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β-Carboline (norharman)

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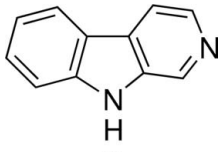
The structure of β-carboline, also called norharman (systematic name: 9*H*-pyrido[3,4-*b*]indole), $C_{11}H_8N_2$, has been determined at 110 K. Norharman is prevalent in the environment and the human body and is of wide biological interest. The structure exhibits intermolecular N—H···N hydrogen bonding, which results in a one-dimensional herringbone motif. The three rings of the norharman molecule collectively result in a C-shaped curvature of 3.19 (13)° parallel to the long axis. The diffraction data show shorter pyridyl C—C bonds than those reported at the STO-3G level of theory.

Comment

Norharman, (I), is the prototypical β-carboline alkaloid that is the basic structural unit for a wide range of important naturally occurring compounds. Norharman is found in numerous plants and animals, including humans (Fekkes *et al.*, 1992). It is also prevalent in the environment, for example, as a constituent of cigarette smoke, and can be absorbed from numerous foodstuffs and other environmental sources (Herraiz, 2004).



(I)

The biological function of norharman appears to be varied and its toxicity and therapeutic uses have been investigated. For example, norharman has been implicated as both a neurotoxin relevant to Parkinson's disease (Kuhn *et al.*, 1996) and a mediator in the mutagenesis of DNA in the presence of other small molecules (Mori *et al.*, 1996). Norharman has also been suggested as a potential neuroprotective agent (Haghdoost-Yazdi *et al.*, 2010). The molecular-based interactions between norharman and biological materials such as DNA and proteins are likely to arise primarily from hydrogen bonding and quadrupolar effects, due to the π-derived electrons. However, no adducts or cocrystals of norharman have been published to date.

Despite considerable investigation into the properties and biological activity of norharman and the calculation of its optimized structure at the STO-3G level of theory (Konschin *et al.*, 1987), a high-quality crystal structure has not yet been reported. Crystallographic studies undertaken by Ray (1957) and later by Roychowdhury & Roychowdhury (1981), determined unit-cell parameters and presented gross structural features. Given the ongoing research into the biological function of norharman and the many related β-carboline derivatives, a single-crystal X-ray structure of norharman would be of use in theoretical modelling and related structural work. A fragment search of the Cambridge Structural Database (CSD, Version 5.32; Allen, 2002) using the unsaturated norharman skeleton returned 48 hits for structures where the three-dimensional coordinates have been reported. The bond lengths and distances were subjected to principal-component and cluster analyses (Barr *et al.*, 2005; Fletcher *et al.*, 1996) and correlation coefficients were calculated, but no meaningful trends were observed. Investigation of the bonding in these molecules is restricted, in part due to the limited number of structures reported. Therefore, the structure of norharman will be of use as a fundamental reference as more β-carboline structures are obtained.

Single crystals of norharman were grown as part of ongoing efforts to explore the metal–ligand bonding and electron distribution in complexes incorporating the norharman motif. The needle-like morphology resulted in poor diffraction, but a data set of sufficient quality to locate the H atoms was obtained. The unit-cell parameters and space group are consistent with those reported previously (Ray, 1957). Upon refinement, the H atoms were observed in the difference map, although all but amino atom H2 (Fig. 1) were refined using a riding model.

The molecular structure of norharman (Fig. 1) exhibits curvature parallel to the longest axis, with angles between the least-squares planes of the benzene/pyrrole and pyrrole/pyridyl rings of 0.68 (14) and 2.60 (14)°, respectively, defining a C- rather than S-shaped geometry. The X-ray structures of other β-carbolines in the CSD generally exhibit curvatures of 0–5°. The bond lengths of the benzene fragment are identical, within experimental error, to those observed for aniline, where the latter exhibits asymmetry about the Ph—N axis due

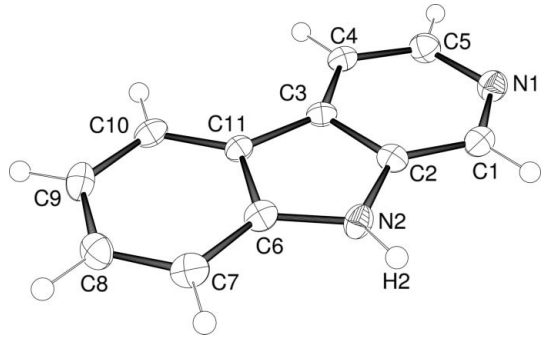


Figure 1
The molecular structure of norharman, (I). Displacement ellipsoids are drawn at the 50% probability level.

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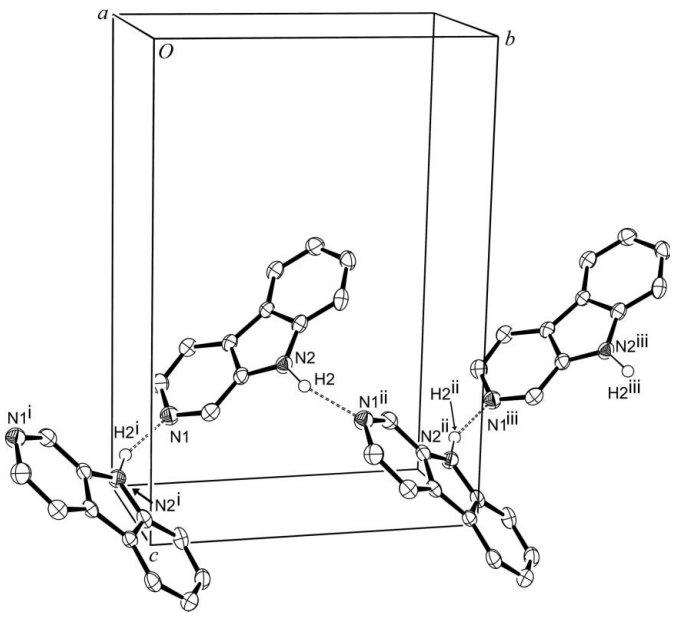

Figure 2
The hydrogen-bonding network of norharman, viewed parallel to the *b* axis. [Symmetry codes: (i) $-x, y-\frac{1}{2}, -z+\frac{3}{2}$; (ii) $-x, y+\frac{1}{2}, -z+\frac{3}{2}$; (iii) $x, y+1, z$.]

to hydrogen bonding in the crystal lattice (Fukuyo *et al.*, 1982). Compared with the structure of 3-aminopyridine (Chao *et al.*, 1975), the pyridyl moiety of (I) exhibits lengthening of the N1—C5 and C2—C3 bonds of 0.26 (9) and 0.24 (8) Å, respectively, reflective of conjugation across the π-system of the entire molecule.

Hydrogen bonding has been implicated as key to the biological activity of β-carbolines (Guan *et al.*, 2006). Norharman exhibits intermolecular hydrogen bonding (Fig. 2 and Table 1), resulting in a one-dimensional herringbone chain motif parallel to the *b* axis. The distance between atoms N2 and N1^{ii} [symmetry code: (ii) $-x, y+\frac{1}{2}, -z+\frac{3}{2}$] is 2.888 (3) Å and the angle between the least-squares planes of adjacent norharman molecules is 71.55 (4)°. The hydrogen-bonding interaction is nonlinear and the location of atom H2 identifies N2—H2 and N1^{ii} as the hydrogen-bond donor and acceptor, respectively. The alternative neutral tautomer of norharman could be derived *via* formal proton migration from N2 to N1, although loss of aromaticity in the pyridyl moiety would suggest this isomer would not be the molecular ground state. However, there are several structures of *N*-alkylated analogues where this alternative tautomer is observed (Bonazzi *et al.*, 2010; Mahboobi *et al.*, 2000). Moreover, in addition to locating atom H2 in the difference map, the C1—N1—C5 angle of 118.0 (2)° is diagnostic of unprotonated substituted pyridines, where on protonation, an angle of 120–122° would be expected (Krygowski *et al.*, 2005). Furthermore, comparison between the experimental and reported theoretical geometric parameters determined at the STO-3 G level of theory (Konschin *et al.*, 1987) shows that the latter generally overestimates the bonds lengths of the pyridyl and five-membered rings. For example, the bonds lengths C3—C11, C2—N2 and N1—C6 were calculated as 1.4643, 1.4029 and 1.3661 Å, whereas using X-ray diffraction the bond lengths are 1.448 (4), 1.381 (3) and 1.357 (4) Å, respectively. For the calculated structure it was suggested that overestimation of the C—N bond lengths may occur due to an insufficiently large basis set (Konschin *et al.*, 1987).

With respect to the hydrogen bonding, related β-carbolines exhibit a range of hydrogen-bonding motifs that are dependent on the stereochemistry about atoms N1 and N2 and any ring substituents that are also capable of hydrogen-bonding interactions. For example, in the structural analogue harman, where atom C1 is substituted with a methyl group, the additional steric interaction induces a helical chain motif (El-Sayed *et al.* 1986), whereas the addition of an ester (Kubicki & Codding, 2001; Bertolasi *et al.*, 1984) or amide (Muir & Codding, 1984) functionality at C5 results in a flat chain motif derived from hydrogen bonding between the ester or amide group and atom H2.

Experimental

Norharman was prepared according to literature methods (Lippke *et al.*, 1983; Hagen *et al.*, 1987). Crystals of (I) suitable for X-ray diffraction were grown from a supersaturated solution of norharman in ethyl acetate at 277 K over a period of 24 h.

Crystal data

$C_{11}H_8N_2$
M_r = 168.19
Orthorhombic, $P2_12_12_1$
a = 5.8272 (4) Å
b = 9.8245 (4) Å
c = 14.3943 (11) Å
V = 824.06 (9) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.08 mm^{-1}
T = 110 K
0.30 × 0.01 × 0.01 mm

Data collection

Oxford SuperNova diffractometer
Absorption correction: multi-scan (*CrysAlis PRO*; Oxford Diffraction, 2010)
T_{min} = 0.899, T_{max} = 1.000
2818 measured reflections
866 independent reflections
676 reflections with $I > 2\sigma(I)$
R_{int} = 0.039

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.073
S = 1.00
866 reflections
122 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

H atoms were found in difference Fourier maps and were subsequently treated as riding, with C—H = 0.95 Å and U_{iso}(H) = 1.2U_{eq}(C), with the exception of atom H2, which was refined. There was insufficient Friedel-pair coverage to determine the absolute structure, so Friedel pairs were merged and the absolute structure was chosen arbitrarily.

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···N1^{ii}	1.00 (3)	1.96 (3)	2.888 (3)	153 (3)

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

Data collection: *CrysAlis PRO* (Oxford Diffraction, 2010); cell refinement: *CrysAlis PRO*; data reduction: *CrysAlis PRO*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *OLEX2*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: KU3050). Services for accessing these data are described at the back of the journal.

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