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The Crystal Structure of 2-Amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole

BY J. D. EKSTRAND AND DICK VAN DER HELM

Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019, USA

The crystal structure of 2-amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole has been determined with three-dimensional X-ray diffraction techniques. The crystals are orthorhombic, space group Pbca, with eight molecules in the unit cell; $a = 6.778$ (1), $b = 21.041$ (2), $c = 17.410$ (1) Å. The structure was refined by block-diagonal least-squares techniques to a final R value of 0.055 for all 2565 reflections. The structure contains hydrogen-bonded dimers across a center of symmetry. The thiazole ring is perfectly planar but the molecule, as a whole, is slightly bent. Two possible resonance forms do not completely explain the bond distances observed in the thiazole ring.

Introduction

The title compound is a highly substituted thiazole derivative synthesized for potential use in cancer chemotherapy by Hashem, Berlin, Chesnut & Durham (1976). Tests conducted by Berlin show complete growth inhibition of Bacillus subtilis at a compound concentration of 25 μg ml^{-1} and 50% growth inhibition of human tumor cells (KB) at a compound concentration of 50 μg ml^{-1} (Hashem et al., 1967). The compound is from a group of pyrazolo, isoxazolo and thiazolo systems containing the A, C, and D rings of a heterosteroid. The structure determination of a pyrazole derivative in this group of compounds has been reported previously (Wu, van der Helm & Berlin, 1977).

Experimental

A yellow block-like crystal showing ten identifiable faces and with approximate dimensions of 0.3 × 0.3 × 0.2 mm was selected from a sample recrystallized from ethanol. The space group was determined as Pbca from systematic absences with a GE manual diffractometer. Unit-cell data (Table 1) were measured with Cu $K\alpha_1$ ($\lambda = 1.54051$ Å) radiation. The 2565 intensity data, comprising all unique reflections with 2θ less than 150°, were collected with Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å) on a Nonius CAD-4 automatic diffractometer using θ–2θ scan techniques. A variable scan width, calculated as $(1.0 + 0.1 \tan \theta)°$, was used. The aperture, located 173 mm from the

Table 1. *Crystallographic data*

$C_{13}H_{14}N_2O_2S$	$V = 2486.7$ Å^3
FW 262.0	$Z = 8$
Space group *Pbca*	$D_o = 1.393$ g cm^{-3} (measured by
$a = 6.788 (1)$ Å*	flotation in hexane/CCl_4)
$b = 21.041 (2)$*	$D_c = 1.400$
$c = 17.410 (1)$*	

* Determined by least-squares fit to the $+2\theta$ and -2θ values of 30 reflections taken from all octants of reciprocal space.

crystal, used a variable width of $(4.0 + 0.86 \tan \theta)$ mm and a constant height of 6.0 mm. Maximum scan time was 60s, $\frac{2}{3}$ of the time being spent scanning the peak and $\frac{1}{6}$ of the time on each of the left and right backgrounds. Of the 2565 reflections the net intensity for 319 reflections was indistinguishable from the background having $I \leq 2\sigma(I)$. They were assigned intensities equal to $1.4(I)$ for use in the least-squares refinement. Lorentz, polarization and absorption corrections were applied to the data. The program of Coppens, Leiserowitz & Rabinovich (1965) was used for the absorption corrections ($\mu = 22.20$ cm^{-1}). The scheme used to assign experimental weights to the amplitudes has been previously described (Ealick & van der Helm, 1975).

Structure determination and refinement

The structure was solved by the heavy-atom method. The S position was located from a Patterson synthesis, and after several cycles of refinement all non-hydrogen atoms were located from a difference Fourier map. Anisotropic temperature factors were given to the S, O, N, and C atoms. All fourteen H atoms were located

from a subsequent difference Fourier synthesis and given isotropic temperature factors. The observed structure factors were corrected for the anomalous dispersion effect of the S atom. Secondary extinction corrections were made according to the equation $I_{corrected} = I_o \exp (-C_{ext}P)$. The constant C_{ext} was determined to be 8.3×10^{-6} from the slope of a plot of log F_c/F_o versus P (net count) for 44 reflections having amplitudes greater than 50 and values for $\sin^2 \theta$ less than 0.2. The least-squares refinement, using the block-diagonal method, converged to a value for $R(= \Sigma ||kF_o| - |F_c||/\Sigma|kF_o|)$ of 0.055. The magnitude, $[\Sigma w(F_o - F_c)^2/(m - n)]^{1/2}$, where m is the number of reflections and n is the number of parameters refined, was 1.78. Final parameters are in Tables 2 and 3. The quantity minimized by the least-squares calculation was

Table 3. *Positional parameters* ($\times 10^3$) *and isotropic temperature factors for hydrogen atoms*

Standard deviations are given in parentheses.

	x	y	z	B (Å^2)
H(4a)	628 (3)	485 (1)	252 (2)	6.7 (7)
H(4b)	775 (4)	515 (1)	181 (1)	6.2 (6)
H(5a)	840 (3)	408 (1)	210 (1)	4.7 (5)
H(5b)	823 (4)	429 (1)	113 (1)	6.1 (7)
H(6)	747 (3)	298 (1)	199 (1)	4.5 (5)
H(9)	155 (3)	358 (1)	76 (1)	3.4 (4)
H(14a)	−28 (4)	563 (1)	18 (1)	5.7 (6)
H(14b)	63 (3)	619 (1)	56 (1)	5.6 (6)
H(17a)	669 (3)	195 (1)	255 (1)	6.2 (6)
H(17b)	665 (3)	132 (1)	208 (1)	6.5 (7)
H(17c)	797 (4)	190 (1)	173 (1)	6.2 (6)
H(18a)	−19 (4)	210 (1)	34 (1)	6.2 (6)
H(18b)	96 (3)	266 (1)	3 (1)	5.4 (6)
H(18c)	−61 (3)	273 (1)	69 (1)	5.7 (6)

Table 2. *Atomic fractional coordinates and thermal parameters* (all $\times 10^4$) *for non-hydrogen atoms*

Calculated standard deviations are given in parentheses. Thermal parameters are of the form:
$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	2159 (2)	4828 (1)	705 (1)	487 (9)	271 (7)	464 (8)	64 (6)	−112 (7)	−18 (6)
C(2)	2119 (3)	5447 (1)	744 (1)	583 (11)	298 (9)	442 (9)	65 (8)	−103 (8)	−9 (7)
S(3)	4112.7 (10)	5788.1 (2)	1226.0 (4)	723 (4)	258 (2)	769 (3)	−11 (2)	−234 (3)	−23 (2)
C(4)	6750 (4)	4875 (1)	1907 (2)	560 (12)	386 (11)	874 (15)	−72 (9)	−257 (12)	−34 (11)
C(5)	7513 (3)	4226 (1)	1712 (1)	410 (10)	410 (11)	808 (14)	−43 (8)	−178 (10)	24 (10)
C(6)	6242 (2)	3097 (1)	1725 (1)	376 (9)	357 (9)	412 (8)	68 (7)	−65 (7)	3 (6)
C(7)	4877 (3)	2640 (1)	1516 (1)	462 (9)	253 (7)	347 (8)	70 (7)	−22 (7)	3 (6)
C(8)	3120 (3)	2823 (1)	1164 (1)	440 (9)	274 (7)	341 (8)	−17 (7)	−52 (7)	−10 (6)
C(9)	2746 (3)	3459 (1)	1024 (1)	377 (8)	287 (7)	362 (8)	37 (7)	−65 (7)	−5 (6)
C(10)	4158 (2)	3919 (1)	1212 (1)	356 (8)	269 (7)	346 (8)	26 (7)	−15 (6)	−12 (6)
C(11)	3820 (2)	4598 (1)	1083 (1)	390 (8)	280 (9)	369 (8)	23 (7)	−33 (7)	−17 (6)
C(12)	5040 (3)	5035 (1)	1394 (1)	489 (10)	278 (9)	556 (11)	−8 (8)	−99 (9)	−3 (7)
C(13)	5918 (2)	3736 (1)	1564 (1)	346 (8)	318 (9)	413 (8)	15 (7)	−39 (7)	−17 (6)
N(14)	708 (3)	5822 (1)	431 (1)	888 (14)	303 (9)	822 (12)	204 (9)	−378 (11)	−84 (8)
O(15)	5133 (2)	1996 (1)	1599 (1)	603 (8)	256 (7)	537 (8)	89 (6)	−119 (7)	25 (6)
O(16)	1888 (2)	2334 (1)	968 (1)	671 (9)	301 (7)	637 (8)	−97 (6)	−288 (8)	58 (6)
C(17)	6795 (4)	1789 (1)	2036 (1)	639 (13)	386 (9)	623 (12)	158 (9)	−77 (11)	115 (9)
C(18)	329 (3)	2470 (1)	461 (1)	505 (10)	478 (11)	564 (11)	−117 (9)	−171 (10)	44 (9)
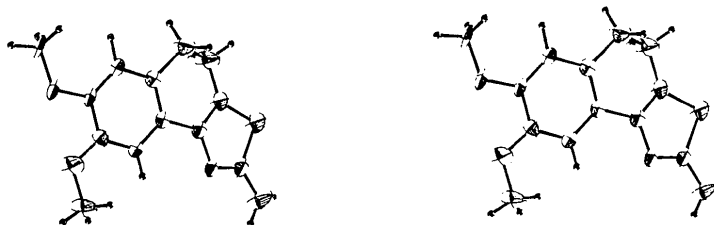
Fig. 1. Stereoview of the molecule generated by the *ORTEP* program (Johnson, 1965).

Table 4. *Least-squares planes and atom deviations* (Å)
from the planes

Atoms with asterisks were used in the calculation of least-squares planes.

(a) Thiazole ring
$$3 \cdot 480x + 0 \cdot 978y - 14 \cdot 926z = 0 \cdot 165$$

N(1)*	0·006	C(4)	−0·185	C(10)	−0·144
C(2)*	−0·005	C(5)	0·308	C(13)	−0·075
S(3)*	0·002	C(6)	−0·264	O(15)	−0·571
C(11)*	−0·003	C(7)	−0·473	O(16)	−0·725
C(12)*	0·002	C(8)	−0·541	C(17)	−0·665
N(14)	0·008	C(9)	−0·399	C(18)	−0·496

(b) Benzene ring
$$2 \cdot 915x - 2 \cdot 082y - 15 \cdot 628z = -1 \cdot 505$$

C(6)*	−0·015	C(10)*	0·007	O(15)	0·086
C(7)*	0·008	C(13)*	0·008	O(16)	0·056
C(8)*	0·008	C(5)	0·141	C(17)	−0·069
C(9)*	−0·015	C(11)	−0·032	C(18)	0·367

$\Sigma\, w_F(kF_o - F_c)^2$. In the last cycle of refinement all parameter shifts of non-hydrogen atoms were less than $0 \cdot 7\sigma$. All 2565 reflections were used in the standard-deviation calculations. A final difference Fourier map showed peaks ranging from −0·43 to 0·42 e Å^{-3} around the S atom location and two peaks (0·43, 0·28 e Å^{-3}) near C(4) and C(5) on opposite sides of the cyclohexadiene ring (see below). The scattering factors for non-hydrogen atoms were taken from *International Tables for X-ray Crystallography* (1962) and those for H from Stewart, Davidson & Simpson (1965). The mean values for $w_F\Delta F^2$ calculated for ranges of F_o were quite constant, validating the weighting scheme used.*

Description and discussion of the structure

A stereoview of the molecule is given in Fig. 1. The molecule contains three fused rings: an aminothiazole

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32182 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

ring, a cyclohexadiene ring and a benzene ring with two attached methoxy groups. Equations of the least-squares planes are given in Table 4. Although the benzene ring itself is planar, the exocyclic atoms are out of this plane, especially C(5) (0·141 Å). The C atoms of the methoxy groups are rotated, to a small extent, out of the plane, in opposite directions. This rotation can also be seen from the torsion angles shown in Fig. 2. The thiazole ring is also planar, while in addition N(14) is in this plane. The other two exocyclic atoms C(4) and C(10) are significantly out of this plane (0·185 and 0·144 Å), and are on the same side of the plane. As a result, all other atoms, with the exception of C(5), are located on that same side of the least-squares plane through the thiazole ring. The cyclohexadiene ring can be considered to be in a half-chair conformation, as can be seen from the torsion angles shown in Fig. 2. Fig. 1 shows the high thermal motion of atoms C(4) and C(5), whose thermal ellipsoids have major axes of 8·2 and 7·1 Å^2. It is even possible that the alternative half-chair conformation exists, to a small extent, in the crystal structure as may be indicated by two small peaks in the final difference Fourier synthesis: one peak of 0·43 e Å^{-3} at 0·97 Å from C(4) and another peak of 0·28 e Å^{-3} at 0·81 Å from C(5), on opposite sides of the C(4)−C(5) bond. It also results in a shortening of the C(4)−C(5) bond [1·501 (3) Å] (Fig. 3).
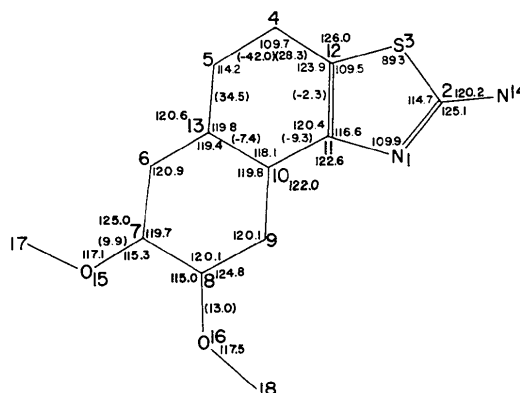

Fig. 2. Bond angles. Standard deviations are between 0·1 and 0·2°. Torsion angles for the cyclohexadiene ring and the methoxy groups are given in parentheses.

The dimensions of various thiazole rings have recently been compared by Form, Raper & Downie (1974). All distances observed (Fig. 3) are within the range of distances cited. The molecule which most closely resembles the present structure is 2-methylamino-benzothiazole (Fehlmann, 1970), in which C(11)—C(12) is fused to a benzene ring. The C(11)—C(12) and the two S—C distances are longer in the benzothiazole structure (distances in square brackets), i.e. C(12)—S(3) 1·729 (2) Å [1·739 (3)], C(2)—S(3) 1·746 (2) Å [1·763 (3)] and C(11)—C(12) 1·352 (3) Å [1·391 (3)], while the other three distances are shorter, i.e. C(11)—N(1) 1·392 (2) Å [1·381 (3)], N(1)—C(2) 1·306 (2) Å [1·297 (3)] and C(2)—N(14) 1·355 (3) Å [1·335 (3)]. Fehlmann considers the C—S bonds in 2-methylaminobenzothiazole to be pure single bonds if shortening due to hybridization is taken into account. We feel, however, that resonance form II, besides the major form (I), needs to be considered in

view of the inequality of the two C—S distances, the actual value of the C(12)—S(3) distance of 1·729 Å, and the C(2)—N(14) distance of 1·355 Å. Even so, neither resonance forms I nor II explains the difference in the C(11)—N(1) and C(2)—N(14) distances.

(I)   (II)
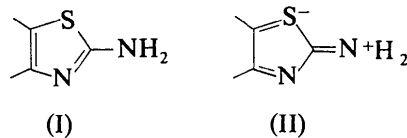
A packing diagram is shown in Fig. 4. Two hydrogen bonds occur across a center of symmetry involving N(14), H(14a) and N(1) ($\bar{x}$, $1 - y$, $\bar{z}$). The N(14)$\cdots$N(1) distance is 3·094 Å, the H(14a)$\cdots$N(1) distance is 2·222 Å, and the N(14)—H(14a)$\cdots$N(1) angle is 163·6°.

Fig. 3. Bond distances. Standard deviations are given in parentheses.

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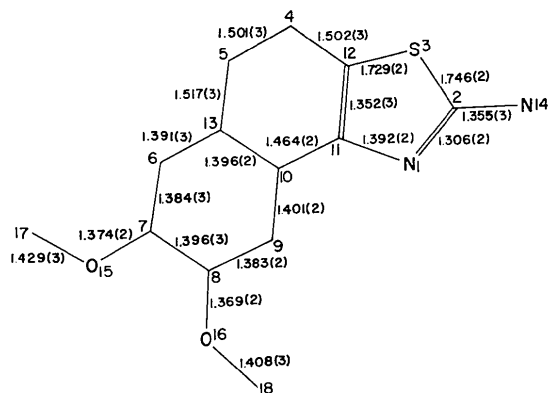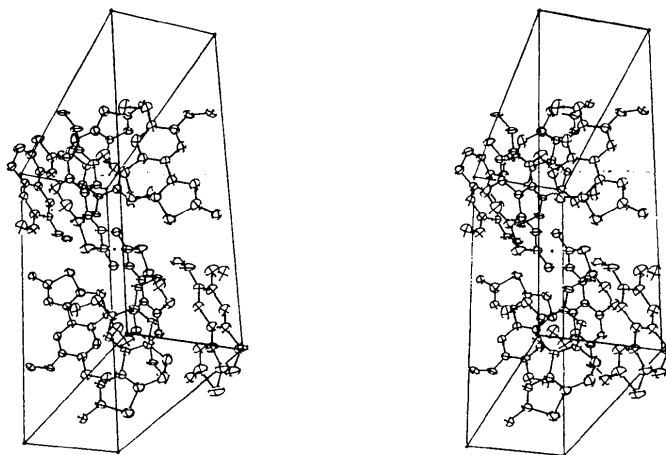Fig. 4. Packing drawing generated by ORTEP (Johnson, 1965) showing hydrogen-bonding across the center of symmetry ($\frac{1}{2}$, $\frac{1}{2}$, $\frac{1}{2}$). Directions of the axes are a →, b ↑, and c ↗.

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The Crystal and Molecular Structures of (+)-Pseudoephedrine and (+)-Pseudoephedrine Hydrochloride

BY M. MATHEW AND GUS J. PALENIK

Center for Molecular Structure, Department of Chemistry, University of Florida, Gainesville, Florida 32611, *USA*
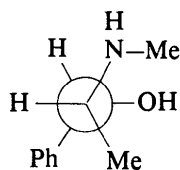
The crystal structures of (+)-pseudoephedrine, I, and (+)-pseudoephedrine hydrochloride, II, have been determined by X-ray diffraction techniques. Both compounds form orthorhombic crystals, with the space group $P2_12_12_1$ and four molecules per unit cell. The unit-cell dimensions are $a = 7.337$ (4), $b = 8.646$ (5) and $c = 16.113$ (7) Å for I and $a = 25.358$ (11), $b = 6.428$ (5) and $c = 6.901$ (5) Å for II. The structures were solved by direct methods and refined by least-squares techniques to R values of 0.065 for I and 0.075 for II. We have demonstrated that protonation does not alter molecular shape since the conformations in I and II are virtually identical. Both molecules, I and II, are in an extended form which is similar to that found in various ephedrines and related phenethylamines.
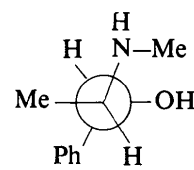
Introduction

The relation between molecular structure and biological activity is intriguing. The possibility of defining the stereochemical requirements of a receptor site by considering the geometry of active drugs has stimulated both theoretical [*e.g.* Pullman, Coubeils, Courrière & Gervois (1972) and Kier (1968*a*) and references therein] and experimental studies. For example, Portoghese (1967) has studied the conformation of ephedrine isomers in solution by NMR techniques, while Hearn, Freeman & Bugg (1973) have reviewed the X-ray work on phenylethanolamines. However, a persistent problem is whether the conformation found by a given physical method is the same as that found at the receptor site. This question is frequently raised in X-ray diffraction studies despite the fact that the drug–receptor interactions are closely related to solid-state effects. An additional complication is introduced if the drug can exist in protonated or deprotonated forms, in which case the conformation may be *p*H dependent. Obviously, the above questions will only be answered by the multifaceted approach. As part of our broad program of studies of antihistamines and bronchodilators, we have undertaken an X-ray study of

(+)-pseudoephedrine and (+)-pseudoephedrine hydrochloride.

Ephedrine and pseudoephedrine can exist as various conformers, and the preferred conformation has been the subject of much controversy. Portoghese (1967) used NMR techniques to assign the conformation 1 to ephedrine and 2 to pseudoephedrine. The crystal structures of various ephedrine salts have been determined and the conformation 1 was found in all cases: the hydrochloride by Bergin (1971), the monohydrogen phosphate by Hearn, Freeman & Bugg (1973) and the dihydrogen phosphate by Hearn & Bugg (1972). However, there are no data on either ephedrine or pseudoephedrine free base or salts of pseudoephedrine. Therefore, we undertook a study of pseudoephedrine free base, I, and pseudoephedrine hydrochloride, II, to