Virgidivarine, a Sparteine-Type Alkaloid

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Abstract

Virgidivarine, $C_{15}H_{26}N_2O_2$, is an alkaloid isolated from the African *Leguminosa Virgilia divaricata*. Its systematic name is 1-(3-butenyl)-5-(2-piperidyl)-3-piperidinecarboxylic acid. The crystals are tetragonal, $a = 8.339$ (2), $c = 43.537$ (5) Å and $Z = 8$. The space group is $P4_12_12$ or $P4_32_12$. The structure was solved by direct methods and refined by full-matrix least squares using 875 diffractometer-collected reflexions (Mo $K\alpha$ radiation) with $I > 2\sigma(I)$, resulting in $R(R_w) = 4.27$ (4.38)%. The molecule contains two piperidine rings connected by the bond C(5)–C(2'). The first ring contains a butenyl group at N(1) and a carboxyl group at C(3). Difference Fourier maps as well as the packing reveal that the molecule is a zwitterion with a COO⁻ and an NH₂⁺ group. Two N–H···O hydrogen bonds [2.685 (5) and 2.740 (5) Å] connect the zwitterion with neighbouring molecules.

Introduction

South African samples of *Leguminosae*, among others *Calpurnia aurea* (van Eijk & Radema, 1977; Radema, van Ejik, Vermin, de Kok & Romers, 1979), contain, among others the alkaloids calpurmenin and its 13α-(2-pyrrolecarboxylic acid) ester. The molecular and crystal structure of the latter was determined by Vermin, de Kok, Romers, Radema & van Eijk (1979). Another African plant, *Virgilia divaricata*, contains as the main alkaloid virgidivarine and some hitherto unknown polar alkaloids related to calpurmenin (see Vermin *et al.*, 1979, and literature cited therein).

Mass spectroscopy and IR spectroscopy suggest a sparteine-like structure with, however, open *B* and *D* rings (see Fig. 1) and the presence of a carboxylic and an HC=CH function, the latter presumably as a butenyl group. The details of the chemical analysis will be published elsewhere (van Eijk, 1982). So far only 25 mg of the new compound has been isolated and it was

not possible to determine physical constants and to verify pharmacological or toxicological properties. To our knowledge there are four more dipiperidine alkaloids, *e.g.* hystrine, adenocarpine, ammodendrine and santiaguine (Harnborne, Boulter & Turner, 1971); however, the link between the sparteine skeleton and the double piperidine system is only evident for virgidivarine. The numbering of atoms of the title compound and its relation with the sparteine ring system is indicated in Fig. 1.

Experimental

The alkaloid with composition $C_{15}H_{26}N_2O_2$ was dissolved in methanol and crystallized on careful mixing with ether. The diffraction experiments were carried out with one specimen with dimensions $0.45 \times 0.4 \times 0.18$ mm, isolated from an extremely small amount of cauliflower-like crystals. No density was measured.

The diffraction pattern was indexed in the tetragonal system. The lattice constants are $a = 8.339$ (2) Å and $c = 43.537$ (5) Å. Reflexions 00*l* and *h*00 are absent for $l \neq 4n$ and $h \neq 2n$, therefore, the space group must be $P4_12_12$ or $P4_32_12$. Mass spectroscopic experiments
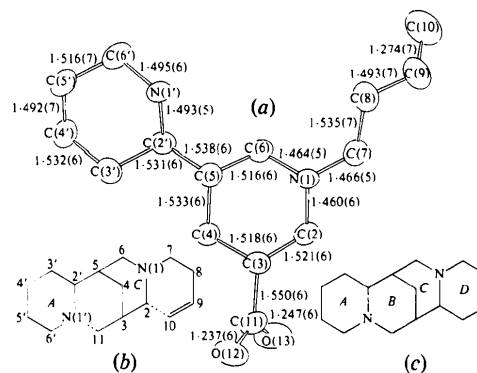

Fig. 1. (*a*) Numbering of atoms of virgidivarine, (*b*) the rearrangement of the molecular framework in comparison with (*c*) the ring system of sparteine.

indicate that the largest fragment has a molecular weight of 266. Assuming $d_x = 1.169$ Mg m^{-3} the unit cell contains eight molecules.

The reflexion data were collected with a CAD-4 diffractometer employing graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.71069$ Å) in the range $2° < \theta < 23°$. The c axis being relatively large, particular care was necessary to avoid overlap of neighbouring reflexions in the direction $\mathbf{c}^*$. A total of 1370 symmetry-independent reflexions were measured of which 875 had $I > 2\sigma(I)$. Standard reflexions 045, 405 and $3\bar{4}0$ were repeatedly measured in order to correct for loss of scattering power by the crystal during exposure. No absorption correction was applied.

were refined in the normal way. The heavy atoms were refined anisotropically. The scattering factors of all atoms were taken from *International Tables for X-ray Crystallography* (1974). The weighting scheme used was $w = 1/\sigma^2(F)$. Discrepancy indices are defined as $R = \sum |\Delta F|/\sum |F_o|$ and $R_w = [\sum w(\Delta F)^2/\sum wF_o^2]^{1/2}$. After five cycles of full-matrix least-squares refinement, the indices $R(R_w)$ converged to 4·27 (4·38)%. The positional parameters and their e.s.d.'s are tabulated in Table 1.*

All calculations were carried out on the Leiden University AMDAHL computer using computer programs written or modified by Mrs E. W. Rutten-Keulemans and Dr R. A. G. de Graaff.

Structure determination and refinement

The structure was solved in a straightforward way using the direct-methods package *MULTAN* 78 (Main, 1978).

With one exception all heavy atoms were found. The missing atom C(10) was located in a difference Fourier map. With the exception of H(N1'1) and H(N1'2), H atoms were introduced at calculated positions. To these H atoms were given the shifts, $\Delta x, \Delta y, \Delta z$, of the parent C atoms, but their isotropic Debye–Waller temperature parameters were refined in the normal way. H(N1'1) and H(N1'2) were located in difference Fourier maps and refined with slack constraints (Waser, 1963) using the following requirements: N(1')–H(N1'1) = 1·0, N(1')–H(N1'2) = 1·0 Å and assuming tetrahedral valency angles around N(1'). The Debye–Waller factors of H(N1'1) and H(N1'2)

Discussion of the structure

Disregarding the carboxyl oxygens and rearranging the framework (Fig. 1*b*), the relationship with sparteine-like alkaloids (Fig. 1*c*) is obvious.

The bond distances and their e.s.d.'s are given in Fig. 1(*a*). The valency and torsion angles are tabulated in Tables 2 and 3. The single bond C(4')–C(5') [1·492 (7) Å] is significantly shorter than the standard value (1·533 Å; *Tables of Interatomic Distances and Configuration in Molecules and Ions*, 1965). In the absence of a thermal-motion correction it is hardly possible to draw a conclusion concerning the presence of a special binding effect. Moreover, the Cambridge Crystallographic Data Base system displays a bewildering variety of single-bond C—C distances between 1·483 and 1·532 Å, with an average of 1·517 Å for 12 selected piperidine and piperidinium compounds published in the last decade (Kashino, Sumida & Haisa, 1972; Kashino, 1973; Tranqui, Cromer &

Table 1. *Positional parameters and equivalent isotropic B values* (Å^2) *of the heavy atoms with e.s.d.'s in digits of the last decimal given in parentheses*

$$B_{eq} = \tfrac{8}{3} \pi^2 \text{ trace } \tilde{U}.$$

	x	y	z	B_{eq}
N(1')	0·7231 (4)	−0·1811 (4)	0·90133 (8)	3·0 (1)
C(2')	0·8167 (6)	−0·0290 (5)	0·89882 (10)	3·0 (1)
C(3')	0·8072 (6)	0·0550 (5)	0·93003 (10)	3·6 (1)
C(4')	0·8707 (7)	−0·0521 (6)	0·95591 (11)	4·3 (1)
C(5')	0·7796 (7)	−0·2060 (6)	0·95694 (11)	4·4 (1)
C(6')	0·7841 (6)	−0·2896 (6)	0·92602 (12)	4·2 (1)
N(1)	0·7619 (5)	0·0746 (4)	0·81411 (8)	3·3 (1)
C(2)	0·8169 (6)	0·2407 (6)	0·81447 (10)	3·5 (1)
C(3)	0·7516 (5)	0·3279 (5)	0·84249 (10)	3·0 (1)
C(4)	0·8005 (6)	0·2432 (6)	0·87190 (10)	3·1 (1)
C(5)	0·7544 (6)	0·0653 (5)	0·87089 (10)	2·9 (1)
C(6)	0·8214 (6)	−0·0069 (5)	0·84161 (10)	3·4 (1)
C(7)	0·8213 (7)	−0·0028 (6)	0·78609 (10)	4·4 (1)
C(8)	0·7510 (7)	−0·1706 (7)	0·78074 (11)	4·8 (1)
C(9)	0·8021 (7)	−0·2419 (7)	0·75085 (12)	5·3 (1)
C(10)	0·8656 (7)	−0·3795 (8)	0·74701 (15)	6·5 (2)
C(11)	0·8028 (8)	0·5062 (6)	0·84464 (13)	3·4 (1)
O(12)	0·7069 (5)	0·5966 (4)	0·85769 (9)	5·0 (1)
O(13)	0·9352 (5)	0·5442 (4)	0·83346 (8)	5·0 (1)

Table 2. *Valency angles* (°) *of virgidivarine with e.s.d.'s in parentheses*

N(1')–C(2')–C(3')	107·3 (4)	N(1)–C(2)–C(3)	110·5 (4)
C(2')–C(3')–C(4')	111·6 (4)	C(2)–C(3)–C(4)	111·0 (4)
C(3')–C(4')–C(5')	110·3 (4)	C(3)–C(4)–C(5)	111·0 (4)
C(4')–C(5')–C(6')	110·9 (5)	C(4)–C(5)–C(6)	108·4 (4)
C(5')–C(6')–N(1')	110·6 (4)	C(5)–C(6)–N(1)	112·2 (4)
C(6')–N(1')–C(2')	112·9 (4)	C(6)–N(1)–C(2)	109·0 (4)
N(1')–C(2')–C(5)	108·4 (4)	C(2)–C(3)–C(11)	114·1 (4)
C(3')–C(2')–C(5)	116·8 (4)	C(4)–C(3)–C(11)	108·8 (4)
C(2')–C(5)–C(6)	109·7 (4)	C(2)–N(1)–C(7)	108·7 (4)
C(2')–C(5)–C(4)	112·8 (4)	C(6)–N(1)–C(7)	111·2 (4)
O(12)–C(11)–O(13)	126·6 (5)	N(1)–C(7)–C(8)	113·5 (4)
O(12)–C(11)–C(3)	115·7 (5)	C(7)–C(8)–C(9)	112·7 (5)
O(13)–C(11)–C(3)	117·6 (5)	C(8)–C(9)–C(10)	126·3 (6)

Table 3. *Torsion angles* (°) *of virgidivarine with e.s.d.'s in parentheses*

Endocyclic

N(1')–C(2')–C(3')–C(4')	57·5 (5)	N(1)–C(2)–C(3)–C(4)	57·2 (5)
C(2')–C(3')–C(4')–C(5')	−57·5 (5)	C(2)–C(3)–C(4)–C(5)	−53·0 (5)
C(3')–C(4')–C(5')–C(6')	55·2 (5)	C(3)–C(4)–C(5)–C(6)	52·5 (5)
C(4')–C(5')–C(6')–N(1')	−55·6 (6)	C(4)–C(5)–C(6)–N(1)	−58·4 (5)
C(5')–C(6')–N(1')–C(2')	58·6 (6)	C(5)–C(6)–N(1)–C(2)	63·3 (5)
C(6')–N(1')–C(2')–C(3')	−58·5 (5)	C(6)–N(1)–C(2)–C(3)	−61·2 (5)

Exocyclic

N(1')–C(2')–C(5)–C(6)	−77·7 (4)	C(2)–N(1)–C(7)–C(8)	−171·5 (4)
C(3')–C(2')–C(5)–C(6)	161·1 (4)	C(6)–N(1)–C(7)–C(8)	68·5 (5)
C(3')–C(2')–C(5)–C(4)	40·1 (5)	N(1)–C(7)–C(8)–C(9)	175·2 (4)
C(12)–C(11)–C(3)–C(4)	−85·3 (5)	C(7)–C(8)–C(9)–C(10)	127·6 (7)
O(13)–C(11)–C(3)–C(4)	94·1 (5)		

Boucherle, 1974; Ducruix & Pascard-Billy, 1974; Bhattacharjee & Chacko, 1977; Jaskólski, Gdaniec & Kosturkiewicz, 1977; Minshall & Sheldrick, 1977; Arte, Feneau-Dupont, Declercq, Germain & Van Meerssche, 1977; Rømming & Songstad, 1978; Jaskólski, Kosturkiewicz, Mickiewicz-Wicklacz & Wiewiórowski, 1979).

The bond lengths of C(11)–O(12) and C(11)–O(13) do not differ significantly: Δl and $\sigma(\Delta l)$ being 0·010 and 0·0085 Å respectively. Since two H atoms were located near N(1') in equatorial and axial positions with respect to the piperidine ring we infer that virgidivarine occurs as a zwitterion. In accordance with this view N(1') donates two H atoms in bridges to O(12) and O(13), see *Packing*.

It can be seen (Table 3) that the piperidine rings are slightly deformed chairs. The degree of puckering is smallest near C(5') in the monosubstituted ring and near C(4) in the trisubstituted ring. The average puckering angles [57·1 (2) and 57·6 (2)° respectively] are larger than in cyclohexane [54·9 (4)°; Bastiansen, Fernholt, Seip, Kambara & Kuchitsu, 1973], in agreement with the average puckering of the piperidinium ion in piperidinium toluate [57·0 (7)°; Kashino, 1973].

Packing

A part of the structure (Fig. 2) is projected along [100]. Only the molecules x,y,z (in part); $\frac{1}{2} + x$, $\frac{1}{2} - y$, $\frac{3}{4} - z$; x, $1 + y$, z (in part); $y,x,\bar{z}$; $\frac{1}{2} - y$, $\frac{1}{2} + x$, $\frac{1}{4} + z$ and y, $1 + x$, $\bar{z}$ are indicated in the figure. N(1') donates two H atoms in bridges to O(12) and O(13) (dashed lines in Fig. 2). The former is very short [2·658 (5) Å] and the latter [2·740 (5) Å] can be considered as being fairly short for N–H···O type hydrogen bonds. Hoogendorp, Verschoor & Romers (1978) found an even shorter N–H···O bond [2·626 (8) Å] in the structure of adenosine 5'-O-methylphosphate and these authors cite a number of similar short distances.

Disregarding the hydrogen bonds the intermolecular interactions are van der Waals contacts between H atoms and the shortest distance is 2·26 Å. Taking as upper limits for H···H contacts the distances 2·9, 2·7
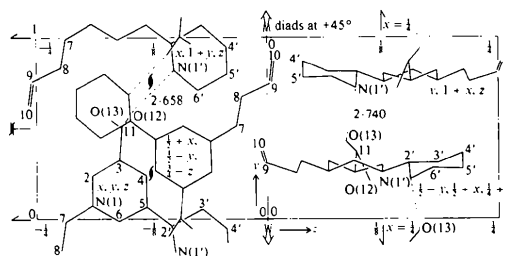

Fig. 2. Projection of the structure along [100]. Only a part is shown between $z = \frac{3}{4}$ and $z = \frac{1}{4}$. The standard deviations of the distances are <0·01 Å.

or 2·6 Å, the molecule is surrounded by 14, 10 or 8 neighbours respectively.

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