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The antifungal agent methyl 2-benzyl-6-diethylamino-4-phenyl-2*H*-1,3,5-thiadiazine-2-carboxylate

Emilio Rodriguez-Fernandez,[a]* Rafael Del-Campo,[a] Julio J. Criado,[a] Jaun L. Manzano[a] and Francisca Sanz[b]

[a]Department of Inorganic Chemistry, Faculty of Chemistry, Plaza de la Merced s/n, Universidad de Salamanca, 37007 Salamanca, Spain, and [b]X-ray Diffraction Service, Faculty of Chemistry, Universidad de Salamanca, 37007 Salamanca, Spain

Correspondence e-mail: erodri@usal.es

Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.005 Å
R factor = 0.047
wR factor = 0.108
Data-to-parameter ratio = 8.8

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

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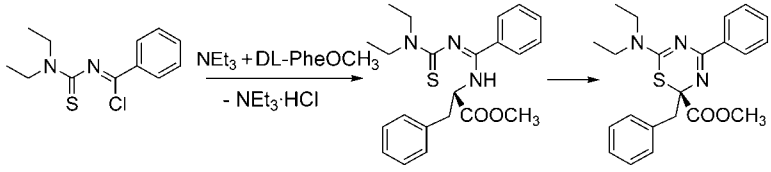
The title compound, $C_{22}H_{25}N_3O_2S$, a new thiourea derivative of phenylalanine, has been synthesized and its antifungal activity investigated against the fungus *Penicillium digitatum* and the yeast *Saccharomyces cerevisiae*.

Comment

Some compounds containing a thiourea moiety have been reported to show antifungal activity against pathogenic fungi of crop plants (Del Campo *et al.*, 2004; Cremlyn *et al.*, 1998; Criado *et al.*, 1998). Compounds containing a 1,3,5-thiadiazine nucleus have also been shown to possess antifungal properties (Aboul-Fadl *et al.*, 2002). The antifungal activity of the title compound, (I), was measured by its effects on the inhibition of spore growth of *P. digitatum*. The percentage of inhibited fungal growth caused by 20 µg of (I) was 65%, with respect to the control. (The dimethyl sulfoxide, used as solvent, showed significant inhibitory effect. Hence, all inhibition values were expressed in comparison with the respective control where only dimethyl sulfoxide was added to the wells.)



(I') (I)

The molecular structure of (I) is shown in Fig. 1. The central thiadiazine ring adopts a boat conformation. The bond lengths N1—C5 [1.304 (3) Å] and N3—C6 [1.279 (3) Å] in the thiadazine ring are characteristic of N=C double bonds. The other N—C distances [N3—C7 = 1.426 (3) Å and N1—C6 = 1.369 (3) Å] are significantly shorter than the average C—N single-bond length of 1.479 Å. The S—C distances are S1—C5 = 1.752 (3) Å and S1—C7 = 1.849 (3) Å. This is in agreement with the distances observed previously (Maier *et al.*, 2001) in a similar compound, also containing a 1,3,5-thiadiazine nucleus. While the phenyl substituent is essentially in the plane of the corresponding C6=N3 bond, the benzyl group is twisted by 112.8 (3)° (C16—C11—C10—C7) out the plane of the heterocyclic ring.

In the crystal structure, no π-stacking interactions were observed between the phenyl groups (Fig. 2). The molecules stack along the *b* axis and are linked by a C—H···O intermolecular hydrogen bond (Table 1).

Experimental

A solution of 3-(chlorophenylmethylene)-1,1-diethylthiourea (19.6 mmol) (Rodriguez-Fernandez *et al.*, 1999) in acetone (50 ml)

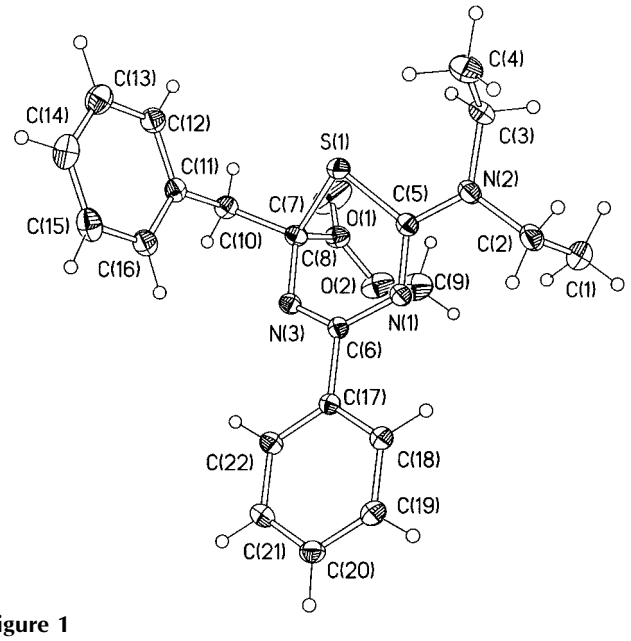


Figure 1
The molecular structure of (I), with atom C7 in an *S* configuration, showing the atom-labelling scheme and displacement ellipsoids drawn at the 50% probability level.

and triethylamine (2.5 ml) was added dropwise to a solution of DL-phenylalanine methyl ester (19.6 mmol) in acetone (20 ml). The resulting solution was refluxed for 6 h, and the precipitate of $Et_3N{\cdot}HCl$ (see scheme) filtered off. The resulting solution was kept at 273 K for two months. Pale-yellow crystals of the desired product, (I), were obtained. Using other amino acids (Del Campo *et al.*, 2002), the NH derivative (I′) instead of the thiadiazine form, similar to (I), was synthesized. Analysis calculated for $C_{22}H_{25}N_3O_2S$: C 66.81, N 10.62, H 6.37, S 8.11%; found: C 66.76, N 10.57, H 6.35, S 8.10%; m.p. 364 (1) K; yield 45%; R_F = 0.58 (*n*-hexane–ethyl ether 1:1); FT–IR (cm^{-1}): ν 1728, 1537, 1470, 1321, 1244, 1216, 1131, 1069, 818, 718, 698; ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, *t*), 1.59 (2H, *s*), 3.75 (4H, *q*), 3.75 (3H, *s*), 7.06–8.47 (9H, *m*); ^{13}C NMR ($CDCl_3$): δ 13.02, 14.50, 43.07, 45.37, 53.00, 126.96, 127.22 (× 2), 127.80 (× 2), 128.07 (× 2), 130.90 (× 2), 135.40, 138.66, 160.23, 161.73, 171.69. FAB+/MS (*m*/*z*): 396.3 $[M+1]^+$, 336 $[M + 1 - COOMe]^+$; λ max, nm (CH_3OH) (ε, M^{-1} cm^{-1}): 220 (27900), 250 (*sh*) (17300), 315 (11000), 325 (11400). Solutions of (I), prepared in dimethyl sulfoxide (DMSO; 1 mg per ml) were tested for the inhibition of *P. digitatum* or *S. cerevisiae* as follows: PDA plates containing 10^4 *P. digitatum spores* and YPD (1% yeast extract, 2% peptone and 2% dextrose) agar plates containing 10^5 *S. cerevisiae* cells per ml agar were prepared and maintained for 8 h at room temperature. Hollow cylinders with a diameter of 5 mm were placed on the plates spread with the target fungi and used as wells. These were loaded with the compound solutions (20 µl) or DMSO (20 µl). The plates were then incubated at 301 K for 24 h. Each well was analyzed in triplicate and photographed using an inverted microscope (Zeiss) and a photographic camera (CoolSnap, RS Photometrics). Captured images were processed with the Leica Qwin program (Copyright Leica Microsystems Imaging Solutions). The degree of inhibition was recorded from the images and numerical values, expressed as a percentage of their respective controls, of the area covered by the fungal growth. Data are expressed as mean values and standard deviations. No appreciable inhibition against *S. cerevisiae* was observed.

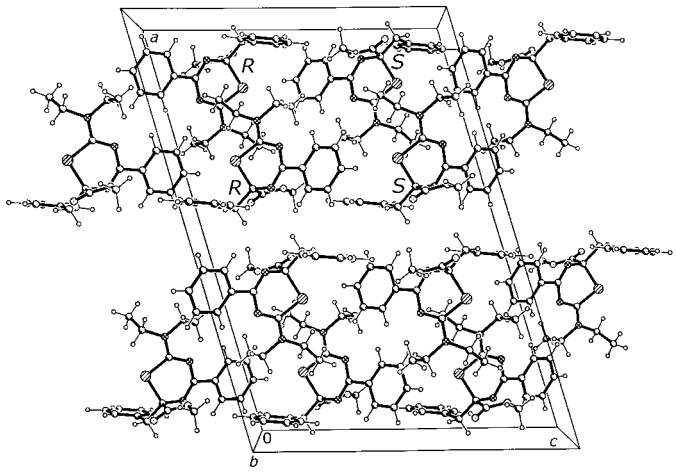


Figure 2
Crystal packing of (I) viewed along the *b* axis, showing the three-dimensional network structure. Four molecules appear marked with the appropriate *R* or *S* configuration at atom C7.

Crystal data

$C_{22}H_{25}N_3O_2S$	D_x = 1.257 Mg m^{-3}
M_r = 395.51	Cu $K\alpha$ radiation
Monoclinic, *C*2/*c*	Cell parameters from 25 reflections
a = 25.671 (5) Å	θ = 8–20°
b = 9.252 (2) Å	μ = 1.55 mm^{-1}
c = 18.329 (4) Å	*T* = 293 (2) K
β = 106.27 (3)°	Prism, pale yellow
V = 4179.1 (15) $Å^3$	0.08 × 0.06 × 0.05 mm
Z = 8	

Data collection

Seifert XRD 3000 *S* diffractometer	θ_{max} = 59.8°
2θ–ω scans	*h* = −27 → 28
Absorption correction: none	*k* = −10 → 10
5943 measured reflections	*l* = −19 → 0
3099 independent reflections	2 standard reflections
2529 reflections with $I > 2\sigma(I)$	every 100 reflections
R_{int} = 0.022	intensity decay: <1%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.047P)^2 + 3.392P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.047	$(\Delta/\sigma)_{max}$ = 0.002
$wR(F^2)$ = 0.118	$\Delta\rho_{max}$ = 0.35 e $Å^{-3}$
S = 1.15	$\Delta\rho_{min}$ = −0.23 e $Å^{-3}$
3098 reflections	Extinction correction: *SHELXL*97
354 parameters	Extinction coefficient: 0.0033 (3)
All H-atom parameters refined	

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C15—H15···O1^{i}	0.93 (4)	2.43 (4)	3.334 (5)	165 (3)

Symmetry code: (i) $x, 1+y, z$.

The H atoms were refined isotropically; C—H 0.91 (4)–1.08 (4) Å.

Data collection: *CRYSOM* (Martinez-Ripoll & Cano, 1996); cell refinement: *CRYSOM*; data reduction: *XRAY*80 (Stewart *et al.*, 1990); program(s) used to solve structure: *SHELXTL* (Siemens, 1996); program(s) used to refine structure: *SHELXTL*; molecular

graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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References

Aboul-Fadl, T., Hussein, M. A., El-Shorbagi, A. N. & Khallil, A. R. (2002). *Arch. Pharm. Pharm. Med. Chem.* **9**, 438–442.

Cremlyn, R. J., Ellam, R. M. & Farouk, S. (1998). *Pesticide Sci.* **52**, 70–74.

Criado, J. J., Rodríguez-Fernández, E., García, E., Hermosa, M. R. & Monte, E. (1998). *J. Inorg. Biochem.* **69**, 113–119.

Del Campo, R., Criado, J. J., García, E., Hermosa, M. R., Jiménez-Sánchez, A., Manzano, J. L., Monte, E., Rodríguez, E. & Sanz, F. (2002). *J. Inorg. Biochem.* **89**, 74–82.

Del Campo, R., Criado, J. J., Gheorghe, R., González, F. J., Hermosa, M. R., Francisca, S., Manzano, J. L., Monte, E. & Rodríguez-Fernández, E. (2004). *J. Inorg. Biochem.* In the press.

Maier, O., Frohlich, R. & Wurthwein, E. U. (2001). *Eur. J. Org. Chem.* pp. 83–92.

Martinez-Ripoll, M. & Cano, F. H. (1996). *CRYSOM*. Institute of Physical Chemistry, Rocasolano, CSIC, Serrano 119, Madrid, Spain.

Rodriguez-Fernandez, E., Garcia, E., Hermosa, M. R., Jimenez-Sanchez, A., Mar-Sanchez, M. M., Monte, E. & Criado, J. J. (1999). *J. Inorg. Biochem.* **75**, 181–188.

Siemens (1996). *SHELXTL*. Version 5.0. Siemens AXS Inc., Madison, Wisconsin, USA.

Stewart, J. M., Kundell, F. A., Baldwin, J. C. (1990). *The X-RAY*80 *System*. Computer Science Center, University of Maryland. College Park, Maryland, USA.