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The Crystal Structure of Colchicine. A New Application of Magic Integers to Multiple-Solution Direct Methods

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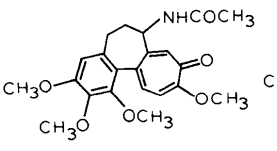
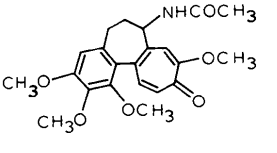
The mitotic spindle inhibitor colchicine, $C_{22}H_{25}NO_6$, crystallizes as a dihydrate in space group $P2_1$, a = 17·08, b = 10·70, c = 13·88 Å, β = 117·9°, $Z = 4(C_{22}H_{25}NO_6.2H_2O)$/unit cell. The crystal structure was solved by a multiple-solution direct method in which unknown starting phases φ_i are represented using 'magic integers': $\varphi_i = m_i x$. An appropriate choice of integers m_i and sampling of the variable x allows a drastic reduction in computing time and a great increase in structure-solving capability compared to the widely used method in which all unknown phases are permuted among the four values 45, 135, 225, 315°. The crystal structure of colchicine dihydrate was refined by least squares to R = 0·052 for 2322 observed X-ray reflections. The two independent colchicine molecules have very similar conformations in the crystal. The troponoid rings have alternating bond lengths, and are not precisely planar. These rings make dihedral angles with the planar benzene rings of 53° in one molecule of colchicine, 51° in the other. The four independent water molecules are all found in a distinct region in the crystal, which is held together by a complex hydrogen-bond network. Two methoxy-group O atoms of colchicine act as hydrogen-bond acceptors, the one on the troponoid ring participating in a bifurcated hydrogen bond.

Colchicine (I), the principal active substance of the autumn crocus, has a remarkable range of biological effects. The most studied of these is its arrest of mitosis, believed to result from the specific strong binding of colchicine to the protein tubulin, preventing the assembly of tubulin into microtubules which form the mitotic spindle (Soifer, 1975). Colchicine is also capable of relieving the pain of gout (for which it has been used since ancient times), of inducing polyploidy in plants, and of causing particular malformations in embryos (Eigsti & Dustin, 1955).



(I)



(II)

To contribute toward understanding the specific interaction with tubulin, and other biological activity,

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we have set out to determine the crystal structures of a series of derivatives of colchicine and closely related compounds (Margulis, 1974, 1975; Koerntgen & Margulis, 1977). By looking at both active and inactive compounds, defining the exact stereochemistry of these molecules and the possible range of conformational variation among them, we hope to isolate those structural features necessary for activity. Of particular interest is the greatly reduced activity of isocolchicine (II) and its derivatives compared to colchicine and its derivatives. The crystal structure of colchicine itself, for which data had been on hand for some time but which it was only recently possible to solve, using a new direct-methods technique, is presented here.*

Experimental

Large crystals were easily grown by slow evaporation from aqueous solution containing tris(hydroxymethyl)-aminomethane (tris) buffer. They were determined to be the dihydrate, $C_{22}H_{25}NO_6.2H_2O$, monoclinic, space group $P2_1$, $a = 17{\cdot}08 \pm 0{\cdot}01$, $b = 10{\cdot}700 \pm 0{\cdot}007$, $c = 13{\cdot}88 \pm 0{\cdot}01$ Å, $\beta = 117{\cdot}9 \pm 0{\cdot}1°$. These crystals are identical to those previously thought to be a complex of tris and colchicine (Margulis, Banerjee & White, 1969). Unit-cell parameters and standard deviations were found from least-squares analysis of diffractometer angle measurements. The measured density, $D_m = 1{\cdot}32$ g cm^{-3}, indicated $Z = 4$ (calculated density $D_x = 1{\cdot}29$ g cm^{-3}), thus requiring that the asymmetric unit consist of two independent colchicine and four water molecules. Intensity data were collected from a crystal of dimensions $0{\cdot}3 \times 0{\cdot}3 \times 0{\cdot}1$ mm with a Syntex $P2_1$ diffractometer, using monochromated Cu $K\alpha$ ($\lambda = 1{\cdot}54178$ Å) X-rays. Of the 2501 measured intensities, 2322 were considered 'observed' [$I > 3\sigma(I)$]. No absorption corrections were made ($\mu = 8{\cdot}3$ cm^{-1}, $\mu r \simeq 0{\cdot}1$).

Structure determination

Repeated attempts to solve the structure with the *MULTAN* direct-methods phasing program (Main, Lessinger, Woolfson, Germain & Declercq, 1976) all failed. A solution was finally achieved by using a more efficient way of representing unknown phases in the multiple-solution approach. *MULTAN*, after defining an origin, chooses in addition a small number of unknown starting phases, representing them either exactly by their two allowed values if they are special, or approximately by the four values 45, 135, 225, 315° if they are general. In noncentrosymmetric space groups the number of combinations to consider thus increases by a factor of 4 for each additional general starting phase. The r.m.s. error in representing general phases in this way is always $\pi/4\sqrt{3}$ radians = 26·0°. The enantiomorph is defined by an appropriate phase restriction.

If unknown general starting phases are represented by 'magic integers', $\varphi_l = m_l x$ (White & Woolfson, 1975), Main (1977) has shown how it is possible to distribute the errors evenly among the φ_l and control the r.m.s. error in phase representation by appropriate choice of integers m_l. All possible combinations of the φ_l can then be explored simply by sampling the variable x. The appropriate sampling interval, and therefore the number of phase sets necessary to develop, again depend on the integers m_l. For magic integers chosen as described by Main, the number of phase sets is conveniently taken as four times the maximum integer, with the variable x sampled at intervals $\Delta x = 360°/4m_{max}$ starting at $x = \frac{1}{2}\Delta x$ and increasing to $x = 360° - \frac{1}{2}\Delta x$. The phase represented by the largest

* Previous crystallographic analysis (King, de Vries & Pepinsky, 1952) of two two-dimensional projections of the colchicine–methylene bromide complex provided confirmation of the molecular structure and a very rough geometry of colchicine.

Table 1. *Number of phase sets (ignoring enantiomorph definition) for n general starting phases*

Column Q: quadrant representation $\varphi_l = 45, 135, 225, 315°$ (r.m.s. phase error 26·0°). Column M: magic-integer representation $\varphi_l = m_l x$ with $m_l = 2^n - 2^{(l-1)}$ (r.m.s. phase error very near $\Delta\varphi_{1b}$).

n	Q	M	$\Delta\varphi_{1b}$	Magic-integer sequences
1	4	4	26·0°	1
2	16	12	29·3	3, 2
3	64	28	32·9	7, 6, 4
4	256	60	35·4	15, 14, 12, 8
5	1024	124	37·2	31, 30, 28, 24, 16
6	4096	252	38·5	63, 62, 60, 56, 48, 32
7	16384	508	39·5	127, 126, 124, 120, 112, 96, 64
8	65536	1020	40·2	255, 254, 252, 248, 240, 224, 192, 128
9	262144	2044	40·8	511, 510, 508, 504, 496, 480, 448, 384, 256
10	1048576	4092	41·2	1023, 1022, 1020, 1016, 1008, 992, 960, 896, 768, 512

integer thus takes on repeatedly the values 45, 135, 225, 315°. This allows enantiomorph definition to be made exactly as before; if an unknown general starting phase is involved in enantiomorph definition, it is assigned the largest integer.

A lower bound to the r.m.s. error made in representing n general phases in this way is

$$\Delta\varphi_{1b} = 2\sqrt{\left(\frac{\pi}{n+2}\right)\left[\frac{\Gamma(n+2)/2}{4m_{max}}\right]^{1/n}}$$

Table 2. *Figures of merit for best* 3 *of* 510 *phase sets; ranges for all* 510 *sets*

Set rank	Combined	Absolute	ψ_o	Residual
1	2·6079	1·0477	240·4	28·37
2	2·5614	1·0431	252·0	28·59
3	1·9575	0·9484	288·2	33·45
Range	Possible 0·0–3·0	0·6994–1·2724	240·4–781·3	28·37–41·45

(Main, 1976). We have found that an acceptable compromise between decreasing the necessary number of phase sets and increasing the r.m.s. error in phase representation can be achieved by using the magic-integer sequence $m_i = 2^n - 2^{(i-1)}$ to represent n general phases.* Each additional general starting phase now increases only by a factor of two the number of phase sets to be developed, just as do additional special phases. This change is very easy to incorporate into *MULTAN*, and program operation is as automatic as before.† A comparison of the two methods of phase representation is set forth in Table 1.

Solving the crystal structure of colchicine dihydrate required the location of 62 C, N, and O atoms. In order to obtain a good convergence map, it was necessary to take the 451 largest normalized structure factors ($|E| \geq$

* Using the same method, we have solved two other structures of comparable difficulty, isocolchicine, $C_{22}H_{25}NO_6$, $P2_12_12_1$, $Z = 8$, and *N*-acetylcolchinol, $C_{20}H_{23}NO_5.H_2O$, $P2_1$, $Z = 4$, to be reported elsewhere.

† A listing of the necessary changes is available on request from TNM.

Table 3. *Atomic coordinates* ($\times 10^4$)

Standard deviations estimated from the least-squares calculations, assuming random errors in the intensity data, are given in parentheses as deviations in the last significant figure.

Molecule *a*				Molecule *b*			
	x	*y*	*z*		*x*	*y*	*z*
C(1)	5867 (6)	8131	3535 (7)	C(1)	528 (5)	5109 (8)	988 (7)
C(2)	5910 (6)	8237 (10)	2512 (7)	C(2)	903 (5)	6198 (8)	1674 (7)
C(3)	5520 (6)	7449 (9)	1637 (6)	C(3)	1230 (5)	6316 (8)	2747 (6)
C(4)	5004 (6)	6367 (9)	1488 (6)	C(4)	1362 (5)	5422 (8)	3543 (6)
C(5)	4768 (5)	5714 (9)	2165 (6)	C(5)	1099 (5)	4187 (7)	3477 (6)
C(6)	5027 (5)	6080 (10)	3296 (7)	C(6)	598 (5)	3556 (7)	2435 (6)
C(7)	5495 (6)	7089 (11)	3823 (7)	C(7)	387 (5)	3965 (8)	1436 (6)
C(8)	4191 (6)	4623 (9)	1727 (6)	C(8)	1345 (5)	3519 (8)	4520 (6)
C(9)	3401 (6)	4547 (10)	1775 (6)	C(9)	1794 (5)	2368 (8)	4693 (6)
C(10)	2830 (6)	3540 (12)	1317 (7)	C(10)	2052 (5)	1749 (8)	5686 (7)
C(11)	3048 (6)	2582 (11)	815 (7)	C(11)	1878 (5)	2277 (9)	6492 (6)
C(12)	3869 (6)	2621 (10)	802 (7)	C(12)	1423 (5)	3376 (8)	6291 (6)
C(13)	4413 (6)	3636 (10)	1222 (6)	C(13)	1160 (5)	3984 (8)	5321 (6)
C(14)	3166 (5)	5556 (10)	2337 (7)	C(14)	1963 (5)	1778 (8)	3835 (6)
C(15)	3728 (6)	5478 (10)	3563 (7)	C(15)	1092 (6)	1299 (8)	2882 (7)
C(16)	4718 (5)	5213 (9)	3903 (6)	C(16)	313 (5)	2228 (8)	2570 (6)
C(17)	5947 (6)	4648 (12)	5658 (8)	C(17)	−1276 (6)	2066 (10)	1448 (7)
C(18)	5890 (6)	2991 (10)	1792 (9)	C(18)	−200 (6)	5077 (12)	4647 (10)
C(19)	4210 (6)	467 (10)	748 (8)	C(19)	580 (8)	3362 (12)	7256 (9)
C(20)	1623 (7)	1627 (13)	85 (10)	C(20)	2526 (6)	491 (9)	7704 (7)
C(21)	6581 (6)	9462 (10)	1623 (7)	C(21)	1342 (7)	8328 (9)	1543 (8)
C(22)	6359 (6)	4831 (12)	6872 (7)	C(22)	−2012 (6)	1488 (11)	455 (7)
N	5216 (5)	5309 (9)	5072 (6)	N	−471 (5)	1787 (6)	1590 (5)
O(1)	6228 (4)	8991 (7)	4236 (5)	C(1)	304 (4)	5149 (6)	−6 (5)
O(2)	6395 (4)	9247 (6)	2524 (4)	O(2)	898 (3)	7179 (6)	1033 (4)
O(3)	5165 (4)	3706 (6)	1089 (4)	O(3)	736 (4)	5119 (5)	5177 (4)
O(4)	4073 (4)	1683 (6)	263 (4)	O(4)	1255 (4)	3920 (6)	7095 (4)
O(5)	2507 (4)	1555 (8)	300 (5)	O(5)	2126 (4)	1708 (6)	7479 (4)
O(6)	6286 (4)	3998 (8)	5254 (5)	O(6)	−1398 (4)	2783 (7)	2067 (5)
O(*W*1)	8016 (4)	3645 (6)	5401 (5)	O(*W*3)	5459 (5)	1839 (9)	3814 (5)
O(*W*2)	8179 (5)	2203 (7)	3685 (5)	O(*W*4)	6893 (9)	1142 (11)	4086 (9)

1·50). Of the 7471 triple phase relationships among these, the strongest 4000 were used to solve the structure. In addition to the origin-defining phases 13,0,6, 1,1,−11, 4,0,−11, all fixed at $\varphi = 0$, eight unknown general phases were used to start. Confining attention to one enantiomorph, $\frac{1}{2}(1020) = 510$ phase sets were developed in the usual way with the tangent formula. The best set was easily picked out, as it had the highest combined figure of merit (see Table 2), and the E map made with those phases showed essentially the entire structure, which was quickly completed by successive Fourier syntheses.

The structure was refined with the least-squares program of P. K. Gantzel, R. A. Sparks & K. N. Trueblood to a final value of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0{\cdot}052$ for the 2322 'observed' reflections. Because of computing limitations, refinement was in three blocks, within which all matrix elements were used: C, N, and O, with anisotropic temperature factors, for each of the two independent colchicine molecules, and the four water O atoms, also with anisotropic temperature factors. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Most of the H atoms were found in difference Fourier maps, the rest located from geometrical considerations. They were included in the structure factor calculations, but not completely refined. The H atom coordinates have large uncertainties, and no conclusions should be drawn based solely on exact H atom positions.*

Results and discussion

Final atomic coordinates for C, N, O are listed in Table 3. Bond distances and angles are shown in Figs. 1 and 2, selected torsion angles in Fig. 3. The three figures show the two independent colchicine molecules to have very similar geometries and conformations.

The troponoid rings *C* exhibit clear alternation of long and short bonds. While both rings *C* are roughly planar (to within 0·06 Å in molecule *a*, 0·07 Å in molecule *b*), a more exact description of their conformation is a very shallow boat, defined by three planes: plane 1: C(3), C(4), C(5), C(6), r.m.s. deviation 0·0035, 0·0036 Å; plane 2: C(2), C(3), C(6), C(7), r.m.s. deviation 0·0013, 0·0040 Å; plane 3: C(1), C(2), C(7), deviation of O(1), 0·08, 0·03 Å. The dihedral angles between plane 1 and plane 2 are 2·5, 6·4°, those between plane 2 and plane 3 are 6·7, 5·4°. The puckering in the rings may alternatively be described by the torsion angles in Fig. 3. The bond-length pattern found here agrees closely with that reported for other structures containing troponoid rings (Margulis, 1974, 1975; Koerntgen & Margulis, 1977; Shimanouchi & Sasada, 1973; Derry & Hamor, 1972; Hamor & Derry, 1973; Karlsson, Pilotti & Wiehager, 1973, 1976; Berg, Karlsson, Pilotti & Wiehager, 1976). However, the pattern of ring puckering and the extent of non-planarity seem to vary among these compounds. Ring *C* of colchicine is non-planar to an extent so far seen only in $-SCH_3$ substituted troponoid rings (Margulis, 1975).

The *N*-acetyl side chains [C(16), N, C(17), O(6), C(22), groups *D*] are more nearly planar, to within 0·03 Å in molecule *a*, 0·04 Å in molecule *b*. Rings *A* are planar (to within 0·02 Å), as expected. The general overall shape of the colchicine molecule, as illustrated in Fig. 3, is governed by the dihedral angles between these planar regions, which are listed below:

Plane	Plane	Molecule *a*	Molecule *b*
Ring *A*	Ring *C*	53°	51°
Ring *A*	Group *D*	67	66
Ring *C*	Group *D*	87	90.

Note particularly that rings *A* and *C* are twisted about the C(5)–C(8) bond.

The exact shape of much of the periphery, and the accessibility of rings *A* and *C* of colchicine, when it binds to the tubulin receptor site, will be governed by the orientations of the four methoxy groups. These are the parts of the molecule which might be expected to show the greatest conformational variability when the various derivatives of colchicine and related compounds are compared. In the colchicine dihydrate crystal, the methoxy group on ring *C* lies almost parallel to the ring plane. On ring *A*, methoxy O(5)–C(20) is almost parallel to the ring, while the other two methoxy groups are more nearly perpendicular to it, both pointing in the same direction. In this conformation, ring *A* and its three methoxy O atoms are quite accessible from one side of the molecule but not the other. This is the same side from which ring *C* is accessible, the other side being blocked by the acetyl group and methoxy O(3)–C(18). It is interesting that the N–H bond also points out toward this same side of the molecule, since hydrogen bonding with this N atom as donor must be considered as a possible part of the mechanism of colchicine binding to tubulin (Margulis, 1974). These points, illustrated in Fig. 3, are particularly apparent in an examination of space-filling molecular models.

The complex hydrogen-bonding system which holds the crystal together is shown in Fig. 4, and further details are given in Table 4. A helical hydrogen-bond system of a common type, with N(*b*) donating to the accepting tropolone keto oxygen O(1)(*b*) of another molecule, binds the crystal along **b** and **c**. A separate,

* Lists of structure factors, anisotropic thermal parameters for C, N and O atoms, and H positional and isotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33035 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

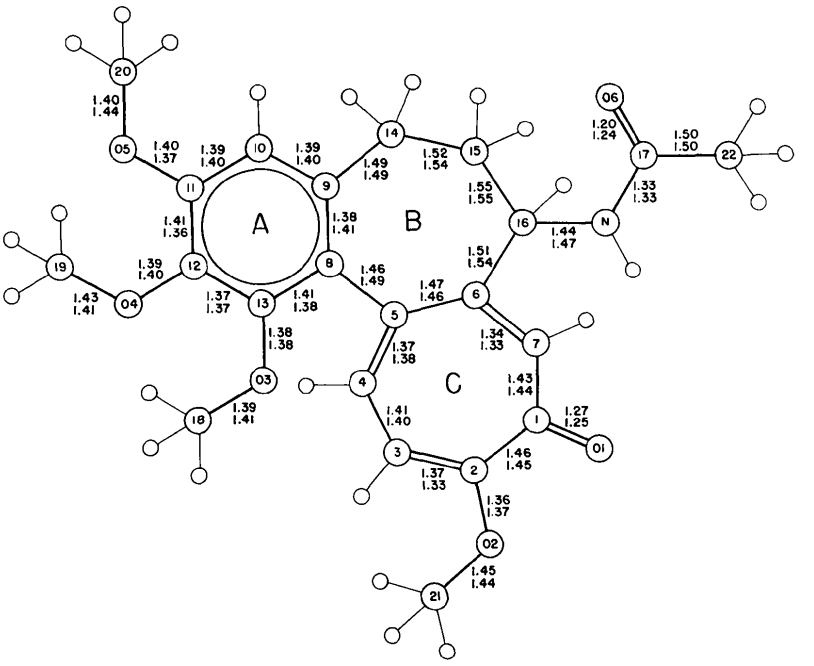

Fig. 1. Bond distances (Å); those for molecule *a* are listed above those for molecule *b*. Standard deviations are approximately 0·01 Å for each bond. Numbered atoms without element symbol are carbon, unlabelled atoms are hydrogen.

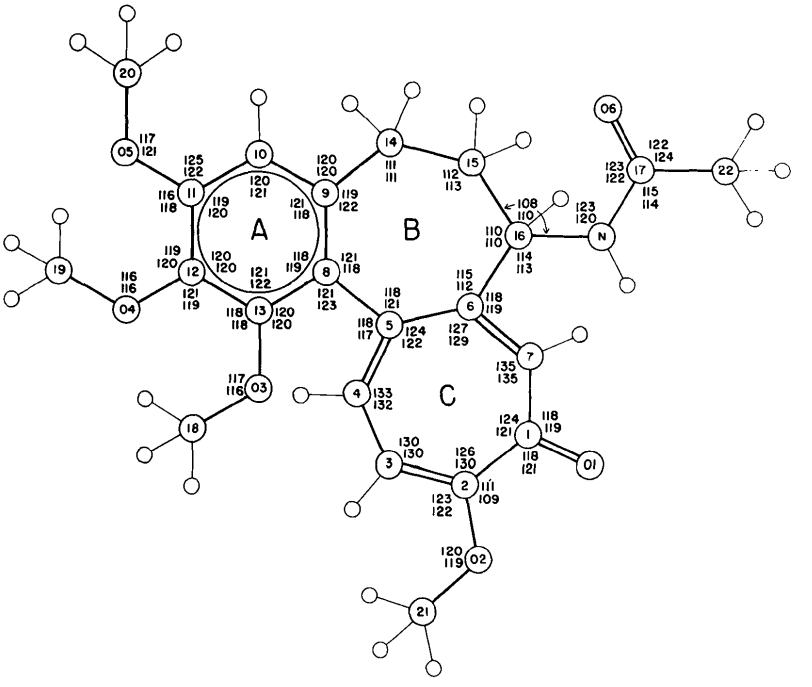

Fig. 2. Bond angles (°); those for molecule *a* are listed above those for molecule *b*. Standard deviations are approximately 1° for each angle. Numbered atoms without element symbol are carbon, unlabelled atoms are hydrogen.

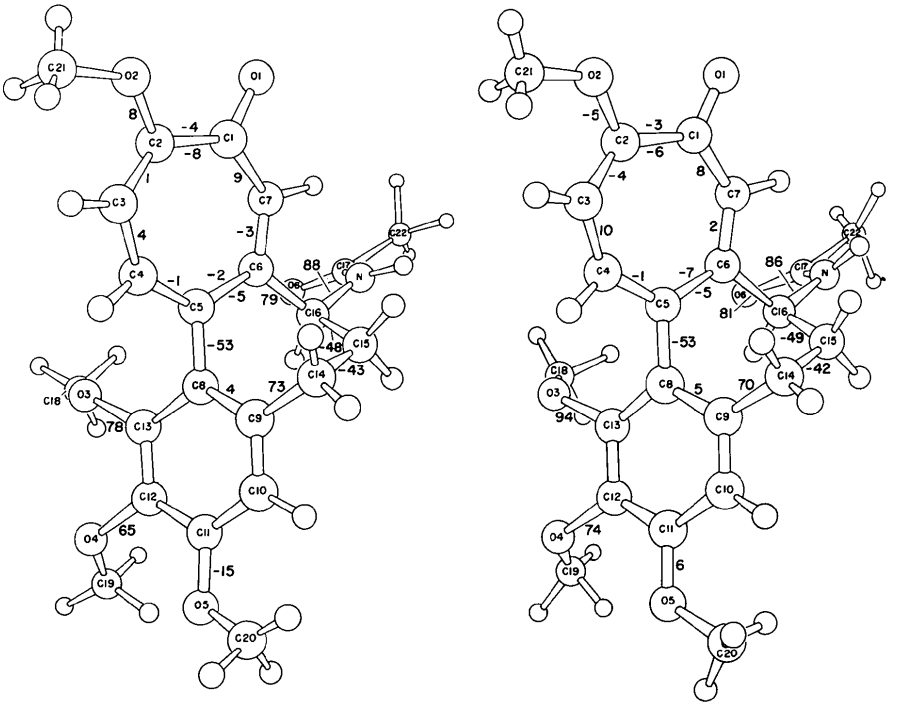

Fig. 3. Experimentally determined conformations of molecule *a* (left) and molecule *b* (right), viewed normal to the planes defined by C(5), C(8), C(15). Torsion angles (°) are given for rings *B* and *C*, for O(1)–C(1)–C(2)–O(2), for C(6)–C(16)–N–C(17), and for the methoxy groups. The latter are taken to be the angles between the planes $COCH_3$ and the least-squares planes for rings *A* and *C*.

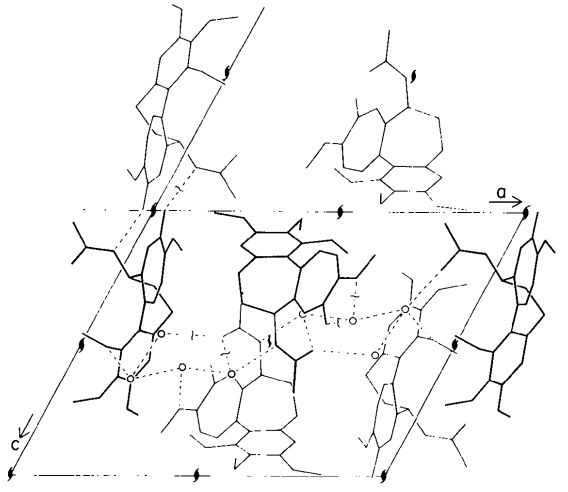

Fig. 4. Projection of the crystal structure down **b**. Circles are water molecules. Hydrogen atoms are omitted for clarity. Lightly inked molecules are related to heavily inked ones by a twofold screw operation. Dashed lines indicate hydrogen bonds. Symbol ~ indicates hydrogen bonds to molecules related to molecules shown by translation up or down in **y**. O(*W*4), O(1)(*a*), and O(2)(*a*) are connected by a single bifurcated hydrogen bond.

more intricate system of hydrogen bonds along **a** and **b** consists of the four independent water molecules and five different colchicine molecules.

Table 4. *Hydrogen-bond system*

Donor (*x*,*y*,*z*)	Acceptor	Position	*d* (Å)
N(*b*)	O(1)(*b*)	$-x, -\frac{1}{2}+y, -z$	2·93
N(*a*)	O(*W*3)	$1-x, \frac{1}{2}+y, 1-z$	2·84
O(*W*3)	O(6)(*a*)	*x*,*y*,*z*	2·95
O(*W*3)	O(*W*4)	*x*,*y*,*z*	2·41
O(*W*4)(bifurcated)	O(1)(*a*)	$x, -1+y, z$	2·62
	O(2)(*a*)	$x, -1+y, z$	2·79
O(*W*4)	O(*W*2)	*x*,*y*,*z*	2·75
O(*W*2)	O(6)(*b*)	$1+x, y, z$	2·73
O(*W*2)	O(3)(*b*)	$1-x, -\frac{1}{2}+y, 1-z$	2·86
O(*W*1)	O(6)(*a*)	*x*,*y*,*z*	2·89
O(*W*1)	O(*W*2)	*x*,*y*,*z*	2·96

There are several noteworthy features of this system. First, all the water molecules are near each other, bound together with hydrogen bonds, in a distinct 'water region' of the crystal. This is interesting in view of the reported unusually high solubility of colchicine in water (Zeisel, 1886). While all other hydrogen-bond donor–acceptor distances fall within the usually observed ranges, there is one apparently extremely short bond, 2·41 Å, between O(*W*3) and O(*W*4). We do not attach much significance to this distance, since the rather large thermal parameters of these two atoms would lead to a corrected bond length up to several tenths of an ångström longer, depending on the model assumed (Hamilton & Ibers, 1968). It is also possible that there is some disorder in the crystal.

A second point is that a methoxy ether oxygen atom, O(3)(*b*), acts as an acceptor in a hydrogen bond with O(*W*2). Hydrogen bonds involving methoxy oxygen atoms have not been frequently observed previously, but have been found in the crystals of thiocolchicine.$6H_2O$ (Koerntgen & Margulis, 1977). In view of the influence of the methoxy groups on the shapes of colchicine and the many other natural products containing such groups, this type of interaction may have an important bearing on the physiological activities of these substances.

The third point to remark is the bifurcated hydrogen bond between O(*W*4) and the two oxygen atoms O(1)(*a*) and O(2)(*a*) on the troponoid ring *C*. O(1) and O(2) also act as receptors in a bifurcated hydrogen bond in the crystal structure of isocolchicine (Lessinger & Margulis, 1978), in which the keto and methoxy positions are interchanged. This underscores the fact that there is a wide latitude in the position of possible hydrogen-bond donors to one or both O atoms on ring *C*. However, not all orientations of the donor with respect to the molecular skeleton which are possible for colchicine are allowed for isocolchicine, and *vice versa*. The greatly diminished biological activity of isocolchicine compared to colchicine remains one of the most interesting, and puzzling, problems in explaining the detailed mechanism of action of these molecules.

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