

(S)-N-(5,6,7,10-Tetrahydro-1,2,3-trimethoxy-11-methylthio-10-oxo-benzo[a]heptalen-7-yl)acetamide (Pseudothiocolchicine)

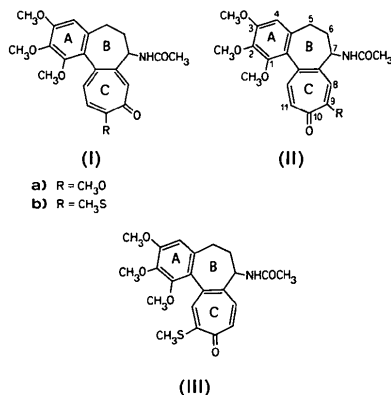
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Abstract. $C_{22}H_{25}NO_5S$, $M_r = 415.5$, hexagonal, $P6_1$, $a = 12.426$ (3), $c = 23.894$ (8) Å, $V = 3195$ (2) Å³, $Z = 6$, $D_x = 1.296$ g cm⁻³; $\lambda(Mo K\alpha) = 0.71069$ Å (graphite-crystal monochromator), $\mu = 1.75$ cm⁻¹, $F(000) = 1320$, room temperature, final $R = 0.048$ for 2022 observed reflections. The steric hindrance between MeO at C(1) and the MeS group cannot explain the difference in the electronic spectra of pseudothiocolchicine with respect to those of less strained thiocolchicine and isothiocolchicine. In fact, the MeS group is nearly coplanar with the tropolone ring and also the conjugation between the π system of that ring and the lone pairs of the S atom is seen from the distance S—C(11) [1.757 (5) Å], in the normal range for conjugated C—S—C=C systems. The unusually long C(10)—C(11) bond [1.480 (5) Å] might lower the conjugation in the tropolone ring, but still cannot explain the surprising result observed in the electronic spectra of the title compound.

Introduction. The interest in colchicine chemistry is mainly due to its high biological activity and anti-inflammatory properties. Upon acid hydrolysis and with addition of diazomethane, colchicine (Ia) is converted to isocolchicine (IIa). Velluz & Muller (1955) noted that isocolchicine with MeSNa in aqueous MeOH yields pseudothiocolchicine (III) as the major product.



A series of colchicine derivatives were recently studied by Danieli, Lesma, Palmisano & Riva (1985), on the basis of ¹H and ¹³C NMR spectra and chemical correlation. The electronic spectra of colchicine and isocolchicine show a band at 325 and 327 nm respectively. The substitution of the MeO with an MeS group on ring C introduces a bathochromic effect of 40–60 nm. In fact, the same band in thiocolchicine (Ib) and isothiocolchicine (IIb) is shifted to 363 and 383 nm respectively. This shift was attributed to the coupling effect between the lone pairs of S and the π system of tropolone ring C. No shift was found in pseudothiocolchicine (III): in this case, Danieli *et al.* (1985) attributed the absence of bathochromic effect to a strong reduction in conjugation, owing to steric hindrance between the MeS group and the MeO group in position 1.

In order to check this hypothesis and also to determine the conformation of the molecule, we have carried out an X-ray diffraction study of (III).

Experimental. Pale-yellow crystals were recrystallized from acetone. A crystal 0.28 × 0.24 × 0.18 mm was selected and mounted on a Nonius CAD-4 diffractometer. The cell parameters were obtained from a least-squares fit of 25 reflections in the range $12 < \theta < 14^\circ$; 2487 unique reflections collected, 2022 observed [criterion $I > \sigma(I)$]; θ range 0.0–27.5°; hkl range: 0 → 13, 0 → 13, 0 → 30; ω - 2θ scan technique.

Three standard reflections showed no significant variation of the intensities. Data were corrected for Lorentz and polarization factors but not for absorption. Structure solved by direct methods using MULTAN80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980); H atoms were located from a difference Fourier synthesis and included isotropically in final refinement based on F , with $w = 4I_0/[\sigma^2(I_0) + 0.0009I_0^2]$ where I_0 is the intensity on absolute scale. Final $R = 0.048$, $wR = 0.034$; $S = 1.08$, residual density = ± 0.2 e Å⁻³, max. shift 0.05 σ on final cycle, extinction coefficient $g = 34$ (6) × 10⁻⁷ [Larson (1967), equation (3)]. Scattering factors from *International Tables for X-ray Crystal-*

Table 1. Fractional coordinates and U_{eq} values

	$U_{eq} = (\sum_i \sum_j \beta_{ij} a_i a_j) / 6\pi^2$			
	x	y	z	$U_{eq}(\text{\AA}^2)$
S	0.22770 (9)	0.72097 (9)	-0.06130	0.0586 (5)
O(1)	0.4897 (2)	0.6761 (3)	0.0596 (1)	0.063 (1)
O(2)	0.7444 (2)	0.7849 (2)	0.0834 (1)	0.055 (1)
O(3)	0.8793 (2)	0.6988 (2)	0.0327 (1)	0.067 (1)
O(4)	0.0295 (3)	0.4929 (3)	-0.0820 (2)	0.092 (2)
O(5)	0.2294 (2)	0.2076 (2)	0.0925 (1)	0.061 (1)
N	0.2522 (3)	0.1575 (3)	0.0052 (1)	0.048 (1)
C(1)	0.5617 (3)	0.6354 (3)	0.0343 (2)	0.043 (2)
C(2)	0.6883 (3)	0.6866 (3)	0.0471 (2)	0.044 (2)
C(3)	0.7566 (3)	0.6420 (3)	0.0191 (2)	0.046 (2)
C(4)	0.7005 (3)	0.5499 (3)	-0.0202 (2)	0.049 (2)
C(5)	0.5192 (4)	0.4028 (4)	-0.0792 (2)	0.052 (2)
C(6)	0.4266 (4)	0.2754 (4)	-0.0561 (2)	0.055 (2)
C(7)	0.3456 (3)	0.2826 (3)	-0.0100 (2)	0.042 (2)
C(8)	0.1674 (4)	0.3070 (4)	-0.0448 (2)	0.053 (2)
C(9)	0.0932 (4)	0.3522 (4)	-0.0612 (2)	0.057 (2)
C(10)	0.1141 (4)	0.4752 (4)	-0.0662 (2)	0.056 (2)
C(11)	0.2365 (3)	0.5850 (3)	-0.0536 (2)	0.046 (2)
C(12)	0.3424 (4)	0.5878 (4)	-0.0375 (1)	0.044 (2)
C(13)	0.5767 (3)	0.5011 (3)	-0.0342 (2)	0.046 (2)
C(14)	0.2933 (3)	0.3659 (3)	-0.0261 (1)	0.041 (2)
C(15)	0.3720 (3)	0.4930 (3)	-0.0235 (1)	0.040 (2)
C(16)	0.5053 (3)	0.5429 (3)	-0.0069 (1)	0.040 (1)
C(17)	0.4941 (5)	0.6925 (6)	0.1180 (2)	0.079 (3)
C(18)	0.7947 (6)	0.7636 (6)	0.1338 (2)	0.078 (3)
C(19)	0.9496 (5)	0.6466 (6)	0.0114 (3)	0.080 (3)
C(20)	0.2008 (3)	0.1283 (3)	0.0559 (2)	0.047 (2)
C(21)	0.1064 (5)	-0.0057 (5)	0.0657 (3)	0.073 (3)
C(22)	0.3751 (4)	0.8417 (4)	-0.0358 (3)	0.071 (3)

Table 2. Bond distances (\AA) and angles ($^\circ$)

S—C(11)	1.757 (5)	S—C(22)	1.797 (4)
O(1)—C(1)	1.369 (6)	O(1)—C(17)	1.407 (5)
O(2)—C(2)	1.371 (4)	O(2)—C(18)	1.441 (7)
O(3)—C(3)	1.361 (4)	O(3)—C(19)	1.418 (9)
O(4)—C(10)	1.236 (7)	O(5)—C(20)	1.230 (5)
N—C(7)	1.446 (4)	N—C(20)	1.332 (5)
C(1)—C(2)	1.404 (5)	C(1)—C(16)	1.406 (5)
C(2)—C(3)	1.395 (7)	C(3)—C(4)	1.371 (6)
C(4)—C(13)	1.383 (5)	C(5)—C(6)	1.521 (6)
C(5)—C(13)	1.512 (6)	C(6)—C(7)	1.525 (7)
C(7)—C(14)	1.521 (6)	C(8)—C(9)	1.355 (8)
C(8)—C(14)	1.428 (6)	C(9)—C(10)	1.422 (7)
C(10)—C(11)	1.480 (5)	C(11)—C(12)	1.355 (7)
C(12)—C(15)	1.438 (7)	C(13)—C(16)	1.394 (6)
C(14)—C(15)	1.382 (4)	C(15)—C(16)	1.503 (5)
C(20)—C(21)	1.500 (6)		
C(11)—S—C(22)	103.9 (2)	C(1)—O(1)—C(17)	120.4 (4)
C(2)—O(2)—C(18)	116.1 (4)	C(3)—O(3)—C(19)	117.6 (4)
C(7)—N—C(20)	122.6 (3)	O(1)—C(1)—C(16)	117.4 (4)
O(1)—C(1)—C(2)	121.8 (4)	C(2)—C(1)—C(16)	120.7 (4)
O(2)—C(2)—C(1)	119.8 (3)	C(1)—C(2)—C(3)	118.8 (4)
O(2)—C(2)—C(3)	121.2 (3)	O(3)—C(3)—C(2)	115.2 (3)
C(2)—C(3)—C(4)	120.3 (4)	O(3)—C(3)—C(4)	124.5 (4)
C(3)—C(4)—C(13)	121.4 (4)	C(6)—C(5)—C(13)	112.9 (4)
C(5)—C(6)—C(7)	112.3 (4)	N—C(7)—C(6)	108.5 (3)
C(6)—C(7)—C(14)	112.1 (4)	N—C(7)—C(14)	114.1 (3)
C(9)—C(8)—C(14)	132.6 (4)	C(8)—C(9)—C(10)	132.3 (5)
O(4)—C(10)—C(9)	120.2 (5)	C(9)—C(10)—C(11)	121.7 (4)
O(4)—C(10)—C(11)	118.1 (4)	S—C(11)—C(10)	109.6 (3)
C(10)—C(11)—C(12)	128.2 (4)	S—C(11)—C(12)	122.1 (3)
C(11)—C(12)—C(15)	133.5 (4)	C(4)—C(13)—C(5)	119.9 (4)
C(5)—C(13)—C(16)	120.1 (4)	C(4)—C(13)—C(16)	119.9 (3)
C(7)—C(14)—C(8)	117.5 (3)	C(8)—C(14)—C(15)	124.6 (4)
C(7)—C(14)—C(15)	117.9 (3)	C(12)—C(15)—C(14)	126.9 (4)
C(14)—C(15)—C(16)	119.2 (3)	C(12)—C(15)—C(16)	113.8 (3)
C(13)—C(16)—C(15)	119.9 (3)	C(1)—C(16)—C(15)	121.2 (3)
C(1)—C(16)—C(13)	118.8 (3)	O(5)—C(20)—N	121.4 (3)
N—C(20)—C(21)	116.5 (4)	O(5)—C(20)—C(21)	122.1 (5)

lography (1974). Programs used include *SDP* (Enraf-Nonius, 1979), *ORTEPII* (Johnson, 1976), *PARST* (Nardelli, 1983) and various in-house programs for refinement and geometrical analysis running on a Gould CONCEPT 32/97 computer.*

Discussion. Atomic coordinates and equivalent isotropic thermal parameters are given in Table 1, bond distances and angles in Table 2 and a view of the molecule with numbering of the atoms in Fig. 1.

Ring *A*, while of course quite flat, is not as precisely planar as would be expected. The total puckering amplitude Q_t (Cremer & Pople, 1975) is equal to 0.019 (4). The methoxy groups, C(1)—O(1)—C(17), C(2)—O(2)—C(18) and C(3)—O(3)—C(19) form dihedral angles with the benzene ring *A* of 45.4 (3), 63.7 (3) and 17.1 (6) $^\circ$, respectively. Ring *C* is less flat than ring *A* [$Q_t = 0.046$ (4)]. It exhibits a definite bond-length alternation with an arrangement quite different from that observed in other troponoid rings. The mean bond distances C(10)—C(11) and C(12)—C(15) for (Ia) (Lessinger & Margulis, 1978a), (Ib) (Koertgen & Margulis, 1977), (IIa) (Lessinger & Margulis, 1978b) and (IV) (Margulis, 1977) are respectively 1.465 (9) and 1.415 (10) \AA whereas they are 1.480 (5) and 1.438 (7) \AA for (III), *i.e.* there is a significant lengthening. The C(22)—S—C(11) group is approximately

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52896 (20 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

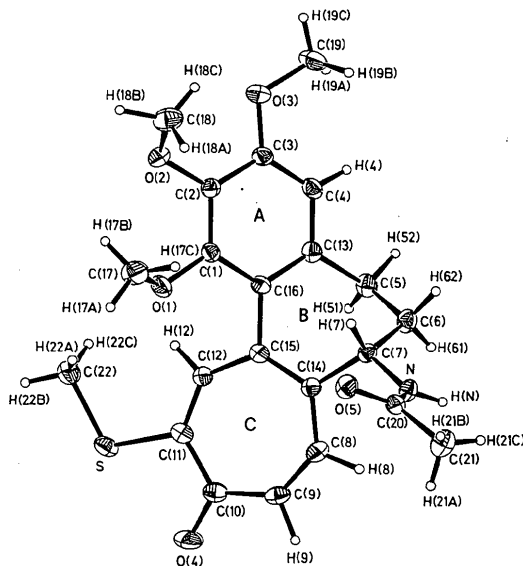


Fig. 1. ORTEPII plot of the molecule with numbering scheme. Thermal ellipsoids at 20% probability. H atoms not to scale.

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

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

	(Ia)	(Ib)	(IIa)	(III)	(IV)
C(13)—C(16)—C(15)—C(14)	-53	-53	-55	-53	-57
C(16)—C(15)—C(14)—C(7)	-5	-5	-3	-6	-4
C(15)—C(14)—C(7)—C(6)	79	81	82	78	79
C(14)—C(7)—C(6)—C(5)	-48	-49	-50	-44	-46
C(7)—C(6)—C(5)—C(13)	-43	-42	-39	-44	-42
C(6)—C(5)—C(13)—C(16)	73	70	68	68	67
C(5)—C(13)—C(16)—C(15)	4	5	7	7	9

References: (Ia) colchicine (Lessinger & Margulis, 1978a); (Ib) thiocolchicine.6H₂O (Koerntgen & Margulis, 1977); (IIa) isocolchicine (Lessinger & Margulis, 1978b); (III) pseudothiocolchicine (present work); (IV) demethylisothiocolchicine (Margulis, 1977).

in the plane of the troponoid ring C [the angle being 7.6 (2)°]. The value of the S—C(11) bond length [1.757 (5) Å] is close to the one corresponding to a conjugated system (Koerntgen & Margulis, 1977; Clark & Margulis, 1980). This fact suggests that the free-electron pairs of the S atom could conjugate with the troponone π system, in contrast to the hypothesis of Danieli *et al.* (1985) based on the absence of bathochromic effect in the electronic absorption spectra of (III).

The A and C rings are considerably twisted: the angle between them, 50.7 (1)°, is necessary to accommodate the fused seven-membered ring B. The conformation of ring B is similar to that found in other

colchicine derivatives (see Table 3); the difference between corresponding torsion angles is within 7°.

References

- CLARK, J. I. & MARGULIS, T. N. (1980). *Life Sci.* **26**, 833–836.
 CREMER, D. & POPE, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
 DANIELI, B., LESMA, G., PALMISANO, G. & RIVA, R. (1985). *Helv. Chim. Acta*, **68**, 2173–2176.
 Enraf-Nonius (1979). *Structure Determination Package*. Enraf-Nonius, Delft, The Netherlands.
International Tables for X-ray Crystallography (1974). Vol. IV, pp. 149–150. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)
 JOHNSON, C. K. (1976). *ORTEP*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
 KOERNTGEN, C. & MARGULIS, T. N. (1977). *J. Pharm. Sci.* **66**, 1127–1131.
 LARSON, A. C. (1967). *Acta Cryst.* **23**, 664–665.
 LESSINGER, L. & MARGULIS, T. N. (1978a). *Acta Cryst.* **B34**, 578–584.
 LESSINGER, L. & MARGULIS, T. N. (1978b). *Acta Cryst.* **B34**, 1556–1561.
 MAIN, P., FISKE, S., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCO, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.
 MARGULIS, T. N. (1977). *Biochem. Biophys. Res. Commun.* **76**, 1293–1298.
 NARDELLI, M. (1983). *Comput. Chem.* **7**, 95–98.
 VELLUZ, L. & MULLER, G. (1955). *Bull. Soc. Chim. Fr.* pp. 198–200.

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Structures of Two Hydrated Cage Diketones

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Abstract. 2,3,5,6-Tetrachloro-8,11-dihydroxy-4,4-dimethoxy-8,11-epoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane, (3a), C₁₃H₁₂Cl₄O₅, *M_r* = 390.05, monoclinic, *P*2₁/*n*, *a* = 7.392 (1), *b* = 12.726 (3), *c* = 16.107 (2) Å, β = 95.64 (1)°, *V* = 1507.8 (5) Å³, *Z* = 4, *D_x* = 1.718 g cm⁻³, $\lambda(\text{Mo } K\alpha)$ = 0.71073 Å, μ = 8.06 cm⁻¹, *F*(000) = 792, *T* = 298 K, *R* = 0.0395 for 2783 reflections. 1,9-Dibromo-11,11-dihydroxy-5-methylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8-one,

(4a), C₁₂H₁₂Br₂O₃, *M_r* = 364.05, triclinic, *P*1̄, *a* = 6.713 (1), *b* = 14.013 (2), *c* = 14.579 (2) Å, α = 113.29 (1), β = 99.58 (1), γ = 99.31 (1)°, *V* = 1202.3 (4) Å³, *Z* = 4, *D_x* = 2.011 g cm⁻³, $\lambda(\text{Mo } K\alpha)$ = 0.71073 Å, μ = 66.68 cm⁻¹, *F*(000) = 712, *T* = 295 K, *R* = 0.0640 for 3888 reflections. The two open-ended cage compounds are composed of four five-membered rings and a four-membered ring. The diketone moieties in the parent compounds have added water to form a dihydrate, (3a), and a monohydrate, (4a). The parent diketone usually contains

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