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Preparation of New Nitrogen-Bridged Heterocycles. XXXI.[1] Cyclization Aptitudes of 2-Acylmethylthio-3-cyanoindolizines Having a Cyano or an Ester Group at the 1-Position

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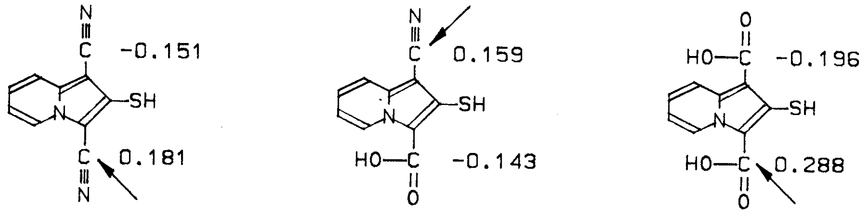
Some 2-acylmethylthio-3-cyanoindolizine derivatives having a cyano or an ethoxycarbonyl group at the 1-position were prepared and their intramolecular cyclization reactions were examined. The alkaline treatment of these polyfunctionalized indolizines in refluxing ethanol gave only 3-aminothieno[2,3-*b*]indolizine derivatives in moderate to good yields regardless of the kind of 1-substituent, and the other possible alternative, a thieno[3,2-*a*]indolizine derivative, could not be obtained at all. The higher reactivity of the 3-cyano group over 1-cyano and 1-ethoxycarbonyl groups coincided well with the results expected from molecular orbital calculations for the model compounds. From our present and previous results, the order (3-CN > 1-CN > 3-ester > 1-ester) of the reactivities of electron-withdrawing groups at the 1- and 3-positions on the indolizine ring was finally established.

Keywords indolizine; 3-cyanoindolizine; thieno[2,3-*b*]indolizine; fused indolizine; cyclization aptitude

Previously, we found smooth and effective transformations of 2-(acylmethylthio)indolizines bearing electron-withdrawing groups at the 1- and 3-positions to the corresponding thieno[3,2-*a*]- and thieno[2,3-*b*]indolizines, and showed that these cyclization modes were readily understandable by a consideration of the electronic and substituent effects of these molecules.[2] The molecular orbital calculations (Pariser, Parr, and Pople (PPP) method)[3] of three model compounds for such polyfunctionalized indolizines showed that the order of electrophilicity of their substituents is 3-CN > 1-CN > 3-COOH > 1-COOH (see Fig. 1). Of these reactivities, the order of 1-CN > 3-COOH > 1-COOH has been experimentally confirmed so far.[2] However, the reactivity of the 3-cyano group is still not established. In this paper, we wish to report the preparation of 2-acylmethylthio-3-cyanoindolizine derivatives possessing the 1-cyano or 1-ethoxycarbonyl group and their cyclization aptitudes under alkaline conditions.

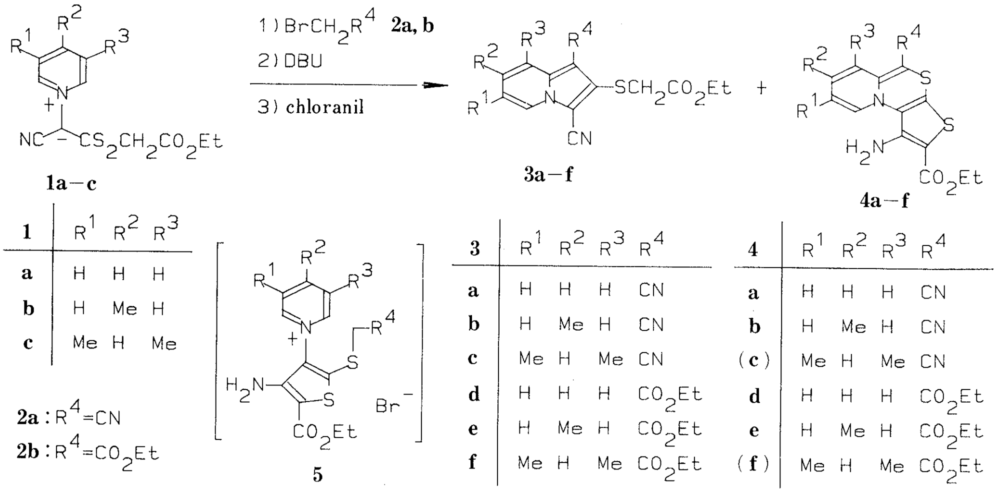
Results and Discussion

Preparations and Reactions of 2-Acylmethylthio-3-cyanoindolizine Derivatives These functionalized 3-cyanoindolizines were synthesized by the use of two procedures reported previously by us[2]: 1,3-indolizinedicarbonitriles **3a**—**c** and ethyl 3-cyano-1-indolizinecarboxylates **3d**—**f** bearing an ethoxycarbonylmethylthio group at the 2-position were synthesized directly from pyridinium 1-(cyano)[(ethoxycarbonylmethylthio)thiocarbonyl]methylides **1a**—**c** (Chart 1). In addition to the expected products **3a**—**f**, ethyl 1-aminopyrido[2,1-*c*]thieno[3,2-*e*][1,4]thia-



A ($E_{\mathrm{LUMO}}=-2.04$) B ($E_{\mathrm{LUMO}}=-2.21$) C ($E_{\mathrm{LUMO}}=-2.34$)

Fig. 1



1	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	Me	H	Me

2a: R^4=CN
2b: R^4=CO_2Et

3	R^1	R^2	R^3	R^4
a	H	H	H	CN
b	H	Me	H	CN
c	Me	H	Me	CN
d	H	H	H	CO_2Et
e	H	Me	H	CO_2Et
f	Me	H	Me	CO_2Et

4	R^1	R^2	R^3	R^4
a	H	H	H	CN
b	H	Me	H	CN
(c)	Me	H	Me	CN
d	H	H	H	CO_2Et
e	H	Me	H	CO_2Et
(f)	Me	H	Me	CO_2Et

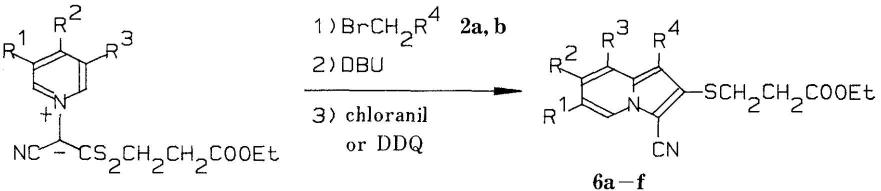
Chart 1

zine-2-carboxylate derivatives **4a, b, d, e** were also obtained in the reactions of the ylides **1a, b**. Mechanistically, the formation of compounds **4a, b, d, e** can be explained in terms of reaction intermediates such as 1-(3-thienyl)pyridinium bromides (**5**), based on our recent results.[4)]

On the other hand, other 2-acylmethylthio-3-cyanoindolizine derivatives were synthesized as follows. Thus, the syntheses of *S*-protected indolizines, 2-(2-ethoxycarbonylethylthio)indolizines **6a—f**, were carried out using pyridinium 1-(cyano)[(2-ethoxycarbonylethylthio)thiocarbonyl]methylides **1d—f** followed by deprotection, and then *S*-alkylation of the resulting 2-indolizinethiols with halides **7a—c**. Through these reactions, only functionalized indolizines **3i, l, o, r, s, u, v, x** were obtained, but interestingly, indolizines **3g, h, j, k, m, n, p, q, t, w** could not be obtained and 3-aminothieno[2,3-*b*]indolizines **8g, h, j, k, m, n, p, q, t, w** were formed in moderate to good yields (Charts 2 and 3).

Indolizines **3a—f, i, l, o, r, s, u, v, x** thus obtained were smoothly converted in good yields to the corresponding 3-aminothieno[2,3-*b*]indolizine derivatives **8a—f, i, l, o, r, s, u, v, x** on heating in ethanol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and formation of 9-cyanothieno[3,2-*a*]indolizine derivatives **9** could not be detected at all (Chart 4).

Structural Elucidation The structures of these functionalized indolizines **3a—f, i, l, o, r, s, u, v, x** and *S*-protected indolizines **6a—f** were determined by elementary analyses, and proton nuclear magnetic resonance (^{1}H-NMR) (Table I) and infrared (IR) spectral inspections and by spectral comparisons with known indolizine derivatives.[2,5)] The structures of pyrido[2,1-*c*]thieno[3,2-*e*][1,4]thiazines **4a, b, d, e** were deduced by the comparison of their physical and spectral data with those of authentic compounds whose structures were recently proved by single-crystal X-ray structural analysis.[4)] On the other

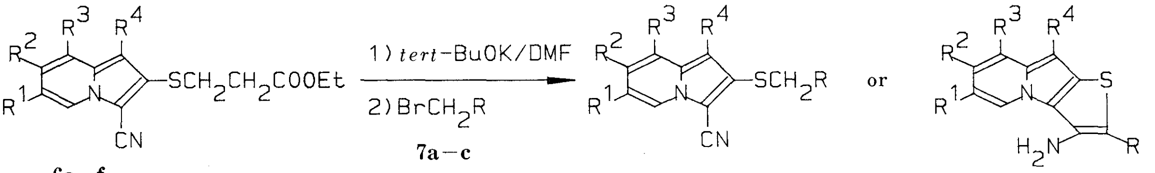


1d–f **6a–f**

1	R^1	R^2	R^3
d	H	H	H
e	H	Me	H
f	Me	H	Me

6	R^1	R^2	R^3	R^4
a	H	H	H	CN
b	H	Me	H	CN
c	Me	H	Me	CN
d	H	H	H	CO$_2$Et
e	H	Me	H	CO$_2$Et
f	Me	H	Me	CO$_2$Et

Chart 2



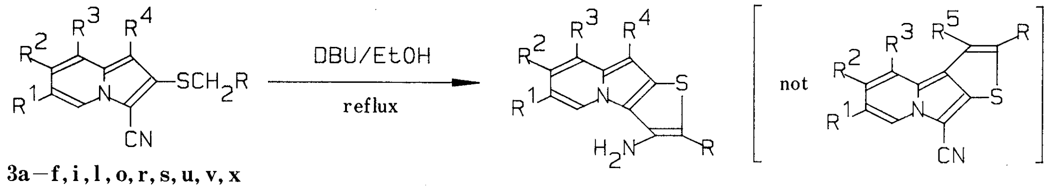
6a–f **3i, l, o, r, s, u, v, x** **8g, h, j, k, m, n, p, q, t, w**

7	R
a	Ac
b	COPh
c	COC$_6$H$_4$Cl-*p*

3, 8	R^1	R^2	R^3	R^4	R
g	H	H	H	CN	Ac
h	H	Me	H	CN	Ac
i	Me	H	Me	CN	Ac
j	H	H	H	CN	COPh
k	H	Me	H	CN	COPh
l	Me	H	Me	CN	COPh
m	H	H	H	CN	COC$_6$H$_4$Cl-*p*
n	H	Me	H	CN	COC$_6$H$_4$Cl-*p*
o	Me	H	Me	CN	COC$_6$H$_4$Cl-*p*

3, 8	R^1	R^2	R^3	R^4	R
p	H	H	H	CO$_2$Et	Ac
q	H	Me	H	CO$_2$Et	Ac
r	Me	H	Me	CO$_2$Et	Ac
s	H	H	H	CO$_2$Et	COPh
t	H	Me	H	CO$_2$Et	COPh
u	Me	H	Me	CO$_2$Et	COPh
v	H	H	H	CO$_2$Et	COC$_6$H$_4$Cl-*p*
w	H	Me	H	CO$_2$Et	COC$_6$H$_4$Cl-*p*
x	Me	H	Me	CO$_2$Et	COC$_6$H$_4$Cl-*p*

Chart 3



3a—f, i, l, o, r, s, u, v, x

8a—f, i, l, o, r, s, u, v, x

9 (R^5=NH_2 or OH)

3, 8	R^1	R^2	R^3	R^4	R
a	H	H	H	CN	CO_2Et
b	H	Me	Me	CN	CO_2Et
c	Me	H	Me	CN	CO_2Et
d	H	H	H	CO_2Et	CO_2Et
e	H	Me	H	CO_2Et	CO_2Et
f	Me	H	Me	CO_2Et	CO_2Et
i	Me	H	Me	CN	Ac
l	Me	H	Me	CN	COPh
o	Me	H	Me	CN	COC_6H_4Cl-*p*
r	Me	H	Me	CO_2Et	Ac
s	H	H	H	CO_2Et	COPh
u	Me	H	Me	CO_2Et	COPh
v	H	H	H	CO_2Et	COC_6H_4Cl-*p*
x	Me	H	Me	CO_2Et	COC_6H_4Cl-*p*

Chart 4

TABLE I. ^{1}H-NMR Spectral Data for Indolizines

Compd. No.[a]	C-5	C-6	C-7	C-8	R^4	$(CH_2)_{1 \text{ or } 2}$	R
3a	8.37 br d	7.14 dt	7.43 br t	7.78 br d	—	3.84 s	1.26 t, 4.21 q
3b	8.23 d	6.97 dd	2.46 s	7.51 br s	—	3.79 s	1.23 t, 4.19 q
3c	8.03 br s	2.37 s	7.02 br s	2.73 s	—	3.78 s	1.27 t, 4.22 q
3d	8.28 br d	7.02 dt	7.33 br t	8.26 br d	1.42 t, 4.42 q	3.94 s	1.22 t, 4.17 q
3e	8.18 d	6.88 dd	2.47 s	8.09 br s	1.47 t, 4.43 q	3.96 s	1.24 t, 4.20 q
3f	8.00 br s	2.33 s	6.92 br s	2.53 s	1.44 t, 4.46 q	3.81 s	1.26 t, 4.21 q
3i	7.98 br s	2.39 s	6.98 br s	2.72 s	—	3.86 s	2.39 s
3l	[b]	2.34 s	6.97 br s	2.70 s	—	4.53 s	7.3—8.2 m
3o	[b]	2.36 s	6.99 br s	2.71 s	—	4.46 s	7.3—8.1 m
3r	7.95 br s	2.34 s	6.90 br s	2.51 s	1.42 t, 4.40 q	3.87 s	2.34 s
3s	8.33 br d	7.01 dt	[b]	8.33 br d	1.43 t, 4.40 q	4.70 s	7.1—8.2 m
3u	[b]	2.35 s	6.90 br s	2.55 s	1.40 t, 4.37 q	4.54 s	7.3—8.2 m
3v	8.25 br d	6.98 dt	[b]	8.25 br d	1.38 t, 4.37 q	4.61 s	7.1—8.0 m
3x	[b]	2.26 s	6.84 br s	2.45 s	1.33 t, 4.31 q	4.40 s	7.1—8.0 m
6a	8.35 br d	6.9—7.6 m		7.75 br d	—	2.67 br t, 3.40 br t	1.28 t, 4.16 q
6b	8.25 d	6.91 dd	2.46 s	7.49 br s	—	2.65 br t, 3.37 br t	1.27 t, 4.16 q
6c	8.00 br s	2.37 s	7.00 br s	2.71 s	—	2.66 br t, 3.35 br t	1.28 t, 4.16 q
6d	8.37 br d	7.02 dt	7.37 br t	8.36 br d	1.42 t, 4.35 q	2.56 br t, 3.36 br t	1.23 t, 4.08 q
6e	8.17 d	6.88 dd	2.43 s	8.10 br s	1.46 t, 4.39 q	2.66 br t, 3.42 br t	1.27 t, 4.12 q
6f	7.96 br s	2.30 s	6.90 br s	2.49 s	1.43 t, 4.40 q	2.59 br t, 3.26 br t	1.25 t, 4.12 q

a) The coupling constants were as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, and $J_{\mathrm{Et}}=7.0$ Hz. *b*) Overlapped with the phenyl proton signals.

TABLE II. ^{1}H-NMR Spectral Data for Thienoindolizines

Compd. No.[a,b]	C-5	C-6	C-7	C-8	NH_2	R^4	R
8a	8.52 br d	7.02 dt	7.41 br t	7.90 br d	5.89 br s	—	1.41 t, 4.42 q
8b	8.38 d	6.84 dd	2.49 s	7.61 br s	5.88 br s	—	1.39 t, 4.45 q
8c	8.14 br s	2.36 s	6.98 br s	2.77 s	5.86 br s	—	1.43 t, 4.41 q
8d	8.35 br d	6.86 br t	7.25 br t	8.33 br d	5.81 br s	1.47 t, 4.44 q	1.40 t, 4.37 q
8e	8.15 d	6.61 dd	2.41 s	8.02 br s	5.77 br s	1.46 t, 4.42 q	1.41 t, 4.35 q
8f	7.92 br s	2.26 s	6.78 br s	2.76 s	5.83 br s	1.46 t, 4.37 q	1.40 t, 4.37 q

a) The coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=2.0$, and $J_{\mathrm{Et}}=7.0$ Hz. *b*) The NMR spectra of compounds **8g—x** could not be measured because of the low solubilities.

hand, the structures of the ethyl 2-acyl-3-aminothieno[2,3-*b*]indolizine derivatives **8d—f, p—x** could be readily determined by observing the disapperarance of the 3-cyano absorption band and the appearance of new primary amino absorption bands in the range of 3258—3470 cm^{-1} in their IR spectra (see Table IV). However, the structures

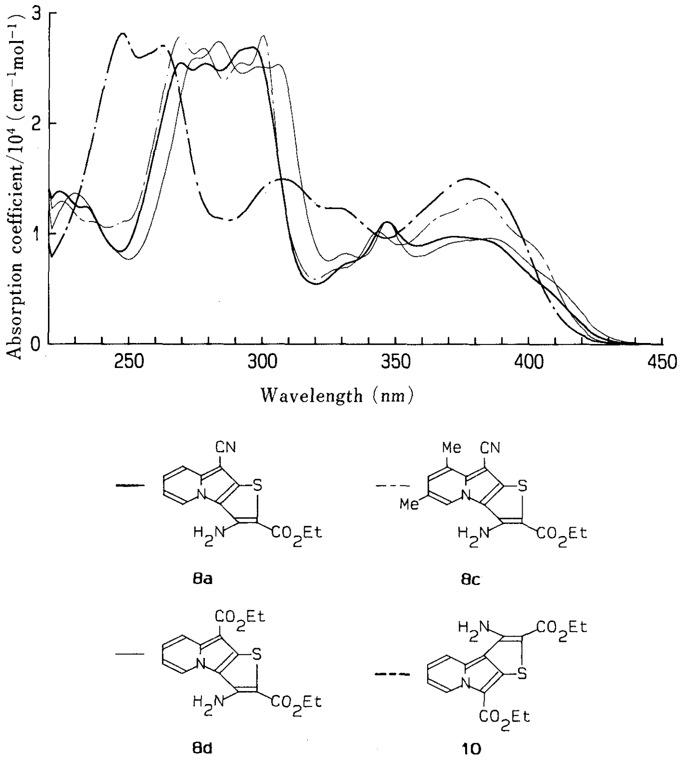


Fig. 2. UV Spectra of Thienoindolizines in Ethanol

of the 2-acyl-3-aminothieno[2,3-*b*]indolizine-9-carbonitriles **8a**—**c**, **g**—**o** could not be deduced only from their physical and spectral data (Table II), since they have one more cyano group in the molecule and this situation is the same in the other possible structures, 2-acyl-3-aminothieno[3,2-*a*]indolizine-9-carbonitriles (**9**). Finally, the structures were determined by comparison of the ultraviolet (UV) spectral patterns of the products **8a**, **c** with those of authentic 3-aminothieno[2,3-*b*]indolizine **8d** and diethyl 3-aminothieno[3,2-*a*]indolizine-2,9-dicarboxylate (**10**). The UV spectra of **8a**, **c**, **d** and **10** are illustrated in Fig. 2. Apparently, the UV spectral patterns of **8a**,**c** is similar to that of **8d** in all regions but greatly different from that of **10**. The similarity in the UV spectra of **8a**, **c**, **d** strongly supported the notion that **8a**, **c** have a 3-amino-2-acylthieno[2,3-*b*]indolizine structure but not the 3-amino-2-acylthieno[3,2-*a*]indolizine structure such as **10**. From these results 2-acyl-3-aminothieno[2,3-*b*]indolizine-9-carbonitrile structures were assigned for the other products **8b**, **g**—**o**.

The preference for the 3-cyano group over the 1-cyano and 1-ethoxycarbonyl groups in these cyclization reactions coincided well with the result expected from molecular orbital calculation.[3] In conclusion, the order (3-CN> 1-CN and 1-ester) of reactivity of the substituents on the indolizine ring was determined through these cyclization reactions, and in combination with our previous results[2] the order (3-CN>1-CN>3-ketone>3-ester>1-ester) of reactivity was established.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The microanalyses were carried out on a Perkin-Elmer 2400 elemental analyzer. The ^{1}H-NMR spectra were determined with a Varian EM360A spectrometer in deuteriochloroform with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The IR and UV spectra were taken with a JASCO FT/IR-5300 infrared spectrophotometer and a Hitachi 220 spectrophotometer.

Materials Pyridinium 1-(cyano)methylides **1a**—**f** were synthesized according to the literature,[6] and some results and properties of the products are as follows: **1a**: 88%, yellow needles, mp 111—112 °C (lit.[6] mp 103 °C). **1b**: 84%, yellow needles, mp 147—149 °C. IR (KBr): 2160 (CN), 1728 (CO) cm^{-1}. *Anal.* Calcd for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52. Found: C, 52.91; H, 4.71; N, 9.52. **1c**: 79%, orange prisms, mp 131—133 °C. IR (KBr): 2171 (CN), 1721 (CO) cm^{-1}. *Anal.* Calcd for $C_{14}H_{16}N_2O_2S_2$: C, 54.52; H, 5.23; N, 9.08. Found: C, 54.54; H, 5.17; N, 9.01. **1d**: 61% orange needles, mp 146—148 °C. IR (KBr): 2175 (CN), 1706 (CO) cm^{-1}. *Anal.* Calcd for $C_{13}H_{14}N_2O_2S_2$: C, 53.04; H, 4.79; N, 9.52. Found: C, 53.13; H, 4.90; N, 9.78. **1e**: 46%, yellow needles, mp 89—91 °C. IR (KBr): 2170 (CN), 1734 (CO) cm^{-1}. *Anal.* Calcd for $C_{14}H_{16}N_2O_2S_2$: C, 54.52; H, 5.23; N, 9.08. Found: C, 54.35; H, 5.18; N, 9.11. **1f**: 52%, yellow needles, mp 120—123 °C. IR (KBr): 2170 (CN), 1732 (CO) cm^{-1}. *Anal.* Calcd for $C_{15}H_{18}N_2O_2S_2$: C, 55.87; H, 5.63; N, 8.69. Found: C, 56.09; H, 5.45; N, 8.89.

Preparation of Functionalized Indolizines General Method A: A chloroform solution (30 ml) of a pyridinium 1-(cyano)methylide **1** (3 mmol) and bromoacetonitrile or ethyl bromoacetate (**2**, 3 mmol) was kept at room temperature until the ylide **1** was no longer detectable by its thin layer chromatographic monitoring. DBU (3 mmol) was added to the resulting solution at 0 °C in an ice bath, and after 10 min, chloranil (3 mmol) was added. The resulting mixture was stirred for 4 h at that temperature. The reaction solution was then filtered to remove insoluble substances and the filtrate was concentrated under reduced pressure. The residue was separated by column chromatography on alumina using chloroform as an eluent. After evaporation of the solvent, the crude indolizine was recrystallized from ethanol.

Indolizines **3a**—**f** and **6a**—**f** were prepared by this method.

General Method B: A mixture of an *S*-protected indolizine **6** (1 mmol) and potassium *tert*-butoxide (1.5 mmol) in *N*,*N*-dimethylformamide (2 ml) was allowed to react at room temperature for 10 min. The ethyl acrylate generated was removed completely from the system using a rotatory evaporator, then a halide **7** (1.2 mmol) was added and the resulting solution was kept for 2—3 h at room temperature. Diluted hydrochloric acid and water (*ca.* 20 ml) were added and the precipitates were collected by suction. The precipitates were dissolved in chloroform and freed from water by filtration through phase-separating filter paper, then the products were separated by column chromatography on alumina using chloroform for indolizines **3** or chloroform–ethanol for thienoindolizines **8**. Recrystallizations were carried out from ethanol for **3** or chloroform for **8**.

In these reactions only indolizines **3i**, **l**, **o**, **r**, **s**, **u**, **v**, **x** were obtained, and instead of the expected **3g**, **h**, **j**, **k**, **m**, **n**, **p**, **q**, **t**, **w**, 3-aminothieno[2,3-*b*]indolizines **8g**, **h**, **j**, **k**, **m**, **n**, **p**, **q**, **t**, **w** were formed directly.

These results and some data for functionalized indolizines **3a**—**f**, **i**, **l**, **o**, **r**, **s**, **u**, **v**, **x** and **6a**—**f** and thienoindolizines **8g**, **h**, **j**, **k**, **m**, **n**, **p**, **q**, **t**, **w** are summarized in Tables I, III, and IV, respectively. Furthermore, other products **4a**, **b**, **d**, **e** were also obtained in the reactions using the pyridinium ylides **1a**,**b** in method A. Some data for these compounds are as follows: **4a**: 13%, violet prisms, mp 159—160 °C (dec). IR (KBr): 3400 and 3305 (NH$_2$), 2165 (CN), 1671 (CO) cm^{-1}. NMR (CDCl$_3$) δ: 1.36 (3H, t, J=7.0 Hz, OCH$_2$C$\underline{H}_3$), 4.32 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 5.49 (2H, br s, NH$_2$), 6.15 (1H, br t, J=7.0, 7.0 Hz, 8-H), 6.79 (1H, br t, J=7.0, 9.0 Hz, 7-H), 7.02 (1H, br d, J=9.0 Hz, 6-H), 7.55 (1H, br d, J=7.0 Hz, 9-H). *Anal.* Calcd for $C_{14}H_{11}N_3O_2S_2$: C, 52.98; H, 3.49; N, 13.24. Found: C, 53.11; H, 3.28; N, 13.32. **4b**: 11%, violet needles, mp 174—175 °C (dec.). IR (KBr): 3410 and 3315 (NH$_2$), 2160 (CN), 1670 (CO) cm^{-1}. NMR (CDCl$_3$) δ: 1.33 (3H, t, J=7.0 Hz, OCH$_2$C$\underline{H}_3$), 2.32 (3H, s, 7-Me), 4.30 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 5.48 (2H, br s, NH$_2$), 6.02 (1H, dd, J=7.0, 2.0 Hz, 8-H), 6.79 (1H, br s, 6-H), 7.50 (1H, d, J=7.0 Hz, 9-H). *Anal.* Calcd for $C_{15}H_{13}N_3O_2S_2$: C, 54.36; H, 3.95; N, 12.68. Found: C, 54.31; H, 3.67; N, 13.01. **4d**: 4%, violet prisms, mp 196—199 °C (dec.). IR (KBr): 3400 and 3310 (NH$_2$), 1669 (CO) cm^{-1}. NMR (CDCl$_3$) δ: 1.28 and 1.32 (each 3H, t, J=7.0 Hz, 2×OCH$_2$C$\underline{H}_3$), 4.19 and 4.28 (each 2H, q, J=7.0 Hz, 2×OC$\underline{H}_2$CH$_3$), 5.48 (2H, br s, NH$_2$), 6.15 (1H, dt, J=7.0, 7.0, 2.0 Hz, 8-H), 6.80 (1H, br t, J=7.0, 9.0 Hz, 7-H), 7.51 (1H, br d, J=7.0 Hz, 9-H), 8.21 (1H, br d, J=9.0 Hz, 6-H). *Anal.* Calcd for $C_{16}H_{16}N_2O_4S_2$: C, 52.73; H, 4.43; N, 7.69. Found: C, 52.56; H, 4.38; N, 7.53. **4e**: 5%, violet needles, mp 136—139 °C (dec.). IR (KBr): 3447 and 3343 (NH$_2$), 1655 (CO) cm^{-1}. NMR (CDCl$_3$) δ: 1.29 and 1.33

TABLE III. Some Data for Indolizines

Compd. No.[a]	Reactants		Yield (%)	mp (°C)	ν^{KBr} cm^{-1}	Formula	Analysis (%) Calcd			Found		
							C	H	N	C	H	N
3a[b]	**1a**	**2a**	14	156—159	2200 1726	$C_{14}H_{11}N_3O_2S$	58.93	3.49	14.73	58.74	3.80	14.50
3b[c]	**1b**	**2a**	25	157—158	2201 1726	$C_{15}H_{13}N_3O_2S$	60.19	4.38	14.04	60.10	4.40	13.96
3c	**1c**	**2a**	46	143—144	2201 1703	$C_{16}H_{15}N_3O_2S$	61.32	4.82	13.41	61.22	4.80	13.65
3d[d]	**1a**	**2b**	78	105—107	2201 1714 1684	$C_{16}H_{16}N_2O_4S$	57.82	4.85	8.43	57.55	4.76	8.32
3e[e]	**1b**	**2b**	75	95—96	2200 1726 1679	$C_{17}H_{18}N_2O_4S$	58.94	5.24	8.09	58.95	5.23	8.09
3f	**1c**	**2b**	62	88—90	2202 1731 1678	$C_{18}H_{20}N_2O_4S$	59.98	5.59	7.77	59.73	5.51	8.07
3i	**6c**	**7a**	99	149—152	2201 1728	$C_{15}H_{13}N_3OS$	63.58	4.62	14.83	63.62	4.62	14.88
3l	**6c**	**7b**	99	139—141	2218 1715	$C_{20}H_{15}N_3OS$	69.54	4.38	12.17	69.57	4.41	12.11
3o	**6c**	**7c**	94	197—199	2203 1688	$C_{20}H_{14}ClN_3OS$	63.24	3.71	11.06	63.19	3.71	11.11
3r	**6f**	**7a**	99	195—198	2211 1738 1682	$C_{17}H_{18}N_2O_3S$	61.80	5.49	8.48	61.84	5.53	8.39
3s	**6d**	**7b**	90	140—143	2201 1688	$C_{20}H_{16}N_2O_3S$	65.92	4.43	7.69	65.86	4.47	7.71
3u	**6f**	**7b**	75	178—181	2201 1699 1684	$C_{22}H_{20}N_2O_3S$	67.33	5.14	7.14	67.47	5.13	7.00
3v	**6d**	**7c**	35	173—176	2199 1684	$C_{20}H_{15}ClN_2O_3S$	60.23	3.79	7.02	60.04	3.71	6.84
3x	**6f**	**7c**	62	139—141	2199 1705 1684	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56	62.03	4.71	6.29
6a	**1d**	**2a**	29	106—108	2216 1724	$C_{15}H_{13}N_3O_2S$	60.19	4.38	14.04	60.21	4.35	14.05
6b	**1e**	**2a**	34	134—136	2211 1725	$C_{16}H_{15}N_3O_2S$	61.32	4.82	13.41	61.19	4.62	13.45
6c	**1f**	**2a**	39	108—110	2218 1723	$C_{17}H_{17}N_3O_2S$	62.37	5.23	12.83	62.57	5.48	12.84
6d	**1d**	**2b**	23	66—68	2209 1738 1692	$C_{17}H_{18}N_2O_4S$	58.94	5.24	8.09	59.10	5.18	7.99
6e	**1e**	**2b**	35	84—86	2197 1728 1682	$C_{18}H_{20}N_2O_4S$	59.98	5.59	7.77	59.92	5.33	8.06
6f	**1f**	**2b**	46	61—63	2214 1734 1699	$C_{19}H_{22}N_2O_4S$	60.94	5.92	7.48	60.82	6.05	7.38

a) These compounds **3a**—**f**, **i**, **l**, **o**, **r**, **s**, **u**, **v**, **x** and **6a**—**f** were obtained as colorless needles. *b*) Plus **4a**. *c*) Plus **4b**. *d*) Plus **4d**. *e*) Plus **4e**.

TABLE IV. Some Data for Thienoindolizines

Compd. No.[a]	Reactants		Yield (%)	mp (°C)	ν^{KBr} cm^{-1}	Formula	Analysis (%) Calcd			Found		
							C	H	N	C	H	N
8a	**3a**		62	235—238	3470 3362 2211 1605	$C_{14}H_{11}N_3O_2S$	58.93	3.89	14.73	58.80	3.88	14.86
8b	**3b**		80	>300	3440 3340 2200 1655	$C_{15}H_{13}N_3O_2S$	60.19	4.38	14.25	60.15	4.30	14.25
8c	**3c**		80	293—296	3405 3320 2200 1655	$C_{16}H_{15}N_3O_2S$	61.32	4.81	13.41	61.16	5.02	13.44
8d	**3d**		76	218—220	3420 3285 1650 1602	$C_{16}H_{16}N_2O_4S$	57.82	4.85	8.43	57.88	4.92	8.30
8e	**3e**		93	202—204	3440 3323 1654 1598	$C_{17}H_{18}N_2O_4S$	58.94	5.24	8.09	58.82	5.16	8.02
8f	**3f**		85	179—181	3440 3340 1706 1593	$C_{18}H_{20}N_2O_4S$	59.98	5.59	7.77	59.81	5.66	7.87
8g	**6a**	**7a**	97	277—280	3387 3293 2211 1587	$C_{13}H_9N_3OS$	61.16	3.55	16.46	61.05	3.53	16.32
8h	**6b**	**7a**	99	>298	3436 3295 2207 1595	$C_{14}H_{11}N_3OS$	62.44	4.12	15.60	62.72	4.07	15.63
8i	**3i**		78	>300	3445 3283 2205 1601	$C_{15}H_{13}N_3OS$	63.58	4.62	14.83	63.62	4.66	14.74
8j	**6a**	**7b**	95	280—283	3434 3268 2211 1595	$C_{18}H_{11}N_3OS$	68.12	3.49	13.24	68.14	3.46	13.26
8k	**6b**	**7b**	68	>298	3399 3268 2205 1593	$C_{19}H_{13}N_3OS$	68.86	3.95	12.68	68.67	4.03	12.78
8l	**3l**		59	>300	3420 3295 2209 1565	$C_{20}H_{15}N_3OS$	69.54	4.38	12.17	69.54	4.33	12.19
8m	**6a**	**7c**	90	283—286	3439 3368 2213 1595	$C_{18}H_{10}ClN_3OS$	61.45	2.87	11.94	61.57	3.06	11.69
8n	**6b**	**7c**	66	>300	3434 3291 2211 1584	$C_{19}H_{12}ClN_3OS$	62.38	3.31	11.49	62.16	3.39	11.62
8o	**3o**		66	>300	3410 3277 2207 1591	$C_{20}H_{14}ClN_3OS$	63.24	3.71	11.06	63.12	3.73	11.16
8p	**6d**	**7a**	86	250—252	3410 3295 1688 1584	$C_{15}H_{14}N_2O_3S$	59.59	4.67	9.27	59.42	4.62	9.07
8q	**6e**	**7a**	66	268—271	3434 3347 1667 1607	$C_{16}H_{16}N_2O_3S$	60.74	5.10	8.85	60.92	5.07	8.71
8r	**3r**		70	273—275	3393 3275 1696 1578	$C_{17}H_{18}N_2O_3S$	61.80	5.49	8.48	61.70	5.71	8.35
8s	**3s**		52	208—210	3436 3258 1665 1588	$C_{20}H_{16}N_2O_3S$	65.92	4.43	7.69	65.88	4.43	7.71
8t	**6e**	**7b**	42	245—247	3428 3274 1659 1586	$C_{21}H_{18}N_2O_3S$	66.65	4.79	7.40	66.56	4.94	7.38
8u	**3u**		52	233—235	3428 3304 1715 1578	$C_{22}H_{20}N_2O_3S$	67.33	5.14	7.14	67.05	5.21	7.09
8v	**3v**		52	252—254	3420 3297 1707 1578	$C_{20}H_{15}ClN_2O_3S$	60.23	3.79	7.02	60.10	3.79	6.77
8w	**6e**	**7c**	52	234—236	3424 3275 1665 1584	$C_{21}H_{17}ClN_2O_3S$	61.09	4.15	6.78	61.34	4.05	6.61
8x	**3x**		54	262—264	3418 3304 1715 1578	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56	62.05	4.68	6.41

a) Compounds **8a**—**x** were obtained as yellow needles.

(each 3H, t, $J=7.0$ Hz, $2\times OC\underline{H}_2CH_3$), 2.10 (3H, s, 7-Me), 4.18 and 4.30 (each 2H, q, $J=7.0$ Hz, $2\times OC\underline{H}_2CH_3$), 5.57 (2H, br s, NH_2), 6.08 (1H, dd, $J=7.0$, 2.0 Hz, 8-H), 7.51 (1H, d, $J=7.0$ Hz, 9-H), 8.08 (1H, br s, 6-H). *Anal.* Calcd for $C_{17}H_{18}N_2O_4S_2$: C, 53.95; H, 4.79; N, 7.40. Found: C, 53.72; H, 4.73; H, 4.73; N, 7.70.

Preparation of Thienoindolizines General Method: An ethanolic solution (30 ml) of a polyfunctionalized indolizine **3** (1 mmol) and DBU (2 mmol) was heated under reflux for 2 h and the resulting mixture was then chilled in a freezer. The precipitates which separated were collected by suction and the crude product was recrystallized from chloroform.

The results and some properties of the products are listed in Tables II and IV.

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References

1) For part XXX of this series, see A. Kakehi, S. Ito, and J. Hakui, *Chem. Lett.*, **1992**, 777.

2) A. Kakehi, S. Ito, T. Fujii, Y. Morimoto, S. Matsumoto, and M. Shiohara, *Bull. Chem. Soc. Jpn.*, **62**, 119 (1989); A. Kakehi, S. Ito, N. Yamada, and K. Yamaguchi, *Chem. Pharm. Bull.*, **38**, 1527 (1990).

3) R. Pariser and R. G. Parr, *J. Chem. Phys.*, **21**, 466 (1953); *idem*, *ibid.*, **21**, 767 (1953); J. A. Pople, *Trans. Faraday Soc.*, **49**, 1375 (1953); H. O. Prichard and H. A. Skinner, *Chem. Rev.*, **55**, 745 (1955).

4) A. Kakehi, S. Ito, Y. Ohno, S. Shiba, and S. Kamata, *Bull. Chem. Soc. Jpn.*, **60**, 3713 (1987); A. Kakehi, S. Ito, J. Hakui, and H. Fukazawa, *ibid.*, **65**, 1244 (1992).

5) F. W. Kröck and F. Kröhnke, *Chem. Ber.*, **102**, 659, 669 (1969); T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Tetrahedron*, **28**, 4947 (1972); Y, Tamura, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2091; A. Kakehi and S. Ito, *Bull. Chem. Soc. Jpn.*, **47**, 938 (1974); J. Alvarez-Builla, M. G. Quintanilla, C. Abril, and M. T. Gandasegui, *J. Chem. Research*, (*S*), **1984**, 202.

6) Y. Tominaga, H. Fujito, H. Norisue, A. Ushirogochi, Y. Masuda, and G. Kobayashi, *Yakugaku Zasshi*, **99**, 1081 (1979).