

CEDRONIN AND 7-EPI-CEDRONIN:  
X-RAY CRYSTAL STRUCTURE ANALYSIS

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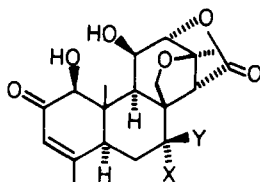
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ABSTRACT.—The structure and stereochemistry of the quassinoid cedronin [**1**] and the previously unreported 7-*epi*-cedronin [**2**] isolated from *Simaba cedron* have been established by X-ray crystal structure analysis. The change in configuration at C-7 produces a minimal change in molecular conformation and crystal packing. Cedronin [7-*epi*-cedronin] crystallizes in the monoclinic space group  $P2_1$  with cell parameters  $a=6.794(2)$  [6.779(1)],  $b=18.684(2)$  [19.029(3)],  $c=7.573(2)$  [7.419(2)]Å,  $\beta=116.67(2)^\circ$  [115.56(1)°],  $U=859$  [863]Å<sup>3</sup>,  $D_x=1.405$  [1.398] g cm<sup>-3</sup> for  $Z=2$ , Mo  $K\alpha$  radiation ( $\lambda=0.71069$ Å); final R factor=0.038 [0.031] for 1766 [1819] observed data with  $I>3\sigma(I)$ .

Quassinoids, bitter principles of simaroubaceous plants, continue to excite interest because of the complexity and diversity of their structures and because they exhibit a wide range of biological properties including, in some cases, antileukemic activity (1). The C<sub>19</sub> quassinoid cedronin was isolated from the seeds of Brazilian *Simaba cedron* Planch. (Simaroubaceae) by J. Polonsky (2), who identified it as 7-dihydrosamaderin B (3) and later assigned it the 7 $\alpha$ -hydroxy configuration (4, 5), but few details of the characterization are available in the primary literature. In our investigation of the seeds and leaves of Guyanese *S. cedron*, we isolated small quantities of two quassinoids. The first, mp 238-240°, was more abundant in the seeds, and appeared to be Polonsky's cedronin<sup>1</sup> [**1**]. The second, mp 232-234°, was more abundant in the leaves, and its spectroscopic characteristics indicated that it was a new stereoisomer of cedronin, almost certainly the C-7 epimer with an equatorial OH group. X-ray crystal structure analysis offered the best method for establishing unequivocally the structure and stereochemistry of each of these compounds, and for making a detailed comparison of the stereochemistry of these two complex, multiply-bridged, polycyclic compounds.

## DISCUSSION

Crystal data and the final atomic positional parameters in the two structures are given in Tables 1 and 2, respectively.<sup>2</sup> The X-ray analysis establishes the two isomers as



- 1** X=OH, Y=H cedronin  
**2** X=H, Y=OH 7-*epi*-cedronin

<sup>1</sup>An authentic sample of the original cedronin is no longer available.

<sup>2</sup>Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

TABLE 1. Crystal Data, Details of Intensity Measurements, and Structure Refinements<sup>a</sup>

Compound	Cedronin [1]	7- <i>epi</i> -Cedronin [2]
System	Monoclinic <sup>b</sup>	Monoclinic <sup>b</sup>
a(Å)	6.794(2)	6.779(1)
b(Å)	18.684(2)	19.029(3)
c(Å)	7.573(2)	7.419(2)
β(deg.)/U(Å <sup>3</sup> )	116.67(2)/859	115.56(1)/863
fw/F(000)/μ(Mo Kα)(cm <sup>-1</sup> )	363.4/386/1.0	363.4/386/1.0
Z/D <sub>x</sub> (gcm <sup>-3</sup> )	2/1.405	2/1.398
Space Group	P2 <sub>1</sub>	P2 <sub>1</sub>
Refns. in cell detmn.	25	25
(No./range in deg.)	12.0<θ<17.1	11.9<θ<16.0
Scan widths (deg.)	0.80+0.35 tan θ	0.70+0.35 tan θ
Max. scan time (sec.)	85	85
Std. Refns. (No./Interval in sec.) <sup>c</sup>	3/6500	3/6500
Max 2θ(deg.)/Octants	55/h,k, ±1	55/h,k, ±1
Total No. Colld. (Inc. Stds.)	2266	2280
Unique Data <sup>d</sup>	1983	2007
No. Data I>3σ(I)	1766	1819
R <sub>1</sub> (R <sub>2</sub> ) <sup>e</sup>	0.0378(0.0410)	0.0311(0.0407)
Max. Δ/σ	0.10	0.45
Weights, value of p	0.00032 <sup>f</sup>	0.040 <sup>g</sup>
Max. peak final ΔF Fourier (eÅ <sup>-3</sup> )	0.23	0.22

<sup>a</sup>Enraf-Nonius CAD 4 diffractometer; θ-2θ mode; Mo Kα radiation (λ=0.71069Å); graphite monochromator; T=298K.

<sup>b</sup>Note that the matrix [1,0,0/1,0,2/0,1,0] results in an apparent C22<sub>1</sub> cell of dimensions 6.792(2) [6.779(1)], 13.535(4) [13.391(2)], 18.689(3) [19.029(3)]Å, γ=90.03(2)° [88.34(3)°] for both compounds but without the required higher Laue symmetry among the reflections. In addition, this cell would require the molecules to have crystallographic symmetry 2. Values for 7-*epi*-cedronin are given in brackets

<sup>c</sup>No systematic variations in the intensities of the standards were observed.

<sup>d</sup>49[44] systematically absent or zero F<sub>obs</sub> data rejected and 147[151] symmetry equivalent data then averaged {R<sub>merge</sub>(F)=0.016[0.012]} to give nos. of data indicated. Values for 7-*epi*-cedronin are given in brackets.

<sup>e</sup>Both structures eventually solved using direct methods after several different choices of the origin and starting reflections and refined using standard least-squares and Fourier methods. Programs: Enraf-Nonius SDP package on PDP 11/23 or SHELX-76 on Gould 9705 computers (7). Scattering curves stored in programs were taken from International Tables for X-ray Crystallography (8).

<sup>f</sup>Weights: w = {σ<sup>2</sup>(F) + pF<sup>2</sup>}<sup>-1</sup>

<sup>g</sup>Weights: w = 4F<sup>2</sup> {σ<sup>2</sup>(I) + (pF<sup>2</sup>)<sup>2</sup>}<sup>-1</sup>

cedronin [1] and 7-*epi*-cedronin [2] (Figures 1 and 2). Surprisingly, the change in configuration at C(7) has minimal effect on the overall molecular conformation and on the crystal packing, as can be seen in the similarity in the unit cell dimensions and space group (Table 1). Thus, there are no differences in analogous bond lengths >3σ and, amongst the bond angles, two small differences are due to the change in configuration at C(7) Δ[C(7)-C(8)-C(30)]=1.8°; Δ[C(8)-C(14)-C(15)]=2.2°, while the remaining two are due to a change in orientation of the O(1)-H(O1) hydroxyl group Δ[C(2)-C(1)-O(1)]=2.0° and Δ[C(1)-C(2)-C(3)]=1.6°. These latter difference also show up in a

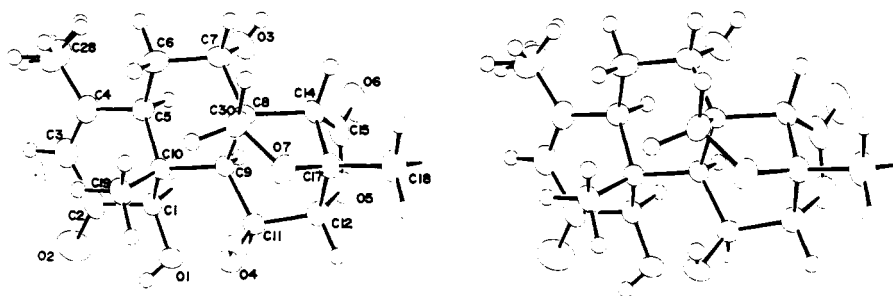


FIGURE 1. Stereoscopic view (ORTEP) of cedronin [1]. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are drawn with uniform isotropic thermal parameters. [Absolute configuration was not determined; that shown follows precedent (1).]

least-squares fit using the program BMFIT (6) of the non-hydrogen atoms [except O(3)] in the two structures, since the maximum derivations are 0.11, 0.22, and 0.19 Å for C(2), O(2), and O(1), respectively (Figure 2). The other large deviation is for O(4) [0.12 Å]. Direction cosines of selected intramolecular vectors with respect to orthogonal axes indicate that, at most, there is only an 8° difference in the orientation of the two epimers.

The crystal packing of both epimers is dictated by interactions involving the hydroxyl groups. Thus, hydroxyl O(1)-H(O1) is involved in an intramolecular contact with O(2) and a weaker C(11)-H(111). . . O(1) contact (Table 3). Similarly O(4)-H(O4) is involved in intramolecular contacts of comparable strength in both epimers to O(7) [2.05-2.06 Å]. The principal intermolecular contacts involve the hydrogen bond O(3)-H(O3). . . O(4). In cedronin this interaction is slightly weaker since O(3) is also involved in another weaker interaction to O(1)-H(O1) [2.24 Å]. Interactions between molecules along the *b* [i.e., long] axis of the molecule are generally weak, the shortest being C(3)-H(31). . . O(7) [2.39 Å] in cedronin.

It is notable, however, that rings B and C are distorted chairs with maximum tor-

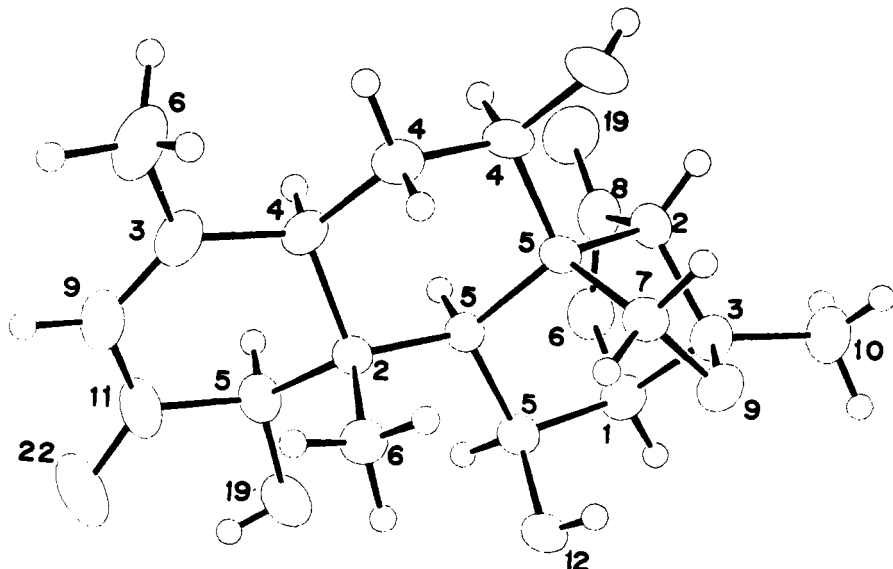


FIGURE 2. ORTEP view of 7-*epi*-cedronin showing the results of a least squares fit of the non-hydrogen atoms [except O(3)] of the two epimers. Numbers shown indicate displacement (in pm) from cedronin. [Atom numbering for Tables, etc. is the same as in Figure 1.]

TABLE 2. Final Atomic Positional Parameters<sup>a</sup>

Atom	x	y	z	$B$ or $B_{eq}(\text{\AA}^2)^b$
O(1) . . . . .	0.0070(3)	0.2682	0.0226(3)	2.76(5)
	-0.0103(3)	0.3466	0.4683(3)	3.42(4)
O(2) . . . . .	0.0555(5)	0.1372(2)	-0.0730(4)	4.88(8)
	-0.0238(3)	0.2119(1)	0.4222(3)	5.52(6)
O(3) . . . . .	0.7984(4)	0.3302(2)	0.6527(3)	3.44(6)
	1.0357(3)	0.4172(1)	1.0291(2)	3.55(4)
O(4) . . . . .	0.1678(3)	0.4157(2)	-0.0723(3)	2.71(5)
	0.2266(2)	0.4819(1)	0.3997(2)	2.44(3)
O(5) . . . . .	0.2557(4)	0.4687(2)	0.4225(3)	2.85(6)
	0.2949(2)	0.5365(1)	0.8967(2)	2.77(3)
O(6) . . . . .	0.5109(5)	0.4443(2)	0.7268(3)	4.11(8)
	0.5272(3)	0.5014(1)	1.2015(2)	3.88(4)
O(7) . . . . .	0.5432(3)	0.4946(2)	0.1301(3)	2.42(5)
	0.6143(2)	0.5459(1)	0.6159(2)	2.40(3)
C(1) . . . . .	0.2129(4)	0.2359(2)	0.1396(4)	2.08(6)
	0.1709(3)	0.3098(1)	0.6094(3)	2.44(4)
C(2) . . . . .	0.2214(6)	0.1620(2)	0.0601(5)	2.88(8)
	0.1523(4)	0.2327(1)	0.5497(3)	3.26(5)
C(3) . . . . .	0.4325(6)	0.1251(2)	0.1470(4)	2.80(8)
	0.3436(4)	0.1886(1)	0.6392(3)	3.24(5)
C(4) . . . . .	0.6170(5)	0.1598(2)	0.2613(4)	2.46(7)
	0.5401(3)	0.2160(1)	0.7521(3)	2.71(4)
C(5) . . . . .	0.6144(4)	0.2371(2)	0.3192(4)	2.02(6)
	0.5642(3)	0.2938(1)	0.8078(3)	2.14(3)
C(6) . . . . .	0.8316(5)	0.2778(2)	0.3807(4)	2.61(7)
	0.7954(3)	0.3223(1)	0.8765(3)	2.54(4)
C(7) . . . . .	0.8263(5)	0.3471(2)	0.4822(4)	2.49(6)
	0.8173(3)	0.3944(1)	0.9700(3)	2.35(4)
C(8) . . . . .	0.6360(4)	0.3954(2)	0.3460(3)	1.82(6)
	0.6543(3)	0.4473(1)	0.8270(2)	1.83(3)
C(9) . . . . .	0.4115(4)	0.3547(2)	0.2545(3)	1.66(6)
	0.4177(2)	0.4169(1)	0.7295(2)	1.70(3)
C(10) . . . . .	0.4160(4)	0.2798(2)	0.1617(3)	1.77(6)
	0.3944(3)	0.3411(1)	0.6407(2)	1.79(3)
C(11) . . . . .	0.2170(4)	0.4057(2)	0.1297(4)	2.01(6)
	0.2493(3)	0.4729(1)	0.5981(3)	2.03(3)
C(12) . . . . .	0.2500(5)	0.4791(2)	0.2300(4)	2.20(6)
	0.3032(3)	0.5445(1)	0.7042(3)	2.39(4)
C(13) . . . . .	0.4783(4)	0.5110(2)	0.2811(4)	2.07(6)
	0.5431(3)	0.5662(1)	0.7640(3)	2.34(4)
C(14) . . . . .	0.6144(4)	0.4633(2)	0.4579(3)	2.08(6)
	0.6524(3)	0.5168(1)	0.9399(2)	2.25(3)
C(15) . . . . .	0.4663(6)	0.4561(2)	0.5578(4)	2.61(8)
	0.4955(3)	0.5160(1)	1.0341(3)	2.66(4)
C(18) . . . . .	0.4940(6)	0.5913(2)	0.3177(4)	2.87(8)
	0.5814(4)	0.6443(1)	0.8057(3)	3.32(5)
C(19) . . . . .	0.4243(5)	0.2818(2)	-0.0386(4)	2.34(6)
	0.4227(3)	0.3349(1)	0.4462(3)	2.28(4)
C(28) . . . . .	0.8337(6)	0.1208(2)	0.3437(6)	3.85(10)
	0.7392(4)	0.1706(1)	0.8298(4)	4.13(6)
C(30) . . . . .	0.6894(4)	0.4339(2)	0.1947(4)	2.23(6)
	0.7292(3)	0.4796(1)	0.6773(2)	2.14(3)

<sup>a</sup>For each atom, top line is cedronin, second line is 7-*epi*-cedronin.<sup>b</sup>All non-hydrogen atoms refined anisotropically.  $B_{eq} = 1/3$  trace B for anisotropically refined atoms.

TABLE 3. Selected Contacts

A-H. . . B	H. . . B (Å)		A-H. . . B (deg.)	
	Cedronin	7- <i>epi</i> -Cedronin	Cedronin	7- <i>epi</i> -Cedronin
O(1)-H(01). . . O(2)	2.27	1.96(4)	105	135(3)
. . . O(3)	2.24	—	121	—
C(11)-H(111). . . O(1)	2.16	2.28(2)	121	121(2)
C(3)-H(31). . . O(7)	2.39	[2.57]	138	[147(2)]
O(3)-H(03). . . O(4)	2.20	1.98(3)	162	166(3)
C(19)-H(191). . . O(3)	—	[2.51]	—	[169(3)]
O(4)-H(04). . . O(7)	2.05	2.06(3)	108	139(2)
O(4)-H(04). . . O(6)	—	2.38(3)	—	137(2)
O(3)-H(03). . . O(1)	[2.44]	—	108	—
C(6)-H(61). . . O(1)	[2.42]	—	153	—
C(30)-H(301). . . O(3)	—	[2.41(2)]	—	—

sion angles of  $62.3^\circ$  [C(10-5-6-7)] and  $80.5^\circ$  [C(8-14-13-12)], respectively, for 7-*epi*-cedronin [values for cedronin are very similar], while ring A adopts a distorted sofa conformation with  $\tau$  [C(1-2-3-4)] and  $\tau$  [C(2-3-4-5)] angles of  $-8.4$  and  $5.7^\circ$  (7-*epi*-cedronin). Finally, the  $\gamma$ -lactone and furanoid rings in *epi*-cedronin are described by the puckering constants (9),  $\Delta = 19.6$ ,  $\phi_m = 41.7^\circ$  ( $\gamma$ -lactone) and  $\Delta = 12.1$ ,  $\phi_m = 44.4^\circ$  (furan) and, thus, have conformations which are intermediate between the symmetrical envelope and twist (half-chair) forms.

## EXPERIMENTAL

**PLANT MATERIAL.**—Plant material was collected in the white sands region near the Soesdyke-Linden Highway, Demerara, Guyana. Voucher specimens are deposited in the University of Guyana Herbarium and in the Institute of Systematic Botany, Utrecht.

**GENERAL EXPERIMENTAL PROCEDURES.**—Melting points were determined on a Thomas-Kofler micro hot stage. A Nicolet 5DX ftr spectrometer (CHCl<sub>3</sub> solutions), a Varian XL-400 nmr spectrometer (CDCl<sub>3</sub> solutions), Bell and Howell CEC 21-490 (lrms), and AEI MS30 (hrms) mass spectrometers, and a Perkin-Elmer 243B polarimeter were used.

**EXTRACTION, ISOLATION, AND CHARACTERIZATION.**—Dried plant material (seeds or leaves) was ground, defatted with hexane, and extracted with hot H<sub>2</sub>O. The aqueous solution was continuously extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> afforded a residue which was chromatographed to provide cedronin (major isomer in seeds) and 7-*epi*-cedronin (major isomer in leaves).

Cedronin [**1**], recrystallized from MeOH, mp 238-240°, [ $\alpha$ ]<sub>D</sub>+70° (*c* 0.44, CHCl<sub>3</sub>),  $-14^\circ$  (*c* 1.2, pyridine) [lit. (2) mp 275-280°, sintering at 240°, [ $\alpha$ ]<sub>D</sub>-12.6° (pyridine)]; ir 3693, 3506, 1775, 1660 cm<sup>-1</sup>; <sup>1</sup>H nmr 6.06 (m, 1H), 4.83 (m, 1H), 4.64 (d, *J*=9, 1H), 4.41 (d, *J*=9, 1H), 4.32 (dd, *J*=3.5, 1, 1H), 4.09 (m, 1H), 3.97 (dd, *J*=3, 3, 1H), 3.71 (dd, *J*=9, 2, 1H), 3.39 (m, 1H), 3.23 (m, 1H), 2.66 (d, *J*=1, 1H), 2.24 (m, 1H), 2.17 (ddd, *J*=14.5, 3, 3, 1H), 1.90 (m, 3H), 1.64 (dd, *J*=14.5, 3, 1H), 1.52 (s, 3H), 1.23 (s, 3H); ms exact mass 364.1509 (C<sub>19</sub>H<sub>24</sub>O<sub>7</sub>). Diacetate, mp 108-110°, [ $\alpha$ ]<sub>D</sub>-3.5° (*c* 0.4, CHCl<sub>3</sub>), ms M<sup>+</sup> 448.

7-*epi*-Cedronin [**2**], recrystallized from EtOAc/hexane, white crystals, mp 232-234°, [ $\alpha$ ]<sub>D</sub>+109.3° (*c* 0.57, CHCl<sub>3</sub>); ir 3474, 1773, 1671 cm<sup>-1</sup>; <sup>1</sup>H nmr 6.04 (m, 1H), 4.76 (m, 1H), 4.44 (d, *J*=8.4, 1H), 4.33 (m, 1H), 4.25 (dd, *J*=5, 1, 1H), 4.20 (dd, *J*=8.4, 1.5, 1H), 3.92 (m, 1H), 3.82 (dd, *J*=11, 5, 1H), 3.50 (d, *J*=9, 1H), 3.05 (d, *J*=1, 1H), 2.46 (d, *J*=11, 1H), 2.17 (ddd, *J*=11, 5, 2, 1H), 1.93 (m, 3H), 1.70 (m, 1H), 1.51 (m, 1H), 1.47 (s, 3H), 1.18 (s, 3H); ms exact mass 364.1521 (calcd. for C<sub>19</sub>H<sub>24</sub>O<sub>7</sub>, 364.1522). Diacetate, mp 229-231°, [ $\alpha$ ]<sub>D</sub>+28.1° (*c* 0.26, CHCl<sub>3</sub>), ms M<sup>+</sup> 448.

## ACKNOWLEDGMENTS

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## LITERATURE CITED

1. J. Polonsky, in: "The Chemistry and Chemical Taxonomy of the Rutales," Ed. by P.G. Waterman and M.F. Grondon, Chap. 8, Academic Press, London, 1983, pp. 247-266.
2. J. Polonsky, *Bull. Soc. Chim. France.*, 1845 (1960).
3. J. Zylber and J. Polonsky, *Bull. Soc. Chim. France.*, 2016 (1964).
4. J. Polonsky, *Fortschr. Chem. Org. Naturstoffe*, **30**, 101 (1973).
5. J. Polonsky, *Fortschr. Chem. Org. Naturstoffe*, **47**, 221 (1985).
6. P.S. Yuen and S.C. Nyburg, *J. Appl. Cryst.*, **12**, 258 (1979).
7. Enraf-Nonius Structure Determination Package (1981). B. A. Frenz and Associates, Inc., College Station, Texas. SHELX 76- G.M. Sheldrick (1976). University of Cambridge, England.
8. International Tables for X-ray Crystallography (1974). Vol. IV., Kynoch Press, Birmingham, England. (Present distributor D. Reidel, Dordrecht.)
9. C. Altona, H.J. Geise, and C. Romers, *Tetrahedron*, **24**, 13 (1968).

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