

Structural Studies of Colchicine Derivatives. II. Structure of Acetyl Anhydrocolchicine, $C_{24}H_{25}NO_6$

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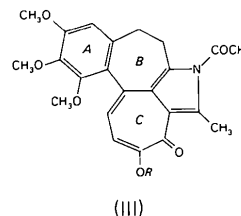
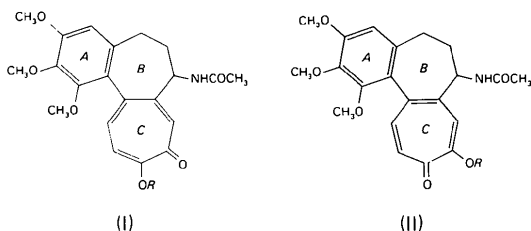
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Abstract. $M_r = 423.19$, triclinic, $P\bar{1}$, $a = 7.927$ (2), $b = 11.731$ (5), $c = 12.949$ (5) Å, $\alpha = 112.04$ (3), $\beta = 97.18$ (3), $\gamma = 71.44$ (3)°, $V = 1058$ (7) Å³, $Z = 2$, $D_m = 1.32$ (2), $D_x = 1.33$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.70926$ Å, $\mu = 0.895$ cm⁻¹, $F(000) = 450$, $T = 298$ K. Final $R = 0.075$ for 3121 unique reflections. The results confirm the pyrrolic structure advanced in a previous publication and chemically define acetyl anhydrocolchicine as the tetracyclo compound 6-acetyl-3,10,11,12-tetramethoxy-5-methyl-7,8-dihydro-4*II*-benzo[1,2]heptalen[5,6-*bc*]pyrrol-4-one (IUPAC name). The benzene and pyrrolic rings are essentially planar while the two seven-membered rings have boat conformations. There are no short intermolecular contacts.

Introduction. Molecular-geometry and conformational studies on a series of colchicine (I) ($R = \text{CH}_3$) (Lessinger & Margulis, 1978*a*) and isocolchicine (II) ($R = \text{CH}_3$) (Lessinger & Margulis, 1978*b*) derivatives and related compounds (Margulis, 1974, 1977; Koerntgen & Margulis, 1977; Clark & Margulis, 1980; Brossi, R3sner, Silverton, Iorio & Hufford, 1980; Silverton, 1979) have been carried out in recent years in order better to understand their selectivity of action, *i.e.* binding to the protein tubulin.

Blad3-Font (1977*a,b*, 1978, 1979) has synthesized new derivatives of colchicine in which the tropolonic structure and the chirality of the starting product were no longer present. For one of these products an X-ray study has already been published (Busetta, Leroy, Hospital, Elguero & Blad3-Font, 1979) and in this connection we deemed it of interest to determine by X-ray diffraction the crystal structures of some other derivatives for which there is some doubt concerning their chemical structures. The present work is the second of a series of this structural study of colchicine derivatives (Miravittles, Solans, Blad3-Font, Germain & Declercq, 1982) and concerns an achiral product acetyl anhydrocolchicine (III) ($R = \text{CH}_3$) thus named for shortness on account of the structure suggested by instrumental analysis and spectroscopic features (Blad3-Font, 1977*a*).



Experimental. Title compound obtained as described (Blad3-Font, 1977*a*) by treatment of (\pm)-8-acetylcolchicine (which adopts a five-membered cyclol form prefiguring the pyrrole ring) with acetic anhydride or mineral acids. Orange single crystals obtained by evaporation of methanol solution of crystalline powder at room temperature; size 0.25 × 0.20 × 0.20 mm.

Unit-cell parameters by least squares from 15 reflections, 2θ from $47\text{--}90^\circ$. Syntex four-circle diffractometer, graphite-monochromatized $\text{Mo K}\alpha$, one standard reflection, 2.9% variation in intensity. No systematic absences. 3121 unique reflections, $\theta < 23.5^\circ$, $-8 \leq h \leq 8$, $-12 \leq k \leq 12$, $0 \leq l \leq 14$; for small intensities, *i.e.* $I < \sigma(I)$, the most probable intensity assumed to be $I = [I + \sigma(I)]/2$. Lorentz and polarization but no absorption correction. Repeated attempts to solve structure with straightforward option of *MULTAN*11/82 direct-methods program (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982) and *YZARC*11/82 (Wright, Declercq, Germain & Woolfson, 1982) all failed, a solution was achieved with *RANTAN* option; 27 non-H atoms found in Fourier map with set of phases presenting better figures of merit given by *RANTAN* (ABSFORM = 1.143, PSIZERO = 1.173 and RESID = 15.69), a new Fourier synthesis showed four remaining C atoms. Refinement on *F* carried out using local version of *CRYSTAN* (Burzlaff, Böhme & Gomm, 1977). Weighted isotropic and anisotropic block-matrix least-squares refinement converged at $R = 0.117$ for all reflections. Difference Fourier synthesis ($\theta_{\text{max}} = 20^\circ$) showed positions of 23 H atoms; three H atoms belonging to methyl groups not found but located after some anisotropic cycles in a new difference map ($\theta_{\text{max}} = 8^\circ$). Final $R = 0.075$, $wR = 0.043$ with $w = 1/\sigma^2(F_o)$ [$\sigma(F_o)$ derived from counting statistics], $S = 2.51$. (Δ/σ) $_{\text{max}} = 0.21$, final $\Delta\rho$ excursions $-0.20\text{--}0.26 \text{ e \AA}^{-3}$.

Discussion. Final atomic coordinates and equivalent isotropic thermal parameters are listed in Table 1;* Fig. 1 shows a view of the molecule with the numbering scheme.

The chemical structure of acetyl anhydrocolchicine as defined by the X-ray crystallographic results corresponds to 6-acetyl-3,10,11,12-tetramethoxy-5-methyl-7,8-dihydro-4*H*-benzo[1,2]heptaleno[5,6-*bc*]pyrrol-4-one (III), thus confirming the previously proposed structure (Bladé-Font, 1977*a*). For easier comparison with other colchicine derivatives studied by X-rays, the colchicine numbering has been used in our drawings and coordinates.

The bond lengths and angles are shown in Fig. 2, torsion angles in Table 2. The benzene ring *A* is nearly planar [r.m.s.d. = 0.005 (5) Å, $\delta_{\text{max}} = 0.008$ (2) Å for C(12b)]. The pyrrolic ring *D* is essentially planar [$\chi^2 = 7.6$ [$= \sum(\delta/\sigma)^2$], r.m.s.d. = 0.003 (3) Å, $\delta_{\text{max}} = 0.004$ (2) Å for C(13)]. The greater planarity of ring

B in comparison to other derivatives of the colchicine series is highly conditioned in this compound by the existence of the additional pyrrolic ring *D* as can be seen from the sum of the torsion angles of ring *B* for colchicine, isocolchicine, colchicine acetate, colchicine and acetyl anhydrocolchicine (305, 300, 291, 296 and 248° , respectively). This is also supported by the fact that only the two more distant torsion angles of this ring, *i.e.* C(6)–C(5)–C(4a)–C(12b) and C(5)–C(4a)–C(12b)–C(12a) take the usual values in these derivatives. Ring *B* has a boat conformation defined by plane (1): C(4a),C(5),C(6); plane (2): C(4a),C(12b),C(7),C(6) [r.m.s.d. = 0.014 (7) Å, $\delta_{\text{max}} =$

Table 1. Atomic coordinates with *e.s.d.*'s in parentheses ($\times 10^4$) and equivalent isotropic temperature factors (\AA^2) for the non-H atoms

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq} *
C(1)	0.6328 (3)	0.7112 (2)	0.9999 (1)	3.1
C(1m)	0.3921 (4)	0.6264 (3)	0.9347 (2)	7.8
C(2)	0.5765 (3)	0.8247 (2)	1.0901 (1)	3.3
C(2m)	0.5079 (4)	0.7784 (3)	1.2388 (2)	7.6
C(3)	0.6466 (3)	0.9255 (2)	1.1075 (1)	3.2
C(3m)	0.6442 (3)	1.1411 (2)	1.2186 (2)	4.8
C(4)	0.7692 (3)	0.9120 (2)	1.0335 (1)	3.4
C(4a)	0.8245 (3)	0.7976 (2)	0.9425 (1)	3.1
C(5)	0.9493 (3)	0.7884 (2)	0.8593 (2)	4.0
C(6)	0.8522 (3)	0.7977 (2)	0.7530 (2)	3.8
C(7)	0.7948 (3)	0.6805 (2)	0.6879 (1)	3.0
C(7a)	0.7994 (2)	0.5768 (2)	0.7151 (1)	2.9
C(8)	0.7712 (3)	0.4777 (2)	0.6132 (1)	3.2
C(9)	0.7730 (3)	0.3462 (2)	0.5949 (2)	4.2
C(10)	0.8811 (3)	0.2775 (2)	0.6667 (2)	3.9
C(10m)	1.0368 (5)	0.0636 (2)	0.6604 (2)	7.1
C(11)	0.9225 (3)	0.3289 (2)	0.7740 (2)	4.0
C(12a)	0.8156 (3)	0.5721 (2)	0.8271 (1)	2.9
C(12)	0.8737 (3)	0.4611 (2)	0.8479 (1)	3.1
C(12b)	0.7591 (3)	0.6948 (2)	0.9246 (1)	3.5
C(13)	0.7514 (3)	0.5228 (2)	0.5273 (1)	3.3
C(13m)	0.7207 (3)	0.4579 (2)	0.4057 (2)	5.2
C(14)	0.7405 (3)	0.7294 (2)	0.5099 (2)	4.6
C(14m)	0.6329 (4)	0.8648 (2)	0.5569 (2)	6.0
N(1)	0.7640 (2)	0.6470 (1)	0.5727 (1)	3.4
O(1)	0.5616 (2)	0.6137 (1)	0.9866 (1)	3.8
O(2)	0.4479 (2)	0.8424 (1)	1.1616 (1)	4.3
O(3)	0.5866 (2)	1.0318 (1)	1.2005 (1)	4.0
O(9)	0.6932 (3)	0.2872 (1)	0.5153 (1)	6.8
O(10)	0.9266 (2)	0.1482 (1)	0.6075 (1)	5.3
O(14)	0.7992 (3)	0.6818 (2)	0.4170 (1)	7.4

$$* B_{\text{eq}} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

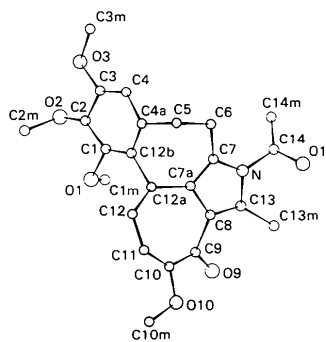


Fig. 1. View of the molecule with atomic numbering.

* Lists of anisotropic thermal parameters, structure factors and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38779 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester, CH1 2HU, England.

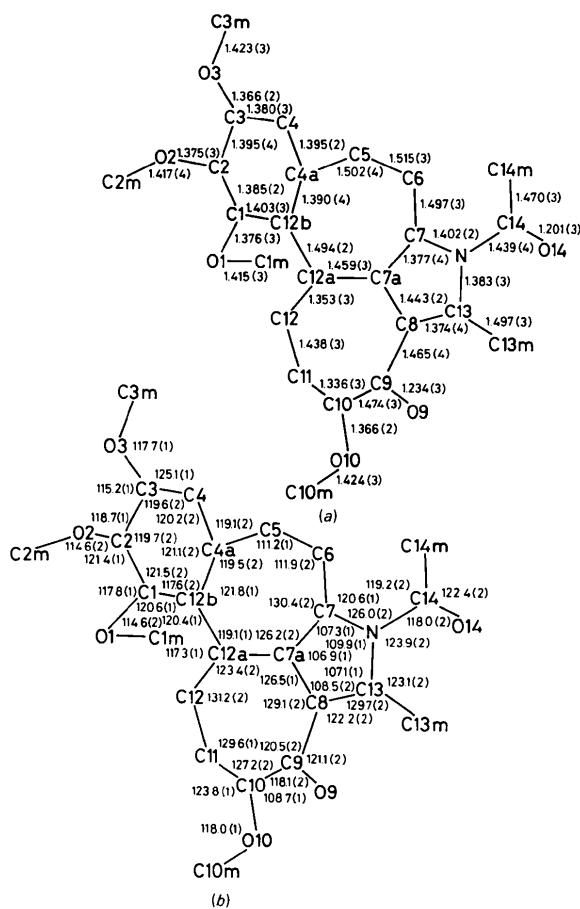


Fig. 2.(a) Bond lengths (Å) and (b) bond angles (°) (e.s.d.'s in parentheses).

Table 2. Selected torsion angles (°)

The maximum value for the e.s.d.'s is 0.3°.

C(2)-C(1)-O(1)-C(1m)	81.5	C(12)-C(12a)-C(12b)-C(1)	-53.1
C(1)-C(2)-O(2)-C(2m)	76.7	C(7a)-C(12a)-C(12)-C(11)	-3.4
C(4)-C(3)-O(3)-C(3m)	4.9	C(12a)-C(12b)-C(4a)-C(5)	2.7
C(4a)-C(5)-C(6)-C(7)	70.1	C(7a)-C(8)-C(9)-C(10)	-28.0
C(6)-C(5)-C(4a)-C(12b)	72.4	C(8)-C(9)-C(10)-C(11)	30.9
C(5)-C(6)-C(7)-C(7a)	7.9	C(9)-C(10)-C(11)-C(12)	0.0
C(6)-C(7)-C(7a)-C(12a)	18.7	C(11)-C(10)-O(10)-C(10m)	5.3
C(7)-C(7a)-C(12a)-C(12b)	23.6	C(10)-C(11)-C(12)-C(12a)	19.9
C(8)-C(7a)-C(12a)-C(12b)	-151.1	C(14m)-C(14)-N-C(7)	41.0
C(12a)-C(7a)-C(8)-C(9)	7.9	O(14)-C(14)-N-C(13)	38.5
C(7a)-C(12a)-C(12b)-C(4a)	53.5		

0.016 (3) Å]; and plane (3): C(12b),C(7),C(7a),-C(12a) [r.m.s.d. = 0.07 (6) Å, δ_{\max} = 0.100 (3) Å]. The angle between the normals to planes (1) and (2) is 119.5 (3)° and that between planes (2) and (3) is 30.5 (4)°. The prow of the boat is C(5). Ring C exhibits bond-length alternation, except for the C(7a)-C(8) bond length [1.443 (2) Å], since as a consequence of the existence of ring D, this is a single bond. As in other compounds belonging to the colchicine series, this ring also has a boat conformation with the prow at C(9), defined by plane (1): C(10),C(9),C(8); plane (2):

C(11),C(10),C(7a),C(8) [r.m.s.d. = 0.014 (7) Å, δ_{\max} = 0.016 (3) Å]; and plane (3): C(11),C(12),C(12a),-C(7a) [r.m.s.d. = 0.010 (9) Å, δ_{\max} = 0.013 (3) Å]. The angles between the normals to planes (1) and (2), and between planes (2) and (3) are 23.2 (3) and 18.7 (4)° respectively.

The overall shape of acetyl anhydrocolchicine is characterized by the dihedral angles between the four planar regions [ring A-ring B, 36.2 (3); ring B-ring C, 32.5 (3); ring C-ring D, 16.2 (2); ring A-ring C, 61.7 (3)°] as well as by the twisting between ring A and ring C, given by the torsion angle C(12)-C(12a)-C(12b)-C(1), not different from the torsion angles formed in colchicine, isocolchicine and colchicine acetate.

The methoxy group C(3m)-O(3)-C(3) is approximately contained in the plane of ring A [-4.6 (3)°], while the other two, C(2)-O(2)-C(2m) and C(1)-O(1)-C(1m), form angles of 75.4 (3) and 81.6 (3)° respectively with ring A, pointing in opposite directions. The methoxy group linked to the C ring is almost [15.8 (3)°] in the plane of this ring as in colchicine and isocolchicine.

No short intermolecular contacts are found.

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