Ir and Pmr Spectra of 2-Aryl-4-thiazolidinones. III. Stereochemical Analysis of 2-Aryl-3-(2-pyridyl)-4-thiazolidinones

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The long-range coupling through the sulphur atom observed in a number of 2-aryl-3-(2-pyridyl)-4-thiazolidinones suggests that the C_2 proton and one of methylene protons are in a *cis* 1,3 diequatorial relationship. Some additional information concerning the preferred orientations of the substituents in this system are given from Eu(fod)$_3$, [tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)]europium, induced shift data.

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The conformational analysis of 2-aryl-4-thiazolidinones (1-2) was investigated after considering a series of 2-aryl-3-(2-pyridyl) derivatives (3-4), which possess activity against *Myc. tubercolosis, Str. pyogenes, St. aureus, Str. equi, Ed. typhi* and *E. coli* (5), in order to obtain further information concening their stereochemistry (6).

In previously investigated 3-arylidenamino derivatives (1), the restricted rotation about the N_3-N_{imine} linkage favoured an equilibrium between two conformers. In one of these conformers the azomethyne proton was intramolecularly H bonded with the 4-carbonyl group. The presence of such an equilibrium did not allow us to determine whether the thiazolidinone ring was involved in conformational equilibria independent of the 3-arylidenamino substituents. We believed that the ir and pmr spectral analysis of the title 3-pyridyl derivatives might enable us to obtain further information concerning the preferred conformation of the thiazolidinone ring system. Very few reports have appeared in the literature concerning the conformation of this ring system (7-8).In fact, the only available crystal data are relative to a 2-phenylimino derivative (7) with a planar structure unlike that of our compounds, which can be considered to have an envelope conformation, where the sulphur atom is the flap of the envelope (1). While awaiting the outstanding X-ray investigations, pmr spectroscopy appeared to be a valuable method to deduce the molecular stereochemistry of these molecules in solution. Further, the application of lanthanide shift reagents (LSR) on the pmr spectra could be of great interest, considering that the lanthanide induced shifts (LIS) are directly related to the lanthanide-substrate complex geometry, thus shedding some light on the substrate geometry.

Results and Discussion.

The ir spectra of the title compounds (Table I) show a single carbonyl absorption in the liquid phase (9). However, in the above mentioned 3-arylidenamino derivatives (1-2), such absorption underwent a clear-cut splitting, with the intensity being varied according to solvent polarity. In the pmr spectra, it was observed that apolar solvents, such as carbon tetrachloride, shifted the azomethyne proton averaged resonance to lower fields than the polar ones, *i.e.* trilfuoroacetic acid. Based on these findings, both carbon tetrachloride and trifluoroacetic acid (TFA) were used as solvents (Table I). The latter of these, which interacts with the 4-carbonyl group and also probably with the sulphur atom (10), might influence the thiazolidinone cyclic conformational equilibrium.

In both solvents the C_2 proton resonance signal appears as a slightly broad singlet. In carbon tetrachloride this signal, in the *ortho*-phenyl substituted derivatives, lies under the aromatic proton resonances; using TFA however, it undergoes a notable diamagnetic shift and becomes evident. The methylene protons resonate as a

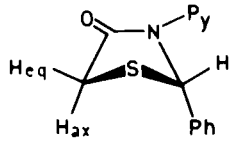

fig 1

clear AB system in carbon tetrachloride. The TFA interactions affect both the chemical shifts, which are shifted to lower fields, and the $\Delta \nu_{AB}/J_{AB}$ ratio, which becomes very small (up to 0.26), suggesting an apparent magnetic equivalence of H_{ax} and H_{eq} in this solvent. From these results it could be deduced that TFA affects the thiazolidinone nucleus conformational equilibrium; however one must observe the interesting feature which sheds light on the cyclic preferred conformation; the signals of the low field part of the S-CH_2 quartet are long-range coupled with the 2-H in all of the solvents used. Such coupling is clearly confirmed by decoupling techniques (Figure 2).

Long-range coupling is normally expected to occur between equatorially situated protons. It is known that the equatorial proton of a methylene group linked to a sulphur atom absorbs at higher field than the axial proton because of the C-S bond shielding properties (12).

However, in the compounds we prepared and in analogous compounds (13), the pseudoequatorial proton

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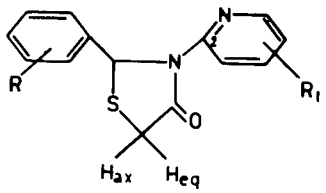
Table I

Ir and Pmr Spectral Data



Compound No.	R	R′	Ir (cm^{-1}) Carbon Tetrachloride	Pmr (δ) Carbon Tetrachloride (TFA)					
				Thiazolidinone		Pyridine (b)			
			ν C=O	5-H_{ax} (a)	5-H_{eq} (a)	2-H	6-H	3-H	CH_3
I	H	H	1707	3.62	3.87	6.73	8.13 d	8.23 d	
				(4.05)	(4.18)	(6.56)			
II	o-NO_2	H	1714	3.64	3.78	x	x	x	
				(4.05)	(4.22)	(7.30)			
III	o-CH_3	H	1705	3.61	3.83	x	8.10 d	8.35 d	2.45
				(4.04)	(4.21)	(6.70)			(2.53)
IV	o-Cl	H	1714	3.62	3.81	x	8.15 d	8.45 d	
				(4.08)	(4.22)	(6.86)			
V	m-Cl	H	1713	3.62	3.87	6.66	8.73 d	8.14 d	
				(4.10)	(4.22)	(6.53)			
VI	p-Cl	H	1713	3.63	3.84	6.66	8.05 d	8.15 d	
				(4.12)	(4.24)	(6.58)			
VII	o-Cl	CH_3(3)	1709	3.70	3.79	x	8.13 d		2.27
				(4.28)	(4.35)	(7.05)			(2.42)
VIII	o-Cl	CH_3(4)	1710	3.56	3.76	x	7.83 d	8.13 s	2.34
				(4.05)	(4.20)	(6.84)			(2.56)
IX	o-Cl	CH_3(5)	1707	3.58	3.78	x	7.88 s	8.21 d	2.20
				(4.06)	(4.20)	(6.83)			(2.53)
X	o-Cl	CH_3(6)	1712	3.57	3.77	x		8.00 d	2.22

(a) These protons appear as a quartet (J = *ca* 16 Hz) with further splitting, sometimes clearly discernable, with J = *ca* 1.5 Hz. (b) The resonances were attributed according to (11). (x) These resonances could not be unambigously assigned.

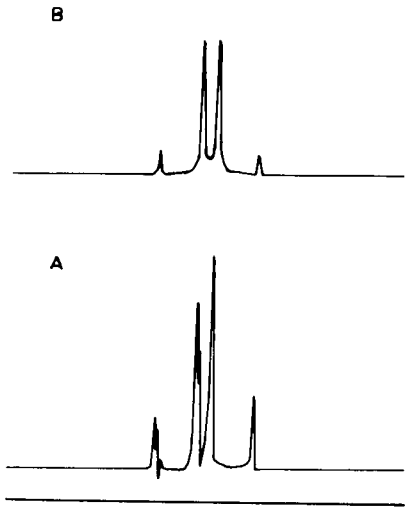


Figure 2. 5-CH_2 AB System of compound I before(A) and after(B) decoupling.

(H_{eq}) gives rise to low field signals, this demonstrating the above mentioned additional splitting of $J_{2,5}$ = about 1.5 Hz. The paramagnetic shift can be attributed to the deshielding effects of the carbonyl group, which in the envelope type conformation is nearly coplanar with H_{eq}, whereas the 2-phenyl group could contribute to shifting of the pseudoaxial proton (H_{ax}) to higher fields. It is known that a phenyl group prefers the equatorial orientation (14). From a molecular model examination in our case, however, such a conformation appears more sterically hindered due to the 3-pyridyl steric demands.

The pseudoaxial orientation, on the other hand, makes possible the arrangement between 2-H and 5-H_{eq} revealed by the above mentioned W long-range coupling through the sulphur atom. Therefore, the decrease of the $\Delta \nu_{AB}/J_{AB}$ ratio observed in TFA can be attributed to an accidental isochrony of the methylenic protons (15).

We determined to ascertain the five-membered ring preferential conformation and at the same time to gain ad-

Table II

Chemical Shifts (δ) in Deuteriochloroform, "Normalized" Chemical Shifts (δ_{ind}) under the Influence of Eu(fod)$_3$ and r in Å for Compounds I, III and VII

Compound No.		5-H$_{ax}$	5-H$_{eq}$	2-H	6-H(Py)	3-H(Py)	CH$_3$	6-H(Ph)
I	δ	3.79	4.03	6.93	8.21	8.25		(c)
	δ_{ind}	8.9	10.0	4.7	6.6	9.2		"
	r	4.2	3.8	6.9	6.0	4.1		"
III	δ	3.77	4.01	7.20 (a)	8.26	8.30	2.5	"
	δ_{ind}	9.1	10.0	4.3	4.8	9.9	1.8	"
	r	4.2	3.8	6.9	6.0	4.1	8.7 (b)	"
VII	δ	3.85	3.98	7.25 (a)	8.23		2.31	7.56
	δ_{ind}	9.1	10.0	4.7	3.0		5.7	1.6
	r	4.2	3.8	6.9	7.7		6.0 (b)	9.1

(a) These values are obtained by extrapolation of the LIS plots. (b) For the methyl group, r is taken as the distace from the lanthanide ion to the center of the circle of rotation of the methyl protons. (c) These resonances could not be unambigously assigned.

ditional information concerning the steric preferences of C_2 and N_3 substituents with the aid of the paramagnetic shift reagent Eu(fod)$_3$, [tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)] europium. We have submitted compound I to this analysis, no substituents, as well as III and VII with a methyl group on the 2-phenyl and 3-pyridyl groups respectively. The measurements were effected in deuteriochloroform as no relevant difference was observed between carbon tetrachloride and deuteriochloroform. The results which were obtained are listed in Table II, where the chemical shifts (δ) observed in the absence of the shift reagent, the induced shifts (δ_{ind}) after extrapolation to an equimolar ratio of Eu(fod)$_3$ to solute (L/S = 1) and normalized to a value of 10.0 for the most shifted signal, and the distances (r) from the lanthanide to the protons investigated, which are measured on the appropriate Drieding molecular models, are reported. The normalization procedure eliminates the need for a precisely defined experimental procedure (16) if the experimental conditions are kept as constant as possible, and the δ_{ind} values are measured in the linear region of the LIS curve. The Eu(fod)$_3$ induced shifts are supposed to be mainly of the pseudocontact type (17) and, according to the McConnell and Robertson (18) equation, are proportional to $(3\cos^2\chi - 1)/r^3$, where r is the corresponding Ld-H distance and χ is the angle between the principal magnetic axis of the complex and the vector of length r.

Our experimental results indicate that the lanthanide complexes with the carbonyl O atom lone pair; coordination to other basic centers of the molecule may be ruled out. In fact the LIS are linear at least up to a *ca* 0.30 LSR/substrate molar ratio (Figure 3).

In the ground state of the carbonyl group, the oxygen atom carries two lone pairs, which reside in diastereomeric

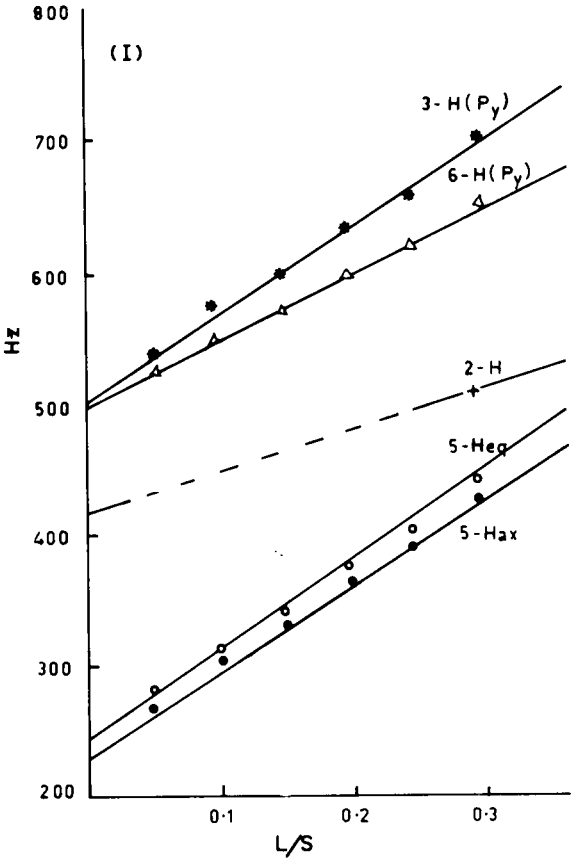


Figure 3. Lanthanide induced shifts of some signals of compounds I, III and VII, plotted against the molar ratios of Eu(fod)$_3$ to substrate (L/S).

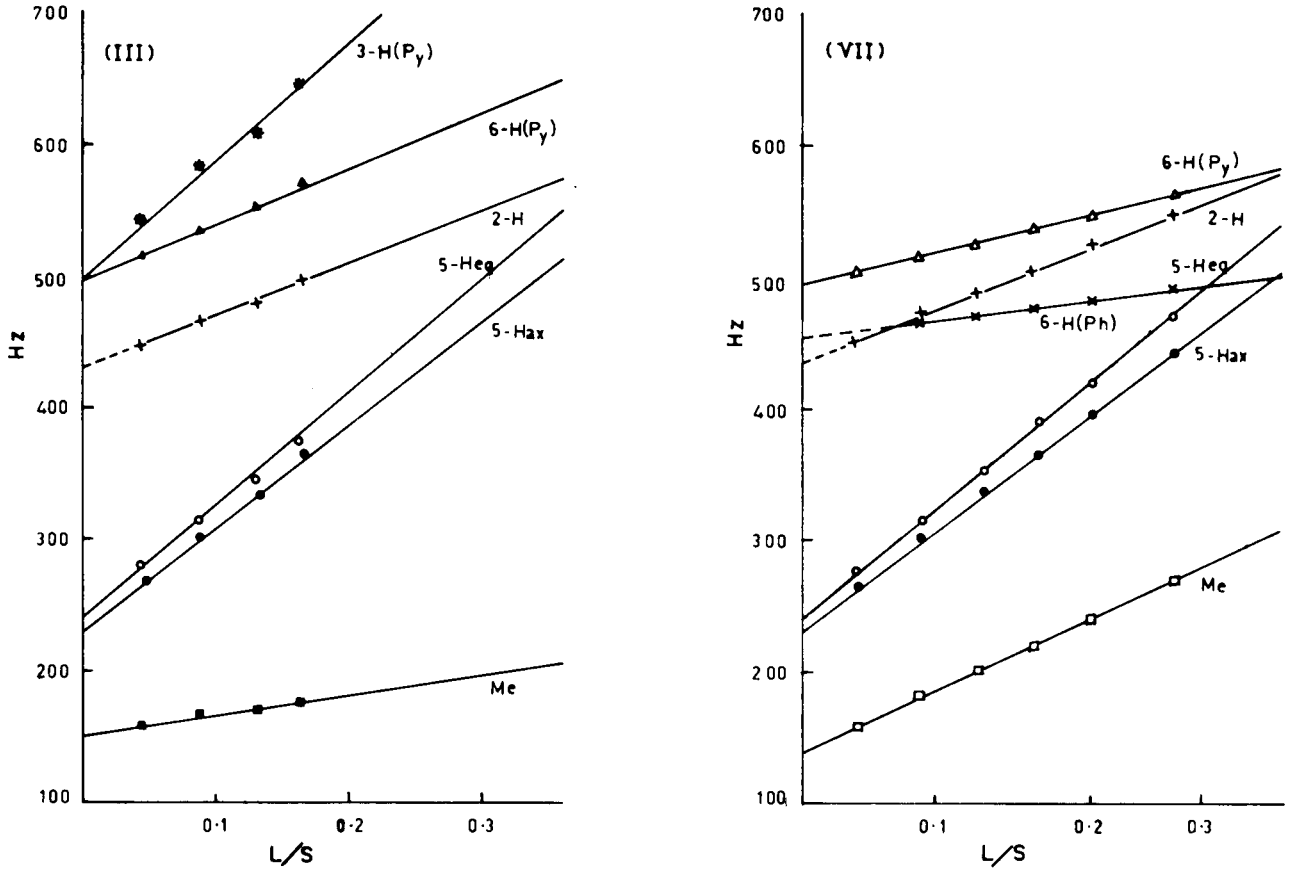


fig 3

environments. Consequently, two different complexation sites are, in principle, possible for the lanthanide ion (19). In relatively rigid molecules like the title compounds, these diastereomeric positions on the carbonyl plane are represented by value of $\varphi = 140°$ and 220°, respectively, where φ is the angle Eu-O-C_4 while the Eu-O internuclear distance is fixed at 3 Å, which is the most widely accepted value (Figure 4) (20-22). In our compounds, the best fit was

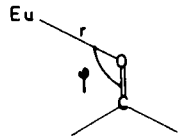


fig 4

obtained for $\varphi = 140°$ and for an Eu-O distance of 3 Å with the lanthanide situated in the direction opposed to the pyridine ring; this actually is the less sterically hindered diastereomeric site. The results, which show a considerable decrease in the isotropic shifts and an increase in the distance of the respective nuclei from the shift reagent (Table II), lead us to propose a preferred envelope type conformation for the thiazolidinone nucleus, with the sulphur atom being situated 0.6 Å out of the plane of the other four ring atoms and with 2-H and 5-H_{eq} in a *cis* 1-3 diequatorial relationship. These results confirm the preferred conformation already observed in the absence of Eu(fod)$_3$.

Further, only for this conformation does the plot of log δ_{ind} against log r give a straight-line, with a slope of about -2.5, suggesting that the distance parameter dominates the shift magnitude (23) and that the LIS can be analyzed ignoring angular dependencies (24).

It was possible, with the aid of Eu(fod)$_3$ to shed some light on the preferred orientation of the C_2 and N_3 substituents. In compound I the LIS evidence that the pyridine ring is free to rotate, seems to also be true for the phenyl ring. The increased steric hindrance owing to substituents on the phenyl or pyridine ring obviously reduces the freedom of rotation with respect to compound I. In compound III, the experimental data suggest that the pyridine ring can rotate freely, whereas the pseudoaxial phenyl ring assumes a preferential orientation where the plane C_{Ph}-C_2-N_3 and C_2-N_3-C_4 make a dihedral angle of about 90°; the methyl group is situated at an average distance of 8.7 Å from the lanthanide in the direction opposed to the

C_2-N_3 bond, and out of the cage-moiety. In compound VII the pyridine ring exhibits a preferential conformation where its plane is nearly perpendicular to the mean plane of the thiazolidinone ring, bisecting the C_5-S bond. In this compound the methyl group is *cis* to the sulphur atom. Also, the *o*-chloro substituted phenyl ring assumes a preferential conformation with the chlorine atom near 5-H_{ax} and with the 6-H (Ph) situated at an average distance of 9.1 Å from the lanthanide.

EXPERIMENTAL

The investigated compounds were synthesized according to the literature (3,4). Ir spectra were taken on a Perkin-Elmer Model 257 Spectrometer in Nujol mulls and in carbon tetrachloride solutions (0.05-0.1*M*). Pmr spectra were recorded on a Varian T-60A Spectrometer (60 MHz) from carbon tetrachloride and trifluoroacetic acid d_1 with tetramethylsilane as an internal standard; chemical shifts are in δ (ppm). Lanthanide induced shifts measurements were performed with Eu(fod)$_3$ at a probe temperature of 30-35° in solutions of *ca.* 0.3*M* in deuteriochloroform. Increasing quantities of Eu(fod)$_3$ were added stepwise from a stock solution up to a value of *ca.* 0.3 L/S ratio.

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