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The Crystal and Molecular Structure of *N*-(Thioacetyl)tryptamine. A Radioprotective Indole Compound

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The crystal structure of N-(thioacetyl)tryptamine, a radioprotective agent, has been determined by the X-ray method. The crystal is monoclinic, space, group $P2_1/c$ with the unit cell dimensions: a=23.761(5), b=5.553(1), c=8.889(2) Å, and β=94.04(4)°. The structure was solved by the direct method and succesive Fourier syntheses, and refined by the block-diagonal least-squares method to give a final R-value of 0.072. In the crystal, the molecules are held together with van der Waals contacts between the nonpolar groups of adjacent molecules, and an intermolecular hydrogen bond between the sulfur and nitrogen atoms of the side chain (N-H···S=3.322 Å). The folded conformation observed in this compound could be related to the protection of DNA against irradiation.

Indolylalkylamines containing sulfur atoms could be expected to be radioprotective agents in living cells, because other indolylalkylamines such as serotonin and tryptamine are well known to act as radioprotective agents,[1–4)] and the sulfur compounds such as cysteine, cysteamine and 2-(2-aminoethyl) thiouronium salts are also used as radioprotective agents.[5–9)] Shinoda *et al.*[10)] examined the relationship between the chemical structures of these indolylalkylamines and their effects in protecting radiation damage, using mice irradiated with X-rays, and confirmed that *N*-(thioacetyl)tryptamine (TATP) was a potent radioprotective agent.

During a series of structural studies of the radioprotective indolylalkylamines,[11)] we have determined the crystal structure of TATP; this will be reported in this paper.

Experimental

Preliminary oscillation and Weissenberg photographs showed the space group to be $P2_1/c$. The density was measured by the floatation method in a benzene–carbon tetrachloride mixture. The unit cell dimensions were refined on a Rigaku Denki automatic four-circle diffractometer with graphite-monochromated Cu $K\alpha$ radiation. The crystal data are shown in Table 1.

The intensity data were collected, using a single crystal with dimensions 0.5×0.3×0.2 mm, on the diffractometer by $\omega/2\theta$ scanning technique within $\sin\theta/\lambda$ less than 0.595 Å^{-1}. Scan speed was 4°/min, background being measured for 5 s.

Table 1. Crystal data

Chemical formula	$C_{12}H_{14}N_2S$
Molecular weight	218.31
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell constant	
a/Å	23.761(5)
b/Å	5.553(1)
c/Å	8.889(2)
β/°	94.04(4)
Volume/Å^3	1169.8(5)
Z	4
D_m/g cm^{-3}	1.233(1)
D_x/g cm^{-3}	1.240
F(0 0 0)	464

Intensities of 2009 independent reflections were corrected for Lorentz and polarization factors, but not for absorption. The intensities of four standard reflections, measured every 100 reflections, showed no deterioration during the course of the data collection.

All numerical calculations were carried out on an ACOS-700 computer of the Computation Center of Osaka University using UNICS program.[12)] Atomic scattering factors in "International Tables for X-Ray Crystallography"[13)] were used.

Determination and Refinement

The structure was solved by the direct method (program MULTAN[14)]). An E-map computed using the 160 reflections with $|E|\geqq 1.20$ (absolute figure of merit=1.14) revealed the positions of sulfur atom and non-hydrogen atoms of the indole ring. The coordinates of all the remaining non-hydrogen atoms were obtained by successive Fourier syntheses. The structure was refined by a block-diagonal least-squares method. From a difference map at the stage of R-value=0.12, the positions of all fourteen hydrogen atoms were

Table 3. Atomic coordinates (×10^4) and their standard deviations

Atom	x	y	z
N(1)	8328(1)	12654(2)	10143(2)
C(2)	7779(1)	11757(3)	10008(2)
C(3)	7747(1)	9828(2)	9084(2)
C(4)	8528(1)	7783(2)	7671(2)
C(5)	9086(1)	7938(3)	7409(2)
C(6)	9426(1)	9732(3)	8069(2)
C(7)	9219(1)	11407(3)	9009(2)
C(8)	8656(1)	11265(2)	9279(2)
C(9)	8299(1)	9468(2)	8616(2)
C(10)	7237(1)	8343(3)	8482(3)
C(11)	6707(1)	9515(3)	8748(3)
N(12)	6231(1)	8178(2)	8083(2)
C(13)	5919(1)	8676(2)	6857(2)
S(13)	6049(0)	10946(1)	5713(1)
C(14)	5425(1)	7045(3)	6544(2)

Table 5. Hydrogen atom coordinates ($\times 10^3$) with their standard deviations

Atom	x	y	z
H(1)	847(1)	1381(3)	1071(2)
H(2)	747(1)	1244(3)	1051(2)
H(4)	828(1)	648(2)	719(2)
H(5)	927(1)	675(3)	669(2)
H(6)	984(1)	973(3)	784(2)
H(7)	946(1)	1269(3)	953(2)
H(10A)	727(1)	662(3)	909(2)
H(10B)	719(1)	834(2)	724(2)
H(11A)	671(1)	1135(3)	817(2)
H(11B)	682(1)	965(3)	1001(2)
H(12)	616(1)	675(3)	861(2)
H(14A)	554(1)	556(3)	622(2)
H(14B)	521(1)	682(4)	739(3)
H(14C)	512(1)	770(4)	574(2)

determined (peak height: 0.25—0.40 e·Å^{-3}); these positions were included in subsequent refinements with isotropic temperature factors.

In the later stage of refinement, the following weighting scheme was used: $w=0.71$ for $F_0=0.0$, $w=1.0$ for $0<F_0\leqq 15.0$ and $w=1.0/[1.0+0.095(F_0-15.0)]$ for $F_0>15.0$. In the last stage of refinement, none of the positional parameters shifted more than one-fourth of the estimated standard deviations. The final R-value excluding $F_0=0$ is 0.072. The residuals in the difference map were within the range of ± 0.2 e·Å^{-3}. The observed and calculated structure factors are listed in Table 2.[15] The final positional and thermal parameters for non-hydrogen atoms are given in Tables 3 and 4,[15] respectively. The coordinates for hydrogen atoms are given in Table 5.

Results and Discussion

Molecular Structure. The bond lengths and angles are given in Fig. 1, together with the atomic numbering used in this work. Their standard deviations are 0.004 to 0.009 Å for lengths and 0.3 to 0.5° for angles. The bond lengths of N–H or C–H are from 0.87 to 1.13 Å. The equations of the least-squares planes for the indole ring and the thioacetyl group and the deviations of atoms from these planes are listed in Table 6.

Table 6.

Equations of the best planes expressed by $m_1X+m_2Y+m_3Z=d$ in an orthogonal space

Plane	m_1	m_2	m_3	d
Indole ring	0.1669	−0.5961	0.7854	6.0448
Thioacetyl group	0.6013	−0.6039	−0.5233	2.0865

Deviations (Å) from the best planes:

Indole ring		Thioacetyl group	
N(1)*	0.025	N(12)*	0.019
C(2)*	0.011	C(13)*	−0.021
C(3)*	−0.004	S(13)*	−0.018
C(4)*	−0.021	C(14)*	0.019
C(5)*	0.012	C(11)	−0.083
C(6)*	0.005	H(12)	0.127
C(7)*	0.013		
C(8)*	0.022		
C(9)*	−0.021		
C(10)	−0.120		
H(1)	0.088		
H(2)	0.006		
H(4)	0.022		
H(5)	−0.018		
H(6)	0.014		
H(7)	0.042		

Atoms with asterisks define the plane.

The bond lengths and angles of the indole ring agree well with those found in the related indole derivatives within their standard deviations,[16] but the bond lengths of the side chain are significantly different: the C(10)–C(11) and C(11)–N(12) bonds are shorter than 1.511 and 1.463 Å of the average bond lengths found in the substituted tryptamine derivatives.[16] The shortening of the N(12)–C(13) bond indicates clearly the contribution of a resonance form:-N(12)⩸C(13)⩸S(13).

The indole ring is planar within a maximum deviation of 0.025 Å at the N(1) atom, whereas the C(10) atom deviates significantly from the plane, probably due to the effect of the crystal packing. The thioacetyl group is also planar and its plane makes a dihedral angle of 87.2° to the indole ring.

The conformation of TATP projected onto the indole ring plane is shown in Fig. 2. The bond sequence of C(3)–C(10)–C(11)–N(12) is the extended form, due

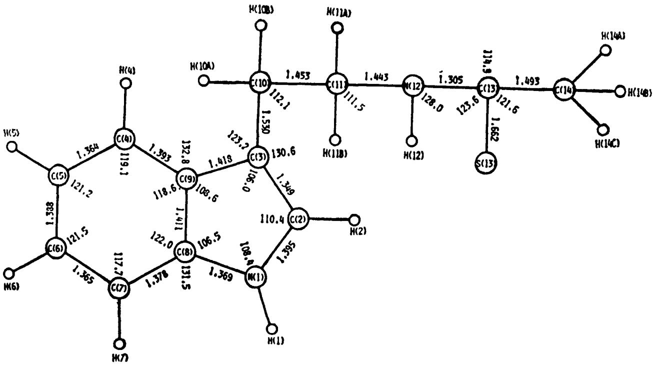

Fig. 1. The bond lengths and angles for non-hydrogen atoms.

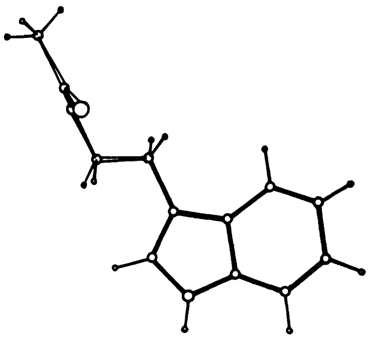

Fig. 2. The conformation of TATP molecule projected onto the indole ring.

to the attachment of the thioacetyl group to the N(12) atom; the torsion angles of C(2)–C(3)–C(10)–C(11) and C(3)–C(10)–C(11)–N(12) are 12.6° and 176.0°, respectively. A similar conformation is also found in the *N*-monosubstituted tryptamine such as melatonin.[17,18] On the other hand, the bond sequence of C(11)–N(12)–C(13)–S(13) takes the folded form: the torsion angles of C(10)–C(11)–N(12)–C(13) and C(11)–N(12)–C(13)–S(13) are −104.4° and 4.9°, respectively.

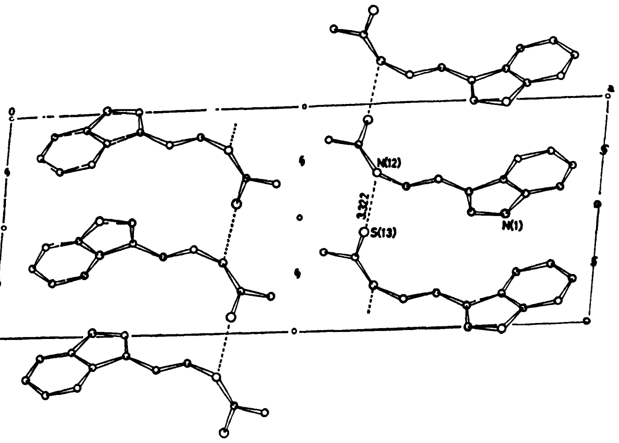

Fig. 3. Crystal packing of TATP viewed along the b-axis. The dotted lines represent possible hydrogen bonds.

Crystal Structure. Figure 3 shows the crystal structure viewed down the b-axis, where the hydrogen bonds are represented by the dotted lines. The indole rings related by c-glide form a zig-zag sheet which is stabilized by the van der Waals contacts with the neighboring sheets related by b-translation and inversion. The N(1) atom does not take part in any hydrogen bond. The 2-(thioacetylamino)ethyl side chains arranged parallel to the c-axis are linked by the hydrogen bonds between the N(12) and S(13) atoms (N(12)···S(13), 3.322 Å, H(12)···S(13), 2.42 Å, ∠N(12)–H(12)···S(13), 159.8°).

No stacking between the indole rings and no contacts shorter than 3.5 Å were observed.

The TATP molecule could exert its radioprotective effect in a manner similar to the mechanism proposed for indolylalkylamines:[19] the formation of the charge-transfer complex between nucleic acid bases and indole ring may protect the formation of peroxide radicals of the bases by irradiation. The role of the sulfur atom is thought to be the stabilization of the charge-transfer complex by the hydrogen bond between S(13) atom and the hydroxyl group of phosphate backbone of DNA, from the CPK model fitting based on the B-type DNA. Since the sulfur atom is said to act as a radical scavenger,[20] it may further protect the cleavage of the phosphodiester linkage of DNA.

References

1) Z. M. Bacq, *Acta Radiologica*, **41**, 47 (1954).
2) Z. M. Bacq and A. Herve, *Strahlentherapie*, **95**, 215 (1954).
3) H. Langendorff and R. Koch, *Strahlentherapie*, **98**, 245 (1955).
4) P. Dukor and R. Shuppli, *Experientia*, **17**, 257 (1961).
5) H. M. Patt, E. B. Tyree, R. L. Straube, and D. E. Smith, *Science*, **110**, 213 (1949).
6) H. Langendorff, R. Koch, and U. Hagen, *Strahlentherapie*, **95**, 238 (1954).
7) A. Herve and Z. M. Bacq, *Brit. J. Radiol.*, **24**, 617 (1951).
8) D. G. Doherty, W. T. Burnett. Jr., and R. Shapira, *Radiat. Res.*, **7**, 13 (1957).
9) B. G. Crough and R. R. Overman, *Science*, **125**, 1092 (1957).
10) M. Shinoda, S. Ohta, T. Hino, and S. Akaboshi, *Yakugaku Zasshi*, **94**, 1620 (1974).
11) M. Inoue, T. Sakaki, A Wakahara, and K. Tomita, *Biochim. Biophys. Acta*, **543**, 123 (1978).
12) The Universal Crystallographic Computing System-Osaka. The Computing Center, Osaka University (1973).
13) "International Tables for X-Ray Crystallography," Kynoch Press, Birmingham (1974), Vol. 4.
14) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
15) Tables 2 and 4 have been deposited at the Chemical Society of Japan (Document No. 8116).
16) T. Ishida, Dissertation, Faculty of Pharm. Sci., Osaka Univ., (1979).
17) A. Mostad and C. Römming, *Acta Chem. Scand., Sect. B*, **28**, 564 (1974).
18) A. Wakahara, T. Fujiwara, and K. Tomita, *Chem. Lett.*, **1972**, 1139.
19) K. Tomita, *Yuki Gosei Kagaku Kyokai Shi*, **31**, 747 (1973).
20) A. Hanaki and S. Akaboshi, *Japan Analyst*, **15**, 518 (1966).