Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Synthesis and absolute configuration of methyl (–)-(3*R*)-8-(4-bromophenyl)-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.006 Å
R factor = 0.044
wR factor = 0.103
Data-to-parameter ratio = 14.7

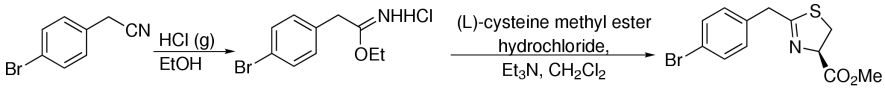
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 19 June 2002
Accepted 28 June 2002
Online 12 July 2002

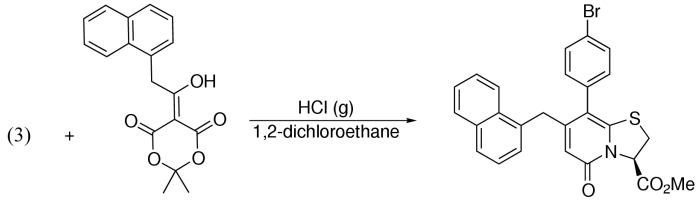
The title molecule, $C_{26}H_{20}BrNO_3S$, contains a ring-fused 2-pyridinone framework substituted with a 4-bromo-phenyl-, a naphthalen-1-ylmethyl and a methoxycarbonyl substituent. The main goal of this work was to confirm the stereochemistry for the methoxycarbonyl substituent, which proved to be 3*R*. Moreover, the 4-bromophenyl substituent was shown to be rotated out of the plane of the 2-pyridinone ring, with a torsion angle of 61.2 (5)°. To allow the best packing arrangement, the naphthalen-1-ylmethyl substituent is positioned to mediate an intermolecular π–π interaction.

Comment

Heterocycles having a 2-pyridinone framework are extensively studied classes of compounds, due partly to their diverse biological activities. These range from antibacterial (Casinovi *et al.*, 1968; Dolle & Nicolaou, 1985; Rigby & Balasubramanian, 1989) and antifungal (Cox & Hagan, 1991) agents to free-radical scavengers (Teshima *et al.*, 1991; Rice-Evans & Burdon, 1994). Ring-fused 2-pyridinones have also attracted attention as angiotensin-converting enzyme (ACE) inhibitors (Mynderse *et al.*, 1985; Hunt *et al.*, 1988; O'Connor & Somers, 1985), as well as inhibitors of Aβ-peptide aggregation (Kuner *et al.*, 2000; Thorsett & Latimer, 2000), which is believed to play an important role in amyloid formation in Alzheimer's disease.



(1) (2) (3)



(4) (5)

As a result of its anticancer properties, the natural product (*S*)-camptothecin, isolated from *Campthoteca acuminata* by Wall *et al.* (1966), is one of the most studied ring-fused 2-pyridinones (Comins & Nolan, 2001). The structure of (*S*)-camptothecin was elucidated two years later by X-ray crystallography (McPhail & Sim, 1968). Previously, we reported a new ketene–imine cycloaddition method for the synthesis of

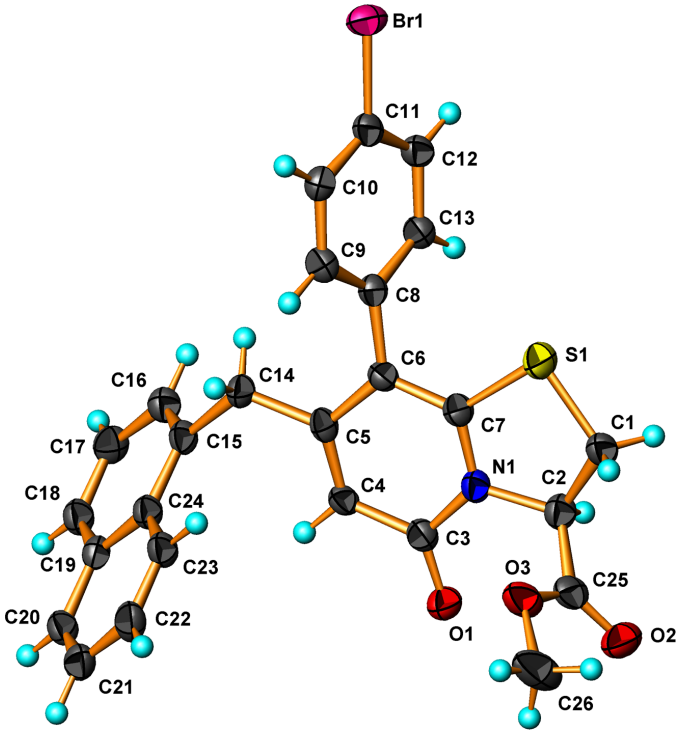


Figure 1
A view of the molecular structure of (5), showing 50% probability displacement ellipsoids.

substituted optically active ring-fused 2-pyridinones (Emtenäs *et al.*, 2001). Although having high enantioselectivity in the reaction, the stereochemistry remained unconfirmed. Therefore, from previous experience of bromine-containing aromatics being easier to crystallize, we synthesized the title compound, (5). Additionally, the Br atom facilitates the determination of the absolute configuration, due to the high anomalous scattering of Mo radiation.

The crystal structure determination of (5) confirmed the 3*R* configuration. In addition, the 8-(4-bromophenyl) substituent was shown to be rotated out of the plane, with a torsion angle of 61.2 (5)° (atoms C13, C8, C6 and C7; see Fig. 1). Although somewhat more pronounced, this arrangement has previously been observed by Jones *et al.* (2000), where their corresponding phenyl substituent was almost perpendicular to the plane, with a torsion angle of 103°. There is a possible weak hydrogen-bond interaction between O1 and C1 in a neighbouring molecule, 3.085 (6) Å. Otherwise, there are no intermolecular interactions shorter than van der Waals distances, except for one, C19—H(C10) of 2.75 and 0.15 Å less than the van der Waals distance. As can be seen in Fig. 2, the naphthalen-1-ylmethyl substituent is positioned to mediate an intermolecular π–π interaction.

Experimental

For the preparation of methyl 4-(*R*)-2-(4-bromobenzyl)-4,5-dihydrothiazole-4-carboxylate, (3), dry HCl(g) was passed through a stirred solution of (1) (5.12 g, 26 mmol) in EtOH—CH_2Cl_2 (1:1, 20 ml) for 4 h at 273 K. The solution was allowed to reach room temperature overnight and was then concentrated, giving (2) as colourless crystals (7.27 g, quant.), which were used in the next step without further purification. Et_3N (2.0 ml, 14 mmol) was added dropwise to a stirred suspension of L-cysteine methyl ester hydrochloride (3.02 g, 11 mmol) in CH_2Cl_2 (15 ml) at 273 K. After 30 min, (2) was added and the suspension was allowed to reach room temperature. After stirring overnight, the suspension was diluted with CH_2Cl_2 (25 ml) and washed with water, aqueous saturated $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Flash column chromatography (heptane–EtOAc, 1:1) gave the thiazoline (3) as an oil (3.37 g, quant.). $[\alpha]_D$ +53° (*c* 0.91, $CHCl_3$).

For the synthesis of the title compound, (5), dry HCl (g) was passed through a 273 K solution of (3) (2.08 g, 7 mmol) and (4) (Emtenäs *et al.*, 2001; 2.71 g, 9 mmol) in 1,2-dichloroethane (45 ml) for 15 min. The solution was stirred for 12 h at 337 K before an additional amount of (4) (1.30 g, 4 mmol) was added. After 3 h, the solution was allowed to reach room temperature and was then diluted with CH_2Cl_2 and washed with water, aqueous saturated $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated, Flash column chromatography (heptane–EtOAc, 1:4) gave (5) as a white solid (1.79 g, 53%). The product (5) was crystallized from EtOH [m.p. 475–476 K; $[\alpha]_D$ −134° (*c* 1.26, $CHCl_3$)].

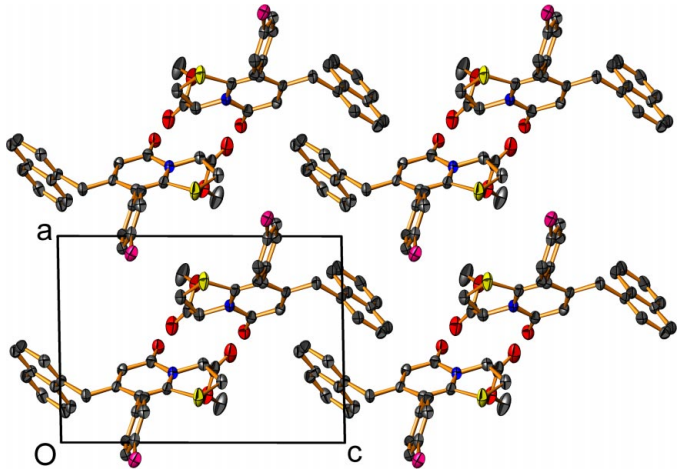


Figure 2
A packing diagram of (5), viewed down the *b* axis.

Crystal data

$C_{26}H_{20}BrNO_3S$
M_r = 506.40
Monoclinic, $P2_1$
a = 9.5502 (5) Å
b = 8.6443 (5) Å
c = 13.1213 (6) Å
β = 91.028 (3)°
V = 1083.05 (10) Å^3
Z = 2
D_x = 1.553 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 8301 reflections
θ = 4.5–27.5°
μ = 2.02 mm^{-1}
T = 120 K
Plate, colourless
0.25 × 0.13 × 0.03 mm

Data collection

KappaCCD diffractometer
ω scans
Absorption correction: numerical (Herrendorf & Bärnighausen, 1997)
T_{min} = 0.566, T_{max} = 0.815
8301 measured reflections
4234 independent reflections
3754 reflections with $I > 2\sigma(I)$
R_{int} = 0.052
θ_{max} = 27.5°
h = −12 → 12
k = −11 → 11
l = −16 → 17

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0225P)^2 + 1.1354P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.044$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.103$	$\Delta\rho_{max} = 0.76$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.52$ e Å^{-3}
4234 reflections	Absolute structure: (Flack, 1983), 1582 Friedel pairs
289 parameters	Flack parameter = 0.013 (10)
H-atom parameters constrained	

The H atoms were refined using a riding model.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ATOMS* (Dowty, 1998); software used to prepare material for publication: *SHELXL*97.

This work was funded by grants from the Knut and Alice Wallenberg Foundation, the Foundation for technology transfer in Umeå and the Swedish Research Council.

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