

C2—C3	1.360 (8)	C13'—C14	1.55 (3)
C3—C4	1.416 (8)	C14—C15	1.476 (9)
C4—O4	1.244 (7)	C15—N16	1.518 (7)
C4—C5	1.506 (7)	N16—C17	1.497 (6)
C5—C6	1.518 (7)	C11—O2B	1.30 (2)
C6—C7	1.518 (7)	C11—O4B	1.35 (2)
C7—C8	1.521 (8)	C11—O1A	1.35 (2)
C7—C17	1.527 (7)	C11—O4A	1.35 (2)
C8—C9	1.517 (8)	C11—O1B	1.37 (2)
C9—C10	1.500 (9)	C11—O3A	1.38 (2)
C9—C11	1.512 (8)	C11—O2A	1.39 (2)
C11—N16	1.515 (7)	C11—O3B	1.40 (2)
C2—N1—C6	116.9 (4)	C12—C13—C14	121.0 (20)
C2—N1—C10	116.3 (5)	C12'—C13'—C14	124.7 (25)
C6—N1—C10	116.5 (4)	C15—C14—C13	105.7 (11)
N1—C2—C3	125.0 (4)	C15—C14—C13'	118.3 (12)
C2—C3—C4	121.0 (5)	C14—C15—N16	114.4 (5)
O4—C4—C3	124.0 (5)	C17—N16—C11	112.4 (4)
O4—C4—C5	120.8 (5)	C17—N16—C15	112.8 (4)
C3—C4—C5	115.1 (5)	C11—N16—C15	107.8 (4)
C4—C5—C6	113.3 (4)	N16—C17—C7	113.5 (4)
N1—C6—C5	109.8 (4)	O2B—C11—O4B	115 (1)
N1—C6—C7	111.2 (4)	O1A—C11—O4A	114 (1)
C5—C6—C7	114.5 (4)	O2B—C11—O1B	107 (1)
C6—C7—C8	110.4 (5)	O4B—C11—O1B	105 (1)
C6—C7—C17	115.0 (4)	O1A—C11—O3A	109 (1)
C8—C7—C17	108.5 (5)	O4A—C11—O3A	118 (1)
C9—C8—C7	106.5 (4)	O1A—C11—O2A	108 (1)
C10—C9—C11	114.1 (5)	O4A—C11—O2A	100 (1)
C10—C9—C8	110.3 (5)	O3A—C11—O2A	107 (1)
C11—C9—C8	111.0 (5)	O2B—C11—O3B	109 (1)
N1—C10—C9	111.0 (5)	O4B—C11—O3B	115 (1)
C9—C11—N16	113.2 (4)	O1B—C11—O3B	106 (1)

D—H...A	D—H	H...A	D...A	D—H...A
N16—H16...O1W ^a	0.86 (6)	1.99 (6)	2.823 (6)	165 (5)
O1W—H1W1...O4	0.83 (8)	1.94 (8)	2.761 (5)	171 (8)
O1W—H1W2...O2A	1.00 (10)	1.84 (10)	2.843 (10)	171 (7)

Symmetry code: (i) $-x, y - \frac{1}{2}, 2 - z$.

Data collection: Kuma KM-4 software (Kuma, 1991). Cell refinement: Kuma KM-4 software. Data reduction: Kuma KM-4 software. Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *Stereochemical Workstation Operation Manual* (Siemens, 1989). Software used to prepare material for publication: *SHELXL93*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AB1207). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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A Morphine Metabolite: (-)-Morphine-3-O-β-D-glucuronide Trihydrate (M3G.3H₂O)

ZOFIA URBANCZYK-LIPKOWSKA

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

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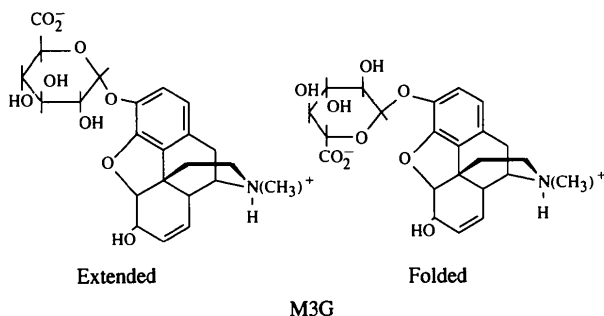
Abstract

The title compound, C₂₃H₂₇NO₉.3H₂O, occurs in the solid state as a zwitterion solvated by three water molecules. The conformation of this morphine conjugate is extended with the strongest proton donor (hydroxyl group at C6) and acceptors (two O atoms of the carboxyl group) located on one side of the molecule. The three-dimensional hydrogen-bonding pattern shows many competing possibilities of bonding and resembles one of the probable dynamic structures in solution.

Comment

The important role of morphine in modern pain therapy, even with its numerous side effects, is unquestionable. However, the role of metabolites in neuropharmacological mechanisms is not yet fully understood. Recently, the two main metabolites of morphine, 3-O-β-D-glucuronide (M3G) and 6-O-β-D-glucuronide (M6G), have been studied at many laboratories. These conjugates of morphine and glucuronic acid, produced in the liver, have been found in blood plasma and the brain, suggesting that, in contrast to morphine itself, they can penetrate the blood-brain barrier (Yoshimura, Ida, Oguri & Tsukamoto, 1973). Other studies have demonstrated that both metabolites of morphine could be formed enzymatically in various parts of the human brain (Wahlström, Windblad, Bixo & Rane, 1988). Morphine glucuronides have adverse effects on the nervous system (Smith, Watt & Cramond, 1990). M6G is a very potent μ-receptor agonist and is much more active *in vivo* than morphine (Shimomura *et al.*, 1971). M3G does not act as an analgesic but plays an important role in developing morphine tolerance (Lipkowski, Langlade, Os-good, Szyfelbein & Carr, 1992). Lipophilicity studies, along with molecular modelling of these compounds,

have shown that under physiological conditions two basic conformations are possible: an extended conformation and a conformation with an intramolecular hydrogen bond between the morphine and glucuronide units (Carrupt *et al.*, 1991).



The higher permeabilities of these two metabolites in comparison with morphine were explained on the basis of the chameleon-like properties of the molecule, possessing significantly different sized hydrophobic and hydrophilic areas in the extended and folded forms. As the conformation of the molecule and hydrogen-bonding pattern seems to be essential in explaining this phenomenon, X-ray diffraction studies of the (-)-morphine-3-*O*- β -D-glucuronide (M3G) crystallized from water were performed.

As shown in the *ORTEP* (Johnson, 1965) diagram (Fig. 1), the compound occurs in the crystal as a zwitterion, with almost equal C—O distances in the carboxyl group and a well localized quaternary H(N) atom. No peculiarities in the geometry were found when compared with that of morphine hydrochloride trihydrate (Gylbert, 1973) or other morphine conjugates,

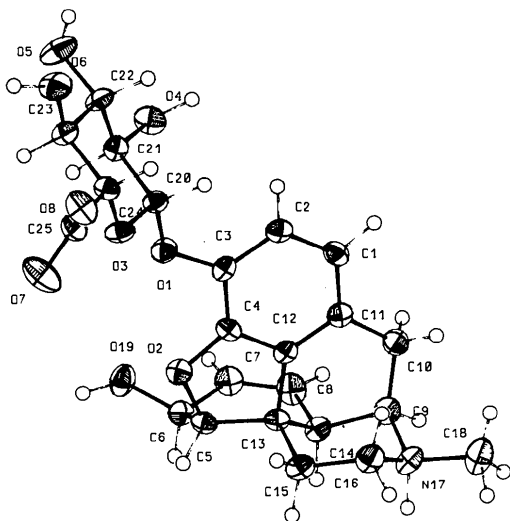


Fig. 1. A view of the molecule showing the atom labels and 50% probability ellipsoids. H atoms are represented by spheres of arbitrary radii.

e.g. naltrexonazine (Urbanczyk-Lipkowska, Lipkowski, Etter, Hahn & Portoghese, 1987) and bimirphinan (Urbanczyk-Lipkowska, Etter, Lipkowski & Portoghese, 1987).

Attempts to explain the interesting biological properties of morphine glucuronates have been made by performing lipophilicity studies, together with molecular modelling (Carrupt *et al.*, 1991). The relatively high lipophilicity of these molecular aggregates suggests that the conformation of the molecules may change significantly when crossing biological barriers. The two critical conformations, proposed by Carrupt *et al.* (1991) on the basis of molecular-modelling studies are: the extended form, with all polar groups exposed to interactions with the solvent (water), and the folded form, bonded by an intramolecular hydrogen bond and showing, outside of the folding, quite a large hydrophobic area suitable for interactions with the biological membrane.

In the crystal, the M3G molecule, like morphine hydrochloride, retains three water molecules. Fig. 2 illustrates the hydrogen-bonding pattern in the crystal, and Table 3 presents the geometry of all short hydrogen-bonding-type interactions. According to Table 3, the O7 and O8 atoms of the carboxyl group of the glucuronic moiety are the strongest hydrogen-bond acceptors, whereas O6 and O19 are the strongest hydrogen-bond donors. These groups form strong intermolecular hydrogen bonds between the molecules. No intramolec-

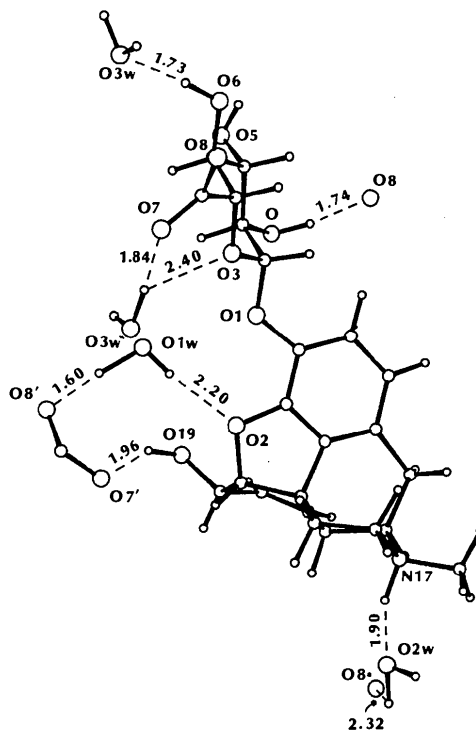


Fig. 2. Short intermolecular interactions (Å) in the hydrogen-bonding range.

ular hydrogen bonds are found; however, two water molecules mediate non-direct hydrogen bonding between the above mentioned groups. As can be seen from Table 3, the hydrogen-bond geometry is not perfect, e.g. the hydroxyl group O5 remains unbonded as a result of competition between many bonding possibilities.

The conformation of the molecule in the crystal is extended [torsion angles C4—C3—O1—C20 and C3—O1—C20—O3 are 158.1 (4) and -121.5 (4)°, respectively]. However, in contrast to the conformation found by molecular modelling (see the scheme above), the glucuronic moiety is rotated in such a way that the carboxyl group and the five-membered ring are located on the same side of the morphine unit. Three molecules of water co-crystallize with the M3G molecule in such a way that most of the hydrogen bonds occur on one side of the molecule. The M3G molecule, even when located in the vicinity of a biological membrane (folded conformation), could probably retain some of its water molecules, thus bringing its two structural elements closer and consequently becoming more lipophilic.

Experimental

The compound was prepared according to the method described by Berrang, Twine, Hennessee & Carroll (1975). The reaction product was dissolved in hot water, stirred for 30 min and left to stand at *ca* 278 K. White prism-like crystals appeared after two weeks.

Crystal data

C₂₃H₂₇NO₉·3H₂O

M_r = 515.512

Orthorhombic

*P*2₁2₁2₁

a = 10.957 (1) Å

b = 12.836 (2) Å

c = 16.466 (3) Å

V = 2315 (1) Å³

Z = 4

D_x = 1.479 Mg m⁻³

Mo *K*α radiation

λ = 0.71069 Å

Cell parameters from 25

reflections

θ = 11.2–21.4°

μ = 0.12 mm⁻¹

T = 298 K

Prism

0.3 × 0.3 × 0.2 mm

White

Data collection

Enraf–Nonius CAD-4
diffractometer

2θ scans

Absorption correction:

none

2097 measured reflections

1995 independent reflections

1995 observed reflections

[*I* > 3σ(*I*)]

θ_{max} = 25°

h = 0 → 12

k = 0 → 15

l = 0 → 18

3 standard reflections

frequency: 60 min

intensity decay: 2%

Refinement

Refinement on *F*

R = 0.046

wR = 0.039

S = 1.348

(Δ/σ)_{max} = 0.12

Δρ_{max} = 0.24 e Å⁻³

Δρ_{min} = -0.17 e Å⁻³

Extinction correction: none

1995 reflections

465 parameters

w = 1/σ²(*F*)

Atomic scattering fac-

tors from *SHELX76*

(Sheldrick, 1976)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

$$B_{eq} = (8\pi^2/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B_{eq}</i>
C1	0.7813 (4)	0.3552 (4)	0.3661 (3)	2.3 (1)
C2	0.7929 (4)	0.4360 (3)	0.4228 (3)	2.1 (1)
C3	0.8271 (4)	0.4151 (3)	0.5027 (3)	1.6 (2)
C4	0.8498 (4)	0.3125 (3)	0.5229 (2)	1.5 (2)
C5	0.8663 (4)	0.1615 (3)	0.5937 (3)	2.1 (1)
C6	0.7415 (4)	0.1222 (3)	0.6289 (3)	2.3 (1)
C7	0.6452 (4)	0.1023 (4)	0.5655 (3)	2.6 (2)
C8	0.6689 (4)	0.0655 (4)	0.4922 (3)	2.8 (2)
C9	0.8164 (4)	0.0541 (3)	0.3735 (3)	2.4 (2)
C10	0.7824 (4)	0.1583 (3)	0.3347 (3)	2.7 (1)
C11	0.8060 (4)	0.2532 (3)	0.3871 (3)	2.0 (1)
C12	0.8457 (4)	0.2368 (3)	0.4654 (3)	1.5 (2)
C13	0.8815 (4)	0.1352 (3)	0.5033 (3)	1.9 (1)
C14	0.8018 (4)	0.0495 (3)	0.4666 (3)	2.3 (1)
C15	1.0174 (4)	0.1096 (4)	0.4843 (3)	2.4 (2)
C16	1.0397 (4)	0.0995 (4)	0.3945 (3)	2.8 (2)
N17	0.9514 (4)	0.0241 (3)	0.3569 (2)	2.8 (1)
C18	0.9783 (5)	0.0084 (4)	0.2685 (3)	3.9 (2)
O19	0.6945 (3)	0.1898 (2)	0.6885 (2)	3.0 (1)
C20	0.8496 (4)	0.5906 (3)	0.5523 (3)	2.0 (1)
C21	0.7414 (4)	0.6511 (3)	0.5855 (3)	2.2 (1)
C22	0.7685 (4)	0.7652 (3)	0.5805 (3)	2.4 (2)
C23	0.8878 (4)	0.7900 (3)	0.6252 (3)	2.4 (1)
C24	0.9885 (4)	0.7207 (3)	0.5906 (3)	2.1 (1)
C25	1.1107 (4)	0.7345 (4)	0.6364 (3)	2.5 (1)
O1	0.8296 (3)	0.4842 (2)	0.5661 (2)	2.4 (1)
O2	0.8738 (3)	0.2751 (2)	0.5990 (2)	2.3 (1)
O3	0.9555 (3)	0.6141 (2)	0.5985 (2)	2.2 (1)
O4	0.6329 (3)	0.6232 (2)	0.5422 (2)	2.7 (1)
O5	0.6678 (3)	0.8214 (2)	0.6170 (2)	3.5 (1)
O6	0.9143 (3)	0.8962 (2)	0.6128 (2)	3.1 (1)
O7	1.1304 (3)	0.6760 (3)	0.6945 (2)	3.6 (1)
O8	1.1789 (3)	0.8058 (3)	0.6119 (2)	3.0 (1)
O1W	0.7836 (4)	0.4197 (3)	0.7409 (2)	4.7 (1)
O2W	0.9156 (4)	-0.1972 (3)	0.3765 (3)	6.1 (2)
O3W	0.9719 (4)	0.9866 (3)	0.7536 (3)	5.7 (2)

Table 2. Selected geometric parameters (Å, °)

C2—C1	1.401 (7)	C13—C12	1.498 (6)
C11—C1	1.381 (6)	C14—C13	1.529 (6)
C3—C2	1.394 (7)	C15—C13	1.557 (6)
C4—C3	1.381 (6)	C16—C15	1.504 (7)
O1—C3	1.370 (5)	N17—C16	1.502 (6)
C12—C4	1.357 (6)	C18—N17	1.499 (6)
O2—C4	1.367 (5)	C21—C20	1.519 (6)
C6—C5	1.569 (6)	O1—C20	1.402 (5)
C13—C5	1.535 (7)	O3—C20	1.420 (6)
O2—C5	1.463 (5)	C22—C21	1.497 (5)
C7—C6	1.506 (7)	O4—C21	1.432 (6)
O19—C6	1.408 (5)	C23—C22	1.534 (6)
C8—C7	1.322 (7)	O5—C22	1.449 (5)
C14—C8	1.530 (6)	C24—C23	1.528 (6)
C10—C9	1.528 (6)	O6—C23	1.409 (5)
C14—C9	1.542 (7)	C25—C24	1.547 (6)
N17—C9	1.553 (6)	O3—C24	1.421 (5)
C11—C10	1.515 (6)	O7—C25	1.235 (6)
C12—C11	1.377 (7)	O8—C25	1.249 (6)
H40—O4	1.02 (4)	H4W—O2W	1.09 (7)
H50—O5	0.88 (5)	H5W—O3W	1.01 (5)
H60—O6	0.94 (4)	H6W—O3W	0.88 (6)
H1W—O1W	0.95 (6)	H6W—H5W	1.41 (8)
H2W—O1W	1.26 (5)	H17N—N17	1.09 (4)
H3W—O2W	0.83 (6)	H19O—O19	0.92 (5)

C1—C2—C3	120.7 (4)	C9—N17—H17N	107 (2)
C2—C1—C11	121.1 (4)	C14—C9—N17	105.3 (3)
C1—C11—C10	125.9 (4)	C9—N17—C16	112.4 (3)
C1—C11—C12	116.2 (4)	C9—N17—C18	113.1 (4)
C2—C3—C4	117.3 (4)	C10—C11—C12	117.7 (4)
C2—C3—O1	126.9 (4)	C11—C12—C13	127.3 (4)
C3—C4—C12	120.6 (4)	C12—C13—C14	108.2 (4)
C3—C4—O2	126.2 (3)	C12—C13—C15	110.5 (4)
C4—C3—O1	115.5 (4)	C14—C13—C15	108.3 (4)
C3—O1—C20	120.7 (4)	C13—C15—C16	111.7 (4)
C4—C12—C11	123.6 (4)	C15—C16—N17	110.8 (4)
C4—C12—C13	108.9 (4)	C16—N17—C18	111.1 (4)
C12—C4—O2	113.2 (3)	C20—C21—C22	109.0 (4)
C4—O2—C5	106.5 (3)	C20—C21—O4	109.9 (4)
C5—C6—C7	114.1 (4)	C21—C20—O1	108.5 (3)
C5—C6—O19	112.2 (3)	C21—C20—O3	109.6 (4)
C6—C5—C13	112.5 (4)	O1—C20—O3	104.3 (3)
C6—C5—O2	110.3 (3)	C20—O3—C24	111.3 (3)
C5—C13—C12	100.6 (3)	C21—C22—C23	110.2 (3)
C5—C13—C14	118.6 (4)	C21—C22—O5	108.2 (3)
C5—C13—C15	110.2 (4)	C22—C21—O4	112.4 (3)
C13—C5—O2	105.7 (3)	C22—C23—C24	108.4 (4)
C6—C7—C8	123.8 (4)	C22—C23—O6	107.8 (3)
C7—C6—O19	109.4 (4)	C23—C22—O5	110.2 (3)
C7—C8—C14	119.1 (4)	C23—C24—C25	112.1 (4)
C8—C14—C9	111.6 (4)	C23—C24—O3	110.0 (3)
C8—C14—C13	109.8 (4)	C24—C23—O6	111.1 (3)
C9—C10—C11	115.1 (4)	C24—C25—O7	117.3 (4)
C10—C9—C14	115.1 (3)	C24—C25—O8	116.3 (4)
C10—C9—N17	112.1 (3)	C25—C24—O3	106.6 (3)
C9—C14—C13	107.8 (3)	O7—C25—O8	126.2 (4)
H1W—O1W—H2W	105 (5)	C16—N17—H17N	112 (2)
H3W—O2W—H4W	82 (5)	C18—N17—H17N	101 (2)
H5W—O3W—H6W	97 (5)	C22—O5—H50	101 (4)
C6—O19—H190	129 (3)	C23—O6—H60	113 (3)

Table 3. Hydrogen-bonding geometry (Å, °)

D—H...A	D—H	H...A	D...A	D—H...A
N17—H17N...O2W	1.09 (4)	1.90 (4)	2.886 (5)	149 (3)
O6—H60...O3W	0.94 (4)	1.73 (4)	2.668 (6)	175 (4)
O1W—H1W...O2	0.95 (6)	2.20 (6)	3.143 (5)	170 (5)
O4—H40...O8 ⁱ	1.02 (4)	1.74 (4)	2.743 (4)	167 (4)
O19—H190...O7 ⁱⁱ	0.92 (5)	1.96 (4)	2.725 (5)	140 (4)
O1W—H2W...O8	1.26 (5)	1.60 (5)	2.860 (5)	175 (4)
O2W—H4W...O8 ⁱⁱⁱ	1.09 (4)	2.37 (5)	2.951 (5)	111 (4)
O3W—H5W...O7 ^{iv}	1.01 (5)	1.84 (5)	2.810 (6)	160 (3)
O3W—H5W...O3	1.01 (5)	2.40 (4)	3.040 (6)	121 (4)
O3W—H6W...O1W	0.88 (6)	2.30 (5)	2.815 (6)	118 (5)

Symmetry codes: (i) $x - \frac{1}{2}, \frac{3}{2} - y, 1 - z$; (ii) $2 - x, y - \frac{1}{2}, \frac{3}{2} - z$; (iii) $x - \frac{1}{2}, \frac{1}{2} - y, 1 - z$; (iv) $2 - x, \frac{1}{2} + y, \frac{3}{2} - z$.

Intensities were corrected for Lp effects and variation in the intensity of the standard reflections. The structure was solved by direct methods (SHELXS86; Sheldrick, 1985) and refined by full-matrix least squares minimizing $\sum w(\Delta F)^2$, where $w = 1/\sigma^2(F)$ and σ was obtained from counting statistics (SHELX76; Sheldrick, 1976). All water, hydroxyl and H(N) atoms were found from ΔF synthesis and refined; otherwise, the atomic parameters were recalculated after every six cycles of refinement. The electron-density maximum always accompanied the O2W atom, showing that the second water molecule is slightly disordered. No fluctuations of electron density above that value were observed on the final $\Delta\rho$ maps. All calculations were performed on a PC/486 computer, using the programs quoted above and our own supporting programs.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: KA1049). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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3-Acetylamino-1,4-benzoquinone 4-Oxime

TRUSHAR ADATIA, HENGAMEH BARJESTEH,*
JOHN CHARALAMBOUS, NICK CHOI AND MARY MCPARTLIN

School of Applied Chemistry, University of North London, Holloway Road, London N7 8DB, England

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Abstract

In the title compound, C₈H₈N₂O₃, the ring system conforms to an almost planar configuration. The mean values of the two short and four long C—C bond distances in the six-membered ring are 1.339 (8) and 1.450 (8) Å, respectively. In the oxime group, the bond dimensions are C—N 1.301 (7), N—O 1.361 (6) and C—N—O 112.5 (4)°. The quinonic C=O bond distance is 1.234 (7) Å, which is similar to the C=O bond length [1.222 (7) Å] of the amide group. The crystal structure is stabilized by intermolecular hydrogen bonding.

Comment

It has been well established that in solution quinone monooximes exhibit nitrosphenolic/quinone oximic tautomerism (Burawoy, Cais, Chamberlain, Liversedge