Crystal structure of serotonin

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The title compound, serotonin or 5-hydroxytryptamine (5-HT) [systematic name: 3-(2-aminoethyl)-1H-indol-5-ol], C₁₀H₁₂N₂O, has one molecule in the asymmetric unit. The conformation of the ethylamino side chain is gauche–gauche [Ca—Cₐ—Cₘ—Cₘ and Ca—Cₘ—Cₘ—N (a = aromatic, m = methylene) torsion angles = −64.2 (3) and −61.9 (2)°, respectively]. In the crystal, the molecules are linked into a three-dimensional network by N—H···O and O—H···N hydrogen bonds.

1. Chemical context

Serotonin, C₁₀H₁₂N₂O, systematic name 3-(2-aminoethyl)-1H-indol-5-ol, is the primary neurotransmitter in humans, regulating mood, anxiety and happiness (Young & Leyton, 2002). While it is best known for its role in the central nervous system, serotonin is found throughout the human body and impacts a wide array of bodily functions. Roughly ninety-five percent of the body’s serotonin is actually found in the gastrointestinal tract, where it regulates intestinal movement (Berger et al., 2009). Serotonin is produced in the human body through biosynthesis from the essential amino acid tryptophan (Fitzpatrick, 1999), and broken down by monoamine oxidase to generate 5-hydroxyindoleacetic acid. As such, monoamine oxidase inhibitors and other compounds that increase serotonin concentration have been used to treat depression (Suchting et al., 2021).

Serotonin is not unique to humans, but is found throughout life on Earth including all bilateral animals, where it also functions as a neurotransmitter (Bacqué-Cazenave et al., 2020). It is found in plants, notably in seeds, where serotonin stimulates the digestive tract of animals, leading to excretion of the seeds (Akula et al., 2011). Serotonin and related tryptamines are well known to be present in a number of fungi (Tyler, 1958; Sherwood et al., 2020). A variety of related tryptamines found in plants, fungi, and toads, which are active at serotonin receptors, have garnered significant attention as psychedelic drugs to treat mood disorders including anxiety, depression, and addiction (Carhart-Harris & Goodwin, 2017). Serotonin was discovered by Vittorio Erspaner in 1935,
characterized as 5-hydroxytryptamine (5-HT) in 1949 by Rapport, and synthesized by Upjohn pharmaceutical in 1951 (Whitaker-Azmitia, 1999). Despite the simplicity of its structure and universally recognized biological significance, the single-crystal structure of pure free base serotonin has never been reported. Herein, we report this structure to fill in the gap from the scientific record.

2. Structural commentary

Serotonin or 5-hydroxytryptamine (5-HT) is an indolamine with a 5-hydroxy substitution. In the solid state, serotonin crystallizes with one molecule in the asymmetric unit (Fig. 1) in the chiral space group $P2_12_12_1$. The 5-hydroxyindole fused-ring unit is almost planar with the non-hydrogen atoms showing an r.m.s. deviation from planarity of 0.030 Å. The ethylamino arm is turned away from the indole ring, with a $C7—C8—C9—C10$ torsion angle of $-64.2 (3)^\circ$. The ethylamino arm itself turns back toward the indole ring with a $C8—C9—C10—N2$ torsion angle of $-61.9 (2)^\circ$.

3. Supramolecular features

In the crystal, the serotonin molecules are linked by a series of hydrogen bonds that produce a three-dimensional network in the solid state. The hydroxy groups form hydrogen bonds to the amine $N$ atoms on an adjacent serotonin molecules forming $O1—H1\cdots N2$ hydrogen bonds. The indole $N$ atoms form hydrogen bonds to the hydroxy groups of adjacent serotonin molecules through $N1—H1A\cdots O1$ hydrogen bonds. Half of the amine $H$ atoms link to the hydroxy groups of nearby molecules through $N2—H2B\cdots O1$ hydrogen bonds. There are no observed $\pi—\pi$ stacking interactions. Fig. 2

\[\begin{array}{cccc}
D—H - A & D—H & H - A & D - A \\
O1—H1\cdots N2 & 0.88 (1) & 1.77 (1) & 2.636 (2) & 170 (3) \\
N1—H1A\cdots O1 & 0.88 (1) & 2.10 (1) & 2.967 (2) & 169 (2) \\
N2—H2B\cdots O1 & 0.91 (1) & 2.19 (1) & 3.092 (3) & 168 (2) \\
\end{array}\]

Symmetry codes: 
(i) $-x + 3/2, -y + 1, z - 1/2$ 
(ii) $-x + 1, -y, z + 1/2$ 
(iii) $-x + 2, y + 1/2, z - 1/2$. 

Figure 1
The molecular structure of serotonin free base showing the atomic labeling. Displacement ellipsoids are drawn at the 50% probability level.

Figure 2
The different hydrogen-bonding interactions between the serotonin molecules. Hydrogen atoms not involved in hydrogen bonding are omitted for clarity. Symmetry codes: (i) $1/2 - x, 1 - y, 1/2 + z$ (ii) $2 - x, 1/2 + y, 1/2 - z$ (iii) $3/2 - x, -y, -1/2 + z$.

Table 1
Hydrogen-bond geometry (Å, °).

![Figure 2](image2)

Figure 3
The crystal packing of serotonin free base viewed along the $a$-axis. Hydrogen bonds are shown as dashed lines. Hydrogen atoms not involved in hydrogen bonds are omitted for clarity.
The two most closely reported free-base structures to serotonin are the natural product bufotenine, 5-hydroxy-1,3,6,8-tetrasulfonatopyrene (Feng et al., 1995: ZILMIQ), and two compounds where it is co-crystallized with the picrate salt has a structure similar to that of the title compound, and the geometrical data are less certain.

4. Database survey

The previous structural reports of serotonin are all complex mixtures containing serotonin in its C_{10}H_{12}N_{2}O^{+} cationic form. These include the creatine sulfate monohydrate (Karle et al., 1965: Cambridge Structural Database refcode HTRCRS), the hydrogen oxalate salt (Amit et al., 1978: SERHOX), the oxadipate salt (Rychkov et al., 2013: VIKWIX), the piconate monohydrate (Thewalt & Bugg, 1972: SERPIC) and two compounds where it is co-crystallized with 1,3,6,8-tetrasulfonatopyrene (Feng et al., 2017: RAWDIF, RAWDOL). The two most closely reported free-base structures to serotonin are the natural product bufotenine, 5-hydroxy-N,N-dimethyltryptamine (Falkenberg, 1972: BUFTEN) and 5-methoxytryptamine (Quarles et al., 1974: MXTRYP). 5-Methoxytryptamine has also been reported as its picrate (Nagata et al., 1995: ZILMIQ) and chloride (Pham et al., 2021: CCDC 2106050) salts. The free base reported here shows the ethylamino arm turned away from the indole plane. The majority of the cationic tryptamine structures show ethylamino arms that are nearly in-plane with the indole ring. Only the picanate salt has a structure similar to that of the title compound, showing an ethylamino arm turned similarly away from the indole ring. The torsion angles associated with the ethylamino arms of the different structures are summarized in Table 2.

5. Synthesis and crystallization

Single crystals suitable for X-ray diffraction studies were grown from the slow evaporation of a tetrahydrofuran solution of a commercial sample of serotonin free base (Chem-Impex).

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 3. Hydrogen atoms H1, H1A, H2A and H2B were found from a difference-Fourier map and were refined isotropically, using DFIX restraints with an N—H(indole) distance of 0.87 (1) Å, N—H(amine) distances of 0.90 (1) Å, and an O—H distance of 0.86 (1) Å. Isotropic displacement parameters were set to 1.2 U_{eq} of the parent nitrogen atoms and 1.5 U_{eq} of the parent oxygen atom. All other hydrogen atoms were placed in calculated positions with C—H = 0.93 Å (sp³) or 0.97 Å (sp²). Isotropic displacement parameters were set to 1.2 U_{eq} of the parent carbon atoms. The absolute structure of the crystal chosen for data collection was indeterminate in the present refinement.

Acknowledgements

Financial statements and conflict of interest: This study was funded by CaaM Tech, Inc. ARC reports an ownership interest in a company (Parsons et al., 2013) that markets a commercial sample of serotonin free base (Chem-Impex).

| Crystal data | C_{10}H_{12}N_{2}O | M_{r} | 176.22 |
| Crystal system, space group | Orthorhombic, P_{2}2_{1}2_{1} | 297 |
| Temperature (K) | 297 |
| a, b, c (Å) | 8.2248 (6), 8.7542 (6), 13.0712 (10) |
| V (Å³) | 941.15 (12) |
| Z | 4 |
| Radiation type | Mo Kα |
| μ (mm⁻¹) | 0.08 |
| Crystal size (mm) | 0.18 × 0.10 × 0.02 |

| Diffractometer | Bruker D8 Venture CMOS |
| Absorption correction | Multi-scan (SADABS: Bruker, 2018) |
| T_{min}, T_{max} | 0.711, 0.745 |
| No. of measured, independent and observed [I > 2σ(I)] reflections | 25138, 1783, 1590 |
| R_{int} | 0.052 |
| (sin θ/λ)_{max} (Å⁻¹) | 0.610 |

| Refinement | |
| R[F² > 2σ(F²)], wR(F²), S | 0.030, 0.073, 1.05 |
| No. of reflections | 1783 |
| No. of parameters | 134 |
| No. of restraints | 4 |
| H-atom treatment | H atoms treated by a mixture of independent and constrained refinement |
| Δρ_{max}, Δρ_{min} (e Å⁻³) | 0.13, −0.13 |

| Absolute structure | Flack x determined using 609 quotients [I(F')−F]/{σ(F) + σ(F')} |
| Absolute structure parameter | −1.2 (6) |

Computer programs: APEX3 (Bruker, 2018), SAINT (Bruker, 2018), SHELXT2014 (Sheldrick, 2015a), SHELXL2018 (Sheldrick, 2015b), OLEX2 (Dolomanov et al., 2009), publICIF (Westrip, 2010).
in CaaMTech, Inc., which owns US and worldwide patent applications, covering new tryptamine compounds, compositions, formulations, novel crystalline forms, and methods of making and using the same.

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Computing details

Data collection: APEX3 (Bruker, 2018); cell refinement: SAINT (Bruker, 2018); data reduction: SAINT (Bruker, 2018); program(s) used to solve structure: SHELXT2014 (Sheldrick, 2015a); program(s) used to refine structure: SHELXL2018 (Sheldrick, 2015b); molecular graphics: OLEX2 (Dolomanov et al., 2009); software used to prepare material for publication: publCIF (Westrip, 2010).

3-(2-Aminoethyl)-1H-indol-5-ol

Crystal data

C₁₀H₁₂N₂O  
Mr = 176.22  
Orthorhombic, P₂₁₂₁₂₁  
\(a = 8.2248\) (6) Å  
\(b = 8.7542\) (6) Å  
\(c = 13.0712\) (10) Å  
\(V = 941.15\) (12) Å³  
\(Z = 4\)  
\(F(000) = 376\)  
\(D_x = 1.244\) Mg m⁻³  
Mo Kα radiation, λ = 0.71073 Å  
Cell parameters from 6263 reflections  
\(θ = 3.1–25.4°\)  
\(μ = 0.08\) mm⁻¹  
\(T = 297\) K  
Block, colourless  
0.18 × 0.10 × 0.02 mm

Data collection

Bruker D8 Venture CMOS diffraetometer  
\(φ\) and \(ω\) scans  
Absorption correction: multi-scan  
(SADABS; Bruker, 2018)  
\(T_{min} = 0.711, T_{max} = 0.745\)  
25138 measured reflections  
1783 independent reflections  
1590 reflections with \(I > 2σ(I)\)  
\(R_{int} = 0.052\)  
\(θ_{max} = 25.7°, θ_{min} = 2.8°\)  
\(h = -10→10\)  
\(k = -10→10\)  
\(l = -15→15\)

Refinement

Refinement on \(F^2\)  
Least-squares matrix: full  
\(R[F^2 > 2σ(F^2)] = 0.030\)  
wR\((F^2)\) = 0.073  
\(S = 1.05\)  
1783 reflections  
134 parameters  
4 restraints  
Hydrogen site location: mixed  
H atoms treated by a mixture of independent and constrained refinement  
\(w = 1/[σ^2(F_c^2) + (0.0372P)^2 + 0.1115P]\)  
where \(P = (F_c^2 + 2F_s^2)/3\)  
\((Δ/σ)_{max} < 0.001\)  
\(Δρ_{max} = 0.13\) e Å⁻³  
\(Δρ_{min} = -0.13\) e Å⁻³  
Absolute structure: Flack x determined using  
609 quotients [(I)−(I)]/[(I)+(I)] (Parsons et al., 2013)  
Absolute structure parameter: −1.2 (6)
Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

| Atom | x     | y     | z     | Uiso*  |
|------|-------|-------|-------|--------|
| O1   | 0.91964 (18) | 0.18734 (16) | 0.08462 (10) | 0.0398 (4) |
| O1A  | 0.6390 (2)  | 0.0903 (2)  | 0.45983 (14) | 0.0445 (5)  |
| O1B  | 0.633 (3)   | 0.012 (2)   | 0.5016 (15)  | 0.051 (7)*  |
| N1   | 0.7279 (2)  | 0.6020 (2)  | 0.47447 (15) | 0.0458 (5)  |
| N2   | 0.8312 (19) | 0.638 (3)   | 0.465 (2)    | 0.072 (9)*  |
| C1   | 0.5533 (3)  | 0.2238 (2)  | 0.47087 (16) | 0.0433 (5)  |
| C2   | 0.487070    | 0.246998    | 0.526412     | 0.052*      |
| C3   | 0.7237 (2)  | 0.0960 (2)  | 0.36910 (15) | 0.0343 (4)  |
| C4   | 0.8552 (2)  | 0.1654 (2)  | 0.39086 (14) | 0.0316 (4)  |
| C5   | 0.7543 (2)  | 0.3534 (2)  | 0.32597 (16) | 0.036*      |
| C6   | 0.8303 (2)  | 0.3077 (2)  | 0.34660 (16) | 0.0388 (5)  |
| C7   | 0.5916 (2)  | 0.2065 (2)  | 0.36536 (16) | 0.0375 (5)  |
| C8   | 0.6150 (2)  | 0.2466 (2)  | 0.30040 (15) | 0.0391 (5)  |
| N2   | 0.7217 (2)  | 0.5542 (2)  | 0.31592 (12) | 0.0316 (4)  |
| N1   | 0.8182 (2)  | 0.5638 (2)  | 0.34684 (12) | 0.0325 (5)  |
| C1   | 0.7220 (2)  | 0.6501 (2)  | 0.38531 (14) | 0.0412 (5)  |
| C2   | 0.7906 (2)  | 0.3782 (2)  | 0.41038 (12) | 0.036*      |
| C3   | 0.6162 (2)  | 0.2562 (2)  | 0.40807 (12) | 0.036*      |
| C4   | 0.5384 (2)  | 0.4263 (2)  | 0.40928 (12) | 0.039*      |
| C5   | 0.4909 (2)  | 0.5440 (2)  | 0.39955 (12) | 0.037*      |
| C6   | 0.5921 (2)  | 0.4832 (2)  | 0.38910 (12) | 0.038*      |
| C7   | 0.6981 (2)  | 0.4232 (2)  | 0.36739 (12) | 0.040*      |

Atomic displacement parameters (Å²)

| Atom | U11  | U22  | U33  | U12  | U13  | U23  |
|------|------|------|------|------|------|------|
| O1   | 0.0473 (8) | 0.0370 (8) | 0.0351 (7) | 0.0049 (7) | 0.0058 (6) | −0.0021 (6) |
| N1   | 0.0536 (11) | 0.0411 (10) | 0.0390 (10) | 0.0009 (9) | 0.0040 (9) | 0.0125 (8) |
| N2   | 0.0465 (11) | 0.0406 (10) | 0.0502 (12) | 0.0012 (9) | −0.0064 (9) | −0.0055 (9) |
| C1   | 0.0441 (11) | 0.0456 (13) | 0.0402 (11) | 0.0009 (10) | 0.0064 (9) | 0.0025 (9) |
| C2   | 0.0378 (10) | 0.0309 (9) | 0.0342 (10) | −0.0019 (8) | −0.0068 (9) | 0.0044 (8) |
| C3   | 0.0434 (11) | 0.0268 (9) | 0.0461 (11) | 0.0031 (8) | −0.0094 (10) | 0.0058 (8) |
| C4   | 0.0366 (10) | 0.0325 (10) | 0.0435 (11) | 0.0061 (8) | −0.0055 (9) | −0.0036 (9) |
| C5   | 0.0322 (9) | 0.0299 (9) | 0.0328 (9) | −0.0033 (7) | −0.0037 (8) | −0.0034 (8) |
| C6   | 0.0360 (9) | 0.0230 (8) | 0.0323 (9) | −0.0004 (8) | −0.0052 (8) | 0.0010 (7) |
| C7   | 0.0304 (9) | 0.0282 (9) | 0.0315 (9) | −0.0012 (7) | −0.0060 (7) | 0.0001 (7) |
### Geometric parameters (Å, °)

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| C8 | 0.0348 (9) | 0.0347 (10) | 0.0353 (10) | 0.0004 (8) | −0.0024 (9) | −0.0004 (8) |
| C9 | 0.0377 (10) | 0.0390 (11) | 0.0406 (11) | 0.0078 (9) | −0.0006 (9) | −0.0009 (9) |
| C10 | 0.0493 (12) | 0.0340 (10) | 0.0404 (11) | 0.0045 (9) | −0.0001 (10) | −0.0003 (9) |

**O1—H1** 0.878 (13)  
C1—N1 1.376 (2)  
N1—H1A 0.879 (12)  
N1—C1 1.373 (3)  
N1—C2 1.376 (3)  
N2—H2A 0.894 (12)  
N2—H2B 0.914 (13)  
C1—H1B 0.9300  
C1—C8 1.358 (3)  
C2—C3 1.391 (3)  
C3—H3 0.9300  
C5—O1—H1 109.1 (19)  
C1—N1—H1A 124.8 (16)  
C2—N1—H1A 126.4 (16)  
H2A—N2—H2B 113 (2)  
C10—N2—H2A 109.3 (16)  
C10—N2—H2B 108.5 (18)  
N1—C1—H1B 124.7  
C8—C1—N1 110.65 (19)  
C8—C1—H1B 124.7  
N1—C2—C3 131.04 (18)  
N1—C2—C7 107.41 (16)  
C3—C2—C7 121.54 (18)  
C2—C3—H3 120.0  
C4—C3—C2 118.04 (17)  
C4—C3—H3 121.0  
C3—C4—H4 119.4  
C3—C4—C5 121.14 (18)  
C5—C4—H4 119.4  
O1—C5—C4 116.80 (17)  
C6—C5—O1 122.29 (17)  
C6—C5—C4 120.90 (17)  

O1—C5—C6—C7 177.03 (16)  
N1—C1—C8—C7 0.2 (2)  
N1—C1—C8—C9 −177.44 (19)  
N1—C2—C3—C4 178.8 (2)  
N1—C2—C3—C7 −178.8 (2)  

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sup-3
N1—C2—C7—C8 0.8 (2) C5—C6—C7—C2 −0.5 (2)
C1—N1—C2—C3 178.3 (2) C5—C6—C7—C8 −178.96 (18)
C1—N1—C2—C7 −0.7 (2) C6—C7—C8—C1 178.0 (2)
C1—C8—C9—C10 113.0 (2) C6—C7—C8—C9 −4.4 (3)
C2—N1—C1—C8 0.3 (3) C7—C2—C3—C4 −2.4 (3)
C2—C3—C4—C5 −0.5 (3) C7—C8—C9—C10 −64.2 (3)
C2—C7—C8—C1 −0.6 (2) C8—C9—C10—N2 −61.9 (2)
C2—C7—C8—C9 177.08 (18)

Hydrogen-bond geometry (Å, °)

\begin{tabular}{lcccc}
\hline
D—H···A & D—H & H···A & D···A & D—H···A \\
\hline
O1—H1···N2 & 0.88 (1) & 1.77 (1) & 2.636 (2) & 170 (3) \\
N1—H1A···O1 & 0.88 (1) & 2.10 (1) & 2.967 (2) & 169 (2) \\
N2—H2B···O1 & 0.91 (1) & 2.19 (1) & 3.092 (3) & 168 (2) \\
\hline
\end{tabular}

Symmetry codes: (i) −x+3/2, −y+1, z−1/2; (ii) −x+3/2, −y, z+1/2; (iii) −x+2, y+1/2, −z+1/2.