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2-(4-Chlorophenyl)-1,3-dicyano-6,7-dihydro-4-imino-9,10-dimethoxybenzo[*a*]quinolizine–water (2/5)

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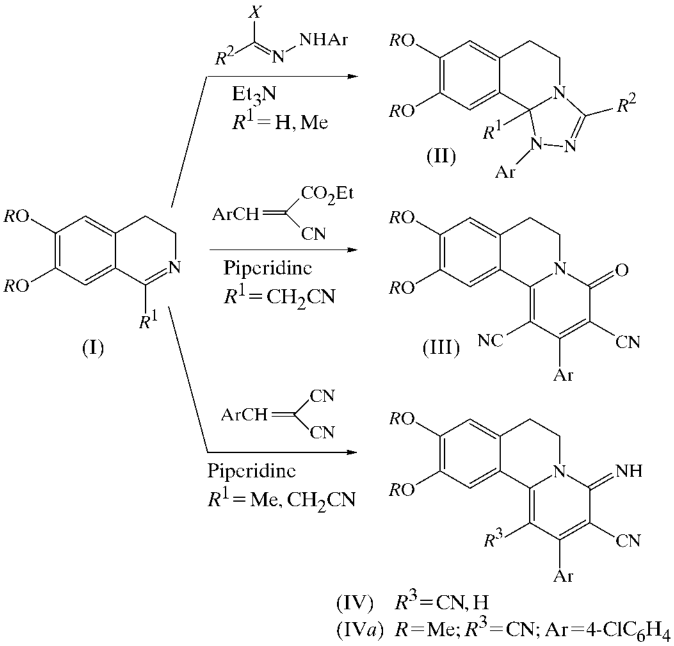
Crystals of the title compound, $C_{23}H_{17}ClN_4O_2 \cdot 2.5H_2O$, contain channels filled with highly disordered water molecules. The best structure refinement was obtained by removing the solvent contribution from the intensity data and refining against a solvent-free model. The central six-membered ring of the quinolizine molecule has a slightly distorted screw-boat conformation.

Comment

Fused isoquinoline derivatives are of considerable pharmaceutical and agricultural interest (Kleeman & Engel, 1982; Dannhardt & Sommer, 1985; Fülöp *et al.*, 1990). Compounds with a fused five-membered ring at the original isoquinoline C═N bond can be prepared conveniently by 1,3-dipolar cycloadditions with 3,4-dihydroisoquinolines, (I) (Shawali, 1993). For example, [1,2,4]triazolo[3,4-*a*]isoquinolines of type (II) were obtained in high yield from cycloadditions with nitrile–imines (*cf.* Caramella & Grünanger, 1984), which were generated *in situ* from the corresponding hydrazonoyl halides by elimination of H*X* on treatment with a base (Dannhardt & Sommer, 1985; Fülöp *et al.*, 1990; Szabó *et al.*, 1992; Abdelhadi *et al.*, 1996; Elwan *et al.*, 1996; Awad *et al.*, 2002). On the other hand, pyrrolo[2,1-*a*]isoquinoline derivatives were obtained from 1-(cyanomethyl)-3,4-dihydroisoquinolines and hydrazonoyl halides in refluxing tetrahydrofuran in the presence of Et_3N (Awad *et al.*, 2001). In none of the reactions was a product with a fused six-membered ring formed (*cf.* Fülöp *et al.*, 1990; Elwan *et al.*, 1996). However, isoquinolines with a fused six-membered ring at the original C═N bond are attractive targets (Fülöp *et al.*, 1997; Fülöp & Bernáth, 1999; Martinek *et al.*, 2000), and several methods for the preparation of benzo[*a*]quinolizines have been reported (Kametani, 1978; Bhattacharjya *et al.*, 1983; Maiti & Pakrashi, 1984; Ninomiya *et al.*, 1984; Akhrem & Chernov, 1988).



(IV) R^3=CN, H
(IV*a*) *R*=Me; R^3=CN; Ar=4-ClC$_6$H$_4$

Recently, we developed a novel and efficient one-pot synthesis for polyfunctional benzo[*a*]quinolizine derivatives (Awad *et al.*, 2002). The reaction of 1-(cyanomethyl)-6,7-diethoxy-3,4-dihydroisoquinoline [(I), R^1 = CH_2CN] with ethyl *β*-aryl-*α*-cyanocinnamates in the presence of piperidine led to 1,3-dicyano-6,7-dihydrobenzo[*a*]quinolizin-4-ones, (III), in high yield, whereas similar reactions with arylidenemalononitriles gave the corresponding 4-iminoquinolizines,

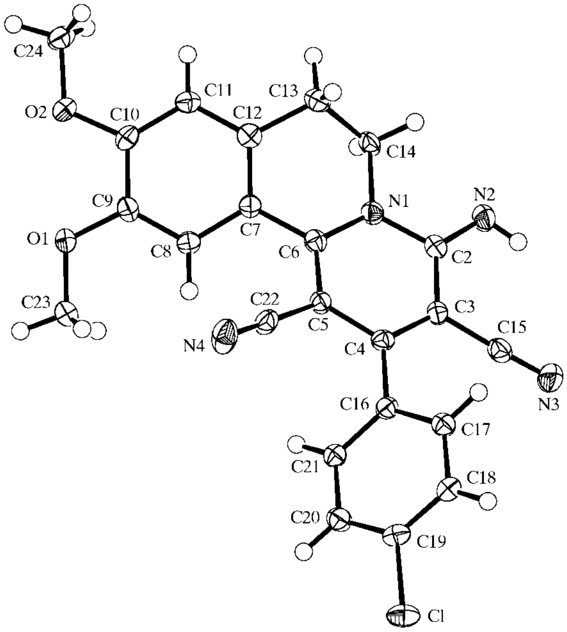


Figure 1
View of the quinolizine molecule of (IV*a*) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of arbitrary size. The solvent molecules were not included in the model.

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(IV) (Awad *et al.*, 2002). The structures of these products have been established on the basis of their spectroscopic data and elemental analyses. With the aim of proving the structure of the imino compounds of type (IV), the low-temperature crystal structure of the title compound, (IV*a*) (R = Me, R^3 = CN, Ar = 4–ClC_6H_4), has been determined.

Compound (IV*a*) crystallizes as a hydrate with approximately 2.5 water molecules for every quinolizine molecule. There are two solvent cavities per unit cell, so that each cavity contains five water molecules. The water molecules appear to be highly disordered and it was difficult to model their positions and distribution reliably. Therefore, the *SQUEEZE* function of *PLATON* (van der Sluis & Spek, 1990; Spek, 2001) was used to eliminate the contribution of the electron density in the solvent region from the intensity data, and the solvent-free model was employed for the final refinement. Further details are given in the *Experimental* section. Due to the omission of the water molecules from the model, it was not possible to analyse the hydrogen-bonding interactions fully. Attempts to model the solvent molecules indicated that they are suitably positioned for a series of water–water hydrogen bonds to exist. The packing diagram (Fig. 2) shows that the solvent cavities are aligned into channels through the structure, so that infinite chains of hydrogen-bonded water molecules are conceivable. Fig. 2 also shows that the imine H atom is far from the solvent channels and is therefore unable to form a hydrogen bond with any of the water molecules. Furthermore, the N2—H2 bond is aligned in the plane of the quinolizine molecule and these molecules are stacked parallel to one another. In this position, the imine H atom does not partake in any hydrogen-bonding interactions.

The central six-membered ring of the quinolizine molecule has a slightly distorted screw-boat conformation (Fig. 1), with puckering parameters (Cremer & Pople, 1975) Q = 0.514 (3) Å, θ = 72.7 (2)° and φ = 263.3 (3)° for the atom sequence N1—C6—C7—C12—C13—C14. For an ideal screw-boat, the nearest ideal values are θ = 67.5° and φ = 270°. Atoms C12 and C13 are 0.409 (4) and 0.887 (4) Å, respectively, from the mean plane defined by atoms N1, C6, C7 and C14, and the r.m.s deviation of these latter four atoms from their plane is 0.035 Å. The r.m.s. deviation of the six atoms of the benzo ring from their mean plane is 0.011 Å, while the cyano-substituted six-membered ring is distorted very slightly from planarity, with an r.m.s. deviation of 0.031 Å; the maximum deviation from this plane is 0.0527 (16) Å for C6. The angle between the mean planes of the benzo and cyano-substituted rings is 29.71 (6)°, while the latter ring makes an angle of 43.25 (6)° with the *p*-chlorophenyl ring. The bond lengths around the cyano-substituted six-membered ring (Table 1) show that there is significant delocalization of the electron density from the C2=N2, C3=C4 and C5=C6 double bonds towards the N1—C2, N1—C6 and C4—C5 bonds. Similar delocalization involving the N1 atom is observed in the structure of the related compound 11,16,16-trimethyl-8-aza-D-homogona-1,3,5(10),9(11),13,17-hexaen-12-one (Lyakhov *et al.*, 1997).

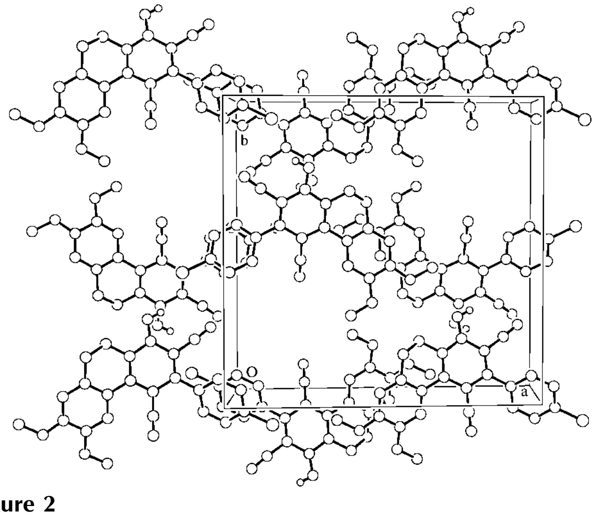

Figure 2
The crystal packing of (IV*a*)·$2.5H_2O$ viewed down the *c* axis showing the channels available to the unmodelled water molecules and the stacking of the quinolizine molecules. H atoms bonded to C atoms have been omitted for clarity.

Experimental

The title compound, (IV*a*)·$2.5H_2O$, was obtained in 82% yield by reacting 1-(cyanomethyl)-3,4-dihydro-6,7-dimethoxyisoquinoline [(I), R = Me, R^1 = CH_2CN; 1.15 g, 5 mmol] with (4-chlorophenyl)-methylidenemalononitrile (0.94 g, 5 mmol) and piperidine (0.5 ml) in refluxing acetonitrile (40 ml) for 3 h. After evaporation of the solvent *in vacuo*, the residue was triturated with methanol (10 ml) and crystallized from ethanol (m.p. 494–496 K). Suitable single crystals of (IV*a*)·$2.5H_2O$ were obtained by recrystallization from diethyl ether.

Crystal data

$C_{23}H_{17}ClN_4O_2 \cdot 2.5H_2O$
M_r = 461.90
Monoclinic, $P2_1/c$
a = 17.4665 (18) Å
b = 17.0031 (16) Å
c = 7.347 (3) Å
β = 94.566 (18)°
V = 2175.1 (9) Å^3
Z = 4
D_x = 1.410 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 17.8–19.4°
μ = 0.22 mm^{-1}
T = 173 (1) K
Prism, orange
0.38 × 0.25 × 0.20 mm

Data collection

Rigaku AFC-5*R* diffractometer
ω–2θ scans
5556 measured reflections
4982 independent reflections
3141 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.034
$\theta_{\rm max}$ = 27.5°
h = −22 → 22
k = −22 → 0
l = 0 → 9
3 standard reflections every 150 reflections intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.151
S = 0.97
4982 reflections
277 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0795P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max}$ = 0.001
$\Delta\rho_{\rm max}$ = 0.31 e Å^{-3}
$\Delta\rho_{\rm min}$ = −0.26 e Å^{-3}

There are two cavities of 178 Å^3 per unit cell which appear to be filled by rather diffuse water molecules. The symmetry-unique cavity is centred at (0.18, 0.25, −0.03). Satisfactory refinement results were

Table 1
Selected interatomic distances (Å).

N1—C6	1.363 (3)	C2—C3	1.463 (3)
N1—C2	1.414 (3)	C3—C4	1.374 (3)
N1—C14	1.482 (3)	C4—C5	1.430 (3)
N2—C2	1.283 (3)	C5—C6	1.403 (3)

obtained when two full-occupancy O atoms and one half-occupancy O atom were defined in the asymmetric unit. This yields five water molecules per cavity. However, the anisotropic displacement parameters of these O atoms were very large. Several trials at defining additional sites or using lower site-occupation factors for these O atoms yielded inferior results. Therefore, it was assumed that the water molecules are highly disordered within their cavities, which results in smeared-out electron density. As an alternative strategy, the *SQUEEZE* function of *PLATON* (van der Sluis & Spek, 1990; Spek, 2001) was used to eliminate the contribution of the electron density in the solvent region from the intensity data. The use of this strategy and the subsequent solvent-free model produced slightly better refinement results, and hence more precise geometric parameters, than the attempt to model the solvent atoms. Therefore, the solvent-free model and intensity data were used for the final results reported here. *PLATON* estimated that each cavity contains approximately 19 electrons, which is almost equivalent to two water molecules. This is contradictory to the results obtained from attempting to model the solvent molecules, which suggested that five water molecules, or 50 e, are present in each cavity. However, the electron count produced by the *SQUEEZE* procedure is very dependent on the low-angle reflections and may be underestimated if some of these are absent from the data set. In the present structure determination, important low-angle reflections such as 100, 200, 020 and 110 are missing because they were obscured by the beam stop, so an underestimated electron count during the *SQUEEZE* procedure is not surprising.

The methoxy H atoms were constrained to an ideal geometry (C—H = 0.98 Å), with $U_{\rm iso}$(H) = $1.5U_{\rm eq}$(C), but were allowed to rotate freely about the C—O bonds. The position of the imine H atom was refined freely along with an isotropic displacement parameter. All other H atoms were placed in geometrically idealized positions (C—H = 0.95–0.99 Å) and constrained to ride on their parent atoms with $U_{\rm iso}$(H) = $1.2U_{\rm eq}$(C).

Data collection: *MSC*/*AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991); cell refinement: *MSC*/*AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1999); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 2001).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1527). Services for accessing these data are described at the back of the journal.

References

Abdelhadi, H. A., Elwan, N. M., Abdallah, T. A. & Hassaneen, H. M. (1996). *J. Chem. Res.* (*S*), pp. 292–293.

Akhrem, A. A. & Chernov, Yu. G. (1988). *Dokl. Akad. Nauk SSSR*, **299**, 128–129; *Chem. Abstr.* (1989), **109**, 128809g.

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Awad, E. M., Elwan, N. M., Hassaneen, H. M., Linden, A. & Heimgartner, H. (2001). *Helv. Chim. Acta*, **84**, 1172–1180.

Awad, E. M., Elwan, N. M., Hassaneen, H. M., Linden, A. & Heimgartner, H. (2002). *Helv. Chim. Acta.* **85**. In the press.

Bhattacharjya, A., Bhattacharya, P. K. & Pakrashi, S. C. (1983). *Heterocycles*, **20**, 2397–2400.

Caramella, P. & Grünanger, P. (1984). *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, edited by A. Padwa, pp. 291–392. New York: J. Wiley.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Dannhardt, G. & Sommer, I. (1985). *Arch. Pharm.* (*Weinheim*), **318**, 556–558.

Elwan, N. M., Abdelhadi, H. A., Abdallah, T. A. & Hassaneen, H. M. (1996). *Tetrahedron*, **52**, 3451–3456.

Fülöp, F. & Bernáth, G. (1999). *Curr. Org. Chem.* **3**, 1–24.

Fülöp, F., Lazar, L., El-Gharib, M. S. A. & Bernáth, G. (1990). *Pharmazie*, **45**, 60–61.

Fülöp, F., Tari, J., Bernáth, G., Sohár, P., Dancsó, A., Argay, G. & Kálmán, A. (1997). *Liebigs Ann. Recl*, pp. 1165–1171.

Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Kametani, T. (1978). Japan Kokai 78 65896; *Chem. Abstr.* (1978), **89**, 215241c.

Kleeman, A. & Engel, J. (1982). *Pharmazeutische Wirkstoffe*, 2nd ed. Stuttgart: Thieme Verlag.

Lyakhov, A. S., Govorova, A. A., Gulyakevich, O. V. & Mikhal'chuk, A. L. (1997). *Kristallografiya*, **42**, 870–876.

Maiti, B. C. & Pakrashi, S. C. (1984). *Heterocycles*, **22**, 2043–2046.

Martinek, T., Forró, E., Günther, G., Sillanpää, R. & Fülöp, F. (2000). *J. Org. Chem.* **65**, 316–321.

Molecular Structure Corporation (1991). *MSC*/*AFC Diffractometer Control Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Molecular Structure Corporation (1999). *TEXSAN*. Version 1.10. MSC, 9009 New Trails Drive, The Woodlands, TX 77381–5209, USA.

Ninomiya, I., Tada, Y., Kiguchi, T., Yamamoto, O. & Naito, T. (1984). *J. Chem. Soc. Perkin Trans.* 1, pp. 2035–2038.

Shawali, A. S. (1993). *Chem. Rev.* **93**, 2731–2777.

Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.

Sluis, P. van der & Spek, A. L. (1990). *Acta Cryst.* A**46**, 194–201.

Spek, A. L. (2001). *PLATON*. University of Utrecht, The Netherlands.

Szabó, J., Fodor, L., Bani-Akoto, E., Talpas, G. S., Bernáth, G. & Sohár, P. (1992). *Tetrahedron*, **48**, 4957–4962.