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Structures of Colchicine Analogues. V. 2-Methoxy-5-(4-methoxyphenyl)cyclohepta-2,4,6-trien-1-one

BY J. M. GULBIS AND M. F. MACKAY

Department of Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia

AND M. G. BANWELL AND J. N. LAMBERT

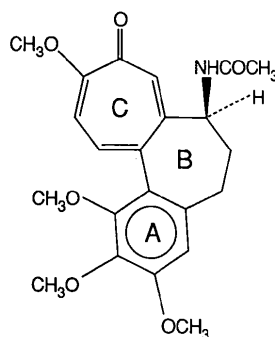
School of Chemistry, University of Melbourne, Parkville, Victoria 3052, Australia

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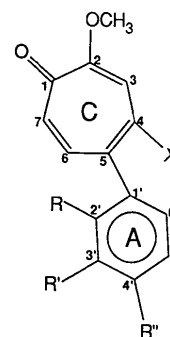
Abstract. C₁₅H₁₄O₃, *M_r* = 242.3, monoclinic, *Pc*, *a* = 13.219 (1), *b* = 7.072 (1), *c* = 6.527 (2) Å, β = 97.23 (1)°, *V* = 605.3 (3) Å³, *Z* = 2, *D_m* (flotation) = 1.33 (1), *D_x* = 1.329 Mg m⁻³, λ(Cu *Kα*) = 1.5418 Å, μ(Cu *Kα*) = 0.66 mm⁻¹, *F*(000) = 256, *T* = 291 (1) K, final *R* = 0.040 for 905 observed data. The bicyclic molecule adopts a conformation similar to the solid-state conformation of isocolchicine, and the dihedral angle between the planes of the two rings is 41.1 (4)°.

Introduction. The alkaloid colchicine (1) is a potent antimitotic agent (Brossi, Yeh, Chrzanowska, Wolff, Hamel, Lin, Quin, Suffness & Silverton, 1988), which exerts its effect by binding to the cytoskeletal protein tubulin. The existence of two partial binding sites on the protein has been established, one for the trimethoxyphenyl *A* ring and one for the troponoid *C* ring. In view of this and the potent antimitotic properties of the *AC*-ring analogues (2) (Fitzgerald, 1976) and (3) (Banwell, Herbert, Buckleton, Clark, Rickard, Lin & Hamel, 1988), comprehensive structure–activity studies of colchicine analogues lacking the central *B* ring could provide important insights into the mode of the colchicine–tubulin interaction. In addition, such systems might represent potentially useful compounds in a therapeutic sense. As part of a continuing conformational study

of colchicine analogues which might have potential as antimitotic agents (Banwell, Gravatt, Buckleton, Clark & Rickard, 1989; Banwell, Collis, Crisp, Lambert, Reum, Scoble, Gable, Mackay & Hamel, 1991), we report here the structure of an *AC*-ring monomethoxyphenyl analogue (4). In earlier studies we reported the structures of the three bicyclic dimethoxyphenyl analogues (5) and (6) (Gable, Mackay, Banwell & Lambert, 1990) and (7) (Banwell *et al.*, 1991).



(1)



- (2) *R* = *R'* = *R''* = OCH₃, *X* = H
 (3) *R* = *R'* = *R''* = OCH₃, *X* = Cl
 (4) *R* = *R'* = *X* = H, *R''* = OCH₃
 (5) *R* = *R'* = OCH₃, *R''* = *X* = H
 (6) *R'* = *R''* = OCH₃, *R* = *X* = H
 (7) *R* = *R''* = OCH₃, *R'* = *X* = H

Experimental. Pale-yellow prismatic crystals of (4) from benzene, $ca\ 0.24 \times 0.21 \times 0.27$ mm, aligned on a Rigaku-AFC diffractometer; cell parameters determined by least-squares from 2θ values for 25 strong reflections ($41 < 2\theta < 78^\circ$); Cu $K\alpha$ radiation (graphite crystal monochromator, $\lambda = 1.5418 \text{ \AA}$); ω - 2θ scan, scan rate 2° min^{-1} , scan range ($\Delta\omega$) $1.2^\circ + 0.5^\circ \tan\theta$, $2\theta_{\text{max}} = 130^\circ$, 10 s stationary background counts; three standard reflections monitored every 50 reflections, no significant intensity variation; 1109 unique data, $h\ 0$ to 15, $k\ 0$ to 8, $l\ -7$ to 7, 905 for which $I > 2\sigma(I)$ used for refinement; intensities corrected for Lorentz and polarization effects and for absorption, transmission factors 0.959 to 0.870. Structure solved by direct methods with *SHELXS86* (Sheldrick, 1985) and refined with *SHELXL76* (Sheldrick, 1976). H-atom sites located by difference, except for those of the methoxy groups, which were included at idealized positions (C—H 1.08 Å); no refinement of H-atom coordinates or temperature factors; full-matrix least-squares refinement with anisotropic temperature factors given to C and O atoms, isotropic for H, converged at $R = 0.040$ and $wR = 0.052$, $S = 1.27$ (162 parameters varied); function minimized $\sum w(|F_o| - |F_c|)^2$, with weights $(\sigma^2|F_o| + 0.0012|F_o|^2)^{-1}$; one reflection, 020, apparently seriously affected by extinction omitted from the final refinement. At convergence, $(\Delta/\sigma)_{\text{max}} = 0.001$; $(\Delta\rho)_{\text{max}}$, $(\Delta\rho)_{\text{min}} = +0.14$, -0.21 e \AA^{-3} . Atomic scattering factors and anomalous-dispersion factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, pp. 99, 149). Figures were prepared from the output of *ORTEPII* (Johnson, 1976). Calculations performed on a VAX11/780 computer.

Discussion. Final atomic coordinates for the non-H atoms are given in Table 1,* bond lengths and angles are listed in Table 2 and the molecular conformation and numbering is illustrated in Fig. 1. The molecule (4) adopts a solid-state conformation that resembles isocolchicine (Lessinger & Margulis, 1978a), an inactive isomer of colchicine, rather than colchicine (Lessinger & Margulis, 1978b) (1). This solid-state conformation has been adopted without exception by all other bicyclic AC-ring analogues so far studied, namely (2) (Rossi, Link & Lee, 1984), (3) (Banwell *et al.*, 1988), (5) and (6) (Gable *et al.*, 1990), and (7) (Banwell *et al.*, 1991). The tropolone A-ring atoms in (4) are coplanar to within 0.04 (1) Å, and

* Lists of structure factors and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54562 (12 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: HA0070]

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

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

	x	y	z	B_{eq} (Å ²)
C(1)	4196	2848 (5)	4979	3.26 (7)
C(2)	4501 (4)	2364 (5)	2932 (8)	3.25 (7)
C(3)	3862 (4)	1968 (5)	1162 (8)	3.17 (6)
C(4)	2783 (4)	1930 (5)	752 (9)	2.99 (6)
C(5)	2043 (5)	2362 (5)	1950 (9)	2.86 (6)
C(6)	2253 (4)	2912 (5)	4066 (8)	2.95 (6)
C(7)	3162 (4)	3144 (5)	5316 (6)	3.30 (6)
O(1)	4872 (4)	3057 (6)	6456 (6)	5.62 (7)
O(2)	5516 (4)	2333 (4)	3034 (6)	3.95 (5)
C(2')	5976 (5)	1956 (8)	1203 (9)	5.46 (10)
C(1')	950 (4)	2359 (4)	1017 (9)	2.71 (6)
C(2')	667 (4)	3099 (5)	-940 (8)	3.13 (6)
C(3')	-349 (4)	3148 (5)	-1855 (8)	3.30 (7)
C(4')	-1093 (5)	2427 (5)	-756 (9)	3.20 (6)
C(5')	-821 (4)	1683 (5)	1214 (9)	3.39 (6)
C(6')	182 (4)	1674 (5)	2084 (8)	3.32 (6)
O(4')	-2115 (4)	2364 (4)	-1491 (9)	4.35 (6)
C(4'')	-2441 (5)	3158 (8)	-3452 (10)	5.35 (10)

Table 2. Bond lengths (Å) and angles (°) with *e.s.d.*'s in parentheses

C(1)—C(2)	1.483 (5)	O(2)—C(2')	1.432 (8)
C(1)—C(7)	1.427 (5)	C(1')—C(2')	1.387 (7)
C(1)—O(1)	1.238 (5)	C(1')—C(6')	1.389 (8)
C(2)—C(3)	1.371 (7)	C(2')—C(3')	1.400 (7)
C(2)—O(2)	1.335 (7)	C(3')—C(4')	1.385 (8)
C(3)—C(4)	1.418 (7)	C(4')—C(5')	1.394 (8)
C(4)—C(5)	1.362 (9)	C(4')—O(4')	1.376 (8)
C(5)—C(6)	1.428 (8)	C(5')—C(6')	1.375 (7)
C(5)—C(1')	1.496 (8)	O(4')—C(4'')	1.414 (8)
C(6)—C(7)	1.375 (7)		
C(2)—C(1)—C(7)	123.2 (5)	C(2)—O(2)—C(2')	119.4 (4)
C(2)—C(1)—O(1)	118.5 (3)	C(5)—C(1')—C(2')	120.6 (4)
C(7)—C(1)—O(1)	118.3 (3)	C(5)—C(1')—C(6')	121.7 (4)
C(1)—C(2)—C(3)	126.7 (3)	C(2')—C(1')—C(6')	117.6 (4)
C(1)—C(2)—O(2)	110.1 (3)	C(1')—C(2')—C(3')	122.4 (4)
C(3)—C(2)—O(2)	123.2 (4)	C(2')—C(3')—C(4')	118.4 (4)
C(2)—C(3)—C(4)	131.4 (4)	C(3')—C(4')—C(5')	119.9 (4)
C(3)—C(4)—C(5)	131.7 (4)	C(3')—C(4')—O(4')	124.1 (4)
C(4)—C(5)—C(6)	123.4 (4)	C(5')—C(4')—O(4')	115.9 (4)
C(4)—C(5)—C(1')	119.5 (4)	C(4')—C(5')—C(6')	120.4 (4)
C(6)—C(5)—C(1')	117.0 (4)	C(1')—C(6')—C(5')	121.3 (4)
C(5)—C(6)—C(7)	131.0 (4)	C(4')—O(4')—C(4'')	118.5 (4)
C(1)—C(7)—C(6)	132.4 (3)		

both methoxy groups are coplanar with their associated rings as reflected by the torsion angles C(1)—C(2)—O(2)—C(2') of $-177.9(4)^\circ$ and C(3')—C(4')—O(4')—C(4'') of $-3.0(8)^\circ$. The dihedral angle between the normals to the two rings in the other bicyclic analogues (see scheme) ranges between $43.4(3)^\circ$ in (6) and $57.4(5)^\circ$ in (2).

As only hydrogen-bond acceptors are present in the analogue molecules and the crystals are not solvated, hydrogen-bond formation is precluded. Thus the molecules are held together in the crystal by van der Waals interactions only, with the shortest intermolecular contacts being C(2')...O(4')(1 + x, y,

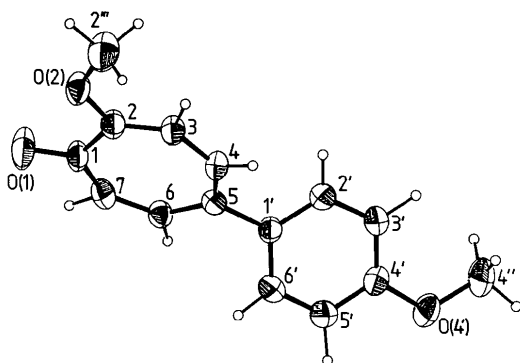


Fig. 1. Perspective view of (4) with thermal ellipsoids scaled to 50% probability. H atoms are denoted by spheres of arbitrary radius.

z) 3.265 (9) Å, and $C(2') \cdots O(1)(x, y, -1 + z)$ 3.346 (7) Å.

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Structure of a Substituted 2-Thiohydantoin

BY M. F. MACKAY

Department of Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia

B. M. DUGGAN AND R. L. LASLETT

Faculty of Applied Chemistry, Swinburne Institute of Technology, Hawthorn, Victoria 3122, Australia

AND J. F. K. WILSHIRE

CSIRO, Division of Biomolecular Engineering, Parkville Victoria 3052, Australia

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Abstract. *S*-[1-(3-Acetyl-5-oxo-2-thioxo-2,3,4,5-tetrahydro-1*H*-imidazol-4-yl)ethyl] ethanethioate, C₉H₁₂N₂O₃S₂, $M_r = 260.3$, monoclinic, $P2_1/n$, $a = 8.643$ (1), $b = 15.554$ (1), $c = 8.898$ (1) Å, $\beta = 92.05$ (1)°, $V = 1195.4$ (3) Å³, $Z = 4$, $D_m(\text{floatation}) = 1.448$ (5), $D_x = 1.446$ Mg m⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu(\text{Cu } K\alpha) = 3.96$ mm⁻¹, $F(000) = 544$, $T = 293$ (1) K, final $R = 0.046$ for 1708 observed data. Atoms of the thiohydantoin nucleus are approximately coplanar, and the N(3) acetyl group is twisted by about 12° from the mean plane. N(1) of the

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thiohydantoin ring is the donor atom in an intermolecular hydrogen bond with the carbonyl oxygen of the N(3) acetyl substituent, the N(1)⋯O(6) distance being 2.873 (3) Å. These interactions link the molecules into chains along the [101] direction in the crystal.

Introduction. Application of the thiocyanate degradation procedure (Schlack & Kumpf, 1926) to a peptide (I) converts the C-terminal amino acid into a substituted thiohydantoin derivative (II), which can