Hexacyclic Indole Alkaloids. The Structure of Cuanzine as an Experimental Test of Molecular Mechanics Calculations

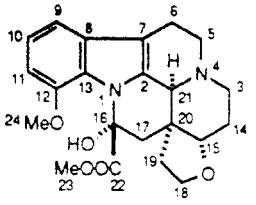
Giovanni Palmisano,*,† Bruno Gabetta,‡ Giordano Lesma,† Tullio Pilati,§ and Lucio Toma*,⊥

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano and Centro CNR di Studio per le Sostanze Organiche Naturali, Via Venezian 21, 20133 Milano, Italy, Inverni Della Beffa, Laboratori Ricerca e Sviluppo, Via Ripamonti 99, 20141 Milano, Italy, Centro CNR per lo Studio delle Relazioni tra Struttura e Reattività Chimica, Via Venezian 21, 20133 Milano, Italy, and Dipartimento di Chimica Organica, Università degli Studi di Pavia, Viale Taramelli 10, 27100 Pavia, Italy

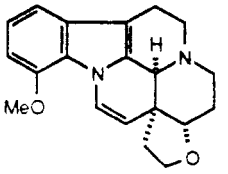
Received August 10, 1989 (Revised Manuscript Received October 30, 1989)

The conformational space of cuanzine was explored by employing MM2 force field for energy calculations and minimization. Location of the global minimum on the potential energy surface furnished a geometry which resembles the literature reported X-ray conformation of vincamine **3**. Moreover, the global minimum of structure **1** was found at a higher energy value than the global minimum of its C(16) epimer **8**, suggesting that the previous assignment of structure **1** to natural cuanzine should be revised into **8**. Reinterpretation of the ^{1}H NMR data reinforced this suggestion which was ultimately confirmed by X-ray analysis of cuanzine hydrochloride.

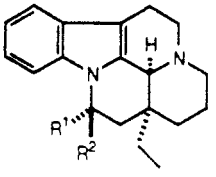
Cuanzine **1** and decarbomethoxyapocuanzine **2** are two hexacyclic indole alkaloids that were first isolated from the root bark of *Voacanga chalotiana* (Apocynaceae) in the early 1970s.[1,2] These compounds are of particular interest because of C(15)–C(18) linkage[3] with interposition of an oxygen atom in the basic eburnane skeleton (e.g., vincamine **3**), although a similar structural feature is not unusual in biogenetically related Aspidosperma alkaloids (e.g., modestamine, vandrikine, beninine, and vobtusine-like bisindoles).[4]



1

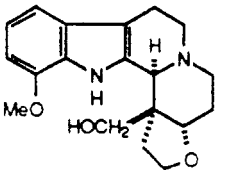


2



3: R^1 = COOMe, R^2 = OH

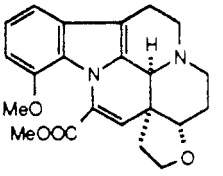
4: R^1 = OH, R^2 = COOMe



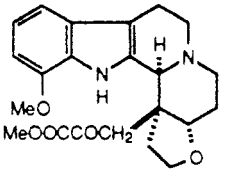
5

The discovery[5] of the vasodilating, antihypertensive, and antiarrhythmic activity of **1** prompted the development of a synthetic plan, which resulted in an expedient and stereocontrolled route to **5** based on intermolecular Diels–Alder formation of ring D.[6] This intermediate represents an attractive precursor to cuanzine because it contains a functionality at C(17) needed for eventual introduction of additional carbons for the completion of ring E.

The structure of cuanzine was elucidated mainly by comparison of ^{1}H and ^{13}C NMR spectra with those of vincamine **3** and 16-epivincamine **4**.[1]. These results led to the assignment of the structure **1** (i.e., 16-epivincamine-like) in which ring E is considered to be in a half-chair conformation ($^{17}H_{16}$) with the α-OH occupying a pseudoaxial position. This hypothesis was advanced in order to explain the fact that the long-range *W* coupling of H(17β) to one of C(19) protons appeared evident after extensive decoupling experiments at low field (100 MHz). As a consequence of the pseudoaxial position of the OH group, cuanzine is very sensitive to acid catalysts due to its propensity to give the apo-derivative **6** through a concerted diaxial elimination process. Moreover, there is



6



7

ample precedent[7] that 16-epivincamine **4** is susceptible to base-induced epimerization (MeONa, MeOH), producing the thermodynamically more stable vincamine **3**, presumably, through the intermediacy of the α-keto ester **7**. Surprisingly, we were unable to detect or induce any reactions that resulted in the inversion at C(16) in cuanzine,[8] and this result prompted a reappraisal of the stereochemistry at C(16) in cuanzine.

† Dipartimento di Chimica Organica e Industriale, Milano.
‡ Inverni Della Beffa, Milano.
§ Centro CNR per lo Studio delle Relazioni tra Struttura e Reattività Chimica, Milano.
⊥ Dipartimento di Chimica Organica, Pavia.

(1) Bombardelli, E.; Bonati, A; Gabetta, B.; Martinelli, E. M.; Mustich, G.; Danieli, B. *Tetrahedron* **1974**, *30*, 4141–4146.
(2) Bombardelli, E.; Bonati, A.; Danieli, B.; Gabetta, B.; Martinelli, E. M.; Mustich, G. *Experientia* **1974**, *30*, 979–980.
(3) The numbering system for the alkaloids used in this paper is based upon the standard skeleton eburnane and corresponds with the proposal by Le Men and Taylor (Le Men, J.; Taylor, N. J. *Experientia* **1965**, *21*, 508–510).
(4) For a general review of the *Aspidosperma* alkaloids, see: Saxton, J. E. In *Heterocyclic Compounds. The Monoterpenoid Indole Alkaloids (The Aspidosperma Alkaloids)*; Saxton, J. E., Ed.; Wiley: New York, 1983; Vol. 25, Part 4, pp 331–437. See also, Cordell G. A. In *The Alkaloids (The Aspidosperma Alkaloids)*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. XVII, Chapter 4, pp 200–384.
(5) Inverni Della Beffa SpA, Fr. Demande 2,303,544, 1976; *Chem. Abstr.* **1977**, *87*, 28999c.
(6) Palmisano, G.; Danieli, B.; Lesma, G.; Passarella, D. *Tetrahedron* **1989**, *45*, 3583–3596.
(7) Szántay, C.; Szabó, L.; Kalaus, G. *Tetrahedron Lett.* **1973**, 191–192. Oppolzer, W.; Hauth, H.; Pfäffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801–1810. Danieli, B.; Lesma, G.; Palmisano, G.; Tollari, S. *J. Org. Chem.* **1983**, *38*, 381–383.
(8) At that time this dichotomous behavior was attributed to steric congestion near the reacting center resulting from the proximity of MeO group at C(12).

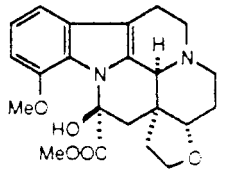
0022-3263/90/1955-2182$02.50/0

Table I. Relative Energies (kcal/mol) and Selected Geometrical Features of Conformations I–VII of 9 and I_S of 8 Compared with the Geometrical Features of the X-ray Structure of Cuanzine Hydrochloride, Vincamine,[11] and Vincamine Hydrobromide[11]

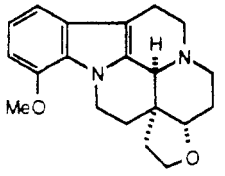
			ring puckering coordinates										
			C ring[a]			D ring[b]			E ring[c]			F ring[d]	
	E_{rel}	C/D fusion	Q	ϕ_2	θ	Q	ϕ_2	θ	Q	ϕ_2	θ	q_2	ϕ_2
I	0.0	cis	0.47	351	131	0.52	238	168	0.47	20	130	0.39	12
II	5.7	cis	0.45	323	130	0.52	259	155	0.57	289	83	0.38	8
III	5.1	cis	0.48	359	128	0.65	136	90	0.46	30	130	0.34	128
IV	12.8	cis	0.51	123	58	0.60	35	82	0.61	278	78	0.39	23
V	10.6	cis	0.57	86	74	0.64	79	84	0.45	31	131	0.31	51
VI	7.4	trans	0.48	346	132	0.67	6	84	0.53	264	68	0.41	13
VII	10.8	trans	0.56	15	123	0.67	29	84	0.43	54	126	0.43	15
I_S	–	cis	0.47	350	131	0.52	240	168	0.46	14	130	0.40	12
8·HCl	–	cis	0.51	350	129	0.52	252	171	0.50	12	131	0.40	17
3	–	cis	0.50	352	127	0.57	275	174	0.50	18	126	–	–
3·HBr	–	cis	0.51	343	133	0.55	314	174	0.47	16	143	–	–

[a] C(7)–C(6)–C(5)–N(4)–C(21)–C(2). [b] N(4)–C(3)–C(14)–C(15)–C(20)–C(21). [c] N(1)–C(2)–C(21)–C(20)–C(17)–C(16). [d] C(20)–C(15)–O–C(18)–C(19).

We asked the reasons of this different configurational preference at an epimerizable center; as this preference should have been dictated by some conformational constraint specifically operating in cuanzine, molecular mechanics calculations on 1 and its epimer at C(16) 8 were performed and the results are herein reported.



8



9

Compounds 1 and 8 possess a certain degree of conformational flexibility so that a number of conformations are possible; while the indole moiety is rigidly planar, rings C–F can pucker in several ways, the N(4) lone pair can invert (*cis* ⇌ *trans*-quinolizidines), and the methoxyl and the methoxycarbonyl groups can rotate around the C(12)–O and C(16)–C(22) bonds, respectively. Thus, in principle, a number of conformers of these diasteromers can be envisaged, and to deal with this problem, we adopted the following strategy.

A preliminar approximation was made to simplify the calculations: the OH and COOMe groups at C(16) were replaced with two hydrogens (→ **9**). By examination of molecular models of **9** we identified the candidate starting geometries. These were energetically minimized by using Allinger's MM2(85) force field,[9] and the final steric energy of the most stable conformer I was set to zero. The relative stabilities of the other conformers II–VII are shown in Table I and the optimized geometries are illustrated in Figure 1.

These results indicated that I is by wide margins the lowest energy, no other minimum being found in a range of 5 kcal/mol above it, so that **9** is predicted to be locked in the conformation I at room temperature. The geometrical feature expressed by ring puckering parameters (Q, θ, ϕ)[10] of conformations I–VII for **9** are reported in Table I in which the results[11] from X-ray crystallography of vincamine **3** are also included for comparison. X-ray analysis of **3** showed[11] that ring E was in an envelope conformation (^{20}E) distorted toward half-chair $^{20}H_{17}$ (with COOMe occupying a pseudoequatorial position) and similarly ring C was intermediate between ^4E and $^4H_5$, while ring D was in a chair conformation. All these features are retained when N(4) is protonated (Table I, compare data of **3** and **3**·HBr). It is noteworthy that among conformations I–VII of compound **9**, it is just the minimum-energy conformation I that corresponds to the X-ray geometry of vincamine **3**, apart from ring F which does not exist in **3** and assumes in I the $^{20}T_{15}$ twisted conformation. On the contrary, conformer II (with a steric energy of 5.7 kcal/mol above the global minimum), while about similar to I in rings C and D, exhibits for ring E about the same geometry (intermediate between $B_{16,21}$ and $^{17}H_{16}$) as earlier proposed[1] for natural cuanzine.

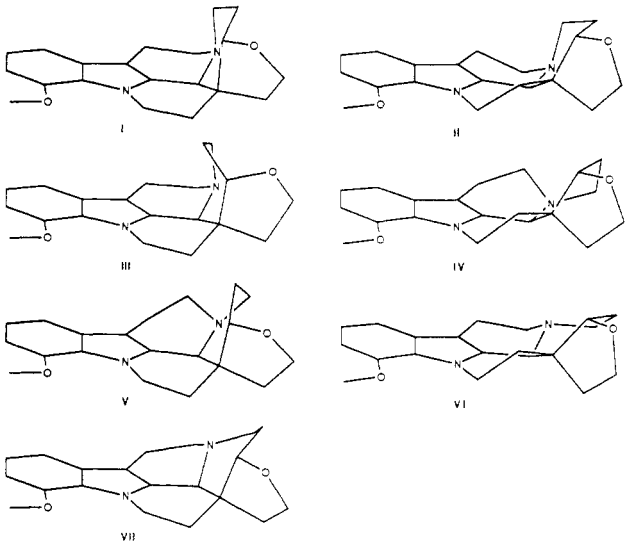


Figure 1. Representation of the MM2 calculated geometries for compound **9** with hydrogen atoms omitted for clarity.

As further improvement of calculations, the hydroxy and the carbomethoxy groups were added in two different orientations (α-COOMe, β-OH, and vice versa) to each of the three low-energy conformations (i.e., I–III) so that six starting geometries [three with 16*S* (I_S–III_S) and three with 16*R* configuration (I_R–III_R)] were obtained. The conformational space relative to the rotation of the methoxycarbonyl group around the C(16)–C(22) bond was fully explored with the DRIVER option of MM2(85), and each of the starting conformations exhibited a 2-fold minima (designated with the subscripts a and b) for this rotation (Table II).[12] The calculated differences in the energies

(9) Tai, J. C.; Allinger, N. L. *J. Am. Chem. Soc.* **1988**, *110*, 2050–2055.
(10) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
(11) Weber, H. P.; Petcher, T. J. *J. Chem. Soc. Perkin Trans. 2* **1973**, 2001–2006. (The crystal structure of vincamine 2-oxoglutarate has been also reported: Fayos, J.; Martñez-Ripoll, M. *Acta, Cryst.* **1981**, *B37*, 760–763.)

Table II. Relative Energies (kcal/mol) and Selected Geometrical Features of Conformations of Compounds 1 and 8 Compared with the Geometrical Features of the X-ray Structure of Cuanzine Hydrochloride, Vincamine,[11] and Vincamine Hydrobromide[11]

compd	conformation	E_{rel}	C(16) configuration	torsional angle N(1)–C(16)–C(22)–O(Me), τ	torsional angle N(1)–C(16)–O–H
8	I_{S_a}	0.0	*S*	−145	+71
8	I_{S_b}	0.0	*S*	+32	+83
1	I_{R_a}	1.3	*R*	+163	−81
1	I_{R_b}	1.3	*R*	−6	−99
8	II_{S_a}	7.9	*S*	+176	+89
8	II_{S_b}	6.9	*S*	−51	+90
1	II_{R_a}	7.2	*R*	+132	−62
1	II_{R_b}	7.5	*R*	−48	−67
8	III_{S_a}	4.5	*S*	−143	+62
8	III_{S_b}	4.6	*S*	+34	+70
1	III_{R_a}	6.3	*R*	+160	−81
1	III_{R_b}	6.0	*R*	−12	−96
8·HCl	–	–	*S*	−148	+75
3	–	–	*S*	+46	+159
3·HBr	–	–	*S*	+41	+129

Table III. ^{1}H NMR Data of Compounds 8 and 8·HCl; the Chemical Shifts Are Expressed in ppm Downfield from Tetramethylsilane, and the Couplings Constants Are Given in Hertz

	compound (solvent)					
	8 (C_6D_6)	8 ($CDCl_3$)	8·HCl ($CDCl_3$)		8 (C_6D_6)	8 ($CDCl_3$)	8·HCl ($CDCl_3$)
H-3α	2.12, ddd		3.26, ddd	$J_{6\alpha,6\beta}$	–	–	17
		2.46–2.56, m		$J_{6\alpha,5\alpha}$	–	–	6.5
H-3β	2.22, ddd		3.02, ddd	$J_{6\alpha,5\beta}$	–	–	2
H-5α			3.70, ddd	$J_{6\beta,5\alpha}$	–	–	11.5
	2.96–3.05, m	3.27–3.36, m		$J_{6\beta,5\beta}$	–	–	6.5
H-5β			3.80, ddd	$J_{5\alpha,5\beta}$	–	–	14
H-6α	2.24–2.39, m	2.50–2.70, m	3.15, dddd	$J_{3\alpha,3\beta}$	11.5	–	12
H-6β	2.61–2.76, m	2.84–3.03, m	3.08, dddd	$J_{3\alpha,14\alpha}$	5	–	4.5
H-9	7.27, d	7.13, dd	7.14, dd	$J_{3\alpha,14\beta}$	3.5	–	3
H-10	7.12, t	7.06, t	7.16, dd	$J_{3\beta,14\alpha}$	12	–	14
H-11	6.44, d	6.65, dd	6.77, dd	$J_{3\beta,14\beta}$	3	–	3
H-14α	1.70, dddd		2.29, dddd	$J_{14\alpha,14\beta}$	13	–	14
		1.58–1.80, m		$J_{14\alpha,15}$	10.5	10.5	11
H-14β	1.52, dddd		1.79, dddd	$J_{14\beta,15}$	6.5	7	6
H-15	4.74, dd	4.41, dd	4.54, dd	$J_{18\alpha,18\beta}$	–	–	8.5
H-17α	1.90, br d	2.01, dd	2.12, dd	$J_{18\alpha,19\alpha}$	–	–	10
H-17β	2.82, d	2.65, d	2.75, d	$J_{18\alpha,19\beta}$	3.5	4	3
H-18α			4.19, ddd	$J_{18\beta,19\alpha}$	–	–	8.5
	3.70–3.95, m	3.96–4.10, m		$J_{18\beta,19\beta}$	8	7.5	8.5
H-18β			4.05, q	$J_{19\alpha,19\beta}$	12	12	13.5
H-19α	2.61–2.76, m	2.72–2.90, m	3.62, ddd	$J_{17\alpha,17\beta}$	14.5	14.5	15
H-19β	1.09, ddd	1.57, ddd	1.76, ddd	$J_{9,10}$	7	7.5	8
H-21	4.04, br s	4.35, t	4.96, br s	$J_{9,11}$	–	1.5	3
Me-23	3.25,[a] s	3.76,[a] s	3.82,[a] s	$J_{10,11}$	7	7.5	6
Me-24	3.34,[a] s	3.87,[a] s	3.91,[a] s	$J_{17\alpha,OH}$	~1	1.5	1.8
OH	4.82, br s	4.52, d	4.68, d	$J_{6\alpha,21}$	~2	2	2
				$J_{6\beta,21}$	~2	2	2

[a] These assignments may be interchanged.

at the two minima ranged from 0.0 (I_{S_a}–I_{S_b} and I_{R_a}–I_{R_b}) to 1.0 kcal/mol (II_{S_a}–II_{S_b}) while the geometrical features of the rings were practically identical and remained about unchanged compared to the corresponding conformers of compound **9** (see, for example, in Table I the ring puckering coordinates of conformation I_{S_a} which are very close to that of I). Interestingly, these calculations led to virtually the same energetic ranking as noted in I–III, thereby implying that only conformations I_{S_a}–I_{S_b} and I_{R_a}–I_{R_b} (generated from I) significantly contribute to the Boltzmann distribution of compounds **8** and **1**, respectively. This indicates that a conformation type I (i.e., vincamine-like) is probably adopted by cuanzine; moreover, as rotamers I_{S_a} (τ = −145°)–I_{S_b} (τ = +32°) are more stable (1.3 kcal/mol) than rotamers I_{R_a}–I_{R_b}, the *S* configuration at C(16) appears to be sterically favored over the *R* configuration (Table II).

While the hexacyclic framework of cuanzine appeared secure on spectroscopic grounds, in light of molecular mechanics results, the stereochemistry at C(16) required at reinterpretation of the ^{1}H NMR data. Spectral data of cuanzine in $CDCl_3$ and C_6D_6 are summarized in Table III. Use of 300-MHz spectroscopy allowed analysis of the spectra by first-order approximations, and all signals were assigned in a straightforward way on the basis of chemical shifts, multiplicity, and ^{1}H–^{1}H correlation spectroscopy (COSY). Also included in Table III are the spectral data of cuanzine hydrochloride, and it is noteworthy that the coupling constants are similar in magnitude regardless of the ionization state of the nitrogen N(4).[13] The ^2J and

(12) Rotation of the OH group around C(16)–O bond was also carried out for each of the 12 minima I–III_{S_a}, I–III_{S_b}, I–III_{R_a}, I–III_{R_b}. Energies reported in Table II refer to the lowest in the three minima obtained for each of these rotations.

(13) As it might be expected, protonation at the bridgehead N(4) in cuanzine hydrochloride influenced the chemical shift of adjacent protons, which displayed a low-field shift in relation to the unprotonated compound.

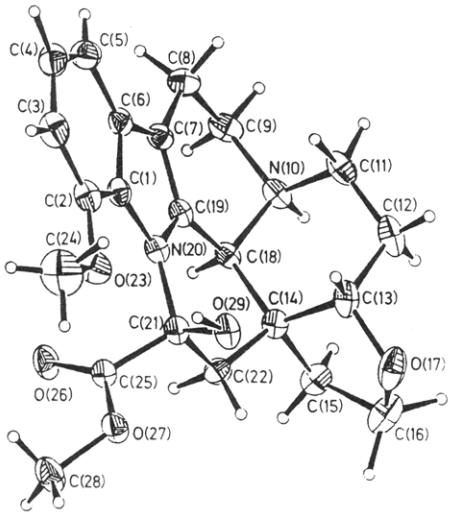


Figure 2. ORTEP[15] drawing of 8·HCl as determined by X-ray crystallography. Thermal ellipsoids are drawn at 20% probability.

^3J coupling pattern previously established[1] was confirmed while the chemical shift of two hydrogen atoms should be reversed [H(3α) and H(6β)]. Moreover, the H(17α) showed a long-range coupling to the alcoholic proton rigidly oriented as a consequence of the hydrogen bonding to the C(12)methoxyl group.[14] This ^4J *W* coupling was confirmed by the disappearance of the coupling itself on D_2O exchange of the sample dissolved either in $CDCl_3$ or in C_6D_6 and by the presence of the proper cross peak in the COSY experiments in both the solvents.

The findings on the structure of cuanzine were ultimately confirmed by X-ray analysis of cuanzine hydrochloride. Figure 2 shows the perspective view of the compound as ethanol solvate and the numbering scheme adopted for crystallographic purposes. There is a very good agreement between the bond distances and angles in the X-ray structure of the hydrochloride of cuanzine and the calculated I_{S_a} conformation of 8 (see Tables I and II for a comparison of the two geometries). The four puckered rings (C–F) were in the same conformation found by calculations and the OH···OMe hydrogen bond was also evident from the analysis.

It can be safely concluded that molecular mechanics calculations, spectral data, and X-ray analysis all agree in defining 8 as the real structure of natural cuanzine.

Experimental Section

NMR Spectroscopy. ^1H NMR spectra were recorded on a Bruker CPX-300 (300MHz) instrument.

Conformational Analysis. Molecular mechanics calculations were performed with the MM2(85)[9] program purchased from QCPE. The parameter set was updated using the parameter list 7-mar-1988 (VAX) kindly furnished by Prof. Allinger. A few parameters involving the N_{sp^2} atom were not found in the list, so these parameters were given the values of the corresponding bending and torsional constants involving a C_{sp^2} atom instead of the N_{sp^2}. Moreover for the stretching C_{sp^3}–N_{sp^2} the values of the C_{sp^3}–N_{sp^2} (amide) bond were assumed (K_s = 3.52 mdyn/Å, l_0 = 1.437 Å). Variation of these parameters over a reasonable range did not significantly affect the results. A value of 4.7 for the dielectric constant was used during the calculations; however, the results were virtually unaffected by use of other values (e.g., the default value of 1.5) or by complete suppression of the dipolar interactions.

X-ray Structure Determination. Crystals suitable for X-ray diffractometry were obtained from ethanol. Cell parameters and reflection intensities were measured with graphite monochromated Mo–Kα radiation on a Enraf-Nonius CAD-4 diffractometer operating at room temperature in the $\omega/2\vartheta$ scan mode for a crystal having approximate dimensions 0.36 × 0.32 × 0.28 mm. The scan range (ω) was calculated from [1.00 + 0.35 tan ϑ]°. Reflections were scanned in the range $0 < \vartheta < 27.5°$. Three standard reflections measured every 2 h showed no appreciable variation with time. The data were corrected for Lorentz and polarisation effects but not for absorption. A total of 3315 unique reflections were collected of which 2514 were considered to be observed [$I > \sigma(I)$] and used in the structure analysis.

Crystal data: $(C_{22}H_{27}N_2O_5)^+Cl^-\cdot C_2H_6O$, M = 481.0, orthorhombic, space group $P2_12_12_1$ (established from systematic absence), a = 8.248 (1) Å, b = 11.833 (1) Å, c = 24.595 (3) Å, V = 2400.4 (5) Å^3, Z = 4, D_c = 1.331 cm^{-3}, μ(Mo-Kα 0.710 69 Å) = 2.0 cm^{-1}.

The structure was solved by direct methods;[16] the "best" E-map gave the positions of the chlorine and other 23 heavy atoms. The remaining six C atoms of cuanzine, those of crystallization ethanol and the most part of hydrogen atoms, were obtained from difference Fourier maps. The ethanol molecule is disordered; we obtained the best rationalization of the disorder by assuming that the COH group is unique, while the remaining atoms are splitted in two positions (with population factor refined to 0.56 and 0.44, respectively); H atoms of this molecule were introduced in structure factor calculations but not refined. Final full-matrix least squares refinement for 416 parameters included atomic positions, temperature factors (anisotropic for non-hydrogen atoms), a secondary extintion parameter, an overall scale factor, and a population factor for the disordered ethanol. The refinement was terminated when all shifts concerning cuanzine were less than 0.02σ, and those of ethanol were less than 0.2σ. The final R was 0.054 (R_w 0.039), GOF = 1.74. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with weight $w = 4F_o^2/[\sigma(F_o^2) + 0.0004F_o^4]$. Final difference Fourier synthesis showed no significant residual electron density. Programs used include SDP,[17] and various in-house programs for refinement and geometrical analysis running on a Gould 32/97 computer.

Acknowledgment. We are grateful to Prof. B. Danieli for helpful discussion during the course of this work. Financial support from Ministero della Pubblica Istruzione (Rome) is also acknowledged.

Registry No. 1, 125132-61-8; 3, 1617-90-9; 3-HBr, 124780-68-3; 8, 53492-09-4; 8·HCl·EtOH, 125072-51-7.

Supplementary Material Available: Tables of final atomic positional coordinates, equivalent isotropic thermal parameters, selected bond lengths, bond angles, and torsion angles for compound 8·HCl (4 pages). Ordering information is given on any current masthead page.

(14) Long-range ^4J couplings for an atomic H–O–C–C–H arrangement were observed in sugars, with the necessary condition of a simultaneous axial position of the OH and the C-H bonds. (Gillet, B.; Nicole, D.; Delpuech, J.-J.; Gross, B. *Org. Magn. Reson.* **1981**, *17*, 28-36.)

(15) Johnson, C. K. *ORTEP II*, Report ORNL 5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.

(16) Main, P.; Fiske, S.; Hull, S. E.; Lessinger, L.; Germain, G.; Declerq, J. P.; Woolfson, M. M. *MULTAN 80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*; Universities of York, England, and Louvain, Belgium, 1980.

(17) Frenz, B. A. *Enraf-Nonius Structure Determination Package*; *User Guide*, version 6; Enraf-Nonius: Delft, The Netherlands, Jan 1983.