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Ethyl 6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

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Abstract. $C_{23}H_{29}NO_6$, M_r = 415·5, orthorhombic, $Pna2_1$, a = 16·8621 (12), b = 14·6638 (20), c = 8·7087 (6) Å, V = 2153·3 (3) Å^3, Z = 4, D_c = 1·281, D_m = 1·27 (1) Mg m^{-3}. The compound is related to papaverine, a major alkaloid of *Papaver somniferum*. The compound was prepared from the corresponding imine, and crystals containing the racemate were obtained by sublimation. The structure was solved by direct methods and refinement converged to a conventional R of 0·048 for the 271 parameters varied and 1661 reflections used in the refinement. In the hetero ring the average displacement from a calculated best-fit plane is 0·15 Å; for the N atom the displacement is 0·29 Å.

Introduction. The title compound is of interest as an intermediate in the synthesis of the aporphine alkaloid glaucine. The compound was prepared by reduction of the double bond in the corresponding imine using $NaBH_4$ in ethyl alcohol, followed by treatment with ethyl chloroformate (Cava, Stern & Wakisaka, 1973). A specimen measuring 0·31 × 0·40 × 0·49 mm was mounted nearly parallel to the a^* axis. The crystal has systematic absences for reflections $0kl$ ($k + l = 2n + 1$) and $h0l$ ($h = 2n + 1$), consistent with space groups $Pna2_1$ and $Pnam$. An acentric distribution of intensities and the successful structure solution showed the former space group to be correct. ω scans of several intense reflections taken with a small take-off angle and an open detector displayed widths at half-height of less than 0·1°. Cell constants were determined by a least-squares refinement of nine reflections (63 < $|2\theta|$ < 76°) measured with Cu $K\alpha$ radiation [λ(Cu $K\alpha_1$) = 1·54050, λ(Cu $K\alpha_2$) = 1·54433 Å]. The density was obtained from neutral buoyancy in aqueous zinc chloride.

Intensities were measured with a Picker FACS-I automated diffractometer and Ni-filtered Cu radiation (40 kV, 12 mA, take-off angle = 2°) at ambient temperatures. Data were collected using the coupled θ:2θ technique from 0·5 to 120°, with a scan rate of 2° min^{-1} and range of 2·4(1 + 0·4 tan θ)°, and with 10 s background measurements at both extremities of the scan. A total of 1863 reflections were measured and 1611 having $|F_o| > 3\sigma_{(F_o)}$ were used in the structure solution and refinement: $\sigma^2_{(F_o)} = 1/w = (F_o/2I_n)^2\,[I_s + (t_s/t_b)^2 I_b + (0{\cdot}02I_n)^2]$, where I, t, s, n and b refer to intensity (counts), time (s), scan, net and background respectively. Three standard reflections measured after every 50 data reflections showed less than 1%

Table 1. *Final positional parameters and equivalent isotropic thermal parameters*

	x	y	z	B_{eq} (Å^2)†
O(1)	0·0639 (2)	0·0514 (2)	0·2500	5·6
O(2)	−0·0050 (2)	0·1675 (2)	0·3553 (6)	3·9
O(3)	0·1663 (2)	0·5372 (2)	−0·2373 (7)	4·5
O(4)	0·0428 (2)	0·5830 (2)	−0·0800 (6)	3·9
O(5)	−0·2914 (2)	0·1816 (3)	0·3938 (7)	6·0
O(6)	−0·3047 (3)	0·0174 (3)	0·2955 (7)	6·3
N	0·0409 (2)	0·1820 (2)	0·1179 (7)	3·2
C(1)	0·0351 (3)	0·1274 (3)	0·2400 (9)	3·7
C(2)	−0·0820 (3)	0·2540 (3)	0·0162 (8)	3·5
C(3)	−0·0013 (3)	0·2685 (3)	0·0996 (7)	3·0
C(4)	0·0818 (3)	0·1476 (3)	−0·0201 (8)	3·6
C(5)	0·1457 (3)	0·2158 (3)	−0·0684 (8)	3·9
C(6)	0·1144 (3)	0·3122 (3)	−0·0714 (8)	3·2
C(7)	0·1547 (3)	0·3786 (3)	−0·1563 (8)	3·3
C(8)	0·1298 (3)	0·4685 (3)	−0·1579 (8)	3·3
C(9)	0·0626 (3)	0·4928 (3)	−0·0755 (8)	3·0
C(10)	0·0224 (3)	0·4276 (3)	0·0089 (7)	3·1
C(11)	0·0473 (3)	0·3366 (3)	0·0109 (8)	2·9
C(12)	−0·1380 (3)	0·1873 (3)	0·0912 (8)	3·3
C(13)	−0·1867 (3)	0·2164 (3)	0·2094 (8)	3·6
C(14)	−0·2408 (3)	0·1587 (3)	0·2782 (8)	4·0
C(15)	−0·2458 (3)	0·0683 (3)	0·2274 (8)	4·1
C(16)	−0·1963 (3)	0·0385 (3)	0·1133 (8)	4·1
C(17)	−0·1413 (3)	0·0978 (3)	0·0451 (8)	3·8
C(18)	0·2352 (3)	0·5153 (4)	−0·3242 (9)	5·0
C(19)	−0·0269 (3)	0·6098 (3)	−0·0014 (9)	4·8
C(20)	−0·2933 (4)	0·2738 (5)	0·4406 (9)	6·8
C(21)	−0·3226 (3)	−0·0676 (4)	0·2359 (10)	5·2
C(22)	−0·0242 (5)	0·1103 (4)	0·4835 (10)	6·5
C(23)	−0·0777 (5)	0·1586 (5)	0·5851 (9)	7·6

† $B_{eq} = \frac{1}{3}\sum_i \sum_j B_{ij}\, a_i^* a_j^*\, \mathbf{a}_i.\mathbf{a}_j$. E.s.d.'s are 0·2–0·5 Å^2.

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average decrease in intensity. Intensities which were corrected for absorption as a function of φ [linear $\mu = 0{\cdot}675\ \text{mm}^{-1}$; maximum/minimum transmission (calculated) = 1·05, (observed) = 1·06] and for Lorentz–polarization effects in the usual manner, were converted to normalized structure magnitudes.

The structure was solved through use of the direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971). Several E maps generated from 300 reflections with $1{\cdot}3 < |E| < 3{\cdot}6$ contained the complete molecule. The structure was refined by means of a full-matrix least-squares program which minimized the function $\sum w(|F_o| - |F_c|)^2$, utilized anisotropic temperature factors and included a correction for secondary extinction [$g = 5{\cdot}4\,(4) \times 10^{-6}$]. Atomic scattering factors for nonhydrogen atoms were taken from tabulations of Cromer & Waber (1965) and were corrected for real and imaginary anomalous-dispersion effects (Cromer & Liberman, 1970). For H atoms the values of Stewart, Davidson & Simpson (1965) were used. A difference Fourier electron density map contained peaks near all expected H atom positions. H atoms with a calculated C—H separation of 1·0 Å and $B = 4{\cdot}0\ \text{Å}^2$ were included in the model structure and held fixed. Refinement converged to $R = [\sum(|F_o| - |F_c|)/\sum(F_o)] = 0{\cdot}048$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2} = 0{\cdot}059$. The largest shift in the last cycle of refinement was $0{\cdot}1\sigma$ and the maximum peak in the final difference Fourier electron density map was 0·3 e Å^{-3}. Atomic coordinates are listed in Table 1, a stereoview of the molecule is shown in Fig. 1, and Fig. 2 shows bond distances and angles for which e.s.d.'s (*via* the least-squares matrix) are less than 0·006 Å and 0·4° respectively. Torsional angles within the hetero ring are listed in Table 2.*

Table 2. *Selected torsion angles* (*e.s.d.'s* ≤0·6°)

The integers refer to C atom labels as shown in Fig. 2.

3–N–4–5	62·1°	2–3–N–1	−91·6°
N–4–5–6	−47·5	11–3–N–1	146·5
4–5–6–11	21·1	6–11–3–2	−109·1
5–6–11–3	−3·9		
6–11–3–N	13·8		
11–3–N–4	−43·7		

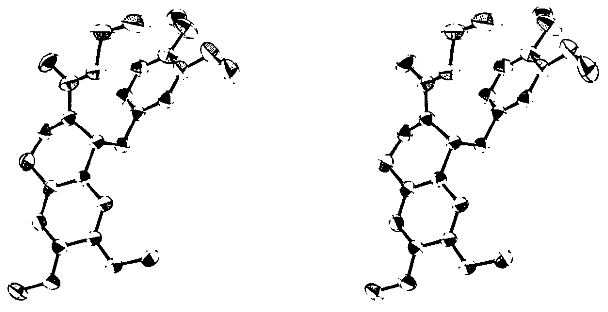

Fig. 1. A stereoview of the $C_{23}H_{29}NO_6$ molecule (*ORTEP*, Johnson, 1965).

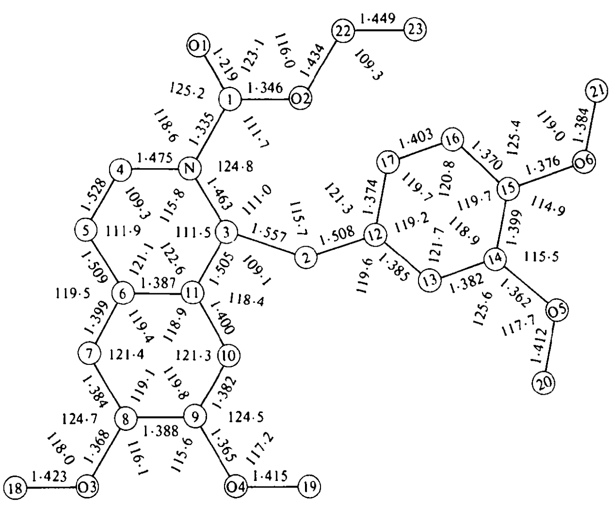

Fig. 2. A schematic representation of the $C_{23}H_{29}NO_6$ molecule containing bond distances (Å) and angles (°).

Discussion. In this structure the molecules are well separated and there are no intermolecular contacts worthy of special mention. Of the two phenyl rings the fused ring (A) is more regular than the benzyl ring (B) as shown by maximum displacements from best-fit planes of 0·004 and 0·02 Å respectively. In addition, the methoxy groups are more nearly coplanar on ring A than B. The dihedral angle between best-fit planes through rings A and B is 28°. The average C—C(ring) distance is 1·388 (21) Å. (E.s.d.'s of average values are calculated from the scatter formula, *viz* $\sigma(\text{ave}) = \{[\sum(m_i - \bar{m})^2]/(i-1)\}^{1/2}$.)

Bond distances and angles in the hetero ring compare well with values reported for other compounds containing a similar ring system (Brown & Trefonas, 1972; Bruderer, Metzger, Brossi & Daly, 1976; Shakked & Kennard, 1977; Wong-Ng & Nyburg, 1979; Brennan, Garafalo & Williams, 1979). The two largest displacements from the best-fit plane are 0·31 and −0·29 Å for the C(4) and N atoms respectively.

The complete set of eight atoms comprising the ethoxycarbonylaminodimethylene group is quite planar with an average displacement from the best-fit plane of 0·06 (5) Å and a maximum of 0·15 Å noted for O(2). Dihedral angles between this plane and rings A and B are 30 and 45° respectively. The relative positions of

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* Lists of structure factors, anisotropic thermal parameters and H atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36051 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

the three planar segments in the molecule result in a rather loosely packed structure consistent with the ease of sublimation of the solid material.

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Structure of (*S*)-*N*-(α-Methylbenzyl)nicotinamide; a Chiral NADH Analog

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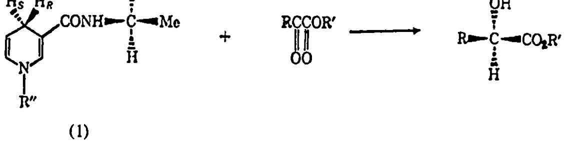
Abstract. $C_{14}H_{14}N_2O$, monoclinic, $C2$, $a = 20{\cdot}651$ (3), $b = 5{\cdot}2276$ (8), $c = 18{\cdot}650$ (3) Å, $\beta = 142{\cdot}70$ (1)°, $Z = 4$, $D_o = 1{\cdot}23$ (1), $D_c = 1{\cdot}23$ Mg m^{-3}. Least-squares refinement (nonhydrogen atoms anisotropic, H atoms isotropic) led to a final unweighted R value (on F; 1392 observed reflections) of 0·038. The carboxamide group is rotated by 34° from the plane of the pyridine ring and oriented such that the carbonyl O atom is directed toward the 4 position of the pyridine ring. The hybridization of the amide N is close to sp^2; the chiral C atom, C(7), is 0·20 Å out of the plane of the carboxamide group. The phenyl group extends toward the B side of the molecule and the methyl group towards the A side. The conformation of the molecule is discussed in relation to studies of stereospecific reduction by models for the reduced pyridine nucleotide, NADH. It is found that the structure leads to predictions of asymmetric induction which are opposite to those experimentally observed.

Introduction. Ohnishi, Kagami & Ohno (1975)* reported the first example of the stereoselective, non-enzymatic reduction of pyruvate esters by a 1,4-dihydronicotinamide; a reaction which mimics that catalyzed by lactate dehydrogenase (Everse & Kaplan, 1973). The reduction was achieved by the use of the chiral dihydronicotinamides (1). It was argued that the stereoselectivity of the reaction was the result of non-bonded, steric interactions between the substrate and the chiral nicotinamide. These interactions favored the approach of the pyruvate ester toward the A side* of the dihydropyridine ring leading to L-lactate as the predominant product.



(1)

(1*a*) $R'' = n$-propyl
(1*b*) R'' = benzyl
(1*c*) R'' = 2,6-dichlorobenzyl

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* For more recent work with chiral nicotinamides see DeVrie & Kellog (1979) and Ohno, Ikeguchi, Kimura & Oka (1979).

* The A side of the nicotinamide ring is the side which faces the viewer when the ring is viewed from a direction perpendicular to the plane of the ring and one travels around the ring in a counter-clockwise direction when taking the shortest path from the ring N atom to the carboxamide group.

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