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Conformational Analysis of a New Analgesic Triazolinethione

Structural Comparisons with Antipyrine

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SUMMARY

Crystals of 3-(2-hydroxyphenyl)-4-methyl-1,2,4-Δ-2-triazoline-5-thione, a new non-narcotic analgesic compound, are monoclinic with the following cell parameters: $a = 5.942$, $b = 17.771$, $c = 10.319$ Å, $\beta = 102.77°$, $Z = 4$, space group $P2_{1/C}$. The structure was determined by the direct-phasing program MULTAN and by Fourier methods. The triazoline ring makes an angle of 62° with the benzene ring, and this result has been compared with the dihedral angle value between the pyrazolone and phenyl planes of antipyrine derivatives. A theoretical calculation of conformational energy is also reported and structure-activity relationships are discussed.

INTRODUCTION

Among a series of new triazolinethiones exhibiting an aspirin-like analgesic activity (1), HMT[4] appeared to be characteristic. This compound, which could be considered as an analogue of salicylic acid in which the carboxyl group is replaced by a less acidic triazolinethione group (Fig. 1), was found to be devoid of anti-inflammatory activity yet retained its analgesic properties: it had the same order of analgesic potency as aspirin, with a lower toxicity. Moreover, it had little effect on the central nervous system, autonomic system, and respiratory system.

We report here the results of a crystal and molecular structure determination of HMT and conformational comparisons of the molecule with the molecular geometry of known derivatives used as pain-relieving drugs.

This investigation was undertaken to provide adequate structural knowledge which might form a basis for an interpretation of the mode of action of these compounds.

METHODS

Colorless single crystals of HMT were obtained by solvent evaporation in the cold from an ethanolic solution.

Crystal data (λ *Mo* $K\alpha = 0.7107$ *A*). HMT: $C_9H_9N_3OS$; monoclinic, $a = 5.942$ [10], $b = 17.771$ [35], $c = 10.319$ [20] Å, $\beta = 102.77$ [20], $Z = 4$; space group $P2_{1/C}$.

A well-formed transparent prism was chosen and the intensities were collected on a Philips PW1100 diffractometer with graphite monochromated radiation at room temperature using the $2\theta/\theta$ scan technique. No absorption corrections were applied. A total of 3205 unique reflections were measured, of which 2025 were considered to be observed [$I > 3\ \sigma(I)$] and were used in the refinement.

Structure determination and refinement. The structure was solved by using the direct-phasing program MULTAN (2). The best set revealed 12 non-hydrogen atoms. A Fourier synthesis was necessary to find the last carbon atoms. The atomic coordinates and thermal parameters were refined by full-matrix least-squares with the program ORION (3). The hydrogen atoms were found by difference Fourier maps. Those of the *methyl* group were placed in their expected positions. All of the hydrogen atoms were given isotropic thermal factors equal to those of the carrier atoms.

A last refinement of all of the parameters of the heavy atoms gave a final R factor of 0.042.

The coordinates and anisotropic thermal parameters for the heavy atoms, the atomic parameters, and isotropic thermal parameters for the hydrogen atoms are available from the authors on request.

Theoretical calculations of the energy of HMT. The energy calculations were made with the semi-empirical function given by Kitajgorodskij (4) with the parameter values proposed by Giglio (5). The approach was based on the calculation of potential energy as a function of the

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[4] The abbreviation used is: HMT, 3-(2-hydroxyphenyl)-4-methyl-1,2,4-Δ-2-triazoline-5-thione.

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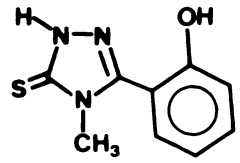

FIG. 1. *3-(2-Hydroxyphenyl)-4-methyl-1,2,4-Δ-2-triazoline-5-thione (HMT)*

orientation around each of the chemical bonds. The torsion angles τ_1, τ_2, and τ_3 are depicted in Fig. 2. They are defined as the angles through which the groups must rotate to coincide with their position in the crystal conformation. Possible deformations of the phenyl and triazole rings were neglected.

Internal molecular energy variations were calculated by varying one torsion angle parameter at a time and keeping the others at observed values.

RESULTS

Description of the structure. Figure 3 is a perspective view of the structure with the atomic numbering. Bond lengths and angles values are given in Tables 1 and 2.

The deviations of the triazole and phenyl rings from planarity are negligible: maximal atomic deviations from the planes are 0.006 Å and 0.004 Å, respectively (Fig. 4). The angle of the two planes is shown by the Newman projection (Fig. 5); its average value is 66°.

The individual distances in the triazoline ring reflect an appreciable delocalization of nonbonded electrons as previously described for similar thioheterocycles (6).

The C(1)—S bond is a partial double bond (1.679 Å), intermediate between the C=S double bond (1.61 Å) and the C—S single bond (1.81 Å). A tautomeric equilibrium thiol ⇌ thione could be involved, but the proton H(N1) has been well positioned by difference Fourier distribution. Such a value, evidence for an electronic delocalization, is in accordance with the reported values for heterocyclic thiones (7–11).

Molecular packing. The molecular arrangement in the unit cell can be described by parallel layers in which intermolecular contacts are one strong hydrogen bond [N(2) ... H—O = 1.83 Å] and Van der Waals contacts [C(3) ... C(6) = 3.483 Å].

The layers are linked by Van der Waals contacts [C(1) ... C(1) = 3.584 Å] and weak hydrogen bonds [N(1) ... H(1)—S = 2.42 Å; S ... H(1)—N(1) = 2.42 Å]. The formation of such "dimers" built, in solution, by these intermolecular hydrogen bonds have already been proposed on the basis of the NMR data (1).

Energy calculations. By calculating the internal energy with variation of torsional parameter τ_2, three maxima and three minima were shown with ΔE = 1 kcal·M^{-1} (Fig. 6). The rotation of the hydroxyl group (τ_3) induced a significant energy change (ΔE = 15 kcal·M^{-1}) with a maximum corresponding to the nearest distance between the hydrogen atom and the triazole ring (Fig. 6). The τ_1 rotation produced the major variation (ΔE = 50 kcal·M^{-1}) and showed two maxima (Fig. 7) corresponding to the rings in a coplanar conformation ($\Delta E \rightarrow \infty$ when C(9) and N(3) are in the *cis* position with respect to the C(2)—C(4) bond; ΔE = 50 kcal·M^{-1} when C(9) and N(3) are in the *trans* position with respect to the C(2)—C(4) bond).

The energy minima are very wide and the rings are

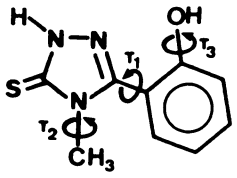

FIG. 2. *Torsional parameters of the conformation of HMT*

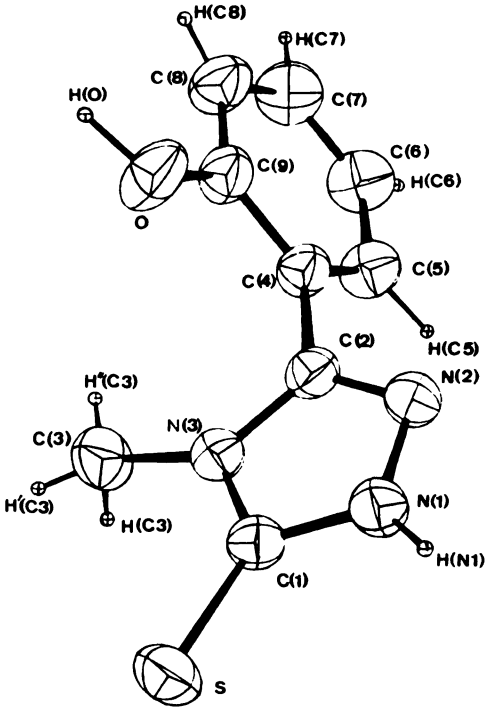

FIG. 3. *Perspective view of HMT*

TABLE 1

Bond lengths of HMT

Bond	Length[a]
	Å
C(1)—N(1)	1.337 (3)
N(1)—N(2)	1.370 (3)
N(2)—C(2)	1.303 (3)
C(2)—N(3)	1.368 (3)
N(3)—C(1)	1.365 (3)
C(1)—S	1.679 (2)
N(3)—C(3)	1.453 (3)
C(2)—C(4)	1.470 (3)
C(4)—C(5)	1.390 (3)
C(5)—C(6)	1.392 (3)
C(6)—C(7)	1.372 (4)
C(7)—C(8)	1.374 (4)
C(8)—C(9)	1.389 (3)
C(9)—C(4)	1.393 (3)
C(9)—O	1.357 (3)

[a] Numbers in parentheses are standard deviations.

TABLE 2

Bond angles of HMT

Bond	Angle[a]
S—C(1)—N(1)	128.8° (2)
S—C(1)—N(3)	127.4° (2)
N(1)—C(1)—N(3)	103.8° (2)
C(1)—N(3)—C(3)	124.9° (2)
C(3)—N(3)—C(2)	126.7° (2)
C(1)—N(3)—C(2)	108.3° (2)
N(3)—C(2)—N(2)	110.6° (2)
C(2)—N(2)—N(1)	104.5° (2)
N(3)—C(2)—C(4)	124.7° (2)
N(2)—C(2)—C(4)	124.7° (2)
C(2)—C(4)—C(5)	121.5° (2)
C(2)—C(4)—C(9)	118.8° (2)
C(4)—C(9)—C(8)	119.9° (2)
C(4)—C(9)—0	116.9° (2)
0—C(9)—C(8)	123.2° (3)
C(9)—C(8)—C(7)	119.6° (3)
C(8)—C(7)—C(6)	121.4° (3)
C(7)—C(6)—C(5)	119.5° (2)
C(5)—C(4)—C(9)	119.7° (2)
C(4)—C(5)—C(6)	120.0° (2)
C(1)—N(1)—N(2)	112.9° (2)

[a] Numbers in parentheses are standard deviations.

free to rotate. Only one electronic delocalization not considered here could limit this mobility.

The two conformations in which the two rings lie in perpendicular planes showed energies closely similar and the curve appears to be nearly symmetrical.

DISCUSSION

HMT, obtained by the cyclization of the salicylhydrazide (1), can be considered as a salicylic acid derivative. It showed a marked analgesic activity comparable to those of non-narcotic aspirin-like drugs.

The mechanism of aspirin-induced analgesia remains unclear, but it is generally assumed that aspirin may act by the inhibition of the biosynthesis of cyclo-oxygenase products such as prostaglandins of the E series and prostacyclin (12–18). Other biochemical mechanisms

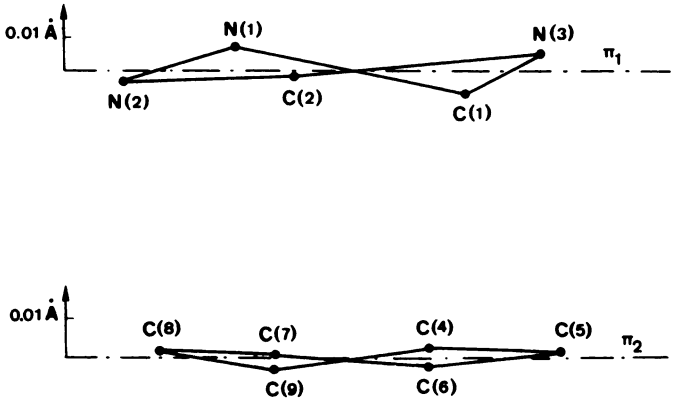

FIG. 4. *Conformations of the planes*

π_1 is defined as C(1), C(2), N(1), N(2), N(3) (triazole ring); $0.755\ X - 0.550\ Y + 0.357\ Z + 3.968 = 0$. π_2 is defined as C(4), C(5), C(6), C(7), C(8), C(9) (phenyl ring); $0.562\ X - 0.424\ Y - 0.710\ Z + 12.063 = 0$.

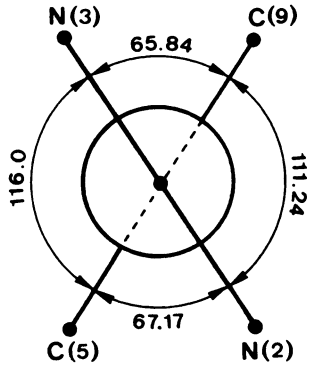

FIG. 5. *Newman projection along the C(2)—C(4) bond*

have been postulated, such as an inhibitory action on cell membrane permeability (19, 20) and inhibition of histamine release (21, 22).

However, the site of action of aspirin and of aspirin-like drugs has not been elucidated. It has been reported that aspirin-like drugs act peripherally at the pain chemoreceptors (23–25). The action of HMT could be explained by its binding at these peripheral nociceptors. The structure of HMT differs from that of salicylic acid by replacement of the carboxylic group responsible for severe ulcerogenic effect (26) by a triazoline ring; therefore, it is of interest to compare stereochemically the phenyltriazole HMT with other analgesic phenyl-substituted heterocycles such as pyrazolone derivatives.

Thus, in the antipyrine molecule, both the phenyl and the pyrazolone rings are planar and are inclined with respect to each other at 52° (27, 28). This dihedral angle reaches values varying from 62 to 68° in the structure of

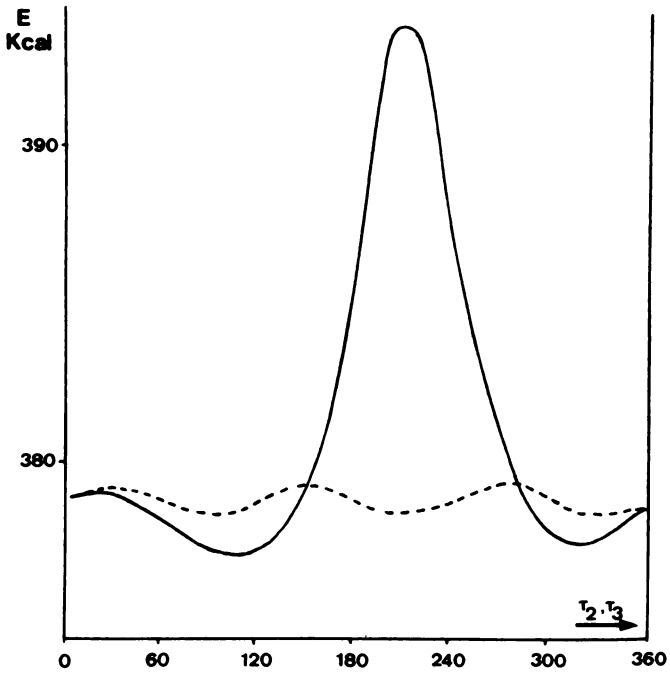

FIG. 6. *Internal molecular energy of HMT calculated by varying the torsional angles* τ_3 (——) *and* τ_2 (– – –)

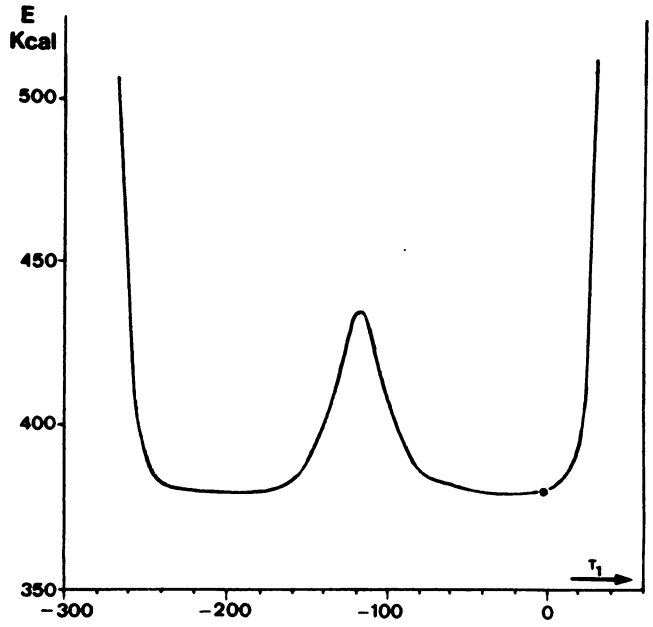

FIG. 7. *Internal molecular energy of HMT calculated by varying the torsional angle* τ_1

some metallic complexes of antipyrine (29). The triazolinethione ring of HMT, structurally comparable to the pyrazolone ring, makes an angle of 66° with that of the benzene ring.

If the relative positionings of aromatic and heterocyclic rings found in the solid state prove to be alike, support is provided for their having similar modes of uptake at the peripheral nociceptors.

In conclusion, HMT shows interesting pain-relieving properties due to its action at a peripheral site; however, it should not be able to cross the blood-brain barrier, which would explain the lack of any central effect.

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