[Chem. Pharm. Bull. 33(11)4775—4782(1985)]

Utilization of Protopine and Related Alkaloids. XVII.[1] Spectroscopic Studies on the Ten-Membered Ring Conformations of Protopine and α-Allocryptopine

HIROSHI TAKAHASHI, MIEKO IGUCHI, and MASAYUKI ONDA*

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

(Received March 20, 1985)

The infrared carbonyl absorptions of protopine and α-allocryptopine in dilute carbon tetrachloride solution and nuclear Overhauser effect experiments in the proton nuclear magnetic resonance spectra have shown that these alkaloids each interconvert between two major conformations of the ten-membered ring. These conformations are discussed on the basis of the observed spectral data.

Keywords——protopine alkaloid; IR; variable-temperature ^{1}H-NMR; NOE; gated decoupling; selective proton decoupling; two-dimensional ^{1}H–^{13}C shift correlation

It is well known that a ten-membered ring exists in a number of conformations. The molecules of the protopine alkaloids contain a hexahydrodibenz[*c*,*g*]azecine ring system. Because of our interest in the conformations of ten-membered cyclic aminoketones, we investigated the spectral properties of protopine (**1**) and α-allocryptopine (**2**).

The infrared (IR) spectrum of **1** showed a carbonyl absorption at 1658 cm^{-1} (Nujol), which was explained by a transannular interaction between the nitrogen atom and the carbonyl carbon.[2]

The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **1** revealed the spectral complexity caused by a slow inversion of the ten-membered ring (B) at low temperatures.[3] In addition, the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **1**, taken in the presence of phenol, showed the occurrence of the transannular interaction between the nitrogen atom and the carbonyl carbon.[4]

The X-ray analysis of **1** provided the following structural features:[5a] (1) Ring B is severely buckled, and a distance between the nitrogen atom and the carbonyl carbon is 2.555 Å. The nitrogen lone pair is directed toward the carbonyl carbon. (2) The carbonyl group is at an angle of 37.4° counterclockwise below the benzene ring (A). The 7-methyl group and the carbonyl oxygen atom are on the same side of ring B. (3) A steric interaction exists between the 5- and 13-hydrogens. The first feature stabilizes the molecule due to the transannular ("amide-type") interaction, and is responsible for a low-frequency shift of the carbonyl group in the IR spectrum. The second feature (slightly) labilizes the molecule due to the (slight) loss of conjugation and causes a high-frequency shift of the carbonyl group. The third feature also labilizes the molecule. It is likely that the transannular interaction outweighs the labilizing factors, and that **1** adopts the above molecular geometry as the most stable conformation of the crystal structure.

IR Spectroscopy

The spectral data for **1**, **2** and related compounds are recorded in Table I. Carbonyl absorptions of **1** and acetopiperone (**3**) were observed at 1654 and 1660 cm^{-1}, respectively, in

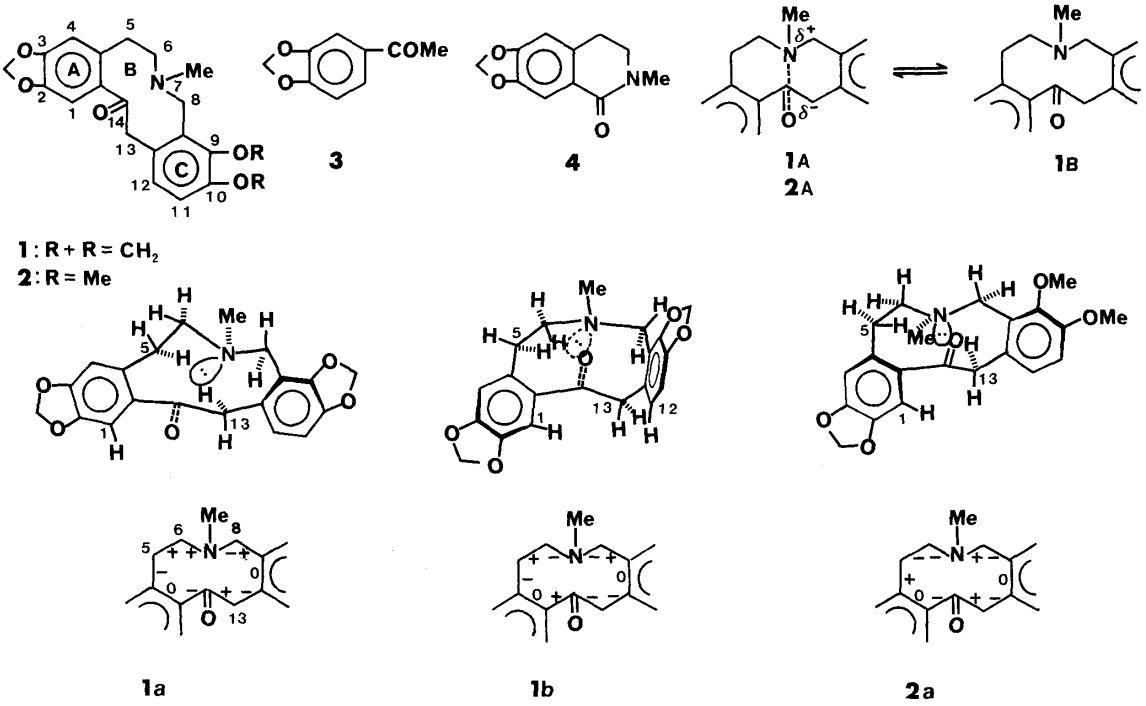

Chart 1

TABLE I. IR Carbonyl Absorptions of **1**, **2** and Related Compounds (cm^{-1}, ε)

	KBr	CCl_4[a)]	$CHCl_3$[b)]
1	1654	1686 (386), 1670 (386)	1652 (471)
2	1640	1662 (287), 1654 (250)	1650 (209)
3	1660	1683 (615)	1670 (307)
4	1636	1658 (645)	1640 (531)
5	1672		
6	1660		

a) $c = 1 \times 10^{-4}$ mol/l. *b*) $c = 1 \times 10^{-3}$ mol/l.

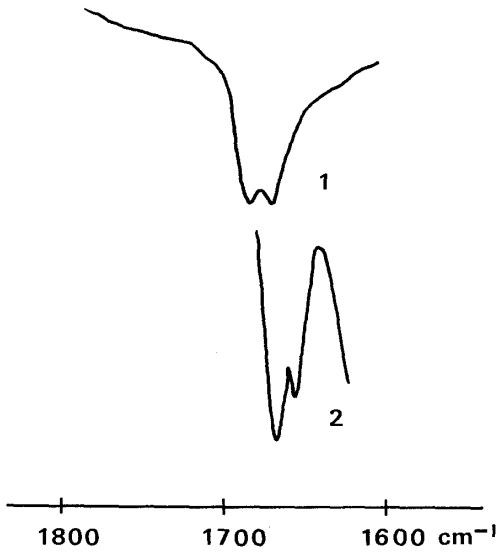

Fig. 1. Carbonyl Absorptions of **1** and **2** ($c = 1 \times 10^{-4}$, CCl_4)

the solid state. A difference $\Delta\nu_{3-1}=6\,cm^{-1}$ in carbonyl frequency proves that the transannular interaction between the nitrogen atom and the carbonyl carbon outweighs any high-frequency shift arising from the loss of conjugation due to non-coplanarity of the carbonyl group and ring A.

Ring B can adopt conformations in solution that are different from that of the crystal structure. Two carbonyl absorptions of **1** were observed at 1686 and 1670 cm^{-1} in dilute carbon tetrachloride solution (Fig. 1). The absorption at 1670 cm^{-1} is due to the modified carbonyl group in the conformation **1a** (corresponding to the crystal structure)[5a] of the interacted form **1A**.[6,7] The other at 1686 cm^{-1} is due to the carbonyl group in the major conformation **1b** of the non-interacted form **1B**,[6] which would have the carbonyl group slightly out of ring A, as compared with a carbonyl absorption (1683 cm^{-1}, CCl_4) of **3**.

Protopine methiodide (**5**) showed a carbonyl absorption at 1672 cm^{-1} in the solid state. Differences $\Delta\nu_{5-1}(KBr)=18$ and $\Delta\nu_{5-3}(KBr)=12\,cm^{-1}$ in carbonyl frequency reveal the non-transannular interaction between the nitrogen atom and the carbonyl carbon as well as non-coplanarity of the carbonyl group and ring A, caused by the 7-methyl groups in **5**.

The crystal structure of **2** is assumed to be similar to that of **1**.[5b] Comparison of a carbonyl absorption (1640 cm^{-1}, KBr) of **2** with that (1636 cm^{-1}, KBr) of oxyhydrastinine (**4**) [$\Delta\nu_{3-2}(KBr)=20\,cm^{-1}$] suggests that the carbonyl group is (nearly) coplanar with ring A in the crystalline form of **2** and that the nitrogen atom and the carbonyl carbon mutually interact across ring B.

Two carbonyl absorptions of **2** were detected at 1662 and 1654 cm^{-1} in dilute carbon tetrachloride solution (Fig. 1). Taking into account a carbonyl absorption (1683 cm^{-1}, CCl_4) of **3**, the two absorptions are considered to correspond to the modified carbonyl groups in two major conformations of the interacted form **2A**. One of the conformations corresponds to that (**1a**-type) of the crystal structure, and the other is the conformation **2a** having the carbonyl group non-coplanar with ring A.

No difference in carbonyl frequency (KBr) between **3** and α-allocryptopine methiodide (**6**) is attributed to (near) coplanarity of the carbonyl group and ring A in the crystalline form of **6**.

Carbonyl absorptions of **1** and **2**, which were observed at 1652 and 1650 cm^{-1} in dilute chloroform solution, respectively, are presumably a result of fast interconversions between two conformations as well as low-frequency shifts due to the polar solvent.[7]

NMR Spectroscopy

The variable-temperature ^1H-NMR spectra of **1** and **2** are shown in Figs. 2 and 3. The methylene protons in ring B appeared as broad and/or complex signals at 32 °C. These signals were sharpended at 50—60 °C and showed the same pattern. The spectra at 32 °C represent slow interconversions between two conformations (*vide supra*) on the NMR time scale. The ones at 60 °C correspond to those of the equilibrating species. However, these observations give no information on the conformation in solution.

The ^1H- and ^{13}C-NMR spectra of **1** and **2** at 60 °C are recorded in Tables II and III. Protons and carbons were assigned by means of gated decoupling and selective proton decoupling experiments. In addition, the two-dimensional ^1H–^{13}C shift correlation technique was used for **1**. Two methylenedioxy protons in **1** and two methoxy protons in **2**, which remained so far ambiguous, were identified. The 12-proton in **1** appeared as a double doublet ($J_{11H,12H}=8.5$ and $J_{8H_A,12H}=1.5$ Hz) at a higher field (δ_H 6.65) than the 11-proton (δ_H 6.67, d, $J=8.5$ Hz). Other things being equal, the 6-proton resonates at a higher field by *ca.* 0.2 ppm than the 5-proton in a 7,8-methylenedioxyisoquinoline.[8] An up-field shift of the 12-proton can be ascribed to the participation of a shielding effect of ring A. Ring A in **1a** is too far away to affect the 12-proton shielding. Thus, **1b** adopts a molecular geometry, in which the 12-

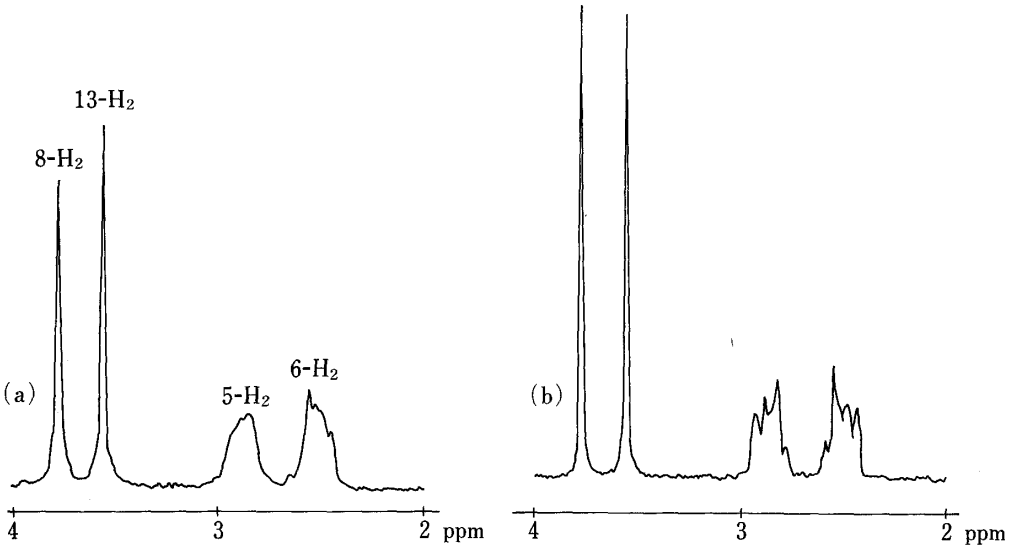

Fig. 2. Partial 90 MHz ^{1}H-NMR Spectra of **1**
(a) at 32 °C; (b) at 60 °C.

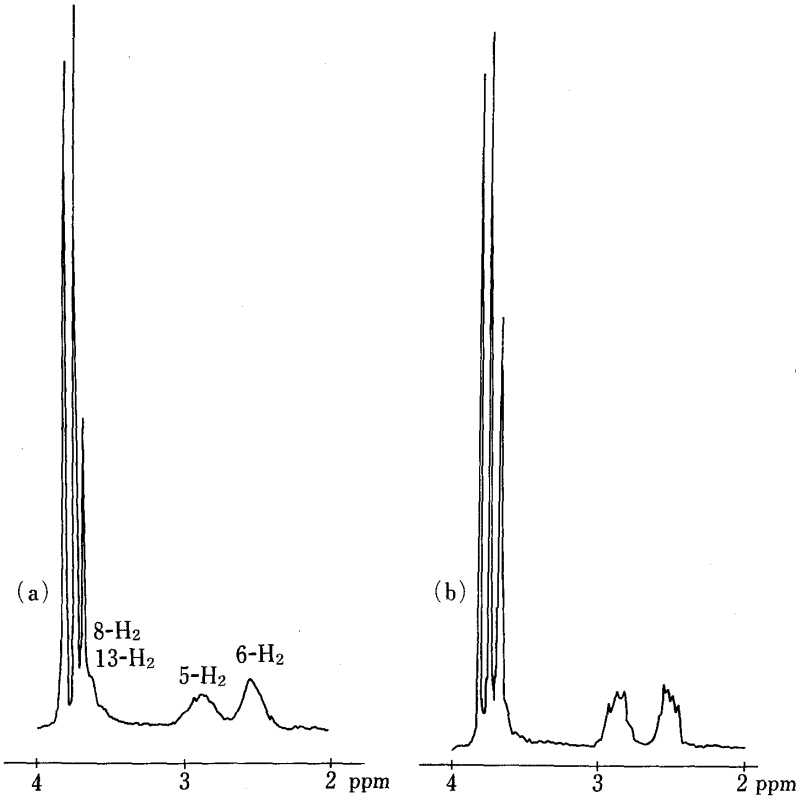

Fig. 3. Partial 90 MHz ^{1}H-NMR Spectra of **2**
(a) at 32 °C; (b) at 60 °C.

hydrogen lies in the vicinity of the shielding zone of ring A. The observed chemical shift of the 12-proton is a result of the contribution of **1b** to be equilibrating species. The carbon chemical shifts observed for **1** and **2** in this work led us to revise the assignments of three aromatic carbons (C-2, -9 and -10) having ether linkages and two aromatic quaternary carbons (C-4a and -14a) described in the literature.[4,9,10]

A Dreiding model of the conformation **1a**, which was constructed on the basis of the

TABLE II. ^{1}H- (300 MHz) and ^{13}C-NMR (75.4 MHz) Data for **1** at 60 °C (ppm, Hz)

	δ_C[a]	$^1J_{CH}$	$^{>1}J_{CH}$	One-bond[b] δ_H	One-bond[b] J_{HH}	Long-range[b]
1	108.0 Ds	164		6.89 s		2,3-OCH_2O,[c] 4-H
2	145.7 Sm					2,3-OCH_2O,[c] 4-H
3	147.8 Sm					1-H,[c] 2,3-OCH_2O[c]
4	110.3 Dt	164	6	6.63 s		5-H_2
4a	132.6 Sdt		7, 5			1-H,[c] 5-H_2
5	31.7 Tq	127	5	2.89 s	W_H 18	4-H, 6-H_2[c]
6	57.7 Tm	135		2.52 t	5	5-H_2, 7-CH_3
8	50.6 Tq	134	5.5	3.57 d	1.5	7-CH_3
8a	117.7 Sdt		7, 3.5			8-H_2,[c] 12-H, 13-H_2
9	146.2 Sm					8-H_2[c] 9,10-OCH_2O, 11-H
10	145.8 Sm					9,10-OCH_2O, 12-H
11	106.6 Ds	163		6.67 d	8.5	
12	124.9 Dt	163	5	6.65 dd	8.5, 1.5	13-H_2
12a	128.8 Sm					8-H_2,[c] 11-H, 13-H_2
13	46.3 Td	126	5	3.79 s		12-H
14	194.8 Sq		5			1-H,[c] 13-H_2
14a	136.0 Sdt		7, 5			4-H, 5-H_2
2,3-OCH_2O	101.1 Ts	173		5.93 s		
7-CH_3	41.3 Qm	135		1.93 s		6-H_2,[c] 8-H_2[c]
9,10-OCH_2O	100.7 Ts	173		5.91 s		

a) Capital and small letters refer to the splittings observed in the off-resonance and the gated decoupled spectra, respectively. *b*) These data were obtained by the two-dimensional ^{1}H–^{13}C shift correlation technique. *c*) Long-range couplings were also confirmed by selective proton decoupling experiments.

crystal structure of **1**,[5a] shows the following approximate shortest internuclear distances: 1-H *ca.* 3.8 Å 13-H_2 and 5-H_2 *ca.* 1.5 Å 13-H_2. The roughly assessed nuclear Overhauser effects (NOE's) are not in accord with NOE's of 15.5 and 3.5% observed between the 1- and 13-protons and between the 5- and 13-protons in **1** at 60 °C.[11] The observed NOE's correspond to those of the equilibrating species between **1a** and **1b**. As mentioned above, **1b** contains the carbonyl group in a slightly non-coplanar relation to ring A in **1B**, and the 12-hydrogen lies in the vicinity of the shielding zone of ring A. The conformation **1b**, which was constructed on the basis of these factors, contains the following features: (1) An internuclear distance between the nitrogen atom and the carbonyl carbon is *ca.* 3.5 Å. (2) The nitrogen lone pair is not directed toward the carbonyl carbon. (3) The carbonyl group is at an angle of *ca.* 45° clockwise below ring A. The 7-methyl group and the carbonyl oxygen atom are on the opposite side of ring B. (4) Ring B is free from steric strain. (5) Assessed shortest internuclear distances: 1-H *ca.* 2.5 Å 13-H_2 and 5-H_2 *ca.* 4 Å 13-H_2. It seems probable that **1b** (strain-free) is a stable conformation, next to **1a**. A large contribution of **1b** to the equilibrating species accounts for the observed NOE's.

It is deduced that **2** interconverts between a conformation similar to **1a** and the one **2a** having the carbonyl group noncoplanar with ring A in **2A**. Owing to a large steric interaction between the 7-methyl and the 9-methoxy groups, **2** cannot exist in the **1b**-type conformation. A stable conformation having the following features can be drawn for **2a**: (1) An internuclear distance between the nitrogen atom and the carbonyl carbon is *ca.* 2.5 Å. (2) The nitrogen lone pair is directed toward the carbonyl carbon. (3) The carbonyl group is at an angle of *ca.* 70° counterclockwise above ring A. The 7-methyl group and the carbonyl oxygen atom are on the opposite side of ring B. (4) A steric interaction exists between the 7-methyl group and the 13-hydrogen. (5) Assessed shortest internuclear distance between the 1- and 13-hydrogens is *ca.*

TABLE III. ^{1}H- (90 MHz) and ^{13}C-NMR (25.2 MHz) Data for **2** at 60 °C (ppm, Hz)

	δ_C[a]	$^1J_{CH}$	$^{>1}J_{CH}$	Irradiated H (δ_H)	Resulting splitting
1	109.4 Ds	165		1-H (6.92 s)	S
2	146.3 Sm			4-H	br s
				2,3-OCH_2O	d (7)
3	148.3 Sm			1-H	d (4)
				2,3-OCH_2O	d (7)
4	110.6 Dt	165	5	4-H (6.60 s)	S
				5-H_2	s
4a	133.1 Sm			1-H	sharpened
				5-H_2	dt (7, 4)
				6-H_2	dt (7, 3.5)
5	32.4 Tq	128	5	5-H_2 (2.88 m)	S
				4-H	t (5)
				6-H_2	d (5)
6	57.8 Tm	135		6-H_2 (2.54 m)	S
				5-H_2	q (4)
				7-CH_3	sharpened
8	50.3 Tq	128	5	8-H_2 (3.68 s)	S
				7-CH_3	s
8a	128.9 Sdt		7, 3	8- and 13-H_2's	d (7)
				12-H	sharpened
9	147.8 Sm			8-H_2	each
				11-H	sharpened
				9-OCH_3[b]	
10	151.9 Sm			12-H	q (4)
				10-OCH_3[c]	d (7)
11	111.0 Ds	162		11-H (6.73 d)[d]	S
12	128.0 Dt	162	5	12-H (6.89 d)[d]	S
				13-H_2	s
12a	129.9 Sm			8- and 13-H_2's	d (7)
				11-H	sharpened
13	46.5 Td	128	5	13-H_2 (3.68 s)	S
				12-H	s
14	193.7 Sq		5	1-H	t (5)
				13-H_2	d (5)
14a	136.3 Sdt		7, 4	4-H	t (4)
				5-H_2	d (7)
2,3-OCH_2O	101.3 Ts	175		2,3-OCH_2O (5.92 s)	S
7-CH_3	41.3 Qm	136		7-CH_3 (1.85 s)	S
				6-H_2	sharpened
				8-H_2	t (5)
9-OCH_3	55.8 Qs	146		9-OCH_3 (3.80 s)[b]	S
10-OCH_3	60.8 Qs	146		10-OCH_3 (3.76 s)[c]	S

a) Capital and small letters refer to the splittings observed in the off-resonance and the gated decoupled spectra, respectively. *b*) A slightly down-field region from δ_H 3.80 was irradiated so as not to affect the 10-methoxy protons. *c*) A slightly up-field region from δ_H 3.76 was irradiated so as not to affect the 9-methoxy protons. *d*) An AB quartet with J_{HH} 8.5 Hz.

2.5 Å. An NOE of 16% was observed between the 1- and 13-protons at 60 °C. A large contribution of **2a** to the equilibrating species also explains the observed NOE. The transannular interaction between the nitrogen atom and the carbonyl carbon outweighs to some extent the labilizing factors, and as a result, **2** adopts **2a** as a stable conformation, next to the **1a**-type one.

For the above-mentioned reasons, the observed differences in the IR and NMR spectra between **1** and **2** can be attributed to conformational changes resulting from the steric interaction between the 7-methyl and the 9-methoxy groups in **2**.

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Spectra were recorded on the following spectrometers: IR, Hitachi 260-30; ^{1}H-NMR, Varian EM-390 (90 MHz) and Varian XL-300 (300 MHz) (in $CDCl_3$); ^{13}C-NMR, JEOL JNM PFT-100 (25.2 MHz) and Varian XL-300 (75.4 MHz) (in $CDCl_3$); mass (MS), JEOL JMS DX-300.

Protopine (1)[12]——Colorless pillars of mp 210—211 °C (from MeOH). ^{1}H-NMR (300 MHz) NOE (%) at 60 °C: 5-H_2→4-H (29.5), 7-Me (2.5), 8-H_2 (5.5), 13-H_2 (3.5); 6-H_2→4-H (5), 7-Me (2), 8-H_2 (2); 8-H_2→5-H_2 (2.5), 6-H_2 (2.5); 13-H_2→1-H (15.5), 12-H (10.5). *Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.01; H, 5.38; N, 3.95.

Protopine Methiodide (5)——A mixture of **1** (35 mg) and methyl iodide (0.4 ml) in chloroform (1.5 ml) was stirred at room temperature for 27 h. The precipitate was collected and recrystallized from methanol to yield **5** (43.9 mg, 90%) as colorless needles of mp 217—218 °C (dec.) [lit.,[2b] mp 213—215 °C (dec.)]. *Anal.* Calcd for $C_{21}H_{22}INO_5$: C, 50.92; H, 4.48; N, 2.83. Found: C, 50.77; H, 4.46; N, 2.78.

α-Allocryptopine (2)[12]——Colorless pillars of mp 160—161 °C (from MeOH). ^{1}H-NMR (300 MHz) NOE (%) at 60 °C: 4-H→5-H_2(3), 6-H_2 (2.5); 5-H_2→4-H (21), 8- and/or 13-H_2's (3); 6-H_2→4-H (6), 7-Me (2), 8- and/or 13-H_2's (1.5); 12-H→11-H (10.5); 13-H→1-H (16), 12-H (10). *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.32; H, 6.31; N, 3.77.

α-Allocryptopine Methiodide (6)——A mixture of **2** (40.2 mg) and methyl iodide (0.4 ml) in carbon tetrachloride (5 ml) was stirred at room temperature for 10 h. Work-up of the reaction mixture gave **6** (51.9 mg, 93.5%) as colorless needles of mp 206—208 °C (dec.). *Anal.* Çalcd for $C_{22}H_{26}INO_5$: C, 51.67; H, 5.13; N, 2.74. Found: C, 51.42; H, 4.98; N, 2.80.

Acetopiperone (3)——A mixture of methyl iodide (0.1 ml) and Mg (38.2 mg) in anhydrous ether (2 ml) was refluxed in a stream of N_2 for 1 h. A solution of piperonal (152.8 mg) in anhydrous ether (0.5 ml) was added dropwise, and the whole was stirred at room temperature for 1 h. After addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with ether. The ethereal solution was dried over Na_2SO_4 and concentrated *in vacuo*, then purified by prep. TLC[13] (silica gel, benzene) to yield α-methylpiperonyl alcohol (122.2 mg, 72%) as a colorless oil, *Rf* 0.23 [IR ($CHCl_3$), 3604, 3464 cm^{-1} (OH); MS, M^+, 166.063 (M, 166.062)].

A solution of the alcohol (98.4 mg) in acetone (0.1 ml) was added to a mixture of $Na_2Cr_2O_7$ (120 mg) and H_2SO_4 (d=1.84) (0.05 ml) in water (1 ml), and the whole was stirred at room temperature for 20 min. The reaction mixture was extracted with ether. Work-up gave **3** (60.5 mg, 61%) as colorless needles of mp 89—90 °C (from EtOH) (lit.,[14] mp 87—88 °C). MS Calcd for $C_9H_8O_3$: M, 164.047. Found *m/z*: M^+, 164.048.

Oxyhydrastinine (4)——A solution of NaCN (20.1 mg) in water (0.5 ml) and 15% aqueous NaOH (0.2 ml) were added to a suspension of hydrastininium iodide[15] (44.7 mg) in benzene (1.5 ml)–methanol (0.8 ml), and the whole was stirred at room temperature for 4 h. The reaction mixture was extracted with benzene. Work-up gave an oil, which was purified by prep. TLC (alumina, benzene) to yield the pseudo-cyanide (27.5 mg, 90%), as a colorless oil, *Rf* 0.44 [IR ($CHCl_3$), 2228 cm^{-1} (C≡N); MS, M^+, 216.090 (M, 216.090)].

A solution of $K_3Fe(CN)_6$ (204.7 mg) in water (1 ml) and a solution of KOH (81.7 mg) in water (1 ml) were added to a solution of the pseudo-cyanide (24.2 mg) in ethanol (3 ml), and the whole was heated at 60 °C in a stream of N_2 for 1 h. The reaction mixture was filtered, and the filtrate was extracted with ethyl acetate. Work-up gave **4** (22.4 mg, 97%) as colorless needles of mp 99—100 °C (from ether) (lit.,[16] mp 95—96 °C). ^{1}H-NMR (90 MHz) δ: 7.52 (1H, s, 8-H), 6.56 (1H, s, 5-H), 5.95 (2H, s, OCH_2O), 3.50, 2.87 (each 2H, t, J=6.5 Hz, 3- and 4-H_2's), 3.10 (3H, s, 2-Me). MS Calcd for $C_{11}H_{11}NO_3$: M, 205.073. Found *m/z*: M^+, 205.074.

References and Notes

1) Part XVI: M. Onda, A. Hatano, H. Yamaguchi, and N. Sato, *Chem. Pharm. Bull.*, **32**, 2503 (1984).
2) *a*) E. H. Mattus, H. Schwarz, and L. Marison, *Can. J. Chem.*, **31**, 1144 (1953); *b*) F. A. L. Anet and L. Marison, *ibid.*, **32**, 452 (1954).
3) F. A. L. Anet and M. A. Brown, *Tetrahedron Lett.*, **1967**, 4881.
4) T. T. Nakashima and G. E. Maciel, *Org. Magn. Reson.*, **5**, 9 (1973).
5) *a*) S. R. Hall and F. R. Ahmed, *Acta Crystallogr., Sect. B*, **24**, 337 (1968); *b*) *Idem, ibid.*, **24**, 346 (1968).
6) N. J. Leonard, M. Ōki, J. Brader, and H. Boaz, *J. Am. Chem. Soc.*, **77**, 6237 (1955).
7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 3rd ed., Chapman and Hall Ltd., London, 1975,

p. 153; A. Ōno, "Shin Jikkenkagaku Koza (in Japanese)," Vol. 13, Maruzen, Tokyo, 1977, pp. 248—249.
8) M. Shamma and H. H. Tomlinson, *J. Org. Chem.*, **43**, 2852 (1978).
9) B. Gözler and M. Shamma, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 2431.
10) K. Iwasa, M. Sugiura, and N. Takao, *J. Org. Chem.*, **47**, 4275 (1982).
11) R. A. Bell and J. K. Saunders, *Can. J. Chem.*, **48**, 1114 (1970); *idem*, "Topics in Stereochemistry," Vol. 7, ed. by N. L. Allinger and E. L. Eliel, John Wiley and Sons, Inc., New York, 1973, p. 1.
12) M. Onda, K. Takiguchi, M. Hirakura, H. Fukushima, M. Akagawa, and F. Naoi, *Nippon Nogeikagaku Kaishi*, **39**, 168 (1965).
13) Preparative thin-layer chromatography.
14) W. Feuerstein and M. Heimann, *Chem. Ber.*, **34**, 1468 (1901).
15) This compound was prepared from *N*-(3,4-methylenedioxyphenethyl)formamide *via* the Bischler-Napieralski reaction and treatment with methyl iodide. Light yellow plates of mp 242—245 °C (dec.) [H. Decker, *Justus Liebigs Ann. Chem.*, **395**, 321 (1913), mp 234 °C]. *Anal.* Calcd for $C_{11}H_{12}INO_2$: C, 41.65; H, 3.81; N, 4.41. Found: C, 41.61; H, 3.83; N, 4.38.
16) M. Freund and W. Will, *Chem. Ber.*, **22**, 2400 (1889).