

# Synthesis and crystal and molecular structure of new *N*-substituted $\gamma$ -hydroxybutyramides

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The *N*-(2-phenylethyl)amide of  $\alpha$ -(1',1'-ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid (**II**) and the *N*-(*p*-methoxybenzyl)amide of  $\alpha$ -(1',1'-ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid (**III**) have been synthesized and the crystal structure of **III** has been solved. Compound **III**, C<sub>16</sub>H<sub>23</sub>O<sub>5</sub>N, crystallizes in the monoclinic space group *P*2<sub>1</sub>/*c* with *a* = 12.572(2), *b* = 11.149(2), *c* = 12.317(2) Å and  $\beta$  = 106.53(1)°. The structure was solved by direct methods, and refined by full-matrix least squares to give *R* = 0.040 (*R*<sub>w</sub> = 0.047) for 2004 intensities. The dioxolane ring has a deformed half-chair conformation.

## Introduction

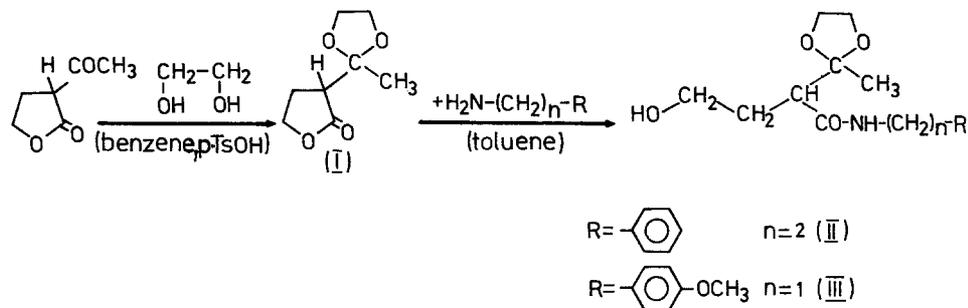
Our interest in central nervous system (CNS) active compounds led us to study  $\gamma$ -hydroxybutyric acid derivatives.  $\gamma$ -Hydroxybutyric acid is a commonly known CNS depressant; it is also one of the metabolites of 4-aminobutyric acid (GABA), the major inhibitory neurotransmitter (Roberts *et al.*, 1976; Snead and Nichols, 1987). Recently, we have prepared some *N*-substituted amides of  $\gamma$ -hydroxybutyric acid. In preliminary pharmacological tests these compounds displayed anticonvulsive properties in pentetrazole induced convulsions (Malawska *et al.*, 1988). Consequently, in order to understand the influence of structural parameters, e.g., the distance between two active centers in the molecule (hydroxyl and amide group) and the conformational mobility of the entire molecule (Krogsgaard-Larsen *et al.*, 1985) on pharmacological properties, we have tried now to examine the crystal structure of above mentioned amides.

## Experimental

*N*-Substituted amides of  $\gamma$ -hydroxybutyric acid were prepared starting from  $\alpha$ -acetylbutyrolactone, in which the acetyl grouping was converted to ethylene ketal derivative (**I**). Aminolysis of **I** with 2-phenylethylamine and 4-methoxybenzylamine in toluene gave the  $\alpha$ -[1'1'-(ethylenedioxy)]-ethyl- $\gamma$ -hydroxybutyramides **II** and **III**, respectively, in good yields (scheme of reaction). In the mass spectra, ion-molecular masses had low intensities but were consistent with theoretical values. The ion at *m/e* 87 (100%) is characteristic of the ethylenedioxy ring at the  $\alpha$ -position. The IR analysis confirmed the presence of the C=O group at 1630 cm<sup>-1</sup> (compound **II**) and 1650 cm<sup>-1</sup> (comp. **III**), with absorption bands at 3260 (**II**) and 3220, 3320 cm<sup>-1</sup> (**III**) to NH and OH groups. Thin-layer chromatography was performed on silica gel GF<sub>254</sub> precoated plates (5 × 10 cm; 0.25 mm) using S<sub>1</sub>: chloroform-acetone (1:1), S<sub>2</sub>: benzene-acetone-methanol (1:1:1) as developing systems. IR spectra were taken on a Specord 80 IR VEB Carl Zeiss Jena spectrophotometer in KBr pellets (concentration 1:300 mg KBr). UV spectra were taken on a Specord UV VIS VEB Carl Zeiss Jena spectrophotometer in methanol solutions *c* = 1.10<sup>-4</sup> mole/liter. The mass spectra were obtained on a GCMS 2091 LKB mass spectrometer operating at ionising energy of 70 eV.

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Scheme 1.

### 2-Oxo-3(1',1'-ethylenedioxy) ethyltetrahydrofuran (I)

To a solution of 33 ml (0.3 mol) of  $\alpha$ -acetylbutyrolactone in anhydrous benzene (150 ml), 20 ml (0.36 mol) of ethylene glycol and 10 mg of *p*-toluene sulfonic acid were added. The mixture was refluxed for several hours and the water was removed azeotropically. The benzene solution was washed with saturated sodium bicarbonate solution and dried over anhydrous sodium carbonate. The solvent was evaporated and the oily residue distilled under reduced pressure, yielding 34.5 g (67%) of I.  $\text{C}_8\text{H}_{12}\text{O}_4$  (172.2) calculated: C-55.8, H-7.02; found: C-55.68, H-7.07.

### *N*-(2-phenylethyl)amide of $\alpha$ -(1',1'-ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid (II)

A mixture of 5.1 g (0.03 mol) compound I in toluene (30 ml) and 3.6 g (0.03 mol) 2-phenylethylamine was heated under reflux for 12 h. After removal of the solvent, the oily residue was cooled. The crude product 4.6 g (yield 52.3%) was filtered and recrystallized from ethyl acetate and cyclohexane m.p. 94.6°C; TLC  $R_f = 0.50$  (solvent  $S_1$ ),  $R_f = 0.86$  (solvent  $S_2$ );  $\text{C}_{16}\text{H}_{23}\text{NO}_4$  (293.4) calculated: C-65.49, H-7.90, N-4.77; found: C-66.08, H-8.07, N-4.80; IR [ $\text{cm}^{-1}$ ]: 3260 (NH + OH), 1630 (C=O); UV  $\lambda_{\text{max}}$  [nm]: 204.5, 215.1;  $\lg\epsilon$ : 4.14, 3.83; MS ( $m/e$ ): 293(2.4), 249(3.5), 232(7.3), 231(25.2), 202(4.1), 173(8.5), 140(10.8), 129(3.3), 127(9.2), 111(7.8), 104(5.8), 88(5.3), 87(100), 43(8.2), 30(9.6).

### *N*-(*p*-methoxybenzyl)amide of $\alpha$ -(1',1'-ethylenedioxy)-ethyl- $\gamma$ -hydroxybutyric acid (III)

Compound III was obtained in a similar way to amide II; m.p. 100–102°C, yield 43.3%;  $\text{C}_{16}\text{H}_{23}\text{NO}_5$  (309.4) calculated: C-62.11, H-7.49, N-4.52; found:

C-62.08, H-7.11, N-4.89; TLC:  $R_f = 0.46$  (solvent  $S_1$ ),  $R_f = 0.86$  (solvent  $S_2$ ); IR [ $\text{cm}^{-1}$ ]: 3320(OH), 3220(NH), 1650(C=O); UV  $\lambda_{\text{max}}$  [nm]: 201, 223.7, 274.7, 282.5,  $\lg\epsilon$ : 4.23, 4.14, 3.26, 3.21; MS ( $m/e$ ): 309(4.3), 247(31.8), 219(38), 176(7.7), 162(5.1), 136(55.9), 121(70.8), 115(13.1), 87(100);

### X-ray determination

Crystals suitable for X-ray investigation were obtained by crystallization of an ethyl acetate solution. The cell parameters and intensities were measured on a Enraf-Nonius CAD 4 diffractometer. The crystals are monoclinic. Accurate cell parameters were determined from a least-squares refinement of the  $(\sin \theta/\lambda)^2$  values for 25 reflections. The intensity data were collected using graphite-monochromated Mo  $K\alpha$  radiation and the  $\omega$ - $2\theta$  scan technique. The measured intensities were corrected for Lorentz and polarization effects, but not for absorption. Crystal data and experimental details are listed in Table 1.

### Solution and refinement of the structure

The 2004 reflections with  $I > 4\sigma(I)$  were used in the subsequent analysis. The structure was solved by direct methods, using the SHELXS-86 program (Sheldrick *et al.*, 1985), and refined by full-matrix least squares. All nonhydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were located from a difference Fourier map, and their positional and individual isotropic thermal parameters were refined. The function  $\Sigma w(|F_o| - |F_c|)^2$  was minimized, and in the final cycles of calculation a weighting scheme based on counting statistics was used;  $w = [\sigma^2(F_o) + 0.0003(F_o)^2]^{-1}$ . An empirical isotropic extinction correction was introduced, and the parameter  $x$  was refined to the value 0.0049(7). Refinement was terminated when the maximum shift in any parameter was  $< 0.1\sigma$ . The

**Table 1.** Crystal data and experimental parameters

Molecular formula	C <sub>16</sub> H <sub>23</sub> O <sub>5</sub> N
<i>M<sub>r</sub></i>	309.36
Space group	<i>P</i> 2 <sub>1</sub> / <i>c</i>
<i>a</i> /Å	12.572(2)
<i>b</i> /Å	11.149(2)
<i>c</i> /Å	12.317(2)
$\beta$ /deg	106.53(1)
<i>V</i> /Å <sup>3</sup>	1655.1(5)
<i>Z</i>	4
<i>F</i> (000)	664
<i>D<sub>x</sub></i> /mg m <sup>-3</sup>	1.240(3)
<i>D<sub>m</sub></i> /mg m <sup>-3</sup>	1.23(2)
$\mu$ (Mo <i>K</i> $\alpha$ )/mm <sup>-1</sup>	0.09
Radiation	Mo <i>K</i> $\alpha$
Scan mode	$\omega - 2\theta$
Crystal size/mm (sphere)	<i>r</i> = 0.35
$2\theta$ range	0–50°
Reflections measured	2794
Reflections with <i>I</i> > 4 $\sigma$ ( <i>I</i> )	2004
<i>R</i>	0.040
<i>R<sub>w</sub></i>	0.047

final difference Fourier map did not show any peaks higher than 0.12 e Å<sup>-3</sup>. Tables 2, 3, and 4 list the final atomic positional and thermal parameters. Most of the computations were performed with SHELX-76 crystal

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

	<i>x</i>	<i>y</i>	<i>z</i>
C(1)	10371(3)	4437(2)	3124(2)
C(2)	11393(2)	4153(2)	4064(2)
C(3)	11457(2)	2817(2)	4369(2)
C(4)	10530(2)	2501(2)	4880(2)
C(5)	8842(2)	1347(3)	4682(2)
C(6)	7885(2)	2158(2)	4132(2)
C(7)	7312(2)	2778(3)	4739(2)
C(8)	6407(2)	3501(3)	4231(2)
C(9)	6076(2)	3621(2)	3085(2)
C(10)	6642(2)	3022(3)	2459(2)
C(11)	7535(2)	2298(3)	2967(2)
C(12)	4509(3)	4850(4)	3053(5)
C(13)	12591(2)	2423(2)	5138(2)
C(14)	13944(3)	1557(3)	4464(4)
C(15)	13180(3)	623(3)	4612(4)
C(16)	12949(3)	3000(3)	6292(3)
O(1)	10333(2)	5684(2)	2822(2)
O(2)	10420(2)	3028(2)	5718(1)
O(3)	5209(1)	4315(2)	2477(2)
O(4)	13393(1)	2647(2)	4541(2)
O(5)	12581(1)	1162(1)	5294(2)
N(1)	9845(1)	1644(2)	4365(2)

**Table 3.** Anisotropic thermal parameters ( $\times 10^3$ ) for the nonhydrogen atoms

	<i>U</i> <sub>11</sub>	<i>U</i> <sub>22</sub>	<i>U</i> <sub>33</sub>	<i>U</i> <sub>23</sub>	<i>U</i> <sub>13</sub>	<i>U</i> <sub>12</sub>
C(1)	97(2)	63(2)	62(2)	10(1)	14(1)	17(1)
C(2)	67(1)	49(1)	65(1)	7(1)	19(1)	-2(1)
C(3)	52(1)	45(1)	53(1)	-2(1)	14(1)	-6(1)
C(4)	52(1)	48(1)	48(1)	1(1)	11(1)	1(1)
C(5)	55(1)	69(2)	69(2)	18(1)	17(1)	-9(1)
C(6)	49(1)	58(1)	52(1)	3(1)	18(1)	-14(1)
C(7)	76(2)	93(2)	53(1)	-1(1)	26(1)	-8(1)
C(8)	75(2)	88(2)	73(2)	-13(1)	32(1)	5(1)
C(9)	51(1)	58(1)	77(2)	-2(1)	19(1)	-5(1)
C(10)	74(2)	105(2)	53(1)	1(1)	14(1)	21(1)
C(11)	71(2)	94(2)	53(1)	-1(1)	20(1)	19(1)
C(12)	77(2)	95(3)	157(4)	-5(3)	43(3)	18(2)
C(13)	52(1)	50(1)	77(1)	10(1)	15(1)	-9(1)
C(14)	82(2)	98(2)	112(3)	18(2)	43(2)	20(2)
C(15)	101(2)	73(2)	151(4)	0(2)	54(3)	7(2)
C(16)	77(2)	87(2)	83(2)	3(2)	-9(2)	-6(2)
O(1)	125(2)	73(1)	68(1)	24(1)	43(1)	32(1)
O(2)	87(1)	88(1)	69(1)	-26(1)	35(1)	-10(1)
O(3)	66(1)	90(1)	109(1)	7(1)	23(1)	17(1)
O(4)	58(1)	75(1)	120(1)	22(1)	34(1)	-7(1)
O(5)	65(1)	51(1)	112(1)	19(1)	29(1)	2(1)
N(1)	51(1)	52(1)	53(1)	0(1)	15(1)	-8(1)

**Table 4.** Positional parameters ( $\times 10^3$ ) and *U*<sub>iso</sub> ( $\times 10^3$ ) for hydrogen atoms

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i>
H(1)	1026(3)	560(3)	217(3)	117(14)
H(2)	992(2)	136(2)	371(2)	64(7)
H(11)	969(2)	428(2)	339(2)	79(8)
H(12)	1044(2)	398(2)	244(2)	86(8)
H(21)	1207(2)	436(2)	382(2)	81(7)
H(22)	1141(2)	464(2)	473(2)	67(7)
H(31)	1133(2)	239(2)	369(2)	50(5)
H(51)	866(2)	53(2)	441(2)	72(7)
H(52)	899(2)	143(2)	555(2)	74(7)
H(71)	750(2)	272(2)	552(2)	95(9)
H(81)	605(2)	394(3)	475(3)	108(9)
H(101)	639(2)	313(2)	170(2)	101(9)
H(111)	797(2)	182(2)	249(2)	86(7)
H(121)	391(3)	518(4)	250(3)	140(14)
H(122)	498(2)	527(3)	371(2)	95(10)
H(123)	416(4)	431(4)	343(3)	165(19)
H(141)	1422(3)	159(3)	374(3)	124(11)
H(142)	1458(4)	161(4)	521(4)	178(18)
H(151)	1358(3)	-1(3)	500(3)	124(12)
H(152)	1265(3)	45(4)	372(3)	174(17)
H(161)	1289(3)	382(3)	625(2)	102(10)
H(162)	1238(3)	293(3)	670(3)	125(13)
H(163)	1370(3)	276(3)	673(2)	101(9)

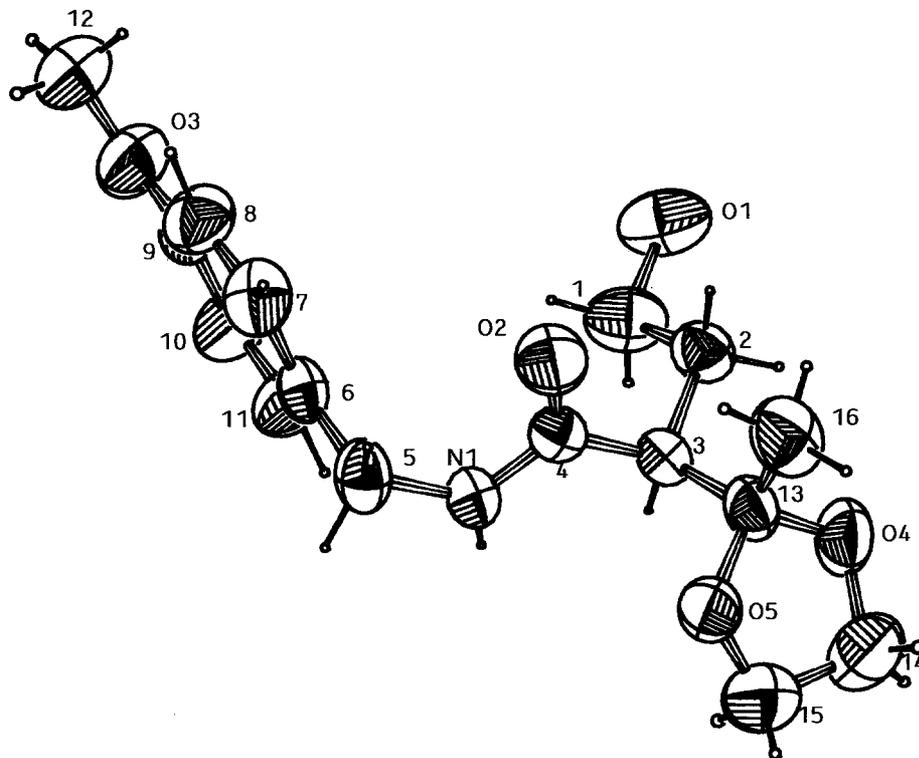


Fig. 1. A view of the molecule showing the atom numbering.

structure determination program (Sheldrick, 1976) on an AMSTRAD 1512 minicomputer.

### Discussion

A view of the molecule is given in Fig. 1. Selected bond lengths and angles are listed in Table 5. The dioxolane ring has a deformed half-chair conformation with C(14)  $-0.184(5)$  Å and C(15)  $0.215(5)$  Å from the least-squares plane of the ring. The asymmetry parameters in relation to a twofold axis (Duax and Norton, 1975) are  $\Delta C_2(13) = 4.2^\circ$  and  $|\phi|_{av} = 18.8^\circ$ . The conformation is in agreement with literature data. In known structures, 1,3-dioxolane rings possess a half-chair or envelope conformation (Ducruix and Pascard-Billy, 1977; Ruzić-Toros and Leban, 1978). The configuration of the dioxolane ring is illustrated by Newman projections in Fig. 2a. An extended conformation of the Fig. 2a O(1)–C(1)–C(2)–C(3)–C(13) chain [O(1)–C(1)–C(2)–C(3) =  $-178.3(2)^\circ$ , C(1)–C(2)–C(3)–C(13) =  $167.6(2)^\circ$ ] is observed. The defor-

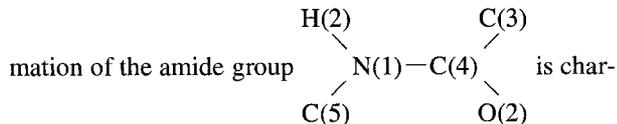


Table 5. Bond lengths/Å and angle/deg

C(1)–C(2)	1.498(3)	C(1)–O(1)	1.438(3)
C(2)–C(3)	1.533(3)	C(3)–C(4)	1.515(4)
C(3)–C(13)	1.534(3)	C(4)–O(2)	1.229(3)
C(4)–N(1)	1.321(3)	C(5)–C(6)	1.502(3)
C(5)–N(1)	1.461(3)	C(6)–C(7)	1.365(4)
C(6)–C(11)	1.385(3)	C(7)–C(8)	1.389(4)
C(8)–C(9)	1.356(3)	C(9)–C(10)	1.363(4)
C(9)–O(3)	1.372(3)	C(10)–C(11)	1.380(4)
C(12)–O(3)	1.410(6)	C(13)–C(16)	1.507(4)
C(13)–O(4)	1.429(3)	C(13)–O(5)	1.419(2)
C(14)–C(15)	1.463(5)	C(14)–O(4)	1.415(4)
C(15)–O(5)	1.412(5)		
C(2)–C(1)–O(1)	111.2(2)	C(2)–C(3)–C(13)	113.8(2)
C(2)–C(3)–C(4)	109.6(2)	C(4)–C(3)–C(13)	111.5(2)
C(3)–C(4)–N(1)	116.2(2)	C(3)–C(4)–O(2)	121.4(2)
O(2)–C(4)–N(1)	122.3(2)	C(6)–C(5)–N(1)	112.6(2)
C(5)–C(6)–C(11)	120.8(2)	C(5)–C(6)–C(7)	122.5(2)
C(7)–C(6)–C(11)	116.7(2)	C(6)–C(7)–C(8)	122.6(2)
C(7)–C(8)–C(9)	119.6(2)	C(8)–C(9)–O(3)	125.6(2)
C(8)–C(9)–C(10)	118.9(2)	C(10)–C(9)–O(3)	115.4(2)
C(9)–C(10)–C(11)	121.2(2)	C(6)–C(11)–C(10)	120.9(2)
C(3)–C(13)–O(5)	108.9(2)	C(3)–C(13)–O(4)	107.5(2)
C(3)–C(13)–C(16)	115.8(2)	O(4)–C(13)–O(5)	106.1(2)
C(16)–C(13)–O(5)	107.9(2)	C(16)–C(13)–O(4)	110.2(2)
C(15)–C(14)–O(4)	104.6(3)	C(14)–C(15)–O(5)	104.6(3)
C(9)–O(3)–C(12)	118.4(3)	C(13)–O(4)–C(14)	108.4(2)
C(13)–O(5)–C(15)	108.3(2)	C(4)–N(1)–C(5)	122.0(2)

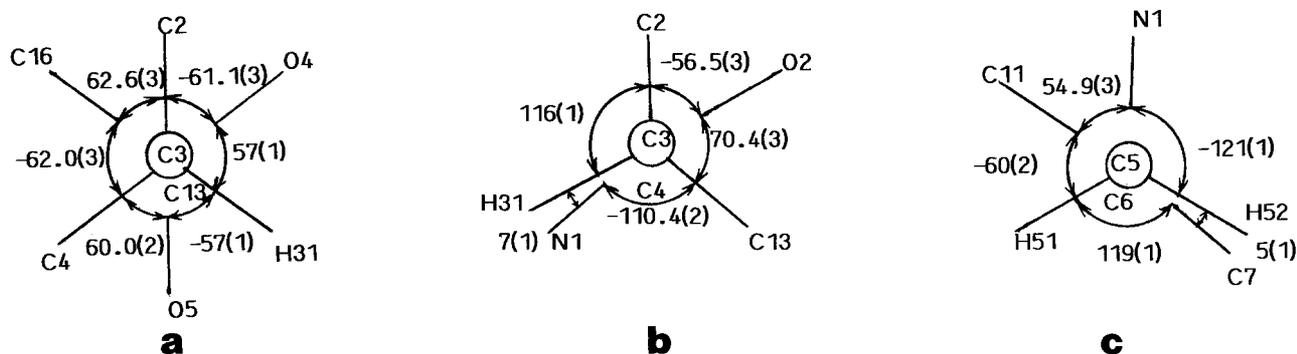


Fig. 2. (a) Configuration of the dioxolane ring. (b) Mutual location of extended chain and amide fragment. (c) Configuration of the methoxyphenyl ring.

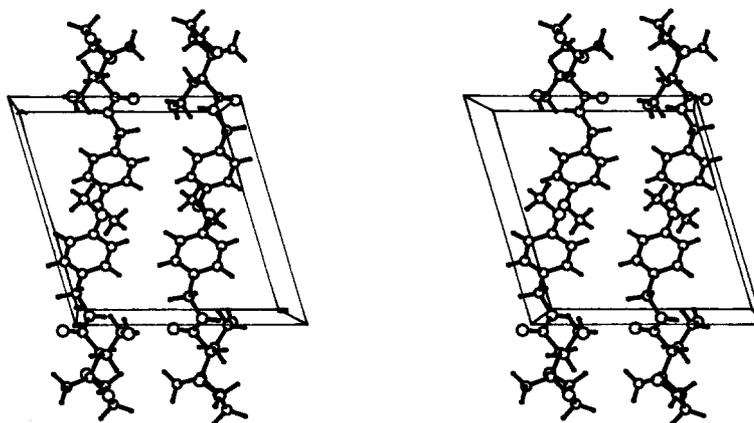


Fig. 3. Molecular packing.

acterized by angles  $\chi_C = 0.9^\circ$ ,  $\chi_N = 14^\circ$  and  $\tau = 0$  (Dunitz, 1976) and indicates that the deviations from planarity of the six atoms are caused mainly by an out-of-plane bending at N(1) atom. The literature information about the non-planar amide groups (Dunitz, 1976; Winkler and Dunitz, 1971), contrary to the observed data, indicate that out-of-plane bending at nitrogen is about as important as pure twisting. Figure 2b presents the mutual location of the extended chain and the amide fragment.

The phenyl ring has normal geometry (1.374 Å and  $120.0^\circ$  for the average bond length and average internal angle), with the methoxy group almost coplanar [the torsion angle C(8)–C(9)–O(3)–C(12) is  $-7.8(4)^\circ$ ]. The configuration of the methoxyphenyl ring is illustrated in Fig. 2c. The distances between two active centres in the molecule (hydroxyl and amide group) is 4.994(3) Å, which does not indicate any interaction between them. Atoms C(15) and C(14) in the

dioxolane ring are probably slightly disordered as indicated by high anisotropic thermal parameters (Fig. 1) and short distances to the neighbouring C and O atoms. External CH<sub>3</sub> and OH groups and O(4), O(5) atoms of dioxolane ring show relatively large temperature factors. In spite of the presence of six electronegative atoms and NH and OH groups in the molecule, no intermolecular or intramolecular hydrogen bonds are observed. The molecular packing in the unit cell is given in Fig. 3. Intermolecular distances do not indicate and interactions stronger than normal van der Waals'.

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Structure factor data have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 60649 (13 pages).