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STRUCTURE AND ABSOLUTE STEREOCHEMISTRY OF PSEUDOREPANDULINE. ^{13}C-NMR STUDIES ON REPANDULINE-TYPE ALKALOIDS

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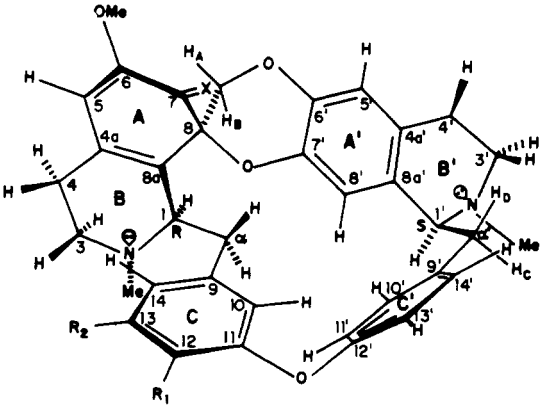
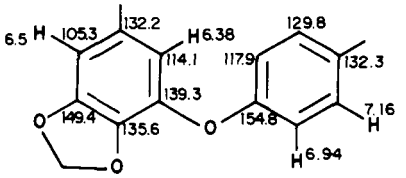
ABSTRACT.—The ^{13}C-nmr spectrum of repanduline was assigned from the known structure **2** by means of ^{13}C-^{1}H (HETCOR) 2D correlation experiments. Using data from repanduline in conjunction with ^{1}H-^{1}H (COSY) and HETCOR 2D studies on pseudorepanduline [**1**], the absolute stereochemistry of **1** has been determined. Some observations are made on the conformation of repanduline-type alkaloids and on their possible mode of biosynthesis.

The unusual yellow bisbenzylisoquinoline alkaloid, repanduline [**2**], was first described in 1947 (1). It was the subject of a number of degradative and spectroscopic studies (2–4) before its structure and absolute stereochemistry were determined unequivocally by the use of long-range differential nOe effects (5), ^{13}C-nmr spectroscopy [F. de A.M. Reis and I.R.C. Bick, unpublished data; see note 20 of Neuhaus *et al.* (5)] and X-ray crystallography [D.J. Williams, D. Neuhaus, and I.R.C. Bick, unpublished data; see note 28 of Neuhaus *et al.* (5)]. Another analogous yellow biscoclaurine alkaloid, pseudorepanduline [**1**], was briefly described in 1975 (6), and recently a third, dielsine, was reported, for which structure **3** has been proposed (7).

In the course of determining the structure of repanduline, the chemical shifts of all its protons had been determined (5). Using these data, a 2D ^{13}C-^{1}H correlation (HETCOR) study of **2** was performed in order to match each carbon with its corresponding signal. The assignments so deduced have been supported by comparison with those of model compounds. The ring A′ carbons of **2** were compared with those of the benzodioxin model **5**, and compound **4** was used for the sp^2 carbons of rings C and C′; in addition, the ring C′ assignments proved to be closely similar to those for members of



1 R^1=OMe, R^2=H, X=O
2 R^1R^2=OCH_2O, X=O
3 R^1=OH, R^2=OMe, X=O
6 R^1R^2=OCH_2O, X=H, OH
8 R^1=OMe, R^2=H, X=H, OH



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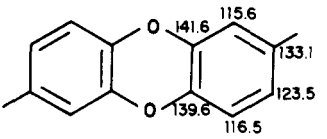

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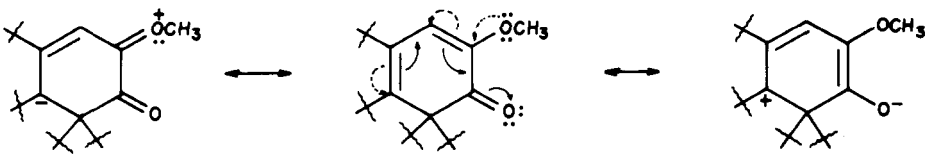
the berbamine series of bisbenzylisoquinolines (8), including tenuipine which, moreover, has the same partial structure as repanduline and similar carbon assignments for ring C.

As for ring A of the repanduline group, its structure is distinguished from that of all the other bisbenzylisoquinoline alkaloids by the simultaneous presence of a cyclohexadienone ring, an enol ether group, and a spiro carbon atom. Carbon C-5, resonating at 112.9 ppm, could be unambiguously correlated with H-5 at δ 5.52, and the assignment of absorptions at 148.0, 193.7, and 83.5 ppm to C-6, C-7, and C-8, respectively, was relatively straightforward.

The signals at 125.7 and 131.8 ppm were ascribed to C-4a and C-8a, the remaining carbons of ring A, on the following basis. Carbon C-8a would be expected to suffer deshielding because of electron withdrawal resulting from the mesomeric effect of the conjugated ketone group (Scheme 1). On the other hand, the enol ether group would have a mesomeric effect in the opposite sense, and chemical evidence indicates that these effects counteract each other in part; whereas repanduline [**2**] shows good stability to aqueous acid despite its enol ether structure, the corresponding secondary alcohol **6** formed by borohydride reduction of **2** is acid-labile and is readily hydrolyzed to the ketone **7**. The shielding effect of the enol ether group in **6** should thus be apparent on C-8a, instead of being masked by the presence of the carbonyl in **2**. On this basis, C-8a is assigned the values 131.8 and 123.5 in **2** and **6**, respectively, while the C-4a value of 125.7 ppm is almost unchanged when **2** is reduced to **6**.

Assignments based on chemical considerations, comparison with model compounds, and the use of homonuclear (COSY) 2D experiments have reinforced the HETCOR 2D correlation study and have allowed the unambiguous assignment of the ^{13}C-nmr signals for repanduline [**2**] (Table 1). The same techniques were then applied to pseudorepanduline [**1**]. The ^{1}H-nmr spectrum of **1**, which was assigned by means of a COSY 2D experiment (Table 2), showed chemical shifts and patterns similar to those of repanduline [**2**]. The major differences between **1** and **2** appear in ring C; in the pseudorepanduline spectrum, the signal for H-14 (δ 7.05, dd, J = 8.3 and 1.8 Hz) has a meta coupling to H-10 (δ 6.52, d, J = 1.8 Hz) and an ortho coupling to a doublet at δ 6.77 (J = 8.3 Hz) which is absent from the repanduline spectrum and is ascribed to H-13. The difference in substitution pattern between **1** and **2** is clearly demonstrated.

The three protons attached to C-1′ and C-α′ form an AMX system, with a signal at δ 3.69 (dd, J = 12 and 4 Hz) assigned to H-1′ and others at δ 3.37 (dd, J = 12 and 4



SCHEME 1

TABLE 1. ^{13}C-nmr Data for Repanduline-type Alkaloids and Derivatives **1**, **2**, and **6–9**.

Carbon	Compound					
	1	**2**	**6**	**8**	**7**	**9**[a]
C-1	62.3	62.7	61.1	60.0	59.3	58.8
C-3	50.0	49.9	49.2	48.2	45.4	48.9
C-4	28.6	29.1	28.4	27.6	27.1	26.7
C-4a	125.8	125.7	125.8	125.7	126.8	126.6
C-5	112.7	112.9	95.2	94.8	42.2	42.5
C-6	147.9	148.0	157.2	157.0	205.5	205.8
C-7	193.0	193.7	76.4	76.1	81.3	81.6
C-8	83.3	83.5	78.5	78.4	76.7	—
C-8a	131.8	131.8	123.5	123.5	125.0	124.2
C-α	37.3	37.7	38.4	37.2	37.7	37.0
C-9	135.7	136.1	136.6	136.2	135.9	135.0
C-10	117.7	111.9	112.7	118.9	112.8	119.2
C-11	146.0	142.8	142.7	146.0	142.5	146.6
C-12	148.6	133.4	134.4	148.2	133.2	148.2
C-13	110.9	147.9	148.1	110.9	148.1	111.3
C-14	123.4	103.4	103.8	122.3	103.6	123.4
C-1′	64.9	64.9	65.0	64.9	64.5	64.9
C-3′	46.1	45.9	46.4	46.3	46.4	45.5
C-4′	25.2	25.1	25.2	25.0	24.5	24.0
C-4a′	128.6	129.0	129.8	129.2	130.1	130.3
C-5′	114.8	114.9	114.8	114.7	114.6	115.1
C-6′	140.0	140.1	141.3	141.1	140.5	141.4
C-7′	139.4	139.4	139.9	139.7	139.2	139.9
C-8′	116.3	116.3	116.8	116.6	116.4	117.0
C-8a′	127.9	127.8	127.5	127.5	127.4	127.2
C-α′	39.1	38.9	39.4	39.6	38.4	38.8
C-9′	131.8	132.4	132.4	132.4	132.4	131.7
C-10′	129.2	129.7	129.7	129.7	129.5	130.0
C-11′	122.2	122.2	122.2	122.8	122.1	122.9
C-12′	153.0	152.6	152.1	153.4	152.4	153.6
C-13′	122.2	122.7	122.7	122.8	122.1	122.9
C-14′	134.8	134.9	134.2	134.2	134.6	135.0
N-Me	43.1	43.2	43.2	43.0	41.6	41.6
N′-Me	42.1	42.1	42.2	42.2	42.2	42.3
6-O-Me	55.2	55.3	55.4	55.3		
12-O-Me	55.8			55.8		56.0
C-CH_2-O	68.2	68.3	63.1	62.9	65.9	66.2
O-CH_2-O		100.9	101.0		100.9	

[a]The chemical shift of C-8 was obscured by the solvent peak.

Hz) and δ 2.68 (t, J = 12 Hz) ascribed to H_C and H_D, respectively. The corresponding protons on C-1 and C-α form a second-order system in the δ 3.01 region.

The protons H-A and H-B of the dioxin residue absorb at δ 4.16 and 3.90, respectively, (each d, J = 11 Hz), and the remaining aliphatic protons attached to C-4 (δ 2.10 and 2.28), C-3 (δ 2.45 and 3.12), and C-3′ (δ 2.90 and 3.27) give signals similar to those of **2** (5).

A HETCOR experiment permitted the complete assignment of all carbon signals of pseudorepanduline [**1**]. The ^{13}C chemical shifts of **1** and its derivatives **8** and **9** (Table 1) in general closely parallel those of **2**, **6**, and **7**, respectively. The data indicate that ring A is similarly constituted in **1** and **2**, and in particular C-8a shows the same shift from 131.8 to 123.5 ppm when **1** is reduced to **8** as that already noted in repanduline.

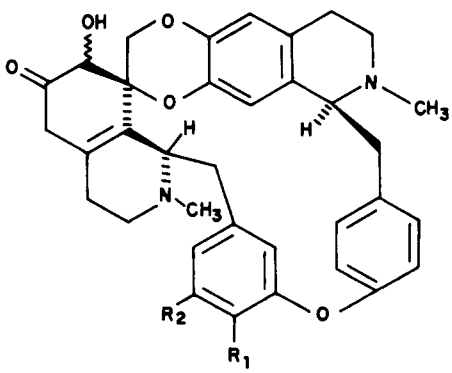
TABLE 2. ^{1}H-nmr Assignments for Pseudorepanduline [**1**] in $CDCl_3$.[a]

Proton	Assignment	Proton	Assignment
H-1	2.87–3.06 m	H-8′	5.13 s
H_{ax}-3	3.12 m	H_C	3.37 dd, J = 12 and 4
H_{eq}-3	2.45 m		
H_{eq}-4	2.28 m	H_D	2.68 t, J = 12
H_{ax}-4	2.10 m	H-10′	7.37 dd, J = 8.2 and 2.1
H-5	5.52 s		
H-α	2.87–3.06 m	H-11′	7.15 dd, J = 8.2 and 2.4
H-10	6.52 d, J = 1.8		
H-13	6.77 d, J = 8.3	H-13′	6.95 dd, J = 8.3 and 2.4
H-14	7.05 dd, J = 8.3 and 1.8	H-14′	6.77 dd, J = 8.3 and 2.1
H-1′	3.69 dd, J = 12 and 4	H_A	4.16 d, J = 11
H_{eq}-3′	3.27 m	H_B	3.90 d, J = 11
H_{ax}-3′	2.90 m	6-OMe	3.63 s
H_{eq}-4′	2.87 m	12-OMe	3.92 s
H_{ax}-4′	2.60 m	N_2-Me	2.42 s
H-5′	6.52 s	N'_2-Me	2.65 s

[a]Coupling constants (J) are given in Hz.

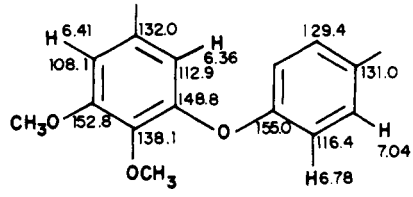
The only significant differences between the spectra of **1** and **2** appear in signals from ring C, where a methylenedioxy group is replaced by an MeO. The signals at 110.9, 117.7, and 123.4 ppm, which were correlated with H-13, H-10, and H-14 resonating at δ 6.77, 6.52, and 7.05, respectively, were assigned to the corresponding carbons C-13, C-10, and C-14. Their chemical shifts closely resemble those recorded for the similarly located carbons of phaeanthine (8).

In previous conformational studies (8–10), we have shown that 18-membered macrocyclic bisbenzylisoquinolines have severe steric constraints. In the repanduline [**2**] series, the presence of a spiro carbon introduces an additional torsional strain which makes the whole molecule less flexible. From Dreiding models it can be seen that rings A, B, and C of **1** and **2** have an extended conformation in which ring C is bent forward to form an interplanar angle close to 90° with ring B. The flexibility of the macro rings of **1** and **2** is clearly diminished as compared with that of a simple bisbenzylisoquinoline alkaloid, and the free rotation of rings C and C′ is further restricted. Some indication of the effect of this restriction on rings C′ is given by the chemical shifts of the protons at-



7 R^1R^2=OCH_2O
9 R^1=OMe, R^2=H

tached to it. In the model compounds **4** and **10**, where there is complete freedom of rotation of each ring about the ether linkage, there is no difference in chemical shift between the two ortho protons in the right-hand rings; the meta protons form a similar pair. In the case of repanduline [**2**], the corresponding pairs H-11′ (δ 7.12)/H-13′ (δ 6.92), and H-10′ (δ 7.37)/H-14′ (δ 6.73) of ring C′ differ in chemical shift by 0.20 and 0.64 ppm (5), respectively, and similar values are observed for **1** and **3** (dielsine) (7).



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The chemical shifts of C-3 and C-4 (50.0 and 28.6 ppm, respectively, for **1** and 49.9 and 29.1 ppm for **2**) suggest that ring B of both compounds adopts a half-chair conformation, with the N-Me and C-α equatorially oriented and anti to C-4 and C-3, respectively. This disposition accords with that observed (9,10) in other bisbenzylisoquinoline alkaloids, and also with that reported (11) for the corresponding carbons (C-5 and C-6) of tetrahydroprotoberberines. The intermediate values found for the ring B′ carbons C-3′ and C-4′ of **1** and **2** are indicative of a mixture between different conformations bearing axial and equatorial N′-Me and C-α′ groups.

In the berbamine type of bisbenzylisoquinolines, the difference in chemical shift of the C-α and C-α′ carbons has been correlated with the stereochemistry at C-1 and C-1′ (8); the difference for alkaloids with an *R,R* or *S,S* configuration is ca. 3.5 ppm, whereas for bases with an *R,S* or an *S,R* stereochemistry, it amounts to ca. 1 ppm. This parameter also appears to hold true for the repanduline series as an indication of the configuration at these centers: the value for **2**, which has been shown to have the *R,S* stereochemistry, is 1.2 ppm, while **1**, with a value of 1.8 ppm and a specific rotation similar in sign and magnitude to **2**, must have the same configuration.

The same *R,S* stereochemistry is associated with berbamine, and a close analogue of this alkaloid could serve as an intermediate in the biosynthesis of **1** by a process of phenolic oxidation leading to the formation of a new carbon-carbon bond, a process similar to that suggested for the biosynthesis of repanduline [**2**] (3). When this proposal was made concerning **2**, its stereochemistry was unknown, and nortenuipine, which has been found to occur in both *S,S* and *R,R* configurations, was suggested as the biosynthetic intermediate (3). However, a more likely alkaloidal starting point for **2** would appear to be a close analogue of isotenuipine (12), a base with the correct *R,S* stereochemistry which has been isolated from a repanduline-containing plant.

In summary, the ^{13}C- and high-resolution ^{1}H-nmr studies provide conclusive evidence for the structural similarity of **1** and **2** except for ring C, where the different substitution pattern is clearly demonstrated. In conjunction with the specific rotation data, the nmr evidence establishes the structure and absolute configuration of pseudorepanduline as **1**.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The ^{13}C-nmr spectra were measured in ca. 0.25 mmol $CDCl_3$ solution in a 10-mm spinning tube with TMS as internal standard. A Varian XL 100 nmr spectrometer at 25.2 MHz interfaced with a Varian 620 L Fourier transform computer with a 16K memory was

employed. The 400 MHz ^{1}H-nmr spectrum of pseudorepanduline was obtained from a $CDCl_3$ solution in a 5-mm spinning tube with TMS as internal standard by means of the experimental spectrometer IEF 400 at the Institut d'Electronique Fondamentale d'Orsay. The ^{1}H- (300.98 MHz) and ^{13}C- (75.46 MHz) nmr spectra of pseudorenpanduline and repanduline were recorded on a Varian Gemini 300 spectrometer in $CDCl_3$ solution using a 5 mm spinning tube and TMS as internal standard. The DEPT pulse sequence to establish the carbon shifts and degree of protonation was measured in a 5 mm ^{13}C/^{1}H dual probe head. The following conditions apply to the ^{1}H-^{1}H COSY 90 experiment: number of increments = 512; number of repetitions = 16; 2D spectral width = 2454.0 Hz. The 2D ^{13}C-^{1}H chemical shift correlated spectra of pseudorepanduline and repanduline were obtained using the standard HETCOR pulse sequence, which incorporated quadrature detection in both domains. The fixed delays corresponded to an average ^1J(^{13}C-^{1}H) coupling of 140 Hz. The other spectroscopic parameters used were: number of increments = 128, number of repetitions = 232, 1D spectral width = 18761.7 Hz, and 2D spectral width = 2454.0 Hz.

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