Table 5. *Hydrogen bonds in cell of N-Ac-Leu-Tyr-OMe*

No H bonds for O(2)*A*, O(2)*B* or O(2)*C*.

Donor	Acceptor	Length	H···O*	Symm. equiv. of acceptor
N(1)*A*	O(1)*C*	3·176†	2·79†	$\frac{1}{2}-x, 2-y, \frac{1}{2}+z$
N(1)*B*	O(1)*A*	2·888	2·22	x, y, z
N(1)*C*	O(1)*B*	3·017	2·63†	$-\frac{1}{2}+x, \frac{3}{2}-y, 1-z$
	O″(2)*C*	3·143	2·47	$\frac{1}{2}+x, \frac{3}{2}-y, -z$
N(2)*A*	O(1)*C*	2·847	2·19	$\frac{1}{2}-x, 2-y, \frac{1}{2}+z$
N(2)*B*	O(1)*A*	3·062	2·41	x, y, z
N(2)*C*	O(1)*B*	2·999	2·17	$-\frac{1}{2}+x, \frac{3}{2}-y, 1-z$
O″(2)*A*	O(0)*A*	2·728	1·83	$x, y, -1+z$
O″(2)*B*	O(0)*C*	2·647	1·85	x, y, z
O″(2)*C*	O(0)*B*	2·709	1·95	$-1+x, y, -1+z$

* The amide and hydroxyl hydrogen atom positions were refined by least squares; H···O e.s.d.'s ~0·05 Å.

† Long values for hydrogen bonds; angles N(1)*A*–H···O(1)*C* and N(1)C–H···O(1)*B* are 113 and 114°, respectively.

provides the peptide with flexibility to adjust to its environment in order to make a maximum number of intermolecular hydrogen bonds for efficient packing. Larger peptides, stabilized by intramolecular attractions, are rarely observed to have more than one conformation in a crystal, except for small changes.

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Structures of Colchicine Analogues. I. Allocolchicine

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Abstract. Methyl 5-acetylamino-6,7-dihydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*]cycloheptene-3-carboxylate, $C_{22}H_{25}NO_6$, $M_r = 399{\cdot}4$, monoclinic, $P2_1$, $a = 7{\cdot}968\ (1)$, $b = 9{\cdot}482\ (1)$, $c = 15{\cdot}063\ (2)$ Å, $\beta = 112{\cdot}95\ (1)°$, $V = 1047{\cdot}9\ (2)$ Å^3, $Z = 2$, D_m(flotation) $= 1{\cdot}27\ (1)$, $D_x = 1{\cdot}266$ Mg m^{-3}, λ(Cu $K\alpha$) $= 1{\cdot}5418$ Å, $\mu = 0{\cdot}68$ mm^{-1}, $F(000) = 424$, $T = 288\ (1)$ K. Final $R = 0{\cdot}050$ for 1765 observed data. The seven-membered ring has the expected boat conformation, and the angle between the normals to the phenyl rings is 48·7 (4)°. The relative orientations of the three adjacent methoxy groups and the acetamido substituent are similar to those observed in crystals of colchicine. Intermolecular hydrogen bonds between the N and O atoms of the acetamido groups link the molecules into infinite spirals along the *b* axis.

Introduction. The tricyclic alkaloid colchicine, (I), exerts a potent antimitotic activity in eukaryotic cells by inhibition of the cytoskeletal tubulin–microtubule equilibrium (Dustin, 1984). The pivotal nature of this equilibrium is a major target for drug design in anticancer agents. While too toxic for clinical use, colchicine (I) plays an essential role in defining the structure–activity relationships of drug action at the 'colchicine binding site' on tubulin. This site is occupied not only by colchicinoids but by a structurally diverse range of compounds such as podophyllotoxin (Kelleher, 1977) and benzimidazole derivatives (Lacey & Watson, 1985).

The complexity of such diverse structural compatibility at the 'colchicine binding site' has led to extensive studies of the solid-state conformations of

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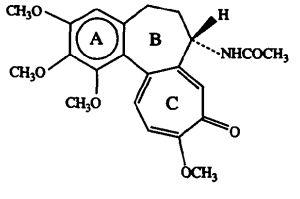
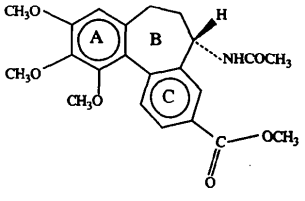
colchicinoids by X-ray crystallography, in an attempt to elucidate the structural features essential for antimitotic activity. Compounds thus far investigated focus on a range of structural variants in the *C*-ring region, a key component to activity, and include colchicine (Lessinger & Margulis, 1978*a*), isocolchicine (Lessinger & Margulis, 1978*b*), colchiceine and isocolchiceine (Silverton, 1979; Mackay, Morrison & Gulbis, 1985), thiocolchicine (Koerntgen & Margulis, 1977) and their respective analogues. In the present study, which is the first in a series of structural studies of allocolchicines that we are undertaking, we report the structure of allocolchicine (II), methyl 5-acetylamino-6,7-dihydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*]cycloheptene-3-carboxylate, the first non-troponoid system of the colchicinoids studied to date. In allocolchicine the *C* ring is chemically rearranged to a methyl benzoate moiety, a change which confers a significant enhancement in both biological activity and affinity for the colchicine site (Fitzgerald, 1976; Lacey, Burden & Watson, 1987).



(I)



(II)

Experimental. Allocolchicine was prepared from colchicine according to the method of Fernholz (1950). Colourless prismatic crystals elongated along **b** from methanol (m.p. 529–530·5 K). A crystal *ca* 0·75 × 0·52 × 0·31 mm was aligned on a Rigaku AFC diffractometer; cell parameters determined by least squares from 2θ values for 25 strong reflections ($45 < 2\theta < 78°$); Cu $K\alpha$ radiation (graphite-crystal monochromator); ω–2θ scan, 2θ scan rate 4° min^{-1}, scan range $(\Delta\omega)$ 1·2° + 0·5°tanθ, 10 s stationary background counts; 3 standard reflections monitored every 50 reflections, no significant intensity variation; 1887 unique data to $2\theta_{max} = 130°$ (h −9 to 9, k 0 to 11, l 0 to 17); 1765 data ($I > \sigma I$) for refinement; corrections for Lorentz and polarization factors and for absorption (transmission factors 0·845 to 0·718). Structure solved by direct methods with *SHELX*76 (Sheldrick, 1976). Methyl H atoms (C–H 1·08 Å) and H of N atom (N–H 0·97 Å) included at idealized positions; other H-atom sites located. Full-matrix least-squares refinement with anisotropic temperature factors for the C, N and O atoms, isotropic for H, converged at $R = 0·050$ and $wR = 0·051$, $S = 3·60$ (299 parameters varied); function minimized $\sum w(|F_o| - |F_c|)^2$ with weights $(\sigma^2|F_o| + 0·00005|F_o|^2)^{-1}$. An isotropic extinction correction of the form $F_c = F[1 - (2·74 \times 10^{-6}|F|^2/\sin\theta)]$ was applied to the calculated structure amplitudes. At convergence $(\Delta/\sigma)_{max} = 0·15$ [z coordinate of H(6*b*)], 0·02 (non-H atoms) and $(\Delta\rho)_{max}$, $(\Delta\rho)_{min} = +0·20$ and −0·21 e Å^{-3}. Atomic scattering factors and anomalous-dispersion corrections from *International Tables for X-ray Crystallography* (1974). Figures were prepared from the output of *ORTEP*II (Johnson, 1976). All calculations were performed on a VAX11/780 computer.

Table 1. *Final atomic coordinates* (× 10^4) *and equivalent isotropic temperature factors for the non-*H *atoms with e.s.d.'s in parentheses*

$B_{eq} = 8\pi^2 U_{eq} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}(Å^2)
C(1)	4378 (6)	3832	6391 (3)	4·3 (1)
C(2)	3171 (6)	2752 (6)	5927 (3)	4·8 (1)
C(3)	1394 (6)	2802 (6)	5855 (3)	5·0 (1)
C(4)	784 (6)	3972 (6)	6203 (3)	4·9 (1)
C(4*a*)	1962 (6)	5082 (6)	6636 (3)	4·3 (1)
C(5)	1253 (6)	6393 (6)	6955 (4)	5·0 (1)
C(6)	1926 (6)	6531 (6)	8050 (3)	5·0 (1)
C(7)	3942 (6)	6142 (6)	8558 (3)	4·3 (1)
C(7*a*)	5125 (5)	6758 (6)	8086 (3)	3·8 (1)
C(8)	6332 (5)	7888 (6)	8512 (3)	4·0 (1)
C(9)	7397 (5)	8443 (6)	8069 (3)	4·1 (1)
C(10)	7276 (6)	7914 (6)	7181 (3)	4·8 (1)
C(12)	6103 (6)	6807 (6)	6756 (3)	4·7 (1)
C(12*a*)	5026 (5)	6220 (6)	7199 (3)	4·2 (1)
C(12*b*)	3772 (5)	5022 (6)	6738 (3)	4·1 (1)
C(13)	5528 (6)	5654 (6)	10297 (3)	4·8 (1)
C(14)	6039 (6)	6186 (6)	11289 (3)	5·8 (1)
C(15)	8683 (6)	9656 (6)	8505 (3)	5·0 (1)
C(17)	9933 (10)	11151 (9)	9842 (5)	8·7 (2)
C(1*M*)	7393 (6)	3370 (8)	7467 (4)	6·8 (2)
C(2*M*)	4057 (10)	348 (8)	5964 (4)	9·4 (2)
C(3*M*)	−1278 (8)	1444 (8)	5601 (4)	7·6 (2)
O(1)	6178 (4)	3722 (6)	6495 (2)	5·2 (1)
O(2)	3780 (5)	1680 (6)	5504 (2)	6·3 (1)
O(3)	313 (5)	1674 (6)	5412 (2)	6·6 (1)
O(13)	5937 (5)	4428 (6)	10134 (2)	6·1 (1)
O(15)	9580 (5)	10197 (6)	8126 (2)	6·9 (1)
O(16)	8705 (4)	10005 (6)	9356 (2)	6·9 (1)
N(1)	4553 (5)	6517 (6)	9587 (2)	4·4 (1)

Discussion. Final atomic coordinates for the non-H atoms are given in Table 1.* The molecular conformation and numbering scheme are illustrated in Fig. 1, while the bond lengths, valence angles and selected torsion angles are given in Table 2.

The overall shape of the molecule is similar to that of colchicine. The angle between the normals to the *A* and *C* rings resulting from a twist about the C(12*a*)–C(12*b*) bond is 48·7 (4)°, compared with the values 51 and 53° in the two independent colchicine molecules

* Lists of structure amplitudes, anisotropic thermal parameters, H-atom coordinates and short intermolecular approaches have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51624 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

(Lessinger & Margulis, 1978*a*). The acetamido side chain at C(7) is disposed to the same side of the molecule as in other colchicinoid structures containing this group. The angles between the normals to the group [atoms C(7), N(1), C(13), O(13), C(14) coplanar to within ±0·01 (1) Å] and the *A* and *C* rings are 73·9 (4) and 72·4 (4)°, respectively. By comparison, the carboxylic ester group [atoms C(9), C(15), O(15), O(16), C(17) coplanar to within ±0·01 (1) Å] lies nearly in the plane of the *C* ring [dihedral angle 2·8 (3)°]. The *B* ring adopts the expected boat conformation as in other colchicinoid structures. However, the phenyl ring *C* in allocolchicine which replaces the troponoid ring in colchicinoids has caused a slight flattening of the *B* ring. This is reflected in the sum of torsion angles in ring *B* which is only 285°, compared with the value 305° for colchicine and values ranging between 291 and 304° for comparable colchicinoids (see Table 3). When the *A* rings of colchicine and allocolchicine are superimposed (Fig. 2), the carbonyl C atom of the *C*-ring ester substituent of (II) is essentially equidistant from the methoxy and keto moieties of the colchicine *C* ring. In fact, the possible free rotation about the C(9)–C(15) bond in (II) suggests that the ester O atoms could occupy similar regions of space with respect to the tropolone O atoms of colchicine. Indeed, it is probable that this greater flexibility of the ester over the more rigid tropolone permits allocolchicine to achieve a better fit to the receptor.

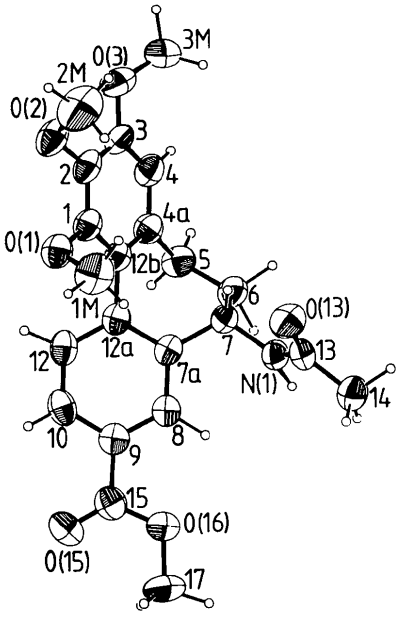


Fig. 1. A perspective view of the allocolchicine molecule with thermal ellipsoids scaled to 50% probability. The C symbol is omitted for carbons and the H atoms are denoted by spheres of arbitrary radius.

Table 2. *Bond lengths* (Å), *valence angles* (°) *and selected torsion angles* (°) *for allocolchicine,* $C_{22}H_{25}NO_6$

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

C(1)–C(2)	1·392 (6)	C(7*a*)–C(12*a*)	1·404 (7)
C(1)–C(12*b*)	1·405 (6)	C(8)–C(9)	1·373 (7)
C(1)–O(1)	1·385 (6)	C(9)–C(10)	1·396 (7)
C(2)–C(3)	1·378 (8)	C(9)–C(15)	1·510 (8)
C(2)–O(2)	1·384 (8)	C(10)–C(12)	1·385 (8)
C(3)–C(4)	1·393 (9)	C(12)–C(12*a*)	1·392 (8)
C(3)–O(3)	1·372 (8)	C(12*a*)–C(12*b*)	1·494 (7)
C(4)–C(4*a*)	1·392 (8)	C(13)–C(14)	1·477 (7)
C(4*a*)–C(5)	1·519 (9)	C(13)–O(13)	1·257 (9)
C(4*a*)–C(12*b*)	1·391 (6)	C(13)–N(1)	1·330 (6)
C(5)–C(6)	1·528 (7)	C(15)–O(15)	1·190 (7)
C(6)–C(7)	1·531 (6)	C(15)–O(16)	1·317 (6)
C(7)–C(7*a*)	1·503 (8)	C(17)–O(16)	1·454 (9)
C(7)–N(1)	1·476 (5)	C(1*M*)–O(1)	1·444 (6)
C(7*a*)–C(8)	1·415 (8)	C(2*M*)–O(2)	1·416 (9)
		C(3*M*)–O(3)	1·420 (8)

C(2)–C(1)–C(12*b*)	120·5 (3)	C(8)–C(9)–C(10)	120·2 (4)
C(2)–C(1)–O(2)	118·9 (3)	C(8)–C(9)–C(15)	121·6 (4)
C(12*b*)–C(1)–O(1)	120·6 (3)	C(10)–C(9)–C(15)	118·2 (4)
C(1)–C(2)–C(3)	120·1 (4)	C(9)–C(10)–C(12)	119·8 (4)
C(1)–C(2)–O(2)	118·3 (4)	C(10)–C(12)–C(12*a*)	112·8 (4)
C(3)–C(2)–O(2)	121·5 (4)	C(7*a*)–C(12*a*)–C(12)	119·7 (4)
C(2)–C(3)–C(4)	119·8 (4)	C(7*a*)–C(12*a*)–C(12*b*)	119·8 (4)
C(2)–C(3)–O(3)	116·2 (4)	C(12)–C(12*a*)–C(12*b*)	120·5 (4)
C(4)–C(3)–O(3)	124·0 (4)	C(1)–C(12*b*)–C(4*a*)	118·9 (4)
C(3)–C(4)–C(4*a*)	120·5 (4)	C(1)–C(12*b*)–C(12*a*)	121·2 (4)
C(4)–C(4*a*)–C(5)	120·1 (4)	C(4*a*)–C(12*b*)–C(12*a*)	119·8 (4)
C(4)–C(4*a*)–C(12*b*)	120·1 (4)	C(14)–C(13)–O(13)	121·6 (4)
C(5)–C(4*a*)–C(12*b*)	119·7 (4)	C(14)–C(13)–N(1)	116·6 (4)
C(4*a*)–C(5)–C(6)	113·2 (4)	O(13)–C(13)–N(1)	121·8 (4)
C(5)–C(6)–C(7)	112·1 (4)	C(9)–C(15)–O(15)	123·6 (4)
C(6)–C(7)–C(7*a*)	113·5 (4)	C(9)–C(15)–O(16)	111·3 (4)
C(6)–C(7)–N(1)	108·6 (4)	O(15)–C(15)–O(16)	125·1 (4)
C(7*a*)–C(7)–N(1)	113·1 (4)	C(1)–O(1)–C(1*M*)	112·7 (3)
C(7)–C(7*a*)–C(8)	121·4 (4)	C(2)–O(2)–C(2*M*)	116·5 (4)
C(7)–C(7*a*)–C(12*a*)	119·8 (4)	C(3)–O(3)–C(3*M*)	117·5 (4)
C(8)–C(7*a*)–C(12*a*)	118·8 (4)	C(15)–O(16)–C(17)	115·4 (4)
C(7*a*)–C(8)–C(9)	120·6 (4)	C(7)–N(1)–C(13)	123·1 (4)

O(1)–C(1)–C(2)–O(2)	−6·2 (7)	C(7)–C(7*a*)–C(12*a*)–C(12)	179·0 (5)
O(1)–C(1)–C(12*b*)–C(12*a*)	1·8 (7)	C(8)–C(9)–C(15)–O(15)	−177·3 (5)
O(2)–C(2)–C(3)–O(3)	5·2 (8)	C(8)–C(9)–C(15)–O(16)	4·1 (7)
C(1)–C(2)–O(2)–C(2*M*)	108·8 (6)	O(13)–C(13)–N(1)–C(7)	−2·8 (8)
C(2)–C(3)–O(3)–C(3*M*)	159·4 (5)	C(9)–C(15)–O(16)–C(17)	178·9 (5)
C(6)–C(7)–N(1)–C(13)	133·5 (5)	O(15)–C(15)–O(16)–C(17)	0·3 (8)

To date the solid-state conformations of those colchicinoids which contain the three methoxy substituents of the *A* ring show that those at C(1) and C(2) are roughly perpendicular to the ring plane whereas the one at C(3) lies close to the ring plane (*cf.* first three torsion angles in Table 3). In allocolchicine, the methoxy groups at C(1) and C(2) point in the same direction, and lie on the same side of the molecule as the acetamido side chain on the *B* ring. This is also observed for colchicine and thiocolchicine (Koerntgen & Margulis, 1977) and in one of the independent molecules in the structures of isocolchicine (Lessinger & Margulis, 1978*b*) and *N*-acetyldemecolcine (Silverton, Sharma & Brossi, 1985). For the other independent molecule in each of the two latter structures, the C(2) methoxy group points in the opposite

Table 3. *Selected torsional angles* (°) *in the solid-state conformations for comparable colchicinoids*

The angles refer to the 7*S* configuration of naturally occurring colchicine.

	(1)		(2)		(3)	(4)		(5)	(6)	(7)	(8)		(9)
C(1*M*)–O(1)–C(1)–C(2)	−79	−94	−73	−100	−97	−90	−85	50	−104	58	−94	−89	−105·2 (5)
C(2*M*)–O(2)–C(2)–C(3)	−68	−76	92	90	97	74	−84	69	−72	61	96	−73	−74·5 (7)
C(3*M*)–O(3)–C(3)–C(4)	14	−4	−3	−4	−3	−8	23	7	0	26	2	−15	−22·1 (8)
C(12*b*)–C(4*a*)–C(5)–C(6)	−73	−70	−71	−74	−69	−68	−67	−71	−69	−70	−73	−72	−73·7 (7)
C(4*a*)–C(5)–C(6)–C(7)	43	42	41	41	36	44	42	39	38	41	43	41	41·8 (6)
C(5)–C(6)–C(7)–C(7*a*)	48	49	48	50	54	44	46	49	50	47	49	50	44·3 (6)
C(6)–C(7)–C(7*a*)–C(12*a*)	−79	−81	−78	−78	−75	−78	−79	−78	−82	−79	−80	−79	−72·1 (6)
C(7)–C(7*a*)–C(12*a*)–C(12*b*)	5	5	4	1	−4	6	3	2	3	4	3	1	−1·1 (7)
C(7*a*)–C(12*a*)–C(12*b*)–C(4*a*)	53	53	50	52	56	53	57	52	54	52	53	54	49·7 (7)
C(12*a*)–C(12*b*)–C(4*a*)–C(5)	−4	−5	−2	1	−2	−7	−9	−1	−6	−3	−3	−3	2·6 (7)
C(7*a*)–C(7)–N(1)–C(13)	−88	−86	−92	−90	−82	−80	−106	−85	−75	−74	−74	−74	−99·5 (6)
C(7)–N(1)–C(13)–O(13)	6	6	−4	0	4	−3	−1	−4.7	8	2	6	1	−2·8 (8)
C(7)–N(1)–C(13)–C(14)	−178	−176	176	177	−176	175	−179	−177	−170	−179	−175	179	178·9 (5)
C(12)–C(12*a*)–C(12*b*)–C(1)	54	52	47	53	55	53	63	57	53	57	54	56	48·9 (7)
Σ torsions ring *B*	305	305	296	297	296	300	304	291	302	298	304	300	285

(1) Colchicine (Lessinger & Margulis, 1978*a*).
(2) Colchiceine (Mackay, Morrison & Gulbis, 1985).
(3) Colchiceine (Silverton, 1979).
(4) Isocolchicine (Lessinger & Margulis, 1978*b*).
(5) Colchiceine acetate (Miravitlles, Solans, Bladé-Font, Germain & Declercq, 1982).
(6) Thiocolchicine (Koerntgen & Margulis, 1977).
(7) Colchiceine benzoate (Molins, Rius, Solans, Miravitlles, Bladé-Font & Germain, 1985).
(8) *N*-Acetyldemecolcine (Silverton, Sharma & Brossi, 1985).
(9) Allocolchicine (this work).

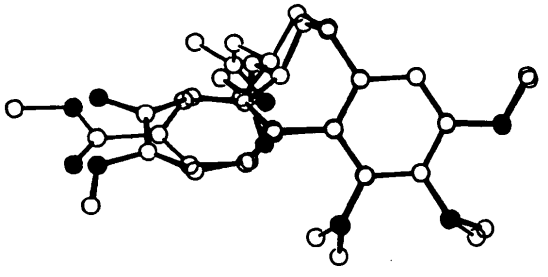


Fig. 2. The molecular structures of allocolchicine and colchicine with their *A* rings superimposed.

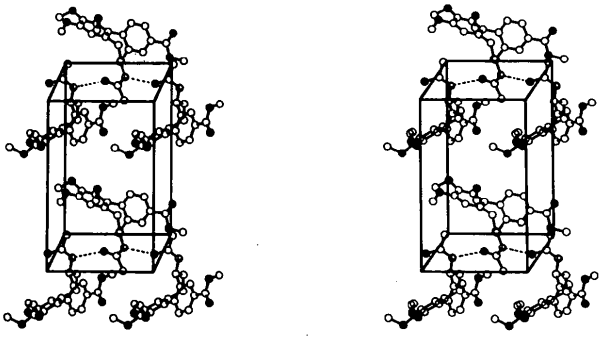


Fig. 3. Stereoview of the crystal packing. Direction of projection *a*, the *c* axis is vertical.

direction, as is also observed in structures of colchiceine (Silverton, 1979; Mackay, Morrison & Gulbis, 1985), whereas in colchiceine acetate (Miravitlles, Solans, Bladé-Font, Germain & Declercq, 1982) both the C(1) and C(2) methoxy groups point away from the acetamido side chain. Free rotation about the O–CH_3 bonds allows flexibility so that the different orientations of the *A*-ring methoxy substituents could arise as a consequence of crystal packing forces. However, in crystals of an ethyl acetate–water solvate of colchiceine (Silverton, 1979) and a hemihydrate of colchiceine (Mackay, Morrison & Gulbis, 1985) in which the packing modes are quite different, the colchiceine molecules adopt essentially identical conformations. As in other colchicinoids the acetamido side chain in allocolchicine has the conformation (Table 3) preferred by equatorial *O*-acetyl groups as first discussed by Mathieson (1965). All bond lengths and angles are similar to those in comparable structures.

The crystal packing is illustrated in Fig. 3. Intermolecular hydrogen bonds, in which N is the donor atom to an acetamido carbonyl O atom related by a 2_1 axis ($1-x$, $\frac{1}{2}+y$, $2-z$), link the molecules into infinite spirals along **b**. The N(1)···O(13) and NH(1)···O(13) distances are 2·842 (8) and 1·90 Å and N(1)–NH(1)···O(13) = 162°. All other intermolecular contacts are normal.

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Structure of a κ-Opioid Receptor Misfit: (1*S*,5*R*,8*R*,9*R*)-2′-Hydroxy-5,9-dimethyl-8,2-epoxyethano-6,7-benzomorphan Hydrochloride*†

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Abstract. $C_{16}H_{22}NO_2^+.Cl^-$, $M_r = 295{\cdot}808$, monoclinic, $P2_1$, $a = 11{\cdot}967$ (1), $b = 12{\cdot}529$ (1), $c = 9{\cdot}9369$ (9) Å, $\beta = 93{\cdot}00$ (1)°, $V = 1487{\cdot}8$ (2) Å^3, $Z = 4$, $D_m = 1{\cdot}32$ (2), $D_x = 1{\cdot}321$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ(Cu $K\alpha$) = 2·289 mm^{-1}, $F(000) = 632$, $T = 291$ K, final $R = 0{\cdot}040$ for 2448 observed reflections. The two molecules present in the asymmetric unit are linked by an extensive network of hydrogen bonds, including several of the less common (C–)H···O and (C–)H···Cl types. This interpretation is substantiated by a Mulliken population analysis resulting from *CNDO*/2 calculations. The major effect of the presence of the epoxyethano bridge is a marked flattening about the N atom of the piperidinium ring. Whether this is sufficient to explain the inactivity of the compound at the opioid κ receptor is not clear.

Introduction. The title compound, although having an equatorial oxygen substituent at the same position as ketazocine [(1*S*,5*R*,9*R*)-2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-8-oxo-6,7-benzomorphan] (Verlinde & De Ranter, 1983) has its keto oxygen, is devoid of the κ-opioid properties of this prototypical molecule. Apart from being about 150 times less active than ketazocine in the writhing test in mice (Merz, 1983), it fails completely to inhibit the contractions of the electrically stimulated rabbit vas deferens (Verlinde & De Ranter, 1988), a preparation containing exclusively opioid receptors of the κ type (Oka, Negishi, Suda, Matsumiya, Inazu & Ueki, 1980). A 2′-methoxy analogue lacking the 9-methyl group was reported to be inactive (Shiotani & Kometani, 1980). Other modifications of the structure of ketazocine, such as the replacement of the carbonyl by an equatorial hydroxy or methoxy group with retention of the *N*-cyclopropylmethyl [Michne & Albertson (1972) and Merz (1983), respectively] led also to inactive compounds.

In 1984 a model was proposed to explain κ-opioid activity in the 6,7-benzomorphan series, establishing a distinct role for this crucial O atom (De Ranter, Verlinde, Blaton & Peeters, 1984). This model explains how ketazocine, with its O atom on the benzomorphan nucleus, and reputed κ-opioid agonists such as bremazocine and Mr2034 where the O atom is incorporated in the *N*-side chain, can interact with the same receptor. Hydrogen bonding to a common group in the receptor is postulated. The main purpose of the present study is to find clues in the crystal structure that might explain the inactivity of the title compound in view of that model.

Experimental. Colourless prismatic crystals obtained at room temperature from an equimolar ethyl acetate–methanol solution. Density measured by flotation in *n*-heptane/CCl_4, ~0·5 × 0·3 × 0·25 mm, Hilger & Watts computer-controlled four-circle diffractometer, Ni-filtered Cu $K\alpha$ radiation, $\omega/2\theta$ scan technique

* *Chemical Abstracts* name: (1*R*,2*S*,6*R*,11*R*)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-1,3-epoxyethano-2,6-methano-3-benzazocin-8-ol hydrochloride.

† Structural Studies of Substituted 6,7-Benzomorphan Compounds. XIV. Part XIII: Verlinde, De Ranter, Blaton & Peeters (1989).

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