Quinolizidines. VII. Structure of O-Methylpsychotrine : The Endocyclic versus the Exocyclic Double Bond Structure in the Dihydroisoquinoline Moiety

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Quinolizidines. VII.[1] Structure of *O*-Methylpsychotrine: The Endocyclic versus the Exocyclic Double Bond Structure in the Dihydroisoquinoline Moiety

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By comparison of its ultraviolet spectra in H_2O at various pH's with those of model compounds, **11**, **14**, **16**, **17**, and **18**, the Ipecac alkaloid *O*-methylpsychotrine has been shown to have the genuine 3,4-dihydroisoquinoline structure (**1**), not the exocyclic double bond structure (**4**), in the free base form as well as in the protonated form. The ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra of the alkaloid have also confirmed this endocyclic double bond structure in the dihydroisoquinoline moiety. These results indicate that the position of the double bond for simple 1-alkyl-3,4-dihydroisoquinolines is endocyclic, and factors that stabilize the exocyclic double bond structure are discussed. 1-*tert*-Butyl-3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide (**30**) has been found to be unstable in H_2O. On heating in H_2O at 90°C for 10 min, it underwent ring opening to give **27** in good yield. The acid dissociation constants for 1-methyl- (**16**) and 1-*tert*-butyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**18**) in H_2O at 20°C were spectrometrically determined to be 9.16 ± 0.02 and 8.80 ± 0.02, respectively.

Keywords——Ipecac alkaloid; 1-alkyl-3,4-dihydroisoquinoline; methiodide; tautomeric shift of double bond; ring opening; UV; ^1H NMR; ^{13}C NMR; pK_a

The Ipecac alkaloid *O*-methylpsychotrine was first discovered by Pyman in 1917.[2] Although it has been assigned[3] structure **1** largely on the basis of chemical interrelation with emetine (**2**) and psychotrine (**5**), there have been conflicting reports in the literature concerning the position of the double bond in its dihydroisoquinoline moiety. It forms an *N*-benzoyl derivative (**3**) and was, therefore, long considered to contain a secondary amino group. Brindley and Pyman[4] allocated the double bond to the position shown in formula **4**. Karrer *et al.*[5] confirmed this exocyclic double bond structure for the *N*-benzoyl derivative **3** by oxidation with perphthalic acid or ozone to give *N*-benzoylcorydaldine (**8**). However, the ultraviolet (UV)[6] and infrared (IR)[3a,7] spectral data of *O*-methylpsychotrine support its endocyclic double bond structure (**1**), but in a somewhat inconclusive manner, and the formation of the *N*-benzoyl derivative **3** was interpreted in terms of a tautomeric shift of the double bond.[8] Nevertheless, Schuij *et al.*[9] recently claimed the double bond in *O*-methylpsychotrine to be exocyclic, as in **4**, on the basis of their mass spectral study.

The position of the double bond in the dihydroisoquinoline moiety thus remains uncertain not only for *O*-methylpsychotrine [and hence for another Ipecac alkaloid psychotrine (**5**)[3]], but also for a whole group of similar compounds as well. The group includes the *Alangium* alkaloids desmethylpsychotrine[10] and alangicine,[10] which have recently been assigned structures **6**[11] and **7**,[12] respectively. We now present nuclear magnetic resonance (NMR) and UV spectroscopic evidence that the double bond in *O*-methylpsychotrine is not exocyclic as in structure **4**, but endocyclic as in structure **1**.

Our previous papers[13,14] have already shown that the quaternary iodide **9** is converted into the readily isolable enamine **10** under strongly alkaline conditions, and that methylation of **10** with methyl iodide gives the *N*-methylated product **11** as well as the *C*-methylated product **12**.[14] We selected compounds **10** and **11** as good models for the exocyclic double bond structure (**4**) in the present spectroscopic study. An additional model was the *N*-acetyl derivative **14**, which was prepared from the tertiary base **17**[15] by adaptation of the procedure[16]

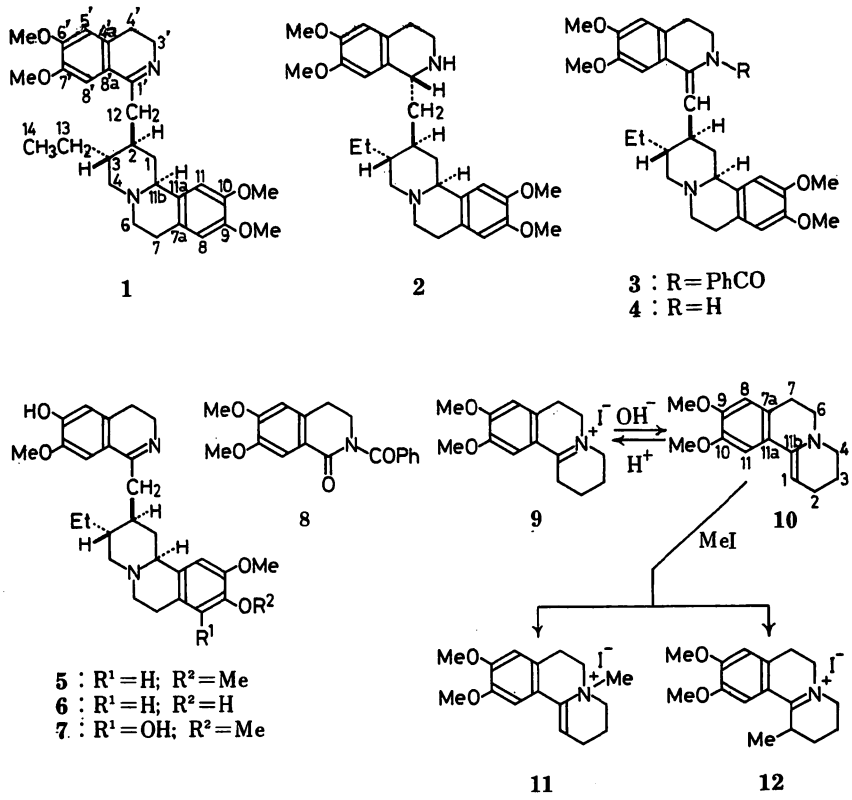


Chart 1

TABLE I. ^{1}H NMR Spectra of the Exocyclic C=C Models **10** and **11**

Compound	Solvent[b]	Temp. (°C)	Chemical shift (δ)[a] $C_{(1)}H$	$C_{(2)}H_2$	$C_{(3)}H_2$	$C_{(4)}H_2$	$C_{(6)}H_2$, $C_{(7)}H_2$	$C_{(8)}H$	$C_{(11)}H$	OMe
10	A	24	5.20(b)	2.26(t) [J=6.0 Hz]	1.95(m)	3.07(m)	2.7—3.1(m)	6.53(s)	7.10(s)	3.85(s) 3.86(s)
10	A	−20	5.32(t) [J=3.9 Hz]	2.27(m)	1.96(m)	3.05(m)	2.7—3.1(m)	6.55(s)	7.10(s)	3.87(s) 3.89(s)
10	B	24	5.24(t) [J=3.9 Hz]	2.17(m)	1.83(m)	2.97(m)	2.6—3.0(m)	6.64(s)	7.10(s)	3.74(s) 3.74(s)
10	C	24	5.35(t) [J=4.0 Hz]	2.23(m)	1.89(m)	3.00(m)	2.7—3.1(m)	6.65(s)	7.34(s)	3.73(s) 3.80(s)
11[c]	B	24	6.74(b)	2.3—2.5(m)	1.9—2.3(m)	3.4—4.0(m)	3.4—4.0(m) 3.0—3.4(m)	6.89(s)	7.11(s)	3.79(s) 3.79(s)

a) Measured in 5—12% (w/v) solutions. The letter in parentheses designates the multiplicity or shape of the signal; the abbreviations are given in "Experimental".
b) The symbol A stands for $CDCl_3$; B, Me_2SO-d_6; C, pyridine-d_5.
c) The $N_{(4)}$-methyl protons resonated at δ 3.19 (s).

of Brossi *et al.* However, its configuration about the exocyclic double bond was undetermined. It may be seen from Table I that the ^{1}H NMR spectrum of **10** in various solvents showed a one-proton triplet at δ 5.20—5.35 assignable to the olefinic proton at $C_{(1)}$. The corresponding proton in **11** resonated at δ 6.74 in Me_2SO-d_6. The olefinic proton of **14** appeared as a doublet at δ 5.34 (J=10.3 Hz) in $CDCl_3$ (see "Experimental"). If *O*-methylpsychotrine has the exocyclic double bond structure (**4**), it should have displayed an olefinic proton doublet in the range of δ 5.2—6.7 by analogy. As shown in Table II, however, neither the free base of *O*-methylpsychotrine nor its di(hydrogen oxalate) salt [**1**•2(CO_2H)$_2$] exhibited such a signal in

Table II. ^{1}H NMR Spectra of *O*-Methylpsychotrine and Its Di(hydrogen oxalate)

Compound	Solvent	Temp. (°C)	Chemical shift (δ)[a]			
			CMe	OMe	Aromatic protons	CO_2H
O-Methylpsychotrine	$CDCl_3$	24[b]	0.98 (t) [J=6.8 Hz]	3.75 (s) 3.82 (s) 3.89 (s) 3.92 (s)	6.49 (s) 6.54 (s) 6.73 (s) 7.03 (s)	—
O-Methylpsychotrine di(hydrogen oxalate)	Me_2SO-d_6	24[c]	0.91 (b)	3.65 (s) 3.71 (s) 3.86 (s) 3.91 (s)	6.62 (s) 6.74 (s) 7.16 (s) 7.43 (s)	9.85 (b, s)
O-Methylpsychotrine di(hydrogen oxalate)	Me_2SO-d_6	80[d]	0.93 (t) [J=7.2 Hz]	3.67 (s) 3.74 (s) 3.86 (s) 3.92 (s)	6.60 (s) 6.73 (s) 7.12 (s) 7.40 (s)	9.53 (b, s)

a) The letter(s) in parentheses designate(s) the multiplicity or shape of the signal; the abbreviations are given in "Experimental".
b) An 11% (w/v) solution.
c) A saturated solution.
d) A 12% (w/v) solution.

Table III. ^{1}H NMR Spectra of 1-Alkyl-3,4-dihydro-6,7-dimethoxyisoquinolines (**16**, **17**, **18**) and Their Methiodides

Compound	Chemical shift (δ)[a] in $CDCl_3$								
	$C_{(4)}H_2$	$C_{(3)}H_2$	OMe	$C_{(5)}H$	$C_{(8)}H$	$C_{(1)}$-Alkyl			N^+Me
						Me	CH_2	CH	
16	2.63(m)	3.64(m)	3.91(s) 3.91(s)	6.69(s)	6.99(s)	2.36(t)[b] [J=1.5 Hz]	—	—	—
17	2.60(t) [J=7.6 Hz]	3.64(t) [J=7.6 Hz]	3.90(s) 3.91(s)	6.70(s)	6.99(s)	0.96(d) [J=6.6 Hz]	2.57(d) [J=6.8 Hz]	2.08(m)	—
18	2.51(m)	3.57(m)	3.90(s) 3.91(s)	6.71(s)	7.35(s)	1.39(s)	—	—	—
28	3.29(t) [J=7.7 Hz]	4.13(t) [J=7.7 Hz]	3.96(s) 4.00(s)	6.97(s)	7.29(s)	2.98(s)	—	—	3.90(s)
29	3.28(t) [J=7.7 Hz]	4.17(t) [J=7.7 Hz]	3.96(s) 4.02(s)	7.02(s)	7.28(s)	1.06(d) [J=6.6 Hz]	3.25(d) [J=7.4 Hz]	2.13(m)	3.97(s)
30	3.19(t) [J=7.0 Hz]	4.08[c]	3.91(s) 4.00(s)	6.98(s)	7.25(s)	1.76(s)	—	—	4.15(s)
18·HCl	2.98(t) [J=7.6 Hz]	4.10[d]	3.93(s) 4.02(s)	6.89(s)	7.53(s)	1.71(s)	—	—	—[e]

a) The letter in parentheses designates the multiplicity or shape of the signal; the abbreviations are given in "Experimental".
b) Long-range coupling with the $C_{(3)}$-methylene protons was confirmed by spin-decoupling experiments.
c) Overlapped with the signals of OMe's and N^+Me.
d) Overlapped with the signal of OMe.
e) The N^+H proton signal appeared at δ 13.30 (b).

TABLE IV. ^{13}C Shieldings of Compounds 9—11 in $CDCl_3$

Carbon	Chemical shift[a] 9	10	11[b]	Carbon	Chemical shift[a] 9	10	11[b]
C (1)	25.8	93.3	119.7	C (9)	155.8	148.5[e]	149.9[f]
C (2)	17.1	22.8	21.8	C (10)	148.5	147.4[e]	148.3[f]
C (3)	21.0	22.4	15.6	C (11)	110.9	106.2	107.7
C (4)	55.0[c]	51.7	62.8[d]	C (11a)	119.1	123.6	118.2
C (6)	52.3[c]	50.0	61.8[d]	C (11b)	173.4	140.7	137.2
C (7)	28.9	29.5	22.7	OMe	56.9	55.8	55.6
C (7a)	132.2	126.7	122.4		56.9	55.9	55.8
C (8)	110.7	110.8	111.3	N^+Me	—	—	46.8

a) In ppm downfield from internal Me_4Si.
b) Measured in Me_2SO-d_6.
c—*f*) Assignments indicated by a given superscript may be reversed.

TABLE V. ^{13}C Shieldings of 3,4-Dihydroisoquinolines and Their Methiodides in $CDCl_3$

Carbon	Chemical shift[a] 16	17	18	21[b]	22[b]	28	29	30
C (1)	163.5	166.1	172.1	159.5	164.6	174.3	177.0	186.8
C (3)	47.0	46.9	47.3	47.4	50.5	53.2	53.5	55.9
C (4)	25.8	26.0	26.7	24.7	25.5	26.0	26.2	26.9
C (4a)	131.1	131.7	133.6	129.8	132.3	132.7	133.3	133.4
C (5)	110.3	110.4	110.4	110.5	111.3	110.9	111.2	110.5
C (6)	150.9	150.7	149.9	151.3	157.6	156.1	156.2	154.6
C (7)	147.5	147.4	146.4	147.9	148.8	148.5	148.5	146.9
C (8)	109.1	109.3	111.3	110.5	115.7	112.5	112.9	112.3
C (8a)	122.5	122.2	121.0	121.6	117.2	119.8	119.2	121.4
OMe	56.0	55.9	55.8	56.0	57.0	57.1	57.0	56.7
	56.2	56.3	56.3	56.1	57.2	57.1	57.0	56.7
					48.1		46.6	50.1
N^+Me	—	—	—	—	—	46.6	23.0(Me)	32.2(Me)
1-Alkyl	23.4(Me)	22.7(Me)	30.2(Me)	—	—	21.0(Me)	29.6(CH)	40.9(C)
		26.9(CH)	39.2(C)				39.9(CH_2)	
		45.1(CH_2)						

a) In ppm downfield from internal Me_4Si.
b) From ref. 32.

this region; apart from four singlets of the aromatic protons (and a broad four-proton singlet of the carboxyl protons in the case of the salt), no signal was observed in the region downfield from the methoxyl proton signals. This led us to favor the endocyclic double bond structure (1) for the alkaloid in both the neutral and the protonated form.

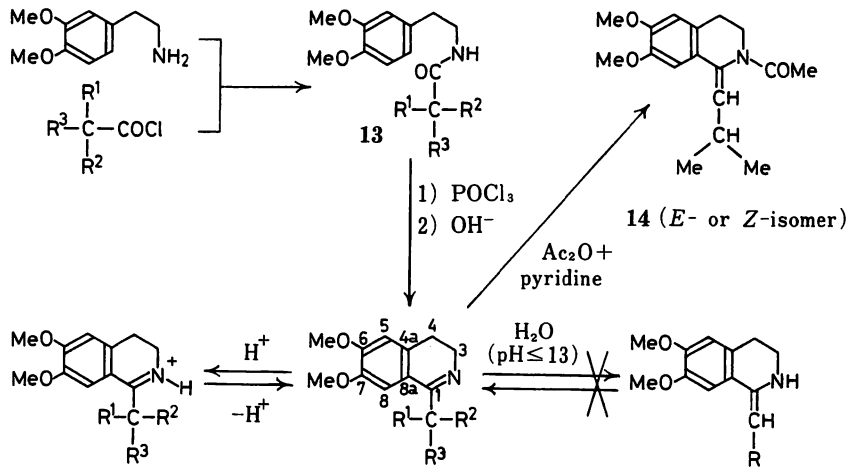
In order to confirm this, we next extended the spectroscopic approach to include ^{13}C NMR spectroscopy. The chemical shift information reported[17] for emetine (2) as well as the data outlined in Table IV for the model compounds 9—11 and in Table V for some 3,4-dihydroisoquinoline models permitted shift assignment for all carbons of *O*-methylpsychotrine. It may be seen from Table VI that the alkaloid under study has sixteen sp^3 carbons and thirteen sp^2 carbons. This differs from the exocyclic double bond structure (4) in having one more sp^3 carbon and one less sp^2 carbon. The di(hydrogen oxalate) [$1 \cdot 2(CO_2H)_2$] has also been found to have carbons similar in kind and in number, aside from the carboxyl carbons. Thus, these ^{13}C NMR spectral data on both the free base and the salt of *O*-methylpsychotrine are consistent with the endocyclic double bond structure (1).

Yet another spectroscopic approach was a closer examination by means of UV spectroscopy. This approach to the problem has met with only qualified success in the past[3a,6] because

TABLE VI. ^{13}C Shieldings of *O*-Methylpsychotrine (1) and Its Di(hydrogen oxalate) [1·2(CO_2H)$_2$]

Carbon	Chemical shift[a] *O*-Methylpsychotrine			Carbon	Chemical shift[a] *O*-Methylpsychotrine		
	Free base at 24°C[b]	Di(hydrogen oxalate) at 24°C[c]	Di(hydrogen oxalate) at 80°C[d]		Free base at 24°C[b]	Di(hydrogen oxalate) at 24°C[c]	Di(hydrogen oxalate) at 80°C[d]
C(1)	37.5	33.8	34.1	C(14)	11.3	10.2	9.8
C(2)	39.3	37.8[f]	37.8[j]	C(1′)	166.0	174.3	172.9
C(3)	42.4	38.6[f]	38.6[j]	C(3′)	47.0	41.4	41.8
C(4)	61.3	56.8	57.3	C(4′)	26.1	24.7[g]	24.5[k]
C(6)	52.5	49.1	49.3	C(4′a)	131.5	133.7	133.2
C(7)	29.1	25.7[g]	25.7[k]	C(5′)	110.4	111.4[h]	111.4[l]
C(7a)	126.6	123.9	124.3	C(6′)	150.8	155.0	154.6
C(8)	111.5	111.7[h]	112.3[l]	C(7′)	147.5[e]	148.1[i]	148.2[m]
C(9)	147.3[e]	147.7[i]	147.7[m]	C(8′)	109.1	112.0	112.3
C(10)	147.0[e]	147.4[i]	147.4[m]	C(8′a)	122.4	118.2	118.5
C(11)	108.2	108.6	109.1	OMe	55.8	55.4	55.5
C(11a)	130.0	124.7	125.3		55.8	55.4	55.5
C(11b)	62.5	60.2	60.3		56.0	56.0	56.0
C(12)	39.7	35.4	35.8		56.2	56.2	56.1
C(13)	23.8	22.2	22.0	CO_2H	—	164.6	163.4

a) In ppm downfield from internal Me_4Si.
b) Determined in $CDCl_3$ at 11% (w/v) concentration.
c) Measured in a saturated Me_2SO-d_6 solution.
d) Measured as a 12% (w/v) solution in Me_2SO-d_6.
e—*m*) Assignments indicated by a given superscript may be reversed.



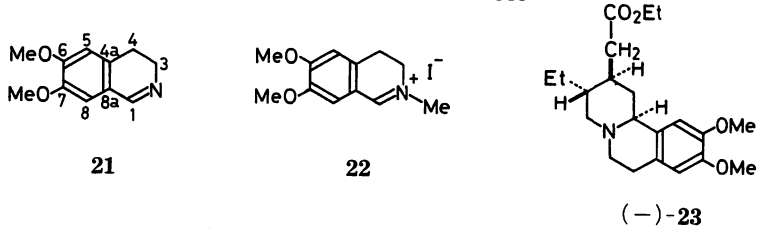


Chart 2

of the imperfect use of model compounds and solvents which failed to rule out the possibility of a tautomeric shift of the double bond. In the present work, we first tried to find UV spectral characteristics of a real 1-substituted 3,4-dihydroisoquinoline in 1-*tert*-butyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**18**), a model in which the endocyclic double bond cannot tautomerize to the exocyclic position. Compound **18**[18] was prepared in the usual manner from 3,4-dimethoxyphenethylamine and pivaloyl chloride through the amide (**13**: $R^1=R^2=R^3=$Me). Compounds **16**[19] and **17**,[15] models for *O*-methylpsychotrine, were likewise obtained, and the structures of the three dihydroisoquinolines were confirmed by ^{1}H NMR (Table III) and ^{13}C NMR spectroscopy (Table V). Fig. 1 shows the UV spectra of the 1-*tert*-butyl derivative **18** in H_2O at various pH's. The spectrum at pH 1 is essentially unchanged at pH 2, indicating that it is the spectrum of pure conjugate acid (type **15**). Similarly, the spectrum at pH 13 represents that of pure base **18**. All other spectra at different pH's go through the same isosbestic points at 234.5, 253, and 285 nm, which confirms that we are dealing with a simple acid–base reaction (**15**$\rightleftarrows$**18**) that is not complicated by further equilibria or other phenomena. On this basis, the acid dissociation constant (pK_a) of **18** in H_2O was spectrometrically determined to be 8.80±0.02 at 20°C and ionic strength 0.05. The observed bathochromic shift in going from the free base (**18**) to the protonated species (**15**) is in agreement with that reported[20] for 1-methyl- and 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline.

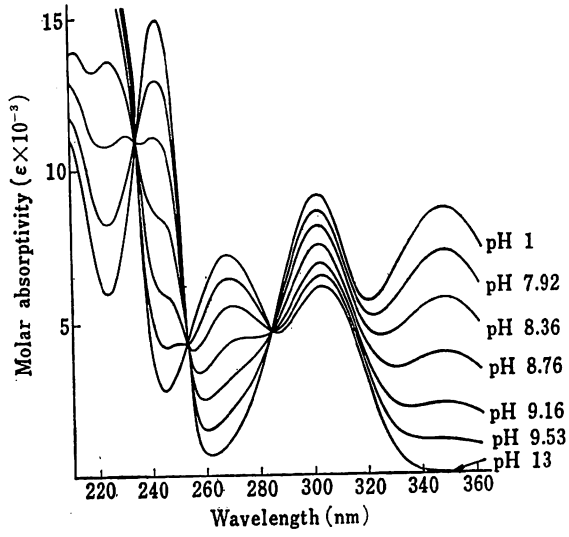


Fig. 1. UV Spectra of **18** in H_2O

Fig. 2 displays the UV curves of the 1-methyl derivative **16** in H_2O at various pH's. The spectra at pH 1—13

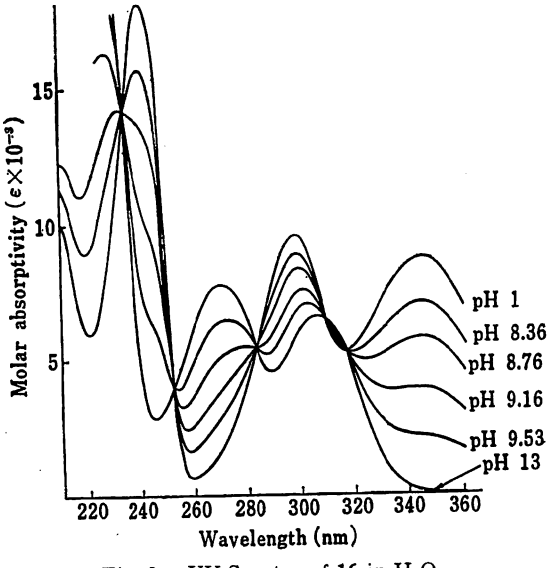


Fig. 2. UV Spectra of **16** in H_2O

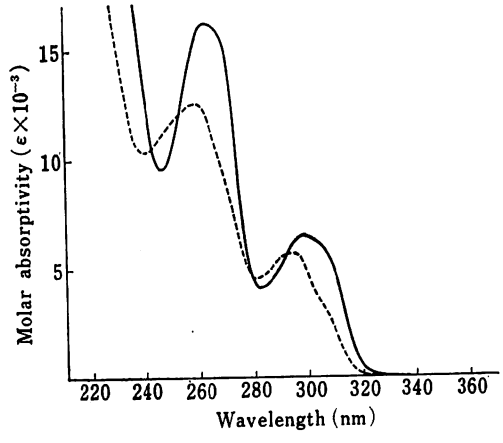


Fig. 3. UV Spectra of **11** and **14**

——: **11** in H_2O at pH 1, 7, or 13.
----: **14** in 80% (v/v) aq. EtOH; unchanged when the solution was made 0.1 N with respect to NaOH or HCl.

are closely similar to those of the 1-*tert*-butyl derivative **18** (Fig. 1), and quite different from those of the exocyclic double bond models **11** and **14** (Fig. 3). It may be seen that all the spectra of **16** cross at the isosbestic points at 234, 252, 283.5, 309.5, and 316.5 nm. Thus, it is clear that the protonated species (type **15**) and neutral species of **16** are equilibrated in H_2O in the range of pH 1—13, and that the species (**19**) with the exocyclic double bond does not exist under such conditions. This observation permitted us to determine the pK_a value (9.16±0.02 in H_2O at 20°C and ionic strength 0.05) for **16** by UV spectrophotometry. Similar spectra of **17**, as summarized in Table VII, also confirmed the absence of the

Table VII. UV Spectra of Dihydroisoquinolines and Benzoquinolizidines in H_2O

Compound	UV Spectra					
	pH 1[a]		pH 7[b]		pH 13[c]	
	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
9	230[d]	4.32	230[d]	4.31	228	4.32
	238	4.32	238	4.32	238[d]	4.28
	298	3.98	298	3.98	298	3.93
	343	3.99	343	3.99	342.5	3.86
11	219	4.50	219	4.50	219	4.49
	262	4.21	262	4.21	262	4.21
	298.5	3.81	298.5	3.81	298.5	3.81
16	241	4.26	241	4.26	225	4.37
	299	3.98	299	3.98	270	3.89
	346	3.94	345	3.93	306.5	3.82
17[e]	242.5	4.23	242.5	4.22	225	4.34
	301.5	3.97	301	3.97	270.5	3.88
	349	3.95	348	3.94	306	3.81
18	243	4.17	243	4.17	224	4.31
	302	3.96	302	3.96	268.5	3.86
	349	3.94	349	3.94	304	3.80
O-Methylpsychotrine[f]	241.5	4.26	239	4.25	226	4.43
	288.5	3.86	288.5	3.87	278.5	3.96
	305	3.92	304	3.90	307	3.77
	354	3.91	353	3.86		
(−)-**23**	231	3.86	230	3.86	223[d]	3.91
	279[d]	3.51	279[d]	3.51	280[d]	3.53
	282	3.53	282	3.53	283.5	3.54
	288[d]	3.49	288[d]	3.49	288	3.50
25	245	4.21	228	4.32	Unstable	
	307	3.98	273	3.89		
	358	3.97	332	4.34		
28[g]	230[d]	4.30	230[d]	4.29	228	4.30
	239	4.31	239	4.30	239[d]	4.27
	301	3.98	301	3.98	301	3.92
	347.5	3.98	347.5	3.98	347.5	3.91
29[h]	229	4.31	229	4.31	228	4.31
	241	4.30	241	4.30	241[d]	4.30
	303.5	4.00	303.5	4.00	303.5	3.99
	350	4.01	350	4.00	350	4.00
30	Unstable		Unstable		Unstable	

a) Measured in 0.1 N aq. HCl.
b) Measured in 0.045 M phosphate buffer.
c) Measured in H_2O containing NaOH at 0.1 M concentration.
d) Shoulder.
e) UV $\lambda_{max}^{H_2O}$ (pH 9.2) 228 nm (log ε 4.18), 246 (sh) (3.93), 278.5 (sh) (3.72), 303 (3.88), 348 (3.58).
f) UV $\lambda_{max}^{H_2O}$ (pH 9.2) 226.5 nm (log ε 4.38), 279 (3.93), 306 (3.80), 351 (3.23).
g) UV $\lambda_{max}^{0.9N\ aq.\ NaOH}$ 225 nm (log ε 4.32), 288 (3.68), 301 (3.68), 347.5 (3.62).
h) UV $\lambda_{max}^{0.9N\ aq.\ NaOH}$ 227 nm (log ε 4.33), 241 (sh) (4.26), 303.5 (3.95), 350 (3.93).

TABLE VIII. UV Spectra of Dihydroisoquinolines and Benzoquinolizidines in Aqueous EtOH

Compound	UV Spectra					
	Solvent A[a]		Solvent N[b]		Solvent B[c]	
	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
9	217	4.35	217	4.35	223.5	4.37
	243	4.26	243	4.26	252	4.12
	301	3.98	301.5	3.98	290	3.80
	349	4.01	350	4.01	306	3.81
11	218	4.54	218	4.54	225	4.42
	266	4.18	266	4.18	266	4.18
	301	3.85	301	3.85	301	3.85
14	258	4.10	258	4.10	258	4.10
	295	3.75	295	3.75	295	3.75
16	243	4.27	226.5	4.31	226.5	4.39
	302	3.98	247[d]	3.83	271	3.90
	351	3.96	271	3.81	278[d]	3.87
			278[d]	3.81	308	3.84
			306	3.86		
			351	3.29		
17	245	4.18	227.5	4.23	227.5	4.30
	304	3.93	247[d]	3.63	272	3.84
	354	3.93	251	3.63	278[d]	3.83
			259.5	3.58	307.5	3.79
			273	3.77		
			278	3.77		
			306	3.81		
			355	3.22		
18	245	4.10	225	4.25	225.5	4.25
	305	3.88	269	3.78	269	3.79
	355	3.89	277[d]	3.74	277[d]	3.75
			304.5	3.74	304.5	3.73
			355	2.46		
O-Methylpsychotrine	243	4.26	228	4.45	228	4.46
	285[d]	3.82	280	3.99	280	4.00
	291	3.88	286[d]	3.93	291[d]	3.87
	306.5	3.94	291[d]	3.87	308	3.81
	359	3.94	308	3.82		
			356	2.84		
(−)-**23**	232	3.90	225[d]	3.92	225	3.91
	280	3.57	281.5	3.58	281.5	3.58
	284	3.58	285.5	3.59	285.5	3.59
	289[d]	3.52	290[d]	3.52	290[d]	3.52
25	246.5	4.23	229	4.38	229	4.38
	308.5	3.99	267[d]	3.91	267[d]	3.92
	362	3.99	274	3.94	274	3.95
			331	4.34	331	4.34
28	217.5	4.34	217.5	4.34	223	4.40
	244.5	4.27	244.5	4.27	253	4.04
	304	3.99	304	3.99	260[d]	4.01
	353	4.01	353	4.01	290	3.75
					301	3.73
29	217.5	4.37	217.5	4.36	225	4.42
	246	4.24	246	4.24	267	3.90
	306.5	3.99	306.5	3.99	304	3.71
	356	4.02	356	4.02		
30	Unstable		Unstable		Unstable	

a) 80% (v/v) Aqueous EtOH containing HCl at 0.1 M concentration.
b) 80% (v/v) Aqueous EtOH.
c) 80% (v/v) Aqueous EtOH containing NaOH at 0.1 M concentration.
d) Shoulder.

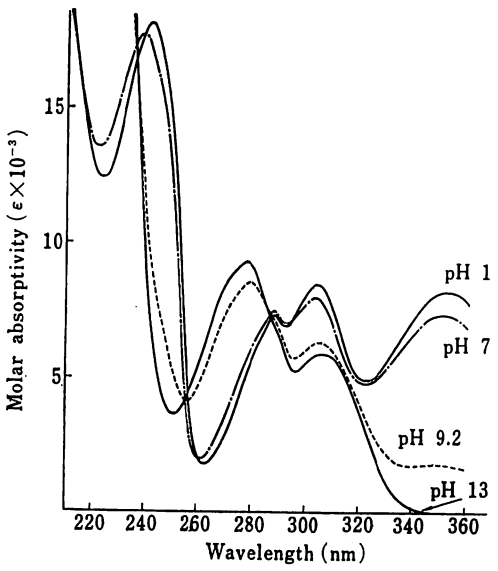


Fig. 4. UV Spectra of *O*-Methylpsychotrine in H_2O

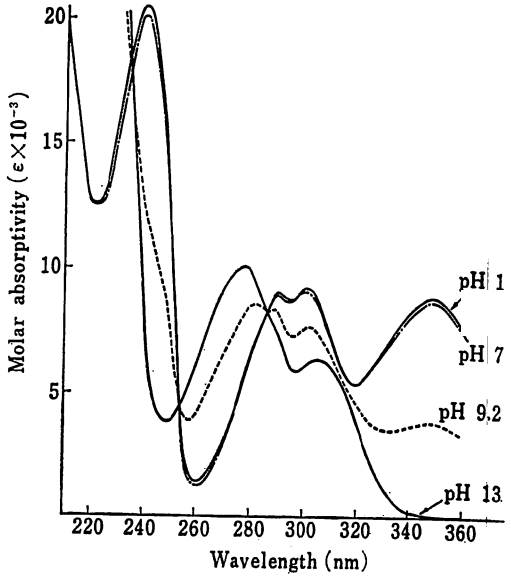
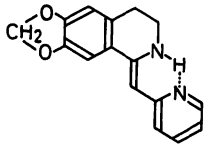


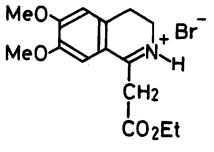
Fig. 5. UV Spectra of an Equimolar Mixture of **17** and (−)-**23** in H_2O

tautomeric form (**20**) in H_2O and indicated that an equilibrium between **17** and **15** exists. As shown in Figs. 4 and 5, the spectra of *O*-methylpsychotrine in H_2O at pH 1, 7, 9.2, and 13 were found to closely resemble those of an equimolar mixture of **17** and the tricycle (−)-**23**,[21] indicating that the dihydroisoquinoline moiety of *O*-methylpsychotrine has the same endocyclic double bond structure as that of **17**. Replacement of the solvent H_2O by 80% (v/v) aqueous EtOH in the above UV measurements gave similar results, which are listed in Table VIII.

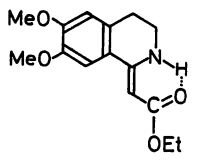
Now that the stability of the endocyclic C=N bond in simple 1-substituted 3,4-dihydroisoquinolines toward tautomeric shift had been confirmed, we were able to check a few cases where tautomeric shift of the C=N bond has been reported to occur. On the basis of their



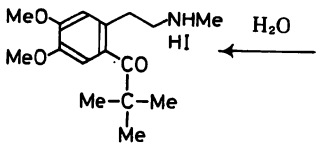
24



25



26



27

28 : $R^1=R^2=R^3=H$
29 : $R^1=R^2=H$; $R^3=CHMe_2$
30 : $R^1=R^2=R^3=Me$

31 : R=H
32 : $R=CHMe_2$

Chart 3

UV spectroscopic studies, Noller and Azima[22] indicated that 1-(α-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline exists in the exocyclic double bond form (**24**),[20] possibly by forming intramolecular hydrogen bonding, whereas the corresponding 1-benzyl[20] and 1-(β-picolyl) analogs have the endocyclic C=N structure. The protonated form of 1-ethoxycarbonylmethyl-3,4-dihydro-6,7-dimethoxyisoquinoline is known to have the endocyclic C=N structure (type **25**),[23] but the free base has the exocyclic C=C structure,[23,24] for which Openshaw and Whittaker[23] suggested a resonance-stabilized interaction of the carbonyl oxygen and the amino hydrogen atom (type **26**) on the basis of IR spectral data. In the present work, we confirmed the endocyclic C=N structure of the hydrobromide **25** by the observation of a two-proton singlet ($C\underline{H}_2CO_2Et$) at δ 4.60 in its ^1H NMR spectrum in $CDCl_3$. Fig. 6 shows the UV spectra of **25** in H_2O at various pH's. Evidently, the endocyclic double bond structure (type **25**) is favored in the pH region below 4 and its importance is superseded by the exocyclic C=C structure (**26**) at higher pH's, suggesting the basicity of **26** to be considerably weaker than that of **16**.

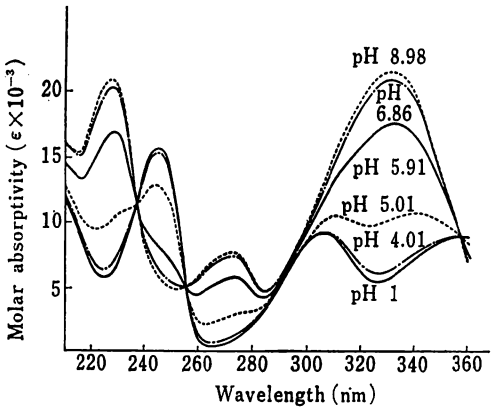


Fig. 6. UV Spectra of **25** in H_2O

Finally, we prepared the methiodides **28**,[19,25] **29**,[15] and **30** from the bases **16**—**18** by quaternization with MeI and confirmed their structures by means of ^1H NMR and ^{13}C NMR spectroscopy (see Tables III and V). It is known that under basic conditions 1,2-dialkyl-3,4-dihydroisoquinolinium salts (type **9**, **28**, or **29**) are converted into the free bases (type **10**, **31**, or **32**) with the exocyclic double bond at the 1-position,[13,20] whereas the reverse change takes place under acidic conditions.[13,26] The UV spectral data (Table VII) suggest that in 0.1 N aqueous NaOH (pH 13) 85% of **28** or 97% of **29** still exists in the quaternary salt form with the endocyclic double bond. However, when a solution of **28** in 80% (v/v) aqueous EtOH was made 0.1 N with respect to NaOH, its UV spectrum (Table VIII) indicated that almost complete conversion of **28** into **31** took place. The salt **29** behaved similarly under the same conditions.

On the other hand, the salt **30** was extremely unstable even in plain water at room temperature. On heating with H_2O at 90°C for 10 min, it produced the ring-opened derivative **27** in 89% yield. The initial step of this transformation must be the nucleophilic attack of H_2O at the 1-position, which is the center of low electron density. A rapid ring opening of the resulting pseudo base by hydrolysis may relieve steric strain between the bulky *tert*-butyl group and the *N*-methyl group.

In conclusion, the present results confirm that simple 1-alkyl-3,4-dihydroisoquinolines and their protonated species have the corresponding endocyclic double bond structures under ordinary circumstances. Activation of the α-hydrogen(s) of the 1-alkyl group by quaternization of the nitrogen at the 2-position makes the exocyclic C=C structure possible under strongly basic conditions. Interestingly, the greatest stability of this exocyclic double bond structure is caused by a 1-substituent that can give extended conjugation and resonance stabilization by forming intramolecular hydrogen bonding with the secondary NH. The UV, ^1H NMR, and ^{13}C NMR spectral data described above for *O*-methylpsychotrine have thus established the structure of this Ipecac alkaloid as **1**, not **4**. It follows that the dihydroisoquinoline moiety of psychotrine, desmethylpsychotrine, and alangicine must have the endocyclic double bond as shown in formulas **5**, **6**, and **7**.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. Spectra reported herein were recorded on a Hitachi 323 UV spectrophotometer, a JASCO IRA-2 IR spectrophotometer, or a JEOL JNM-FX-100 spectrometer, equipped with a ^{13}C FT NMR system, at 24°C wtih Me_4Si as an internal standard. Determinations of acid dissociation constants by UV spectrophotometry were carried out according to the general procedure of Albert and Serjeant.[17] Unless otherwise noted, buffer solutions used for the measurements of UV spectra were at 0.009 M concentration and the ionic strength was maintained at 0.05. The pH regions covered by individual buffer systems at 20°C or 24°C were 3.21—4.01, HCO_2H–HCO_2Na; 5.01—5.91, AcOH–AcONa; 7.92—9.99, H_3BO_3–Na_2CO_3. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, sh=shoulder, t=triplet.

Materials——The known test compounds selected for the spectroscopic study were taken from stock or were synthesized according to published procedures: **9**,[13,14] **10**,[13,14] **11**,[14] **16**,[19] **17**,[15,18] **18**,[18] (−)-**23**,[21] **28**,[19,25] **29**.[15] *O*-Methylpsychotrine and its di(hydrogen oxalate) were prepared from (−)-emetine (**2**) by following the procedure of Openshaw and Whittaker,[28] and the synthetic base was identified by direct comparison with an authentic sample[29] of *O*-methylpsychotrine. Other test compounds were obtained as described below.

2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-methylpropylidene)isoquinoline (**14**)——A mixture of **17**[15,18] (495 mg, 2.0 mmol), pyridine (4 ml), and Ac_2O (2 ml) was stirred at room temp. for 24 h. The reaction mixture was then concentrated *in vacuo*, and the oily residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed successively with 5% aq. HCl, sat. aq. $NaHCO_3$, and sat. aq. NaCl, dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to leave a yellow oil (570 mg), which solidified on standing for a few days. Recrystallization of the solid from benzene–hexane (1: 3, v/v) gave **14** (427 mg, 74%) as colorless prisms, mp 112—113°C; UV (Fig. 3 and Table VIII); IR ν_{max}^{Nujol} cm^{-1}: 1655, 1637 (amide CO and C=C or *vice versa*); ^1H NMR ($CDCl_3$) δ: 1.15 (6H, d, J=6.6 Hz, $CH\underline{Me}_2$), 2.14 (3H, s, COMe), 2.83 (2H, t, J=6.6 Hz, $ArC\underline{H}_2$), 2.65—3.05 (1H, m, $C\underline{H}Me_2$), 3.84 (2H, t, J=6.6 Hz, NCH_2), 3.88 and 3.89 (6H, s each, two MeO's), 5.34 (1H, d, J=10.3 Hz, C=CH), 6.69 (1H, s, $H_{(5)}$), 6.92 (1H, s, $H_{(8)}$). *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.81; H, 8.11; N, 4.81. The configuration about the double bond in this compound was uncertain.

1-(1,1-Dimethylethyl)-3,4-dihydro-6,7-dimethoxyisoquinoline Hydrochloride (**18**·**HCl**)——The base **18** (2.00 g, 8.1 mmol) was dissolved in 10% (w/w) ethanolic HCl (10 ml), and dry ether (20 ml) was added. The mixture was kept in a refrigerator overnight, and the colorless crystals that resulted were filtered off to give **18**·HCl (2.03 g, 88%). Recrystallization from EtOH–ether (1: 2, v/v) afforded an analytical sample as colorless pillars, mp 204—204.5°C (dec.); IR ν_{max}^{Nujol} 1638 cm^{-1} ($C=N^+$); ^1H NMR (Table III). *Anal.* Calcd for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.39; H, 8.05; N, 5.16.

1-Ethoxycarbonylmethyl-3,4-dihydro-6,7-dimethoxyisoquinoline Hydrobromide (**25**)——This salt was prepared by the procedure of Osbond.[30] It was recrystallized from EtOH–ether (1: 1, v/v) and dried over P_2O_5 at 2 mmHg and room temp. for 15 h to yield **25**·$1/4H_2O$ as yellow prisms, mp 161—162°C (dec.) [lit.[30] mp 160°C (dec., sintered at 155°C) for a hemihydrate]; UV (Fig. 6 and Tables VII and VIII); IR ν_{max}^{Nujol} cm^{-1}: 1736 (ester CO), 1645 ($C=N^+$); ^1H NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.1 Hz, $OCH_2\underline{Me}$), 1.99 (0.5H, H_2O), 3.14 (2H, t, J=8.2 Hz, $ArC\underline{H}_2$), 3.92 and 4.03 (6H, s each, two MeO's), 4.20 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 4.60 (2H, s, $C\underline{H}_2CO_2Et$), 6.90 (1H, s, $H_{(5)}$), 7.16 (1H, s, $H_{(8)}$), 13.95 (1H, b, N^+H). *Anal.* Calcd for $C_{15}H_{20}BrNO_4 \cdot 1/4H_2O$: C, 49.67; H, 5.70; N, 3.86. Found: C, 49.95; H, 5.54; N, 3.58.

1-(1,1-Dimethylethyl)-3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium Iodide (**30**)——A mixture of **18**[18] (4.95 g, 20 mmol) and MeI (15 ml) was refluxed for 144 h. The excess of MeI was removed by distillation *in vacuo* to leave a yellow solid, which was triturated with ether (20 ml). An insoluble solid was collected by filtration and washed with ether (10 ml) to give **30** (7.32 g, 94%). Recrystallization from MeOH yielded an analytical sample as yellow prisms, mp 187—189°C (dec.); UV (Tables VII and VIII); ^1H NMR (Table III); ^{13}C NMR (Table V). *Anal.* Calcd for $C_{16}H_{24}INO_2$: C, 49.37; H, 6.21; N, 3.60. Found: C, 49.36; H, 6.34; N, 3.58.

1-[4,5-Dimethoxy-2-(2-methylaminoethyl)phenyl]-2,2-dimethyl-1-propanone Hydriodide (**27**)——A mixture of **30** (100 mg, 0.26 mmol) and H_2O (0.5 ml) was heated in a water bath kept at 90°C for 10 min. The reaction mixture was then kept standing at room temp. for 1 h, and the precipitate that resulted was collected by filtration and dried to give **27** (92.8 mg, 89%), mp 153.5—155°C. Recrystallization from H_2O furnished an analytical sample as slightly yellowish pillars, mp 154—155°C; UV λ_{max} [80% (v/v) aq. EtOH] 221 nm (log ε 4.45), 274 (3.63), 287 (sh) (3.60); λ_{max} [0.1 N HCl–80% (v/v) aq. EtOH] 221 (4.45), 274 (3.62), 287 (sh) (3.60); λ_{max} [0.1 N NaOH–80% (v/v) aq. EtOH] 222 (4.44), 285 (3.58); IR ν_{max}^{Nujol} 1657 cm^{-1} (ArCO); ^1H NMR ($CDCl_3$) δ: 1.30 (9H, s, CMe_3), 2.68 (3H, t, J=5.7 Hz, N^+Me), 2.97 (2H, t, J=7.0 Hz, $ArC\underline{H}_2$), 3.39 (2H, m, N^+CH_2), 3.87 and 3.96 (6H, s each, two MeO's), 6.87 (1H, s, aromatic $H_{(3)}$), 7.03 (1H, s, aromatic $H_{(6)}$), 8.50 (2H, b, N^+H_2); ^1H NMR (D_2O) δ[31]: 1.21 (9H, s, CMe_3), 2.78 (3H, s, N^+Me), 2.80 (2H, t, J=7.6 Hz, $ArC\underline{H}_2$), 3.31

(2H, t, J=7.6 Hz, N^+CH_2), 3.81 and 3.89 (6H, s each, two MeO's), 6.88 (1H, s, aromatic $H_{(3)}$), 7.05 (1H, s, aromatic $H_{(6)}$); ^{13}C NMR (D_2O) δ[31]: 33.3 (N^+Me), 56.1 (MeO's), 217.3 (CO). *Anal.* Calcd for $C_{16}H_{26}INO_3$: C, 47.18; H, 6.43; N, 3.44. Found: C, 47.02; H, 6.52; N, 3.63.

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