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A new amidrazone derivative with antimycobacterial activity

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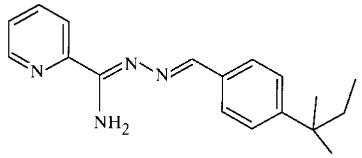
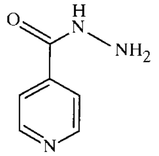
Of a series of pyridine-2-carboxamidrazone derivatives with activity against mycobacteria, the N^1-[4-(1,1-dimethylpropyl)-benzylidene] derivative reported here, $C_{18}H_{22}N_4$, is one of the most active. The predicted *E* isomer about the C11═N12 double bond is confirmed and intramolecular hydrogen bonding involving both amino H atoms helps to keep the molecule flat. The same donor and acceptor atoms also form intermolecular hydrogen bonds.

Comment

Benzylidenepyridylcarboxamidrazones with hydrophobic groups attached to the benzylidene moiety have attracted interest for their antimycobacterial activity (Billington *et al.*, 1998). The title compound, (I), with its 1,1-dimethylpropyl substituent, is particularly active. Its minimum inhibitory concentation of 8–10 µg ml^{-1} against *Mycobacterium fortuitum* approaches the 3 µg ml^{-1} of the established drug isoniazid, (II).



(I)



(II)

We sought confirmation of the structure of (I), in particular, the configuration about the C11═N12 double bond. The reaction used for the synthesis allows both *Z* and *E* isomers, but proton NMR spectrometry and steric considerations suggested the *E* form, which is now verified. Other structural features, which appear to be similar in further members of this class of compounds currently under investigation, involve torsion angles in the chain joining the two rings (Table 1). Small twists about successive bonds, especially about formally single bonds, create an angle of 12.7 (2)° between least-squares planes through the two ring systems. The inclination of the rings must limit the π-electron overlap achievable. Compared to the average $Csp^2—C_{ar}$ bond length of 1.483 (15) Å (Allen *et al.*, 1987), the C1—C11 bond is considerably shorter [1.446 (4) Å], while the C1*P*—C14 bond at the opposite end is not [1.473 (4) Å]. A degree of double-bond character in the former is perhaps substantiated by its greater planarity: torsion angles C2—C1—C11—N12 and N13—C14—C1*P*—N2*P* are 178.1 (3) and 172.4 (3)°, respectively.

The amino group is expected to be a hydrogen-bond donor. Its C14—N141 distance of 1.337 (4) Å suggests considerable double-bond character consistent with sp^2 hybridization at N. Thus, electron density could migrate to the adjacent N13 atom, facilitating resonance-assisted intermolecular N—H···N hydrogen bonding. However, N2*P* not N13 is the hydrogen acceptor, and N12 makes a distant contact to the other amino H atom. In addition, intramolecular N—H···N interactions to N12 in the chain and N2*P* in the heterocycle, though kinked, fulfil the criteria used by Taylor *et al.* (1984) for three-centre hydrogen bonds (Table 2). Preventing an even closer intramolecular approach of N141 to N12, angle N13—C14—N141 is 8–10° larger than the other angles at C14.

The main problem encountered with the structure was disorder in the dimethylpropyl group. Although this should not affect the major structural features described so far, it almost certainly had an effect on what was a difficult refinement leading to a fairly high *wR*.

Experimental

Crystal data

$C_{18}H_{22}N_4$
$M_r = 294.40$
Orthorhombic, *Pbca*
$a = 21.957$ (4) Å
$b = 20.518$ (2) Å
$c = 7.522$ (1) Å
$V = 3388.8$ (8) Å^3
$Z = 8$
$D_x = 1.154$ Mg m^{-3}

Cu *Kα* radiation
Cell parameters from 25 reflections
$\theta = 8.64$–25.83°
$\mu = 0.549$ mm^{-1}
$T = 293$ (2) K
Plate, yellow
0.65 × 0.33 × 0.15 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω/2θ scans
Absorption correction: ψ scan (*CADABS*; Gould & Smith, 1986)
$T_{\min} = 0.469$, $T_{\max} = 0.921$
6157 measured reflections
3316 independent reflections

1635 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.072$
$\theta_{\max} = 72.07°$
$h = 0 \rightarrow 27$
$k = -25 \rightarrow 0$
$l = -9 \rightarrow 9$
3 standard reflections
frequency: 120 min
intensity decay: 3.1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.072$
$wR(F^2) = 0.231$
$S = 1.001$
3316 reflections
204 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.1267P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.37$ e Å^{-3}
$\Delta\rho_{\min} = -0.25$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0011 (3)

Table 1
Selected geometric parameters (Å, °).

C1—C11	1.446 (4)	C14—N141	1.337 (4)
C11—N12	1.284 (4)	C14—C1*P*	1.473 (4)
N12—N13	1.393 (4)	C1P—N2*P*	1.344 (4)
N13—C14	1.303 (4)	N2*P*—C3*P*	1.327 (4)
N13—C14—N141	126.0 (3)	N141—C14—C1*P*	117.8 (3)
N13—C14—C1*P*	116.2 (3)		
C2—C1—C11—N12	178.1 (3)	N12—N13—C14—C1*P*	177.4 (2)
C1—C11—N12—N13	175.1 (3)	N13—C14—C1*P*—N2*P*	172.4 (3)
C11—N12—N13—C14	−173.9 (3)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N141—H141···N12	0.86	2.35	2.636 (4)	100
N141—H142···N2*P*	0.86	2.37	2.712 (4)	104
N141—H141···N2*P*^{i}	0.86	2.31	3.085 (4)	149
N141—H142···N12^{ii}	0.86	2.61	3.368 (4)	148

Symmetry codes: (i) $\frac{3}{2} - x, 2 - y, \frac{1}{2} + z$; (ii) $\frac{3}{2} - x, 2 - y, z - \frac{1}{2}$.

H atoms were treated as riding with N—H = 0.86 Å and C—H = 0.93–0.97 Å. Two separate positions were refined for each terminal methyl C atom using *PART*.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *CADABS* (Gould & Smith, 1986); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); software used to prepare material for publication: *SHELXL*97.

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