Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

3-Hydroxy-2-[4-(2-hydroxyethyl)piperazin-1-ylmethyl]-6-methylpyran-4-one

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Key indicators

Single-crystal X-ray study
T = 296 K
Mean σ(C–C) = 0.002 Å
R factor = 0.033
wR factor = 0.073
Data-to-parameter ratio = 17.5

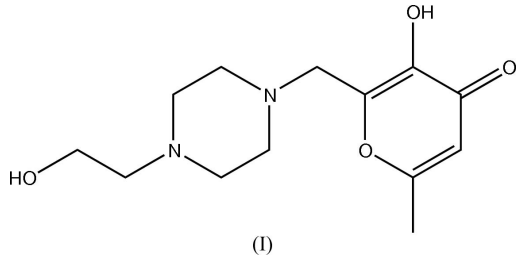
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 16 May 2005
Accepted 25 May 2005
Online 31 May 2005

In the title compound, $C_{13}H_{20}N_2O_4$, the piperazine ring displays a chair conformation. The occurrence of O—H···N hydrogen bonding results in the formation of a layer-like structure, which extends parallel to the *ac* plane.

Comment

Epilepsy, one of the most frequent neurological disorders, is a major public health issue, affecting about 4% of individuals over their lifetime (Browne & Holmes, 2001). Although a number of antiepileptic drugs are currently on the market, they have some adverse effects. Therefore, there is a definite need for more selective and less toxic anticonvulsant drugs (Krall *et al.*, 1978). In our previous work, 3-hydroxy-6-methyl-2-substituted-4*H*-pyran-4-one derivatives were synthesized for the evaluation of their potential anticonvulsant activity. Their anticonvulsant activities were determined by maximal electroshock (MES), subcutaneous metrazol (scMet) and rotorod toxicity tests for neurological deficits. Some Mannich bases were shown to have a high level of protection against MES and scMet tests (Aytemir *et al.*, 2004). X-ray crystallography studies were also carried out. The conformation of the compounds is induced by intra- and intermolecular hydrogen bonds (Köysal *et al.*, 2004; Ocak *et al.*, 2004). According to activity studies, the title compound, (I), has been found to show activity against MES at 300 mg kg^{-1} doses after half an hour, whereas no neurotoxicity was observed. The bidentate chelating ligand 2-hydroxymethyl-5-hydroxypyran-4-one (kojic acid), which is analogous to the catechol-like function, forms stable complexes with several metal ions (Petrola & Repetti, 1985; Masoud *et al.*, 1989).



(I)

The title compound consists of 2-methyl-5-hydroxypyran-4-one (allomaltol) and a piperazine ring, which are connected through a methylene bridge. The piperazine is further connected through the second N atom to the ethanol group.

The bond lengths and angles observed in the allomaltol group are comparable to those found in ethyl-4-(3-hydroxy-6-methyl- 4-oxo-4*H*-pyran-2-ylmethyl)piperazine-1-carboxylate (Ocak *et al.*, 2004).

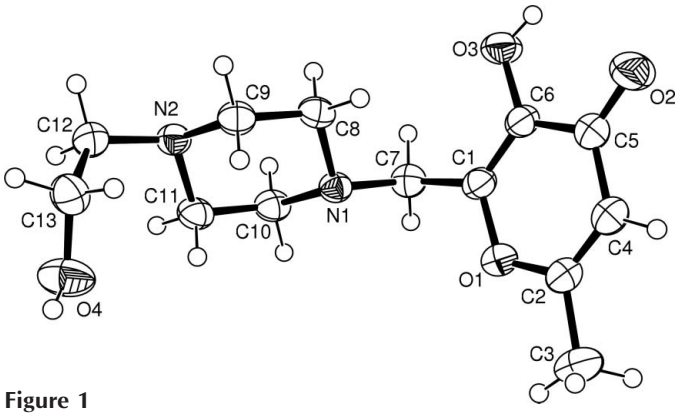


Figure 1
An *ORTEPIII* (Burnett & Johnson, 1996) drawing of the title compound, showing the atomic numbering scheme. Displacement ellipsoids of non-H atoms are shown at the 50% probability level.

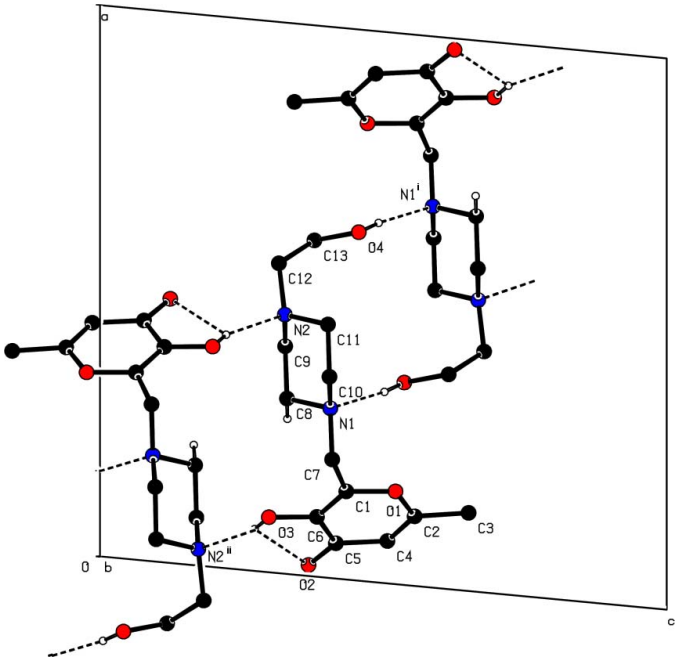


Figure 2
A packing view (*PLATON*; Spek, 2003) showing the O—H···N hydrogen-bond (dashed lines) network. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$.]

In the piperazine ring, the bond lengths and angles conform to those found previously (Yogavel *et al.*, 2003; Ocak *et al.*, 2004). The piperazine ring adopts a chair conformation, with a total puckering amplitude of Q_T = 0.5848 (16) Å (Cremer & Pople, 1975). The bond angles around atoms N1 and N2 are indicative of sp^3-hybridization. The plane through the C atoms of the piperazine ring makes a dihedral angle of 83.96 (5)° with the allomaltol group.

There are one intramolecular O—H···O and two intermolecular O—H···N hydrogen bonds in the crystal structure. Atom O2 is involved as an acceptor in one intra- and two intermolecular biifurcated hydrogen bonds. The O—H···N hydrogen bond generates a layer-like network, extending parallel to the *ac* plane. Some weak C—H···O intramolecular interactions help to stabilize the structure.

Experimental

All chemicals used in this study were supplied by Merck (Darmstadt, Germany) or the Aldrich Chemical Co. (Steinheim, Germany). Allomaltol (5-hydroxy-2-methylpyran-4-one) was synthesized from kojic acid according to the report by Ellis *et al.* (1996). 2-Chloromethyl-5-hydroxypyran-4-one (chlorokojic acid) was prepared in good yield (75%) by chlorination of kojic acid using thionyl chloride at room temperature. Allomaltol was produced by reduction of chlorokojic acid with zinc powder in concentrated hydrochloric acid. Compound (I) was prepared as a Mannich base by reaction of 4-(2-hydroxyethyl)piperazine (0.01 mol) and allomaltol (0.01 mol) in methanol (20 ml) with 37% formalin (1 ml). The resulting mixture was stirred vigorously for 30 min at room temperature and concentrated under reduced pressure. After drying under vacuum, a pale-yellow oil was obtained. The oil product was recrystallized from ethyl acetate to give a beige crystalline solid. Yield 47%, m.p. 406–407 K. IR (cm^{-1}): 1632 (C═O, *st*) and 1460 (C═C, *st*). ^{1}H NMR (DMSO, 400 MHz, p.p.m.): δ 2.30 (3H, *s*, 6-CH_3), 2.56–2.74 (9H, *m*, –CH_2—CH_3, piperazine and –OH), 3.63–3.72 (4H, *m*, piperazine, –CH_2–), 6.20 (1H, *s*, H^5). Analysis calculated for $C_{13}H_{20}N_2O_4$ (MA 268.31): C 58.19, H 7.51, N 10.44%; found: C 58.33, H 7.90, N 10.35%.

Crystal data

$C_{13}H_{20}N_2O_4$	D_x = 1.273 Mg m^{-3}
M_r = 268.31	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 10945 reflections
a = 15.256 (2) Å	θ = 1.8–29.3°
b = 5.8527 (5) Å	μ = 0.10 mm^{-1}
c = 15.7510 (19) Å	T = 296 K
β = 95.373 (10)°	Prism, beige
V = 1400.2 (3) $Å^3$	0.58 × 0.34 × 0.11 mm
Z = 4	

Data collection

Stoe IPDS-II diffractometer	1705 reflections with $I > 2\sigma(I)$
φ scans	R_{int} = 0.049
Absorption correction: integration (*X-RED32*; Stoe & Cie, 2002)	θ_{max} = 27.0°
T_{min} = 0.955, T_{max} = 0.992	$h = -19 \rightarrow 19$
13472 measured reflections	$k = -7 \rightarrow 7$
3057 independent reflections	$l = -20 \rightarrow 20$

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)]$ = 0.033	$w = 1/[\sigma^2(F_o^2) + (0.0394P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.074	$(\Delta/\sigma)_{max}$ = 0.001
S = 0.78	$\Delta\rho_{max}$ = 0.14 e $Å^{-3}$
3057 reflections	$\Delta\rho_{min}$ = −0.12 e $Å^{-3}$
175 parameters	

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

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O2	0.82	2.35	2.7548 (15)	112
O4—H4···N1^{i}	0.82	2.09	2.9024 (15)	174
O3—H3···N2^{ii}	0.82	2.03	2.7859 (14)	154

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

H atoms were included in calculated positions and treated using a riding model [C—H(aromatic) = 0.93 Å and C—H(CH_2) = 0.97 Å, with U_{iso}(H) = 1.2U_{eq}(C); C—H(CH_3) = 0.96 Å and O—H = 0.82 Å, with U_{iso}(H) = 1.5U_{eq}(C,O)].

Data collection: *X-AREA* (Stoe & Cie, 2002); cell refinement: *X-AREA*; data reduction: *X-RED32*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996) and *PLATON* (Spek, 2003); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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