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Molecular Modelling of the Isothiazolo[5,4-*b*]pyridin-3(2*H*)-one Derivatives

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Abstract: The performance of several semiempirical (MNDO, AM1, PM3, and SAM1) and *ab initio* (HF and MP2/6-31G*) methods for describing the structural and electronic features of a series of isothiazolopyridines, some of them bearing a hypervalent sulphur, is compared. Most of semiempirical methods calculate reasonable molecular structures, as compared with X-Ray structures, even in the case of *S*-oxides and *S,S*-dioxides. However, dipole moments are barely reproduced by these methods, even in the case of SAM1, which includes *d* orbitals. Hartree–Fock *ab initio* calculations do not lead to good dipole moment values in the case of *S,S*-dioxides. The agreement with experimental values is much better in the case of second order Møller–Plesset calculations, but this seems to be due to the systematic differences found between HF and MP2 values. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The 1,2-benzisothiazolin-3(2*H*)-one 1,1-dioxide system is the central nucleus of some pharmacological products as Supidimide[1] (CNS depressor), Ipsapirone[1] (anxiolytic) as well as in new candidates for proteolytic enzyme inhibitors[2]. Additionally, many 1,2-benzisothiazolin-3(2*H*)-one 1,1-dioxide derivatives present other interesting biological activities[3]. However the related isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxide system has still been studied very little[4-7], but analogs of saccharin[8] and ipsapirone[9] are already known.

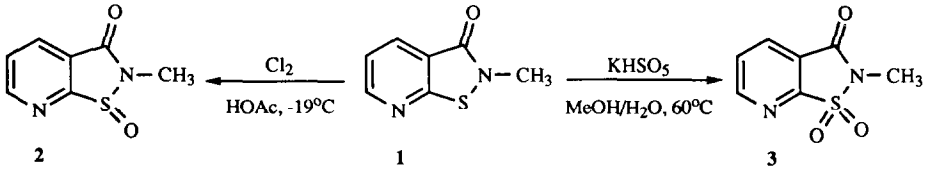
Molecular orbital calculations on these pyrido fused isothiazol-3(2*H*)-one derivatives are necessary to predict chemical reactivity, enzyme-substrate docking or quantitative structure-activity relationships. Previously, isothiazole and its 1,1-dioxide have only been studied using extended basis set (STO-3G*) *ab initio* molecular orbital theory methods and the results compared with X-ray data.[10] In this paper we report calculated and experimental geometric and electronic properties of a series of small isothiazolo[5,4-*b*]pyridin-3(2*H*)-one derivatives in their three different sulphur oxidation states. Calculations were carried out using semiempirical and *ab initio* (6-31G*) molecular orbital methods.

RESULTS AND DISCUSSION

Synthesis

2-Methylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**1**) was synthesised in a single step (83% yield) by reacting 2-chlorothio-3-pyridinecarbonyl chloride[11] with methylamine. 2-Methylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1-oxide (**2**) was quantitatively obtained by treating **1** with chlorine in aqueous acetic acid. On the other hand, the oxidation of **1** with potassium hydrogen persulphate ($KHSO_5$, commercially available as oxone®) at 60 °C in

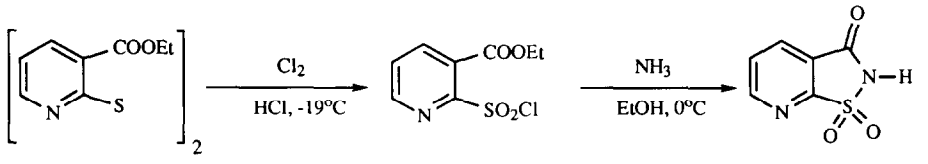
aqueous methanol gave 81% yield of 2-methylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxide (**3**) in a single step. No *C*-halogenation nor *N*-oxidation processes were detected under reaction conditions (Scheme 1).



2 **1** **3**

Scheme 1

Oxone®/MeOH, 3-chloroperoxybenzoic acid/CH_2Cl_2 or $KMnO_4$/AcOH applied on isothiazolo[5,4-*b*]pyridin-3(2*H*)-one[12] gave poor yields of isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxide (**4**). This compound was synthesised in 80% yield from 2,2'-dithiobis(ethyl 3-pyridinecarboxylate)[12] (**5**) following scheme 2. The treatment of **5** with chlorine in aqueous HCl yielded 88% of ethyl 2-chlorosulfonyl-3-pyridinecarboxylate (**6**). Subsequently, **6** reacted with 2N ammonia in ethanol to give **4** (91% yield).



5 **6** **4**

Scheme 2

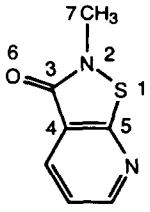
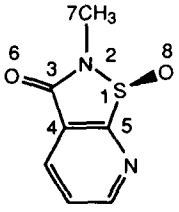
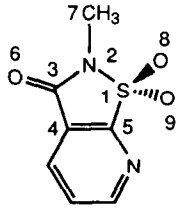
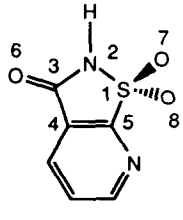
Theoretical Calculations

Several semiempirical (MNDO,[13] AM1,[14] PM3,[15] and SAM1[16]) and *ab initio* (Hartree–Fock, with a split valence 6-31G* basis set) methods have been used to optimise the molecular structures of compounds **1–4**. Some selected geometrical parameters are gathered in Table 1.

In order to compare the theoretical results with experimental ones, X-ray diffraction structures were determined for compounds **1** and **2**. In the case of compounds **3** and **4**, reported X-ray data of the saccharin[17] were used instead to assess the quality of the theoretical results. As can be seen in Table 1, in general, all calculated geometries are in good agreement with the known X-ray structures. Some discrepancies will be discussed below.

A deeper insight on the quality of the calculated geometries was carried out by means of two types of numerical analyses. The first one consisted of least squares fits forced to intercept thru (0.0) between experimental and calculated bond distances (Å) and bond angles (°). The second one is a least squares fit between the atomic Cartesian coordinates of the experimental and calculated structures (molecular fit in Table 2). The quality of the molecular fit was expressed as the root mean squares (RMS). In the case of compounds **1** and **2**, all ten heavy atoms of the isothiazolo[5,4-*b*]pyridin-3(2*H*)-one nucleus and the eleven heavy atoms of the isothiazolo[5,4-*b*]pyridin3(2*H*)-one 1-oxide were included in the fit. Whereas for compound **4** (structurally more similar to saccharin than compound **3**), only the eight heavy atoms of the isothiazol-3(2*H*)-one 1,1-dioxide moiety were superimposed those from the experimental structure of saccharin. The results of these analyses are gathered in Table 2.

Table 1. Representative bond distances (Å) and angles (degrees) of the isothiazole nucleus in compounds **1–4**.

Compound	Internal Coord.	MNDO	AM1	PM3	SAM1	6-31G*	X-ray[a]
 **1**	S1–N2	1.665	1.667	1.778	1.710	1.719	1.719
	N2–C3	1.424	1.403	1.451	1.414	1.365	1.364
	C3–C4	1.489	1.480	1.480	1.513	1.475	1.450
	C4–C5	1.429	1.429	1.412	1.450	1.382	1.396
	C5–S1	1.684	1.710	1.760	1.788	1.753	1.747
	N2–C7	1.460	1.422	1.470	1.437	1.448	1.452
	C3–O6	1.222	1.239	1.214	1.257	1.200	1.230
	C5–S1–N2	94.0	94.8	91.9	92.3	90.0	89.7
	S1–N2–C3	114.6	114.0	119.9	115.9	116.6	117.0
	N2–C3–C4	108.0	108.9	109.9	109.4	108.2	108.1
	C3–C4–C5	111.4	112.7	113.6	111.9	113.6	113.8
	C4–C5–S1	111.8	109.4	112.2	110.5	111.5	111.3
	S1–N2–C3–C7	177.0	−179.4	144.6	−179.3	179.9	−177.5
 **2**	S1–N2	1.705	1.682	1.789	1.732	1.707	1.704
	N2–C3	1.424	1.405	1.448	1.418	1.376	1.382
	C3–C4	1.496	1.491	1.488	1.519	1.483	1.475
	C4–C5	1.419	1.421	1.407	1.441	1.372	1.379
	C5–S1	1.756	1.766	1.821	1.880	1.798	1.807
	N2–C7	1.463	1.427	1.475	1.441	1.455	1.465
	C3–O6	1.221	1.237	1.213	1.252	1.192	1.213
	S1–O8	1.494	1.460	1.518	1.436	1.460	1.473
	C5–S1–N2	91.6	93.4	89.8	88.9	88.2	88.0
	S1–N2–C3	115.6	114.7	113.9	118.0	118.0	118.0
	N2–C3–C4	108.7	109.4	109.8	109.7	108.2	108.8
	C3–C4–C5	111.9	112.8	113.6	111.8	112.6	112.2
	C4–C5–S1	112.2	109.4	112.5	111.2	112.6	112.7
	O8–S1–N2	105.4	111.0	105.0	109.8	109.9	110.6
	S1–N2–C3–C7	171.0	171.7	153.6	−173.9	169.7	−176.7
	O8–S1–N2–C5	108.4	111.0	107.7	109.8	109.2	107.0
 **3**	S1–N2	1.709	1.671	1.784	1.726	1.673	1.663
	N2–C3	1.425	1.409	1.437	1.425	1.377	1.369
	C3–C4	1.496	1.493	1.493	1.520	1.487	1.474
	C4–C5	1.416	1.420	1.407	1.442	1.372	1.369
	C5–S1	1.772	1.741	1.806	1.872	1.779	1.758
	N2–C7	1.468	1.431	1.478	1.444	1.459	—
	C3–O6	1.219	1.233	1.213	1.284	1.189	1.214
	S1–O8(9)	1.517	1.389	1.430	1.433	1.424	1.429
	C5–S1–N2	92.3	93.0	89.2	89.6	91.5	92.2
	S1–N2–C3	114.8	115.0	115.3	117.7	116.2	115.0
	N2–C3–C4	109.2	108.6	109.0	109.7	108.8	109.6
	C3–C4–C5	112.7	112.0	113.4	111.9	113.3	112.9
	C4–C5–S1	111.0	110.7	113.2	111.0	110.2	110.0
	O8–S1–N2	108.7	111.0	108.9	110.8	109.4	109.0
	S1–N2–C3–C7	180.0	179.7	180.0	180.0	180.0	—
	O8(9)–S1–N2–C5	115.4	113.8	113.8	111.7	113.7	115.0
 **4**	S1–N2	1.692	1.659	1.772	1.702	1.672	1.663
	N2–C3	1.415	1.405	1.430	1.422	1.379	1.369
	C3–C4	1.497	1.493	1.492	1.520	1.487	1.474
	C4–C5	1.420	1.421	1.409	1.444	1.374	1.369
	C5–S1	1.777	1.744	1.809	1.878	1.783	1.758
	C3–O6	1.219	1.233	1.213	1.247	1.186	1.214
	S1–O8(9)	1.516	1.389	1.430	1.433	1.422	1.429
	C5–S1–N2	91.0	92.9	89.0	89.2	90.4	92.2
	S1–N2–C3	117.3	116.0	115.9	119.0	117.9	115.0
	N2–C3–C4	107.7	108.5	108.9	109.9	107.8	109.6
	C3–C4–C5	112.7	111.8	113.2	111.6	113.3	112.9
	C4–C5–S1	114.3	110.7	113.0	111.0	110.9	110.0
	O7–S1–N2	108.3	111.0	108.6	110.7	109.7	109.0
	O7(8)–S1–N2–C5	115.5	113.9	113.9	111.9	113.3	115.0

[a] X-ray data assigned to compounds **3** and **4** were extracted from saccharin (ref. 17).

As a general conclusion, the experimental (in the solid state) geometries are better approximated by the *ab initio* HF/6-31G* calculations. Not only are the slopes closest to one in regression analyses, but standard errors of the regressions (SE) and RMS of superimposed structures are the lowest. With regard to semiempirical methods, all give slopes reasonably close to one and similar SE for compounds **1** and **2**, although the RMS of the superimposed structures is always lower for MNDO and AM1 methods. In the case of compound **4**, AM1 behaves better than the rest, giving rise to good values of slope, standard error and RMS. As a conclusion, AM1 geometries are good alternatives to *ab initio* ones. Only in the case of compound **2**, MNDO performs slightly better than AM1.

The calculation of dihedral angles also deserves a comment. The rings of all three X-ray structures are almost planar. However, the PM3 method gave a notable pyramidalization of the isothiazole nitrogen atom in compounds **1** and **2** . Otherwise, *ab initio* HF/6-31G* and the rest of the semiempirical methods described as planar the isothiazole rings of compound **1** and 1,1-dioxides (**3** and **4**), whereas they gave a slight *N*-pyramidalization in the 1-oxide **2** (Table 1).

Table 2. Comparison between X-ray (d_X, α_X) and calculated geometries (d_i, α_i) for compounds **1**, **2** and **4**.

Compound	Method	Distances[a] ($d_X = m \cdot d_i$)		Angles[b] ($\alpha_X = m \cdot \alpha_i$)		Molecular fit
		slope (*m*)	SE	slope (*m*)	SE	RMS (Å)
	MNDO	0.994	0.040	1.001	1.9	0.050
	AM1	0.995	0.031	1.000	2.3	0.038
1	PM3	0.983	0.028	1.002	2.7	0.058
	SAM1	0.978	0.025	1.000	2.3	0.060
	HF/6-31G*	1.001	0.018	0.998	0.9	0.024
	MNDO	0.991	0.025	1.001	1.5	0.069
	AM1	0.996	0.023	0.999	2.5	0.083
2	PM3	0.982	0.026	1.001	2.5	0.104
	SAM1	0.980	0.027	0.999	2.6	0.103
	HF/6-31G*	1.005	0.009	0.998	0.9	0.052
	MNDO	0.970	0.036	0.997	1.0	0.070
	AM1	0.996	0.031	1.002	2.0	0.033
4	PM3	0.973	0.033	0.995	2.4	0.060
	SAM1	0.966	0.031	0.999	1.9	0.070
	HF/6-31G*	0.996	0.015	0.995	1.7	0.019

[a] CO, SO and all of the bond distances (Å) of the nucleus were used in the analyses. [b] NCO, NSO, OSO and all inner angles (°) of the nucleus were used in the analyses.

The calculated dipole moments of compounds **1**–**4**, as well as the corresponding experimental values (in dioxane solution) are gathered in Table 3. First, the full semiempirical values calculated using the same Hamiltonian for geometry optimisation and wavefunction calculation are given. Next, the *ab initio* HF/6-31G* values obtained through different geometries: 6-31G*//MNDO, 6-31G*//AM1, 6-31G*//PM3, 6-31G*//SAM1, and 6-31G*//6-31G* are given. In this way, the influence of both geometrical and electronic factors can be established by comparison between the different values calculated.

Table 3. Experimental and calculated dipole moments (in Debyes) of compounds **1–4**.

Compound	Wavefunction	Geometry					Exper.
		MNDO	AM1	PM3	SAM1	HF/6-31G*	
	MNDO	1.69					
	AM1		1.00				
1	PM3			1.61[a]			1.72
	SAM1				1.03		
	HF/6-31G*	1.58	1.55	1.79[b]	1.78	1.49	
	MP2/6-31G*					0.81	
	MNDO	4.33					
	AM1		3.15				
2	PM3			3.44[c]			4.05
	SAM1				2.94		
	HF/6-31G*	4.45	4.02	4.26[d]	4.33	3.96	
	MP2/6-31G*					3.26	
	MNDO	6.04				5.04	
	AM1		3.99			3.81	
3	PM3			4.10		4.09	4.43
	SAM1				3.89		
	HF/6-31G*	6.22	4.92	5.10	4.89	5.08	
	MP2/6-31G*					4.31	
	MNDO	6.49				5.29	
	AM1		4.33			4.04	
4	PM3			4.45		4.26	4.56
	SAM1				4.24		
	HF/6-31G*	6.93	5.43	5.75	5.41	5.54	
	MP2/6-31G*					4.76	

[a] 1.15 with a planar geometry. [b] 1.54 with a planar geometry. [c] 3.62 with a planar geometry. [d] 4.33 with a planar geometry.

In the case of compound **1**, most calculated dipole moments are in a good agreement with the experimental value. The only exception seems to be the low AM1 and SAM1 values (MP2 results will be discussed later). These values do not come, however, from particularly bad geometries. In fact, the 6-31G*//AM1, 6-31G*//SAM1 and the 6-31G*//6-31G* calculated dipole moments are similar, indicating that no dramatic changes in geometry affecting the charge distribution are produced. This was expected from the structural analysis described above (Table 2).

In conclusion, the AM1 and SAM1 Hamiltonians tend to underestimate the dipole moment of this compound. On the other hand, MNDO and PM3 calculations lead to reasonable values. However, as already mentioned, inspection of the calculated geometries reveals that in the case of PM3, the isothiazole nitrogen is piramidalized (dihedral angle $\approx 145^{o}$), unlike *ab initio* and X-ray results. If the planarity of this nitrogen is forced, the calculated dipole moment drops to 1.15 D, a value close to those of AM1 and SAM1. Thus, surprisingly,

MNDO is the only semiempirical method that gives simultaneously good descriptions of geometrical and electronic features of compound **1**, close to those determined by *ab initio* calculations.

In the case of compound **2**, AM1, PM3 and SAM1 methods lead to underestimated dipole moments, whereas the MNDO and 6-31G*//6-31G* calculations are in much better agreement with the experimental values. Again, this fact is not due to geometrical reasons (Table 1). Indeed, the 6-31G*//AM1 and 6-31G*//SAM1 values are closer to the 6-31G*//6-31G* value (and to the experimental one) than the 6-31G*//MNDO, which is somewhat high. In the case of the PM3 method, a pyramidalisation in the isothiazole nitrogen is observed (dihedral angle = 154°). However, in this case, forcing the planarity does not change very much the calculated dipole moment (from 3.44 to 3.62 D), which is probably due to the dominant effect of the S=O bond in the total dipole moment. Also the single points 6-31G*//PM3 give rise to similar values with both nonplanar and planar geometries (4.26 and 4.33 D, respectively). Again, the MNDO method seems to be the best one among the semiempirical methods for this compound, bearing a hypervalent S(IV) sulphur atom.

The situation is reversed in the case of compounds **3** and **4**. Here, the AM1, PM3 and SAM1 values seem to be the best ones, even better than the *ab initio* 6-31G*//6-31G* value. In this case, the PM3 geometry is fully planar. This agreement between experimental and calculated dipole moment, however, seems to be due to an artifact of these methods, which tends to underestimate the dipole moments of these compounds. This is shown by comparison of the AM1, PM3 and SAM1 values with the corresponding 6-31G*//AM1, 6-31G*//PM3 and 6-31G*//SAM1 ones. In all cases the calculated dipole moment increases by *ca.* 1 Debye giving rise to values virtually identical to the 6-31G*//6-31G* value. This also indicates that the AM1, PM3 and SAM1 geometries are close to the 6-31G* one (Table 1). In order to corroborate these hypotheses, AM1//6-31G* and PM3//6-31G* single point calculations were carried out. The calculated dipole moments are almost the same as the full semiempirical ones, which indicates that the wavefunctions and not the geometries are responsible for the low values obtained. On the other hand, the MNDO method displays the reverse behaviour. The calculated dipole moment is high with the MNDO geometry, with both the MNDO and the 6-31G* wavefunctions. However, the MNDO//6-31G* value is close to the 6-31G*//6-31G* one. In this case, the geometric differences seem to be responsible for the behaviour observed.

With regard to the Møller–Plesset correlation correction, the MP2/6-31G*//6-31G* calculations systematically reduce the dipole moment by *ca.* 0.7 D. This leads to a value close to the experimental one in the case of compounds **3** and **4** but to worse values in the case of compounds **1** and **2**. Thus, unlike the conclusion drawn in a recent work,[18] the MP2 results are not systematically better than the Hartree–Fock ones.

In summation, from a practical viewpoint, MNDO is the best semiempirical method for S(II) and S(IV) in this type of compounds, whereas HF/6-31G* is superior to MP2/6-31G*//6-31G* in these cases. On the other hand, the reverse is true for the S(VI) compounds: the correlation correction is necessary in order to approach the experimental value. In this case, the PM3 calculations lead to better values, although this is probably due to an artifact in the method. The use of semiempirical AM1 geometries together with *ab initio* wavefunctions constitute a valuable alternative to pure *ab initio* calculations for these rather complex systems.

EXPERIMENTAL

General

Melting points were determined in a Mettler FP82HT+FP80 apparatus and are uncorrected. Elemental analyses were obtained in a Carlo Erba EA1108 CHNS analyser from vacuum-dried samples (over phosphorus pentoxide at 3–4 mm Hg, 6–12 hours at about 30-70 °C). Infrared spectra were recorded on a Nicolet 510M FT-IR apparatus, using potassium bromide tablets for solid products and sodium chloride plates for liquid products; the frequencies are expressed in cm^{-1}. The ^{13}C-NMR spectra were obtained on a Varian Gemini 200 instrument (50 MHz) at 20 °C, with tetramethylsilane as the internal reference, at a concentration of about 0.1 g/ml and deuteriochloroform or dimethylsulphoxide-d_6 as solvent; the chemical shifts are reported in ppm from tetramethylsilane and are in δ units. Thin-layer chromatography (tlc) was carried out on silica gel (Schleicher & Schuell F1500/LS 254) with ethyl acetate:cyclohexane (2:1) as solvent and the plates were scanned under 254 and 366 nm ultraviolet light. Solvents were usually removed under vacuum, when stated, in a rotatory evaporator.

2-Chlorothio-3-pyridinecarbonyl chloride[11] and 2,2'-dithiobis(ethyl 3-pyridinecarboxylate)[12] were prepared according to previously described procedures.

Synthetic Procedures

• 2-Methylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**1**)

To a mixture of 2-chlorothio-3-pyridinecarbonyl chloride[11] (5.20 g, 25.0 mmol) in dioxane (20 ml), a solution of methylamine (2.33 g, 75.0 mmol) in water (60 ml) was dropwise added with stirring at 0 °C. After the addition was completed, stirring was continued at room temperature for a further 3 hours. After the addition of CH_2Cl_2 (150 ml), the organic layer was separated, washed with H_2O (2 x 30 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was recrystallized from 2-propanol to give **1** (3.44 g, 83%) as pale yellow needles. mp 130.5–131.5 °C (128–130 °C from isooctane/ethanol[12]); IR 1645 (CON) cm^{-1}; ^{13}C-NMR (50 MHz, $CDCl_3$): 30.1 ($\underline{C}H_3$), 118.7 (C_{3a}), 120.3 (C_5), 134.2 (C_4), 153.0 (C_6), 161.4 (C_{7a}), 163.3 (C_3). Anal. Calcd for $C_7H_6N_2OS$: C, 50.56; H, 3.65; N, 16.86; S, 19.30. Found: C, 50.32; H, 3.76; N, 16.71; S, 18.99.

• 2-Methylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1-oxide (**2**)

For 30 min. chlorine was passed through a stirred mixture of **1** (1.50 g, 9.0 mmol) in 8M acetic acid (50 ml) at -19 °C. The mixture was concentrated (25 ml) under vacuum and subsequently, 0.5M NaOH was added to bring pH 6. The resulting solid material was collected, dried and recrystallized in 2-propanol to give 1.41 g of **2**. An additional amount of **2** (0.19 g) was obtained by extraction of the aqueous filtrate with CH_2Cl_2 (3 x 50 ml). Overall yield 98%. mp 113–114 °C; IR 1714 (CON), 1106 (SO) cm^{-1}; ^{13}C-NMR (50 MHz, $CDCl_3$): 27.0 ($\underline{C}H_3$), 122.4 (C_{3a}), 127.1 (C_5), 134.2 (C_4), 154.5 (C_6), 163.9 (C_{7a}), 164.9 (C_3). Anal. Calcd for $C_7H_6N_2O_2S$: C, 46.14; H, 3.33; N, 15.38; S, 17.60. Found: C, 46.31; H, 3.37; N, 15.42; S, 17.89.

• 2-Methylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxide (**3**)

To a stirred mixture of **1** (1.50 g, 9.0 mmol) in 50% aqueous MeOH (30 ml) at 20 °C, oxone® (1.66 g, 27.0 mmol of $KHSO_5$) was added in small portions. Stirring was continued at 60 °C for a further 24 hours. When the reaction had been completed, 0.5M NaOH was added at 0 °C to bring pH to 7. The insoluble material was collected and recrystallized from 2-propanol to give 1.44 g (81%) of **3**. mp 140–142 °C; IR 1730 (CON), 1338,

1163 (SO_2) cm^{-1}; ^{13}C-NMR (50 MHz, $CDCl_3$): 23.3 ($\underline{C}H_3$), 122.4 (C_{3a}), 128.2 (C_5), 133.6 (C_4), 155.2 (C_6), 155.8, 156.6 (C_3, C_{7a}). Anal. Calcd for $C_7H_6N_2O_3S$: C, 42.41; H, 3.06; N, 14.14; S, 16.17. Found: C, 42.65; H, 3.13; N, 14.10; S, 16.46.

• Ethyl 2-chlorosulphonyl-3-pyridinecarboxylate (**6**)

For 30 min. chlorine was passed through a mixture of 2,2'-dithiobis(ethyl 3-pyridinecarboxylate)[12] (1.00 g, 2.75 mmol) in 17% aqueous HCl (50 ml) at -19 °C with stirring. The resulting white solid was collected, washed with cold water and dried to give 1.21 g (88%) of **6** which was utilised without further purification. Crude **6** gave correct CHNS elemental analysis but it slowly lost sulphur dioxide when it was dissolved in organic solvents at room temperature. mp 29.5–30.4 °C; IR 1730 (CON), 1370, 1184 (SO_2) cm^{-1}; ^{13}C-NMR (50 MHz, $CDCl_3$): 13.7, 63.3, 128.3, 128.5, 138.9, 150.6, 155.0, 164.0. Anal. Calcd for $C_8H_8ClNO_4S$: C, 38.47; H, 3.21; N, 5.61; S, 12.85. Found: C, 38.52; H, 3.05; N, 5.66; S, 12.67.

• Isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxide (**4**)

To a stirred solution of 2N ethanolic ammonia (30 ml) at 0 °C, freshly prepared solid **6** (1.00 g, 4.0 mmol) was added in small portions. Stirring was continued at 0 °C for 2 hours and at 20 °C for a further 5 hours. Solvents were removed in vacuum and the residual material was dispersed in 1M aqueous HCl (75 ml). The resulting solid material was collected, washed with cold water, dried and recrystallised from *n*-butanol to give 0.67 g (91%) of **4**. mp 195–196 °C; IR 1743 (CON), 1339, 1142 (SO_2) cm^{-1}; ^{13}C-NMR (50 MHz, DMSO-d_6): 123.2 (C_{3a}), 129.0 (C_5), 134.4 (C_4), 155.5 (C_6), 157.3 (C_{7a}), 159.5 (C_3). Anal. Calcd for $C_6H_4N_2O_3S$: C, 39.12; H, 2.19; N, 15.21; S, 17.41. Found: C, 39.28; H, 2.08; N, 15.27; S, 17.19.

X-ray Data

• 2-Methylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**1**)

$C_7H_6N_2OS$. Mt=166.20, monoclinic, space group $P2_1/c$, a=7.782(1) Å, b=12.185(2) Å, c=7.412(2) Å, β=90.79(1)°, V=702.7 $Å^3$, Z=4, Calcd. density=1.572 $g \cdot cm^{-3}$, Cu Kα radiation, λ=1.54178 Å, μ=34.4 cm^{-1}, F(000)=324. The structure was determined by direct methods and refined by full-matrix least squares analysis using 921 with $F_o > 3.0\ \sigma(F_o)$ from 1328 independent reflections measured at 293(1) °K with a Enraf-Nonius CAD-4 diffractometer, final R1=0.066 and wR2=0.091.

• 2-Methylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1-oxide (**2**)

$C_7H_6N_2O_2S$. Mt=182.20, monoclinic, space group $P2_1/c$, a=7.730(1) Å, b=11.611(5) Å, c=9.186(2) Å, β=110.80(1)°, V=770.8 $Å^3$, Z=4, Calcd. density=1.570 $g \cdot cm^{-3}$, Cu Kα radiation, λ=1.54184 Å, μ=33.4 cm^{-1}, F(000)=376. The structure was determined by direct methods and refined by full-matrix least squares analysis using 1291 with $F_o > 3.0\ \sigma(F_o)$ from 1452 independent reflections measured at 296(1) °K with a Enraf-Nonius CAD-4 diffractometer, final R1=0.042 and wR2=0.046.

Dipole Moment Measurements

Dipole Moments were measured in dioxane at 25 °C. The Debye formula was used following Halverstadt and Kumler extrapolation method[19] for calculation of total polarisation, with $\alpha = \left(\frac{d\varepsilon}{d\omega_2}\right)_{\omega_2 \to 0}$, $\beta = \left(\frac{dv}{d\omega_2}\right)_{\omega_2 \to 0}$ and $0.0001 < \omega_2 < 0.0500$ and where ε is the dielectric constant, ω_2 the massic fraction of the sample and v the massic volume. Electronic polarisation can be replaced by molecular refraction R_{MD}. Experimental data are collected in Table 4.

Table 4: Experimental dipole moments μ (in Debyes) measured in dioxane

Compd.	α	β	R_{MD}	$P_{2\infty}$	μ
1	2.31	≈ 0	40.29	100.46	1.72
2	11.95	≈ 0	42.41	378.50	4.05
3	13.01	≈ 0	44.53	446.24	4.43
4	14.86	≈ 0	39.88	464.49	4.56

Computational Procedures

Semiempirical calculations were carried out with the MOPAC 6.0[20] and AMPAC 5.0[21] packages, using the MNDO,[13] AM1,[14] PM3,[15] and SAM1[16] Hamiltonians. Full geometrical optimisations were performed in all cases by means of the BFGS algorithm as implemented in the above-mentioned programs.

Ab initio calculations were performed with the GAUSSIAN 94 package,[22] using the 6-31G* basis set. Full geometrical optimisations were carried out at this level of theory by means of Schlegel's algorithm, and then some single point calculations were performed within the second-order Møller-Plesset perturbation theory. Additionally, some HF/6-31G* single points were also carried out using the semiempirical geometries.

The data processing was done on a SGI PowerIndigo2 workstation.

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REFERENCES AND NOTES

1. Craig, P. N. *In* Comprehensive Medicinal Chemistry: Drug Compendium. Vol. 6. *Edited by* C. Hansch, Pergamon Press, Oxford, **1990**, pp. 237 - 965.
2. Hlasta, D. J.; Desai, R. C.; Subramanyam, C.; Lodge, E. P.; Dunlap, R. P.; Boaz, N. W.; Mura, A. J.; Latimer, L. *Eur. Pat. Appl.* EP 542372 (**1993**). *Chem. Abstr.* **1994,** *120*, 191707. Hlasta, D. J.; Desai, R. C.; Subramanyam, C.; Court, J. J.; Bell, M. R.; Kumar, V.; Dunlap, R. P.; Latimer, L. *Eur. Pat. Appl.* EP 550511 (**1993**). Chem. Abstr. **1994,** *120*, 106989.
3. Davis, M. *In* Advances in Heterocyclic Chemistry: Recent Advances in the Chemistry of Benzisothiazoles and Other Policyclic Isothiazoles. Vol. 38. *Edited by* A. R. Katrizky, Academic Press, Inc., London, **1985**, pp.105 - 133.
4. Schaper, V. *Synthesis* **1985,** 861.

5. Zawisza, T.; Malinka, W. *Il Farmaco Ed. Sci.* **1986,** *41,* 676.
6. Krauze, A.; Rumler, A.; Hagen, F.; Jansch, I.; Sturm, I.; Dubur, G. *Khim. Geterotsikl. Soedin.* **1992,** 75. *Chem. Abstr.* **1993,** *118,* 233839.
7. Martinez-Merino, V.; Gil, M.J.; Zabalza, J.M.; Gonzalez, A. *Heterocycles* **1995,** *41,* 2737.
8. Chiang, G.C.S. US 5,043,181 (**1991**). *Chem. Abstr.* **1992,** *116,* 40104.
9. Malinka, W. *Acta Pol. Pharm.* **1991**, *48*, 19. *Chem. Abstr.* **1993,** *118,* 80890.
10. Rozas, I. *J. Phys. Org. Chem.* **1992**, *5*, 74.
11. Martinez-Merino, V.; Gil, M.J.; Gonzalez, A.; Zabalza, J.M.; Navarro, J.; Mañu, M.A. *Heterocycles* **1994,** *38,* 333.
12. Monge, A.; Martinez-Merino, V.; Fernandez-Alvarez, E. *J. Heterocyclic Chem.* **1988,** *25,* 23.
13. Dewar, M. J. S.; Thiel, W. H. *J. Am. Chem. Soc.* **1977,** *99,* 4917.
14. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985,** *107,* 3902.
15. Stewart, J. J. P. *J. Comput. Chem.* **1989,** *10,* 209 and 221.
16. Dewar, M. J. S.; Jie, C.; Yu, J. *Tetrahedron*, **1993,** *49,* 5003.
17. Okaya,Y. *Acta Crystallogr. Sect. B*, **1969,** *25,* 2257.
18. Alkorta, I. *Theor. Chim. Acta* **1994,** *89,* 1.
19. Halverstadt, I. F.; Kumler, D. *J. Amer. Chem.Soc.* **1942,** *64,* 2988.
20. Stewart, J. J. P. MOPAC 6.0, *QCPE 455* (**1990**).
21. AMPAC 5.0, 30 days demostration version, Semichem, Inc. (**1995**).
22. GAUSSIAN 94 (SGI-Revision C.3), Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andrés, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.;Head-Gordon, M.; González, C.; Pople, J. A. Gaussian, Inc., Pittsburgh PA **1995**.

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