SYNTHESIS AND MOLECULAR STRUCTURE OF 1,4-DIMETHYL-4,5,7,8-TETRAHYDRO-6H-IMIDAZO[4,5-e][1,4]-DIAZEPINE-5,8-DITHIONE

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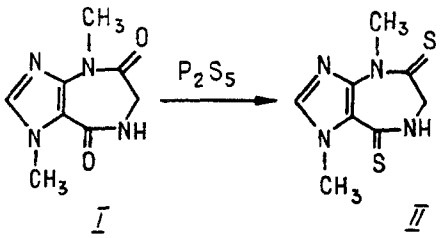
1,4-dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]-diazepine-5,8-dithione was synthesized by boiling 1,4-dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]-diazepine-5,8-dione (a cyclic homolog of theobromine) with P_2S_5. Its molecular and crystal structures were determined by X-ray structure analysis, PMR spectroscopy and the calculations using the MM2 program. The crystals are monoclinic, sp. gr. $P\,2_1/n$ with $a = 9.305(4)$, $b = 9.464(3)$, $c = 11.628(3)$ Å, $\gamma = 90.49(3)°$, $Z = 4$ for $C_8H_{10}N_4S_2$. M.p. 268-269 °C. The 7-membered heterocycle has a boat conformation in the crystal, while in solution at room temperature it undergoes interconversion. The geometrical parameters of the molecule obtained by X-ray structure analysis, by PMR spectroscopy below the coalescence temperature (290 K), and by MM2 calculations are in good agreement.

This article is concerned with the synthesis and molecular structure determination of 1,4-dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dithione (II) by X-ray structure analysis, PMR spectroscopy and molecular-mechanics calculations. Compound II was obtained by boiling 1,4-dimethyl-4,5,7,8-tetrahydro-6H-imidazo [4,5-e][1,4]diazepine-5,8-dione, a cyclic homolog of theobromine [1], with P_2S_5 in dry pyridine.



I II

EXPERIMENTAL

1,4-Dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]-diazepine-5,8-dithione was obtained by the following procedure. A mixture of 0.5 g (2.6 mmoles) of imidazodiazepine (I) and 0.6 g (2.7 mmoles) of phosphorus pentasulfide in 5 ml of dry pyridine was boiled for 1.5 h. Pyridine was distilled off on a rotary evaporator to dryness. The residue was carefully ground with water and filtered off. Then it was recrystallized from methanol. Yield 0.4 g (68.6%); m.p. 268-269 °C.

The NMR spectra were obtained on a Bruker AM-250 spectrometer equipped with an Aspect 3000 computer in the Fourier transform mode. The ^1H NMR spectra of the 0.01 M $CDCl_3$ solution (low concentration was chosen to reduce the influence of intermolecular interactions) were recorded at an operating frequency of 250 MHz. Pulse

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TABLE 1. Coordinates of Basic Atoms ($\times 10^4$)

Atom	x/a	y/b	z/c
S1	6717(2)	–4528(2)	–2200(2)
S2	2867(2)	–740(2)	641(1)
N1	789(4)	–2978(4)	–778(4)
N3	1480(5)	–5071(4)	–1436(4)
N4	4021(4)	–4759(4)	–1503(4)
N7	4409(4)	–1665(4)	–1097(4)
C1	–216(6)	–1858(6)	–466(6)
C2	394(6)	–4276(6)	–1144(5)
C3	4212(7)	–6296(6)	–1298(6)
C5	5084(5)	–3963(5)	–1908(4)
C6	4688(6)	–2441(5)	–2150(5)
C8	3203(5)	–1769(5)	–498(4)
C9	2279(5)	–2909(5)	–869(4)
C10	2649(5)	–4221(5)	–1287(4)

TABLE 2. Bond Lengths (Å) in 1,4-Dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dithione

Bond	r, Å		Bond	r, Å	
	X-ray structure analysis	MM2 calculation		X-ray structure analysis	MM2 calculation
C3–S2	1.675(5)	1.68	C5–S1	1.650(5)	1.68
N4–C5	1.324(6)	1.36	N4–C10	1.401(6)	1.39
C5–C6	1.516(7)	1.52	C6–C7	1.452(7)	1.45
N7–C8	1.323(6)	1.34	C8–C9	1.440(7)	1.44
N3–C2	1.311(7)	1.28	N3–C10	1.358(6)	1.29
N4–CH_3	1.486(7)	1.48	C2–N1	1.348(7)	1.35
N1–C9	1.391(6)	1.38	N1–C1	1.464(7)	1.46
C9–C10	1.380(7)	1.36			

width 15 μsec, response time 3.05 sec, number of acquisitions 8, pulse delay 4 sec. The sample was placed in a 5 mm diam. ampul. Chemical shifts were measured relative to the signal of TMS used as an internal reference, with an error of ±0.003 ppm. The temperature was varied within 273-320 K and kept constant with an accuracy of 0.5 K. The field was stabilized with solvent deuterium nuclei.

The molecular-mechanics calculations were performed on an IBM PC/AT(286) using the MM2 program.

The X-ray structure analysis was carried out on a crystal grown from the saturated methanol solution.

The crystals are monoclinic, with unit cell dimensions refined by 12 pinacoidal reflections: a = 9.305(4), b = 9.464(3), c = 11.628(3) Å; γ = 90.49(3)°. Space group is $P2_1/n$, Z = 4 for $C_8H_{10}N_4S_2$.

The crystal data were collected on a RED-4 diffractometer (monochromated MoK_α radiation, $\sin\theta/\lambda \leq 0.6$ Å^{-1}, ω-scan at a constant rate of 8 deg/min). A total of 1487 reflections were measured with $I \geq 3\sigma(I)$ of which 1391 independent reflections were used for crystallographic calculations.

The structure was solved by the heavy atom method and refined by the least-squares technique in an anisotropic approximation for the S, N, and C atoms. The H atoms were located by a standard difference Fourier technique and refined using only isotropic thermal parameters. The final $R(hkl)$ = 0.043. The coordinates of the basic atoms and molecular geometry are given in Tables 1-4.

DESCRIPTION OF STRUCTURE

A projection of the structure on the xy plane is shown in Fig. 1. The crystal structure includes the centrosymmetric dimers formed by the NH... hydrogen bonds (N7...S2 = 3.433(4), N7–H = 0.93 and H...S2 = 2.52 Å,

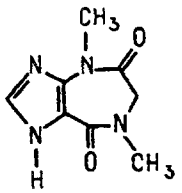
TABLE 3. Bond Angles in 1,4-Dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dithione

Angle	deg		Angle	deg	
	X-ray analysis	MM2 calculation		X-ray analysis	MM2 calculation
C5–N4–C3	121.2(4)	121.2	C10–N4–C3	116.3(4)	116.7
C5–N4–C10	122.3(4)	121.9	N4–C5=S1	125.0(4)	119.8
C6–C5=S1	120.0(4)	122.1	N4–C5–C6	114.8(4)	118.0
C5–C6–N7	111.6(4)	110.4	C6–N7–C8	124.1(4)	121.5
N7–C8=S2	122.3(4)	118.6	C9–C8=S2	123.9(4)	121.6
N7–C8–C9	113.5(4)	120.0	N1–C9–C8	126.9(4)	129.1
N1–C9–C10	103.9(4)	106.6	C8–C9–C10	128.8(5)	124.2
N4–C10–N3	119.2(4)	122.9	N4–C10–C9	128.7(5)	128.9
N3–C10–C9	111.8(4)	108.1	C9–N1–C2	106.4(4)	105.3
C9–N1–C1	128.8(4)	128.7	C2–N1–C1	124.5(5)	125.9
C10–N3–C2	104.1(4)	111.8	N3–C2–N1	113.5(5)	108.3

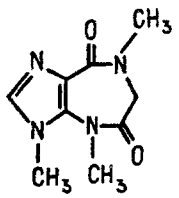
TABLE 4. Torsion Angles in 1,4-Dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dithione

Angle	deg		Angle	deg	
	X-ray analysis	MM2 calculation		X-ray analysis	MM2 calculation
N4C5–C6N7	69.0	68.4	C10N4–C5C6	–1.5	–1.8
C5C6–N7C8	–77.8	–67.7	C9C10–N3C2		0.4
C6N7–C8C9	10.4	–0.1	C10N3–C2N1		0.5
N7C8–C9C10	34.6	41.2	N3C2–N1C9		–1.1
C8C9–C10N4	–2.9	–0.3	C2N1–C9C10		1.3
C9C10–N4C5	–36.4	–39.0			

the N7HS2 angle is 167°). The dimers are held together by van der Waals forces. The dimeric centrosymmetric associates formed by hydrogen bonds between the amide NH...O groups of the neighboring molecules are typical of 1,4-benzdiazepines [2]. Substitution of O by S does not lead to any essential changes in the packing mode.



III



IV

In molecule II, the 7-membered heterocycle has a boat conformation; the conjugated 5-membered heterocycle is planar. The torsion angles are listed in Table 4. They are virtually the same as those found for I and III [3]; only their values differ, specifying the depth of the boat. We emphasize that the conformation of the 7-membered cycle found in the three structures is essentially identical and differs only slightly from that for 1,4-benzdiazepines. It appears to be determined by the size of the cycle and its set of heteroatoms.

The interatomic distances (see Fig. 1 and Table 2) show a significant π-delocalization in the 5-membered cycle and in the C5–N5...C8–N7 moiety of the 7-membered cycle. In the imidazole cycle, the distances N1–C9 = 1.391 Å, N1–C2 = 1.348 Å, N3–C2 = 1.3111 Å, N3–C10 = 1.358 Å, and C9–C10 = 1.380 Å do not differ from those obtained for I and III.

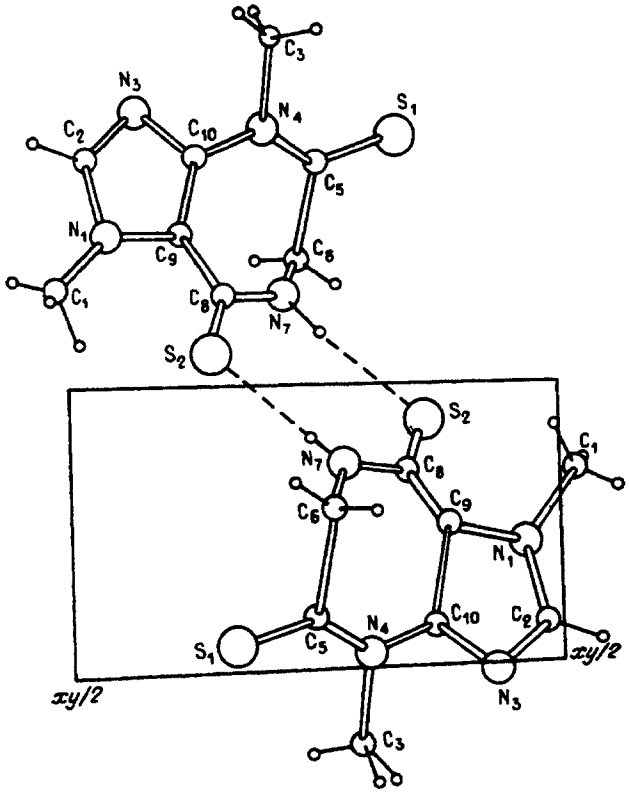


Fig. 1. A projection of the structure of 1,4-dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dithione on the *xy* plane.

In the 7-membered cycle, the distances are normal [3]; in the thioamide groups, the C5–S1 and C8–S2 distances are 1.650 and 1.675 Å, respectively.

The sum of the angles at N4 is 360°, precluding the pyramidal form of the thiomethylamide group. It has a *cis*-conformation, as well as the thioamide group. The *cis*-geometry just gives rise to the above H bond.

Tables 2-4 give a comparison of bond lengths, as well as bond and torsion angle values obtained by the X-ray structure analysis and by the molecular-mechanics calculation using the MM2 program [4]. The calculation was carried out for a monomeric form, but the calculated and experimental data agree fairly well. The relative errors of bond length and bond angle determination are less than 5% (Table 2) and 6% (Table 3), respectively. The largest difference is observed for the N3–C10 bond length, and for the N7–C8–C9 and C10–N3–C2 bond angles.

The agreement between the calculated and measured torsion angles (Table 4) about the C5–C6, C10–N4, and N4–C5 bonds is ideal. However, the difference between the torsion angle values for the C6–N7, N7–C8, and C8–C9 bonds is rather large, indicating an essential influence of the intermolecular hydrogen bond and the packing effects in the crystal.

The PMR spectrum of compound II in $CDCl_3$ at 295 K shows the following signals: N^4CH_3 (3.88 ppm), N^1CH_3 (4.08 ppm), a partially coalesced multiplet of CH_2 protons in the form of two broadened signals at 4.41 and 4.65 ppm, $=CH^{im}$ (7.53 ppm) and NH (7.88 ppm). At the same time, in the spectrum of compound I having the C=O instead of C=S groups, the signals of the N^4CH_3, N^1CH_3, and CH_2 protons are shifted upfield (3.39, 3.90, and 3.98 ppm); the signal of the $=CH^{im}$ proton is shifted downfield (7.67 ppm). This may be explained by the larger electronegativity of carbonyl compared to C=S, resulting in screening of the N^4CH_3, N^1CH_3, and CH_2 protons. Deshielding of the $=CH^{im}$ proton in II is due to the opposite sign of polarization of the S=C bond relative to carbonyl.

To determine the inversion barrier of the 7-membered cycle in compound II, we have studied the evolution of signals in the PMR spectra in the temperature range of 273-320 K. At an elevated temperature (305 K), the signals of the spin multiplet of the ABX type coalesce. At decreased temperatures, we can find the coalescence point of spin multiplets of the CH_2 and NH protons. The spin multiplets coalesce at 290 K. Subsequent decrease of temperature

results in the appearance of a doublet of the AB quartets of the CH_2 protons and a broadened doublet of doublets of the NH protons. Based on the multiplicity of the signals, we can find the geminal and vicinal spin-spin coupling constants, $^2J_{HH}$ = –14.8 Hz and $^3J_{NH-CH}$ = 6.2 Hz. Taking into account the correction for substituent electronegativity, we obtain the corrected value of $^3J_{NH-CH}$ = 6.8 Hz. Using the Karplus-Bystrov relation for the glycyl protons [5], one can obtain the value of the torsion angle φ about the NH–CH_2 (N7–C6) bond. For compound II in chloroform at temperatures below the coalescence point, the angle φ is ±40°.

This angle is smaller in magnitude than that obtained by the X-ray structure analysis (–77.8°). It means that in a crystal, the 7-membered cycle has a less flattened bath conformation than in solution. Such a deformation can be attributed to formation of a pair of C=S...HN hydrogen bonds in a crystal or the stacking interaction of the neighboring molecules.

The inversion barrier value for the 7-membered cycle obtained from the known equations [6] amounts to 61.6 ± 0.2 kJ/mole at the inversion frequency of 62.4 sec^{-1} in compound II. This value exceeds that for the oxygen-containing compound I by 13.7 kJ/mole and approaches the barrier value for compound IV, 63.2 kJ/mole. The high value of the inversion barrier for the 7-membered cycle in compound IV was earlier explained by steric hindrance caused by the N^1CH_3 and N^8CH_3 methyl groups [7]. One can suggest that the increased inversion barrier in passing from the cycle with carbonyl groups to that with C=S groups is also due to steric reasons because of the large radius of the sulfur atom.

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