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4,4-Dibenzyl-1,4-dihydroisoquinoline

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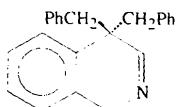
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Abstract

The title compound, 4,4-dibenzyl-1,4-dihydroisoquinoline, $C_{23}H_{21}N$, is one of the few stable derivatives of 1,4-dihydroisoquinoline for which structures have been reported so far. In the solid state the compound exhibits an interesting conformation with both benzyl groups at C4 folded symmetrically toward the heterocyclic system.

Comment

The nitrogen-containing ring of the 1,4-dihydroisoquinoline moiety is in the flattened boat conformation with C1 and C4 deviating from the least-squares plane by 0.183 and 0.124 Å, respectively. The deviation of the remaining atoms ranges from 0.036 to 0.077 Å.



Almost all C–C and C–N bond distances as well as intra-annular bond and torsion angles in the 1,4-dihydroisoquinoline moiety do not differ significantly from the corresponding distances and angles in other compounds reported (Gieren, Burger & Einhellig, 1973; Weidner, Maas & Würthwein, 1989; Vogel, Delavier, Jones & Doring, 1991; Richter-Addo, Knight, Dewey, Arif & Gladysz, 1993; Pich, Bishop, Craig & Scudder,

1994). The most noticeable difference in the geometry of the 1,4-dihydroisoquinoline system is the significant enlargement of the intra-annular bond angle N2—C3—C4 to $129.0(2)^\circ$ versus 121.5 – 125.0° reported for other structures. The relative enlargement of the angle may result from the presence of two bulky benzyl groups at the adjacent C atom (C4).

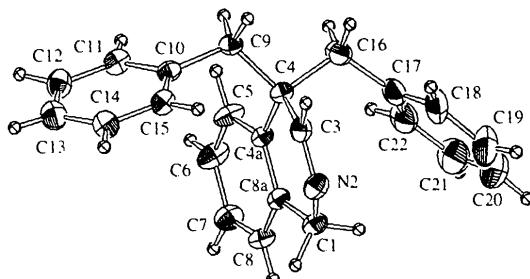


Fig. 1. Molecular structure showing 30% probability displacement ellipsoids. Displacement ellipsoids for H atoms are of arbitrary size.

Both benzyl substituents at C4 are twisted toward the isoquinoline moiety in a similar fashion, yet they are not equivalent. The C4—C9 bond is shorter by 0.015 Å (5σ) than the C4—C16 bond. Also, the C4—C16—C17 angle is significantly smaller (3.2° or 16σ) than its counterpart, C4—C9—C10. The two phenyl rings of the benzyl groups are twisted differently with respect to the isoquinoline system. Whereas the torsion angles around the first single bond (*i.e.* C4—C9 and C4—C16) are virtually equivalent for both groups, the torsion angles around the second bond (C9—C10 and C16—C17) differ by about 20° . Thus, the dihedral angle between the benzene ring and the plane dissecting the methylene group is 68.1° for one benzyl substituent (C9—C15) and 89.0° for the other (C16—C22). The planes dissecting the methylene groups are almost perpendicular to the isoquinoline moiety for both benzyl substituents. The discussed angular differences between the two benzyl groups can be rationalized by different packing interactions acting on both phenyl rings.

The isoquinoline moieties are arranged in a parallel pattern in the crystal (Fig. 2) with the distance between

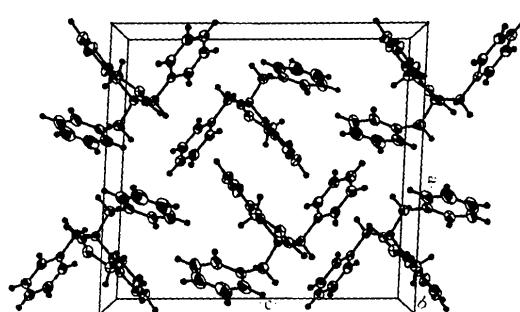


Fig. 2. Packing diagram viewed down the *b* axis.

the least-squares planes of the two adjacent aromatic rings being 3.42 Å. Benzene rings from one of the benzyl groups (C17–C22) are also packed parallel, with the distance between the adjacent rings being 3.52 Å.

Experimental

4,4-Dibenzyl-1,4-dihydroisoquinoline was prepared from sequential benzylations of the boron-activated enamines derived from the reaction of isoquinoline with sodium triethylborohydride (Minter & Re, 1988). The product was purified by recrystallization from THF/ligroin. Colorless crystals with melting point 389–390 K were obtained.

Crystal data

$C_{23}H_{21}N$
 $M_r = 311.43$
 Monoclinic
 $P2_1/n$
 $a = 14.891 (2)$ Å
 $b = 7.3102 (11)$ Å
 $c = 16.1682 (10)$ Å
 $\beta = 92.380 (7)^\circ$
 $V = 1758.5 (4)$ Å³
 $Z = 4$
 $D_x = 1.176$ Mg m⁻³

Data collection

Rigaku AFC-6S diffractometer
 $\omega/2\theta$ scans
 Absorption correction:
 ψ scan (North, Phillips & Mathews, 1968)
 $T_{\min} = 0.927$, $T_{\max} = 1.000$
 5575 measured reflections
 3710 independent reflections

Refinement

Refinement on F^2
 $R(F^2) = 0.0603$
 $wR(F^2) = 0.1022$
 $S = 2.26$
 3710 reflections
 301 parameters
 All H-atom parameters refined
 $w = 1/\sigma^2(F^2)$

$Cu K\alpha$ radiation
 $\lambda = 1.54178$ Å
 Cell parameters from 25 reflections
 $\theta = 34.2$ – 39.9°
 $\mu = 0.51$ mm⁻¹
 $T = 295$ K
 Prismatic
 $0.50 \times 0.30 \times 0.20$ mm
 Colorless

3710 observed reflections
 $[I > \sigma(I)]$
 $R_{\text{int}} = 0.040$
 $\theta_{\max} = 79.3^\circ$
 $h = -4 \rightarrow 18$
 $k = 0 \rightarrow 9$
 $l = -20 \rightarrow 20$
 3 standard reflections monitored every 150 reflections
 intensity decay: 1.0%

$(\Delta/\sigma)_{\max} = 0.003$
 $\Delta\rho_{\max} = 0.29$ e Å⁻³
 $\Delta\rho_{\min} = -0.27$ e Å⁻³
 Extinction correction: none
 Atomic scattering factors from International Tables for X-ray Crystallography (1974, Vol. IV, Table 2.3.1)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

$$U_{\text{eq}} = (1/3) \sum_j \sum_{ij} U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}
N2	0.2088 (1)	0.2527 (2)	0.0605 (1)	0.0490 (6)
C1	0.1529 (2)	0.2797 (3)	-0.0144 (1)	0.0470 (8)
C3	0.2507 (1)	0.3888 (3)	0.0907 (1)	0.0423 (6)
C4	0.2530 (1)	0.5831 (3)	0.0591 (1)	0.0375 (6)
C4a	0.1744 (1)	0.6188 (3)	-0.0006 (1)	0.0350 (6)
C5	0.1490 (2)	0.7959 (3)	-0.0233 (1)	0.0503 (8)
C6	0.0786 (2)	0.8259 (3)	-0.0799 (1)	0.0597 (8)

C7	0.0311 (2)	0.6804 (3)	-0.1140 (1)	0.0565 (10)
C8	0.0562 (2)	0.5058 (3)	-0.0921 (1)	0.0482 (6)
C8a	0.1276 (1)	0.4737 (3)	-0.0358 (1)	0.0373 (6)
C9	0.2567 (1)	0.7169 (3)	0.1337 (1)	0.0395 (6)
C10	0.1747 (1)	0.7262 (3)	0.1859 (1)	0.0372 (6)
C11	0.1229 (2)	0.8825 (3)	0.1869 (1)	0.0476 (8)
C12	0.0505 (2)	0.8944 (4)	0.2377 (1)	0.0561 (10)
C13	0.0292 (2)	0.7493 (4)	0.2878 (1)	0.0591 (10)
C14	0.0808 (2)	0.5939 (3)	0.2869 (1)	0.0536 (10)
C15	0.1532 (2)	0.5829 (3)	0.2366 (1)	0.0455 (6)
C16	0.3436 (2)	0.6059 (4)	0.0142 (2)	0.0567 (10)
C17	0.3549 (2)	0.4750 (4)	-0.0559 (2)	0.0600 (8)
C18	0.3960 (2)	0.3070 (5)	-0.0418 (2)	0.0823 (14)
C19	0.3999 (3)	0.1785 (6)	-0.1039 (3)	0.1115 (17)
C20	0.3675 (3)	0.2204 (7)	-0.1824 (3)	0.1199 (19)
C21	0.3282 (3)	0.3867 (7)	-0.1980 (2)	0.1026 (18)
C22	0.3222 (2)	0.5133 (5)	-0.1350 (2)	0.0742 (14)

Table 2. Selected geometric parameters (Å, °)

N2—C1	1.454 (3)	C4a—C8a	1.379 (3)
N2—C3	1.262 (2)	C5—C6	1.380 (3)
C1—C8a	1.504 (3)	C6—C7	1.380 (3)
C3—C4	1.510 (3)	C7—C8	1.372 (3)
C4—C4a	1.509 (2)	C8—C8a	1.391 (3)
C4—C9	1.552 (3)	C9—C10	1.514 (2)
C4—C16	1.567 (3)	C16—C17	1.498 (4)
C4a—C5	1.394 (3)		
C1—N2—C3	118.2 (2)	C5—C6—C7	120.3 (2)
N2—C1—C8a	116.7 (2)	C6—C7—C8	119.0 (2)
N2—C3—C4	128.9 (2)	C7—C8—C8a	121.2 (2)
C3—C4—C4a	110.6 (2)	C1—C8a—C4a	120.9 (2)
C9—C4—C16	106.8 (2)	C1—C8a—C8	119.2 (2)
C4—C4a—C5	121.6 (2)	C4a—C8a—C8	120.0 (2)
C4—C4a—C8a	119.8 (2)	C4—C9—C10	117.3 (2)
C5—C4a—C8a	118.6 (2)	C4—C16—C17	114.1 (2)
C4a—C5—C6	120.8 (2)		
C3—N2—C1—C8a	-17.6 (3)	C3—C4—C16—C17	58.4 (3)
C1—N2—C3—C4	-1.0 (3)	C4a—C4—C16—C17	-61.7 (3)
N2—C1—C8a—C4a	17.5 (3)	C4—C4a—C8a—C1	1.0 (2)
N2—C3—C4—C4a	18.7 (2)	C4—C9—C10—C11	-112.8 (2)
C3—C4—C4a—C8a	-17.3 (2)	C4—C9—C10—C15	70.7 (2)
C3—C4—C9—C10	-67.0 (2)	C4—C16—C17—C18	-90.5 (3)
C4a—C4—C9—C10	56.5 (2)	C4—C16—C17—C22	87.0 (3)

All non-H atoms were refined with anisotropic displacement parameters. The H atoms were refined isotropically. The C—H distances range from 0.90 (2) to 1.05 (4) Å and B_{eq} for the H atoms ranges from 3.4 (4) for H9A to 12 (1) Å² for H18 and H19. The range of the aromatic C—C bonds for the two benzene rings is 1.368 (7)–1.387 (5) Å, with an average of 1.378 Å and e.s.d. of 0.005 Å. The average experimental e.s.d. for the 12 bonds is 0.005 Å. The range of the C—C—C angles in the benzene rings is 118.0 (3)–121.1 (3)°, with an average of 120.0° and e.s.d. of 1.0°. The average experimental e.s.d. for the 12 angles is 0.3°.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *PROCESS* in *TEXSAN* (Molecular Structure Corporation, 1985). Program(s) used to solve structure: *MITHRIL* in *TEXSAN* (Gilmore, 1984). Program(s) used to refine structure: *LS* in *TEXSAN*. Molecular graphics: *ORTEPII* (Johnson, 1976), *PLUTO* (Motherwell & Clegg, 1978). Software used to prepare material for publication: *PLATON* (Spek, 1990).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1166). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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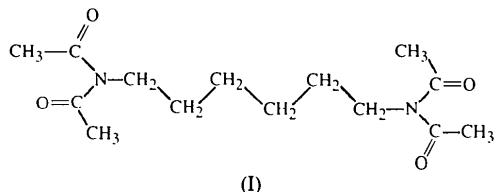
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to have this type of activity. HMBA, as an effective differentiating agent, is used in Phase II clinical trials (Andreeff *et al.*, 1992). The title compound, (I), is slightly more potent and somewhat more effective than HMBA. As a step towards understanding the molecular mechanism by which this compound initiates cell differentiation, identifying the structure–activity relationship and providing structural data for drug design, its crystal structure has been determined.



(I)

Each acetyl group can assume one of the two possible conformations with respect to the central hydrocarbon chain: one with the carbonyl O atom *cis* to the chain and the other with the methyl group *cis* to the chain. In the observed structure (Fig. 1), the two acetyl groups at each end have different conformations. The molecule is centrosymmetric and the asymmetric unit of the crystal contains only half the molecule. The *N,N*-bisacetylamine group is planar, but the possibility of twofold symmetry about the N—C(3) bond is not realised.

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Anti-Cancer Agents. I. *N,N,N',N'-Tetraacetylhexamethylenediamine*

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Abstract

The centrosymmetric molecule *N,N,N',N'-tetraacetylhexamethylenediamine*, C₁₄H₂₄N₂O₄, occupies a special position, with only half of the molecule in the asymmetric unit. Each terminal *N,N*-bisacetylamine group is planar but not twofold symmetric.

Comment

Since the discovery that dimethyl sulfoxide (DMSO) induces erythroid differentiation in murine virus-induced erythroleukemic cells (Friend, Scher, Holland & Sato, 1971), numerous chemical compounds such as butyric acid (Leder & Leder, 1975), *N,N*-dimethylacetamide, hexamethylenebisacetamide (HMBA) (Reuben, Wife, Breslow, Rifkind & Marks, 1976) and retinoic acid (Strickland & Mahdavi, 1978) have been demonstrated

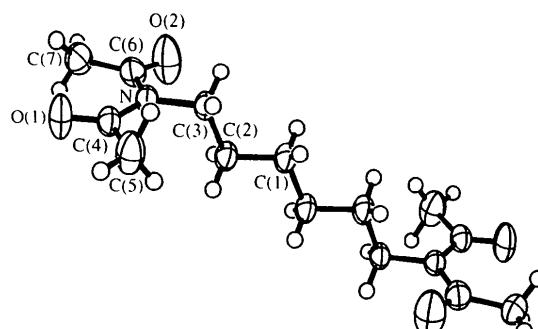


Fig. 1. Molecular structure showing 50% probability displacement ellipsoids for non-H atoms.

Experimental

The title compound was synthesized by the reaction of HMBA with excess acetic anhydride (Haces, Breitman & Driscoll, 1987). The product was recrystallized in ether.

Crystal data

C ₁₄ H ₂₄ N ₂ O ₄	Mo $K\alpha$ radiation
$M_r = 284.4$	$\lambda = 0.71073 \text{ \AA}$
Monoclinic	Cell parameters from 20 reflections
$P2_1/n$	$\theta = 6\text{--}10^\circ$
$a = 8.978(2) \text{ \AA}$	$\mu = 0.081 \text{ mm}^{-1}$
$b = 8.689(2) \text{ \AA}$	$T = 295 \text{ K}$
$c = 10.702(2) \text{ \AA}$	Block
$\beta = 106.98(3)^\circ$	