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3-Cyano-5-(4-methoxybenzyl)-6-(4-methoxyphenyl)-4-methylthio-2H-pyran-2-one†

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Abstract

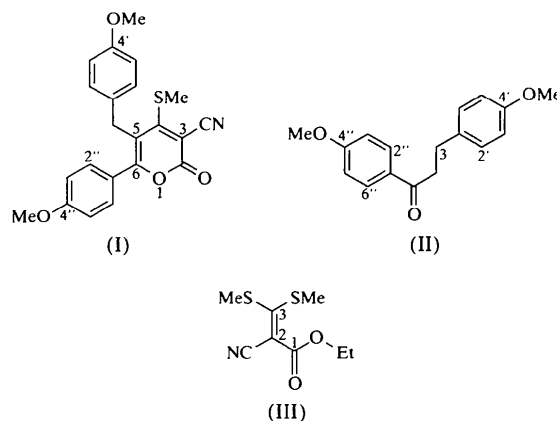
The synthesis of the title compound, C₂₂H₁₉NO₄S, is described. The methyl group of the methylthio substituent points towards the CN group, as has been noted before when bulky substituents occupy the 5-position. The phenyl groups in the 5- and 6-positions are twisted at angles of 75.7 (1) and 36.5 (1)°, respectively, from the plane of the pyrone ring.

Comment

Substituted δ -lactones are useful intermediates in the synthesis of various bioactive, naturally occurring, pyrones such as anibine, phenylcoumalin, paracotoin, *etc.* (Tominaga *et al.*, 1977, 1984, 1987). We have synthesized several 3-cyano-4-methylthio-6-aryl-2H-pyran-2-ones as synthons for the synthesis of different classes of heterocyclic systems such as pyrazoles, isoxazoles, pyrazolo/isoxazolocoumarins and triazoles (Singh *et al.*, 1995; Kumar *et al.*, 1996). Such δ -lactones, with a benzyl group at the C-5 position, have not been reported previously, but we have synthesized several novel 3-cyano-5-benzyl-4-methylthio-6-aryl-2H-pyran-2-ones, with a view to screening them for antibacterial and antifungal activities and in order to study structure–activity relationships. This paper reports the synthesis of a novel lactone, (I), prepared by the addition of the enolate anion derived from 1,3-bis(4-methoxyphenyl)propanone, (II), to ethyl 2-cyano-3,3-bis(methyl-

† IUPAC name: 5-(4-methoxybenzyl)-6-(4-methoxyphenyl)-4-methylthio-2-oxo-2H-pyran-3-carbonitrile.

thio)acrylate, (III). The structure of this novel δ -lactone is confirmed by single-crystal X-ray diffraction.



The molecular structure of the title compound (I) is illustrated in Fig. 1. The bond lengths and angles are largely unexceptional (Allen *et al.*, 1987). The Csp²—S distance [1.742 (2) Å] is shorter than the Csp³—S distance [1.789 (3) Å]; this behaviour has been previously noted (Azim *et al.*, 1997) and is indicative of some double bonding in the sp² case. The structure of the 3-cyano-4-methylthio-2H-pyran-2-one fragment has been reported previously by our group (Kumar *et al.*, 1996; Malhotra *et al.*, 1997; Azim *et al.*, 1997), and in all cases the methylthio substituent is approximately co-planar with the pyrone ring [in this instance, the C8—S1—C4—C5 torsion angle is 169.09 (18)°]. As in the title compound, bulky substituents in the 5-position cause the methyl group to point towards the CN group. In com-

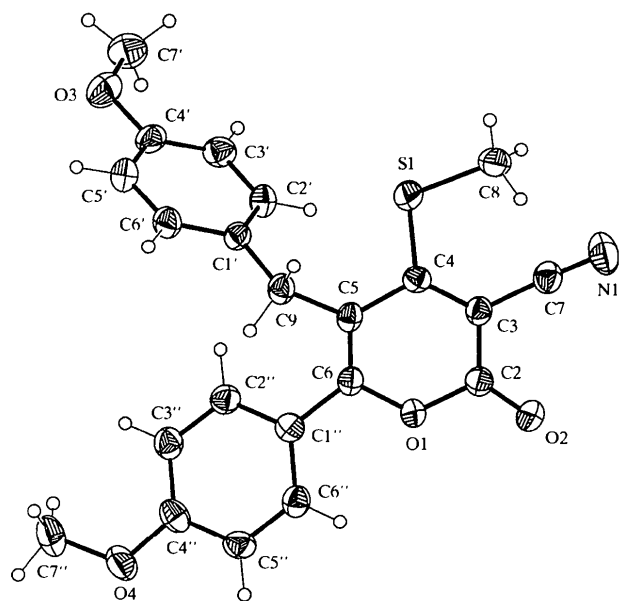


Fig. 1. View of the title molecule showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level. H atoms are shown as circles of an arbitrary radius.

pound (I), the two methoxy substituents are also approximately aligned in the planes of their attached phenyl groups [C7'—O3—C4'—C3' = 2.0 (4) and C7''—O4—C4''—C5'' = 170.5 (3)°]. The phenyl groups in the 5- and 6-positions are twisted at angles of 75.7 (1) and 36.5 (1)°, respectively, from the plane of the pyrone ring.

Experimental

The precursor, 1,3-bis(4-methoxyphenyl)propanone, (II), was obtained by the catalytic hydrogenation of 1,3-bis(4-methoxyphenyl)propenone and crystallized as white plates from ethanol [m.p. 319–320 K; literature m.p. 318–321 K (*Beilstein Handbuch der Organischen Chemie*, 1948)]; the 1,3-bis(4-methoxyphenyl)propanone was obtained by the condensation of *p*-methoxyacetophenone and anisaldehyde as a yellow solid [m.p. 375 K; literature m.p. 373–374 K (Tallman & Stuart, 1948)]. To prepare the title compound, a mixture of ethyl 2-cyano-3,3-bis(methylthio)acrylate [(III), 2.17 g, 0.01 mol], 1,3-bis(4-methoxyphenyl)propanone [(II), 2.70 g, 0.01 mol], KOH (1.12 g, 0.02 mol) and dimethylformamide (20 ml) was stirred for 16 h at 301–303 K. The red–brown supernatant was poured onto crushed ice (200 g) and the contents stirred for 6 h. The yellow solid that separated out was filtered, dried and crystallized from chloroform to give (I) as yellow needles (2.4 g, yield 61%, m.p. 467 K). Spectroscopic data for (I): IR ν_{\max} (KBr, cm⁻¹): 3448, 2930, 2367, 2219 (CN), 1717 (C=O), 1605, 1587, 1511, 1482, 1305, 1261, 1244, 1185, 1020, 908, 843, 803, 750 and 577; UV (MeOH) λ_{\max} : 329 and 370 nm; ¹H NMR (CDCl₃, 250 MHz, p.p.m.): δ 2.86 (s, 3H, -SCH₃), 3.81 and 3.83 (2 × s, 3H each, 2 × OCH₃), 4.00 (s, 2H, -CH₂Ph), 6.87 (*d*, *J* = 8.96 Hz, 4H, C3'-H, C5'-H, C3''-H and C5''-H), 7.02 (*d*, *J* = 8.64 Hz, 2H, C2'-H and C6'-H) and 7.48 (*d*, *J* = 8.76 Hz, 2H, C2'' and C6''-H); ¹³C NMR (CDCl₃, 62.9 MHz, p.p.m.): δ 171.13 (C2), 162.03 (C4''), 159.85 (C4'), 158.54 (C6), 158.47 (C1''), 130.57 (C2'' and C6''), 129.62 (C4), 128 (C2' and C6'), 123.38 (-CN), 114.66 (C1'), 114.44 (C3' and C5'), 114.10 (C3'' and C5''), 113.98 (C3), 94.40 (C5), 55.43 and 55.25 (2 × OCH₃), 33.14 (-CH₂Ph) and 18.45 (-SCH₃); EIMS (electron impact MS) *m/z* (relative intensity): 395 (*M*⁺ + 2)(10), 393 (*M*⁺)(40), 318 (10), 284 (10), 191 (7), 135 (100), 108 (65) and 77 (12).

Crystal data

C ₂₂ H ₁₉ NO ₄ S	Mo K α radiation
<i>M_r</i> = 393.44	λ = 0.71073 Å
Orthorhombic	Cell parameters from 5771 reflections
<i>Pna</i> 2 ₁	θ = 1.67–27.00°
<i>a</i> = 20.5254 (13) Å	μ = 0.199 mm ⁻¹
<i>b</i> = 15.1311 (10) Å	<i>T</i> = 180 (2) K
<i>c</i> = 6.1276 (4) Å	Needle
<i>V</i> = 1903.1 (2) Å ³	0.46 × 0.08 × 0.06 mm
<i>Z</i> = 4	Yellow
<i>D_x</i> = 1.373 Mg m ⁻³	
<i>D_m</i> not measured	

Data collection

Siemens SMART CCD area-detector diffractometer	3282 reflections with <i>I</i> > 2 σ (<i>I</i>)
ω scans	<i>R</i> _{int} = 0.040

Absorption correction: multi-scans (*SADABS*; Sheldrick, 1996)
 T_{\min} = 0.913, T_{\max} = 0.988
 10 889 measured reflections
 4105 independent reflections

Refinement

Refinement on *F*²
 $R[F^2 > 2\sigma(F^2)] = 0.047$
 $wR(F^2) = 0.094$
 $S = 1.049$
 4105 reflections
 257 parameters
 H-atoms constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0353P)^2 + 0.424P]$
 where $P = (F_o^2 + 2F_c^2)/3$

$\theta_{\max} = 27^\circ$
 $h = -20 \rightarrow 26$
 $k = -18 \rightarrow 19$
 $l = -7 \rightarrow 7$
 Intensity decay: none

$(\Delta/\sigma)_{\max} = 0.001$
 $\Delta\rho_{\max} = 0.218 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.221 \text{ e } \text{Å}^{-3}$
 Extinction correction: none
 Scattering factors from *International Tables for Crystallography* (Vol. C)
 Absolute structure: Flack (1983)
 Flack parameter = 0.07 (9)

Table 1. Selected geometric parameters (Å, °)

S1—C4	1.742 (2)	S1—C8	1.789 (3)
C4—S1—C8	109.35 (12)		
C8—S1—C4—C5	169.09 (18)	C5—C6—C1''—C6''	-144.0 (3)
C6—C5—C9—C1'	-97.9 (3)	O1—C6—C1''—C2''	-142.6 (2)
C7'—O3—C4'—C3'	2.0 (4)	C7''—O4—C4''—C5''	170.5 (3)

The temperature of the crystal was controlled using an Oxford Cryosystems Cryostream Cooler (Cosier & Glazer, 1986). Data were collected over a hemisphere of reciprocal space, by a combination of three sets of exposures. Each set had a different φ angle for the crystal and each exposure of 10 s covered 0.3° in ω . The crystal-to-detector distance was 5.01 cm. Coverage of the unique set was over 99% complete to at least 27° in θ . Crystal decay was monitored by repeating the initial frames at the end of the data collection and analyzing the duplicate reflections. H atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all non-H atoms; H atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl H atoms) times the equivalent isotropic displacement parameter of the atom to which they were attached.

Data collection: *SMART* (Siemens, 1994). Cell refinement: *SAINT* (Siemens, 1995). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL/PC* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *SHELXTL/PC*. Software used to prepare material for publication: *SHELXTL/PC*.

We wish to acknowledge the use of the EPSRC's Chemical Database Service at the Daresbury Laboratory (Fletcher *et al.*, 1996) for access to the Cambridge Structural Database (Allen & Kennard, 1993). We also thank the Council for Scientific and Industrial Research (CSIR, New Delhi, India) for financial assistance.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1285). Services for accessing these data are described at the back of the journal.

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(±)-3-Oxo-1,2,3,9,10,10a-hexahydro-phenanthrene-10a-carboxylic acid: catemeric hydrogen bonding in a δ -keto acid

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Abstract

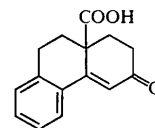
The crystal structure of the title compound (C₁₅H₁₄O₃) involves hydrogen-bonding catemers, with hydrogen bonds progressing from the carboxyl group of each mol-

ecule to the ketone group of a screw-related neighbor [O...O = 2.604 (3) Å]. This creates two parallel centrosymmetrically related single-strand hydrogen-bonding helices proceeding in the *b* direction through the chosen cell. Two intermolecular C=O...H—C close contacts were found, one involving the acid (2.39 Å) and one, the ketone (2.58 Å). A close contact was also found between a methylene C—H and the center of the aromatic π -cloud in a centrosymmetrically related molecule.

Comment

Our continuing interest in the crystal structures of keto carboxylic acids lies in elucidating and predicting their hydrogen-bonding behavior. Beyond the acid-to-acid dimer and catemer modes characteristic of unadorned acids, keto acids display an additional three hydrogen-bonding patterns of the carboxyl-to-ketone type. Over 40 instances are now known of acid-to-ketone catemers, while internal hydrogen bonds and acid-to-ketone dimers are much rarer. The intra-chain units in keto-acid catemers may be categorized as homochiral (translationally or screw-related) or heterochiral (glide-related), and for such catemers overall, the order of prevalence observed thus far is: screw > translation > glide. Several cases are also known of hydrates with more complex hydrogen-bonding patterns. We have previously referenced and discussed numerous examples of these hydrogen-bonding modes (Thompson *et al.*, 1992, 1998; Coté *et al.*, 1996; Lalancette *et al.*, 1998).

Compound (I) belongs to the category of δ -keto acids, which embraces examples of standard acid dimers (Lalancette *et al.*, 1997) and internal hydrogen bonds (Abell *et al.*, 1991), as well as both anhydrous (Coté *et al.*, 1997) and hydrated (Winkler *et al.*, 1986) acid-to-ketone catemers. Compound (I) was of interest to us as a benzo-annulated version of a carboxyoctalone whose structure and catemeric hydrogen-bonding behavior we had described previously (Lalancette *et al.*, 1991). Experience has led us often to anticipate similar hydrogen-bonding behavior among structurally similar compounds, and we report here that, like its simpler analog, (I) forms carboxyl-to-ketone catemers in which the intra-chain units are screw-related.



(I)

The asymmetric unit for (I), with its numbering, is shown in Fig. 1. The only skeletal option available for full rotation in (I) involves the C10A—C11 bond,