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1,2-Diethyl-3-hydroxy-6-phenylthiopyridin-4(1*H*)-one

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Key indicators

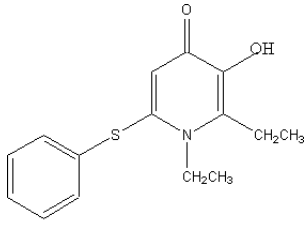
Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
Disorder in main residue
R factor = 0.047
wR factor = 0.127
Data-to-parameter ratio = 16.4

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

The title compound, $C_{15}H_{17}NO_2S$, synthesized as an inhibitor for 5-lipoxygenase, comprises the neutral 1,2-diethyl-3-hydroxy-6-phenylthiopyridin-4(1*H*)-one molecule. The H atom of the hydroxy group and the carbonyl O atom form intermolecular hydrogen bonds with another molecule in a head-to-head fashion. The resulting dimers pack along the *b* axis and form hydrophobic channels.

Comment

3-Hydroxypyridin-4(1*H*)-one derivatives demonstrate various pharmacological effects, such as antineoplastic, anti-hypertensive, cardiotonic, anti-inflammatory and analgesic effects (Hwang *et al.*, 1980; Hershko *et al.*, 1992; Feng *et al.*, 1993; Williams, 1976), and favourable effects in Parkinson's and Thalassemia diseases (Waldmerir *et al.*, 1993; Tondury *et al.*, 1990). In particular, 1,2-dimethyl- and 1,2-diethyl-3-hydroxypyridin-4(1*H*)-one derivatives have been shown to have a potent chelating effect (Hider *et al.*, 1990). They can effectively remove iron from iron-overloaded animals, including man (Porter *et al.*, 1990, 1994), and have been used clinically. These results prompted us to prepare new 3-hydroxypyridin-4(1*H*)-one derivatives and assay them for new medicinal effects.



(I)

We have synthesized 6-substituted-*N*-alkyl-3-hydroxypyridin-4(1*H*)-ones, including the title compound, (I), and examined them for inhibition of 5-lipoxygenase. 5-Lipoxygenase is a cytosolic enzyme which contains a non-heme Fe atom at the active site (Percival, 1991) and catalyses the oxidation of arachidonic acid to leukotrienes, which can cause asthma, inflammatory and rheumatoid arthritis *etc.* We have found that the title compound exhibits strong inhibitory activity on 5-lipoxygenase. Interestingly, the substitution at the 6-position is essential for inhibition of the enzyme. Removal of the substituent at the 6-position, such as in the derivative 1,2-diethyl-3-hydroxypyridin-4(1*H*)-one, diminished the enzyme inhibitory activity. This is related to both the ability of coor-

dination and hydrophobic discrimination of the title compound.

The carbonyl C—O bond length is 1.259 (2) Å, which is longer than the pyridinone average C═O double bond (1.20 Å) and slightly shorter than those found in 1,2-dimethyl-3-hydroxypyridin-4(1*H*)-one and 1-ethyl-2-methyl-3-hydroxypyridin-4(1*H*)-one (Xiao *et al.*, 1992; Clarke *et al.*, 1992). The phenolic hydroxy C—O distance is 1.354 (2) Å, which is quite close to 1.356 (1) Å, and the C2—C3—C4 bond angle is 114.9 (2)°, which is also close to the value of 114.7 (1)° observed by Xiao *et al.* (1992). The S—C bond lengths are 1.775 (2) and 1.779 (2) Å, and the C—S—C bond angle is 102.52 (9)°. The H atom of the hydroxyl group and the carbonyl O atom of compound (I) are hydrogen bonded to the carbonyl O and the hydroxyl H atom, respectively, from another molecule, resulting in head-to-head dimers. The packing of the dimers generates hydrophobic channels along the *b* axis. Compared with other structurally characterized pyridinone compounds (Nelson *et al.*, 1988), the hydrophobic channels observed in compound (I) possibly result from the addition of the auxiliary phenylthio group.

Experimental

1,2-Diethyl-3-hydroxypyridin-4(1*H*)-one (0.84 g, 5.0 mmol) and Ag_2O (6.0 mmol) were stirred in ethanol (40 ml) at 318 K for 4 h. The solid phase was removed by filtration and the solvent was evaporated. The crude product and thiophenol (0.66 g, 6.0 mmol) were stirred in acetone (20 ml) for 48 h at 308 K. The resulting precipitate was collected by evaporation of the solvent, and was recrystallized from acetone/petroleum ether to afford 0.66 g (2.4 mmol, 48%) of the title compound. Then the compound was dissolved in acetone, and the resulting solution was allowed to stand at room temperature. After 3 d, colorless block crystals of (I) were collected.

Crystal data

$C_{15}H_{17}NO_2S$
M_r = 275.36
Monoclinic, $P2_1/n$
a = 12.980 (7) Å
b = 8.482 (5) Å
c = 14.189 (8) Å
β = 110.165 (9)°
V = 1466.4 (14) Å^3
Z = 4
D_x = 1.247 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 820 reflections
θ = 3.0–26.6°
μ = 0.22 mm^{-1}
T = 293 (2) K
Block, colorless
0.46 × 0.26 × 0.20 mm

Data collection

Bruker CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (Blessing, 1995)
T_{min} = 0.906, T_{max} = 0.958
8374 measured reflections
3200 independent reflections
2277 reflections with $I > 2\sigma(I)$
R_{int} = 0.022
θ_{max} = 27.2°
$h = -16 \rightarrow 16$
$k = -10 \rightarrow 6$
$l = -18 \rightarrow 17$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.127
S = 1.06
3200 reflections
195 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0454P)^2 + 0.6466P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.016 (2)

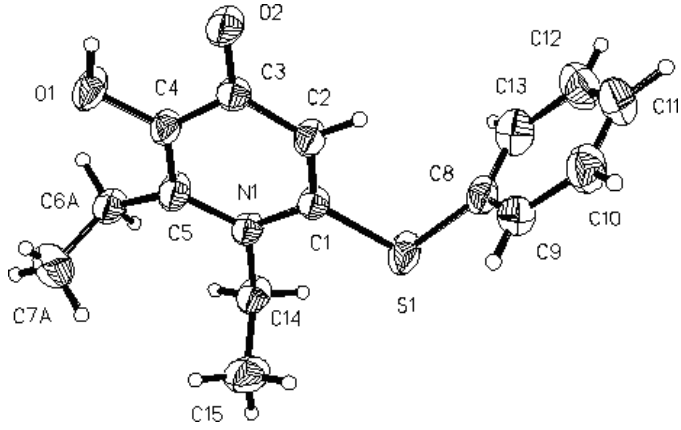


Figure 1
The structure of the title compound, showing 30% probability displacement ellipsoids. The occupancies of the disordered ethyl atoms C6*A* and C7*A* is 0.70; the alternative positions (C6*B* and C7*B*) have been omitted for clarity.

Table 1
Selected geometric parameters (Å, °).

S1—C8	1.775 (2)	O1—C4	1.354 (2)
S1—C1	1.779 (2)	O2—C3	1.259 (2)
C8—S1—C1	102.52 (9)	O1—C4—C3	118.91 (16)
C2—C3—C4	114.94 (16)	C5—C4—C3	122.39 (18)
O1—C4—C5	118.68 (18)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1*A*···O2^{i}	0.84 (3)	1.89 (3)	2.638 (2)	147 (3)
O1—H1*A*···O2	0.84 (3)	2.31 (3)	2.727 (2)	111 (2)

Symmetry code: (i) $2-x, -y, 1-z$.

All H atoms bonded to C atoms were placed in idealized positions (C—H = 0.97, 0.96 and 0.93 Å for CH_2, CH_3 and CH, respectively) and refined as riding atoms. The hydroxyl H atom was located from a difference map and was refined. One of the ethyl groups (C6 and C7) is disordered and was refined in two positions C6*A*/C7*A* and C6*B*/C7*B*.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT-Plus* (Bruker, 1999); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1998); software used to prepare material for publication: *SHELXTL*.

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