New Tetracyclic Colchicinoids from the Reaction of *N*-Deacetylthiocolchicine and *N*-Deacetylcolchicine with Nitrous Acid and *tert*-Butyl Nitrite

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Dedicated to Professor *Paola Vita Finzi* on the occasion of her 70th birthday

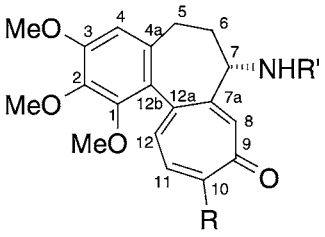
Reaction of *N*-deacetylthiocolchicine (**3**) and *N*-deacetylcolchicine (**4**) with nitrous acid (HONO) furnished the new tetracyclic colchicinoids **5** and **6**, as well as the *Demyanov*-rearrangement products **7** and **8**. Starting from **3**, the pyrazole-containing tetracycle **9** was obtained. The novel compounds were characterized spectroscopically, and an X-ray crystal-structure analysis of **5** allowed us to establish the absolute configurations at the stereogenic centers.

Introduction. – (a*R*,7*S*)-Colchicine (**1**) [1], the major alkaloid of *Colchicum autumnale* and *Gloriosa superba*, displays interesting anti-inflammatory and antimitotic activities [2] associated with its capacity to inhibit microtubule assembly substoichiometrically. Unfortunately, the therapeutic use of **1** and its analog, thiocolchicine (**2**), is hampered by their toxicities [3].

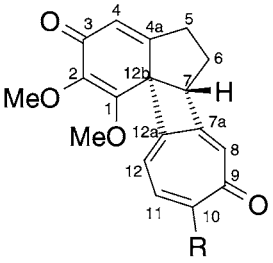
Extensive studies [4] have been carried out to modify the structural motif of colchicine to find less-toxic but still biologically active analogs. The interactions of colchicine with its molecular target, tubulin, have been thoroughly investigated [3]. Among the important observations are findings indicating that the configuration of colchicinoids plays a crucial role in tubulin recognition [5].

Recently, attention has been focused on effects arising from changes in the conformation and dimensions of ring B, and of the orientation of the C(7) side chain [6]. The novel thiocolchicine congener **7** [7] and some of its analogs were found to be potent inhibitors of tubulin polymerization. They are characterized by a six-membered ring, (replacing the usual seven-membered ring B), by a pseudoaxially oriented hydroxymethyl side chain at C(6), and by an (a*S*,6*S*) configuration[1]). Compound **7** has

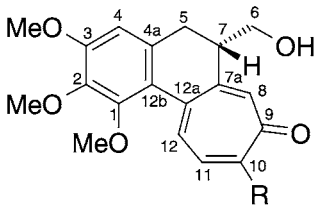
[1]) According to [1], the *correct* (axial) configuration.



1 R= OMe; R'= Ac
2 R= SMe; R'= Ac
3 R= SMe; R'= H
4 R= OMe; R'= H



5 R= SMe
6 R= OMe



7 R= SMe
8 R= OMe

been synthesized in moderate yield, starting from deacetylthiocolchicine (**3**) [8], by means of a *Demyanov* rearrangement [9].

With the aim to prepare and study new molecules and to further evaluate the importance of ring B and of C(7) substitution, we have re-examined the above reaction. We found that, besides the expected compound **7**, the new thiocolchicine derivative **5** was formed, which possesses an unusual tetracyclic structure in which the seven-membered ring B has been transformed to a bicyclic [3.2.0] system and the trimethoxybenzene ring A to a dimethoxydienone moiety. Deacetylcolchicine (**4**) behaved similarly, providing the tetracyclic analog **6**, together with the expected derivative **8**. Here, we present the details of the structure determination of several new compounds, including an X-ray crystallographic analysis of **5**, to unambiguously establish the absolute configuration at C(7) and at the newly created C(12b) stereocenter[2]). Moreover, by changing the deamination reagent from nitrous acid (HON=O) to *tert*-butyl nitrite (^{t}BuON=O), another novel tetracyclic colchicinoid, **9**, was formed.

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[2]) For the novel compounds **5**, **6**, and **8**, we retained the usual colchicine numbering. For systematic names and numbering, see *Exper. Part.*

Results and Discussion. – Flash chromatography of the reaction mixture obtained after treatment of an aqueous AcOH solution of **3** in the presence of a slight excess of $NaNO_2$ at room temperature afforded the tetracyclic compound **5** in 40% isolated yield (less-polar product), together with 45% of **7**.

The HR-EI mass spectrum of **5** indicates a molecular composition of $C_{19}H_{18}O_4S$, suggesting the formal loss of $MeNH_2$ from the starting compound. Accordingly, the ^{1}H-NMR spectrum shows no exchangeable H-atoms and the presence of only two MeO groups at δ (H) 3.76 and 4.02 ppm, in addition to the signals of an intact (methylsulfanyl)tropone ring. The H–C(4) signal appears at δ(H) 6.05, (*d*, $J = 2.3$ Hz), in a shielded position, and with a coupling never found before in colchicinoids [10]. Resolution of the five-spin system of the ring-B H-atoms indicates vicinal-coupling-constant values compatible with the presence of a five-membered ring. H–C(7) Shows a signal at δ(H) 4.04 (*d*, $J = 7.4$ Hz), due to the coupling to H–C(6) at δ(H) 2.19 (*tdd*). The complex coupling pattern of this H-atom is generated by identical large geminal couplings ($J = 12.8$ Hz) to H–C(6) at 2.06 and to the vicinal H–C(5) at 2.57 ppm, respectively, thus, suggesting a *trans*-diaxial relationship. The remaining 6.8-Hz coupling of H–C(6) at δ(H) 2.19 is due to the second vicinal atom, H–C(5) at δ(H) 2.44, which does not show any coupling with H–C(6) at δ(H) 2.06. H–C(5) at 2.57 couples with H–C(6) at 2.06 ppm and is related to the above-mentioned unusual splitting of H–C(4). Strong NOE interactions between H–C(6) and H–C(7) indicates an almost eclipsed relationship between these protons, whereas the relative *trans* configuration of H–C(6) at δ(H) 2.19 and H–C(5) at δ(H) 2.57 is confirmed by the absence of any measurable contact. Furthermore, no interaction is observed between H–C(4) and the MeO groups.

The ^{13}C-NMR spectrum of **5** contains *a*) the signals typical for the tropone moiety, which appear very close to those of thiocolchicine, *b*) two methylene resonances at δ(C) 30.9 and 29.8, *c*) an upfield methine resonance at δ(C) 49.2, and *d*) only four sp^2 C-atom resonances at δ(C) 123.9, 156.2, 158.8, and 159.8 the remaining two ring-A C-atoms corresponding to a C=O group at δ(C) 185.0 and a quaternary C-atom resonating at δ(C) 59.3. All these data suggest that the seven-membered ring B of **3** has been transformed to a bicyclic [3.2.0] system (formation of a new bond between C(7) and C(12b) in **5**). This process is accompanied by the elimination of the NH_2 function at C(7) and of the Me group of MeO–C(3).

The similar behavior displayed by *N*-deacetylcolchicine (**4**) on reaction with HONO was confirmed by close inspection of the spectroscopic data of **6** (36% yield) and **8** (47% yield) (see *Exper. Part*). The structure of **5** was unequivocally established by X-ray crystallographic analysis, confirming the absolute (7R,12b*R*) configuration, see the (*Figure*). An in-depth examination of the *Cambridge Crystallographic Database* (CCD), as of October 2002 indicated that no crystal structure has been reported so far with a connectivity of rings similar to that found in **5**.

As expected, the troponoid ring of **5** is almost planar, with a total puckering amplitude [11] of 0.073(3) Å and a maximum distance from the mean plane of 0.04 Å for C(10). The geometrical parameters of this ring and of its methylthio and oxo substituents (*Table 1*) are very similar to those observed in other thiocolchicine derivatives [12][13]: C(15)–S(1)–C(10) lies approximately in the plane of the ring, and the C(10)–S(1) bond length is close to that found in conjugated systems (1.751 Å) [14]. The troponoid ring exhibits a clear alternation of long and short bonds (see *Table 1*) similarly to colchicine [15] and thiocolchicine (*CCD* refcode *TCOLCH*). Only the C(9)–C(10) bond distance, 1.485(3) Å, is significantly lengthened compared with thiocolchicine (1.458 Å) or related compounds [12] but lies not too far from those in pseudothiocolchicine [13] (1.480 Å) and demethylthiocolchicine [16] (1.475 Å).

The six-membered ring exhibits a strongly flattened boat conformation, the total puckering amplitude *Q* being 0.132(2) Å with the φ_2 angle close to $-180°$ ($\varphi_2 = -178.7(9)°$). The orientation of the two adjacent MeO substituents is very different: the C(14)–O(2) bond is almost perpendicular to the plane of the ring, while C(13) lies not far from that plane (causing a very short C(13)···O(2) contact of 2.829 Å). Consequently, the C(14)–O(2) and O(2)–C(2) distances (1.431(3) and 1.384(3) Å, respectively) are significantly longer than the corresponding ones of the more-conjugated C(13)–O(1)–C(1) fragment (1.405(4) and 1.349(2) Å, respectively). The dihedral angle between the planes of the dienone and troponoid rings, connected *via* the C(12b)–C(12a) bond, is 81.43(6)°, *i.e.*, considerably longer than in colchicine (53°), thiocolchicine (53.8°), or pseudothiocolchicine (50.7°). This difference is certainly caused by the novel fused ring.

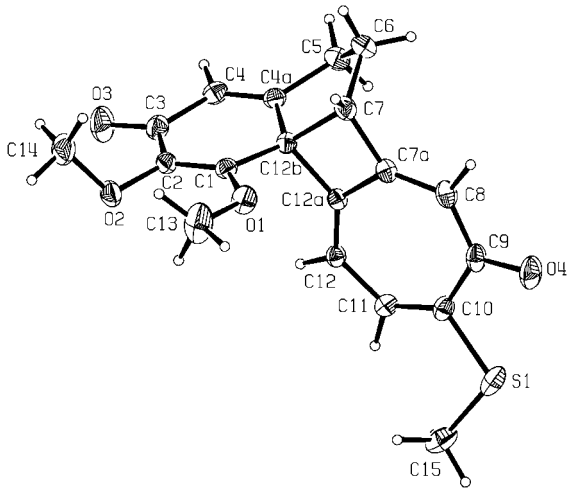


Figure. *ORTEP Plot of* **5** (20%-probability level)

Table 1. *Selected Bond Lengths* [Å], *Bond Angles* [°], *and Torsion Angles* [°] *of* **5**

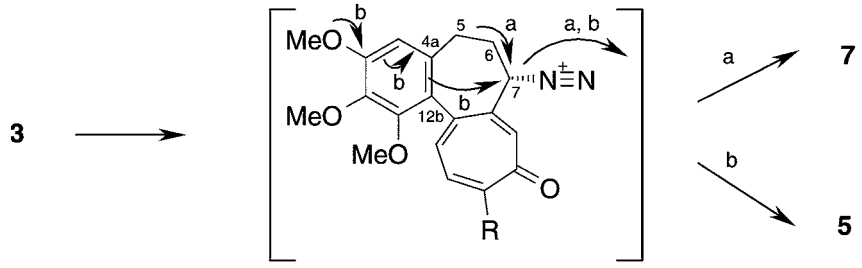
C16–C1	1.541(3)	C2–C1–C16	111.5(2)	C2–C1–C16–C15	61.2(3)
C1–C9	1.596(3)	C2–C1–C6	116.0(2)	C6–C1–C9–C10	– 118.9(2)
C9–C10	1.520(3)	C6–C1–C9	105.3(2)	C11–C10–C16–C1	173.3(2)
C10–C16	1.411(3)	C16–C1–C9	85.4(1)	C10–C11–C12–C13	1.5(4)
C10–C11	1.358(3)	C1–C9–C10	87.5(2)	C9–C10–C16–C1	– 5.6(2)
C11–C12	1.438(3)	C9–C10–C16	93.0(2)	C1–C9–C10–C16	5.4(2)
C12–C13	1.485(3)	C10–C16–C1	93.6(2)	C1–C6–C7–C8	– 35.5(3)
C13–C14	1.372(3)	C12–C13–C14	130.9(2)	C6–C1–C9–C8	– 1.9(3)
C14–C15	1.410(3)	C12–C13–S1	108.7(2)	C17–S1–C13–C12	171.8(2)
C15–C16	1.340(3)	C14–C13–S1	120.4(2)	S1–C13–C12–C11	176.0(2)
C12–O4	1.236(3)	C11–C12–C13	122.9(2)	C18–O1–C2–C1	172.9(3)
C13–S1	1.759(2)	C11–C12–O4	119.8(2)	C19–O2–C3–C2	108.5(3)
S1–C17	1.801(4)	C13–C12–O4	117.3(2)		
C1–C6	1.493(3)	C13–S1–C17	102.9(1)		
C1–C2	1.484(3)				
C2–C3	1.341(3)				
C3–C4	1.465(3)				
C4–C5	1.470(3)				
C5–C6	1.320(3)				

The cyclobutane ring is characterized by a single puckering parameter of $q = 0.070(2)$ Å, corresponding to a displacement of the C-atoms from the reference plane by 0.035(1) Å. One of the four C–C bonds is very long (C(12b)–C(7) = 1.596(3) Å), but a cursory survey of the *CCD* showed that such a value is not unusual in fused compounds (*e.g.*, *CCD* refcodes *DEDYOA* and *MXBCUO*). The cyclobutane ring is roughly coplanar with the troponoid ring, the dihedral angle between their mean-square planes being 6.34(9)°, and the angle between the planes of the four- and six-membered rings 82.86(8)°. The cyclopentane ring exhibits a slightly distorted envelope conformation, (puckering amplitude $q_2 = 0.346(3)$ Å), C(12b), C(4a), C(6), and C(7) being nearly coplanar, with C(5) protruding by 0.534(4) Å from their plane. The φ_2 angle is 110.6(4)°, to be compared with 108°, the closest value of a pure envelope conformation.

The absolute configuration was established on the basis of the *Flack* parameter [17], which is 0.00(8) for the stereoisomer depicted in the *Figure*.

Mechanistically, the products **7** and **8** are clearly formed by N_2 elimination from the intermediate diazo derivative followed by migration of the antiperiplanar C(5)–C(6) bond (*Demyanov* rearrangement; *Scheme 1,* path *a*). Conversely, the highly stereo- and regioselective formation of **5** and **6** could invoke a concerted mechanism (path *b)* in which the transannular participation of the π electrons of ring A, leading to the formation of the C(12b)–C(7) bond, is concomitant with the departure of N_2.

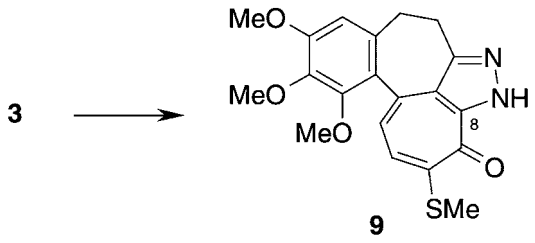
Scheme 1



Moreover, the participation of the neighboring electron-rich ring system should be largely favored by the low degree of stabilization of the potential C(7) carbocation, which is adjacent to the electron-withdrawing tropone ring. Finally, although steric factors cannot be fully excluded, the regioselectivity of the reaction may also depend on the higher electronic density at C(12b) relative to C(4a) due to the three MeO substituents on ring A.

Next, we altered the deamination conditions subjecting deacetylthiocolchicine (**3**) to *tert*-butyl nitrite and a small amount of AcOH in anhydrous THF. This route yielded predominantly the tetracycle **9** (*Scheme 2)*, with an additional pyrazole ring. This result can be rationalized by a different reaction pathway not involving a diazonium salt. When *tert*-butyl nitrite is used, rather a diazo ether is the probable intermediate, affording the fused pyrazole ring by nucleophilic attack of C(8) at the terminal N-atom under loss of the ^{t}BuO[3]).

Scheme 2



[3]) A similar compound featuring an isoxazole instead of a pyrazole ring has been reported by *Berg et. al.* [18] upon treating 7-oxo-deacetamidothiocolchicine with 'hydroxylamine-*O*-sulfonic' ((aminooxy)sulfonic acid) in HCO_2H/H_2SO_4.

Conclusions. – We have described the preparation of novel colchicinoids with a tetracyclic skeleton derived by the transformation of the seven-membered ring B to a bicyclic [3.2.0] system. In spite of the impressive number of functionally and structurally modified colchicinoids that have been prepared in the context of the structure/activity investigations, the tetracyclic compounds **5** and **6** have never been described before. Until now, bicyclic [3.2.0] systems in colchicinoids were found only in β-, γ and α-lumicolchicines, which, however, arise from the photo-isomerization of tropolone methyl-ether rings. In addition, the tetracyclic compound **9** was obtained incorporating a new structural motif in the form of a pyrazole ring.

In-vitro pharmacological tests performed with **5** and **6** showed no biological activity at all, which highlights the central role of an intact benzenoid ring (ring A). Interestingly, compound **9** is cytotoxic against a broad range of cellular lines, being, in some cases, basically as active as *paclitaxel*, another important natural product endowed with peculiar properties. A detailed investigation of the pharmacological properties of **9** and of other new colchicinoids will be presented elsewhere.

Experimental Part

General. Colchicine (**1**) and *thiocolchicine* (**2**) were a gift of *Indena*, *S.p.A.*, Milan. All solvents were distilled and properly dried prior to use. During workup, all organic extracts were dried (Na_2SO_4) and evaporated. Thin-layer chromatography (TLC): *Merck* silica gel *60 F_{254}* plates. Flash column chromatography (FC): Merck silica gel *60* (230–400 mesh). M.p.: *Kofler* hot-bench apparatus. CD Spectra: *Jasco* model *J500*. ^{1}H- and ^{13}C-NMR spectra: *Bruker AC-300* (300 and 75.4 MHz, resp.); in $CDCl_3$; chemical shifts δ in ppm rel. to Me_4Si, coupling constants *J* in Hz (apparent values). MS: *VG-7070EQ-HF* instrument (EI, 70 eV); *m/z* (rel. intensity in %).

*(6a*R, *11b*R*)-6,6a-Dihydro-1,2-dimethoxy-9-(methylsulfanyl)-3*H*-cyclohepta[3,4]cyclobuta[1,2-*C*]indene-3,8(5*H*)-dione* (**5**) and *(6*S*)-5,6-Dihydro-6-(hydroxymethyl)-1,2,3-trimethoxy-9-(methylsulfanyl)-8*H*-cyclohepta[*a*]naphthalen-8-one* (**7**)[4]. To a soln. of **3** (430 mg, 1.16 mmol) in H_2O (40 ml), $NaNO_2$ (110 mg, 1.58 mmol) in H_2O (10 ml) and glacial AcOH (150 µl) was added (evolution of N_2). The mixture was stirred at r.t. for 24 h, extracted with CH_2Cl_2, and washed with aq. $NaHCO_3$ soln. The org. phase was dried and evaporated, and the crude product was purified by FC (CH_2Cl_2/MeOH 9:1). A less-polar fraction yielded 158 mg (40%) of **5**. M.p. 191°. R_f (CH_2Cl_2/MeOH 9:1) 0.68. CD ($\Delta\varepsilon$ (λ)) 21.2 (250), −0.4 (294), 1.5 (322), −0.3 (349), 3.1 (376), 3.7 (392). ^{1}H-NMR: 6.84 (*d*, *J* = 10.0; 1 H), 6.83 (s, 1 H); 6.60 (*d*, *J* = 10.0, 1 H); 6.05 (*d*, *J* = 2.3, 1 H); 4.04 (*d*, *J* = 7.4, 1 H); 4.02 (*s*, 3 H); 3.76 (*s*, 3 H); 2.59 (*dddd*, *J* = 15.2, 12.8, 7.3, 2.3, 1 H); 2.44 (*dd*, *J* = 15.2, 6.8, 1 H); 2.35 (*s*, 3 H); 2.19 (*tdd*, *J* = 12.8, 7.4, 6.8, 1 H); 2.06 (*dd*, *J* = 12.8, 7.3, 1 H). ^{13}C-NMR: 185.0; 183.0; 160.5; 159.8; 158.8; 156.2; 146.9; 137.1; 127.1; 125.6; 123.9; 122.0; 60.9; 60.5; 59.3; 49.2; 30.9; 29.8; 15.9. EI-MS: 342 (23, M^+), 314 (17), 286 (38). HR-EI-MS: 342.0938 (M^+, $C_{19}H_{18}O_4S_1^+$; calc. 342.0926).

A second, more-polar fraction gave 195 mg (45%) of **7**. M.p. 200°. R_f (CH_2Cl_2/MeOH 9:1) 0.48. CD ($\Delta\varepsilon$ (λ)): −15.0 (210), 5.3 (250), −4.0 (300), 6.3 (387), 6.0 (410). ^{1}H-NMR: *cf.* [7]. HR-EI-MS: 374.1194 (M^+, $C_{20}H_{22}O_5S_1^+$; calc. 374.1188).

(*6a*R, *11b*R)-*6,6a-Dihydro-1,2,9-trimethoxy-3*H*-cyclohepta[3,4]cyclobuta[1,2-c]indene-3,8(5*H*)-dione* (**6**), and *(6*S*)-5,6-dihydro-6-(hydroxymethyl)-1,2,3,9-tetramethoxy-8*H*-cyclohepta[a]naphthalen-8-one* (**8**)[4]). Deacetylcolchicine (**4**; 400 mg, 1.12 mmol) was allowed to react with $NaNO_2$ as described above. The mixture was separated by FC (CH_2Cl_2/MeOH 9:1). A less-polar fraction yielded 131 mg (36%) of **6**. M.p. 161°. R_f (CH_2Cl_2/MeOH 9:1) 0.58. CD ($\Delta\varepsilon$ (λ): −11.1 (219), 27.9 (244), 0.7 (276), 5.4 (313), 2.1 (337), 4.6 (364). ^{1}H-NMR: 6.99 (*s*, 1 H); 6.61 (*s*, 2 H); 6.06 (*d*, *J* = 2.2, 1 H); 4.03 (*s*, 3 H); 3.90 (*s*, 3 H); 3.87 (*d*, *J* = 7.7, 1 H); 3.75 (*s*, 3 H); 2.56 (*dddd*, *J* = 15.4, 12.8, 7.4, 2.2, 1 H), 2.45 (*dd*, *J* = 15.4, 7.2, 1 H); 2.17 (*tdd*, *J* = 12.8, 7.7, 7.2, 1 H); 2.08 (*dd*, *J* = 12.8, 7.4, 1 H). HR-EI-MS: 326.1144 (M^+, $C_{19}H_{18}O_5^+$; 326.1154).

A second, more-polar fraction gave 188 mg (47%) of **8**. M.p. 174° R_f (CH_2Cl_2/MeOH 9:1) 0.31. CD ($\Delta\varepsilon$ (λ)): 16.3 (236), −12.3 (269), −2.4 (290), −4.9 (306), 7.0 (351). ^{1}H-NMR: 7.94 (*d*, *J* = 11.8, 1 H); 7.38 (*s*, 1 H); 6.80 (*d*, *J* = 11.8, 1 H), 6.58 (*s*, 1 H); 3.97 (*s*, 3 H); 3.89 (*s*, 6 H); 3.67 (*s*, 3 H); 3.56 (*dd*, *J* = 15.3, 9.5, 1 H), 3.42

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[4]) Systematic numbering different from that shown in the formulae.

Table 2. *Crystal Data and Refinement Details*

Formula	$C_{19}H_{18}O_4S$
Z	4
Molecular mass (M_r)	342.419
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
D_{calc} [g cm^{-3}]	1.331
μ [mm^{-1}]	0.209
a [Å]	8.0377(5)
b [Å]	10.7555(9)
c [Å]	19.7768(21)
V[Å^3]	1709.1(2)
Diffractometer	*Siemens P4*
Radiation	MoK_α (0.71073 Å)
Scan type	$\omega/2\theta$
Scan rate (2θ) [deg min^{-1}]	3
Reflections collected	6477
$2\theta_{max}$ [°]	50
Independent reflections	3003
Observed data [$I < 2\sigma$]	2482
Refinement method	full-matrix least-squares on F^2
No. of parameters	290
Extinction coefficient[a])	0.0109(15)
$R(F)$, w$R(F^2)$	0.0430, 0.0778
Max. and min. $\Delta\rho$[eÅ^{-3}]	0.10, −0.18
R indices [$I < 2\sigma$]	
$R(F)$, w$R(F^2)$	0.0313, 0.0722
Goodness-of-fit	1.003

[a]) According to [19b].

(*dd*, $J = 15.3$, 11.4, 1 H); 3.03 (*m*, 1 H); 2.92 (*m*, 2 H); 1.75 (br. *s*, 1 H). HR-EI-MS 358.1414 (M^+, $C_{20}H_{22}O_6^+$; calc. 358.1416).

*7,8-Dihydro-10,11,12-trimethoxy-3-(methylsulfanyl)benzo[4,5]heptaleno[1,10-*cd*]pyrazol-4(5*H*)-one* (**9**).To a soln. of **3** (100 mg, 0.27 mmol) in anh. THF (5 ml), *tert*-butyl nitrite (44 mg, 0.42 mmol) and glacial AcOH (1 ml) were added. The resulting mixture was stirred at reflux for 1 h, poured into H_2O, extracted with CH_2Cl_2, and washed with aq. $NaHCO_3$ soln. The org. phase was dried and evaporated, and the crude product was purified by FC (CH_2Cl_2/MeOH 9:1), yielding 54 mg (52%) of **9**. M.p. 237°. R_f (CH_2Cl_2/MeOH 9:1) 0.77; ^{1}H-NMR: 7.23 (*s*, 2 H); 6.61 (*s*, 1 H); 3.92 (*s*, 3 H); 3.90 (*s*, 3 H); 3.44 (*s*, 3 H); 3.00 (*m*, 4 H); 2.49 (*s*, 3 H). ^{13}C-NMR: 173.25; 153.48; 153.02; 152.92; 145.70; 141.76; 140.43; 137.83; 132.96; 128.82; 128.42; 125.30; 120.44; 107.76; 61.34; 61.17; 55.97; 34.49; 30.38; 14.84. EI-MS: 384 (67, M^+). HR-EI-MS: 384.1157 ($M+$, $C_{20}H_{20}N_2O_4S_1^+$; (calc. 384.1144).

X-Ray Structure Determination of **5**[5]). A crystal of dimensions $0.425 \times 0.4 \times 0.175$ mm was obtained at the separation surface of a biphasic system of MeOH and diisopropyl ether. Unit-cell parameters were obtained by least-squares fitting of the $\sin^2\theta$ values of 46 reflections, centered in both negative and positive 2θ regions. Details of data collection are reported in *Table 2*. Check reflections were measured every 97 reflections, showing a maximum decay of 2.7% after 75 h of exposure. Intensities were then corrected for decay and for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods using SHELX86 [19a];

[5]) Crystallographic data (excluding structure factors) for compound **5** have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-110020. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: +44(1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk)

all H-atoms were located in subsequent difference density maps, and their positions were allowed to refine. Results of the least-squares refinement [19b] (non-H atoms anisotropic, H atoms isotropic) are given in *Table 2*.

TLS Thermal-motion analysis [20] indicated that the fused ring system behaves as a rigid body to a first approximation, the root mean-square (rms) difference between TLS and experimental anisotropic displacement parameters being 0.003(1) Å^2. The rms libration amplitudes are 4.7, 2.4 and 1.7°, and the implied correction to the bond lengths lies in the range of 0.002 – 0.007 Å.

REFERENCES

[1] U. Berg, H. Bladh, *Helv. Chim. Acta* **1999**, *82*, 323.
[2] H. G. Capraro, A. Brossi, 'Tropolonic Colchicum Alkaloids', in 'The Alkaloids', Ed. A. Brossi, Academic Press, New York, 1984, Vol. 23, p. 1 – 70.
[3] A. Brossi, H. J. C. Yeh, M. Chrzanowska, J. Wulff, E. Hamel, C. M. Lin, F. Quinn, M. Suffness, J. Silverton, *Med. Res. Rev.* **1988**, *8*, 77.
[4] A. Brossi, *J. Med. Chem.* **1990**, *33*, 2311.
[5] O. Boyè, A. Brossi, 'Tropolonic Colchicum Alkaloids' and Allo Congeners', in 'The Alkaloids', Ed. A. Brossi, Accademic Press, New York, 1992, Vol. 41, p. 125.
[6] P. Lincoln, J. Nordh, J. Deinum, J. Amgstrom, B. Nordan, *Biochemistry* **1991**, *30*, 1179.
[7] L. Sun, A. T. McPhail, E. Hamel, C. M. Lin, S. B. Hastie, J.-J. Chang, K.-H. Lee, *J. Med. Chem.* **1993**, *36*, 544.
[8] L. Velluz, G. Muller, *Bull. Soc. Chim. Fr.* **1954**, 1072.
[9] R. Kotani, *J. Org. Chem.* **1965**, *30*, 350.
[10] F. Clerici, S. Mottadelli, M. L. Rossi, *J. Nat. Prod.* **1995**, *58,* 259.
[11] D. Cremer, J. A. Pople, *J. Am. Chem. Soc.* **1975**, *97*, 6.
[12] P. Kerekes, A. Brossi, J. L. Flippen-Anderson, C. F. Chignell, *Helv. Chim. Acta* **1985**, *68*, 571.
[13] T. Pilati, R. Bianchi, G. Casalone, *Acta Crystallogr., Sect. C* **1990**, *46*, 1873.
[14] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.
[15] J. J. Mayerle, J. B.Torrance, J. I. Crowley, *Acta Crystallogr., Sect. B* **1979**, *35,* 2988.
[16] J. V. Silverton, R. Dumont, A. Brossi, *Acta Crystallogr., Sect. C* **1987**, *43*, 1802.
[17] H. D. Flack, *Acta Crystallogr., Sect. A* **1983**, *39*, 876.
[18] U. Berg, H. Bladh, M. Hoff, C. Svensson, *J. Chem. Soc., Perkin Trans. 2* **1997**, 1697.
[19] a) G. M. Sheldrick, SHELX-86, Program for the Solution of Crystal Structures, University of Göttingen, 1985. b) G. M. Sheldrick, SHELX-93, Program for the Refinement of Crystal Structures, University of Göttingen, 1993.
[20] V. Schomaker, K. N. Trueblood, *Acta Crystallogr., Sect B* **1968**, *24*, 63; J. D. Dunitz, V. Schomaker, K. N. Trueblood, *J. Phys. Chem.* **1988**, *92*, 856.

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