

**CRYSTAL STRUCTURE OF
5,6,8,12b-TETRAHYDRODIOXOLO[4,5-g]ISOINDOLO[1,2-a]ISOQUINOLIN-8-ONE (C₁₇H₁₃NO₃)**

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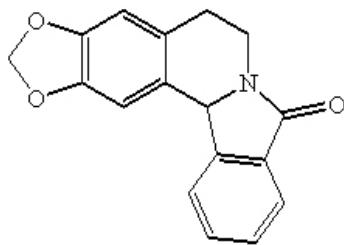
ABSTRACT

The title compound was prepared by cyclization of 2-(3,4-methylenedioxyphenyl)ethyl-3-hydroxyisoindolin-1-one in concentrated hydrochloric acid. The compound crystallizes in the orthorhombic space group *Pca*2₁ (No. 29) with *a* = 27.034(5) Å, *b* = 4.5093(9) Å, *c* = 10.667(2) Å, *V* = 1300.4(4) Å³ and *Z* = 4. The crystal consists of a single enantiomer. The molecule consists of two essentially flat moieties forming an dihedral angle of 116.3(2)°. The crystal structure has intermolecular C-H...O interactions resulting in chains that run along the crystallographic *c*-axis.

Keywords: crystal structure, isoindolo[1,2-*a*]isoquinolin-8-one, X-ray diffraction

INTRODUCTION

Although the isoindolo[1,2-*a*]isoquinoline structure has been known for more than four decades,¹ and its rigid tetracyclic skeleton may be expected to support a wide variety of drug-like compounds, no pharmacological studies have been published on the (unknown) parent substance or its easily accessible 8-oxo derivatives. To fill this gap we have prepared a series of 5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinoline-8-ones substituted with one to three methoxy or a methylenedioxy group, all on ring A. These compounds are generally crystalline solids, and we have selected the 2,3-methylenedioxy analogue 5,6,8,12b-tetrahydrodioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8-one (**1**) for definitive proof of its structure by X-ray crystallography.



1

EXPERIMENTAL

Synthesis

To a solution of phthalic anhydride (5.0 g, 33.7 mmol) in ethanol (50 mL) was added homopiperonylamine (5.6 g, 33.7 mmol). The mixture was stirred at 80 °C for one hour, cooled to room temperature and filtered. The solid product was dissolved in dioxane-methanol (1:1, 80 mL), sodium borohydride (1.2 g, 31.3 mmol) was added in small portions at 0 °C, stirred for 30 minutes and subsequently heated under reflux for 3 hours, concentrated (to 15 mL) and finally diluted with water (150 mL) and filtered. The precipitate was dissolved in 37% hydrochloric acid (50 mL), stirred at reflux temperature for one hour, and diluted with ice-water (100 mL). Crystallization in methanol gave 5,6,8,12b-tetrahydrodioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8-one (2.8 g, overall yield 35%) as colorless, blocky crystals (Scheme 1).

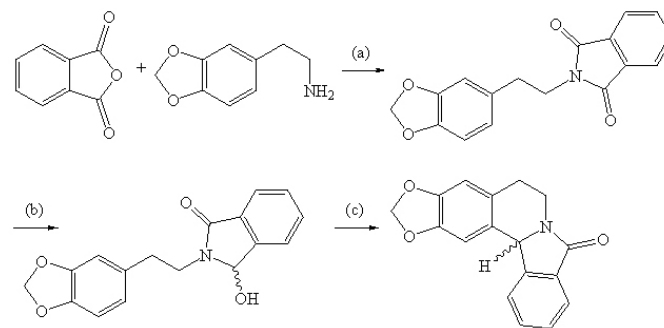
Structure determination

Single-crystal X-ray diffraction data were obtained with the use of graphite monochromatized MoK α radiation ($\lambda = 0.71073$ Å) at 293 K on a Bruker AXS SMART CCD area detector diffractometer. The collection of the intensity data was carried out with the SMART program.² Cell refinement and data reduction were done using SAINT.² The observed Laue symmetry and systematic extinctions clearly pointed to the space group *Pca*2₁ (No. 29). The structure was solved by direct methods and refined on *F*² by full-matrix least-squares. All H atoms were found in difference Fourier maps and refined freely [C-H = 0.94(2)-1.08(2)]. The final cycle of refinement included all anisotropic displacement parameters and converged to a final *R* = 0.0362 and *wR*₂ =

0.0472. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.105 eÅ⁻³ and -0.105 eÅ⁻³. The SHELXL package of crystallographic programs was used to solve and refine the structure.³ Atomic scattering factors were taken from SHELXTL/PC. The molecular graphics used to prepare material for publication were drawn using DIAMOND.⁴

RESULTS AND DISCUSSION

Although the synthetic route used (Scheme 1) can only lead to the racemic compound, the crystal contains a single enantiomer.



Scheme 1. Reagents and conditions: (a) EtOH, 80°C; (b) NaBH₄, MeOH / dioxane (1:1), reflux, 3 h; (c) 37% HCl, reflux, 1 h.

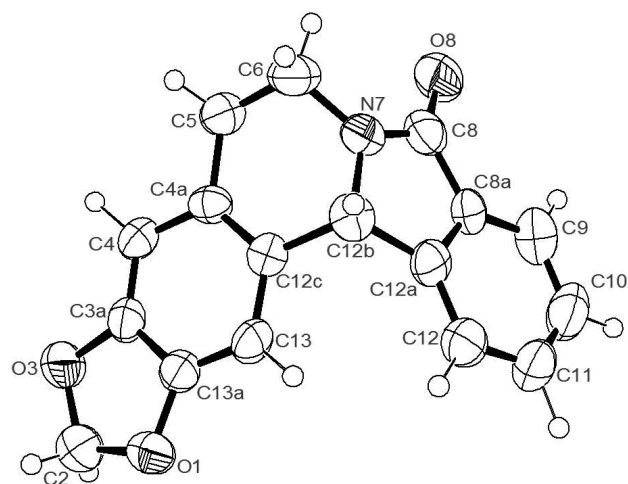


Figure 1: A view of the structure of **1** showing the atom numbering scheme. Ellipsoids are shown at the 50% probability level.

Table 1. Crystal data and structure refinement

Formula; molecular mass	C ₁₇ H ₁₃ NO ₃ ; 279.28
Crystal	white block, 0.2 × 0.09 × 0.3 mm
Space group; Z	Orthorhombic, <i>Pca</i> 2 ₁ (No. 29); 4
Lattice parameters	<i>a</i> = 27.034(5) <i>b</i> = 4.5093(9) Å <i>c</i> = 10.667(2) Å
Volume	1300.4(4) Å ³
F(000)	584
Wavelength, λ (MoKα)	0.71073 Å
Absorption coefficient, μ	0.099 mm ⁻¹
Data Collection	
Diffractometer	Bruker AXS SMART CCD
Scan mode	φ/ω
<i>T</i>	293 K
θ max	25.00 °
θ min	2.43 °
Measured reflections	8584 (<i>R</i> _{int} = 0.0687)
Independent reflections	2264
Reflections with <i>I</i> > 2σ (<i>I</i>)	1287
Refinement	
<i>R</i> _{gt} (<i>F</i>)	0.0362
<i>wR</i> _{ref} (<i>F</i> ²)	0.0472
GooF=S	0.768
Flack's parameter	0.00
parameters	187
Δρ _{max}	0.105 e Å ⁻³
Δρ _{min}	-0.105 e Å ⁻³

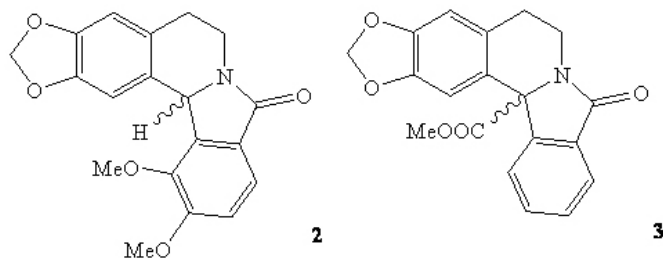
Table 2. Selected geometric parameters: bond lengths [Å], torsion angles and bond angles [°].

O1-C2	1.436(4)	N7-C6-C5	109.3(3)
O8-C8	1.234(4)	C8-N7-C6	124.6(3)
N7-C6	1.447(4)	C13-C13a-C3a	121.5(3)
N7-C12b	1.458(3)	C6-N7-C12b-C12a	170.4(3)
C13-C12c	1.398(4)	C4a-C5-C6-N7	38.7(5)

The crystal data are summarized in Table 1. Selected bond lengths and angles with their estimated standard deviations (esd's) are given in Table 2. A perspective view of the molecular structure with the atom labels is depicted in Figure 1.

The structure of the molecule is essentially angular and shows two main planes. Plane A, defined by N7, C8, C8a, C9, C10, C11, C12, C12a and C12b, has a maximum deviation of 0.0383 Å, where atoms C5 and C6 are displaced by 1.49(5) Å and 0.107(5) from the mean plane, respectively. The plane B, defined by C2, O3, O1, C13a, C3a, C13, C4, C4a and C12c, presents a maximum deviation of 0.0296 Å. The dihedral angle formed with the previous plane is 116.3(2)°.

The X-ray crystal structures of the alkaloid nuevamine (11,12-dimethoxy-5,6,8,12b-tetrahydrodioxolo[4,5-g]isoindolo[1,2-*a*]isoquinolin-8-one) (**2**) and the synthetic intermediate 12b-methoxycarbonyl-5,6,8,12b-tetrahydrodioxolo[4,5-g]isoindolo[1,2-*a*]isoquinolin-8-one (**3**) have been reported quite recently.⁵

**Figure 2:** Structures of nuevamine (**2**) and 12b-methoxycarbonyl-5,6,8,12b-tetrahydrodioxolo[4,5-g]isoindolo[1,2-*a*]isoquinolin-8-one (**3**).

In view of the fact that the crystal of **1** studied here contained a single enantiomer, it is of interest to note that synthetic racemic nuevamine (**2**) was resolved spontaneously by recrystallization.⁵ The C8-N7-C6 bond angle [124.6(3)°] in **5,6,8,12b-tetrahydrodioxolo[4,5-g]isoindolo[1,2-*a*]isoquinolin-8-one (**1**)** is very similar to the corresponding angles in **2** and **3**, 123.53(15)° and 122.85(13)°, respectively. The C6-N7-C12b-C12a torsion angle [170.4(3)°] in **1** and the corresponding torsion angle in **3** [172.30(14)°] are also similar. However, the geometry at N7 [C8-N7-C6-C5 = 100.3(4)°] in **1** is quite different in **3** [169.95(15)°], as in **1** the conformation of the tetrahydropyridine ring is a half-chair, while in **3** it is a half-boat. All the other relevant structural parameters (bond distances and angles) are as expected and in acceptable agreement with the recently described analogues.

The crystal packing results in intermolecular C2-H2β...O8 interactions (Fig. 3 and Table 3), with H-acceptor distances which are less than the sum of the van der Waals radii. These interactions result in chains that run along the crystallographic *c*-axis.

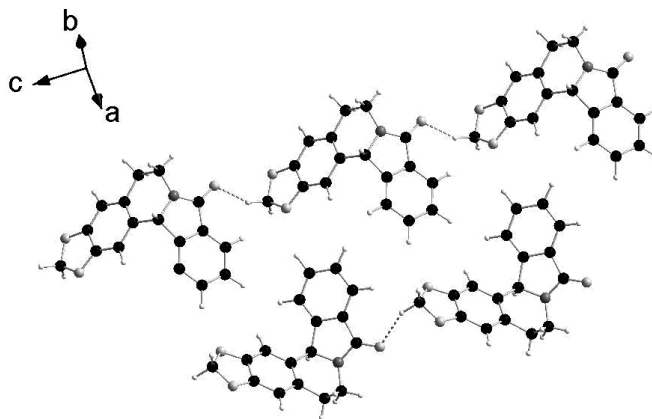
**Figure 3:** Crystal packing showing the intermolecular C2-H2β...O8 interaction.

Table 3. Intermolecular contacts (Å, °)

D-H...A	d(D-H)	d(H...A)	d(D...A)	< DHA
C(2)-H(2β)...O(8)*	0.99(3)	2.42(3)	3.383(5)	162(2)

*Symmetry code: $x, y, z+1$ **ACKNOWLEDGMENTS**

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Supplementary Information: Crystallographic data (excluding structure factors) for the structural analysis have been deposited in the Cambridge Crystallographic Data Centre, CCDC 717800. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre; Postal Address: CCDC, 12 Union Road, Cambridge CB21EZ, UK, Telephone: (44) 01223 762910, Fax: (44) 01223 336033, e-mail: deposit@ccdc.cam.ac.uk).

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