

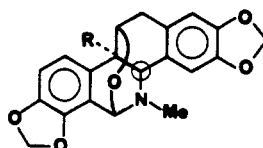
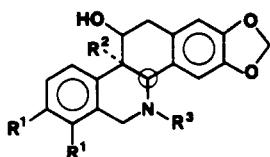
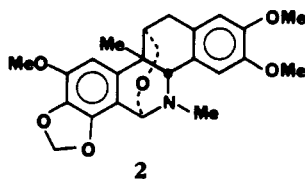
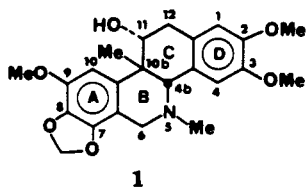
ABSOLUTE STEREOCHEMISTRY OF (-)-AMBININE

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ABSTRACT.—The absolute stereochemistry of the corynoline-type alkaloid (-)-ambinine [1] has been determined to be 4bS, 10bS, 11R by means of cd and X-ray analyses.

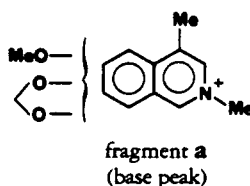
Corydalis ambigua Cham. et Schlt. (Papaveraceae), distributed in northeastern China, is known as a folk medicine for analgesic, antispasmodic, and sedative actions. Our investigations (Chinese group) led to the isolation of the benzo[*c*]phenanthridine alkaloid (-)-ambinine [1], C₂₃H₂₇NO₆ (1). The presence of a methoxyl and a methylenedioxy in ring A and two methoxyls in ring D was confirmed by a characteristic mass spectral fragment **a** (*m/z* 232) for corynoline-type alkaloids. The substitution pattern was determined by the ¹H-nmr spectrum, which included three one-proton singlets in the aromatic region, and by an nOe (20%) between the aromatic H-10 and the angular 10b-Me. The relative stereochemistry of **1** was determined to incorporate a B/C *cis*-steroidal ring juncture and an 11-axial hydroxyl because of an nOe (20%) between H-4b and 10b-Me and an intramolecular H bonding (3200 cm⁻¹) for N-5 and the 11 α -OH as well as the preparation of a derivative, (-)-ambinoxine [2], by the Hg(OAc)₂ oxidation of **1**. This paper is concerned with the elucidation of the absolute stereochemistry of (-)-ambinine [1] by means of cd and X-ray analyses.



- 3 R¹, R¹=OCH₂O, R²=R³=Me corynoline
 4 R¹, R¹=OCH₂O; R²=H; R³=Me chelidonine
 5 R¹, R¹=OCH₂O; R²=R³=H norchelidonine
 6 R¹=OMe; R²=H; R³=Me homochelidonine

- 7 R=Me
 8 R=H

(The stereostructures shown refer to the (+)-form.)



RESULTS AND DISCUSSION

It is known that the corynoline-type alkaloids **3–6** show characteristic cd Cotton effects in the 1L_b -band region, and that a negative Cotton effect corresponds to the $4bR$, $10bR$, $11S$ configuration and a positive one to the enantiomeric arrangement (2). Presently, a positive Cotton effect at 285.7 nm for (-)-ambinine [**1**] suggested its absolute stereochemistry to be $4bS$, $10bS$, $11R$ (Figure 1). Furthermore, the cd spectra of (-)-ambinoxine [**2**] taken in MeOH and HCl/MeOH were the mirror images of (+)-corynoxine [**7**] and (+)-didehydrochelidonine [**8**] at ca. 325 nm, supporting the above configuration assigned for **1** (2) (Figure 2).

An X-ray analysis of (-)-ambinine·HBr was also carried out. The absolute stereochemistry was determined using the anomalous scattering of Br atoms. The crystal structure and parameters obtained are given in Figure 3 and Table 1, respectively. As can be seen, rings B and C are fused in a *cis* arrangement, with each in a half-chair conformation, while the 11-hydroxyl is α (axial) oriented. Thus, the $4bS$, $10bS$, $11R$ configuration has been determined for **1**.

To our knowledge this is the first report of a corynoline-type alkaloid with five oxygen functions in the aromatic rings, three in ring A and two in ring D, as a natural substance.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's (uncorrected) were determined on a micro hot-stage apparatus. Specific rotations were taken on a JASCO DPI-181 polarimeter. Spectra were recorded on the following spectrometers: ir, Hitachi 260-30; uv, Hitachi EPS-2U; cd, JASCO J-20; 1H nmr, JEOL JNM FX-500S (500 MHz) (reference, TMS); hrms, JEOL JMS DX-300; elemental analysis, Perkin-Elmer 240B.

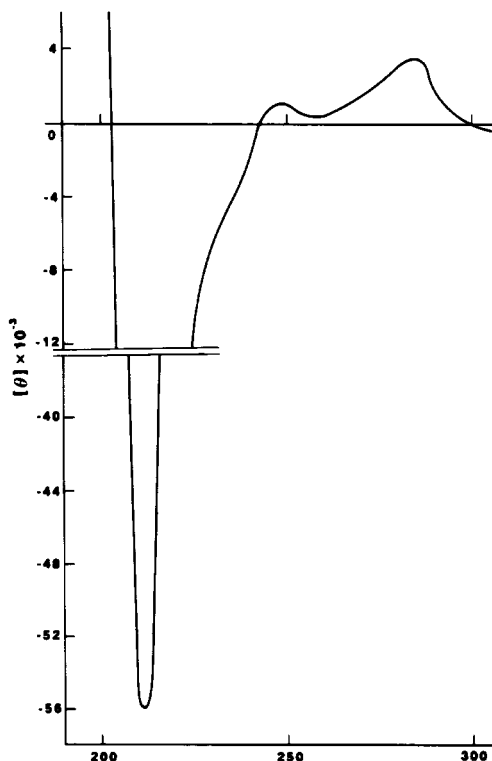


FIGURE 1. Cd spectrum of (-)-ambinine [**1**] (in MeOH).

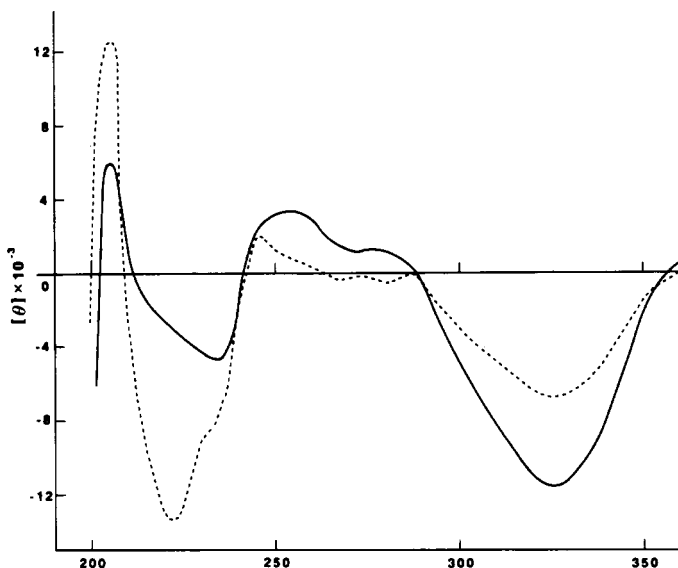


FIGURE 2. Cd spectra of (-)-ambinoxine [2] (—in MeOH, ----in HCl/MeOH).

(-)-AMBININE [1].—Colorless prisms, mp 218–219° (EtOH); specific rotation ($c = 1.30$, CHCl_3) $[\alpha]^{22}$ (nm) -106.0° (589), -112.7° (577), -131.2° (546), -233.0° (435), -374.0° (365); ir ν max cm^{-1} (ϵ) 3200 (105.17) ($c = 7.14 \times 10^{-4}$, CCl_4); uv λ max (MeOH) (log ϵ) 288 (sh) (4.475), 281 (4.539), 228 (sh) (5.115), 207 (5.586); cd ($c = 1.5 \times 10^{-4}$, MeOH) $[\theta]^{30.5}$ (nm) 0 (299.0), +3442 (285.7) (positive maximum), +2891 (279.1) (sh), +358 (259.4) (negative maximum), +1156 (248.5) (positive maximum), 0 (243.0), ($c = 7.5 \times 10^{-5}$, MeOH) -56158 (211.0) (negative maximum), 0 (203.0); ^1H nmr (CDCl_3) δ 6.67, 6.64 (each 1H, s, H-1 and H-4), 6.59 (1H, s, H-10), 5.99, 5.95 (each 1H, d, $J = 1.5$ Hz, OCH_2O), 4.01 (1H, m, H-11), 3.99, 3.41 (each 1H, d, $J = 15.0$ Hz, H₂-6), 3.91, 3.90 (each 3H, s, $\text{OMe} \times 2$), 3.88 (3H, s, 9-OMe), 3.32 (1H, s, H-4b), 3.17 (1H, d, $J = 18.0$ Hz, Ha-12),

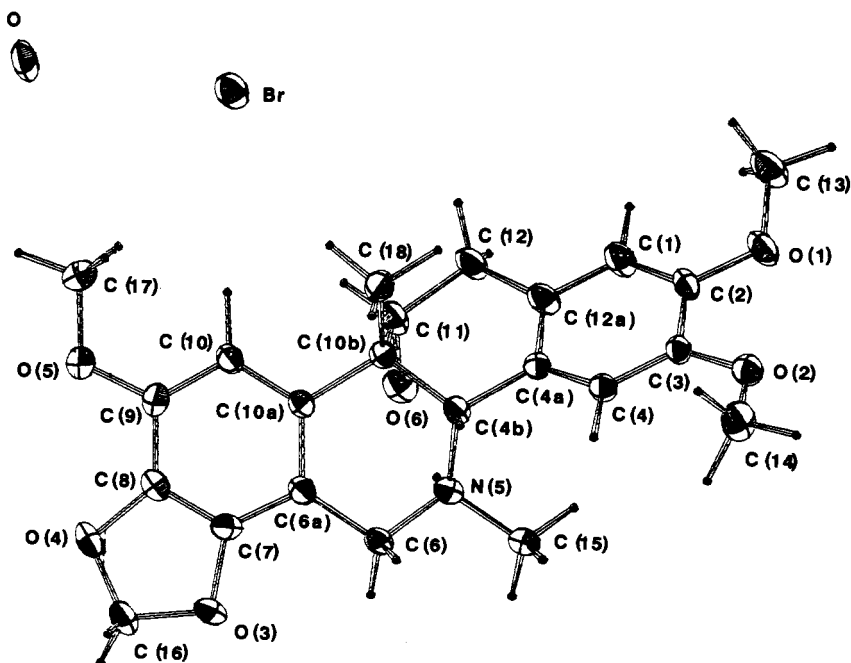


FIGURE 3. Molecular structure of (-)-ambinine [1].

TABLE 1. Atomic Parameters ($\times 10^4$) of (-)-Ambinine [1].

Atom	x	y	z	Beq/Å ^{2a}
BR-1	-62 (1)	3760(1)	9581 (1)	4.7
O-1	6682 (6)	5229(4)	8173 (6)	5.0
O-2	6824 (5)	6039(4)	10228 (6)	3.8
O-3	2817 (5)	3400(4)	16629 (5)	4.1
O-4	1130 (5)	2906(4)	16396 (6)	4.7
O-5	39 (6)	2845(4)	14040 (6)	5.1
O-6	4126 (5)	2795(4)	11871 (6)	4.1
O-7	-2561(11)	3297(8)	10586(14)	4.7
N-5	4804 (6)	3929(4)	13349 (6)	2.9
C-1	5384 (8)	4391(5)	9089 (8)	4.0
C-2	6052 (8)	5003(6)	9145 (9)	3.9
C-3	6130 (7)	5448(5)	10252 (8)	3.1
C-4	5518 (7)	5239(5)	11266 (8)	3.0
C-4a	4871 (7)	4604(5)	11240 (7)	3.2
C-4b	4225 (7)	4427(5)	12389 (7)	2.8
C-6	4241 (7)	3950(5)	14575 (8)	3.2
C-6a	3114 (7)	3712(5)	14389 (7)	3.0
C-7	2506 (7)	3443(5)	15367 (9)	3.2
C-8	1511 (7)	3165(5)	15246 (8)	3.3
C-9	1034 (7)	3145(6)	14079 (9)	3.4
C-10	1586 (7)	3428(5)	13062 (8)	3.3
C-10a	2614 (7)	3700(5)	13215 (8)	2.8
C-10b	3198 (7)	3995(5)	12035 (8)	3.0
C-11	3442 (8)	3290(5)	11187 (8)	3.8
C-12	3966 (9)	3536(6)	9961 (8)	4.7
C-12a	4762 (8)	4175(5)	10123 (7)	3.7
C-13	6443(11)	4932(7)	6952(10)	5.5
C-14	6751(10)	6608(6)	11207(11)	4.9
C-15	5929 (8)	4130(6)	13545 (8)	3.7
C-16	1908 (9)	3139(8)	17286(10)	5.4
C-17	-523(10)	2957(9)	12912(11)	6.6
C-18	2495 (8)	4593(6)	11363(10)	4.0

$$^a \text{Beq} = \frac{1}{3} \sum_i \sum_j \beta_{ij} \alpha_i \alpha_j$$

3.10 (1H, dd, $J = 18.0, 4.0$ Hz, Hb-12), 2.19 (3H, s, 5-Me), 1.15 (3H, s, 10b-Me); nOe 10b-Me \rightarrow H-4b (20%), H-10 (20%), 9-OMe \rightarrow H-10 (18%); hrms m/z [M]⁺ 413.1851 (413.1839 for C₂₃H₂₇NO₆). *Anal.* calcd for C₂₃H₂₇NO₆ · ½ H₂O, C 65.39, H 6.68, N 3.32; found C 65.74, H 6.64, N 3.13.

(-)-AMBININE·HBr.—Colorless fine needles, mp 199–202° (EtOH).

(-)-AMBINOXINE [2].—This compound was obtained on oxidation of 1 with Hg(OAc)₂ in 6% HOAc at 100° for 4 h. Colorless prisms, mp 176–177° (EtOH); specific rotation ($c = 1.17, \text{CHCl}_3$) [α]_D²² (nm) -80.0° (589), -85.1° (577), -98.8° (546), -178.6° (435), ($c = 0.117, \text{CHCl}_3$) -239.3 (365); uv λ max (MeOH) (log ϵ) 380 (3.686), 332 (4.678), 284 (4.194), 224 (sh) (4.740), 204 (5.262), (HCl/MeOH) (log ϵ) 380 (4.281), 332 (5.106), 284 (4.495), 224 (sh) (5.064), 204 (5.663); cd ($c = 1.7 \times 10^{-4}, \text{MeOH}$) [θ]_D^{31.2} (nm) 0 (361.5), -6769 (361.1) (negative maximum), -97 (287.1) (positive maximum), -532 (280.5) (negative maximum), -387 (276.0) (positive maximum), -435 (270.0) (negative maximum), 0 (263.2), +1983 (246.6) (positive maximum), 0 (242.0), -8220 (233.5) (sh), -13297 (222.8) (negative maximum), 0 (209.0), +12572 (205.5) (positive maximum), 0 (200.6), ($c = 1.1 \times 10^{-4}, \text{HCl/MeOH}$) 0 (356.0), -11583 (325.0) (negative maximum), 0 (288.0), +1121 (276.1) (positive maximum), +1046 (272.1) (negative maximum), +3288 (256.7) (positive maximum), 0 (241.0), -4783 (234.2) (negative maximum), 0 (211.0), +6352 (204.5) (positive maximum), 0 (202.0); hrms m/z [M]⁺ 411.1679 (411.1681 for C₂₃H₂₅NO₆). *Anal.* calcd for C₂₃H₂₅NO₆ · ½ H₂O, C 65.70, H 6.23, N 3.33; found C 65.67, H 6.05, N 3.36.

X-RAY CRYSTALLOGRAPHIC DATA FOR (-)-AMBININE·HBr.—C₂₃H₂₉O₇·HBr · ½ H₂O, formula weight = 511.37, orthorhombic, space group $P2_12_12_1$; $a = 12.805$ (2), $b = 17.234$ (2), $c = 10.649$ (2) Å;

$D_c = 1.454 \text{ g}\cdot\text{cm}^{-3}$, $\mu (\text{CuK}\alpha) = 17.711 \text{ cm}^{-3}$, $Z = 4$, 2503 independent reflections were measured out of 2θ , $\max = 150^\circ$ with a Rigaku AFC-4 four cycle diffractometer using $\text{CuK}\alpha$ radiation ($\lambda = 1.54789 \text{ \AA}$) with an incident beam graphite monochromator. The data were collected at 296K from a colorless crystal ($0.2 \times 0.3 \times 0.2 \text{ mm}$) using the ω - 2θ scan technique.

The structure was solved by the direct method (MULTAN) (3) and refined by the block-diagonal least-squares method. Hydrogen atoms other than those attached to C-13, C-14, C-17, and C-18 could be identified in a difference map. The coordinates of twelve hydrogen atoms were calculated, assuming an ideal geometry, and were included in the refinement with the isotropic temperature factors.

The absolute configuration was determined by the anomalous scattering technique. When the refinements were carried out by use of the atomic parameters obtained from the result of the direct method, the residual values converged to $R = 0.061$ and $R_w = 0.063$, respectively. On the contrary, the refinements in the enantiomeric atomic parameters resulted in the residual values of $R = 0.067$ and $R_w = 0.067$, respectively. These facts indicated that the former configuration is probably the correct choice (Figure 3).

The atomic scattering factors and anomalous scattering corrections were taken from *International Tables for X-ray Crystallography* (4). The final atomic parameters are listed in Table 1. The calculations were carried out on a HITAC M-680H computer at the Computer Center of University of Tokyo, using the Universal Crystallographic Computer Program System UNICS III (5).¹

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¹Atomic coordinates for this structure 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, UK.