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Structure of a New Colchicine Derivative, 5,6-Dihydro-6-hydroxymethyl-1,2,3-trimethoxy-9-methylthio-8*H*-cyclohepta[*a*]naphthalen-8-one

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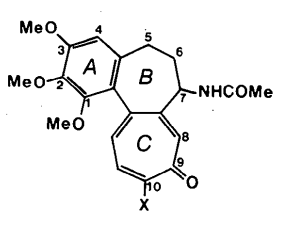
Abstract. $C_{20}H_{22}O_5S$, $M_r = 374{\cdot}4$, monoclinic, $P2_1$, $a = 11{\cdot}125$ (6), $b = 8{\cdot}749$ (3), $c = 9{\cdot}378$ (5) Å, $\beta = 95{\cdot}62$ (4)°, $V = 908{\cdot}4$ (7) Å^3, $Z = 2$, $D_x = 1{\cdot}369$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 1{\cdot}964$ cm^{-1}, $F(000) = 396$, $T = 293$ K. Least-squares refinement based on 2132 observed reflections gave $R = 0{\cdot}046$. The title compound has a dihedral angle of 29·8 (1)° between the planes of the two rings *A* and *C*. The hydroxymethyl substituent is in an axial position on the six-membered *B* ring. The compound is the first published biologically active colchicinoid with an *A*–*C* ring twist of less than 50°.

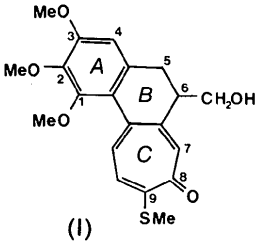
Introduction. Colchicine, the major alkaloid of *Colchicum autumnale*, is a powerful mitotic inhibitor. Its activity has been shown to be due to specific binding to tubulin, the main subunit of the microtubule cytoskeleton, thus preventing it from assembling into microtubules under physiological conditions (Dustin, 1978).

The binding of colchicine to tubulin is remarkable in the sense that it is slow, highly temperature dependent, and although practically irreversible, non-covalent in nature.



X = OMe Colchicine

X = SMe Thiocolchicine



(I)

Recent studies have focused on the role of the *B* ring and its substituents in the binding (Bane, Puett, Macdonald & Williams, 1984; Andreu, Gorbunoff, Lee & Timasheff, 1984; Bhattacharyya, Howard, Maity, Brossi, Sharma & Wolff, 1986; Engelborghs & Fitzgerald, 1987). Kinetic studies of the colchicine–tubulin interaction have shown multiphase binding kinetics, indicating a conformational change of an initially formed loosely bound complex in order to achieve tight binding (Garland, 1978; Lambeir & Engelborghs, 1981). In a CD study (Detrich, Williams, Macdonald, Wilson & Puett, 1981) of colchicine-bound tubulin, the negative CD band at 340 nm of colchicine was found to be absent in the complex. This was interpreted as an indication of a conformational change in the colchicine molecule, in which the *A*–*C* ring dihedral angle is diminished from 53° in solution to 19° in the bound state.

The X-ray diffraction studies of colchicinoids hitherto reported, have given no indication of more than one colchicine conformation in the solid state. The basic colchicine skeleton conformation appears to be at a global energy minimum, as shown by the similarities of the *B*-ring torsion angles for a number of colchicinoids (Sharma, Brossi & Silverton, 1985). Interestingly, a bicyclic colchicine analogue devoid of the *B* ring also crystallizes with an *A*–*C* ring twist of 57° (Rossi, Link & Lee, 1984).

Therefore, it was of much interest to study a compound with a more planar phenyltropone chromophore. Taking advantage of an unusual nitrous acid deamination rearrangement in the colchinol series (Cohen, Cook & Roe, 1940; Cook, Jack & Loudon, 1952), the title compound (I) was synthesized. Its structure was established by NMR (Lincoln 1989). (I) was found to be a potent microtubule inhibitor, with a fast and reversible binding action to the colchicine binding site of tubulin. To establish the conformation, a crystal-structure determination was undertaken.

Experimental. The details of the synthesis of the title compound (I) will be described elsewhere (Lincoln, 1989). Single crystals of (I) were obtained by recrys-

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tallization from ethyl acetate, m.p. 473 K (uncorrected). A yellow prismatic crystal (0·26 × 0·22 × 0·56 mm) was mounted on a glass pin and data were collected on a Syntex $P2_1$ diffractometer with graphite-monochromatized Mo $K\alpha$ radiation using ω–2θ scan mode. The lattice parameters were determined by least-squares fit of 14 reflections with $8<2\theta<20°$. A total of 2933 reflections were collected, 2132 with $I>3\sigma(I)$ were considered observed. $2\theta_{max} = 55·0°$, hkl range: 0→18, 0→15, −15→15. Integrated intensities were calculated by the program *LELA* (Lehmann & Larsen, 1974). The data were corrected for Lorentz and polarization effects (Andersen, 1985), but not for absorption. Three standard reflections ($\bar{1}1\bar{1}$, $\bar{2}30$, $\bar{1}1\bar{2}$), remeasured after every 47 reflections, showed no significant change in intensity.

The structure was solved by direct methods using *MITHRIL* (Gilmore, 1983). An anisotropic full-matrix least-squares refinement was based on $|F_{hkl}|$ using *SHELX76* (Sheldrick, 1976). All H-atom positions were located, and the positional and isotropic thermal parameters were refined. H atoms on the methyl groups were constrained to have the same isotropic temperature factor [$U = 0·093$ (5) Å^2]. 308 parameters were refined, $R = 0·046$, $wR = 0·051$; $w = 1/[\sigma^2(F^2) + 0·0016F^2]$. Max. and min. residual electron densities in the final difference Fourier map were 0·22 and −0·24 e Å^{-3}, respectively. The mean and max. shift/e.s.d. were 0·005 and 0·022. Molecular parameters were calculated with *PARST*83 (Nardelli, 1983). The atomic scattering factors were derived from *International Tables for X-ray Crystallography* (1974). The drawings were made using *ORTEP* (Johnson, 1965).

Discussion. The final atomic coordinates and equivalent isotropic thermal parameters for the non-H atoms are listed in Table 1.* Fig. 1 shows the molecule with the atomic labeling. The bond distances, angles and selected torsion angles are listed in Table 2.

Preliminary results from the NMR and CD properties of (I) in solution indicate that the absolute configuration of the compound is 6*R*. Interpretation of the NMR spectrum shows an axial arrangement of the *B*-ring substituent in solution and the CD spectrum suggests that the helicity of the *A*–*C* ring twist in (I) is the same as in thiocolchicine, derived from natural (−)-colchicine (Lincoln, 1989).

* Lists of structure factors, anisotropic thermal parameters, torsion angles and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51954 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional coordinates* (× 10^4) *and equivalent isotropic thermal parameters* (Å^2) *for the non*-H *atoms; e.s.d.'s in parentheses*

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

	x	*y*	*z*	B_{eq}
S	−4300 (1)	4372	2859 (1)	4·47 (2)
C(1)	−9859 (3)	7893 (4)	3726 (3)	3·16 (7)
C(2)	−1027 (3)	8409 (4)	3813 (3)	3·30 (7)
C(3)	−1655 (3)	9153 (4)	2662 (3)	3·39 (8)
C(4)	−1099 (3)	9375 (5)	1425 (3)	3·57 (7)
C(4a)	−9943 (3)	8836 (4)	1317 (3)	3·23 (6)
C(5)	−9314 (3)	9092 (5)	−12 (3)	3·95 (9)
C(6)	−7987 (3)	9487 (5)	377 (3)	3·73 (8)
C(6a)	−7373 (3)	8189 (4)	1267 (3)	3·20 (7)
C(7)	−6221 (3)	7863 (5)	985 (4)	3·67 (8)
C(8)	−5359 (3)	6706 (5)	1468 (4)	3·78 (8)
C(9)	−5581 (3)	5532 (4)	2509 (4)	3·48 (7)
C(10)	−6637 (3)	5273 (4)	3074 (4)	3·76 (8)
C(11)	−7734 (3)	6081 (4)	2966 (4)	3·63 (7)
C(11a)	−8083 (3)	7423 (4)	2262 (3)	3·14 (7)
C(11b)	−9303 (2)	8049 (4)	2435 (3)	3·06 (6)
C(12)	−7869 (3)	1033 (5)	1157 (4)	4·38 (10)
C(1*m*)	−9168 (4)	7961 (7)	6232 (4)	5·56 (12)
C(2*m*)	−2214 (5)	6789 (7)	4999 (6)	6·65 (16)
C(3*m*)	−3508 (3)	252 (6)	1720 (5)	5·23 (11)
C(9*m*)	−4679 (4)	3149 (8)	4264 (6)	6·67 (16)
O(1)	−9257 (2)	7176 (4)	4880 (2)	4·60 (7)
O(2)	−1590 (2)	8156 (4)	5038 (2)	3·87 (6)
O(3)	−2792 (2)	9599 (4)	2888 (3)	4·70 (7)
O(8)	−4369 (2)	6669 (4)	943 (3)	5·44 (8)
O(12)	−6685 (2)	1449 (4)	1625 (3)	5·00 (8)

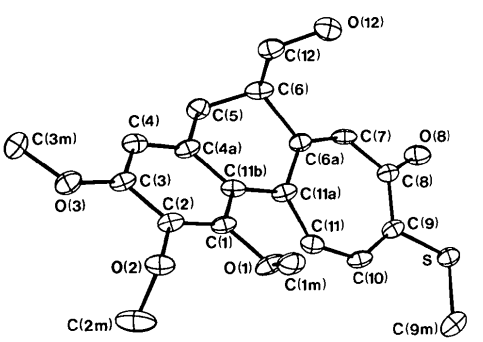

Fig. 1. Thermal-ellipsoid (50% probability) plot of (I) showing the numbering scheme employed. H atoms have been omitted for clarity.

In the crystal structure it is found that the hydroxymethyl group on the six-membered *B* ring is in an axial position, while corresponding seven-membered *B*-ring substituents in colchicinoid crystal structures are always found in a pseudo-equatorial orientation.

The overall conformation of (I) is similar to that of the natural colchicinoids with seven-membered *B* rings, although it is flatter due to the smaller *A*–*C* ring twist. The dihedral angle between the least-squares planes of the benzene ring and the tropone ring is 29·8 (1)° compared to the average of 53 ±4° [torsion angle C(4a)—C(12b)—C(12a)—C(7a) = C(4a)—C(11b)—C(11a)—C(6a) in (I)] found in all

Table 2. *Bond distances* (Å), *angles* (°) *and selected torsion angles* (°) *with e.s.d.'s in parentheses*

S—C(9)	1·754 (4)	C(6)—C(12)	1·537 (6)
S—C(9*m*)	1·780 (6)	C(6a)—C(7)	1·364 (5)
C(1)—C(2)	1·386 (5)	C(6a)—C(11a)	1·445 (5)
C(1)—C(11b)	1·419 (4)	C(7)—C(8)	1·437 (6)
C(1)—O(1)	1·368 (4)	C(8)—C(9)	1·455 (6)
C(2)—C(3)	1·389 (4)	C(8)—O(8)	1·250 (4)
C(2)—O(2)	1·379 (4)	C(9)—C(10)	1·354 (5)
C(3)—C(4)	1·381 (4)	C(10)—C(11)	1·405 (5)
C(3)—O(3)	1·360 (4)	C(11)—C(11a)	1·384 (5)
C(4)—C(4a)	1·383 (5)	C(11a)—C(11b)	1·487 (4)
C(4a)—C(5)	1·505 (4)	C(12)—O(12)	1·395 (4)
C(4a)—C(11b)	1·391 (4)	C(1*m*)—O(1)	1·437 (5)
C(5)—C(6)	1·525 (5)	C(2*m*)—O(2)	1;382 (7)
C(6)—C(6a)	1·530 (5)	C(3*m*)—O(3)	1·411 (5)

C(9)—S—C(9*m*)	103·8 (2)	C(7)—C(6a)—C(11a)	127·7 (3)
C(11b)—C(1)—O(1)	119·9 (3)	C(6a)—C(7)—C(8)	134·2 (4)
C(2)—C(1)—O(1)	119·5 (3)	C(7)—C(8)—O(8)	118·7 (4)
C(2)—C(1)—C(11b)	120·6 (3)	C(7)—C(8)—C(9)	123·8 (4)
C(1)—C(2)—O(2)	120·1 (3)	C(9)—C(8)—O(8)	117·4 (4)
C(1)—C(2)—C(3)	120·7 (3)	S—C(9)—C(8)	110·2 (3)
C(3)—C(2)—O(2)	119·2 (3)	C(8)—C(9)—C(10)	126·3 (3)
C(2)—C(3)—O(3)	114·7 (3)	S—C(9)—C(10)	123·4 (3)
C(2)—C(3)—C(4)	119·1 (3)	C(9)—C(10)—C(11)	131·9 (4)
C(4)—C(3)—O(3)	126·2 (3)	C(10)—C(11)—C(11a)	131·5 (4)
C(3)—C(4)—C(4a)	120·7 (3)	C(6a)—C(11a)—C(11)	123·8 (3)
C(4)—C(4a)—C(11b)	121·7 (3)	C(11)—C(11a)—C(11b)	118·5 (3)
C(4)—C(4a)—C(5)	121·4 (3)	C(6a)—C(11a)—C(11b)	117·5 (3)
C(5)—C(4a)—C(11b)	116·9 (3)	C(4a)—C(11b)—C(11a)	120·4 (3)
C(4a)—C(5)—C(6)	110·7 (2)	C(1)—C(11b)—C(11a)	122·4 (3)
C(5)—C(6)—C(12)	110·4 (3)	C(1)—C(11b)—C(4a)	117·2 (3)
C(5)—C(6)—C(6a)	109·4 (3)	C(6)—C(12)—O(12)	114·4 (3)
C(6a)—C(6)—C(12)	112·4 (3)	C(1)—O(1)—C(1*m*)	117·7 (3)
C(6)—C(6a)—C(11a)	117·0 (3)	C(2)—O(2)—C(2*m*)	112·6 (3)
C(6)—C(6a)—C(7)	115·3 (3)	C(3)—O(3)—C(3*m*)	117·3 (3)

C(11a)—C(11b)—C(4a)—C(5)	−3·5 (5)	C(10)—C(11)—C(11a)—C(6a)	9·6 (6)
C(11b)—C(4a)—C(5)—C(6)	−39·9 (4)	C(11)—C(11a)—C(6a)—C(7)	−8·6 (6)
C(4a)—C(5)—C(6)—C(6a)	58·5 (4)	C(11a)—C(6a)—C(7)—C(8)	2·9 (7)
C(5)—C(6)—C(6a)—C(11a)	−36·2 (4)	C(2)—C(1)—O(1)—C(1*m*)	−54·0 (5)
C(6)—C(6a)—C(11a)—C(11b)	−5·5 (5)	C(3)—C(2)—O(2)—C(2*m*)	88·9 (5)
C(6a)—C(11a)—C(11b)—C(4a)	27·6 (5)	C(4)—C(3)—O(3)—C(3*m*)	4·9 (6)
C(6a)—C(7)—C(8)—C(9)	−1·5 (7)	C(10)—C(9)—S—C(9*m*)	−9·7 (4)
C(7)—C(8)—C(9)—C(10)	6·0 (6)	C(12)—C(6)—C(6a)—C(7)	−95·2 (4)
C(8)—C(9)—C(10)—C(11)	−7·1 (7)	C(6a)—C(6)—C(12)—O(12)	54·2 (4)
C(9)—C(10)—C(11)—C(11a)	−1·2 (7)	O(8)—C(8)—C(9)—S	3·7 (5)

other solid-state colchicinoid structures (Sharma *et al.*, 1985).

Despite the increased planarity the structure of the phenyltropone chromophore in (I) remains similar to those of other thiocolchicine derivatives. Comparble bond angles and bond lengths generally lie within the range of values reported for the following compounds: *N*-desacetylthiocolchicine (Koerntgen & Margulis, 1977), 1,2-di-*O*-acetyl-1,2-di-*O*-demethylthiocolchicine and 2,3-di-*O*-acetyl-2,3-di-*O*-demethylthiocolchicine (Kerekes, Brossi, Flippen-Anderson & Chignell, 1985). Otherwise, deviations from the range do not exceed 2° or 0·017 Å, except for those of the 2-methoxy group. However, the steric congestion in the flattened molecule is evident from the distances O(1)···C(11), 2·758 (4) Å, and O(1)···H(11), 2·15 (4) Å, the latter being considerably shorter than the sum of the van der Waals radii, 2·6 Å.

The benzene *A* ring appears to be somewhat distorted [$\chi^2 = 107$, r.m.s.d. = 0·015 (4) Å, δ_{max} = 0·022 (3) Å for C(11b)] from the least-squares plane through its six C atoms, and has a significantly lengthened C(1)—C(11b) bond. Furthermore, the tropone *C* ring deviates significantly from planarity [$\chi^2 = 627$, r.m.s.d. = 0·033 (4) Å, δ_{max} = 0·050 (3) Å for C(11a)]. The ring can be described as a shallow distorted chair, or by the angles between three defined planes: plane (1): C(6a), C(7), C(8), C(10), C(11) [$\chi^2 = 4·3$, r.m.s.d. = 0·004 (4) Å, δ_{max} = 0·007 (4) Å for C(7)], plane (2): C(8), C(9), C(10), plane (3): C(6a), C(11), C(11a). The dihedral angles between the planes are: (1)–(2) = 5·4 (3), (1)–(3) = 7·4 (3), (2)–(3) = 12·5 (4)°. Planes (2) and (3) are tilted in the same direction as the 6-hydroxymethyl group, relative to plane (1). The puckering of the *C* ring, although in a distinctly different conformation from the colchicinoids hitherto studied, is comparable in magnitude to what has been found in most other thiocolchicine derivatives.

As indicated by the bond lengths, the extent of π-electron delocalization in the tropone ring of (I) is similar to the delocalization in the above-mentioned thiocolchicine derivatives, with formal single and formal double bonds averaging 1·436 and 1·367 Å, respectively. Further, the only significant differences in the tropone-ring bond lengths between (I) and the thiocolchicines are a longer C(11)—C(11a) and a shorter C(9)—C(10) formal double bond in (I), probably an effect of increased conjugation with the benzene ring.

The molecular packing is illustrated in Fig. 2. There is one intermolecular hydrogen bond, O(12)—H(12′)···O(8^{i}) (i = $-x-1$, $y+\frac{1}{2}$, $-z$) [O(12)—H(12′) = 0·81 (4), O(12)···O(8) = 2·784 (4), H(12′)···O(8) = 2·01 (4) Å, O(12)—H(12′)···O(8) = 158 (4)°], arranging the molecules along a screw axis. The characteristics of the hydrogen bond are in good accord with the previously reported tropone carbonyl hydrogen bonds in other colchicinoids (*e.g.* Sharma *et al.*, 1985). There are no other intermolecular contacts less than 3·30 Å.

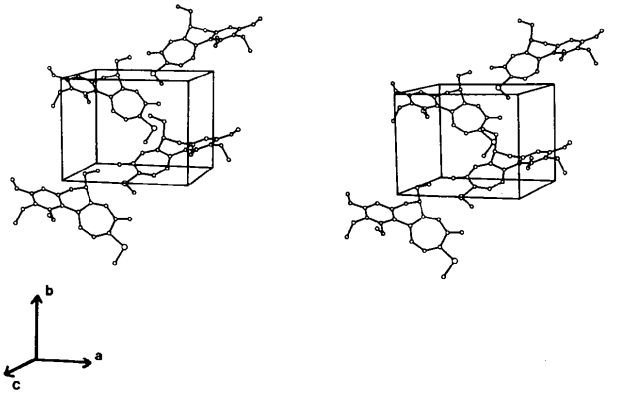

Fig. 2. Stereoview showing the crystal packing.

This is the first example of a less twisted (30°), biologically active colchinoid having a conformation similar to the one proposed for the colchicine–tubulin complex (Detrich *et al.*, 1981).

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Structure of Ethyl 2-Chloro-4-methyl-6-(1-pyrrolidinyl)benzoate

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Abstract. $C_{14}H_{18}ClNO_2$, $M_r = 267{\cdot}7$, orthorhombic, *Pbca*, $a = 10{\cdot}571$ (3), $b = 12{\cdot}081$ (5), $c = 21{\cdot}384$ (6) Å, $V = 2731$ Å^3, $Z = 8$, $D_x = 1{\cdot}30$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 3{\cdot}59$ cm^{-1}, $F(000) = 1136$, $T = 293$ K, $R = 0{\cdot}0357$ for 716 observed reflections. In molecules of the title compound the ester substituent is forced from conjugation with the aromatic ring and nitrogen lone pair by steric interaction with the adjacent chlorine.

Introduction. The selective preparation of highly functionalized vinylogous urethanes (Schlessinger, Doss & Richardson, 1986) has attracted widespread interest over the years, and such substances have a variety of applications in agriculture and medicine.

Our interest in the stereoelectronic effects of related enaminones (Natale, 1982) and vinylogous imidates (Natale, McKenna, Niou, Borth & Hope, 1985) has led us to examine the solid-state structure of the title compound. The title compound is readily available by the phosphorus-oxychloride-promoted dimerization of enamines (Harris, Huppatz & Phillips, 1975). We have also observed that the title compound is produced as a by-product in the preparation of ethyl 3,5-dimethylisoxazolecarboxylate (McMurry, 1973) when $POCl_3$ is used to dehydrate nitroethane to the nitrile oxide in the presence of an enamine (Quincy & Natale, 1985).

Experimental. The title compound was isolated as a by-product of the nitrile oxide cycloaddition of the pyrrolidine enamine of ethyl acetoacetate (McMurry, 1973; Quincy & Natale, 1985). Suitable crystals, $0{\cdot}45 \times 0{\cdot}25 \times 0{\cdot}3$ mm, were obtained by slow evaporation from a 1:1 mixture of ethanol and ethyl acetate. The data were collected on a Nicolet *R3/m* diffractometer by the ω-scan technique (Campana, Shepard & Litchman, 1980) using graphite-

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