Preparation of New Nitrogen-bridged Heterocycles. 21.[1] A Facile Synthesis of 2-Indolizinethiols Using New Protecting Groups

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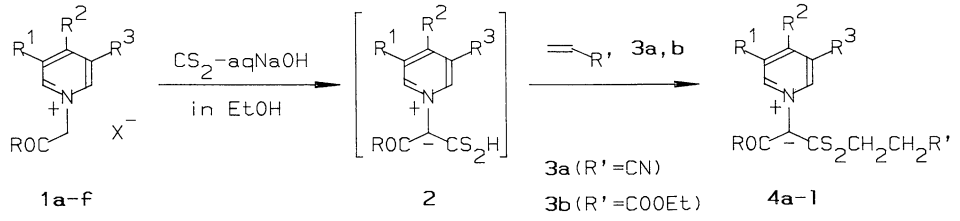
Some indolizine derivatives having (2-cyanoethyl)thio or (2-ethoxycarbonylethyl)thio group at the 2-position were prepared in moderate to good yields starting from the corresponding pyridinium 1-(thiocarbonyl)methylides. The treatment of these indolizines with a strong base such as potassium *t*-butoxide in *N*,*N*-dimethylformamide (DMF) gave smoothly title compounds, 2-indolizinethiols, with the elimination of acrylonitrile or ethyl acrylate.

In our previous papers,[2] we have reported the preparations of 2-[(ethoxycarbonylmethyl)thio]indolizines possessing cyano and/or acyl groups at the 1- and 3- positions and their facile and regiospecific cyclizations to thieno[3,2-*a*]- and thieno[2,3-*b*]indolizine derivatives. However, it has become apparent that the application of this method for the preparations of polyfunctionalized indolizines other than 2-[(ethoxycarbonylmethyl)thio]indolizines described above is very difficult or synthetically useless from the following reasons. 1) The cis-trans isomerization of the 1-vinyl group in the pyridinium salt leads to the formation of regioselective cyclization products. 2) There is the possibility of strong intra- and intermolecular interactions between the active methylenes and the acyl or the cyano group on the 1-vinyl moiety in the pyridinium salt. 3) There are two different types of reaction routes, the ring contraction-desulfulization and the ring contraction-rearrangement,[3] depending upon the 1-substituent of pyrido[2,1-*c*][1,4]thiazine intermediates. Hence, we focused our attention on the preparations of indolizines with the protected mercapto group at the 2-position, which are obtainable from the regiospecific cyclizations of the corresponding pyridinium salts and are convertible to versatile thiol derivatives by their deprotections. After considerations of some subjects such as the reaction conditions, mechanisms, and ready availability of reagents, we selected 2-cyanoethyl and 2-ethoxycarbonylethyl groups as the protecting groups for the mercapto function. Namely, the reaction sequence employed by us is a combination of the introduction of the protecting group by Michael addition and of its deprotection by β-elimination.[4] In this paper we wish to report the preparations of 2-[(2-cyanoethyl)thio]- and 2-[(2-ethoxycarbonylethyl)thio]indolizines and their facile derivation to the corresponding 2-indolizinethiols.

Results and Discussion

Preparations of Pyridinium 1-(Thiocarbonyl)methylides. Pyridinium 1-(thiocarbony)methylides **4a—l** bearing a (2-cyanoethyl)thio or (2-ethoxycarbonylethyl)-thio group were prepared in 40-67% yields by the Michael addition of pyridinium 1-(dithiocarboxy)-methylides **2**, generated in situ by the reactions of 1-



1a-f 2 4a-l

1	R^1	R^2	R^3	R	X
a	H	H	H	OEt	Br
b	H	Me	H	OEt	Cl
c	Me	H	Me	OEt	Cl
d	H	H	H	Me	Cl
e	H	Me	H	Me	Cl
f	Me	H	Me	Me	Cl

4	R^1	R^2	R^3	R	R'
a	H	H	H	OEt	CN
b	H	Me	H	OEt	CN
c	Me	H	Me	OEt	CN
d	H	H	H	OEt	COOEt
e	H	Me	H	OEt	COOEt
f	Me	H	Me	OEt	COOEt

4	R^1	R^2	R^3	R	R'
g	H	H	H	Me	CN
h	H	Me	H	Me	CN
i	Me	H	Me	Me	CN
j	H	H	H	Me	COOEt
k	H	Me	H	Me	COOEt
l	Me	H	Me	Me	COOEt

Scheme 1.

(ethoxycarbonylmethyl)- and 1-acetonylpyridinium halides **1a—f** with carbon disulfide in the presence of a base, to acrylonitrile (**3a**) or ethyl acrylate (**3b**) (Scheme 1).

These methylides **4a—l** showed clearly the characteristic absorption bands due to a cyano (2238—2248 cm^{-1}) or an ester carbonyl group (1719—1728 cm^{-1}) attached to the tetrahedral carbon in the (2-cyanoethyl)thio or (2-ethoxycarbonylethyl)thio group in their IR spectra, and also exhibited the ethylene protons as two methylene triplets at δ near 2.8 and near 3.6 in their ^1H NMR spectra.

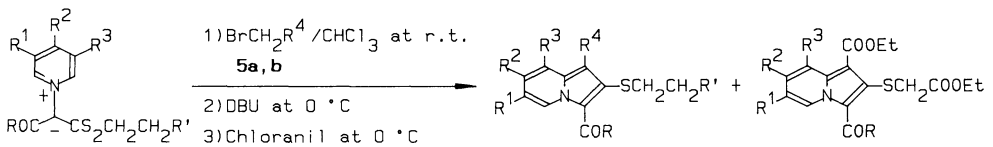
Preparations of 2-[(2-Substituded Ethyl)thio]indolizines. According to our previous papers,[2] these pyridinium methylides **4a—l** were treated with bromoacetonitrile (**5a**) or ethyl bromoacetate (**5b**) in chloroform at room temperature for ca. 3—6 d and the resulting pyridinium salts were allowed to react with 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU) as a base and then with chloranil as a dehydrogenating agent in the same solvent at 0 °C for 5—12 h to afford the corresponding 2-[(2-cyanoethyl)thio]- **6a—c, g—i, m—o** and 2-[(2-ethoxycarbonylethyl)thio]indolizine derivatives **6d—f, j—l, p—r** in moderate to good yields. Only when ethyl bromoacetate **5b** was used, small amount of 2-[(ethoxycarbonylmethyl)thio]indolizines (**7a—f**) could be also detected by means of their ^1H NMR spectral inspections (Scheme 2). The formations of these compounds **7a—f** could be almost suppressed by performing the *S*-alkylations at low temperature (below 20 °C), and were increased considerably on heating. Thus, compounds **7a—f** must be generated via the transalkylation of the (2-cyanoethyl)thio or (2-ethoxycarbonylethyl)thio group in the corresponding pyridinium salts with the excess alkylating agent **5b**.

The ^1H NMR spectra (Table 1) of these compounds **6a—r** exhibited the ethylene proton signals at δ 2.58—2.79 (2H) and 3.21—3.53 (2H) as slightly broad triplets. The skeletal proton and methyl proton signals appeared in the range of δ 6.83—10.07 and δ 2.30—2.78, respectively. Their IR spectra showed a distinct absorption band due to a cyano (2230—2240 cm^{-1} or a

Table 1. ^1H NMR Spectral Data of 2-(Substituted Ethylthio)indolizines

Compd[a] No.	$\delta(CDCl_3)$ C-5	C-6	C-7	C-8	CH_2CH_2S	R′	R and R^4
6a	9.60	7.09	7.44	7.78	2.79 3.53	—	1.44 4.60
	br d	dt	br t	br d	br t br t		t q
6b	9.48	6.93	2.49	7.52	2.77 3.51	—	1.43 4.51
	d	dd	s	br s	br t br t		t q
6c	9.31	2.38	7.02	2.78	2.70 3.38	—	1.49 4.51
	br s	s	br s	s	br t br t		t q
6d	9.69	7.03	7.41	7.78	2.71 3.52	1.26 4.13	1.46 4.44
	br d	dt	br t	br d	br t br t	t q	t q
6e	9.43	6.87	2.48	7.48	2.73 3.53	1.26 4.18	1.46 4.47
	d	dd	s	br s	br t br t	t q	t q
6f	9.28	2.33	6.97	2.73	2.63 3.38	1.23 4.13	1.46 4.47
	br s	s	br s	s	br t br t	t q	t q
6g	9.50	7.00	7.38	8.36	2.59 3.31	—	1.47 1.48 4.47 4.52
	br d	dt	br t	br d	br t br t		t t q q
6h	9.38	6.83	2.44	8.12	2.58 3.29	—	1.16 1.46 4.47 4.49
	d	dd	s	br s	br t br t		t t q q
6i	9.28	2.33	6.90	2.45	2.60 3.21	—	1.46 1.49 4.50 4.52
	br s	s	br s	s	br t br t		t t q q
6j	9.56	7.00	7.34	8.39	2.58 3.32	1.21 4.10	1.48 1.48 4.48 4.50
	br d	dt	br t	br d	br t br t	t q	t t q q
6k	9.40	6.79	2.43	8.13	2.54 3.27	1.18 4.08	1.44 1.44 4.44 4.44
	d	dd	s	br s	br t br t	t q	t t q q
6l	9.29	2.30	6.83	2.43	2.56 3.18	1.20 4.11	1.41 1.44 4.43 4.47
	br s	s	br s	s	br t br t	t q	t t q q
6m	10.07	7.01	7.43	8.42	2.58 3.32	—	2.94 1.44 4.41
	br d	dt	br t	br d	br t br t		s t q
6n	9.70	6.84	2.46	8.13	2.58 3.33	—	2.96 1.46 4.45
	d	dd	s	br s	br t br t		s t q
6o	9.70	2.33	6.96	2.45	2.61 3.15	—	2.93 1.43 4.46
	br s	s	br s	s	br t br t		s t q
6p	9.95	7.01	7.40	8.41	2.58 3.33	1.20 4.10	2.94 1.47 4.47
	br d	dt	br t	br d	br t br t	t q	s t q
6q	9.85	6.88	2.44	8.18	2.56 3.30	1.18 4.09	2.91 1.45 4.46
	d	dd	s	br s	br t br t	t q	s t q
6r	9.73	2.31	6.94	2.45	2.59 3.17	1.22 4.12	2.93 1.43 4.49
	br s	s	br s	s	br t br t	t q	s t q

a) The coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=2.0$, $J_{Et}=7.0$, and $J_{ethylene}=7.0$ and 7.0 Hz.

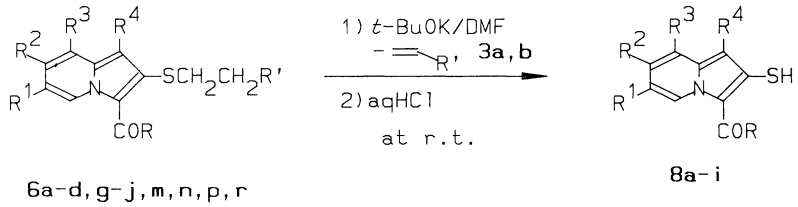


6	R^1	R^2	R^3	R^4	R	R'
a	H	H	H	CN	OEt	CN
b	H	Me	H	CN	OEt	CN
c	Me	H	Me	CN	OEt	CN
d	H	H	H	CN	OEt	COOEt
e	H	Me	H	CN	OEt	COOEt
f	Me	H	Me	CN	OEt	COOEt
g	H	H	H	COOEt	OEt	CN
h	H	Me	H	COOEt	OEt	CN
i	Me	H	Me	COOEt	OEt	CN

6	R^1	R^2	R^3	R^4	R	R'
j	H	H	H	COOEt	OEt	COOEt
k	H	Me	H	COOEt	OEt	COOEt
l	Me	H	Me	COOEt	OEt	COOEt
m	H	H	H	COOEt	Me	CN
n	H	Me	H	COOEt	Me	CN
o	Me	H	Me	COOEt	Me	CN
p	H	H	H	COOEt	Me	COOEt
q	H	Me	H	COOEt	Me	COOEt
r	Me	H	Me	COOEt	Me	COOEt

7	R^1	R^2	R^3	R
a	H	H	H	OEt
b	H	Me	H	OEt
c	Me	H	Me	OEt
d	H	H	H	Me
e	H	Me	H	Me
f	Me	H	Me	Me

Scheme 2.



8	React(6)	R^1	R^2	R^3	R^4	R
a	a or d	H	H	H	CN	OEt
b	b	H	Me	H	CN	OEt
c	c	Me	H	Me	CN	OEt
d	g or j	H	H	H	COOEt	OEt
e	h	H	Me	H	COOEt	OEt

8	React(6)	R^1	R^2	R^3	R^4	R
f	i	Me	H	Me	COOEt	OEt
g	m or p	H	H	H	COOEt	Me
h	n	H	Me	H	COOEt	Me
i	r	Me	H	Me	COOEt	Me

Scheme 3.

Table 2. ^{1}H NMR Spectral Data of 2-Indolizinethiols

Compd[a] No.	δ(CDCl3) C-5	C-6	C-7	C-8	SH	R and R4			
8a	9.57	6.97	7.37	7.68	4.39	1.47	4.42		
	br d	dt	br t	br d	s	t	q		
8b	9.49	6.79	2.40	7.41	4.36	1.44	4.40		
	d	dd	s	br s	s	t	q		
8c	9.36	2.28	6.94	2.65	4.34	1.45	4.42		
	br s	s	br s	s	s	t	q		
8d	9.61	6.93	7.33	8.25	7.12	1.48	1.48	4.46	4.48
	br d	dt	br t	br d	s	t	t	q	q
8e	9.40	6.73	2.40	7.97	7.06	1.45	1.45	4.44	4.44
	d	dd	s	br s	s	t	t	q	q
8f	9.34	2.31	6.94	2.50	5.98	1.43	1.48	4.43	4.47
	br s	s	br s	s	s	t	t	q	q
8g	10.16	6.94	7.39	8.21	8.25	2.70	1.48	4.41	
	br d	dt	br t	br d	br s	s	t	q	
8h	10.05	6.77	2.67	8.20	7.97	2.69	1.48	4.40	
	d	dd	s	br s	br s	s	t	q	
8i	9.89	2.30	6.99	2.46	6.38	2.73	1.41	4.42	
	br s	s	br s	s	br s	s	t	q	

a) The coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=2.0$, $J_{Et}=7.0$.

carbonyl (1715—1733 cm^{-1}) group attached to a tetrahedral carbon in the 2-substituents. The chemical shifts and signal patterns of the protons and methyl protons attached to the pyridine ring were, in particular, quite similar to those of 2-(alkylthio)indolizine derivatives prepared earlier by us[2,3] and other investigators.[5] The structures of minor products **7a—f** were determined by the comparisons of their ^1H NMR spectral data with those of authentic samples[2] and partially by their independent syntheses (vide post).

Preparations of 2-Indolizinethiols. When a small excess of potassium *t*-butoxide was added to the DMF solution of ethyl 1-cyano-2-[(2-cyanoethyl)thio]-3-indolizinecarboxylate (**6a**) at room temperature, the rapid evolution of acrylonitrile **3a** was observed by its odor: the quenching of the resulting mixture with aqueous hydrochloric acid gave ethyl 1-cyano-2-mercapto-3-indolizinecarboxylate (**8a**) in 52% yield. The same product **8a** could also be obtained in 67% yield by the similar reactions of 2-[(2-ethoxycarbonylethyl)thio]indolizine derivative **6d** with the evolution of ethyl acrylate **3b**. Analogously, 2-indolizinethiols **8b—i** were prepared from the basic treatment of the protected indolizines **6b, c, 6g** and **6j, 6h, i, 6m** and **6p**, and **6n, r**, respectively (Scheme 3). During these deprotection reactions no attack of the base or solvent to the other functional groups such as cyano, ethoxycarbonyl, and acetyl groups could be observed.

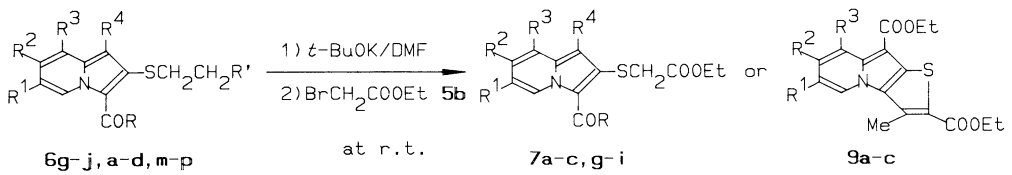
The structures of compounds **8a—i** could be easily determined by the indications of the proton signals that appeared in the range of δ 4.34—8.25 in their ^1H NMR spectra (Table 2) and of the weak absorption bands shown at 2370—2520 cm^{-1} due to the mercapto group in their IR spectra (Table 5).

These 2-indolizinethiol derivatives **8a—i** are considerably stable and can be stored at room temperature for a few months without appreciable decomposition. Presumably, the high stability of these compounds **8a—i** is owing to the presence of the favorable hydrogen-bonding between the 2-mercapto and the 1- or 3-acyl carbonyl groups.

***S*-Alkylation of 2-Indolizinethiol Derivatives.** Since the facile elimination of the protecting groups from indolizines **6** could be confirmed, the possibility of the functionalization of the mercapto group was examined by using ethyl bromoacetate (**5b**) as an alkylating agent. The addition of **5b** to a DMF suspension of ethyl 1-cyano-2-[(2-cyanoethyl)thio]-3-indolizinecarboxylate (**6a**) and potassium *t*-butoxide caused a rapid exothermal reaction to give the expected ethyl 1-cyano-2-[(ethoxycarbonylmethyl)thio]-3-indolizinecarboxylate (**7g**) in 56% yield. The same compound **7g** could be also obtained in 64% yield by the similar treatment of indolizine **6d** with **5b**. Analogously, the *S*-alkylated indolizines **7a—c, h, i** were prepared from the reactions of indolizines **6g** and **6j**, and **6h, i, b, c** with **5b** in the presence of base. On the other hand, the similar treatment of indolizines **6m** and **6p**, and **6n, o** possessing a 3-acetyl group did not afford any 2-[(ethoxycarbonylmethyl)thio]indolizine derivatives (**7d—f**), but provided 3-methylthieno[2,3-*b*]indolizines (**9a—c**) in good yields (Scheme 4). These tricyclic indolizine derivatives **9a—c** must be formed via the intramolecular condensations between the 3-acetyl carbonyl and the active methylene group in **7d—f** generated in situ initially. Recently, we have observed the actual conversions of indolizines **7d—f** to thienoindolizines **9a—c** under the alkaline conditions.[2]

Indolizines **7g—i** and thienoindolizines **9a—c** were completely in accord with the authentic samples[2] synthesized by us in all respects.

The chief advantages of our method stated above are 1) the easy introduction of the protecting groups by the Michael addition, 2) the smooth deprotection by the β-elimination, 3) the ready availability of reagents, and 4) if necessary, the removal of the vinyl component formed is quite simple. On the other hand, the ability and the readiness for the β-eliminations of these 2-cyanoethyl and 2-ethoxycarbonylethyl groups are approximately equal but, as long as their handlings



6g-j, a-d, m-p

7a-c, g-i

9a-c

7	React(6)	R^1	R^2	R^3	R^4	R
a	g or j	H	H	H	COOEt	OEt
b	h	H	Me	H	COOEt	OEt
c	i	Me	H	Me	COOEt	OEt
g	a or d	H	H	H	CN	OEt
h	b	H	Me	H	CN	OEt
i	c	Me	H	Me	CN	OEt

9	React(6)	R^1	R^2	R^3
a	m or p	H	H	H
b	n	H	Me	H
c	o	Me	H	Me

Scheme 4.

are concerned, the latter is slightly superior to the former because of its high solubility for organic solvents.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The microanalyses were carried out on a Perkin-Elmer 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 spectra were taken with a Hitachi 260-10 infrared spectrophotometer.

Preparations of Pyridinium 1-[(2-Substituted Ethylthio)-thiocarbonyl]methylides. General Method: To the stirred ethanolic solution (100 ml) of 1-(ethoxycarbonylmethyl)-pyridinium halides (0.1 mol), an aqueous solution (10 ml) of sodium hydroxide (4.4 g, 0.11 mol) was added dropwise in a period of 10 min and the resulting dark red solution was stirred for further 30 min. Acrylonitrile **3a** (8 g, 0.15 mol) or ethyl acrylate **3b** (15 g, 0.15 mol) was then added, and the reaction mixture was allowed to react at room temperature for 2 h under stirring. The reaction solution was poured into 500 ml of ice-water, and the product that precipitated was collected by filtration and air-dried. Recrystallization from chloroform–ether gave the corresponding pyridinium methylide.

Pyridinium methylides **4a**, **c**, **f**, **i** were obtained as yellow prisms, **4b**, **e**, **q**, **l** as yellow needles, and **4d**, **h**, **j**, **k** as yellow flakes. Some physical and spectral data of these pyridinium methylides are listed in Table 3.

Preparations of 2-[(2-Substituted Ethyl)thio]indolizines. General Method: A chloroform solution (10 ml) of pyridinium methylide **4** (4 mmol) and bromoacetonitrile **5a** or ethyl bromoacetate **5b** (5 mmol) was kept on standing at room temperature until the material **4** was completely alkylated (ca. 3—6 d). After further 20 ml of chloroform was added, the resulting solution was allowed to react with DBU (0.76 g, 5 mmol) and then chloranil (0.98 g, 4 mmol) in an ice

Table 3. Some Data of Pyridinium Ylides

Compd No.	Reactants	Yield %	Mp °C	ν(KBr)/cm^{-1} CO and CN	δ($CDCl_3$)[a] CH_2CH_2S	Formula[b]
4a	**1a 3a**	63	147—148	1640 2242	2.88 3.58	$C_{13}H_{14}N_2O_2S_2$
4b	**1b 3a**	40	197—198	1625 2248	2.85 3.56	$C_{14}H_{16}N_2O_2S_2$
4c	**1c 3a**	46	182—184	1647 2240	2.88 3.57	$C_{15}H_{18}N_2O_2S_2$
4d	**1a 3b**	59	175—177	1654 1720	2.81 3.60	$C_{15}H_{19}NO_4S_2$
4e	**1b 3b**	45	147—148	1608 1728	2.79 3.59	$C_{16}H_{21}NO_4S_2$
4f	**1c 3b**	55	190—192	1641 1721	2.80 3.59	$C_{17}H_{23}NO_4S_2$
4g	**1d 3a**	50	200—202	1575 2238	2.84 3.58	$C_{12}H_{12}N_2OS_2$
4h	**1e 3a**	67	196—197	1577 2242	2.84 3.58	$C_{13}H_{14}N_2OS_2$
4i	**1f 3a**	59	204—205	1575 2240	2.85 3.55	$C_{14}H_{16}N_2OS_2$
4j	**1d 3b**	64	161—163	1575 1722	2.79 3.60	$C_{14}H_{17}NO_3S_2$
4k	**1e 3b**	62	176—178	1584 1726	2.77 3.57	$C_{15}H_{19}NO_3S_2$
4l	**1f 3b**	58	189—191	1573 1719	2.78 3.59	$C_{16}H_{21}NO_3S_2$

a) The proton signals of these methylene groups appeared as triplets or almost triplets coupled with 7.0 Hz.
b) Satisfactory analytical data (within 0.3% for C, H, and N) were obtained for all new compounds.

Table 4. Some Data of 2-(Substituted Ethylthio)indolizines

Compd No.	Reactants	Yield %	Mp °C	ν(KBr)/cm^{-1} CO and CN	Formula[a]
6a	**4a 5a**	50	129—130	1673 2210 2240	$C_{15}H_{13}N_3O_2S$
6b	**4b 5a**	65	130—131	1673 2205 2240	$C_{16}H_{15}N_3O_2S$
6c	**4c 5a**	51	149—151	1674 2210 2236	$C_{17}H_{17}N_3O_2S$
6d	**4d 5a**	52	76—77	1676 1733 2200	$C_{17}H_{18}N_2O_4S$
6e	**4e 5a**	65	95—96	1675 1717 2200	$C_{18}H_{20}N_2O_4S$
6f	**4f 5a**	59	105—107	1670 1715 2200	$C_{19}H_{22}N_2O_4S$
6g	**4a 5b**	69	81—82	1675 1685 2230	$C_{17}H_{18}N_2O_4S$
6h	**4b 5b**	84	94—95	1670 1685 2230	$C_{18}H_{20}N_2O_4S$
6i	**4c 5b**	76	52—53	1667 1705 2233	$C_{19}H_{22}N_2O_4S$
6j	**4d 5b**	72	88—89	1670 1688 1730	$C_{19}H_{23}NO_6S$
6k	**4e 5b**	81	69—70	1668 1685 1725	$C_{20}H_{25}NO_6S$
6l	**4f 5b**	83	51—52	1668 1720	$C_{21}H_{27}NO_6S$
6m	**4g 5b**	43	89—91	1624 1691 2240	$C_{16}H_{16}N_2O_3S$
6n	**4h 5b**	38	117—118	1611 1683 2240	$C_{17}H_{18}N_2O_3S$
6o	**4i 5b**	51	75—76	1606 1718 2240	$C_{18}H_{20}N_2O_3S$
6p	**4j 5b**	32	61—63	1620 1690 1720	$C_{18}H_{21}NO_5S$
6q	**4k 5b**	36	55—56	1619 1690 1720	$C_{19}H_{23}NO_5S$
6r	**4l 5b**	61	47—48	1626 1725	$C_{20}H_{25}NO_5S$

a) Satisfactory analytical data (within 0.3% for C, H, and N) were obtained for all new compounds.

Table 5. Some Data of 2-Indolizinethiols

Compd No.	React.	Yield %	Mp °C	ν(KBr)/cm^{-1} CO, CN, and SH	Formula[a]
8a	**6a**	52	130—131	1685 2200 2450	$C_{12}H_{10}N_2O_2S$
	6d	67			
8b	**6b**	75	143—146	1680 2200 2500	$C_{13}H_{12}N_2O_2S$
8c	**6c**	80	149—151	1670 2197 2520	$C_{14}H_{14}N_2O_2S$
8d	**6g**	70	80—82	1680 2500	$C_{14}H_{15}NO_4S$
	6j	66			
8e	**6h**	75	83—85	1650 1675 2450	$C_{15}H_{17}NO_4S$
8f	**6i**	62	52—53	1675 2470	$C_{16}H_{19}NO_4S$
8g	**6m**	94	114—116	1605 1641 2370	$C_{13}H_{13}NO_3S$
	6p	78			
8h	**6n**	84	151—152	1610 1657 2380	$C_{14}H_{15}NO_3S$
8i	**6r**	50	73—75	1610 1668 2490	$C_{15}H_{17}NO_3S$

a) Satisfactory analytical data (within 0.3% for C, H, and N) were obtained for all new compounds.

bath for 5—12 h. The solution was then concentrated under reduced pressure and the residue was separated by column chromatography (alumina) using chloroform as an eluent. Recrystallizations from ethanol afforded the corresponding indolizine derivatives **6a—r** having the (2-cyanoethyl)thio or (2-ethoxycarbonylethyl)thio group at the 2-position.

When ethyl bromoacetate **5b** was used as an alkylating agent, the presence of 2-[(ethoxycarbonylmethyl)thio]indolizine derivatives **7a—f** were also detected by the ^{1}H NMR spectral inspections of the crude products, but the isolations of pure **7a—f** from them were unsuccessful because of their low yields (below 3%) and like solubilities. The formations of these **7a—f** could be almost suppressed by lowering the temperature of the *S*-alkylations to below 20 °C. All compounds **6a—r** were obtained as colorless needles. These results and some physical and spectral data are summarized in Tables 1 and 4.

Preparations of 2-Indolizinethiols. General Method: To a DMF solution (1—2 ml) of 2-[(2-cyanoethyl)thio]- or 2-[(2-ethoxycarbonylethyl)thio]indolizine **6** (1 mmol), potassium *t*-butoxide (0.14 g, 1.25 mmol) was added at room temperature and, after the sufficient stirring using a spatula, the resulting mixture was kept on standing for additional 15 min. The reaction mixture was acidified with dilute hydrochloric acid (5 ml), and the precipitates that separated were collected by filtration and washed twice with water (20 ml). The crude product was again dissolved in chloroform (30 ml) and freed from water by the filtration through a phase-separating filter paper. The chloroform layer was concentrated under reduced pressure and the residue was purified by column chromatography (alumina) using chloroform as an eluent. Recrystallizations from ethanol gave the corresponding 2-indolizinethiol derivatives **8a—i** as colorless needles.

When potassium *t*-butoxide was added to indolizines **6**, the rapid elimination of the protecting group could be easily confirmed by the characteristic odor of acrylonitrile **3a** or ethyl acrylate **3b**. These results and some physical and spectral data are listed in Tables 2 and 5.

***S*-Alkylations of 2-Indolizinethiol Derivatives. General Method:** To a DMF suspension (1—2 ml) of indolizine **6** (1 mmol) and potassium *t*-butoxide (0.14 g, 1.25 mmol), ethyl bromoacetate **5b** (0.20 g, 1.2 mmol) was added at room temperature and the resulting solution was then kept on standing at room temperature for 1 h with occasional stirring. The usual work-ups gave the corresponding 2-[(ethoxycarbonylmethyl)thio]indolizines **7a—c, g—i** and 3-methylthieno[2,3-*b*]indolizines **9a—c**.

Products **7a—c, g—i** and **9a—c** were in accord with authentic samples synthesized earlier[2] in all respects. These results are shown below: **7a**, 68% from **6g** or 71% from **6j**, mp 53 °C. **7b**, 67% from **6h**, mp 59—60 °C. **7c**, 76% from **6i**, mp 103—104 °C. **7g**, 56% from **6a** or 64% from **6d**, mp 88—89 °C. **7h**, 50% from **6b**, mp 101—102 °C. **7i**, 74% from **6c**, mp 107—109 °C. **9a**, 69% from **6m** or 64% from **6p**, mp 194—195 °C. **9b**, 67% from **6n**, mp 173—174 °C. **9c**, 77% from **6o**, mp 127—128 °C.

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