References

Clegg, W. (1981). *Acta Cryst.* A**37**, 22–28.

Gould, R. O., McNab, H. & Walkinshaw, M. D. (1983). *Acta Cryst.* C**39**, 1097–1101.

Jones, A. J., McNab, H. & Hanisch, P. (1978). *Aust. J. Chem.* **31**, 1005–1010.

McNab, H. (1978). *J. Chem. Soc. Perkin Trans.* 1, pp. 1023–1029.

Nagel, M. & Allmann, R. (1981). *Cryst. Struct. Commun.* **10**, 905–908.

Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.

Sheldrick, G. M. (1992). *SHELXTL/PC User's Manual.* Release 4.3. Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.

Sheldrick, G. M. (1993). *SHELXL93. Program for Crystal Structure Refinement.* Univ. of Göttingen, Germany.

Stoe & Cie (1988*a*). *DIF4. Diffractometer Control Program.* Version 6.2. Stoe & Cie, Darmstadt, Germany.

Stoe & Cie (1988*b*). *REDU4. Data Reduction Program.* Version 6.2. Stoe & Cie, Darmstadt, Germany.

Acta Cryst. (1994). C**50**, 1501–1503

Structure and Absolute Configuration of (−)-(3*S*,4*R*)-4-Carboxy-1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenylpiperidinium Bromide (Levocabastine Hydrobromide)†

N. M. Blaton, O. M. Peeters and C. J. De Ranter

Laboratorium voor Analytische Chemie en
Medicinale Fysicochemie,
Faculteit Farmaceutische Wetenschappen,
Katholieke Universiteit Leuven,
Van Evenstraat 4, B-3000 Leuven, Belgium

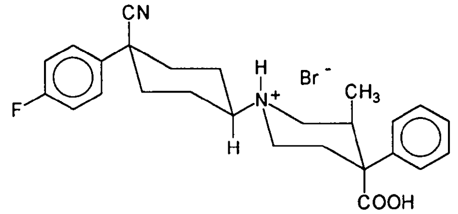
(*Received* 4 *February* 1994; *accepted* 14 *March* 1994)

Abstract

Levocabastine is a potent H_1 antihistamine agent. Both the piperidine and cyclohexane rings in the title compound, $C_{26}H_{30}FN_2O_2^+.Br^-$, have conformations close to an ideal chair. The piperidine and fluorophenyl rings are positioned equatorially on the cyclohexane ring, while the cyano group is oriented axially, resulting in a *cis* configuration. The phenyl moiety on the piperidine ring is in an equatorial orientation while the methyl and carboxyl substituents are placed axially. This corresponds to a *trans* configuration. The molecules are linked together in the **c** direction by N—H···Br···H—O hydrogen bonds.

Comment

The title compound (I) contains a 1,4-substituted cyclohexane ring and a 3,4-substituted piperidine ring. As such substituted rings give rise to *cis* and *trans* isomers and, moreover, 3,4-substituted piperidines are chiral, eight isomers are possible. The geometry of the four racemates was derived from the NMR spectra of the benzyl esters (Stokbroekx *et al.*, 1986). Here we report the structure of levocabastine, the most potent histamine H_1 antagonist of the series.



(I)

The absolute configuration is (3*S*,4*R*). The bond distances and angles lie within the expected ranges. The cyclohexane and piperidine rings have confromations close to an ideal chair. The fluorophenyl and phenyl substituents are placed equatorially, while the cyano, methyl and carboxyl groups are oriented axially. The conformation of the cyclohexane–piperidine connection is staggered. The carboxyl substituent is almost perpendicular to the phenyl ring [80.2 (2)°], while the fluorophenyl moiety is nearly coplanar with it [9.8 (2)°]. The molecules are linked together by N15—H15···Br [N15···Br 3.248 (4), H15···Br 2.272 Å, N15—H15···Br 145.7°] and $O23^i$—$H23^i$···Br [$O23^i$···Br 3.118 (4), $H23^i$···Br 2.070 Å, $O23^i$—$H23^i$···Br 148.4°; symmetry code: (i) $\frac{3}{2} - x, -y, \frac{1}{2} + z$] hydrogen bonds, forming infinite chains in the **c** direction.

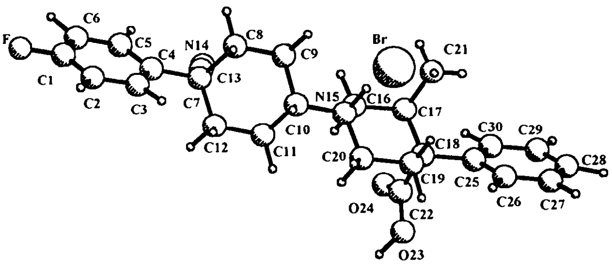


Fig. 1. *PLUTO* (Motherwell & Clegg, 1978) diagram of the molecule showing the atomic numbering scheme.

Experimental

Crystal data

$C_{26}H_{30}FN_2O_2^+.Br^-$
$M_r = 501.44$

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å

---

† Internal code of the Janssen Research Foundation: R53474.

Acta Crystallographica Section C
ISSN 0108-2701 ©1994

Orthorhombic
$P2_12_12_1$
$a = 6.592$ (1) Å
$b = 21.621$ (4) Å
$c = 16.894$ (4) Å
$V = 2407.8$ (9) Å^3
$Z = 4$
$D_x = 1.383$ Mg m^{-3}

Cell parameters from 24 reflections
$\theta = 20–25°$
$\mu = 2.593$ mm^{-1}
$T = 293$ K
Plate
0.5 × 0.3 × 0.1 mm
Colourless

Data collection

Syntex $P2_1$ four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3414 measured reflections
3002 independent reflections
2264 observed reflections [$I > 3.0\sigma(I)$]

$R_{\rm int} = 0.0129$
$\theta_{\rm max} = 54.97°$
$h = 0 \rightarrow 7$
$k = 0 \rightarrow 22$
$l = -17 \rightarrow 17$
3 standard reflections monitored every 50 reflections intensity variation: < 2%

Refinement

Refinement on F
$R = 0.0293$
$wR = 0.0380$
$S = 0.91$
2264 reflections
289 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F) + 0.00100F^2]$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.27$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.21$ e Å^{-3}

Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2B and 2.3.1)
Absolute configuration: the Bijvoet coefficient was 0.961(1) and exactly 1 for the 227 and 13 most significant Bijvoet pairs, respectively

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
Br	0.49207 (9)	−0.03452 (2)	0.64381 (3)	0.0559 (2)
F	0.9975 (9)	0.4465 (1)	0.7362 (2)	0.095 (1)
C1	1.011 (1)	0.3876 (2)	0.7092 (3)	0.062 (2)
C2	0.841 (1)	0.3618 (3)	0.6786 (4)	0.082 (3)
C3	0.8543 (8)	0.3004 (3)	0.6499 (4)	0.071 (2)
C4	1.0346 (7)	0.2677 (2)	0.6542 (3)	0.049 (2)
C5	1.1981 (9)	0.2970 (3)	0.6880 (3)	0.060 (2)
C6	1.187 (1)	0.3567 (3)	0.7160 (4)	0.066 (2)
C7	1.0477 (6)	0.2021 (2)	0.6207 (3)	0.044 (2)
C8	0.9524 (7)	0.1537 (2)	0.6784 (3)	0.049 (2)
C9	0.9601 (7)	0.0875 (2)	0.6451 (3)	0.047 (2)
C10	0.8573 (7)	0.0845 (2)	0.5637 (3)	0.044 (2)
C11	0.9538 (8)	0.1300 (2)	0.5062 (3)	0.048 (2)
C12	0.9429 (7)	0.1958 (2)	0.5394 (3)	0.052 (2)
C13	1.2642 (9)	0.1855 (2)	0.6104 (3)	0.057 (2)
N14	1.4288 (7)	0.1725 (2)	0.5991 (3)	0.085 (2)
N15	0.8541 (6)	0.0193 (2)	0.5330 (2)	0.044 (1)
C16	1.0629 (7)	−0.0077 (2)	0.5198 (3)	0.048 (2)
C17	1.0524 (7)	−0.0762 (2)	0.4980 (3)	0.049 (2)
C18	0.9242 (7)	−0.0857 (2)	0.4228 (3)	0.046 (2)
C19	0.7142 (7)	−0.0564 (2)	0.4353 (3)	0.047 (2)
C20	0.7282 (8)	0.0113 (2)	0.4589 (3)	0.053 (2)
C21	0.979 (1)	−0.1156 (2)	0.5676 (3)	0.059 (2)
C22	1.0319 (9)	−0.0557 (2)	0.3514 (3)	0.062 (2)
O23	0.9088 (6)	−0.0454 (2)	0.2925 (2)	0.086 (2)
O24	1.2089 (6)	−0.0450 (3)	0.3487 (3)	0.120 (3)
C25	0.9105 (8)	−0.1550 (2)	0.4004 (3)	0.051 (2)
C26	0.7291 (9)	−0.1830 (3)	0.3811 (3)	0.063 (2)
C27	0.723 (1)	−0.2453 (3)	0.3599 (4)	0.077 (3)
C28	0.895 (1)	−0.2804 (3)	0.3615 (5)	0.090 (3)
C29	1.074 (1)	−0.2534 (3)	0.3797 (5)	0.102 (4)
C30	1.0832 (9)	−0.1901 (3)	0.3997 (4)	0.086 (3)

Table 2. *Selected geometric parameters* (Å, °)

F—C1	1.357 (5)	N15—C16	1.512 (5)
C1—C2	1.35 (1)	N15—C20	1.512 (6)
C1—C6	1.34 (1)	C16—C17	1.528 (6)
C2—C3	1.415 (9)	C17—C18	1.539 (6)
C3—C4	1.385 (7)	C17—C21	1.531 (6)
C4—C5	1.374 (7)	C18—C19	1.538 (6)
C4—C7	1.529 (6)	C18—C22	1.543 (7)
C5—C6	1.378 (8)	C18—C25	1.548 (6)
C7—C8	1.563 (6)	C19—C20	1.520 (6)
C7—C12	1.543 (6)	C22—O23	1.302 (6)
C7—C13	1.482 (7)	C22—O24	1.190 (7)
C8—C9	1.538 (6)	C25—C26	1.380 (8)
C9—C10	1.535 (6)	C25—C30	1.367 (8)
C10—C11	1.520 (6)	C26—C27	1.393 (7)
C10—N15	1.503 (5)	C27—C28	1.36 (1)
C11—C12	1.533 (6)	C28—C29	1.35 (1)
C13—N14	1.137 (7)	C29—C30	1.41 (1)
F—C1—C6	119.6 (5)	C10—N15—C16	113.6 (3)
F—C1—C2	117.6 (5)	C16—N15—C20	109.5 (4)
C2—C1—C6	122.8 (5)	N15—C16—C17	111.6 (3)
C1—C2—C3	117.8 (6)	C16—C17—C21	111.7 (4)
C2—C3—C4	120.9 (6)	C16—C17—C18	110.7 (4)
C3—C4—C7	120.2 (4)	C18—C17—C21	112.7 (4)
C3—C4—C5	117.3 (5)	C17—C18—C25	111.3 (4)
C5—C4—C7	122.5 (4)	C17—C18—C22	109.6 (4)
C4—C5—C6	122.2 (5)	C17—C18—C19	109.0 (4)
C1—C6—C5	118.9 (6)	C22—C18—C25	104.0 (4)
C4—C7—C13	108.8 (4)	C19—C18—C25	112.4 (4)
C4—C7—C12	112.6 (4)	C19—C18—C22	110.4 (4)
C4—C7—C8	111.6 (4)	C18—C19—C20	112.3 (4)
C12—C7—C13	107.8 (4)	N15—C20—C19	111.1 (4)
C8—C7—C13	107.4 (4)	C18—C22—O24	124.2 (5)
C8—C7—C12	108.5 (4)	C18—C22—O23	112.5 (4)
C7—C8—C9	112.4 (4)	O23—C22—O24	123.3 (5)
C8—C9—C10	110.6 (3)	C18—C25—C30	119.4 (5)
C9—C10—N15	110.7 (4)	C18—C25—C26	122.2 (5)
C9—C10—C11	111.1 (4)	C26—C25—C30	118.4 (5)
C11—C10—N15	113.1 (4)	C25—C26—C27	120.5 (6)
C10—C11—C12	110.3 (4)	C26—C27—C28	120.7 (6)
C7—C12—C11	112.7 (4)	C27—C28—C29	119.2 (6)
C7—C13—N14	177.1 (6)	C28—C29—C30	120.8 (7)
C10—N15—C20	113.6 (3)	C25—C30—C29	120.2 (6)
C3—C4—C7—C8	−78.9 (6)	C11—C10—N15—C20	−63.0 (5)
C3—C4—C7—C12	43.4 (6)	C10—N15—C16—C17	173.4 (4)
C3—C4—C7—C13	162.8 (5)	N15—C16—C17—C21	−68.2 (5)
C4—C7—C8—C9	178.9 (4)	C16—C17—C18—C22	66.0 (5)
C13—C7—C12—C11	60.7 (5)	C16—C17—C18—C25	−179.5 (4)
C8—C9—C10—N15	−176.8 (3)	C17—C18—C25—C26	132.9 (5)
C9—C10—N15—C16	−62.6 (5)	C17—C18—C22—O24	21.9 (7)
C9—C10—N15—C20	171.5 (4)	C22—C18—C25—C26	−109.1 (5)
C11—C10—N15—C16	62.9 (5)	C25—C18—C22—O23	80.4 (5)

Data were collected using a variable scan speed with a scan range of 1° below $K\alpha_1$ to 1° above $K\alpha_2$. The ratio of total background time to scan time was unity. The structure was solved by a combination of Patterson and direct methods for difference structures and was refined using a full-matrix least-squares method. H atoms were calculated at geometrical positions except those of the methyl and hydroxyl groups, which were obtained from a difference Fourier synthesis. The absolute configuration was determined by calculating the Bijvoet coefficient according to a selection procedure of Beurskens, Noordik & Beurskens (1980). Data collection and cell refinement: $P2_1$ *Diffractometer Program* (Syntex, 1975). Data reduction: *REDU4* (Stoe & Cie, 1992). Program(s) used to solve structure: *DIRDIF* (Beurskens *et al.*, 1981). Program(s) used to refine structure: *NRCVAX* (Gabe, Le Page, Charland, Lee & White, 1989). Molecular graphics: *PLUTO* (Motherwell & Clegg, 1978). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

The authors thank Dr J. Tollenaere of Janssen Research Foundation (Beerse, Belgium) for providing the title compound.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1090). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Beurskens, G., Noordik, J. H. & Beurskens, P. T. (1980). *Cryst. Struct. Commun.* **9**, 23–28.

Beurskens, P. T., Bosman, W. P., Doesburg, H. M., Gould, R. O., van den Hark, Th. E. M., Prick, P. A., Noordik, J. H., Beurskens, G. & Parthasarathi, V. (1981). *DIRDIF*. Technical Report 1981/2. Crystallography Laboratory, Univ. of Nijmegen, The Netherlands.

Gabe, E. J., Le Page, Y., Charland, J.-P., Lee, F. L. & White, P. S. (1989). *J. Appl. Cryst.* **22**, 384–387.

Motherwell, W. D. S. & Clegg, W. (1978). *PLUTO. Program for Plotting Molecular and Crystal Structures*. Univ. of Cambridge, England.

Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.

Stoe & Cie (1992). *REDU4. Data Reduction Program*. Version 7.03. Stoe & Cie, Darmstadt, Germany.

Stokbroekx, R. A., Luyckx, M. J. M., Willems, J. J. M., Janssen, M., Bracke, J. O. M. M., Joosen, R. L. P. & Van Wauwe, J. P. (1986). *Drug Develop. Res.* **8**, 87–93.

Syntex (1975). *P*2$_1$ *Diffractometer Program*. Version 1. Syntex Analytical Instruments, Cupertino, California, USA.

Acta Cryst. (1994). **C50**, 1503–1505

Methyl 5-Cyano-1-[2-(methoxycarbonyl)phenyl]-4,5-dihydro-3-pyrazolecarboxylate

TULLIO PILATI AND GIANLUIGI CASALONE

CNR - Centro per lo Studio delle Relazioni,
fra Struttura e Reattività Chimica, Via Golgi 19,
20133 Milano, Italy

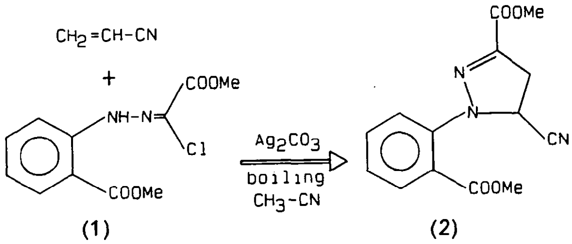
(*Received* 8 *February* 1994; *accepted* 21 *March* 1994)

Abstract

The title compound, $C_{14}H_{13}N_3O_4$, has two molecules in the asymmetric unit which have quite different geometries, in spite of the absence of strong intramolecular contacts. This is a result of the flexibility of the 4,5-dihydropyrazole ring. Similar compounds which show the same ring variability can be found in the literature.

Comment

Continuing a series of 1,3-dipolar cycloaddition reactions, Garanti (1993) added the chlorohydrazone (1) and Ag_2CO_3 (to generate the corresponding nitrilimmine) to acrylonitrile in boiling acetonitrile, obtaining the title compound (2).



(1) (2)

The present work confirms the expected conformation of the reaction product. There are two crystallographically independent molecules in the asymmetric unit of (2) and there is no particular relation between them. Fig. 1 shows molecule *A*, with the numbering scheme of the heavy atoms. The same numbering is applied to molecule *B*. The intermolecular packing interactions are not particularly relevant. In fact only three weak hydrogen bonds are present: C18*A*···O13*B*$^{\rm i}$ = 3.232 (3), H181*A*···O13*B*$^{\rm i}$ = 2.52 (3) Å and C18*A*—H181*A*···O13*B*$^{\rm i}$ = 129 (3)°; C4*A*···O17*B*$^{\rm ii}$ = 3.328 (3), H42*A*···O17*B*$^{\rm ii}$ = 2.62 (3) Å and C4*A*—H42*A*···O17*B*$^{\rm ii}$ = 128 (2)°; C4*B*···O17*A*$^{\rm iii}$ = 3.485 (3), H41*B*···O17*A*$^{\rm iii}$ = 2.67 (3) Å and C4*B*—H41*B*···O17*A*$^{\rm iii}$ = 142 (2)° [symmetry codes: (i) $1-x, -y, 1-z$; (ii) $-x, 1-y, 1-z$; (iii) $-x, -y, 1-z$]. Nevertheless, the two molecules are quite different, as can be seen from Fig. 2.

The main difference between the molecules is in the conformation of the heterocycle (N1, N2, C3, C4, C5), which is practically planar in molecule *A* [total puckering amplitude Q_t = 0.029 (2) Å (Cremer &

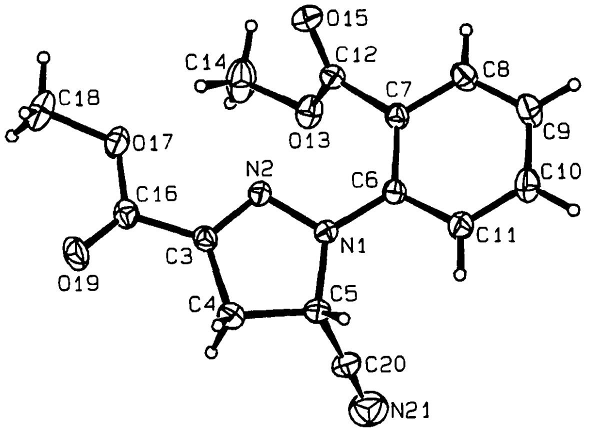


Fig. 1. *ORTEP*II (Johnson, 1976) drawing of molecule *A* with the numbering scheme of the heavy atoms, the same numbering was applied to molecule *B*. Displacement ellipsoids are drawn at the 20% probability level; H atoms are not to scale.