^{1}H Nuclear Magnetic Resonance Spectra of the Imidazo[2,1-*b*]thiazole System

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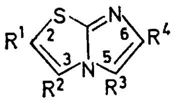
Some imidazo[2,1-*b*]thiazoles have been subjected to a ^{1}H n.m.r. investigation. The aromatic character of this ring system, in connection with proton shielding, has been tested with coupled Hartree–Fock calculations of ring current effects, and it seems that the main differences in the chemical shifts relative to the single ring heterocycles are due to this kind of perturbation. A long-range coupling constant over six bonds has also been observed which implies a coupling mechanism involving the sulphur atom.

THERE have been many reports of the chemical and spectroscopic properties of fused heterocyclic systems. Imidazo[1,2-*a*]pyridines [1,2] and imidazo[1,2-*a*]pyrimidines,[1,3,4] which have a bridgehead nitrogen atom, have been extensively examined both for their chemical and n.m.r. spectral properties. The reactivity and chemical properties of imidazo[2,1-*b*]thiazole (1), imidazo[2,1-*b*]benzothiazole, and their derivatives have already been elucidated.[5,6] In this system electrophilic substitution occurs at C-5 while no reaction is observed at C-2.[5,6]



(1) $R^1 = R^2 = R^3 = R^4 = H$
(2) $R^1 = R^2 = R^4 = H, R^3 = Me$
(3) $R^1 = R^2 = R^3 = H, R^4 = Me$
(4) $R^1 = R^2 = R^3 = H, R^4 = Ph$
(5) $R^1 = R^2 = R^3 = H, R^4 = Et$
(6) $R^1 = Me, R^2 = R^3 = H, R^4 = Ph$
(7) $R^1 = R^3 = H, R^2 = Me, R^4 = Ph$
(8) $R^1 = R^2 = H, R^3 = Me, R^4 = Ph$
(9) $R^1 = R^2 = H, R^3 = R^4 = Me$

This paper reports the n.m.r. spectra of imidazo[2,1-*b*]thiazole and some of its derivatives; furthermore, the n.m.r. parameters of this system are discussed in terms of spectroscopic analysis of its aromatic character according to the ring current model.[7]

RESULTS AND DISCUSSION

The ^{1}H n.m.r. spectra of compounds (1)—(9) were all easily analysable by direct inspection. For compounds (1)—(5), however, an iterative determination of the best parameters by means of the LAOCN 3 program [8] was performed. The probable error on computed chemical shifts and coupling constants never exceeded 0·02 Hz, while experimental error was probably restricted to within 0·2 Hz. Assignments of the resonances were made by analogy with substituted compounds of known structure. The results are shown in Table 1. Only in the case of 6-H was a slightly broad band observed, due probably to the presence of the nitrogen atom, which has a quadrupole moment. This effect appears to be produced by N-7 and not by N-4. This is probably due to the particular chemical environment of N-4, which acquires a more symmetrical character than N-7.

The methyl group always shows a coupling with the proton attached to the vicinal carbon atom which is higher than that observed in toluene but of a similar order of magnitude as that observed in methyl-substituted single-ring heterocycles. This should be related to the localization of π electrons being higher than in benzene derivatives. This kind of coupling is also present with the methylene protons of the 6-ethyl derivative (5).

A long-range coupling constant has also been observed between 2- and 6-H; this coupling, which extends over

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six bonds, has been detected even in the cases [9] of indolizine and azaindolizine with a magnitude of 0·5 Hz. The higher value found here is due to the presence of the sulphur atom and the most probable mechanism of this coupling involves an electronic interaction through this atom.

TABLE 1

Chemical shifts (δ) * and coupling constants * of imidazo-[2,1-*b*]thiazole derivatives recorded in 0·5M-deuteriochloroform solution

Compound	δ_{2-H}	δ_{3-H}	δ_{5-H}	δ_{6-H}	δ_{CH_3}	$J_{2.3}$/Hz	$J_{2.6}$/Hz	$J_{5.6}$/Hz	Other couplings	(Hz)
(1)	6·754	7·405	7·431	7·289		4·47	1·15	1·34		
(2)	6·736	7·208		6·974	2·340	4·49	1·10		$J_{CH_3.6-H}$	1·06
(3)	6·640	7·225	7·123		2·313	4·43			$J_{CH_3.5-H}$	1·00
(4)	6·651	7·236	7·600			4·50				
(5)	6·683	7·324	7·152		CH_3 1·259	4·41			$J_{CH_2.5-H}$	0·93
					CH_2 2·710					
									$J_{CH_3.CH_2}$	7·49
(6)		7·004	7·459		2·334				$J_{CH_3.3-H}$	1·41
(7)	6 245		7·482		2·253				$J_{CH_3,2-H}$	1·28
(8)	6·725	7·216			2·259	4·50				
(9)	6·623	7·119			2·228	4·47				

* The r.m.s. error on the parameters never exceeds 0·02 Hz whilst the experimental error is probably restricted to 0·2 Hz.

TABLE 2

Charge densities obtained from CNDO/2 and PPP methods and SCF ring current contributions for substituted imidazo[2,1-*b*]thiazoles

		CNDO q_C			CNDO	PPP	
Compound	Ring position	Total	σ	π	q_H	q_C	σ_{ring}
(1)	2	−0·0874	−0·0170	−0·0704	0·0458	−0·0620	1·619
	3	0·1246	0·0863	0·0383	0·0162	−0·0816	1·591
	5	0·0069	0·1179	−0·1110	0·0190	−0·1745	3·028
	6	0·0059	0·0811	−0·0752	0·0108	−0·0841	2·868
(2)	2	−0·0902			0·0444	−0·0626	1·524
	3	0·1271			0·0144	−0·0846	1·513
	6	−0·0238			0·0118	−0·1393	2·844
(3)	2	−0·0909			0·0449	−0·0701	1·638
	3	0·1262			0·0158	−0·0801	1·602
	5	−0·0150			0·0206	−0·2289	2·989

The proton chemical shifts of the compounds fall substantially in two distinct regions; that of 2-H is at higher field than those of 3-, 5-, and 6-H, which lie in the neighbourhood of nitrogen atoms. The lower values are for the protons near the bridgehead nitrogen atom, namely 3- and 5-H. Comparison with the parent heterocycles imidazole [10] and thiazole [10] shows that in the fused system the signals for 5- and 6-H appear at lower and those of 2- and 3-H at higher field than in the former compounds. This has been explained [1] for imidazo[1,2-*a*]pyridine by admitting a mutual ring current effect of the two rings which provide an upfield shift of the pyridine protons, due to the electron-rich imidazole ring, and a downfield shift of imidazole protons, caused by the more electron-deficient pyridine ring. In order to explain this ring current effect a planar structure for imidazo[1,2-*a*]pyridine has been postulated. Since this explanation is also likely to apply to the system studied here, we have tried to justify this assumption in a more quantitative fashion. Furthermore, we have tried to ascertain whether local diamagnetic contributions from electron densities on protons or carbon atoms and ring current effects are likely to be the only factors which determine the main differences in this fused system with respect to the parent one-ring compounds. Calculations of net charges on protons and on carbon atoms were performed by the CNDO/2 [11] and PPP [12] methods. Ring currents were calculated by the coupled Hartree–Fock perturbation theory [13] which we recently applied [14] to heterocyclic molecules. The parameter set employed in the latter calculation is that proposed by Shug [15] with the inclusion of sulphur parameters tested by us for substituted benzenes.[16] The net charges and ring current values, calculated for compounds (1)—(3), are reported in Table 2. Computations were carried out only on compounds with the smaller number of atoms in order to have a smaller number of second-order effects to take into account. In order to determine the quantities reported in Table 2 the recently reported [17] geometrical

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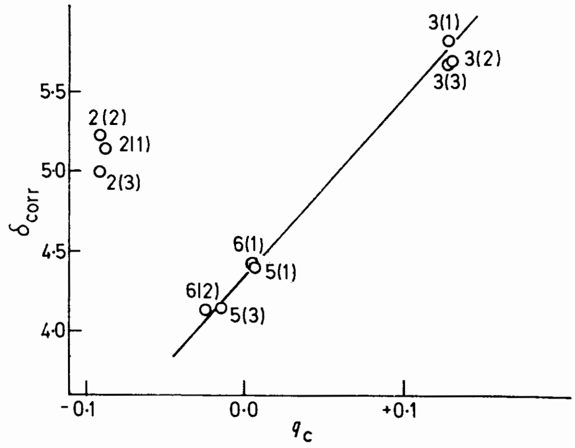
factors for the imidazo[2,1-*b*]thiazole ring were employed. The fused heterocyclic system proved to be planar within the limits of experimental error.[17]

Regarding the reactivity of this system, it is observed that CNDO/2 calculations provide the highest negative total net charge on C-2 and not on C-5, the latter being the only position in which electrophilic reactivity is observed. The trend of PPP net charges seems more realistic, since a more negative character is assigned to the imidazole ring, and C-5 is that bearing the highest negative charge, in agreement with the experimentally observed reactivity.[5,6] It should be borne in mind, however, that total charge densities, namely $\sigma + \pi$, are obtained from CNDO, while from PPP only the π contribution is evaluated; very probably the π charge better represents the reactivity of one position in a heteroaromatic ring. When the σ and π contributions are separated from the total charge given by CNDO, as reported in Table 2 for compound (1), the highest π negative character is assigned to C-5 by this method as well.



Plot of ^{1}H chemical shifts corrected for ring current contributions against total electron density on carbon given by CNDO/2 for imidazo[2,1-*b*]thiazole derivatives. Main numbering refers to the ring position; that in parentheses to the compound

None of the sets of net charges in Table 2 agrees with the trend of experimental chemical shifts. When chemical shifts are corrected for the ring current effect a proportionality is found only with the total charge density on carbon as given by the CNDO/2 method: 2-H, which lies near the sulphur atom, is not included in this proportionality as shown in the Figure, and the deviation is of the order of 1 p.p.m. Most probably the deviation is due to magnetic anisotropy effects caused by the sulphur atom, which should have a greater effect than nitrogen. If this effect is present it should also act on the proton chemical shifts of thiazole. In this context, if we consider the difference in chemical shift between protons of imidazo[2,1-*b*]thiazole and those in equivalent positions of thiazole and imidazole we should find the contribution of ring currents from one ring to the protons of the other in the fused system. These differences, which are reported in Table 3, can be compared with the corresponding differences in calculated ring current effects (the values for thiazole and imidazole are from ref. 7), $\Delta\sigma_{ring}$, and a proportionality is found between the two sets of values, $\Delta\sigma_{ring} \simeq 1{\cdot}5\Delta\delta$. Assuming that the ring current contribution given by the coupled technique is higher than the ' experimental ' value, and that for benzene a proportionality factor of *ca.* 1·6 is found,[18] we conclude that the major effect influencing the proton chemical shift of fused heterocyclic systems with respect to the individual single-ring heterocycles is due to the difference in ring current contributions.

TABLE 3

Differences in proton chemical shift ($\Delta\delta$) and in calculated ring current effect ($\Delta\sigma_{ring}$) between equivalent positions of imidazo[2,1-*b*]thiazole and those of thiazole and imidazole

Proton	$\Delta\delta$	$\Delta\sigma_{ring}$
2-H	−0·29	−0·09
3-H	−0·46	−0·20
5-H	0·30	0·86
6-H	0·13	0·55

Substituents at C-2 and -6 affect only the adjacent proton, the methyl group causing a shift to high field and the phenyl group to low field. When the methyl group is attached to C-5 3-H is also affected, and this should be due to steric interactions or field effects owing to the particular geometry of the molecule.

Finally, the vicinal coupling constants $J_{2,3}$ and $J_{5,6}$ deserve some comment. With respect to the parent heterocycles thiazole ($J_{4,5}$ 3·1 Hz)[19] and *N*-alkylimidazole ($J_{4,5}$ 1·4 Hz)[10] in the fused system, $J_{2,3}$ is increased while $J_{5,6}$ remains approximately the same. According to the interpretation of proton–proton coupling constants which, in an empirical fashion, seem to depend[20] both on the electronegativity of the neighbouring atoms and on the π bond order, it seems that in the case of the imidazo[2,1-*b*]thiazole a higher localization of π bond should be found between C-2 and -3. This is also in agreement with π bond orders which can be calculated by the PPP procedure ($p_{2,3}$ 0·8705, $p_{5,6}$ 0·6924) for compound (1) and shows that, with respect to thiazole ($p_{4,5}$ 0·7915), there is an increase of bond order, while a similar value is found in the case of *N*-alkylimidazole ($p_{4,5}$ 0·7017). The higher bond localization in rings containing sulphur atoms is in agreement with the lower aromatic character of these systems as predicted by the ring current model.[14]

EXPERIMENTAL

The spectra were recorded on a JEOL JNM–C60–HL spectrometer in the internal lock mode. Sample solutions were *ca.* 0·5M in deuteriochloroform and a small amount of tetramethylsilane was added as internal standard and lock signal.

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Materials.—Preparation and properties of 6-phenyl- (4), 2-methyl- (6), 3-methyl-6-phenyl- (7), and 5-methyl-6-phenyl- (8) imidazo[2,1-*b*]thiazoles have been previously reported.[5,6] New derivatives and modified procedures are described.

Imidazo[2,1-b]*thiazole* (1). A solution of 2-aminothiazole (4 g) in absolute ethanol (30 ml) was added with bromoacetaldehyde (4·9 g) and refluxed for 12 h on a steam-bath. The hydrobromide, m.p. 73 °C, separated on cooling, was collected, and dissolved in saturated aqueous Na_2CO_3. The solution was then saturated in the cold with KOH and extracted with chloroform. After drying and removal of the solvent, the residue was chromatographed in benzene on Al_2O_3, eluting with benzene–ethyl acetate (4 : 1) to give an oil, b.p. 103° at 2 mmHg; picrate, m.p. 206° (lit.,[21] b.p. 106° at 2 mmHg; picrate, m.p. 205°).

5-*Methylimidazo*[2,1-b]*thiazole* (2). 2-Aminothiazole (2 g) was added to α-bromopropanal (2·8 g) with cooling in an ice-bath, and the mixture was heated for 6 h on a steam-bath; the hydrobromide was worked-up as above. Removal of the solvent gave a solid residue which on crystallization from ligroin gave *needles*, m.p. 99—100° (Found: C, 52·0; H, 4·4; N, 20·2. $C_6H_6N_2S$ requires C, 52·15; H, 4·4; N, 20·3%).

6-*Methylimidazo*[2,1-b]*thiazole* (3). This was prepared from neat 2-aminothiazole (2 g) and bromoacetone (2·8 g), and was an oil, b.p. 100° at 2 mmHg; picrate, m.p. 205° (lit.,[22] b.p. 81—85° at 0·15 mmHg; picrate, m.p. 203—204°).

5,6-*Dimethylimidazo*[2,1-b]*thiazole* (9). This was prepared from neat 2-aminothiazole (2 g) and α-bromoethyl methyl ketone * (3 g), giving the hydrobromide, m.p. 195°. The free base was chromatographed on Al_2O_3 eluting with benzene–ethyl acetate (4 : 1) and crystallized from ligroin to give *needles*, m.p. 92° (Found: C, 55·18; H, 5·1; N, 18·0. $C_7H_8N_2S$ requires C, 55·25; H, 5·3; N, 18·35%).

6-*Ethylimidazo*[2,1-b]*thiazole* (5). 2-Aminothiazole (2 g) and bromomethyl ethyl ketone * were mixed in the cold; after 15 min absolute ethanol (10 ml) was added and the mixture was refluxed for 4 h to give an oil, b.p. 116° at 2 mmHg; picrate, m.p. 202° (Found: C, 55·1; H, 5·2; N, 18·2. $C_7H_8N_2S$ requires C, 55·25; H, 5·3; N, 18·35%).

[3/630 *Received*, 26th *March*, 1973]

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* The mixture of isomers of bromoethyl methyl ketone obtained by the method of Catch and his co-workers [23] was distilled on a 50 cm Vigreaux column. The fraction with b.p. 42° at 14 mmHg contained mainly α-bromoethyl methyl ketone and that with b.p. 50° at 14 mmHg mainly bromomethyl ethyl ketone.

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