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7-Nitroindazole

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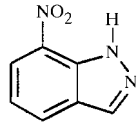
The title compound, $C_7H_5N_3O_2$, is an inhibitor of nitric oxide synthase and monoamine oxidase. The N1H tautomer crystallized as a dimer and adopts a planar conformation assisted by intramolecular hydrogen bonding.

Comment

7-Nitroindazole, (I), is an inhibitor of nitric oxide synthase (NOS), the enzyme responsible for the generation of the ubiquitous neurotransmitter nitric oxide (Moore *et al.*, 1993). In the early 1990s, it was discovered that (I) exhibited selectivity for neuronal NOS (nNOS) (Babbedge *et al.*, 1993; MacKenzie *et al.*, 1994) and it soon became the standard investigative tool for the study of effects related to nNOS (Rivier, 1998). Shortly after these findings, it became clear that (I) may have utility as a neuroprotecting agent when it was found that it protected against MPTP-induced neurotoxicity in the mouse (Schulz *et al.*, 1995; Przedborski *et al.*, 1996) and baboon (Hantraye *et al.*, 1996). Although initial arguments suggested that nNOS may mediate, in part, MPTP-induced neurotoxicity (Przedborski *et al.*, 1996), more recent studies in the mouse (Castagnoli *et al.*, 1997) and rat (Desvignes *et al.*, 1999) provided evidence that (I) is also an inhibitor of monoamine oxidase B (MAO-B), which may contribute to the protective effect of this compound against MPTP neurotoxicity (Di Monte *et al.*, 1997). It has now been suggested and that this action on MAO-B, rather than NOS inhibition, is the mechanism by which (I) prevents MPTP-induced ATP depletion (Royland *et al.*, 1999).

The conformation of (I) is of interest because of its unique ability to inhibit both MAO-B and nNOS, two biologically important enzyme systems. Furthermore, its general use as an investigative drug to study the inhibition of nNOS makes a structural study of this molecule important. Several reversible inhibitors of MAO have planar structures, including the endogenous indole derivative isatin, (Medvedev *et al.*, 1995) an MAO-B selective inhibitor, and the commercially available (in Europe) phenyloxazolidinone toloxatone, an MAO-A selective inhibitor (Moureau *et al.*, 1992, 1995).



(I)

Von Auwers, in 1891 (Von Auwers & Meyenburg, 1891), was the first to report that indazoles exist in a tautomeric equilibrium. Evidence obtained from molecular refractivity measurements in Von Auwers' laboratory later suggested the predominance of the tautomer possessing the benzenoid structure (Von Auwers *et al.*, 1937). It was also shown by UV spectroscopy (Rousseau & Linwall, 1950) as well as by proton (Elguero *et al.*, 1966) and ^{14}N NMR (Witanowski *et al.*, 1972) that the data from indazole more closely resemble those obtained from 1-methylindazole than those from 2-methylindazole, further supporting evidence for the predominance of the benzenoid structure. The crystal structure of indazoles (Escande *et al.*, 1974; Escande & Lapasset, 1974) also supported these conclusions. *Ab initio* studies by the group of Elguero (Catalan & Elguero, 1994; Catalan *et al.*, 1996) suggested that indazole occurs in the N1H tautomeric form in the gas phase and in solution both in the ground and excited states and that the N1H tautomer is more stable than its N2H congener by 4 kcal mol^{-1}.

Compound (I) adopts, in the solid state, a planar conformation assisted by intramolecular hydrogen bonding between the 7-nitro group and a H atom on N1 of the indazole structure. An H atom was unambigously detected from the Fourier difference map on N1 but not on N2. This H atom is further engaged in an intermolecular hydrogen bond leading to the formation of stable dimers in the crystal packing (Table 1). A planar conformation would have been less likely if the N2H tautomer had formed.

Experimental

The title compound was purchased from Research Biochemicals International (lot ZXY-296C) as a crystalline sample.

Crystal data

$C_7H_5N_3O_2$
M_r = 163.14
Monoclinic, $P2_1/n$
a = 5.020 (1) Å
b = 9.636 (1) Å
c = 14.506 (1) Å
β = 98.232 (4)°
V = 694.46 (16) Å^3
Z = 4
D_x = 1.560 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 40–45°
μ = 1.013 mm^{-1}
T = 293 (2) K
Needle, orange–yellow
0.70 × 0.25 × 0.18 mm

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Data collection

Enraf–Nonius diffractometer	$R_{int} = 0.010$
$\theta/2\theta$ scans	$\theta_{max} = 71.87^\circ$
Absorption correction: analytical (*HELENA*; Spek, 1997)	$h = 0 \rightarrow 6$
	$k = -8 \rightarrow 11$
$T_{min} = 0.537$, $T_{max} = 0.839$	$l = -17 \rightarrow 17$
1877 measured reflections	3 standard reflections
1355 independent reflections	frequency: 60 min
1223 reflections with $I > 2\sigma(I)$	intensity decay: 2%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0544P)^2 + 0.1541P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.037$	
$wR(F^2) = 0.109$	
$S = 1.097$	$(\Delta/\sigma)_{max} = 0.001$
1355 reflections	$\Delta\rho_{max} = 0.20$ e Å^{-3}
110 parameters	$\Delta\rho_{min} = -0.15$ e Å^{-3}
H-atom parameters constrained	Extinction correction: *SHELXL*97
	Extinction coefficient: 0.0079 (12)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···N2^{i}	0.86	2.28	2.941 (2)	134
N1—H1···O9	0.86	2.29	2.749 (2)	114

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

The H atom on N1 was located by difference synthesis (N—H = 0.86 Å). All H atoms were treated as riding atoms (C—H = 0.93 Å).

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997).

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