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Studies on Antispasmodics. V.[1] Synthesis and Anticholinergic Activity of N-Alkyl 1- and 2-Diarylmethylene-indolizidinium Bromides[2]

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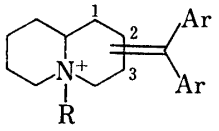
In a search for new antispasmodics, we have synthesized N-alkyl 2- and 1-diarylmethyleneindolizidinium bromides (**6**—**13**), which can be regarded as conformationally rigid derivatives of prifinium bromide (**14**) or the basic compound (**15**) of the pyrrolidine antispasmodics. Condensation of ethoxycarbonylindolizidines (**20** and **26**) with phenyllithium or 2-thienylmagnesium bromide, followed by dehydration, afforded diarylmethyleneindolizidines (**23**, **24**, **29** and **30**). Quaternization of the 2-substituted derivatives (**23** and **24**) with methyl bromide afforded two isomeric methobromides, the *trans*-(**6a** and **7a**) and the *cis*-methobromides (**6b** and **7b**), while the 1-substituted derivatives (**29** and **30**) afforded only the *cis*-methobromides (**10** and **11**). 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 2- and 1-diarylhydroxymethylindolizidines (**21**, **22**, **27** and **28**) were also determined from the IR spectra and by X-ray analysis.

The quaternary ammonium salts (**6**—**13**) exhibited anticholinergic activity more potent than that of **15**, and the activities of several compounds were equal to that of **14**. The structure-activity relationships of these compounds are discussed.

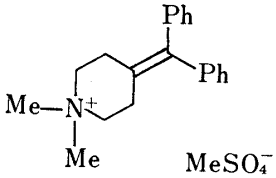
Keywords——antispasmodics; N-alkyl diarylmethyleneindolizidinium bromides; conformationally rigid derivatives; substituted indolizidines; stereochemistry; X-ray analysis; ^1H- and ^{13}C-NMR; anticholinergic activity; structure-activity relationships

We have previously reported the synthesis of N-alkyl 1-, 2- and 3-diarylmethylenequinolizidinium bromides (**1**—**3**)[4] and found that they have more potent anticholinergic activities than the piperidine antispasmodics such as diphemanil methylsulfate (**4**) and timepidium bromide (**5**), presumably because of the rigidity of their conformation compared to those of **4** and **5**. As a continuation of our studies on structure-activity relationships of bicyclic hetero ring compounds, we tried to synthesize compounds with the indolizidine ring system, N-alkyl 2- and 1-diarylmethyleneindolizidinium bromides (**6**—**13**), which can be regarded as conformationally rigid derivatives of prifinium bromide (**14**) or the basic compound (**15**)[5] of the pyrrolidine antispasmodics. This paper deals with the synthesis, stereochemistry and anticholinergic activities of **6**—**13**. The stereochemistries of 2- and 1-diarylhydroxymethylindolizidines (**21**, **22**, **27** and **28**) are also described.

1) Part IV: E. Koshinaka, N. Ogawa, K. Yamagishi, H. Kato, and M. Hanaoka, *Yakugaku Zasshi*, **100**, 100 (1980).
2) A part of this work was presented at the 47th Meeting of the Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, November, 1978.
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) *a)* M. Hitomi, H. Nojima, and S. Uchida, *Nippon Yakurigaku Zasshi*, **62**, 427 (1966); *b)* S. Ohki, *Yuki Gosei Kagaku Kyokai Shi*, **30**, 1 (1972).



1 : 1-subst. deriv.
2 : 2-subst. deriv.
3 : 3-subst. deriv.



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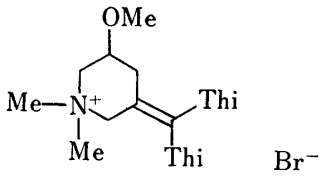

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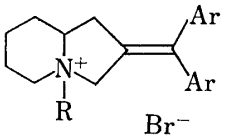
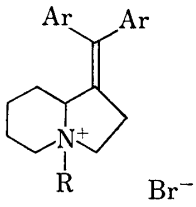
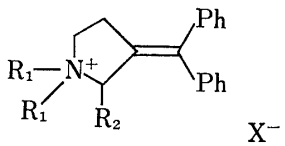


6 : Ar=Ph, R=Me
7 : Ar=Thi, R=Me
8 : Ar=Ph, R=Et
9 : Ar=Thi, R=Et



10 : Ar=Ph, R=Me
11 : Ar=Thi, R=Me
12 : Ar=Ph, R=Et
13 : Ar=Thi, R=Et



14 : R_1=Et, R_2=Me, X=Br
15 : R_1=Me, R_2=H, X=I

R=Me, Et
Ar=Ph (phenyl), Thi (2-thienyl)

Chart 1

2-Diarylmethyleneindolizidines (23 and 24)

We have already reported an alternative and convenient synthesis of 3-ethoxycarbonylquinolizidine *via* cyclization of 3-[2-(2-chloroethyl)piperidin-1-yl]propionitrile.[6] This synthetic method was applied here to the synthesis of 2-ethoxycarbonylindolizidine (**20**).

The addition product (**17**) of 2-piperidinemethanol (**16**) to acrylonitrile was chlorinated with thionyl chloride to afford the chloronitrile (**18**), bp_2 129—130°, in 82% overall yield from **16**. Treatment of **18** with sodium hydride (NaH) or potassium *tert*-butoxide (*tert*-BuOK) effected cyclization to give a 61% or 68% yield of the 2-cyanoindolizidine (**19**), bp_3 91—95°, which was shown to be a mixture of two diastereoisomers (**19a** and **19b**) in a 1:1 ratio by gas chromatography–mass spectroscopy (GC–MS). Column chromatographic separation of **19** afforded **19a**, *m/e* 150 (M^+), the picrate, mp 189—192°, and **19b**, *m/e* 150 (M^+), the picrate, mp 215—218°. The former showed bands at 2800, 2760, 2730 (Bohlmann bands), 2240 cm^{-1} (CN), and the latter at 2800, 2760, 2730 (Bohlmann bands), 2230 cm^{-1} (CN) in the infrared (IR) spectra.

Heating of the nitriles (**19a** and **19b**) in ethanolic hydrogen chloride (HCl–EtOH) gave the desired esters, **20a**, bp_7 118—120°, IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2750, 2720 (Bohlmann bands), 1730 (CO), *m/e* 197 (M^+), the picrate, mp 137—138°, and **20b**, bp_7 119—120°, IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2750, 2720 (Bohlmann bands), 1730 (CO), *m/e* 197 (M^+), the picrate, mp 152°, in 68% and 46% yields, respectively. Thus, the ester (**20**) could be obtained in 4 steps from **16** in 23—38% overall yield.

Condensation of the esters (**20a** and **20b**) with phenyllithium (PhLi) afforded the 2-diphenylmethanols, **21a**, mp 132—134°, *m/e* 307 (M^+), and **21b**, mp 136—138°, *m/e* 307 (M^+), in excel-

6) *a*) Part II: E. Koshinaka, N. Ogawa, K. Yamagishi, H. Kato, and M. Hanaoka, *Yakugaku Zasshi*, **99**, 1021 (1979); *b*) Part III: *idem*, *ibid.*, **100**, 88 (1980).

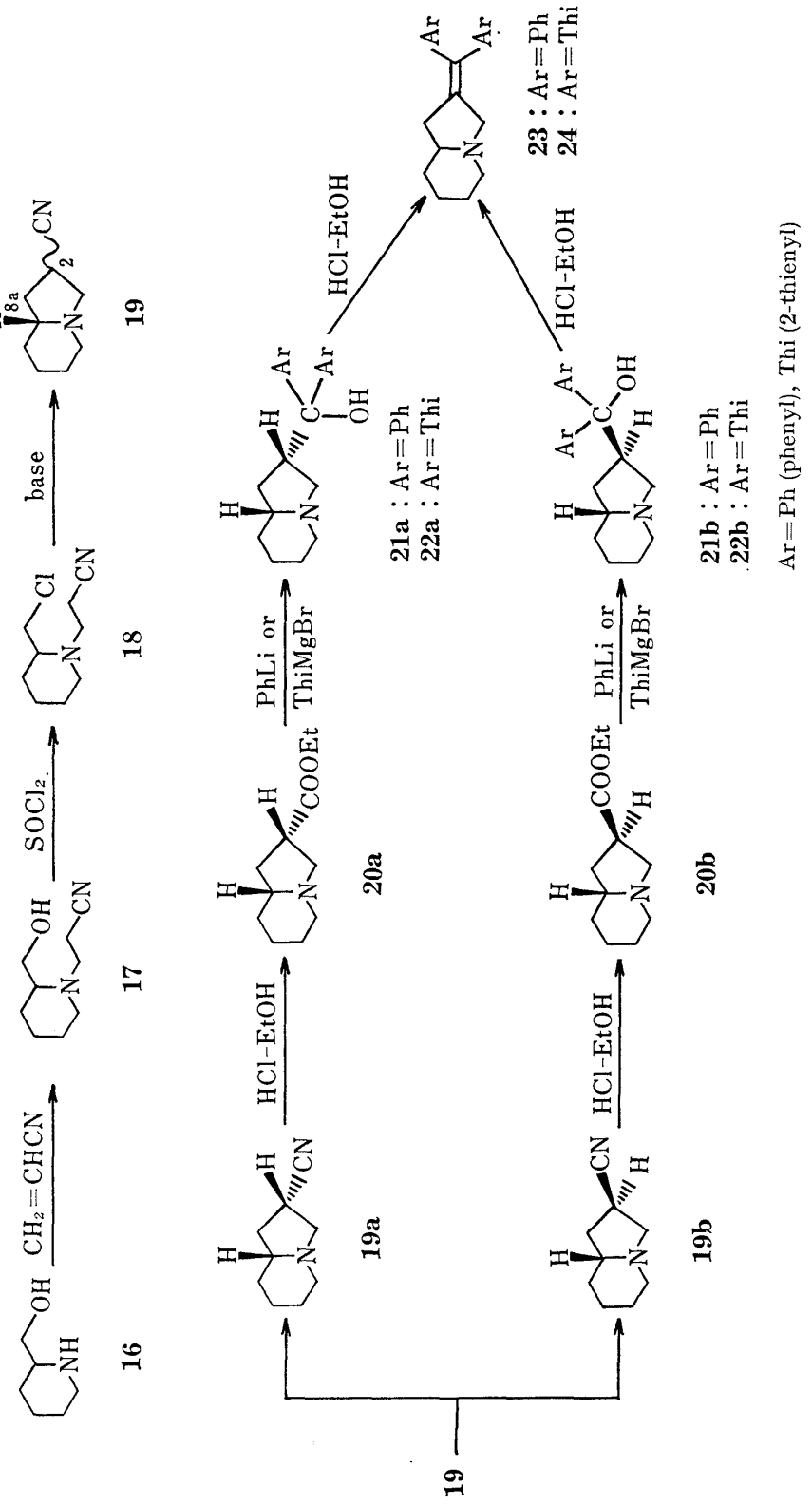
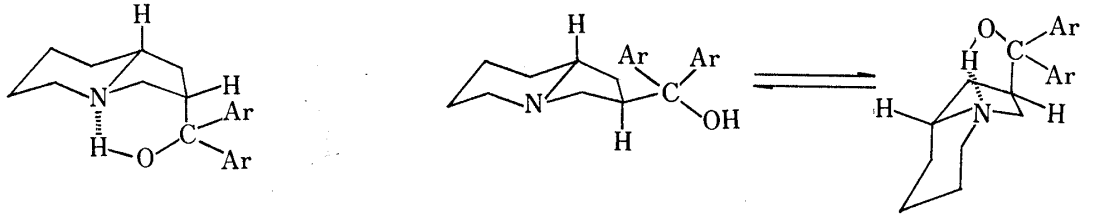


Chart 2



21a′ : Ar=Ph
22a′ : Ar=Thi

21b′ : Ar=Ph
22b′ : Ar=Thi

21b″ : Ar=Ph
22b″ : Ar=Thi

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

Chart 3

lent yields. The IR spectrum of **21a** in dilute carbon tetrachloride solution (5×10^{-3} M solution) showed bands at 3250 (hydrogen-bonded OH), 2800, 2740, 2720 cm^{-1} (Bohlmann bands) and that of **21b** showed bands at 3630 (free OH), 3300 (hydrogen-bonded OH), 2780, 2740, 2710 cm^{-1} (Bohlmann bands).

The *cis*- and *trans*-fused conformations of indolizidine are in equilibrium in favor of the *trans*-fused conformation,[7] and the Bohlmann bands are useful for stereochemical assignment of the ring fusion of indolizidine systems, as in the case of quinolizidine systems.[8] On the basis of the observations that both isomers (**21a** and **21b**) showed strong Bohlmann bands, that **21a** showed only a hydrogen-bonded hydroxyl band, and that **21b** showed a free hydroxyl band, the stereochemistries of **21a** and **21b** could be assigned as *cis* (2*H*, 8a*H*)- and *trans*(2*H*, 8a*H*)-2-diphenylhydroxymethylindolizidine, respectively. **21a** would exist in the conformer **21a′**, and **21b** in the conformer **21b′** together with the conformer **21b″** in some extent, of which the latter would be responsible for the hydrogen-bonded hydroxyl band in the IR spectrum of **21b**.

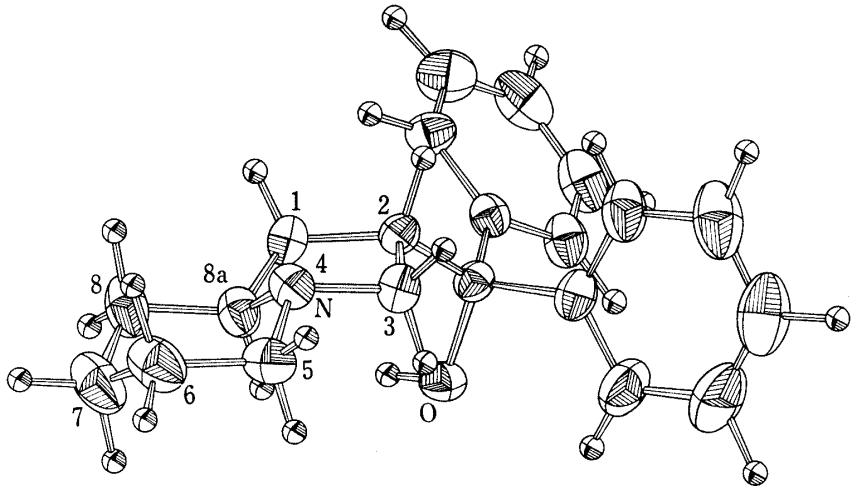


Fig. 1. Perspective View of the Structure of Racemic **21b**

In general, the stereochemistry of indolizidine ring systems has not been studied as extensively as that of quinolizidine ring systems. Therefore, in order to confirm the above stereochemical assignments, an X-ray diffraction study of **21b** was performed. The X-ray analysis data for **21b** (as shown in Fig. 1) indicated that the above assignments are correct

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

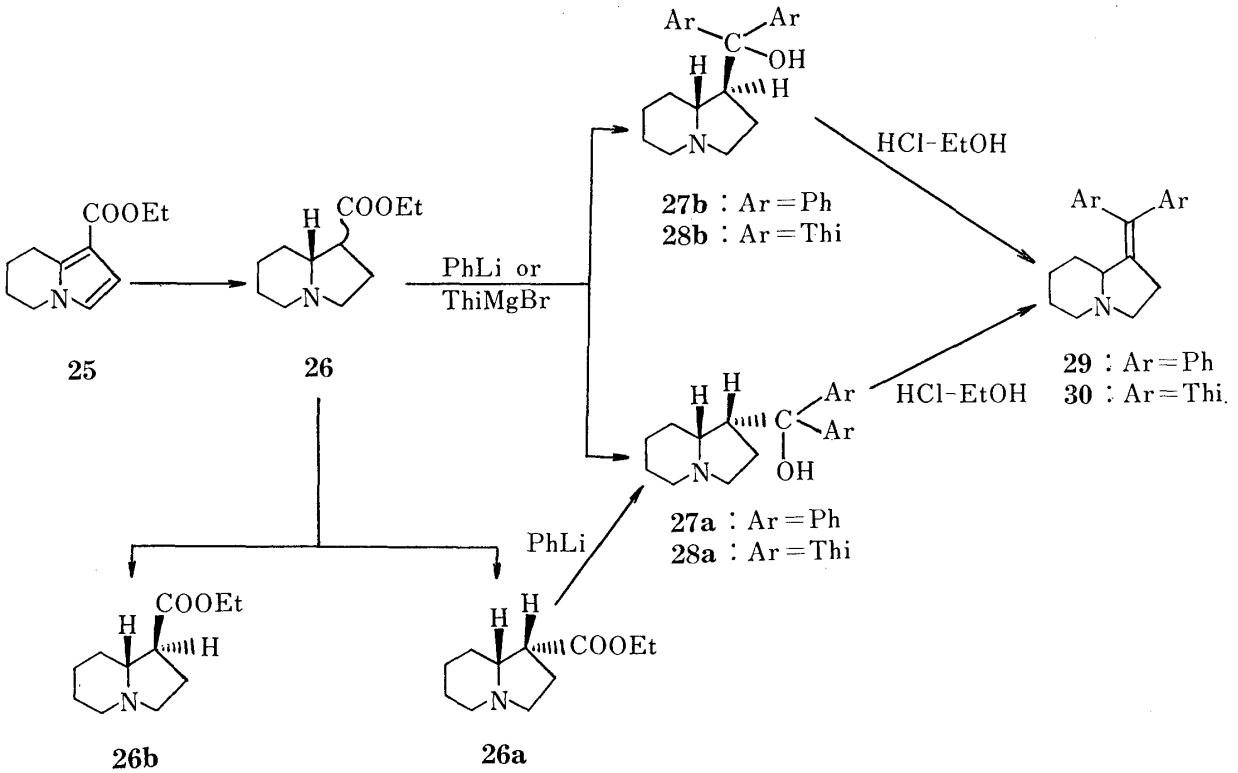
and that the Bohlmann bands and the hydroxyl bands in the IR spectrum are thus useful for stereochemistry determination in indolizidine systems. Consequently, the stereochemistries of the esters (**20a** and **20b**) and the nitriles (**19a** and **19b**) were also established.

Treatment of **20a** and **20b** with 2-thienylmagnesium bromide (ThiMgBr) gave the 2-dithienylmethanols, **22a**, mp 130—131°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3250 (hydrogen-bonded OH), 2810, 2750, 2730 (Bohlmann bands), *m/e* 319 (M^+), and **22b**, mp 101—102°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3610 (free OH), *ca.* 3200 (hydrogen-bonded OH), 2780, 2740, 2710 (Bohlmann bands), *m/e* 319 (M^+), respectively. The IR spectra of **22a** and **22b** in dilute carbon tetrachloride solution were similar to those of **21a** and **21b**, respectively.

Heating of both 2-diphenylmethanols (**21a** and **21b**) with HCl–EtOH effected dehydration to give 2-diphenylmethyleneindolizidine (**23**), mp 76—79°, IR ν_{max}^{KBr} cm^{-1}: 2780, 2750, 2720 (Bohlmann bands), 1640 (C=C), *m/e* 289 (M^+), and both 2-dithienylmethanols (**22a** and **22b**) gave 2-dithienylmethyleneindolizidine (**24**), bp_3 195—197°, IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2750, 2720 (Bohlmann bands), *m/e* 301 (M^+), the hydrochloride, mp 197—200° (dec.), in excellent yields.

1-Diarylmethyleneindolizidines (29 and 30)

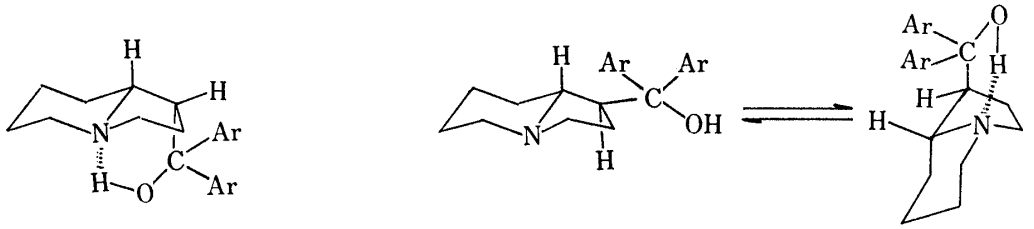
Catalytic hydrogenation of 1-ethoxycarbonyl-5,6,7,8-tetrahydroindolizine (**25**)[9] over palladium on carbon in ethanol gave a 41% yield of 1-ethoxycarbonylindolizidine (**26**), bp_3 88—90°, which was shown to be a mixture of two diastereoisomers (**26a** and **26b**) in a 2:3 ratio by GC–MS. Condensation of **26** with PhLi followed by chromatographic separation gave two isomeric 1-diphenylmethanols, **27a**, mp 106—108°, *m/e* 307 (M^+), and **27b**, mp 128—129°, *m/e* 307 (M^+).



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

Chart 4

9) M.T. Pizzorno and S.M. Albonico, *J. Org. Chem.*, **42**, 909 (1977).



27a' : Ar=Ph
28a' : Ar=Thi

27b' : Ar=Ph
28b' : Ar=Thi

27b'' : Ar=Ph
28b'' : Ar=Thi

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

Chart 5

The IR spectrum of **27a** in dilute carbon tetrachloride solution (5×10^{-3} M solution)showed bands at 3250 (hydrogen-bonded OH), 2800, 2740, 2720 cm^{-1} (Bohlmann bands), while that of **27b** showed bands at 3640 (free OH), *ca.* 3250 (hydrogen-bonded OH), 2790, 2730 cm^{-1} (Bohlmann bands). On the basis of the observations that both isomers (**27a** and **27b**) showed strong Bohlmann bands, that **27a** showed only a hydrogen-bonded hydroxyl band, and that **27b** showed a free hydroxyl band, **27a** and **27b** could be assigned as *cis* (1*H*, 8a*H*)- and *trans* (1*H*, 8a*H*)-1-diphenylhydroxymethylindolizidine, respectively. **27a** would exist in the conformer **27a'**, and **27b** in the conformer **27b'** together with the conformer **27b''** in some extent, of which the latter would be responsible for the hydrogen-bonded hydroxyl band in the IR spectrum of **27b**.

Treatment of **26** with ThiMgBr gave two isomeric 1-dithienylmethanols, **28a**, mp 116.5—118°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3200 (hydrogen-bonded OH), 2800, 2740, 2720 (Bohlmann bands), *m/e* 319 (M^+), and **28b**, mp 144—145.5°, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (free OH), *ca.* 3200 (hydrogen-bonded OH), 2790, 2710 (Bohlmann bands), *m/e* 319 (M^+).

Chromatographic separation of the ester (**26**) gave *cis*(1*H*, 8a*H*)-1-ethoxycarbonylindolizidine (**26a**), IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2720 (Bohlmann bands), 1730 (CO), the picrate, mp 105.5—106°, and the condensation product of **26a** with PhLi was identified as **27a** from the IR spectrum and by mixed melting point determination. Attempts to isolate the other ester (**26b**) were unsuccessful.

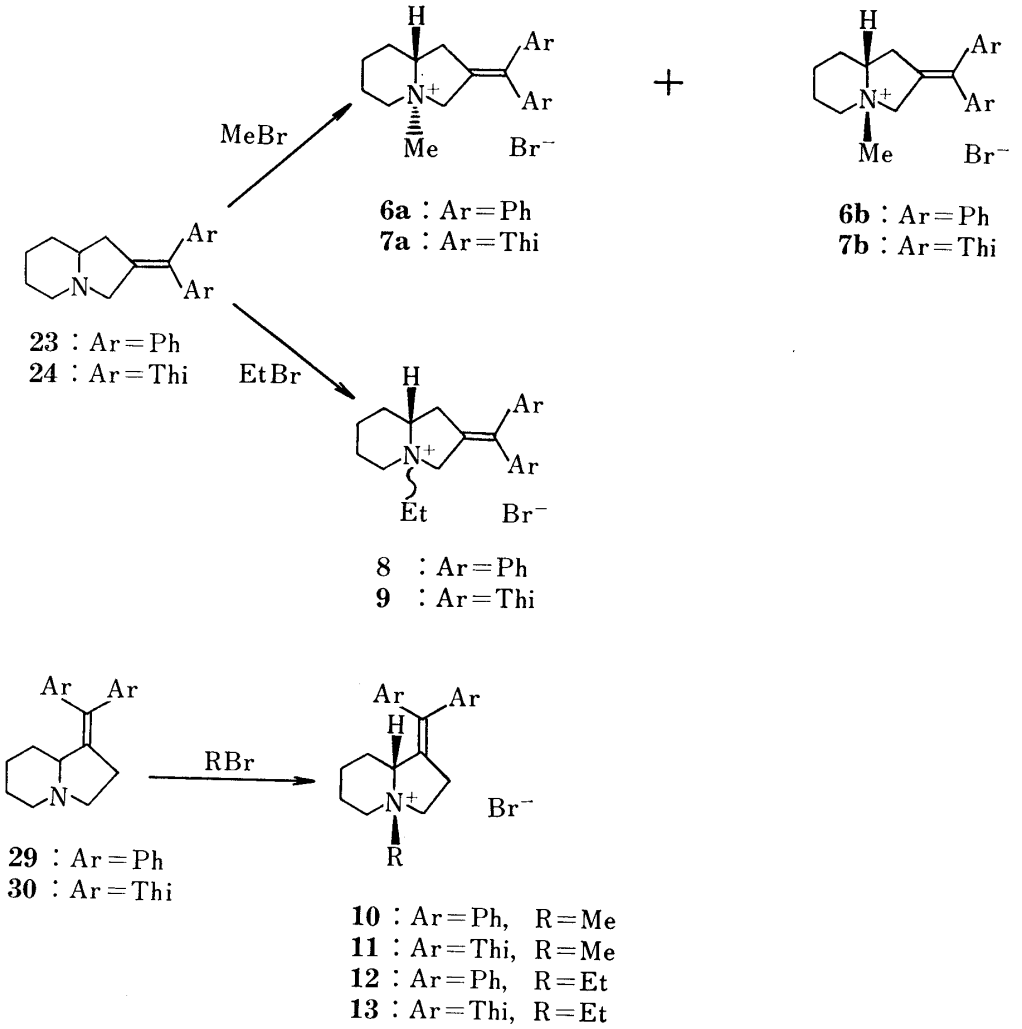
On treatment with HCl–EtOH, both 1-diphenylmethanols (**27a** and **27b**) gave 1-diphenylmethyleneindolizidine (**29**), $bp_{1.5}$ 160—161°, IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2720 (Bohlmann bands), 1635 (C=C), *m/e* 289 (M^+), and both 1-dithienylmethanols (**28a** and **28b**) gave 1-dithienylmethyleneindolizidine (**30**), mp 80.5—81.5°, IR ν_{max}^{KBr} cm^{-1}: 2810, 2790, 2740 (Bohlmann bands), *m/e* 301 (M^+), in excellent yields.

N-Alkyl 2- and 1-Diarylmethyleneindolizidinium Bromides (6—13)

Quaternization of **23** with methyl bromide afforded two isomeric methobromides, **6a**, mp 259—261°, NMR δ: 3.03 (N^+ —Me), and **6b**, mp 221—224°, NMR δ: 3.53 (N^+ —Me), in a 1 : 1 ratio. On similar treatment, **24** also gave two isomeric methobromides, **7a**, mp 205—206°, NMR δ: 3.04 (N^+ —Me), and **7b**, mp 213—215°, NMR δ: 3.55 (N^+ —Me), in a 1 : 1.5 ratio. On the basis of the report[10] that the N^+—methyl signal of indolizidine *cis*-methiodide appeared at lower field than that of the corresponding *trans*-methiodide in the ^{1}H-NMR spectrum, the stereochemistries of **6a** and **7a** were assigned as *trans* and those of **6b** and **7b** as *cis*. Quaternization of **23** and **24** with ethyl bromide gave the ethobromides, **8**, mp 123—127°, and **9**, mp 212—214°, respectively. The stereochemistries of **8** and **9** remained undetermined.

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

Quaternization of **29** and **30** with methyl bromide produced only the *cis*-methobromide (**10**), mp 210—211°, NMR δ: 3.51 (N^+ —Me) and the *cis*-methobromide (**11**), mp 286—287°, NMR δ: 3.45 (N^+ —Me), respectively, the stereochemistries of which were established by analysis of their ^{13}C-NMR spectra, as described later. The formation of only the *cis*-methobromide was anticipated in view of the presence of strong steric interaction between one of the aromatic rings and the C_8-methylene in the *trans*-fused methobromide. Similarly, quaternization of **29** and **30** with ethyl bromide provided the *cis*-ethobromide (**12**), mp 163—164°, and the *cis*-ethobromide (**13**), mp 252—253°, respectively.



6a : Ar=Ph
7a : Ar=Thi

6b : Ar=Ph
7b : Ar=Thi

23 : Ar=Ph
24 : Ar=Thi

8 : Ar=Ph
9 : Ar=Thi

29 : Ar=Ph
30 : Ar=Thi

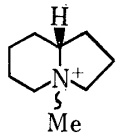
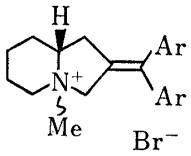
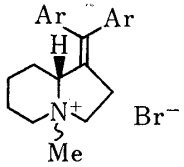
10 : Ar=Ph, R=Me
11 : Ar=Thi, R=Me
12 : Ar=Ph, R=Et
13 : Ar=Thi, R=Et

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

Chart 6

The stereochemistries of all the methobromides assigned above were confirmed to be correct by their ^{13}C-NMR spectra. As shown in Table I, the N^+-methyl groups of the *trans*-methobromides appeared at higher field (40.5—41.0 ppm) than those of the *cis*-methobromides (48.0—53.0 ppm). These observations are compatible with the data for indolizidine methiodides (**31**, see Table I) and N-methyl diarylmethylenequinolizidinium bromides (the N^+-methyl signals of the *trans* form appeared at 37.5—39.5 ppm and those of the *cis* form at 50.0—51.5 ppm).[4] The difference in the chemical shifts of the N^+-methyl groups between the *trans* (**6a** and **7a**) and the corresponding *cis* (**6b** and **7b**) compounds was *ca.* 7—8 ppm, and

Table I. ^{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*
 **31**		3.06[a] (2.82[b])	3.43[a] (3.12[b])	39.18[a]	47.64[a] (49.51[c])	1 : 1
	Ph	3.03	3.61	40.76	48.24	1 : 1
	Thi	3.04	3.64	40.70	48.50	1 : 1.5
	Ph	—	3.51	—	52.60	0 : 1
	Thi	—	3.45	—	53.05	0 : 1

a) Measured with a mixture of *trans*- and *cis*-methiodides in a 1 : 1 ratio.
b) In D_2O.[10]
c) In D_2O (using dioxane as an internal standard).

this value is smaller than that observed in N-methyl 2- and 3-diarylmethylenequinolizidinium bromides (*ca.* 11—13 ppm).

The quaternization ratio of the *cis*- and *trans*-methobromides from 2-diarylmethyleneindolizidines (**23** and **24**) was similar to that from indolizidine, indicating that the 2-diarylmethylene group had no significant effect on the quaternization ratio.

Pharmacology

N-Alkyl 2- and 1-diarylmethyleneindolizidinium bromides (**6**—**13**) prepared in this study were tested for anticholinergic activity by the Magnus method using isolated guinea pig ileum. The results are shown in Table II.

Table II. Anticholinergic Activities of the Synthesized Compounds

Compd.	Anti-Ach[a] ED_{50}(g/ml)	Relative potency (atropine = 1)	Compd.	Anti-Ach[a] ED_{50}(g/ml)	Relative potency (atropine = 1)
6a	6.7×10^{-8}	0.16	**7a**	4.9×10^{-8}	0.31
6b	3.3×10^{-8}	0.33	**7b**	4.3×10^{-8}	0.35
8	1.0×10^{-7}	0.15	**9**	5.4×10^{-8}	0.11
10	7.5×10^{-8}	0.09	**11**	1.1×10^{-7}	0.10
12	1.4×10^{-7}	0.05	**13**	4.9×10^{-7}	0.02
14	1.8×10^{-8}	0.34			
15		0.02[5]			

a) Protective activity against the action of acetylcholine (1×10^{-7} g/ml) on isolated guinea pig ileum.

Among the compounds tested, the activities of **6b**, **7a** and **7b** were equal to that of **14**, and about one-third of that of atropine. The pA_2 values of **7a**, **7b** and atropine were 8.39, 8.36 and 8.92, respectively, and these compounds antagonized acetylcholine competitively.

Based on the above results, some structure-activity relationships of N-alkyl diarylmethyleneindolizidinium bromides can be summarized as follows.

(1) The anticholinergic activity increased according to the substitution position of indolizidine in the order 2- >1-.

(2) No difference of activity between a thienyl group and a phenyl group was observed except in the case of the 2-diarylmethyleneindolizidine *trans*-methobromides (**6a** and **7a**).

(3) Among the substituents on the quaternary nitrogen atom, a methyl group was more effective than an ethyl group.

(4) In the 2-diphenylmethyleneindolizidine methobromides, the activity of the *cis* form was twice that of the *trans* form, while in the 2-dithienylmethyleneindolizidine methobromides, that of the *trans* form was equal to that of the *cis* form.

The N-alkyl diarylmethyleneindolizidinium bromides were also found to have more potent effects than **15**. The potent anticholinergic activities of the indolizidine derivatives compared to **15** might be due to the rigidity of their conformations compared to that of **15**. These pharmacological data suggest that the methyl group of **14** plays an effective role in fixing the conformation of the pyrrolidine ring.[5]

Investigations of the synthesis and structure-activity relationships of other bicyclic hetero ring systems are in progress.

Experimental[11]

3-(2-Chloromethylpiperidin-1-yl)propionitrile (18)——A mixture of 2-piperidinemethanol (**16**, 20.0 g) and acrylonitrile (12.0 g) was heated at 70—80° for 1 hr, then the excess acrylonitrile was evaporated off *in vacuo*. The residue (**17**) was dissolved in $CHCl_3$ (30 ml) and $SOCl_2$ (21.0 g) was added dropwise. After refluxing for 2 hr, the solvent was evaporated off *in vacuo*. The residue was made alkaline with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was distilled to give **18** (26.5 g, 82%) as a colorless oil, bp 129—130° (2 mmHg). IR ν_{max}^{liq} cm^{-1}: 2250 (CN). MS *m/e*: 186, 188 (3: 1, M^+).

Cyclization of 18 (Formation of *cis*(2*H*,8a*H*)-2-Cyanoindolizidine (19a) and *trans*(2*H*,8a*H*)-2-Cyanoindolizidine (19b))——Compound **18** (3.73 g) was added dropwise to a suspension of 50% NaH (1.92 g) or *tert*-BuOK (4.48 g) in DMF (30 ml) with stirring. The reaction 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 residue was distilled to give **19** in 61%[12] or 68% yield as a colorless oil, bp 91—95° (3 mmHg). The product (**19**) showed two peaks on GC (column temperature, 130°, t_R (retention time): 1.00 (**19b**) and 1.41 min (**19a**)) in a 1: 1 ratio. GC–MS of both fractions: *m/e*: 150 (M^+).

The product (**19**, 4.00 g) was chromatographed on a silica gel column using ether as an eluent. The first fraction gave **19a** (1.85 g) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2800, 2760, 2730 (Bohlmann bands), 2240 (CN). MS *m/e*: 150 (M^+). The picrate: yellow prisms, mp 189—192° (MeOH). *Anal.* Calcd for $C_{15}H_{17}N_5O_7$: C, 47.50; H, 4.52; N, 18.46. Found: C, 47.49; H, 4.45; N, 18.17.

The second fraction gave **19b** (1.70 g) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2800, 2760, 2730 (Bohlmann bands), 2230 (CN). MS *m/e*: 150 (M^+). The picrate: yellow prisms, mp 215—218° (MeOH). *Anal.* Calcd for $C_{15}H_{17}N_5O_7$: C, 47.50; H, 4.52; N, 18.46. Found: C, 47.53; H, 4.42; N, 18.21.

***cis*(2*H*,8a*H*)-2-Ethoxycarbonylindolizidine (20a) and *trans*(2*H*,8a*H*)-2-Ethoxycarbonylindolizidine (20b)**——1) From **19a**: A solution of **19a** (1.85 g) in abs. EtOH (30 ml) was saturated with HCl gas, refluxed for 0.5 hr, then concentrated *in vacuo*. The residue was made alkaline with aq. K_2CO_3 and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was distilled to give **20a** (1.64 g, 68%) as a colorless oil, bp 118—120° (7 mmHg). The product (**20a**) showed one peak on

11) 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. ^{1}H-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 at 25.05 MHz, 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, m=multiplet, q=quartet, s=singlet, t=triplet.

12) A much higher yield (77%) was obtained in a large-scale experiment using **18** (26.2 g).

GC (column temperature, 110°, t_R=1.84 min). IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2750, 2720 (Bohlmann bands), 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS m/e: 197 (M^+). The picrate: yellow needles, mp 137—138° (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, 5.15; N, 12.95.

2) From **19b**: Compound **19b** (1.70 g) was treated by the procedure described for **20a** to give **20b** (1.02 g, 46%) as a colorless oil, bp 119—120° (7 mmHg). GC (column temperature, 110°): one peak (t_R= 1.63 min). IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2750, 2720 (Bohlmann bands), 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.14 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS m/e: 197 (M^+). The picrate: yellow needles, mp 152° (EtOH). *Anal.* Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.79; H, 5.18; N, 12.86.

***cis*(2*H*,8a*H*)-2-Diphenylhydroxymethylindolizidine (21a) and *trans*(2*H*,8a*H*)-2-Diphenylhydroxymethylindolizidine (21b)——1)** From **20a**: A solution of **20a** (1.07 g) in abs. ether (5 ml) was added dropwise to a stirred solution of PhLi in abs. ether (10 ml) (prepared from Li (0.23 g) and PhBr (2.56 g)) with cooling. The reaction mixture was refluxed for 1 hr, 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 **21a** (1.46 g, 88%). Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless needles, mp 132—134°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3250 (bonded OH), 2800, 2740, 2720 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 5.94 (1H, br, OH, disappeared on addition of D_2O), 7.03—7.70 (10H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$) δ: 149.05, 147.68, 128.01, 127.92, 126.06, 125.92, 80.38, 64.72, 57.59, 52.32, 42.80 (C_2), 32.90, 30.94, 25.53, 24.50. *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81 87; H, 8.06; N, 4.33.

2) From **20b**: Compound **20b** (1.10 g) in abs. ether (5 ml) was treated with a solution of PhLi in abs. ether (10 ml) (prepared from Li (0.24 g) and PhBr (2.63 g)) by the procedure described for **21a** to give **21b** (1.42 g, 83%). Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless needles, mp 136—138°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3630 (free OH), 3300 (bonded OH), 2780, 2740, 2710 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 2.88 (1H, s, OH, disappeared on addition of D_2O), 7.07—7.62 (10H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$) δ: 147.29, 147.15, 128.26, 128.07, 126.65, 126.41, 126.02, 125.53, 79.41, 63.94, 55.83, 52.32; 43.83 (C_2), 34.07, 30.89, 24.74, 24.50. *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.91; H, 8.23; N, 4.44.

***cis*(2*H*,8a*H*)-2-(Di-2-thienylhydroxymethyl)indolizidine (22a) and *trans*(2*H*,8a*H*)-2-(Di-2-thienylhydroxymethyl)indolizidine (22b)——1)** From **20a**: A solution of **20a** (1.50 g) in abs. ether (10 ml) was added dropwise to a solution of ThiMgBr in abs. ether (40 ml) (prepared from Mg (0.55 g) and ThiBr (3.72 g)) with cooling. The reaction mixture was refluxed for 1 hr, then decomposed by addition of sat. aq. NH_4Cl. 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 **22a** (2.40 g, 99%). Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless needles, mp 130—131°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3250 (bonded OH), 2810, 2750, 2730 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 6.43—6.50 (1H, br, OH, disappeared on addition of D_2O), 6.77—7.20 (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, 63.61; H, 6.65; N, 4.13.

2) From **20b**: Compound **20b** (1.50 g) in abs. ether (10 ml) was treated with a solution of ThiMgBr in abs. ether (40 ml) (prepared from Mg (0.55 g) and ThiBr (2.23 g)) by the procedure described for **22a** to give **22b** (2.23 g, 92%), which was recrystallized from $(iso\text{-}Pr)_2O$ to give colorless needles, mp 101—102°. IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3610 (free OH), *ca.* 3200 (bonded OH), 2780, 2740, 2710 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 3.78 (1H, br, OH, disappeared on addition of D_2O), 6.78—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, 63.84; H, 6.74; N, 4.31.

2-Diphenylmethyleneindolizidine (23)——1) From **21a**: A solution of **21a** (2.00 g) in EtOH (20 ml) saturated with HCl was refluxed for 1 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 residue was recrystallized from hexane to give **23** (1.80 g, 96%) as colorless needles, mp 76—79°. IR ν_{max}^{KBr} cm^{-1}: 2780, 2750, 2720 (Bohlmann bands), 1640 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 3.08, 3.60 (2H, AB-q, J=14 Hz, C_3–H_2), 7.22 (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, 87.08; H, 8.14; N, 4.76.

2) From **21b**: A solution of **21b** (0.50 g) in EtOH (5 ml) saturated with HCl was treated by the procedure described for **23** from **21a** to give **23** (0.43 g, 91%) as colorless needles, mp 76—79° (hexane); this material was identical with that obtained from **21a** (IR and NMR spectra and mixed melting point).

2-(Di-2-thienylmethylene)indolizidine (24)——1) From **22a**: A solution of **22a** (0.50 g) in EtOH (5 ml) saturated with HCl was treated by the procedure described for **23** to give **24** (0.45 g, 95%) as a colorless oil, bp 195—197° (3 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2750, 2720 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 3.00, 3.74 (2H, AB-q, J=15 Hz, C_3–H_2), 6.76—7.36 (6H, m, aromatic protons). MS m/e: 301 (M^+). The hydrochloride: yellow prisms, mp 197—200° (dec.) (iso-PrOH). *Anal.* Calcd for $C_{17}H_{19}NS_2\cdot HCl$: C, 60.42; H, 5.97; N, 4.14. Found: C, 60.17; H, 6.12; N, 3.87.

2) From **22b**: A solution of **22b** (0.50 g) in EtOH (5 ml) saturated with HCl was treated by the procedure described for **23** to give **24** (0.47 g, 98%) as a colorless oil, bp 195—197° (3 mmHg). The hydrochloride: yellow prisms, mp 197—200° (dec.) (iso-PrOH); this material was identical with that obtained from **22a**, judging from the IR and NMR spectra.

2-Diphenylmethylene-4-methyl-*trans*-indolizidinium Bromide (6a) and 2-Diphenylmethylene-4-methyl-*cis*-indolizidinium Bromide (6b)——A solution of **23** (5.78 g) and MeBr (10 ml) in MeOH (50 ml) was kept standing at room temperature for 36 hr then concentrated *in vacuo*, and the residue was washed with ether to give a mixture of **6a** and **6b** (6.97 g, 91%) in a 1:1 ratio. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (3/2H, s, N^+–CH_3), 3.53 (3/2H, s, N^+-CH_3).

The mixture was washed with acetone (50 ml) and recrystallized twice from MeOH–ether to give **6a** (2.56 g) as colorless prisms, mp 259—262°. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (3H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 40.76 (N^+-CH_3). *Anal.* Calcd for $C_{22}H_{26}BrN$: C, 68.75; H, 6.82; N, 3.64. Found: C, 68.62; H, 6.82; N, 3.43.

The acetone washing was concentrated *in vacuo* and the residue was recrystallized three times from acetone to give **6b** (0.66 g) as colorless crystals, mp 221—224°. ^{1}H-NMR ($CDCl_3$) δ: 3.53 (N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 48.24 (N^+-CH_3). *Anal.* Calcd for $C_{22}H_{26}BrN$: C, 68.75; H, 6.82; N, 3.64. Found: C, 68.54; H, 6.68; N, 3.48.

2-(Di-2-thienylmethylene)-4-methyl-*trans*-indolizidinium Bromide (7a) and 2-(Di-2-thienylmethylene)-4-methyl-*cis*-indolizidinium Bromide (7b)——A solution of **24** (4.23 g) and MeBr (7 ml) in MeOH (35 ml) was treated by the procedure described for **6** to give a mixture of **7a** and **7b** (5.51 g, 99%) in a 1:1.5 ratio. ^{1}H-NMR ($CDCl_3$) δ: 3.04 (6/5H, s, N^+–CH_3), 3.55 (9/5H, s, N^+-CH_3).

The mixture was recrystallized twice from MeOH–acetone to give **7b** (1.49 g) as colorless prisms, mp 213—215°. ^{1}H-NMR ($CDCl_3$) δ: 3.55 (3H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 48.50 (N^+-CH_3). *Anal.* Calcd for $C_{18}H_{22}BrNS_2$: C, 54.54; H, 5.59; N, 3.53. Found: C, 54.45; H, 5.62; N, 3.44.

The mother liquor was evaporated to dryness *in vacuo* and the residue was recrystallized twice from MeOH–acetone to give **7a** (0.10 g) as colorless crystals, mp 205—206°. ^{1}H-NMR ($CDCl_3$) δ: 3.04 (3H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 40.70 (N^+-CH_3). *Anal.* Calcd for $C_{18}H_{22}BrNS_2$: C, 54.54; H, 5.59; N, 3.53. Found: C, 54.28; H, 5.72; N, 3.34.

2-Diphenylmethylene-4-ethylindolizidinium Bromide (8)——A solution of **23** (0.50 g) and EtBr (5 ml) was kept standing at 50—60° for 36 hr then concentrated *in vacuo*, and the residue was washed with ether to give **8** (0.64 g, 93%) as colorless crystals, mp 123—127°.

2-(Di-2-thienylmethylene)-4-ethylindolizidinium Bromide (9)——A solution of **24** (0.50 g) and EtBr (6 ml) in acetone (20 ml) was kept standing at 50° for 24 hr then concentrated *in vacuo*, and the residue was washed with acetone to give **9** (0.56 g, 83%) as yellow prisms, mp 212—214° (iso-PrOH–acetone). *Anal.* Calcd for $C_{19}H_{24}BrNS_2$: C, 55.60; H, 5.89; N, 3.41. Found: C, 55.33; H, 5.91; N, 3.16.

***cis*(1*H*,8a*H*)-1-Ethoxycarbonylindolizidine (26a) and *trans*(1*H*,8a*H*)-1-Ethoxycarbonylindolizidine (26b)**——A solution of 1-ethoxycarbonyl-5,6,7,8-tetrahydroindolizine (**25**,[10] 24.4 g) in EtOH (200 ml) was hydrogenated over 5% Pd-C catalyst (25 g) at 90 kg/cm^2 and 80° for 9 hr. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether and shaken with 10% HCl. The aq. layer 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 distilled to give **26** (10.1 g, 41%), as a colorless oil, bp 88—90° (3 mmHg). IR ν_{max}^{liq} cm^{-1}: 2780, 2720 (Bohlmann bands), 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). The product (**26**) showed two peaks on GC (column temperature, 110°, t_R=1.33 (**26b**), 1.80 min (**26a**)) in a 3:2 ratio. GC–MS of both fractions: *m/e* 197 (M^+). The starting material (**25**, 6.1 g, 25%) was recovered from the ether layer on 10% HCl extraction. The mixture **26** (3.00 g) was chromatographed on a silica gel column using $CHCl_3$–MeOH (95:5, v/v) as an eluent. The first fraction gave **26a** (0.43 g) as a colorless oil. GC: one peak (t_R=1.80 min). IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2720 (Bohlmann bands), 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, OCH_2-$C\underline{H}_3$), 4.14 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e*: 197 (M^+). The picrate: yellow needles, mp 105.5—106° (EtOH). *Anal.* Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.77; H, 5.26; N, 13.00. An attempt to isolate **26b** was unsuccessful.

***cis*(1*H*,8a*H*)-1-Diphenylhydroxymethylindolizidine (27a) and *trans*(1*H*,8a*H*)-1-Diphenylhydroxymethylindolizidine (27b)**——1) A solution of **26** (2.00 g) in abs. ether (10 ml) was added dropwise to a stirred solution of PhLi in abs. ether (30 ml) (prepared from Li (0.43 g) and PhBr (5.20 g)) with cooling. The reaction mixture was refluxed for 1 hr, 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 ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. A small amount of hexane was added to the residue and the precipitate was collected by filtration to give **27** (2.95 g, 95%), which was chromatographed on an alumina column using $CHCl_3$ as an eluent. The first fraction gave **27a** (1.14 g, 37%) as colorless prisms, mp 106—108° ((iso-Pr)$_2$O). IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3250 (bonded OH), 2800, 2740, 2720 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 6.60 (1H, br, OH, disappeared on addition of D_2O), 6.99—7.79 (10H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$) δ: 149.78, 149.64, 127.92, 127.77, 125.58, 125.43, 125.28,

125.14, 79.85, 67.45, 54.13, 53.74, 46.41 (C_1), 29.48, 25.18, 25.09, 24.70. MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.18; H, 8.26; N, 4.44.

The second fraction gave **27b** (0.88 g, 28%) as colorless needles, mp 128—129° ((iso-pr)$_2$O). IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3640 (free OH), *ca.* 3250 (bonded OH), 2790, 2730 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 4.70 (1H, s, OH, disappeared on addition of D_2O), 7.04—7.62 (10H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$) δ: 147.98, 147.68, 128.07, 127.87, 126.26, 125.97, 125.67, 79.85, 63.40, 49.88, 49.68, 51.15 (C_1), 27.62, 25.53, 24.45, 21.33. MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.85; H, 8.20; N, 4.61.

2) From **26a**: Compound **26a** (0.20 g) was treated with a solution of PhLi in abs. ether (5 ml) (prepared from Li (43 mg) and PhBr (0.52 g)) by the procedure described for **27** to give **27a** (0.24 g, 77%), which was identical with **27a** obtained in 1) on the basis of IR and NMR spectral comparison and mixed melting point determination.

***cis*(1*H*,8a*H*)-1-(Di-2-thienylhydroxymethyl)indolizidine (28a) and *trans*(1*H*,8a*H*)-1-(Di-2-thienylhydroxymethyl)indolizidine (28b)**——A solution of **26** (2.00 g) in abs. ether (10 ml) was added dropwise to a stirred solution of ThiMgBr in abs. ether (40 ml) (prepared from Mg (0.74 g) and ThiBr (5.00 g)) with cooling. The reaction mixture was refluxed for 1 hr, then decomposed by addition of sat. aq. NH_4Cl. 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 ether. The extract was washed with H_2O, dried, and concentrated *in vacuo* to give **28** (3.12 g, 96%) as a brownish oil, which was chromatographed on a silica gel column using ether and ether–MeOH (95: 5, v/v) as eluents. The fraction eluted with ether gave **28a** (1.04 g, 32%) as colorless plates, mp 116.5—118° ((iso-Pr)$_2$O). IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3200 (bonded OH), 2800, 2740, 2720 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 6.78—7.18 (6H, m, aromatic protons), 7.60 (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, 63.77; H, 6.48; N, 4.42.

The fraction eluted with ether–MeOH gave **28b** (1.10 g, 34%) as colorless prisms, mp 144—145.5° (MeOH-(iso-Pr)$_2$O). IR $\nu_{max}^{CCl_4}$ cm^{-1} (5×10^{-3} M solution): 3600 (free OH), *ca.* 3200 (bonded OH), 2790, 2710 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 6.00 (1H, br, OH, disappeared on addition of D_2O), 6.81—7.28 (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, 63.59; H, 6.63; N, 4.42.

1-Diphenylmethyleneindolizidine (29)——1) From **27a**: A solution of **27a** (0.50 g) in EtOH (5 ml) saturated with HCl was treated by the procedure described for **23** to give **29** (0.39 g, 83%) as a pale yellow oil, bp 160—161° (1.5 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2780, 2720 (Bohlmann bands), 1635 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 7.22 (10H, s, aromatic protons). MS *m/e*: 289 (M^+). High resolution MS: Calcd for $C_{21}H_{23}N$: 289.1829. Found: 289.1818.

2) From **27b**: A solution of **27b** (0.50 g) in EtOH (5 ml) saturated with HCl was treated by the procedure described for **23** to give **29** (0.41 g, 87%) as a pale yellow oil, bp 160—161° (1.5 mmHg); this was identical with the oil obtained from **27a** (IR and NMR spectra).

1-(Di-2-thienylmethylene)indolizidine (30)——1) From **28a**: A solution of **28a** (0.50 g) in EtOH (5 ml) saturated with HCl was treated by the procedure described for **23** to give **30** (0.41 g, 87%) as yellow plates, mp 80.5—81.5° ((iso-Pr)$_2$O). IR ν_{max}^{KBr} cm^{-1}: 2810, 2790, 2740 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 6.75—7.06 (4H, m, aromatic protons), 7.13—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, 67.64; H, 6.26; N, 4.61.

2) From **28b**: A solution of **28b** (0.50 g) in EtOH (5 ml) saturated with HCl was treated by the procedure described for **23** to give **30** (0.42 g, 89%) as yellow plates, mp 80.5—81.5° ((iso-Pr)$_2$O); this material was identical with that obtained from **28a** (IR and NMR spectra and mixed melting point).

1-Diphenylmethylene-4-methyl-*cis*-indolizidinium Bromide (10)——A solution of **29** (0.50 g) and MeBr (2 ml) in acetone (10 ml) was kept standing at room temperature for 0.5 hr then concentrated *in vacuo*, and the residue was washed with a small amount of acetone to give **10** (0.50 g, 82%). ^{1}H-NMR ($CDCl_3$) δ: 3.51 (N^+-CH_3). Recrystallization from EtOH–acetone gave colorless plates, mp 210—211°. ^{13}C-NMR ($CDCl_3$) δ: 52.60 (N^+-CH_3). *Anal.* Calcd for $C_{22}H_{26}BrN$: C, 68.75; H, 6.82; N, 3.64. Found: C, 68.56; H, 6.85; N, 3.51.

1-(Di-2-thienylmethylene)-4-methyl-*cis*-indolizidinium Bromide (11)——A solution of **30** (3.10 g) and MeBr (5 ml) in acetone (30 ml) was treated by the procedure described for **10** to give **11** (4.00 g, 98%). ^{1}H-NMR ($CDCl_3$) δ: 3.45 (N^+-CH_3). Recrystallization from EtOH–acetone gave colorless plates, mp 286—287°. ^{13}C-NMR ($CDCl_3$) δ: 53.05 (N^+-CH_3). *Anal.* Calcd for $C_{18}H_{22}BrNS_2$: C, 54.54; H, 5.59; N, 3.53. Found: C, 54.45; H, 5.63; N, 3.59.

1-Diphenylmethylene-4-ethyl-*cis*-indolizidinium Bromide (12)——A solution of **29** (0.50 g) and EtBr (5 ml) in acetone (10 ml) was kept standing for 15 hr then concentrated *in vacuo*, and the residue was washed with a small amount of acetone to give **12** (0.29 g, 42%). Recrystallization from EtOH–acetone gave colorless plates, mp 163—164°. *Anal.* Calcd for $C_{23}H_{28}BrN\cdot1/5H_2O$: C, 68.72; H, 7.12; N, 3.48. Found: C, 68.83; H, 7.24; N, 3.26.

1-(Di-2-thienylmethylene)-4-ethyl-*cis*-indolizidinium Bromide (13)——A solution of **30** (1.90 g) and EtBr (10 ml) in acetone (30 ml) was treated by the procedure described for **12** to give **13** (2.30 g, 89%).

Recrystallization from EtOH–acetone gave colorless plates, mp 252—253°. *Anal.* Calcd for $C_{19}H_{24}BrNS_2$: C, 55.60; H, 5.89; N, 3.41. Found: C, 55.54; H, 5.85; N, 3.43.

4-Methylindolizidinium Iodide (31)——4-Methylindolizidinium iodide was obtained as a mixture of the *trans*- and the *cis*-methiodide in a 1:1 ratio by the method of Meyer *et al.*[10] ^{1}H-NMR ($CDCl_3$) δ: 3.06 (3/2H, s, N^+-CH_3), 3.43 (3/2H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 39.18 (N^+-CH_3), 47.64 (N^+-CH_3).

The mixture was recrystallized four times from acetone to give the *cis*-methiodide as colorless needles, mp>300° (lit.[10] mp 333—334°). ^{1}H-NMR ($CDCl_3$) δ: 3.43 (3H, s, N^+-CH_3). ^{13}C-NMR (D_2O) δ: 49.51 N^+-CH_3).

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