*Data collection*

Siemens *P*4 diffractometer
$2\theta/\theta$ scans
Absorption correction: face-indexed numerical (Sheldrick, 1994)
$T_{min}$ = 0.961, $T_{max}$ = 0.983
4800 measured reflections
1943 independent reflections
999 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.060
$\theta_{max}$ = 25.05°
$h = -10 \rightarrow 1$
$k = -13 \rightarrow 1$
$l = -26 \rightarrow 26$
3 standard reflections every 97 reflections intensity decay: 1.84%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.135
$S$ = 1.001
1942 reflections
147 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.055P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.182 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.132 e Å$^{-3}$
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

| | | | |
|---|---|---|---|
| O1—C2 | 1.214 (3) | O3—C10 | 1.321 (3) |
| O2—C10 | 1.205 (3) | | |
| O2—C10—C9 | 124.5 (3) | O3—C10—C9 | 114.2 (2) |

Table 2. *Hydrogen-bonding geometry (Å, °)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O3—H3···O1$^{i}$ | 0.94 (3) | 1.78 (3) | 2.715 (3) | 174 (1) |
| C4—H4*B*···O2$^{ii}$ | 0.97 | 2.66 | 3.566 (3) | 155 |
| C9—H9*B*···O2$^{ii}$ | 0.97 | 2.69 | 3.537 (3) | 146 |

Symmetry codes: (i) $x-1, y, z$; (ii) $\frac{1}{2}-x, \frac{1}{2}+y, z$.

All non-carboxyl H atoms were found in electron-density difference maps, but were replaced in calculated positions and allowed to refine as riding models on their appropriate C atoms. Displacement parameters for methylene H-atom pairs were allowed to refine independently, as was the single methine H atom. The carboxyl H atom was found in an electron-density difference map, but was replaced in a calculated position, and the O—H distance and displacement parameter allowed to refine.

Data collection: *XSCANS* (Fait, 1991). Cell refinement: *XSCANS* (Siemens, 1996). Data reduction: *XSCANS* (Siemens, 1996). Program(s) used to solve structure: *SHELXTL/PC* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL/PC*. Molecular graphics: *SHELXTL/PC*. Software used to prepare material for publication: *SHELXTL/PC*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1471). Services for accessing these data are described at the back of the journal.

## References


Abell, A. D., Morris, K. B. & McKee, V. (1990). *Aust. J. Chem.* **43**, 765–771.
Berkovitch-Yellin, Z. & Leiserowitz, L. (1982). *J. Am. Chem. Soc.* **104**, 4052–4064.
Borthwick, P. W. (1980). *Acta Cryst.* B**36**, 628–632.
Brunskill, A. P. J., Lalancette, R. A. & Thompson, H. W. (1997). *Acta Cryst.* C**53**, 903–906.
Cambridge Structural Database (1998). Version 5.15. Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, England.
Chadwick, D. J. & Dunitz, J. D. (1979). *J. Chem. Soc. Perkin Trans.* 2, pp. 276–284.
Coté, M. L., Thompson, H. W. & Lalancette, R. A. (1996). *Acta Cryst.* C**52**, 684–687.
Coté, M. L., Thompson, H. W. & Lalancette, R. A. (1997). *Acta Cryst.* C**53**, 102–106.
Fait, J. (1991). *XSCANS User's Manual.* Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Gula, M. J. & Spencer, T. A. (1980). *J. Org. Chem.* **45**, 805–809.
Jönsson, P.-G. (1972). *Acta Chem. Scand.* **26**, 1599–1619.
Lalancette, R. A., Thompson, H. W. & Brunskill, A. P. J. (1998). *Acta Cryst.* C**54**, 421–424.
Lalancette, R. A., Thompson, H. W. & Coté, M. L. (1997). *Acta Cryst.* C**53**, 901–903.
Lalancette, R. A., Thompson, H. W. & Vanderhoff, P. A. (1991). *Acta Cryst.* C**47**, 986–990.
Leiserowitz, L. (1976). *Acta Cryst.* B**32**, 775–802.
Moffitt, W., Woodward, R. B., Moscowitz, A., Klyne, W. & Djerassi, C. (1961). *J. Am. Chem. Soc.* **83**, 4013–4018.
Sheldrick, G. M. (1994). *SHELXTL/PC User's Manual.* Version 5. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Siemens (1996). *XSCANS User's Manual.* Version 2.2. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Stork, G., Brizzolara, A., Landesman, H., Szmuszkovicz, J. & Terrell, R. (1963). *J. Am. Chem. Soc.* **85**, 207–222.
Thompson, H. W., Brunskill, A. P. J. & Lalancette, R. A. (1998). *Acta Cryst.* C**54**, 829–831.
Thompson, H. W., Lalancette, R. A. & Vanderhoff, P. A. (1992). *Acta Cryst.* C**48**, 66–70.
Vanderhoff, P. A., Thompson, H. W. & Lalancette, R. A. (1986). *Acta Cryst.* C**42**, 1766–1769.


*Acta Cryst.* (1998). C**54**, 1653–1659

# *Amaryllidaceae* Alkaloids: (+)-Tazettine, (+)-3-*O*-Demethylcriwelline and (+)-3-Epimacronine at 173 K


Anthony Linden,[a] Gülnur Akineri,[b] Seda Noyan,[b] Tekant Gözler[b] and Manfred Hesse[a]

[a]*Institut of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland, and* [b]*Faculty of Pharmacy, Ege University, Bornova 35100, Izmir, Turkey. E-mail: alinden@oci.unizh.ch*

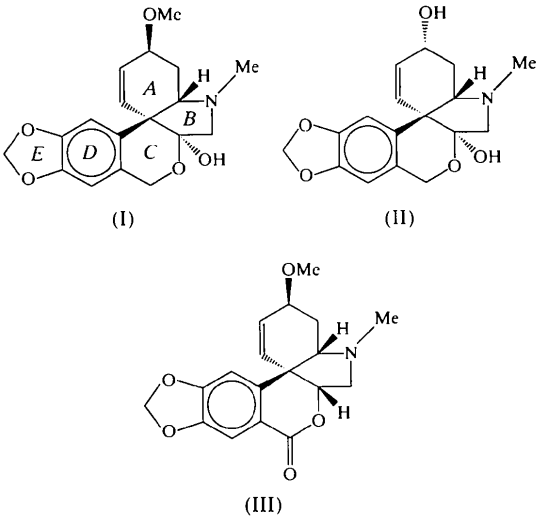

(*Received 13 March 1998; accepted 15 May 1998*)

## Abstract


The *Amaryllidaceae* alkaloids (+)-tazettine [(+)-(3*S*,4a*S*,-6a*S*,13b*S*)-3-methoxy-5-methyl-3,4,4a,5,6,6a-hexahydro-8*H*,11*H*-[1,3]dioxolo[6,7][2]benzopyrano[3,4-*c*]indol-


© 1998 International Union of Crystallography
Printed in Great Britain – all rights reserved

6a-ol, $C_{18}H_{21}NO_5$] and partially hydrated (+)-3-epimacronine [(+)-(3*S*,4a*S*,6a*R*,13b*S*)-3-methoxy-5-methyl-3,4,4a,5,6,6a-hexahydro-8*H*,11*H*-[1,3]dioxolo[6,7][2]-benzopyrano[3,4-*c*]indol-8-one 0.066-hydrate, $C_{18}H_{19}NO_5.0.066H_2O$] have been extracted from *Galanthus plicatus* subsp. *byzantinus*, while (+)-3-*O*-demethylcriwelline [(+)-(3*R*,4a*S*,6a*S*,13b*S*)-5-methyl-3,4,4a,5,6,6a-hexahydro-8*H*,11*H*-[1,3]dioxolo[6,7][2]benzopyrano[3,4-*c*]indole-3,6a-diol, $C_{17}H_{19}NO_5$] has been isolated from the plant *Galanthus gracilis*. These compounds have the ring skeleton of the tazettine or [2]benzopyrano-[3,4-*c*]indole subgroup. (+)-3-*O*-Demethylcriwelline is a new alkaloid and is the 3-*O*-demethyl C3-epimer of (+)-tazettine. The geometrical features of the compounds differ predominantly in the conformations of the pyrrolidine and pyran rings.




## Comment

The *Amaryllidaceae* alkaloids encompass a functionally and structurally diverse group of bases (Martin, 1987). Plants of the *Amaryllidaceae* family are generally considered to be sources for potential drugs having a wide range of pharmacological activities, including antiviral (Martin, 1987; Gabrielsen *et al.*, 1992), antineoplastic (Suffness & Cordell, 1985; Ghosal *et al.*, 1988; Pettit *et al.*, 1990), immunostimulant (Ghosal *et al.*, 1984), analgesic (Kametani *et al.*, 1971), insect antifeedant (Ghosal *et al.*, 1985; Martin, 1987) and antimalarial properties (Likhitwitayawuid *et al.*, 1993). In particular, galanthamine inhibits cholinesterase activity and is undergoing clinical trials for the treatment of Alzheimer's disease (Han *et al.*, 1992). Therefore, the investigation of new sources and new relatives of these important alkaloids and the determination of their three-dimensional structures are crucial objectives.

Among the tazettine subgroup of *Amaryllidaceae* alkaloids, which are those compounds possessing the [2]benzopyrano[3,4-*c*]indole nucleus, few single-crystal X-ray diffraction analyses have been reported. The absolute configuration of (+)-tazettine, (I), a well known *Amaryllidaceae* alkaloid (Wildman, 1968), has been confirmed by the determination of the crystal structure of *N*-methyltazettine iodide (Sato & Koyama, 1971) and agrees with the absolute structure that had previously been postulated from chemical degradation experiments (Highet & Highet, 1966). Subsequently, the crystal structure of pure (+)-tazettine has been determined (İde *et al.*, 1996), although it appears that the wrong enantiomer has inadvertently been employed in the refinement and the structural parameters lack precision because of the refinement strategy. The structure of (±)-(6a$\beta$)-5-demethyl-6a-deoxydihydro-5-(methoxycarbonyl)tazettinone has also been reported (Abelman *et al.*, 1990). This communication reports a significantly more precise redetermination of the structure of (+)-tazettine, (I), as well as the first X-ray crystal structure determinations of (+)-3-*O*-demethylcriwelline, (II), and (+)-3-epimacronine, (III). Compounds (I) and (III) were isolated from *Galanthus plicatus* Bieb. subsp. *byzantinus* (Baker) D. A. Webb growing in Bolu, Abant, Turkey, while compound (II) was isolated from *Galanthus gracilis* Celak growing on Nif Mountain, Izmir, Kemalpasa, Turkey (Ünver *et al.*, 1998). Compound (III) has been detected previously in *Sprekalia formosissima* (Wildman & Bailey, 1968) and *Hymenocallis rotata* (Kihara *et al.*, 1987), but compound (II) has not previously been isolated from natural sources, although it has been obtained as one of the products formed by refluxing tazettine in 10% HCl for 4 h (Keda *et al.*, 1956). Ünver *et al.* (1998) have confirmed that compound (II) is a true alkaloid and not a product of the isolation procedures.

The structure of compound (I) (Fig. 1) was refined using the enantiomer which matches that found for *N*-methyltazettine iodide (Sato & Koyama, 1971). This is the antipode of the one used, presumably erroneously, by İde *et al.* (1996). The s.u.'s in the present results are a factor of three smaller than those in the former work and, therefore, a more detailed comparison can be made between the structures of compounds (I), (II) and (III). The bond lengths and angles in (I) are generally within the normally expected ranges. The only slightly unusual values are the relatively short C6a—O6a bond in the tertiary hydroxy group (Table 1) and the asymmetrical nature of the bonds about N5, which range from 1.462 (3) to 1.496 (2) Å. The bond angles about N5 clearly display the $sp^3$ pyramidalization of this atom and the methyl substituent is in the orientation which avoids steric interactions with the cyclohexene ring. The overall geometrical features of (I) do not differ significantly from those reported by İde *et al.* (1996). Those authors found that the bond lengths about N5 were almost equal, but the large s.u.'s in their report make fine comparisons difficult.

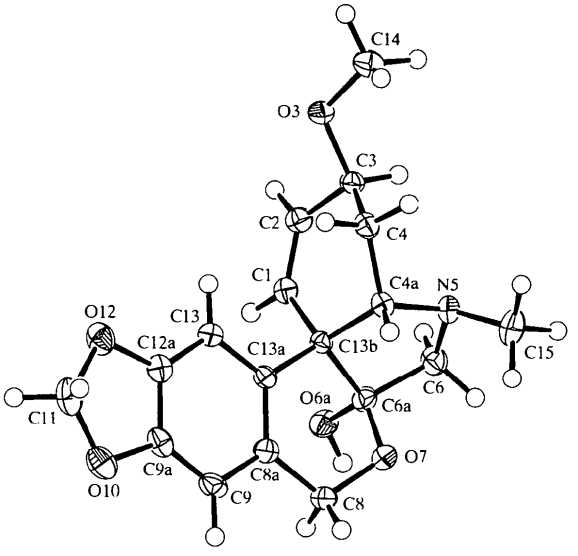



Fig. 1. View of the molecule of compound (I) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by spheres of arbitrary size.

The cyclohexene ring, *A*, in (I) has a distorted half-chair conformation in which atoms C4 and C4a lie on opposite sides of the plane defined by atoms C13b, C1, C2 and C3, and deviate therefrom by 0.515 (3) and −0.175 (3) Å, respectively. The puckering parameters (Cremer & Pople, 1975) are given in Table 6. The half-chair conformation is distorted towards a C4-envelope. The pyran ring, *C*, is close to an ideal half-chair conformation in which C6a and O7 lie on opposite sides of the plane defined by C8, C8a, C13a and C13b, and deviate therefrom by 0.347 (4) and −0.386 (4) Å, respectively. The pyrrolidine ring, *B*, has a half-chair conformation twisted on C6a—C13b, with C6a and C13b −0.307 (5) and 0.321 (5) Å, respectively, from the plane defined by C4a, N5 and C6. If C11 is excluded, the fused dioxolobenzene rings, *D* and *E*, form a planar system in which the r.m.s. deviation is 0.012 Å. Atom C11 lies 0.171 (3) Å from this plane. All of these ring conformations agree with those found by İde *et al.* (1996). In *N*-methyltazettine iodide (Sato & Koyama, 1971), the cyclohexene ring is a more distorted half-chair, with C4a being the only atom that is significantly out of the ring plane.

The hydroxy substituent at C6a of (I) is the donor for an intermolecular hydrogen bond with the 3-methoxy group of a neighbouring molecule (Table 2). This interaction links the molecules into infinite one-dimensional chains which run parallel to the *x* axis and have a graph set with the *C*(8) motif (Bernstein *et al.*, 1995).

The structure of (+)-3-*O*-demethylcriwelline, (II) (Fig. 2), shows that this compound is the 3-*O*-demethyl C3-epimer of (+)-tazettine. In the refinement, the enantiomorph was chosen by assuming that all chiral centres, except that at C3, are the same as in (I). This assumption is supported by the fact that the CD spectrum of compound (II) is almost superimposable upon that of (+)-tazettine (Ünver *et al.*, 1998). The bond lengths and angles are very similar to those in compound (I), including the relatively short C6a—O6a bond in the tertiary hydroxy group and the asymmetrical nature of the bonds about N5 (Table 3).

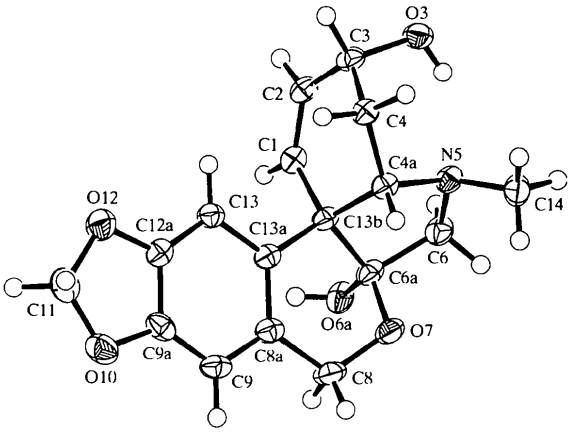


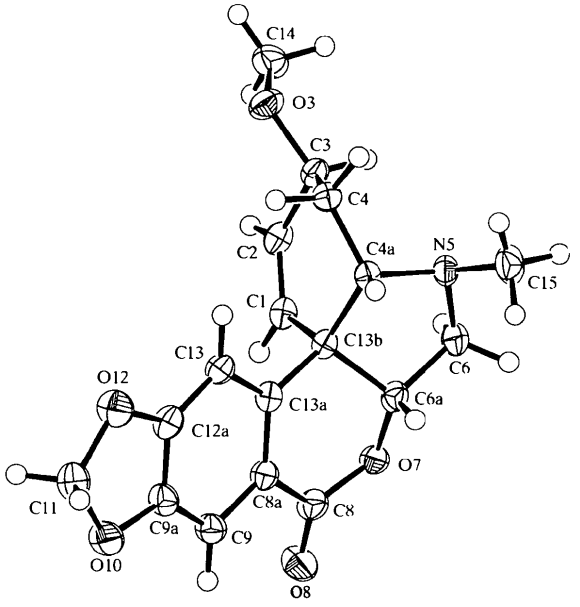

Fig. 2. View of the molecule of compound (II) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by spheres of arbitrary size.

The ring conformations in (II) are very similar to those in (I), except that the pyrrolidine ring in (II) has the envelope conformation (Table 6), with C13b as the envelope flap at a distance of 0.632 (4) Å from the plane defined by C4a, N5, C6 and C6a. In the cyclohexene ring of (II), which has a slightly more ideal half-chair conformation than that in compound (I), C4 and C4a lie 0.405 (5) and −0.303 (5) Å, respectively, from the plane defined by C13b, C1, C2 and C3. The pyran ring has an almost identical half-chair conformation to that in compound (I); C6a and O7 lie −0.391 (5) and 0.378 (5) Å, respectively, from the plane defined by C8, C8a, C13a and C13b. In the fused dioxolobenzene ring system, C11 lies 0.066 (4) Å from the plane defined by the eight remaining atoms, whose r.m.s. deviation from the plane is 0.019 Å.

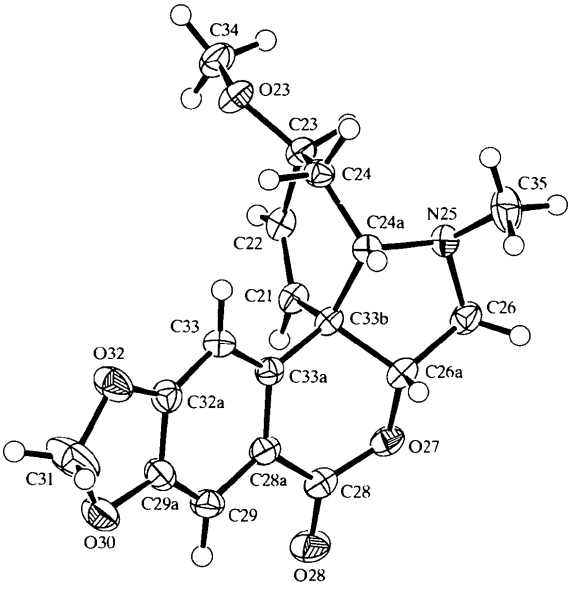
The hydroxy group at C3 of (II) forms an intramolecular hydrogen bond with N5 (Table 4) to give the graph set *S*(6) . The hydroxy substituent at C6a is the donor for an intermolecular hydrogen bond with the 3-hydroxy group of a neighbouring molecule. This interaction links the molecules into infinite one-dimensional chains which run parallel to the *y* axis and have a graph set with the *C*(8) motif.

The structure of (+)-3-epimacronine, (III) (Fig. 3), is also related to (+)-tazettine, except that the hydroxy

group at C6a is absent and has been replaced by a carbonyl group at C8. The enantiomer used in the refinement was chosen by assuming that C3, C4a and C13b have the same configuration as in (+)-tazettine, while C6a is inverted. This stereochemistry is in agreement with that previously postulated from chemical and spectroscopic evidence (Wildman & Bailey, 1968; Kobayashi *et al.*, 1980). The asymmetric unit contains two symmetry-independent molecules of the alkaloid plus a partially occupied site containing a water molecule. The molar fraction of water in the crystal lattice is only 6.6 (5)%. The bond lengths and angles in the two independent molecules show no significant differences and are generally very similar to those in compounds (I) and (II) (Table 5). The O7—C8 and O27—C28 bonds are shorter than in compounds (I) and (II) due to conjugation with the carbonyl group. The bond angles around C13b show larger deviations from tetrahedral angles than the corresponding angles in compounds (I) and (II).




(*a*)




(*b*)

Fig. 3. Views of (*a*) molecule *A* and (*b*) molecule *B* of compound (III) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by spheres of arbitrary size.

The independent molecules in (III) differ slightly from each other in the puckering of the various rings (Table 6). The pyrrolidine ring in molecule *A* of (III) has a half-chair conformation twisted on C6a—C13b, which is distorted slightly towards a C6a-envelope conformation. Molecule *B* has the same half-chair conformation, but with a slightly greater distortion towards a C13b-envelope. For molecule *A*, C6a and C13b are 0.495 (6) and −0.235 (6) Å, respectively, from the plane defined by C4a, N5 and C6, while for molecule *B*, C26a and C33b are 0.180 (6) and −0.543 (6) Å from the plane defined by C24a, N25 and C26. For the cyclohexene ring, molecule *A* has a half-chair conformation twisted on C4—C4a, but distorted towards a C4-envelope, with C4 and C4a −0.548 (4) and 0.124 (4) Å, respectively, from the plane defined by C13b, C1, C2 and C3. Molecule *B* has a more ideal half-chair conformation twisted on C24—C24a, with C24 and C24a 0.319 (5) and −0.339 (5) Å, respectively, from the plane defined by C33b, C21, C22 and C23. The conformation of the pyran ring differs from those in compounds (I) and (II) because of the influence of the carbonyl group at C8. In both independent molecules, this ring has a distorted skew-boat conformation. In molecule *A*, C6a and O7 lie 0.893 (4) and 0.338 (4) Å, respectively, from the plane defined by C8, C8a, C13a and C13b, while in molecule *B*, C26a and O27 lie 0.923 (4) and 0.410 (4) Å, respectively, from the plane defined by C28, C28a, C33a and C33b. In the fused dioxolobenzene rings of molecule *A*, C11 lies 0.026 (3) Å from the plane defined by the eight remaining atoms, whose r.m.s. deviation from the plane is 0.004 Å. The corresponding system in molecule *B* is less planar with C31 0.074 (6) Å from the plane whose eight defining atoms have an r.m.s. deviation of 0.020 Å.

## Experimental

The isolation, purification and spectroscopic data of the title compounds are described by Ünver *et al.* (1998). The compounds were crystallized from their solutions in acetone–methanol by slow evaporation.

**Compound (I)**

*Crystal data*

$C_{18}H_{21}NO_5$
$M_r$ = 331.37
Orthorhombic
$P2_12_12_1$
$a$ = 13.342 (2) Å
$b$ = 16.839 (1) Å
$c$ = 7.052 (2) Å
$V$ = 1584.5 (5) Å$^3$
$Z$ = 4
$D_x$ = 1.389 Mg m$^{-3}$
$D_m$ not measured

Mo $K\alpha$ radiation
$\lambda$ = 0.71069 Å
Cell parameters from 25 reflections
$\theta$ = 18.5–20.0°
$\mu$ = 0.102 mm$^{-1}$
$T$ = 173 (1) K
Prism
0.40 × 0.27 × 0.27 mm
Colourless

*Data collection*

Rigaku AFC-5*R* diffractometer
$\omega$–$2\theta$ scans
Absorption correction: none
3176 measured reflections
3072 independent reflections
2661 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.014

$\theta_{max}$ = 30°
$h = 0 \rightarrow 18$
$k = -1 \rightarrow 23$
$l = -1 \rightarrow 9$
3 standard reflections every 150 reflections intensity decay: insignificant

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.109
$S$ = 1.034
3072 reflections
221 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0596P)^2 + 0.2133P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001

$\Delta\rho_{max}$ = 0.28 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.21 e Å$^{-3}$
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0061 (18)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °) for (I)*

| | | | |
|---|---|---|---|
| O3—C3 | 1.446 (2) | N5—C6 | 1.469 (3) |
| O6a—C6a | 1.402 (2) | N5—C15 | 1.462 (3) |
| O7—C6a | 1.429 (2) | C1—C2 | 1.331 (3) |
| O7—C8 | 1.428 (2) | | |
| C6—N5—C4a | 108.50 (14) | C1—C13b—C13a | 109.63 (14) |
| C15—N5—C4a | 111.02 (15) | C4a—C13b—C6a | 101.02 (14) |
| C15—N5—C6 | 114.57 (16) | C4a—C13b—C13a | 112.92 (15) |
| C1—C13b—C4a | 112.07 (14) | C6a—C13b—C13a | 111.22 (13) |
| C1—C13b—C6a | 109.71 (15) | | |
| C1—C2—C3—C4 | −21.2 (2) | O7—C8—C8a—C13a | 16.1 (3) |
| C2—C1—C13b—C4a | −6.9 (2) | C8a—C13a—C13b—C6a | 12.9 (2) |
| C6—N5—C4a—C13b | −12.40 (19) | C11—O10—C9a—C12a | −8.4 (2) |
| C4a—N5—C6—C6a | −12.1 (2) | C11—O12—C12a—C9a | 7.4 (2) |

Table 2. *Hydrogen-bonding geometry (Å, °) for (I)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O6a—H6a···O3$^{i}$ | 0.84 | 1.97 | 2.7656 (19) | 158.6 |

Symmetry code: (i) $x - \frac{1}{2}, \frac{1}{2} - y, 1 - z$.

**Compound (II)**

*Crystal data*

$C_{17}H_{19}NO_5$
$M_r$ = 317.34
Monoclinic
$P2_1$
$a$ = 7.297 (5) Å
$b$ = 11.083 (2) Å
$c$ = 9.531 (3) Å
$\beta$ = 104.30 (3)°
$V$ = 746.8 (5) Å$^3$
$Z$ = 2
$D_x$ = 1.411 Mg m$^{-3}$
$D_m$ not measured

Mo $K\alpha$ radiation
$\lambda$ = 0.71069 Å
Cell parameters from 24 reflections
$\theta$ = 19–20°
$\mu$ = 0.104 mm$^{-1}$
$T$ = 173 (1) K
Prism
0.50 × 0.30 × 0.23 mm
Colourless

*Data collection*

Rigaku AFC-5*R* diffractometer
$\omega$–$2\theta$ scans
Absorption correction: none
1938 measured reflections
1806 independent reflections
1574 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.031

$\theta_{max}$ = 27.5°
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 14$
$l = -12 \rightarrow 12$
3 standard reflections every 150 reflections intensity decay: insignificant

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.095
$S$ = 1.036
1806 reflections
212 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0454P)^2 + 0.1561P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001

$\Delta\rho_{max}$ = 0.29 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.18 e Å$^{-3}$
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.006 (3)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 3. *Selected geometric parameters (Å, °) for (II)*

| | | | |
|---|---|---|---|
| O3—C3 | 1.452 (3) | N5—C6 | 1.484 (3) |
| O6a—C6a | 1.390 (3) | N5—C14 | 1.463 (4) |
| O7—C6a | 1.438 (3) | C1—C2 | 1.329 (4) |
| O7—C8 | 1.427 (4) | | |
| C6—N5—C4a | 107.9 (2) | C1—C13b—C13a | 110.6 (2) |
| C14—N5—C4a | 112.4 (2) | C4a—C13b—C6a | 100.3 (2) |
| C14—N5—C6 | 112.9 (2) | C4a—C13b—C13a | 112.8 (2) |
| C1—C13b—C4a | 110.4 (2) | C6a—C13b—C13a | 112.2 (2) |
| C1—C13b—C6a | 110.2 (2) | | |
| C1—C2—C3—C4 | −17.9 (4) | O7—C8—C8a—C13a | 16.9 (4) |
| C2—C1—C13b—C4a | −13.4 (3) | C8a—C13a—C13b—C6a | 15.9 (3) |
| C6—N5—C4a—C13b | −22.2 (3) | C11—O10—C9a—C12a | −3.9 (3) |
| C4a—N5—C6—C6a | −3.5 (3) | C11—O12—C12a—C9a | 0.8 (3) |

Table 4. *Hydrogen-bonding geometry (Å, °) for (II)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O3—H3···N5 | 0.84 | 2.05 | 2.749 (3) | 140.4 |
| O6a—H6a···O3$^{i}$ | 0.84 | 1.89 | 2.685 (3) | 157.5 |

Symmetry code: (i) $2 - x, y - \frac{1}{2}, 1 - z$.

**Compound (III)**

*Crystal data*

$C_{18}H_{19}NO_5.0.066H_2O$
$M_r$ = 330.54

Mo $K\alpha$ radiation
$\lambda$ = 0.71069 Å

Monoclinic
$P2_1$
$a$ = 8.176 (2) Å
$b$ = 17.666 (2) Å
$c$ = 11.0743 (9) Å
$\beta$ = 95.054 (9)°
$V$ = 1593.3 (3) Å$^3$
$Z$ = 4
$D_x$ = 1.378 Mg m$^{-3}$
$D_m$ not measured

Cell parameters from 25 reflections
$\theta$ = 19–20°
$\mu$ = 0.101 mm$^{-1}$
$T$ = 173 (1) K
Prism
0.50 × 0.35 × 0.32 mm
Colourless

*Data collection*

Rigaku AFC-5*R* diffractometer
$\omega$–$2\theta$ scans
Absorption correction: none
4033 measured reflections
3781 independent reflections
3413 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.015

$\theta_{max}$ = 27.5°
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 22$
$l = -14 \rightarrow 14$
3 standard reflections every 150 reflections intensity decay: insignificant

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.090
$S$ = 1.031
3781 reflections
448 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0458P)^2 + 0.3026P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001

$\Delta\rho_{max}$ = 0.22 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.21 e Å$^{-3}$
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0051 (13)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 5. *Selected geometric parameters (Å, °) for (III)*

| | | | |
|---|---|---|---|
| O3—C3 | 1.432 (3) | O23—C23 | 1.443 (3) |
| O7—C6a | 1.436 (3) | O27—C26a | 1.448 (3) |
| O7—C8 | 1.366 (3) | O27—C28 | 1.355 (3) |
| O8—C8 | 1.199 (3) | O28—C28 | 1.214 (3) |
| N5—C4a | 1.501 (3) | N25—C24a | 1.494 (3) |
| N5—C6 | 1.486 (3) | N25—C26 | 1.489 (3) |
| N5—C15 | 1.459 (3) | N25—C35 | 1.454 (3) |
| C1—C2 | 1.331 (3) | C21—C22 | 1.328 (3) |
| C6—N5—C4a | 109.30 (18) | C26—N25—C24a | 109.41 (19) |
| C15—N5—C4a | 111.8 (2) | C35—N25—C24a | 111.5 (2) |
| C15—N5—C6 | 112.8 (2) | C35—N25—C26 | 113.8 (2) |
| C1—C13b—C4a | 111.42 (18) | C21—C33b—C24a | 110.75 (19) |
| C1—C13b—C6a | 112.96 (19) | C21—C33b—C26a | 112.90 (19) |
| C1—C13b—C13a | 108.15 (18) | C21—C33b—C33a | 108.43 (19) |
| C4a—C13b—C6a | 99.07 (17) | C24a—C33b—C26a | 99.24 (19) |
| C4a—C13b—C13a | 119.69 (19) | C24a—C33b—C33a | 120.3 (2) |
| C6a—C13b—C13a | 105.19 (17) | C26a—C33b—C33a | 104.83 (18) |

| | |
|---|---|
| C1—C2—C3—C4 | −23.3 (3) |
| C2—C1—C13b—C4a | −5.6 (3) |
| C6—N5—C4a—C13b | −9.0 (2) |
| C4a—N5—C6—C6a | −19.5 (2) |
| O7—C8—C8a—C13a | 16.5 (3) |
| C8a—C13a—C13b—C6a | −37.0 (3) |
| C11—O10—C9a—C12a | 0.9 (3) |
| C11—O12—C12a—C9a | −1.5 (3) |
| C21—C22—C23—C24 | −14.1 (3) |
| C22—C21—C33b—C24a | −14.7 (3) |
| C26—N25—C24a—C33b | −21.4 (2) |
| C24a—N25—C26—C26a | −7.0 (2) |
| O27—C28—C28a—C33a | 14.9 (3) |
| C28a—C33a—C33b—C26a | −42.9 (3) |
| C31—O30—C29a—C32a | −3.7 (4) |
| C31—O32—C32a—C29a | 1.2 (3) |

Table 6. *Ring puckering parameters in compounds (I), (II) and (III)*

| | $Q$ (Å) | $\theta$ (°) | $\varphi_2$ (°) |
|---|---|---|---|
| Ideal values[a] | | | |
| Five-membered envelope | – | – | $n \times 36$ |
| Five-membered half-chair | – | – | $(n \times 36) + 18$ |
| Six-membered half-chair | – | 50.8 | $(n \times 60) + 30$ |
| Six-membered envelope | – | 54.7 | $n \times 60$ |
| Six-membered skew-boat | – | 67.5 | $(n \times 60) + 30$ |
| Compound (I) | | | |
| Cyclohexene ring | 0.462 (2) | 50.7 (2) | 134.4 (3) |
| Pyran ring | 0.485 (2) | 51.3 (2) | 328.7 (3) |
| Pyrrolidine ring | 0.379 (2) | – | 89.4 (3) |
| Compound (II) | | | |
| Cyclohexene ring | 0.463 (3) | 48.4 (4) | 145.3 (5) |
| Pyran ring | 0.508 (3) | 50.2 (3) | 331.1 (4) |
| Pyrrolidine ring | 0.408 (3) | – | 76.8 (4) |
| Compound (III) – molecule *A* | | | |
| Cyclohexene ring | 0.458 (3) | 50.6 (4) | 130.1 (4) |
| Pyran ring | 0.549 (2) | 63.1 (2) | 82.8 (3) |
| Pyrrolidine ring | 0.455 (3) | – | 96.4 (3) |
| Compound (III) – molecule *B* | | | |
| Cyclohexene ring | 0.429 (3) | 48.4 (4) | 151.1 (5) |
| Pyran ring | 0.557 (3) | 61.4 (2) | 89.7 (3) |
| Pyrrolidine ring | 0.450 (3) | – | 81.1 (3) |

Notes: (*a*) Cremer & Pople (1975).

For compounds (II) and (III), the origin was fixed according to the method of Flack & Schwarzenbach (1988). In each structure, all H atoms were initially located in a difference electron-density map, but their positions were subsequently geometrically optimized. The methyl and hydroxy groups were refined as rigid groups which were allowed to rotate but not to tip, and $U_{iso}$(H) was set equal to $1.5U_{eq}$(parent atom). All other H atoms were allowed to ride on their parent atoms with $U_{iso}(H) = 1.2U_{eq}(C)$. An extinction correction was applied for each structure, but the magnitudes of the s.u.'s of the extinction coefficients indicate that these corrections have negligible effects on the structural results. The presence of water in the crystal lattice of (III) was indicated by a residual electron density peak of 0.67 e Å$^{-3}$ when the water-free model was employed, while all other peaks were less than 0.24 e Å$^{-3}$. This peak was 2.84, 2.87 and 2.91 Å from O3, O32 and O10, respectively, which are appropriate O···O distances for hydrogen-bonded water molecules. Furthermore, an analysis of the water-free model with *PLATON* (Spek, 1998) showed that the structure contained 9 Å$^{-3}$ holes. Although these holes are quite small, they are further evidence for there being sufficient space in the crystal lattice to accommodate water molecules. Inclusion of an O atom in the model, together with refinement of its site occupation factor, led to an improvement in the $R$ factors [$wR(F^2)$ = 0.0975 for the water-free model] and a site-occupation factor for the O atom of 0.132 (9). The H atoms of the partial occupancy water molecule were not included in the model.

For all compounds, data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1989); program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structures: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *OR-*

*TEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

The authors are grateful to the Swiss National Science Foundation for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1465). Services for accessing these data are described at the back of the journal.

## References


Abelman, M. M., Overman, L. E. & Tran, V. D. (1990). *J. Am. Chem. Soc.* **112**, 6959–6964.

Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Flack, H. D. & Schwarzenbach, D. (1988). *Acta Cryst.* A**44**, 499–506.

Gabrielsen, B., Monath, T. P., Huggins, J. W., Kirsi, J. J., Hollingshead, M., Shannon, W. M. & Pettit, G. R. (1992). *Natural Products as Antiviral Agents*, edited by C. K. Chu & H. G. Cutler, pp. 121–135. New York: Plenum Press.

Ghosal, S., Saini, K. S. & Arora, V. K. (1984). *J. Chem. Res.* **5**, 232–233.

Ghosal, S., Saini, K. S. & Razdan, S. (1985). *Phytochemistry*, **24**, 2141–2156.

Ghosal, S., Singh, S. K., Kumar, Y., Unnikrishnan, S. & Chattopadhyay, S. (1988). *Planta Med.* **54**, 114–116.

Han, S. Y., Sweeney, J. E., Bachman, E. S., Schweiger, E. J., Forloni, G., Coyle, J. T., Davis, B. M. & Joullie, M. M. (1992). *Eur. J. Med. Chem.* **27**, 673–687.

Highet, R. J. & Highet, P. F. (1966). *Tetrahedron Lett.* **34**, 4099–4101.

İde, S., Şener, B., Temizer, H. & Könükol, S. (1996). *Cryst. Res. Technol.* **31**, 617–624.

Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Kametani, T., Seino, C., Yamaki, K., Shibuya, S., Fukumoto, K., Kigasawa, K., Satoh, F., Hiiragi, M. & Hayasaka, T. (1971). *J. Chem. Soc. C*, pp. 1043–1047.

Keda, T., Taylor, W. I., Tsuda, Y., Uyeo, S. & Yajuna, H. (1956). *J. Chem. Soc.* pp. 4749–4761.

Kihara, M., Koike, T., Imakura, Y., Kida, K., Shingu, T. & Kobayashi, S. (1987). *Chem. Pharm. Bull.* **35**, 1070–1075.

Kobayashi, S., Kihara, M., Shingu, T. & Shingu, K. (1980). *Chem. Pharm. Bull.* **28**, 2924–2932.

Likhitwitayawuid, K., Angerhofer, C. K., Chai, H., Pezzuto, J. M. & Cordell, G. A. (1993). *J. Nat. Prod.* **56**, 1331–1338.

Martin, S. F. (1987). *The Alkaloids: Chemistry and Pharmacology*, Vol. 30, edited by A. Brossi, pp. 251–376. New York: Academic Press.

Molecular Structure Corporation (1989). *TEXSAN. Single Crystal Structure Analysis Software.* MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Molecular Structure Corporation (1991). *MSC/AFC Diffractometer Control Software.* MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Pettit, G. R., Cragg, G. M., Singh, S. B., Duke, J. A. & Doubek, D. L. (1990). *J. Nat. Prod.* **53**, 176–178.

Sato, T. & Koyama, H. (1971). *J. Chem. Soc. B*, pp. 1070–1073.

Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.

Sheldrick, G. M. (1997). *SHELXL*97. *Program for the Refinement of Crystal Structures.* University of Göttingen, Germany.

Spek, A. L. (1998). *PLATON. Program for the Analysis of Molecular Geometry.* Version of January 1998. University of Utrecht, The Netherlands.

Suffness, M. & Cordell, G. A. (1985). *The Alkaloids: Chemistry and Pharmacology*, Vol. 25, edited by A. Brossi, pp. 198–212. New York: Academic Press.

Ünver, N., Noyan, S., Gözler, T., Önür, M. A., Gözler, B. & Hesse, M. (1998). *Planta Med.* Submitted.

Wildman, W. C. (1968). *The Alkaloids*, Vol. 11, edited by R. H. F. Manske, pp. 308–405. New York: Academic Press.

Wildman, W. C. & Bailey, D. T. (1968). *J. Org. Chem.* **33**, 3749–3753.


© 1998 International Union of Crystallography
Printed in Great Britain – all rights reserved

*Acta Cryst.* (1998). C**54**, 1659–1662

# 3-(Dimethylamino)-5,6,7,8,9,10-hexahydro-12,13-dimethoxy-4*H*-spiro[benzo-1-thia-2,5-diazacyclododecene-4,1′-cyclobutan]-6-one 1,1-Dioxide Dichloromethane Solvate (1/1) at 173 K

ANTHONY LINDEN, TONYA R. MIHOVA AND HEINZ HEIMGARTNER

*Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland. E-mail: alinden@oci.unizh.ch*

*(Received 17 April 1998; accepted 19 June 1998)*


## Abstract

The 12-membered ring in the title compound, $C_{20}H_{29}N_3O_5S.CH_2Cl_2$, has conformational disorder with the two C atoms adjacent to the fused benzene ring each occupying two sites. The major conformer is present in 74.3 (8)% of the molecules. The formal N2=C bond in the 12-membered ring and the adjacent C—N bond of the dimethylamino substituent have almost identical lengths, indicative of the electron donor character of the dimethylamino group. The amide group has the *trans* conformation and forms an intramolecular hydrogen bond with one of the sulfonyl O atoms. The solvent molecule forms C—H···O hydrogen bonds with the organic substrate. This novel heterocycle has been formed by a ring enlargement reaction of the corresponding nine-membered 1,2-benzothiazonin-3-one 1,1-dioxide and 2-(dimethylamino)-1-azaspiro[2.3]hex-1-ene.


## Comment

Cyclic oxosulfonamides of the type (I) and 3-amino-2*H*-azirines, (II), react to give ring-enlarged heterocycles of the type (III) (Heimgartner, 1991; Orahovats *et al.*, 1992, 1996; Villalgordo *et al.*, 1992; Mihova *et al.*, 1996, 1998). This reaction proceeds *via* the formation of an aziridine intermediate, *A*, and the regioselective nucleophilic attack of the aziridine N atom onto the carbonyl group. This mechanism has been proven in the case of a five-membered starting material, (I), by using $^{15}$N-labelled (II) (Ametamey *et al.*, 1988). In some