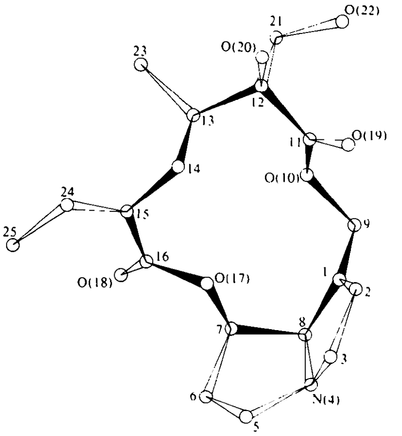

Fig. 1. A perspective view of the molecule showing the numbering scheme. The macrocyclic ring is shaded.

The carbonyl bonds are nearly parallel in all three PA's. The angle between the planes defined by C(7)—O(17)—C(16)—O(18) and C(9)—O(10)—C(11)—O(19) is 12·2 (2)° in retrorsine and 15° in jacobine, but 25° in swazine. This difference is explained by the slightly different conformation of the macro-ring, and also accounts for the shorter intramolecular distance O(10)—O(17) in swazine. In retrorsine and jacobine these distances are 3·23 and 3·25 Å respectively, with dihedral angles C(9)—O(10)—C(11)—C(12) of 177·5 (7)° and 179°. In swazine the corresponding distance is 3·16 Å and the dihedral angle is −178°.

It has been suggested that the potency of these alkaloids depends in some way on the accessibility to attack of the C(1)—C(2) double bond, regarded in terms of the size of the C(2)—C(1)—C(9)—O(10) dihedral angle (Sussman & Wodak, 1973). This angle is −87·0 (5)° in retrorsine, −106° in jacobine, 108° in swazine, −64° in fulvine, −63° in monocrotaline, −88° in axillarine and −12° in heliotrine (Wodak, 1975), a monoester PA. A direct comparison of the toxicity of all these alkaloids is a difficult and costly study. However, one should note that for retrorsine and axillarine which have similar dihedral angles (*ca* −88°) the former is by far the more toxic. Also, retrorsine, which contains two hydroxyl substituents and has a dihedral angle of −87·0 (5)°, is twice as toxic as jacobine (Bull *et al.*, 1968) which is less water soluble (containing only one hydroxyl substituent) and has a larger dihedral angle of −106°.

The author wishes to thank Dr D. H. G. Crout (Exeter) for supplying the sample of retrorsine hydrobromide and its UV spectrum, and the continued interest he has shown in this work, Dr M. Laing (Durban, South Africa) for supplying the atomic coordinates of swazine, Miss Kim Do (Neuchâtel) for technical assistance, and, finally, the Swiss National Science Foundation for financial support.

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The Structure of Colchiceine Ethyl Acetate–Water Solvate

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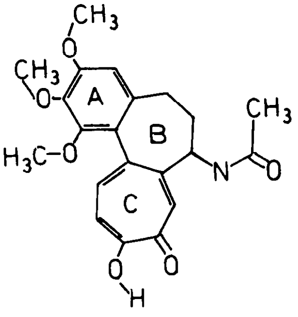
Abstract. $C_{21}H_{23}NO_6.C_4H_8O_2.H_2O$, monoclinic, $P2_1$, $Z = 2$, $a = 8{\cdot}329$ (1), $b = 12{\cdot}795$ (1), $c = 12{\cdot}571$ (1) Å, $\beta = 106{\cdot}57$ (1)°, $M_r = 492{\cdot}5$, $D_m = 1{\cdot}26$ (1), $D_x = 1{\cdot}273$ Mg m^{-3} at 296 K. Cell dimensions were obtained by least-squares refinement of angles measured at $\pm\theta$. Intensity data were collected with an Enraf–Nonius

CAD-4 diffractometer to a maximum sin θ/λ of 0·62 $Å^{-1}$ (2638 unique reflections, 384 unobserved at the 1σ level). The structure was solved by direct methods making use of the technique of negative-quartet frequencies to determine the starting set. The final R factor was 5·2%. The results show an unusual multiply solvated structure and confirm the chemical structure of colchiceine.

Introduction. Iorio, Brossi & Silverton (1978) reported the structure of 7-oxodesacetimidocolchicine which showed an unusual 3:2 mixture of the two possible tropolone structures. Because colchiceine (I) shows similar chemical properties, it was decided to investigate its structure crystallographically. A preliminary study of the Cu salt of colchiceine is described by Morrison (1951) who reported an electron density projection compatible with (I) although the molecular formula in the paper has the hydroxyl and carbonyl functions reversed.



(I)

Crystals of colchiceine were prepared (Cook & Loudon, 1952), and recrystallized from ethyl acetate, as pale-yellow needles, m.p. 450–452 K. The cell dimensions are not the same as those reported by Morrison (1951) who quoted a triclinic cell, a = 8·23 (1), b = 8·36 (1), c = 16·93 (4) Å, α = 90°52′, β = 93°52′, γ = 118°48′. Morrison's crystals were presumably a simple hydrate or were unsolvated.

Attempts were made to grind spherical crystals for data collection, but, because of cleavage, only an ellipsoid (0·3 × 0·2 × 0·2 mm) was obtained. During data collection, three standard reflections were measured after each two-hour period of X-ray exposure and no significant deterioration of the crystal was observed. Programs used in this investigation were *MULTAN* 78 of Main, Hull, Lessinger, Germain, Declercq & Woolfson (1978), XRAY 72 of Stewart, Kruger, Ammon, Dickinson & Hall (1972), and local programs for negative quartets and data reduction. *MULTAN* 78 is the latest version of *MULTAN* and was used to solve the phase problem, although not by an unthinking automatic application. Even with the increased number of variable phases allowed by the 'magic integer' technique incorporated in *MULTAN* 78, no satisfactory solutions were obtained. All E maps generated had one peak at least twice the height of any other. The situation persisted with up to eight variable phases. The negative quartet method of Silverton, Kabuto & Akiyama (1978) was then employed to select origin and variable phases (the two-dimensional phases used in origin selection were identical to those employed in the automatic approaches but the other planes were quite different). It was apparent, after one or two preliminary runs, that six variables would suffice. The negative-quartet approach gave a uniquely indicated solution which was confirmed by the NQEST test of DeTitta, Edmonds, Langs & Hauptman (1975). The corresponding E map showed all the heavier atoms of the colchiceine molecule.

The weighting used in the least-squares refinement was that of Peterson & Levy (1957). From density measurements, it had been suspected that the crystals contained solvent and, after the first three cycles of isotropic least-squares refinement, a difference map was calculated which indicated several peaks compatible with the solvent of crystallization: ethyl acetate. It was, however, surprising to find another isolated peak, of considerably greater height than those of the solvent. The only possible explanation seemed to be that the peak was the O atom of an unsuspected water molecule (later refinement and location of the appropriate H atoms confirmed this surmise). The presence of two different molecules of solvent of crystallization, while not unique, is distinctly unusual.

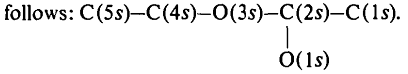
Further refinement was fairly routine and all H atoms were found in difference maps although the apparent thermal parameters of the ethyl acetate atoms were very large and refinement of the appropriate H atoms was inconclusive. For the final cycles of refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic parameters for the H atoms. The parameters for the H atoms of the ethyl acetate molecule were calculated and not refined. Temperature factors for the H atoms of the methyl groups were also held constant but the positions were refined. The fairly large structure was refined to convergence by dividing the atoms into two groups and alternately holding all parameters for one group constant and refining those of the other group. The origin is thus effectively fixed by the unrefined group. Standard blocked-matrix refinement, with one y parameter fixed, led to considerable oscillation of parameters, although no significant bond-length variation was apparent. The final R factor of 5·2% is rather large but the high value can probably be attributed to the difficulty with the ethyl acetate molecule whose anisotropic thermal parameters are so large as to suggest disorder either of position or conformation. Apart from a hydrogen bond to the water of crystallization, the ethyl acetate appears to be held only by van der Waals forces although the crystals showed no signs of efflorescence during the whole time required for X-ray experimental work. The final atomic positions for the heavier atoms are given in Table 1.*

Discussion. The bond lengths and angles for the various molecules are given in Tables 2 and 3. The reported molecular dimensions of the ethyl acetate molecule are not unreasonable given the large thermal motions or disorder. Fig. 1 shows the crystal conformation of the colchiceine molecule. The three methoxy groups have different conformations in the crystal but the differences can be explained in terms of molecular packing since C(3*m*) would have short intermolecular contacts were it to adopt an orientation similar to those of C(1*m*) and C(2*m*). The *B* ring has essentially a boat conformation, as described by Bucourt (1974), but some of the torsion angles are flattened because of the fused benzene and tropolone rings. The tropolone ring shows alternant bond lengths, and dimensions are similar to the average values given by Silverton, Kabuto, Buck & Cava (1977). Unlike 7-oxodesacetimidocolchicine, the molecule is not a mixture of the two possible tropolones and the accepted structure of colchiceine is confirmed. It is not possible to eliminate the possibility that a chemical equilibrium exists in solution.

The molecules appear to be held together in the crystal by an extensive three-dimensional network of reasonably strong hydrogen bonds (Table 4, Fig. 2) mostly involving the water molecules. The H atom

Table 1. *Positional parameters for the heavier atoms* (× 10^4)

The letters *s* and *w* refer to the ethyl acetate and water molecules respectively. The atoms of the ethyl acetate molecule are numbered as follows:



$C(5s)\text{—}C(4s)\text{—}O(3s)\text{—}\underset{\overset{|}{O(1s)}}{C(2s)}\text{—}C(1s).$

	x	*y*	*z*		*x*	*y*	*z*
C(1)	7579 (3)	1913 (2)	4466 (2)	O(1)	8101 (2)	1033 (1)	4019 (1)
C(1*m*)	7183 (6)	851 (3)	2903 (3)	C(2)	6471 (3)	1769 (2)	5093 (2)
O(2)	5847 (2)	795 (1)	5204 (1)	C(2*m*)	6882 (6)	215 (3)	6084 (3)
C(3)	5916 (4)	2637 (2)	5566 (2)	O(3)	4802 (3)	2414 (2)	6146 (2)
C(3*m*)	4107 (7)	3271 (4)	6575 (4)	C(4)	6479 (4)	3630 (2)	5405 (2)
C(4a)	7608 (3)	3768 (2)	4772 (2)	C(5)	8176 (4)	4846 (2)	4561 (2)
C(6)	7434 (4)	5189 (2)	3354 (2)	C(7)	7252 (3)	4302 (2)	2526 (2)
C(7a)	8902 (3)	3720 (2)	2675 (2)	C(8)	9788 (3)	3918 (2)	1927 (2)
C(9)	11332 (3)	3522 (3)	1796 (2)	O(9)	11874 (3)	3841 (3)	1027 (2)
C(10)	12365 (3)	2741 (2)	2536 (2)	O(10)	13720 (3)	2454 (2)	2257 (2)
C(11)	12127 (4)	2311 (3)	3463 (3)	C(12)	10804 (3)	2451 (2)	3944 (2)
C(12a)	9358 (3)	3038 (2)	3617 (2)	C(12b)	8166 (3)	2900 (2)	4299 (2)
N	6503 (3)	4704 (2)	1410 (2)	C(13)	5592 (4)	4099 (2)	594 (2)
O(13)	5419 (3)	3148 (2)	732 (2)	C(14)	4797 (6)	4627 (4)	−482 (3)
O(*w*)	3245 (4)	1914 (3)	9054 (3)	C(1*s*)	9014 (12)	5011 (6)	8368 (8)
O(1*s*)	10589 (9)	3513 (6)	8158 (6)	C(2*s*)	9472 (7)	3932 (5)	8394 (5)
O(3*s*)	8353 (5)	3295 (3)	8677 (3)	C(4*s*)	8671 (9)	2237 (5)	8789 (6)
C(5*s*)	7381 (10)	1667 (6)	9051 (7)				

Table 2. *Bond lengths* (Å)

Estimated standard deviations are given in parentheses.

C(1*s*)–C(2*s*)	1·43 (1)	C(2*s*)–O(1*s*)	1·18 (1)	C(2*s*)–O(3*s*)	1·36 (1)
O(3*s*)–C(4*s*)	1·38 (1)	C(4*s*)–C(5*s*)	1·41 (1)	C(1)–O(1)	1·383 (4)
C(1)–C(2)	1·386 (5)	C(1)–C(12b)	1·392 (4)	O(1)–C(1*m*)	1·412 (4)
C(2)–O(2)	1·372 (4)	C(2)–C(3)	1·399 (5)	O(2)–C(2*m*)	1·405 (5)
C(3)–O(3)	1·364 (5)	C(3)–C(4)	1·389 (5)	O(3)–C(3*m*)	1·416 (6)
C(4)–C(4a)	1·405 (5)	C(4a)–C(5)	1·506 (5)	C(4a)–C(12b)	1·400 (4)
C(5)–C(6)	1·531 (5)	C(6)–C(7)	1·518 (5)	C(7)–N	1·458 (4)
C(7)–C(7a)	1·527 (4)	C(7a)–C(8)	1·374 (5)	C(7a)–C(12a)	1·433 (4)
C(8)–C(9)	1·435 (5)	C(9)–O(9)	1·246 (5)	C(9)–C(10)	1·465 (5)
C(10)–O(10)	1·325 (5)	C(10)–C(11)	1·354 (5)	C(11)–C(12)	1·411 (5)
C(12)–C(12a)	1·379 (4)	C(12a)–C(12b)	1·496 (5)	N–C(13)	1·335 (4)
C(13)–O(13)	1·242 (5)	C(13)–C(14)	1·489 (5)		

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* A complete table of atomic positional and thermal parameters for all atoms and a list of structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34649 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Bond angles* (°)

E.s.d.'s are given in parentheses.

C(1*s*)–C(2*s*)–O(1*s*)	131·0 (8)	C(1*s*)–C(2*s*)–O(3*s*)	112·7 (7)
O(1*s*)–C(2*s*)–O(3*s*)	116·1 (7)	C(2*s*)–O(3*s*)–C(4*s*)	119·3 (6)
O(3*s*)–C(4*s*)–C(5*s*)	113·2 (7)	O(1)–C(1)–C(2)	117·4 (3)
O(1)–C(1)–C(12b)	120·9 (3)	C(2)–C(1)–C(12b)	121·7 (3)
C(1)–O(1)–C(1*m*)	113·2 (3)	C(1)–C(2)–O(2)	120·8 (3)
C(1)–C(2)–C(3)	119·3 (3)	O(2)–C(2)–C(3)	119·8 (3)
C(2)–O(2)–C(2*m*)	113·3 (3)	C(2)–C(3)–C(4)	119·9 (3)
C(2)–C(3)–O(3)	114·7 (3)	O(3)–C(3)–C(4)	125·4 (3)
C(3)–O(3)–C(3*m*)	117·1 (3)	C(3)–C(4)–C(4a)	120·4 (3)
C(4)–C(4a)–C(5)	120·6 (3)	C(4)–C(4a)–C(12b)	119·8 (3)
C(5)–C(4a)–C(12b)	119·5 (3)	C(4a)–C(5)–C(6)	112·3 (3)
C(5)–C(6)–C(7)	113·4 (3)	C(6)–C(7)–C(7a)	111·8 (2)
C(6)–C(7)–N	109·1 (3)	N–C(7)–C(7a)	114·4 (3)
C(7)–C(7a)–C(8)	117·8 (3)	C(7)–C(7a)–C(12a)	114·5 (3)
C(8)–C(7a)–C(12a)	127·6 (3)	C(7a)–C(8)–C(9)	133·4 (3)
C(8)–C(9)–O(9)	120·6 (3)	C(8)–C(9)–C(10)	123·5 (3)
O(9)–C(9)–C(10)	116·0 (3)	C(9)–C(10)–C(11)	128·3 (3)
C(9)–C(10)–O(10)	114·3 (3)	O(10)–C(10)–C(11)	117·3 (3)
C(10)–C(11)–C(12)	129·9 (3)	C(11)–C(12)–C(12a)	131·6 (3)
C(12)–C(12a)–C(7a)	125·5 (3)	C(7a)–C(12a)–C(12b)	118·9 (3)
C(12)–C(12a)–C(12b)	115·6 (3)	C(12a)–C(12b)–C(4a)	120·4 (3)
C(12a)–C(12b)–C(1)	120·8 (3)	C(4a)–C(12b)–C(1)	118·8 (3)
C(7)–N–C(13)	121·9 (3)	N–C(13)–C(14)	116·3 (3)
N–C(13)–O(13)	121·6 (3)	O(13)–C(13)–C(14)	122·1 (3)

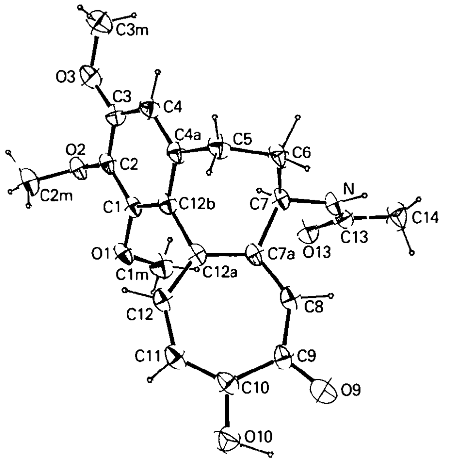

Fig. 1. *ORTEP* (Johnson, 1965) drawing of the colchiceine molecule in its crystal conformation. The thermal ellipsoids indicate 40% probability. The H atoms are represented by arbitrary spheres.

attached to O(10), H(10), appears to form a bifurcated hydrogen bond, intermolecularly to O(13) in the acetimido side chain and intramolecularly to the tropolone carbonyl O(9) atom. As may be seen from Table 4, although the O–H–O angles are fairly far from 180°, the formally non-bonded O···H distances are quite short. While the H atom might be forced into close contact with O(9) by an intermolecular bond, the non-linear character of this bond would seem to preclude the possibility since there appears to be no reason why the H atom should not be rotated away from the observed stereochemically unfavorable situation. If the intramolecular hydrogen bond persists in solution, the H atom would be positioned favorably for an equilibrium between the two tropolone forms.

Table 4. *Probable hydrogen bonds*

X–H···*Y*	*X*···*Y* (Å)	H···*Y* (Å)	∠*X*–H–*Y* (°)	Symmetry operation
O(10)···O(9)	2·559 (4)	1·95 (6)	113 (5)	None
O(10)···O(13)	2·832 (4)	1·98 (7)	136 (4)	*a*
O(*w*)···O(13)	2·836 (4)	1·79 (6)	169 (6)	*c*
N···O(*w*)	2·907 (5)	1·96 (6)	169 (3)	2_1
O(*w*)···O(1*s*)	2·987 (9)	1·89 (7)	164 (5)	*a*

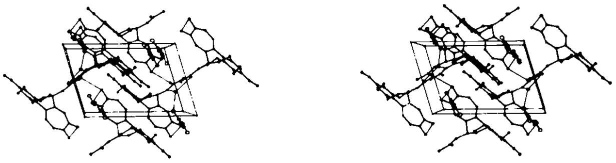

Fig. 2. Molecular packing showing the hydrogen bonds.

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