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cis-3-Phenyl-3,3a,4,5-tetrahydrobenzo[*g*]-indazole-2-carboxamide

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Key indicators

Single-crystal X-ray study
T = 123 K
Mean σ(C–C) = 0.003 Å
R factor = 0.031
wR factor = 0.082
Data-to-parameter ratio = 8.2

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

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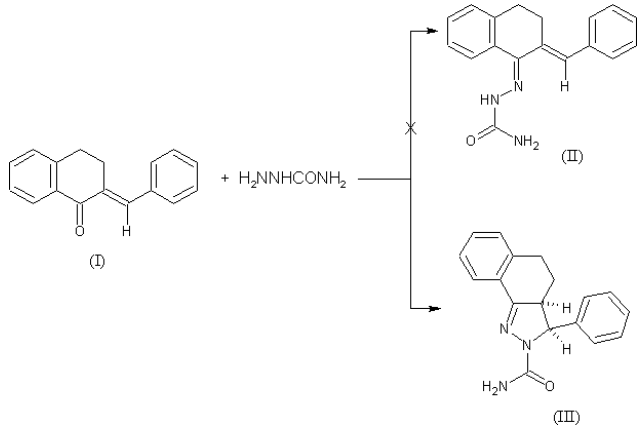
The title compound, $C_{18}H_{17}N_3O$, crystallizes in a conformation where the phenyl group is almost orthogonal to the aromatic part of the tetrahydronaphthalene moiety. In the crystal structure, molecules form one-dimensional extended chains *via* N—H···O hydrogen bonds.

Comment

In an attempt to prepare 2-phenylmethylene-1-tetralone semicarbazone, (II), a potential anticancer drug, from 2-phenylmethylene-1-tetralone, (I), and semicarbazide, an unexpected product, namely *cis*-3-phenyl-3,3a,4,5-tetrahydrobenzo[g]indazole-2-carboxylic acid amide, (III) (Fig. 1), was obtained. Compound (III) exhibits *cis* stereochemistry at atoms C3 and C3*A*.



The conversion of (I) to (II) was suggested because a previous study reported that replacement of the O atom of various acyclic α,β-unsaturated ketones by a substituted hydrazine group diminished the electrophilicity of the olefinic C atoms (Dimmock *et al.*, 1981). This investigation also

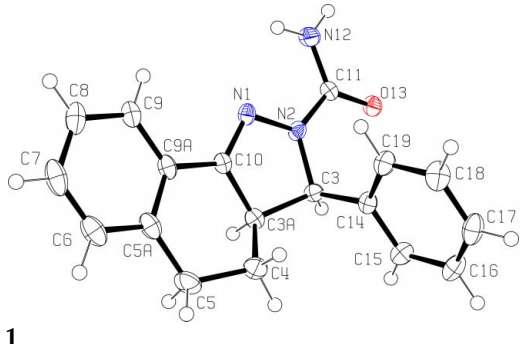


Figure 1
View of (III) (Farrugia, 1997), with non-H-atom displacement ellipsoids drawn at the 50% probability level. For clarity, H atoms are drawn as small spheres of arbitrary size.

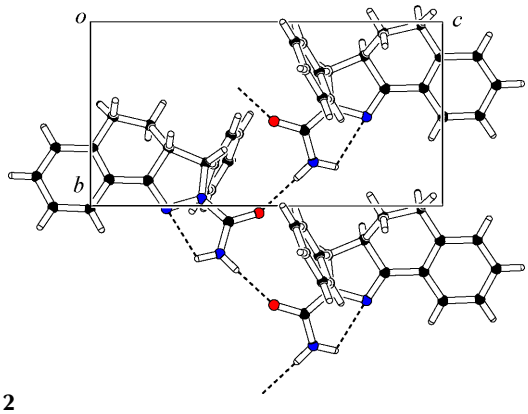


Figure 2
Plot (Spek, 1997) of the hydrogen bonding in (III), viewed down the *a* axis.

disclosed that nucleophilic attack of semicarbazide took place on the carbonyl C atom, with retention of the olefinic double bond. The straightforward conversion of (I) to (II) was therefore envisaged, permitting its evaluation against a panel of four tumor cell lines. However, the product isolated was shown by X-ray crystallography to be the substituted indazole (III) and not the desired semicarbazone (II). It is likely that the intermediate semicarbazone exists as an equilibrium mixture of *E* and *Z* isomers in solution (Dimmock *et al.*, 1990; Karabastos *et al.*, 1964). In contrast to acyclic α,β-unsaturated ketones, the olefinic C atoms in (II) will be immobile and in close proximity to the secondary amine group of the Z isomer, leading to ring closure.

A review of the literature disclosed that structure (III) had been proposed previously, mainly on the basis of ^{1}H and ^{13}C NMR spectroscopy (Lóránd *et al.*, 1985; Szöllösy *et al.*, 1991); subsequently, *cis–trans* isomerization studies of (III) were described (Lóránd *et al.*, 1996). The present report, therefore, provides unequivocal proof of the identity of the product produced by Lóránd *et al.* (1996). Cytotoxic evaluation of (III) revealed that, at the maximum concentrations used, namely 50 μ*M* (P388 screen) or 500 μ*M* (L1210, Molt 4/C8 and CEM tests), inhibition of 50% of the growth of the cells was not accomplished, in contrast to the situation for (I), in which case the IC_{50} values in these four screens were 30.2, 121, 32.4 and 7.42 μ*M*, respectively (Dimmock *et al.*, 1999). For many molecules with cytotoxic properties, their activity depends on their bonding into the major and minor grooves in DNA. The fact that the molecules of (III) have a conformation where the phenyl group is almost orthogonal [88.93 (11)°] to the aromatic part of the tetrahydronaphthalene moiety may be significant in explaining the low cytotoxicity of (III) (Patrick, 1995).

The crystal structure of (III) is stabilized by both classical and non-classical hydrogen bonds. An intramolecular hydrogen bond links the N12/H12*B* group to atom N1 [N···N = 2.693 (3) Å]. The molecules of (III) are linked into one-dimensional extended chains by intermolecular N12—H12*A*···O13($1-x,\frac{1}{2}+y,1-z$) bonds, lying approximately in the *bc* plane and pointing in the *b*-axis direction, as show in Fig. 2. The phenyl groups point in the *a*-axis direction. In addition, there are two non-classical hydrogen bonds, *viz*. C3···O13($1-x,-\frac{1}{2}+y,1-z$) at 3.349 (4) Å and C17···O13($2-x,-\frac{1}{2}+y,1-z$) at 3.304 (4) Å (see Table 1.).

Experimental

Semicarbazide hydrochloride (30 mmol) was added to a suspension of 2-phenylmethylene-1-tetralone (10 mmol) prepared by a literature procedure (Smith *et al.*, 1973), ethanol (95%, 109 ml) and hydrochloric acid (36.5% *w*/*w*, 11 ml). The mixture was heated under reflux for 72 h. On cooling, the precipitate was collected, washed with ethanol (25 ml) and water (50 ml), and recrystallized from ethanol (95%), giving (III) as a racemic product [m.p. 543–544 K; literature m.p. 548 K (Lóránd *et al.*, 1985)] in 62% yield. Analysis calculated for $C_{18}H_{17}N_3O$: C 74.20, H 5.88, N 14.43%; found: C 74.00, H 5.90, N 14.45%. The evaluation using P388 cells was accomplished using a literature procedure (Phillips *et al.*, 1989), whereas the L1210, Molt 4/C8 and CEM assays were conducted by a previously described method (Balzarini *et al.*, 1982).

Crystal data

$C_{18}H_{17}N_3O$
M_r = 291.35
Monoclinic, $P2_1$
a = 7.902 (7) Å
b = 7.004 (5) Å
c = 13.736 (12) Å
β = 102.38 (8)°
V = 742.6 (11) Å^3
Z = 2
D_x = 1.303 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 7.3–18.3°
μ = 0.08 mm^{-1}
T = 123 (2) K
Prism, colorless
0.38 × 0.23 × 0.13 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω scans
1697 measured reflections
1632 independent reflections
1473 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
θ_{max} = 26.3°
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 8$
$l = -17 \rightarrow 16$
3 standard reflections
every 200 reflections
frequency: 120 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.082
S = 1.06
1632 reflections
199 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0434P)^2 + 0.117P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N12—H12*B*···N1	0.88	2.33	2.693 (3)	105
N12—H12*A*···O13^{i}	0.88	1.98	2.850 (3)	171
C3—H3···O13^{ii}	1.00	2.36	3.350 (4)	171
C17—H17···O13^{iii}	0.95	2.59	3.304 (3)	132

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

All H atoms on C atoms were placed in calculated positions (C—H = 1.00 Å on methine aliphatic C atoms, 0.99 Å for methylene aliphatic H atoms and 0.95 Å on aromatic C atoms) and refined as riding. The U_{iso}(H) values were set equal to 1.2U_{eq} of the attached C atoms. The positions of the H atoms on N atoms were found in ΔF maps and refined to establish the geometry of the –NH_2 group. These H atoms were then placed in ideal positions, with N—H bond lengths

of 0.88 Å and U_{iso}(H) values set at 1.2U_{eq} of the attached N atoms. In the absence of significant anomalous dispersion effects, Friedel pairs were merged.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1992); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *Xtal*3.7 (Hall *et al.*, 2000); program(s) used to solve structure: *Xtal*3.7; program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997) and *PLATON*97 (Spek, 1997); software used to prepare material for publication: *SHELXL*97.

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