

The packing of the molecules is shown in Fig. 2. This is a stereoview looking down the *b* axis. There is no unusual intermolecular distance in this structure.

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Calpurmenin and its 13 α -(2'-Pyrrolicarboxylic Acid) Ester

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Abstract

Calpurmenin and its 13 α -(2'-pyrrolicarboxylic acid) ester, C₂₀H₂₇N₃O₄, are alkaloids with a sparteine molecular framework, isolated from the South African *Leguminosa*, *Calpurnia aurea*. Crystals of the ester compound are orthorhombic with space group *P*2₁2₁2₁ and *Z* = 4. The lattice dimensions are *a* = 8.128 (4), *b* = 12.423 (3) and *c* = 18.467 (5) Å. The structure was solved with direct methods and refined with least squares using 1339 reflexions of which 805 had intensities with *I* > 2 σ (*I*). The keto oxygen atom is bound to C(2), the hydroxyl group is bound to C(12) in a β axial orientation, the ester moiety is bound to C(13) in an axial orientation. Ring *A* is a distorted sofa, rings *B* and *D* are slightly distorted chairs, while ring *C* has a nearly ideal boat conformation.

Introduction

During our research into the alkaloids of Ethiopian and South African *Leguminosae*, *inter alia* *Calpurnia*

aurea, we discovered in the South African *Calpurnia* two hitherto unknown alkaloids, which were not observed in the Ethiopian material (van Eijk & Radema, 1977). Thin-layer chromatography and column chromatography were employed to isolate these alkaloids. Mass spectroscopy (MS) showed one of them to be a pyrrolicarboxylic acid ester of the other compound (named calpurmenin); their molecular weights were 373 and 280, respectively (Radema, van Eijk, Vermin, de Kok & Romers, 1979). As was to be expected, MS proved these compounds to contain the sparteine skeleton with four six-membered fused rings *A*, *B*, *C* and *D* (see Fig. 1*a*). Furthermore, MS indicated that the keto oxygen atom is located either at C(2) in ring *A*, or at C(10) in ring *B*, while one hydroxyl group (or its corresponding ester moiety) is bound to C(13). According to MS and IR spectra the second hydroxyl group should be bound to C(12), C(11), C(15) or to C(17).

In the molecular framework of sparteine and its diastereoisomers, ring *C* (or *B*) can adopt either the chair or the boat conformation. The former occurs in α -

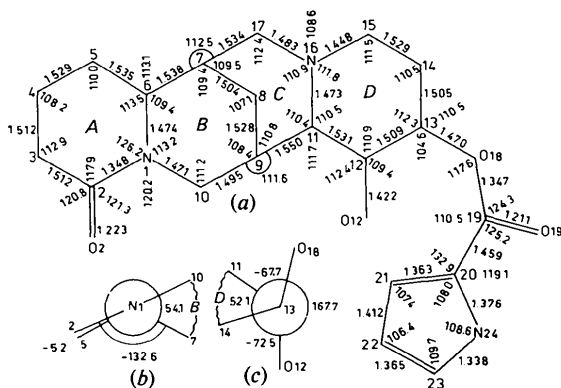


Fig. 1. (a) Bond lengths and angles for (I). (b) Conformation about N(1). (c) Conformation about C(13). E.s.d.'s are 0.007, 0.006 and 0.005 Å for C–C, C–N and C–O bond lengths respectively and 0.2° for valency angles.

isosparteine (Przybylska & Barnes, 1953), 7-hydroxy- β -isosparteine (Pinkerton & Steinrauf, 1967), β -isosparteine copper chloride (Childers, Foltz, Merritt & Streib, 1975) and sparteine *N*(16)-oxide (Srivastava & Przybylska, 1969); the latter exists in the lupin alkaloids lupanine *N*(16)-oxide (compound II: Kałuski, Gusiev, Struchkov, Skolik, Baranowski & Wiewiórowski, 1972), (+)-lupanine hydrochloride dihydrate (compound III: Skrzypczak-Jankun & Kałuski, 1978) and (\pm)-lupanine (compound IV: Doucerain, Chiaroni & Riche, 1976).

The purpose of the present investigation is the structure determination of the 13-(2'-pyrrolocarboxylic acid) ester of calpurmenin (hereafter I) by X-ray diffraction in order to establish the position and orientation of the substituents and to determine the overall shape of the molecular framework. It turns out that ring C has a nearly ideal boat conformation, which offers the opportunity to compare the geometries of compounds (I), (II), (III) and (IV). The numbering of atoms of (I) (disregarding hydrogen) is indicated in Fig. 1.

Experimental

The alkaloid (I) with molecular composition $C_{20}H_{27}N_3O_4$ was crystallized repeatedly. The compound was dissolved in a weakly acidified mixture of methanol/acetic acid (0.3%). By dropping a mixture of CH_2Cl_2 /EtOEt (1:1) into the solution up to slight turbidity, crystallization set in after 1 h. The cluster of very small crystals contained one fragment with dimensions 0.45 \times 0.15 \times 0.08 mm. This fragment proved to be a single crystal and was used during all diffraction measurements on a Nonius CAD-4 diffractometer.

The unit cell is orthorhombic with space group $P2_12_12_1$ and the lattice dimensions are $a = 8.128$ (4), $b = 12.423$ (3) and $c = 18.467$ (5) Å. Assuming a density $d_x = 1.33$ Mg m $^{-3}$, the unit cell contains four molecules of (I).

The reflexion intensities were measured with the ω scanning mode in the range between $\theta = 2$ and $\theta = 22^\circ$, employing graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.71069$ Å). A total of 1339 symmetry-independent reflexions were measured of which 805 had intensities with $I > 2\sigma(I)$. At time intervals, repeated measurements of standard reflexions were used to correct for loss of scattering power of the crystal during the total exposure. No absorption correction was applied.

Structure determination and refinement

In order to unravel the structure with direct methods, use was made of the new version of the multiple solution program package *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1979). Since the number of reflexions available was rather small, we added chemical information to the program part *NORMAL* in order to allow for a better normalization of structure factors, an improved weighting scheme and a proper convergence in the subsequent tangent refinement. The additional information consisted of the occurrence of a cyclohexane and a pyrrole ring, both moieties being assumed in random orientation. The solution with the best combined figure of merit produced all heavy atoms derived from the positions of the 27 highest peaks in the *E* Fourier map. It is interesting to note that without chemical information the program failed to find a proper solution. The carbonyl oxygen atom is bound to C(2), the hydroxyl atom O(12) is bound to C(12) and ring C occurs in a boat conformation. Apparently, alkaloid (I) and calpurmenin belong to the family of lupanine derivatives.

The structural parameters were improved with a block-diagonal (3 \times 3 + 6 \times 6 blocks) least-squares refinement. The scattering factors of the heavy atoms were taken from *International Tables for X-ray Crystallography* (1974) and those of H from Stewart, Davidson & Simpson (1965). The H atoms were introduced at fixed calculated positions and only their isotropic temperature factors were refined. During the final cycles, the matrix of normal equations was divided into three blocks and the non-significant reflexions [$I < 2\sigma(I)$] were taken into account. The first block contained the pyrrolocarboxylate moiety, the second contained ring A, C(7) and C(10), and the third the remaining atoms.* Based on the expressions for anisotropic temperature factors and definitions of reliability indices in de Graaff, Martens & Romers (1978), the final weighted and unweighted indices are $R_w = 2.6$ and

* The weights used during the refinement were $\sigma^{-2}[F(hkl)]$, where σ is the standard deviation as derived from the instrument-measured reflexions.

$R = 10.0\%$ for all reflexions* and $R_w = 2.5$ and $R = 3.3\%$ for significant reflexions only.

Molecular geometry

The positional parameters of the heavy atoms are listed in Table 1. The mean e.s.d.'s are 0.0044, 0.0034 and 0.0030 Å for C, N and O, respectively. Neglecting errors in cell constants and, tentatively, taking into account a 10% underestimation due to the refinement

* Tables of hydrogen positions, thermal parameters of heavy atoms and observed and calculated structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34404 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Fractional coordinates ($\times 10^4$) of the heavy atoms

E.s.d.'s referring to the last digit are given in parentheses.

| | x | y | z |
|-------|-----------|-----------|----------|
| C(2) | 5174 (6) | -291 (4) | 4763 (3) |
| C(3) | 6118 (5) | 312 (4) | 4186 (3) |
| C(4) | 5771 (6) | -99 (4) | 3431 (3) |
| C(5) | 3914 (5) | -44 (4) | 3302 (2) |
| C(6) | 3016 (5) | -779 (3) | 3842 (2) |
| C(7) | 1171 (5) | -522 (3) | 3908 (2) |
| C(8) | 362 (5) | -1349 (4) | 4386 (2) |
| C(9) | 1138 (5) | -1245 (3) | 5136 (2) |
| C(10) | 2926 (5) | -1513 (3) | 5077 (2) |
| C(11) | 871 (5) | -98 (3) | 5446 (2) |
| C(12) | -43 (5) | -126 (3) | 6170 (2) |
| C(13) | -351 (5) | 998 (4) | 6448 (2) |
| C(14) | -1170 (5) | 1704 (4) | 5892 (2) |
| C(15) | -221 (5) | 1670 (3) | 5178 (2) |
| C(17) | 853 (5) | 607 (4) | 4215 (2) |
| C(19) | 1389 (6) | 2201 (4) | 7128 (2) |
| C(20) | 3105 (5) | 2465 (4) | 7278 (2) |
| C(21) | 4558 (6) | 2061 (4) | 7030 (2) |
| C(22) | 5835 (5) | 2619 (4) | 7387 (3) |
| C(23) | 5091 (6) | 3340 (4) | 7838 (2) |
| N(1) | 3767 (4) | -778 (3) | 4568 (2) |
| N(16) | -21 (4) | 577 (3) | 4920 (2) |
| N(24) | 3456 (4) | 3245 (3) | 7785 (2) |
| O(2) | 5672 (4) | -321 (3) | 5388 (2) |
| O(12) | -1562 (3) | -691 (2) | 6125 (1) |
| O(18) | 1292 (3) | 1415 (2) | 6627 (1) |
| O(19) | 212 (4) | 2608 (3) | 7422 (2) |

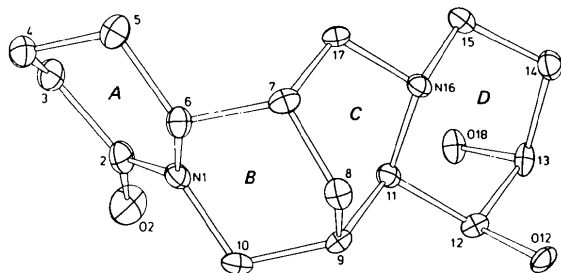


Fig. 2. An ORTEP (Johnson, 1965) projection of (I).

with three blocks we arrive at e.s.d.'s of 0.007, 0.006 and 0.005 Å for C—C, C—N and C—O bond lengths respectively. The e.s.d.'s of valency and dihedral angles are about 0.2 and 0.3° respectively. The geometry of (I) is depicted in Fig. 1. The overall molecular shape (omitting H atoms and the pyrrolocarboxylate group) is shown in an ORTEP projection (Johnson, 1965) in Fig. 2.

The observed bond lengths and valency angles (see Fig. 1) hardly need comment. The short bond distance N(1)—C(2) (1.348 Å) is indicative of a partial double-bond character of this link (see below). The pyrrolocarboxylate moiety, including O(18), is planar within 0.02 Å. The skeleton is A shaped (see Fig. 2) with bridge atoms C(7), C(8) and C(9) at the top of the molecule. Fig. 2 shows that rings C and D are *trans* fused. It also demonstrates that hydroxyl atoms O(12) and O(18) are bonded in an axial orientation to C(12) and C(13). Following IUPAC rules (IUPAC Inf. Bull. *Appnd. Tentative Nomencl. Symb. Units Stand.* 1976), the name of (I) is 12 β -hydroxy-13 α -(2'-pyrrolyl-carboxyloxy)lupanine.

The endocyclic torsion angles of the rings A, B, C and D are collected in Table 2 for compounds (I), (II),

Table 2. Selected dihedral angles (°) of the title compound (I), lupanine N-oxide (II), (+)-lupanine-HCl.2H₂O (III) and (±)-lupanine (IV)

E.s.d.'s are approximately 0.3°.

| Ring A | (I) | (II) | (III) | (IV) |
|-------------------------|-------|------|-------|------|
| N(1)—C(2)—C(3)—C(4) | -24.4 | -15 | -23.9 | -34 |
| C(2)—C(3)—C(4)—C(5) | 55.9 | 47 | 54.4 | 56 |
| C(3)—C(4)—C(5)—C(6) | -62.2 | -66 | -62.1 | -60 |
| C(4)—C(5)—C(6)—N(1) | 37.2 | 49 | 38.8 | 40 |
| C(5)—C(6)—N(1)—C(2) | -5.2 | -20 | -8.1 | -18 |
| C(6)—N(1)—C(2)—C(3) | -1.8 | 3 | 0.2 | 15 |
| Ring B | | | | |
| N(1)—C(6)—C(7)—C(8) | -58.2 | -60 | -58.4 | -59 |
| C(6)—C(7)—C(8)—C(9) | 63.0 | 67 | 64.5 | 63 |
| C(7)—C(8)—C(9)—C(10) | -63.3 | -65 | -64.1 | -61 |
| C(8)—C(9)—C(10)—N(1) | 59.3 | 59 | 59.3 | 57 |
| C(9)—C(10)—N(1)—C(6) | -55.9 | -55 | -56.1 | -53 |
| C(10)—N(1)—C(6)—C(7) | 54.1 | 54 | 55.4 | 54 |
| Ring C | | | | |
| C(9)—C(8)—C(7)—C(17) | -60.7 | -62 | -60.0 | -60 |
| C(8)—C(7)—C(17)—N(16) | -5.0 | 12 | 6.7 | 1 |
| C(7)—C(17)—N(16)—C(11) | 55.0 | 48 | 51.4 | 58 |
| C(17)—N(16)—C(11)—C(9) | -55.8 | -56 | -53.1 | -55 |
| N(16)—C(11)—C(9)—C(8) | -1.4 | 4 | -3.5 | -6 |
| C(11)—C(9)—C(8)—C(7) | 59.5 | 53 | 58.4 | 63 |
| Ring D | | | | |
| C(11)—N(16)—C(15)—C(14) | -59.3 | -56 | -58.8 | -61 |
| N(16)—C(15)—C(14)—C(13) | 55.0 | 54 | 56.1 | 58 |
| C(15)—C(14)—C(13)—C(12) | -51.8 | -54 | -53.7 | -54 |
| C(14)—C(13)—C(12)—C(11) | 52.1 | 56 | 55.7 | 54 |
| C(13)—C(12)—C(11)—N(16) | -54.5 | -60 | -58.3 | -56 |
| C(12)—C(11)—N(16)—C(15) | 58.8 | 59 | 59.1 | 59 |

(III) and (IV). The dihedral angles of ring *A* (see also Fig. 2) indicate that this ring adopts in (I) a sofa conformation with C(4) outside the plane of C(5), C(6), N(1), C(2), C(3) and O(2). Rings *B* and *D* constitute normal, slightly distorted chairs, but ring *C* occurs in a nearly ideal boat conformation with symmetry C_{2v} .

Although flexible sofas and half chairs frequently occur in 3-oxo- Δ^4 steroids (Romers, Altona, Jacobs & de Graaff, 1974), it is surprising that these forms are also observed for lupanine alkaloids. The listed torsion angles for ring *A* indicate that (I), (III) and (IV) are *S*(4) sofas with C(4) *above* (mean value 0.57 Å) the planar part of the *A* ring, whereas (II) is more or less a half chair with C(4) *above* (0.33 Å) and C(5) *below* (−0.44 Å) the planar moiety. The observed differences for the corresponding *A* ring dihedral angles in (I), (III) and (IV) demonstrate that the sofa form in lupanines is also flexible. Some flexibility also exists in ring *C*. Inspection of Table 2 reveals small but nevertheless significant variations in its torsion angles. Following the characterization proposed by Buys & Geise (1968) and counting clockwise $\phi_0 = (7-17-16-11)$, $\phi_1 = (17-16-11-9)$... $\phi_5 = (8-7-17-16)$, one calculates pseudorotation phase angles of 28.4, 37.4, 30.8 and 27.8° for (I), (II), (III) and (IV), respectively.

Pyramidal atomic inversion of nitrogen in piperazines (McKenna, 1970; Lambert, 1971) and the planar coordination of nitrogen in trisilylamine (Beagley & Conrad, 1970) and in tetrasilylhydrazine (Glidewell, Rankin, Robiette & Sheldrick, 1970) are experimental evidence that, notwithstanding the presence of a lone electron pair, this element is able to adopt a planar or nearly planar hybridization. In compound (I), N(1) is only 0.046 Å outside the plane of its neighbours C(2), C(6) and C(10) and exists in a nearly planar trigonal configuration. Presumably the planar coordination is enhanced by some π bonding in the short bond between N(1) and C(2), thus imposing planarity on the fragment containing C(3), C(2), O(2), N(1), C(6) and C(10) and, consequently, inducing the sofa conformation in ring *A*.

Since the *all-chair* conformation prevails in sparteine and its diastereoisomers it is puzzling why the boat conformation of ring *C* occurs in the quoted lupanine derivatives. Although Dreyding models give indication of severe steric hindrance for (I) with ring *C* in the chair conformation, force-field calculations might give a better insight before definite conclusions can be drawn.

Within an upper limit of 3.9 Å, each molecule is surrounded by twelve neighbours at positions $\pm 1 + x$, y , z ; $-\frac{1}{2} + x$, $\pm\frac{1}{2} - y$, $1 - z$; $-x$, $\pm\frac{1}{2} + y$, $\frac{1}{2} - z$; $\frac{1}{2} + x$, $\pm\frac{1}{2} - y$, $1 - z$; $\frac{1}{2} - x$, $-y$, $\pm\frac{1}{2} + z$ and $1 - x$, $\pm\frac{1}{2} + y$, $\frac{1}{2} - z$. The stacking is governed by hydrogen bridges of the type O(12)—H...O(2) and N(24)—H...O(12) with

length 2.668 and 2.858 Å, respectively. The molecule at position x, y, z donates hydrogen in the bonds O(12)—H...O(2) and N(24)—H...O(12) to molecules at positions $1 + x$, y , z and $1 - x$, $\frac{1}{2} + y$, $\frac{1}{2} - z$; it accepts hydrogen in the bonds O(2)...H—O(12) and O(12)...H—N(24) from molecules at $-1 + x$, y , z and $1 - x$, $\frac{1}{2} + y$, $\frac{1}{2} - z$.

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