A Multinuclear NMR Study of Derivatives of Thiazolidine

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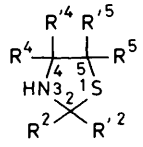
The structure of mono- and poly-(alkyl or aryl) substituted thiazolidines has been studied using ^1H and ^{13}C NMR spectroscopy: the N–H hydrogen is axial and the order of preference for the equatorial position of substituent is 4 > 2 > 5. These results have been used to parametrize the ^{15}N chemical shifts. These compounds display stereoelectronic interactions related to the anomeric effect. Several conformations may exist in solution: (**3**),(**4**) half-chair, (**3**) and (**4**) envelopes.

The thiazolidine ring is an important heterocyclic system in biology and medicine: it is the backbone of the penicillin structure and an integral part of some antiradiation drugs; it is formed *in vivo* from cysteine with endogenous aldehydes.

The structure of the thiazolidine ring has been studied by Larice[1] and Guiliano[2] (NMR, IR and force-field calculations): the results of the two last methods seem to favour the (**3**),(**4**) half-chair form with a pseudoequatorial substituent for 2- or 5-monomethyl derivatives and with axial methyl for 4-methyl thiazolidine. A more or less puckered geometry has been advanced for 2,2-dimethylthiazolidine[3] and several 1,3-thiazolidine spirochromenes[4] from NMR investigations. Wilson and Bazzone[5] have proposed (**3**) and (**4**) envelope forms from NMR studies of thiazolidine and its 2-t-butyl derivative. Thiazolidine-4-carboxylic acid is present in (S) envelope form in the solid state[6,7] or in solution:[8] its derivatives present other conformations. We here report ^1H and ^{13}C NMR studies of a series of mono- and poly-(alkyl or aryl) substituted thiazolidines; structural conclusions have been used to increment the ^{15}N NMR spectra of these compounds.

Results and Discussion

^3J(HCNH).—^1H Spectra of some derivatives of thiazolidine (Table 1) exhibit broadened signals (H-2, H-3, and H-4) above room temperature. Cooling gives new spectra with different signal multiplicities for these hydrogen atoms: new couplings arise from N–H hydrogen atom as expected by selective decoupling of this proton, which restores the original spectrum. All the compounds studied below 273 K have at least one coupling constant ($J_{2,3}$ or $J_{3,4}$) larger than 12 Hz; for 2-unsubstituted compounds, the value of coupling constant between H-3 and the second H-2 is included between 6.5 and 7.5 Hz. So using the stereochemical dependence of vicinal coupling constants in the HCNH fragment, it is possible to determine in those compounds the orientation of the N–H bond and of the 2- and 4-substituents: the values observed in thiazolidines are only consistent with an axial N–H bond. Stabilization of the N–H axial orientation with respect to the equatorial one has been assigned by Booth and Lemieux[9] (for diazanes and tetrahydrooxazines) to the presence of a highly negative geminal heteroatom which lowers the basicity of the NH group; as noted by Samitov *et al.*,[10] the dependence of this process on the concentration is also due to the formation of auto-associates through intermolecular hydrogen bonds between the N–H hydrogens and the electron lone pairs on the heteroatoms. In monosubstituted (**2**), (**3**), (**18**), and trisubstituted (**14**), (**16**) compounds, the 2- (or 4-) substituent prefers the equatorial orientation. It is the same for the more abundant isomers of the



	R^2	R'^2	R^4	R'^4	R^5	R'^5
(**1**)	H	H	H	H	H	H
(**2**)	Me	H	H	H	H	H
(**3**)	H	H	Me	H	H	H
(**4**)	H	H	H	H	Me	H
(**5**)	Me	Me	H	H	H	H
(**6**)	H	H	Me	Me	H	H
(**7**)	H	H	H	H	Me	Me
(**8**) and (**9**)	Me	H	Me	H	H	H
(**10**) and (**11**)	Me	H	H	H	Me	H
(**12**) and (**13**)	H	H	Me	H	Me	H
(**14**)	Me	H	Me	Me	H	H
(**15**)	Me	H	H	H	Me	Me
(**16**)	Me	Me	Me	H	H	H
(**17**)	Me	Me	H	H	Me	H
(**18**)	H	H	Pr^i	H	H	H
(**19**)	H	H	H	H	Pr^i	H
(**20**) and (**21**)	Me	H	Pr^i	H	H	H
(**22**)	H	H	Bu^t	H	H	H
(**23**) and (**24**)	Bu^t	H	Me	H	H	H
(**25**) and (**26**)	Bu^t	H	H	H	Me	H
(**27**) and (**28**)	Me	H	Bu^t	H	H	H
(**29**)	Ph	H	H	H	H	H
(**30**)	H	H	Ph	H	H	H
(**31**)	H	H	H	H	Ph	H
(**32**) and (**33**)	Ph	H	Me	H	H	H
(**34**) and (**35**)	Ph	H	H	H	Me	H
(**36**) and (**37**)	Me	H	Ph	H	H	H
(**38**) and (**39**)	Me	H	H	H	Ph	H

2,4-disubstituted compounds (**8**), (**20**), (**23**), and (**32**) which exhibit larger values of coupling $J_{2,3}$; the coupling constant $J_{3,4}$ is only evaluated for (**32**) but the similitude of the (H-4,H-5) part of the spectra of these four compounds allows us to assume that, for each, the 4-substituent is equatorial. In the 2,5-disubstituted compounds (**25**) and (**26**), (**34**) and (**35**), the 2-substituent prefers the equatorial orientation in *cis* and *trans* isomers; consequently they only differ by the 5-substituent position. The coupling $J_{3,4}$ is only evaluated in the isomer (**13**) of 4,5-dimethyl thiazolidines, compound in which the 4-methyl is equatorial.

^3J(H-4,H-5).—Several approaches have been used to translate the vicinal coupling constants of thiazolidines into structural information, often by parametrization of the Karplus

Table 1. ^{1}H NMR of thiazolidines. (H-2,H-4,H-5 are the pseudoequatorial hydrogens, and H-2′,H-4′,H-5′ are the pseudoaxial ones or are strongly indicative of this. The protons which reside either in an equatorial or in an axial position have been arbitrarily classified with the equatorial hydrogens in the coupling constant part of the table).

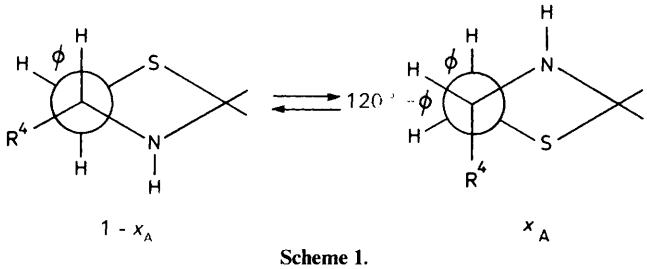
Compounds	Frequency/ MHz	Temperature/K	Solvent	δ H-2	δ H-2′	δ H-4	δ H-4′	δ H-5	δ H-5′	δ H-3	δ R-2	δ R-4	δ R-5	| J(2,2′) |	| J(4,4′) |
(1)	360	298	$CDCl_3$		4.17		3.19		2.87	1.76					
(2)	360	298	$CDCl_3$	4.56		2.91–3.07(3)		3.50–3.59(1)		1.64	1.56				
	80	198	CD_2Cl_2												
(3)	500	298	$CDCl_3$	4.26	4.10		3.24	3.05	2.38	1.60		1.33		9.4	
	80	213	CD_2Cl_2												
(4)	500	298	$CDCl_2$	4.28	4.16	3.23	2.72	3.51		2.07			1.30		12.3
(5)	360	298	$CDCl_3$			3.36			3.07	1.93	1.60				
(6)	80	298	$CDCl_3$		4.19				2.66	1.05		1.28			
	80	203	CD_2Cl_2												
(7)	80	298	$CDCl_3$		4.31		2.05			2.38			1.45		
(8)	250	308	CD_2Cl_2		4.55		3.18	3.10	2.47	*a*	1.51	1.32			
	80	193	CD_2Cl_2												
(9)	250	308	CD_2Cl_2		4.69		3.60		3.05	2.52	*a*	1.44	1.21		
(10)	250	308	CD_2Cl_2		4.67	3.47	2.50		3.58	2.27	1.46		1.29		12.6
(11)	250	308	CD_2Cl_2		4.54	2.99	3.03	3.58		2.27	1.51		1.24		12.5
(12)	80	298	CD_2Cl_2		4.16		2.70		2.94	1.88		1.23	1.31		
(13)	80	298	CD_2Cl_2	4.24	4.01		3.12	3.43		1.90		1.18	1.07	9.2	
	80	193	CD_2Cl_2												
(14)	80	298	$CDCl_3$		4.62			2.88	2.72	1.60	1.55	1.39; 1.21			
	80	203	CD_2Cl_2												
[b](15)	60	298	CCl_4		4.60	2.91	2.66				1.45		1.42; 1.36		12
(16)	80	298	$CDCl_3$				3.53	3.22	2.69	1.70	1.66; 1.5	1.35			
	80	203	CD_2Cl_2												
(17)	80	298	$CDCl_3$			3.41	2.88	3.65		2.42	1.61;1.56		1.31		13.2
(18)	60	298	CD_2Cl_2	4.26	4.03		2.71	3.01	2.38	*a*		1.74		9.3	
	80	233	CD_2Cl_2												
(19)	60	298	$CDCl_3$		4.16		2.58	3.45		2.23			1.63		
(20)	80	298	$CDCl_3$		4.58		2.47	3.20		1.4	1.56	1.79			
	80	223	$CDCl_3$												
(21)	80	298	$CDCl_3$	4.69			2.47	3.20		1.4	1.47	1.79			
(22)	250	308	$CDCl_3$	4.32	4.06		2.95	2.77	2.51	1.65				9.4	
(23)	500	298	$CDCl_3$		4.47		3.20	3.04	2.25	1.42		1.35			
	80	193	CD_2Cl_2												
(24)	500	298	$CDCl_3$		4.44		3.68		2.88	2.55	1.42		1.18		
(25)	360	298	$CDCl_3$		4.57	3.55	2.50			3.35	1.87		1.35		12.2
	80	213	CD_2Cl_2												
(26)	360	298	$CDCl_3$		4.44	3.10	3.02	3.55			1.87		1.20		12.3
	80	213	CD_2Cl_2												
(27)	500	298	$CDCl_3$		4.56		2.98	2.91	2.70	1.03	1.56				
(28)	500	298	$CDCl_3$	4.72			3.08	3.02	2.63	1.03	1.44				
(29)	400	298	CD_2Cl_2		5.53	3.00–3.15(3)		3.50–3.65(1)		2.00					
(30)	250	308	$CDCl_3$				4.21	3.35	2.83	2.15					
(31)	250	308	$CDCl_3$	4.48	4.33	3.51	3.01		4.53	2.15				9.5	12.5
(32)	500	298	$CDCl_3$		5.57		3.35	3.21	2.62	1.89		1.38			
	80	193	CD_2Cl_2												
(33)	500	298	$CDCl_3$		5.68		3.61		3.17	2.63	1.89		1.28		
(34)	500	298	$CDCl_3$		5.67	3.55	2.65			3.67	2.31		1.37		12.3
	80	178	CD_2Cl_2												
(35)	500	298	$CDCl_3$		5.56	3.09	3.16	3.69			2.31		1.33		12.4
	80	178	CD_2Cl_2												
(36)	250	308	$CDCl_3$				4.24	3.43	2.95	2.06	1.62				
(37)	250	308	$CDCl_3$					3.40	3.06	2.06	1.55				
(38)	250	308	$CDCl_3$		4.91	3.72	2.90		4.61	2.06	1.58				12.7
(39)	250	308	$CDCl_3$		4.72	3.27	3.33	4.67		2.06	1.68				12.5

Table 1 (*continued*).

Compounds	Frequency/ MHz	Temperature/K	Solvent	| $J(5,5')$ |	$J(2,3)$	$J(2',3)$	$J(3,4')$	$J(4,5)$	$J(4,5')$	$J(4',5)$	$J(4',5')$	$J(R_n,H_n)$	δ Others
(1)	360	298	$CDCl_3$						6.3				
(2)	360	298	$CDCl_3$									6.2	
	80	198	CD_2Cl_2			12.0				6.0	8.3	6.4	
(3)	500	298	$CDCl_3$	10.0									
	80	213	CD_2Cl_2		7.4	12.5	11.8						
(4)	500	298	$CDCl_3$					6.1		5.6		6.6	
(5)	360	298	$CDCl_3$						6.2				
(6)	80	298	$CDCl_3$										
	80	203	CD_2Cl_2		10.3								
(7)	80	298	$CDCl_3$										
(8)	250	308	CD_2Cl_2	10.1						5.8	10.1	6.1 (n = 2), 6.2 (n = 4)	
	80	193	CD_2Cl_2			13.0							
(9)	250	308	CD_2Cl_2	10.1				5.9	6.1			6.2 (n = 2), 6.6 (n = 4)	
(10)	250	308	CD_2Cl_2						6.0		8.5	6.2 (n = 2), 6.3 (n = 5)	
(11)	250	308	CD_2Cl_2					2.8		6.1		6.2 (n = 2), 6.8 (n = 5)	
(12)	80	298	CD_2Cl_2								7.7	6.5 (n = 4), 6.2 (n = 5)	
(13)	80	298	CD_2Cl_2							5.4		6.6 (n = 4), 6.8 (n = 5)	
	80	193	CD_2Cl_2		7.2	12.6	12.3						
(14)	80	298	$CDCl_3$	10.1								6.2 (n = 2)	
	80	203	CD_2Cl_2			13.0							
[b](**15**)	60	298	CCl_4									6.0 (n = 2)	
(16)	80	298	$CDCl_3$							5.5	10.1	6.1 (n = 4)	
	80	203	CD_2Cl_2				13.6						
(17)	80	298	$CDCl_3$					5.8	6.5			6.4 (n = 5)	
(18)	60	298	CD_2Cl_2										Me:0.99; 1.07
	80	233	CD_2Cl_2		6.6	12.9	13.6						
(19)	60	298	$CDCl_3$										Me:0.97; 1.02
(20)	80	298	$CDCl_3$									6.2 (n = 2)	Me:1.00; 1.09
	80	223	$CDCl_3$			12.1							
(21)	80	298	$CDCl_3$										Me:0.98; 1.05
(22)	250	308	$CDCl_3$	10.1						6.0	9.7		Bu^t:1.03
(23)	500	298	$CDCl_3$	10.1						5.6	10.1	6.3 (n = 4)	Bu^t:1.04
	80	193	CD_2Cl_2			13.4							
(24)	500	298	$CDCl_3$	10.1				5.6	4.7			6.5 (n = 4)	Bu^t:1.00
(25)	360	298	$CDCl_3$						5.8		9.2	6.4 (n = 5)	Bu^t:1.03
	80	213	CD_2Cl_2			12.5							
(26)	360	298	$CDCl_3$					1.5		6.0		6.8 (n = 5)	Bu^t:1.05
	80	213	CD_2Cl_2			13.0							
(27)	500	298	$CDCl_3$	10.0						6.1	9.8	6.1 (n = 2)	Bu^t:1.01
(28)	500	298	$CDCl_3$	10.5						6.1	9.7	6.5 (n = 2)	Bu^t:0.99
(29)	400	298	CD_2Cl_2										φ:7.2–7.4(3); 7.4–7.5(2)
(30)	250	308	$CDCl_3$	10.3						6.2	8.9		φ:7.10–7.55
(31)	250	308	$CDCl_3$					6.4		6.2			φ:7.10–7.55
(32)	500	298	$CDCl_3$	9.9						5.9	9.6	6.3 (n = 4)	φ:7.2–7.5
	80	193	CD_2Cl_2			13.6	12.5						
(33)	500	298	$CDCl_3$	10.0				5.8	6.2			6.5 (n = 4)	φ:7.2–7.5
(34)	500	298	$CDCl_3$						6.0		8.2	6.4 (n = 5)	φ:7.25–7.5
	80	178	CD_2Cl_2			12.0							
(35)	500	298	$CDCl_3$					2.7		6.1		6.8 (n = 5)	φ:7.25–7.5
	80	178	CD_2Cl_2			13.0							
(36)	250	308	$CDCl_3$	10.1						6.2	10.1	6.1 (n = 2)	φ:7.15–7.4
(37)	250	308	$CDCl_3$	10.6				6.3	6.8			6.4 (n = 2)	φ:7.15–7.4
(38)	250	308	$CDCl_3$						6.3		8.8	6.2 (n = 2)	φ:7.15–7.4
(39)	250	308	$CDCl_3$					3.2		6.4		6.2 (n = 2)	φ:7.15–7.4

[a] Obscured by the methyl signal; [b] ref. 1.

equation. We first used the methods formulated by Elguero and Fruchier[11] and previously applied by Maguet[4] to 1,3-thiazolidine spirochromenes: in spite of a larger number of approximations, this calculation allows an evaluation of the torsion angle φ and of the population x_A of the conformer family with axial 4- (or 5-) substituents.



Scheme 1.

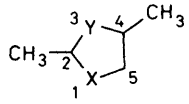
To use the mathematical treatment of Elguero and Fruchier, one can evaluate in the vicinal coupling constant of the parent compound (**1**) the contribution independent of the torsion angle; this calculation may be achieved if the two families of conformers are assumed to be equally populated. This contribution is corrected by the increment of the substituent in the derivatives of thiazolidine (for methyl and phenyl substituents, we have used the values reported by Abraham and Pachler;[12] the t-butyl increment derives from the vicinal coupling constant measured in 2,2-dimethylbutane J 7.51 ± 0.1).

Good agreement is obtained between the two methods (differences and ratios). The value of the torsion angle included is between 39 and 43° (it is impossible to distinguish J_{cis} and J_{trans} for the compounds (**4**), (**31**), (**9**), and (**33**) initially, but the results change little from one set of parameters to the next). Data have been collected in Table 2. For the compounds which have a value of x_A close to 0 or 100, we have then analysed the coupling constant by a generalized Karplus equation. Among all the existing relations, we have chosen the equation formulated by Altona *et al.*[13] [relation due to Gandour *et al.*[14] leads to aberrant data for (**13**)]. The research of the dihedral angle amounts to resolve a fourth-degree equation the only two solutions of which are consistent with the chemical structure. The exploitation of the vicinal coupling constants $J_{4,5}$ confirms the results obtained with the ^3J(HCNH) couplings.

^3J(R*s*,H*s*) *with s* = 2, 4, *or* 5.—Numerous reports[15] suggest that couplings between methyl groups attached to cyclic systems and methine hydrogens have a value characteristic of their orientation. Thus for a given pair of six-membered cyclic compounds, splitting of an axial methyl group by an equatorial methine group is larger than that of an equatorial methyl by an axial methine (for instance, 7.2 and 6.5 Hz respectively for the 4-methyl-1-t-butyl cyclohexane[16]). Though the origin of this effect has not been cleared up, the application of such a criterion follows our previous conclusions: in 2,4-disubstituted derivatives, compounds (**8**), (**23**) and (**32**) have their methyl group in a more pronounced equatorial orientation than compounds (**9**), (**24**), and (**33**) respectively; in 2,5-disubstituted derivatives, the 2-methyl groups have the same orientation in the two isomers whereas the 5-methyl group is more equatorial in compounds (**10**), (**25**), and (**34**) than in (**11**), (**26**), and (**35**) respectively; lastly, the 4,5-dimethylthiazolidines differ in the 5-methyl position, more axial in (**13**) than in (**12**).

Chemical Shifts of H-2, H-4, *and* H-5.—Anteunis and Danneels[17] have shown that chemical shift criteria lead to structural elucidation of pseudorotational systems. Application of their '*syn* upfield rule' to thiazolidines leads to the following conclusions. In the 2,4-dimethyl derivative (**9**), H-2 and H-4 are more deshielded than in (**8**) and so are, on an average, closer to the 4- and 2-methyl groups respectively than in (**8**); this is in agreement with the criterion proposed by MacMillan and Stoodley[18] concerning derivatives of thiazolidine-4-carboxylic acids. In the 4,5-dimethyl compound (**12**), the two substituents shield their vicinal hydrogen atoms: this compound is then the *trans* isomer with an equatorial methyl group; the H-2 protons are not differentiated and are, on average, more deshielded than in (**13**). In the 2,5-dimethyl thiazolidine (**11**), the equatorial H-4 proton is shielded by the (pseudoaxial) 5-substituent; in its isomer (**10**), the (pseudoaxial) H-2 atom is deshielded and is then *syn* with the 5-substituent: the methyl groups of (**10**) are consequently equatorial (the pseudoaxial H-2 proton is deshielded by the *syn* pseudoequatorial 5-methyl group) and the 5-substituent is pseudoaxial in (**11**) (and so the conformations advanced by Elz *et al.*[19] are erroneous).

Chemical Shifts of C-2, C-4, *and* C-5 (see Table 3).—Simple chemical shift criteria allow the assignment of most of the signals. Inseparable diastereoisomers are analysed as a mixture; when the compounds are in different ratios, signals are assigned by means of their intensities, otherwise the 2D heteronuclear correlated spectrum removes all ambiguity. The five-membered ring is notoriously conformationally mobile; despite this, the five-membered ring can be parametrized[20] and in the compounds having the structure below (see Table 4), C-2 and



C-4 resonate at lower field and C-5 at higher field in the *cis*-disubstituted species than in the corresponding *trans* isomers. This regularity has been used as an assignment rule in the five-membered ring system[21] but application of this rule to 2,4-dimethyl thiazolidines leads to conclusions opposite to those of Llinares.[22]

Chemical Shifts of 2-, 4-, 5-*Methyl Groups.*—The signals of 4-methyl groups in (**8**) and (**9**) (18.96 and 19.09 ppm respectively) are assigned by comparison with those of (**23**) and (**24**) (19.06 and 19.22 ppm), methyl t-butyl derivatives where the assignment is easy; the same work is performed with the signals of 5-methyl groups of (**10**) and (**11**) (20.75 and 23.63 ppm respectively) and those of (**25**) and (**26**) (20.47 and 23.32 ppm). Interactions between substituents are larger in the *cis*-4,5-dimethyl derivative than in the corresponding *trans* isomer: accordingly the methyl groups are more shielded in (**13**) than in (**12**); in the latter, the signals may be close to the average values of chemical shift of a 5-methyl group (20.7–23.6 ppm) and of a 4-methyl group (18.4–19.1 ppm); and so the following assignment seems to be logical: in (**12**), the 4- and 5-substituents resonate at 17.29 and 19.84 ppm respectively, whereas these two signals are shielded in (**13**) at 14.67 and 18.27 ppm respectively. This is in agreement with the assignments in 2,3-dimethylthiolanes.[26]

In the six-membered heterocyclic ring, the chemical shifts of methyl substituents can be calculated as a function of their position and of the nature of the heteroatom (see Table 4). These results display the marked deshielding of axial methyl groups located on a carbon α to the sulphur atom and the shielding of equatorial methyl groups located on a carbon β to a nitrogen or oxygen atom: this γ anti-effect[34] would be transmitted, at least partially, by the axial hydrogen atoms located on the carbon α and γ[35,36] to the heteroatom and its intensity would be subject to the electronegativity of the heteroatom. As the axial or equatorial feature of the substituents is less marked in the five-membered ring systems, this increment is more prob-

Table 2. Treatments of ^3J(H-4,H-5) by the relations of Elguero and Fruchier, and by the relation of Altona *et al.*

			Relations of Elguero and Fruchier					
			Differences method		Ratios method		Relation of Altona *et al.*	
Compounds	J_{cis}	J_{trans}	φ/°	x_A	φ/°	x_A	φ *cis*[a]/°	φ *trans*[a]/°
(1)	6.3	6.3	43	0.5	42.5	0.5		
(3)	6.2	8.4	39.5	0.13	40	0.23	(37 and) 41	(141 and) 148
(4)	6.1	5.6	39	0.46	40	0.49		
	5.6	6.1	42.5	0.43	43	0.46		
(5)	6.2	6.2	43	0.5	42.5	0.49		
(8)	5.8	10.1	41	0	42	0.1	(40 and) 44	(152 and) 159
(9)	5.9	6.1	40	0.41	41.5	0.46		
	6.1	5.9	39	0.42	41	0.46		
(10)	6.0	8.5	39	0.10	41	0.23	(37 and) 44	(142 and) 148
(11)	6.1	2.8	39	0.80	41	0.74	(37 and) 44	(59 and) 66
(12)		7.7						(144 and) 147
(13)	5.4						(38 and) 42	
(16)	5.5	10.1	43	0	43	0.11	(42 and) 46	(151 and) 159
(17)	5.8	6.5	41	0.36	42	0.42		
(22)	6.0	9.7	41	0	42	0.16	(38 and) 42	(150 and) 156
(23)	5.6	10.1	42	0	43	0.11	(41 and) 45	(153 and) 159
(24)	5.6	4.7	42	0.59	43	0.59		
(25)	5.8	9.2	41	0.04	42	0.18	(39 and) 46	(147 and) 153
(26)	6.0	1.5	39	0.96	41	0.87	(37 and) 44	(72 and) 80
(27)	6.1	9.8	40.5	0	42	0.15	(38 and) 42	(150 and) 157
(28)	6.1	9.7	40.5	0	42	0.16	(38 and) 42	(150 and) 156
(30)	6.2	8.9	39	0.07	40	0.20	(37 and) 41	(144 and) 151
(31)	6.2	6.4	39	0.38	40	0.42		
	6.4	6.2	38	0.38	39.5	0.43		
(32)	5.9	9.6	40.5	0	42	0.14	(40 and) 44	(149 and) 156
(33)	5.8	6.2	40.6	0.40	42	0.45		
	6.2	5.8	38	0.42	40	0.46		
(34)	6.0	8.2	39.6	0.14	41	0.25	(37 and) 44	(140 and) 147
(35)	6.1	2.7	39	0.82	40	0.74	(36 and) 44	(59 and) 67
(36)	6.2	10.1	39	0	40.5	0.10	(38 and) 42	(152 and) 159
(37)	6.3	6.8	38	0.32	40	0.39		
(38)	6.3	8.8	38	0.07	40	0.21	(35 and) 42	(143 and) 150
(39)	6.4	3.2	37	0.75	39	0.69	(34 and) 42	(55 and) 63

[a] The less probable values are in brackets.

Table 3. ^{13}C NMR data of methylated thiazolidines at 303 K ($^1J_{C,H}$ in parentheses).

	Solvent	C-2	C-4	C-5	Me-2	Me-4	Me-5
(1)	C_6D_6[a]	55.64(154.6)	52.96(140.6)	34.09(142.8)			
(2)	without	66.57(153.1)	52.43(140.2)	36.32(142.8)	21.91(126.9)		
(3)	without	54.42(154.7)	60.75(140.8)	40.54(138.6)		18.40(126.6)	
(4)	$CDCl_3$	56.03(154.7)	60.22(139.7)	45.62(141.9)			21.74(126.9)
(5)	without	76.04	51.35(140.2)	37.56(141.7)	31.50(126.8)		
(6)	without	53.15(154.4)	64.77	45.35(140.6)		25.64(125.7)	
(7)	$CDCl_3$	56.49(?)	66.12(?)	56.19(?)			30.26(?)
(8)	$CDCl_3$	65.89(157.7)	61.33(141.9)	43.09(139.9)	21.35(127.4)	18.96(126.3)	
(9)	$CDCl_3$	64.25(154.4)	58.58(?)	42.57(?)	24.07(127.1)	19.90(?)	
(10)	$CDCl_3$	66.77(155.7)	60.25(137.9)	48.45(140.2)[b]	21.93(126.9)		20.75(126.6)
(11)	$CDCl_3$	67.34(155.7)	59.35(139.2)	47.18(142.5)[b]	22.52(127.1)		23.63(126.5)
(12)	$CDCl_3$	53.25(154.6)	67.56(139.2)	52.59(141.2)		17.29(126.0)	19.84(127.1)
(13)	$CDCl_3$	53.38(154.0)	62.74(138.6)	47.45(141.5)		14.67(126.3)	18.27(126.7)
(14)	without	64.15(157.7)	65.56	47.52(140.2)	21.74(127.1)	25.44(125.8)	
						27.90(?)	
(15)	C_6D_6[c]	67.80(?)	66.20(?)	58.30(?)	22.70(?)		29.60(?)
							31.80(?)
(16)	without	75.42	59.40(137.3)	44.47(139.7)	31.50(126.9)	19.06(124.1)	
					33.30(126.9)		
(17)	$CDCl_3$	76.73	58.62(136.1)	49.32(141.9)	31.76(127.2)		21.68(127.0)
					32.55(127.0)		

[a] Ref. 2. [b] Possible assignment interchange. [c] Ref. 23. (?) Imprecise or unknown values.

lematical; however, the relative values of chemical shifts of methyl substituents in thiazolidines have been calculated with regard to the chemical shift of a methyl group in cyclopentane which is close to 21 ppm whereas its pseudoequatorial or pseudoaxial feature:

Methyl substituent on	Orientation	Effect[a]
(2)	Pseudoequatorial	$(\alpha_S)_e + (\alpha_N)_e = -0.7$
	Pseudoaxial	$(\alpha_S)_a + (\alpha_N)_a = +4$
(4)	Equatorial	$(\alpha_N)_e + (\beta_S)_e = +0.4$
	Axial	$(\alpha_N)_a + (\beta_S)_a = +0.3$
(5)	Pseudoequatorial	$(\alpha_S)_e + (\beta_N)_e = -3.6$
	Pseudoaxial	$(\alpha_S)_a + (\beta_N)_a = +2.4$

[a] − Is shielding, + is deshielding.

These results display the deshielding of 2- or 5-pseudoaxial methyl substituents with regard to their pseudoequatorial counterparts and the close values of the chemical shifts of 4-methyl substituents. Our data are in agreement with these calculations.

^{15}N *Chemical Shifts.*—Martin *et al.*[37] have reported the ^{15}N chemical shifts of (**1**), (**2**), (**3**), (**4**), (**15**), and (**16**). The ^{15}N chemical shift is subject to conformational factors tied to steric surroundings of the atom, to the position of the lone pair and to its interactions; the solvent plays an important part by its ability to create some bonds with the nitrogen atom and so to reduce its electronic potential. Studies on piperidines[38] and decahydroquinolines[39] have shown that the orientation of the lone pair has an effect upon the shifts of tertiary amines, but not upon the shifts of secondary amines (as for ^{1}H and ^{13}C NMR[33]). The ^{15}N shifts of *N*-unsubstituted thiazolidines are well correlated, where the N–H hydrogen is axial for nearly all the studied compounds, with the ^{13}C chemical shifts in the corresponding thiolanes, of the carbon located in the position corresponding to the nitrogen atom in thiazolidines (Figure) and so can be expressed by substituent parameters to the same degree as the ^{13}C shifts. We have tried to extract these substituent parameters from the structures established by ^{1}H and ^{13}C NMR spectroscopy:

Substituent	Increment
2e-Me	19.5
4e-Me	16.0
5e-Me	1.1
5a-Me	−6.5
gem-5	5.5

The effects of 2e-Me and 4e-Me are calculated by comparison of the shifts of (**14**) and (**6**), (**16**) and (**5**) respectively; 5e-Me, 5a-Me and *gem*-5 are extracted from (**10**), (**11**), and (**7**). These values are in agreement with the chemical shifts of (**8**) and (**13**). One can estimate the value of 2a-Me and 4a-Me close to 11 ppm and *gem*-2, *gem*-4 and *vic* 4e,5a slightly lower than the values of piperidines (−3 ppm).

Conclusions

^{1}H and ^{13}C NMR data have allowed us to establish the order of preference for the equatorial position of alkyl or aryl substituents: 4 > 2 > 5; in the latter, axial and equatorial positions are nearly equivalent. We have previously reported the structure of 2-phenylthiazolidine[40] the conformation of which in the solid state at 132 K is close to an envelope with N at the summit. So, in solution, other forms play a part in the structure of thiazolidines: examination of Dreiding models indicates that these conformations can be an envelope with C-4 at the summit and a half-chair with N and C-4 twisted out of the plane on opposite sides.

The N–H hydrogen is axial, for nearly all the studied thiazolidines and then n_N and $\sigma^*_{C\text{-}S}$ orbitals are in the synclinal position ideal for their overlapping: these compounds display stereoelectronic interactions related to the anomeric effect. This is corroborated by other data: larger values of ^1J(C-2,H-2) indicate stronger s-character of the hybrid orbital of C-2; in 2-phenyl thiazolidine, the (C-2,N) bond (1.454 Å) is shorter than the (C-4,N) one (1.472 Å) as (C-5,S) (1.827 Å) and (C-2,S) (1.882 Å) which display a strengthening of the (C-2,N) bond and a weakening of the (C-2,S) bond (Scheme 2).

Table 4. ^{13}C NMR data of 2,4-dimethylated derivatives, $\overbrace{XCH_2CH(CH_3)Y}^{CH_3}$.

X	Y	Isomer	C-2	C-4	C-5	Me-2	Me-4	Reference
CH_2	CH_2	*cis*	35.5	35.5	34.4	21.2	21.2	24
		trans	33.6	33.6	35.3	21.5	21.5	
O	CH_2	*cis*[a]	81.6	34.5	74.5		18.1	25
		trans[a]	80.2	33.4	76.0		18.0	
S	CH_2	*cis*	43.3	40.2	39.5	22.1	18.7	26
		trans	41.4	37.2	39.7	24.1	18.7	
N	CH_2	*cis*	55.3	35.2	54.7	22.1	20.2	27
		trans	53.7	33.9	55.7	22.2	19.7	
O	O	*cis*	101.5	72.9	71.0	20.2	18.8	25
		trans	100.6	71.9	71.7	20.2	18.5	
S	S	*cis*	48.6	51.6	45.4	24.2	20.4	21
		trans	47.7	49.8	46.0	25.6	20.2	
S	NH	*cis*	66.2	61.6	43.2	21.5	18.8	Opposite
		trans	64.6	58.8	42.7	24.3	19.0	to 22

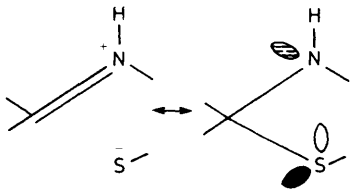
[a] 2-Ethylated derivative.

Table 5. ^{13}C Chemical shifts of methyl substituents in six-membered ring systems—parametrization test.

$\overbrace{CH_2(CH_2)_4X}$	δ Me-2e	δ Me-2a	δ Me-3e	δ Me-3a	$(\alpha_X)_e$	$(\alpha_X)_a$	$(\beta_X)_e$	$(\beta_X)_a$
Cyclohexane (X = CH_2)[28]	22.7	17.5	22.7	17.5				
Piperidine (X = N)[29]	23.0[a]	18.6[a]	20.1	17.0	+0.3	+11	−2.6	−0.5
Tetrahydropyran (X = O)[30]	21.7	16.9	17.9	16.6	−1.0	−0.6	−4.8	−0.9
Thiane (X = S)[31]	21.7	20.4	22.8	16.8	−1.0	+2.9	+0.1	−0.7

$\overbrace{X(CH_2)_3XCH_2}$		δ Me-2e	δ Me-2a	δ Me-4e	δ Me-4a	δ Me-5e	δ Me-5a
1,3-Dioxane (X = O)	Th	20.7	16.3	21.7	16.9	13.1	15.7
	Exp[32]	21.2	17.0	22.0	(?)	12.4	15.9
1,3-Dithiane (X = S)	Th	20.7	23.3	21.7	20.4	22.9	16.1
	Exp[32]	20.3	23.6	21.7	20.2	22.2	16.4

[a] Extracted from *trans*-2-methyldecahydroquinoline.[33] (?): unknown value.



Scheme 2.

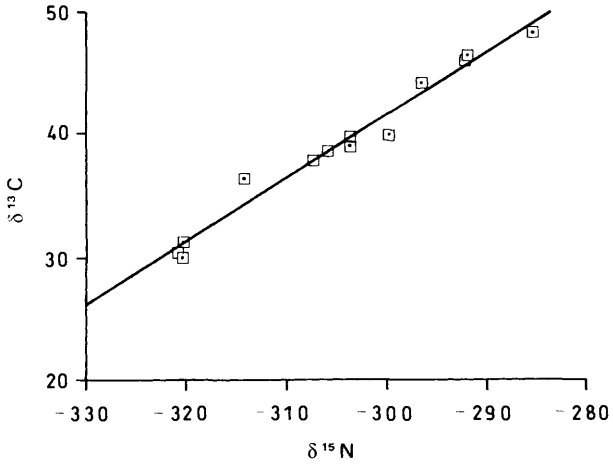


Figure. ^{13}C Thiolane = *f*(15 N thiazolidine).

Table 6. ^{15}N Chemical shifts of thiazolidines at 303 K (nitromethane scale).

	δ	δ–δ[compound (1)]	$^{13}C^{a}$
(1)	−320.5	0.0	31.2
(2)	−303.3	17.2	39.6
(3)	−306.1	14.4	38.6
(4)	−320.9	−0.4	30.4
(5)	−292.6	27.9	46.0
(6)	−296.8	23.7	44.2
(7)	−320.4	0.1	30.0
(8)	−285.6	34.9	48.3
(9)	−292.3	28.2	46.5
(10)	−299.9	20.6	39.9
(11)	−307.5	13.0	37.9
(12)	−303.8	16.7	39.0
(13)	−314.3	6.2	36.4
(14)	−277.3	43.2	unknown
(15)	−304.6	15.8	unknown
(16)	−279.6	43.9	unknown
(17)	−293.2	27.3	unknown

[a] Chemical shift in thiolane[26] of the carbon located in the position corresponding to the nitrogen atom in thiazolidine. [b] Value reported by Martin *et al.*[37]

Experimental

All the compounds have been previously described.[1,22,41–46] ^{1}H NMR spectra were performed on different Bruker spectrometers: WM 250, AM 400, AM 500, WM 360, WP 80, and WP 60; the products were examined in 5 mm tubes with tetramethylsilane as an internal reference; the (H-4,H-5) part of the spectra of 4- (or 5-) monosubstituted derivatives were analysed as an ABX system (with decoupling when necessary); in most cases, observation of the H-2 (or H-3) part of the low temperature spectra allows the evaluation of ^{3}J(HCNH). ^{13}C NMR spectra were recorded on a Bruker WP 80 (20.15 MHz, 10 mm tubes) or AM 400 instrument (100.614 MHz, 5 mm tubes) with standard pulse sequences. ^{15}N NMR spectra were recorded on a Bruker WP 80 spectrometer (8.12 MHz); the products were examined in the pure liquid state in 20 mm tubes with a concentric tube containing ^{15} N-enriched nitric acid in deuterium oxide, providing both the external reference and the field-frequency lock. The reference shift was calibrated by recording spectra of pure nitromethane and saturated aqueous ammonium nitrate. Chemical shifts are reported using the nitromethane scale.

References

1 J. L. Larice, Phys. Sc. Thesis, University of Marseille, 1972.
2 M. Guiliano, Phys. Sc. Thesis, University of Marseille, 1977.
3 V. Kulkarni and G. Govil, *J. Pharm. Sci.*, 1977, **66**, 483.
4 M. Maguet, Phys. Sc. Thesis, University of Brest, 1980.
5 G. Wilson and T. Bazzone, *J. Am. Chem. Soc.*, 1974, **96**, 1465.
6 M. Goodman and K. C. Su, *Biopolymers*, 1972, **11**, 1773.
7 J. Loscalzo, R. Kallen, and D. Voet, *Arch. Biochem. Biophys.*, 1973, **157**, 426.
8 F. Piriou, K. Lintner, H. Lam-Thanh, F. Toma, and S. Fermandjian, *Tetrahedron*, 1978, **34**, 553.
9 H. Booth and R. Lemieux, *Can. J. Chem.*, 1971, **49**, 777.
10 Y. Samitov, O. Danilova, B. Unkovsky, and I. Boiko, *Magn. Reson. Chem.*, 1986, **24**, 480.
11 J. Elguero and A. Fruchier, *An. Quim.*, 1974, **70**, 141.
12 R. Abraham and K. Pachler, *Mol. Phys.*, 1964, **7**, 165.
13 C. Haasnoot, F. De Leeuw, and C. Altona, *Tetrahedron*, 1980, **36**, 2783.
14 W. Colucci, S. Jungk, and R. Gandour, *Magn. Reson. Chem.*, 1985, **23**, 335.
15 L. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon Press, Oxford, 1969.
16 D. Danneels and M. Anteunis, *Org. Magn. Reson.*, 1974, **6**, 617.
17 M. Anteunis and D. Danneels, *Org. Magn. Reson.*, 1975, **7**, 345.
18 I. MacMillan and R. Stoodley, *Chem. Commun.*, 1968, 11.
19 S. Elz, M. Drager, H. J. Sattler, and W. Schunack, *Z. Naturforsch., Teil B*, 1987, **42**, 617.
20 E. Eliel and K. Pietrusiewicz, 'Topics in Carbon-13 NMR Spectroscopy,' vol. 3, Wiley, New York, 1979.
21 K. Pihlaja, M. Eskonmaa, R. Keskinen, A. Nikkila, and T. Nurmi, *Org. Magn. Reson.*, 1981, **17**, 246.
22 J. Llinares, Ing.-Doct. Thesis, University of Marseille, 1975; J. Llinares, R. Faure, and E. J. Vincent, *C.R. Seances Acad. Sci., Ser. C*, 1979, **289**, 133.
23 R. Faure, J. R. Llinas, E. J. Vincent, and J. L. Larice, *C.R. Acad. Sci., Ser. C*, 1974, **279**, 717.
24 M. Christl, H. Reich, and J. Roberts, *J. Am. Chem. Soc.*, 1971, **93**, 3463.
25 E. Eliel, V. Rao, and K. Pietrusiewicz, *Org. Magn. Reson.*, 1979, **12**, 461.
26 G. Barbarella and P. Dembech, *Org. Magn. Reson.*, 1980, **13**, 282.
27 D. Barbry and B. Hasiak, unpublished work.
28 R. Willer, unpublished work. See ref. 30.
29 E. Eliel, D. Kandasamy, C. Yen, and K. Hargrave, *J. Am. Chem. Soc.*, 1980, **102**, 3698.
30 E. Eliel, K. Hargrave, M. Pietrusiewicz, and M. Manoharan, *J. Am. Chem. Soc.*, 1982, **104**, 3635.
31 R. Willer and E. Eliel, *J. Am. Chem. Soc.*, 1977, **99**, 1925.
32 E. Eliel, V. Rao, and F. Riddell, *J. Am. Chem. Soc.*, 1976, **98**, 3583.
33 E. Eliel and F. Vierhapper, *J. Org. Chem.*, 1976, **41**, 199.
34 E. Eliel, W. Bailey, L. Kopp, R. Willer, D. Grant, R. Bertrand, K. Christensen, D. Dalling, M. Duch, E. Wenkert, F. Schell, and D. Cochran, *J. Am. Chem. Soc.*, 1975, **97**, 322.
35 H. Bejerbeck and J. Saunders, *Can. J. Chem.*, 1976, **54**, 2985.
36 H. Duddeck and M. Rabiul Islam, *Org. Magn. Reson.*, 1981, **16**, 32; 1983, **21**, 727.
37 G. Martin, M. Martin, and J. P. Gouesnard, '^{15}N NMR Spectroscopy,' Springer Verlag, Berlin, 1981.
38 R. Duthaler, K. Williamson, D. Giannini, W. Bearden, and J. Roberts, *J. Am. Chem. Soc.*, 1977, **99**, 8407.
39 F. Vierhapper, G. Furst, R. Lichter, S. Fanso-Free, and E. Eliel, *J. Am. Chem. Soc.*, 1981, **103**, 5629.

40 F. Baert, M. Muller, D. Barbry, and D. Couturier, *Acta Crystallogr., Sect. B*, 1987, **43**, 538.
41 E. Bergmann and A. Kaluszyner, *Recl. Trav. Chim. Pays-Bas*, 1959, **78**, 289.
42 I. Schmolka and P. Spoerri, *J. Am. Chem. Soc.*, 1957, **79**, 4716.
43 J. Piper and T. Johnston, *J. Org. Chem.*, 1964, **29**, 1657.
44 R. Malkina, *Radiobiol.*, 1984, **24**, 651.
45 D. Barbry and D. Couturier, *Chem. Ber.*, 1987, **120**, 1073.
46 D. Barbry, G. Ricart, and D. Couturier, *Org. Mass Spectrom.*, 1988, **23**, 493.

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