[Chem. Pharm. Bull. 28(9)2783—2795(1980)]

Studies on Antispasmodics. VI.[1] Synthesis of N-Alkyl 6- and 7-Diarylmethyleneindolizidinium Bromides[2]

KAGARI YAMAGISHI, EIICHI KOSHINAKA, NOBUO OGAWA, KAZUYA MITANI, TOMOYASU NISHIKAWA, HIDEO KATO,[3a] and MIYOJI HANAOKA[3b]

Research Laboratories, Hokuriku Seiyaku Co., Ltd.[3a] *and Faculty of Pharmaceutical Sciences, Kanazawa University*[3b]

(Received April 7, 1980)

As part of a search for new antispasmodics, we have synthesized N-alkyl 6- and 7-diarylmethyleneindolizidinium bromides (**1**—**8**), which might be expected to exhibit potent anticholinergic activities due to the rigid piperidine ring structure, by analogy with N-alkyl 2- and 3-diarylmethylenequinolizidinium bromides (I). Treatment of ethoxycarbonylindolizidines (**13** and **22**) with phenyllithium or 2-thienylmagnesium bromide, followed by dehydration, afforded diarylmethyleneindolizidines (**25**, **26**, **29** and **30**). Quaternization of the 6-substituted derivatives (**25** and **26**) with methyl bromide afforded two isomeric methobromides, the *trans*- (**1a** and **2a**) and the *cis*-methobromides (**1b** and **2b**), and the 7-substituted derivatives (**29** and **30**) also afforded the corresponding *trans*- (**5a** and **6a**) and *cis*-methobromides (**5b** and **6b**). The stereochemistries of these methobromides were confirmed by the chemical shifts of the N^+-methyl signals in the ^1H- and ^{13}C-NMR spectra. The stereochemistries of 6- and 7-diarylhydroxymethylindolizidines (**23**, **24**, **27** and **28**) were also determined from their IR and ^{13}C-NMR spectra.

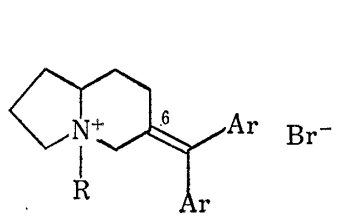
Keywords——antispasmodics; N-alkyl diarylmethyleneindolizidinium bromides; conformationally rigid derivatives; ethoxycarbonylindolizidines; diarylhydroxymethylindolizidines; stereochemistry; ^1H- and ^{13}C-NMR

In a previous paper[4] N-alkyl 2- and 3-diarylmethylenequinolizidinium bromides (I) were reported to have more potent anticholinergic activities than the piperidine antispasmodics such as diphemanil methylsulfate (II)[5] and timepidium bromide (III)[6] owing to their rigid piperidine conformations caused by the fusion of piperidine with another piperidine. As indolizidine, piperidine fused with pyrrolidine, might also have a rigid piperidine ring structure, N-alkyl 6- and 7-diarylmethyleneindolizidinium bromides (**1**—**8**) might also exhibit potent activities. This paper deals with the synthesis of **1**—**8** and the stereochemistries of various 6- and 7-diarylhydroxymethylindolizidines (**23**, **24**, **27** and **28**).

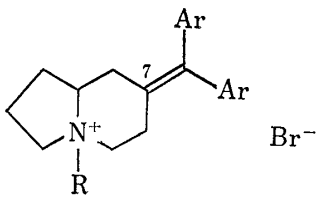
6- and 7-Ethoxycarbonylindolizidines (13 and 22)

The synthesis of 6-ethoxycarbonylindolizidine (**13**) was attempted by a new synthetic method developed for 3-ethoxycarbonylquinolizidine.[7] The chloronitrile (**11**), derived from 2-pyrrolidineethanol (**9**)[8] *via* the hydroxy-nitrile (**10**), was treated with sodium hydride (NaH) to give the cyclization product (**12**) in 53% yield as a mixture of two diastereoisomers in a

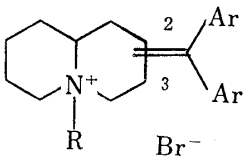
1) Part V: H. Kato, E. Koshinaka, N. Ogawa, K. Yamagishi, K. Mitani, S. Kubo, and M. Hanaoka, *Chem. Pharm. Bull.*, **28**, 2194 (1980).
2) A part of this work was presented at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, August, 1979.
3) Location: *a) Inokuchi, Katsuyama, Fukui, 911, Japan*; *b) Takara-machi, Kanazawa, 920, Japan.*
4) Part I: E. Koshinaka, N. Ogawa, S. Kurata, K. Yamagishi, S. Kubo, I. Matsubara, and H. Kato, *Chem. Pharm. Bull.*, **27**, 1454 (1979).
5) N. Sperber, F.J. Villani, M. Sherlock, and D. Papa, *J. Am. Chem. Soc.*, **73**, 5010 (1951).
6) N. Kawazu, T. Kanno, S. Saito, and H. Tamaki, *J. Med. Chem.*, **15**, 914 (1972).
7) Part II: E. Koshinaka, N. Ogawa, K. Yamagishi, H. Kato, and M. Hanaoka, *Yakugaku Zasshi*, **99**, 1021 (1979).
8) B.R. Baker, R.E. Schaub, and J.H. Williams, *J. Org. Chem.*, **17**, 116 (1952).



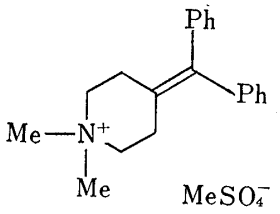
1 : Ar=Ph, R=Me
2 : Ar=Thi, R=Me
3 : Ar=Ph, R=Et
4 : Ar=Thi, R=Et



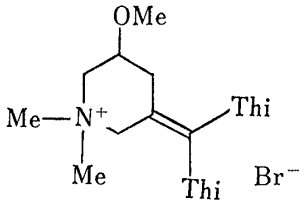
5 : Ar=Ph, R=Me
6 : Ar=Thi, R=Me
7 : Ar=Ph, R=Et
8 : Ar=Thi, R=Et



I



II



III

Ar=Ph(phenyl), Thi(2-thienyl)

Chart 1

1: 1 ratio. The cyclization yield of **11** was inferior to that (75%) of 3-cyanoquinolizidine.[7] Separation of the mixture by column chromatography (CCG) afforded **12a** and **12b**. Heating of the nitriles (**12a** and **12b**) in ethanolic hydrogen chloride (HCl–EtOH) gave the desired esters (**13a** and **13b**, respectively).

On the other hand, following the cyclization method for 2-cyanoquinolizidine,[9] the chloronitrile (**16**), derived from 2-pyrrolidinemethanol (**14**) *via* the hydroxy-nitrile (**15**), was treated with potassium *tert*-butoxide (*tert*-BuOK) to give only 2-methylenepyrrolidine (**17**), NMR δ: 5.70 (2H, m, $>C=CH_2$), instead of the cyclization product (**18**), probably due to easy formation of an exocyclic olefin from pyrrolidine in comparison with that from piperidine. Therefore, the ester (**22**) was synthesized according to the conventional method for 2-ethoxycarbonylquinolizidine.[10]

Reduction of the ketoester (**19**)[11] with sodium borohydride ($NaBH_4$) followed by dehydration with phosphorus oxychloride in pyridine afforded the unsaturated ester (**21**). Catalytic hydrogenation of **21** over the Adams catalyst gave the desired ester (**22**) as a mixture of two diastereoisomers (**22a** and **22b**; 5: 1), which was separated by CCG to give the major ester (**22a**) and the minor ester (**22b**).

6- and 7-Diarylmethyleneindolizidines (25, 26, 29 and 30)

Treatment of the esters (**13a** and **13b**) with phenyllithium (PhLi) afforded the 6-diphenylmethanols (**23a** and **23b**) in 86% and 87% yields, respectively. Since both isomers (**23a** and

9) Part III: E. Koshinaka, N. Ogawa, K. Yamagishi, H. Kato, and M. Hanaoka, *Yakugaku Zasshi*, **100**, 88 (1980).
10) N.J. Leonard, K. Conrow, R.W. Fulmer, *J. Org. Chem.*, **22**, 1445 (1957).
11) T. Kunieda, K. Koga, S. Yamada, *Chem. Pharm. Bull.*, **15**, 337 (1967).

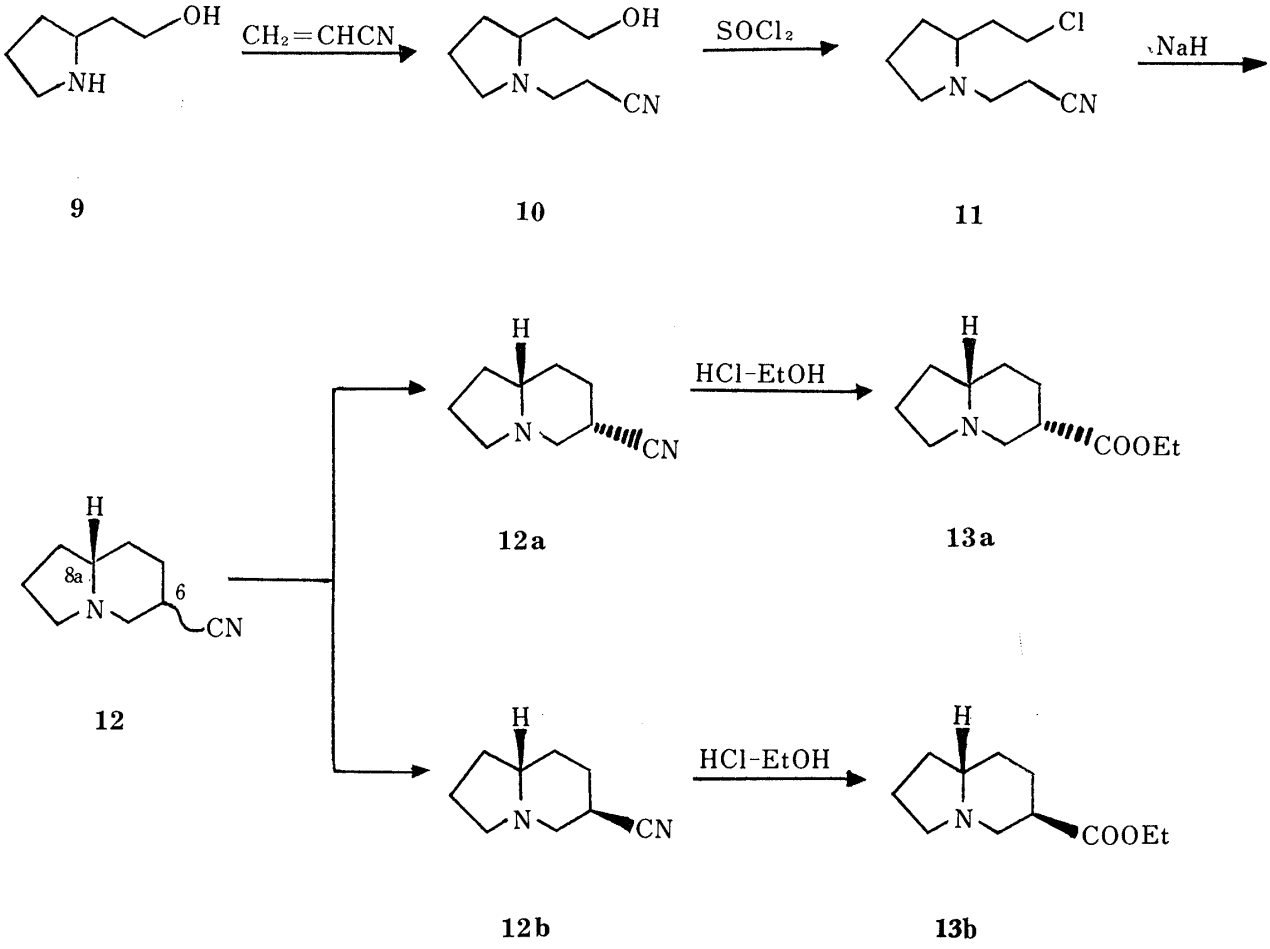


Chart 2

23b) showed strong Bohlmann bands, and **23a** showed a hydrogen-bonded hydroxyl band (*ca.* 3150 cm^{-1}), while **23b** showed a free hydroxyl band (3640 cm^{-1}) in the IR spectra, the stereochemistries of **23a** and **23b** could be assigned as *cis*(6*H*, 8a*H*)- and *trans*(6*H*, 8a*H*)-6-diphenylhydroxymethylindolizidine, respectively.[1,12] Consequently, the stereochemistries of the esters (**13a** and **13b**) and the nitriles (**12a** and **12b**) were also established as depicted in Chart 2.

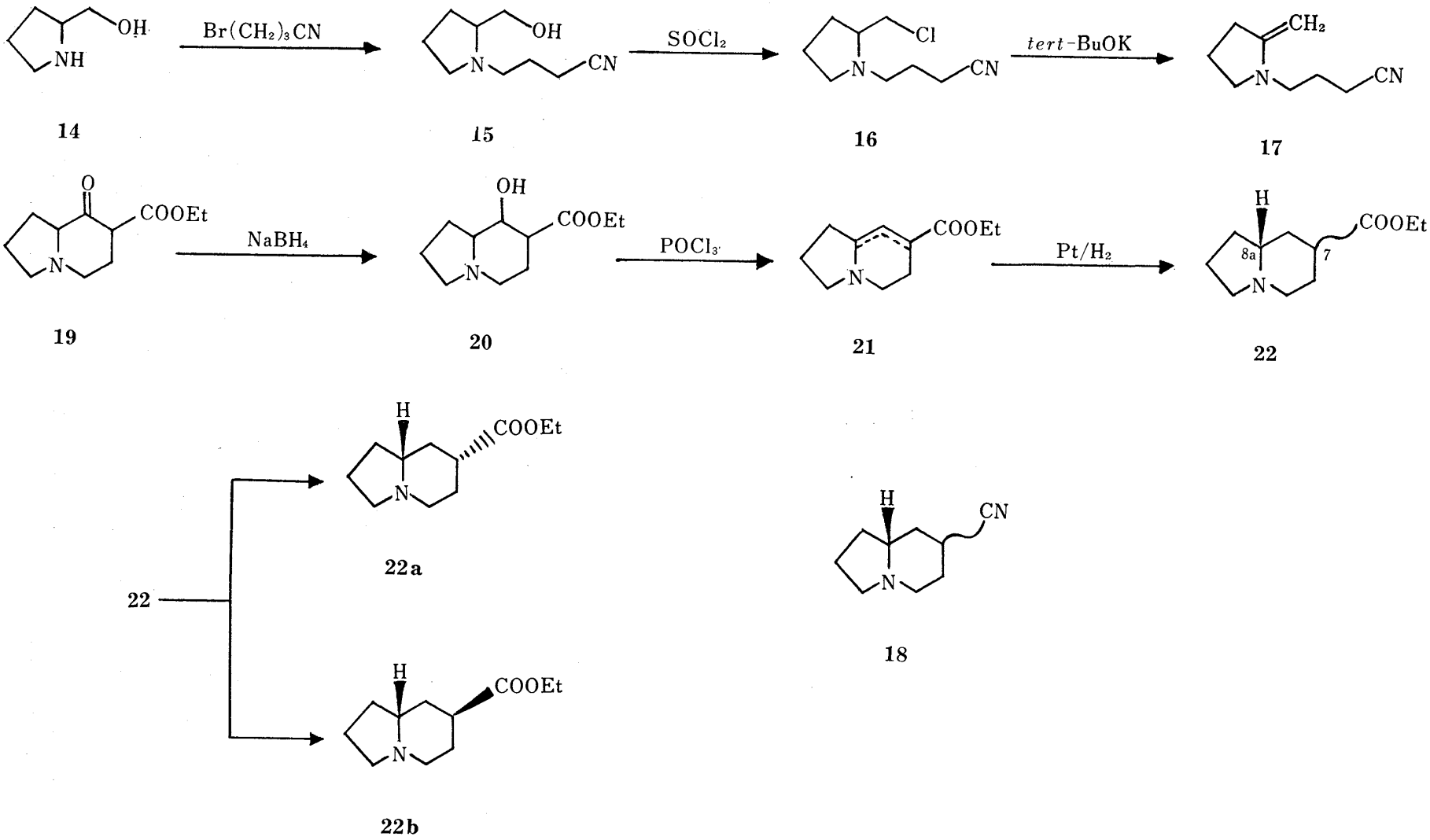
Similar treatment of the esters (**13a** and **13b**) with 2-thienylmagnesium bromide (ThiMgBr) gave the 6-dithienylmethanols, **24a** and **24b**, respectively.

On the other hand, treatment of the esters (**22a** and **22b**) with PhLi afforded 7-diphenylmethanols, **27a** and **27b**, respectively, the stereochemistries of which could be assigned as *cis* (7*H*, 8a*H*)- and *trans*(7*H*, 8a*H*)-7-diphenylhydroxymethylindolizidine, respectively, from their IR spectra as in the case of 2-diphenylhydroxymethylquinolizidines (**32a** and **32b**).[9] Consequently, the stereochemistries of the esters (**22a** and **22b**) were also established.

Similar treatment of the major ester (**22a**) with ThiMgBr gave 7-dithienylmethanol (**28a**).

The stereochemistries of 6- and 7-diphenylhydroxymethylindolizidines (**23** and **27**) assigned above were confirmed by the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra. The summarized ^{13}C-NMR data (Table I) for the corresponding 3- and 2-diphenylhydroxymethylquinolizidines (**31**[7] and **32**[9]) indicated that C_3 of **31a** (*trans*-quinolizidine with an axial

12) *a*) H.S. Aaron and C.P. Ferguson, *Tetrahedron Lett.*, **1968**, 6191; *b*) C.P. Rader, R.L. Young, Jr., and H.S. Aaron, *J. Org. Chem.*, **30**, 1536 (1965); *c*) H.S. Aaron, C.P. Rader, and G.E. Wicks, Jr., *ibid.*, **31**, 3502 (1966).



14 **15** **16** **17**

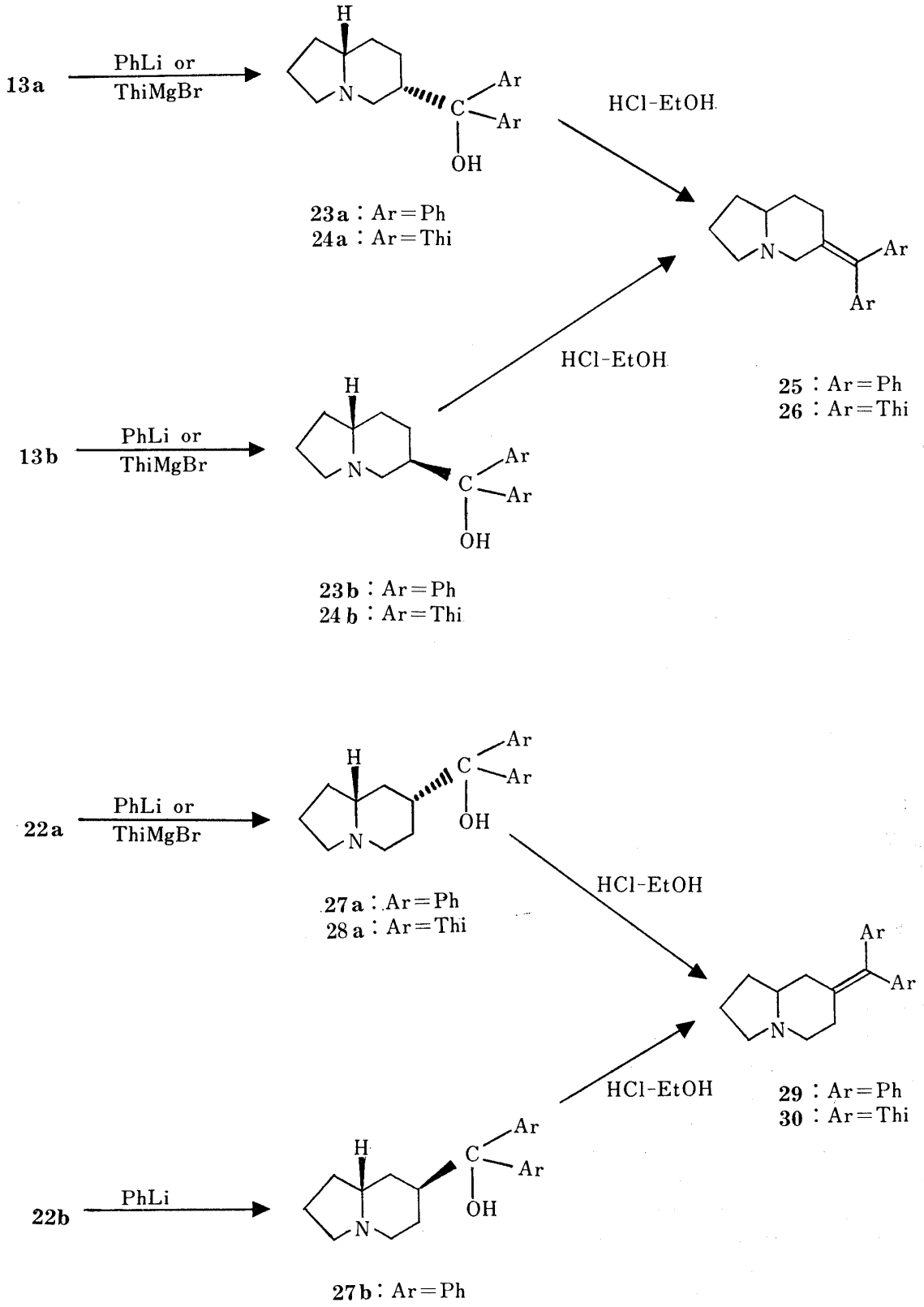
19 **20** **21** **22**

22a

18

22b

Chart 3



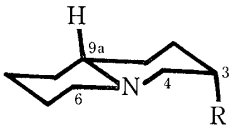
Ph=phenyl, Thi=2-thienyl

Chart 4

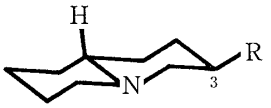
Table I. ^{13}C-NMR Chemical Shifts (ppm) of Diphenylhydroxymethylquinolizidines (**31** and **32**)

Compd.[a] No.	C_{9a}	C_4	C_6	C_2 or C_3	Δ C_2 or C_3 (**b-a**)
31a	62.52	58.08	56.18	38.70 (C_3)	5.18
31b	62.81	57.35	56.76	43.88 (C_3)	
32a	62.62	56.37[b]	56.27[b]	44.32 (C_2)	−6.74
32b	57.45	49.20	55.40	37.58 (C_2)	

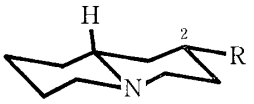
a) Compound numbers were as follows.



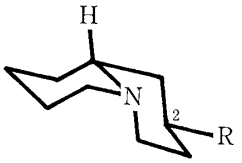
31a



31b



32a



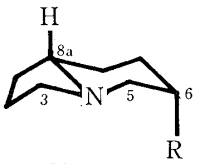
32b
R = C(OH) Ph_2

b) Assignments may be reversed.

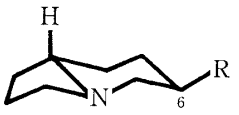
Table II. ^{13}C-NMR Chemical Shifts (ppm) of Diphenylhydroxymethylindolizidines (**23** and **27**)

Compd.[a] No.	C_{8a}	C_3 and C_5		C_6 or C_7	Δ C_6 or C_7 (**b-a**)
23a	64.47	54.57	53.69	38.75 (C_6)	5.27
23b	64.28	54.17	53.54	44.02 (C_6)	
27a	64.52	53.74	52.22	44.76 (C_7)	−6.89
27b	59.49	54.47	48.56 (C_5)	37.87 (C_7)	

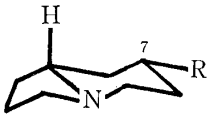
a) Compound numbers were as follows.



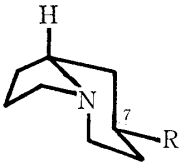
23a



23b



27a

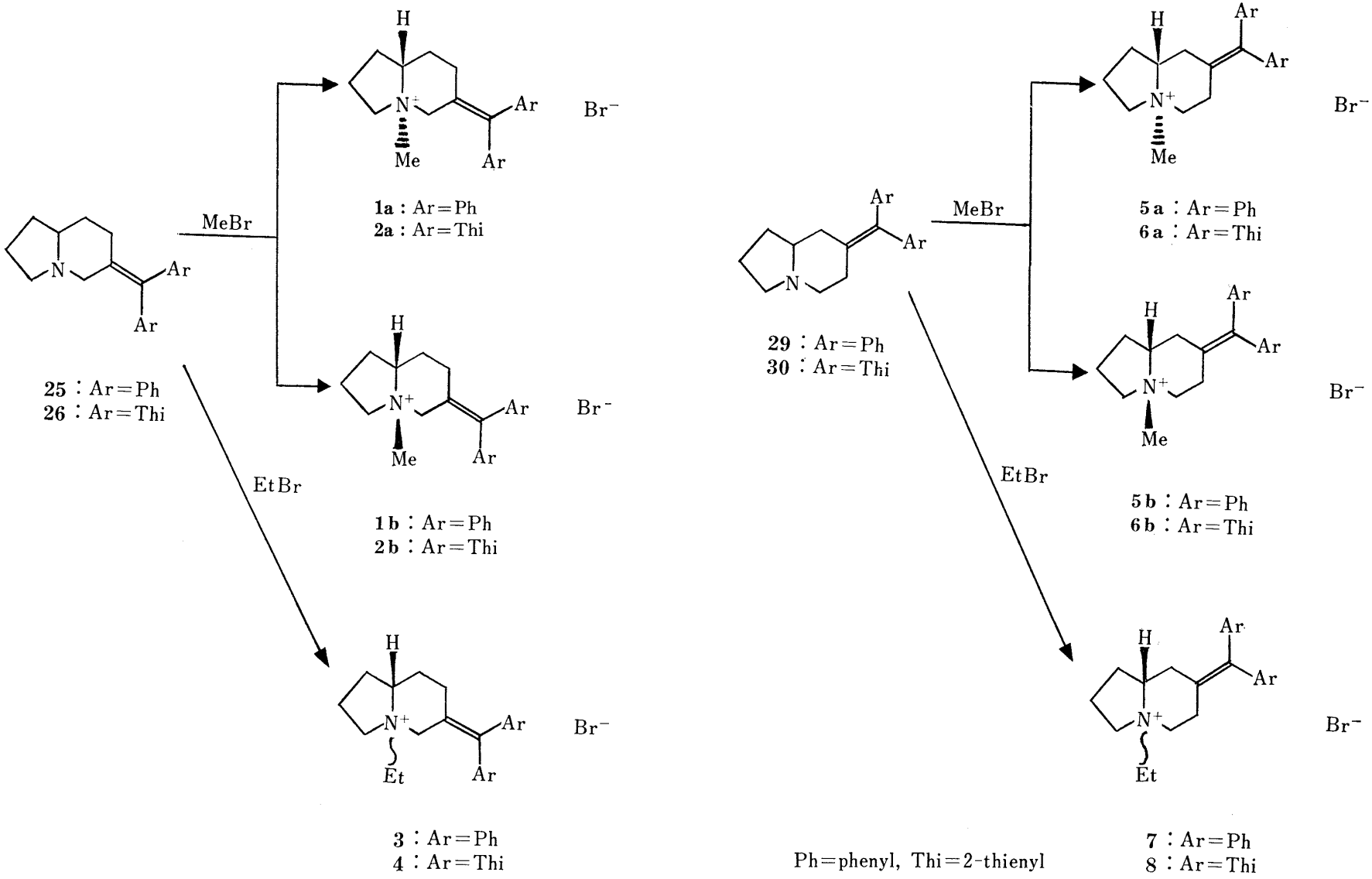


27b
R = C(OH)Ph_2

substituent) appeared at higher field than C_3 of **31b** and C_2 of **32a** (*trans*-quinolizidine with an equatorial substituent), as in the case of methylquinolizidines.[13] On the other hand, C_2 of **32b** (*cis*-quinolizidine with an equatorial substituent) appeared at higher field than that of **32a**, and the higher field shifts of C_4 and C_{9a} are characteristic of *cis*-quinolizidine.[14] By analogy with the above assignment, **23b** and **27a** were confirmed to have a *trans*-indolizidine structure with an equatorial substituent and **23a** to have a *trans*-indolizidine structure with an axial substituent, judging from the chemical shift of C_6 or C_7. The higher chemical shifts of C_5, C_7 and C_{8a} of **27b** indicated it to be a *cis*-indolizidine with an equatorial substituent (Table II).

Heating of both 6-diphenylmethanols (**23a** and **23b**) with HCl–EtOH effected dehydration to give 6-diphenylmethyleneindolizidine (**25**), and similarly, both 6-dithienylmethanols (**24a** and **24b**) gave 6-dithienylmethyleneindolizidine (**26**), in excellent yields.

13) R.T. LaLonde and T.N. Donvito, *Can. J. Chem.*, **52**, 3778 (1974).
14) *a*) M. Sugiura and Y. Sasaki, *Chem. Pharm. Bull.*, **24**, 2988 (1976); *b*) M. Sugiura, N. Takao, and Y. Sasaki, *ibid.*, **25**, 960 (1977).



Ph=phenyl, Thi=2-thienyl

Chart 5

On similar treatment, both 7-diphenylmethanols (**27a** and **27b**) gave the 7-diphenylmethyleneindolizidine (**29**), and 7-dithienylmethanol (**28a**) gave the 7-dithienylmethyleneindolizidine (**30**), in excellent yields.

N-Alkyl 6- and 7-Diarylmethyleneindolizidinium Bromides (1—8)

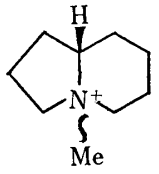
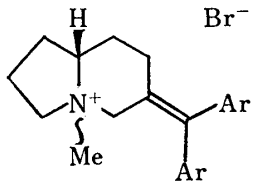
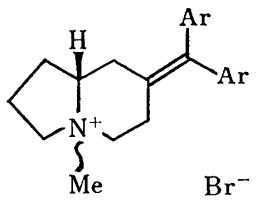
Quaternization of **25** with methyl bromide afforded the *trans*-(**1a**) and the *cis*-methobromide (**1b**) in a 1: 1 ratio. On similar treatment, **26** afforded the *trans*- (**2a**) and the *cis*-methobromide (**2b**) in a 1: 1 ratio.

On the other hand, quaternization of **29** with methyl bromide afforded the *trans*- (**5a**) and the *cis*-methobromide (**5b**) in a 1: 3.5 ratio. Similar treatment of **30** gave the *trans*- (**6a**, not isolated) and the *cis*-methobromide (**6b**) in a 1: 4 ratio. The stereochemistries of the above methobromides were assigned from the chemical shifts of the N^+ —methyl signals in the ^{1}H-NMR spectra on the basis of the report[15] on *cis*- and *trans*-indolizidine methiodides (see Table III).

The ethobromides (**3**, **4**, **7** and **8**) were isolated on quaternization of **25**, **26**, **29** and **30**, respectively, with ethyl bromide, but their stereochemistries remain undetermined.

The quaternization ratios of the *trans*- and *cis*-methobromides from 6-diarylmethyleneindolizidines (**25** and **26**) were the same as that from indolizidine. However, on quaternization of 7-diarylmethyleneindolizidines (**29** and **30**), the amounts of the *cis*-methobromides

Table III. ^{1}H- and ^{13}C-NMR N^+-Methyl Signals of Diarylmethyleneindolizidine Methobromides and the Quaternization Ratios of *trans*- and *cis*-Methobromides

Compd.	Ar	^{1}H-NMR chemical shift of N^+—Me (δ in $CDCl_3$)		^{13}C-NMR chemical shift of N^+—Me (δ in $CDCl_3$)		Ratio
		trans	*cis*	*trans*	*cis*	*trans* : *cis*
 **33**		2.82[a]	3.12[a]	39.18[b]	47.64[b]	1 : 1
	Ph	2.84	3.25	40.85	49.32	1 : 1
	Thi	2.86	3.29	40.66[c]	50.51	1 : 1.5
	Ph	3.20	3.55	39.44	48.37	1 : 3.5
	Thi	3.20[d]	3.57	39.65[d]	48.90	1 : 4

a) In D_2O.[16]
b) Measured with a mixture of *trans*- and *cis*-methiodides in a 1:1 ratio.[1]
c) In CD_3OD.
d) Measured with a mixture of *trans*- and *cis*-methobromides in a 1: 4 ratio.

15) W.L. Meyer and N. Sapianchiary, *J. Am. Chem. Soc.*, **86**, 3343 (1964).

formed were greater than those of the *trans*-methobromides. Thus, the substitution position of the diarylmethylene group has a significant effect on the quaternization ratio.

The stereochemistries of all methobromides assigned above were confirmed by their ^{13}C-NMR spectra. As shown in Table III, the N^+-methyl signals of the *trans*-methobromides appeared at higher field (39.0—41.0 ppm) than those of the *cis*-methobromides (48.0—51.0 ppm). These observations are compatible with the data for indolizidine methiodides (**33**, see Table III), N-methyl diarylmethylenequinolizidinium bromides (I)[4a] (the *trans* form appeared at 37.5—39.5 ppm and the *cis* form at 50.0—51.5 ppm), and N-alkyl 1- and 2-diarylmethyleneindolizidinium bromides[1] (the *trans* form appeared at 40.5—41.0 ppm and the *cis* form at 48.0—53.0 ppm).

N-Alkyl 6- and 7-diarylmethyleneindolizidinium bromides (**1**—**8**) prepared in this study were tested for anticholinergic activity by the Magnus method using isolated guinea pig ileum. Among the compounds tested, **6b** exhibited potent activity; its activity was equal to that of atropine. The pharmacological data will be reported in detail in the next paper.

Experimental[16]

3-[2-(2-Chloroethyl)pyrrolidin-1-yl]propionitrile (11)——A mixture of 2-pyrrolidineethanol (**9**,[8] 36.7 g) and acrylonitrile (20.3 g) was stirred at room temperature for 20 min and then the excess acrylonitrile was removed by evaporation *in vacuo*. The residue (**10**) was dissolved in $CHCl_3$ (120 ml) and $SOCl_2$ (41.7 g) was added dropwise. After refluxing for 30 min, the solvent was removed by evaporation *in vacuo*. The residue was made alkaline with aq. NaOH and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*.

The residual oil was distilled to give **11** (43.4 g, 73%) as a colorless oil, bp 120—124° (2.5 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2250 (CN). MS *m/e*: 186, 188 (3: 1, M^+).

***cis*(6*H*,8a*H*)-6-Cyanoindolizidine (12a) and *trans*(6*H*,8a*H*)-6-Cyanoindolizidine (12b)**——Compound **11** (28.8 g) was added dropwise to a suspension of 50% NaH (14.8 g) in DMF (150 ml) containing EtOH (0.5 ml), with stirring. The reaction mixture was heated at 50—60° for 1 hr and then poured into ice-water (1.5 l), and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give **12** (12.3 g, 53%) as a colorless oil, bp 75—78° (2 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2250 (CN). The product (**12**) showed two peaks on GC (column temperature, 130°, t_R=1.04 (**12b**), 1.61 min (**12a**)) in a 1: 1 ratio.

The product (**12**, 9.4 g) was recrystallized twice from petroleum ether to give **12a** (1.11 g), as colorless plates, mp 53—55°. IR ν_{max}^{KBr} cm^{-1}: 2800, 2760, 2730 (Bohlmann bands), 2250 (CN). MS *m/e*: 150 (M^+). *Anal.* Calcd for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65. Found: C, 71.78; H, 9.65; N, 18.63. The picrate: yellow needles, mp 174—176° (MeOH). *Anal.* Calcd for $C_{15}H_{17}N_5O_7$: C, 47.50; H, 4.52; N, 18.46. Found: C, 47.31; H, 4.36; N, 18.27.

The mother liquor was concentrated *in vacuo* and the residue was chromatographed on a silica gel column using $(iso\text{-}Pr)_2O$ as an eluent. The first fraction gave **12a** (2.62 g) and the second fraction gave **12b** (3.65 g) as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 2810, 2730 (Bohlmann bands), 2250 (CN). MS *m/e*: 150 (M^+). The picrate: yellow prisms, mp 201—204° (MeOH). *Anal.* Calcd for $C_{15}H_{17}N_5O_7$: C, 47.50; H, 4.52; N, 18.46. Found: C, 47.41; H, 4.37; N, 18.33.

***cis*(6*H*,8a*H*)-6-Ethoxycarbonylindolizidine (13a)**——A solution of **12a** (2.00 g) in EtOH (30 ml) saturated with HCl was refluxed for 5 hr and then concentrated *in vacuo*. The residue was made alkaline with aq. NaOH and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give **13a** (2.03 g, 77%) as a colorless oil, bp 76—77° (3 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2800, 2730 (Bohlman bands), 1735 (CO). ^1H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $-OCH_2\underline{CH_3}$), 4.16 (2H, q, J=7 Hz, $-O\underline{CH_2}CH_3$). MS *m/e*: 197 (M^+). The picrate: yellow needles, mp 167—169° (MeOH). *Anal.* Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 48.04; H, 5.12; N, 13.12.

16) All melting points were measured with a Yanagimoto micro melting point apparatus. Melting points and boiling points are uncorrected. The extracts were dried over anhydrous Na_2SO_4. IR spectra were measured with an IRA-2 spectrophotometer, Japan Spectroscopic Co. ^1H-NMR spectra were measured with Hitachi R-20B, and JEOL FX-90Q and FX-100 spectrometers, using TMS as an internal standard, ^{13}C-NMR spectra were measured with JEOL FX-90Q and FX-100 units, using TMS as an internal standard. MS and GC-MS were carried out with Hitachi RMU-6MG and RMU-7M machines and GC with a Hitachi 063 unit employing a 2% QF-1 column. The following abbreviations are used: br=broad, d=doublet, d-d=doublet of doublets, m=multiplet, q=quartet, s=singlet, t=triplet.

***trans*(6*H*,8a*H*)-6-Ethoxycarbonylindolizidine (13b)**——Compound **12b** (2.00 g) was treated by the procedure described for **13a** to give **13b** (1.61 g, 61%) as a colorless oil, bp 74—79° (3 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2800, 2730 (Bohlmann bands), 1735 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $-OCH_2\underline{C}H_3$), 4.12 (2H, q, J=7 Hz, $-OC\underline{H}_2CH_3$). MS *m/e*: 197 (M^+). The picrate: yellow needles, mp 206—208° (MeOH). *Anal.* Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.94; H, 5.13; N, 12.98.

(−)-4-(2-Hydroxymethylpyrrolidin-1-yl)butyronitrile (15)——A solution of 4-bromobutyronitrile (12.10 g) in DMF (20 ml) was added dropwise to a mixture of 2-pyrrolidinemethanol (**14**, 6.90 g) ($[\alpha]_D^{22}$ +10.2° (*c*=1.0, EtOH) and anhyd. K_2CO_3 (6.60 g) in DMF (50 ml). The mixture was heated at 80° for 2.5 hr with stirring and then poured into water (600 ml), and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give **15** (5.76 g, 50%) as a colorless oil, bp 118—124° (3 mmHg). $[\alpha]_D^{22}$ −85.6° (*c*=1.0, EtOH).

(−)-4-(2-Chloromethylpyrrolidin-1-yl)butyronitrile (16)——Thionyl chloride (6.59 g) was added dropwise to a solution of compound **15** (4.66 g) in $CHCl_3$ (100 ml). After refluxing for 1 hr, the solvent was concentrated *in vacuo*. The residue was made alkaline with 10% aq. K_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give **16** (3.81 g, 74%) as a colorless oil, bp 117—119° (3 mmHg). $[\alpha]_D^{22}$ −14.2° (*c*=1.0, EtOH).

4-(2-Methylenepyrrolidin-1-yl)butyronitrile (17)——Compound **16** (3.25 g) was added dropwise to a suspension of *tert*-BuOK (3.91 g) in DMF (40 ml) with stirring. The mixture was heated for 30 min at 50°, then poured into water (600 ml), and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give **17** (1.36 g, 52%) as a colorless oil, bp 130—135° (17 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 3050 (>C=CH_2), 2250 (CN). ^{1}N-NMR ($CDCl_3$) δ: 5.70 (2H, m, W_H=4 Hz, >C=CH_2). MS *m/e*: 150 (M^+). The picrate: yellow plates, mp 93—94° (EtOH). *Anal.* Calcd for $C_{15}H_{17}N_5O_7$: C, 47.50; H, 4.52; N, 18.46. Found: C, 47.38; H, 4.60; N, 18.15.

(−)-7-Ethoxycarbonyl-8-hydroxyindolizidine (20)——An ice-cooled, stirred solution of 7-ethoxycarbonyl-8-oxoindolizidine (**19**, 28.0 g) ($[\alpha]_D^{23}$ −3.0° (*c*=1.0, EtOH), prepared from L-proline *via* 3 steps according to the literature[11]) in MeOH (300 ml) was treated portionwise with $NaBH_4$ (3.00 g). After stirring for 3 hr under ice-cooling, the mixture was poured into ice-water (600 ml) and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give **20** (21.1 g, 75%) ($[\alpha]_D^{23}$ −3.6° (*c*=1.0, EtOH) as a colorless oil, bp 125—127° (2 mmHg), which was triturated with cold hexane and the precipitate was collected by filtration to give a colorless solid (6.83 g), mp 70—71°. Recrystallization from hexane gave colorless plates, mp 72—73°. $[\alpha]_D^{23}$ −1.3° (*c*=1.0, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 2800, 2760 (Bohlmann bands), 1730 (CO). MS *m/e*: 213 (M^+). *Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61,95; H, 8.98; N, 6.57. Found: C, 61.78; H, 9.15; N, 6.71.

Dehydration of 20 (Formation of 21)——Phosphorus oxychloride (4 ml) was added dropwise to an ice-cooled, stirred solution of **20** (5.00 g, $[\alpha]_D^{23}$ −1.3°) in pyridine (40 ml) under an N_2 atmosphere. After stirring at room temperature for 3 days, the mixture was made alkaline with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give **21** (2.56 g, 56%) as a pale yellow oil, bp 114—116° (4 mmHg). $[\alpha]_D^{23}$ ±0° (*c*=1.0, EtOH). IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2720 (Bohlmann bands), 1710 (CO). MS *m/e*: 195 (M^+).

***cis*(7*H*,8a*H*)-7-Ethoxycarbonylindolizidine (22a) and *trans*(7*H*,8a*H*)-7-Ethoxycarbonylindolizidine (22b)**——A solution of **21** (8.10 g) in acetic acid (60 ml) was hydrogenated over the Adams catalyst (1.00 g) at 20° and atmospheric pressure for 1 hr, absorbing *ca.* one equivalent of H_2. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was made alkaline with 10% aq. K_2CO_3 and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give **22** (7.60 g, 93%) as a colorless oil, bp 89—91° (2 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 1730 (CO). The product (**22**) showed two peaks on GC (column temperature, 125°, t_R=1.34 (**22a**), 1.09 min (**22b**)) in a 5:1 ratio.

The mixture of **22a** and **22b** was chromatographed on a silica gel column using $CHCl_3$–MeOH (19:1, v/v) as an eluent. The first fraction gave **22a** (5.80 g) as a colorless oil, bp 97—99° (3 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2790, 2740, 2710 (Bohlmann bands), 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $-OCH_2\underline{C}H_3$), 4.14 (2H, q, J=7 Hz, $-OC\underline{H}_2CH_3$). MS *m/e*: 197 (M^+). The picrate: yellow needles, mp 190—191° (EtOH). *Anal.* Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.60; H, 5.19; N, 12.82.

The second fraction gave **22b** (0.50 g) as a colorless oil, bp 98—100° (3 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2800, 2730 (Bohlmann bands), 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $-OCH_2\underline{C}H_3$), 4.16 (2H, q, J=7 Hz, $-OC\underline{H}_2CH_3$). MS *m/e*: 197 (M^+). The picrate: yellow prisms, mp 163—165° (EtOH). *Anal.* Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.70; H, 5.22; N, 12.94.

***cis*(6*H*,8a*H*)-6-Diphenylhydroxymethylindolizidine (23a)**——A solution of **13a** (0.50 g) in abs. ether (10 ml) was added dropwise to a stirred solution of PhLi in abs. ether (30 ml) (prepared from Li (0.11 g) and PhBr (1.79 g)). The reaction mixture was stirred at room temperature for 0.5 hr and then decomposed by addition of H_2O. The ether layer was separated and the aq. layer was extracted with ether. The separated ether layer and the extract were combined, washed with H_2O, dried, and concentrated *in vacuo*. A small amount of $(iso\text{-}Pr)_2O$ was added to the residue and the precipitate was collected by filtration to give **23a** (0.67 g, 86%). Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless pillars, mp 169—170°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution):

ca. 3150 (bonded OH), 2800, 2740, 2720 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 7.00—7.68 (10H, m, aromatic protons), 7.59 (1H, s, OH, disappeared on addition of D_2O). MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.91; H, 8.22: N, 4.61.

***trans*(6*H*,8a*H*)-6-Diphenylhydroxymethylindolizidine (23b)**——Compound **13b** (0.50 g) was treated by the procedure described for **23a** to give **23b** (0.68 g, 87%). Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless plates, mp 172—173°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3640 (OH), 2800, 2730 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (1H, s, OH, disappeared on addition of D_2O), 7.03—7.60 (10H, m, aromatic protons). MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.15; H, 8.23; N, 4.64.

***cis*(6*H*,8a*H*)-6-(Di-2-thienylhydroxymethyl)indolizidine (24a)**——A solution of **13a** (0.50 g) in abs. ether (10 ml) was added dropwise to a stirred solution of ThiMgBr in abs. ether (50 ml) (prepared from Mg (0.18 g) and ThiBr (1.24 g)). The reaction mixture was refluxed for 1 hr and then decomposed by addition of H_2O. The ether layer was separated and the aq. layer was extracted with ether. The separated ether layer and the extract were combined and shaken with 10% HCl. The aq. layer was made alkaline with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. A small amount of $(iso\text{-}Pr)_2O$ was added to the residue and the precipitate was collected by filtration to give **24a** (0.60 g, 74%). Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless pillars, mp 139—142°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): *ca.* 3150 (bonded OH), 2810, 2750, 2720 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 6.79—7.27 (6H, m, aromatic protons), 8.79 (1H, br, OH, disappeared on addition of D_2O). MS *m/e*: 319 (M^+). *Anal.* Calcd for $C_{17}H_{21}NOS_2$: C, 63.91; H, 6.63; N, 4.38. Found: C, 64.04; H, 6.89; N, 4.25.

***trans*(6*H*,8a*H*)-6-(Di-2-thienylhydroxymethyl)indolizidine (24b)**——Compound **13b** (0.50 g) was treated by the procedure described for **24a** to give **24b** (0.58 g, 72%). Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless needles, mp 168°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3610 (OH), 2790, 2730 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 3.12 (1H, br, OH, disappeared on addition of D_2O), 6.82—7.27 (6H, m, aromatic protons). MS *m/e*: 319 (M^+). *Anal.* Calcd for $C_{17}H_{21}NOS_2$: C, 63.91; H, 6.63; N, 4.38. Found: C, 64.12; H, 6.63; N, 4.44.

6-Diphenylmethyleneindolizidine (25)——1) From **23a**: A solution of **23a** (0.40 g) in EtOH (15 ml) saturated with HCl was refluxed for 1.5 hr and then concentrated by evaporation *in vacuo*. The residue was made alkaline with aq. NaOH and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was recrystallized from hexane to give **25** (0.36 g, 96%) as colorless pillars, mp 97—99°. IR ν_{max}^{KBr} cm^{-1}: 2780, 2740, 2710 (Bohlmann bands), 1630 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 2.61 (1H, d, J=12 Hz, C_5–H_{ax}), 3.80 (1H, d-d, J=12, 2 Hz, C_5–H_{eq}), 7.19 (10H, s, aromatic protons). MS *m/e*: 289 (M^+). *Anal.* Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.04; H, 8.24; N, 4.96.

2) From **23b**: Compound **23b** (0.40 g) was treated by the procedure described for the preparation of **25** from **23a** to give **25** (0.34 g, 91%) as colorless pillars, mp 97—99°; this material was identical with that obtained from **23a** (IR and NMR spectra and mixed melting point).

6-(Di-2-thienylmethylene)indolizidine (26)——1) From **24a**: A solution of **24a** (0.40 g) in EtOH (15 ml) saturated with HCl was refluxed for 1 hr, then concentrated *in vacuo*. The residue was made alkaline with aq. NaOH and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. A small amount of $(iso\text{-}Pr)_2O$ was added to the residue and the precipitate was collected by filtration to give **26** (0.34 g, 90%). Recrystallization from $(iso\text{-}Pr)_2O$ gave pale brownish pillars, mp 117—119°. IR ν_{max}^{KBr} cm^{-1}: 2800, 2740, 2720 (Bohlmann bands), 1610 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 2.65 (1H, d, J= 12 Hz, C_5–H_{ax}), 4.05 (1H, d-d, J=12, 2 Hz, C_5–H_{eq}), 6.75—7.05 (4H, m, aromatic protons), 7.08—7.35 (2H, m, aromatic protons). MS *m/e*: 301 (M^+). *Anal.* Calcd for $C_{17}H_{19}NS_2$: C, 67.73; H, 6.35; N, 4.65. Found: C, 67.74; H, 6.43; N, 4.56.

2) From **24b**: Compound **24b** (0.40 g) was treated by the procedure described for the preparation of **26** from **24a** to give **26** (0.33 g, 88%), which was identical with that obtained from **24a** (IR and NMR spectra and mixed melting point).

***cis*(7*H*,8a*H*)-7-Diphenylhydroxymethylindolizidine (27a)**——A solution of **22a** (3.70 g) in abs. ether (30 ml) was added dropwise to a stirred solution of PhLi in abs. ether (100 ml) (prepared from Li (0.80 g) and PhBr (8.90 g)). The reaction mixture was refluxed for 10 min and then decomposed by addition of H_2O. The ether layer was separated and the aq. layer was extracted with ether. The separated ether layer and the extract were combined and washed with H_2O, then 10% HCl was added to the ether layer. The precipitate was collected by filtration to give **27a**·HCl (6.19 g, 96%) as colorless prisms, mp>300° (MeOH). *Anal.* Calcd for $C_{21}H_{26}ClNO$: C, 73.35; H, 7.62; N, 4.07. Found: C, 73.14; H, 7.71; N, 4.00.

The free base was obtained in the usual way as colorless needles, mp 140—141° ((iso-$Pr)_2O$). IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3630 (OH), 2780, 2730 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 2.24 (1H, s, OH, disappeared on addition of D_2O), 7.08—7.63 (10H, m, aromatic protons). MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.96; H, 8.27; N, 4.38.

***trans*(7*H*,8a*H*)-7-Diphenylhydroxymethylindolizidine (27b)**——Compound **22b** (0.41 g) was treated with a solution of PhLi in abs. ether (20 ml) (prepared from Li (0.15 g) and PhBr (1.63 g)) by the procedure described for **27a** to give **27b**·HCl (0.47 g, 66%) as colorless prisms, mp 284—285° (MeOH–ether). *Anal.* Calcd for $C_{21}H_{26}ClNO$: C, 73.35; H, 7.62; N, 4.07. Found: C, 73.06; H, 7.73; N, 3.77.

The free base was obtained in the usual way as colorless plates, mp 134—135° ((iso-Pr)$_2$O). IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3630 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.94 (1H, br, OH, disappeared on addition of D_2O), 7.10—7.61 (10H, m, aromatic protons). MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.93; H, 8.42; N, 4.49.

***cis*(7*H*,8a*H*)-7-(Di-2-thienylhydroxymethyl)indolizidine (28a)**——Compound **22a** (0.50 g) was treated by the procedure described for **24** to give **28a** (0.63 g, 78%). Recrystallization from (iso-Pr)$_2$O gave colorless plates, mp 122—123°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3610 (OH), 2780, 2730 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 3.09 (1H, s, OH, disappeared on addition of D_2O), 6.80—7.30 (6H, m, aromatic protons). MS *m/e*: 319 (M^+). *Anal.* Calcd for $C_{17}H_{21}NOS_2$: C, 63.91; H, 6.63; N, 4.38. Found: C, 63.81; H, 6.70; N, 4.25.

7-Diphenylmethyleneindolizidine (29)——1) From **27a**: A solution of **27a**·HCl (2.65 g) in EtOH (10 ml) saturated with HCl was treated by the procedure described for **25** to give **29** (2.18 g, 98%) as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 2790, 2730 (Bohlmann bands), 1630 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 6.90—7.35 (10H, m, aromatic protons). MS *m/e*: 289 (M^+). The hydrochloride: colorless scales, mp 221—223° (acetone–ether). *Anal.* Calcd for $C_{21}H_{24}ClN$: C, 77.40; H, 7.42; N, 4.30. Found: C, 77.00; H, 7.48; N, 4.16. The picrate: yellow plates, mp 165—166° (ethyl acetate). *Anal.* Calcd for $C_{27}H_{26}N_4O_7$: C, 62.54; H, 5.05; N, 10.81. Found: C, 62.30; H, 5.01; N, 10.55.

2) From **27b**: A solution of **27b**·HCl (0.25 g) in EtOH (2 ml) saturated with HCl was refluxed for 1 hr and then concentrated *in vacuo* to give **29**·HCl (0.23 g, 97%) as colorless scales, mp 221—223° (acetone–ether); this material was identical with that obtained from **27a**·HCl (IR and NMR spectra and mixed melting point).

7-(Di-2-thienylmethylene)indolizidine (30)——A solution of **28a** (3.54 g) in EtOH (15 ml) saturated with HCl was treated by the procedure described for **25** to give **30** (3.15 g, 94%) as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2730 (Bohlmann bands), 1610 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 6.75—7.30 (6H, m, aromatic protons). MS *m/e*: 301 (M^+). High resolution MS: Calcd for $C_{17}H_{19}NS_2$: 301.0958. Found: 301.0969. The picrate: yellow prisms, mp 132—133° (ethyl acetate). *Anal.* Calcd for $C_{23}H_{22}N_4O_7S_2$: C, 52.07; H, 4.18; N, 10.56. Found: C, 51.79; H, 4.28; N, 10.50.

6-Diphenylmethylene-4-methyl-*trans*-indolizidinium Bromide (1a) and 6-Diphenylmethylene-4-methyl-*cis*-indolizidinium Bromide (1b)——A solution of **25** (1.00 g) and MeBr (3 ml) in MeOH (10 ml) in a sealed tube was kept standing at room temperature for 24 hr and then concentrated *in vacuo*, and the residue was washed with ether to give a mixture of **1a** and **1b** (1.25 g, 94%) in a 1:1 ratio. ^{1}H-NMR ($CDCl_3$) δ: 2.84 (3/2H, s, N^+–CH_3), 3.25 (3/2H, s, N^+–CH_3).

The mixture was washed with acetone (10 ml) and recrystallized from $CHCl_3$–acetone to give **1a** (0.30 g) as colorless needles, mp 245—247°. ^{1}H-NMR ($CDCl_3$) δ: 2.84 (3H, s, N^+–CH_3). ^{13}C-NMR ($CDCl_3$) δ: 40.85 (N^+–CH_3). *Anal.* Calcd for $C_{22}H_{26}BrN\cdot H_2O$: C, 65.67; H, 7.01; N, 3.48. Found: C, 65.72; H, 6.90; N, 3.44.

The acetone washing was concentrated *in vacuo* and the residue was recrystallized twice from MeOH–acetone–ether to give **1b** (0.26 g) as colorless needles, mp 205—207°. ^{1}H-NMR ($CDCl_3$) δ: 3.25 (3H, s, N^+–CH_3). ^{13}C–NMR ($CDCl_3$) δ: 49.32 (N^+–CH_3). *Anal.* Calcd for $C_{22}H_{26}BrN$: C, 68.75; H, 6.82; N, 3.64. Found: C, 68.59; H, 6.78; N, 3.51.

6-(Di-2-thienylmethylene)-4-methyl-*trans*-indolizidinium Bromide (2a) and 6-(Di-2-thienylmethylene)-4-methyl-*cis*-indolizidinium Bromide (2b)——A solution of **26** (3.78 g) and MeBr (10 ml) in MeOH (50 ml) in a sealed tube was treated by the procedure described for **1** to give a mixture of **2a** and **2b** (4.70 g, 95%) in a 1:1.5 ratio. ^{1}H-NMR ($CDCl_3$) δ: 2.86 (6/5H, s, N^+-CH_3), 3.29 (9/5H, s, N^+-CH_3).

The mixture was recrystallized three times from MeOH–acetone–ether to give **2a** (1.34 g) as colorless needles, mp 239—241°. ^{1}H–NMR ($CDCl_3$) δ: 2.86 (3H, s, N^+-CH_3). ^{13}C–NMR (CD_3OD) δ: 40.66 (N^+-CH_3). *Anal.* Calcd for $C_{18}H_{22}BrNS_2$: C, 54.54; H, 5.59; N, 3.53. Found: C, 54.22; H, 5.67; N, 3.47.

The mother liquor was concentrated *in vacuo* and the residue was recrystallized six times from MeOH–acetone–ether to give **2b** (0.43 g) as colorless plates, mp 228—230°. ^{1}H–NMR ($CDCl_3$) δ: 3.29 (3H, s, N^+-CH_3). ^{13}C–NMR ($CDCl_3$) δ: 50.51 (N^+-CH_3). *Anal.* Calcd for $C_{18}H_{22}BrNS_2$: C, 54.54; H, 5.59; N, 3.53. Found: C, 54.16; H, 5.61; N, 3.57.

6-Diphenylmethylene-4-ethylindolizidinium Bromide (3)——A solution of **25** (0.46 g) and EtBr (2 ml) in MeOH (5 ml) was heated at 50° for 3 days in a sealed tube and then concentrated *in vacuo*. A mixture of acetone and ether was added to the residue and the precipitate was collected by filtration to give **3** (0.17 g, 28%). Recrystallization from MeOH–acetone gave colorless prisms, mp 237—238°. *Anal.* Calcd for $C_{23}H_{28}BrN$: C, 69.34; H, 7.08; N, 3.52. Found: C, 69.17; H, 7.05; N, 3.35.

6-(Di-2-thienylmethylene)-4-ethylindolizidinium Bromide (4)——A solution of **26** (0.50 g) and EtBr (2 ml) in MeOH (5 ml) was treated by the procedure described for **3** to give **4** (0.29 g, 43%) as colorless prisms, mp 210—211° (MeOH–acetone). *Anal.* Calcd for $C_{19}H_{24}BrNS_2$: C, 55.60: H, 5.89; N, 3.41. Found: C, 55.48; H, 5.89; N, 3.26.

7-Diphenylmethylene-4-methyl-*trans*-indolizidinium Bromide (5a) and 7-Diphenylmethylene-4-methyl-*cis*-indolizidinium Bromide (5b)——A solution of **29** (1.50 g) and MeBr (3 ml) in MeOH (10 ml) was treated by the procedure described for **1** to give a mixture of **5a** and **5b** (1.95 g, 98%) in a 1:3.5 ratio. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (2/3H, s, N^+-CH_3), 3.55 (7/3H, s, N^+-CH_3).

The mixture was washed with acetone (20 ml) and recrystallized twice from MeOH–acetone to give **5b** (1.05 g) as colorless needles, mp 233—234°. ^{1}H-NMR ($CDCl_3$) δ: 3.55 (N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 48.37 (N^+-CH_3). *Anal.* Calcd for $C_{22}H_{26}BrN \cdot 1/2H_2O$: C, 67.17; H, 6.92; N, 3.56. Found: C, 67.17; H, 6.95; N, 3.57.

The acetone washing was concentrated *in vacuo* and the residue was recrystallized four times from MeOH–acetone to give **5a** (0.19 g) as colorless prisms, mp 229—230°. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 39.44 (N^+-CH_3). *Anal.* Calcd for $C_{22}H_{26}BrN$: C, 68.75; H, 6.82; N, 3.64. Found: C, 68.48; H, 6.87; N, 3.63.

7-(Di-2-thienylmethylene)-4-methyl-*trans*-indolizidinium Bromide (6a) and 7-(Di-2-thienylmethylene)-4-methyl-*cis*-indolizidinium Bromide (6b)——A solution of **30** (1.80 g) and MeBr (3 ml) in MeOH (10 ml) was treated by the procedure described for **1** to give a mixture of **6a** and **6b** (2.25 g, 95%) in a 1 : 4 ratio. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (3/5H, s, N^+-CH_3), 3.57 (12/5H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 39.65 (N^+-CH_3), 48.90 (N^+-CH_3).

The mixture was washed with acetone (20 ml) and recrystallized three times from MeOH–acetone to give **6b** (1.17 g) as colorless pillars, mp 224—226° (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.57 (N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 48.90 (N^+-CH_3). *Anal.* Calcd for $C_{18}H_{22}BrNS_2$: C, 54.54; H, 5.59; N, 3.53. Found: C, 54.62; H, 5.55; N, 3.35.

7-Diphenylmethylene-4-ethylindolizidinium Bromide (7)——A solution of **29** (0.25 g) and EtBr (1 ml) in MeOH (9 ml) was treated by the procedure described for **3** to give **7** (0.12 g, 34%) as colorless needles, mp 230—232° (acetone). *Anal.* Calcd for $C_{23}H_{28}BrN \cdot 1/4H_2O$: C, 68.57; H, 7.13; N, 3.48. Found: C, 68.57; H, 7.16; N, 3.41.

7-(Di-2-thienylmethylene)-4-ethylindolizidinium Bromide (8)——A solution of **30** (0.47 g) and EtBr (2 ml) in MeOH (8 ml) was treated by the procedure described for **3** to give **8** (0.23 g, 36%) as colorless needles, mp 215—217° (MeOH–acetone). *Anal.* Calcd for $C_{19}H_{21}BrNS_2$: C, 55.60; H, 5.89; N, 3.41. Found: C, 55.57; H, 6.00; N, 3.35.

Acknowledgement The authors are very grateful to Prof. Y. Arata, School of Pharmacy, Hokuriku University, for his guidance throughout the course of this work. Thanks are also due to Japan Electron Optics Lab. Co. for measurement of the ^{13}C-NMR spectra, and to Mr. S. Kurata of our Laboratories for technical assistance.