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Structure of a New Gastric-Acid-Inhibiting Agent, 11-[(4-Methyl-1-piperazinyl)acetyl]pyrido[2,3-*b*][1,4]benzodiazepin-6(5*H*)-one Monohydrate (Pirenzepine Free Base), $C_{19}H_{21}N_5O_2.H_2O$

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Abstract. $M_r = 369{\cdot}43$, monoclinic, $P2_1/c$, $a = 13{\cdot}160\,(7)$, $b = 12{\cdot}766\,(9)$, $c = 12{\cdot}439\,(7)$ Å, $\beta = 113{\cdot}2\,(4)°$, $U = 1920{\cdot}8$ Å^3, $Z = 4$, $D_c = 1{\cdot}277$ Mg m^{-3}, μ(Mo $K\alpha$) = $0{\cdot}128$ mm^{-1}. Final $R = 0{\cdot}045$ for 2681 observed reflexions. The intramolecular geometry is in agreement with the atom type involved, hybridization and conjugation. The diazepine ring is in the boat form. The water molecule is involved in hydrogen bonds with the amide group of the diazepine ring, N(5)—H$\cdots$O(*W*) [2·800 (3) Å] and O(*W*)—H$\cdots$O(6)[2·907 (3) Å]. N(4′) of the piperazine ring is hydrogen-bonded to the water molecule by O(*W*)—H$\cdots$N(4′)[2·821 (3) Å].

Introduction. Pirenzepine dihydrochloride (LS-519) produced by Dr Karle Thomae GmbH under the proprietary name Gastrozepin was introduced in 1977 as a new gastric-acid-inhibiting agent (Prous, 1979). The crystal-structure determinations of pirenzepine hydrochloride and the hydrobromide of 11-(3-diethylaminopropyl)-6-(methyl)pyrido[2,3-*b*][1,5]benzodiazepin-5(6*H*)-one were reported by Luger (1981). The crystal and molecular structure of pirenzepine monohydrate free base is described in this paper.

Experimental. Space group determined from Weissenberg photographs, Cu $K\alpha$, diffraction symmetry and extinctions indicated space group $P2_1/c$, Philips PW 1100 computer-controlled four-circle diffractometer, ω-scan mode, scan width = $1{\cdot}60°\theta$, scan speed = $0{\cdot}04°(\theta)$ s^{-1}, graphite-monochromated Mo $K\alpha$, 2681 independent reflexions [$I > 2\sigma(I)$], range $2 < \theta < 30°$, three standard reflexions measured every 2 h; overall temperature ($B = 2{\cdot}47$ Å^2) and scale factors determined (Wilson, 1942) and used to compute normalized structure amplitudes, routine *NORMAL* in *MULTAN* 80, structure solved with *MULTAN* 80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) based on 304 reflexions, $|E| \geq 1{\cdot}50$, least-squares, minimizing $\sum W||F_o| - |F_c||^2$, $W = 1$; anisotropic refinement and a subsequent difference synthesis located H atoms; a scale factor, atomic coordinates of all atoms, anisotropic thermal parameters of non-H and isotropic parameters of H (336 variables in all) refined, anisotropic thermal parameters in usual range, maximum values U_{11} for O(*W*)[0·0985 (2)], U_{22}[0·0949 (3)] and U_{33}[0·0919 (2)Å^2] for C(7′), $F(000) = 784$; scattering factors for non-H given by Cromer & Mann (1968), for H by Stewart, Davidson & Simpson (1965); Univac 1110 computer, University Computing Centre, Zagreb, XRAY system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Discussion. Atomic coordinates and equivalent isotropic thermal parameters are listed in Table 1.* The structural formula and atom numbering are given in Fig. 1. Bond lengths and angles are listed in Table 2. The conformation of the molecule is shown in Fig. 2 and Table 3.

Bond distances and angles in the three fused rings, benzene, diazepine, and pyridine, are affected by the conjugation. Deviation from the values expected for the given atom type and hybridization could not be explained by the thermal vibrations of the atoms. The shortening of C(7)—C(8), 1·372 (4) Å, in the benzene ring could be attributed to intermolecular contacts, involving these atoms, with N(1) [3·352 (3); 3·470 (3) Å].

The seven-membered diazepine ring exhibits a boat conformation with the fold at N(5)—C(6) and N(11). Boat and chair conformations are possible for the seven-membered ring although results about the barriers to ring reversal in some benzodiazepine derivatives indicate the boat structure as the more stable one (Raban, Carlson, Szumuszkovicz, Slomp, Chidester & Duchamp, 1975). X-ray structure determinations of many inactive and active 1,4-benzodiazepines confirm this statement (Ružić-Toroš, Kojić-Prodić, Bresciani-Pahor, Nardin & Randaccio, 1982; Bandoli & Clemente, 1976; Gilli, Bertolasi, Sacerdoti & Borea, 1977, 1978).

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* Lists of structure factors, anisotropic thermal parameters, displacements of the atoms from least-squares planes, intermolecular contacts and hydrogen bonds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38114 (29 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final atomic coordinates* ($\times 10^4$ *for* C, N *and* O; $\times 10^3$ *for* H) *and isotropic thermal parameters* ($\times 10^2$)

U_{eq} is derived from the anisotropic thermal parameters by $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	*y*	*z*	U_{eq} or U(Å^2)
N(1)	6263 (1)	1423 (1)	6087 (1)	4·2 (2)
C(2)	6199 (1)	1306 (1)	4985 (1)	4·6 (2)
C(3)	6380 (1)	372 (2)	4557 (1)	4·7 (2)
C(4)	6615 (1)	−503 (1)	5255 (1)	4·3 (2)
N(5)	7023 (1)	−1266 (1)	7162 (1)	4·3 (2)
C(6)	6726 (1)	−1540 (1)	8057 (1)	4·2 (2)
O(6)	7131 (1)	−2330 (1)	8634 (1)	6·4 (2)
C(7)	5060 (1)	−1465 (1)	8510 (1)	4·8 (3)
C(8)	4228 (2)	−932 (2)	8677 (1)	5·1 (3)
C(9)	4186 (1)	143 (2)	8615 (1)	5·1 (3)
C(10)	4978 (1)	698 (1)	8379 (1)	4·5 (2)
N(11)	6635 (1)	716 (1)	7947 (1)	3·7 (2)
C(12)	6537 (1)	588 (1)	6761 (1)	3·4 (2)
C(13)	6695 (1)	−404 (1)	6403 (1)	3·5 (2)
C(14)	5866 (1)	−922 (1)	8266 (1)	3·9 (2)
C(15)	5818 (1)	162 (1)	8216 (1)	3·7 (2)
C(16)	7373 (1)	1361 (1)	8752 (1)	4·2 (2)
O(16)	7400 (1)	1426 (1)	9749 (1)	6·2 (2)
C(17)	8146 (1)	1997 (1)	8376 (2)	4·6 (3)
N(1′)	8712 (1)	1375 (1)	7805 (1)	3·8 (2)
C(2′)	9214 (1)	2042 (1)	7195 (2)	4·9 (3)
C(3′)	9766 (2)	1377 (2)	6583 (2)	5·8 (3)
N(4′)	10604 (1)	696 (1)	7417 (1)	5·0 (2)
C(5′)	10082 (2)	28 (1)	8008 (2)	5·4 (3)
C(6′)	9536 (2)	688 (2)	8627 (2)	4·7 (2)
C(7′)	11162 (3)	63 (3)	6827 (3)	8·4 (4)
O(*W*)	2165 (2)	2153 (1)	8845 (2)	7·9 (2)
H(2)	603 (2)	195 (2)	451 (2)	6·1 (7)
H(3)	632 (2)	32 (2)	375 (2)	5·2 (6)
H(4)	676 (2)	−118 (2)	499 (2)	3·9 (6)
H(5)	737 (2)	−175 (2)	696 (2)	4·3 (6)
H(7)	509 (2)	−222 (2)	854 (2)	5·7 (7)
H(8)	366 (2)	−133 (2)	886 (2)	7·1 (8)
H(9)	363 (2)	53 (2)	871 (2)	5·2 (6)
H(10)	496 (2)	143 (2)	834 (2)	4·2 (6)
H(17)1	868 (2)	237 (2)	909 (2)	6·3 (7)
H(17)2	768 (2)	259 (2)	780 (2)	5·7 (7)
H(2′)1	857 (2)	248 (2)	661 (2)	6·0 (7)
H(2′)2	978 (2)	255 (2)	777 (2)	6·6 (8)
H(3′)1	918 (2)	91 (2)	594 (2)	6·6 (9)
H(3′)2	1017 (2)	184 (2)	621 (2)	8·3 (9)
H(5′)1	951 (2)	−46 (2)	741 (2)	6·6 (7)
H(5′)2	1068 (2)	−44 (2)	857 (2)	7·0 (8)
H(6′)1	1012 (2)	112 (2)	929 (2)	5·1 (6)
H(6′)2	917 (2)	21 (2)	904 (2)	7·5 (8)
H(7′)1	1175 (3)	−45 (3)	747 (3)	11 (1)
H(7′)2	1152 (3)	55 (3)	648 (3)	9 (1)
H(7′)3	1057 (3)	−38 (3)	615 (3)	10 (1)
H(*W*)1	162 (3)	167 (3)	843 (3)	10 (1)
H(*W*)2	223 (4)	217 (4)	950 (4)	14 (2)

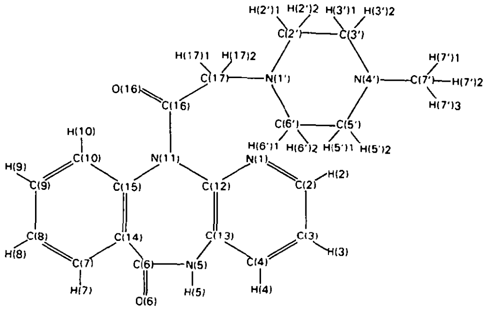

Fig. 1. Structural formula with the atom numbering.

Table 2. *Bond distances* (Å) *and angles* (°)

N(1)—C(2)	1·348 (3)	C(14)—C(15)	1·388 (3)
N(1)—C(12)	1·315 (3)	C(16)—O(16)	1·229 (3)
C(2)—C(3)	1·364 (4)	C(16)—C(17)	1·513 (4)
C(2)—H(2)	0·99 (2)	C(17)—N(1′)	1·452 (3)
C(3)—C(4)	1·375 (3)	C(17)—H(17)1	1·01 (2)
C(3)—H(3)	0·97 (2)	C(17)—H(17)2	1·05 (2)
C(4)—C(13)	1·395 (3)	N(1′)—C(2′)	1·460 (3)
C(4)—H(4)	0·97 (2)	N(1′)—C(6′)	1·454 (3)
N(5)—C(6)	1·362 (3)	C(2′)—C(3′)	1·505 (4)
N(5)—C(13)	1·403 (3)	C(2′)—H(2′)1	1·04 (2)
N(5)—H(5)	0·86 (2)	C(2′)—H(2′)2	1·04 (2)
C(6)—O(6)	1·231 (3)	C(3′)—N(4′)	1·465 (3)
C(6)—C(14)	1·484 (4)	C(3′)—H(3′)1	1·05 (2)
C(7)—C(14)	1·397 (4)	C(3′)—H(3′)2	1·01 (3)
C(7)—H(7)	0·97 (2)	N(4′)—C(5′)	1·462 (4)
C(7)—C(8)	1·372 (4)	N(4′)—C(7′)	1·468 (5)
C(8)—C(9)	1·377 (4)	C(5′)—C(6′)	1·502 (4)
C(8)—H(8)	1·00 (3)	C(5′)—H(5′)1	1·03 (2)
C(9)—C(10)	1·383 (4)	C(5′)—H(5′)2	1·01 (2)
C(9)—H(9)	0·92 (2)	C(6′)—H(6′)1	1·04 (2)
C(10)—C(15)	1·381 (3)	C(6′)—H(6′)2	1·03 (3)
C(10)—H(10)	0·94 (2)	C(7′)—H(7′)1	1·09 (3)
N(11)—C(12)	1·438 (3)	C(7′)—H(7′)2	0·97 (4)
N(11)—C(15)	1·433 (3)	C(7′)—H(7′)3	1·05 (3)
N(11)—C(16)	1·362 (2)	O(*W*)—H(*W*)1	0·93 (3)
C(12)—C(13)	1·387 (3)	O(*W*)—H(*W*)2	0·78 (5)

C(2)—N(1)—C(12)	116·7 (2)	C(12)—N(11)—C(16)	124·9 (2)
N(1)—C(2)—C(3)	122·9 (2)	C(15)—N(11)—C(16)	120·6 (2)
N(1)—C(2)—H(2)	115 (1)	N(1)—C(12)—N(11)	117·0 (2)
C(3)—C(2)—H(2)	121 (1)	N(1)—C(12)—C(13)	125·0 (2)
C(2)—C(3)—C(4)	119·6 (2)	N(11)—C(12)—C(13)	118·0 (2)
C(2)—C(3)—H(3)	120 (1)	C(4)—C(13)—N(5)	119·8 (2)
C(4)—C(3)—H(3)	120 (1)	C(4)—C(13)—C(12)	116·8 (2)
C(3)—C(4)—C(13)	118·7 (2)	N(5)—C(13)—C(12)	123·1 (2)
C(3)—C(4)—H(4)	123 (1)	C(6)—C(14)—C(7)	118·1 (2)
C(13)—C(4)—H(4)	118 (1)	C(6)—C(14)—C(15)	123·2 (2)
C(6)—N(5)—C(13)	129·8 (2)	C(7)—C(14)—C(15)	118·6 (2)
C(6)—N(5)—H(5)	114 (1)	C(10)—C(15)—N(11)	120·5 (2)
C(13)—N(5)—H(5)	115 (1)	C(10)—C(15)—C(14)	120·9 (2)
N(5)—C(6)—O(6)	119·3 (2)	N(11)—C(15)—C(14)	118·5 (2)
N(5)—C(6)—C(14)	119·3 (2)	N(11)—C(16)—O(16)	120·8 (2)
O(6)—C(6)—C(14)	121·2 (2)	N(11)—C(16)—C(17)	117·9 (2)
C(8)—C(7)—C(14)	120·5 (2)	O(16)—C(16)—C(17)	121·3 (2)
C(8)—C(7)—H(7)	121 (2)	C(16)—C(17)—N(1′)	113·2 (2)
C(14)—C(7)—H(7)	118 (2)	C(17)—N(1′)—C(2′)	111·0 (2)
C(7)—C(8)—C(9)	120·2 (3)	C(17)—N(1′)—C(6′)	111·7 (2)
C(7)—C(8)—H(8)	120 (2)	C(2′)—N(1′)—C(6′)	110·6 (2)
C(9)—C(8)—H(8)	120 (2)	N(1′)—C(2′)—C(3′)	109·9 (2)
C(8)—C(9)—C(10)	120·4 (2)	C(2′)—C(3′)—N(4′)	110·8 (2)
C(8)—C(9)—H(9)	123 (1)	C(3′)—N(4′)—C(5′)	109·3 (2)
C(10)—C(9)—H(9)	117 (1)	C(3′)—N(4′)—C(7′)	110·9 (2)
C(9)—C(10)—C(15)	119·4 (2)	C(5′)—N(4′)—C(7′)	110·9 (2)
C(9)—C(10)—H(10)	121 (1)	N(4′)—C(5′)—C(6′)	110·1 (2)
C(15)—C(10)—H(10)	119 (1)	N(1′)—C(6′)—C(5′)	110·6 (2)
C(12)—N(11)—C(15)	114·3 (1)	H(*W*)1—O(*W*)—H(*W*)2	110 (4)

Table 3. *Torsion angles* (°)

C(12)—N(1)—C(2)—C(3)	1·4 (3)	C(14)—C(15)—N(11)—C(12)	69·5 (2)
N(1)—C(2)—C(3)—C(4)	1·5 (4)	N(11)—C(12)—C(13)—N(5)	−4·7 (3)
C(2)—C(3)—C(4)—C(13)	−2·0 (3)	C(12)—C(13)—N(5)—C(6)	38·3 (3)
C(3)—C(4)—C(13)—C(12)	−0·4 (3)	C(13)—N(5)—C(6)—C(14)	5·3 (3)
C(3)—C(4)—C(13)—N(5)	−174·7 (2)	C(15)—N(11)—C(12)—C(13)	−64·5 (2)
C(4)—C(13)—C(12)—N(1)	3·6 (3)	C(13)—N(5)—C(6)—O(6)	−178·8 (2)
C(4)—C(13)—C(12)—N(11)	−178·9 (2)	C(12)—N(11)—C(16)—O(16)	179·8 (2)
C(13)—C(12)—N(1)—C(2)	−4·1 (3)	C(12)—N(11)—C(16)—C(17)	0·2 (3)
C(7)—C(8)—C(9)—C(10)	0·3 (3)	N(11)—C(16)—C(17)—N(1′)	−50·0 (2)
C(8)—C(9)—C(10)—C(15)	−0·5 (3)	C(16)—C(17)—N(1′)—C(2′)	165·2 (1)
C(9)—C(10)—C(15)—C(14)	1·1 (3)	C(17)—N(1′)—C(2′)—C(3′)	−178·4 (1)
C(9)—C(10)—C(15)—N(11)	178·7 (2)	N(1′)—C(2′)—C(3′)—N(4′)	−57·9 (2)
C(10)—C(15)—C(14)—C(7)	−1·4 (3)	C(2′)—C(3′)—N(4′)—C(5′)	58·7 (3)
C(10)—C(15)—C(14)—C(6)	177·8 (2)	C(2′)—C(3′)—N(4′)—C(7′)	−178·7 (2)
C(15)—C(14)—C(7)—C(8)	1·1 (3)	C(3′)—N(4′)—C(5′)—C(6′)	−58·6 (2)
C(14)—C(7)—C(8)—C(9)	−0·6 (3)	N(4′)—C(5′)—C(6′)—N(1′)	58·6 (2)
N(5)—C(6)—C(14)—C(15)	−42·4 (3)	C(5′)—C(6′)—N(1′)—C(2′)	−57·7 (2)
C(6)—C(14)—C(15)—N(11)	0·2 (3)		

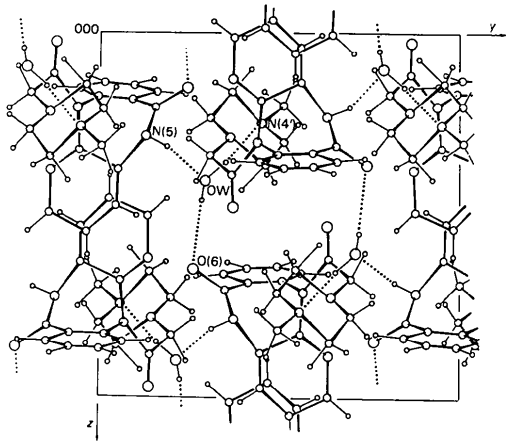

Fig. 2. A view of the crystal structure along **a** showing the packing, hydrogen bonds, and conformation of the benzodiazepine and piperazine rings.

The pyridine and benzene rings are planar in the limits of the experimental errors whereas the piperazine ring is in a chair conformation. The dihedral angle between the benzene and the pyridine ring is 60·9 (4)°.

The water molecule is involved in hydrogen bonds with the amide group of the diazepine ring, N(5)–H(5)···O(*W*)[2·800 (3)] and O(*W*)–H(*W*)2 ···O(6)[2·907 (3) Å]. N(4′) of the piperazine ring is hydrogen-bonded to the water molecule by O(*W*)–H(*W*)1···N(4′)[2·821 (3) Å]. Molecular packing is also influenced by van der Waals interactions. The relative orientation of the pyridine and piperazine ring [with a dihedral angle of 22·2 (4)°] enables a short intramolecular contact N(1)···N(1′) of 3·087 (2) Å.

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References

BANDOLI, G. & CLEMENTE, D. A. (1976). *J. Chem. Soc. Perkin Trans.* 2, pp. 413–418.

CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A**24**, 321–324.

GILLI, G., BERTOLASI, V., SACERDOTI, M. & BOREA, P. A. (1977). *Acta Cryst.* B**33**, 2664–2667.

GILLI, G., BERTOLASI, V., SACERDOTI, M. & BOREA, P. A. (1978). *Acta Cryst.* B**34**, 2826–2829, 3793–3795.

LUGER, P. (1981). *Acta Cryst.* A**37**, C60.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J. P. & WOOLFSON, M. M. (1980). *MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

PROUS, J. R. (1979). Editor, *Annual Drug Data Report,* Vol. II, p. 180. Barcelona: J. R. Prous Publishers.

RABAN, M., CARLSON, E. H., SZUMUSZKOVICZ, J., SLOMP, G., CHIDESTER, C. G. & DUCHAMP, D. J. (1975). *Tetrahedron Lett.* pp. 139–142.

RUŽIĆ-TOROŠ, Ž., KOJIĆ-PRODIĆ, B., BRESCIANI-PAHOR, N., NARDIN, G. & RANDACCIO, L. (1982). *Acta Cryst.* B**38**, 2977–2981.

STEWART, J. M., MACHIN, P. A., DICKINSON, C., AMMON, H. L., HECK, H. & FLACK, H. (1976). The XRAY 76 system. Tech. Rep. TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

WILSON, A. J. C. (1942). *Nature* (*London*), **150**, 151–152.

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(23*R*,25*R*)- and (23*S*,25*S*)-3β-Methoxymethoxy-5α,8α-(3,5-dioxo-4-phenyl-1,2,4-triazole-1,2-diyl)-25-hydroxycholest-6-eno-26,23-lactone, $C_{37}H_{49}N_3O_7$

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Abstract. $M_r = 647\cdot8$, (23*R*,25*R*) isomer: monoclinic, $P2_1$, $a = 12\cdot939$ (2), $b = 9\cdot909$ (2), $c = 13\cdot517$ (2) Å, $\beta = 100\cdot46$ (1)°, $V = 1704\cdot3$ (5) Å^3, $Z = 2$, $D_x = 1\cdot262$ Mg m^{-3}, $F(000) = 696$, μ(Cu $K\alpha$) = 0·6 mm^{-1}; (23*S*,25*S*) isomer: orthorhombic, $P2_12_12_1$, $a = 9\cdot946$ (2), $b = 29\cdot966$ (7), $c = 11\cdot189$ (2) Å, $V = 3334\cdot8$ (8) Å^3, $Z = 4$, $D_x = 1\cdot290$ Mg m^{-3} $F(000) = 1392$, μ(Cu $K\alpha$) = 0·6 mm^{-1}. The structures were determined by Patterson-search and direct methods and refined to R_w values of respectively 0·051 and 0·047 for 2650 and 3005 observed reflections. The molecules are T-shaped with the 4-phenyltriazole moiety perpen-

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