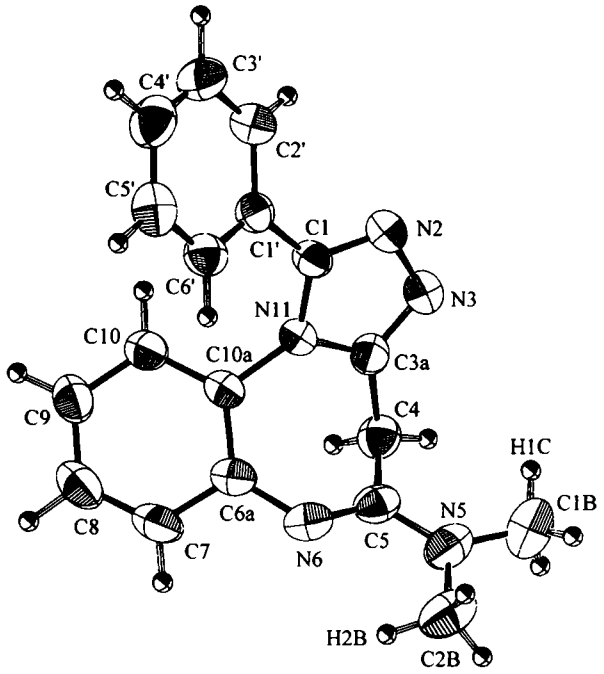
Crystal structure of *N,N*-dimethyl-1-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,5]-benzodiazepin-5-amine, $C_{18}H_{17}N_5$

A. Borassi[I], M. Di Braccio[II], G. C. Grossi[II], G. Izzo[I] and A. Mugnoli*[I]

[I] Dipartimento di Chimica e Chimica Industriale, Università degli Studi di Genova, Via Dodecaneso, 31, I-16146 Genova, Italy
[II] Dipartimento di Scienze Farmaceutiche, Università degli Studi di Genova, Viale Benedetto XV, 3, I-16132 Genova, Italy

Received April 9, 2001, CCDC-No. 1267/650



Abstract

$C_{18}H_{17}N_5$, orthorhombic, $P2_12_12_1$ (No. 19), $a = 8.769(5)$ Å, $b = 9.500(3)$ Å, $c = 18.916(8)$ Å, $V = 1575.8$ Å^3, $Z = 4$, $R_{gt}(F) = 0.036$, $wR_{ref}(F^2) = 0.089$, $T = 294$ K.

Source of material

The compound was crystallized from a mixture of cyclohexane and ethyl acetate.

Experimental details

With the exception of the C1B hydrogen atoms, which were localized by means of a circular Fourier synthesis, all the H atoms were obtained experimentally and their positions and thermal factors were refined.

Discussion

Several [1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines are known to possess pharmacological activities. For instance, we have recently described the crystal structure of RL202, an anticonvulsant compound of this family [1]. On the other hand, a number of *N*-substituted [1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines were reported to exhibit anti-inflammatory and analgesic activities [2,3] or anti-convulsant properties [4], depending on their substitution pattern. As a further part in the study of these novel biologically active amino derivatives, we have now investigated the crystal structure of the title compound, an anti-inflammatory agent [2] indicated here as RL142.

As in RL202, the diazepine ring shows a boat conformation, the ring asymmetry parameters [5,6] evidencing a pseudo mirror plane through atom C4 [$\Delta C_s = 0.0390(9)$]. The (acute) dihedral angles between the central plane (N11, C3a, C5, N6) and the planes defined by atoms C3a, C4, C5 and by N6, C6a, C10a, N11 respectively, known as 'bow' and 'stern' angles [7], are 52.7(1)° and 39.0(1)° for RL142, to be compared with 55.1(1)° and 37.1(1)°, respectively, for RL202. Atoms C5, C1B, C2B, N5 are coplanar within 0.008 Å. In both methyl groups C1B and C2B, there is an H atom not far from an eclipsed orientation with respect to the C5—N5 bond, the involved C5–N5–C1B–H1C and C5–N5–C2B–H2B torsion angles being 25° and 17°, respectively. For this last methyl group, a short intramolecular contact should be noticed, the H2B···N6 distance being only 2.31(3) Å. Other conformational parameters in RL142 are the torsion angles of the C1-phenyl ring and of the C5-dimethylamino moiety.

In order to obtain the molecular conformation in absence of crystal forces, the geometry of the isolated molecule of RL142 has been optimized with DFT methods at the B3LYP/6-31G** level (full optimization, 430 basis functions) [8]. The same level of theory and basis set have been used even to optimize the molecular geometry in a water continuum, following the Onsager approach [9,10]. Both calculations show that the system C5, C1B, C2B, N5 preserves a roughly planar geometry (within 0.076 Å in the gas phase, within 0.058 Å in solution). Considering the phenyl- and the dimethylamino-group the experimental and the calculated conformations are very similar, the involved torsion angles in the crystal, in the isolated molecule and in the water solution being: N2-C1-C1′-C2′, 35.2°, 33.2° and 32.6°, respectively; N6–C5–N5–C2B, 2.8°, –1.8° and –0.2°, respectively.

On the whole, essentially the same conformation is found in the three phases, the only difference involving the rotation of the methyl groups. In particular the torsion angle C5–N5–C2B–H2B (17°, 34° and 31° in the experimental, isolated and solvated molecule, respectively) seems to be stabilized by a weak intramolecular H2B···N6 electrostatic interaction. In fact in the optimized models the calculated Mulliken charges for the most negatively charged atoms are –0.58 a.u. (N6 and N11) and for the most positive H atoms 0.15 a.u. (H2B) and 0.16 a.u. (H1C). Correspondingly, the H2B···N6 distance in the isolated molecule and in water solution is 2.37 Å and 2.36 Å, respectively.

* Correspondence author (e-mail: mugnoli@unige.it)

Table 1. Data collection and handling.

Crystal:	colourless, rounded prism, size 0.36 × 0.39 × 0.42 mm
Wavelength:	Mo K_α radiation (0.7107 Å)
μ:	0.80 cm^{-1}
Diffractometer, scan mode:	Enraf-Nonius CAD4, ω/θ
$2\theta_{max}$:	54.84°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	2070, 2070
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 1659
$N(param)_{refined}$:	266
Programs:	PARST [5], SIR97 [11], SHELXL-97 [12], ORTEP-II [13]

Table 2. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	x	y	z	U_{iso}
H(1A)	4a	0.8194	0.6613	0.1077	0.106
H(1B)	4a	0.9627	0.7335	0.1416	0.106
H(1C)	4a	0.7990	0.7705	0.1692	0.106
H(2A)	4a	1.036(5)	0.485(4)	0.152(2)	0.11(1)
H(2B)	4a	0.997(4)	0.407(4)	0.227(2)	0.09(1)
H(2C)	4a	1.093(5)	0.545(4)	0.222(2)	0.13(1)
H(41)	4a	0.535(3)	0.583(2)	0.257(1)	0.050(6)
H(42)	4a	0.604(3)	0.694(2)	0.210(1)	0.059(7)
H(7)	4a	0.707(3)	0.223(3)	0.342(1)	0.068(8)
H(8)	4a	0.540(4)	0.154(3)	0.432(2)	0.089(9)
H(9)	4a	0.422(3)	0.327(2)	0.501(1)	0.062(7)
H(10)	4a	0.460(3)	0.567(3)	0.473(1)	0.055(6)
H(2′)	4a	0.558(3)	0.969(3)	0.520(1)	0.062(7)
H(3′)	4a	0.592(4)	0.975(3)	0.644(2)	0.088(9)
H(4′)	4a	0.726(3)	0.788(3)	0.698(2)	0.082(8)
H(5′)	4a	0.838(3)	0.601(3)	0.628(1)	0.074(8)
H(6′)	4a	0.796(3)	0.605(3)	0.506(1)	0.057(6)

Table 3. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	4a	0.6542(2)	0.7932(2)	0.4249(1)	0.046(1)	0.0333(9)	0.050(1)	-0.0016(9)	0.004(1)	-0.0042(9)
N(2)	4a	0.6559(2)	0.9096(2)	0.3881(1)	0.064(1)	0.0385(9)	0.057(1)	-0.0038(9)	0.009(1)	-0.0003(8)
N(3)	4a	0.6393(3)	0.8740(2)	0.31709(9)	0.067(1)	0.042(1)	0.053(1)	-0.0002(9)	0.008(1)	0.0043(8)
C(3A)	4a	0.6291(3)	0.7372(2)	0.3146(1)	0.046(1)	0.045(1)	0.044(1)	0.0018(9)	0.005(1)	0.0039(9)
C(4)	4a	0.6214(3)	0.6434(3)	0.2525(1)	0.055(1)	0.055(1)	0.040(1)	0.001(1)	-0.003(1)	0.001(1)
C(5)	4a	0.7668(2)	0.5572(2)	0.2523(1)	0.049(1)	0.053(1)	0.041(1)	-0.002(1)	-0.001(1)	-0.014(1)
N(6)	4a	0.7921(2)	0.4600(2)	0.29869(9)	0.051(1)	0.054(1)	0.0463(9)	0.0079(9)	-0.0004(8)	-0.0111(9)
C(6A)	4a	0.6875(3)	0.4326(2)	0.3529(1)	0.048(1)	0.042(1)	0.043(1)	0.0080(9)	-0.0070(9)	-0.0064(9)
C(7)	4a	0.6601(3)	0.2914(2)	0.3708(1)	0.076(2)	0.037(1)	0.056(1)	0.010(1)	-0.009(1)	-0.009(1)
C(8)	4a	0.5618(4)	0.2540(2)	0.4239(1)	0.086(2)	0.037(1)	0.060(1)	-0.001(1)	-0.012(1)	0.005(1)
C(9)	4a	0.4864(3)	0.3554(2)	0.4628(1)	0.069(2)	0.045(1)	0.051(1)	-0.008(1)	-0.004(1)	0.008(1)
C(10)	4a	0.5124(3)	0.4954(2)	0.4481(1)	0.049(1)	0.040(1)	0.047(1)	0.003(1)	-0.001(1)	-0.0018(9)
C(10A)	4a	0.6134(2)	0.5331(2)	0.3948(1)	0.044(1)	0.0334(9)	0.043(1)	0.0023(8)	-0.0043(9)	-0.0014(8)
N(11)	4a	0.6383(2)	0.6799(2)	0.38087(8)	0.0466(9)	0.0329(8)	0.0415(8)	0.0012(7)	0.0033(8)	-0.0006(7)
C(1′)	4a	0.6743(2)	0.7882(2)	0.5022(1)	0.044(1)	0.040(1)	0.047(1)	-0.0084(9)	0.0052(9)	-0.0040(9)
C(2′)	4a	0.6154(3)	0.8964(2)	0.5434(1)	0.064(1)	0.045(1)	0.057(1)	0.001(1)	0.004(1)	-0.007(1)
C(3′)	4a	0.6367(4)	0.8966(3)	0.6157(1)	0.086(2)	0.065(2)	0.052(1)	-0.005(2)	0.012(1)	-0.016(1)
C(4′)	4a	0.7202(4)	0.7904(3)	0.6474(1)	0.082(2)	0.077(2)	0.044(1)	-0.017(2)	0.002(1)	-0.002(1)
C(5′)	4a	0.7791(3)	0.6823(3)	0.6073(1)	0.060(1)	0.062(2)	0.059(1)	-0.009(1)	-0.007(1)	0.009(1)
C(6′)	4a	0.7562(3)	0.6811(2)	0.5349(1)	0.046(1)	0.048(1)	0.057(1)	-0.004(1)	0.002(1)	-0.004(1)
N(5)	4a	0.8729(2)	0.5843(2)	0.2020(1)	0.059(1)	0.074(1)	0.049(1)	-0.005(1)	0.0094(9)	-0.011(1)
C(1B)	4a	0.8627(4)	0.6969(4)	0.1508(2)	0.095(2)	0.099(2)	0.072(2)	-0.008(2)	0.025(2)	0.012(2)
C(2B)	4a	1.0107(3)	0.4998(4)	0.1986(2)	0.056(2)	0.099(2)	0.064(2)	-0.001(2)	0.011(1)	-0.021(2)

Acknowledgments. We wish to thank Professor G. Roma (University of Genova) for his continuous interest in this work and for discussions. Financial support from the Italian C.N.R. is gratefully acknowledged. This work was partially supported by the Fondazione Cassa di Risparmio di Genova e Imperia.

References

1. Borassi, A.; Carnasciali, M. M.; Mugnoli, A.; Roma, G.: 8-Chloro-6-phenyl-4H-[1,2,4]-triazolo[4,3-a][1,5]benzodiazepin-5(6*H*)-one. Acta Crystallogr. C**56** (2000) 258-259.
2. Di Braccio, M.; Roma, G.; Grossi, G. C.; Ghia, M.; Mereto, E.: 1,5-Benzodiazepines VIII. Novel 4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine derivatives with analgesic or anti-inflammatory activity. Eur. J. Med. Chem. **25** (1990) 681-687.
3. Roma, G.; Grossi, G. C.; Di Braccio, M.; Ghia, M.; Mattioli, F.: 1,5-Benzodiazepines IX. A new route to substituted 4*H*-[1,2,4]triazolo-[4,3-a][1,5]benzodiazepin-5-amines with analgesic and/or anti-inflammatory activities. Eur. J. Med. Chem. **26** (1991) 489-496.
4. Grossi, G. C.; Di Braccio, M.; Roma, G.; Ghia, M.; Brambilla, G.: 1,5-Benzodiazepines XI 5-(Dialkylamino) or 5-(alkylthio) substituted 8-chloro-6-phenyl-6*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines with anticonvulsant activity. Eur. J. Med. Chem. **28** (1993) 577-584.
5. Nardelli, M.: PARST. A system of FORTRAN routines for calculating molecular structure parameters from results of crystal structure analyses. Computers and Chemistry **7** (1983) 95-98.
6. Nardelli, M.: Ring asymmetry parameters from out-of-plane atomic displacements. Acta Crystallogr. C**39** (1983) 1141-1142.
7. Hamor, T. A.; Martin, I. L.: The Benzodiazepines. In: *Progress in Medicinal Chemistry* (Eds. G. P. Ellis and G. B.West), Elsevier Science Publishers 1983, Vol. 20, p.157-233.
8. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.;Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D.J., Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.: GAUSSIAN98, Revision A9. Gaussian, Inc., Pittsburgh PA, USA 1998.

9. Onsager, L.: Electric moments of molecules in liquids. J. Amer. Chem. Soc. **58** (1936) 1486-1493.
10. Wong, M. W.; Frisch, M. J.; Wiberg, K. B.: Solvent effects 1. The mediation of electrostatic effects by solvents. J. Amer. Chem. Soc. **113** (1991) 4776-4782.
11. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R.: SIR97: A new tool for crystal structure determination and refinement. J. Appl. Crystallogr. **32** (1999) 115-119.
12. Sheldrick, G. M.: SHELXL-97: A program for refinement of crystal structures. Germany, University of Göttingen, Germany 1997.
13. Johnson, C. K.: ORTEP-II. A FORTRAN thermal-ellipsoid plot program for crystal structure illustrations. Report ORNL-5138. TN, USA: Oak Ridge National Laboratory, USA 1976.