Tetrahedron Vol. 25, pp. 3413 to 3428. Pergamon Press 1969. Printed in Great Britain

STUDIES ON CONFORMATION AND REACTIVITY—1
SUGARS WITH POTENTIAL ANTIVIRAL ACTIVITY—4

THE CONFORMATIONS OF SOME ACYCLIC SUGAR DERIVATIVES[1]

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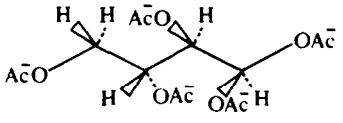
(*Received in the UK* 26 *February* 1969; *Accepted for publication* 4 *March* 1969)

Abstract—An examination of the conformations adopted by acyclic sugar derivatives has been made. It is shown that 1,3-eclipsed rather than 1,2-*gauche* interactions are important in determining relative conformer population and that the observed conformer distribution, as determined by analysis of PMR spectra, is close to that calculated from consideration of non-bonded interactions.

INTRODUCTION

THE chemical[2a] and physiological[2b] activity of molecules may be greatly influenced by their stereochemistry and it has been appreciated in recent years that the *conformations* of molecules may strongly influence their behavior.[3]

Numerous studies[4] have been made of the conformations adopted by alicyclic rings, and by carbohydrates in their furanose and pyranose forms.[5] These cases are somewhat simplified, since only a limited number of conformers possess reasonable stability. The conformation of the acyclic forms of the sugars presents a more complex problem, since in theory a range of situations are possible, varying from rapid rotation around each bond of the chain to a rigid adoption of a single conformation. There have been a number of tentative attempts to relate reactivity to conformation for the acyclic forms of carbohydrates;[6] it was concluded that the sugar adopts the fully extended zig-zag chain form (as exemplified in I for penta-O-acetyl-D-arabitol)



I

with the vicinal groups fully staggered. Barker, *et al.*[7] concluded from their results on cyclic acetal formation that this is the most favourable situation thermodynamically. In principle, analysis of PMR spectra may throw light upon the conformations of molecules, since it is possible to obtain, in suitable situations, an estimate of the relative angles subtended by H atoms on adjacent C atoms by examination of the coupling constants found in their spectra and similarly the observed chemical shifts of signals in these spectra may give an indication of the spatial relationships between the H atoms and other groups in the molecule.

A second physical property, which is affected by the conformation of the molecule,

is the optical activity, and in sugars it should be possible to relate the observed molecular rotations to the actual conformations adopted by the molecules.

The papers in this series represent an attempt to determine the relative importance of the different factors affecting the conformations of acyclic systems, comparing results obtained in PMR and optical rotation measurements with the different possible calculated situations. From this it should prove possible to develop guide-lines to successful prediction of conformation in these systems, which may be of use in explaining effects observed in some virus-enzyme reactions.

RESULTS AND DISCUSSION

Since the commencement of this work[8] a number of PMR studies of sugars have appeared,[9] but none have dealt with conformer distribution in acyclic systems.* A number of papers have appeared which deal with simpler acyclic systems.[10,11]

In pyranose rings equatorial and axial acetyl groups can be identified by the chemical shift of the Me protons.[12,13] We have examined a large number of acetylated straight chain sugars and have noted similar variations in the chemical shift of the acetyl protons. Although we were able, in a limited number of cases, to assign particular signals to particular acetyl groups, there is no general simple relationship between chemical shift and conformation. More fruitful was analysis of the coupling between methine protons. In this paper calculations made of the coupling expected for a number of different conformational models are compared with the values we have obtained experimentally for the compounds. Applying the conformational principles already well-established for cyclic systems, there is surprisingly good agreement between calculated and observed values, confirming the validity of the method, and showing that, *in suitably modified form*, the Karplus equation[14] can be used in this series of compounds. The original, simpler, suggestion that the sugars adopt the fully-extended zig-zag chain form (I) gives reasonable agreement only when there are no large 1,3-interactions. The results of measurements of variation in coupling constant with temperature provide additional evidence both for the adoption of favoured conformations in general and for the correctness of the values of coupling constant calculated to be associated with these conformations in particular.

The Karplus equation and conformation. In his analysis of the coupling constants between vicinal hydrogens, Karplus[14] showed that the relationship of coupling constant to subtended angle can be expressed as

$$J = A + B\cos\phi + C\cos\phi$$

(where ϕ is the dihedral angle subtended and A, B and C, are constants). Taking the values suggested by Karplus for these constants,[15] the coupling constant expected for a 180° relationship (J_t) is 9·5 c/s, and for a 60° angle (J_g) 4·5 c/s. Karplus suggested a number of minor corrections which could be applied, chiefly a correction for the electronegativity (X) of substituents

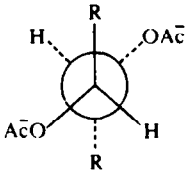
$$\text{viz. } J^c_{H'} = J^u_{HH'}\,(1 - 0{\cdot}07\,X)$$

* Since this work was completed a paper by H. S. El Khadem, D. Horton and T. F. Page, Jr., *J. Org. Chem.* **33**, 374 (1968) has appeared which discusses conformation of some non-acetylated sugar derivatives in dimethyl sulphoxide (d_6).

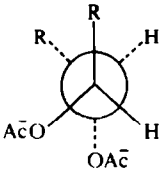
where $J^{c}_{HH'}$ is the corrected average coupling constant and $J^{u}_{HH'}$ is the uncorrected average value from the original Karplus equation.

If we apply this to an acetylated sugar, using Pauling's electronegativity values, we arrive at values for $J_{HH'} = 9{\cdot}2$ c/s ($\phi = 180°$): $J_{HH'} = 4{\cdot}2$ c/s ($\phi = 60°$). However, the observed values vary considerably. Thus Stevens and Lemieux[16] found, for some acetylated pyranoses, a range of 5–8 c/s for *trans* diaxial vicinal protons (angle approximately 180°), and of 2–3 c/s for those with a 60° angle. These variations are not unexpected since the rings are not completely rigid in any case. These values are in line with those calculated by Cohen, *et al.*,[17] viz. $J_{HH'} = 9{\cdot}4$ c/s ($\phi = 180°$) and 2·7 c/s ($\phi = 60°$), for the 1,4-dioxan system.

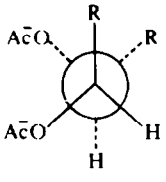
It would seem reasonable to assume that the acetylated straight chain sugars would show similar values, and hence a coupling constant of approximately 9·5 c/s will indicate a *trans* arrangement (as e.g. in II) and of approximately 2·0 c/s a *gauche* arrangement (as III and IV).



II



III



IV

The situations one might consider are:

(a) Complete and rapid free rotation with no preferred conformations.

(b) The adoption of one or other favoured conformation with little or no rotation to any other conformation.

(c) Free rotation, but with most of the molecules existing in one of the energy minima at the point(s) of least interaction.

(d) Equal population of the three conformations II, III, and IV with little or no rotation to the other forms.

(e) Free rotation, but with most of the molecules existing equally distributed between the conformations II, III, and IV. Situations (b) and (d), which are unlikely as they require an energy barrier to rotation of around 20 kcals/mole, are incompatible with the low temperature NMR measurements. Further, the high temperature NMR measurements rule out (a). The observed coupling constants will be given by

$$J_{obs} = \frac{J_t + 2J_g}{3} = 4{\cdot}5 \text{ c/s},$$

if the conformer distribution is as described by (e) and if situation (c) pertains the coupling constants will be close to 2 c/s or 9·5 c/s.

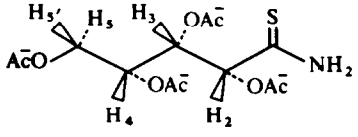
At low temperatures the population of the lowest energy conformer increases and the coupling constants should approach 2 c/s or 9·5 c/s. At high temperatures as the free energy difference between the conformers becomes less important, the conformer distribution should tend to a purely statistical one and the coupling constants should approach 4·5 c/s.

In most of the cases which we have examined we find values for coupling constants which indicate that the molecule exists mainly in one or other preferred conformation, i.e. situation (b) or (c). This is supported by observations at different temperatures. In few cases were values corresponding to those expected in situations (a), (d) or (e) found, and we now discuss the possible arrangements to be found in situations (b) or (c), taking as first example tetra-O-acetyl-D-xylono-thioamide. The simplest arrangement, that found for cyclic-acetal formation[7] and periodate oxidation,[6] and usually assumed to hold, is the fully extended zig-zag chain form (V). One may predict the PMR to have coupling constants as listed in Table 1, where the observed coupling constants are given for comparison.

TABLE 1.

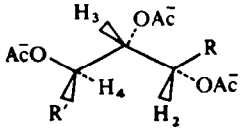
Predicted and observed coupling constants for V

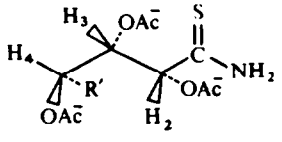
Coupling constant	Dihedral angle	Predicted J value	Observed J value
$J_{H_2H_3}$	$\phi = 60°$	2·0 c/s	3·0 c/s
$J_{H_3H_4}$	$\phi = 60°$	2·0 c/s	7·0 c/s
$J_{H_4H_5}$	$\phi = 180°$	9·5 c/s	6·8 c/s
$J_{H_4H_5'}$	$\phi = 60°$	2·0 c/s	3·8 c/s



V

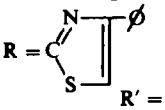
Clearly the observed $J_{H_3H_4}$ is far from the calculated value. A possible explanation is that rotation occurs around the C_3—C_4 bond; there are two other possible conformers and these are shown as VIa and VII. In conformer VI the angle subtended





VII

VIa : R = $CSNH_2$; R' = CH_2OAc

VIb : R = 

R' = CH_2OAc

$\phi_{H_3H_4} = 180°$, requiring $J_{H_3H_4} = 9{\cdot}5$ c/s, while in VII $\phi_{H_3H_4} = 60°$, requiring $J_{H_3H_4} = 2{\cdot}0$ c/s. Hence conformation VI must be highly populated. On the basis of the calculated coupling constants the population fraction may also be calculated, since $7{\cdot}0 = 9{\cdot}5\ p_{VI} + 2{\cdot}0\ (1 - p_{VI})$ and therefore $p_{VI} = 0{\cdot}7$.*

* Calculations of this type based on PMR spectra can only be expected to give approximate agreement of course, since a number of assumptions are involved.

At first sight such a result may seem surprising in view of the usual assumption that the extended zig-zag chain gives rise to the most stable arrangement. It has been assumed[6] that this conformation is adopted since it will minimize 1,2-interactions. However, it is well known that in the 6-membered cyclic systems axial 1,3-interactions are highly unfavourable.[18] In the acyclic system the situation at the 1,3-positions is closely similar, since the distances between groups are of the same order, and the groups are fully eclipsed. Hence the assumption previously made[6] would only be valid *if* these 1,3-interactions were small enough to be ignored.

Eliel *et al.* quote[19] values for non-bonded interactions (reproduced in Table 2). One can use these values to calculate the expected conformer distribution in these acyclic systems. We have done this, and have found that very reasonable agreement is obtained with the values of coupling constant calculated from the observed spectra.†

TABLE 2.

Group	Vicinal *gauche* interaction kcal/mole			1,3-Eclipsed interaction kcal/mole		
	RR, CH	OAc	H	RR, CH	OAc	H
RR, CH	(0·35)*	0·35	0	3·7	2·2	0·9
OAc	0·35	0·35	0	2·2	2·0	0·45
H	0	0	0	0·9	0·45	0

* This value has not been determined but is probably of the right order.

If a calculation is made on the assumption[6] that only 1,2-interactions are important a conformer ratio V:VI:VII of about 26:48:26 (which would correspond to a coupling constant of approximately 5·8 c/s) is arrived at.* This ratio is derived by substituting the values from Table 2 for the 1,2-interactions in V, VI and VII (respectively 1·05, 0·7 and 1·05 kcal/mole) in the expressions

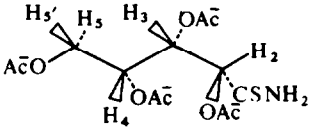
$$\Delta G^* = \Delta H - T\Delta S \quad \text{and} \quad K = \exp(-\Delta G/RT)$$

If we now recalculate taking into account the 1,3-eclipsed interactions between C_2 and C_4 we arrive at an expected ratio of 15:80:5 for the relative percentages of V:VI:VII, for which a coupling constant of 8 c/s is expected. (The calculation of this value is outlined in the Experimental).

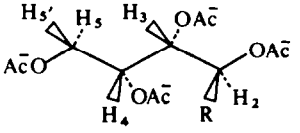
A further refinement may be made to this calculation, since it has been assumed above that rotation has not occurred around C_2–C_3. That this is qualitatively true is

* In this analysis a number of assumptions are made, as follows. (a) In general, the C-attached atom in a group dominates the group's effective interactions. (b) The 1,3-diaxial interactions of cyclohexane systems are of the same order as 1,3-eclipsed interactions in a zig-zag chain conformation. (c) Interactions apart from 1,2-*gauche* and 1,3-eclipsed are small and are therefore ignored. (d) 1,2-*Gauche* interactions in acyclic systems are of the same order as axial-equatorial interactions in cyclohexane and its derivatives. (e) Only small changes in entropy are caused by the conversion of one conformer into another.

indicated by the low coupling constant observed ($J_{H_2H_3}$ = 3 c/s); if rotation occurs we have two further conformations (VIII and IX) to consider. However, conformer VIII will have a 1,3-interaction between an acetyl group (on C_4) and a thioamide group (on C_2); since these are large groups we may assume that this conformation must be a minor contributor. Conformer IX will contribute a coupling constant of



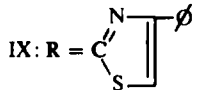
VIII



IX

IXa: R = $CSNH_2$

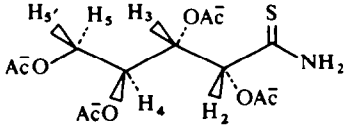
IX: R =



$J_{H_2H_3}$ = 9·5 c/s while conformers V, VI and VII, require $J_{H_2H_3}$ = 2·0 c/s, so we may calculate the population of conformer IX.

If we now recalculate the expected coupling constant for C_3C_4, we have $J_{H_3H_4}$ = 7·2 c/s, a value in good agreement with the observed one of 7·0 c/s. If the total interactions for the conformers IXa and VIa are calculated, we are left with a value of about 2 kcals per mole for the 1,3-interaction of thioamide and hydrogen, which is not unreasonable.

We may conclude from the foregoing that 1,3-eclipsed interactions are large compared with 1,2-*gauche*, and that these 1,3-interactions largely determine which conformer is most populated. This suggestion is readily tested, since in the fully extended zig-zag chain form of 2,3,4,5-tetra-O-acetyl-L-arabinothioamide (X) there are no large 1,3-interactions, and the observed coupling constants should correspond



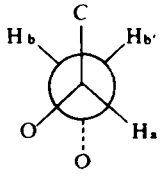
X

TABLE 3.

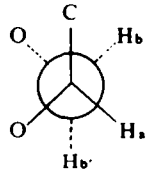
Tetra-O-acetyl-L-arabonothioamide (X)		
Coupling constant	Predicted J value	Observed J value
$J_{H_2H_3}$	2·0 c/s	2·4 c/s
$J_{H_3H_4}$	9·5 c/s	8·8 c/s
$J_{H_4H_5}$	9·5 c/s	6·0 c/s
$J_{H_4H_5'}$	2·0 c/s	3·0 c/s

to those forecast from this model. Table 3 summarizes these figures and it can be seen that $J_{H_2H_3}$ and $J_{H_3H_4}$ are almost as predicted.

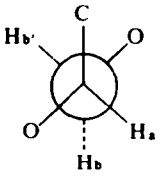
Conformation at terminal group. So far the conformational arrangement of the terminal group has not been considered. The conformers XI, XII and XIII, represent the possible staggered forms, and we may calculate their expected relative populations



XI



XII



XIII

from the size of the non-bonded interactions as above. This is illustrated in Table 4.

In the case where an *erythro* arrangement is present on the terminal three carbons the predicted values for the coupling constants are $J_{H_aH_b'} = 7{\cdot}6$ c/s: $J_{H_aH_b} = 2{\cdot}5$ c/s. There is fair agreement between these values and the ones observed.*

Effect of size of $C_{(1)}$ *group.* In considering the spectrum and conformations of

TABLE 4.

Configuration	Conformer	1,2-Interactions kcal/mole	1,3-Interactions kcal/mole	Total Interactions kcal/mole	Conformer distribution
AcO, AcO, OR, OAc, OAc, CH_2OAc, CH_2OAc	XI	0·35	0·45	0·8	75%
	XII	0·70	0·90	1·6	19%
	XIII	0·35	2·0	2·35	6%
AcO, OAc, CH_2OAc	XI	0·35	0·45	0·8	67%
	XII	0·70	2·0	2·70	1%
AcO, OR, OAc, CH_2OAc	XIII	0·35	0·90	1·25	32%

tetra-O-acetyl-D-xylono-thioamide, it was considered that the large size of the thioamide group reduced the population of form IX.

It follows that, if this group is replaced by a less bulky group, this restriction will

* For the purpose of analysis the protons H_4, H_5 and $H_{5'}$, have been considered as an isolated ABX system, and the coupling between H_4(=X in ABX) and H_3 treated as simple first order coupling. The calculated values in practice are found to be quite close to those obtained by direct reading from the spectrum. (An example of a calculated and observed spectrum is given in the Experimental). Since the chemical shift difference between H_5 and $H_{5'}$ (or the corresponding protons in another system) will generally be small, it is not always possible to measure the intensity and line positions accurately and in these cases analysis is not possible.

The nomenclature and methods adopted are those described by J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution* NMR. McGraw-Hill, New York, N.Y. (1959).

be removed. We examined the spectrum of the corresponding nitrile, which meets this requirement, but the spectrum was unfortunately not amenable to first order analysis.

We considered that the effective size of the thioamide group could be reduced if the N—C—S system were to be incorporated in a 5-membered ring. One possible arrangement is the thiazole system, and we therefore prepared and examined some 4-aryl thiazole derivatives. These compounds gave spectra which were amenable to analysis. The observed and predicted coupling constants for the conformer IXb are compared in Table 5. Since the 1,3-interaction between hydrogen and the thiazole

TABLE 5.

2-[D-*Xylo*-tetra-O-acetylbutyl]4-phenyl-1,3-thiazole (IXb)

Coupling constant	Predicted J value	Observed J value
$J_{H_2H_3}$	9·5 c/s	6·8 c/s
$J_{H_3H_4}$	2·0 c/s	4·0 c/s
$J_{H_4H_5'}$	7·0 c/s	6·5 c/s
$J_{H_4H_5}$	4·3 c/s	5·1 c/s

ring is less than that between hydrogen and a thioamide group, the population of conformation VI should decrease in favour of conformation IX, while the remaining conformers will still be relatively unfavourable.

From the coupling constants, the population is divided *approximately* in the order; conformer IXb, 64% ($J_{H_2H_3}$ = 6·8 c/s) conformer VIb, 27% ($J_{H_3H_4}$ = 4 c/s).

Further examples. We have applied these principles to a number of related compounds, and in Table 6 are listed the observed coupling constants for these com-

TABLE 6

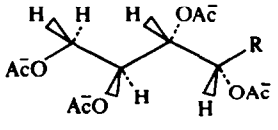
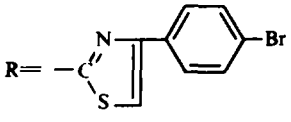
Sugar-major conformer predicted from steric interaction	Coupling constant	Predicted J for major conformer	Observed J value
Tetra-O-acetyl-L-arabono-			
 R=CN	$J_{H_2H_3}$	2·0 c/s	3·0 c/s
	$J_{H_3H_4}$	9·5 c/s	7·8 c/s
	$J_{H_4H_5}$	2·5 c/s	3·6 c/s
	$J_{H_4H_5'}$	7·6 c/s	4·8 c/s
R=CSNH^2	$J_{H_2H_3}$	2·0 c/s	2·4 c/s
	$J_{H_3H_4}$	9·5 c/s	8·8 c/s
	$J_{H_4H_5}$	2·5 c/s	3·0 c/s
	$J_{H_4H_5'}$	7·6 c/s	6·0 c/s
	$J_{H_2H_3}$	2·0 c/s	3·0 c/s
	$J_{H_3H_4}$	9·5 c/s	8·6 c/s
	$J_{H_4H_5}$	2·5 c/s	3·2 c/s
	$J_{H_4H_5'}$	7·6 c/s	5·0 c/s

TABLE 6—*continued*

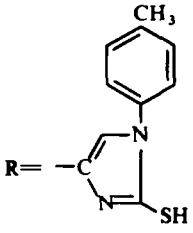
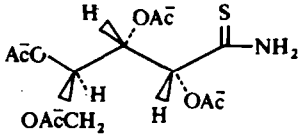
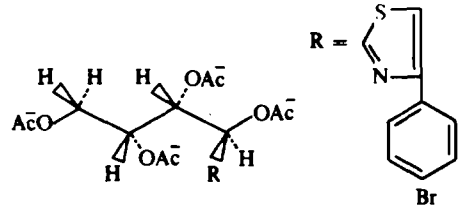
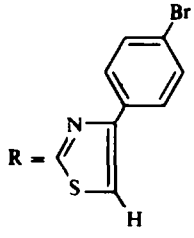
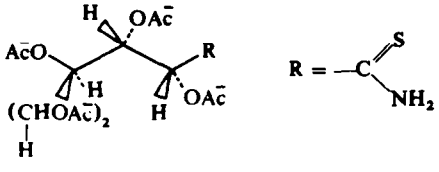
Sugar-major conformer predicted from steric interaction	Coupling constant	Predicted J for major conformer	Observed J value
	$J_{H_2H_3}$	2·0 c/s	4·0 c/s
	$J_{H_3H_4}$	9·5 c/s	8·0 c/s
	$J_{H_4H_5}$	2·5 c/s	3·0 c/s
	$J_{H_4H_5}$	7·6 c/s	5·0 c/s
Tetra-O-acetyl-D-xylonothioamide			
	$J_{H_2H_3}$	2·0 c/s	3·0 c/s
	$J_{H_3H_4}$	9·5 c/s	7 c/s
	$J_{H_4H_5}$	4 c/s	3·8 c/s
	$J_{H_4H_5'}$	6 c/s	6·8 c/s
2-[D-*Xylo*-tetra-O-acetylbutyl]4-aryl-1,3-thiazole			
	$J_{H_2H_3}$	9·5 c/s	6·8 c/s
	$J_{H_3H_4}$	2·5 c/s	4·0 c/s
	$J_{H_4H_5}$	4·3 c/s	5·1 c/s
	$J_{H_4H_5'}$	7·0 c/s	6·5 c/s
	$J_{H_2H_3}$	9·5 c/s	6·8 c/s
	$J_{H_3H_4}$	2·0 c/s	4·0 c/s
	$J_{H_4H_5}$	4·3 c/s	5·1 c/s
	$J_{H_4H_5'}$	7·0 c/s	6·5 c/s
Penta-O-acetyl-D-gluco			
	$J_{H_2H_3}$	2·0 c/s	3·6 c/s
	$J_{H_3H_4}$	9·5 c/s	5·8 c/s
	$J_{H_4H_5}$	4·6 c/s	5·6 c/s
	$J_{H_5H_6}$	2·5 c/s	4·2 c/s
	$J_{H_5H_6'}$	7·6 c/s	6·0 c/s

TABLE 6—*continued*

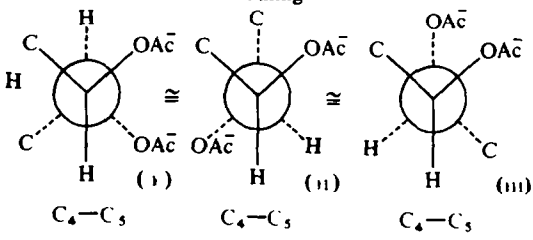
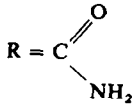
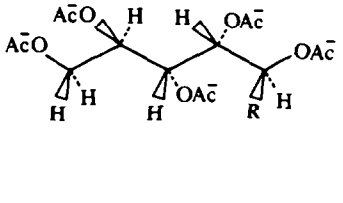
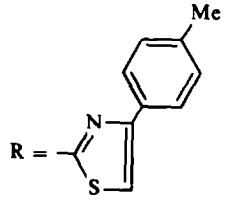
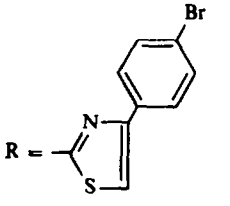
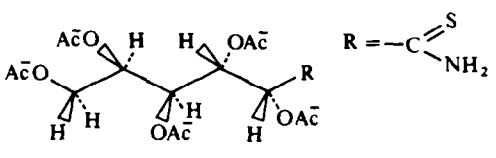
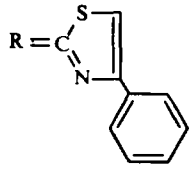
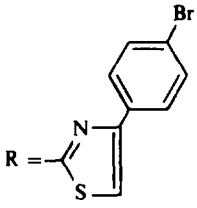
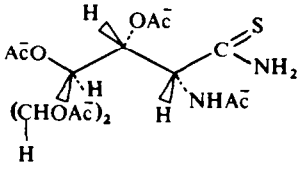
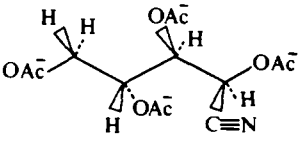
Sugar-major conformer predicted from steric interaction	Coupling constant	Predicted J for major conformer	Observed J value
Assuming 			
	$J_{H_2H_3}$	2·0 c/s	4·3 c/s
	$J_{H_3H_4}$	9·5 c/s	—
	$J_{H_4H_5}$	4·6 c/s	—
	$J_{H_5H_6}$	2·5 c/s	4·2 c/s
	$J_{H_5H_6'}$	7·6 c/s	5·8 c/s
	$J_{H_2H_3}$	9·5 c/s	7·2 c/s
	$J_{H_3H_4}$	2·0 c/s	3·6 c/s
	$J_{H_4H_5}$	9·5 c/s	7·0 c/s
	$J_{H_5H_6}$	2·5 c/s	3·5 c/s
	$J_{H_5H_6'}$	7·6 c/s	6·0 c/s
	$J_{H_2H_3}$	9·5 c/s	7·2 c/s
	$J_{H_3H_4}$	2·0 c/s	3·6 c/s
	$J_{H_4H_5}$	9·5 c/s	7·2 c/s
	$J_{H_5H_6}$	2·5 c/s	3·5 c/s
	$J_{H_5H_6'}$	7·6 c/s	6·0 c/s
	$J_{H_2H_3}$	9·5 c/s	7·0 c/s
	$J_{H_3H_4}$	2·0 c/s	3·6 c/s
	$J_{H_4H_5}$	9·5 c/s	7·2 c/s
	$J_{H_5H_6}$	2·5 c/s	3·5 c/s
	$J_{H_5H_6'}$	7·6 c/s	6·0 c/s
Penta-O-acetyl-D-galactono- 	$J_{H_2H_3}$	2·0 c/s	2·0 c/s
	$J_{H_3H_4}$	9·5 c/s	9·4 c/s
	$J_{H_4H_5}$	2·0 c/s	—
	$J_{H_5H_6}$	4·3 c/s	5·1 c/s
	$J_{H_5H_6'}$	7·0 c/s	6·8 c/s

TABLE 6—*continued*

Sugar-major conformer predicted from steric interaction	Coupling constant	Predicted J for major conformer	Observed J value
Penta-O-acetyl-D-galactono- 	$J_{H_2H_3}$	2·0 c/s	2·3 c/s
	$J_{H_3H_4}$	9·5 c/s	9·4 c/s
	$J_{H_4H_5}$	2·0 c/s	2·0 c/s
	$J_{H_5H_6}$	4·3 c/s	5·0 c/s
	$J_{H_5H_6'}$	7·0 c/s	7·0 c/s
	$J_{H_2H_3}$	2·0 c/s	2·2 c/s
	$J_{H_3H_4}$	9·5 c/s	9·4 c/s
	$J_{H_4H_5}$	2·0 c/s	2·0 c/s
	$J_{H_5H_6}$	4·3 c/s	5·0 c/s
	$J_{H_5H_6'}$	7·0 c/s	7·0 c/s
N-Acetyl-tetra-O-acetyl-D-glucosaminothioamide. 	$J_{H_2H_3}$	2·0 c/s	5 c/s
	$J_{H_3H_4}$	9·5 c/s	4·0 c/s
	$J_{H_4H_5}$	4·6 c/s	7·0 c/s
	$J_{H_5H_6}$	2·5 c/s	3·6 c/s
	$J_{H_5H_6'}$	7·6 c/s	6·5 c/s
Tetra-O-acetyl-D-ribononitrile 	$J_{H_2H_3}$	2·0 c/s	2·0 c/s
	$J_{H_3H_4}$	9·5 c/s	—
	$J_{H_4H_5}$	2·5 c/s	—
	$J_{H_4H_5'}$	7·6 c/s	—

pounds. The values we predict for the *major* conformation based on calculations of 1,3-eclipsed and 1,2-*gauche* interactions are also quoted. Agreement is closest in those cases where the major conformer has the largest (calculated) stability relative to other conformers. In some cases one (or more) of the alternative conformers approaches more closely to the stablest conformation in stability, and the values may be recalculated to take account of this, in which case even closer agreement is observed.

Further evidence of the correctness of the assumed values for the *trans* and *gauche* coupling constants should be available from an examination of the effect of temperature variation on the spectra. At higher temperatures where conformers will be more equally populated, the observed coupling constants should approach 4·5 c/s, while at lower temperatures values nearer to 9·5 c/s (*trans*) and 2·0 c/s (*gauche*) should finally result. In Tables 7 and 8 examples are given of the effect of temperature upon coupling constants. It can be seen that the values do behave as expected. In examining

TABLE 7. VARIATION OF COUPLING CONSTANT WITH TEMPERATURE (SEE TEXT).
2-[L-*Arabino*-tetra-O-acetylbutyl]4-*p*-bromophenyl-1,3-thiazole

	Temperature				
	Chloroform (d_1)			DMSO (d_6)	
	−60°C	−10°C	+30°C	+30°C	+150°C
$J_{H_2H_3}$	2·1 c/s	3·0 c/s	3·3 c/s	3·3 c/s	4·5 c/s
H_2	3·5 τ	3·57 τ	3·58 τ	3·67 τ	3·69 τ
$J_{H_3H_5}$	9·5 c/s	8·9 c/s	8·4 c/s	8·4 c/s	6·5 c/s
H_3	4·15 τ	4·16 τ	4·19 τ	4·34 τ	4·36 τ
$J_{H_4H_5}$	—	3 c/s	3·0 c/s	3·5 c/s	4·0 c/s
$J_{H_4H_5'}$	—	5 c/s	5·0 c/s	5·5 c/s	5·5 c/s
OAc	7·96 τ	8·00 τ	8·01 τ	8·01 τ	8·02 τ (3)
	7·88	7·92 τ	7·95 τ	7·99 τ	
	7·82 τ	7·88 τ	7·91 τ	7·95 τ	
	7·74 τ	7·78 τ	7·81 τ	7·82 τ	7·88 τ

TABLE 8. VARIATION OF COUPLING CONSTANT WITH TEMPERATURE (SEE TEXT)
2-[D-*Gluco*-penta-O-acetylpentyl]4-*p*-bromophenyl-1,3-thiazole

	Temperature				
	Chloroform (d_1)			DMSO (d_6)	
	−60°C	−10°C	+30°C	+30°C	+150°C
$J_{H_2H_3}$	7·4 c/s	7·2 c/s	7·0 c/s	6·4 c/s	6·2 c/s
H_2	3·73 τ	3·73 τ	3·74 τ	3·78 τ	3·80 τ
$J_{H_3H_4}$	3·0 c/s	3·4 c/s	3·5 c/s	3·8 c/s	4·0 c/s
H_3	4·10 τ	4·10 τ	4·11 τ	4·24 τ	4·28 τ
$J_{H_4H_5}$	8·0 c/s	7·5 c/s	7·0 c/s	6·5 c/s	6·0 c/s
H_4	4·61 τ	4·56 τ	4·54 τ	4·64 τ	4·64 τ
$J_{H_5H_6}$	—	3·5 c/s	3·7 c/s	3·5 c/s	4·0 c/s
$J_{H_5H_6'}$	—	5·5 c/s	5·5 c/s	5·8 c/s	5·5 c/s
OAc	8·97 τ	8·00 τ	8·04 τ	8·07 τ	8·10 τ
	7·89 τ(2)	7·93 τ(2)	7·96 τ(2)	8·00 τ(2)	8·05 τ
	7·82 τ	7·84 τ(2)	7·91 τ	7·94 τ	8·03 τ
	7·79 τ		7·88 τ	7·90 τ	8·01 τ
					7·94 τ

the spectra of the thioamides it was interesting to note that the signal for the H_3 proton occurred at lower field than that for H_2. The most likely explanation for this is that H_3 is in the deshielding cone of the C═S group.

It is clear from these results that 1,3-eclipsed interactions play an important part in determining the conformer distribution in the acyclic sugar derivatives, that these compounds do exist largely in preferred conformations, and that calculations of conformer distribution based on approximate values for group interactions do lead to valid descriptions of the situation in these systems, even though these interaction values were derived from cyclic systems.

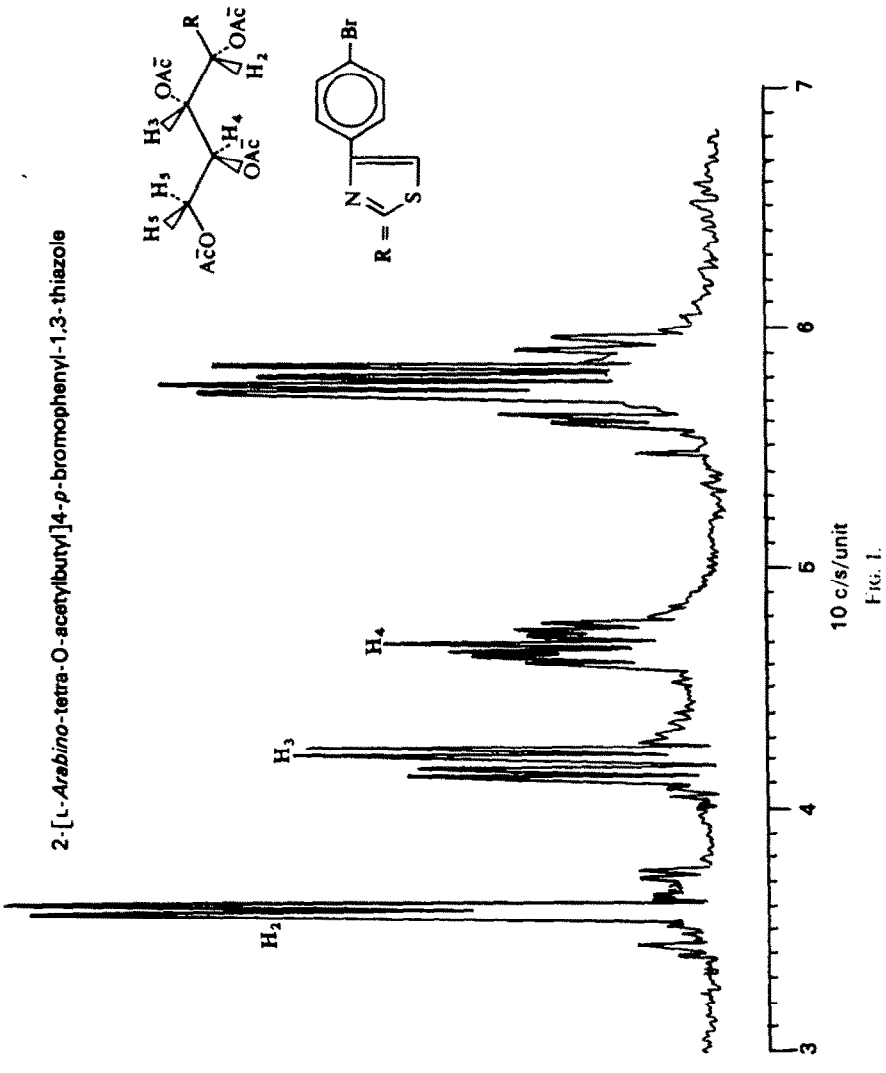

2-[L-Arabino-tetra-O-acetylbutyl]4-p-bromophenyl-1,3-thiazole
H2
H3
H4
R = N S Br
3
4
5
6
7
10 c/s/unit

FIG. 1.

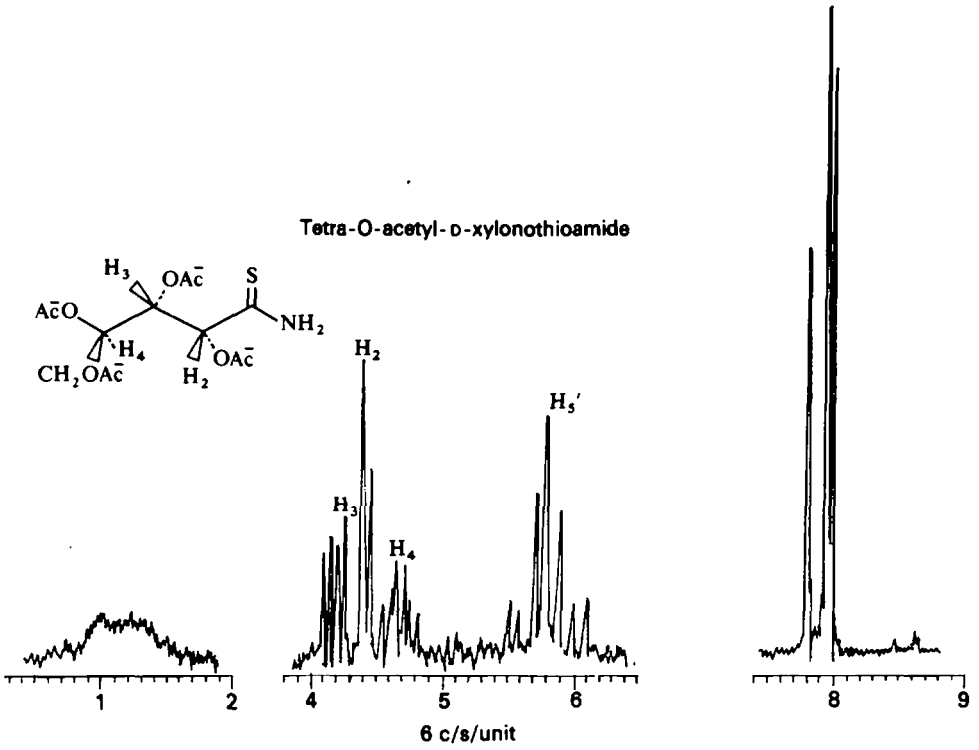

Tetra-O-acetyl-D-xylonothioamide
H3
OAc
S
AcO
NH2
H4
CH2OAc
OAc
H2
H2
H5'
H3
H4
1
2
4
5
6
8
9
6 c/s/unit

FIG. 2.

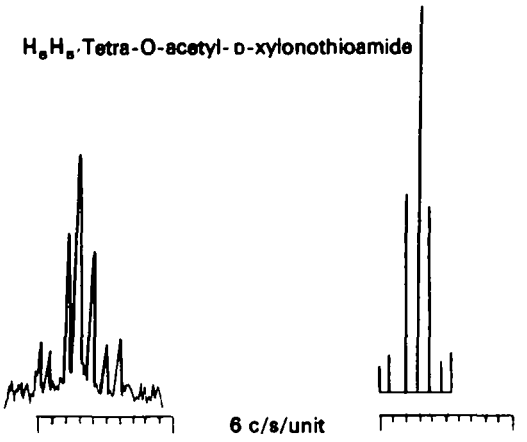

H6H6'-Tetra-O-acetyl-D-xylonothioamide
6 c/s/unit

FIG. 3.

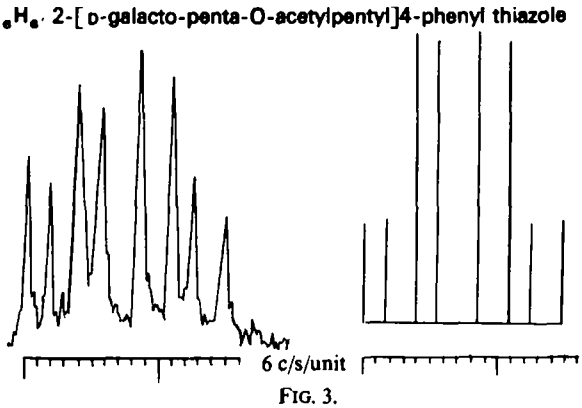


FIG. 3.

EXPERIMENTAL

The synthesis of compounds examined in this work will be described in a succeeding communication, as part of some wider synthetic studies.[20]

Calculation of approximate conformer populations

For the three conformations V, VI and VII, we have interactions as follows:

Conformer V. 1,2 vicinal interactions 1·05 kcal/mole; 1,3 eclipsed interactions (H/H═O, OAc/OAc = 2·0), 2·0 kcal/mole; Total interactions 3·05 kcal/mole.

Conformer VI. 1,2 vicinal interactions 0·7 kcal/mole; 1,3 eclipsed interactions (C/H 0·9, O/H 0·45) 1·35 kcal/mole; Total interactions 2·05 kcal/mole.

Conformer VIII. 1,2 vicinal interactions 1·05 kcal/mole; 1,3 eclipsed interactions (C/OAc = 2·2, OAc/H = 0·45) 2·65 kcal/mole. Total interactions 3·7 kcals/mole.

Taking the relative populations as N_V, N_{VI} and N_{VII}, where these are the mole fractions of conformers V, VI and VII, respectively, we have

$$N_V + N_{VI} + N_{VIII} = 1$$

$$\frac{N_V}{N_{VI}} = K = \exp\left[-\frac{G(V-VI)}{RT}\right] \quad \text{i.e.} \quad \frac{N_{VI}}{N_V} = \exp\left[-\frac{1000}{RT}\right]$$

$$\log N_V/N_V = 0{\cdot}73 \qquad N_V/N_V = 5{\cdot}4$$

Likewise

$$N_{VI}/N_{VII} = 16{\cdot}5 \quad \text{and} \quad N_V/N_{VII} = 3{\cdot}1$$

Hence

$$N_{VI}/N_V + N_{VI}/N_{VII} = 5{\cdot}4 + 16{\cdot}5$$

$$\frac{N_V + N_{VII}}{N_{VI}} = 0{\cdot}25$$

$$N_{VI}:(N_V + N_{VII}) = 4:1.$$

Since

$$N_V = 3{\cdot}1\ N_{VII}$$

$$N_{VI}:N_V:N_{VII} = 0{\cdot}8:0{\cdot}15:0{\cdot}05$$

and the calculated coupling constant is

$$J_{H_3H_4} = 9{\cdot}5 \times 0{\cdot}8 + 2{\cdot}0 \times 0{\cdot}2 = 8{\cdot}0 \text{ c/s.}$$

Analysis of ABX spectra. By the application of the standard method the following parameters were

calculated for (A) tetra-O-acetyl-D-xylonothioamide and (B) 2-(D-galacto-penta-O-acetylpentyl)-4-phenyl-1,3-thiazole.
(A) $J_{AX} = 6{\cdot}4$ c/s. $J_{BX} = 3{\cdot}6$ c/s.
$\nu_A = 22{\cdot}5$ c/s (from arbitrary zero) $\nu_B = 10{\cdot}5$ c/s.
(B) $J_{AB} = 11{\cdot}5$ c/s. $J_{AX} = 7{\cdot}1$ c/s $J_{BX} = 4{\cdot}9$ c/s.
$\nu_A = 33{\cdot}5$ c/s $\nu_B = 10$ c/s.

Line spectra, calculated from the above values, and the observed spectra are shown in Fig. 2. The energy and intensity values are given in the Table below:

Line no.	(A)		(B)	
	Energy	Intensity	Energy	Intensity
1	0	0·25	0	0·55
2	4	0·33	5	0·58
3	12	1·75	11·5	1·45
4	16	1·67	16·5	1·42
5	16	1·75	25·5	1·45
6	22	1·67	32·5	1·42
7	28	0·25	37·0	0·55
8	34	0·33	44	0·58

Acknowledgements—One of us (B.S.) thanks Loughborough University for financial assistance.

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