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Structure Analysis of Anticonvulsant Drugs: 5-(*p*-Chlorophenylmethyl)-3-methyl-2-pyrrolidinone, *cis* (I) and *trans* (II) Isomers

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Abstract. $C_{12}H_{14}ClNO$, *cis* (I) and *trans* (II) isomers. (I): $M_r = 223{\cdot}7$, monoclinic, $P2_1$, $a = 12{\cdot}844$ (4), $b = 8{\cdot}396$ (6), $c = 5{\cdot}351$ (4) Å, $\beta = 94{\cdot}3$ (4)°, $V = 577{\cdot}9$ Å^3, $Z = 2$, $D_x = 1{\cdot}29$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 2{\cdot}58$ mm^{-1}, $F(000) = 236$, $T = 293$ K, $R = 0{\cdot}040$ for 1078 observed reflections. (II): $M_r = 223{\cdot}7$, monoclinic, $P2_1/n$, $a = 11{\cdot}621$ (1), $b = 15{\cdot}601$ (1), $c = 6{\cdot}507$ (1) Å, $\beta = 92{\cdot}1$ (1)°, $V = 1179{\cdot}0$ Å^3, $Z = 4$, $D_x = 1{\cdot}26$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 2{\cdot}53$ mm^{-1}, $F(000) = 472$, $T = 293$ K, $R = 0{\cdot}046$ for 1168 observed reflections. For the two structures, the corresponding bond lengths, valence angles and torsion angles are very similar except around the methylene group between the phenyl and the pyrrolidinone rings. Cohesion is assumed mainly by intermolecular hydrogen bonds between the O atom and the N–H group of the pyrrolidinone amide functions. Spatial equivalence of the three putative pharmacophoric elements can be assumed for both isomers.

Introduction. This work is part of a more general study on the structural and molecular properties of anticonvulsant drugs. In usual pharmacological tests (maximal electroshock, bicuculline-induced seizures), the *trans* isomer (II) is only slightly more active. Surprisingly, the equimolecular mixture of both diastereoisomers [(I) and (II)] is observed to be more active on photoepileptic baboons than a pure isomer alone (Molimard, Jeanjean, Chambon & Bizière, 1986). In order to confirm the nature of the two asymmetric centres and to specify the conformation of each molecule, their structures were resolved by X-ray diffraction.

Experimental. Compound (I): suitable crystals obtained by slow evaporation of an ethanol/ethyl acetate solution at 293 K. Colourless, transparent, prismatic crystal, dimensions: 0·42 × 0·19 × 0·18 mm for all X-ray measurements by an Enraf–Nonius CAD-4 diffractometer. Graphite monochromator. Lattice parameters from least-squares refinement of 25 medium-angle reflections. ω–θ scan method, $4 \le 2\theta \le 56°$, $(\sin\theta/\lambda)_{max} = 1{\cdot}17$ Å^{-1}, $-17 \le h \le 17$, $0 \le k \le 11$, $0 \le l \le 7$. Lorentz and polarization corrections; no correction for absorption. 1469 unique reflections measured and 1078 observed [$I \ge 2{\cdot}5\sigma(I)$]. Variation in intensity of standard reflection less than 0·6%. Direct methods (*MULTAN*80: Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) used to find all 15 non-H atoms in the best figure of merit E map. Full-matrix least-squares refinement on F by using *SHELX*76 (Sheldrick, 1976). All 14 H atoms revealed in difference Fourier maps. Anisotropic temperature factors (U_{ij}) for heavy atoms and isotropic ones (with constraint to the carrier atoms) for H atoms. $R = 0{\cdot}040$, $wR = 0{\cdot}047$ given by final least-squares cycle, $S = 0{\cdot}24$, $w = 1/[\sigma^2(F) + 0{\cdot}01F^2]$, $(\Delta/\sigma)_{max} = 0{\cdot}05$ [x parameter of Cl(15)], max. and min. heights in final difference Fourier map: 0·27 and −0·17 e Å^{-3}. Atomic scattering factors from *SHELX*76 and structural analysis by *XRAY*76 (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Compound (II): crystallized from ethanol at 293 K. Colourless, transparent, prismatic crystal, dimensions: 0·40 × 0·25 × 0·16 mm for all X-ray measurements by an Enraf–Nonius CAD-4 diffractometer. Lattice parameters from least-squares refinement of 25 medium-angle reflections. ω–θ scan method, $4 \le 2\theta \le 50°$, $(\sin\theta/\lambda)_{max} = 1{\cdot}08$ Å^{-1}, $-13 \le h \le 13$, $0 \le k \le 18$, $0 \le l \le 7$. Lorentz and polarization corrections, no correction for absorption. 2069 unique reflections measured and 1168 observed [$I \ge 2{\cdot}5\sigma(I)$]. Maximal variation in intensity of the standard reflection: 0·9%. Direct methods using *SHELX*76. The 14 H atoms found in a difference Fourier map. Full-matrix least-squares anisotropic refinement on F using *SHELX*76 (H atoms isotropic). $R = 0{\cdot}046$, $wR = 0{\cdot}063$, $S = 0{\cdot}38$, $w = 1/[\sigma^2(F) + 0{\cdot}01F^2]$, $(\Delta/\sigma)_{max} = 0{\cdot}05$ [y parameter of Cl(15)], $-0{\cdot}26 \le \Delta\rho \le 0{\cdot}21$ e Å^{-3} in final difference map. Atomic scattering factors from *SHELX*76 and structural analysis by *XRAY*76.

*MULTAN*80, *SHELX*76 and *XRAY*76 programs are implemented on the IBM 4341-2 computer (running under VM/CMS operating system) of the Scientific Computing Facility Centre, Namur, Belgium.

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Discussion. For heavy atoms, atom numbering, bond lengths and valence angles are presented in Fig. 1 (figure drawn using the *CHEMDRAW* software; Cambridge Scientific Computing Inc., 1986), while atomic parameters and equivalent anisotropic thermal factors are given in Table 1.*

A statistical study using the Cambridge Crystallographic Database (Allen, Bellard, Brice, Cartwright, Doubleday, Higgs, Hummelink, Hummelink-Peters, Kennard, Motherwell, Rodgers & Watson, 1979; Allen, Kennard & Taylor, 1983) gives mean values and statistical standard deviations (different from the deduced crystallographic e.s.d.'s and indicated here in square brackets) for distances in 42 pyrrolidinone moieties. The values of the N(1)–C(2) bond lengths are 1·336 (4) and 1·331 (4) Å for compounds (I) and (II) respectively, compared to 1·354 [32] Å as the mean value; the C(2)–O(6) bond lengths are 1·225 (4) and 1·230 (3) Å, compared to 1·229 [21] Å. The distances for the amide function are thus in the range of the standard deviations around the mean values. The same observation is made for all distances in the pyrrolidinone ring: C(2)–C(3) 1·521 (4), 1·511 (4) and 1·503 [27] Å; C(3)–C(4) 1·533 (4), 1·543 (5) and 1·510 [53] Å; C(4)–C(5) 1·534 (4), 1·533 (5) and 1·522 [34] Å; C(5)–N(1) 1·461 (3), 1·454 (4) and 1·419 [44] Å.

Both compounds present a network of intermolecular hydrogen bonds (Fig. 2) between the O and N atoms of the amide function in neighbouring cells (Table 2). The parameters of these hydrogen bonds agree with the mean values computed by Taylor, Kennard & Versichel (1984). In spite of the apparent difference between the two N–H···O angles [174·5 and 149·8° for compounds (I) and (II) respectively], they remain close to the mean value calculated from 1357 intermolecular bonds, 162·1°. The crystalline cohesion is achieved by van der Waals contacts.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters, and stereoscopic views of molecular conformation have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51452 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

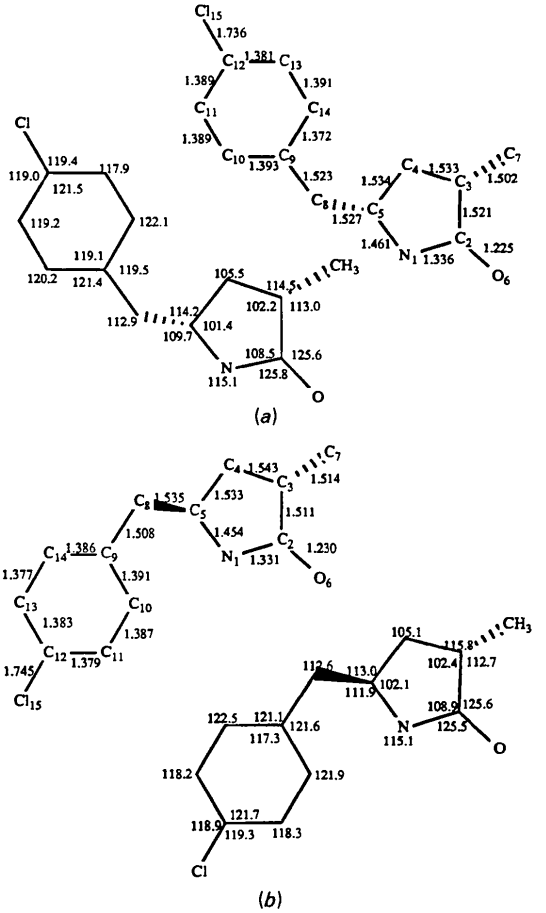

Fig. 1. Atom numbering, bond lengths (Å) and valence angles (°) for both isomers: (*a*) (I) (*cis* isomer) and (*b*) (II) (*trans* isomer); maximum e.s.d.'s are 0·006 Å and 0·4°.

Table 1. *Final atomic coordinates* ($\times 10^4$) *and* B_{eq} *values with e.s.d.'s in parentheses for the two isomers* (I) *and* (II)

$B_{eq} = 8\pi^2 U_{eq}$ and $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	*y*	*z*	B_{eq}(Å^2)
(*a*) *cis* isomer (I)				
N(1)	748 (1)	229 (2)	−7886 (5)	5·08 (1)
C(2)	439 (1)	−1288 (4)	−7881 (5)	4·92 (1)
C(3)	1003 (1)	−2124 (5)	−5652 (6)	5·75 (1)
C(4)	1904 (1)	−979 (5)	−4951 (5)	6·00 (1)
C(5)	1524 (1)	662 (4)	−5874 (5)	4·69 (1)
O(6)	−223 (1)	−1888 (4)	−9347 (5)	7·01 (1)
C(7)	1333 (4)	−3788 (5)	−6244 (12)	8·96 (1)
C(8)	2365 (1)	1692 (5)	−6924 (5)	5·54 (1)
C(9)	3295 (1)	1966 (4)	−5049 (5)	4·56 (1)
C(10)	3227 (1)	2951 (4)	−2975 (5)	5·44 (1)
C(11)	4089 (2)	3191 (5)	−1306 (5)	5·64 (1)
C(12)	5020 (1)	2444 (5)	−1743 (5)	5·49 (1)
C(13)	5105 (2)	1456 (5)	−3781 (5)	5·84 (1)
C(14)	4226 (2)	1244 (4)	−5419 (5)	5·32 (1)
Cl(15)	6100 (1)	2757 (1)	335 (1)	8·15 (1)
(*b*) *trans* isomer (II)				
N(1)	4169 (1)	−606 (1)	3029 (4)	5·30 (1)
C(2)	3479 (2)	−651 (1)	4613 (4)	5·12 (1)
C(3)	2411 (2)	−1150 (1)	3971 (5)	6·22 (1)
C(4)	2448 (2)	−1132 (1)	1603 (5)	6·98 (1)
C(5)	3720 (2)	−1000 (1)	1140 (5)	6·12 (1)
O(6)	3683 (1)	−342 (1)	6327 (2)	7·39 (1)
C(7)	1331 (2)	−789 (2)	4879 (5)	8·57 (1)
C(8)	4344 (2)	−1841 (1)	669 (5)	7·53 (1)
C(9)	5618 (2)	−1718 (1)	417 (5)	6·12 (1)
C(10)	6399 (4)	−1776 (2)	2081 (5)	7·79 (1)
C(11)	7562 (4)	−1607 (2)	1887 (5)	7·92 (1)
C(12)	7947 (2)	−1402 (1)	−32 (6)	7·28 (1)
C(13)	7202 (2)	−1345 (1)	−1733 (5)	7·21 (1)
C(14)	6050 (2)	−1506 (1)	−1474 (5)	6·71 (1)
Cl(15)	9406 (1)	−1191 (1)	−326 (2)	11·88 (1)

Table 2. *Parameters for the intermolecular hydrogen bond in both isomers* (I) *and* (II) *and mean values calculated from* 1357 *intermolecular* N–H···O *hydrogen bonds* (*Taylor, Kennard & Versichel*, 1984)

N–H···O	N–H (Å)	N···O (Å)	H···O (Å)	∠N–H···O (°)
cis isomer (I)				
N(1)–H(1)^{i}···O(6)^{ii}	1·019	2·996	1·901	174·5
trans isomer (II)				
N(1)–H(1)^{i}···O(6)^{iii}	0·911	2·892	2·068	149·8
Mean values				
N–H···O	–	2·892	1·934	162·1

Symmetry codes: (i) = x, y, z; (ii) = $1-x, -y, 1-z$; (iii) = $-x, \frac{1}{2}+y, -2-z$.

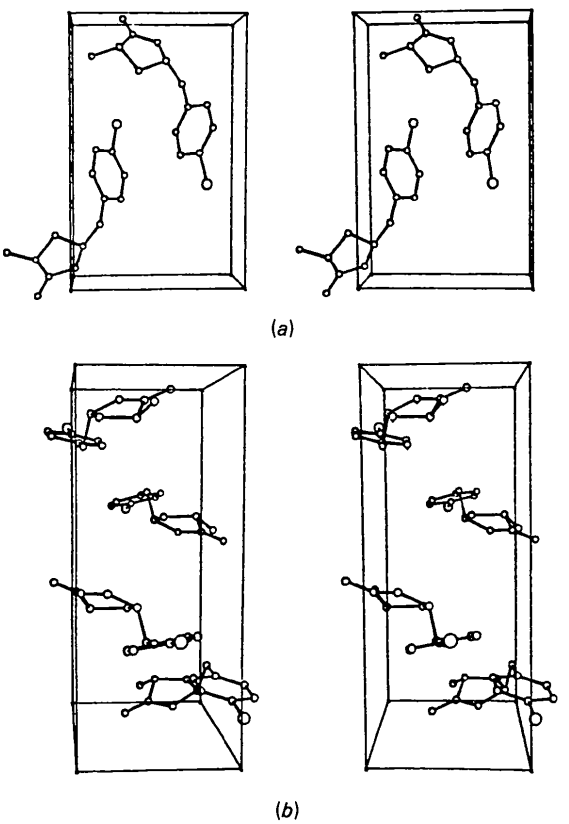

Fig. 2. Stereoscopic views of molecular conformations and crystal packings of both isomers: (*a*) *cis* (I) and (*b*) *trans* (II).

In the case of the $P2_1$ space group (I), we retained the set of coordinates with the lowest R factor corresponding to the 3*S*,5*S* stereoisomer, separated during crystallization. The second crystal, space group $P2_1/n$, contains both enantiomers (3*S*,5*R* and 3*R*,5*S*).

In order to compare the two diastereoisomers retained [3*S*,5*S* (I), and 3*S*,5*R* (II)], we attempted to fit their crystal structures considering two of their potential pharmacophoric elements: on the one hand, the amide function which could form the link with a putative receptor; on the other hand, the C(5) substituent increasing the specificity of the drug by its hydrophobic and steric characters. Superimposing the amide functions (*IFMFIT* program; Lejeune, Michel & Vercauteren, 1986) (Fig. 3*a*), we observed that the pyrrolidinone rings and their 3-methyl substituents adopt the same conformation, both C(4) atoms lying in the same orientation.

As both isomers (I) and (II) are present as racemic mixtures, it is obvious that the differences of activity (Molimard, Jeanjean, Chambon & Bizière, 1986) of the two drugs might be due to different spatial occupations of the phenylmethyl group and/or of the methyl substituent. This fact is directly governed by the stereochemistry of the C(3) and C(5) asymmetric centres. Considering the 3*R*,5*S* enantiomer of (II), even if its phenylmethyl group could adopt the same conformation as (I), the methyl groups and the C(4) atoms will not then be superimposed.

On the other hand, we can consider that free rotation around the C(5)–C(8) and C(8)–C(9) bonds is allowed for both molecules (I) and (II); the phenyl rings may then converge to the same plane (Fig. 3*b*). This borderline case is unique and the resulting conformations might be the active ones, thereby explaining that the differences between the activities of isomers (I) and (II) are finally not so marked. Concerning the observation of the higher activity of the equimolecular mixture of both drugs, crystallography is not able to provide a satisfactory explanation.

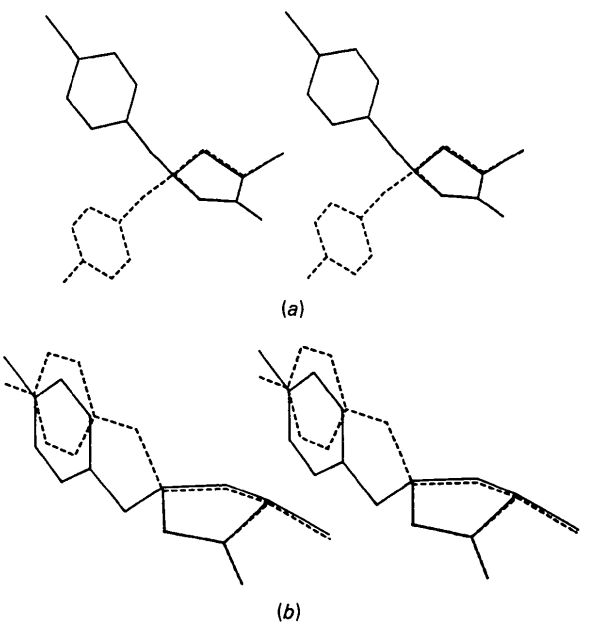

Fig. 3. Stereoscopic views of the fitting of the two diastereoisomers. (I) (3*S*,5*S* *cis* isomer) full line and (II) (3*S*,5*R* *trans* isomer) dotted line; (*a*) rigid fitting of the pyrrolidinone rings and (*b*) flexible fitting [rotations around the C(5)–C(8) and C(8)–C(9) bonds].

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References

ALLEN, F. H., BELLARD, S., BRICE, M. D., CARTWRIGHT, B. A., DOUBLEDAY, A., HIGGS, H., HUMMELINK, T., HUMMELINK-PETERS, B. G., KENNARD, O., MOTHERWELL, W. D. S., RODGERS, J. R. & WATSON, D. G. (1979). *Acta Cryst.* B**35**, 2331–2339.

ALLEN, F. H., KENNARD, O. & TAYLOR, R. (1983). *Acc. Chem. Res.* **16**, 146–153.

Cambridge Scientific Computing Inc. (1986). *CHEMDRAW*, a structure drawing program for the Apple Macintosh. Cambridge Scientific Computing Inc.

LEJEUNE, J., MICHEL, A. & VERCAUTEREN, D. P. (1986). *J. Comput. Chem.* **7**, 739–744.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain-la-Neuve, Belgium.

MOLIMARD, J.-C., JEANJEAN, F., CHAMBON, J.-P. & BIZIÈRE, K. (1986). *IXth Symposium on Medicinal Chemistry*, p. 219. European Federation for Medicinal Chemistry, September 14–18, West Berlin, Germany.

SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

STEWART, J. M., MACHIN, P. A., DICKINSON, C. W., AMMON, H. L., HECK, H. & FLACK, H. (1976). The *XRAY76* system. Tech. Rep. TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland, USA.

TAYLOR, T., KENNARD, O. & VERSICHEL, W. (1984). *Acta Cryst.* B**40**, 280–288.

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Short S···O Contacts: Structure of 2,5-Bis(*p*-methoxyphenylhydroxymethyl)thiophene

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Abstract. $C_{20}H_{20}O_4S$, $M_r = 356{\cdot}4$, monoclinic, $P2_1/c$, $a = 5{\cdot}045$ (3), $b = 29{\cdot}115$ (7), $c = 11{\cdot}924$ (2) Å, $\beta = 94{\cdot}82$ (3)°, $V = 1745{\cdot}2$ Å^3, $Z = 4$, $D_x = 1{\cdot}357$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 17{\cdot}86$ cm^{-1}, $F(000) = 752$, $T = 298$ K, $R = 0{\cdot}038$, $wR = 0{\cdot}044$ for 1212 reflections, $I > 3\sigma(I)$. In the crystal, the molecule adopts a conformation in which one of the two hydroxymethyl fragments is synplanar to S and the other is anticlinal to S. Although the two fragments are otherwise equivalent, the C—C—O bond angles in the two hydroxymethyl fragments are significantly different from each other [106·7 (3) and 110·7 (3)°]. The decrease of 4° in the bond angle is for the C—C—OH fragment that makes a short S···O contact and must indicate a non-bonded attractive interaction between the two atoms.

Introduction. The approach of presumed electrophiles and nucleophiles has been shown to exhibit a preferred geometry and angular orientation towards a divalent sulfur center (Rosenfield, Parthasarathy & Dunitz, 1977; Guru Row & Parthasarathy, 1981; Chatterjee & Parthasarathy, 1983). These interactions, though not very strong, exhibit directional preferences at distances close to or less than the sum of van der Waals radii of the two interacting atoms. Most of these interactions occur in crystal structures along with stronger overwhelming interactions like coordination, H bonding *etc.* We have undertaken crystal structure determinations of compounds which are likely to exhibit intra- and/or intermolecular interactions where the complexity of other stronger interactions is minimized. In the present paper we discuss the structure of one such compound.

Experimental. The title compound was prepared following a reported procedure (Ulman & Manassen, 1979); needle-shaped crystals obtained from ethanol at room temperature; crystal used: 0·55 × 0·30 × 0·15 mm; CAD-4 diffractometer; unit-cell dimensions from least-squares fit of 25 reflections ($16 < 2\theta < 42°$); intensity data [$2\theta_{max} = 154°$ for λ(Cu $K\alpha$)]; $\omega/2\theta$ scan; ω scan width $(1{\cdot}20 + 0{\cdot}14\tan\theta)°$; aperture width $(3{\cdot}0 + 1{\cdot}2\tan\theta)$ mm; maximum time spent on any reflection is 100 s; faster scan for strong reflections;

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