

Fig. 1. A PLUTO diagram of the structure showing the atom-labelling scheme.

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## Structure of 5-Hydroxyindole-3-acetic Acid

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**Abstract.** C<sub>10</sub>H<sub>9</sub>NO<sub>3</sub>, *M<sub>r</sub>* = 191.19, monoclinic, *P*2<sub>1</sub>/*c*, *a* = 5.892 (1), *b* = 5.141 (1), *c* = 29.305 (6) Å, β = 102.61 (3)°, *V* = 866.3 (3) Å<sup>3</sup>, *Z* = 4, *D<sub>m</sub>* = 1.439 (2), *D<sub>x</sub>* = 1.466 g cm<sup>-3</sup>, λ(Cu *K*α) = 1.5418 Å, μ = 8.74 cm<sup>-1</sup>, *F*(000) = 400, *T* = 293 K, final *R* = 0.053 for 1420 (*|F<sub>o</sub>* > 0.0) independent reflections. The molecule takes a planar conformation, in which the dihedral angle between the indole ring and the carboxyl group is 175.5 (3)°. The molecules in the crystal are held by hydrogen bonds between the centrosymmetrically related carboxyl groups (forming 'cyclic dimers'), between the hydroxyl groups, and between NH(indole) and O(carboxyl).

**Introduction.** Indole derivatives, widely distributed in living cells as tryptophan metabolites, have important biological functions.

5-Hydroxyindole-3-acetic acid (5-HIAA) is excreted into urine as a major metabolite of serotonin. Since the biological activity (plant growth hormone) of indole-3-acetic acid (IAA), a related

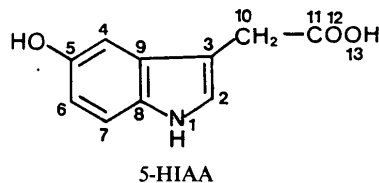
the OH oxygen to another OH group. For 5-hydroxy-7,4'-dimethoxyflavanone (Miles, Main & Nicholson, 1989*b*) the CO...H—O angle is 148°.

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### References

- MILES, C. O., MAIN, L. & NICHOLSON, B. K. (1989*a*). *Aust. J. Chem.* **42**, 1103–1113.  
 MILES, C. O., MAIN, L. & NICHOLSON, B. K. (1989*b*). *Acta Cryst.* **C45**, 681–683.  
 OLD, K. B. & MAIN, L. (1982). *J. Chem. Soc. Perkin Trans. 2*, pp. 1309–1312.  
 SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

final metabolite of tryptophan, is closely related to the molecular conformation (Kaethner, 1977; Farrimond, Elliott & Clack, 1978), it is important to investigate the molecular conformation of 5-HIAA in considering its biological functions.



**Experimental.** Crystals were grown as needles from an ethanol/butanol (1:1) mixture by slow evaporation at 293 K. Crystal density was measured by the flotation method using a C<sub>6</sub>H<sub>6</sub>–CCl<sub>4</sub> mixture. A single crystal with approximate dimensions 0.2 × 0.1 × 0.4 mm was mounted on a Rigaku AFC-5 diffractometer with graphite-monochromated Cu *K*α radiation. Cell parameters were refined by the

least-squares method using  $2\theta$  angles of 25 reflections ( $45 < 2\theta < 60^\circ$ ). Intensities were measured by the  $\omega$ - $2\theta$  scan technique with a scan rate of  $3^\circ \text{ min}^{-1}$  in  $2\theta$  and a scan width of  $\Delta(2\theta) = (1.05 + 0.15 \tan \theta)^\circ$ ; background was counted for 5 s at both sides of each reflection. Four standard reflections (300, 020, 0,0,16, 228) were remeasured every 100 reflections and showed no significant variations ( $\pm 2\%$ ). A total of 1460 independent reflections within  $\theta_{\text{max}} = 65^\circ$  ( $\sin \theta / \lambda < 0.588 \text{ \AA}^{-1}$ ) were collected ( $h - 6$  to  $6$ ,  $k 0$  to  $6$ ,  $l 0$  to  $34$ ), and corrected for Lorentz and polarization effects; neither absorption nor extinction corrections were applied.

The structure was solved by direct methods with *MULTAN87* (Debaerdemaeker, Germain, Main, Tate & Woolfson, 1987) and successive Fourier syntheses, and refined by a block-diagonal least-squares procedure using anisotropic thermal parameters for the non-H atoms. 1420 reflections having  $|F_o| > 0.0$  were used for the refinement. The refinement was carried out to minimize  $\sum w(|F_o| - |F_c|)^2$ . Positions of all the H atoms were calculated and were verified on a difference Fourier map. The H atoms were included in further refinement with isotropic thermal parameters. The weighting function was  $w = 1.0 / [\sigma(F_o)^2 + 0.04024|F_o| - 0.00029|F_o|^2]$ . The number of observations per refined parameter is 8.66 and  $S = 1.653$ . The final  $R$  and  $wR$  values are 0.053 and 0.067, respectively.  $(\Delta/\sigma)_{\text{max}} = 0.12$  for non-H positional parameters.  $\Delta\rho = -0.28$ – $0.31 \text{ e \AA}^{-3}$ . The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). For all crystallographic computations, *The Universal Crystallographic Computation Program System - Osaka* (1979) was used. All the computations were performed on a MicroVAXII computer at the Computation Center, Osaka University of Pharmaceutical Sciences. The final atomic parameters are listed in Table 1.\*

**Discussion.** The molecular conformation of 5-HIAA drawn by *ORTEPII* (Johnson, 1976) is shown in Fig. 1. Bond lengths and angles for non-H atoms are given in Table 2.

The C(2)—C(3)—C(10) angle is about  $10^\circ$  larger than the C(9)—C(3)—C(10) angle, and this may be explained by the repulsion between the C(2) and C(11) atoms caused by the *cis* orientation of C(10)—C(11) with respect to C(2)—C(3) around

\* Lists of anisotropic temperature factors for non-H atoms, atomic parameters and isotropic temperature factors for H atoms, bond lengths involving H atoms, torsion angles, and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53171 (10 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Fractional atomic coordinates and equivalent isotropic temperature factors ( $\text{\AA}^2$ ) for non-H atoms with e.s.d.'s in parentheses

$$B_{\text{eq}} = (4/3) \sum_i \sum_j \beta_{ij} a_i \cdot a_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	$B_{\text{eq}}$
N(1)	1.0302 (3)	0.8955 (4)	0.59836 (7)	3.38 (9)
C(2)	0.8937 (4)	0.6980 (5)	0.57518 (8)	2.90 (9)
C(3)	0.7214 (3)	0.6411 (4)	0.59766 (7)	2.40 (8)
C(4)	0.6225 (4)	0.8489 (4)	0.67210 (8)	2.58 (9)
C(5)	0.6976 (4)	1.0402 (4)	0.70477 (8)	2.74 (9)
O(5)	0.5871 (3)	1.0850 (3)	0.74125 (6)	3.79 (7)
C(6)	0.8884 (4)	1.2015 (5)	0.70331 (8)	3.0 (1)
C(7)	1.0117 (4)	1.1686 (5)	0.66887 (8)	3.2 (1)
C(8)	0.9405 (4)	0.9728 (4)	0.63569 (8)	2.72 (9)
C(9)	0.7481 (3)	0.8140 (4)	0.63682 (7)	2.34 (9)
C(10)	0.5297 (4)	0.4407 (4)	0.58770 (8)	2.77 (9)
C(11)	0.5214 (4)	0.2598 (4)	0.54768 (8)	2.65 (9)
O(12)	0.6680 (3)	0.2567 (3)	0.52305 (6)	3.69 (7)
O(13)	0.3451 (3)	0.1017 (3)	0.54051 (6)	3.71 (7)

Table 2. Bond distances ( $\text{\AA}$ ) and angles ( $^\circ$ ) for non-H atoms with e.s.d.'s in parentheses

N(1)—C(2)	1.379 (3)	C(5)—C(6)	1.405 (3)
N(1)—C(8)	1.374 (3)	C(6)—C(7)	1.377 (3)
C(2)—C(3)	1.357 (3)	C(7)—C(8)	1.399 (3)
C(3)—C(9)	1.433 (3)	C(8)—C(9)	1.403 (3)
C(3)—C(10)	1.509 (3)	C(10)—C(11)	1.489 (3)
C(4)—C(5)	1.377 (3)	C(11)—O(12)	1.241 (3)
C(4)—C(9)	1.408 (3)	C(11)—O(13)	1.300 (3)
C(5)—O(5)	1.387 (3)		
C(2)—N(1)—C(8)	108.7 (1)	N(1)—C(8)—C(7)	130.7 (1)
N(1)—C(2)—C(3)	109.7 (1)	N(1)—C(8)—C(9)	107.7 (1)
C(2)—C(3)—C(9)	107.0 (1)	C(7)—C(8)—C(9)	121.6 (1)
C(2)—C(3)—C(10)	131.3 (1)	C(3)—C(9)—C(4)	133.1 (1)
C(9)—C(3)—C(10)	121.7 (1)	C(3)—C(9)—C(8)	106.9 (1)
C(5)—C(4)—C(9)	117.5 (1)	C(4)—C(9)—C(8)	120.0 (1)
C(4)—C(5)—O(5)	121.4 (1)	C(3)—C(10)—C(11)	118.2 (1)
C(4)—C(5)—C(6)	122.6 (1)	C(10)—C(11)—O(12)	124.0 (1)
O(5)—C(5)—C(6)	116.0 (1)	C(10)—C(11)—O(13)	113.9 (1)
C(5)—C(6)—C(7)	120.3 (1)	O(12)—C(11)—O(13)	122.1 (1)
C(6)—C(7)—C(8)	118.1 (1)		

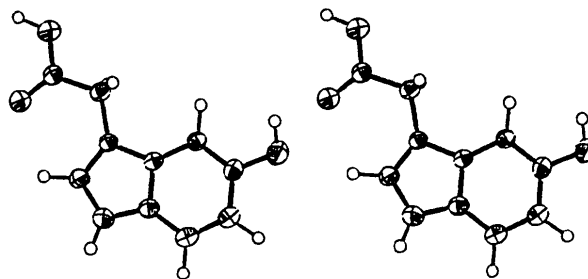


Fig. 1. A stereoscopic view of the 5-HIAA molecule.

C(3)—C(10). On the other hand, the external angles at C(5) differ significantly [ $C(4)—C(5)—O(5) = 121.4^\circ$  and  $C(6)—C(5)—O(5) = 116.0^\circ$ ] in a manner corresponding to that found at the OH group in phenols in which the H atom is situated in the plane of aromatic ring; the *cis* orientation between the H(5) and C(4) atoms results in the opening of the

C(4)—C(5)—O(5) bond angle. The same phenomenon is observed in the 5-hydroxytryptophan molecule (Wakahara, Kido, Fujiwara & Tomita, 1973), while the reverse is true in the serotonin molecule (Karle, Dragonette & Brenner, 1965; Thewalt & Bugg, 1972; Amit, Mester, Klewe & Furberg, 1978). The bond lengths and angles compare well with those reported for IAA (Sakaki, Sogo, Wakahara, Kanai, Fujiwara & Tomita, 1976; Inoue, Sakaki, Fujiwara & Tomita, 1978; Ishida & Inoue, 1981; Chandrasekhar & Raghunathan, 1982; Ishida, Doi, Ueda, Inoue & Sheldrick, 1988) and 5-methoxyindole-3-acetic acid (5-MIAA) (Sakaki, Wakahara, Fujiwara & Tomita, 1975; Sakaki, Sogo, Wakahara, Kanai, Fujiwara & Tomita, 1976) within their e.s.d.'s. The indole ring is planar with a maximum deviation of  $-0.018(2)$  Å at N(1) and the atoms attached to the ring lie almost on the plane; the fluctuation is  $-0.047$  to  $0.038$  Å.

The 5-HIAA molecule takes an extended conformation, where the torsion angles C(2)—C(3)—C(10)—C(11) ( $=\chi$ ) and C(3)—C(10)—C(11)—O(12) ( $=\varphi$ ) are  $2.5(2)$  and  $3.0(2)^\circ$ , respectively; the dihedral angle between the indole ring and the carboxyl group is  $175.5(3)^\circ$ . The molecular conformations hitherto reported for IAA and 5-MIAA are classified into two types of conformations, *i.e.* type I ( $\chi = 87-126^\circ$ ,  $\varphi = -30-0^\circ$ ) and type II ( $\chi = 2-11^\circ$ ,  $\varphi = 60-86^\circ$ ). Thus the present *cis* planar conformation of 5-HIAA is, to the best of our knowledge, the first example of this conformation in an indolecarboxylic acid.

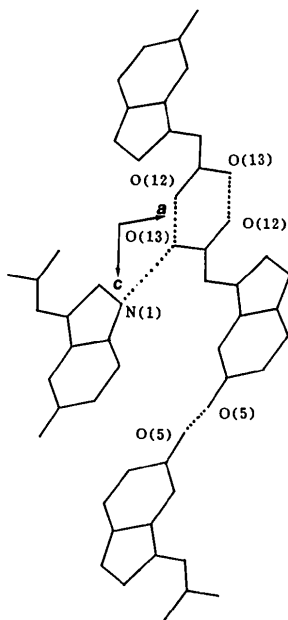


Fig. 2. Molecular packing in the 5-HIAA crystal, viewed along the *b* axis.

Conformational-energy analysis of the 5-HIAA molecule was carried out using the semiquantum-chemical MNDO method (Dewar & Thiel, 1977), in order to investigate the conformational stability. As a result, it was proposed that the planar conformation observed corresponds to the energetically metastable form and is about  $4.19-6.28$  kJ mol $^{-1}$  less stable than types I and II. This suggests that the 5-HIAA conformation is largely affected by the external factors such as the crystal packing force and the intermolecular hydrogen-bond formation.

Fig. 2 shows the crystal packing mode of 5-HIAA molecules. They are tightly held by the hydrogen bonds formed between the neighboring polar atoms. Between the two adjacent molecules related by the center of symmetry, a dimer is formed at the carboxyl end with an O—H $\cdots$ O hydrogen bond [O(13) $\cdots$ O(12) (at  $1-x, -y, 1-z$ ) =  $2.609(2)$ , H $\cdots$ O =  $1.61(3)$  Å and O—H $\cdots$ O =  $177(3)^\circ$ ]. This dimer is further hydrogen bonded to the indole NH group [N(1) $\cdots$ O(13) (at  $1+x, 1+y, z$ ) =  $2.969(3)$ , H $\cdots$ O =  $2.08(3)$  Å and N—H $\cdots$ O =  $152(2)^\circ$ ], and 5-hydroxy groups related by a diad screw axis are connected by the O—H $\cdots$ O hydrogen bond to form an infinite chain elongated along the *b* axis [O(5) $\cdots$ O(5) (at  $1-x, 0.5-y, 1.5-z$ ) =  $2.855(2)$ , H $\cdots$ O =  $1.92(3)$  Å and O—H $\cdots$ O =  $159(3)^\circ$ ].

#### References

- AMIT, A., MESTER, L., KLEWE, B. & FURBERG, S. (1978). *Acta Chem. Scand. Ser. A*, **32**, 267–270.
- CHANDRASEKHAR, K. & RAGHUNATHAN, S. (1982). *Acta Cryst.* **B38**, 2534–2435.
- DEBAERDEMAEKER, T., GERMAIN, G., MAIN, P., TATE, C. & WOLFSON, M. M. (1987). *MULTAN87. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.
- DEWAR, M. J. S. & THIEL, W. (1977). *J. Am. Chem. Soc.* **99**, 4899–4917.
- FARRIMOND, J. A., ELLIOTT, M. C. & CLACK, D. W. (1978). *Nature (London)*, **274**, 401–402.
- INOUE, M., SAKAKI, T., FUJIWARA, T. & TOMITA, K. (1978). *Bull. Chem. Soc. Jpn*, **51**, 1118–1122.
- ISHIDA, T., DOI, M., UEDA, H., INOUE, M. & SHELDRIK, G. M. (1988). *J. Am. Chem. Soc.* **110**, 2286–2294.
- ISHIDA, T. & INOUE, M. (1981). *Acta Cryst.* **B37**, 2117–2120.
- JOHNSON, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
- KAETHNER, T. M. (1977). *Nature (London)*, **267**, 19–23.
- KARLE, I. L., DRAGONETTE, K. S. & BRENNER, S. A. (1965). *Acta Cryst.* **19**, 713–716.
- SAKAKI, T., SOGO, A., WAKAHARA, A., KANAI, T., FUJIWARA, T. & TOMITA, K. (1976). *Acta Cryst.* **B32**, 3235–3242.
- SAKAKI, T., WAKAHARA, A., FUJIWARA, T. & TOMITA, K. (1975). *Bull. Chem. Soc. Jpn*, **48**, 536–540.
- The Universal Crystallographic Computation Program System - Osaka* (1979). The Computation Center, Osaka Univ., Japan.
- THEWALT, U. & BUGG, C. E. (1972). *Acta Cryst.* **B28**, 82–92.
- WAKAHARA, A., KIDO, M., FUJIWARA, T. & TOMITA, K. (1973). *Bull. Chem. Soc. Jpn*, **46**, 2475–2480.