

## Structure of Khellinium Hydrogensulfate

BY SAMIA BOUTIBA\* AND AHMED KALLEL

Laboratoire de Cristallographie, Faculté des Sciences de Tunis, Département de Physique,  
Campus Belvédère, 1060 Tunis, Tunisia

JALEL EDDINE HILA

Pharmacie Centrale de Tunisie, 2040 Rades, Tunisia

AND ERICH F. PAULUS

Hoechst AG, D-6230 Frankfurt am Main 80, Federal Republic of Germany

(Received 8 February 1988; accepted 16 January 1989)

**Abstract.**  $C_{14}H_{13}O_5^+ \cdot HSO_4^-$ ,  $M_r = 358.32$ , monoclinic,  $P2_1/c$ ,  $a = 8.146$  (1),  $b = 7.797$  (1),  $c = 23.363$  (1) Å,  $\beta = 90.13$  (2)°,  $V = 1483.9$  (5) Å<sup>3</sup>,  $Z = 4$ ,  $D_x = 1.60$  Mg m<sup>-3</sup>,  $\lambda(\text{Mo } K\alpha) = 0.71069$  Å,  $\mu = 0.254$  mm<sup>-1</sup>,  $F(000) = 744$ ,  $T = 296$  K, final  $R(F) = 0.083$ ,  $wR = 0.039$  for 2958 observed reflections. The benzofuran heterocycle is planar as in khellin. The two methoxy groups are more twisted towards the heterocycle plane in comparison to khellin. Under the influence of the sulfuric acid the carbonyl group is protonated. The O atoms in the hydrogensulfate anion are statistically disordered.

**Introduction.** Khellin (or 4,9-dimethoxy-7-methyl-5H-furo[3,2-g][1]benzopyran-5-one) is found in seeds of Eastern Mediterranean plants (Späth, Dengel & Gruber, 1938). It exhibits spasmolytic activity and it is used in therapeutics (Leger, Goursolle, Gadret & Carpy, 1978) despite its toxicity. Recently, IR and <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic studies of khellinium hydrogensulfate (Hila, Likforman, Mahuteau, Kirkiacharian & Hamon, 1985) were reported but the site of protonation and the electronic delocalization could not be deduced without ambiguity. We determined the crystal structure of khellinium hydrogensulfate by single-crystal X-ray diffraction and compared it with the khellin structure (Carpy, Hickel & Leger, 1979).

**Experimental.** Crystals were grown as described previously (Hila, 1983). Samples are very sensitive to moisture and to any solvent more basic than khellin, such as water or methanol. To protect the crystals, they are kept in ethyl acetate. A specimen of parallelepiped form with approximate dimensions 0.37 × 0.19 × 0.13 mm was chosen for X-ray diffrac-

tion and sealed in a Lindemann-glass capillary. Oscillation photographs indicate monoclinic symmetry. Nicolet R3 computer-controlled diffractometer was used for data collection. 25 reflections with  $2\theta > 17.3^\circ$  were used for cell refinement;  $2\theta/\theta$  scan;  $\theta_{\text{max}} = 28^\circ$ ; scan speed 3 to 20° min<sup>-1</sup>; 1 standard reflection;  $h - 10 \rightarrow 10$ ,  $k 0 \rightarrow 10$ ,  $l - 30 \rightarrow 4$ ; 4180 reflections were measured, averaging gave 3580 independent with  $R_{\text{int}} = 0.03$ ; 2958 having  $I > \sigma(I)$  were used for structure determination; no correction for absorption or extinction; the least-squares refinement was performed by the cascade method (Sheldrick, 1983); all H atoms were located in a difference Fourier map and refined with an isotropic thermal parameter; final  $R = 0.083$  and  $wR = 0.039$ ;  $S = 1.79$ ; the poor quality of the crystal and the disorder of the O atoms prevent better  $R$  values; the 10 largest peaks in the final difference Fourier map were between 0.29 and 0.35 e Å<sup>-3</sup>; the refinement was based on  $F$  and the weighting scheme used was  $w = 1/\sigma^2(F_o)$ , where  $\sigma(F_o)$ , based on counting statistics, are the e.s.d.'s of  $F_o$ ;  $(\Delta/\sigma)_{\text{max}}$  in the last cycle of refinement was 0.02; scattering factors from *International Tables for X-ray Crystallography* (1974). All calculations were performed with a Nova 3/12 computer and *SHELXTL* (Sheldrick, 1983).†

**Discussion.** The atomic coordinates and  $U_{\text{eq}}$  for non-H atoms are listed in Table 1. Bond lengths and angles are given in Table 2. The molecular structure can be seen in Fig. 1.

† Lists of structure factors, H-atom and disordered O-atom coordinates, anisotropic temperature coefficients, bond lengths and angles involving H atoms and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51871 (26 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

\* Permanent address: Faculté des Sciences et Techniques, Monastir, Tunisia.

Table 1. Atomic coordinates and thermal parameters for non-H atoms

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> <sub>eq</sub> (Å <sup>2</sup> )
C(1)	0.6751 (3)	0.8642 (4)	0.5266 (2)	0.036 (1)
C(2)	0.6284 (4)	0.8131 (4)	0.4726 (2)	0.038 (2)
C(3)	0.4856 (4)	0.7276 (4)	0.4579 (2)	0.037 (2)
C(4)	0.3737 (4)	0.6846 (4)	0.5007 (2)	0.033 (1)
C(5)	0.4172 (3)	0.7283 (4)	0.5583 (2)	0.035 (1)
C(6)	0.5633 (4)	0.8184 (4)	0.5684 (2)	0.042 (2)
C(8)	0.5089 (4)	0.8367 (4)	0.6675 (2)	0.041 (2)
C(9)	0.3708 (4)	0.7481 (4)	0.6610 (2)	0.036 (1)
C(10)	0.3200 (3)	0.6878 (4)	0.6071 (2)	0.053 (2)
C(12)	0.6345 (4)	0.7733 (5)	0.3800 (2)	0.047 (2)
C(13)	0.4947 (4)	0.7041 (4)	0.3961 (2)	0.081 (3)
C(15)	0.9381 (4)	0.8812 (5)	0.5673 (2)	0.071 (2)
C(17)	0.1503 (5)	0.6083 (5)	0.4404 (2)	0.061 (2)
C(19)	0.5779 (5)	0.9105 (5)	0.7211 (2)	0.050 (1)
S(1)	0.0882 (2)	0.5367 (2)	0.2851 (1)	0.048 (1)
O(1)*	-0.0742 (4)	0.5306 (7)	0.3087 (2)	0.054 (1)
O(11)	0.7226 (3)	0.8426 (3)	0.4252 (1)	0.051 (1)
O(14)	0.8097 (3)	0.9609 (3)	0.5358 (1)	0.075 (2)
O(16)	0.2333 (3)	0.6025 (3)	0.4935 (1)	0.077 (2)
O(18)	0.1882 (3)	0.5982 (3)	0.6015 (1)	0.061 (2)
O(2)	0.0730 (3)	0.4705 (4)	0.2227 (1)	0.042 (1)
O(3)†	0.2039 (4)	0.4318 (4)	0.3144 (2)	
O(4)‡	0.1445 (3)	0.7128 (4)	0.2790 (2)	
O(7)	0.6075 (3)	0.8725 (3)	0.6225 (1)	

\* Occupancy = 0.85.

† Occupancy = 0.89.

‡ Occupancy = 0.82.

Table 2. Bond lengths (Å) and angles (°) in khellinium hydrogensulfate

C(1)—O(14)	1.348 (3)	C(8)—C(9)	1.329 (4)
C(1)—C(2)	1.377 (3)	C(8)—C(19)	1.489 (4)
C(1)—C(6)	1.384 (3)	C(9)—C(10)	1.405 (3)
C(2)—O(11)	1.366 (3)	C(10)—O(18)	1.288 (3)
C(2)—C(3)	1.384 (4)	C(12)—O(11)	1.387 (3)
C(3)—C(4)	1.396 (3)	C(12)—C(13)	1.316 (4)
C(3)—C(13)	1.456 (3)	C(15)—O(14)	1.421 (4)
C(4)—O(16)	1.322 (3)	C(17)—O(16)	1.412 (3)
C(4)—C(5)	1.433 (3)	S(1)—O(1)	1.436 (3)
C(5)—C(6)	1.401 (3)	S(1)—O(2)	1.550 (2)
C(5)—C(10)	1.425 (3)	S(1)—O(3)	1.422 (3)
C(6)—O(7)	1.379 (3)	S(1)—O(4)	1.455 (3)
C(8)—O(7)	1.352 (3)		
C(2)—C(1)—C(6)	113.2 (2)	C(13)—C(12)—O(11)	112.8 (2)
C(2)—C(1)—O(14)	122.1 (2)	C(3)—C(13)—C(12)	106.2 (3)
C(6)—C(1)—O(14)	124.6 (2)	C(9)—C(10)—O(18)	121.2 (2)
C(1)—C(2)—C(3)	126.6 (2)	C(9)—C(8)—C(19)	127.9 (2)
C(1)—C(2)—O(11)	122.6 (2)	C(9)—C(8)—O(7)	121.5 (2)
C(3)—C(2)—O(11)	110.7 (2)	C(19)—C(8)—O(7)	110.5 (2)
C(2)—C(3)—C(4)	119.2 (2)	C(8)—C(9)—C(10)	121.6 (2)
C(2)—C(3)—C(13)	105.1 (2)	C(5)—C(10)—C(9)	118.6 (2)
C(4)—C(3)—C(13)	135.6 (2)	C(5)—C(10)—O(18)	120.2 (2)
C(3)—C(4)—C(5)	117.1 (2)	O(1)—S(1)—O(2)	106.2 (2)
C(3)—C(4)—O(16)	126.3 (2)	O(3)—S(1)—O(4)	112.4 (2)
C(5)—C(4)—O(16)	116.6 (2)	O(1)—S(1)—O(3)	113.9 (2)
C(4)—C(5)—C(6)	119.0 (2)	O(1)—S(1)—O(4)	111.1 (2)
C(4)—C(5)—C(10)	124.2 (2)	O(2)—S(1)—O(3)	108.2 (1)
C(6)—C(5)—C(10)	116.8 (2)	O(2)—S(1)—O(4)	104.3 (1)
C(1)—C(6)—C(5)	124.8 (2)	C(2)—O(11)—C(12)	105.1 (2)
C(1)—C(6)—O(7)	113.4 (2)	C(1)—O(14)—C(15)	115.8 (2)
C(5)—C(6)—O(7)	121.8 (2)	C(4)—O(16)—C(17)	120.6 (2)
C(6)—O(7)—C(8)	119.3 (3)		

The O(1), O(3), O(4) atoms in the hydrogensulfate anion exhibit some disorder; nevertheless, O(4) and O(1) are involved in hydrogen bonding. They occupy two sites O(1) and O(q1), O(3) and O(q3), O(4) and

O(q4) with different site occupation factors as shown in Table 1.

The packing of the molecules in the unit cell is shown in the projection along the *a* axis in Fig. 2.

The benzofuran heterocycle is planar as observed in khellin (Carpy, Hickel & Leger, 1979). The torsion angles of the methoxy groups at C(1) and C(4) (Fig. 1) are quite different in khellin and khellinium, namely: C(2)—C(1)—O(14)—C(15) = -114.7 (3)° in khellinium and 29.2 (3)° in khellin, C(3)—C(4)—O(16)—C(17) = -25.5 (4)° in khellinium and 102.2 (2)° in khellin. However, the methyl group at C(8) has the same orientation with respect to the ring in both compounds: C(19)—C(8)—C(9)—C(10) = 179.3 (3)° in khellinium and 178.3 (4)° in khellin.

The carbonium ion connected to the hydroxyl group seems to be energetically quite similar to an enolic group. This fact is corroborated by a large band at 2500 cm<sup>-1</sup> in the IR spectrum which corresponds to an enolic vibration (Hila, 1983).

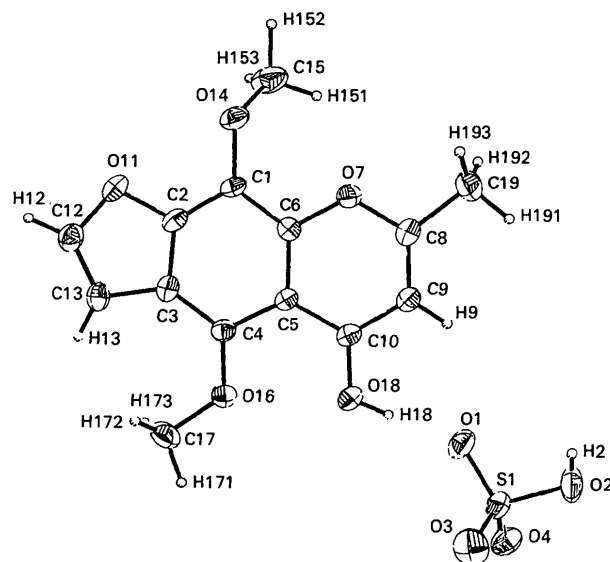


Fig. 1. Molecular structure showing 30% probability thermal ellipsoids for the non-H atoms and atom-numbering scheme.

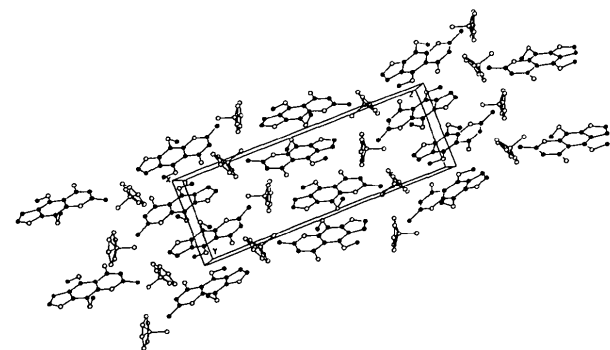


Fig. 2. Projection along the *a* axis showing the packing of the molecules in the unit cell.

The protonation of O(18) and the relatively strong hydrogen bond O(18)—H(18)···O(1) = 2.506 (5) Å with the hydrogensulfate anion decrease the electronegativity of O(18) and contribute to the enhancement of the attractive force between O(16) and O(18) [2.55 (3) Å in khellinium hydrogensulfate and 2.79 (2) Å in khellin] and narrow the angle C(5)—C(4)—O(16) to 116.6 (2)°. The bond length C(10)—O(18) = 1.288 (3) Å in khellinium, longer than in khellin [1.229 (3) Å], is in agreement with this protonation.

The bonds C(8)—C(9) = 1.329 (4) and 1.335 (3) Å and C(9)—C(10) = 1.405 (4) and 1.446 (4) Å in khellinium and khellin, respectively, show a small variation which can be explained by delocalized double bonds in the C(8)—C(9)—C(10) group at the carbonium ion.

The crystalline cohesion is ensured by a strong hydrogen bond between the benzofuran and the anion: O(18)—H(18)···O(1) = 2.506 (5) Å and an intermediate one O(2)—H(2)···O(4) ( $-x, y - 1/2, 1/2 - z$ ) = 2.68 (5) Å between two hydrogensulfate anions. The angles of these bonds are 166 (4) and

176 (3)°, respectively. The anions and the cations are on separate planes parallel to (001).

One of the authors (AK) thanks the Deutscher Akademischer Austauschdienst for financial support and Professor H. Fuess for helpful discussions. We also thank Professor M. Hamon for his interest in this work.

#### References

- CARPY, A., HICKEL, D. & LEGER, J.M. (1979). *Cryst. Struct. Commun.* **8**, 835–838.  
 HILA, J. E. (1983). Thesis, Univ. Paris XI, France.  
 HILA, J. E., LIKFORMAN, J., MAHUTEAU, J., KIRKIACHARIAN, S. & HAMON, M. (1985). *Bull. Soc. Chim. Fr.* **6**, 1275–1279.  
*International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)  
 LEGER, J. M., GOURSOLLE, M., GADRET, M. & CARPY, A. (1978). *Acta Cryst.* **B34**, 1203–1208.  
 SHELDRIK, G. M. (1983). *SHELXTL. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data*. Univ. of Göttingen, Federal Republic of Germany.  
 SPÄTH, E., DENGEL, F. & GRUBER, W. (1938). *Chem. Ber.* **71**, 106.

*Acta Cryst.* (1989). **C45**, 1522–1524

## Structure of Tetrahydrozoline Hydrochloride

BY SUTAPA GHOSE AND J. K. DATTA GUPTA

*Crystallography & Molecular Biology Division, Saha Institute of Nuclear Physics, I/AF Bidhannagar, Calcutta-700 064, India*

(Received 31 October 1988; accepted 24 January 1989)

**Abstract.** 2-(1,2,3,4-Tetrahydro-1-naphthyl)-4,5-dihydro-1H-imidazole hydrochloride,  $C_{13}H_{17}N_2^+ \cdot Cl^-$ ,  $M_r = 236.77$ , triclinic,  $P\bar{1}$ ,  $a = 9.9932$  (9),  $b = 8.0417$  (5),  $c = 7.9269$  (5) Å,  $\alpha = 106.68$  (1),  $\beta = 86.32$  (1),  $\gamma = 98.73$  (1)°,  $V = 603.01$  (8) Å<sup>3</sup>,  $Z = 2$ ,  $D_x = 1.304$  g cm<sup>-3</sup>,  $\lambda(Cu K\alpha) = 1.5418$  Å,  $\mu = 26.089$  cm<sup>-1</sup>,  $F(000) = 252$ , room temperature,  $R = 0.079$  for 1891 observed reflections. The imidazole ring is involved in protonation and the structure is stabilized by hydrogen bonds of the form N(1)—N(1H)···Cl···N(2H)—N(2) that link the molecules in continuous chains parallel to the  $b$  axis. The dihedral angle between the aromatic and the imidazole rings is 88.2 (2)°. Structural differences between the phenethylamines and the  $\alpha$ -adrenergic imidazoli(di)ne agonists and antagonists are discussed.

**Introduction.** Most of the sympathomimetic amines influence both the  $\alpha$ - and the  $\beta$ -adrenergic receptors, but the ratio of  $\alpha$  to  $\beta$  activity varies between drugs

from almost pure  $\alpha$  activity to almost pure  $\beta$  activity (Weiner, 1985). The adrenergic action of the 2-substituted imidazoli(di)nes is selective for the  $\alpha$ -adrenergic receptors only. Structurally, a typical adrenergic imidazoli(di)ne consists of a substituted phenyl ring separated from an imidazole ring by a carbon or nitrogen bridge. The title compound, tetrahydrozoline hydrochloride, is an imidazole ring containing an  $\alpha$ -sympathomimetic amine. When applied topically to the nasal mucosa, it causes vasoconstriction. It is also useful in a 0.05% solution as an ocular decongestant (Weiner, 1985). The crystal structure analysis of the title compound has been undertaken in order to obtain an idea of the structural and conformational differences, if any, between the phenethylamines and the  $\alpha$ -adrenergic imidazoli(di)ne agonists and antagonists.

**Experimental.** Commercially available compound recrystallized at 277 K, from a solution of dilute