Enraf–Nonius (1989). *CAD*-4 *Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
Frenz, B. A. (1985). *Enraf–Nonius SDP-Plus Structure Determination Package*. Version 3.0. Enraf–Nonius, Delft, The Netherlands.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Paixão, J. A., Andrade, L. C. R., de Almeida, M. J., Tavares da Silva, E. J., Sá e Melo, M. L. & Campos Neves, A. S. (1998). *Acta Cryst.* C**54**, 92–93.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL*97. *Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Spek, A. L. (1995). *PLATON. Molecular Geometry Program*. University of Utrecht, The Netherlands.
Tavares da Silva, E. J., Sá e Melo, M. L., Campos Neves, A. S., Paixão, J. A., Andrade, L. C. R., Almeida, M. J. & Costa, M. M. R. (1997). *J. Chem. Soc. Perkin Trans.* 1, pp. 3487–3489.

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Racemic 3-(3,4-dimethoxyphenyl)-5a,6,8,9-tetrahydro-1*H*,7*H*-pyrano[4,3-*b*][1]benzopyran-1-one, an active antitumor agent†

Paul D. Robinson,[a] Alicia Beatty,[b] Duy H. Hua,[b] Yi Chen,[b] Cal Y. Meyers,[c] Elisabeth M. Perchellet,[d] James B. Ladesich[d] and Jean-Pierre Perchellet[d]

[a]*Department of Geology, Southern Illinois University-4324, Carbondale, IL 62901, USA,* [b]*Department of Chemistry, Kansas State University, Manhattan, KS 66506, USA,* [c]*Department of Chemistry and Biochemistry, Southern Illinois University-4409, Carbondale, IL 62901, USA, and* [d]*Department of Biology, Kansas State University, Manhattan, KS 66506, USA. E-mail: robinson@geo.siu.edu*

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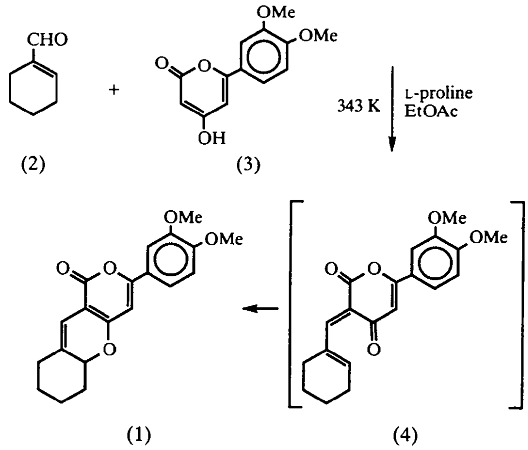
Abstract

The title racemic compound, $C_{20}H_{20}O_5$, an antitumor agent, was obtained from the condensation reaction of 2-cyclohexenecarboxaldehyde and 4-hydroxy-6-(3,4-dimethoxyphenyl)-2-pyrone in the presence of L-proline. The X-ray structure (173 K) shows a linear tricyclic skeleton in which the cyclohexane ring has a chair conformation, with the junction H atom axially oriented on the lone asymmetric C atom. The structure is disordered, such that the two enantiomers lie on the same site. The dimethoxyphenyl ring is virtually coplanar with the 2-pyrone ring, the angle between these two planes being 4.56 (11)°.

Comment

In search of structurally unique anticancer agents, we have synthesized several compounds of a class of tricyclic pyranopyrones *via* the condensation reactions of cyclohexenecarboxaldehydes and 6-substituted 4-hydroxy-2-pyrones (Hua, Chen, Sin *et al.*, 1997; Hua, Chen, Robinson & Meyers, 1997). During *in vitro* anticancer screening, several tricyclic pyranopyrones have exhibited pronounced activity (Newell *et al.*, 1998). The product from the reaction of 1-cyclohexenecarboxaldehyde, (2), with 4-hydroxy-6-(3,4-dimethoxyphenyl)-2-pyrone, (3), in the presence of L-proline (see reaction scheme) was found to possess exceptional inhibitory activity against DNA, RNA and protein synthesis. Purification of this product through silica gel column chromatography with a gradient mixture of hexane–diethyl ether as eluant afforded an orange product whose absolute structure could not be determined from its elemental and spectral analysis alone. It was necessary to turn to X-ray crystal-structure analysis for unambiguous characterization. The isolated material exhibited zero optical rotation. It was crystallized from diethyl ether as orange single crystals, shown by X-ray diffraction to be racemic 3-(3,4-dimethoxyphenyl)-5a,6,8,9-tetrahydro-1*H*,7*H*-pyrano[4,3-*b*][1]benzopyran-1-one, (1), formed *via* electrocyclization of the intermediate, (4).



The molecular structure of (1) at 173 K, with the atom-numbering scheme (Fig. 1), shows the compound to have the predicted tricyclic linear skeleton with near-coplanarity of the C3-dimethoxyphenyl and pyrone rings, the angle between these two planes being 4.56 (11)°, similar to that in biphenyl (Baudour & Sanquer, 1983). The *meta*-methoxy group (C14-methoxy) is *syn* to the pyrone carbonyl. The structure is disordered, such that both enantiomers of (1) lie on the same site and most of their equivalent atoms are superimposed and occupy the same positions. With the exception of the C7 atoms, the atoms of the cyclohexane rings, which

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† Alternative name: 3-(3,4-dimethoxyphenyl)-5a,6,8,9-tetrahydro-1*H*,5a*H*-pyrano[4,3-*b*]chromen-1-one.

contain the asymmetric center, are not superimposed and were refined with group occupancies.

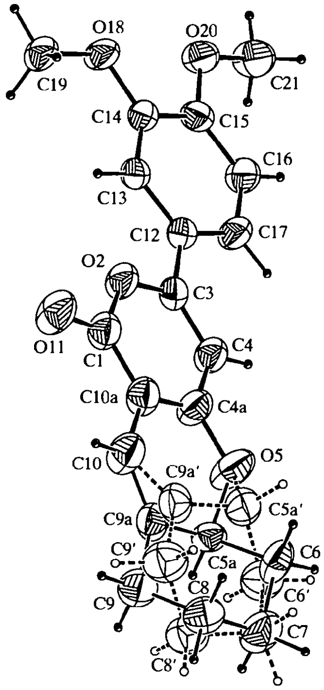

Fig. 1. The molecular structure of (1) with the atom-numbering scheme, showing the two enantiomers occupying the same site. Where equivalent atoms are not superimposed, the two enantiomers are differentiated by unshaded *versus* shaded ellipsoids, dashed *versus* solid bonds and primed *versus* unprimed atom labels. Displacement ellipsoids are at the 50% probability level and H atoms are shown as spheres of arbitrary radii.

The refinement produced an occupancy of 0.534 (6) for the enantiomer with the unprimed atom labels; since the total occupancy was constrained to 1.0, the occupancy of the other enantiomer is 0.466 (6). The enantiomeric H atoms on C5a and C5a′ are axially oriented. Although the two C7 atoms are superimposed, the four corresponding H atoms, with occupancies and geometry appropriate for each of the two enantiomers, all ride on C7. As the space group is centrosymmetric, the unit cell occupancy for each enantiomer will be 50%, preserving the overall racemic nature of the compound.

The two overlapping molecules shown in Fig. 1 are enantiomeric, but they are not mirror images from a crystallographic viewpoint because some small differences in corresponding distances and angles exist within the two cyclohexane rings. However, these differences may be a result of imperfections in the refinement resulting from the disorder, since all non-H atoms were refined anisotropically with no constraints or restraints. An alternative refinement procedure could constrain the two enantiomers to be geometrically identical but we prefer to allow all parameters to vary, where possible.

Experimental

A solution of 1-cyclohexenecarboxaldehyde [(2); 0.67 g, 6.05 mmol], 4-hydroxy-6-(3,4-dimethoxyphenyl)-2-pyrone [(3); 1.00 g, 4.03 mmol] and L-proline (0.46 g, 4.03 mmol) in ethyl acetate (50 ml) was heated at 343 K under argon for 5 d. The mixture was cooled to room temperature, diluted with methylene chloride (80 ml), washed with water (80 ml), dried with $MgSO_4$, filtered and concentrated to give 1.931 g of crude product. Column chromatography on silica gel using a gradient mixture of hexane and ether as eluant gave 0.85 g (62% yield) of orange–yellow solids, (1). Recrystallization of (1) from diethyl ether provided orange crystals used for the X-ray study (m.p. 387–388 K). UV absorption: λ_{max} = 373 nm; ε = 7.411 m^2 mol^{-1} ($CHCl_3$). The compound exhibited zero optical rotation.

Crystal data

$C_{20}H_{20}O_5$
M_r = 340.36
Monoclinic
$P2_1/c$
a = 8.1017 (12) Å
b = 22.918 (4) Å
c = 8.9358 (11) Å
β = 94.453 (8)°
V = 1654.1 (4) $Å^3$
Z = 4
D_x = 1.367 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 30 reflections
θ = 5.14–12.43°
μ = 0.098 mm^{-1}
T = 173 (2) K
Prism
0.6 × 0.5 × 0.4 mm
Orange

Data collection

Siemens *P*4 diffractometer
$2\theta/\omega$ scans
Absorption correction: none
3171 measured reflections
2915 independent reflections
2249 reflections with $I > 2\sigma(I)$
R_{int} = 0.016

θ_{max} = 25°
$h = -9 \rightarrow 1$
$k = -27 \rightarrow 1$
$l = -10 \rightarrow 10$
3 standard reflections every 97 reflections intensity decay: 2.1%

Refinement

Refinement on F^2
$R(F)$ = 0.054
$wR(F^2)$ = 0.150
S = 1.056
2915 reflections
274 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.0716P)^2 + 0.6728P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.270 e $Å^{-3}$
$\Delta\rho_{min}$ = −0.151 e $Å^{-3}$
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

O5—C5a	1.535 (4)	C7—C8	1.592 (7)
O5—C5a′	1.520 (6)	C7—C8′	1.486 (8)
C10—C9a	1.364 (7)	C8—C9	1.513 (9)
C10—C9a′	1.329 (9)	C8′—C9′	1.505 (12)
C5a—C6	1.508 (9)	C9—C9a	1.519 (8)
C5a′—C6′	1.472 (12)	C9′—C9a′	1.518 (11)

C6—C7	1.518 (9)	C9a—C5a	1.500 (8)
C6′—C7	1.601 (11)	C9a′—C5a′	1.511 (10)
O5—C5a—C6	103.1 (5)	C8—C9—C9a	111.7 (5)
O5—C5a′—C6′	100.5 (6)	C8′—C9′—C9a′	112.4 (7)
C5a—C6—C7	107.8 (6)	C9—C9a—C5a	110.8 (5)
C5a′—C6′—C7	107.5 (7)	C9′—C9a′—C5a′	116.3 (6)
C6—C7—C8	108.1 (4)	C9a—C5a—C6	111.4 (5)
C6′—C7—C8′	108.6 (5)	C9a′—C5a′—C6′	114.2 (6)
C7—C8—C9	107.5 (5)	C10—C9a—C9	127.9 (6)
C7—C8′—C9′	109.2 (6)	C10—C9a′—C9′	121.1 (7)

The occupancy factors for the two enantiomers were determined by refining the occupancies of the non-overlapping atoms. The orientations of the methyl groups were refined by the circular Fourier method available in *SHELXL*97 (Sheldrick, 1997*a*). All H atoms were riding.

Data collection: *XSCANS* (Siemens, 1991). Cell refinement: *XSCANS*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1997). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*b*). Program(s) used to refine structure: *TEXSAN* and *SHELXL*97. Molecular graphics: *ORTEP* (Johnson, 1965) and *PLATON* (Spek, 1990). Software used to prepare material for publication: *TEXSAN*, *SHELXL*97 and *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1082). Services for accessing these data are described at the back of the journal.

References

Baudour, J. L. & Sanquer, M. (1983). *Acta Cryst.* B**39**, 75–84.

Hua, D. H., Chen, Y., Robinson, P. D. & Meyers, C. Y. (1997). *Acta Cryst.* C**53**, 1995–1997.

Hua, D. H., Chen, Y., Sin, H.-S., Maroto, M. J., Robinson, P. D., Newell, S. W., Perchellet, E. M., Ladesich, J. B., Freeman, J. A., Perchellet, J.-P. & Chiang, P. K. (1997). *J. Org. Chem.* **62**, 6888–6896.

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

Molecular Structure Corporation (1997). *TEXSAN. Single Crystal Structure Analysis Software*. Version 1.03. *TEXSAN for Windows*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Newell, S. W., Perchellet, E. M., Ladesich, J. B., Freeman, J. A., Chen, Y., Liu, L., Hua, D. H., Kraft, S. L., Basaraba, R. J. & Perchellet, J.-P. (1998). *Int. J. Oncol.* **12**, 433–442.

Sheldrick, G. M. (1997*a*). *SHELXL97. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Sheldrick, G. M. (1997*b*). *Program for the Solution of Crystal Structures*. University of Göttingen, Germany.

Siemens (1991). *XSCANS. X-ray Single Crystal Analysis System*. Version 2.20. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Spek, A. L. (1990). *Acta Cryst.* A**46**, C-34.

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2-(Isopropylthio)benzoic acid

Roger E. Gerkin

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, USA. E-mail: gerkin@chemistry.ohio-state.edu

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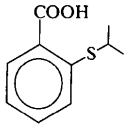
Abstract

The title acid, $C_{10}H_{12}O_2S$, crystallized in the centrosymmetric space group $P2_1/c$ with one molecule in the asymmetric unit. There is a single hydrogen bond, in which the O and H atoms are ordered and $O_D\cdots O_A$ is 2.658 (2) Å. The hydrogen bond forms a cyclic dimer, with graph-set descriptor $R_2^2(8)$, about a center of symmetry. The dihedral angle between the best-fit planes of the benzene ring and the carboxyl group is 13.6 (1)°.

Comment

This study of the title acid, (I), is one of a series of studies of hydrogen bonding in aromatic carboxylic acids. Our previous studies of substituted benzoic acids include *ortho*-(1-naphthoyl)benzoic acid and 3-[2-(1,3-dioxolan-2-yl)ethyl]-2-methylbenzoic acid (Gerkin, 1998, 1999). (I) crystallized in the centrosymmetric space group $P2_1/c$ with one molecule in the asymmetric unit. The refined molecule, with our numbering scheme, is shown in Fig. 1. In the single hydrogen bond, O1—H1$\cdots$O2$(1-x, 1-y, 2-z)$, the O and H atoms are ordered, with O—H = 0.88 (2), H$\cdots$O = 1.78 (2), $O_D\cdots O_A$ = 2.658 (2) Å, and with O—H$\cdots$O = 177 (2)°. This bond forms a cyclic dimer about a center of symmetry as shown in the packing diagram, Fig. 2. The first-level graph (Bernstein *et al.*, 1995) for the hydrogen bond is thus a ring, with descriptor $R_2^2(8)$, and there are no higher-level graphs. A single noteworthy intermolecular C—H$\cdots$O interaction, C5—H5$\cdots$O1$^{ii}(1-x, -\frac{1}{2}+y, \frac{5}{2}+z)$, occurs, for which H$\cdots$O = 2.69 (2), C$\cdots$O = 3.646 (3) Å and C—H$\cdots$O = 169 (2)°. This forms a first-level chain, with descriptor $C(6)$, which propagates along [010].



(I)