The Biological Activity and Crystal Structure of 2-Allylamino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]thiazole (1)

A. Rahman and Dick van der Helm

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

Melvin D. Herd, M. M. Hashem and K. Darrell Berlin

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

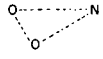
Received January 7, 1980

Screening data for the carcinostatic activity of 2-allylamino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]-thiazole is reported. Significant T/C values (survival ratio) were found when the title compound was used to treat colon 38 tumors in the testing program of the National Cancer Institute. A single crystal X-ray diffraction analysis was made of the compound and revealed an essentially planar arrangement of the aromatic and heterocyclic rings. The compound crystallizes in the space group $P2_1/c$ with cell dimensions a = 7.9177(27) Å, b = 14.999(10) Å, c = 13.237(4) Å, β = 107.56(2)°, Z = 4 at −135 ± 2°C. The intensity data were collected at low temperature using CuK$\bar{\alpha}$ radiation. The structure was determined by direct methods and refined to an R-factor of 0.036 for the 2606 observed data. The internuclear distances were calculated between the two oxygen atoms and N(1) for comparison with such "triangulation" data of other systems with known inhibitory characteristics of cell growth.

J. Heterocyclic Chem., **17**, 1549 (1980).

Introduction.

In studies concerned with a range of biological action in certain polycyclic heterocycles (2-6), a potentially useful structure-activity relationship appeared to exist when methoxy groups were specifically located in the system (2). Cheng and co-workers had suggested earlier (7) that a possible correlation could be present between anti-leukemic activity and critical distances involving a nitrogen and two oxygen atoms situated in a "triangular" arrangement in a specific family of heterocycles. We wish to report herein screening data from the National Cancer



Institute (NCI) on the title compound **1** as well as a single crystal, X-ray diffraction analysis of the structure.

Crystal and Intensity Data.

Yellow single crystals of **1** (m.p. 133°-134°) were obtained by recrystallization from dry ether. A suitable crystal of size (0.24 × 0.14 × 0.10)mm^3 was chosen for data collection. The crystal system is monoclinic, space group $P2_1/c$ with four molecules in the unit-cell; a = 7.9177(27), b = 14.999(10), c = 13.237(4) Å, β = 107.56(2)°. Unit-cell data (Table 1) were measured with CuKα_1 radiation (λ = 1.54051 Å). A total of 3071 reflections comprising all unique data with $2\theta \leq 150°$ were collected with CuK$\bar{\alpha}$ radiation (λ = 1.5418 Å) on a Nonius CAD-4 automatic diffractometer equipped with Enraf-Nonius, cold-stream cooling device, using θ-2θ scan technique. A variable scan width of (0.9 + 0.14 tanθ)°, as determined from the crystal mosaic, and a variable horizontal aperture width of (4.0 + 0.86 tanθ)mm with constant vertical width of 6 mm were used. A maximum of 90 s was spent on each reflection (60 s for scanning the peak and 15 s for each of the left and right backgrounds). The intensity of a monitor reflection, measured after every 3000 seconds of X-ray exposure showed a maximum variation of 4%. The orientation matrix was checked after every 200 observations. 432 reflections were considered indistinguishable from background on the basis that net count was less than 2 σ(I). Lorentz, polarization and absorption corrections were applied to the data. The program of Coppens, Leiserowitz and Rabinovich (8) was used for the absorption correction (μ = 17.18 cm^{-1}). An experimental weight, based on counting statistics, was assigned to each structure factor (9).

Table 1

Crystallographic Data

$C_{16}H_{18}N_2O_2S$	
MW = 302.14	
Space Group $P2_1/c$	
Z = 4	
Cell dimensions *(−135°C)	(25°C)
a = 7.9177(27) Å	a = 8.1503(16) Å
b = 14.999(10) Å	b = 14.825(4) Å
c = 13.237(4) Å	c = 13.860(3) Å
β = 107.56(2)°	β = 106.96(1)°
V = 1498.8 Å^3	V = 1544.0 Å^3
	D_o = 1.305 g/cm^3 (hexane/CCl_4)
	D_c = 1.301 g/cm^3

*Determined by a least-squares fit to the $+2\theta$ and -2θ values of 48 reflections taken for all octants of reciprocal space.

Structure Determination and Refinement.

The structure was solved by direct methods using the

0022-152X/80/071549-04$02.25

Table 2

Positional parameters ($x10^5$) of non-hydrogen atoms. The standard deviations for the last digit are in parentheses.

Atom	x	y	z
N(1)	36576(17)	79352(8)	37944(10)
C(2)	26330(21)	83670(10)	29857(12)
S(3)	22355(6)	78254(3)	17563(3)
C(4)	41305(25)	61645(11)	18917(12)
C(5)	46348(23)	53964(11)	26847(12)
C(6)	68723(21)	50885(10)	44676(12)
C(7)	77171(20)	53178(10)	55141(12)
C(8)	73571(20)	61414(10)	59120(11)
C(9)	62022(21)	67351(10)	52531(12)
C(10)	53870(20)	65121(10)	41873(12)
C(11)	41802(21)	71307(10)	34567(12)
C(12)	35674(22)	69497(10)	24036(12)
C(13)	56922(21)	56802(10)	37962(12)
N(14)	19572(18)	91953(9)	30355(10)
C(15)	20358(23)	95385(11)	40853(12)
C(16)	11153(24)	104145(12)	40029(13)
C(17)	17773(23)	111154(12)	45910(16)
O(18)	89372(16)	48004(7)	62323(9)
O(19)	82357(15)	62829(7)	69643(8)
C(20)	92848(23)	39311(11)	58967(14)
C(21)	77200(26)	70362(11)	74526(13)

Table 3

Positional parameters ($x10^3$) and isotropic temperature factors for hydrogen atoms. Standard deviations for the last digit are given in parentheses.

Atom	x	y	z	B(Å²)
H(4a)	319(2)	595(1)	124(2)	2.5(4)
H(4b)	520(3)	637(1)	165(2)	3.6(3)
H(5a)	530(2)	493(1)	243(1)	2.2(3)
H(5b)	347(3)	511(1)	274(2)	3.0(4)
H(6)	707(2)	451(1)	418(1)	1.8(4)
H(9)	595(2)	728(1)	552(1)	1.5(4)
H(14)	104(3)	933(1)	254(2)	2.6(4)
H(15a)	331(3)	961(1)	452(2)	2.8(5)
H(15b)	146(3)	908(1)	445(2)	3.2(5)
H(16)	−10(3)	1043(1)	350(2)	4.4(5)
H(17a)	116(3)	1165(1)	454(2)	3.2(4)
H(17b)	299(3)	1109(1)	510(2)	3.5(4)
H(20a)	1014(3)	369(1)	653(2)	3.7(4)
H(20b)	819(3)	357(1)	566(2)	3.2(4)
H(20c)	980(2)	397(1)	531(1)	2.4(5)
H(21a)	844(3)	700(1)	822(2)	3.0(5)
H(21b)	799(3)	761(1)	715(2)	3.7(5)
H(21c)	648(3)	697(1)	741(2)	3.6(4)

computer program MULTAN (10). All non-hydrogen atoms were located from the E-map. The structure was refined using a block-diagonal least squares program. The quantity minimized was $\Sigma w(|kFo| - |Fc|)^2$. After several cycles of refinement, a difference Fourier map was calculated which showed all the H positions. The structure was further refined with anisotropic thermal parameters for C, N, O and S atoms and isotropic thermal parameter for H atoms. The R-factor, defined as

$$R = \frac{\Sigma \| kFo | - | Fc \|}{\Sigma | kFo |}$$

based on final parameters (Tables 2 and 3*) (*Anisotropic thermal parameters and structure factors are available from the authors.) is 0.036 for 2606 observed reflections (0.046 for all reflections). In the last cycle of refinement, all shifts were less than 0.3 σ. All 3071 reflections were used for the calculation of standard deviations. A final difference Fourier map showed a maximum residual electron density of $\pm$ 0.2 e Å^{-3}. The magnitude $[\Sigma w(Fo - Fc)^2/(m - n)]^{1/2}$, where m is the number of reflections and n is the number of parameters refined, was 1.66. The scattering factors for non-hydrogen atoms were taken from International Tables for X-ray Crystallography (11) and those

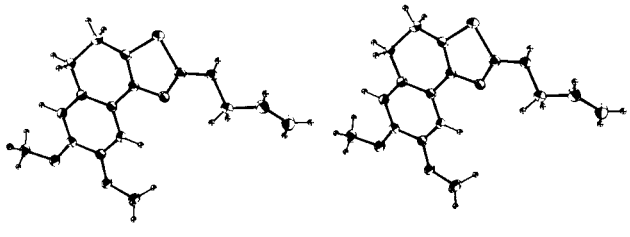


Figure 1. Stereoview of the molecule generated by the ORTEP program (Johnson, 1965).

Table 4

Screening Data for Antitumor Activity of **1** (NSC-251207)

Tumor	Dose/Inj.(mg/kg) (a)	T/C
B16 melanocarcinoma	100 (b)	100
	50	107
	25	116
	12.5	103
L-1210 lymphoid leukemia	100 (c)	97
	50	97
	25	101
	12.5	97
Lewis lung carcinoma	100 (b)	117
	50	99
	25	99
	12.5	98
$CD8F_1$ mammary tumor	100 (c)	122
	50	105
	25	105
	12.5	100
Colon 38 tumor	100 (c)	196
	50 (c)	152
	25 (c)	163
	12.5 (b)	128

(a) The dose/injection refer to mg. or compound injected per kilogram of animal weight. (b) Male mice. (c) Female mice.

for H from Stewart, Davidson and Simpson (12). The observed structure factors were corrected for anomalous dispersion of the S atoms.

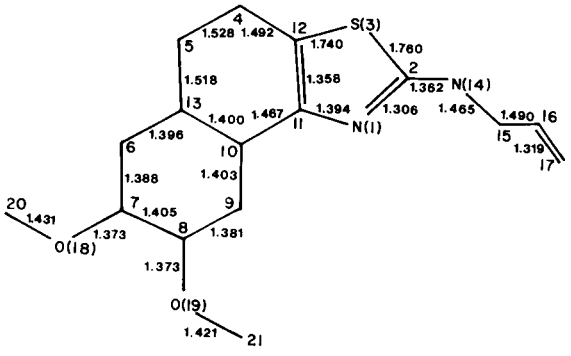


Figure 2. Bond distances. Standard deviations are .002 Å.

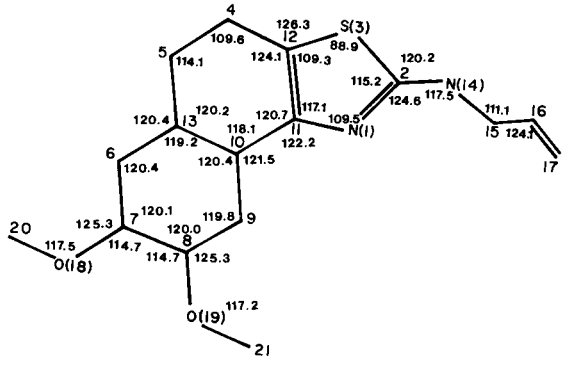


Figure 3. Bond angles. Standard deviations are 0.1°.

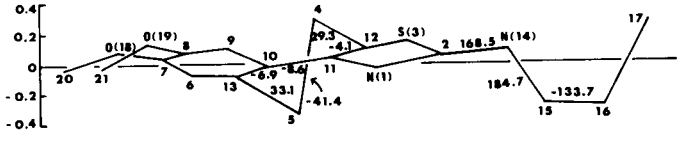


Figure 4. Conformational angles around the cyclohexadiene ring and allyl group. View is with respect to the least-squares plane through the molecule.

Discussion.

Since **1** exhibited cidal action against *Bacillus subtilis* and KB cells (2), the thiazole (NSC-251207) was tested in several tumor systems by NCI. The data are provided in Table 4 and are standard screens at NCI. Although the T/C (survivor ratio) was inadequate with several tumor systems examined, the colon 38 tumor appears vulnerable to destruction by **1**. The highest T/C was 196 at a dose/injection of 100 mg/kg weight of the test mice. Additional screening is in progress.

In view of these findings, it seemed advisable to perform an X-ray diffraction analysis of a single crystal of **1**. Moreover, the heterocyclic system of **1** is part of a program to determine structures in a series of bi- or tricyclic molecules with known or potential biological utility, which contain a pyrazole, isoxazole, or thiazole unit (6). A stereoview of the molecule and schematic diagrams with numbering system, bond lengths and bond angles are shown in Figures 1, 2 and 3. The molecule contains three fused rings: allylaminothiazole, a cyclohexadiene ring and a benzene ring with two methoxy groups attached to it. The thiazole ring is perfectly planar with a maximum atom deviation of less than 0.001 Å. The exocyclic atom N(14) and the allyl carbon atoms (C(15), C(16) and C(17)) are relatively close to this plane with distances of respectively 0.061, −0.199, −0.207 and 0.415 Å. This result is reflected in the conformatinal angles of the side chain which are given in Figure 4. The benzene ring is approximately planar with individual atom deviations between 0.003 and 0.015 Å. The exocyclic atoms C(5), C(11), O(18) and O(19) are −0.163, +0.045, +0.061 and +0.025 Å away from this plane. The molecule as a whole is approximately planar and this is shown in Figure 4. The largest deviations are C(4) and C(17) which are 0.283 and 0.270 Å above the plane and C(5), C(15) and C(16) which are 0.350, 0.276 and 0.287 Å below the plane. The cyclohexadiene ring is in a half-chair-conformation, as can be seen from the torsion angles (Figure 4).

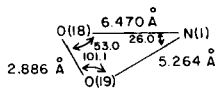
The bond lengths and bond angles in compound **1** are similar to those found in 2-amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]thiazole (**2**)(6c). The differences which are larger than 0.010 Å for the two compounds are the C(2)-S(3), C(12)-S(3), C(4)-C(5) and O(19)-C(21) bonds, which are all longer in compound **1** by respectively, 0.014, 0.011, 0.027 and 0.013 Å. We believe that all these distances in **1** are more reliable and that the apparent shortening of these bonds in thiazole **2** are caused by the thermal motion of the atoms involved in view of the fact that the data for compound **2** were taken at room temperature, while those for the present compound were taken at −138°C.

As in compound **2**, we conclude from the bond distances of the thiazole ring in **1**, that this ring exists primarily in the resonance form with double bonds between C(11)-C(12) and N(1)-C(2) with a small contribution of the resonance form with double bonds between C(11)-N(1) and C(12)-S(3), resulting in a small negative charge on S(3) and a small positive charge on N(14).

The hydrogen atom on N(14) is involved in a weak bifurcated hydrogen bond system with ether oxygen atoms O(18) and O(19) of the molecule at (x − 1, 1½ − y, z − ½). The dimensions are N(14)...O(18) : 3.20 Å, N(14)...O(19) : 2.95 Å, while the N-H...O angles are 160° and 133° respectively.

For the sake of comparison, a calculation was made of the triangulation data, as shown below, from the X-ray analysis. The corresponding 2-amino-4,5-dihydro-7,8-

dimethoxynaphtho[1,2-*d*]thiazole (**2**) (3,13) gave values



for O(18)-N of 6.63 Å and for O(19)-N of 5.37 Å from a simple triangulation calculation. This compound had displayed inhibition of *B. subtilis* and KB cell growth (3). Work is in progress to determine the scope of the activity of this group of thiazoles.

REFERENCES AND NOTES

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