Preparation of New Nitrogen-Bridged Heterocycles. 25.[1] A Smooth Synthesis of [1,4]Thiazino[3,4,5-*cd*]indolizine Derivatives

Akikazu KAKEHI,* Suketaka ITO, Tsuneo FUJII, Tosio SAKURAI,† Kunio URUSHIDO,†
Susumu HATANAKA, Toshiaki MABUCHI, and Shun-ichiro MATSUSHITA
Department of Chemistry and Material Engineering, Faculty of Engineering,
Shinshu University, Wakasato, Nagano 380
†Department of Chemistry, Faculty of Education, Shinshu University, Nishinagano, Nagano 380
(Received May 1, 1990)

The title compounds were prepared smoothly in moderate yields by the reactions of 3-(mercaptomethylene)-2(3*H*)-indolizinones with various alkylating agents such as bromoacetonitrile, bromoacetates, and phenacyl bromides in the presence of base. The structural assignments of these products were accomplished by their spectral inspections, and the structure for one compound was distinctly proven by its X-ray crystallography. In order to explain the regioselectivity in this reaction, a molecular orbital calculation (CNDO/2) was also performed using a model compound.

In a preliminary communication[2] we described the preparation of some 4(1*H*)-8,8a-dihydro[1,4]-thiazino[3,4,5-*cd*]indolizinones by the reactions of 3-(mercaptomethylene)-2(3*H*)-indolizinone with bromoacetonitrile or phenacyl bromide in the presence of a base at room temperature. A possible intermediate involved in this reaction is an ionic species such as **A** (see Fig. 1), and the driving force for its smooth cyclization to cycloadduct **B** seems to be the increased electrophilicity of the C-5 carbon in the 2(3*H*)-indolizinone, as compared with that in indolizine.[3] Recently, we have also found that a zwitterionic intermediate such as **C**, whose structure is very like species **A**, cyclized easily under extremely mild conditions to give the corresponding 1,4-thiazine.[4] The ready formation of these [1,4]thiazino[3,4,5-*cd*]indolizines and the pharmaceutical interest for some fused 1,4-thiazine derivatives[5] prompted us to further investigate the generality and the usefulness of this reaction. In this paper we report on the preparation of 4(1*H*)-8,8a-dihydro[1,4]thiazino[3,4,5-*cd*]indolizinone derivatives from reactions of 3-(mercaptomethylene)-2(3*H*)-indolizinones with some alkylating agents in the presence of a base; we also give our consideration concerning on the regioselectivity in these reactions on the basis of a molecular orbital calculation[6] of a model compound.

Results and Discussion

Preparation of 3-(Mercaptomethylene)-2(3*H*)-indolizinones. These 3-(mercaptomethylene)-2(3*H*)-

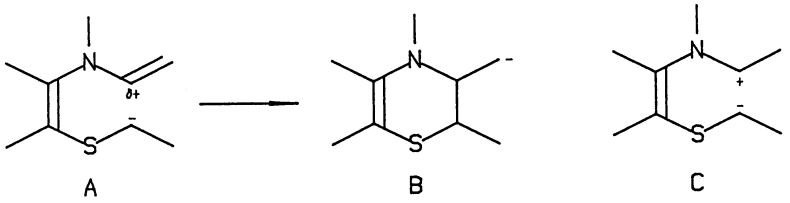
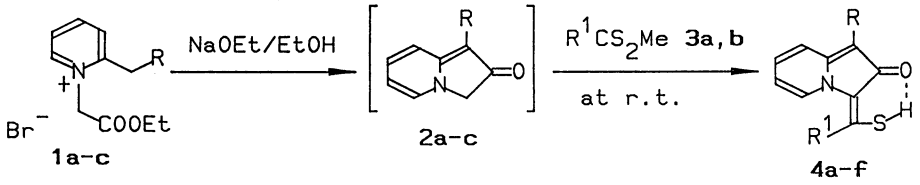


Fig. 1.



1,2	R
a	Me
b	Ph
c	*p*-ClC$_6$H$_4$

3	R¹
a	Me
b	Ph

4	R	R¹
a	Me	Me
b	Ph	Me
c	*p*-ClC$_6$H$_4$	Me
d	Me	Ph
e	Ph	Ph
f	*p*-ClC$_6$H$_4$	Ph

Scheme 1.

Table 1. ^{1}H NMR Data of 3-Methylene-2(3*H*)-indolizinones

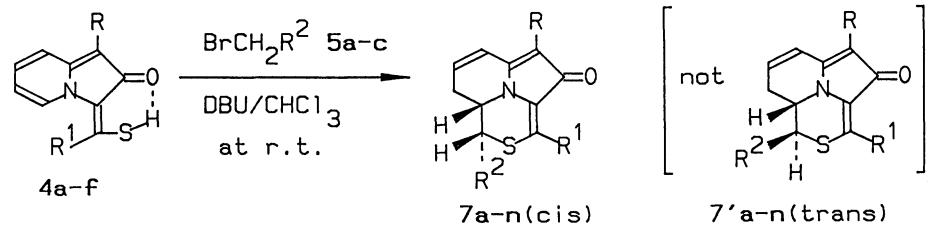
Compd	δ(CDCl$_3$)						
4	5-H	6-H	7-H	8-H	SH	R	R^1
a	8.42 br d	6.78 m	7.0—7.5 m		13.58 br s	2.09 s	3.01 s
b	8.64 br d	6.81 dt	b)	b)	14.03 s	7.1—7.9 m	3.09 s
c	8.62 br d	6.95 dt	b)	b)	13.81 s	7.2—7.9 m	3.09 s
d	b)	6.36 m	b)	b)	13.07 s	2.15 s	7.0—7.7 m
e	b)	6.36 m	b)	b)	13.34 br s	7.0—7.9 m	7.0—7.9 m
f	b)	6.39 dt	b)	b)	13.39 br s	7.0—7.8 m	7.0—7.8 m

a) The coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{5,7}=2.0$ Hz. b) Overlapped with the phenyl proton signals.

indolizinones **4a—f** were prepared in 40—66% yields by reactions of the corresponding 2(3*H*)-indolizinones **2a—c**, generated in situ from an alkaline treatment of 2-ethyl- (**1a**), 2-benzyl- (**1b**), and 2-(*p*-chlorobenzyl)-1-(ethoxycarbonylmethyl)pyridinium bromide (**1c**), with methyl dithioacetate (**3a**) and methyl dithiobenzoate (**3b**) at room temperature with the elimination of methanethiol (Scheme 1).

The structures of these compounds **4a—f** were determined by the physical and spectral means and by their spectral comparisons with those of 3-[(alkylthio)-mercaptomethylene]-2(3*H*)-indolizinone derivatives prepared previously by us.[7] The elemental analyses of **4a—f** were in good accord with our proposed compositions. The IR spectra showed characterisric absorption bands in the ranges of 2280—2550 and 1579—1598 cm^{-1}, attributable to the mercapto and the carbonyl groups, respectively; the ^{1}H NMR spectra (Table 1) exhibited mercapto proton signals at very low magnetic field (δ=13.07—14.03), which indicated the presence of the hydrogen-bonding between this group and the 2-oxo oxygen atom. These spectral features were almost the same as those of 3-[(alkylthio)mercaptomethylene]-2(3*H*)-indolizinones.[7]

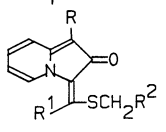
Preparation of [1,4]Thiazino[3,4,5-*cd*]indolizines. Since 3-methylene-2(3*H*)-indolizinone has the 2-methylene-1,2-dihydropyridine and the trienone structures, a considerable increase in the electrophilicity of the C-5 carbon, as compared with that in indolizine,[3] can be expected. However, the exo-methylene moiety of compounds **6** (see Scheme 2) available directly from the *S*-functionalization of 3-(mercaptomethylene)-2(3*H*)-indolizinones (**4a—f**) does not have the proper geometry for cyclization to the corresponding [1,4]thiazino[3,4,5-*cd*]indolizines. For these reasons, the formation of **6** in the reactions of **4a—f** with alkylating agents **5a—f** was initially expected. However, the treatment of **4a—f** with bromoacetonitrile (**5a**) in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in chloroform at room temperature gave directly the corresponding 4(1*H*)-8,8a-dihydro-1-cyano[1,4]thiazino[3,4,5-*cd*]indolizinones (**7a—f**) in which the hydrogens at the 1- and 8a-position have a cis configuration, and did not afford any 3-[(cyanomethylthio)methylene]-2(3*H*)-



5	R^2
a	CN
b	COOEt
c	COO*t*-Bu

7	R	R^1	R^2
a	Me	Me	CN
b	Ph	Me	CN
c	*p*-ClC$_6$H$_4$	Me	CN
d	Me	Ph	CN
e	Ph	Ph	CN
f	*p*-ClC$_6$H$_4$	Ph	CN
g	Me	Me	COOEt

7	R	R^1	R^2
h	Ph	Me	COOEt
i	*p*-ClC$_6$H$_4$	Me	COOEt
j	Me	Ph	COOEt
k	Ph	Ph	COOEt
l	*p*-ClC$_6$H$_4$	Ph	COOEt
m	Me	Me	COO*t*-Bu
n	*p*-ClC$_6$H$_4$	Ph	COO*t*-Bu



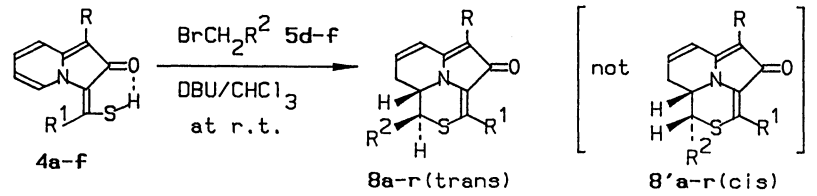
6

Scheme 2.

Table 2. ^{1}H NMR Data of Thiazinoindolizines

Compd	δ(CDCl$_3$)[a,b]							
No.	1-H	8a-H	8-H	7-H	6-H	R	R^1	R^2
7a	3.92 d	4.04 m	2.3—3.0 m	6.27 m	6.57 dd	1.78 s	2.49 s	—
7b	3.95 d	4.18 m	2.3—3.0 m	6.31 m	6.74 dd	7.1—7.7 m	2.54 s	—
7c	3.96 d	4.20 m	2.4—3.0 m	6.38 m	6.69 dd	7.41 s	2.56 s	—
7d	4.00 d	4.20 m	2.3—3.1 m	6.29 m	6.57 dd	1.72 s	7.2—7.8 m	—
7e	3.99 d	4.25 m	2.3—3.0 m	6.33 m	6.77 dd	7.1———7.8 m		—
7f	4.05 d	4.38 m	2.3—3.2 m	6.48 m	6.79 dd	7.37 s	7.2—7.7 m	—
7g	c)	c)	2.3—3.2 m	6.19 m	6.46 dd	1.76 s	2.47 s	1.32 t 4.24 q
7h	c)	c)	2.2—3.1 m	6.25 m	6.67 dd	7.1—7.6 m	2.51 s	1.30 t 4.25 q
7i	4.13 d	c)	2.0—3.1 m	6.29 m	6.62 dd	7.39 s	2.50 s	1.33 t 4.24 q
7j	c)	c)	2.2—3.2 m	6.23 m	6.50 dd	1.76 s	7.0—7.8 m	1.36 t 4.28 q
7k	c)	c)	2.2—3.2 m	6.30 m	6.75 dd	7.1———7.8 m		1.28 t 4.26 q
7l	c)	c)	2.2—3.1 m	6.30 m	6.63 dd	7.30 s	7.0—7.7 m	1.28 t 4.21 q
7m	4.00 d	4.02 m	2.3—3.2 m	6.18 m	6.47 dd	1.77 s	2.48 s	1.51 s
7n	4.16 d	4.20 m	2.1—3.2 m	6.28 m	6.63 dd	7.30 s	7.0—7.7 m	1.44 s
8a	5.12 d	4.30 m	2.0—3.2 m	6.09 m	6.40 dd	1.72 s	2.40 s	7.3—8.3 m
8b	5.16 d	4.45 m	2.0—3.0 m	6.16 m	6.69 dd	7.1—8.3 m	2.50 s	7.1—8.3 m
8c	5.17 d	4.43 m	2.0—3.1 m	6.22 m	6.60 dd	7.41 s	2.46 s	7.2—8.4 m
8d	5.17 d	4.45 m	1.9—3.1 m	6.30 m	6.50 dd	1.68 s	7.3———8.3 m	
8e	5.17 d	4.60 m	2.1—3.2 m	6.22 m	6.71 dd	7.0————————8.3 m		
8f	5.18 d	4.60 m	2.1—3.3 m	6.27 m	6.66 dd	7.1————————8.3 m		
8g	5.03 d	4.40 m	2.0—3.2 m	6.15 m	6.47 dd	1.77 s	2.46 s	7.3—8.3 m
8h	5.12 d	4.48 m	2.0—3.2 m	6.23 m	6.69 dd	7.2—8.3 m	2.52 s	7.2—8.3 m
8i	5.10 d	4.45 m	2.0—3.2 m	6.37 m	6.72 dd	7.40 s	2.50 s	7.3—8.2 m
8j	5.10 d	4.46 m	1.9—3.1 m	6.26 m	6.49 dd	1.73 s	7.2———8.2 m	
8k	5.19 d	4.65 m	2.0—3.2 m	6.28 m	6.75 dd	7.1————————8.3 m		
8l	5.11 d	4.58 m	1.9—3.2 m	6.29 m	6.66 dd	7.1————————8.3 m		
8m	5.00 d	4.35 m	2.0—3.2 m	6.28 m	6.50 dd	1.75 s	2.45 s	7.5—8.3 m
8n	5.15 d	4.54 m	2.1—3.2 m	6.27 m	6.68 dd	7.2—8.2 m	2.57 s	7.2—8.2 m
8p	5.09 d	4.35 m	1.9—3.1 m	6.18 m	6.49 dd	1.67 s	7.2———8.1 m	
8q	5.19 d	4.62 m	2.0—3.2 m	6.35 m	6.80 dd	7.0————————8.1 m		
8r	5.25 d	4.71 m	2.2—3.3 m	6.29 m	6.69 dd	7.4————————8.6 m		

a) The coupling constants are as follows: $J_{1,8a}$=2.0 (cis) or 10.0 (trans), $J_{6,8}$=2.5, and $J_{6,7}$=10.0 Hz. b) The spectrum of **8o** could not be measured because of its low solubility. c) Overlapped with the methylene proton signals of the ethoxyl group.



5	R^2
d	PhCO
e	*p*-ClC_6H_4CO
f	*p*-BrC_6H_4CO

8	R	R^1	R^2
a	Me	Me	PhCO
b	Ph	Me	PhCO
c	*p*-ClC_6H_4	Me	PhCO
d	Me	Ph	PhCO
e	Ph	Ph	PhCO
f	*p*-ClC_6H_4	Ph	PhCO
g	Me	Me	*p*-ClC_6H_4CO
h	Ph	Me	*p*-ClC_6H_4CO
i	*p*-ClC_6H_4	Me	*p*-ClC_6H_4CO

8	R	R^1	R^2
j	Me	Ph	*p*-ClC_6H_4CO
k	Ph	Ph	*p*-ClC_6H_4CO
l	*p*-ClC_6H_4	Ph	*p*-ClC_6H_4CO
m	Me	Me	*p*-BrC_6H_4CO
n	Ph	Me	*p*-BrC_6H_4CO
o	*p*-ClC_6H_4	Me	*p*-BrC_6H_4CO
p	Me	Ph	*p*-BrC_6H_4CO
q	Ph	Ph	*p*-BrC_6H_4CO
r	*p*-ClC_6H_4	Ph	*p*-BrC_6H_4CO

Scheme 3.

indolizinone derivatives (**6**) and isomeric thiazino[3,4,5-*cd*]indolizines **7'a—n** (trans form). Similarly, the reactions of **4a—f** with ethyl bromoacetate (**5b**) and *t*-butyl bromoacetate (**5c**) provided the same type of products (**7g—n**) in 36—58% yields (Scheme 2). On the other hand, the reactions of **4a—f** with phenacyl (**5d**), *p*-chlorophenacyl (**5e**), and *p*-bromophenacyl bromide (**5f**) in the presence of DBU gave only trans isomers **8a—r** in 23—77% yields, and the cis isomers (**8'a—r**) could not be obtained at all (Scheme 3).

These [1,4]thiazino[3,4,5-*cd*]indolizines **7a—n** and **8a—r** were very stable compounds in contrast with pyrido[2,1-*c*][1,4]thiazines which were prepared earlier by us,[4] and did not decompose even in boiling chloroform.

These elementary analyses coincided well with the compositions expected both for our proposed thiazinoindolizines **7a—n** and **8a—r** and for *S*-alkylated 3-methylene-2(3*H*)-indolizinones **6**. However, their ^{1}H NMR spectra (Table 2) definitely excluded the possibility of structure **6** because of the absence of the singlet proton signal attributable to the *S*-methylene group. For example, the ^{1}H NMR spectrum of **7a** showed proton signals at δ=1.78 (3H, s, 5-Me), 2.49 (3H, s, 3-Me), 2.3—3.0 (2H, m, 8-H×2), 3.92 (1H, d, J=2.0 Hz, 1-H), 4.04 (1H, m, 8a-H), 6.27 (1H, m, 7-H), and 6.57 (1H, dd, J=10.0 and 2.5 Hz, 6-H); those of other compounds (**7b—n** and **8a—n, p—r**) were very similar to each other, except for the 1-H signals which appeared at δ near 4.0 as a doublet coupled with 2.0 Hz in compounds **7a—f, i, m, n**, and δ near 5.1 as a doublet coupled with 10.0 Hz in compounds **8a—n, p—r**. The inspection on the stereochemistry at the 1- and 8a-position using Dreiding models suggested that the dihedral angle for the cis isomer is about 60° and that for the trans one is about 180°. Evidently, the coupling constants expected from these dihedral angles are cis<trans,[8] and, hence, products **7a—n** are concluded to be cis isomers and **8a—r** to be trans ones. This conclusion was also supported by an X-ray analysis for one compound (**7b**) (see below). On the other hand, the structures of compounds **7g, h, j—l**, and **8o**, whose 5-H signals could not be clearly shown in their ^{1}H NMR spectra, were assigned by analogy of the reactivity of indolizinones **4a—f** toward similar alkylating agents **5b—f**.

Though the reactions of compounds **7** and **8** with some dehydrogenating agents such as chloranil and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone were also examined, the isolation of any significant products was unsuccessful.

Crystallography of Thiazinoindolizine 7b. The single crystal was grown from an ethanol solution. A red rhombic crystal of approximate size of 0.4×0.2×0.4 mm was used. The X-ray analysis data are shown in Table 3. Tables of coordinates, bond lengths, bond and torsion angles, and F_o-F_c tables are deposited as Document No. 9087 at the Office of the Editor of Bull. Chem. Soc. Jpn. The PLUTO drawing is shown in Fig. 2. As expected by the coupling constant (J=2.0 Hz) between the 1- and 8a-protons in the ^{1}H NMR spectrum of **7b**, the configuration for these protons is gauche and the calculated torsion angle (H3-C9-C10-H12 in Fig. 2) is 62°.

Reaction Mechanisms and Molecular Orbital Calculations. These reactions can be considered to proceed via the *S*-alkylation of 3-(mercaptomethylene)-2(3*H*)-indolizinone (**4a—f**) with alkylating agents **5a—f** in the presence of alkali, the cis-trans isomerization[10] of the 3-*exo*-methylene group in the resulting **6**, the abstraction of a hydrogen from the active methylene group in **9**, followed by a ring closure between the anionic and C-5 carbons in the intermediate **10** accompanied by the addition of a proton to the C-6 carbon (Scheme 4). In particular, **7a—n** (cis form) and **8a—r** (trans form) can be derived only from the ionic species **11** and **12**, respectively. In the cyclization of a similar

Table 3. Crystal and Structure Analysis Data of **7b**

Formula:	$C_{18}H_{14}N_2OS$
Formula weight:	306.38
Crystal system:	Orthorhombic
Space group:	*Pbca*; Z=8
Lattice parameters:	a=14.22(1) Å
	b=15.824(4) Å
	c=13.543(5) Å
	V=3048(3) Å^3
D_c:	1.34 g cm^{-3}
Diffractometer:	Rigaku AFC5S
Radiation:	Mo$K\alpha$ (λ=0.71069 Å)
Monochrometer:	Graphite
Scan type:	ω-2θ
2θ Max:	55°
Computer program:	TEXSAN System[a)]
Structure solution:	Direct method; MITHRIL
Hydrogen atom treatment:	Calculated, not refined
Refinement:	Full-matrix, Anisotropic
Least-squares weight:	$4F_o^2/\sigma^2(F_o^2)$
No. of observations:	1235
No. of variables:	199
Residuals R; R_w:	0.049; 0.060
Max Shift/Error:	0.03

a) See Ref. 9.

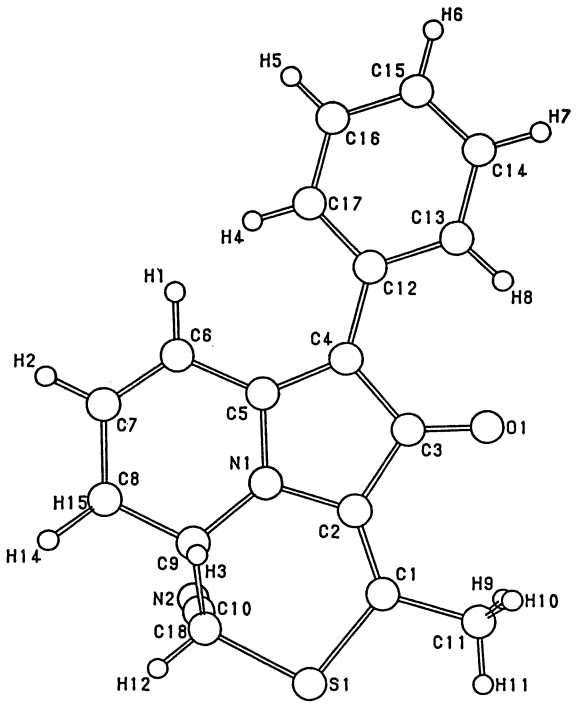
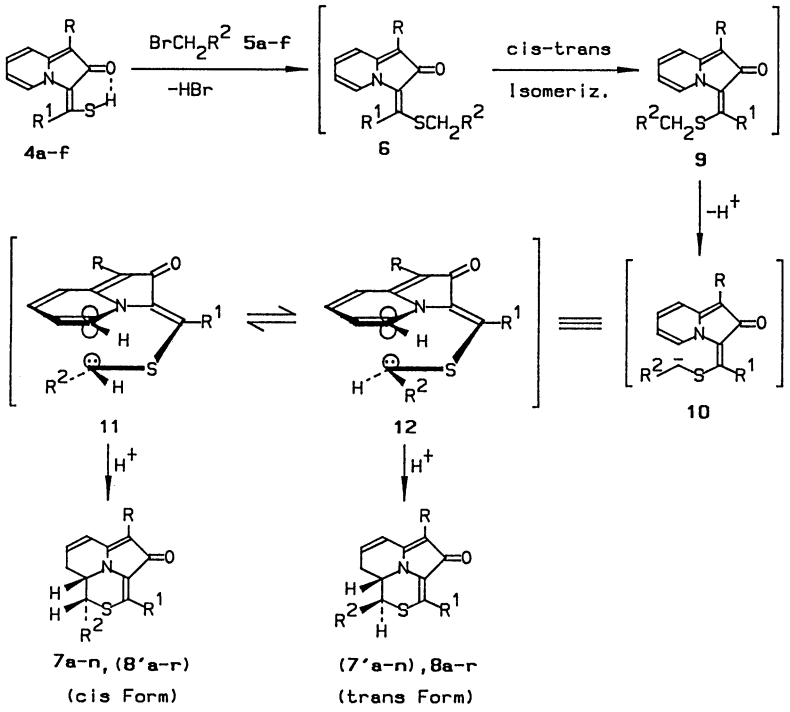


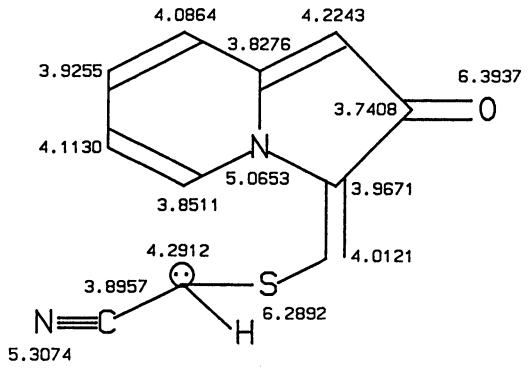
Fig. 2. The PLUTO drawing of thiazinoindolizine **7b**.

zwitterionic system **C** as shown in Fig. 1,[4] the preferential formation of 1,4-thiazine (cis form) is observed when the substituent on the carbanion is a cyano group: a preferential or exclusive one of 1,4-thiazine (trans form) is also observed when the group is an aroyl.

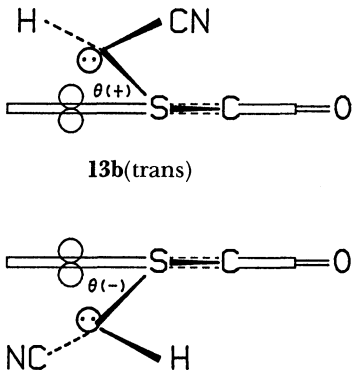
In order to explain the regioselectivity of these reactions, we performed molecular orbital calculations (CNDO/2)[6] for a model compound, 3-[(cyanomethylthio)methylene]-2(3*H*)-indolizinone (**13**) (see Fig. 3). The total energies accompanying the changes of the 3-methylene carbon-sulfur-anionic carbon angle (θ°) are listed in Table 4; from these values, the energy minima were found to be at near θ=±70°. The structure of **13** and the transition states **13a** and **13b** which correspond to intermediates **11** and



Scheme 4.



13



13b(trans)

13a(cis)

Fig. 3. The numerals on the structural formula are the total electron densities of compound **13** ($\theta = -70°$) and those of the hydrogens were omitted.

Table 4. Total Energy Changes for the Methylene Carbon-Sulfur-Anionic Carbon Angles ($\theta°$)

θ[a)]/°	Total energy/eV
80	−135.655897
75	−135.662925
70	−135.666724
67	−135.663927
66	−135.661529
65	Divergency
60	Divergency
50	Divergency
0	Divergency
−30	Divergency
−43	Divergency
−44	−135.475389
−50	−135.602564
−60	−135.640478
−65	−135.642930
−70	−135.643184
−75	−135.642655
−80	−135.641744

a) See Fig. 3 for the sign of the angle (θ).

12 in Scheme 4, respectively, are shown in Fig. 3. As might be expected, the lowered total electron density (3.8511) at the C-5 carbon in **13** ($\theta = -70°$) could be confirmed. Though the total energies of **13a** are slightly smaller than that of **13b**, the apparent predominance toward the cyclization from **13** to cis isomers such as **7a—f** can be seen because the convergent range (below $\theta = -44°$) in the cis transition state **13a** is considerably wider than that (from $\theta = 66°$) in the trans one **13b**. A similar situation seems to apply to the case of ester substituents (R^2), since compounds **7a—n** which have a cis configuration were only isolated. On the other hand, the increase in the bulkiness of the substituent (R^2=COAr) should cause a severe steric hindrance in the cis-type approach **13a** and, hence, cyclization via the trans-type approach **13b** which has no significant hindrance may be preferred exclusively.

In conclusion, a simple and convenient preparative method for [1,4]thiazino[3,4,5-*cd*]indolizine derivatives using a new reactive species was developed.

Experimental

The melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. 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; the chemical shifts are expressed in δ values. The IR spectra were taken with a Hitachi 260-10 infrared spectrophotometer.

Preparation of 3-(Mercaptomethylene)-2(3*H*)-indolizinones. General Method: An ethanolic solution (50 ml) of 1-(ethoxycarbonylmethyl)pyridinium bromide[7] (**1**, 10 mmol) was treated with a small excess of ethanolic sodium

Table 5. Some Data of 3-Methylene-2(3*H*)-indolizinones

Compd	Reactants		Yield	Mp	ν(KBr)/cm^{-1}		Formula[b)]
4[a)]	**1**	**3**	%	°C	SH	CO	
a	**a**	**a**	66	183—185	2300	1598	$C_{11}H_{11}NOS$
b	**b**	**a**	55	172—173	2285	1589	$C_{16}H_{13}NOS$
c	**c**	**a**	56	155	2280	1585	$C_{16}H_{12}ClNOS$
d	**a**	**b**	40	169—170	2550	1593	$C_{16}H_{13}NOS$
e	**b**	**b**	65	171—172	2520	1579	$C_{21}H_{15}NOS$
f	**c**	**b**	57	205—210	2500	1579	$C_{21}H_{14}ClNOS$

a) Compounds **4a**,**e** were obtained as red needles, **4b** as red flakes, **4c** as orange needles, and **4f** as red prisms. b) Satisfactory analytical data (within 0.3% for C, H, N) were obtained for all new compounds.

Table 6. Some Data of Thiazinoindolizines

Compd[a]	Reactants		Yield	Mp	ν(KBr)/cm^{-1}		Formula[b]
	4	5	%	°C	CO	CN	
7a	**a**	**a**	39	192—193	1588	2240	$C_{13}H_{12}N_2OS$
7b	**b**	**a**	45	207—210	1580	2238	$C_{18}H_{14}N_2OS$
7c	**c**	**a**	42	214—219	1585	2240	$C_{18}H_{13}ClN_2OS$
7d	**d**	**a**	39	182—183	1560	2232	$C_{18}H_{14}N_2OS$
7e	**e**	**a**	33	199—200	1587	2240	$C_{23}H_{16}N_2OS$
7f	**f**	**a**	25	195—198	1583	2240	$C_{23}H_{15}ClN_2OS$
7g	**a**	**b**	45	123—125	1593 1725		$C_{15}H_{17}NO_3S$
7h	**b**	**b**	54	171—172	1591 1727		$C_{20}H_{19}NO_3S$
7i	**c**	**b**	45	186—187	1594 1716		$C_{20}H_{18}ClNO_3S$
7j	**d**	**b**	37	107—110	1570 1729		$C_{20}H_{19}NO_3S$
7k	**e**	**b**	58	170—173	1583 1728		$C_{25}H_{21}NO_3S$
7l	**f**	**b**	53	183—184	1585 1728		$C_{25}H_{20}ClNO_3S$
7m	**a**	**c**	52	158—161	1597 1729		c)
7n	**f**	**c**	36	202—203	1581 1722		$C_{27}H_{24}ClNO_3S$
8a	**a**	**d**	62	191—193	1587 1680		$C_{19}H_{17}NO_2S$
8b	**b**	**d**	74	210—212	1600 1677		$C_{24}H_{19}NO_2S$
8c	**c**	**d**	77	215—216	1580 1669		$C_{24}H_{18}ClNO_2S$
8d	**d**	**d**	23	178—181	1564 1679		$C_{24}H_{19}NO_2S$
8e	**e**	**d**	62	181—182	1549 1666		$C_{29}H_{21}NO_2S$
8f	**f**	**d**	51	180—181	1559 1661		$C_{29}H_{20}ClNO_2S$
8g	**a**	**e**	57	214—216	1583 1677		$C_{19}H_{16}ClNO_2S$
8h	**b**	**e**	76	220—223	1566 1680		$C_{24}H_{18}ClNO_2S$
8i	**c**	**e**	64	222—228	1584 1682		$C_{24}H_{17}Cl_2NO_2S$
8j	**d**	**e**	23	126—129	1586 1675		$C_{24}H_{18}ClNO_2S$
8k	**e**	**e**	67	205—207	1587 1674		$C_{29}H_{20}ClNO_2S$
8l	**f**	**e**	71	196—198	1585 1675		$C_{29}H_{19}Cl_2NO_2S$
8m	**a**	**f**	76	205—210	1588 1678		$C_{19}H_{16}BrNO_2S$
8n	**b**	**f**	30	219—223	1580 1677		$C_{24}H_{18}BrNO_2S$
8o	**c**	**f**	74	234—239	1580 1681		d)
8p	**d**	**f**	26	192—194	1583 1679		$C_{24}H_{18}BrNO_2S$
8q	**e**	**f**	66	217—218	1584 1671		$C_{29}H_{20}BrNO_2S$
8r	**f**	**f**	64	216—220	1581 1661		$C_{29}H_{19}BrClNO_2S$

a) Compounds **7a,b** were obtained as brown prisms, **7c,g—i,m** and **8b,g,h,m** as orange needles, **7d—f,j—l,n** and **8f,l,r** as red needles, **8a,i,n,o** as orange prisms, and **8c—f,j,k,p,q** as red prisms. b) Satisfactory analytical data (within 0.3% for C, H, and N) were obtained for compounds except **7m** and **8o**. c) Found: C, 64.24; H, 6.68; N, 4.11%. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39%. d) Found: C, 57.92; H, 3.61; N, 2.50%. Calcd for $C_{24}H_{17}BrClNO_2S$: C, 57.79; H, 3.44; N, 2.81%.

ethoxide (12 mmol in 12 ml of ethanol) under stirring at room temperature for 15 min. To this reaction solution methyl dithioester (**3**, 12 mmol) was then added and the resulting mixture allowed to react under stirring for an additional hour. The reaction solution was poured into 300 ml of water and the solution was extracted twice with chloroform (150 ml). The combined chloroform layer was freed from water by filtration through phase-separating filter paper; the filtrate was concentrated under reduced pressure. The filtrate was then separated by column chromatography on alumina using chloroform as an eluent. Evaporation of the solvent and recrystallization of the crude product from ethanol gave the corresponding 3-[(mercapto)methylmethylene]- or 3-[(mercapto)phenylmethylene]-2(3*H*)-indolizinone derivatives (**4a—f**).

These results and some spectral data are listed in Tables 1 and 5.

Preparation of [1,4]Thiazino[3,4,5-*cd*]indolizines. General Method: A chloroform solution (30 ml) of 3-(mercaptomethylene)-2(3*H*)-indolizinone (**4**, 1 mmol) and an alkylating agent (**5**, 1.2 mmol) was treated with DBU (0.18 g, 1.2 mmol) under stirring at room temperature for 4—6 h. The resulting mixture was then concentrated under reduced pressure and the residue was separated by column chromatography on alumina using chloroform as an eluent. Evaporation of the solvent and recrystallization of the crude product from chloroform gave the corresponding 4(1*H*)-8,8a-dihydro[1,4]thiazino[3,4,5-*cd*]indolizinone derivatives (**7a—n** and **8a—r**).

These results and some spectral data are summarized in Tables 2 and 6.

Although several attempts to obtain the dehydro compounds from the reactions of above dihydrothiazinoindolizines **6**, and **9** with some dehydrogenating agents such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone and chloranil were carried out, the isolation of any significant products from them was unsuccessful.

References

1) For part 24 of this series, see A. Kakehi, S. Ito, T. Sakurai, K. Urushido, H. Isawa, and T. Takashima, *Chem. Pharm. Bull.*, **38**, 2667 (1990).

2) A. Kakehi, S. Ito, and S. Hatanaka, *Chem. Lett.*, **1989**,

2229.

3) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 453 (1961).

4) A. Kakehi, S. Ito, S. Yonezu, K. Maruta. and K. Yuito, *Heterocycl.*, **23**, 33 (1985); A. Kakehi, S. Ito, S. Yonezu, K. Maruta, K. Yuito, M. Shiohara, and K. Adachi, *Bull. Chem. Soc. Jpn.*, **60**, 1867 (1987); A. Kakehi, S. Ito, Y. Ohno, S. Shiba, and S. Kamata, *ibid.*, **60**, 3713 (1987).

5) C. Bodea and I. Silverg, "Advanced Heterocyclic Chemistry," John Wiley and Sons, Inc. (1968), p. 321.

6) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **44**, 3289 (1966). The program used here is an extention of the Q. C. P. E. 141.

7) A. Kakehi, S. Ito, K. Nakanishi, K. Watanabe, and M. Kitagawa, *Bull. Chem. Soc. Jpn.*, **53**, 1115 (1980).

8) R. M. Silverstain and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc. (1967), p. 131.

9) TEXSAN TEXRAY, Structure Analysis Package, Molecular Structure Corporation (1985).

10) Smooth cis-trans isomerization of the 3-methylene moiety may be owing to the contribution of the ionic structure as seen in enamines.