Gelsamydine, an Indole Alkaloid from *Gelsemium elegans* with Two Monoterpene Units

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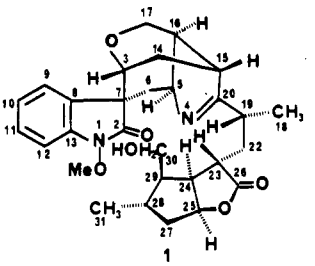
An extract of the whole plant of *Gelsemium elegans* (Loganiaceae) has afforded gelsamydine (1), a novel oxindole alkaloid whose structure and stereochemistry were deduced by spectral and X-ray crystallographic analyses. Gelsamydine (1) represents a new class of indole alkaloid containing two monoterpene units.

Gelsemium elegans (Gardn. and Champ.) Benth. (Loganiaceae) is a well-known toxic plant in Southeastern Asia and is used in Chinese traditional medicine as an analgesic, antispasmodic, and as a remedy for certain skin ulcers. In previous investigations on *Gelsemium elegans*, we have reported the isolation of several new indole alkaloids.[3-5] In this report, we describe the isolation, structure determination through X-ray crystallography, and unambiguous proton and carbon-13 NMR assignments[6] of a biogenetically novel oxindole alkaloid, gelsamydine (1).

Alkaloid 1 was obtained as white needles, mp 194–196 °C, $[\alpha]_D$ −126.9° (*c* 0.026, MeOH). The mass spectrum displayed a molecular ion at *m/z* 508, analyzing for $C_{29}H_{36}N_2O_6$, and a base peak at *m/z* 326 (M^+ − 182) for $C_{19}H_{22}N_2O_3$, which is the same as the molecular ion of gelsenicine (2), previously isolated from this plant.[7,8] The lost fragment, therefore, had the formula $C_{10}H_{14}O_3$. The UV absorptions of 1 at 206 and 257 nm suggested a gelsenicine type oxindole skeleton, and the IR spectrum showed absorptions for carbonyl (1716 cm^{-1}) and C=N (1635 cm^{-1}) groups as in 2, as well as hydroxyl (3413 cm^{-1}) and lactone (1751 cm^{-1}) functionalities which should be in the 10-carbon unit. The ^1H NMR spectrum displayed four aromatic proton signals (δ 7.50, 7.28, 7.09 and 6.90), one methoxy (δ 3.88), six aliphatic methylenes, 10 aliphatic methines, and two methyls as doublets at δ 0.90 (H-31) and 1.19 (H-18). The first methyl group was coupled to a multiplet at δ 1.72 (H-28), and the second was coupled to a multiplet at δ 3.58 (H-19). In 2, a triplet was observed at δ 1.33, consequently, attachment of the C_{10} unit should be at C-19, and this unit should also contain a secondary methyl, three methylene, and five methine groups in 1.

The ^{13}C NMR and APT spectra of 1 indicated the presence of two carbonyl, three quaternary, one olefinic, 14 methine, six methylene, one methoxy, and two methyl carbon atoms. Comparison of the carbon-13 NMR resonances of 1 and 2 (see Table I) showed that both compounds had nearly the same carbon-13 NMR signals as 1 except for C-18 and C-19, both of which were shifted



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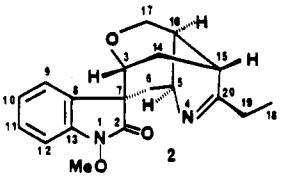

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substantially downfield; 10 additional carbon atoms were also observed. Thus gelsamydine is comprised of gelsenicine (2) with a monoterpene unit of unknown structure attached at C-19.

In order to obtain the ^1H and ^{13}C NMR assignments of 1, the unambiguous ^1H and ^{13}C NMR assignments of gelsenicine (2) were required, and for this purpose COSY, APT, HETCOR,[9,10] and selective INEPT[6,11] techniques were used; the results are shown in Table I. The present carbon-13 NMR data require revision of the previous assignments[7,8] for C-2, C-3, C-5, C-14, C-19, and C-20.

The COSY spectrum of 1 was nearly identical, in part, with the corresponding spectrum of 2. But several additional resonances were also observed, including a methine triplet at δ 4.93 (H-25) coupled to a methylene signal at δ 2.10 (H-27) and the resonance at δ 2.85 assigned to H-24. The methylene signal for H-27 was also coupled to H-28, which was itself coupled to the H-31 methyl and the H-29 methine signal at δ 2.35. The H-29 resonance was coupled to the H-30 methylene signals at δ 3.35, and the H-24 methine was coupled to the H-23 methine signal at δ 1.90. The latter signal was also coupled to the H-22 methylene signal at δ 2.36. These proton coupling arrangements confirmed the presence of an additional monoterpene unit, and from the coupling between the H-22 methylene and the H-19 methine, this moiety could be firmly placed at the C-19 position.

The carbon-13 NMR spectrum of 1 provided some additional structure information regarding the nature of the monoterpene unit. Thus, the carbonyl signal at δ 181.95 (C-26) and the methine carbon signal at δ 81.85 (C-25) suggested that the monoterpene unit had a lactone moiety, and an oxygenated methylene carbon at δ 60.18 indicated the presence of a primary alcohol, which the IR spectrum had previously suggested. The skeletal relationship between the functionalized carbons in the additional monoterpene unit, and the unambiguous assignment of the

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Table I. ^1H and ^{13}C NMR Assignments of Gelsamydine (1) and Gelsenicine (2)[a]

	^1H		^{13}C	
carbon	1	2	1	2
2			171.34	171.20
3	4.43 (m)	4.42 (m)	71.95	72.46
5	3.66 (m)	3.75 (m)	74.72	74.82
6α	2.39 (m)	2.38 (m)	37.02	37.66
6β	2.39 (m)	2.38 (m)		
7			56.03	55.77
8			131.73	132.22
9	7.50 (d, 7.8)	7.53 (d, 7.9)	124.98	124.63
10	7.09 (t, 7.8)	7.07 (d, 7.9)	123.40	123.25
11	7.28 (t, 7.8)	7.24 (t, 7.9)	128.19	127.98
12	6.90 (d, 7.8)	6.89 (t, 7.9)	106.76	106.48
13			138.26	138.00
14α	2.48 (m)	2.17 (m)	26.54	26.97
14β	2.12 (m)	2.17 (m)		
15	2.75 (m)	2.61 (m)	39.29	39.76
16	2.80 (m)	2.81 (m)	40.06	42.48
17α	4.30 (m)	4.34 (m)	61.80	62.01
17β	4.27 (m)	4.27 (m)		
18	1.19 (d, 7.5)	1.33 (t, 6.7)	20.15	9.96
19α	3.58 (m)	2.75 (m)	35.72	25.62
19β		2.37 (m)		
20			187.81	184.16
N_a-OMe	3.88 (s)	3.96 (s)	63.15	63.26
22α	2.36 (m)		37.47	
22β	2.36 (m)			
23	1.90 (m)		52.53	
24	2.85 (m)		48.51	
25	4.93 (t, 6.0)		81.85	
26			181.95	
27α	2.10 (m)		42.43	
27β	1.40 (m)			
28	1.72 (m)		33.02	
29	2.35 (m)		33.11	
30α	3.65 (m)		60.18	
30β	3.35 (m)			
31	0.90 (d, 6.9)		17.17	

[a] Recorded in $CDCl_3$, chemical shift values are reported as δ values (ppm) from internal TMS at 300 MHz, signal multiplicity and coupling constants (Hz) are shown in parentheses. Carbon chemical shifts are reported as δ values (ppm) at 75.6 MHz.

^{13}C NMR spectrum of 1 were obtained using a combination of APT, HETCOR, and selective INEPT pulse programming sequences. The HETCOR spectrum indicated all of the one bond proton–carbon assignments as shown in Table I. This spectrum also led to the assignment of the following methylene group resonances, which had not been possible from the COSY spectrum: H-6 and C-6 at δ 2.39 and 37.02; H-14 and C-14 at δ 2.12, 2.48, and 26.54; H-17 and C-17 at δ 4.27, 4.30, and 61.80; H-22 and C-22 at δ 2.36 and 37.47; H-27 and C-27 at δ 1.40, 2.10, and 42.43; H-30 and C-30 at δ 3.65, 3.35, and 60.18. The remaining quaternary carbons of 1 were assigned using the *J*-modulated selective INEPT technique. Polarization transfer from H-9 (δ 7.50) enhanced C-13 (δ 138.26), C-7 (δ 56.03) and C-10 (δ 123.40), and irradiation of H-10 (δ 7.09) enhanced C-8 (δ 131.73) and C-12 (δ 106.76). Selective INEPT irradiation of H-25 (δ 4.93) resulted in enhancements of C-26 (δ 181.95), C-23 (δ 52.53) and C-28 (δ 33.02), and irradiation of H-3 enhanced C-17 (δ 61.80), C-15 (δ 39.29) and C-6 (δ 37.02). Irradiation of H-18 (δ 1.19) enhanced C-20 (δ 187.81) and C-22 (δ 37.47), confirming the union of the gelsenicine and the monoterpene moieties to have occurred between C-19 and C-22. The complete assignment of the ^{13}C NMR spectrum of 1 is shown in Table I. The CD spectrum of 1 was identical with that of gelsenicine (2), indicating that they have the same configuration at C-7. But some ambiguities remained in the nature of the monoterpene unit.

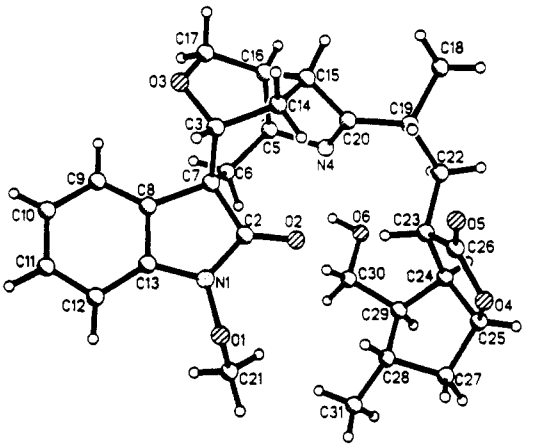

Figure 1. Molecular structure of 1.

Table II. Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å² × 10³)[a] for Gelsamydine (1)

atom	x	y	z	U (equiv)
N(1)	7716 (4)	721 (3)	1143 (4)	85 (2)
C(2)	8194 (4)	1486 (4)	704 (3)	60 (2)
C(3)	8481 (5)	1308 (5)	-900 (3)	71 (2)
N(4)	10310 (3)	3077 (3)	101 (3)	57 (1)
C(5)	10562 (4)	2068 (5)	-272 (3)	66 (2)
C(6)	10029 (4)	1181 (4)	166 (4)	68 (2)
C(7)	8864 (4)	998 (4)	8 (3)	66 (2)
C(8)	8622 (6)	-139 (4)	156 (5)	91 (3)
C(9)	8995 (8)	-997 (6)	-246 (6)	128 (4)
C(10)	8706 (12)	-1932 (10)	11 (12)	196 (10)
C(11)	8017 (10)	-2009 (9)	690 (11)	203 (11)
C(12)	7629 (7)	-1191 (6)	1145 (8)	132 (4)
C(13)	7947 (6)	-238 (5)	854 (6)	99 (3)
C(14)	8391 (4)	2432 (5)	-1108 (4)	72 (2)
C(15)	9444 (4)	2961 (5)	-1207 (3)	69 (2)
C(16)	10314 (4)	2172 (5)	-1226 (4)	78 (2)
C(17)	10046 (6)	1219 (7)	-1717 (4)	103 (3)
C(18)	9839 (6)	5316 (6)	-955 (5)	99 (3)
C(19)	9370 (4)	4631 (4)	-284 (3)	62 (2)
C(20)	9725 (4)	3559 (4)	-417 (3)	58 (2)
C(21)	7616 (7)	833 (7)	2604 (5)	119 (4)
C(22)	9568 (4)	5058 (4)	602 (3)	61 (2)
C(23)	8911 (3)	4629 (3)	1318 (3)	51 (2)
C(24)	9300 (4)	4876 (4)	2220 (3)	59 (2)
C(25)	8366 (4)	5323 (6)	2677 (4)	86 (2)
C(26)	7822 (4)	5044 (4)	1284 (4)	63 (2)
C(27)	8080 (5)	4597 (8)	3374 (4)	106 (3)
C(28)	8616 (5)	3602 (6)	3158 (4)	82 (2)
C(29)	9627 (4)	3958 (5)	2765 (3)	67 (2)
C(30)	10194 (5)	3102 (4)	2302 (4)	72 (2)
C(31)	8744 (6)	2871 (8)	3919 (5)	133 (4)
O(1)	7050 (4)	881 (4)	1817 (4)	109 (2)
O(2)	8084 (3)	2374 (3)	868 (2)	65 (1)
O(3)	9067 (4)	789 (4)	-1519 (3)	98 (2)
O(4)	7532 (3)	5393 (4)	2054 (3)	92 (2)
O(5)	7250 (3)	5085 (4)	694 (3)	87 (2)
O(6)	11016 (3)	3465 (3)	1809 (3)	83 (2)

[a] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized U_{ij} tensor.

The configuration for the remaining 10 asymmetric centers and conclusive evidence for the structure were obtained by single-crystal X-ray analysis. A drawing of the final X-ray model is given in Figure 1. The absolute configuration was not determined in the X-ray analysis, but was set to agree with the known absolute configuration of gelsenicine (2). The entire molecule is roughly U-shaped with a planar oxindole fragment at one end and a perpendicular set of five-membered rings at the other. Tables II–IV list the atomic coordinates and equivalent isotropic displacement parameters, bond lengths, and bond angles,

Table III. Bond Lengths of Gelsamydine (1)

bond	length, Å	bond	length, Å
N(1)–C(2)	1.368 (7)	N(1)–C(13)	1.373 (9)
N(1)–O(1)	1.382 (8)	C(2)–C(7)	1.536 (8)
C(2)–O(2)	1.205 (6)	C(3)–C(7)	1.561 (8)
C(3)–C(14)	1.520 (8)	C(3)–O(3)	1.409 (7)
N(4)–C(5)	1.487 (7)	N(4)–C(20)	1.281 (7)
C(5)–C(6)	1.519 (8)	C(5)–C(16)	1.536 (8)
C(6)–C(7)	1.552 (8)	C(7)–C(8)	1.545 (8)
C(8)–C(9)	1.381 (11)	C(8)–C(13)	1.407 (12)
C(9)–C(10)	1.347 (16)	C(10)–C(11)	1.395 (24)
C(11)–C(12)	1.385 (16)	C(12)–C(13)	1.396 (11)
C(14)–C(15)	1.542 (8)	C(15)–C(16)	1.534 (8)
C(15)–C(20)	1.512 (8)	C(16)–C(17)	1.512 (10)
C(17)–O(3)	1.424 (9)	C(18)–C(19)	1.512 (9)
C(19)–C(20)	1.498 (8)	C(19)–C(22)	1.520 (7)
C(21)–O(1)	1.437 (10)	C(22)–C(23)	1.518 (7)
C(23)–C(24)	1.536 (7)	C(23)–C(26)	1.516 (7)
C(24)–C(25)	1.526 (8)	C(24)–C(29)	1.539 (8)
C(25)–C(27)	1.498 (10)	C(25)–O(4)	1.460 (7)
C(26)–O(4)	1.345 (7)	C(26)–O(5)	1.187 (7)
C(27)–C(28)	1.520 (12)	C(28)–C(29)	1.524 (8)
C(28)–C(31)	1.541 (11)	C(29)–C(30)	1.527 (8)
C(30)–O(6)	1.401 (7)		

respectively. Anisotropic displacement parameters, H-atom coordinates, and isotropic displacement parameters are available from the authors.[12]

Gelsamydine represents a new class of oxindole alkaloid in which the C-19 of the oxindole moiety is connected to a biogenetically unusual monoterpene lactone. This monoterpene lactone can be considered to be formed from two isoprene units by connection of 1 to 4′ and 3 to 3′, with the lactone formed from a 5′-carboxyl group and a 4′-hydroxyl group. A recent communication from Thai and Japanese workers[13] reports the isolation of a similar compound, elegansamine, in which the added monoterpene unit has a δ-lactone unit. We have also isolated this compound and will report on this and several related derivatives elsewhere.

Experimental Section

General Experimental Procedures. The melting point was determined by means of a Kofler hot plate and is uncorrected. Optical rotation was measured with a Perkin-Elmer 241 polarimeter. The UV spectrum was obtained on a Beckman DU-7 spectrometer and the IR spectrum measured on a Nicolet MX-1 FT-IR (KBr) interferometer. ^{1}H NMR, homonuclear COSY, ^{13}C NMR, APT, and HETCOR spectra were recorded in $CDCl_3$, with TMS as internal standard, employing a Varian XL-300 instrument. Standard Varian pulse sequences were used. Selective INEPT NMR experiments were performed at 90.8 MHz using a Nicolet NMC-360 spectrometer. Data sets of 16K covering a spectral width of 10 MHz were acquired. Proton pulse widths were calibrated by using a sample of acetic acid in 10% C_6D_6 (^1J = 6.7 Hz) in a 5-mm NMR tube.[14] The radio frequency field strength for the soft proton pulse was on the order of 25 Hz for these experiments. Eight hertz and 6 Hz were used as $^3J_{C\text{-}H}$ for aromatic protons, and 6 Hz and 4 Hz for aliphatic protons. Low-resolution mass spectrum was obtained with a Varian MAT 112S instrument operating at 70 eV. CD spectrum was run in MeOH with a JASCO J-40A spectropolarimeter. X-ray data were recorded on a Nicolet R3 diffractometer and analyzed on a Microvax II c.p.u. using the SHELXTL series of programs.

Plant Material. Whole plants of *Gelsemium elegans* were collected in Guangxi Province of China in February, 1987, and voucher specimens are deposited in the herbarium of Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, People's Republic of China.

Table IV. Bond Angles of Gelsamydine (1)

angle	degree	angle	degree
C(2)–N(1)–C(13)	114.3 (6)	C(2)–N(1)–O(1)	123.8 (5)
C(13)–N(1)–O(1)	121.9 (6)	N(1)–C(2)–C(7)	107.8 (5)
N(1)–C(2)–O(2)	123.5 (5)	C(7)–C(2)–O(2)	128.7 (5)
C(7)–C(3)–C(14)	118.4 (5)	C(7)–C(3)–O(3)	109.2 (5)
C(14)–C(3)–O(3)	111.4 (5)	C(5)–N(4)–C(20)	108.9 (4)
N(4)–C(5)–C(6)	114.1 (4)	N(4)–C(5)–C(16)	104.9 (5)
C(6)–C(5)–C(16)	114.4 (5)	C(5)–C(6)–C(7)	119.4 (5)
C(2)–C(7)–C(3)	110.9 (4)	C(2)–C(7)–C(6)	111.9 (4)
C(3)–C(7)–C(6)	114.5 (5)	C(2)–C(7)–C(8)	110.5 (5)
C(3)–C(7)–C(8)	109.0 (5)	C(6)–C(7)–C(8)	109.0 (5)
C(7)–C(8)–C(9)	130.6 (7)	C(7)–C(8)–C(13)	109.5 (6)
C(9)–C(8)–C(13)	119.8 (7)	C(8)–C(9)–C(10)	120.8 (11)
C(9)–C(10)–C(11)	118.2 (12)	C(10)–C(11)–C(12)	124.7 (11)
C(11)–C(12)–C(13)	115.0 (10)	N(1)–C(13)–C(8)	107.9 (6)
N(1)–C(13)–C(12)	130.8 (8)	C(8)–C(13)–C(12)	121.3 (7)
C(3)–C(14)–C(15)	113.1 (5)	C(14)–C(15)–C(16)	110.5 (5)
C(14)–C(15)–C(20)	111.5 (4)	C(16)–C(15)–C(20)	101.0 (4)
C(5)–C(16)–C(15)	101.3 (4)	C(5)–C(16)–C(17)	118.0 (6)
C(15)–C(16)–C(17)	113.7 (5)	C(16)–C(17)–O(3)	115.1 (5)
C(18)–C(19)–C(20)	109.8 (5)	C(18)–C(19)–C(22)	110.3 (5)
C(20)–C(19)–C(22)	115.1 (4)	N(4)–C(20)–C(15)	113.9 (5)
N(4)–C(20)–C(19)	124.1 (5)	C(15)–C(20)–C(19)	122.0 (5)
C(19)–C(22)–C(23)	116.3 (4)	C(22)–C(23)–C(24)	114.6 (4)
C(22)–C(23)–C(26)	111.4 (4)	C(24)–C(23)–C(26)	105.2 (4)
C(23)–C(24)–C(25)	104.6 (4)	C(23)–C(24)–C(29)	115.8 (4)
C(25)–C(24)–C(29)	105.1 (4)	C(24)–C(25)–C(27)	107.0 (5)
C(24)–C(25)–O(4)	107.5 (5)	C(27)–C(25)–O(4)	110.1 (5)
C(23)–C(26)–O(4)	110.7 (5)	C(23)–C(26)–O(5)	128.8 (5)
O(4)–C(26)–O(5)	120.6 (5)	C(25)–C(27)–C(28)	105.9 (5)
C(27)–C(28)–C(29)	102.7 (6)	C(27)–C(28)–C(31)	114.5 (6)
C(29)–C(28)–C(31)	114.3 (5)	C(24)–C(29)–C(28)	103.2 (4)
C(24)–C(29)–C(30)	116.5 (4)	C(28)–C(29)–C(30)	112.4 (5)
C(29)–C(30)–O(6)	112.3 (5)	N(1)–O(1)–C(21)	109.2 (5)
C(3)–O(3)–C(17)	116.1 (5)	C(25)–O(4)–C(26)	111.7 (4)

Extraction and Fractionation. The air-dried plant material (20 kg) was percolated with EtOH (200 L) at room temperature, and the EtOH extract was concentrated in vacuo at 50 °C to afford a thick dark syrup. The syrup was redissolved in 1% aqueous HCl solution, and the residual solid was treated with 1% aqueous HCl until the solution gave a negative Dragendorff's test. After extraction three times with $CHCl_3$, the acidic layer was basified with NH_3 and extracted five times with $CHCl_3$ to give crude alkaloid extract A (112 g).

Isolation of Gelsamydine (1). A portion of the 10% methanol in chloroform eluent (1.20 g) from the column chromatography on Si gel[1] of the alkaloid extract was subjected to repeated preparative TLC using cyclohexane–EtOAc–diethylamine (6:4:1, v/v) as a solvent system, and the first band at R_f 0.75 was eluted with acetone to afford white needles of 1 (30 mg, 0.000 15%): mp 194–196 °C; $[\alpha]_D$ −126.9° (*c* 0.26, MeOH); UV λ_{max} (log ε) 206 (4.47) and 257 (3.91) nm; IR ν_{max} (KBr) 3413, 2913, 2904, 1751, 1716, 1635, 1575, 1425, 1042, and 762 cm^{-1}; ^{1}H and ^{13}C NMR, see Table I; MS *m/z* (rel int) 508 (M^+, 89), 479 (12), 477 (79), 339 (28), 333 (13), 332 (36), 327 (24), 326 (100), 304 (18), 295 (24), 150 (56), 146 (13), 144 (14), 134 (12), 132 (17), 130 (15), 122 (18), 120 (16), 108 (16), 107 (21), 106 (12), 94 (50), and 81 (32); HRMS obsd 508.2574 for $C_{29}H_{36}N_2O_6$, calcd 508.2573; CD (MeOH) Δε (nm) +11.39 (235) and −7.39 (263).

Single-Crystal X-ray Diffraction Analysis of Gelsamydine (1). A colorless prism with dimensions of 0.25 × 0.25 × 0.45 mm was used for all diffraction experiments. Preliminary X-ray photographs showed orthorhombic symmetry, and accurate lattice constants of a = 12.982 (3), b = 13.156 (4), and c = 15.671 (3) Å were determined on a diffractometer. Systematic extinctions and a calculated density of 1.26 g/cm^3 were uniquely accommodated with one molecule of composition $C_{29}H_{36}N_2O_6$ forming the asymmetric unit in space group $P2_12_12_1$. All unique diffraction maxima with $2\theta \geq 112°$ were collected with a 2θ scan technique and Cu Kα radiation (1.541 78 Å). Of the 1990 unique reflections measured, 1695 (85%) were judged observed ($|F_o| \geq 4\sigma(F_o)$) after correction for Lorentz, polarization, and background effects. The structure was solved by direct methods and refined by full-matrix least-squares techniques. In the final least-squares cycles, the

(12) The main library of programs used for data collection and analysis were the Nicolet/SHELXTL Library distributed by Nicolet Instruments Division, Madison, WI.

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model included anisotropic non-hydrogen atoms and fixed isotropic hydrogens. The final crystallographic residual was 0.049 and additional crystallographic information can be found in Tables II-IV.[12]

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Notes

Optically Active Tetrahydro-α-phenyl-6,7-dimethoxyisoquinoline-1-methanols from (1-Phenylethyl)ureas. Absolute Configuration of (-)- and (+)-Isomers of the Erythro Series

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Introduction

1,2,3,4-Tetrahydro-α-phenylisoquinoline-1-methanols (1-(α-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines, TIQM) are less known than their 1-benzyl analogues, which represent an important group of the isoquinoline alkaloids.[1-3] TIQM occur as optically active alkaloids in plants,[4,5] and the (±)-erythro isomers prepared by synthesis have shown interesting pharmacological properties.[6] This suggested that a general strategy for a practical synthesis of optically active TIQM could be designed and the absolute configurations of the optical isomers could be determined.

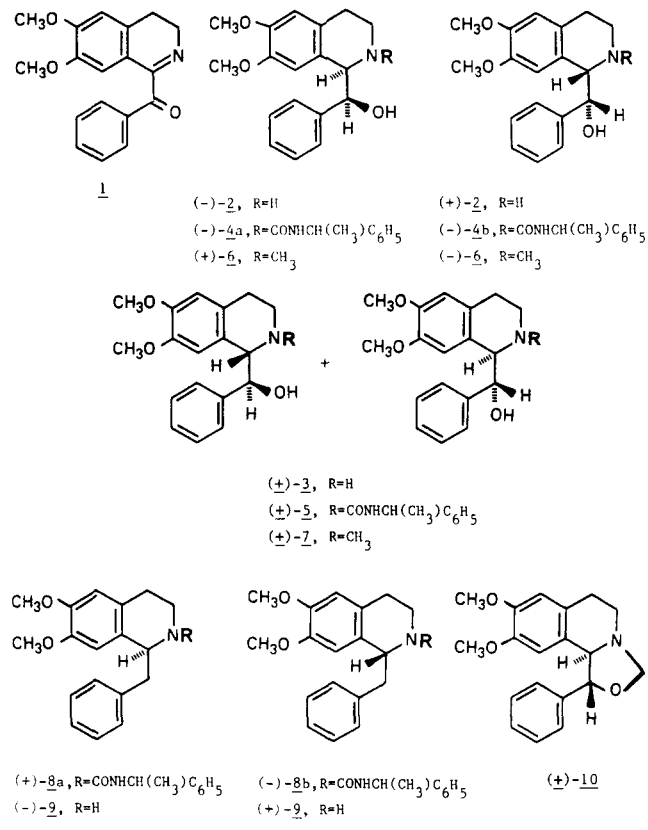
The resolution of the erythro isomer ((±)-**2**) and the threo isomer ((±)-**3**) could be accomplished by reaction of each of the racemic amines with an optically active 1-phenylethyl isocyanate to give the diastereomeric (1-phenylethyl)ureas (**4** and **5**, respectively), followed by separation and subsequent hydrolysis.

This method applied before to prepare optically active tetrahydroisoquinolines[7] is now extended to a synthesis of optically active amino alcohols. Catalytic deoxygenation of the optically active alcohol to the deoxy congener of known absolute configuration, together with assignments of erythro and threo stereochemistry established by ^1H NMR spectroscopy, seem to offer a method for determination of absolute configuration. The results of this investigation, which show (-)-**2** to have the 1*R*,α*S* configuration and (+)-**2** the 1*S*,α*R* configuration are reported here.

Results and Discussion

A convenient starting material for the synthesis of optically active TIQM is the known 1-benzoyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**1**).[8-11] Reduction of **1** with sodium borohydride in methanol at room temperature afforded a 77:23 mixture of erythro alcohol (±)-**2** and threo isomer (±)-**3**, which were separated by crystallization followed by flash chromatography. A high degree of stereospecificity in the reduction of 1-benzoyl-3,4-dihydroisoquinolines with sodium borohydride in methanol, leading predominantly to erythro isomers, has frequently been observed.[11-14]

Chart I



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