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2:1 Adduct of Colchiceine Acetate and Ethyl Acetate

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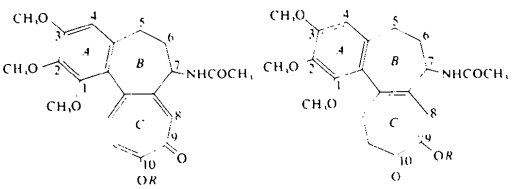
Abstract

$C_{23}H_{25}NO_7.\frac{1}{2}C_4H_8O_2$, $M_r = 471{\cdot}49$, is orthorhombic, $P2_12_12_1$, with $a = 9{\cdot}299$ (3), $b = 10{\cdot}534$ (4), $c = 27{\cdot}084$ (6) Å, $V = 2653$ (4) Å^3, $Z = 4$, λ(Mo $K\alpha$) = 0·71069 Å, $D_c = 1{\cdot}180$, $D_m = 1{\cdot}16$ (2) Mg m^{-3}. The structure was solved by the Patterson search approach where the molecular structure of isocolchicine was used as the search model and refined by full-matrix least-squares methods. The final R value was 0·077 for 1552 observed reflections. The ethyl acetate molecule shows an occupation factor of 0·5, and the acetamido O atom is disordered. The position of the acetoxy group in the solid state defines the molecule as belonging to the isocolchicine series. The conformation of colchiceine acetate may explain its lack of accessibility at the tubulin binding site and therefore its decreased biological activity.

Introduction

Colchicine, $C_{22}H_{25}NO_6$, is an alkaloid extracted from the meadow saffron or autumn crocus (*Colchicum autumnale* L.) and other *Liliaceae*. It presents a large number of biological effects, but the most important of these is doubtless its inhibiting action in the process of mitosis, believed to result from the specific strong binding of colchicine to tubulin. This process interferes with the assembly of this protein into the microtubules of the mitotic spindle. Thus, colchicine and some of its derivatives which bind well to tubulin behave as powerful antimitotics and therefore have potential antitumor activity.

In order to try to clarify the relationships between structure and biological activity in the products of the colchicine series the crystal structures of colchicine (I) ($R = CH_3$) (Lessinger & Margulis, 1978*a*), its inactive isomer, isocolchicine (II) ($R = CH_3$) (Lessinger & Margulis, 1978*b*), and other derivatives (Margulis, 1974, 1977; Koerntgen & Margulis, 1977; Clark & Margulis, 1980; Brossi, Rösner, Silverton, Iorio & Hufford, 1980; Margulis & Lessinger, 1978; Margulis, 1975; Silverton, 1979) have recently been determined. On the other hand, Bladé-Font (1977*a*,*b*, 1978, 1979) has synthesized some new derivatives of colchicine with the same aim in view. Among these the crystal structure of the *O*,*N*-diacetate of the enolic form of colchicine was solved (Busetta, Leroy, Hospital, Elguero & Bladé-Font, 1979).



(I) (II)

Structural variations of colchicine have shown that the arrangement of the tropolone ether function is critical, isocolchicine derivatives of the general formula (II) being considerably less active biologically (Rösner, Caparo, Jacobson, Atwell, Brossi, Iorio, Williams, Sik & Chignell, 1981; Santavý, 1979). In this connection we deemed it of interest to determine by X-ray diffraction the crystal structure of colchiceine acetate (II) ($R = COCH_3$) to contribute toward the understanding of the specific interactions of colchicine

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derivatives with tubulin. On the other hand, we wanted to confirm that in the solid state the acetoxy group is exclusively at C(9), *i.e.* that crystalline colchiceine acetate belongs to the isocolchicine series (Bellet, 1954). In a recent ^{13}C NMR study, Elguero, Muller, Bladé-Font, Faure & Vincent (1980) have discussed the prototropy (I ⇄ II) (R = H) of colchiceine and the acylotropy (I ⇄ II) (R = $COCH_3$) of colchiceine acetate, showing that, in solution, there is in both cases a slight predominance of the isocolchicine-form tautomer. Contrary to what had been assumed from some physical data (Horowitz & Ullyot, 1952; Delaroff & Rathle, 1965), crystalline colchiceine has recently been found to belong to the colchicine ('normal') series (Silverton, 1979); it is therefore (I) (R = H). In the case of a related compound, 7-oxo-deacetamidocolchiceine, it has been determined by X-ray analysis (Iorio, Brossi & Silverton, 1978) that the crystal contains an approximately equimolecular random mixture of the two dimensionally very similar isomeric molecules of the isocolchicine and colchicine series.

Colchiceine acetate was obtained by acetylation of colchiceine with acetic anhydride and pyridine (Santavý, 1952). The crystals were obtained by evaporation of an ethyl acetate solution of crystalline powder at room temperature, and the majority of the crystals obtained were poor in quality. A crystal of 0·2 × 0·1 × 0·7 mm was isolated and used for data collection. The cell parameters were determined by least squares from the settings of 15 reflexions measured on a Syntex four-circle diffractometer with Mo $K\alpha$ radiation.

Intensities of 2267 reflections in the $2\theta \leq 47°$ range were collected with graphite-monochromatized Mo $K\alpha$ radiation using an ω-scan technique, but only 1552 were considered observed [$I \geq 2{\cdot}5\sigma(I)$]. The data were corrected for Lorentz–polarization effects.

The structure was solved using the Patterson search program (Braun, Hornstra & Leenhouts, 1969) with the molecular structure of isocolchicine as the search model.

Refinements were carried out using the *SHELX* program system (Sheldrick, 1976). Weighted isotropic and anisotropic full-matrix least-squares refinement on $\sum w(F_o - F_c)^2$ converged at R = 0·110 for all observed reflections. A difference Fourier synthesis at this point showed the presence of one ethyl acetate molecule and statistical disorder in the acetamido O atom. A final full-matrix refinement including H atoms in calculated positions and starting from occupancy factors of 0·5 for O(13*A*) and O(13*B*) gave a final R value of 0·077 for 1552 observed reflections (these occupancy factors remained finally very close to 0·5 but, on the other hand, the ethyl acetate molecule was constrained to 0·5 occupancy factor, according to the chemical analysis; their temperature factors were refined isotropically). The weights were $w = K[\sigma^2(F) + 0{\cdot}0009|F_o|^2]^{-1}$ where $\sigma(F)$ was the standard deviation

Table 1. *Atomic coordinates* (×10⁴) *and equivalent isotropic temperature factors* (Å²) *with e.s.d.'s in parentheses*

	x	y	z	B_{eq}*
C(1)	3270 (12)	2231 (12)	6696 (4)	3·7 (7)
C(1*m*)	1536 (19)	3787 (15)	6979 (7)	7·9 (8)
C(2)	2525 (13)	1108 (13)	6777 (4)	3·7 (7)
C(2*m*)	434 (14)	731 (17)	7277 (5)	7·1 (8)
C(3)	3270 (14)	−25 (13)	6785 (4)	4·2 (7)
C(3*m*)	3174 (21)	−2290 (14)	6917 (7)	7·4 (8)
C(4)	4751 (14)	−33 (12)	6721 (4)	4·3 (7)
C(4*a*)	5492 (12)	1069 (12)	6637 (4)	3·6 (6)
C(5)	7091 (12)	1059 (12)	6558 (4)	4·4 (7)
C(6)	7494 (12)	1370 (11)	6018 (4)	4·4 (6)
C(7)	6550 (11)	2400 (10)	5800 (4)	3·5 (6)
C(7*a*)	6441 (12)	3580 (10)	6150 (4)	3·3 (6)
C(8)	7309 (13)	4632 (11)	6030 (4)	4·1 (7)
C(9)	7440 (14)	5782 (13)	6243 (5)	4·8 (7)
C(10)	6799 (15)	6357 (14)	6678 (5)	5·4 (7)
C(11)	5856 (15)	5566 (13)	6987 (5)	5·0 (7)
C(12)	5337 (13)	4380 (12)	6930 (4)	4·1 (7)
C(12*a*)	5542 (12)	3464 (11)	6546 (4)	3·4 (7)
C(12*b*)	4767 (12)	2229 (11)	6626 (4)	3·5 (6)
C(13)	6208 (15)	3128 (16)	4951 (4)	5·3 (7)
C(14)	6828 (15)	3356 (16)	4460 (4)	6·5 (7)
C(15)	9407 (19)	7150 (18)	6191 (6)	7·2 (9)
C(16)	9957 (19)	8307 (13)	5953 (7)	7·3 (8)
N	7075 (9)	2723 (10)	5305 (3)	4·0 (5)
O(1)	2593 (9)	3373 (8)	6637 (3)	4·4 (4)
O(2)	1043 (8)	1123 (9)	6800 (3)	5·0 (4)
O(3)	2454 (10)	−1083 (9)	6854 (4)	6·4 (4)
O(9)	8253 (12)	6702 (10)	5979 (4)	7·1 (6)
O(10)	7042 (12)	7468 (9)	6798 (4)	7·5 (6)
O(13*A*)	5068 (92)	3139 (72)	5046 (26)	9·1 (25)
O(13*B*)	4752 (75)	3411 (62)	5043 (26)	4·7 (27)
O(15)	9975 (13)	6607 (13)	6537 (5)	9·2 (6)
C(1*EA*)	1511 (56)	4404 (42)	655 (16)	22·2 (22)
C(2*EA*)	2615 (52)	4923 (44)	321 (17)	14·6 (21)
C(3*EA*)	4659 (57)	4146 (54)	−77 (18)	21·1 (25)
C(4*EA*)	5318 (52)	3394 (41)	−442 (16)	18·1 (24)
O(1*EA*)	3432 (34)	3959 (27)	93 (10)	15·9 (16)
O(2*EA*)	5045 (33)	5385 (30)	89 (10)	18·7 (14)

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

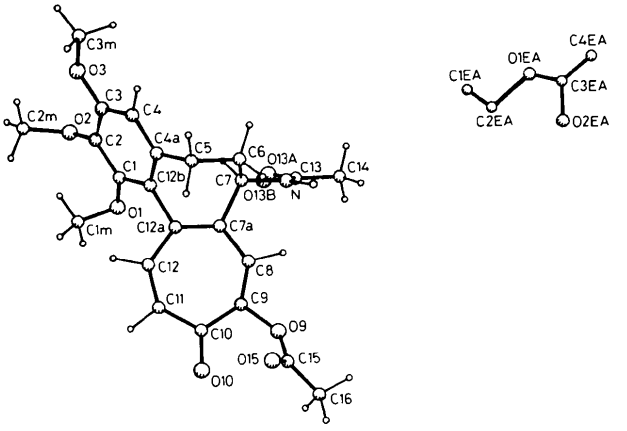

Fig. 1. View of the molecule, with the atomic numbering.

in the observed amplitudes derived from counting statistics.

Final atomic coordinates* are listed in Table 1; Fig. 1 shows the numbering system and a view of the molecules drawn by *PLUTO* (Motherwell & Clegg, 1978).

Discussion

The bond lengths and angles are shown in Fig. 2.

The troponoid ring *C* is not quite planar and shows a definite alternation in bond lengths with an arrangement corresponding to an isocolchicine-like structure.

* Lists of structure factors, anisotropic thermal parameters, and H-atom positional parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36740 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

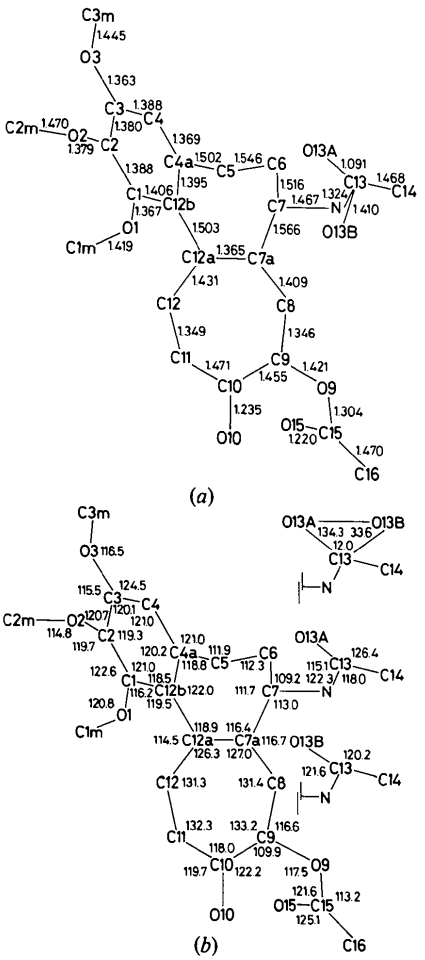

Fig. 2. (*a*) Bond lengths (Å) [the maximum value for the e.s.d.'s is 0·02 Å except for the distances of the disordered atom O(13*A*) and O(13*B*)]. (*b*) Bond angles (°) [the maximum value for the e.s.d.'s is 0·9° except for the angles of the disordered atoms O(13*A*) and O(13*B*)].

According to our data two shallow boat conformations are equally possible. One is defined by the planes:

plane (1): C(9), C(10), C(11);
plane (2): C(9), C(11), C(12), C(8)

(r.m.s.d.: 0·01 and maximum deviation from the plane 0·01 Å);

plane (3): C(8), C(7*a*), C(12*a*), C(12)

(r.m.s.d.: 0·006 and maximum deviation 0·008 Å).

The dihedral angle between planes (1) and (2) is 3·8° and that between planes (2) and (3) is 3·4°. The other boat conformation is defined by the following planes:

plane (4): C(9), C(7*a*), C(8);
plane (5): C(9), C(7*a*), C(12*a*), C(10)

(r.m.s.d.: 0·004 and maximum deviation 0·005 Å);

plane (6): C(10), C(11), C(12), C(12*a*)

(r.m.s.d.: 0·002 and maximum deviation 0·003 Å).

The dihedral angle between planes (4) and (5) is 2·7° and that between planes (5) and (6) is 5·0°. However, the torsion angles (Table 2) define a skew boat conformation with the carbonyl at the prow of the boat. This favours the first conformation previously mentioned.

The puckering of ring *C* is comparable to that found in colchicine (Lessinger & Margulis, 1978*a*) as evidenced by the sum of these torsion angles.

Concerning other structural features of colchiceine acetate it is possible to define the *N*-acetyl side chain by two very rough planes: D_1: C(7), N, C(13), O(13*A*), C(14) (r.m.s.d. 0·03 and maximum deviation 0·05 Å) and D_2: C(7), N, C(13), O(13*B*), C(14) (r.m.s.d. 0·05 and maximum deviation 0·08 Å). The angle between the normals to planes D_1 and D_2 is 4·9°. The lack of planarity in this group is attributed to the disorder of O(13).

Ring *A* exhibits a greater planarity than in colchicine and isocolchicine as the plane defined by the atoms C(12*b*), C(4*a*), C(4), C(3), C(2) and C(1) presents an r.m.s.d. of 0·005 and a maximum deviation from the plane of 0·008 Å for C(4).

Comparison of the torsion angles of the *B* rings in colchicine, isocolchicine and colchiceine with those of colchiceine acetate shows (Table 3) that the most significant differences are in C(12*b*)–C(12*a*)–C(7*a*)–C(7) and C(5)–C(4*a*)–C(12*b*)–C(12*a*). Therefore the conformation of the *B* ring in colchiceine acetate differs from that found in the aforementioned molecules and in other colchicine derivatives, being more flattened, as can be seen from the sum of the torsion angles of ring *B* for colchicine, isocolchicine, colchiceine acetate and colchiceine (305, 300, 291 and 295·9°, respectively).

Table 2. *Selected torsion angles* (°)

The maximum value for the e.s.d.'s is 2°.

C(8)–C(9)–C(10)–C(11)	3·8	C(12*a*)–C(7*a*)–C(8)–C(9)	−3·9	C(4)–C(3)–O(3)–C(3*m*)	6·7
O(9)–C(9)–C(10)–O(10)	−4·1	C(8)–C(7*a*)–C(7)–N	−22·8	C(3)–C(2)–C(1)–C(12*b*)	0·0
C(10)–C(9)–C(8)–C(7*a*)	2·9	C(1)–C(12*b*)–C(4*a*)–C(4)	−0·8	O(2)–C(2)–C(1)–O(1)	0·0
C(10)–C(9)–O(9)–C(15)	66·8	C(12*a*)–C(12*b*)–C(1)–O(1)	6·4	C(3)–C(2)–O(2)–C(2*m*)	69·3
C(9)–C(10)–C(11)–C(12)	−6·4	C(4*a*)–C(12*b*)–C(1)–C(2)	0·0	C(2)–C(1)–O(1)–C(1*m*)	50·1
C(10)–C(11)–C(12)–C(12*a*)	0·9	C(12*b*)–C(4*a*)–C(4)–C(3)	1·6	C(7*a*)–C(7)–N–C(13)	−85·2
C(11)–C(12)–C(12*a*)–C(7*a*)	5·0	C(4*a*)–C(4)–C(3)–C(2)	−1·8	O(13*A*)–C(13)–N–C(7)	−4·2
C(12)–C(12*a*)–C(7*a*)–C(8)	−2·2	C(4)–C(3)–C(2)–C(1)	1·3	O(13*B*)–C(13)–N–C(7)	7·3
C(12)–C(12*a*)–C(12*b*)–C(1)	56·5	O(3)–C(3)–C(2)–O(2)	−4·7	O(15)–C(15)–O(9)–C(9)	17·5

Table 3. *Torsion angles in ring B* (°)

The maximum value for the e.s.d.'s is 2°.

	(I)	(II)		(III)		(IV)
C(4*a*)–C(12*b*)–C(12*a*)–C(7*a*)	−52	−53	−57	−53	−53	−56·4
C(12*b*)–C(12*a*)–C(7*a*)–C(7)	−1·7	−6	−7	−5	−5	4·3
C(12*a*)–C(7*a*)–C(7)–C(6)	77·6	78	79	79	81	75·2
C(7*a*)–C(7)–C(6)–C(5)	−49·2	−44	−46	−48	−49	−53·8
C(7)–C(6)–C(5)–C(4*a*)	−39·2	−44	−42	−43	−42	−35·6
C(6)–C(5)–C(4*a*)–C(12*b*)	70·7	68	70	73	70	68·8
C(5)–C(4*a*)–C(12*b*)–C(12*a*)	1·0	7	9	4	5	1·8

(I) Colchiceine acetate (present work, with reversed signs); (II) isocolchicine (Lessinger & Margulis, 1978*b*); (III) colchicine (Lessinger & Margulis, 1978*a*); (IV) colchiceine (Silverton, 1979).

The overall shape of the colchiceine acetate molecule is governed by the dihedral angles between the planar regions. Ring *A*–ring *C*, 54; ring *A*–group D_1, 66·6; ring *A*–group D_2, 66·7; ring *C*–group D_1, 88·9; ring *C*–group D_2, 84·4° and shows a great similarity with colchicine and isocolchicine. As in these molecules, rings *A* and *C* of colchiceine acetate are twisted about the C(12*a*)–C(12*b*) bond.

The activity of colchicine derivatives in the presence of tubulin depends on the accessibility to the binding site and this is governed by the orientations of the groups with a greater variability of conformation, which in the case of colchiceine acetate are the three methoxy groups and the acetoxy group. The plane determined by the latter forms an angle of 104° with the *C* ring; of the three methoxy groups the C(3)–O(3)–C(3*m*) is almost parallel to the plane of ring *A*, while the other two, C(2)–O(2)–C(2*m*) and C(1)–O(1)–C(1*m*), form angles of 65 and 47°, respectively, with the *A* ring, both pointing in the same direction. The conformation and orientation of the three methoxy groups of ring *A* in colchiceine acetate are similar to those in colchicine but the accessibility of our molecule is decreased owing to the relative position of the acetoxy group. In colchicine and isocolchicine the methoxy group linked to the *C* ring is parallel to this ring, whereas in our case the acetoxy group is almost perpendicular to ring *C*, pointing to the opposite side from the *N*-acetyl group.

Colchiceine and colchiceine acetate, although existing in solution (Elguero *et al.*, 1980) as mixtures of tautomers (I) and (II), crystallize in exclusively one form. This work shows that the crystal structure of colchiceine acetate corresponds to the isocolchicine form (II), in contrast to its parent molecule, colchiceine, which crystallizes in the colchicine-like tautomer (I). A third possibility, *i.e.* the existence of a colchicine analogue with a crystalline structure consisting of a mixture of the two tautomeric forms, is represented by 7-oxo-deacetamidocolchiceine (Iorio *et al.*, 1978).

Further work is now in progress in order to determine the influence of the acyl groups in the acylotropic tautomerism of colchiceine esters and its relation with their crystal structure.

The shortest intermolecular distances are N–O(13B^{ii}) = 2·91 (8); O(13*A*)–O(9^{iii}) = 2·92 (8); O(13*B*)–C(1EA^{i}) = 3·06 (8); N–O(13A^{ii}) = 3·07 (8); C(13)–O(2EA^{iii}) = 3·11 (2); C(2*EA*)–O(13B^{i}) = 3·16 (9); C(1*EA*)–C(4EA^{ii}) = 3·202 (5); N–O(2EA^{iii}) = 3·31 (2) Å, where (i) = 0·5 − *x*, −*y*, 0·5 + *z*; (ii) = 0·5 + *x*, 0·5 − *y*, −*z*; (iii) = −*x*, 0·5 + *y*, 0·5 − *z*.

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On the Conformation of Methoxy Groups in the Crystal Structures of *o*-Dimethoxybenzene Derivatives

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Abstract

Among 32 crystal structures of compounds bearing *o*-methoxy substituents, the planar conformation is preferred in 30 cases; only two structures contain a non-planar methoxy group. The present work tries to explain these differences in conformational properties.

I. Introduction

It is remarkable that, in spite of the absence of steric hindrance, *o*-dimethoxybenzene derivatives exist with a non-planar conformation in the gas phase. Partition coefficients, dipole moments and dielectric relaxation times also indicate the presence of a non-planar conformation. *Ab initio* STO3G calculations for non-planar *o*-dimethoxybenzene derivatives are in much better agreement with the photoelectron spectra of the compounds studied than are the calculations for the planar compounds (Anderson, Kollman, Domelsmith & Houk, 1979).

On the other hand, crystal structures of numerous methoxy-substituted aromatics have been examined but, of 32 crystals studied, only two exhibit non-planar *o*-dimethoxy structures. It was interesting to study these two and some of the other 30 structures for comparison, with the aim of explaining why one conformation is preferred over another for a given crystal structure.

The only non-planar compounds are trimethylated catechinic acid (McCandlish, Hanson & Stout, 1976) and mesembranol (Luhan & McPhail, 1973). Among the planar conformations, we have chosen four structures: (1) *N*-demethyl-*N*-formylmesembrenone (Karle, 1977); (2) polycarpine (Damak & Riche, 1977); (3) tetra-*O*-methyldehydrodicaffeic acid dilactone (Nakamura, Iitaka, Kumada, Takeuchi & Umezawa, 1977); (4) 2-amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]thiazole (Ekstrand & van der Helm, 1977).

The use of only four of the planar compounds was motivated by computation-time considerations: the large sizes of the molecules demanded a significant amount of time for each case. No systematic consideration was involved in the choice of the molecules themselves, however.

II. Method

The method of computing the crystal lattice energy has been described extensively in preceding papers (Caillet

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