Refinement

Refinement on F^2
$R(F) = 0.0248$
$wR(F^2) = 0.0658$
$S = 1.085$
1823 reflections
146 parameters
$w = 1/[\sigma^2(F_o^2) + (g_1P)^2 + g_2P]$
where $P = [\max F_o^2, 0) + 2F_c^2]/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.157$ e Å^{-3}
$\Delta\rho_{\min} = -0.162$ e Å^{-3}
Extinction correction:
$F_c^* = F_ck[1 + (0.001\chi \times F_c^2\lambda^3/\sin2\theta)]$
Extinction coefficient:
$\chi = 0.177\ (9)$
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	*y*	*z*	$U_{\rm eq}$
C(1)	−0.5779 (3)	0.4773 (2)	−0.6549 (2)	0.029 (1)
C(2)	−0.5047 (3)	0.5182 (2)	−0.7866 (2)	0.029 (1)
N(3)	−0.3463 (2)	0.4081 (1)	−0.8054 (1)	0.024 (1)
C(4)	−0.4425 (3)	0.2579 (2)	−0.8263 (2)	0.026 (1)
C(5)	−0.5191 (3)	0.2163 (2)	−0.6958 (2)	0.029 (1)
N(6)	−0.6749 (2)	0.3277 (2)	−0.6748 (1)	0.028 (1)
C(1′)	0.1048 (2)	0.3610 (2)	−0.4015 (2)	0.027 (1)
O(11′)	−0.0590 (2)	0.3588 (2)	−0.5162 (1)	0.050 (1)
O(12′)	0.2969 (2)	0.3290 (2)	−0.3946 (1)	0.038 (1)
C(2′)	0.0716 (2)	0.4078 (2)	−0.2529 (2)	0.024 (1)
O(21′)	0.2753 (2)	0.4254 (1)	−0.1377 (1)	0.031 (1)
C(3′)	−0.0698 (2)	0.2957 (2)	−0.2043 (2)	0.022 (1)
O(31′)	0.0288 (2)	0.1556 (1)	−0.1869 (1)	0.030 (1)
C(4′)	−0.1082 (2)	0.3450 (2)	−0.0579 (1)	0.022 (1)
O(41′)	−0.2368 (2)	0.4501 (1)	−0.0665 (1)	0.031 (1)
O(42′)	−0.0096 (2)	0.2744 (1)	0.0589 (1)	0.031 (1)

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

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
N(3)—H···O(41′$^{\rm i}$)	1.760 (2)	2.780 (2)	170 (4)
N(3)—H···O(11′)	1.936 (2)	2.777 (2)	153 (3)
N(6)—H···O(12′$^{\rm ii}$)	1.907 (2)	2.688 (2)	156 (3)
N(6)—H···O(42′$^{\rm iii}$)	1.859 (2)	2.759 (2)	160 (3)
O(31′)—H···O(42′$^{\rm iv}$)	2.105 (2)	2.627 (2)	125 (3)
O(21′)—H···O(12′$^{\rm v}$)	2.207 (1)	2.607 (1)	110 (3)

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

Data collection: *XSCANS* (Fait, 1991). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SHELXTL/PC* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *XP SHELXTL/PC*.

Many thanks to DRA (Fort Halstead) for generous financial support.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: PT1032). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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One Bicyclic β-Lactam and Two Bicyclic γ-Lactam Compounds

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Abstract

The crystal structures of the bicyclic β-lactam, *rac*-(2*R**,4*S**,6*S**)-4-chloro-4-methyl-8-oxo-1-azabicyclo[4.2.0]octane-2-carboxylic acid methyl ester, $C_{10}H_{14}ClNO_3$ (1), and the bicyclic γ-lactams, *rac*-(5*R**,7*S**,9*S**)-7-chloro-7-methyl-3-oxooctahydroindolizine-5-carboxylic acid methyl ester, $C_{11}H_{16}ClNO_3$ (2), and *rac*-(5*R**,6*S**,10*R**)-3-oxo-6-vinyloctahydro-1*H*-pyrrolo[1,2-*a*]azepine-5-carboxylic acid methyl ester, $C_{13}H_{19}NO_3$ (3), have been established by X-ray crystallography. In (1) and (2) the α-amino ester function and the Cl atom occupy an axial position in a chair-like piperidine ring. In (3) the methyl ester and the vinyl group are equatorially placed on the chair-like seven-

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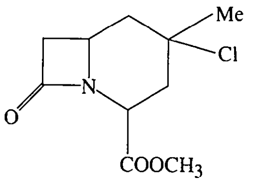
membered ring. The criteria defined by Foces-Foces, Cano & Garciá-Blanco [*Acta Cryst.* (1976), **B32**, 3029–3033] to determine the conformation of a six-membered ring are compared with those defined by Duax, Weeks & Rohrer [*Top. Stereochem.* (1976), **9**, 271–383]. It can be seen that the former cannot be used to determine the conformation of a six-membered ring correctly in the case of strain imposed by a four-membered fused ring such as in (1).

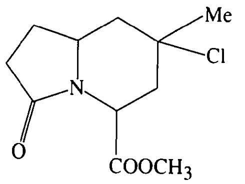
Comment

Bicyclic β-lactam systems are of major interest in industrial research on penicillin and related compounds. As part of a project dealing with systems of this type and of the closely related bicyclic γ-lactams, the three compounds have been synthesized and the crystal structures determined.

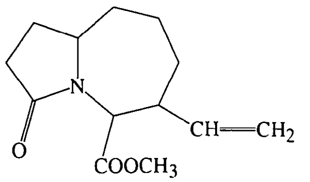
The present X-ray study of these compounds was undertaken to establish the relative stereochemical configuration and to obtain geometrical details of the β-lactam [from (1)] and the γ-lactam [from (2) and (3)] systems.



(1)



(2)



(3)

The observed bond distances and angles are within the expected range of previously reported data (Allen *et al.*, 1987). The N1—C8 bond distance of 1.357 (4) Å in (1) is significantly shorter than the average value (1.385 Å; Allen *et al.*, 1987) but is comparable to the distance of 1.361 (4) Å observed in benzyl 1α-hydroxy-3-methyl-8-oxo-7β-phenoxyacetamido-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (Sim, 1985).

The endocyclic angles in the lactam ring at the N and C atoms compare well with the values for 54 β- and 41 γ-lactams reported by Norskov-Lauritsen, Bürgi, Hoffmann & Schmidt (1985). For the β-lactam (1) the values are 95.3 (3) at N and 91.7 (3)° at C *versus* 94.4 (17) and 91.7 (14)°; for the γ-lactams the values are 113.9 (3)° for (2) [114.1 (2) (14)° for (3)] at N and 107.9 (4)° [108.7 (2) (14)° for (3)] at C *versus* 114.9 (13) and 108.4 (13)°.

The exocyclic C═O angles of the lactam rings are significantly different, the N—C═O angle being smaller than the C—C═O angle [132.4 (4) *versus* 135.9 (4)° in (1), 125.1 (4) *versus* 127.0 (4)° in (2) and 123.8 (2) *versus* 127.5 (3)° in (3)], which should be accredited to an anomeric interaction of the *p*-type lone pair on the carbonyl O atom and the antibonding C—N orbital as interpreted from molecular orbital calculations by Norskov-Lauritsen, Bürgi, Hoffmann & Schmidt (1985). These authors noted that the carbonyl group in lactams tends to show a C—C═O angle that is larger than the N—C═O angle, the difference increasing in magnitude as the ring size decreases. The difference of 3.5° in (1) compares very well to their value of 4.0 (25)°. However, the difference of 1.9 and 3.7° in (2) and (3), respectively, is quite different from the value of −0.1 (21)° obtained by Norskov-Lauritsen, Bürgi, Hoffmann & Schmidt (1985). In particular, the value in (3) is remarkable since the difference increases in magnitude as the ring size increases when compared with (1).

In each of the compounds the lactam carbonyl C atom is planar, the sum of the angles around this atom being 360.0 (6), 360.0 (7) and 360.0 (4)° for (1), (2) and (3), respectively. The N atom in (1) has a more pyramidal geometry than in (2) [sum of the angles around N is 355.4 (5) and 358.4 (6)°, respectively] whereas it can be considered to be planar within the limits of accuracy in (3) [Σ = 359.9 (3)°]. The sum of the angles is in agreement with the distance of the N atom from the least-squares plane defined by the three C atoms bonded to it: 0.171 (3), 0.105 (4) and 0.028 (2) Å for (1), (2)

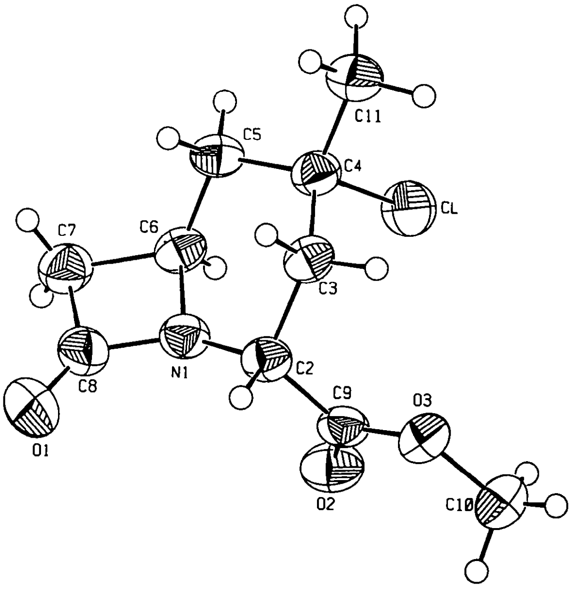


Fig. 1. *ORTEP* diagram showing the molecular structure and atom-numbering scheme of compound (1). Non-H atoms are shown as 50% probability ellipsoids, the H atoms (not labelled) as arbitrary spheres.

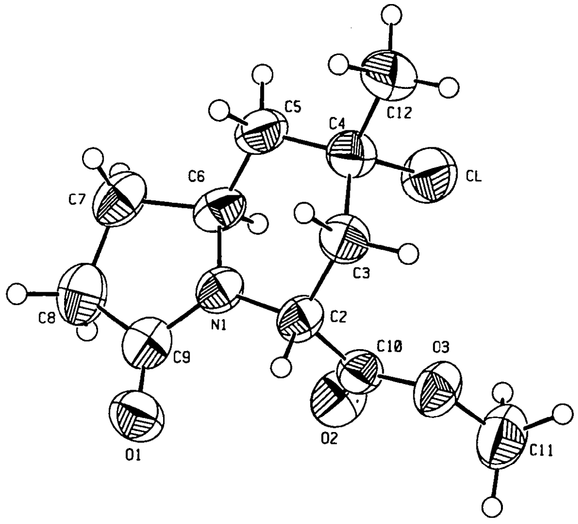


Fig. 2. *ORTEP* diagram showing the molecular structure and atom-numbering scheme of compound (2). Non-H atoms are shown as 50% probability ellipsoids, the H atoms (not labelled) as arbitrary spheres.

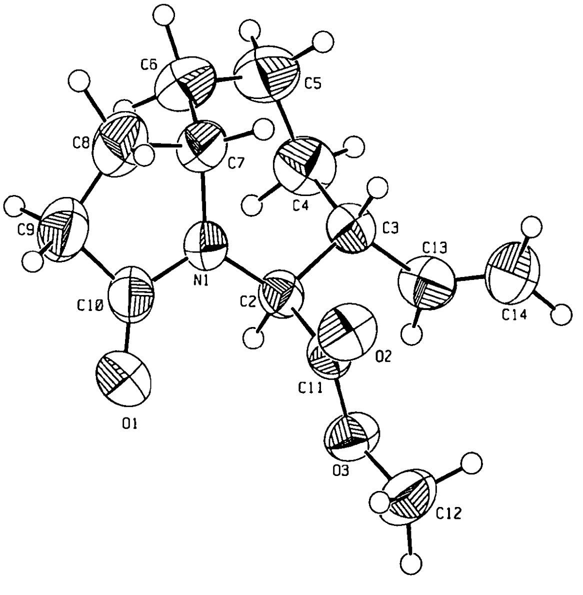


Fig. 3. *ORTEP* diagram showing the molecular structure and atom-numbering scheme of compound (3). Non-H atoms are shown as 50% probability ellipsoids, the H atoms (not labelled) as arbitrary spheres.

and (3), respectively. It may be noted that Page (1984) has reported that pyramidal geometry at the β-lactam N atom is not necessary for antibiotic activity.

In both chlorinated lactams [(1) and (2)] the Cl atom at C4 is axially located, which corroborates the ^{13}C NMR spectra (Esch, Boska, Hiemstra, de Boer & Speckamp, 1991). The methyl ester at C2 is also in an axial position which is in agreement with ^{1}H NMR spectra (Esch, Boska, Hiemstra, de Boer & Speckamp, 1991).

According to Hoffmann (1989) the axial orientation of the α-amino ester function is imposed by the presence of the *N*-carbonyl function, which would cause excessive allylic 1,3-strain in the case of an equatorial ester function. An identical conformation is also found in the structure of the following piperidine compounds having an *N*-carbonyl and an α-amino ester function: the *cis* and *trans* isomers of *N*-[(*tert*-butyloxy)carbonyl]-4-methyl-4-phenylpipecolic acid (Sugg, Griffin & Portoghese, 1985) and 6-phenylcarbamoylpipecolate (Irie, Aoe, Tanaka & Saito, 1985). In (3) both the methyl ester at C2 and the vinyl group at C3 are found in the equatorial position.

The criteria defined by Foces-Foces, Cano & Garciá-Blanco (1976) to determine the conformation of a six-membered ring show an ambiguity in the case of compound (1); the values calculated in Table 7 indicate a conformation between chair and half-chair. According to these authors a six-membered ring adopts a chair conformation when (II) = 2 × (III) and (III) = (IV) but with (I) greater than about 95° and a half-chair conformation when the former two relationships are identical but with (I) less than about 95°. The e.s.d.'s for criterion (I) calculated by Foces-Foces, Cano & Garciá-Blanco (1976) for 15 chair and 11 half-chair conformations were 1 and 2°, respectively, which indicates that the six-membered ring in (1) adopts a half-chair conformation. In order to determine the conformation of this ring in (1), the asymmetry parameters defined by Duax, Weeks & Rohrer (1976) were calculated (Table 8) from which it follows that the six-membered ring adopts an $_{\mathrm{N1}}C^{\mathrm{C4}}$ chair conformation. This conformation is assigned due to the fact that the six-membered ring has six symmetry elements for which the asymmetry parameters are small. The notation $_{\mathrm{N1}}C^{\mathrm{C4}}$ indicates that the degree of departure from ideal chair (denoted by *C*) symmetry is the smallest along N1···C4. Presumably the criteria of Foces-Foces, Cano & Garciá-Blanco (1976) fail due to the strain imposed by the four-membered fused ring. The maximum deviation of an atom from the least-squares plane through the atoms of the four-membered ring in (1) is 0.034 (5) Å for C8. This ring shows a tetrahedral distortion, C7 and N1 being below and C6 and C8 above the least-squares plane. According to the criteria defined by Foces-Foces, Cano & Garciá-Blanco (1976) the six-membered ring in (2) is unambiguously determined as having a chair conformation (Table 7). From the asymmetry parameters (Duax, Weeks & Rohrer, 1976) it follows that the six-membered ring has a $_{\mathrm{C2}}C^{\mathrm{C5}}$ chair conformation (Table 8). The assignment $_{\mathrm{C2}}C^{\mathrm{C5}}$ is based on the same arguments as for (1). A six-membered ring with an ideal chair conformation has torsion angles of ±60°. If the e.s.d. of each torsion angle is assumed to be 0.6°, which is comparable to the observed values in Tables 2 and 4, the e.s.d. of an asymmetry parameter is equal to 0.5°. Taking this value as the e.s.d. of the asymmetry parameters calculated in Table 8, it can be observed that the asymmetry parameters of the six-membered ring in (2) are significantly smaller than in (1). Since the criteria defined by Foces-Foces, Cano & Garciá-Blanco (1976) on the one hand and the asymmetry parameters introduced by Duax, Weeks & Rohrer (1976) on the other hand are both based on endocyclic torsion angles, they are not independent from each other. It can be seen from Table 8 that for high values of the asymmetry parameters, *i.e.* when there is a large deviation from ideal symmetry, the five criteria of Foces-Foces, Cano & Garciá-Blanco (1976) are not able to distinguish the proper conformation.

Following the criteria defined by Altona, Geise & Romers (1968), the five-membered ring in (2) is classified as a half-chair with the twofold axis passing through C9 and the midpoint of the C6—C7 bond ($\varphi_m = -26.6°$, $\Delta = 6.0°$). The Duax, Weeks & Rohrer (1976) asymmetry parameter for this ring is ΔC_2(C6—C7) = 2.4°. The calculation of the same parameters for the five-membered ring in (3) gives the following values: φ_m = 26.0°, Δ = 17.7° and ΔC_s(C8) = 5.1°, from which it follows that this ring has a distorted envelope configuration with the mirror plane going through C8 and the midpoint of the N1—C10 bond.

The seven-membered ring in (3) adopts a distorted chair conformation in which the atoms C3, C4, C6 and C7 form the seat; N1, C2, C3 and C7 form the back and C4, C5 and C6 form the legs of the chair. The mirror plane passes through C5 and the midpoint of the N1—C2 bond. The asymmetry parameter is ΔC_s(N1—C2) = 15.4°.

In the crystal structures of the three compounds there are a number of short intermolecular distances which are summarized in Table 9. In compounds (1) and (2), two or one, respectively, of the O atoms of the carboxylic acid substituent are involved whereas in (3) the methyl ester group is in close contact with the keto O atom of the lactam ring.

Experimental

Compound (2) was grown from hexane/ether solution according to the procedure described by Esch, Boska, Hiemstra, de Boer & Speckamp (1991); compound (1) was prepared following a similar procedure starting from 4-benzoyloxy-2-azetidinone and (2-methyl-2-propenyl)trimethylsilane. Compound (3) was synthesized from 5-[6-trimethylsilyl-4-(*Z*)-hexenyl]-2-pyrrolidinone (Esch, 1991; Esch, Hiemstra, Klaver & Speckamp, 1987) in hexane.

Compound (1)

Crystal data

$C_{10}H_{14}ClNO_3$
$M_r = 231.68$
Monoclinic
$P2_1/c$
$a = 10.456\,(2)$ Å
$b = 12.237\,(2)$ Å
$c = 9.531\,(1)$ Å
$\beta = 111.00\,(1)°$
$V = 1138.5\,(3)$ Å^3
$Z = 4$
$D_x = 1.352$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71069$ Å
Cell parameters from 23 reflections
$\theta = 17.9–20.7°$
$\mu = 0.32$ mm^{-1}
$T = 293$ K
Plate
0.38 × 0.32 × 0.10 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2134 measured reflections
2100 independent reflections
1398 observed reflections
[$I > 2.5\sigma(I)$]

$\theta_{\max} = 24.89°$
$h = -12 \rightarrow 12$
$k = 0 \rightarrow 14$
$l = 0 \rightarrow 11$
2 standard reflections
frequency: 83 min
intensity decay: none

Refinement

Refinement on F
$R = 0.049$
$wR = 0.049$
$S = 0.87$
1397 reflections
137 parameters
H atoms: restrained at 1.00 Å from their carrier atom with $U_{\rm eq} = 0.10$ Å^2
$w = 1/[1.5 + 0.02\sigma(F)^2 + 0.0001/\sigma(F)]$
$(\Delta/\sigma)_{\max} = 0.002$

$\Delta\rho_{\max} = 0.347$ e Å^{-3}
$\Delta\rho_{\min} = -0.302$ e Å^{-3}
Extinction correction: Zachariasen (1967)
Extinction coefficient: 4.4 (3) × 10^{-5}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2*B* and 2.3.1)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (1)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
N1	0.5560 (3)	0.6577 (2)	0.2094 (3)	0.043 (2)
C2	0.6935 (4)	0.6695 (3)	0.2117 (4)	0.042 (2)
C3	0.7666 (3)	0.5575 (3)	0.2473 (4)	0.044 (2)
C4	0.7364 (4)	0.4912 (3)	0.3675 (4)	0.044 (2)
C5	0.5836 (4)	0.4790 (3)	0.3335 (4)	0.046 (2)
C6	0.5135 (4)	0.5894 (3)	0.3129 (4)	0.045 (2)
C7	0.3657 (4)	0.5990 (3)	0.1981 (5)	0.054 (2)
C8	0.4301 (4)	0.6616 (3)	0.0998 (5)	0.049 (2)
C9	0.7690 (4)	0.7615 (3)	0.3178 (4)	0.043 (2)
C10	0.9825 (5)	0.8495 (3)	0.4278 (5)	0.074 (3)
C11	0.8085 (4)	0.3811 (3)	0.3909 (5)	0.062 (2)
O1	0.3897 (3)	0.6994 (3)	−0.0251 (3)	0.067 (2)
O2	0.7165 (3)	0.8257 (2)	0.3750 (3)	0.059 (2)
O3	0.9010 (3)	0.7633 (2)	0.3322 (3)	0.054 (1)
Cl	0.8095 (1)	0.56524 (9)	0.5476 (1)	0.0605 (6)

Table 2. *Selected geometric parameters (Å, °) for (1)*

N1—C2	1.437 (5)	C4—Cl	1.847 (4)
N1—C6	1.478 (5)	C5—C6	1.516 (5)
N1—C8	1.357 (4)	C6—C7	1.545 (5)
C2—C3	1.548 (5)	C7—C8	1.538 (7)
C2—C9	1.529 (5)	C8—O1	1.204 (5)
C3—C4	1.526 (6)	C9—O2	1.196 (5)
C4—C5	1.519 (6)	C9—O3	1.337 (5)
C4—C11	1.521 (5)	C10—O3	1.453 (5)
C2—N1—C6	125.8 (3)	C4—C5—C6	111.3 (3)
C2—N1—C8	134.3 (3)	N1—C6—C5	110.1 (3)
C6—N1—C8	95.3 (3)	N1—C6—C7	87.0 (3)

N1—C2—C3	109.1 (3)	C5—C6—C7	118.3 (3)
N1—C2—C9	111.2 (3)	C6—C7—C8	85.7 (3)
C3—C2—C9	114.2 (3)	N1—C8—C7	91.7 (3)
C2—C3—C4	114.6 (3)	N1—C8—O1	132.4 (4)
C3—C4—C5	112.2 (3)	C7—C8—O1	135.9 (4)
C3—C4—C11	110.8 (4)	C2—C9—O2	124.9 (4)
C3—C4—Cl	108.0 (2)	C2—C9—O3	110.5 (3)
C5—C4—C11	111.9 (3)	O2—C9—O3	124.6 (3)
C5—C4—Cl	107.4 (3)	C9—O3—C10	115.4 (3)
C11—C4—Cl	106.3 (2)		
C6—N1—C2—C3	39.0 (4)	C5—C6—N1—C2	−44.0 (4)
N1—C2—C3—C4	−40.5 (3)	C8—N1—C6—C7	−4.4 (3)
C2—C3—C4—C5	52.2 (4)	N1—C6—C7—C8	3.9 (3)
C3—C4—C5—C6	−55.6 (4)	C6—C7—C8—N1	−4.2 (3)
C4—C5—C6—N1	48.3 (4)	C7—C8—N1—C6	4.4 (3)

Compound (2)

Crystal data

$C_{11}H_{16}ClNO_3$
$M_r = 245.71$
Monoclinic
$P2_1/a$
$a = 9.732\ (2)$ Å
$b = 13.903\ (3)$ Å
$c = 9.116\ (2)$ Å
$\beta = 99.99\ (1)°$
$V = 1214.7\ (5)$ Å^3
$Z = 4$
$D_x = 1.343$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71069$ Å
Cell parameters from 23 reflections
$\theta = 15–19°$
$\mu = 0.30$ mm^{-1}
$T = 293$ K
Plate
0.35 × 0.30 × 0.13 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2257 measured reflections
2221 independent reflections
1172 observed reflections [$I > 2.5\sigma(I)$]

$\theta_{max} = 24.92°$
$h = -11 \rightarrow 11$
$k = 0 \rightarrow 16$
$l = 0 \rightarrow 10$
2 standard reflections frequency: 60 min intensity decay: none

Refinement

Refinement on F
$R = 0.048$
$wR = 0.047$
$S = 0.783$
1172 reflections
146 parameters
H atoms: restrained at 1.00 Å from their carrier atom with $U_{eq} = 0.10$ Å^2
$w = 1/[1.5 + 0.02\sigma(F)^2 + 0.0001/\sigma(F)]$
$(\Delta/\sigma)_{max} = 0.009$

$\Delta\rho_{max} = 0.206$ e Å^{-3}
$\Delta\rho_{min} = -0.252$ e Å^{-3}
Extinction correction: Zachariasen (1967)
Extinction coefficient: 1.1 (2) × 10^{-5}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2*B* and 2.3.1)

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (2)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
N1	0.3242 (3)	0.6502 (3)	−0.0053 (4)	0.044 (2)
C2	0.4149 (4)	0.6742 (3)	0.1334 (5)	0.043 (2)
C3	0.4587 (4)	0.5828 (3)	0.2221 (4)	0.050 (3)
C4	0.3390 (5)	0.5119 (3)	0.2312 (5)	0.054 (3)
C5	0.2532 (5)	0.4934 (3)	0.0770 (5)	0.056 (3)
C6	0.2058 (4)	0.5840 (3)	−0.0078 (5)	0.050 (3)
C7	0.1563 (4)	0.5693 (4)	−0.1758 (5)	0.062 (3)
C8	0.2017 (5)	0.6617 (4)	−0.2459 (5)	0.065 (3)
C9	0.3201 (5)	0.7006 (4)	−0.1328 (5)	0.050 (3)
C10	0.3499 (5)	0.7513 (3)	0.2181 (5)	0.044 (2)
C11	0.3744 (5)	0.8342 (4)	0.4486 (5)	0.081 (4)
C12	0.3968 (5)	0.4190 (3)	0.3105 (5)	0.077 (4)
O1	0.4011 (3)	0.7648 (3)	−0.1514 (3)	0.063 (2)
O2	0.2483 (3)	0.7978 (2)	0.1685 (3)	0.059 (2)
O3	0.4255 (3)	0.7649 (2)	0.3531 (3)	0.058 (2)
Cl	0.2226 (2)	0.5671 (1)	0.3462 (2)	0.0736 (9)

Table 4. *Selected geometric parameters (Å, °) for (2)*

N1—C2	1.450 (5)	C5—C6	1.508 (6)
N1—C6	1.472 (6)	C6—C7	1.537 (7)
N1—C9	1.352 (6)	C7—C8	1.534 (7)
C2—C3	1.526 (6)	C8—C9	1.507 (6)
C2—C10	1.521 (6)	C9—O1	1.222 (6)
C3—C4	1.539 (7)	C10—O2	1.202 (5)
C4—C5	1.527 (6)	C10—O3	1.333 (5)
C4—C12	1.537 (7)	C11—O3	1.444 (6)
C4—Cl	1.840 (5)		
C2—N1—C6	120.9 (3)	C4—C5—C6	113.6 (4)
C2—N1—C9	123.6 (4)	N1—C6—C5	110.2 (3)
C6—N1—C9	113.9 (3)	N1—C6—C7	102.0 (4)
N1—C2—C3	110.0 (3)	C5—C6—C7	114.5 (4)
N1—C2—C10	111.2 (3)	C6—C7—C8	103.9 (4)
C3—C2—C10	114.8 (4)	C7—C8—C9	104.9 (4)
C2—C3—C4	114.7 (3)	N1—C9—C8	107.9 (4)
C3—C4—C5	110.9 (4)	N1—C9—O1	125.1 (4)
C3—C4—C12	110.2 (4)	C8—C9—O1	127.0 (4)
C3—C4—Cl	108.0 (3)	C2—C10—O2	125.1 (4)
C5—C4—C12	112.9 (4)	C2—C10—O3	110.9 (4)
C5—C4—Cl	107.6 (3)	O2—C10—O3	123.9 (4)
C12—C4—Cl	107.1 (3)	C10—O3—C11	117.3 (3)
C6—N1—C2—C3	47.7 (5)	C9—N1—C6—C7	22.1 (5)
N1—C2—C3—C4	−45.8 (5)	N1—C6—C7—C8	−26.6 (4)
C2—C3—C4—C5	49.2 (5)	C6—C7—C8—C9	23.3 (5)
C3—C4—C5—C6	−51.0 (5)	C7—C8—C9—N1	−10.6 (5)
C4—C5—C6—N1	49.4 (5)	C8—C9—N1—C6	−7.5 (5)
C5—C6—N1—C2	−50.0 (5)		

Compound (3)

Crystal data

$C_{13}H_{19}NO_3$
$M_r = 237.28$
Monoclinic
$P2_1/n$
$a = 10.5793\ (5)$ Å
$b = 13.5240\ (8)$ Å
$c = 10.4365\ (6)$ Å
$\beta = 118.305\ (5)°$
$V = 1314.7\ (1)$ Å^3
$Z = 4$
$D_x = 1.199$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 23 reflections
$\theta = 36.5–47.0°$
$\mu = 0.65$ mm^{-1}
$T = 293$ K
Block
0.50 × 0.30 × 0.15 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2634 measured reflections
2596 independent reflections
1937 observed reflections [$I > 2.5\sigma(I)$]

$\theta_{max} = 69.81°$
$h = -11 \rightarrow 12$
$k = -5 \rightarrow 16$
$l = -9 \rightarrow 12$
2 standard reflections frequency: 83 min intensity decay: 5.4%

Refinement

Refinement on F
$R = 0.047$
$wR = 0.042$
$S = 0.643$
1933 reflections
155 parameters
H atoms: restrained at 1.00 Å from their carrier atom with $U_{eq} = 0.10$ Å^2
$w = 1/[0.75 + 0.01\sigma(F)^2 + 0.0001/\sigma(F)]$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.217$ e Å^{-3}
$\Delta\rho_{min} = -0.171$ e Å^{-3}
Extinction correction: Zachariasen (1967)
Extinction coefficient: $6.7\ (3) \times 10^{-6}$
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2*B* and 2.3.1)

Table 5. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (3)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
N1	0.2351 (2)	0.6031 (1)	0.5360 (2)	0.0510 (9)
C2	0.2827 (2)	0.5047 (2)	0.5960 (2)	0.045 (1)
C3	0.2529 (2)	0.4262 (2)	0.4781 (2)	0.049 (1)
C4	0.0906 (3)	0.4202 (2)	0.3685 (3)	0.071 (1)
C5	0.0435 (3)	0.4894 (3)	0.2388 (3)	0.086 (2)
C6	0.0502 (3)	0.5988 (2)	0.2740 (3)	0.083 (2)
C7	0.1971 (3)	0.6366 (2)	0.3877 (2)	0.061 (1)
C8	0.2004 (3)	0.7505 (2)	0.4060 (3)	0.085 (2)
C9	0.1778 (3)	0.7687 (2)	0.5364 (3)	0.080 (2)
C10	0.2312 (3)	0.6752 (2)	0.6236 (3)	0.062 (1)
C11	0.4418 (2)	0.5068 (2)	0.7031 (2)	0.045 (1)
C12	0.6215 (3)	0.4396 (2)	0.9217 (3)	0.079 (2)
C13	0.3077 (3)	0.3267 (2)	0.5479 (2)	0.061 (1)
C14	0.4044 (4)	0.2770 (2)	0.5327 (3)	0.082 (2)
O1	0.2652 (2)	0.6629 (1)	0.7520 (2)	0.087 (1)
O2	0.5299 (2)	0.5499 (1)	0.6832 (2)	0.0625 (9)
O3	0.4716 (2)	0.4521 (1)	0.8197 (2)	0.0578 (8)

Table 6. *Selected geometric parameters (Å, °) for (3)*

N1—C2	1.455 (3)	C6—C7	1.528 (3)
N1—C7	1.474 (3)	C7—C8	1.551 (4)
N1—C10	1.351 (3)	C8—C9	1.510 (5)
C2—C3	1.540 (3)	C9—C10	1.502 (4)
C2—C11	1.516 (3)	C10—O1	1.223 (3)
C3—C4	1.550 (3)	C11—O2	1.198 (3)
C3—C13	1.509 (3)	C11—O3	1.329 (3)
C4—C5	1.522 (4)	C12—O3	1.441 (3)
C5—C6	1.518 (5)	C13—C14	1.295 (5)
C2—N1—C7	126.8 (2)	N1—C7—C8	101.4 (2)
C2—N1—C10	119.0 (2)	C6—C7—C8	112.5 (2)
C7—N1—C10	114.1 (2)	C7—C8—C9	105.6 (3)
N1—C2—C3	112.9 (2)	C8—C9—C10	103.6 (2)
N1—C2—C11	109.7 (2)	N1—C10—C9	108.7 (2)
C3—C2—C11	109.7 (2)	N1—C10—O1	123.8 (2)
C2—C3—C4	111.2 (2)	C9—C10—O1	127.5 (3)
C2—C3—C13	110.1 (2)	C2—C11—O2	124.4 (2)
C4—C3—C13	110.3 (2)	C2—C11—O3	111.3 (2)
C3—C4—C5	113.9 (2)	O2—C11—O3	124.3 (2)
C4—C5—C6	115.3 (2)	C3—C13—C14	123.3 (3)
C5—C6—C7	115.3 (2)	C11—O3—C12	116.3 (2)
N1—C7—C6	112.5 (2)		
C7—N1—C2—C3	−15.6 (3)	C6—C7—N1—C2	75.6 (3)
N1—C2—C3—C4	−58.6 (3)	C10—N1—C7—C8	12.1 (3)
C2—C3—C4—C5	89.7 (3)	N1—C7—C8—C9	−23.0 (3)
C3—C4—C5—C6	−67.9 (4)	C7—C8—C9—C10	25.7 (3)
C4—C5—C6—C7	56.5 (4)	C8—C9—C10—N1	−18.8 (3)
C5—C6—C7—N1	−72.5 (4)	C9—C10—N1—C7	4.0 (3)

Table 7. *Criteria of Foces-Foces, Cano & Garciá-Blanco (1976) for determination of conformation (°) in the six-membered rings of (1) and (2)*

Criterion	(1)	(2)
(I) = $\langle\lvert\varphi_i-\varphi_{i+3}\rvert\rangle$	93.2	97.7
(II) = $\sum\lvert\varphi_i-\varphi_{i+1}\rvert$	559.2	586.2
(III) = $\sum\lvert\varphi_i\rvert$	279.6	293.1
(IV) = $\sum\lvert\varphi_i-\varphi_{i+3}\rvert$	279.6	293.1
(V) = $\sum\lvert(\lvert\varphi_i\rvert-\lvert\varphi_{i+1}\rvert)\rvert$	33.2	11.6

φ_i denote the endocyclic torsion angles (i = 1–6).

Table 8. *Asymmetry parameters (°) of Duax, Weeks & Rohrer (1976) for (1) and (2)*

$$\Delta C_s = \left[\frac{\sum_{i=1}^{3}(\varphi_i + \varphi_i')^2}{3}\right]^{1/2} \qquad \Delta C_2 = \left[\frac{\sum_{i=1}^{2}(\varphi_i - \varphi_i')^2}{2}\right]^{1/2}$$

	ΔC_s	ΔC_2
Compound (1)		
	5.7 (N1)	3.7 (N1—C2)
	6.4 (C2)	12.4 (C2—C3)
	12.0 (C3)	12.5 (C3—C4)
Compound (2)		
	2.7 (N1)	3.0 (N1—C2)
	1.5 (C2)	1.3 (C2—C3)
	2.8 (C3)	3.9 (C3—C4)

φ_i and φ_i' denote the symmetry-related endocyclic torsion angles (°).

Table 9. *Close intermolecular contacts (Å) for the title compounds*

(1)		(3)	
C2···O2^{i}	3.304 (5)	C12···O1^{iv}	3.329 (3)
O3···Cl^{ii}	3.289 (3)		
(2)			
C2···O2^{iii}	3.229 (5)		

Symmetry codes: (i) $x, \frac{3}{2} - y, -\frac{1}{2} + z$; (ii) $x, \frac{3}{2} - y, \frac{1}{2} + z$; (iii) $\frac{1}{2} + x, \frac{3}{2} - y, z$; (iv) $1 - x, 1 - y, 2 - z$.

Crystals of the title compounds are weakly diffracting. For all three compounds the non-H atoms were found in the E maps. The H-atom positions were calculated on the basis of standard geometry and kept fixed in the structure-factor calculations.

For all compounds, data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *LATCON* (local program). Data reduction: *Xtal SORTRF*, *ADDREF* (Hall & Stewart, 1990) for (1); *Xtal ADDREF* for (2) and (3). For all compounds, program(s) used to solve structures: *Xtal SIMPEL*; program(s) used to refine structures: *Xtal CRYLSQ*; molecular graphics: *Xtal ORTEP*; software used to prepare material for publication: *Xtal BONDLA*, *CIFIO*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: JZ1068). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Oxyacanthine

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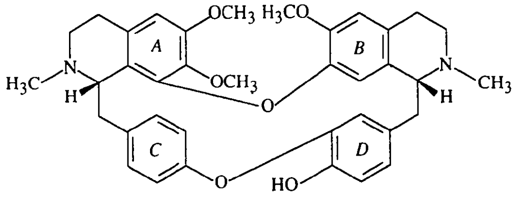
Abstract

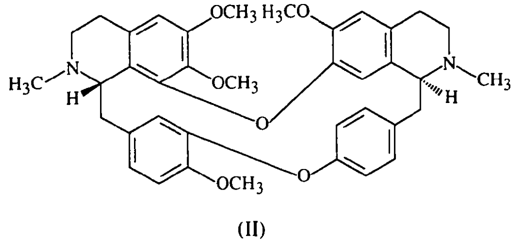
The crystal structure of the title compound (IUPAC name: 6,6′,7-trimethoxy-2,2′-dimethyloxyacanthan-12′-ol), $C_{37}H_{40}N_2O_6$, consists of helical chains, the principal intrachain interaction being hydrogen bonding between the hydroxyl group and one of the amine N atoms. The molecular structure is analysed in detail and results are compared with those reported previously for structurally related tetrandrine. One heterocycle of the molecule assumes a half-boat conformation while the other exists in a conformation intermediate between a half-boat and a half-chair. By analogy with tetrandrine, one amine N atom is predicted to have unrestricted access to its lone pair, whereas the other should display reduced reactivity in reactions dependent on accessibility to a lone pair.

Comment

Oxyacanthine, (I), is a representative member of a subgroup of bisbenzyltetrahydroisoquinoline (BBTI) alkaloids in which the two benzyltetrahydroisoquinoline units are linked by two ether bridges in a head-to-head, tail-to-tail fashion. Interest in BBTI alkaloids stems from their widespread occurrence and their broad spectrum of biological activities, vasodilatory (and hence antihypertensive) activity being one of the most important. For structurally related tetrandrine, (II), which differs from (I) in the mode of ether linkage in the benzyl portion of the molecule and in the configuration at one of the two chiral C atoms, it has been reported (King *et al.*, 1988) that its vasodilator effect results from direct interaction at the diltiazem binding site on voltage-operated Ca^{2+} channels. In another study, some oxyacanthine subgroup alkaloids (*e.g.* aromoline, cepharanthine) have also been reported to relax vascular smooth muscle (Kamiya, Sugimoto & Yamada, 1993) and the mechanism of this activity is likely to be similar to that of tetrandrine. Consequently, the conformational rigidity of (I) and (II), imposed by two ether bridges, makes these molecules useful probes for modelling of the diltiazem binding site. Since accurate structural and conformational information is indispensable for performing such studies and since (II) is the only head-to-head BBTI alkaloid so far studied by X-ray crystallography (Gilmore, Bryan & Kupchan, 1976), we report herein on the crystal structure of (I).



(I)



(II)

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