{2,3}$ in **1–9**. Also, in **1–9**, H-3 resonated at somewhat higher field than H-2, near τ 4.6 as a well-resolved multiplet split by H-2 and the protons on C-4; this signal appeared as a quintet in the spectrum of **8** because $J_{2,3}$ and $J_{3,4}$ were fortuitously equal. The methylene protons of the terminal acetoxymethyl group (at C-4 of **1–9**, C-3 of **10–12**) resonated at highest field of the protons on the chain, near τ 5.6 and 5.9, as the A and B portions of an ABX systerm, from which the remaining coupling constants were measured. The proton resonating at higher field of the methylene protons is indicated by a primed number. The protons of the C-4 methyl group (in **8** and **9**) gave rise to a doublet at τ ~8.75 showing the coupling $J_{3,4}$.

In all examples the ratio of chemical-shift difference to coupling constant for coupled protons was of sufficient magnitude to ensure that the spacings measured approximate closely to the true coupling constants. The results are discussed for each configurational series in turn.

Tetra-*O*-acetyl-D-*arabino*-hexulose Phenylosotriazole (1), *p*-Bromophenylosotriazole (2), and *p*-Nitrophenylosotriazole (3).—The spin couplings and chemical shifts for protons on the chain in **1–3** vary only slightly as a function of the para substituent on the phenyl group. The magnitudes of $J_{1,2}$ and $J_{3,4}$ are small, indicating gauche relationships between H-1 and H-2, and between H-3 and H-4, and the large (8 Hz) $J_{2,3}$ coupling indicates that H-2 and H-3 are antiparallel in the favored conformer. The $J_{3,4'}$ coupling is rather small (4.5–6.0 Hz) and shows that, as found in the *aldehydo*-pentose tetraacetates,[14] C-3–C-4 rotamer states having H-3 gauche disposed to H-4′ compete with the antiparallel conformer; the effectiveness of this competition appears to decrease somewhat as the electronegativity of the para substituent increases, but detailed speculation on this point is not warranted. Compounds **1–3** thus favor the extended, planar, zigzag conformations **1a–3a** (Chart II), respectively, in line with earlier results[2,9–13,15–18] for acetylated, acyclic carbohydrate derivatives having the arabino stereochemistry.

In the absence of potential hydrogen-bonding interactions,[11] the bulky triazole ring structure would be

expected to extend away from the acyclic side chain in the favored conformation. The relative invariance of chemical shift of the acetoxyl methyl signals (and of the protons along the chain) as the para substituent is changed supports this hypothesis.

Tetra-*O*-acetyl-D-*lyxo*-hexulose Phenylosotriazole (4) and *p*-Nitrophenylosotriazole (5).—The coupling data for **4** and **5** accord with invocation of the anticipated[2,9-13,15-17] extended planar, zigzag structures **4a** and **5a**, respectively, as the favored conformations. The required, small value of $J_{2,3}$ and the predictably large values of $J_{1,2}$ and $J_{3,4}$, accord completely with this formulation, and the slight increase in magnitude of $J_{3,4}$ suggests a moderate representation by the C-3–C-4 rotamer state having H-3 antiparallel to H-4, although possible effects from slight bond distortion cannot be excluded.

Tetra-*O*-acetyl-L-*xylo*-hexulose Phenylosotriazole (6) and *p*-Nitrophenylosotriazole (7).—In acetylated, acyclic sugar chains that in the extended form would have an eclipsed, 1,3 interaction between substituent groups it is now well established[2,9,11-14,16,18] that rotation about an internal carbon–carbon bond to alleviate this interaction generates a "sickle" conformation as the favored form. In systems having the xylo configuration and having only tetrahedrally hybridized carbon atoms along the chain, rotation occurs[10-13] largely along C-2–C-3. Data from the literature indicate that introduction of a trigonally hybridized center into such molecules leads to unpredictable conformational behavior. In tetra-*O*-acetyl-D-xylonothioamide,[18] rotation appears to be favored about the C-3–C-4 bond, but in 2-(D-*xylo*-tetraacetoxybutyl)-4-(*p*-bromophenyl)-1,3-thiazole[18] the C-1–C-2 bond (of the side chain) appears to be the axis for rotation. Coupling data measured for *aldehydo*-D-xylose tetraacetate,[14] D-*xylo*-3,4,5,6-tetraacetoxy-*trans*-1-nitro-1-hexene,[16] and methyl 2,3,4,6-tetra-*O*-acetyl-D-*xylo*-hex-5-ulosonate[9] are best reconciled in terms of a conformational equilibrium between two sickle conformers. A method proposed[18] for quantitative prediction of the carbon–carbon bond along which rotation will occur appears altogether speculative when reliable values for the energies of interaction between substituents are lacking.

The coupling data for **7** indicate that, as in the tetra-*O*-acetyl-D-xylose dithioacetals,[12,13] the favored conformation is derived from the extended form **7a** by rotation about the second C–C bond of the chain removed from the larger end group; in compound **7** this bond is C-2–C-3 and the favored form is the sickle conformation **7b**. The relative magnitudes of $J_{1,2}$ (3.6 Hz) and $J_{2,3}$ (8.0 Hz) are consistent with **7b** and indicate a considerable degree of conformational homogeneity. However, in **6** the magnitudes of $J_{1,2}$ (7.5 Hz) and $J_{2,3}$ (3.8 Hz) are interchanged, indicating that the corresponding sickle form (**6b**) does not contribute significantly to the conformational equilibrium[28] of **6** and that there preponderates the alternative sickle form **6c**, obtained by rotation about the C-1–heterocycle bond in **6a**, which likewise provides relief from 1,3 interactions. It is surprising, and somewhat disconcerting in attempts to generalize, to note the radical change in the conformational behavior of the chain that results from such an apparently minor change as nitration at the remote para position of the phenyl moiety. A similar drastic change is observed in the 6-deoxy-L-*arabino*-hexulose derivatives considered next.

Tri-*O*-acetyl-6-deoxy-L-*arabino*-hexulose Phenylosotriazole (8) and *p*-Nitrophenylosotriazole (9).—The coupling data observed for **8** ($J_{1,2}$ = 5.4 Hz, $J_{2,3}$ = 6.2 Hz) are in qualitative accord with the planar, zigzag conformation **8a**, but the intermediate magnitudes of these couplings indicate substantial contributions by other rotameric forms. The corresponding couplings in the *p*-nitro derivative **9** are, however, altogether inconsistent with the planar, zigzag conformation **9a**. The large value of $J_{1,2}$ (7.8 Hz) and the small value (3.4 Hz) of $J_{2,3}$ suggest that **9** may adopt a conformation **9b**, obtained by rotating **9a** along C-1–C-2 and along the C-2–C-3 bond and in which H-2 is antiparallel to H-1 and gauche disposed to H-3. This conformation is free of eclipsed 1,3 interactions and corresponds to an extended, planar zigzag form if the steric requirement at the 1- and 3-acetoxyl groups be reckoned greater than that of the methyl and *p*-nitrophenylosotriazolyl groups. If the *p*-nitrophenylosotriazolyl group has a steric effect smaller than the unsubstituted phenylosotriazolyl group, as already suggested for **5** and **6**, the conformational behavior of **8** can be rationalized in terms of an equilibrium between **8a** and **8b**.

Tri-*O*-acetyl-L-*erythro*-pentulose Phenylosotriazole (10) and *p*-Fluorophenylosotriazole (11).—It has been suggested by Angyal and James[9] that the acetylated, four-carbon sugar chains are conformationally less predisposed toward a single, favored conformation than are five-carbon analogs wherein a terminal hydrogen atom has been replaced by a terminal acetoxymethyl group. The data for **10** and **11** accord with this view; the magnitudes of $J_{1,2}$ indicate extensive, but definitely not exclusive, population of the planar, zigzag forms **10a** and **11a** wherein H-1 is antiparallel to H-2. The argument of stabilization by prolongation of the chain would also seem to predispose **10** and **11** (and **12**) to moderate torsional deviations from ideal geometry, an important consideration before making any attempt to calculate conformational populations. The intermediate values of $J_{2,3}$ and $J_{2,3'}$ suggest that the rotamers about C-2–C-3, especially the two having H-2 antiparallel to one C-3 proton, are separated by relatively small energy differences, so that there is substantial population of more than one rotameric state along this terminal C–C bond, as previously suggested for tetra-*O*-acetyl-*aldehydo*-L-arabinose.[14]

Tri-*O*-acetyl-D-*threo*-pentulose Phenylosotriazole (12).—Considerations made for **10** and **11** also apply to **12**, with a notable exception that the coupling data do not support the planar, zigzag form **12a** as the major conformer. This molecule appears to represent a situation where vicinal, gauche interactions are sufficient to dictate rotational alteration. The large magnitude (6.4 Hz) of $J_{1,2}$ is accommodated only by a major representation from the form **12b**, in which H-1 and H-2 are antiparallel, and in which the 1,2-gauche interaction between the phenylosotriazolyl group and the acetoxymethyl group on C-2 is alleviated. Again the idea of conformational stabilization by chain extension[9] is supported by comparing the behavior of **12** with that of its 3-acetoxymethyl homolog **1**, which favors the fully extended form to a much greater extent.

Conclusions

These data further establish that rotamers of acyclic carbohydrate derivatives that involve an eclipsed 1,3 interaction between substituents are energetically disfavored, a situation that is generally alleviated by rotation about an internal carbon–carbon bond to a different, gauche rotamer (sickle form). The short (three carbon) chains are more prone to populate more than one conformational state to a substantial extent, whereas prolongation of the chain tends to cause the molecule to favor one conformation more exclusively, this being the most extended arrangement compatible with avoidance of 1,3 interactions.

It is suggested that application of the Karplus equation, to quantitative determinations of dihedral angles on rotamer populations, from data obtainable by present methods, is less likely to advance the understanding of conformational behavior of polysubstituted, acyclic chains in solution than a conservative, qualitative treatment, at least until experimental methods of greater finesse are developed.

Registry No. —**1**, 7770-63-0; **2**, 34297-73-9; **3**, 34297-74-0; **4**, 16346-56-8; **5**, 34297-75-1; **6**, 34297-76-2; **7**, 34290-22-7; **8**, 34297-77-3; **9**, 34297-78-4-**10**, 7599-11-3; **11**, 34288-31-8; **12**, 6631-64-7.

A Convenient Synthesis of Myosmine

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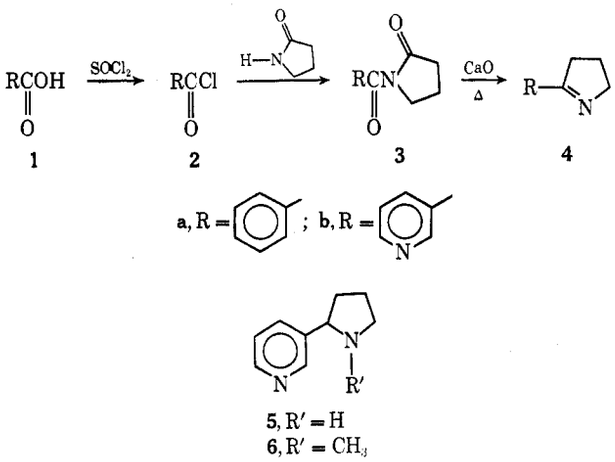
A three-step synthesis of myosmine, one of the pyrrolidine alkaloids found in various *Nicotiana species*, is described.

Myosmine (**4b**) is one of the tobacco alkaloids, and its structure has been elucidated by degradation[2] and spectral methods.[3] It has been previously synthesized by other research groups.[2b,4] We wish now to report a convenient three-step synthesis of this alkaloid (Scheme I).

The envisioned synthesis required, as the critical step, the pyrolysis of *N*-nicotinoyl-2-pyrrolidone (**3b**). Because of the wealth of data available for 2-phenylpyrroline (**4a**),[5] this proved to be a useful model for the initial evaluation of synthetic procedures. The reaction of benzoyl chloride with 2-pyrrolidone yielded the expected product, *N*-benzoyl-2-pyrrolidone (**3a**). Pyrolysis of an equal weight mixture of **3a** and calcium oxide resulted in a crude distillate, shown to be primarily 2-pyrrolidone.[6] However, the simplicity of the procedure more than compensated for the low yield of **4a** and encouraged us to apply the method, without trying to maximize yields, to the synthesis of myosmine.

Nicotinoyl chloride (**2b**) was prepared by treating nicotinic acid with an excess of thionyl chloride. Acylation of 2-pyrrolidone with **2b** afforded **3b**, which when subjected to the conditions of pyrolysis resulted in a crude product mixture which contained 67% **4b** and 33% 2-pyrrolidone.[7] The identity of **4b** was confirmed by analysis of its nmr spectrum, mass spectrum,[8] and the melting point of the picrate derivative.[4] The reported conversion of myosmine to nornicotine (**5**) and nicotine (**6**)[8] thus realizes a simple synthesis of the tobacco alkaloids.

SCHEME I
SYNTHESIS OF MYOSMINE



Experimental Section[9]

N-**Benzoyl-2-pyrrolidone** (**3a**).—A solution of 2-pyrrolidone (85.1 g) and pyridine (158 g) was added to 140 g of benzoyl chloride. After 3 days at room temperature, the pyridine was removed and the residue was suspended in benzene. This solution was washed with water, dried, and concentrated. The crude product was crystallized from hot ethanol to give 81.2 g (56%) of **3a**, mp 91° (lit.[5] mp 92°).

2-Phenylpyrroline (**4a**).—The general procedure for carrying out the pyrolysis involved intimately mixing **3a** with an equal weight of calcium oxide and placing the reactants in a distilling flask. After being heated with a free flame, the crude product mixture was collected and purified. The melting point (35–39°, lit.[5] mp 44°) and the melting point of the picrate derivative (198°, lit.[5] mp 198°), buttressed by nmr, ir, and uv spectral data, confirmed the identity of the product from this sequence.

(1) Undergraduate research participant during the summer of 1970 (NSF Grant GY 7358).

(2) (a) E. Späth, A. Wenusch, and E. Zajic, *Ber.*, **69**, 393 (1936); (b) C. F. Woodward and A. Eisner, *J. Amer. Chem. Soc.*, **66**, 911 (1944).

(3) B. Witkop, *ibid.*, **76**, 5597 (1954).

(4) E. Späth and L. Mamoli, *Ber.*, **69**, 757 (1936).

(5) F. Korte and H.-J. Schulze-Steiner, *Chem. Ber.*, **95**, 2444 (1962).

(6) We have not thoroughly investigated the mechanistic course of this reaction. However, we have noted considerable reductive cleavage occurring, finding benzene, toluene, and trimethylamine in low yields in the reaction products. The yield of **4a** was generally in the order of 15–20%, as much as 85% 2-pyrrolidone having been observed in the reaction product.

(7) This constitutes a 65% yield of **4b**, based on **3b**.

(8) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 2926 (1965).

(9) The boiling points and melting points are uncorrected.