[Chem. Pharm. Bull. 32(7)2503—2515(1984)]

Utilization of Protopine and Related Alkaloids. XVI.[1] Nuclear Magnetic Resonance Spectroscopy on the Cycloadducts of Anhydromethylberberines with Dienophiles

MASAYUKI ONDA,* AKIKO HATANO, HIROKO YAMAGUCHI, and NORIKO SATO

School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo 108, Japan

(Received September 22, 1983)

Proton assignments of the cycloadducts of anhydromethylberberines with dienophiles have been made by reference to the carbon-13 nulcear magnetic resonance spectra. The correlation between the molecular geometries and the proton chemical shifts is discussed on the basis of the variable-temperature nuclear magnetic resonance spectral data.

Keywords——benzo[*c*]phenanthridine; bicyclo[2.2.2]octane; ^{1}H-NMR; spin decoupling; nuclear Overhauser effect; ^{13}C-NMR; gated decoupling; selective proton decoupling; variable-temperature NMR (^{1}H-, ^{13}C-)

In the course of our investigations on the transformation of the protopine and related alkaloids to the benzo[*c*]phenanthridine alkaloids, several cycloadducts (**4**—**11**) of the bicyclo[2.2.2]octane type were obtained by the photolysis of the anhydromethylberberines (**1**—**3**) with nitrosobenzene, diethyl azodicarboxylate and dimethyl acetylenedicarboxylate.[1-4] The stereochemistry of the B/C ring junctures in these compounds was deduced by nuclear magnetic resonance (NMR) spectroscopy. The spectral data for group I indicated that the A ring and D ring protons in the *cis* series (**4** and **6**) absorb at higher fields than those in the *trans* series (**5** and **7**). The spectral data for groups II and III showed that the A ring protons are shifted upfield compared with those in **4** and **6**, but the 1-protons absorb in the same region as those in **5** and **7**. It is likely that these spectral features are related to the boat forms of the C rings and to the orientations of the 13-substituents as well as conformations of the bicyclo[2.2.2]octane systems. We reappraised the ^{1}H-NMR spectra together with the ^{13}C-NMR spectra. As a result, this has resulted in the correction of some previous proton assignments. Furthermore, examination of the variable-temperature ^{1}H- and ^{13}C-NMR spectra has permitted us to correlate the molecular geometries of these compounds with the proton chemical shifts.

Group I

The precise assignments of aromatic protons are required first. Although some previous assignments were ambiguous and erroneous, the A ring and D ring protons were clearly assigned in this work by correlation with the ^{13}C-NMR spectra (Tables I—IV). The ^{1}H-NMR spectra were assigned by comparison with those of related compounds as well as by spin decoupling and nuclear Overhauser effect (NOE) experiments. Carbon assignments were made by gated decoupling and selective proton decoupling experiments.

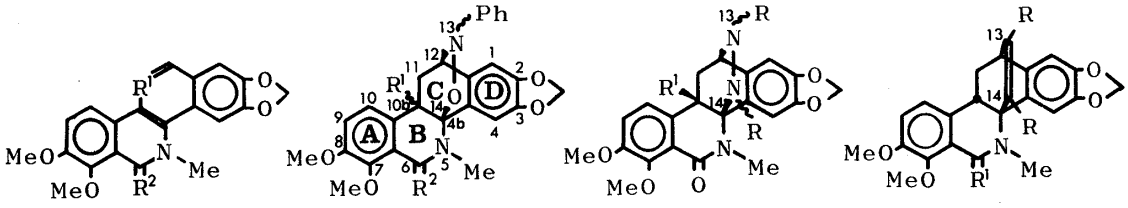
Compound (4)——The ^{1}H-NMR spectrum showed two one-proton singlets (δ_H 6.52 and 6.30) and two one-proton doublets (δ_H 6.87 and 6.66) in addition to the 13-phenyl protons in the aromatic region. The singlet proton (δ_H 6.30) was correlated to an aromatic carbon (δ_C 105.1, C-1) with J_{CH} 166 Hz, which is coupled to the 12-proton (δ_H 4.64) with J_{CH} 3 Hz, and

thus was assigned to the 1-proton. The remaining singlet proton (δ_H 6.52) was assigned to the 4-proton. Assignments of the 9- (δ_H 6.87)[5] and 10-protons (δ_H 6.66)[5] were made by referring to the ^{1}H- and ^{13}C-NMR spectra of **6** (*vide infra*).

Compound (5)——A one-proton singlet (δ_H 6.64) was assigned to the 1-proton on the basis of a coupling (J_{CH} 3 Hz) observed between the 12-proton (δ_H 4.84) and an aromatic carbon (δ_C 105.5, C-1) corresponding to the singlet proton with J_{CH} 166 Hz. An NOE (14%), observed between the 1- and 12-protons, supports the above assignment. Saturation of the 5-methyl protons (δ_H 3.47) gave an increase (20%) in the signal area of a one-proton singlet (δ_H 6.93, 4-H).[5] The 9- and 10-protons appeared as a two-proton singlet (δ_H 7.07). Assignments of the 4-, 9- and 10-protons were made by differentiation of the signals from the proton signals of the 13-phenyl group by gated decoupling and selective proton decoupling experiments.

Compound (6)——A one-proton singlet (δ_H 6.44) was assigned to the 1-proton[5] on the basis of a coupling (J_{CH} 3 Hz) observed between the 12-proton (δ_H 4.77) and an aromatic carbon (δ_C 105.4, C-1) corresponding to the singlet proton with J_{CH} 166 Hz. An NOE (7.5%) was observed between a one-proton singlet (δ_H 6.54, 4-H)[5] and the 5-methyl protons (δ_H 3.42). The gated decoupled spectrum showed a coupling (J_{CH} 2 Hz) between the 10b-proton (δ_H *ca.* 3.78) and an aromatic carbon (δ_C 119.7, C-10) corresponding to a one-proton doublet (δ_H 6.63, 10-H)[6] with J_{CH} 160 Hz. Another one-proton doublet (δ_H 6.91) was assigned to the 9-proton.[6]

Compound (7)——A one-proton singlet (δ_H 6.58) was assigned to the 1-proton on the basis of a coupling (J_{CH} 3 Hz) observed between the 12-proton (δ_H 4.75) and an aromatic carbon (δ_C 105.5, C-1) corresponding to the singlet proton with J_{CH} 166 Hz. An NOE (11%)

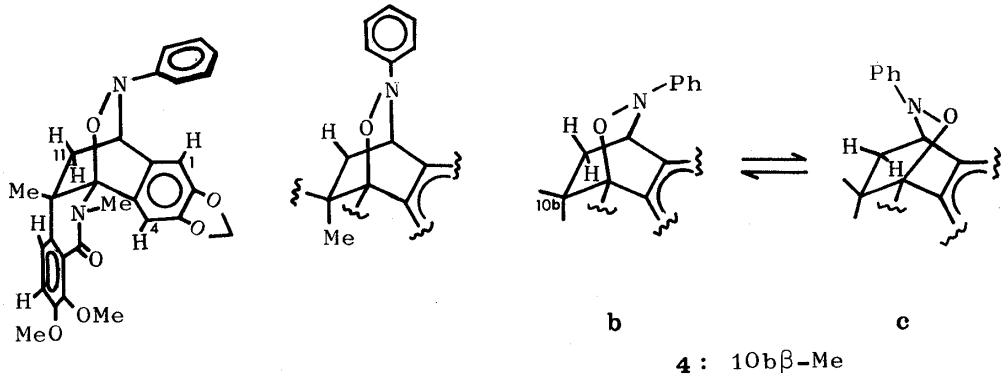


1: R^1 = Me, R^2 = O
2: R^1 = Me, R^2 = H_2
3: R^1 = H, R^2 = O

group I
4: R^1 = —Me, R^2 = O
5: R^1 = ····Me, R^2 = O
6: R^1 = —H, R^2 = O
7: R^1 = ····Me, R^2 = H_2

group II
R = COOEt
8: R^1 = Me
9: R^1 = H

group III
R = COOMe
10: R^1 = O
11: R^1 = H_2



4a **5a** **b** **c**

4: 10bβ-Me
5: 10bα-Me

Chart 1

TABLE I. ^{1}H- and ^{13}C-NMR Spectral Data for **4** (ppm and Hz)

Position	^{13}C			^{1}H		
	δ_C[a]	$^1J_{CH}$	$^{>1}J_{CH}$	δ_H[b]	δ_H	J_{HH}
1	105.1 Dd	166	3	6.30 s		
2	150.2 Sm[c]					
3	151.2 Sm[c]					
4	103.6 Ds	166		6.52 s		
4a	129.4 Sdd		7 and 3			
4b	90.6 Sm					
6	162.8 Sq		3			
6a	122.3 Sd		7			
7	147.6 Sm[d]					
8	152.7 Sm					
9	115.7 Ds	160		6.87 d		9
10	119.2 Ds	160		6.66 d		9
10a	138.2 Sm					
10b	40.9 Sm					
11	38.8 Tm	132			α: 2.28 dd	13 and 2
					β: 2.68 dd	13 and 4
12	62.2 Dq	146	3	4.64 dd		4 and 2
12a	129.1 St		6			
2,3-OCH_2O–	101.1 Ts	174			5.69 d	1
					5.65 d	1
5-Me	27.6 Qs	140			3.39 s	
7-OMe	61.5 Qs	146			3.96 s	
8-OMe	56.0 Qs	146			3.73 s	
10b-Me	28.8 Qt	130	3	1.62 s		
1′	148.0 Sm[d]					
2′ (6′)	117.8 Dt	162	7	6.83 d		7
3′ (5′)	128.8 Dd	162	7	7.03 t		7
4′	123.4 Dt	162	7	6.77 t		7

a) Capital and small letters refer to the splittings observed in the off-resonance and gated decoupled spectra, respectively.
b) These protons were correlated by one-bond proton decoupling.
c, d) Assignments may be reversed.

was observed between the 1- and 12-protons. Also, an NOE (15.5%) was observed between a one-proton singlet (δ_H 7.02, 4-H)[5] and the 5-methyl protons (δ_H 3.03). Two one-proton doublets (δ_H 6.98 and 6.84) corresponded to two aromatic carbons (δ_C 123.0 and 111.7) with each J_{CH} 160 Hz, respectively. The carbon-9′s absorbed higher by 3.5—4.8 ppm than the carbon-10′s in the compounds (**4**—**6**). Considering the deshielding effect of the 6-oxo groups on the carbon-9′s in these compounds, the carbon (δ_C 123.0) can be assigned to the 10-position and the carbon (δ_C 111.7) to the 9-position. Thus, assignments of the 9- (δ_H 6.84)[5] and 10-protons (δ_H 6.98)[5] were made.

The variable-temperature (−50—32 °C) ^{1}H-NMR spectra of all the compounds showed no changes in the signal patterns, so that the observed spectra are compatible with those of equilibrating species between possible conformations as a result of fast interconversions on the NMR time scale. The equilibrating species is relatively contributed from the population of each conformation depending mainly on the steric stability.

Inspection of Dreiding models of **4**, **5** and **7** indicated that the C rings exist in rigid boat forms owing to the bridge between the 4b- and 12-positions and that the B rings in the equilibrating species preferentially adopt half-chair forms, in which the 5-methyl groups are equatorially orientated in order to avoid 1,3-diaxial interaction with the 10b-methyl groups.

TABLE II. ^1H- and ^{13}C-NMR Spectral Data for **5** (ppm and Hz)

Position	^{13}C			^1H		
	δ_C [a]	$^1J_{CH}$	$^{>1}J_{CH}$	δ_H [b]	δ_H	J_{HH}
1	105.5 Dd	166	3	6.64 s		
2	150.6 Sm[c]					
3	151.6 Sm[c]					
4	106.1 Ds	166		6.93 s		
4a	129.5 Sdd		7 and 3			
4b	95.3 Sm					
6	165.5 Sq		2			
6a	120.2 Sd		7			
7	147.2 Sm[d]					
8	153.6 Sm					
9	117.4 Ds	160		7.07 s		
10	122.2 Ds	160		7.07 s		
10a	139.5 Sm					
10b	42.0 Sm					
11	40.1 Tm	134			α: 2.04 dd	13 and 4
					β: 3.08 dd	13 and 2.5
12	59.0 Dq	148	3	4.84 dd		4 and 2.5
12a	128.8 St		6			
2,3-OCH_2O–	101.3 Ts	174			5.88 s	
5-Me	35.2 Qs	140			3.47 s	
7-OMe	61.4 Qs	146			3.95 s	
8-OMe	56.5 Qs	142			3.83 s	
10b-Me	32.3 Qt	128	3		0.70 s	
1′	148.0 Sm[d]					
2′ (6′)	116.1 Dt	162	7	6.82 d		8
3′ (5′)	128.8 Dd	162	7	7.00 t		8
4′	121.9 Dt	162	7	6.71 t		8

a) Capital and small letters refer to the splittings observed in the off-resonance and gated decoupled spectra, respectively.
b) These protons were correlated by one-bond proton decoupling.
c, *d*) Assignments may be reversed.

The 1,3-diplanar forms of the B rings in **4** and **5**, in which the Me–5–6=0 bonds are planar, would be excluded because of severe nonbonded interaction between the 4b–14 bond and the 5-methyl group and between the 4-proton and the 5-methyl group, respectively. Possible conformational changes in these compounds are as follows: rotations about the 5-*methyl,* 10b-*methyl,* 13-phenyl and *methoxy group* bonds; nitrogen-13 inversion; *inversion of the methylenedioxy ring*; flipping of the azaoxy-bridge. At first glance, the italicized interconverting processes are simple and common to all these compounds, and thus are excluded from the following consideration. Although the occurrence of azaoxy-bridge flipping in bicyclo[2.2.2]octane systems has not been reported, it may occur.

Comparison of 4 with 5——The 9-, 10-protons and the 8-methoxy protons in **4** are situated in the shielding zone of the D ring and the 4-proton in the shielding zone of the 6-oxo group. Thus, the protons under consideration must be shielded. Table V shows that chemical shift differences of these protons in **4** and **5** are as expected [$\Delta\delta_{5-4}$ (4-H)=0.41, (9-H)=0.20, (10-H)=0.39 and (8-OMe)=0.10 ppm]. The differences among the latter three seem to paralell the distances between the protons and the shielding zone.

It is known that the 2-methyl-3,4,5,6-tetrahydro-1,2-oxazine ring is more puckered than the corresponding cyclohexane ring.[7] The 13-phenyl group in **4** would be preferentially *endo*[8] because of nonbonded interaction with the 10b-methyl group[9] and on average, as a less

TABLE III. ^1H- and ^{13}C-NMR Spectral Data for **6** (ppm and Hz)

Position	^{13}C			^1H		
	δ_C [a]	$^1J_{CH}$	$^{>1}J_{CH}$	δ_H [b]	δ_H	J_{HH}
1	105.4 Dd	166	3	6.44 s		
2	150.3 Sm [c]					
3	151.2 Sm [c]					
4	103.7 Ds	166		6.54 s		
4a	130.6 Sdt		7 and 2			
4b	89.5 Sm					
6	162.8 Sq		3			
6a	122.8 Sd		7			
7	147.7 Sm [d]					
8	153.3 Sm					
9	115.6 Ds	160		6.91 d		8
10	119.7 Dd	160	2	6.63 d		8
10a	129.8 Sm					
10b	39.6 Dm	134				
11	29.6 Td	137	3		α: 1.95 ddd	14, 6 and 2
					β: 3.06 ddd	14, 10 and 4
12	61.1 Dq	148	3		4.77 dd	4 and 2
12a	127.4 St		6			
2,3-OCH_2O–	101.2 Ts	174			5.76 d	1.5
					5.73 d	1.5
5-Me	28.0 Qs	140		3.42 s		
7-OMe	61.6 Qs	146			3.98 s	
8-OMe	56.1 Qs	146			3.76 s	
1′	148.4 Sm [d]					
2′ (6′)	117.6 Dt	162	7	*ca.* 6.86		
3′ (5′)	128.9 Dd	162	7	*ca.* 7.10		
4′	123.3 Dt	162	7	*ca.* 6.86		

a) Capital and small letters refer to the splittings observed in the off-resonance and gated decoupled spectra, respectively.
b) These protons were correlated by one-bond proton decoupling.
c, d) Assignments may be reversed.

hindered conformation, the 13-phenyl group would lie nearly perpendicular to the 12–13 bond as shown in the drawing (**4a**), where it would be expected to shield the 1-proton and the 2,3-methylenedioxy protons [$\Delta\delta_{5-4}$ (1-H)=0.34 and (OCH_2O)=*ca.* 0.21 ppm]. The steric stabilities of the 13*endo*-phenyl and 13*exo*-phenyl conformations in **5** are supposed to be nearly the same. As a result of fast interconversion between the two conformations of approximately equal populations, the nitrogen-13 atom in **5** is thought in effect to be in a nearly planar state,[10] the 13-phenyl bond probably having a certain amount of double bond character as shown in the drawing (**5a**). Thus, the shielding effect of the 13-phenyl group is not operative on the A ring protons, the 11β-proton (*exo*-phenyl)[11] and the D ring proton (*endo*-phenyl), whereas the 11β- and 12-protons are deshielded [$\Delta\delta_{5-4}$ (11β-H)=0.40 and (12-H)=0.20 ppm].

The 10b-methyl protons (δ_H 0.70) in **5** absorbed at higher field than those (δ_H 1.62) in **4**. The anomalously higher field position of this resonance in **5** is compatible only with the structure having the 10b-methyl group in the shielding zone of the D ring[12] and decided the *trans* B/C ring juncture.[1]

Assignments of the 11α- (higher) and 11β-protons (lower) in **4** and **5** were made on the basis of the shielding effect of the D ring.[13] The 10b-methyl group in **4** might be bent outward in order to be remote from the nitrogen-13 atom and also to remove partially eclipse

TABLE IV. ^1H- and ^{13}C-NMR Spectral Data for **7** (ppm and Hz)

Position	^{13}C			^1H		
	δ_C [a]	$^1J_{CH}$	$^{>1}J_{CH}$	δ_H [b]	δ_H	J_{HH}
1	105.5 Dd	166	3	6.58 s		
2	146.6 Sm [c]					
3	147.1 Sm [c]					
4	106.8 Ds	166		7.02 s		
4a	129.6 Sdd		7 and 3			
4b	95.4 Sm					
6	49.8 Tq	141	4			
6a	126.4 St		6			
7	144.0 Sm					
8	152.6 Sm					
9	111.7 Ds	160		6.84 d		8
10	123.0 Ds	160		6.98 d		8
10a	135.9 Sm					
10b	42.0 Sm					
11	41.7 Tm	134			α: 1.99 dd	14 and 4
					β: 2.92 dd	14 and 2.5
12	59.6 Dq	148	3		4.75 dd	4 and 2.5
12a	130.6 St		6			
2,3-OCH_2O–	100.9 Ts	176			5.88 d	1
					5.85 d	1
5-Me	41.4 Qd	138	4		3.03 s	
7-OMe	59.9 Qs	145			3.89 s	
8-OMe	55.9 Qs	145			3.84 s	
10b-Me	32.9 Qt	130	3		0.68 s	
1′	150.0 Sm					
2′ (6′)	116.3 Dt	162	7	6.90 d		7
3′ (5′)	128.4 Dd	162	7	7.02 t		7
4′	121.3 Dt	162	7	6.75 t		7

a) Capital and small letters refer to the splittings observed in the off-resonance and gated decoupled spectra, respectively.
b) These protons were correlated by one-bond proton decoupling.
c) Assignments may be reversed.

TABLE V. Proton Chemical Shift Differences in **4**, **5** and **6** (ppm)

	1-H	OCH_2O	4-H	8-OMe	9-H	10-H	10b-Me	11α-H	11β-H	12-H
$\Delta\delta_{5-4}$	0.34	*ca.* 0.21	0.41	0.10	0.20	0.39	−0.92	−0.24	0.40	0.20
$\Delta\delta_{6-4}$	0.14	*ca.* 0.08	0.02	0.03	0.04	0.03	—	−0.33	0.38	0.13

interaction with the 11β-hydrogen. As a result, the 11α-hydrogen closely approaches the deshielding zone of the A ring and is deshielded ($\Delta\delta_{5-4} = -0.24$ ppm). On the other hand, if azaoxy-bridge flipping is operative, the bicyclo[2.2.2]octane rings in **4** and **5** are deformed by transmission of the torsion angle changes. The 10b-methyl groups in the conformations **4b** and **4c** are bent, and eclipse interaction with the 11β-hydrogens is partially released. However, nonbonded interaction between the 10b-methyl and 13-phenyl groups would destabilize **4c**. The equilibrating species would have a larger contribution from **4b** than **4c**. This is in accord with the outward-bending of the 10b-methyl group assumed above. The equilibrating species in **5** would have approximately equal contributions from **5b** and **5c**. Thus, the possibility of azaoxy-bridge flipping rather supports the above consideration regarding the relationship

between the molecular geometries and the proton chemical shifts.

Comparison of 4 with 6——The conformations of the B and C rings in **6** are thought to be the same as those in **4**. As predicted from the *cis* B/C ring juncture, the 4-, 9-, 10-protons and the 8-methoxy protons in **6** were shielded similarly to those in **4**. Since the chemical shifts of the 5-methyl protons and the 5-methyl carbon as well as the surrounding proton (4-H) and carbons (C-4, -4a and -4b) are similar to those in **4**, the 5-methyl group in **6** should be preferentially equatorial. The 13*endo*-phenyl conformation would be slightly more stable than the 13*exo*-phenyl conformation in **6** owing to nonbonded interaction between the 10b-hydrogen and the 13-phenyl group, which does not exist in **5**. As a result, the 13*endo*-phenyl conformation would be somewhat favored. Fast interconversion between the two conformations would result in an equilibrating species intermediate between those in **4** and **5**. This explains why the chemical shifts of the 1-, 12-protons and the 2,3-methylenedioxy protons in **6** are intermediate between those in **4** and **5** (Table V). A downfield shift (-0.33 ppm) of the 11α-proton in **4** can be attributed to the outward-bending of the 10b-methyl group (*vide supra*). It is of interest that the 11β-proton in **6** was deshielded by the 13-phenyl group to the same extent as that in **5** ($\Delta\delta_{6-4}=0.38$ and $\Delta\delta_{5-4}=0.40$ ppm).

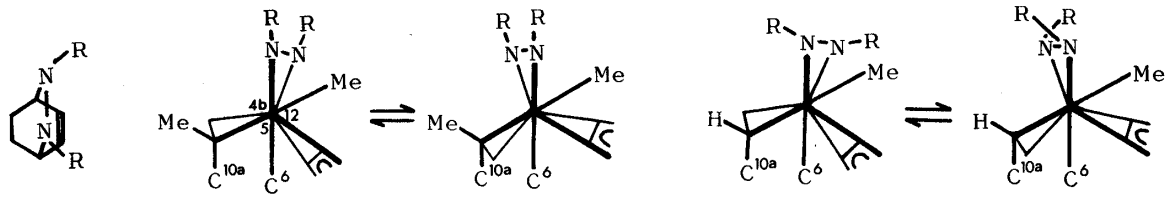
Comparison of 5 with 7——Chemical shift differences observed in several corresponding protons and carbons in **5** and **7** can be ascribed to the effect of the 6-oxo group in **5**, so that the molecular geometry for **7** is supposed to be similar to that for **5**. Nonequivalency observed between the 6-protons in **7** is in accord with a half-chair form of the B ring with the 5eq-methyl group (δ_H 4.38 and 4.10, each d, J_{HH} 16 Hz).

Group II

The 1- and 4-protons in these compounds were assigned by the observations of NOE's between the 1- and 12-protons and between the 4-protons and the 5-methyl protons, respectively. Aromatic protons were correlated to the corresponding aromatic carbons by the gated decoupled spectra. Assignments of the remaining protons and carbons were made by comparison with the spectral data for group I (Tables VI and VII).

Lehn *et al.*[14] examined the molecular geometry for diethyl 2,3-diazabicyclo[2.2.2]oct-5-ene-2,3-dicarboxylate (**12**) by dynamic ^{1}H-NMR spectroscopy, and the results can be as follows. (1) Nitrogen inversions are fast on the NMR time scale, and the nitrogen sites are in planar or nearly planar states, the N–CO bonds having some double bond character. (2) The spectral changes at low temperatures (below 0 °C) are ascribed to slow rotations about the N–CO bonds. (3) The spectral changes at high temperatures are due to diaza-bridge flipping, **12** existing in an equilibrium between two twisted conformations of equal populations.

The following conformational changes are present in group II in addition to those in **12**: rotations about the 5-methyl, 10b-methyl and methoxy group bonds; nitrogen-5 inversion; inversions of the B and methylenedioxy rings. These interconverting processes in group I were fast and were not observed even at -50 °C (*vide supra*). On the basis of this finding, the



12 R = COOEt **8a** R = COOEt **8b** **9a** R = COOEt **9b**

Chart 2

TABLE VI. ^{1}H- and ^{13}C-NMR Spectral Data for **8**[a] (ppm and Hz)

Position	δ_C[b]	δ_H	J_{HH}
1	103.7 d	6.58 s	
2	147.5 s		
3	147.9 s[c]		
4	106.4 d	6.38 s	
4a	129.5 s		
4b	83.1 s		
6	159.5 s		
6a	120.3 s		
7	147.5 s[c]		
8	153.2 s		
9	116.0 d	6.75 d	9
10	117.4 d	6.50 d	9
10a	137.7 s		
10b	45.3 s		
11	36.7 t	α: 2.35 dd	15 and 3
		β: 2.57 dd	15 and 3
12	54.9 d	5.16 t	3
12a	125.6 s		
2,3-OCH_2O–	101.4 t	5.79 d	1
		5.76 d	1
5-Me	30.6 q	3.42 s	
7-OMe	61.6 q	3.90 s	
8-OMe	56.3 q	3.73 s	
10b-Me	34.6 q	1.44 s	
13- and 14-COOEt's			
CH_2	62.6 t	4.21 q	7
		4.00 q	7
Me	14.5 q	1.24 t	7
		1.14 t	7
CO	156.6 s		
	155.2 s		

a) ^{1}H-NMR (90 MHz): at 50 °C. ^{13}C-NMR (25.2 MHz): at 60 °C.
b) Splittings were observed in the off-resonance spectrum.
c) Assignments may be reversed.

additional interconversions in group II were excluded from the following consideration, and the B rings in the equilibrating species were assumed to adopt preferentially half-chair forms with the 5 eq-methyl groups as those in group I.

The ^{1}H-NMR spectrum of **8** showed at −30 °C[15] complex signals (CH_2) and four triplets (Me) of unequal intensities for the ethyl protons of the two ethoxycarbonyl groups in addition to complex signals for the 1-, 4-, 11β-, 12-protons and the 5-methyl protons.[16] At 32 °C the methylene proton signals remained unchanged but the methyl proton signals changed to two triplets of equal intensities. Also, a broad triplet was observed for the 12-proton and a two-peak signal for the 5-methyl protons. At 50 °C the methylene proton signals coalesced to two quartets of equal intensities, and the 12-proton and 5-methyl proton signals changed to a sharp triplet and a singlet, respectively. The spectral changes observed for **8** are similar to those for **12**.[14] Following Lehn's documentation, these results can be interpreted as follows. (1) At −30 °C nitrogen-13 and -14 inversions are already equilibrated, and the nitrogen sites are in planar or nearly planar states, the N–CO bonds having some double bond character. Slow rotations about the N–CO bonds complicate the ethyl proton signals and

TABLE VII. ^{1}H- and ^{13}C-NMR Spectral Data for **9**[a] (ppm and Hz)

Position	δ_C[b]	δ_H	J_{HH}
1	103.9 d	6.65 s	
2	148.2 s[c]		
3	150.8 s[c]		
4	106.5 d	6.48 s	
4a	130.2 s		
4b	80.0 s		
6	162.6 s		
6a	123.2 s		
7	147.7 s		
8	153.5 s		
9	115.2 d	6.76 d	9
10	118.9 d	6.48 d	9
10a	134.9 s		
10b	37.9 d	4.05 dd	10 and 3
11	26.6 t	α: 2.13 dt	14 and 3
		β: 2.62 ddd	14, 10 and 3
12	53.8 d	5.18 t	3
12a	126.9 s		
2,3-OCH_2O–	101.4 t	5.80 d	1
		5.78 d	1
5-Me	31.1 q	3.32 s	
7-OMe	61.6 q	3.91 s	
8-OMe	56.1 q	3.73 s	
13- and 14-COOEt's			
CH_2	63.1 t[d]	4.24 q[d]	7
	62.5 t[d]	3.94 q[d]	7
Me	14.4 q	1.30 t	7
		1.14 t	7
CO	157.8 s		

a) ^{1}H-NMR (90 MHz): at 32 °C. ^{13}C-NMR (25.2 MHz): at 32 °C.
b) Splittings were observed in the off-resonance spectrum.
c) Assignments may be reversed.
d) Carbons and protons were not correlated.

affect the shieldings of several surrounding protons of the diaza-bridge. (2) At 32 °C rotations about the N–CO bonds are averaged, and the spectral complexity is caused by slow diaza-bridge flipping between two conformations (**8a** and **8b**) having planar or nearly planar nitrogen atoms. This situation can account for the spectral characteristic that the 12-proton and the 5-methyl protons are still affected at this stage. (3) At 50 °C all conformational interconversions are equilibrated. This summary clearly correlates the observed ^{1}H-NMR spectral data to the conformational interconversions.

The ^{13}C-NMR spectrum of **8** at 32 °C, corresponding to slow diaza-bridge flipping process, showed broad complex signals for the carbon-12 and the 5-methyl carbon. At 60 °C these signals changed to sharp signals (Fig. 1).

In the molecular geometry for the equilibrating species at 50 °C, derived from the above consideration, the 14-ethoxycarbonyl group is located in an intermediate position between the 5-methyl and 10b-methyl groups, reflecting a balance of steric interactions in the molecule.

As shown in Tables VIII and IX, the signal changes for the ethyl protons of the two ethoxycarbonyl groups in **9** at various temperatures are similar to those in **8**, although the coalescence temperature of the final stage is lower. However, the signal changes for the surrounding protons of the diaza-bridge are different. The 1-proton appeared as two singlets

TABLE VIII. Variable-Temperature ^{1}H-NMR Spectral Data for **8**[a]

	1-H	4-H	11β-H	12-H
−30 °C	6.64 s, 6.55 s (*ca.* 1/2)	6.40 s, 6.35 s (*ca.* 1/2)	2.63 br d	5.28—5.14 (6 peaks)
32 °C	6.58 s	6.38 s	2.57 dd	5.17 br t
50 °C	6.58 s	6.38 s	2.56 dd	5.16 t

	5-Me	COOEt	
		CH_2	Me
−30 °C	3.45—3.35 (4 peaks)	4.38—3.88 (several q)	1.29 t, 1.23 t 1.17 t, 1.11 t (unequal)
32 °C	3.44, 3.40	4.39—3.90 (several q)	1.24 t, 1.14 t (1/1)
50 °C	3.42 s	4.21 q, 4.00 q (1/1)	1.24 t, 1.14 t

a) 90 MHz; δ, ppm.

TABLE IX. Variable-Temperature ^{1}H-NMR Spectral Data for **9**[a]

	1-H	12-H	COOEt	
			CH_2	Me
0 °C	6.68 s, 6.62 s (*ca.* 1/1)	5.20 br t	4.36—3.85 (several q)	1.30 t, 1.23 t 1.20 t, 1.13 t (unequal)
10 °C	6.65 br s	5.20 br t	4.36—3.85 (several q)	1.30 t, 1.15 t (1/1)
32 °C	6.65 s	5.18 t	4.24 q, 3.94 q (1/1)	1.30 t, 1.15 t (1/1)

a) 90 MHz; δ, ppm.

of approximately equal intensities at 0 °C[17] and coalesced to a broad singlet at 10 °C, then to a sharp singlet at 32 °C. The 12-proton appeared as a broad triplet at 0—10 °C and changed to a sharp triplet at 32 °C. No signal changes were observed for the 4-, 11β-protons and the 5-methyl protons. This suggests that the two ethoxycarbonyl groups are orientated as remotely as possible from these protons, being in different orientations from the ethoxycarbonyl groups in **8**. The existence of 13*endo*-ethoxycarbonyl and 14*exo*-ethoxycarbonyl groups would explain the spectral complexity at 0 °C, which is supposed to be caused by slow rotations about the ethoxycarbonyl group bands as well as slow diaza-bridge flipping. Accordingly, the nitrogen sites would be in pyramidal states (no nitrogen inversions). At 10 °C rotations about the ethoxycarbonyl group bonds are averaged, and the spectral complexity would be caused by slow diaza-bridge flipping between two conformations (**9a** and **9b**) having the pyramidal nitrogen atoms.

The ^{13}C-NMR spectrum of **9** at 10 °C, corresponding to slow diaza-bridge flipping process, showed broad complex signals for the carbon-1 and -12. At 32 °C these signals

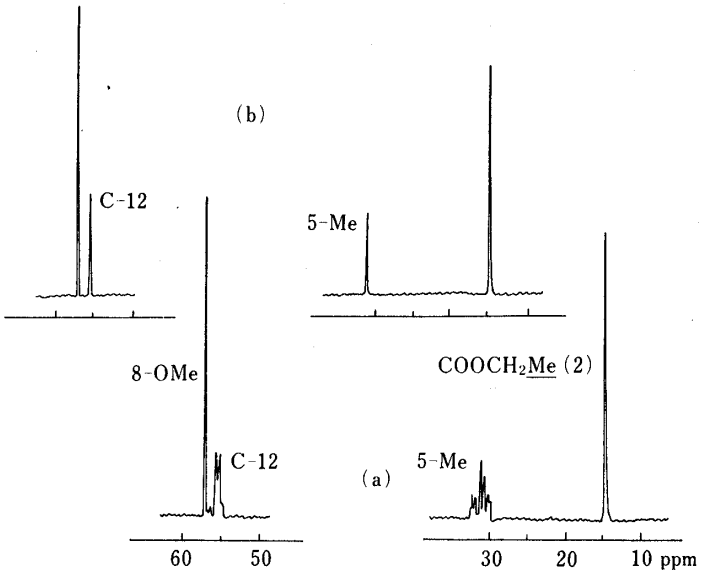


Fig. 1. Partial 25.2 MHz Noise-Decoupled ^{13}C-NMR Spectra of **8**
(a) at 32 °C; (b) at 60 °C. Spectra were taken at different amplifications.

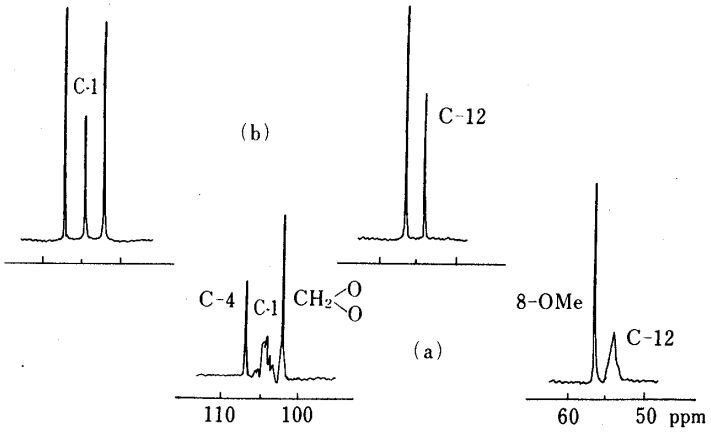


Fig. 2. Partial 25.2 MHz Noise-Decoupled ^{13}C-NMR Spectra of **9**
(a) at 10 °C; (b) at 32 °C. Spectra were taken at different amplifications.

changed to sharp signals (Fig. 2).

The molecular geometry for the equilibrating species at 32 °C, based on the above considerations, has the two ethoxycarbonyl groups *trans*, and the 14-ethoxycarbonyl group *trans* (*ca.* 120°) to the 5-methyl group with respect to the 5–4b–14 bond. This situation is in accord with steric stability of the molecule.

Diaza-bridge flippings deform the bicyclo[2.2.2]octane rings in **8** and **9** by transmission of the torsion angle changes. Considering the access of the 10b-methyl group to the 13-ethoxycarbonyl group in **8b**, **8a** should be more stable than **8b**. Thus, the ^{1}H- and ^{13}C-NMR spectra of **8** at 50 and 60 °C, respectively, represent those of the equilibrating species with **8a** as the predominant contributor. The ^{1}H- and ^{13}C-NMR spectra of **9** at 32 °C, are those of the equilibrating species corresponding to interconversion between **9a** and **9b** of approximately equal populations.

As mentioned above, the molecule of **8** is more puckered than that of **9**. As a result, the 4-

and 11α-protons in **8** closely approach the shielding zone of the 6-oxo group and the deshielding zone of the A ring, respectively [$\Delta\delta_{8-9}$ (4-H) = −0.10 and (11α-H) = 0.22 ppm]. Differences in the configurations of the nitrogen atoms might explain the differences (although slight) in the chemical shifts of the 1-, 11β-protons and the 5-methyl protons in **8** and **9** [$\Delta\delta_{8-9}$ (1-H) = −0.07, (11β-H) = −0.05 and (5-Me) = 0.10 ppm]. It was suggested above that the 9-, 10-protons and the 8-methoxy protons in the *cis* series (**4** and **6**) of group I are shielded by the D rings. Similar upfield shifts were observed for the corresponding protons in **8** and **9** as follows: **8**; 9-H (δ_H 6.75),[5] 10-H (δ_H 6.50)[5] and 8-OMe (δ_H 3.73). **9**; 9-H (δ_H 6.76),[6] 10-H (δ_H 6.48)[6] and 8-OMe (δ_H 3.73).

Group III

It is thought that the B ring in **10** preferentially adopts a half-chair form with the 5 eq-methyl group as those in **4** and **6**. The conformation of the B ring in **11** was earily established by ^{1}H-NMR spectroscopy:[2] the B ring preferentially exists in a flattened (1,3-diplanar) form with the 5 eq-methyl group in order to avoid nonbonded interaction between the 4- and 6α-protons, and this would be in accord with equivalency observed for the 6-protons (δ_H 4.35, s). The 4-proton in **10** was shielded by the 6-oxo group (δ_H 6.44). Upfield shifts of the 10-protons in **10** and **11** can be ascribed to shieldings by the D rings (**10**: δ_H 6.57; **11**: δ_H 6.53). Assignments of the 11α- (higher) and 11β-protons (lower) in **10** and **11** were based on that aromatic rings more strongly shield *endo*-protons than double bonds and *cis* couplings are larger than *trans* couplings in bicyclo[2.2.2]octadiene systems.[13]

Experimental

^{1}H-NMR spectra were taken on Varian EM-390 (90 MHz) and JEOL JNM PS-100 (100 MHz) in deuteriochloroform. ^{13}C-NMR spectra were recorded on a JEOL JNM PFT-100 (25.2 MHz) in deuteriochloroform.

4bβ,12β-(*N*-Phenylepoxyimino)-10bβ-methyl-4b,10b,11,12-tetrahydrooxychelerythrine (4)[1]——Colorless prisms of mp 249.5—251 °C (ethanol). ^{13}C-NMR decoupling: δ_H 4.64 (12-H)→δ_C 105.1 (d, J_{CH} 3 Hz→s, C-1), 129.1 (t, J_{CH} 6 Hz→d, J_{CH} 6 Hz, C-12a), 129.4 (dd, J_{CH} 7 and 3 Hz→d, J_{CH} 7 Hz, C-4a).

4bβ,12β-(*N*-Phenylepoxyimino)-10bα-methyl-4b,10b,11,12-tetrahydrooxychelerythrine (5)[1]——Light yellow prisms of mp 235—235.5 °C (ethanol). ^{1}H-NMR (90 MHz) NOE: δ_H 6.64 (1-H) $\underset{14\%}{\overset{11.5\%}{\rightleftarrows}}$ δ_H 4.84 (12-H); δ_H 3.47 (5-Me) $\xrightarrow{20\%}$ δ_H 6.93 (4-H).

4bβ,12β-(*N*-Phenylepoxyimino)-4b,10bβ,11,12-tetrahydrooxychelerythrine (6)[3]——Colorless plates of mp 138.5—139.5 °C (ether). ^{1}H-NMR (90 MHz) decoupling: δ_H 3.78 (10b-H)→δ_H 3.06 (ddd, J_{HH} 14, 10 and 4 Hz→dd, J_{HH} 14 and 4 Hz, 11β-H), 1.95 (ddd, J_{HH} 14, 6 and 2 Hz→dd, J_{HH} 14 and 2 Hz, 11α-H); δ_H 3.06 and 1.95 (11-H_2)→δ_H 4.77 (dd, J_{HH} 4 and 2 Hz→s, 12-H). NOE: δ_H 3.42 (5-Me) $\xrightarrow{7.5\%}$ δ_H 6.54 (4-H).

4bβ,12β-(*N*-Phenylepoxyimino)-10bα-methyl-4b,5,6,10b,11,12-hexahydrochelerythrine (7)[4]——Colorless needles of mp 188.5—189.5 °C (methanol). ^{1}H-NMR (90 MHz) NOE δ_H: 6.58 (1-H) $\xrightarrow{11\%}$ δ_H 4.75 (12-H); δ_H 3.03 (5-Me) $\xrightarrow{15.5\%}$ δ_H 7.02 (4-H). ^{13}C-NMR decoupling: δ_H 4.75 (12-H)→δ_C 105.5 (d, J_{CH} 3 Hz→s, C-1), 129.6 (dd, J_{CH} 7 and 3 Hz→d, J_{CH} 7 Hz, C-4a), 130.6 (t, J_{CH} 6 Hz→d, J_{CH} 6 Hz, C-12a).

4bβ,12β-[13,14-Bis(carboethoxy)hydrazo]-10bβ-methyl-4b,10b,11,12-tetrahydrooxychelerythrine (8)[1]——Colorless granules of mp 126—129 °C (ether/petr. ether). ^{1}H-NMR (90 MHz) decoupling: δ_H 2.57 and 2.35 (11-H_2)→δ_H 5.16 (t, J_{HH} 3 Hz→s, 12-H). NOE: δ_H 6.58 (1-H) $\xrightarrow{6\%}$ δ_H 5.16 (12-H); δ_H 3.42 (5-Me) $\xrightarrow{33\%}$ δ_H 6.38 (4-H). ^{13}C-NMR gated decoupling: δ_C 103.7, Dd, J_{CH} 166 and 3 Hz (C-1); δ_C 106.4, Ds, J_{CH} 166 Hz (C-4); δ_C 116.0 and 117.4, each Ds, J_{CH} 160 Hz (C-9 and -10).

4bβ,12β-[13,14-Bis(carboethoxy)hydrazo]-4b,10bβ,11,12-tetrahydrooxychelerythrine (9)[3]——Colorless granules of mp 121.5—123 °C (benzene). ^{1}H-NMR (90 MHz) decoupling: δ_H 5.18 (12-H)→δ_H 2.61 (ddd, J_{HH} 14, 10 and 3 Hz→dd, J_{HH} 14 and 10 Hz, 11β-H), 2.13 (dt, J_{HH} 14 and 3 Hz→dd, J_{HH} 14 and 3 Hz, 11α-H); δ_H 4.05 (10b-H)→δ_H 2.61 (ddd, J_{HH} 14, 10 and 3 Hz→dd, J_{HH} 14 and 3 Hz, 11β-H), 2.13 (dt, J_{HH} 14 and 3 Hz→dd, J_{HH} 14 and 3 Hz, 11α-H). NOE: δ_H 6.65 (1-H) $\xrightarrow{10.5\%}$ δ_H 5.18 (12-H); δ_H 3.32 (5-Me) $\xrightarrow{15.5\%}$ δ_H 6.48 (4-H). ^{13}C-NMR gated decoupling: δ_C 103.9, Dd, J_{CH} 166 and 3 Hz (C-1); δ_C 106.5, Ds, J_{CH} 166 Hz (C-4); δ_C 115.2, Ds, J_{CH} 160 Hz (C-9); δ_C 118.9, Dd, J_{CH} 160 and 2 Hz (C-10).

4bβ,12β-[13,14-Bis(carbomethoxy)etheno]-4b,10bβ,11,12-tetrahydrooxychelerythrine (10)[3]——Light yellow granules of mp 135.5—137 °C (ether). ^{1}H-NMR (100 MHz) δ_H: 6.82 (1H, d, J_{HH} 8 Hz, 9-H),[6] 6.72 (1H, s, 1-H), 6.57 (1H, d, J_{HH} 8 Hz, 10-H),[6] 6.44 (1H, s, 4-H), 5.80 and 5.77 (each 1H, d, J_{HH} 1 Hz, 2,3-OCH_2O–), 4.45 (1H, dd, J_{HH} 4 and 2 Hz, 12-H), 3.95 (3H, s, 7-OMe), 3.83 (3H, s, 8-OMe), 3.78 and 3.75 (each 3H, s, 13- and 14-COOMe's), 3.63 (1H, dd, J_{HH} 10 and 7 Hz, 10b-H), 3.26 (3H, s, 5-Me), 2.45 (1H, ddd, J_{HH} 13, 10 and 4 Hz, 11β-H), 1.75 (1H, ddd, J_{HH} 13, 7 and 2 Hz, 11α-H).

4bβ,12β-[13,14-Bis(carbomethoxy)etheno]-4b,5,6,10bβ,11,12-hexahydrochelerythrine (11)[2]——An oil. ^{1}H-NMR (100 MHz) δ_H: 6.73 (2H, s, 1- and 4-H's), 6.61 (1H, d, J_{HH} 9 Hz, 9-H),[6] 6.53 (1H, d, J_{HH} 9 Hz, 10-H),[6] 5.78 (2H, s, 2,3-OCH_2O–), 4.42 (1H, dd, J_{HH} 4 and 2.5 Hz, 12-H), 4.35 (2H, s, 6-H_2), 3.83 and 3.81 (each 3H, s, 7- and 8-OMe's), 3.78 (6H, s, 13- and 14-COOMe's), 3.25 (1H, dd, J_{HH} 10 and 7 Hz, 10b-H), 2.96 (3H, s, 5-Me), 2.32 (1H, ddd, J_{HH} 12, 10 and 4 Hz, 11β-H), 1.70 (1H, ddd, J_{HH} 12, 10 and 2.5 Hz, 11α-H).

References and Notes

1) Part XV: H. Yamaguchi and M. Onda, *Chem. Pharm. Bull.*, **32**, 909 (1984).
2) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.*, **19**, 1 (1971); M. Onda, K. Yonezawa, K. Abe, H. Toyama, and T. Suzuki, *ibid.*, **19**, 317 (1971).
3) M. Onda and H. Yamaguchi, *Chem. Pharm. Bull.*, **27**, 2076 (1979).
4) M. Onda, H. Yamaguchi, and Y. Harigaya, *Chem. Pharm. Bull.*, **28**, 866 (1980).
5) Previous assignments were ambiguous.
6) Previous assignments were reversed.
7) W. L. F. Armarego, "Stereochemistry of Heterocyclic Compounds," Part 2, John Wiley and Sons, New York, 1977, pp. 284—287.
8) *Endo* and *exo* refer to the D ring.
9) H. Hart, S. K. Ramaswami, and R. Willer, *J. Org. Chem.*, **44**, 1 (1979).
10) J. E. Anderson and J. M. Lehn, *J. Am. Chem. Soc.*, **89**, 81 (1967).
11) T. A. Eaton, K. N. Houk, S. F. Watkins, and F. R. Fronczek, *J. Med. Chem.*, **26**, 479 (1983).
12) Guradata and J. B. Stothers, *Can. J. Chem.*, **47**, 3515 (1969).
13) K. Tori, Y. Takano, and K. Kitahonaki, *Chem. Ber.*, **97**, 2798 (1964). Assignments of the 11-protons in the compounds (**6**—**9**) were made by the same criteria as employed in the cases of the compounds (**4**—**5**).
14) J. E. Anderson and J. M. Lehn, *Tetrahedron*, **24**, 123 (1968).
15) The spectrum at −30°C was the same as that at −50°C.
16) B. J. Price and I. O. Sutherland, *J. Chem. Soc.* (*B*), **1967**, 573.
17) The spectrum at 0°C was the same as that at −30°C.