proton abstraction by the ester carbonyl from the neighboring carboxylic acid, followed by the attack of the carboxylate anion on the activated carbonyl group as shown in Chart 1.

Conclusions

Mono(2-ethylhexyl)phthalate (monoester) shows considerable thermolability, and the decomposition was a monomolecular reaction. The reaction began at about 80°, and was 50% complete at 150°, and 90% complete at 250°.

The monoester did not undergo hydrolysis or ester exchange reaction, which are commonly observed in the thermal decomposition of ordinary esters. In addition, *cis*-elimination did not occur, though it was observed in the thermal decomposition of BEHP.

The finding that BEHP and PA were produced by thermal decomposition of the monoester suggests that a mechanism involving neighboring group participation operates, as discussed above.

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Stereochemistry of Quinolizidines. VI.[1] Conformation of Benzo[*a*]quinolizidines and Their ^{13}C Chemical Shifts. (2)

Makiko Sugiura, Narao Takao, Kinuko Iwasa,[2a] and Yoshio Sasaki[2b]

Kobe Women's College of Pharmacy[2a] *and Faculty of Pharmaceutical Sciences, Osaka University*[2b]

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The conformations of six benzo[*a*]quinolizidine derivatives were studied in terms of the ^{13}C chemical shifts at the C-6 and other positions.

The 9,10,11-trimethoxyl derivatives (IV, V and VI) predominantly adopt the *cis*"a" conformation, whereas I, II and III are predominantly in the *trans* conformation. The equilibrium state "*trans*⇄*cis*"a"" is discussed in terms of the population of the *trans* conformer, using an empirical approach.

Keywords——^{13}C chemical shift; benzo[*a*]quinolizidine derivatives; conformation; equilibrium state "*trans cis*"a""; population of *trans* conformer;

Introduction

In our previous work,[3,4] we described the correlation between the conformation of benzo[*a*]quinolizidines and their ^{13}C chemical shifts. Benzo[*a*]quinolizidines are well known to have three possible conformations at room temperature, and an equilibrium exists, as illustrated in Chart 1. The ^{13}C chemical shifts of C-6 and C-7 can be used to distinguish these three conformations,[3] and, in particular, the displacement of C-6 chemical shift reflects well the state of the "*trans*⇄*cis* "a"".[4] Namely, when the *trans* conformation is predominant, C-6 chemical shifts appear in the vicinity of 52 ppm and C-7 in *ca.* 29 ppm. On the

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[1] Part V: M. Sugiura, N. Takao, H. Fujiwara, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 2555 (1978).

[2] Location: *a) Motoyamakita-machi 4-19-1, Higashinada-ku, Kobe 658, Japan*; *b) Yamadakami 133-1, Suita, Osaka 565, Japan.*

[3] M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 1168 (1978).

[4] M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 1901 (1978).

other hand, C-6 undergoes a high field shift up to 46 ppm in the *cis*"a" conformation, while there is little difference for C-7 from the *trans* conformer. In a *cis*"b" conformer, on the other hand, a slight change at C-6 is seen compared to the *trans* conformer (*ca.* 51 ppm), but C-7 shows higher shift up to *ca.* 25 ppm.

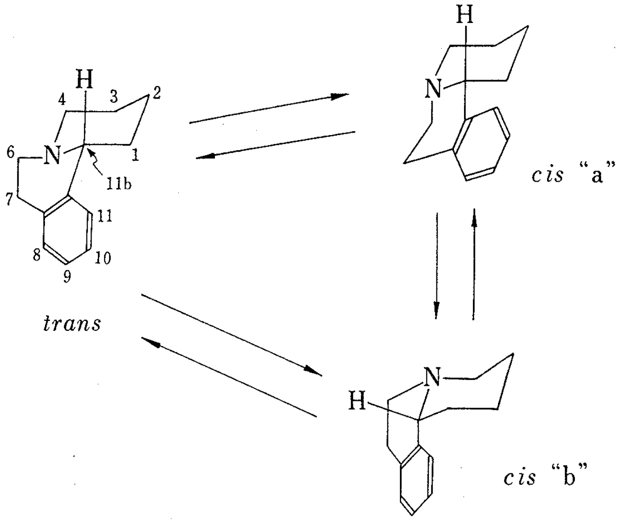
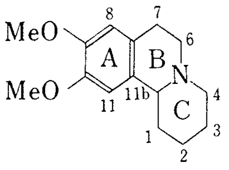


Chart 1

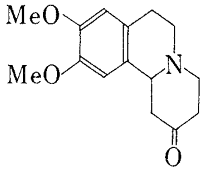
In this work, five additional analogs of benzo[*a*]quinolizidine were prepared and their ^{13}C chemical shifts were measured. The results are consistent with the conclusions previously reached by us. The compounds used are the 9,10-dimethoxyl (I and III) and 9,10,11-trimethoxyl (IV, V and VI) derivatives. 9,10-Dimethoxy-2-oxo-1,2,3,4,6,7,11b-heptahydrobenzo[*a*]quinolizidine (II) was studied in our earlier paper,[3] but is included in this paper for comparison.

On the basis of ^{13}C chemical shifts, I, II and III are confirmed to adopt predominantly *trans* conformations, whereas the 9,10,11-trimethoxyl derivatives (IV, V and VI) are predominantly in the *cis*"a" conformation. Moreover, based on the C-6 chemical shifts, "*trans* ⇄ *cis*"a" " equilibrium is present for all six derivatives.

Thus, the validity and generality of our previous conclusions[3,4] are confirmed.



I



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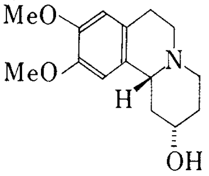
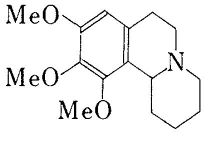
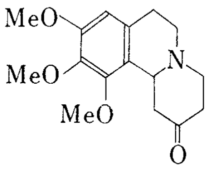


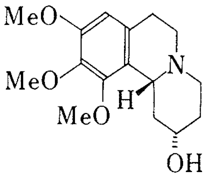
III



IV



V



VI

Experimental

Measurements of ^{13}C NMR spectra were carried out as described in the preceding papers.[1,3,4] Assignments of ^{13}C chemical shifts were made by off-resonance decoupling and by analogy with those of other benzo[*a*]quinolizidines.[3] All pertinent chemical shifts are summarized in Table I; some ambiguity remains, and assignments marked with asterisks may be reversed.

Materials——9,10-Dimethoxy-(II)[3] and 9,10,11-trimethoxy-2-oxo-1,2,3,4,6,7,11*b*-heptahydrobenzo[*a*]-quinolizidine (V)[4] were obtained as described in the preceding papers.

9,10-Dimethoxy-(I) and 9,10,11-trimethoxy-1,2,3,4,6,7,11b-heptahydrobenzo[*a*]quinolizidine (IV) were prepared by Wolf-Kishner reduction of II and V, respectively, by the reported procedures.[5] 9,10-Dimeth-

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[5] J. Parello, *Bull. Soc. Chim. Fr.*, **1968**, 1117.

oxy-(III) and 9,10,11-trimethoxy-*trans*-2-hydroxy-1,2,3,4,6,7,11b-heptahydrobenzo[*a*]quinolizine (VI) were obtained by $NaBH_4$ reduction of II and V in MeOH, followed by silica-gel column chromatography.

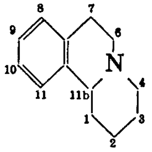
I: MS *m/e*: 246, 247 (M^+), 218, 191.
IV: MS *m/e*: 276, 277 (M^+), 248, 221.
III: MS *m/e*: 262, 263 (M^+), 218, 191.
VI: MS *m/e*: 292, 293 (M^+), 235, 248, 221.

Table I. ^{13}C Chemical Shifts[a] of Benzo[*a*]quinolizidine Derivatives (in $CDCl_3$)

Compound	Carbon[b]							
	11a	7a	8	9	10	11	1	2
I	130.62	126.93	111.65	147.49*	147.24*	108.40	31.62	25.18
II	128.75	126.26	111.62	147.90*	147.67*	108.07	47.52	208.17
III	129.59	126.54	111.64	147.61*	147.22*	108.21	40.47	69.42
IV	125.49	130.37	107.35	150.93*	140.19	151.77*	27.90	25.79
V	123.05	129.64	107.25	150.41*	140.23	152.49*	44.96*	208.95
VI	124.27	129.82	107.30	150.44*	140.11	152.04*	36.51	69.54

Compound	Carbon[b]								
	3	4	6	7	11b	OMe			P_{trans}[c]
I	25.56	56.96	52.96	29.22	63.32	56.01	55.84		96%
II	41.08	54.74	50.78	29.39	61.50	55.94	55.83		74%
III	34.67	54.40	51.69	29.22	60.22	56.01	55.84		83%
IV	22.14	56.14	46.41	30.43	58.23	60.67	60.56	55.85	32%
V	38.86	54.18	45.41*	30.25	57.41	60.66	60.55	55.90	(22%)
VI	30.01	53.24	44.80	30.07	55.84	60.59	60.59	55.26	16%

a) The assignments with asterisks are ambiguous (ppm relative to TMS).
b) Carbons are numbered as follows:

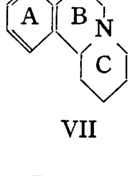


c) Population of *trans* conformer estimated from the C-6 chemical shift.

Results and Discussion

1) 9,10-Dimethoxy-benzo[*a*]quinolizidines

Figure 1 shows stick diagrams of the chemical shifts of three 9,10-dimethoxyl derivatives (I, II and III), together with those of the non-substituted form (1,2,3,4,6,7,11b-heptahydrobenzo[*a*]quinolizidine (VII)) for reference.



VII

Little deviation is observed for aromatic or methoxyl carbon chemical shifts in these three derivatives, irrespective of the substituents on ring C. This observation suggests that ring A is not affected by the variation of substituents on ring C, and rules out conformations that would affect the chemical shifts of ring A carbons. Furthermore, C-6 chemical shifts appear at low field over 50 ppm, while the C-7 carbons appear at low field over 29 ppm. This suggests that all of these derivatives take the *trans* conformation predominantly.[3]

In comparing the chemical shifts of I and VII (*cf.* Fig. 1 and Table I), there is good agreement in the aliphatic region within 0.4 ppm. This suggests that methoxyl groups on ring A have little effect on rings B and C, and that both derivatives take the same conformation.

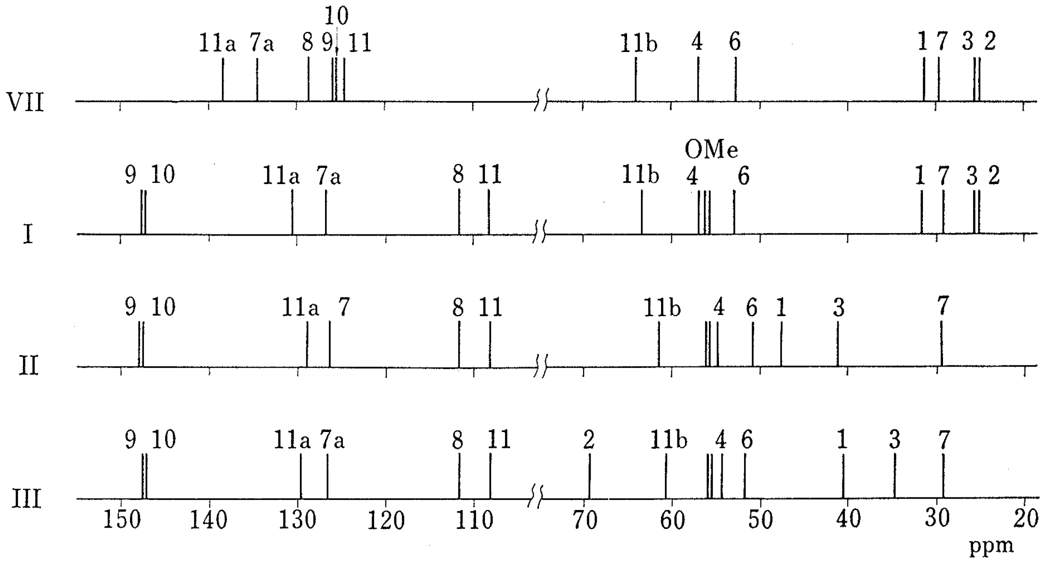


Fig. 1. Stick Diagram of ^{13}C Chemical Shifts of 9,10-Dimethoxy-benzo[*a*]quinolizidines (I, II and III) and 1,2,3,4,6,7,11b-Heptahydrobenzo[*a*]quinolizine (VII) in $CDCl_3$

Since III is obtained by reduction of II, the configuration of the hydroxyl group remains unsettled. The ^{1}H chemical shift of *ca.* 3.6 ppm[6] at C-2 suggests an equatorial hydroxyl group,[5] that is, a *trans* configuration between –OH and 11b-H. This is supported by the following observations. Table II summarizes the aliphatic ^{13}C chemical shifts of I and IV together with the substituent parameters[7] of equatorial and axial hydroxyl groups on C-2 ($\delta_{\mathrm{I}}+\Delta_{\mathrm{eq.-OH}}$, $\delta_{\mathrm{I}}+\Delta_{\mathrm{ax.-OH}}$ $\delta_{\mathrm{IV}}+\Delta_{\mathrm{eq.-OH}}$ and $\delta_{\mathrm{IV}}+\Delta_{\mathrm{ax.-OH}}$), and the observed shifts of III and VI (δ_{III} and δ_{IV}). The observed shifts of III approximate to $\delta_{\mathrm{I}}+\Delta_{\mathrm{eq.-OH}}$ indicating an equatorial orientation of the hydroxyl group on C-2 for III.

Table II. Comparison of Observed and Estimated ^{13}C Chemical Shifts (ppm) for III and VI

Carbon	δ_{III}	$\delta_{\mathrm{I}}+\Delta_{\mathrm{eq.-OH}}$[a]	$\delta_{\mathrm{I}}+\Delta_{\mathrm{ax.-OH}}$[a]	δ_{VI}	$\delta_{\mathrm{IV}}+\Delta_{\mathrm{eq.-OH}}$[a]	$\delta_{\mathrm{IV}}+\Delta_{\mathrm{ax.-OH}}$[a]
1	40.47	40.52	39.02	36.51	36.80	35.30
2	69.42	65.48	61.28	69.54	66.09	61.89
3	34.67	34.46	32.96	30.01	31.04	29.54
4	54.40	54.16	50.06	53.24	53.34	50.06
6	51.69	52.46	52.86	44.80	45.91	46.31
7	29.22	29.22	29.22	30.07	30.43	30.43
11b	60.72	60.82	55.22	55.84	50.73	45.13

a) ref. 6).

2) 9,10,11-Trimethoxy-benzo[*a*]quinolizidines

In tetrahydroprotoberberine-type alkaloids, the substitution of an oxygen functional group on C-1 (corresponding to C-11 of benzo[*a*]quinolizidines) has been confirmed to shift the equilibrium in favor of the *cis*"a" conformation, because of steric repulsion between the substituents on C-1 and an equatorial proton on C-13.[8] Similar effect is expected for benzo[*a*]quinolizidines.

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6) The exact chemical shift could not be determined because of the overlap of methoxyl group signals.

7) S.H. Grover and J.B. Stothers, *Can. J. Chem.*, **52**, 870 (1974).

8) *a*) N. Takao and K. Iwasa, *Chem. Pharm. Bull.* (Tokyo), **24**, 3185 (1976); *b*) N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.* (Tokyo), **25**, 1426 (1977).

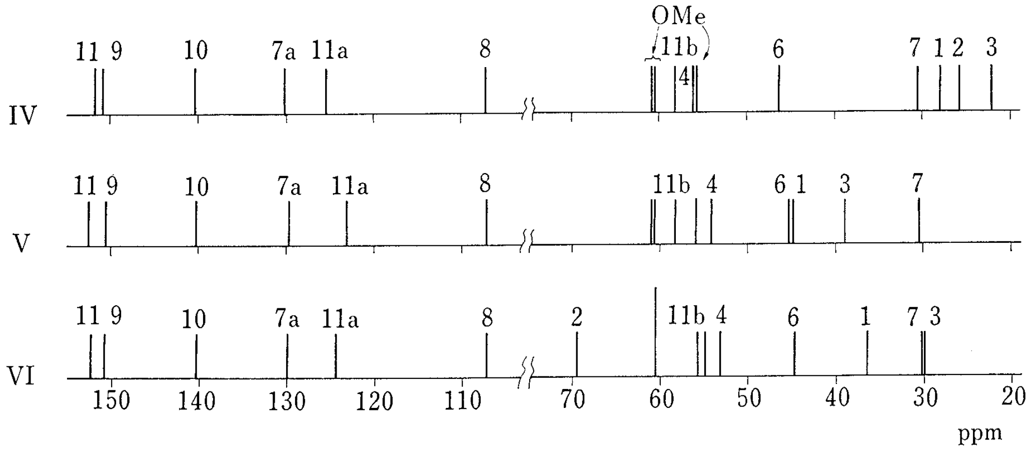

Fig. 2. Stick Diagram of ^{13}C Chemical Shifts of 9,10,11-Trimethoxy-benzo[*a*]quinolizines in $CDCl_3$

In Fig. 2, stick diagrams of the ^{13}C chemical shifts of three trimethoxy-benzo[*a*]quinolizidines (IV, V and VI) are presented. As expected, their C-6 carbon signals are shifted to higher field, which supports a preferred *cis*"a" conformation.[3] As in the case of the dimethoxyl derivatives, there is little difference of aromatic or methoxyl carbon chemical shifts among these derivatives. This rules out differences of conformation among these three derivatives and shows that a substituent on ring C has little effect on ring A.

Just as in the case of III, it was necessary to determine the configuration of the hydroxyl group of VI. As shown in Table II, the observed chemical shifts of VI (δ_{VI}) are rather closer to $\delta_{IV}+\Delta_{eq.-OH}$ than to $\delta_{IV}+\Delta_{ax.-OH}$. Therefore, VI is assumed to have an equatorial hydroxyl group at C-2, with a *trans* configuration between –OH and 11b-H.

3) Relationship between ^{13}C Chemical Shift and Conformation

Previously,[3] we discussed the chemical shift differences (Δ_{C-T}), between *trans* and *cis*"a" or "b" conformers of benzo[*a*]quinolizidines and compared the observed values with those estimated using the methyl substituent parameter piperidine.[9] Table III shows the chemical shift differences ($\Delta^{obs.}_{C-T}$) of IV—I, V—II and VI—III with the estimated differences between trans and *cis*"a" ($\Delta^{estm.}_{C-T}$).[3] The three observed results, though the values are all small, agree well with the estimates in sign and trend of magnitude. This supports the

TABLE III. Estimated and Observed Values of Chemical Shift Difference,[a] Δ_{C-T} (ppm)

Carbon	$\Delta^{obs.b)}_{C-T}$			$\Delta^{estm.c)}_{C-T}$
	(IV−I)	(V−II)	(VI−III)	
1	−3.72	−2.56	−3.96	−5.9
2	0.61	0.78	0.12	0
3	−3.42	−2.22	−4.66	−5.9
4	0.82	−0.56	−1.16	−2.4
6	−6.55	−5.37	−6.89	−9.0
7	1.21	0.86	0.85	0
11b	−5.09	−4.09	−4.88	−5.0

a) A minus sign indicates a high field shift.
b) $\Delta^{obs.}_{C-T}$: observed chemical shift difference between *trans* and *cis* "a" conformations.
c) $\Delta^{estm.}_{C-T}$: estimated chemical shift difference between *trans* and *cis* "a" conformations (*cf.* ref. 3)).

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9) M. Tsuda, *Farumashia*, **9**, 756 (1973).

assigned chemical shifts and conformations. Namely, for I. II and III, the preferred conformations are *trans*, while for IV, V and VI they are *cis*"a."

In Table III, however, all the observed values seem to be smaller than the estimated ones. This suggests a small contribution of the *cis*"a" conformer for I, II and III and/or the *trans* conformer for IV, V and VI.

As shown in the previous report,[4] the C-6 chemical shift acts as an indicator of the equilibrium state "*trans*$\rightleftharpoons$*cis*"a" " of benzo[*a*]quinolizidines and can be used to determine the population of *trans* conformer (P_{trans}). Based on the data[4] that the C-6 chemical shifts are 53.4 ppm and 43.2 ppm for the 100% *trans* conformation and the 100% *cis*"a" conformer, the *trans* population (P_{trans}) can be estimated from eq. (1), where $\delta_{\text{C-6}}$ is the C-6 chemical shift.

$$\frac{\delta_{\text{C-6}}-43.2}{53.4-43.2} \times 100 = P_{trans} \qquad (1)$$

In this work, this approach has been applied to six benzo[*a*]quinolizidine derivatives and estimated P_{trans} values are presented in the last column of Table I. These values show that the state of equilibrium is affected by the position and/or the kind of substituent, as might be expected.

Our approach, employing $\Delta_{\text{C-T}}$ or the C-6 chemical shift, represents a valuable empirical approach which should aid in determining the stereochemistries of new benzo[*a*]quinolizidine derivatives which may be prepared in the future.

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Atropine-like Activities of 2-Substituted 5-Piperidinomethylfuran Derivatives

KAZUKO OHTA,[1a] ISSEI TAKAYANAGI,[1b] ETSUKO HIBI,[1a]
and KEIJIRO TAKAGI[1c]

Department of Organic Chemistry, Tokyo Women's Medical College,[1a] Department of Chemical Pharmacology, Toho University School of Pharmaceutical Sciences[1b] and Department of Pharmacotherapeutics, Faculty of Pharmaceutical Sciences, Science University of Tokyo[1c]

(Received May 16, 1979)

2-Substituted 5-piperidinomethylfuran derivatives were synthesized and their atropine-like and antihistamine activities were tested. The pA_2 values of the tested compounds for atropine-like activity were 7.50 to 5.21, less than that for atropine. The antihistamine activities (pA_2 values: 6.64 to 4.31) were much less than that of chlorpheniramine. Methylation of piperidine essentially did not affect the atropine-like activities but considerably decreased both the competitive and noncompetitive antihistamine activities.

Keywords——atropine-like activity; antihistamine activity; papaverine-like activity; 2-substituted 5-piperidinomethylfuran; effect of methylation of piperidine

2-Furfuryltrimethylammonium (furmethide) and its 5-methylderivative were found to have potent muscarinic activities.[2,3] It is well known that in a series of cholinergic drugs agonistic activity is replaced by antagonistic activity on replacing a part of the

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1) Location: *a) Kawada-cho, Shinjuku-ku, Tokyo*; *b) Miyama, Funabashi, Chiba*; *c) Sadohara-cho, Shinjuku-ku, Tokyo.*
2) E.J. Fellows and A.E. Livingston, *J. Pharmacol. Exp. Ther.*, **68**, 231 (1940).
3) H.R. Ing, P. Kordik and D.P.H.T. Williams, *Brit. J. Pharmacol.*, **7**, 103 (1952).