ω–2θ scans
Absorption correction:
none
2715 measured reflections
2705 independent reflections
1261 observed reflections
$[I > 2\sigma(I)]$

$h = -34 \rightarrow 0$
$k = 0 \rightarrow 34$
$l = 0 \rightarrow 11$
5 standard reflections
frequency: 120 min
intensity decay: 2%

Refinement

Refinement on F^2
$R(F) = 0.0554$
$wR(F^2) = 0.1040$
$S = 1.076$
2701 reflections
40 parameters
All H-atom parameters
refined
$w = 1/[\sigma^2(F_o^2) + (0.045P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.87$ e Å^{-3}
$\Delta\rho_{\min} = -0.45$ e Å^{-3}
Extinction correction: none
Atomic scattering factors
from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
S1	0.12756 (2)	0.42611 (2)	−0.00817 (6)	0.01645 (8)
C1	0.25648 (7)	0.57146 (7)	−0.3339 (2)	0.0108 (2)
C2	0.17428 (8)	0.46913 (8)	−0.3324 (2)	0.0125 (2)
H1	0.2075 (17)	0.4515 (17)	0.088 (5)	0.039 (6)
H21	0.1199 (12)	0.4625 (13)	−0.428 (4)	0.013 (4)
H22	0.1942 (14)	0.4292 (14)	−0.405 (4)	0.019 (5)

Table 2. *Selected geometric parameters (Å, °)*

S1—C2	1.8340 (13)	C1—C1$^{\rm i}$	1.4074 (10)
S1—H1	1.24 (3)	C1—C2	1.5107 (15)
C2—S1—H1	94.7 (11)	C1—C2—S1	112.72 (8)
C1$^{\rm i}$—C1—C1$^{\rm ii}$	120	S1$^{\rm iii}$···H1—S1	165.7 (5)
C1$^{\rm i}$—C1—C2	119.77 (9)		

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

Data collection: *CAD*-4 *Express* (Enraf–Nonius, 1995). Cell refinement: *CAD*-4 *Express*. Data reduction: *GX* (Mallinson & Muir, 1985). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Software used to prepare material for publication: *SHELXL*93.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BM1105). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1997). C**53**, 92–95

Methyl 4-Hydroxy-3-[4-methoxy-2-(methoxymethyleneoxy)phenyl]-2-{[4-methoxy-2-(methoxymethyleneoxy)phenyl]methyl}-5-oxo-2,5-dihydrofuran-2-carboxylate

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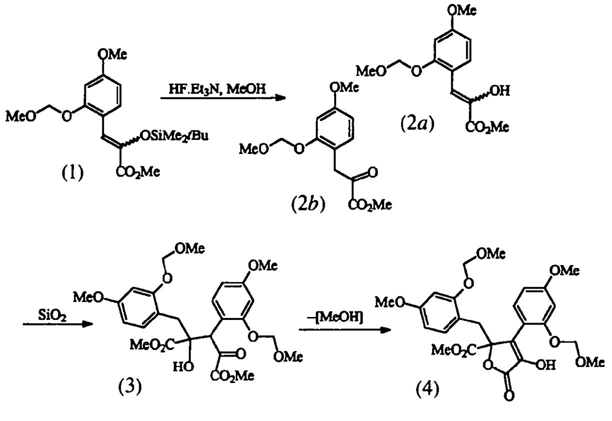
Abstract

The title compound, $C_{25}H_{28}O_{11}$, is formed by a homo-aldol condensation of methyl [4-methoxy-2-(methoxymethyleneoxy)phenyl]pyruvate followed by lactonization. The structure consists of a butenolide ring substituted at the 2 position by an arylmethyl and a methyl carboxylate group, at the 3 position by an aryl group and at the 2 position by a hydroxyl group. The solid-state structure contains a hydrogen-bonded cyclic dimer. The hydrogen bonds are formed between the enol H atom of one molecule and the lactone carbonyl O atom of another.

Comment

In a continuing effort towards the synthesis of some sponge secondary metabolites (Boehlow & Spilling 1995), we proposed a synthetic route involving methyl [4-methoxy-2-(methoxymethyleneoxy)phenyl]pyruvate, (2), as the key intermediate. A Wadsworth–Emmons reaction of 4-methoxy-2-(methoxymethyleneoxy)benzaldehyde with methyl 2-dimethoxyphosphoryl-2-(*tert*-butyldimethylsilyloxy)acetate (Plantier-Royon, Anker & Robert-Baudouy, 1991) gave the silylenol ether (1) in quantitative yield. Treatment of (1) with the complex triethylamine tris(hydrogen fluoride) in methanol yielded methyl [4-methoxy-2-(methoxymethyleneoxy)-phenyl]pyruvate. Attempted isolation of pyruvate (2) by SiO_2 chromatography yielded a white crystalline solid, (4), with a melting point of 425.7–426.0 K. ^{1}H NMR, ^{13}C NMR and mass spectroscopy indicated a dimeric structure, but it proved difficult to unambiguosly assign a structure from the spectral data alone.



The X-ray crystal structure showed butenolide (4) (Fig. 1) to be substituted at the 2 position by arylmethyl and methyl carboxylate groups, at the 3 position by an aryl group and at the 2 position by a hydroxyl group. The butenolide (4) is formed by a homo-aldol condensation of methyl [4-methoxy-2-(methoxymethyleneoxy)-phenyl]pyruvate in the enol form, (2*a*), with keto form (2*b*), followed by lactonization of the intermediate (3). In the solid-state structure, two molecules form a dimer with a hydrogen-bonded ten-membered ring. The hydrogen bonds are formed between the enol H atom of one molecule and the lactone carbonyl O atom of another; the H3*A*···O2 distance is 1.88 (5) Å. The structure of a similar butenolide has been reported (Brown, Jackson, McCarthy & Fallon, 1992) and was formed by dimerization of methyl 4-methoxyphenylpyruvate.

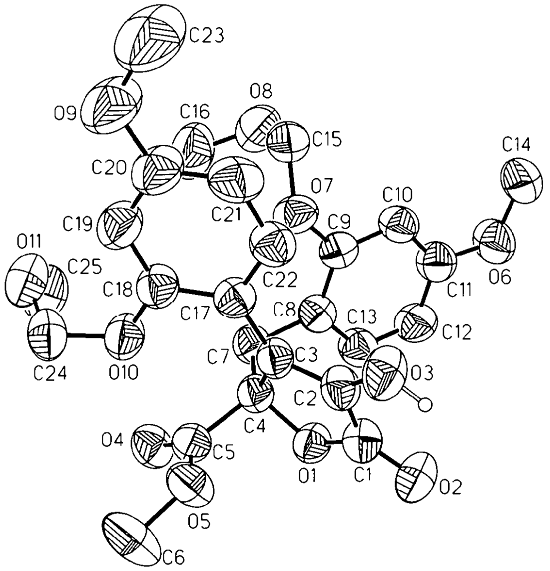


Fig. 1. The molecular structure of compound (4) shown with 50% probability displacement ellipsoids (peripheral H atoms have been omitted for clarity).

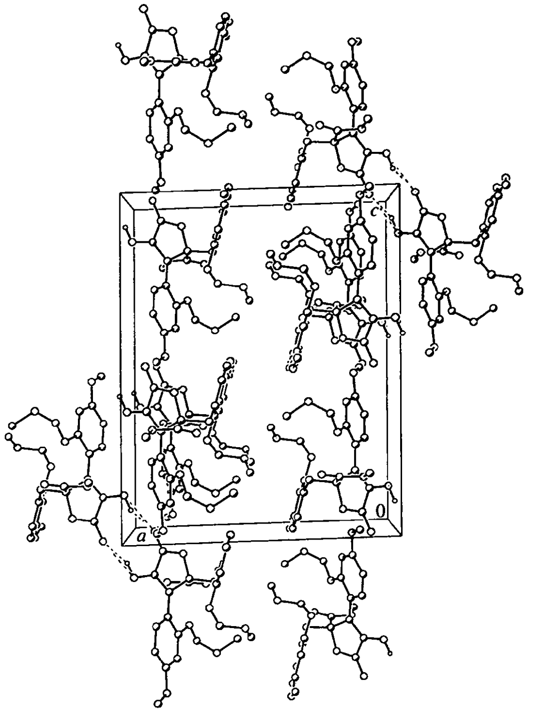


Fig. 2. A molecular packing diagram showing the dimers containing two intermolecular hydrogen bonds in a ten-membered ring (peripheral H atoms have been omitted for clarity).

Experimental

The title compound, (4), was recrystallized from ethyl acetate at room temperature.

Crystal data

$C_{25}H_{28}O_{11}$
$M_r = 504.47$
Monoclinic
$P2_1/c$
$a = 14.6057\ (2)$ Å
$b = 9.2370\ (1)$ Å
$c = 18.6333\ (3)$ Å
$\beta = 91.790\ (1)^\circ$
$V = 2512.64\ (6)$ Å^3
$Z = 4$
$D_x = 1.334$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 8192 reflections
$\theta = 2.0$–14.5°
$\mu = 0.105$ mm^{-1}
$T = 298\ (2)$ K
Hexagonal
0.5 × 0.4 × 0.3 mm
Colorless

Data collection

Siemens SMART CCD diffractometer

2577 observed reflections $[I > 2\sigma(I)]$

ω scans
Absorption correction: none
18 756 measured reflections
3275 independent reflections

$R_{\rm int} = 0.0624$
$\theta_{\rm max} = 22.5°$
$h = -17 \rightarrow 17$
$k = -10 \rightarrow 9$
$l = -21 \rightarrow 21$

Refinement

Refinement on F^2
$R(F) = 0.0753$
$wR(F^2) = 0.2500$
$S = 1.095$
3249 reflections
330 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.1602P)^2 + 1.2573P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} = -0.010$

$\Delta\rho_{\rm max} = 0.544$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.289$ e Å^{-3}
Extinction correction: *SHELXTL* (Sheldrick, 1994)
Extinction coefficient: 0.011 (3)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
O1	0.1981 (2)	0.6965 (3)	0.06868 (12)	0.0615 (7)
O2	0.0916 (2)	0.6013 (3)	−0.00656 (14)	0.0780 (8)
O3	0.0198 (2)	0.4621 (3)	0.1215 (2)	0.0777 (9)
O4	0.2809 (2)	0.9251 (3)	0.17939 (15)	0.0734 (8)
O5	0.1289 (2)	0.8928 (3)	0.1673 (2)	0.0788 (9)
O6	0.3880 (2)	0.1315 (3)	−0.0131 (2)	0.0923 (10)
O7	0.3062 (2)	0.3545 (3)	0.21339 (13)	0.0700 (8)
O8	0.4390 (2)	0.2702 (4)	0.2721 (2)	0.0933 (10)
O9	0.1447 (3)	0.3961 (4)	0.4663 (2)	0.1260 (15)
O10	0.2184 (2)	0.7532 (3)	0.29535 (13)	0.0741 (8)
O11	0.3245 (2)	0.8063 (4)	0.38881 (15)	0.0888 (9)
C1	0.1237 (2)	0.6137 (4)	0.0542 (2)	0.0640 (10)
C2	0.0940 (2)	0.5494 (4)	0.1208 (2)	0.0610 (9)
C3	0.1482 (2)	0.5910 (4)	0.1772 (2)	0.0549 (9)
C4	0.2213 (2)	0.6887 (4)	0.1459 (2)	0.0557 (9)
C5	0.2151 (3)	0.8491 (4)	0.1679 (2)	0.0613 (9)
C6	0.1136 (3)	1.0452 (5)	0.1831 (4)	0.110 (2)
C7	0.3200 (2)	0.6325 (4)	0.1540 (2)	0.0609 (9)
C8	0.3382 (2)	0.4964 (4)	0.1123 (2)	0.0599 (9)
C9	0.3325 (2)	0.3593 (4)	0.1423 (2)	0.0602 (9)
C10	0.3483 (2)	0.2348 (4)	0.1026 (2)	0.0639 (10)
C11	0.3715 (3)	0.2478 (4)	0.0318 (2)	0.0716 (11)
C12	0.3796 (3)	0.3832 (5)	−0.0001 (2)	0.0782 (12)
C13	0.3625 (3)	0.5042 (4)	0.0403 (2)	0.0724 (10)
C14	0.3744 (4)	−0.0099 (5)	0.0142 (3)	0.0955 (14)
C15	0.3458 (3)	0.2493 (4)	0.2598 (2)	0.0785 (12)
C16	0.4606 (4)	0.3997 (7)	0.3088 (3)	0.115 (2)
C17	0.1443 (2)	0.5428 (4)	0.2521 (2)	0.0583 (9)
C18	0.1804 (3)	0.6231 (4)	0.3116 (2)	0.0638 (10)
C19	0.1780 (3)	0.5707 (5)	0.3809 (2)	0.0801 (12)
C20	0.1402 (3)	0.4373 (5)	0.3942 (2)	0.0853 (13)
C21	0.1026 (3)	0.3562 (5)	0.3382 (2)	0.0812 (12)
C22	0.1052 (3)	0.4095 (4)	0.2680 (2)	0.0686 (10)
C23	0.1178 (7)	0.2533 (9)	0.4817 (4)	0.186 (4)
C24	0.2454 (3)	0.8498 (5)	0.3530 (2)	0.0800 (12)
C25	0.4047 (3)	0.8277 (6)	0.3493 (3)	0.101 (2)

Table 2. *Selected geometric parameters (Å, °)*

O1—C1	1.349 (4)	O9—C20	1.395 (5)
O1—C4	1.469 (4)	O9—C23	1.409 (8)
O2—C1	1.216 (5)	O10—C18	1.362 (4)
O3—C2	1.351 (4)	O10—C24	1.441 (5)
O4—C5	1.204 (4)	O11—C24	1.377 (5)
O5—C5	1.322 (4)	O11—C25	1.416 (6)
O5—C6	1.456 (5)	C1—C2	1.456 (5)
O6—C11	1.387 (5)	C2—C3	1.352 (5)
O6—C14	1.418 (6)	C3—C17	1.468 (5)
O7—C9	1.392 (4)	C3—C4	1.528 (5)
O7—C15	1.412 (5)	C4—C7	1.536 (5)
O8—C15	1.387 (5)	C4—C5	1.541 (5)
O8—C16	1.409 (6)	C7—C8	1.505 (5)
C1—O1—C4	109.1 (3)	O4—C5—O5	125.4 (3)
C5—O5—C6	116.4 (3)	O4—C5—C4	123.7 (3)
C11—O6—C14	117.9 (3)	O5—C5—C4	110.8 (3)
C9—O7—C15	119.0 (3)	C8—C7—C4	114.3 (3)
C18—O10—C24	119.0 (3)	C9—C8—C7	122.7 (3)
O2—C1—O1	121.6 (3)	C13—C8—C7	120.4 (3)
O2—C1—C2	129.7 (3)	C8—C9—O7	115.7 (3)
O1—C1—C2	108.7 (3)	C10—C9—O7	122.4 (3)
O3—C2—C3	127.8 (3)	C10—C11—O6	124.3 (3)
O3—C2—C1	120.9 (3)	O6—C11—C12	114.8 (3)
C3—C2—C1	111.4 (3)	C12—C13—C8	122.6 (4)
C2—C3—C17	127.8 (3)	O8—C15—O7	112.8 (3)
C2—C3—C4	105.7 (3)	C22—C17—C18	116.1 (3)
C17—C3—C4	126.3 (3)	C22—C17—C3	119.9 (3)
O1—C4—C3	105.2 (2)	C18—C17—C3	123.9 (3)
O1—C4—C7	107.4 (3)	O10—C18—C19	122.7 (3)
C3—C4—C7	115.3 (3)	O10—C18—C17	115.6 (3)
O1—C4—C5	101.6 (3)	C19—C20—O9	114.3 (4)
C3—C4—C5	114.8 (3)	C21—C20—O9	125.8 (4)
C7—C4—C5	111.2 (3)	O11—C24—O10	112.7 (3)

Data collection was carried out using a Siemens SMART CCD diffractometer at 298 K. Preliminary cell constants were obtained from 60 narrow frames (frame width = 0.3° in ω) data. Final cell parameters were obtained by global refinement of reflections obtained from integration of all the frame data. A total of 2371 frames of intensity data were collected with a frame width of 0.3° in ω and a counting time of 10 s per frame at a crystal-to-detector distance of 3.889 cm. The double-pass method of scanning was used to exclude any noise. The collected frames were integrated using the preliminary cell-orientation matrix. The integration process yielded a total of 18 756 reflections (less than fivefold redundancy), of which 3275 were independent reflections ($2\theta_{\rm max} = 45.0°$). The first 50 frames of data were recollected at the end of data collection (11.2 h total data collection time) to monitor crystal decay. No crystal decay was observed for this data set. The non-H atoms were refined anisotropically to convergence. The hydroxyl H atom was refined isotropically, whereas other H atoms were treated using an appropriate riding model. The relatively high R value and low resolution are related to the weak diffraction and poor crystal quality.

Data collection: *SMART* (Siemens, 1994). Cell refinement: *SAINT* (Siemens, 1994). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL*. Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL*.

The authors are grateful to the University of Missouri–St. Louis RIA Fund for support of this project, and the National Science Foundation for a grant to purchase the X-ray diffractometer (CHE-9309690).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SK1033). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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5-(4-Fluorophenyl)-1,8-dimethyl-2-(*p*-toluoylaminomethyl)-2,3-dihydro-1*H*-1,4-benzodiazepine Monohydrate

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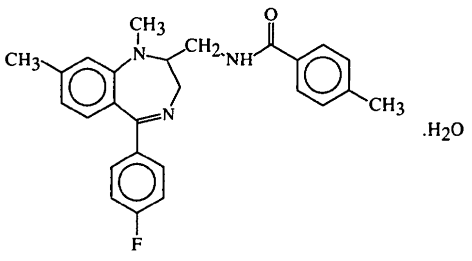
Abstract

The title compound, *N*-{[5-(4-fluorophenyl)-1,8-dimethyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-yl]methyl}-*p*-toluamide monohydrate, $C_{26}H_{26}FN_3O.H_2O$, a benzodiazepine derivative with κ-opioid activity, crystallizes as a hydrate with two almost identical molecules in the asymmetric unit. The observed conformation, stabilized by two hydrogen bonds involving the H_2O molecule, is common for the 2-(acylaminomethyl)benzodiazepines. Hydrogen bonds between H_2O molecules and amidic O atoms link the non-equivalent molecules, with formation of endless chains in the **a** direction.

Comment

The title compound, (I), belongs to a series of 2-(acylaminomethyl)benzodiazepine derivatives with κ-opioid activity. Apart from the structure of tifluadom hydrate (Codding, Zeugner & Finner, 1987), the structures of this series were obtained as either chloride or toluenesulfonate salts (Petcher, Widmer, Maetzel & Zeugner, 1985; Blaton, Peeters & De Ranter, 1996, and references therein). As both the protonation and the ionic crystalline environment may influence the conformation of the molecule, the structure determination of a free base seems worthwhile. Unfortunately, the title compound crystallizes as a hydrate and the H_2O molecule mimics the anion site of the salts, as can be seen from the conformation given in Fig. 1.



(I)

The two molecules in the asymmetric unit of (I) are almost identical, as can be deduced from the geometric parameters of the molecules (Table 2) and the puckering parameters of the diazepine rings [q_2 = 0.798 (5) and 0.797 (5); q_3 = 0.226 (6) and 0.233 (6); Q_T = 0.829 (6) and 0.830 (6) Å; φ_2 = −26.0 (4) and 154.9 (3); φ_3 = −128 (1) and 51 (1); θ_2 = 74.2 (4) and 73.8 (4)°, for molecules *A* and *B*, respectively, considering the atomic sequence N1—C2—C3—N4—C5—C5*A*—C9*A*]. The geometric and puckering parameters are close to those of tifluadom hydrate. The main difference between the hydrates and the salts is the value of the endocyclic angle of the N4 atom. Protonation causes the angle to open by *ca* 8°. The diazepine ring exhibits a boat conformation flattened at the stern with a pseudosymmetry plane through the C3 atom [asymmetry parameter ΔC_s(C3) = 0.004 (2) and 0.008 (2) for *A* and *B*, respectively]. Each H_2O molecule is hydrogen bonded with the N4 and N12 atoms of the same

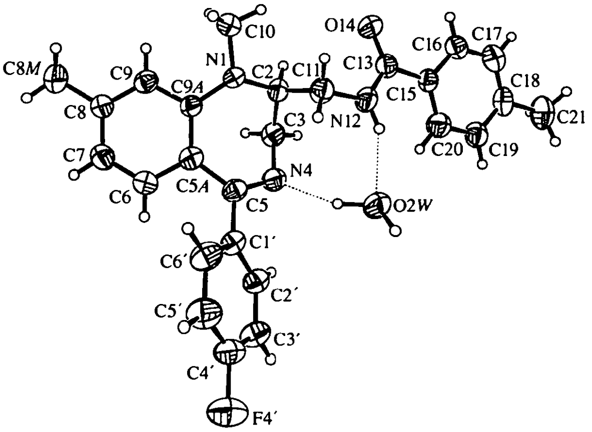


Fig. 1. Perspective view of the title compound (molecule *A*) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.