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Structure of an Orellanine*–Trifluoroacetic Acid Complex: Evidence of a Very Short O—H···O Hydrogen Bond

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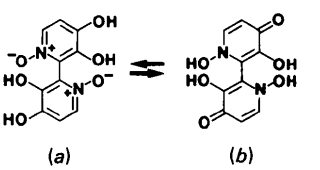
Abstract. $C_{10}H_8N_2O_6.C_2HF_3O_2$, $M_r = 366{\cdot}20$, monoclinic, Cc, $a = 6{\cdot}019\ (2)$, $b = 21{\cdot}158\ (6)$, $c = 12{\cdot}277\ (3)$ Å, $\beta = 97{\cdot}90\ (5)°$, $V = 1422$ Å^3, $Z = 4$, $D_x = 1{\cdot}71$ Mg m^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71069$ Å, $\mu = 0{\cdot}085$ mm^{-1}, $F(000) = 744$, $T = 293$ K, $wR = 0{\cdot}059$ for 703 observed reflexions. The crystal structure is in agreement with that predicted from previous studies in solution. The two pyridine rings of orellanine are nearly perpendicular. Short intermolecular OH···O bonds are formed. A very short one, of 2·45 Å, links two molecules of orellanine through their N—O groups, along the *a* axis. This suggests the existence, in the present complex, of a protonated form of orellanine. One orellanine is bonded to one trifluoroacetic acid molecule through a hydrogen bond. No intramolecular hydrogen bonds are observed. IR and NMR spectra are given and are in agreement with the orellanine crystal structure.

Introduction. Several species of *Cortinarius* mushrooms have been reported to be highly toxic for animal and man (literature reviewed by Schumacher & Høiland, 1983). Among them, *C. orellanus* Fr. and *C. speciosissimus* Kühn & Romagn. were found to contain a toxic substance called orellanine (Grzymala, 1962; Antkowiak & Gessner, 1975, 1985). Using different spectroscopic methods, including incompletely resolved NMR spectra, Antkowiak & Gessner (1979) assigned to this compound the structure of [2,2′-bipyridine]-3,3′,4,4′-tetrol-1,1′-dioxide (Fig. 1). The extraction and the purification of orellanine were previously developed (Klein, Richard & Satre, 1986); its chemical structure was discussed on the basis of toxicological results (Richard, Taillandier & Benoit-Guyod, 1985); Dehmlow & Schulz (1985) described the synthesis of that molecule which they identified to be orellanine. Our work gives the crystal structure of a hydrogen-bonded complex between orellanine and trifluoroacetic acid, the solvent used for crystallization.

The IR spectrum in the solid state is discussed in terms of this structure and NMR data are given.

Experimental. Orellanine was extracted from dried carpophores of *C. orellanus* collected locally. The extraction and purification procedure was according to our already published method (Klein *et al.*, 1986), with boiling methanol as extracting solvent.

Colourless 0·3 × 0·2 × 0·15 mm crystal obtained by slow evaporation at 293 K from a solution in trifluoroacetic acid (TFA); one molecule of orellanine is associated with one molecule of TFA within the crystal. Measurements with a Nicolet *P3F* diffractometer, monochromatized Mo $K\alpha$ radiation, ω-scan mode, no absorption correction. Lattice parameters refined with 24 reflexions, $8 \le \theta \le 10°$. 703 reflexions with $I > 2\sigma(I)$ (1227 measured), sin $\theta/\lambda < 0{\cdot}5$ Å^{-1}, hkl, $hk\bar{l}$, h: 0 to 7, k: 0 to 23, l: −12 to 12. Standard reflexions: 261, 08$\bar{2}$, 20$\bar{4}$ (1% variation). Multisolution direct



(*a*) (*b*)

Fig. 1. General formula of orellanine.

* *Chemical Abstracts* name: [2,2′-bipyridine]-3,3′,4,4′-tetrol-1,1′-dioxide.

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methods (Germain, Main & Woolfson, 1971), least-squares refinement minimizing $\sum w(|F_o| - |F_c|)^2$ (Busing & Levy, 1962). Positional and anisotropic parameters refined for heavy atoms; H-atom positional parameters calculated (not refined); H assumed to be 1 Å from O on the O···O bond, for O(1)···O(4) H at the middle of the bond; isotropic temperature factors for H estimated (not refined). Approximately linear weighting scheme obtained empirically by plotting $(F_o - F_c)^2$ as a function of F_o (Rollett, 1965). Final R values: $R = 0{\cdot}061$, $wR = 0{\cdot}059$ for 703 reflexions. $(\Delta/\sigma)_{max} = 1{\cdot}0$, final $\Delta\rho < 0{\cdot}3$ e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974).

IR spectrum of solid orellanine–TFA in KBr recorded on a Philips Pye Unicam SP3-100-spectrophotometer.

NMR spectra of orellanine in solution in deuterated TFA recorded at room temperature on a Bruker AM400 spectrometer at 100·4 MHz; tetramethylsilane as reference.

Discussion. The atomic parameters are listed in Table 1, interatomic distances, valence and torsion angles in Table 2.* The conformation of the molecule is shown in Fig. 2.

Chemical structure of orellanine and NMR spectra

The structure is in agreement with that predicted and is identical to that of the synthetic compound (Antkowiak & Gessner, 1979; Dehmlow & Schulz, 1985). In solution, the orellanine molecule exhibits such a symmetry that only five resonances are observed on the NMR spectra, such a resonance corresponding to two equivalent C atoms. These resonances were unambiguously assigned on the basis of ^{13}C–^{1}H coupling constants ($J_{1,4} = J_{4,5} = 3$, $J_{1,5} = J_{3,5} = 8$, $J_{5,5} = 196$, $J_{5,4} = 2$, $J_{2,4} = 6$, $J_{4,4} = 175$ Hz). As for the chemical shifts at 160·2, 148·3, 138·8, 127·1 and 114·7 p.p.m.,

* Lists of structure factors, anisotropic thermal parameters, H-atom calculated parameters and mean-plane equations have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43468 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

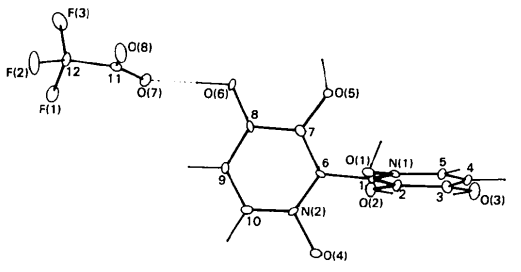

Fig. 2. Orellanine–trifluoroacetic acid: projection on the C(1)C(6)C(7) plane.

Table 1. *Orellanine–trifluoroacetic acid: atomic coordinates* ($\times 10^4$) *with e.s.d.'s in parentheses and equivalent isotropic thermal parameters*

$B_{eq} = 8\pi^2(U_1U_2U_3)^{2/3}$.

	x	y	z	B_{eq}(Å^2)
C(1)	7143	−766 (6)	4734	2·1
C(2)	6000 (31)	−1278 (6)	4164 (16)	2·8
C(3)	6979 (32)	−1886 (8)	4352 (18)	3·5
C(4)	8999 (31)	−1942 (7)	5049 (16)	3·4
C(5)	10076 (31)	−1424 (6)	5615 (15)	3·0
C(6)	6330 (31)	−113 (6)	4518 (16)	1·7
C(7)	7163 (31)	258 (6)	3682 (17)	2·9
C(8)	6172 (29)	864 (6)	3382 (16)	2·3
C(9)	4349 (31)	1033 (5)	3968 (15)	2·2
C(10)	3644 (34)	657 (7)	4810 (17)	3·5
N(1)	9128 (23)	−851 (5)	5453 (14)	2·0
N(2)	4662 (29)	102 (5)	5067 (14)	2·2
O(1)	10045 (25)	−347 (4)	6063 (14)	2·6
O(2)	4063 (26)	−1133 (4)	3494 (14)	3·5
O(3)	6060 (27)	−2414 (5)	3826 (15)	4·9
O(4)	4079 (25)	−273 (4)	5968 (13)	3·0
O(5)	8916 (28)	49 (4)	3170 (14)	3·4
O(6)	7067 (27)	1210 (4)	2613 (14)	2·8
F(1)	1855 (26)	3193 (5)	1456 (15)	5·9
F(2)	4471 (32)	3783 (6)	1941 (18)	7·9
F(3)	4271 (33)	3341 (7)	316 (15)	7·1
C(11)	5377 (31)	2694 (7)	1968 (17)	2·9
C(12)	4058 (37)	3252 (6)	1387 (17)	3·1
O(7)	4613 (26)	2171 (4)	1798 (14)	3·2
O(8)	7265 (27)	2856 (5)	2473 (16)	5·2

Table 2. *Orellanine–trifluoroacetic acid: interatomic distances* (Å), *valence and torsion angles* (°)

E.s.d.'s are in parentheses.

C(1)–C(2)	1·39 (2)	C(6)–C(7)	1·37 (2)
C(2)–C(3)	1·42 (2)	C(7)–C(8)	1·43 (2)
C(3)–C(4)	1·35 (2)	C(8)–C(9)	1·40 (2)
C(4)–C(5)	1·38 (2)	C(9)–C(10)	1·35 (2)
N(1)–C(5)	1·34 (1)	N(2)–C(10)	1·34 (2)
N(1)–C(1)	1·36 (1)	N(2)–C(6)	1·33 (1)
N(1)–O(1)	1·35 (1)	N(2)–O(4)	1·37 (1)
C(2)–O(2)	1·33 (1)	C(7)–O(5)	1·35 (1)
C(3)–O(3)	1·35 (2)	C(8)–O(6)	1·31 (1)
C(1)–C(6)	1·48 (2)		
C(11)–C(12)	1·52 (2)	C(12)–F(1)	1·34 (2)
C(11)–O(7)	1·20 (1)	C(12)–F(2)	1·29 (2)
C(11)–O(8)	1·25 (1)	C(12)–F(3)	1·25 (2)

C(1)–C(2)–C(3)	118 (1)	C(6)–C(7)–C(8)	119 (1)
C(2)–C(3)–C(4)	119 (1)	C(7)–C(8)–C(9)	116 (1)
C(3)–C(4)–C(5)	121 (1)	C(8)–C(9)–C(10)	121 (1)
C(4)–C(5)–N(1)	119 (1)	C(9)–C(10)–N(2)	119 (3)
C(5)–N(1)–C(1)	121 (1)	C(10)–N(2)–C(6)	123 (1)
C(5)–N(1)–O(1)	121 (1)	C(10)–N(2)–O(4)	121 (1)
C(1)–N(1)–O(1)	118 (1)	C(6)–N(2)–O(4)	116 (1)
C(1)–C(2)–O(2)	115 (1)	C(6)–C(7)–O(5)	119 (1)
C(3)–C(2)–O(2)	127 (1)	C(8)–C(7)–O(5)	121 (1)
C(2)–C(3)–O(3)	123 (1)	C(7)–C(8)–O(6)	117 (1)
C(4)–C(3)–O(3)	117 (1)	C(9)–C(8)–O(6)	126 (1)
N(1)–C(1)–C(2)	120 (1)	N(2)–C(6)–C(7)	120 (1)
C(6)–C(1)–C(2)	121 (1)	C(1)–C(6)–C(7)	120 (1)
C(6)–C(1)–N(1)	118 (1)	C(1)–C(6)–N(2)	120 (1)
C(12)–C(11)–O(7)	119 (1)	F(1)–C(12)–F(2)	100 (2)
C(12)–C(11)–O(8)	112 (1)	F(1)–C(12)–F(3)	108 (2)
O(7)–C(11)–O(8)	129 (2)	F(2)–C(12)–F(3)	107 (2)
C(11)–C(12)–F(1)	111 (1)		
C(11)–C(12)–F(2)	114 (1)		
C(11)–C(12)–F(3)	115 (2)		

N(1)–C(1)–C(6)–N(2) −104 (1)

they correspond to resonances of nuclei C(1), C(3), C(5), C(2) and C(4), respectively.

Geometry of the orellanine molecule in the complex

The two pyridine rings are planar (maximum deviation from the planes, 0·02 Å), the O of the *N*-oxide groups being slightly off the planes (0·13 Å). The two rings are nearly perpendicular, their mean planes making an angle of 80 (1)°. The F atoms in TFA are probably disordered, as shown by their high *B* values. This may affect the accuracy of the results. The C–O bond lengths of 1·31–1·35 Å are in agreement with those for C–OH groups. As orellanine is chiral, the existence of inverse symmetry elements in the space group found (*c* mirror) involves a racemic crystal. The occurrence of both right-handed and left-handed molecules in this compound is quite surprising, owing to the fact that this molecule was extracted from mushrooms. One would expect to deal with an enantiomer but it is assumed that racemization occurs upon heating during the extraction procedure. In agreement with this result, no rotatory power was found for this compound.

Hydrogen bonds and IR spectra

Several intermolecular O–H···O hydrogen bonds link orellanine molecules; each of these molecules is also bound to one TFA through a hydrogen bond (Table 3, Fig. 3). The very short O(1)···O(4) hydrogen bond along the *a* axis (2·45 Å) involves two N–O groups. This suggests the existence, in the present complex, of a protonated form (*a*) (Fig. 1), one H being shared by the two *N*-oxide functions. The N–O bond lengths of 1·35–1·37 Å are in agreement with this result.

Such a short hydrogen bond, although quite unusual, has already been observed in acid salts of carboxylic acids (Hadži, Orel & Novak, 1973). In the IR spectrum of solid orellanine–TFA (Fig. 4), a broad absorption band is found to be centred around 2900 cm^{-1} and corresponds to the *νs* (O–H···O) vibration of 2·60–2·67 Å hydrogen-bond lengths (Novak, 1974). The existence of Evan's transmission windows in the 800–1100 cm^{-1} region are also characteristic of hydrogen bonds (Bratos, Lascombe & Novak, 1980).

Moreover, a very broad band whose centre of gravity is around 1200 cm^{-1} is characteristic of the *νs* vibration of a very short O–H···O hydrogen bond of less than 2·50 Å (Novak, 1974). Such a broadening effect has already been observed in $KH(CF_3COO)_2$ which exhibits an O–H···O bond of 2·43 Å (Hadži *et al.*, 1973). No intramolecular hydrogen bonds are observed.

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The X-ray data were collected within the 'Groupe Grenoblois de Diffractométrie'.

Table 3. *Orellanine–trifluoroacetic acid:* O–H···O *hydrogen bonds* (Å)

O(1)···O(4^{i})	2·45 (1)	O(3)···O(8^{iii})	2·63 (1)
O(1)···O(5^{ii})	2·64 (1)	O(6)···O(7)	2·61 (1)
O(2)···O(8^{iii})	2·59 (1)		

Symmetry codes: (i) $1+x, y, z$; (ii) $x, \bar{y}, \frac{1}{2}+z$; (iii) $x-\frac{1}{2}, y-\frac{1}{2}, z$.

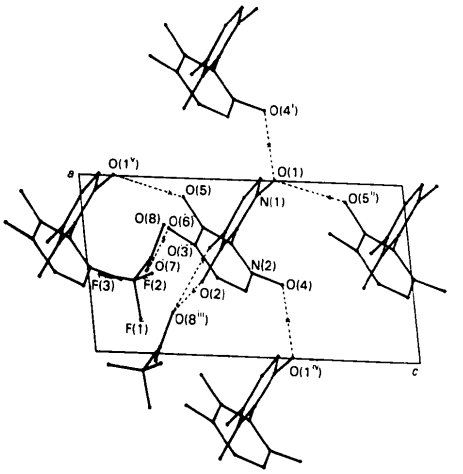

Fig. 3. Orellanine–trifluoroacetic acid: O–H···O hydrogen bonds; projection on the *ac* plane. Symmetry codes: (i) $1+x, y, z$; (ii) $x, \bar{y}, \frac{1}{2}+z$; (iii) $x-\frac{1}{2}, y-\frac{1}{2}, z$; (iv) $-1+x, y, z$; (v) $x, \bar{y}, z-\frac{1}{2}$.

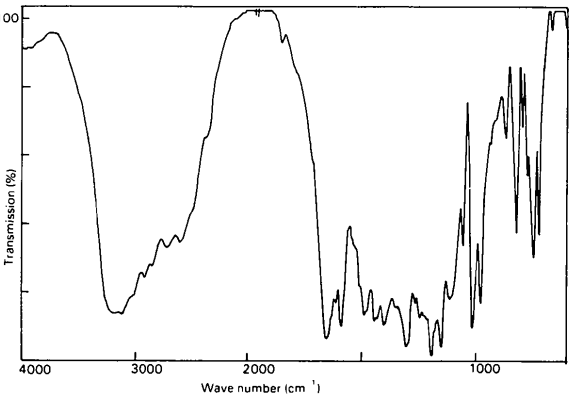

Fig. 4. Orellanine–trifluoroacetic acid: IR spectrum in KBr.

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Structural Researches on H_2 Agonists: the Structures of the Dipicrates of 2-(2-Amino-4-imidazolyl)ethylamine, its 5-Methyl Derivative and *N,N*-Dimethyl-2-(2-amino-1,3-thiazol-5-yl)ethylamine*

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Abstract. To acquire structural information for understanding the effect of the amino group in 2-aminohistamine derivatives, the structures of the dipicrates of 2-(2-amino-4-imidazolyl)ethylamine (I), its 5-methyl analogue (II) and *N,N*-dimethyl-2-(2-amino-1,3-thiazol-5-yl)ethylamine (III) have been studied. Crystal data are: (I) $C_5H_{10}N_4.2C_6H_3N_3O_7.H_2O$, $M_r = 602{\cdot}4$, $P2_1/c$, $a = 21{\cdot}897\ (4)$, $b = 5{\cdot}107\ (1)$, $c = 21{\cdot}769\ (11)$ Å, $\beta = 104{\cdot}34\ (1)°$, $V = 2358\ (1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}696$ Mg m^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1{\cdot}54178$ Å, $\mu = 1{\cdot}2719$ mm^{-1}, $F(000) = 1240$, $T = 293\ (2)$ K, $R = 0{\cdot}0410$ for 2739 reflections. (II) $C_6H_{12}N_4.2C_6H_3N_3O_7.\frac{1}{2}C_2H_6O$, $M_r = 621{\cdot}4$, $Fdd2$, $a = 25{\cdot}044\ (4)$, $b = 40{\cdot}178\ (5)$, $c = 10{\cdot}143\ (2)$ Å, $V = 10{\cdot}206\ (3)$ Å^3, $Z = 16$, $D_x = 1{\cdot}618$ Mg m^{-3}, Cu $K\bar{\alpha}$, $\mu = 1{\cdot}1794$ mm^{-1}, $F(000) = 5136$, $T = 293\ (2)$ K, $R = 0{\cdot}0381$ for 1480 reflections. (III) $C_7H_{13}N_3S.2C_6H_3N_3O_7$, $M_r = 629{\cdot}5$, $P\bar{1}$, $a = 13{\cdot}074\ (4)$, $b = 13{\cdot}853\ (6)$, $c = 8{\cdot}206\ (4)$ Å, $\alpha = 105{\cdot}88\ (11)$, $\beta = 103{\cdot}36\ (3)$, $\gamma = 64{\cdot}90\ (2)°$, $V = 1283\ (1)$ Å^3, $Z = 2$, $D_x = 1{\cdot}629$ Mg m^{-3}, Cu $K\bar{\alpha}$, $\mu = 1{\cdot}8916$ mm^{-1}, $F(000) = 648$, $T = 293\ (2)$, $R = 0{\cdot}0497$ for 1958 reflections. In all these compounds the cation is formed by protonation of a ring N atom and the side-chain amine group. π conjugation along the guanidine and isothiourea systems makes the *juxta*-NH_2 group coplanar with the ring. The conformation of the side chain is heavily influenced by the presence of the methyl group at the 5-imidazole position in the case of (II), and by the presence of sulfur in the ring and methyls on the side-chain amino N atom in the case of (III).

Introduction. The study of imidazolylalkylamine chemical properties, related to their histaminergic activity, has confirmed that the amidine component of the heterocycle is a fundamental part of the H_2-agonistic structure. Likewise it was shown that the factors promoting the formation of the monoprotonated base τ-NH tautomer in the ionic equilibrium are also able to cause the pharmacological dissociation between the H_1 and H_2 properties, making the molecule suitable in general for H_2 activity and in particular as gastric-acid-secretion stimulant (Black, Duncan, Durant, Ganellin & Parsons, 1972; Durant, Emmett & Ganellin, 1973; Durant, Ganellin & Parsons, 1975; Vitali, Bertaccini, Impicciatore & Plazzi, 1972, 1979; Durant, Emmett, Ganellin, Roe & Slatter, 1976; Hepp, Dziuron & Schunack, 1979; Vitali, Impicciatore, Plazzi, Bordi & Vitto, 1984). These properties are observed even when the amidine group is not included in a ring system, so substances like *S*-(aminoalkyl)-isothioureas can still stimulate the H_2 receptors and, in this case, their action is not connected with the

* An account of this work was communicated at the IXth European Crystallographic Meeting, Torino, 2–6 September 1985.

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