at −45 °C, and the resulting solution was warmed to −20 °C for 0.5 h, quenched with saturated ammonium chloride, and extracted with ether. The combined extracts were washed with saturated ammonium chloride, dried ($MgSO_4$), and evaporated. The residue was subjected to silica gel column chromatography with hexane–ether (3:1) as an eluant to yield **5** (906 mg, 91%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, CH_2CH_3), 1.27 (br s, 12 H, CH_2), 1.26 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 1.45–2.20 (m, 6 H, CH_2), 2.20–2.65 (m, 3 H, $CHCH_3$ and CH_2), 3.79 (s, 3 H, $COOCH_3$); IR (CCl_4) 1745, 1765 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.52; H. 10.37.

2-Methyl-5-nonyl-5-carboxypentanolide (6). To a solution of **5** (475 mg, 1.59 mmol) in dry pyridine (5 mL) was added lithium iodide (1.50 g, 11.21 mmol). The resulting solution was refluxed for 8 h, poured into water, acidified with 0.1 N hydrochloric acid, and extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to yield **6** (440 mg, 98%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, 3 H, CH_2CH_3), 1.27 (br s, 15 H, CH_2 and $CHCH_3$), 1.45–2.20 (m, 6 H, CH_2), 2.20–2.65 (m, 3 H, CH_2 and $CHCH_3$), 9.40 (br, 1 H, COOH); IR (CCl_4) 3150 (OH), 1730, 1710 (C=O) cm^{-1}.

***dl*-Malyngolide (1a) and 2-Epimalyngolide (1b).** To a solution of **6** (246 mg, 0.86 mmol) in ether (5 mL) at 0 °C were added triethylamine (104 mg, 1.03 mmol) and ethyl chloroformate (118 mg, 1.03 mmol). After 0.5 h of stirring at 0 °C, freshly prepared zinc borohydride in ether (0.45 M, 2.3 mL, 1.04 mmol) was added. The resulting solution was stirred at 0 °C for 0.5 h, poured into saturated ammonium chloride, and extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was subjected to silica gel column chromatography with hexane–ethyl acetate (7:3) to yield 129 mg (55%) of **1a** (R_f 0.35; hexane–ethyl acetate, 6:4) and 58 mg (25%) of **1b** (R_f 0.47; hexane–ethyl acetate, 6:4). **1a**: ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, 3 H, CH_2CH_3), 1.27 (br s, 16 H, CH_2), 1.26 (d, J = 6.5 Hz, 3 H, $CHCH_3$), 1.45–2.25 (m, 4 H, CH_2), 2.25–2.65 (m, 1 H, $CHCH_3$), 2.80 (br s, 1 H, OH), 3.46 (d, J = 12 Hz, 1 H, CH_2OH), 3.70 (d, J = 12 Hz, 1 H, CH_2OH); IR (neat) 3420 (OH), 1730, 1715 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.49; H, 11.28. **1b**: ^1H NMR ($CDCl_3$) δ 0.89 (br t, J = 5 Hz, 3 H, CH_2CH_3), 1.27 (br s, 19 H, CH_2 and $CHCH_3$), 1.45–2.25 (m, 4 H, CH_2), 2.25–2.65 (m, 1 H, $CHCH_3$), 2.86 (br s, 1 H, OH), 3.58 (s, 2 H, CH_2OH); IR (neat) 3400 (OH), 1730, 1715 (C=O) cm^{-1}.

Acknowledgment. We are grateful to the Korean Traders Scholarship Foundation for financial support.

Registry No. 1a, 74742-19-1; **1b**, 76984-84-4; **2** K salt, 62791-43-9; **3**, 82798-02-5; **4**, 82808-05-7; **5**, 82838-26-4; **6**, 82838-27-5; *n*-nonyl bromide, 693-58-3.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy and Conformational Analysis of the Daphnoline–Repandine Class of Bis(benzylisoquinoline) Alkaloids

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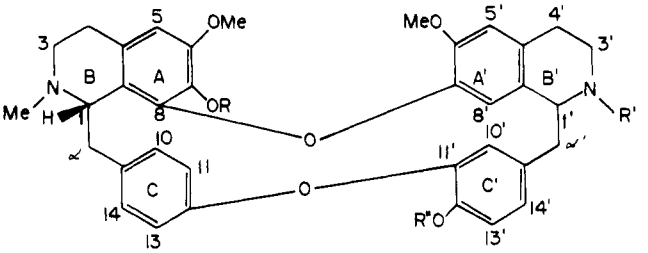
The conformation of macrocyclic compounds are a challenge which has normally been solved by using X-ray crystallography. On the basis of previous works on bis(benzylisoquinoline) alkaloids[1b,2] and conscious that ^1H and ^{13}C NMR data are reliable tools for conformational analysis, we decided to carry out a careful analysis of the 18-membered macrocyclic alkaloids of the dapnoline–repandine class in order to contribute to the determination of related unknown compounds as well as to stimulate similar studies on other macrocyclic compounds.

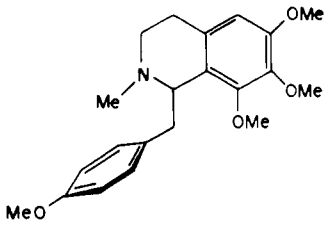
The ^{13}C NMR shifts for daphnoline and some of its derivatives (**1–4**) are listed in Table I. Assignments for



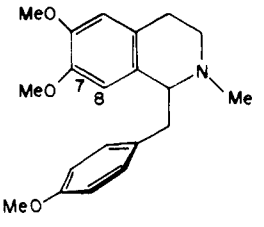
(1) R=R'=R"=H, 1'= R
(2) R=R"=H,R'=Me, 1'= R
(3) R=R'=H,R"=Me, 1'= R
(4) R=R"=Me,R'=H, 1'= R
(5) R=R'=Me,R"=H, 1'= S
(6) R=R'=R"=Me, 1'= S
(13) R=R'=R"=Me, 1'= R

two alkaloids which belong to a diastereomeric series, repandine (**5**) and *O*-methylrepandine (**6**), are also listed. The values have been derived from standard chemical shift theory and from a study of the SFORD and the fully coupled ^{13}C NMR spectra. We have also taken into account analyses which have been reported previously for various mono-[1] and bis(benzylisoquinoline)[1b,2] alkaloids. It has been possible to resolve most of the uncertainties in assignment by selective heteronuclear irradiations and by a consideration of the known effects of O- and N-alkylation.

In the case of monobenzylisoquinoline alkaloids, it is known from ^1H NMR data[3] that a base such as *N,O,O*-trimethylcoclaurine (**7**) preferentially adopts a folded conformation in solution, but if a substituent such as methoxyl is inserted at C-8 as in **8**, an extended conformation is preferred.



(8)



(7)

These facts can only be used for the bis(benzylisoquinoline) conformational analysis, taking into consideration that new steric interactions arise when the macrocycle is formed by the coupling of two benzylisoquinoline

(1) (a) Wenkert, E.; Buckwalter, B. L.; Burffit, I. R.; Gasić, M. J.; Gottlieb, H. E.; Hagaman, E. W.; Schell, F. M.; Wovkulich, P. M. In "Topics in Carbon-13 NMR Spectroscopy"; Levy, G. C., Ed.; Wiley-Interscience: New York, 1976, p 105. (b) Marsaioli, A. J.; Rûveda, E. A.; Reis, F. de A. M. *Phytochemistry* **1978**, *17*, 1655.

(2) (a) Koike, L.; Marsaioli, A. J.; Rûveda, E. A.; Reis, F. de A. M.; Bick, I. R. C. *Tetrahedron Lett.* **1979**, 3765. (b) Koike, L.; Marsaioli, A. J.; Reis, F. de A. M. *J. Org. Chem.* **1981**, *46*, 2385.

(3) (a) Tomita, M.; Shingu, T.; Fujitani, K.; Furukawa, H. *Chem. Pharm. Bull.* **1965**, *13*, 921. (b) Dalton, D. R.; Cava, M. P.; Buck, K. T. *Tetrahedron Lett.* **1965**, 2687.

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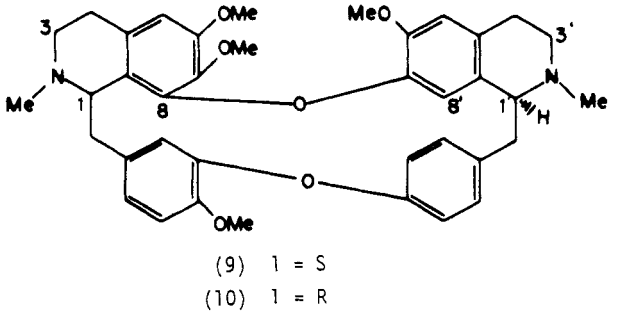
Table I[a]

carbons	chemical shift, ppm					
	1	2	3	4	5	6
1	60.8	60.9	61.3	61.5	59.7	60.5
3	44.6	45.0	45.3	45.3	43.8	44.4
4	23.6	24.4	24.8	25.2	25.9	26.4
4a	121.9	122.9	122.9	127.5	127.0	127.6
5	104.5	104.7	104.7	105.7	106.5	106.8
6	147.9	146.7	147.0	151.3	151.2	151.9
7	133.6	133.4	133.6	137.5	136.0	136.0
8	141.2	141.3	141.7	147.9	148.3	148.5
8a	121.9	122.7	123.4	122.7[b]	121.1	121.9
α	39.9	40.0	39.8	39.8	40.7	40.6
9	130.2	130.6	130.9	130.7	132.3	133.9
10	127.7	128.6	127.9	127.6	129.9	129.9
11	121.7	121.4	121.9	122.1[b]	120.1	120.3
12	151.6	152.6	151.9	151.6	155.0	155.4
13	120.4	120.5	120.8	120.8	121.6	121.7
14	130.9	131.3	131.0	131.1	131.4	131.4
1′	54.7	64.3	55.0	54.8	65.4	65.5
3′	38.5	43.6	39.3	38.9	46.1	46.6
4′	29.0	28.4	29.9	29.6	22.5	23.2
4a′	128.0	128.7	129.1	128.2	130.9	131.1
5′	111.8	111.2	112.2	111.7	112.1	112.5
6′	148.3	148.2	148.5	148.3	148.9	149.0
7′	144.0	143.3	144.1	144.7	144.2	144.5
8′	116.3	117.3	116.4	115.7[c]	119.8	120.3
8a′	127.2	124.3	127.9	127.9	127.2	127.6
α′	42.0	38.3	42.6	42.3	43.8	43.6
9′	138.7	138.6	139.3	139.3	137.5	137.9
10′	115.8	116.8	116.2	115.9[c]	119.4	120.3
11′	144.0	143.7	146.2	147.0	146.5	148.5[b]
12′	145.9	146.0	149.5	149.5	145.9	148.6[b]
13′	114.7	114.2	110.9	110.8	116.7	113.3
14′	123.2	124.5	123.0	123.0	123.7	123.4
NCH_3	41.8	41.8	41.9	41.3	41.8	41.6
N'-CH_3		41.8			41.1	42.2
OCH_3	55.9	55.3	56.1	55.9	54.9	56.3
	55.0	56.1	55.2	54.8	55.4	55.7
C7-OCH_3				60.3	59.4	59.7

[a] The spectra were obtained in $CDCl_3$ solutions. Chemical shifts are expressed on the Me_4Si scale according to the following equation: $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b,c] Signals within a vertical column may be reversed.

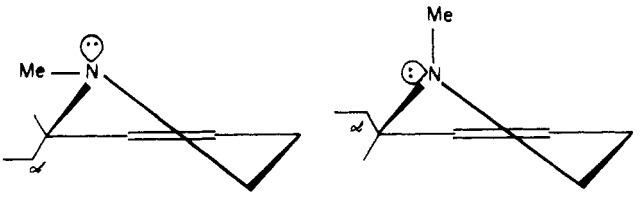
units. In bis(benzylisoquinoline) alkaloids of the tetrandrine (9) series, one of the coclaurine units is substituted at position 8 while the other is not, and here too the coclaurine residues adopt extended and folded conformations, respectively.[2a,4,5] This appears to be broadly true also in the enantiomeric isotetrandrine (10) series,[2a] as well as for the curine class,[2b] although in some cases molecular crowding may result in the distinction between fully folded and fully extended conformations being less sharp.



(9) 1 = S
(10) 1 = R

The observation that O-7-methylation of daphnandrine (3; 3 to 4) affects in a predicted way[1b] the shifts of carbons belonging to ring A, while the remaining carbons show little or no effect, has led us to compare carbon shifts for rings AA′, BB′, and CC′ of *N*-methyldaphnoline (2) and repandine (5) in order to detect different conformational aspects in these two diastereomeric compounds.

The methylenes and methine $\Delta\delta$s for 2 and 5 appear to be due to stereochemical and conformational effects associated with the B and B′ rings. A half-chair conformation with an equatorial *N*-methyl group must be assigned to B′ of 2 to account for the virtual absence of a γ-gauche effect at C-4′ (δ 28.4) as compared to the corresponding carbons of daphnoline (1, δ 29.0). On the other hand, C-α′ is considerably shielded in *N*-methyldaphnoline (2, δ 38.3) as compared to that in daphnoline (1, δ 42.0), and pseudoaxial conformation cis to the methylimino group is thus to be attributed to the benzyl substituent (see structure I). This in turn produces in the case of *N*-methyldaphnoline (2) a distinct shielding at C-3′ (δ 43.6) as compared to C-3 (δ 45.0), and the latter value suggests that the benzyl group is substituted pseudoequatorially at C-1 (structure II).



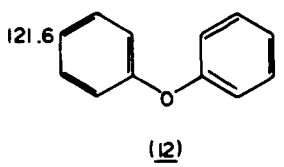
I II

In the diastereomeric repandine (5) series, ring B carbon shifts show little difference as compared to those in 2, suggesting that ring B has the same conformation in both the repandine and daphnoline series. There are, however, differences between the two series in the signals associated with ring B′; thus C-4′ is considerably shielded in repandine (5, δ 22.5), which indicates an axial conformation for the *N*′-methyl group. On the other hand, C-3′ is not shielded (δ 46.1), suggesting that C-α′ is substituted pseudoequatorially at C-1′ and cis to the methylimino group (structure II).

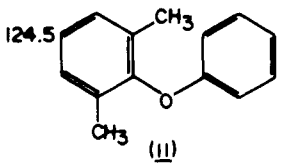
From the experimental data on bis(benzylisoquinoline) alkaloids[1b,2] 21.4 and 28.4 ppm (for C-4 and C-4′) are, so far, the extreme values observed when the *N*-methyl group is axial and equatorial, respectively. The intermediate values more frequently observed for C-4 and C-4′ are indicative of the ratio between different conformations bearing axial and equatorial *N*-methyl groups.

Comparison between sp^2 carbon resonances in the daphnoline and repandine series discloses some interesting features concerning the diphenyl ether moieties. The deshieldings of C-9 ($\Delta\delta$ 1.7) and C-12 ($\Delta\delta$ 2.4) in 5 as compared to the same sites in 2, which are ipso and para to the ring C ether linkage, are most probably attributable to a modification in electron conjugation with the phenyl moieties. These facts are consistent with a deshielding of 2.9 ppm for C-4 in 2,6-dimethylphenyl phenyl ether (11) in comparison to a similar site in diphenyl ether (12), which is caused by an average interplanar angle modification from 33° (in 12) to 67° (in 11).[6]

(4) Gilmore, C. J.; Bryan, R. F.; Kupchan, S. M. *J. Am. Chem. Soc.* **1976**, *98*, 1947.
(5) (a) Bick, I. R. C.; Harley-Mason, J.; Sheppard, N.; Vernengo, M. J. *J. Chem. Soc.* **1961**, 1896. (b) Monograph [on bis(benzylisoquinoline) alkaloids, in Japanese] commemorating the retirement of Professor Masao Tomita: Ageo, S., Ed.; Tomita Memorial Committee, Kyoto University Faculty of Pharmacy, Kyoto, Japan, 1967, p 44.



(12)



(11)

The above observation has led us to propose that analogous conformational changes occur with respect to rings C and C′ of **2** (1*S*,1′*R*) and **5** (1*S*,1′*S*).

Dreiding model analysis of **2** and **5** reveals that the A and A′ diphenyl ether moieties also suffer conformational changes in these two diastereomeric compounds. The fact that C-5 and C-4a′ (para to ether linkages) resonate at lower fields in **5** than in **2** indicates the occurrence of wider interplanar angles between A and A′ in the repandine series.

The lack of ^{13}C NMR data for obaberine (**13**), which would be comparable to *O*-methylrepandine (**6**), was compensated for by ^{1}H NMR spectroscopic observations. The 6′- and 7-methoxy groups of **13** resonate at δ 3.63 and 3.20, while those of **6** resonate at δ 3.42 and 3.03, respectively.[5] Molecular models of these two diastereomeric compounds, together with ^{1}H NMR spectroscopy observations, reveal that the planes of rings A and A′ are tilted at an angle of about 70° to one another in **13**. As a result, the protons of the 7-methoxyl groups are brought above the shielding zone of ring A′, but the 6′-methoxy group remains outside the shielding zone of A. On the other hand, in compound **6** the larger interplanar angle between A and A′ brings both the 7- and 6′-methoxyl groups above the aromatic shielding zones.

The chemical shifts of the H-8′ protons further confirm the angular modifications in both AA′ and CC′ ether linkages which occur in the 1*S*,1′*R* and 1*S*,1′*S* series. In obaberine (**13**), H-8′ appears at an abnormally high field (δ 5.48)[5] as a consequence of the anisotropic shielding of rings C and C′, while H-8′ of **6** lies in the shielding zone of ring C and deshielding zone, of C′; these two effects evidently cancel each other out, and the proton resonates further downfield (δ 6.38).

From the foregoing considerations, it is suggested that none of the benzylisoquinoline moieties in this series acquires a fully folded conformation in solution. This results in less flexible molecules, and the difference in absolute configuration at C-1′ for the repandine series causes an increase in the interplanar angles between rings AA′ and CC′ as compared to those for the daphnoline series. It would appear from this and previous conformational studies[2] that in order to acquire a folded conformation, the coclaurine units of a bis(benzylisoquinoline) must be unsubstituted at C-8, and their benzyl groups should have a para diphenyl ether link. These conditions do not occur in the daphnoline–repandine series, so that the extended conformation prevails.

Experimental Section

The ^{13}C NMR spectra were obtained in a 10-mm spinning tube from solutions of approximately 0.5 mmol of compound in 1 mL of solvent. The instrument employed was Varian XL-100 NMR spectrometer operating at 25.2 MHz and interfaced with a Varian 620-L Fourier transform computer with a 16K memory. The chemical shifts (±0.05 ppm) were measured at a 5-kHz spectral width, with an acquisition time of 0.8 s and a 15-μs pulse width, by using an internal deuterium lock.

Registry No. 1, 479-36-7; 2, 519-53-9; 3, 1183-76-2; 4, 24306-66-9; 5, 518-92-3; 6, 4021-17-4.

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Conformational Analysis. 43. A Boat-Shaped Piperidine Ring in 3-Thia-7-aza-6,8-diphenylbicylco[3.3.1]nonan-9-ol[1]

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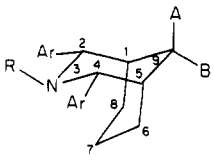
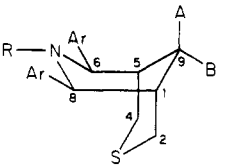
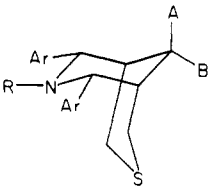
On the basis of an extensive tabulation[2] of the ^{13}C NMR spectra of a series of 2,4-diarylazabicyclo[3.3.1]nonanes and the corresponding 9-ones and 9-ols (two epimers; 1) it was concluded, in accordance with other evidence[3] that these compounds exist largely or entirely in double-chair conformations. An exception was found, however, in the corresponding 7-thia compounds **2** (properly named 3-thia-7-aza-6,8-diarylbicyclo[3.3.1]nonanes). The salient ^{13}C NMR data[2] for the nonaromatic carbons are reproduced in Table I.



1



2



3

A = B = H; A = OH, B = H
A = H, B = OH, A, B = =O; R = H or Me

In comparing the 9-keto compounds (**1a,b** vs. **2a,b**; see Table I for definitions of **a–d**) one notes a palpable upfield shift of the benzylic carbons C(2,4) (numbering for **1**; ca. 1.3 ppm) in going from the carbons compounds (**1a**, **1b**) to the thia compounds (**2a**, **2b**) and an even larger upfield shift (4 ppm or more) for C(9), the carbonyl carbon. The shifts for C(9) and also for C(1,5) and C(6,8) should properly be compared to similar shifts as one goes from cyclohexanone to 4-thiacyclohexanone; the comparison is as follows (cyclohexanone – thiacyclohexanone differences in parentheses):[4] C(6,8), 8.3–8.4 (2.9); C(1,5), 1.0–1.2 (2.1); C(9), −4.0 to −4.4 (−3.3). It is especially the large discrepancy at C(6,8) [C(2,4) in the thia system] that suggests that compounds **2a** and **2b** are not chair–chair conformations.

This hypothesis is corroborated by the chemical shifts in the alcohols **2c** and **2d**. When an axial hydroxyl group

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