CRYSTAL STRUCTURES OF α- AND β-ALLOCRYPTOPINE*

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Crystals of α- and β-allocryptopine were studied by X-ray diffraction analysis and have been found to be crystal modifications of allocryptopine. They are both monoclinic with a = 18.401(4) Å, b = 7.1590(10) Å, c = 14.084(3) Å, β = 108.98(3)°, $P2_1/c$, Z = 4, V = 1 754.5(6) Å^3 for α-allocryptopine and a = 11.407(2) Å, b = 11.5890(10) Å, c = 14.6673(3) Å, β = 107.82(2)°, $P2_1/n$, Z = 4, V = 1 845.9(5) Å^3 for β-allocryptopine. No major differences in the conformations were found, slight differences are only in the positions of dioxolane rings.

Key words: α-Allocryptopine; β-Allocryptopine; Isoquinoline alkaloids; Crystal structure; X-Ray diffraction analysis.

Allocryptopine (**1**) is an isoquinoline alkaloid of the protopine group occurring mainly in the *Papaveraceae* and *Fumariaceae* families and in some species of the *Berberidaceae*, *Ranunculaceae*, and *Rutaceae*[2,3]. Alkaloids of this group are usually formulated as free bases, *i.e.*, by formula **1** with a ten-membered heterocycle ring, a carbonyl group and a tertiary nitrogen atom. However, these structures may be considered as artifacts since it is known that under acid conditions of plant tissues the alkaloids take the form of salts with quaternary nitrogen atom. Salts **2** are derived from free bases **1** by transannular interaction between the carbon of the oxo group and the tertiary nitrogen atom (see for example refs[3–6]).

The alkaloid allocryptopine was discovered at the end of the last century. Originally, it was called β-homochelidonine[7] and γ-homochelidonine[8], and finally renamed α- and β-allocryptopine by Gadamer[9] who determined its structure. Allocryptopine displays a significant antiarrhytmic activity comparable with that of quinidine and a stronger local anaesthetic effect than procaine (*cf.* ref.[10]).

* Part XCVIII in the series Alkaloids of the *Papaveraceae*; Part XCVII: see ref.[1].

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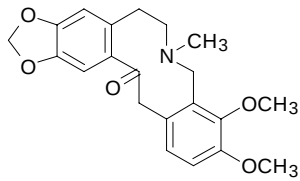
Two forms of allocryptopine of different melting points were described in literature: α-allocryptopine (β-homochelidonine), m.p. 160–161 °C, and β-allocryptopine (γ-homochelidonine), m.p. 171–172 °C, which crystallizes with or without 0.5 molecule of a solvent[8,11,12] (ethanol or ethyl acetate). Both forms are interconvertible by crystallization of free bases or *via* salts[11,12].



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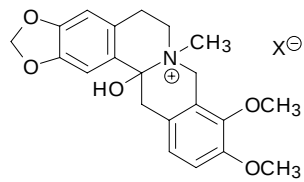

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α-Allocryptopine is the main form reported in the literature. β-Allocryptopine has been obtained from *Sanguinaria canadensis* L.[8], *Chelidonium majus* L.[12], *Eschscholtzia californica* CHAM.[11], *Bocconia frutescens* L.[13], and *Argemone squarrosa* GREENE[14] (all species belong to *Papaveraceae*), and in *Zanthoxylum brachyacanthum* F. MUELL.[15] (*Rutaceae*). Manske[16] has not encountered the higher-melting β-modification.

In our laboratory, we have occasionally obtained the β-form by crystallization of the crude allocryptopine fractions isolated from *Chelidonium majus*[17], *Eschscholtzia californica*[18], *Macleaya microcarpa*[19], and *Argemone albiflora* HORNEM. (*A. alba* LESTIB.)[20] in addition to α-allocryptopine. The nature of the differences between α- and β-allocryptopine has remained unexplained till now. In an attempt to solve this problem, we studied both the allocryptopine forms by X-ray diffraction analysis.

EXPERIMENTAL

Melting points were determined on a Mettler FP 51 apparatus and are not corrected. Both α- and β-allocryptopine have been isolated from the roots of *Chelidonium majus* L. as described previously[17,21]. The crude allocryptopine fraction crystallized from ethanol yielded α-allocryptopine, in the most cases as the main product. From concentrated mother liquors, β-allocryptopine crystallized spontaneously during several days or weeks. Recrystallization from ethanol furnished either the β-form when induced by inoculation with crystals of the same form, or the α-form without inoculation (*cf.* refs[8,11,12,17–20]). α-Allocryptopine: colourless prisms, m.p. 160–161 °C; β-allocryptopine: large colourless columns, m.p. 171–172 °C.

The difraction data were collected on a KUMA KM-4 four-circle single crystal diffractometer using the ω–2θ scan mode. The both structures were solved by the direct method using SHELXS86 program[22]. Using the SHELXL93 program package[23], all non-hydrogen atoms were refined anisotropically by the weighted full-matrix least-squares procedure on F^2 with the weight $w = 1/[\sigma^2(F_o^2) + mP^2 + nP]$, where $P = (F_o^2 + 2F_c^2)/3$ and the coefficients m, n as in Table I. All hydrogen atoms were localized from the difference Fourier map and refined isotropically. The figures were drawn by ORTEP (ref.[24]), the planarity of rings was checked by PARST (ref.[25]). Details about the measurement and refinement are summarized in Table I. Atomic coordinates, thermal parameters, bond lengths and angles of both structures have been deposited at the Cambridge Crystallographic Data

TABLE I
Crystal data and structure refinement parameters for α- and β-allocryptopine

Parameter	α-Allocryptopine	β-Allocryptopine
Diffractometer	KUMA KM-4	KUMA KM-4
Melting point	160–161 °C (EtOH)	171–172 °C (EtOH)
Formula, m.w.	$C_{21}H_{23}NO_5$, 369.40	$C_{21}H_{23}NO_5$, 369.40
Temperature	150(2) K	291(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/n$
Unit cell dimensions	a = 18.401(4) Å b = 7.1590(10) Å c = 14.084(3) Å β = 108.98(3)°	a = 11.407(2) Å b = 11.5890(10) Å c = 14.667(3) Å β = 107.82(2) Å
Volume	1 754.5(6) Å^3	1 845.9(5) Å^3
Z	4	4
Density (calculated)	1.399 Mg/m^3	1.329 Mg/m^3
Absorption coefficient	0.100 mm^{-1}	0.095 mm^{-1}
F(000)	784	784
Crystal size	0.70 × 0.70 × 0.60 mm	0.60 × 0.50 × 0.40 mm
θ range for data collection	1.17 to 24.14°	1.99 to 25.08°
Index ranges	$0 \le h \le 20$, $-7 \le k \le 0$, $-15 \le l \le 15$	$-13 \le h \le 13$, $-13 \le k \le 13$, $-17 \le l \le 4$
Reflections collected	2 775	8 394
Independent reflections	2 684 [R(int) = 0.0394]	3 288 [R(int) = 0.0323]
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Data; restraints; parameters	2 684; 0; 336	3 288; 0; 336
Goodness-of-fit on F^2	1.006	0.960
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0412, $wR2$ = 0.1042	$R1$ = 0.0354, $wR2$ = 0.0852
R indices (all data)	$R1$ = 0.0764, $wR2$ = 0.1255	$R1$ = 0.0520, $wR2$ = 0.0946
Largest difference peak and hole	0.217 and –0.237 e Å^{-3}	0.191 and –0.132 e Å^{-3}
Weighting scheme coefficients: m, n	0.0436, 2.6	0.04, 0.7

Centre (CCDC), Cambridge, U.K. Any request to the CCDC for this material should quote the name of the compound and the Reference No. 100838.

RESULTS AND DISCUSSION

Allocryptopine (**1**) possesses a ten-membered nitrogen heterocycle fused with two ortho substituted aromatic rings. Bond lengths and bond angles are listed in Tables II and III. The weighted least-squares planes through the aromatic rings C1–C2–C3–C4–C4a–C14a (Plane 1) and C8a–C9–C10–C11–C12–C12a (Plane 2) of both allocryptopine forms are quite planar within 0.01 Å including the dioxolane ring in α-allocryptopine. However, the dioxolane C2–O1–C16–O2–C3 ring in β-allocryptopine is significantly deviated from planarity: δ for the C16 atom is 0.14(3) Å.

The ten-membered nitrogen-heterocycle is severely puckered (Fig. 1). The torsion angles C9–C8a–C8–N7 and C12–C12a–C13–C14 showing the displacement of the N7 and C14 atoms from the dimethoxyphenylene plane are 126(6)°, 125(2)° and –105(6)°, –105(2)° for α- and β-allocryptopine, respectively. The dihedral angle between the

TABLE II
Bond lengths in α- and β-allocryptopine

Atoms	Distances, Å		Atoms	Distances, Å	
	α-allo-cryptopine	β-allo-cryptopine		α-allo-cryptopine	β-allo-cryptopine
C1–C2	1.361(4)	1.362(2)	C8–C8a	1.501(4)	1.508(2)
C1–C14a	1.413(4)	1.404(2)	C8a–C9	1.386(4)	1.386(2)
C2–C3	1.369(4)	1.370(3)	C8a–C12a	1.403(4)	1.407(2)
C2–O1	1.384(3)	1.378(2)	C9–O3	1.390(3)	1.385(2)
O1–C16	1.432(4)	1.419(3)	C9–C10	1.406(4)	1.403(2)
C16–O2	1.433(4)	1.431(3)	C10–O4	1.367(3)	1.364(2)
O2–C3	1.379(3)	1.377(2)	C10–C11	1.381(4)	1.380(2)
C3–C4	1.365(4)	1.362(3)	C11–C12	1.388(4)	1.387(3)
C4–C4a	1.416(4)	1.404(2)	C12–C12a	1.383(4)	1.377(2)
C4a–C14a	1.404(4)	1.409(2)	C12a–C13	1.498(4)	1.503(2)
C4a–C5	1.506(4)	1.511(2)	C13–C14	1.520(4)	1.515(2)
C5–C6	1.529(4)	1.524(3)	C14–O5	1.226(3)	1.222(2)
C6–N7	1.456(4)	1.457(2)	C14–C14a	1.504(4)	1.507(2)
N7–C15	1.457(4)	1.445(2)	O3–C17	1.428(4)	1.428(2)
N7–C8	1.469(4)	1.465(2)	O4–C18	1.432(4)	1.419(2)

Plane 1 and the Plane 2 is 137(3)° and 139.2(5)° in α- and β-allocryptopine, respectively.

The N7–C15 (*N*-methyl), O3–C17 (*O*-methyl), and C14–O5 (oxo) groups protrude on the same side of the molecule, the first two bonds being almost parallel. The C18–O4 methoxy group lies in the plane of the adjacent aromatic ring while the C17–O3 methoxy group deviates significantly from the Plane 2 in both allocryptopine forms.

The carbonyl group C14–O5 has the length of 1.226(3) Å and 1.222(2) Å in α- and β-allocryptopine, respectively; the mean bond angles around C14 are 119.2° and

TABLE III
Bond angles in α- and β-allocryptopine

Atoms	Angles, °		Atoms	Angles, °	
	α-allo-cryptopine	β-allo-cryptopine		α-allo-cryptopine	β-allo-cryptopine
C2–C1–C14a	117.9(3)	118.8(2)	C12a–C8a–C8	119.1(2)	119.35(14)
C1–C2–C3	122.0(3)	121.1(2)	C8a–C9–O3	119.3(2)	120.01(14)
C1–C2–O1	128.2(3)	129.2(2)	C8a–C9–C10	120.9(2)	120.99(14)
C3–C2–O1	109.8(2)	109.7(2)	O3–C9–C10	119.6(2)	118.93(14)
C2–O1–C16	105.8(2)	105.3(2)	O4–C10–C11	125.0(3)	125.5(2)
O1–C16–O2	108.2(2)	107.7(2)	O4–C10–C9	115.6(2)	115.39(14)
C3–O2–C16	105.7(2)	104.9(2)	C11–C10–C9	119.3(2)	119.1(2)
C4–C3–C2	121.9(3)	121.9(2)	C10–C11–C12	119.6(3)	119.7(2)
C4–C3–O2	127.6(3)	128.3(2)	C12a–C12–C11	121.7(3)	121.9(2)
C2–C3–O2	110.4(2)	109.8(2)	C12–C12a–C8a	119.0(2)	118.7(2)
C3–C4–C4a	118.4(3)	119.2(2)	C12–C12a–C13	121.5(3)	121.5(2)
C14a–C4a–C4	119.1(3)	118.7(2)	C8a–C12a–C13	119.4(2)	119.77(14)
C14a–C4a–C5	123.8(2)	123.89(14)	C12a–C13–C14	113.8(2)	113.92(13)
C4–C4a–C5	116.6(3)	117.07(14	O5–C14–C14a	119.2(2)	119.11(14)
C4a–C5–C6	112.1(2)	112.07(14)	O5–C14–C13	119.4(2)	120.0(2)
N7–C6–C5	110.7(2)	110.65(14)	C14a–C14–C13	119.0(2)	118.92(13)
C6–N7–C15	113.0(2)	112.79(14)	C4a–C14a–C1	120.6(3)	120.3(2)
C6–N7–C8	111.2(2)	112.18(13)	C4a–C14a–C14	126.3(2)	126.30(14)
C15–N7–C8	111.8(2)	110.80(14)	C1–C14a–C14	113.1(2)	113.40(14)
N7–C8–C8a	112.0(2)	117.72(12)	C9–O3–C17	113.5(2)	113.28(13)
C9–C8a–C12a	119.4(2)	119.44(14)	C10–O4–C18	116.7(2)	117.8(2)
C9–C8a–C8	121.5(2)	121.19(14)			

119.3°, respectively, indicating the sp^2 hybridization of the C14 atom. The O5 oxygen atom is deviated from the Plane 1 by 0.59(6) Å in α-allocryptopine and 0.66(2) Å in β-allocryptopine. The torsion angle C12a–C13–C14–O5 is 37(3)° in both forms.

The N7···C14 distance within the heterocycle is 2.435(4) Å and 2.498(2) Å in α- and β-allocryptopine, respectively. This is substantially shorter than the sum of van der Waals radii of these atoms. Therefore, after protonization in acid media, the quaternary salt of allocryptopine **2** possesses four rings with the N7–C14 single bond[26,27]. The mean value of the three C–N–C bond angles is 112°. The distance of C15···C17 methyl groups is 4.04(5) Å for α- and 3.89(3) Å for β-allocryptopine.

As it is seen in the superposition of α- and β-allocryptopine (Fig. 2), there are no significant differences in the conformation of the central ten-membered heterocycle and of the aromatic rings. The differences in the positions of the methyl groups C15, C17, C18, and the previously described difference in the conformation of the dioxolane C2–O1–C16–O2–C3 ring are probably the result of different crystal packings of α- and

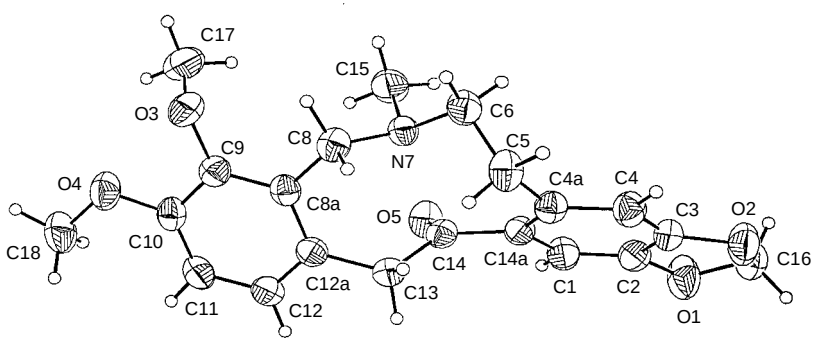

FIG. 1
A perspective view of β-allocryptopine with atom numbering

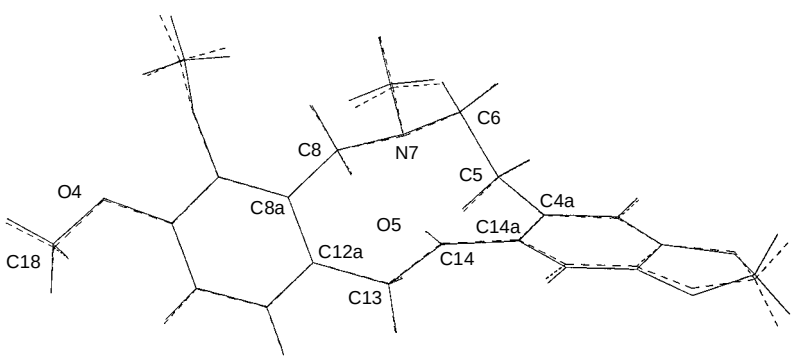

FIG. 2
A drawing of the superposition of α-allocryptopine (full lines) and β-allocryptopine (dashed lines)

β-forms (see Figs 3 and 4). The crystal packing in α-allocryptopine (Fig. 3) is slightly closer then the one in β-form (Fig. 4). This is probably a consequence of stronger van der Waals interactions in α-form. For α-allocryptopine, there were determined five

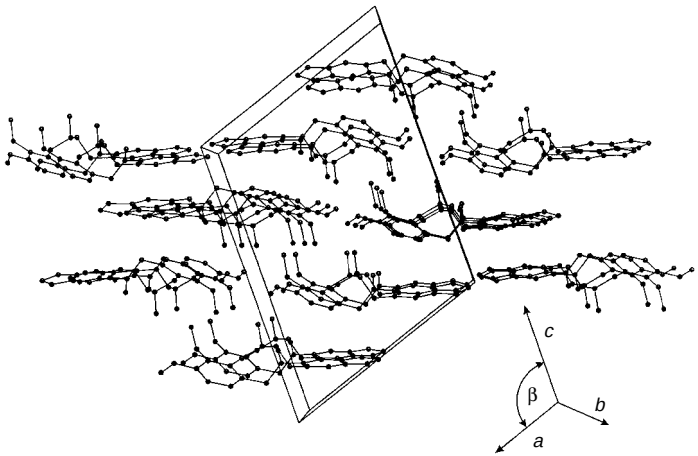

FIG. 3
Crystal packing of the molecules in α-allocryptopine. View in direction [010]

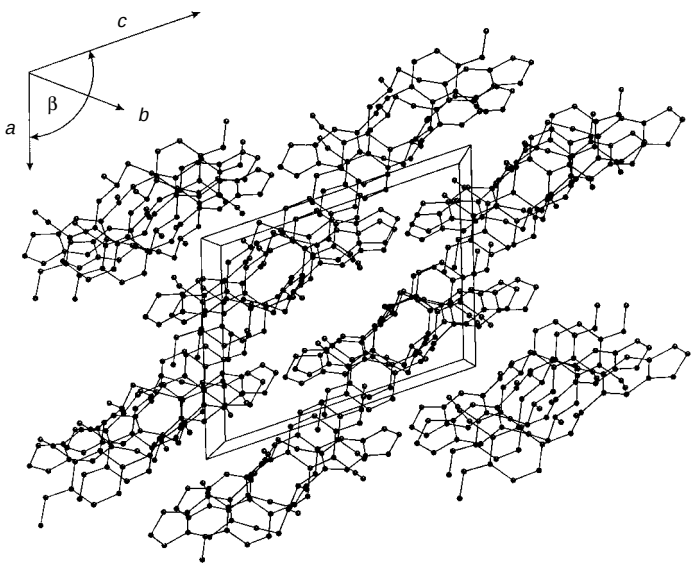

FIG. 4
Crystal packing of the molecules in β-allocryptopine. View in direction [010]

possible intermolecular contacts shorter than 2.75 Å and only two such interactions in β-form (Table IV).

TABLE IV
Intermolecular contacts shorter than 2.75 Å (with esd's except fixed and riding H)

D–H	H···A	D···A	<(DHA)	
		α-Allocryptopine		
1.03(3)	2.63(3)	3.167(4)	112(2)	C16–H16A···O2 (a)
1.03(3)	2.68(3)	3.275(4)	116.7(18)	C6–H6B···O5 (b)
1.05(3)	2.70(3)	3.681(4)	155(2)	C18–H18A···O3 (c)
0.99(3)	2.72(3)	3.434(4)	129(2)	C5–H5A···O5 (b)
1.03(4)	2.72(3)	3.007(4)	96(2)	C16–H16B···O1 (d)
		β-Allocryptopine		
1.00(2)	2.54(2)	3.281(3)	131.4(16)	C16–H16B···O4 (e)
0.97(2)	2.72(2)	3.668(2)	166.4(15)	C6–H6B···O3 (f)

Operators for generating equivalent atoms

(a) $-x + 2, -y + 1, -z + 2$; (b) $x, y + 1, z$; (c) $-x + 1, -y, -z$; (d) $-x + 2, -y, -z + 2$; (e) $x, y, z + 1$; (f) $-x, -y + 1, -z + 2$

Takahashi *et al.*[5] studied the conformations of a ten-membered ring in α-allocryptopine in solution. They deduced, on the basis of IR and NMR measurements, that allocryptopine interconverts between two major conformations. For the stable conformation in solution, they state that the NMe and C=O groups are on the opposite sides of the heterocycle. The molecular and crystal structure of allocryptopine was reported by Sakai *et al.*[28]. However, they specified neither the α/β type nor the melting point. The comparison to our data shows that the α-form was in fact studied.

Thus, we have come to the conclusion that α- and β-allocryptopine differ in their crystal packings and they are crystal modifications of allocryptopine. We have found no major differences in the conformations of the skeleton.

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