bonds to each N atom are coplanar rather than in a pyramidal arrangement. As in the other thiuram disulfides, the C—N bond adjacent to the S atom is quite short while the other C—N bond lengths are long. No intermolecular short contacts are observed. In summary, there are two unusual structural features with respect to the previously reported thiuram disulfides. Whether the long S—S bond leads to greater chemical reactivity is being investigated.

One of the authors, VK, thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for the award of a fellowship.

References

BODE, H., TUSCHE, K. J. & WAHRHAUSEN, H. F. (1962). *Z. Anal. Chem.* **190**, 48–60.

BOR, G., GERVASIO, G., ROSSETTI, R. & STANGHELLINI, P. L. (1978). *J. Chem. Soc. Chem. Commun.* pp. 841–843.

FABIANI, C., SPAGNA, R., VACIAGO, A. & ZAMBONELLI, L. (1971). *Acta Cryst.* B**27**, 1499–1504.

GEOFFREY, A. W., STATHAM, R. J. & WHITE, A. H. (1983). *Aust. J. Chem.* **36**, 1371–1377.

HORDVIK, A. (1966). *Acta. Chem. Scand.* **20**. 1885–1891.

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

KARLE, I. L., ESTLIN, J. A. & BRITTS, K. (1967). *Acta Cryst.* **22**, 273–280.

MAROY, K. (1967). *Acta. Chem. Scand.* **19**, 1509.

ROUT, G. C., SESHASAYEE, M. & ARAVAMUDAN, G. (1982). *Cryst. Struct. Commun.* **11**, 1389–1393.

SCHNABEL, W., DEUTEN, K. V. & KLAR, G. (1980). *Phosphorus Sulfur*, **9**, 93–98.

SHEFTER, E. (1970). *J. Chem. Soc. B*, pp. 903–906.

SHELDRICK, G. M. (1986). *SHELXS*86. Program for crystal structure solution. Univ. of Göttingen, Federal Republic of Germany.

SIMMONS, C. J., LUNDEEN, M. & SEFF, K. (1979). *Inorg. Chem.* **18**, 3444–3452.

Acta Cryst. (1990). C**46**, 676–678

Structure of κ-Agonist, U-50488

BY MITSUNOBU DOI, TOSHIMASA ISHIDA AND MASATOSHI INOUE

Osaka University of Pharmaceutical Sciences, 2-10-65 *Kawai, Matsubara, Osaka* 580, *Japan*

(*Received* 24 *April* 1989; *accepted* 14 *August* 1989)

Abstract. $C_{19}H_{26}Cl_2N_2O.CH_3SO_3H.CH_3OH$, M_r = 497·44, triclinic, $P\bar{1}$, a = 12·276 (4), b = 12·398 (4), c = 8·841 (2) Å, α = 99·37 (6), β = 90·86 (8), γ = 109·64 (4)°, V = 1246 (2) Å^3, Z = 2, D_x = 1·326 Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ(Cu $K\alpha$) = 34·28 mm^{-1}, $F(000)$ = 528, T = 295 K, R = 0·0482 for 3813 reflections with $F > 3\sigma F$. *trans*-(+)-3,4-Dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide (U-50488) methane sulfonic acid was cocrystallized with methanol. The pyrrolidine ring is in a protonated state and forms an ion pair with methanesulfonate. The latter molecule is further linked with methanol solvent *via* a hydrogen bond. The molecule takes an opened conformation to avoid short contacts among the three bulky rings.

Introduction. Conformational studies for μ- and δ-opioid receptor selective antagonists or agonists have provided much information on the structure–function relationship of opioid receptors (Hansen & Morgan, 1984). However, it is well known that there are several opioid sub-receptors other than μ- and δ-receptors. To understand the multifarious functions of the opioid receptor, the stable conformation of the ligand which exhibits high selectivity to each opioid sub-receptor should be elucidated. Some morphine derivatives display analgesic actions, and one of them, U-50488, has high selectivity to the so-called κ-opioid receptor (Vonvoigtlander, Lahti & Ludens, 1983). As part of a series of structural studies of opioid ligands, we report here the crystal structure of U-50488.

Experimental. Cubic crystals were grown from a methanol/ethyl acetate solution of U-50488 methanesulfonic acid. Unit-cell parameters were refined using 22 reflections ($47 \le 2\theta \le 58°$) on a Rigaku AFC-5 diffractometer. Intensity data were collected to $\sin\theta/\lambda = 0{\cdot}588$ Å^{-1} using Cu $K\alpha$ radiation with the θ–2θ scan mode, from a crystal of dimensions 0·4 × 0·4 × 0·3 mm. The data were corrected for Lorentz and polarization effects. An absorption correction was not applied. 4275 independent reflections were measured for $-14 \le h \le 14$, $-14 \le k \le 14$ and $-10 \le l \le 0$, in which 3813 had $F > 3\sigma(F)$. Four reflections monitored periodically during the data correction showed negligible variation indicating instrumental and crystal stability. The structure was solved by direct methods using *MULTAN*87 (Debaerdemaeker, Germain, Main,

0108-2701/90/040676-03$03.00

Table 1. *Positional and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

	x	y	z	B_{eq}(Å^2)
C(1)	−0·1593 (2)	0·5219 (2)	0·6533 (2)	2·99 (6)
C(2)	−0·2714 (2)	0·4214 (2)	0·5901 (2)	3·04 (6)
C(3)	−0·2676 (2)	0·3068 (2)	0·6303 (3)	3·89 (8)
C(4)	−0·2486 (2)	0·3176 (2)	0·8036 (3)	4·79 (9)
C(5)	−0·1364 (2)	0·4155 (2)	0·8656 (3)	4·99 (9)
C(6)	−0·1392 (2)	0·5300 (2)	0·8270 (3)	4·54 (9)
N(7)	−0·1605 (1)	0·6320 (1)	0·6145 (2)	3·29 (6)
C(8)	−0·2446 (2)	0·6828 (2)	0·6827 (3)	4·27 (8)
C(9)	−0·0780 (2)	0·6880 (2)	0·5271 (3)	3·31 (7)
O(10)	−0·0104 (1)	0·6440 (1)	0·4664 (2)	5·04 (6)
C(11)	−0·0735 (2)	0·8079 (2)	0·5055 (3)	4·19 (8)
C(12)	0·0163 (2)	0·8603 (2)	0·3994 (3)	3·80 (8)
C(13)	−0·0133 (2)	0·8391 (2)	0·2437 (3)	4·60 (9)
C(14)	0·0674 (2)	0·8881 (2)	0·1433 (3)	4·71 (9)
Cl(15)	0·02654 (9)	0·85810 (8)	−0·0487 (1)	7·74 (4)
C(16)	0·1764 (2)	0·9614 (2)	0·2005 (3)	4·70 (9)
Cl(17)	0·27589 (7)	1·02539 (7)	0·0792 (1)	7·47 (4)
C(18)	0·2071 (2)	0·9819 (2)	0·3561 (4)	4·9 (1)
C(19)	0·1278 (2)	0·9315 (2)	0·4550 (3)	4·53 (9)
N(20)	−0·2905 (1)	0·4153 (2)	0·4201 (2)	3·38 (6)
C(21)	−0·2061 (2)	0·3777 (2)	0·3194 (3)	4·44 (8)
C(22)	−0·2756 (3)	0·2639 (2)	0·2205 (4)	6·2 (1)
C(23)	−0·3926 (3)	0·2773 (3)	0·1977 (4)	6·6 (1)
C(24)	−0·4125 (2)	0·3359 (2)	0·3550 (3)	4·81 (9)
Methanesulfonate				
S(1)′	0·38411 (6)	0·36013 (6)	0·74701 (8)	5·10 (2)
O(2)′	0·2887 (1)	0·4019 (2)	0·7238 (3)	6·37 (8)
O(3)′	0·3686 (3)	0·2545 (2)	0·6421 (3)	9·7 (1)
O(4)′	0·4949 (2)	0·4483 (2)	0·7424 (3)	8·0 (1)
C(5)′	0·3761 (3)	0·3265 (3)	0·9284 (4)	7·3 (1)
Methanol				
C(1)″	0·4888 (4)	0·0510 (4)	0·7553 (8)	11·9 (3)
O(2)″	0·3809 (5)	0·0382 (4)	0·6819 (8)	19·2 (3)

Table 2. *Bond lengths* (Å) *and angles* (°)

C(1)—C(2)	1·534 (3)	Cl(14)—Cl(15)	1·708 (3)
C(1)—C(6)	1·534 (3)	C(14)—C(16)	1·372 (4)
C(1)—N(7)	1·466 (3)	C(16)—Cl(17)	1·714 (3)
C(2)—C(3)	1·534 (3)	C(16)—C(18)	1·381 (4)
C(2)—N(20)	1·504 (3)	C(18)—C(19)	1·377 (4)
C(3)—C(4)	1·523 (4)	N(20)—C(21)	1·517 (3)
C(4)—C(5)	1·519 (4)	N(20)—C(24)	1·531 (3)
C(5)—C(6)	1·525 (4)	C(21)—C(22)	1·500 (4)
N(7)—C(8)	1·469 (3)	C(22)—C(23)	1·516 (5)
N(7)—C(9)	1·353 (3)	C(23)—C(24)	1·524 (4)
C(9)—O(10)	1·223 (3)	S(1)′—O(2)′	1·455 (2)
C(9)—C(11)	1·512 (3)	S(1)′—O(3)′	1·429 (3)
C(11)—C(12)	1·505 (3)	S(1)′—O(4)′	1·436 (3)
C(12)—C(13)	1·378 (4)	S(1)′—C(5)′	1·717 (4)
C(12)—C(19)	1·386 (3)	C(1)″—O(2)″	1·415 (8)
C(13)—C(14)	1·392 (4)		

C(2)—C(1)—C(6)	110·39 (6)	C(13)—C(14)—Cl(15)	118·74 (5)
C(2)—C(1)—N(7)	111·31 (5)	C(13)—C(14)—C(16)	119·65 (9)
C(6)—C(1)—N(7)	111·93 (6)	Cl(15)—C(14)—C(16)	121·58 (5)
C(1)—C(2)—C(3)	110·40 (5)	C(14)—C(16)—Cl(17)	120·37 (5)
C(1)—C(2)—N(20)	109·75 (5)	C(14)—C(16)—C(18)	119·98 (9)
C(3)—C(2)—N(20)	112·70 (5)	Cl(17)—C(16)—C(18)	119·63 (5)
C(2)—C(3)—C(4)	110·51 (6)	C(16)—C(18)—C(19)	120·24 (9)
C(3)—C(4)—C(5)	110·70 (6)	C(12)—C(19)—C(18)	120·38 (8)
C(4)—C(5)—C(6)	110·02 (7)	C(2)—N(20)—C(21)	116·38 (6)
C(1)—C(6)—C(5)	111·39 (6)	C(2)—N(20)—C(24)	112·82 (6)
C(1)—N(7)—C(8)	118·87 (6)	C(21)—N(20)—C(24)	106·74 (6)
C(1)—N(7)—C(9)	118·73 (6)	N(20)—C(21)—C(22)	106·41 (7)
C(8)—N(7)—C(9)	122·17 (7)	C(21)—C(22)—C(23)	102·41 (8)
N(7)—C(9)—O(10)	122·02 (8)	C(22)—C(23)—C(24)	104·31 (8)
N(7)—C(9)—C(11)	116·99 (7)	N(20)—C(24)—C(23)	103·51 (7)
O(10)—C(9)—C(11)	120·99 (8)	O(2)′—S(1)′—O(3)′	110·53 (7)
C(9)—C(11)—C(12)	113·09 (6)	O(2)′—S(1)′—O(4)′	111·99 (6)
C(11)—C(12)—C(13)	119·44 (7)	O(2)′—S(1)′—C(5)′	106·19 (7)
C(11)—C(12)—C(19)	121·51 (7)	O(3)′—S(1)′—O(4)′	113·20 (7)
C(13)—C(12)—C(19)	119·04 (9)	O(3)′—S(1)′—C(5)′	106·84 (7)
C(12)—C(13)—C(14)	120·65 (8)	O(4)′—S(1)′—C(5)′	107·66 (7)

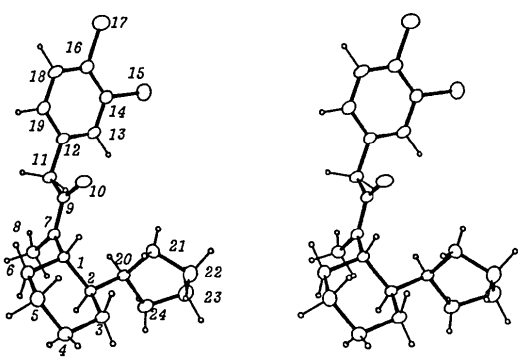

Fig. 1. Molecular conformation and numbering of U-50488.

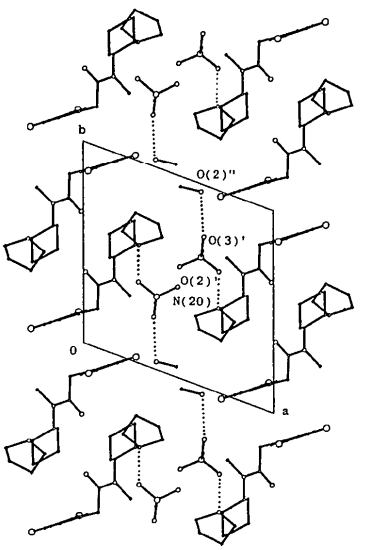

Fig. 2. Packing diagram viewed down the *c* axis.

Tate & Woolfson, 1987). The structure was refined by full-matrix least-squares method with isotropic thermal parameters, and by block-diagonal least-squares method with anisotropic thermal parameters minimizing $\sum w(|F_o| - |F_c|)^2$, where $w = 1/[\sigma(F_o)^2 + aF_o + bF_o^2]$. Hydrogens were included in the calculation of the structure factors with isotropic thermal parameters, but were not refined. Refinement converged to $R = 0{\cdot}0482$, $wR = 0{\cdot}0574$, $a = 0{\cdot}10449$, $b = -0{\cdot}00057$, $(\Delta/\sigma)_{max} = 0{\cdot}29$. Residual electron density in the final difference Fourier map was within 0·44 e Å^{-3}. The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The calculations were carried out using *The Universal Crystallographic Computing System* (1979).

The final atomic parameters are listed in Table 1,* and the bond lengths and angles are listed in Table 2. The molecular conformation is indicated in Fig. 1 and the packing diagram is indicated in Fig. 2.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52496 (14 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion. The *N*-methyl amide bond takes a *trans* form and its plane is almost vertical to the dichlorobenzene ring (Fig. 1). The cyclohexyl ring which takes a 'chair' form is separated from the aromatic ring by the amide bond. The pyrrolidine N(20) atom is in a protonated state and forms an ion pair with the methanesulfonate O(2)′ atom: N(20)—O(2)′ = 2·768 (3) Å. The S(1)′—O(2)′ bond of the methanesulfonate molecule is meaningfully longer than other S—O bonds (Table 2), and this would indicate the localization of a negative charge. The methanesulfonate molecule is further linked to a methanol solvent by a hydrogen bond: O(3)′—O(2)″ = 2·813 (6) Å. The methanesulfonate and methanol molecules compose a layer expanding along the *bc* plane, which is alternately arranged with the hydrophobic layer of U-50488 as shown in Fig. 2.

The U-50488 molecule assumes an 'opened' conformation to avoid intermolecular short contacts among the three bulky rings. Such a conformation would be expected in the absence of the organic acid (non-ionized state), and consequently the relative distance between the aromatic ring and the nitrogen N(20), which is very important to the analgesic activity of morphine, would be invariably kept. Tifluadom, a related κ-agonist which also has a protonated nitrogen and bulky rings like U-50488, was crystallized with a similar conformation (Petcher, Winder, Maetzel & Zeugner, 1985). Thus, such an 'opened' conformation would be closely related with the emergence of κ-agonist activity.

References

DEBAERDEMAEKER, T., GERMAIN, G., MAIN, P., TATE, C. & WOOLFSON, 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.

HANSEN, P. E. & MORGAN, B. A. (1984). *The Peptides*, edited by S. UDENFRIEND & J. MEIENHOFER, Vol. 6, pp. 269–321. New York: Academic Press.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

PETCHER, T. J., WINDER, A., MAETZEL, U. & ZEUGNER, H. (1985). *Acta Cryst.* C**41**, 909–912.

The Universal Crystallographic Computing System (1979). *UNICS.* The Computation Center, Osaka Univ., Japan.

VONVOIGTLANDER, P. F., LAHTI, R. A. & LUDENS, J. H. (1983). *J. Pharmacol. Exp. Ther.* **224**, 7–12.

Acta Cryst. (1990). C**46**, 678–682

Structure of the Tetrahydrate of the N-Terminal Tetrapeptide from Angiotensin II

BY SCOTT H. FELDMAN AND DRAKE S. EGGLESTON

Smith Kline & French Laboratories, Department of Physical and Structural Chemistry, L-950, PO Box 1539, King of Prussia, PA 19406, USA

(*Received* 28 *February* 1989; *accepted* 11 *July* 1989)

Abstract. L-Aspartyl-L-arginyl-L-valyl-L-tyrosine tetrahydrate, $C_{24}H_{37}N_7O_8.4H_2O$, $M_r = 623{\cdot}67$, triclinic, $P1$, $a = 4{\cdot}796\ (2)$, $b = 11{\cdot}791\ (5)$, $c = 13{\cdot}681\ (6)$ Å, $\alpha = 91{\cdot}91\ (2)$, $\beta = 92{\cdot}75\ (2)$, $\gamma = 90{\cdot}94\ (2)°$, $V = 772{\cdot}2\ (10)$ Å^3, $Z = 1$, $D_x = 1{\cdot}341$ Mg m^{-3}, λ(Cu $K\bar{\alpha}$) = 1·54184 Å, $\mu = 8{\cdot}714$ mm^{-1}, $F(000) = 334$, $T = 196$ K, $R = 0{\cdot}041$ for 2740 observations. The tetrapeptide comprises the first four residues of human angiotensin II. Crystals were grown *via* hanging-drop vapor diffusion against various high molarity salt solutions. The tetrapeptide is a double zwitterion in the crystal and adopts an extended conformation. Principal backbone torsion angles are $\psi_1 = 153{\cdot}2\ (2)$, $\omega_2 = 162{\cdot}0\ (2)$, $\varphi_2 = -106{\cdot}5\ (3)$, $\psi_2 = 120{\cdot}8\ (3)$, $\omega_3 = -168{\cdot}2\ (2)$, $\varphi_3 = -129{\cdot}6\ (3)$, $\psi_3 = 120{\cdot}1\ (3)$, $\omega_4 = -176{\cdot}0\ (2)$, $\varphi_4 = -107{\cdot}6\ (3)°$. The aspartyl side chain [$\chi_1^1 = -65{\cdot}4\ (3)°$] is hydrogen bonded intramolecularly to the N terminus. The tyrosyl ring sits over the preceeding peptide bond; the dihedral angle between phenolic and peptide planes is 38·9 (3)°. An extensive hydrogen bonding network exists in the crystals. The peptide backbone amides are hydrogen bonded in a parallel β-sheet motif. The guanidinum group of arginine participates in both a type *B* and a type *C* interaction.

Introduction. The renin–angiotensin system plays a key role in cardiovascular homeostasis with inappropriate activity implicated in the development of essential hypertension, renal disease and congestive heart failure (Capponi, Aquilera, Fakunding & Catt, 1981). Angiotensin II, an octapeptide first isolated in the 1950's (Peach, 1981) and an element of this system, is a potent endogenous vasoconstrictor with direct arterial action.

0108-2701/90/040678-05$03.00