The Methylation, Oxidation and Crystallographic Characterization of Imidazole Derivatives

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Compounds **2**, **3** and **4** were synthesized and the crystal and molecular structures of **1** and **4** were determined. An hptlc technique for studying the methylation rate of **1** and the oxidation rate of **2** was applied.

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Imidazole derivatives are an important class of heterocyclic compounds which exhibit antihistaminic [1], antibacterial [2], and antiprotozoal activity [3].

The aim of this study was to investigate the methylation rate of 1,3-dihydro-1-methylimidazole-2-thione (**1**) (metimazole®), and the oxidation rate of 1-methyl-2-methylthioimidazole (**2**), and to determine the crystallographic parameters of **1** and 1-methyl-2-methylsulphonylimidazole (**4**).

For this purpose, we prepared **2** by methylating **1** with methyl iodide and **4** by oxidating **2** with hydrogen peroxide (Scheme 1). During the oxidation reaction, the intermediates 1-methyl-2-methylsulphinylimidazole (**3**) and **4** were separated out by medium-pressure liquid chromatography (mplc).

The methylation reaction of **1** to **2**, at different concentrations of the starting product **1**, and the oxidation reaction of **2** to **3** and **4**, at different temperatures and with different amounts of hydrogen peroxide, were monitored by means of a high-performance thin-layer chromatographic (hptlc) technique. The identity of the compounds obtained was verified on the basis of their R_f values and by means of a computerized identity check whereby their uv spectra, obtained by scanning the hptlc plate, were compared with standard spectra.

The results indicate that, at high concentrations of **1** (Figure 1), the methylation reaction is over only after 5'; the oxidation reactions of **2** to **3** with 2 or 4 equivalents of hydrogen peroxide (Figures 2-3), both at 50° and 90°, take place immediately, but **4** occurs only at 90°.

Description of Crystal Structures of 1 and 4.

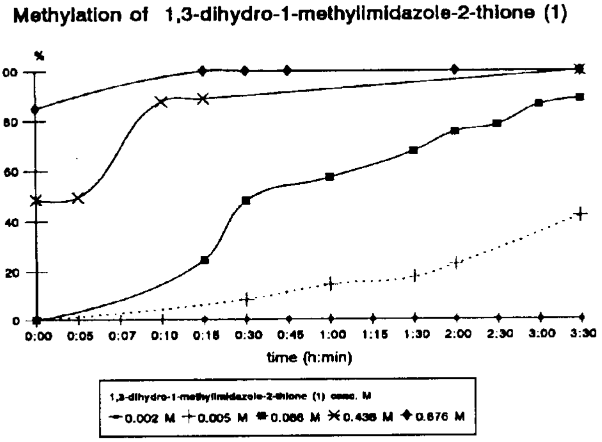


Figure 1: Methylation rate graph.

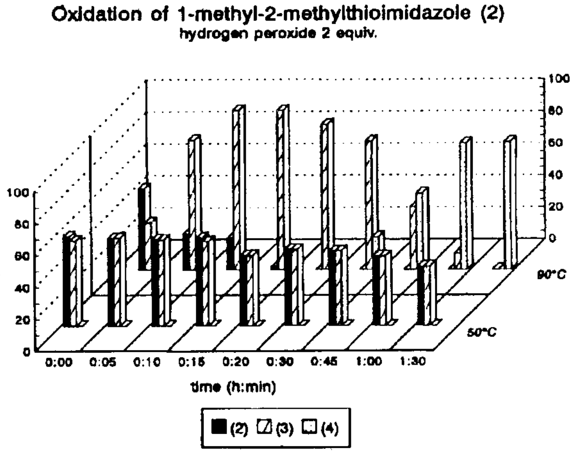
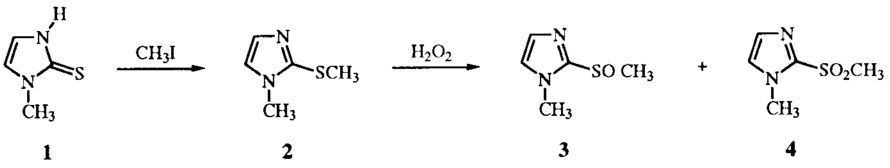


Figure 2: Oxidation rate graph at 2 equivalents of hydrogen peroxide.

Scheme 1



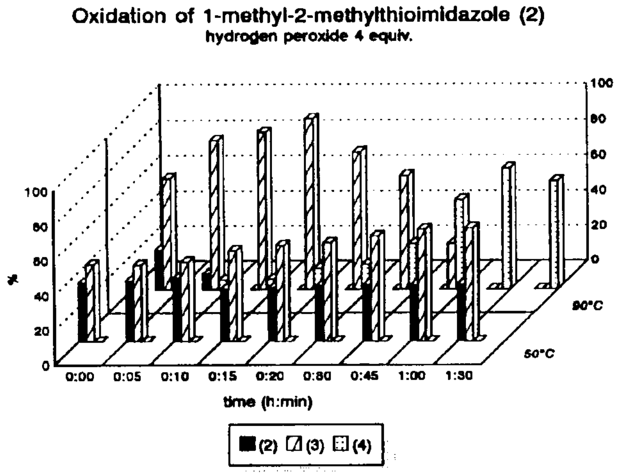


Figure 3: Oxidation rate graphic at 4 equivalents of hydrogen peroxide.

The unit cell of compound **1** contains two crystallographically-independent molecules linked as hydrogen-bonded pairs by two N-H·····S interactions (Figure 4). Both molecules are affected by the same type of statistical disorder due to two alternative orientations of their methyl groups, which differ by a rotation of about 60° around the N(1)-C(6) bonds.

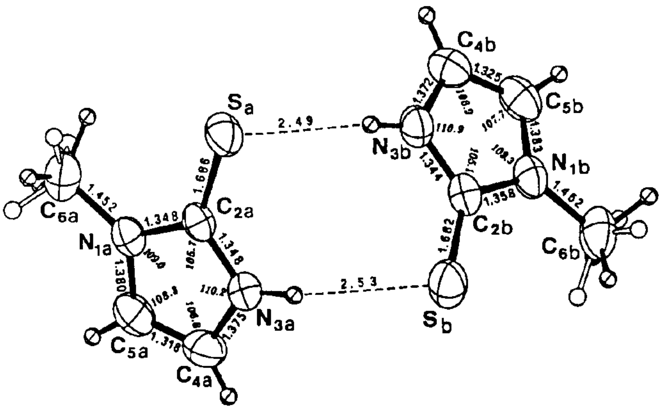


Figure 4: ORTEP [13] drawing showing atom numbering scheme, thermal motion ellipsoids (40%), interatomic distances (Å), and ring bond angles (°) for compound **1**.

The extent of the disorder (occupancy factors of 0.53(2) and 0.47(2) for major and minor sites, respectively) is the same for both the independent molecules.

There are no significant differences between corresponding values of bond lengths and bond angles in the two molecules (Table 1). The largest differences are 0.010 Å for bond distances, and 0.7° in bond angles. Furthermore, these values compare very well with those reported for a closely-related derivative like the 1,3-dimethylimidazole-2(3*H*)-thione (DMIT) [5]. In particular, our C-S bond lengths of 1.686(2) and 1.682(2) Å are close to that of 1.696(5) found in DMIT [4], and of 1.693(13) and 1.699(16) Å reported for **3** bonded to a Co (II) ion [5]. Comparison between the dimensions of our imidazole rings and those found in the neutron study of imidazole at 103 K [6] shows some relevant differences involving either bond lengths or bond angles. The C(4)-C(5) bond distances of 1.318(4) and 1.325(4) Å observed in compound **1** are considerably shorter than that of 1.368(1) found in imidazole [6].

Table 1

Bond Distances (Å) and Bond Angles (deg)

	Compound 1		Compound 4
Bonds	Molecule a	Molecule b	
N(1)-C(2)	1.348(3)	1.358(3)	1.355(3)
N(1)-C(5)	1.380(3)	1.383(3)	1.360(3)
N(1)-C(6)	1.452(3)	1.452(4)	1.466(3)
C(2)-N(3)	1.348(2)	1.344(3)	1.328(3)
C(2)-S	1.686(2)	1.682(2)	1.747(2)
N(3)-C(4)	1.375(3)	1.372(3)	1.367(3)
C(4)-C(5)	1.318(4)	1.325(4)	1.345(3)
S-O(1)	—	—	1.428(2)
S-O(2)	—	—	1.433(2)
S-C(7)	—	—	1.751(3)
C(2)-N(1)-C(5)	109.0(2)	109.3(2)	106.1(2)
C(2)-N(1)-C(6)	124.7(2)	124.5(2)	129.4(2)
C(5)-N(1)-C(6)	126.2(2)	126.2(3)	124.5(2)
N(3)-C(2)-N(1)	105.7(2)	105.1(2)	112.3(2)
N(1)-C(2)-S	126.8(1)	127.0(2)	125.8(2)
N(3)-C(2)-S	127.5(2)	127.8(2)	121.5(2)
C(2)-N(3)-C(4)	110.2(2)	110.9(2)	103.8(2)
C(5)-C(4)-N(3)	106.8(2)	106.9(2)	111.1(2)
C(4)-C(5)-N(1)	108.3(2)	107.7(2)	106.7(2)
O(1)-S-C(2)	—	—	108.8(1)
O(2)-S-C(2)	—	—	107.1(1)
O(2)-S-O(1)	—	—	118.7(1)
C(7)-S-C(2)	—	—	103.9(1)
C(7)-S-O(1)	—	—	108.6(1)
C(7)-S-O(2)	—	—	108.7(1)

It is interesting to note that a more localized double bond between these atoms is also present in DMIT, where the corresponding bond length is 1.325 Å. The extended exocyclic conjugation, which involves the sulfur atom of **1**, appears to affect mainly the ring bond angles. With respect to the imidazole molecule [6], we observe relevant closing of the ring angle at C(2) (from 111.9 (1)° [6] to 105.7 (2)° and 105.1 (2)°) and opening of the adjacent ring angles at N atoms (about 2° at N(1) and 5° at N(3)). Bond angles of DMIT show the same trend [4]. A common feature of imidazole derivatives, also observed in our case, is that the five-ring atoms are closely coplanar, with maximum deviations from least-squares mean planes within ±0.004 Å (Table 9).

The two crystallographically independent molecules of **1** interact through two N-H·····S hydrogen bonding contacts (Table 2) to form dimeric units. Their mean planes make a dihedral angle of 76.7°. No short van der Waals contacts are present in the crystal packing (Figure 6) of these dimeric units.

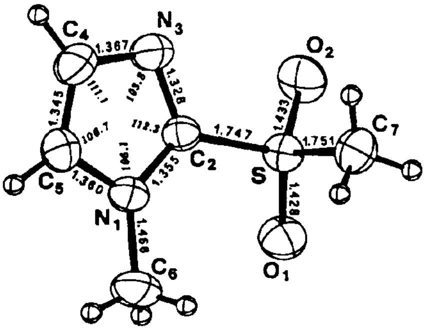


Figure 5: Atom-numbering scheme, thermal ellipsoids (40%), bond distances (Å), and ring bond angles (°) for compound **4**.

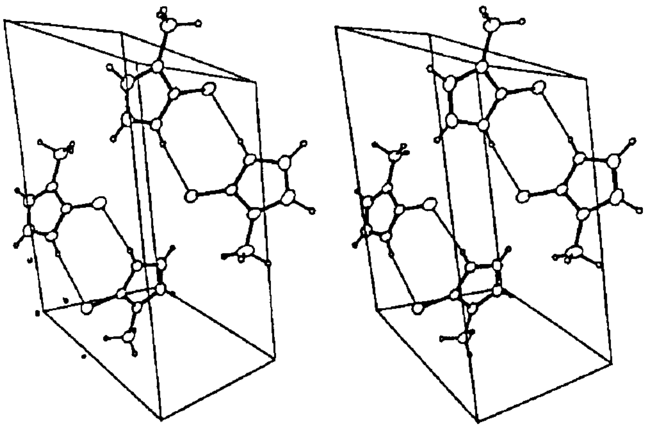


Figure 6: Stereoview of the molecular packing of compound **1**. Still lines represent hydrogen bonds.

Table 2

Hydrogen Bonding Interactions

Atoms 1 2 3	1·····3	1—2	2·····3	∠1-2·····3
Compound **1**				
N(3a)-H(N3a)·····S(b^i)	3.370(2)	0.86(3)	2.53(3)	167(2)
N(3b)-H(N3b)·····S(a^i)	3.324(2)	0.85(3)	2.49(2)	167(2)
Compound **4**				
C(7)—H(7b)·····O(1^{ii})	3.278(3)	0.98(3)	2.38(3)	153(2)

i) Symmetry transformation 1-x, 1-y, 1-z of the reference coordinates.
ii) Symmetry transformation -0.5+x, y, 1.5-z of the references coordinates.

The crystals of **4** are built up of one crystallographically-independent molecule, whose bond distances and angles are reported in Table 1, the atoms being labelled as shown in Figure 5. Comparison of the dimensions of the imidazole moiety with those of the unsubstituted imidazole [6] shows only small, perhaps not significant, differences. The exocyclic C(2)-S bond length of 1.747(2) Å is only slightly less than the mean value of 1.763 Å, retrieved from the Cambridge Crystallographic Database for this type of bond [7]. The absence of exocyclic conjugation is consistent with the "normal" bond distances and angles observed in the imidazole ring. The atoms of the imidazole moiety are coplanar within ±0.004 Å, and the S atom is significantly displaced (0.153 Å) from their mean plane (Table 13). The orientation of the methylsulphonyl group with respect to the imidazole ring may be defined by means of the N(1)- or N(3)-C(2)-S-C(7) torsion angles (Table 12). Their values, both fairly close to ±90°, show that the plane which contains the C(2), S, and C(7) atoms is almost perpendicular to the imidazole ring.

The most interesting result of the structural determination of compound **4** is perhaps the crystal packing of its molecules. These are tied onto linear chains, which parallel the *a* cell axis through one quite rare C-H·····O hydrogen bond interaction involving methyl carbons and sulphonic oxygens (see Table 1 and Figure 7). The interatomic separations and the subtented angle are consistent with the values reported by Taylor and Kennard for this type of hydrogen bonding [8]. Further contributions to the crystal packing arise from many short (less than 3.60 Å) van der Waals contacts involving C, N, or O atoms (Table 14).

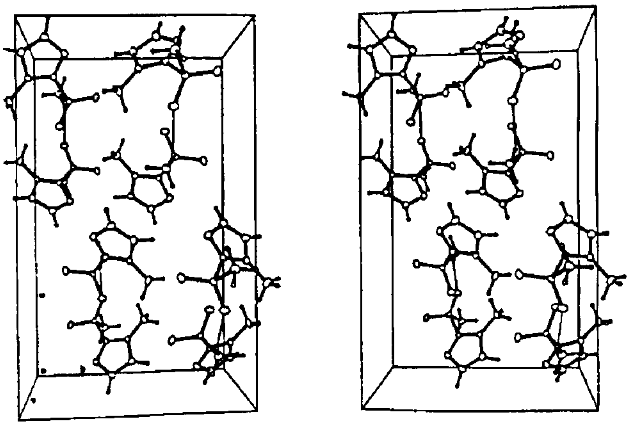


Figure 7: Stereoview of the unit cell contents of compound **4**. Still lines represent hydrogen bonds.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. The uv spectra were recorded on a Perkin Elmer Lambda 5 spectrophotometer using 1 cm quartz cells in a 10^{-5} *M* ethanol solution. The wavelength absorption maxima are reported in nanometer.

The ^{1}H and decoupled ^{13}C nmr spectra were recorded with a Bruker AMX-400 WB (Centro Interdipartimentale Grandi Strumenti, Modena, University) operating at 400.13 and 100.61 Mhz, respectively. Chemical shifts are reported in ppm from

Table 3

Crystallographic Data

	Compound **1**	Compound **4**
Formula	$C_4H_6N_2S$	$C_5H_8N_2O_2S$
Molecular Weight	114.16	160.19
Crystal System [a]	triclinic	orthorhombic
Space Group	$P\bar{1}$ (No. 2)	Pbca (No. 61)
a, Å	7.066(1)	7.088(2)
b, Å	7.339(1)	10.924(3)
c, Å	11.594(1)	18.572(4)
α, deg	99.76(1)	90
β, deg	106.83(1)	90
γ, deg	93.22(1)	90
V, Å^3	563.6(9)	1438.0(7)
Z	4	8
D_{calcd}, g•cm^{-3}	1.345	1.480
D_{obsd}, g•cm^{-3}	1.36	1.50
F(000)	240	672
Radiation (λ, Å)	graphite monochromated MoKα (0.71069)	
Reflections measured	$-9\leq h\leq 9$, $-9\leq k\leq 9$, $0\leq l\leq 14$	$-1\leq h\leq 8$, $-1\leq k\leq 13$, $0\leq l\leq 23$
Scan Type	ω-2θ	ω-2θ
θ Limits, deg	2.0 - 27.0	2.0 - 27.0
Scan Width, deg	0.55 + 0.35 tan θ	0.65 + 0.35 tan θ
Scan Speed Limits, deg•min^{-1}	0.92 - 5.50	0.92 - 5.50
Standard Reflections	2 every 2 h (no changes)	2 every 2 h (no changes)
Collected Reflections	2574	1983
Observed Reflections	1605 with $I \geq 3\sigma(I)$	1145 with $I \geq 3\sigma(I)$
Independent Reflections	1517 (R_{int} = 0.011)	878 (R_{int} = 0.018)
Crystal Dimensions, mm	0.31 x 0.28 x 0.19	0.35 x 0.27 x 0.20
μ, cm^{-1}	3.9	3.3
Transmission [b] max-min	0.996 - 0.967	0.999 - 0.971
No. of Varied Parameters	184	119
R	0.029	0.028
R_w	0.033	0.030
w	$1.56/[\sigma^2(F) + 0.0024F_o^2]$	$1.85/[\sigma^2(F) + 0.00037F_o^2]$
$\Delta\rho$: max-min, e•Å^{-3}	+0.22 -0.21	+0.23 -0.27

[a] Unit cell parameters were derived from least-squares fit to the setting angles of 25 automatically centered reflections from various regions of reciprocal space. [b] Based on empirical ψ scan [12].

tetramethylsilane used as internal standard, and are given in δ units. Microanalyses were carried out by R. Gallesi in the Microanalysis Laboratory of the Dipartimento di Scienze Farmaceutiche, Modena, University. The compounds were separated by a Büchi model 685 (mplc) glass column (460 x 36 mm I.D.), dry-filled with silica gel 60 (particle size 0.015-0.040 mm) (Merck) and connected to an LKB Multirac 2111 fraction collector. The fractions were monitored using 5 x 10 cm tlc plates (Merck).

High Performance Thin Layer Chromatography (hptlc).

Samples were applied to the plates by means of a Linomat IV (Camag) spotter on 10 x 20 cm hptlc plates (Merck). All the plates were developed at room temperature using the ascending mode.

For the separation of **1** from **2** and of **2** from **3** and **4** the solvent system used was toluene/acetone (1:6, v/v and 1:9, v/v respectively). The layers were analyzed at 254 nm by the fluorescence-quenching method using a Camag TLC Scanner II equipped with an Olivetti M280 PC operating the "Cats 3.04" scanning program. The scanner was set up as follows: band width, 10 nm; span, 25; slit, 5 x 0.2 mm; and scanning speed 5 mm/second.

The calibration graphs were plotted for each plate using the linear regression equation obtained from the area values under the peaks for different amounts of standard solution. The linearity correlation coefficient was between 0.9985 and 0.9998 for all compounds. The reproducibility of the method was assessed from 12 repeated analyses of spots containing 100 ng (RSD%: **1** = 3.5, **2** = 3.7, **3** = 3.2, **4** = 3.0), 200 ng (RSD%: **1** = 2.8, **2** = 3.2, **3** = 2.9, **4** = 2.6), 500 ng (RSD%: **1** = 2.4, **2** = 3.1, **3** = 2.5, **4** = 2.3) per spot. The limit of detections [9] were 1.06 ng for **1**, 0.93 ng for **2**, 0.62 ng for **3** and 1.29 ng for **4**.

Crystallography.

Crystals suitable for X-ray analysis were grown from acetone/petroleum ether (bp 60-80°) for **1** and methanol for **4**. In both cases, colorless, well-shaped, prismatic crystals were obtained.

The sample of compound **1** was glued to a glass fiber, whereas that of compound **4**, which sublimates slowly, was sealed into a glass capillary. In both cases, the crystals were directly transferred to an Enraf-Nonius CAD4 diffractometer. All measurements were carried out at room temperature, under the conditions listed in Table 3, which also contains some details of data reduction and structure determination.

The structures were solved by direct methods (SHELX86 program

Table 4

Final Fractional Coordinates and Equivalent Isotropic Temperature Factors [a] for 1-Methyl-1,3-dihydro-2*H*-imidazole-2-thione (**1**)

Atom	x	y	z	B_{eq}, Å^2
N(1a)	0.2735(2)	0.5274(2)	0.0352(2)	3.66(7)
C(2a)	0.2884(3)	0.3988(3)	0.1069(2)	3.39(8)
N(3a)	0.3590(3)	0.4946(2)	0.2234(2)	3.93(7)
C(4a)	0.3857(4)	0.6820(3)	0.2246(3)	4.8(1)
C(5a)	0.3333(4)	0.7015(3)	0.1090(3)	4.8(1)
C(6a)	0.2003(5)	0.4865(5)	-0.0981(2)	5.0(1)
S(a)	0.2260(1)	0.16724(8)	0.05964(6)	5.03(3)
N(1b)	1.0608(3)	0.7916(2)	0.5587(2)	4.09(8)
C(2b)	0.9142(3)	0.7953(3)	0.6129(2)	3.72(9)
N(3b)	1.0055(3)	0.8689(3)	0.7319(2)	4.23(8)
C(4b)	1.2062(4)	0.9091(4)	0.7533(3)	5.2(1)
C(5b)	1.2407(4)	0.8617(4)	0.6463(3)	5.2(1)
C(6b)	1.0303(6)	0.7223(5)	0.4290(3)	5.8(2)
S(b)	0.67215(9)	0.7170(1)	0.54540(6)	5.60(3)
H(N3a)	0.373(4)	0.442(4)	0.286(2)	5.5(2) [c]
H(C4a)	0.431(4)	0.759(4)	0.296(2)	5.5(2)
H(C5a)	0.336(4)	0.809(3)	0.078(2)	5.5(2)
H(1C6a) [b]	0.290(7)	0.452(8)	-0.132(4)	4.7(3) [c]
H(2C6a)	0.108(7)	0.612(7)	-0.121(4)	4.7(3)
H(3C6a)	0.089(8)	0.377(7)	-0.126(4)	4.7(3)
H(1*C6a)	0.266(8)	0.584(8)	-0.123(5)	4.7(3)
H(2*C6a)	0.231(9)	0.356(8)	-0.140(5)	4.7(3)
H(3*C6a)	0.063(8)	0.498(8)	-0.128(5)	4.7(3)
H(N3b)	0.942(4)	0.879(4)	0.784(2)	5.5(2)
H(C4b)	1.293(4)	0.969(3)	0.829(2)	5.5(2)
H(C5b)	1.365(4)	0.873(3)	0.628(2)	5.5(2)
H(1C6b) [b]	1.072(9)	0.616(7)	0.418(4)	4.7(3)
H(2C6b)	1.119(8)	0.812(7)	0.404(4)	4.7(3)
H(3C6b)	0.867(7)	0.735(7)	0.371(4)	4.7(3)
H(1*C6b)	0.918(8)	0.608(8)	0.395(4)	4.7(3)
H(2*C6b)	1.00(1)	0.805(8)	0.382(5)	4.7(3)
H(3*C6b)	1.152(8)	0.69(1)	0.423(5)	4.7(3)

[a] B_{eq} is defined as one-third of the trace of the orthogonalized B_{ij} tensor. [b] The methyl groups are affected by statistical disorder, due to two alternative positions of their hydrogen atoms. The refined occupancy factors of major and minor (asterisked atoms) sites are 0.53(2) and 0.47(2), respectively. [c] Common isotropic temperature factors were refined for hydrogen atoms bonded to ring or to methyl carbons.

Table 5

Final Fractional Coordinates and Equivalent Isotropic Temperature Factors [a] for 1-Methyl-2-methylsulfonylimidazole (**4**)

Atom	x	y	z	B_{eq}, Å^2
N(1)	0.6363(3)	0.5196(2)	0.6194(1)	2.81(8)
C(2)	0.5608(3)	0.6325(2)	0.6106(1)	2.55(8)
N(3)	0.6236(3)	0.6875(2)	0.5515(1)	3.57(9)
C(4)	0.7469(4)	0.6048(3)	0.5227(1)	4.0(1)
C(5)	0.7556(4)	0.5026(2)	0.5629(1)	3.6(1)
C(6)	0.6099(6)	0.4319(3)	0.6783(2)	4.4(1)
S	0.38121(8)	0.69660(5)	0.66292(3)	2.81(2)
O(1)	0.3963(3)	0.6504(2)	0.73463(8)	4.10(8)
O(2)	0.3875(3)	0.8264(1)	0.65196(9)	3.97(8)
C(7)	0.1738(4)	0.6394(3)	0.6243(2)	3.6(1)
H(4)	0.820(4)	0.627(2)	0.481(1)	4.8(6)
H(5)	0.828(4)	0.425(2)	0.561(1)	3.3(5)
H(6a)	0.632(5)	0.461(3)	0.724(2)	7.2(5) [b]
H(6b)	0.681(5)	0.368(4)	0.672(2)	7.2(5)
H(6c)	0.487(6)	0.409(3)	0.681(2)	7.2(5)
H(7a)	0.174(4)	0.667(3)	0.577(2)	5.1(4) [b]
H(7b)	0.071(4)	0.663(3)	0.656(1)	5.1(4)
H(7c)	0.177(4)	0.557(3)	0.627(2)	5.1(4)

[a] B_{eq} is defined as one-third of the trace of the orthogonalized B_{ij} tensor. [b] Common temperature factors were refined for methyl hydrogens bonded to the same carbon atom.

[10]), and were refined through full-matrix least-squares calculations (SHELX76 program [11]) with $\Sigma w(|F_o| - |F_c|)^2$ being minimized. In both cases, the non-hydrogen atoms were refined anisotropically; the hydrogen atoms, located in ΔF maps, were refined isotropically, with common B for those bonded to the same atom. The methyl groups of both the two crystallographically independent molecules of compound **1** were found to be affected by statistical disorder. This is due to two alternative orientations of the methyl protons, arising from a rotation of *c.a.* 60° around the N-C bonds. Least-squares refinement of the occupancy factors led to the values, for both the groups, of 0.53(2) and 0.47(2) for major and the minor sites, respectively. During the refinement of compounds **1**, zero weight was assigned to four strong low-order reflections, which may be affected by secondary extinction. The weighting schemes, reported in Table 1, gave satisfactory agreement analyses in both cases.

Table 6

Anisotropic Temperature Factors [a] for 1-Methyl-1,3-dihydro-2*H*-imidazole-2-thione (**1**)

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1a)	3.40(7)	3.77(7)	4.25(8)	0.57(6)	1.32(6)	1.62(6)
C(2a)	2.98(8)	3.65(8)	4.13(9)	0.49(6)	1.70(7)	1.21(7)
N(3a)	4.18(8)	3.95(8)	3.79(8)	0.09(6)	1.29(7)	1.08(7)
C(4a)	5.0(1)	3.6(1)	5.3(1)	-0.33(8)	1.4(1)	0.27(9)
C(5a)	5.1(1)	3.46(9)	6.2(1)	0.39(8)	1.8(1)	1.77(9)
C(6a)	4.6(1)	6.8(2)	4.5(1)	1.3(1)	1.8(1)	2.4(1)
S(a)	7.25(4)	3.31(2)	5.36(3)	0.19(2)	3.33(3)	0.69(2)
N(1b)	4.69(9)	3.83(8)	4.70(9)	0.73(7)	2.67(8)	1.15(7)
C(2b)	4.13(9)	3.65(9)	4.2(1)	0.75(7)	2.00(8)	1.53(8)
N(3b)	4.23(9)	4.89(9)	4.19(9)	0.35(7)	2.02(7)	1.30(7)
C(4b)	4.2(1)	5.5(1)	5.5(1)	-0.53(9)	1.3(1)	1.1(1)
C(5b)	4.1(1)	5.3(1)	7.1(2)	0.29(9)	2.8(1)	1.5(1)
C(6b)	8.3(2)	5.1(1)	5.6(1)	1.7(1)	4.3(1)	1.4(1)
S(b)	3.85(3)	8.48(4)	4.81(3)	0.28(3)	1.22(2)	2.48(3)

[a] The form of the anisotropic thermal parameter is $\exp[-1/4(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$.

Table 7

Bond Distances (Å) and Bond Angles (°) involving Hydrogen Atoms of 1-Methyl-1,3-dihydro-2*H*-imidazole-2-thione (**1**)

N(3a)-H(N3a)	0.86(3)	N(3b)-H(N3b)	0.85(3)
C(4a)-H(C4a)	0.88(2)	C(4b)-H(C4b)	0.94(2)
C(5a)-H(C5a)	0.92(3)	C(5b)-H(C5b)	0.96(3)
C(6a)-H(1C6a)	0.86(6)	C(6b)-H(1C6b)	0.85(6)
C(6a)-H(2C6a)	1.18(5)	C(6b)-H(2C6b)	1.01(6)
C(6a)-H(3C6a)	1.03(5)	C(6b)-H(3C6b)	1.18(5)
C(6a)-H(1*C6a)	0.96(6)	C(6b)-H(1*C6b)	1.06(5)
C(6a)-H(2*C6a)	1.06(6)	C(6b)-H(2*C6b)	0.88(6)
C(6a)-H(3*C6a)	0.95(6)	C(6b)-H(3*C6b)	0.93(6)
C(2a)-N(3a)-H(N3a)	122(2)	C(2b)-N(3b)-H(N3b)	121(1)
C(4a)-N(3a)-H(N3a)	127(2)	C(4b)-N(3b)-H(N3b)	128(1)
N(3a)-C(4a)-H(C4a)	118(2)	N(3b)-C(4b)-H(C4b)	123(2)
C(5a)-C(4a)-H(C4a)	135(2)	C(5b)-C(4b)-H(C4b)	129(2)
N(1a)-C(5a)-H(C5a)	123(1)	N(1b)-C(5b)-H(C5b)	123(1)
C(4a)-C(5a)-H(C5a)	129(1)	C(4b)-C(5b)-H(C5b)	129(1)
N(1a)-C(6a)-H(1C6a)	113(3)	N(1b)-C(6b)-H(1C6b)	110(3)
N(1a)-C(6a)-H(2C6a)	103(2)	N(1b)-C(6b)-H(2C6b)	105(3)
N(1a)-C(6a)-H(3C6a)	109(3)	N(1b)-C(6b)-H(3C6b)	111(2)
H(1C6a)-C(6a)-H(2C6a)	123(5)	H(1C6b)-C(6b)-H(2C6b)	107(6)
H(1C6a)-C(6a)-H(3C6a)	106(5)	H(1C6b)-C(6b)-H(3C6b)	117(4)
H(2C6a)-C(6a)-H(3C6a)	101(4)	H(2C6b)-C(6b)-H(3C6b)	106(4)
N(1a)-C(6a)-H(1*C6a)	105(3)	N(1b)-C(6b)-H(1*C6b)	111(3)
N(1a)-C(6a)-H(2*C6a)	115(3)	N(1b)-C(6b)-H(2*C6b)	115(4)
N(1a)-C(6a)-H(3*C6a)	112(3)	N(1b)-C(6b)-H(3*C6b)	106(3)
H(1*C6a)-C(6a)-H(2*C6a)	109(5)	H(1*C6b)-C(6b)-H(2*C6b)	107(5)
H(1*C6a)-C(6a)-H(3*C6a)	105(5)	H(1*C6b)-C(6b)-H(3*C6b)	111(5)
H(2*C6a)-C(6a)-H(3*C6a)	110(4)	H(2*C6b)-C(6b)-H(3*C6b)	108(6)

Table 8

Torsion Angles (°) in 1-Methyl-1-3-dihydro-2*H*-imidazole-2-thione (**1**)

N(1a)-C(5a)-C(4a)-N(3a)	0.1(3)	N(1b)-C(5b)-C(4b)-N(3b)	-0.1(3)
N(1a)-C(2a)-N(3a)-C(4a)	0.7(2)	N(1b)-C(2b)-N(3b)-C(4b)	-0.7(3)
C(2a)-N(1a)-C(5a)-C(4a)	0.4(3)	C(2b)-N(1b)-C(5b)-C(4b)	-0.3(3)
C(2a)-N(3a)-C(4a)-C(5a)	-0.5(3)	C(2b)-N(3b)-C(4b)-C(5b)	0.5(3)
N(3a)-C(2a)-N(1a)-C(5a)	-0.7(2)	N(3b)-C(2b)-N(1b)-C(5b)	0.6(2)
N(3a)-C(2a)-N(1a)-C(6a)	-179.0(2)	N(3b)-C(2b)-N(1b)-C(6b)	180.0(3)
C(4a)-C(5a)-N(1a)-C(6a)	178.7(3)	C(4b)-C(5b)-N(1b)-C(6b)	-179.7(3)
C(4a)-N(3a)-C(2a)-S(a)	-177.9(2)	C(4b)-N(3b)-C(2b)-S(b)	177.3(2)
C(5a)-N(1a)-C(2a)-S(a)	178.0(2)	C(5b)-N(1b)-C(2b)-S(b)	-177.4(2)
C(6a)-N(1a)-C(2a)-S(a)	-0.3(3)	C(6b)-N(1b)-C(2b)-S(b)	2.0(4)

Table 9

Selected Least-Squares Planes and Atomic Deviations (Å) Therefrom for 1-Methyl-1,3-dihydro-2*H*-imidazole-2-thione (**1**)

Atom [a]	Dev	Atom	Dev	Atom	Dev
1) Equation [b]: -0.9965x + 0.1377y + 0.2908z = -1.2713					
N(1a)	-0.003	C(2a)	0.004	N(3a)	-0.004
C(4a)	0.002	C(5a)	0.001	*C(6a)	0.022
*S(a)	0.050	*H(N3a)	0.052	*H(C4a)	0.004
*H(C5a)	-0.014				
2) Equation: 0.1540x - 0.9785y + 0.3060z = -2.5462					
N(1b)	-0.003	C(2b)	0.004	N(3b)	-0.003
C(4b)	0.002	C(5b)	0.000	*C(6b)	0.002
*S(b)	0.063	*H(N3b)	0.041	*H(C4b)	-0.062
*H(C5b)	-0.010				

Dihedral Angle between Mean Planes = 76.7°

[a] Asterisked atoms were not used in calculating the plane. [b] x, y, z are fractional crystal coordinates.

Complex neutral atom scattering factors, including anomalous dispersion terms for non-H atoms, were taken from reference [11]. Major calculations were carried out on a VAX 6310 computer.

Final atomic coordinates are given in Tables 4 and 5, and bond distances and angles involving non-hydrogen atoms in Table 1. Anisotropic thermal parameters are reported in Table 6 and 10, bond distances and bond angles involving hydrogen atoms in Table 7 and 11, torsion angles in Table 8 and 12, and selected least-squares planes in Table 9 and 13, for compound **1** and **4**, respectively; Table 14 contains the shortest nonbonded distances in compound **4**.

1-Methyl-2-methylthioimidazole (**2**).

Ten g of **1** (0.087 mole) were dissolved in a 100 ml (0.31 *M*) of sodium carbonate solution, to which 6.6 ml of methyl iodide (0.053 moles) were added dropwise with constant stirring for 60 minutes at room temperature. The reaction mixture was extracted three times with chloroform (30 ml).

The organic phase was evaporated to dryness at 40° to yield the oil **2**, 10.66 g yield (95%); uv (ethanol): λ_{max} 250 nm (log ε 3.68); ^{1}H nmr (deuteriochloroform): δ 2.44 (s, 3H, S-CH_3), 3.44

Table 10

Anisotropic Temperature Factors [a] for 1-Methyl-2-methylsulfonylimidazole (**4**)

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)	3.11(9)	2.29(7)	3.03(8)	-0.03(8)	0.01(7)	0.27(6)
C(2)	2.87(9)	2.12(8)	2.68(8)	-0.15(8)	0.04(8)	0.12(7)
N(3)	4.0(1)	3.19(8)	3.50(8)	0.17(9)	0.60(8)	0.73(8)
C(4)	4.2(1)	4.0(1)	3.8(1)	0.6(1)	1.4(1)	0.6(1)
C(5)	3.4(1)	3.3(1)	4.0(1)	0.57(9)	0.5(1)	0.01(9)
C(6)	5.6(2)	2.8(1)	5.0(1)	0.4(1)	0.8(1)	1.4(1)
S	3.45(3)	2.49(2)	2.49(2)	0.08(2)	-0.05(2)	-0.29(2)
O(1)	4.8(1)	4.96(9)	2.56(6)	0.67(8)	-0.11(7)	0.05(6)
O(2)	4.9(1)	2.46(7)	4.53(8)	0.29(7)	0.06(8)	-0.64(6)
C(7)	3.5(1)	3.9(1)	3.5(1)	-0.2(1)	0.2(1)	-0.4(1)

[a] The form of the anisotropic thermal parameter is $\exp[-1/4(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$.

Table 11

Bond Distances (Å) and Bond Angles (°) involving Hydrogen Atoms of 1-Methyl-2-methylsulfonylimidazole (**4**)

H(4)-C(4)	0.97(3)	H(5)-C(5)	0.99(2)
H(6a)-C(6)	0.93(4)	H(6b)-C(6)	0.87(4)
H(6c)-C(6)	0.90(4)	H(7a)-C(7)	0.92(3)
H(7b)-C(7)	0.98(3)	H(7c)-C(7)	0.90(3)
H(4)-C(4)-N(3)	120(2)	H(4)-C(4)-C(5)	129(2)
H(5)-C(5)-N(1)	118(1)	H(5)-C(5)-C(4)	135(1)
H(6a)-C(6)-N(1)	116(2)	H(6b)-C(6)-N(1)	110(2)
H(6b)-C(6)-H(6a)	108(3)	H(6c)-C(6)-N(1)	110(2)
H(6c)-C(6)-H(6a)	102(3)	H(6c)-C(6)-H(6b)	110(3)
H(7a)-C(7)-S	105(2)	H(7b)-C(7)-S	107(2)
H(7b)-C(7)-H(7a)	119(2)	H(7c)-C(7)-S	108(2)
H(7c)-C(7)-H(7a)	113(3)	H(7c)-C(7)-H(7b)	104(3)

Table 12

Torsion Angles (°) in 1-Methyl-2-methylsulfonylimidazole (**4**)

N(1)-C(5)-C(4)-N(3)	-0.4(3)	N(1)-C(2)-N(3)-C(4)	-0.9(3)
N(1)-C(2)-S-O(1)	31.7(2)	N(1)-C(2)-S-O(2)	161.2(2)
N(1)-C(2)-S-C(7)	-83.8(2)	C(2)-N(1)-C(5)-C(4)	-0.2(3)
C(2)-N(3)-C(4)-C(5)	0.7(3)	N(3)-C(2)-N(1)-C(5)	0.7(3)
N(3)-C(2)-N(1)-C(6)	177.4(3)	N(3)-C(2)-S-O(1)	-155.9(2)
N(3)-C(2)-S-O(2)	-26.5(2)	N(3)-C(2)-S-C(7)	88.5(2)
C(4)-C(5)-N(1)-C(6)	-177.1(3)	C(4)-N(3)-C(2)-S	-174.2(2)
C(5)-N(1)-C(2)-S	173.6(2)	C(6)-N(1)-C(2)-S	-9.6(4)

Table 13

Selected Least-Squares Planes and Atomic Deviations (Å) Therefrom for 1-Methyl-2-methylsulfonylimidazole (**4**)

Atom [a]	Dev	Atom	Dev	Atom	Dev
1) Equation [b]: $0.7477x + 0.4000y + 0.5301z = 11.7427$					
N(1)	-0.002	C(2)	0.004	N(3)	-0.004
C(4)	0.003	C(5)	-0.001	*C(6)	0.054
*S	-0.153	*O(1)	0.431	*O(2)	0.341
*C(7)	-1.882	*H(C4)	0.076	*H(C5)	0.024
2) Equation: $0.7530x + 0.4132y + 0.5121z = 11.6500$					
N(1)	-0.017	C(2)	0.006	C(5)	0.005
C(6)	0.006				
3) Equation: $0.7060x + 0.4246y + 0.5668z = 12.1282$					
N(1)	-0.014	C(2)	0.039	N(3)	-0.013
S	-0.012				

Dihedral Angle between Mean Planes

1·····2	1.3°	1·····3	3.5°

[a] Asterisked atoms were not used in calculating the plane. [b] x, y, z are fractional crystal coordinates.

Table 14

Shortest Nonbonded Distances (Å) in 1-Methyl-2-methylsulfonylimidazole (**4**)

Atoms		Distance	Symmetry Transformation (on second atom)
N(1)	O(1)	3.576(2)	0.5+x, y, 1.5-z
N(3)	C(S)	3.553(3)	1.5-x, 0.5+y, z
C(4)	O(2)	3.475(3)	0.5+x, 1.5-y, 1-z
C(4)	C(7)	3.586(4)	1+x, y, z
C(5)	C(7)	3.510(4)	1+x, y, z
C(5)	O(2)	3.584(3)	1.5-x, -0.5+y, z
C(6)	O(2)	3.356(4)	1-x, -0.5+y, 1.5-z
C(6)	O(1)	3.475(3)	1-x, -0.5+y, 1.5-z
C(6)	O(1)	3.526(4)	0.5+x, y, 1.5-z
O(1)	C(7)	3.278(3)	0.5+x, y, 1.5-z
O(1)	O(1)	3.590(1)	0.5+x, y, 1.5-z
O(1)	O(1)	3.590(1)	-0.5+x, y, 1.5-z
O(2)	C(7)	3.485(3)	0.5-x, 0.5+y, z

(s, 3H, N-CH_3), 6.77 (d, 1H, H_4, $J_{H4\text{-}H5}$ = 1.2 Hz), 6.89 (d, 1H, H_5, $J_{H4\text{-}H5}$ = 1.2 Hz).

Anal. Calcd. for $C_5H_8N_2S$: C, 46.84; H, 6.29; N, 21.86; S, 25.01. Found: C, 46.58; H, 6.34; N, 21.51; S, 25.29.

1-Methyl-2-methylsulphinylimidazole (**3**).

Two g (0.016 mole) of **2** were dissolved in ml 20 of acetic acid; hydrogen peroxide 30% (20 ml, 4 equivalents) was then added and the solution stirred at room temperature for 4 hours. After the addition of water (200 ml) the reaction mixture was extracted three times with dichloromethane (30 ml). The organic phase formed by **2**, **3**, **4** was evaporated to a low volume and separated on mplc by mobile phase toluene/acetone (1:9, v/v) to give 0.67 g (30%) of **3** (oil); uv (ethanol): λ_{max} 246.4 (log ε 3.76); ^1H nmr (deuteriochloroform): δ 3.10 (s, 3H, $SOCH_3$), 3.94 (s, 3H, NCH_3), 7.01 (d, 1H, H_4, $J_{H4\text{-}H5}$ = 1.0 Hz), 7.12 (d, 1H, H_5, $J_{H4\text{-}H5}$ = 1.0 Hz); ^{13}C nmr (deuteriochloroform): δ 29.1 (NCH_3), 38.1 ($SOCH_3$), 125.0 (C_5), 129.2 (C_4), 145.8 (C_2).

Anal. Calcd. for $C_5H_8N_2OS$: C, 41.65; H, 5.59; N, 19.43; S, 22.23. Found: C, 41.45; H, 5.81; N, 19.20; S, 22.40.

1-Methyl-2-methylsulphonylimidazole (**4**).

The same procedure as described for **3** was followed; the reaction mixture was heated under reflux for 20 minutes. The organic phase was evaporated and the residue was recrystallized from methanol to give 2.20 g (89%), mp 116-117° (lit 117-118° [14]): uv (ethanol): λ_{max} 235.2 nm (log ε 3.93); ^{1}H nmr (deuteriochloroform): δ 3.36 (s, 3H, SO_2CH3), 3.98 (s, 3H, NCH_3), 6.98 (d, 1H, H_4, J_{H4-H5} = 1.0 Hz), 7.09 (d, 1H, H_5, J_{H4-H5} = 1.0 Hz).

Anal. Calcd. for $C_5H_8N_2O_2S$: C, 37.49; H, 5.03; N, 17.49; S, 19.98. Found: C, 37.66; H, 4.87; N, 17.54; S, 19.75.

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