# Synthesis, crystal and molecular structure of *N*-(*p*-chlorobenzylamide) of $\alpha$ -(1,1-ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid

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*N*-(*p*-chlorobenzylamide) derivative of  $\alpha$ -(1,1-ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid has been synthesized and the its crystal structure was solved. The dioxolane ring adopts a half-chair conformation, with asymmetry parameter  $\Delta C_2(13) = 5.4^\circ$ . Deformation of the amide group is caused mainly by twist around the C4–N bond.

#### Introduction

Gamma hydroxybutyric acid (GHB) is a well known central nervous system (CNS) depressant; it was introduced into clinics in the 60s as a general anaesthetic (sodium oxybate, Somsanit R). GHB, which is one of the metabolites of  $\gamma$ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the mammalian CNS (Roberts et al., 1976), is present in the mammalian brian. It was recently suggested that it played a role as a neurotransmitter in the central nervous system (Charlier et al., 1988). Extensive structure-activity studies, conformational flexibility and electronic factors of GABA and a number of structurally related compounds have been discussed (Krogsgaard-Larsen, 1989; Pooler and Steward, 1988). Recently we have prepared (Malec et al., 1990) some N-substituted amides of  $\alpha$ -ethylenedioxyethyl- $\gamma$ -hydroxybutyric acid, which were given preliminary pharmacological testing for their central nervous system (CNS) activity. We have presently synthesized a new N-substituted amide of an  $\alpha$ -ethylenedioxyethyl GHB derivative with a 4-chlorobenzylamine residue in the *N*-position. *N*-(*p*-chlorobenzylamide) of  $\alpha$ -(1,1-ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid (I) displayed anticonvulsive properties in pentetrazole induced convulsions, and showed some activity in the hot-plate test; a similar action was found for GHB (Malec *et al.*, 1990). In the course of our investigation concerning the structure-activity relationship of GHB derivatives, we present here the crystal and molecular structure of the amide (I).

# **Experimental**

The amide (I) was obtained by the aminolysis of 2oxo-3(1',1'-ethylenedioxy)ethyltetrahydrofuran (Scheme 1). The purity and homogenity of the amide (I) was investigated by thin-layer chromatography (TLC), and the structure was confirmed by elemental and physicochemical analyses. In the MS spectra the peak of molecular ion was not detected; however, the strong peak at m/z 87(100%) is characteristic of the dioxolane ring. The IR spectra confirm the presence of the carbonyl group at 1640 cm<sup>-1</sup>, and show the absorptions of the N-H and O-H groups at 3400-3230 cm<sup>-1</sup> and 3580-3440 cm<sup>-1</sup>. In <sup>1</sup>H NMR spectra, the signal of the protons appears at about 4.41 ppm, indicating the presence of the benzyl group; the signals of the protons ethylenodioxy group occurs at 3.47 and 3.70 ppm, and

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are in agreement with the structure. TLC was performed with silica gel GF<sub>254</sub> precoated TLC plates (5 × 10 cm, 0.25 mm), using: solvent (1) chloroform : acetone (1:1) and solvent(2) benzene : acetone : methanol (1:1:1) as a developing system. The melting point was determined with a Boetius Micro melting point apparatus (VEB Analytic Dresden). Infrared Spectra were taken on a Specord 71 IR (VEB Carl Zeiss, Jena) using KBr disks (1:300 mg KBr). <sup>1</sup>H NMR spectra were recorded on a Brucker spectrometer at 250 MHz using TMS as internal standard. UV spectra was taken on a Specord UV-VIS (VEB Carl Zeiss, Jena) in methanol solutions. The mass spectra were obtained on a GCMS 2091 LKB mass spectrometer operating at ionising energy of 70 eV.

# *N*-(*p*-chlorobenzyl)amide derivative of $\alpha$ -(1,1ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid (I)

A mixture of 5.1 g (0.03 mol) 2-oxo-3-(1',1'-ethylenedioxy)-ethyltetrahydrofuran in toluene (30 ml) and 4.3 g (0.03 mol) 4-chlorobenzylamine was heated under reflux for 12 h. After removal of the solvent the oily residue was cooled. The crude product 3.8 g (yield 41%) was filtered, crystallized from ethyl acetate and cyclohexane (1:1), and recrystallized from ethyl acetate (m.p. 90–91°C).

Analysis: Calculated for  $C_{15}H_{20}NO_4Cl$  (313.8): C = 57.41 H = 6.42 N = 4.46, Found: C = 57.40 H = 6.52 N = 4.08. TLC:  $R_f = 0.46$  (solvent  $S_1$ ),  $R_f = 0.83$  (solvent  $S_2$ ) MS, m/z: 83.8(9.73%), 87.1(100), 89.3(11.11), 105.3(8.20), 115.3(9.90), 125.3(38.97), 127.2(14.74), 140.2(26.91), 251.3(21.74), 253.3(7.34), 269.1(3.06). IR [cm<sup>-1</sup>]: 3440-3580 (O-H), 3400-3230 (N-H), 1640 (C=O). UV  $\lambda$ max [nm]: 201.6, 219.3, lg $\epsilon$ : 4.14, 4. <sup>1</sup>H NMR: 1.31 (m), CH<sub>3</sub> (C15), 1.95 (m), 2.24 (s), CH<sub>2</sub> (C2), 2.75 (m) CH(C3), 3.47 (s), 3.70 (m) -CH<sub>2</sub>CH<sub>2</sub>- (C13, C14), 3.97 (m) CH<sub>2</sub>/CH(C1), OH(O1), 4.41 (m) CH<sub>2</sub> (C5), 7.28 (m)-C<sub>6</sub>H<sub>4</sub> (C7, 8, 10, 11/NH).

#### X-ray determination

A crystal with approximate dimensions of 0.3, 0.2, 0.25 mm, obtained by slow evaporation of an ethyl acetate solution, was used for data collection. Accurate unitcell dimensions were obtained by the least-squares fit to the  $\theta$  values of 25 reflections measured on the Enraf-Nonius CAD 4 diffractometer. The intensity data were collected using graphite-monochromated Cu  $K\alpha$  radiation and the  $\omega$ -2 $\theta$  scan technique. The measured intensities were corrected for Lorentz and polarization effects, but not for absorption. Crystal and experimental details are listed in Table 1.

## Solution and refinement

The 2843 reflections with  $I > 4\sigma(I)$  were used in the subsequent analysis.

The structure was solved by direct methods, using

Table 1. Crystal data and experimental parameters

Formula	C <sub>15</sub> H <sub>20</sub> NO <sub>4</sub> Cl
M <sub>r</sub>	313.780
a/Å	11.813(1)
b/Å	11.433(1)
c/Å	12.053(1)
β/deg	100.38(1)
$V_e/\text{\AA}^3$	1601.2(2)
Z	4
F(000)	664
$\mu(Cu K\alpha)/cm^{-1}$	22.6
Space group	$P2_1/c$
$D_x/Mg m^{-3}$	1.302(3)
$D_m/{\rm Mg}~{\rm m}^{-3}$	1.30(2)
Radiation	Cu Kα
Scan mode	$\omega - 2\theta$
$\theta$ range	1 – 75°
Reflections with $I \ge 4\sigma(I)$	2843
R	0.049
$R_{W}$	0.059

the SHELXS 86 program (Sheldrick *et al.*, 1985) and refined by the full-matrix least-squares method. The function  $\Sigma w(|F_o| - |F_c|)^2$  was minimized, and in the final cycles of refinement a weighting scheme based on counting statistics was used with  $w = [\sigma^2(F_o) + 0.00001(F_o)^2]^{-1}$ . An empirical isotropic extinction correction was introduced, and the parameter x was refined to the value 0.020(1).

During the refinement of the nonhydrogen atoms with anisotropic thermal parameters, the hydrogen atom contributions (with exception of the hydroxyl and methyl hydrogens) were included in the structure factors after calculation of their positions on the basis of idealized geometry; the positions of the hydroxyl and methyl hydrogens were found from a difference map. H atoms were refined in the riding mode. Refinement was terminated when the maximum shift in any parameter was less than  $0.1\sigma$ . The final difference Fourier map showed no peaks higher than  $0.16 \text{ e} \text{Å}^{-3}$ . Convergence was obtained at R = 0.049 and  $R_w = 0.059$ .

Most of the computations were performed with SHELX-76 crystal structure determination program (Sheldrick, 1976) on an AMSTRAD 1512 personal computer.

Tables 2, 3, and 4 list the final atomic positional and thermal parameters.

**Table 2.** Positional parameters  $(\times 10^4)$  for the nonhydrogen atoms

	x	у	z
CI	4845(1)	366(1)	7736(1)
Ν	9695(1)	3373(1)	9375(1)
<b>O</b> (1)	10246(2)	-529(1)	7702(1)
O(2)	10148(1)	1957(1)	10657(1)
O(3)	12542(1)	3784(1)	10171(1)
O(4)	13413(1)	2282(1)	9411(2)
C(1)	10279(3)	665(2)	8038(2)
C(2)	11322(2)	910(1)	8940(2)
C(3)	11377(1)	2203(1)	9279(1)
C(4)	10362(1)	2503(1)	9836(1)
C(5)	8622(2)	3664(2)	9754(2)
C(6)	7660(2)	2842(2)	9267(1)
C(7)	7146(2)	2936(2)	8144(2)
C(8)	6284(2)	2177(2)	7670(2)
C(9)	5932(2)	1322(2)	8325(2)
C(10)	6408(2)	1210(2)	9450(2)
C(11)	7278(2)	1975(2)	9907(2)
C(12)	12518(2)	2543(2)	10024(2)
C(13)	14042(2)	3295(2)	9304(2)
C(14)	13239(2)	4265(2)	9440(3)
C(15)	12767(2)	1986(2)	11182(2)

#### Discussion

The structure of *N*-(*p*-chlorobenzyl)amide of (1,1ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid (I) is very similar to that of the *N*-(*p*-methoxybenzyl)amide of  $\alpha$ -(1,1-ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid (II) (Malawska *et al.*, 1990). A view of molecule I and the numbering of the atoms are given in Fig. 1. Selected bond lengths and angles are listed in Table 5.



Scheme 3

Differences between all corresponding bond lengths in molecules I and II are contained in the range  $4\sigma$ . The dioxolan ring is in a half-chair conformation, and deformed similarly to molecule **II**. The asymmetry parameters (Duax and Norton, 1975) in relation to the twofold axis  $\Delta C_2(C12)$  equals 5.4° in this molecule and 4.2° in molecule II. Similarly as in molecule II, a shortening of the C14-O3 and C13-O4 bonds (1.418(3), 1.391(3) Å), and much shorter C13-C14 bond (1.488(3) Å) is observed. These atoms, and the outer atoms O1, C1, O2, Cl, exhibit relatively high thermal motions resulting from the lack of strong intermolecular interactions (Fig. 2). In spite of the existence of electronegative atoms and the groups NH and OH, no hydrogen bonds are found. Also, the deformation of the amide group indicates that the deviations from planarity of the six atoms C3, C4, O2, N, H2, C5 are caused mainly by a twist around the C4–N bond ( $\chi_{\rm C} = 1.5^{\circ}, \chi_{\rm N} = 1^{\circ}$ ,  $\tau = 6^{\circ}$ ; Dunitz, 1976). The chlorophenyl ring and the dioxolan ring are situated on the opposite side of the amide group plane, and the dihedral angles between

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	$U_{11}$	U <sub>22</sub>	U <sub>33</sub>	<i>U</i> <sub>23</sub>	$U_{13}$	$U_{12}$
CI	72(0)	94(0)	132(1)	-26(0)	2(0)	-5(0)
Ν	58(1)	45(1)	59(1)	2(1)	15(1)	9(1)
O(1)	191(2)	59(1)	52(1)	-15(1)	34(1)	-43(1)
O(2)	89(1)	75(1)	64(1)	25(1)	26(1)	8(1)
O(3)	66(1)	48(1)	109(1)	-23(1)	32(1)	0(1)
O(4)	66(1)	69(1)	129(1)	-27(1)	34(1)	13(1)
C(1)	129(2)	54(1)	56(1)	-3(1)	0(1)	-19(1)
C(2)	88(1)	40(1)	58(1)	-4(1)	12(1)	5(1)
C(3)	60(1)	39(1)	50(1)	0(1)	10(1)	7(1)
C(4)	59(1)	42(1)	45(1)	2(1)	9(1)	1(1)
C(5)	63(1)	60(1)	73(1)	-12(1)	20(1)	11(1)
C(6)	54(1)	58(1)	58(1)	-4(1)	15(1)	15(1)
C(7)	75(1)	84(1)	62(1)	10(1)	12(1)	0(1)
C(8)	75(1)	97(2)	62(1)	4(1)	5(1)	3(1)
C(9)	56(1)	67(1)	81(1)	-9(1)	10(1)	12(1)
C(10)	73(1)	72(1)	79(1)	10(1)	18(1)	4(1)
C(11)	68(1)	77(1)	56(1)	4(1)	13(1)	9(1)
C(12)	59(1)	45(1)	76(1)	-11(1)	12(1)	10(1)
C(13)	71(1)	85(1)	105(2)	-11(1)	32(1)	5(1)
C(14)	82(2)	63(1)	133(2)	-3(1)	45(2)	-1(1)
C(15)	89(2)	89(2)	75(1)	-1(1)	-17(1)	13(1)

**Table 3.** Anisotropic temperature factors ( $\mathring{A}^2 \times 10^3$ )

Table 4. Hydrogen atom positional parameters ( $\times 10^4)$  with isotropic temperature factors (Å  $\times 10^2)$ 

	x	у	z	U
H(1)	9978	-884	8225	15(1)
H(2)	9954	3881	8707	10(1)
H(11)	9509	865	8365	11(1)
H(12)	10316	1211	7312	10(1)
H(21)	11273	382	9674	7(1)
H(22)	12092	685	8620	10(1)
H(31)	11294	2712	8514	6(1)
H(51)	8378	4547	9491	10(1)
H(52)	8758	3611	10662	9(1)
H(71)	7423	3615	7629	10(1)
H(81)	5890	2259	6792	12(1)
H(101)	6110	544	9966	10(1)
H(111)	7667	1890	10787	9(1)
H(131)	14802	3332	9951	16(1)
H(132)	14288	3333	8483	15(1)
H(141)	12724	4506	8638	14(1)
H(142)	13704	5023	9815	12(1)
H(151)	12825	1050	11093	13(1)
H(152)	13573	2318	11643	13(1)
H(153)	12083	2193	11636	13(1)



Fig. 1. Molecular structure of (I) with the atom labeling scheme.

Table 5. Bond lengths/Å and bond angles/deg

ClC(9)	1.738(3)	NC(4)	1.327(2)
NC(5)	1.461(3)	O(1)C(1)	1.422(3)
O(2)C(4)	1.234(2)	O(3)C(12)	1.429(3)
O(3)C(14)	1.421(3)	O(4)C(12)	1.426(3)
O(4)C(13)	1.395(3)	C(1)C(2)	1.515(4)
C(2)C(3)	1.532(2)	C(3)C(4)	1.515(2)
C(3)C(12)	1.529(2)	C(5)C(6)	1.510(3)
C(6)C(7)	1.384(3)	C(6)C(11)	1.381(3)
C(7)C(8)	1.381(3)	C(8)C(9)	1.368(3)
C(9)C(10)	1.377(3)	C(10)C(11)	1.386(3)
C(12)C(15)	1.514(3)	C(13)C(14)	1.488(3)
C(5) = N = C(4)	121.5(1)	C(14) - O(3) - C(12)	107.9(2)
C(13) = O(4) = C(12)	109.3(2)	C(2) - C(1) - O(1)	111.0(2)
C(3) = C(2) = C(1)	111.1(2)	C(4) - C(3) - C(2)	109.7(1)
C(12) - C(3) - C(2)	113.1(1)	C(12) - C(3) - C(4)	111.5(1)
O(2) - C(4) - N	121.5(1)	C(3) - C(4) - N	116.2(1)
C(3) - C(4) - O(2)	122.2(1)	C(6) - C(5) - N	111.8(2)
C(7) - C(6) - C(5)	119.9(2)	C(11) - C(6) - C(5)	121.9(2)
C(11) - C(6) - C(7)	118.2(2)	C(8) - C(7) - C(6)	121.1(2)
C(9) - C(8) - C(7)	119.2(2)	C(8) - C(9) - Cl	119.5(2)
C(10) - C(9) - Cl	119.0(2)	C(10) - C(9) - C(8)	121.5(2)
C(11) - C(10) - C(9)	118.3(2)	C(10) - C(11) - C(6)	121.6(2)
O(3) - C(12) - O(4)	105.8(2)	C(3) - C(12) - O(4)	107.4(2)
C(3) - C(12) - O(3)	108.7(2)	C(15) - C(12) - O(4)	110.5(2)
C(15) - C(12) - O(3)	107.9(2)	C(15) - C(12) - C(3)	116.0(2)
C(14) - C(13) - O(4)	104.4(2)	C(13) - C(14) - O(3)	103.4(2)



Fig. 2. Packing of the molecules in the unit cell.

them and the amide group are  $77^{\circ}$  and  $44^{\circ}$ , respectively.

The location of the phenyl ring relative to the amide group is very different from that in structure **II**. The dihedral angle between their best planes is, in the case of the methoxybenzyl derivative, considerably larger and equal  $104.8(1)^{\circ}$ . An extended conformation of the 01-C1-C2-C3-C12 chain is observed  $[01-C1-C2-C3 = 178.4(2), C1-C2-C3-C12 = 169.6(2)^{\circ}].$ 

The conformation of the molecule can be described by torsion angles (Table 6). The orientation of the dioxolan ring relative to the extended chain and the amide group is described by the torsion angles about C3-C12.

Table 6. Torsion angles/deg describing the conformation about C3-C12, C3-C4, and C5-C6 bonds

C2-C3-C12-O4	58.5(2)	C2-C3-C4-O2	54.8(2)
H31-C3-C12-O4	-60	C12-C3-C4-O2	-71.4(2)
H31-C3-C12-O3	54	C12-C3-C4-N	110.1(1)
C4-C3-C12-O3	-63.2(2)	H31-C3-C4-N	-7
C4-C3-C12-C15	58.6(2)	C2-C3-C4-N	-123.7(1)
C2-C3-C12-C15	-65.7(2)		
N-C5-C6-C7	-74.1(2)		
N-C5-C6-C11	105.0(2)		
H51-C5-C6-C11	-134		
H51-C5-C6-C7	46		
H52-C5-C6-C11	-15		
H52-C5-C6-C7	165		

A typical staggered conformation is observed. The mutual location of this chain and the amide fragment is presented by the torsion angles about C3-C4. The torsion angle H31-C3-C4-N of  $-7^{\circ}$  indicates screening of the H31 and N atoms. The conformation of the chlorophenyl ring indicates different screening of the atoms H51 and H52 by atoms C11 and C7. The molecular packing in the unit cell is given in Fig. 2. There are no shortened intermolecular contacts less than the sums of van der Waals' radii.

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Structure factor data have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 60766 (18 pages).