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P.M.R. STUDIES OF SOME OPEN-CHAIN DERIVATIVES OBTAINED FROM L-ARABINOSE AND L-CYSTEINE

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ABSTRACT

Accurate p.m.r. parameters for methyl 2(*R*)- and 2(*S*)-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)thiazolidine-4(*R*)-carboxylate (**1** and **2**), 3-acetyl-2(*R*)-(L-*arabino*-2,3,4-triacetoxy-1-hydroxybutyl)thiazolidine-4(*R*)-carboxylic acid 4,1′-lactone (**3**), and *N*,*N*-dimethyl-3-acetyl-2(*R*)-(L-*arabino*-2,3,4-triacetoxy-1-hydroxybutyl)thiazolidine-4(*R*)-carboxamide (**4**) were obtained by computer-assisted analysis of their spectra. The polyacetoxyalkyl side-chain was shown to possess a planar zig-zag conformation in each compound, although some distortions occurred in **3** and **4**. The configurations at C-2 in the diastereoisomers **1** and **2** were ascertained on the basis of the $J_{NH,CH}$ coupling-constants.

INTRODUCTION

P.m.r. spectroscopy is an established method in the study of the conformations of acyclic sugar derivatives in solution. These studies rely upon the analysis of vicinal $^1H/^1H$ coupling constants. It is therefore of prime importance to obtain a complete set of accurate coupling-constants. This objective sometimes cannot be easily realized for carbohydrates, the skeletal protons of which generally form tightly coupled, six- or seven-spin systems that very often give degenerate spectra that are not amenable to analysis either by first-order techniques or computation. Therefore, it is not surprising that, although a considerable body of literature exists on this subject[1–4,18], accurate p.m.r. data obtained by iterative fitting of experimental to theoretical spectra are rarely found[5,6].

Iterative computer analysis of spectra is warranted, as (*a*) data obtained in this way are generally considered to be the most reliable and accurate, and (*b*) a good fit between calculated and experimental spectra is, in itself, a strong confirmation of the assignment.

In connection with our studies[7] on open-chain sugar derivatives derived from L-cysteine, we now report some conformational and configurational characteristics of methyl 2(*R*)- and 2(*S*)-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)thiazolidine-4(*R*)-

carboxylate (**1** and **2**), 3-acetyl-2(*R*)-(L-*arabino*-2,3,4-triacetoxy-1-hydroxybutyl)-thiazolidine-4(*R*)-carboxylic acid 4,1′-lactone (**3**), and *N*,*N*-dimethyl-3-acetyl-2(*R*)-(L-*arabino*-2,3,4-triacetoxy-1-hydroxybutyl)thiazolidine-4(*R*)-carboxamide (**4**), as deduced from the computer-assisted analysis of their p.m r spectra in different solvents

RESULTS AND DISCUSSION

The 100-MHz p m r data are summarized in Tables I and II, and parameters obtained from the iterative calculation are given in Table III Comparison of the first-order and calculated coupling constants shows a reasonable agreement between the two sets of data, except for $J_{2',3'}$ and $J_{3',4b}$ for compound **1** (difference, 0 77 and 0 56 Hz, respectively) Smaller deviations ($\leqslant$0 3 Hz) can be attributed to experimental inaccuracies in measuring the line positions and to the consequence of the almost degenerate nature of the transitions in complex spectra, as recently pointed out by Coxon[8] Inaccuracies in the first-order, chemical-shift data are as much as 5 Hz in some cases

Although there are considerable differences between the chemical-shift values obtained in different solvents (Table I), the coupling constants do not vary significantly on changing the solvent (Table II, $J_{2',3'}$ for compound **4** is an exception, see below) Given this lack of sensitivity of the coupling constants to the solvents, we have recorded all spectra for solutions in pyridine-d_5, as there is a greater spread of the chemical shifts than for chloroform, thus facilitating the spectral analysis In comparison with chloroform, pyridine generally causes a non-uniform downfield-shift for all of the signals, with a few exceptions (H-4b′ and H-5a in compound **4**).

The analysis of the coupling-constant data was based on the well-established principles[1] that these couplings represent average values for rapidly interconverting rotameric species and that the Karplus equation is qualitatively valid for the averaged couplings

Methyl 2(*R*)-(L-*arabino*-1,2,3,4-tetraacetoxybutyl)thiazolidine-4(*R*)-carboxylate (**1**) did not give a satisfactory spectrum in chloroform, but in pyridine afforded a fully analyzable spectrum Experimental and computed spectra are shown in Fig 1. The most-striking feature of the spectrum is a clearly resolved doublet of doublets at 4 90 p p.m (J 12 and 5 2 Hz), which collapsed to a doublet (J 5 2 Hz) on adding deuterium oxide (Fig. 1) Simultaneously, a partially hidden "triplet" (J 12 Hz) at 3 25 p p m disappeared and the complex multiplet at 3 96 p p m simplified to a four-line pattern that was assigned to H-4 on the basis of its chemical shift[9] and by double irradiation (of H-5a) The doublet at 4 90 p p m in the spectrum of the D_2O-treated sample was assigned to H-2, as this is the only proton that is coupled to only one other proton Irradiation of this signal caused the double doublet at 5.72 p p m to collapse to a doublet, indicating that it should be assigned to H-1′ The double doublet at 5 80 p p m is assigned to H-2′, because the smaller spacing equals that found in the H-1′ multiplet and also because all other protons give more-

TABLE I

FIRST-ORDER CHEMICAL-SHIFT DATA FOR COMPOUNDS 1–4

Compound	*Solvent (temperature)*	*Chemical shift (δ)*									
		H-2	*H-1'*	*H-2'*	*H-3'*	*H-4a'*	*H-4b'*	*H 4*	*H-5a*	*H-5b*	*Others*
1	C_5D_5N										NH 3 35
	(70°)	4 90	5 72	5 80	5 40	4 46	4 30	3 96	3 26	2 95	OCH_3 3 65
2	C_5D_5N	5 14	5 44	5 99	5 45	4 55	4 32	4 19	3 30	2 97	OCH_3 3 62
	C_6D_6	4 71	5 19	5 82	5 24	4 32	4 12	3 73	2 64	2 92	OCH_3 3 24
											NH 3 00
	$CDCl_3$	4 68	4 98	5 60	5 07	4 27	4 09	4 03	3 25	2 92	OCH_3 3 78
3	C_5D_5N (100°)	6 07	4 71	5 57	5 40	4 43	4 17	5 4	3 27	3 1	
	$CDCl_3$	4 7–6 3[a]	4 60	5 46	5 26	4 39	4 14	5 2	3 38	3 19	
4	C_5D_5N	5 20	4 20	5 83	5 71	4 74	4 48	5 51	3 62	3 20	NCH_3 2 84, 3 08
	$CDCl_3$	4 77	3 77	5 20	5 35	4 60	4 25	5 3	3 44	3 07	NCH_3 2 99, 3 18
											OH 5 66

[a]Very broad signal, see text

TABLE II

FIRST-ORDER COUPLING CONSTANT DATA FOR COMPOUNDS **1–4**

Compound	*Solvent (temperature)*	*Coupling constant (Hz)*									
		$J_{2,1'}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4a'}$	$J_{3',4b'}$	$J_{4a',4b'}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$	*Others*
1	C_5D_5N (70°)	5 2	2 4	9 0	3 2	4 8	12 8	6 8	9 2	10 0	$J_{NH,H-2}$ 12 0, $J_{NH,H-4}$ 12 0
2	C_5D_5N	9 8	2 3	8 0	3 2	5 5	12 5	6 4	7 5	10 5	
	C_6D_6	10 0	2 0	9 0	2 5	5 0	12 5	6 5	7 0	10 5	$J_{NH,H-2}$ 8 0, $J_{NH,H-4}$ 7 7
	$CDCl_3$	9 5	2 0	8 6	3 2	5 0	12 4	6.5	6 8	10 8	
3	C_5D_5N (100°)	0 7	3 8	6 5	3 5	5 5	12 5	1 3	5 6	10 8	
	$CDCl_3$	0 7	3 6	6 8	3 2	5 0	12 8	1 0	5 6	10 8	
4	C_5D_5N	10 0	1 0	6 5	2 5	6.0	12 0				
	$CDCl_3$	10 0	1–2	9 4	2 2	5 8	13 0	9 2	9 5	12 5	$J_{OH,H-1'}$ 2–3

TABLE III

P M R PARAMETERS (100 MHz) OF COMPOUNDS 1–4 OBTAINED BY ITERATIVE CALCULATION[a,b]

Compound	*Solvent (temperature)*	*Chemical shift (Hz from Me_4Si)*						*Coupling constant (Hz)*					
		H-2	*H-1'*	*H-2'*	*H-3'*	*H-4a'*	*H-4b'*	$J_{2,1'}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4a'}$	$J_{3',4b'}$	$J_{4a',4b'}$
1	C_5D_5N (100°)	490 976 (0 041)	568 546 (0 039)	576 988 (0 041)	540 119 (0 034)	446 285 (0 044)	429 404 (0.041)	5 218 (0 060)	2 469 (0 054)	8 225 (0 053)	3 040 (0 058)	5 357 (0 055)	−12 227 (0 049)
2	C_6D_6	471 164 (0 037)	518 323 (0 038)	582 340 (0 025)	523 675 (0 024)	430 390 (0 033)	413 937 (0 033)	9 764 (0 059)	1 936 (0 041)	8 853 (0 036)	2 510 (0 039)	4 780 (0 039)	−12 502 (0 037)
	$CDCl_3$	469 818 (0 032)	497 905 (0 031)	559.725 (0.031)	507 546 (0 030)	425 773 (0 039)	412 472 (0 041)	9 490 (0 044)	2 003 (0 044)	8 463 (0 043)	2.917 (0 057)	5 235 (0 060)	−12 554 (0.059)
3	C_5D_5N (100°)	612 600 (0 046)	474 467 (0 039)	557 366 (0 037)	540 503 (0 028)	442 357 (0.037)	418 008 (0 037)	0 594 (0 060)	3 459 (0 054)	6 592 (0.040)	3 413 (0 046)	5.545 (0.044)	−12 417 (0 050)
4	C_5D_5N	519 941 (0 089)	419 245 (0 051)	581 850 (0 065)	571 088 (0 057)	481.977 (0 056)	449 208 (0 053)	9.784 (0 101)	1 084 (0 083)	6 446 (0 076)	2 418 (0.080)	6 352 (0 086)	−12.375 (0 073)

[a]Errors are probable errors as given by the LAOCN3 program (in parentheses). [b]R m s. errors **1**, 0 166, **2**, 0 093, 0 111, **3**, 0 136; **4**, 0 179.

complex patterns (H-3′ is coupled to three neighbours, and H-4a′ and H-4b′ give an eight-line pattern around 4 30 and 4 46 p p m characteristic of the AB part of an ABX subsystem) The eight-line multiplet at ~3 p p m is unequivocally assigned[7,10] to H-5a and H-5b of the thiazolidine ring The large coupling (J 12 Hz) of the NH-proton to both H-2 and H-4 is indicative[9,11–13] of the *trans,trans* arrangement of the H-2–NH–H-4 segment Since C-4 has the *R* configuration (L-cysteine), the *trans,trans* relationship establishes the configuration at C-2 as *R* It is to be noted, in this connection, that the NH–CH coupling could not be observed in chloroform solution because of the enhanced NH proton-exchange rate The other coupling constants (Tables II and III) of the polyacetoxyalkyl side-chain are compatible[1,14] with an extended, planar, zig-zag arrangement (P conformation[1]), which is the favoured conformation for open-chain derivatives having the *arabino* configuration The intermediate value (5 2 Hz) of $J_{2,1}$ indicates, however, that rotamers **1b** and **1c** contribute to a significant extent to the rotamer equilibrium around the C-2–C-1′ bond, although they contain a "1,3-dipolar interaction" between AcO-2′ and the N or S atoms, respectively, of the thiazolidine ring, rotamer **1a** is free of such an interaction

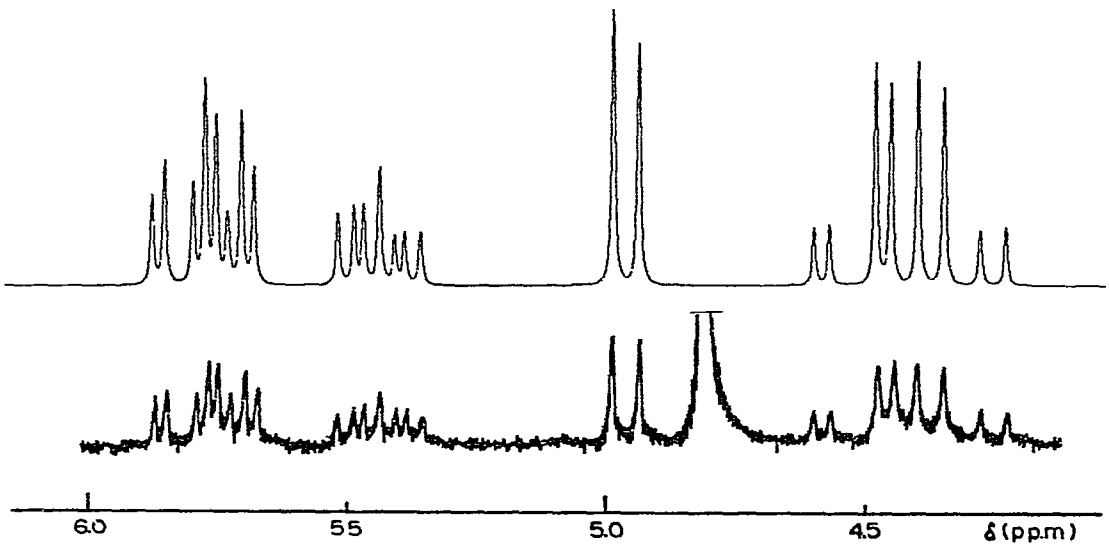
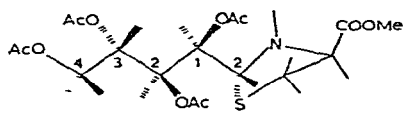
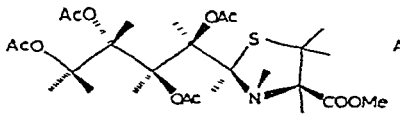


Fig 1 Partial 100-MHz ^{1}H-n m r spectra of **1** in pyridine-d_5–D_2O, top, calculated, bottom, experimental (the truncated peak at ~4 8 p p m arises from HOD)

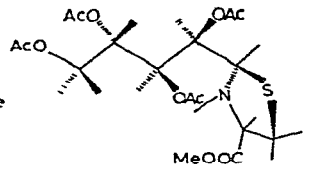
Methyl 2(*S*)-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)thiazolidine-4(*R*)-carboxylate (**2**) displays, in three different solvents, a large $J_{2,1}$ value (Tables II and III), which shows that conformation **2a** is practically exclusive for this compound This conformational preference cannot be understood simply in terms of 1,3-dipolar interactions In attempting to rationalize the $J_{2,1}$ value of the 2(*R*) diastereoisomer **1**,



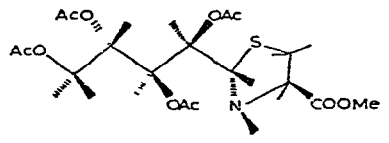
1a



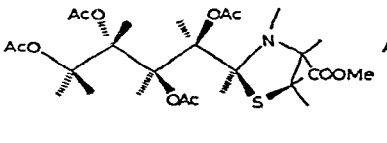
1b



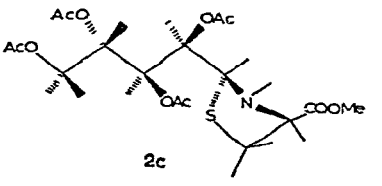
1c



2a



2b



2c

it is assumed that both the N/OAc (occurring in **1b**) or S/OAc (occurring in **1c**) 1,3-dipolar interactions are, or at least one of them is, too small to destabilize conformations **1b** or **1c** On the other hand, both interactions are important if one tries to explain the quasi absence of rotamers **2b** or **2c** for the 2(*S*)-compound **2** This is another piece of evidence that, in addition to others[15], shows that "there is considerable evidence to dictate caution in the formulation of hard and fast rules to predict conformational behaviour in these acyclic molecules[1]"

The configuration at C-2 in compound **2** was also determined on the basis of the NH–CH coupling constant This coupling could not be measured in chloroform or pyridine solution because of rapid proton-exchange In benzene-d_6 solution, however, the splitting of the H-2 doublet could be seen clearly, and $J_{2\ NH}$ was ~8 0 Hz Such a coupling constant requires[9,11,12] the H-2–NH dihedral angle to be ~30°, which is in agreement with the angle measured on a Dreiding model When C-2 has the *S* configuration, the NH–H-2 dihedral angle is 30° in both of the most-probable conformations[16] of the thiazolidine ring

As judged from the data in Tables II and III, compound **2** otherwise displays very similar side-chain couplings as its *R* diastereoisomer, hence, it should adopt the expected P conformation in the solvents studied.

The spectrum calculated for this compound with the data given in Table III fits the experimental spectrum well (Fig 2)

The side-chain coupling constants for 3-acetyl-2(*R*)-(L-*arabino*-2,3,4-triacetoxybutyl)thiazolidine-4(*R*)-carboxylic acid 4,1′-lactone (3) (Tables II and III), in both pyridine and chloroform, deviate significantly from those expected for the P conformation However, it is considered more reasonable to attribute the change in the $J_{1',2'}$ and $J_{2',3'}$ values to a distortion of the tetrahedral CH-angles rather than to a change in the conformer equilibrium This assumption is supported, to some extent, by the unusually small value (0 6–0 7 Hz) of $J_{2,1'}$, which requires the H-2–H-1′ dihedral angle to be ~100° This angle was found to be actually 90–100° when measured on a Dreiding model. In this case, the six-membered lactone ring adopts a

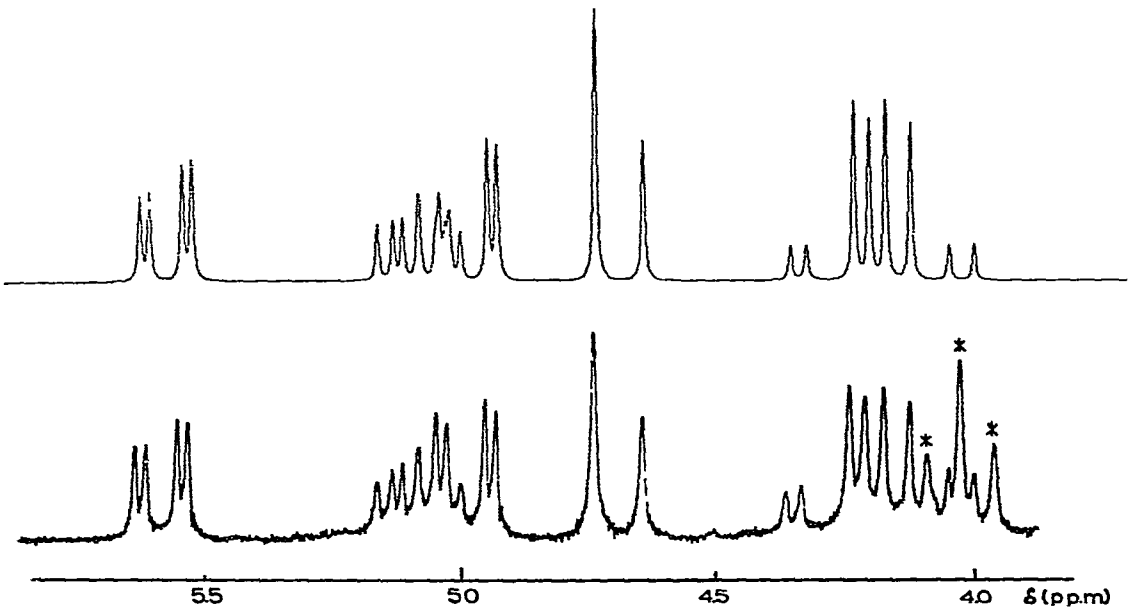


Fig 2 Partial 100-MHz ^{1}H-n.m.r. spectrum of **2** in $CDCl_3$–D_2O top, calculated, bottom, experimental (peaks marked * arise from H-4)

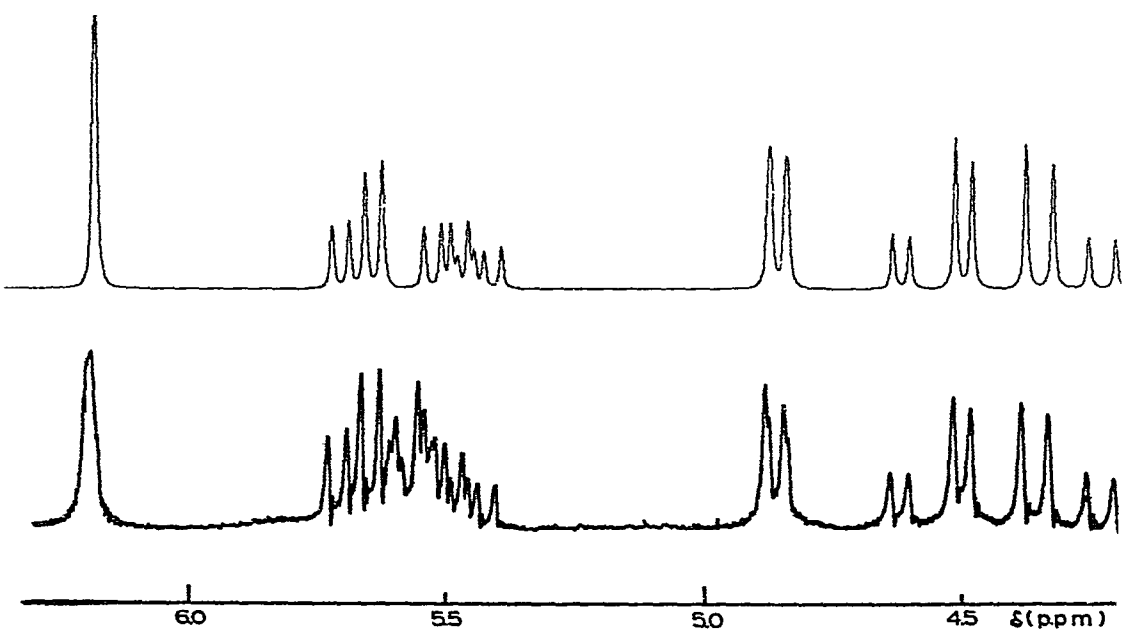


Fig 3 Partial 100-MHz ^{1}H-n.m.r. spectrum of **3** in pyridine-d_5 at 100°, top, calculated; bottom, experimental (the extra peaks in the multiplet at ~5.5 p.p.m. arise from H-4)

flattened-boat conformation, and the side-chain assumes a quasi-equatorial orientation Since the C-2 and C-1′ bond-angles are distorted on account of the flattened-boat geometry of the tetrahydro-1,4-oxazinone ring, it seems to be a plausible assumption that the bond-angle distortion is propagated along the side-chain through C-2′ and C-3′, thereby causing the H-1′–H-2′ and H-2′–H-3′ dihedral angles to depart from the ideal values of 60° and 120°, respectively.

The spectrum of **3** in chloroform-*d* solution displays a very broad, one-proton signal at 4 7–6 3 p p m , in pyridine-d_5 solution, this signal is somewhat narrower. In both spectra, there is a broadened doublet at 4 6–4 7 p p m , which, on closer inspection on the expanded spectrum, reveals an additional splitting of ~0 7 Hz On increasing the probe temperature, the very broad signal becomes much sharper, the other signals being virtually unaffected Irradiation of this temperature-dependent resonance (6 07 p p m in pyridine-d_5 at 100°) removes the ~0 7-Hz splitting, and the signal at 4 7 p p m collapses to a sharp doublet Irradiation of this doublet causes the signal at 5 57 p p m to collapse to a doublet (J 6 5 Hz) On the basis of these spin-decoupling experiments, the temperature-dependent signal at 6 07 p.p m was assigned to H-2, and those at 4 7 and 5 57 p p m to H-1′ and H-2′, respectively. The computed spectrum, based on this assignment, fits well with the experimental one (Fig 3)

The temperature dependence of the H-2 signal can be attributed to the hindered rotation of the *N*-acetyl group Accordingly, a broad acetyl-methyl signal at

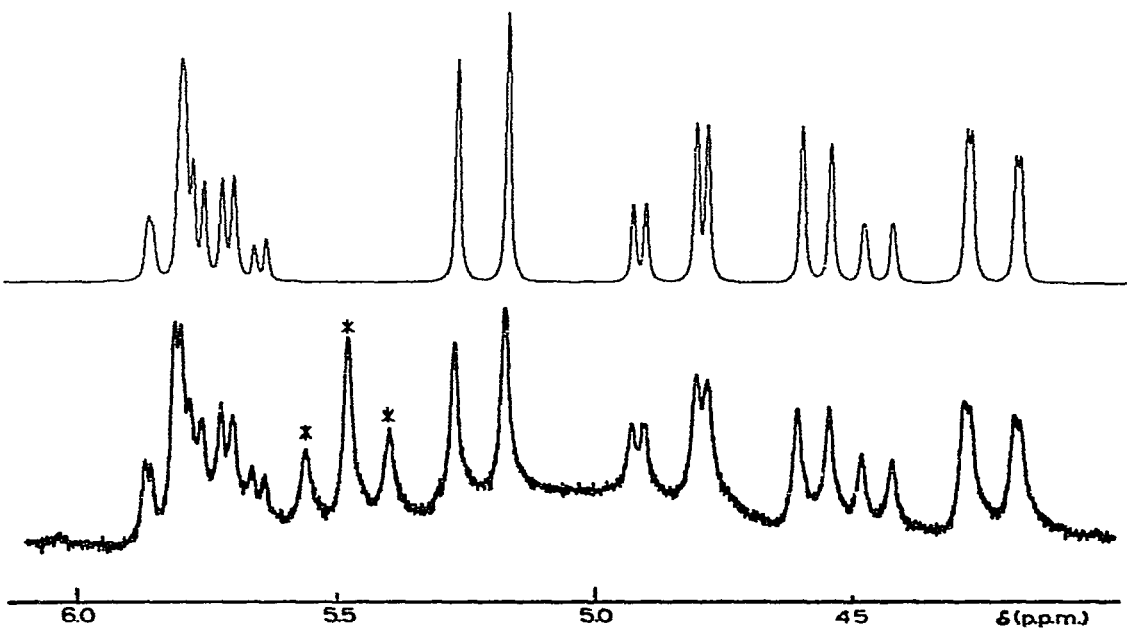
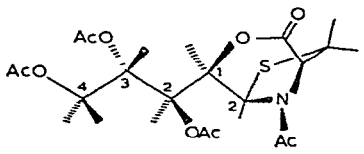


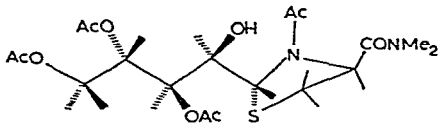
Fig 4 Partial 100-MHz ^{1}H-n m r spectrum of **4** in pyridine-d_5, top, calculated; bottom, experimental (peaks marked * arise from H-4)

2.31 p p m. becomes considerably sharper when the temperature of the sample is increased. The unusually large downfield-shift (6 07 p p m) of H-2 in **3**, as compared to **1** or **2**, is also indicative of the strong shielding arising from the *N*-acetyl carbonyl group

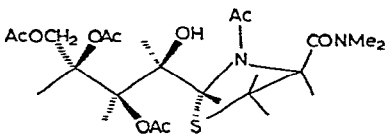
The experimental and computed spectra for *N,N*-dimethyl-3-acetyl-2(*R*)-(L-*arabino*-2,3,4-triacetoxy-1-hydroxybutyl)thiazolidine-4(*R*)-carboxamide (**4**) are shown in Fig 4. The H-2 signal is readily identified as a sharp doublet at 5 20 p p m A much broader "doublet" at 4 20 p p m becomes sharper on adding D_2O Irradiation of this signal results in the collapse of the 5 20-p p m signal to a singlet. Thus, the signal for H-1′ occurs at 4 20 p p m and, moreover, since it was shown to be coupled to an OH-group (D_2O-exchange), this OH-group is located at C-1′.



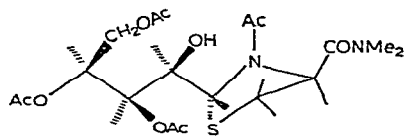
3a



4a



4b



4c

Inspection of the coupling-constant data (Tables II and III) reveals that the side-chain conformation of **4** is close to the predicted P conformation. Furthermore, the large (10 Hz) $J_{2,1'}$ value shows that **4a** is the favored rotamer around the C-2–C-1′ bond in both chloroform and pyridine solutions The decrease in $J_{2,3'}$ (6 5 Hz) in pyridine solution, as compared to 9 4 Hz in chloroform, is somewhat puzzling It suggests some contribution from the bent rotamers **4b** and **4c** in the conformer equilibrium It is equally possible, however, that the free OH-group interacts specifically with the pyridine through a hydrogen bond and that it is the consequent distortion of the H-2′–H-3′ dihedral angle that is reflected in the value of $J_{2',3'}$.

EXPERIMENTAL

The compounds studied were prepared as described[7] earlier P m r spectra were recorded on a JEOL MH-100 instrument for solutions containing ~5% of tetramethylsilane as an internal lock substance. For computation, the required spectral regions were expanded to 50 Hz and recorded at least three times Line positions were measured with the aid of a Hewlett–Packard model 5300A/5301A digital frequency counter R m s error of the line-frequency measurements was

0 05 Hz. In one case (compound 1), the spectrum was recorded at 70° (probe temperature), because the accuracy of the frequency measurement was better at this temperature. Except for a uniform sharpening of all spectral lines, no change could be detected in the spectrum upon heating

Iterative calculations were done with the aid of the LAOCN3 program[17] modified with a plotting routine that allows a Gaussian or Lorentzian line-shape, or an arbitrary mixture, to be used for the plot In each case, the calculation was done on the six-spin system that comprised the side-chain backbone protons plus H-2 Of some 200 transitions obtained after the trial calculation, 40–50 transitions were generally assigned to 20–25 measured frequencies The calculation converged after 2–3 iterations All of the criteria put forward by Coxon[8] for the validity of the spectrum analysis were satisfied by the present computations

ACKNOWLEDGMENTS

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