Preparation of New Nitrogen-Bridged Heterocycles. 40.[1] Synthesis of 1,4-Dihydropyrido[2,3-*b*]indolizin-4-one Derivatives

Akikazu Kakehi,* Suketaka Ito, Shigetoshi Hayashi, and Takashi Fujii

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380

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The title compounds, 1,4-dihydropyrido[2,3-*b*]indolizin-4-one derivatives, were prepared in moderate to good yields via the *N*-formylation of some 3-acetyl-2-(alkylamino)indolizines with triethyl orthoformate and acetic anhydride in the presence of zinc chloride followed by the intramolecular dehydration of the resulting 3-acetyl-2-(*N*-alkylformamido)indolizines under strong alkaline conditions.

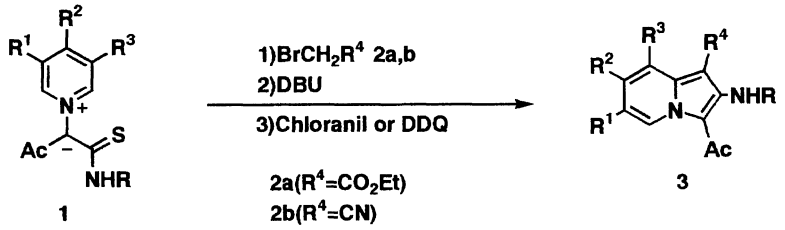
In our previous papers we described a novel and convenient preparative method for some functionalized indolizine derivatives, which are useful precursors for some fused indolizines, via ring contraction and the desulfurization or rearrangement of the corresponding pyrido[2,1-*c*][1,4]thiazine intermediate.[2] To extend this reaction sequence and confirm its utility, we examined the application to syntheses of 2-(alkylamino)indolizine derivatives with electron-withdrawing substituents at the 1- and 3-positions, which were also expected to lead easily to tricyclic indolizines fused with nitrogen-containing heterocycles such as pyrrole and pyridine. As might be expected, such 2-(alkylamino)indolizine derivatives could be synthesized starting from the corresponding acetyl[(*N*-alkyl)thiocarbamoyl](1-pyridinio)-methylides and ethyl bromoacetate or bromoacetonitrile. However, we faced a problem of severe steric hindrance in the *N*-functionalization step of these 2-(alkylamino)indolizines, and all our attempts to obtain their *N*-functionalized derivatives in the reactions with several alkylating agents, such as phenacyl halides and ethyl bromoacetate, in various alkaline conditions were unsuccessful. To avoid this severe steric hindrance, we next investigated the possibility of the introduction of smaller functional groups on the 2-substituent in these molecules, and could find its smooth *N*-formylation. In this paper we wish to report the preparation of some 3-acetyl-2-(alkylamino)indolizine derivatives and their transformation to 1,4-dihydropyrido[2,3-*b*]indolizin-4-ones via the *N*-formylation followed by the intramolecular dehydration.

Results and Discussion

Preparation of 3-Acetyl-2-(alkylamino)indolizine Derivatives. Ethyl 3-acetyl-2-(alkylamino)indolizine-1-carboxylates (**3a**—**k**) or 3-acetyl-2-(alkylamino)indolizine-1-carbonitriles (**3l**—**t**) were prepared in low to moderately yields (10—60%) via the *S*-alkylation of acetyl[(*N*-alkyl)thiocarbamoyl](1-pyridinio)methylides (**1a**—**k**) with ethyl bromoacetate (**2a**) or bromoacetonitrile (**2b**) followed by alkaline treatment of the resulting pyridinium salts and then dehydrogenation (Scheme 1), according to the procedure reported for the synthesis of 2-(alkylthio)indolizine derivatives.[2b,2c,2d,2e]

The elemental analyses of these compounds **3a**—**t** were in accord with the proposed compositions, and their IR spectra had characteristic absorption bands at 3220—3308, 1589—1628, and 1657—1701 or 2193—2205 cm^{-1} due to an amino, an acetyl carbonyl, and an ester carbonyl or a cyano group, respectively. Interestingly, the chemical shifts (δ=9.62—9.99) for the 5-proton in **3a**—**k** in the ^1H NMR spectra (see Experimental) were considerably lower than those (δ=8.36−8.72) in **3l**—**t**. This finding may show a diminished anisotropic effect of the 3-acetyl carbonyl group through a hydrogen-bonding with the 2-alkylamino groups.[3]

Preparation of 3-Acetyl-2-(*N*-alkylformamido)indolizine Derivatives. As described above, we initially examined the *N*-functionalization of these 2-(alkylamino)indolizines **3a**—**t** using some alkylating agents, such as ethyl bromoacetate (**2a**) and phenacyl bromide (**2c**). In contrast with the smooth *S*-alkylation of 2-indolizinethiols,[2e] no *N*-alkylated product **5** and/or its dehydrated pyrrolo[2,3-*b*]indolizine **6** (see Scheme 2) could be obtained, though these reactions were tried under various reaction conditions.[4] From these results, we concluded that the inaccessibility of the desired products, such as **5** and **6**, is owing to the crowding of the 2-alkylamino group. Therefore, we next examined the introduction of smaller functional substituents to the 2-alkylamino group in **3a**—**t**. After

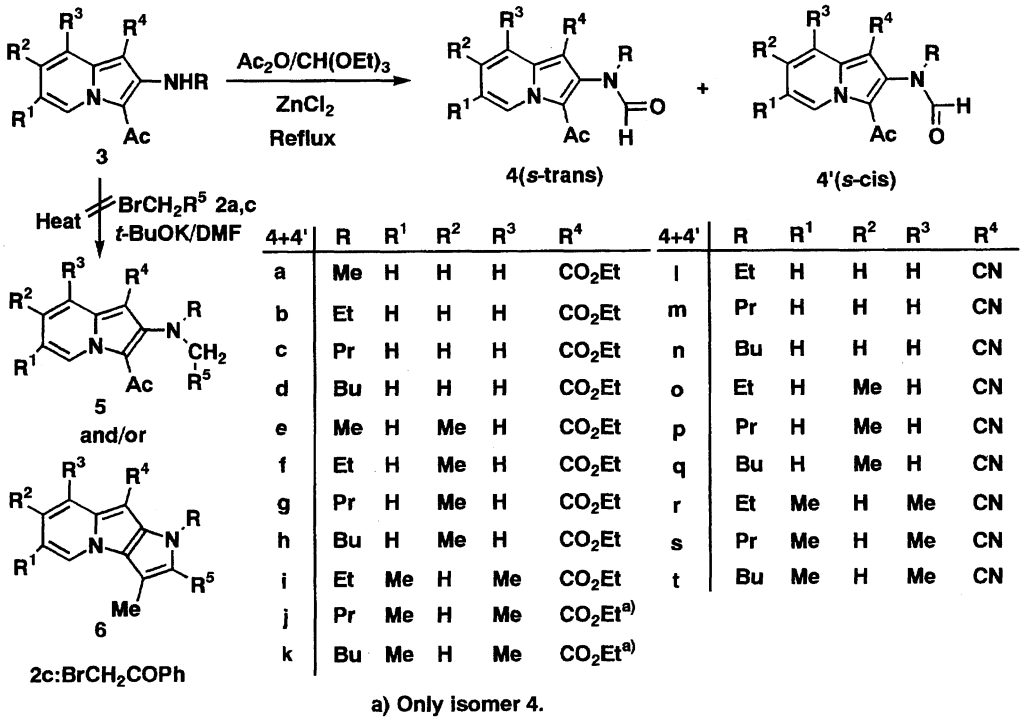


1	R	R^1	R^2	R^3
a	Me	H	H	H
b	Et	H	H	H
c	Pr	H	H	H
d	Bu	H	H	H
e	Me	H	Me	H
f	Et	H	Me	H
g	Pr	H	Me	H
h	Bu	H	Me	H
i	Et	Me	H	Me
j	Pr	Me	H	Me
k	Bu	Me	H	Me

3	R	R^1	R^2	R^3	R^4
a	Me	H	H	H	CO_2Et
b	Et	H	H	H	CO_2Et
c	Pr	H	H	H	CO_2Et
d	Bu	H	H	H	CO_2Et
e	Me	H	Me	H	CO_2Et
f	Et	H	Me	H	CO_2Et
g	Pr	H	Me	H	CO_2Et
h	Bu	H	Me	H	CO_2Et
i	Et	Me	H	Me	CO_2Et
j	Pr	Me	H	Me	CO_2Et
k	Bu	Me	H	Me	CO_2Et

3	R	R^1	R^2	R^3	R^4
l	Et	H	H	H	CN
m	Pr	H	H	H	CN
n	Bu	H	H	H	CN
o	Et	H	Me	H	CN
p	Pr	H	Me	H	CN
q	Bu	H	Me	H	CN
r	Et	Me	H	Me	CN
s	Pr	Me	H	Me	CN
t	Bu	Me	H	Me	CN

Scheme 1.



4+4'	R	R^1	R^2	R^3	R^4
a	Me	H	H	H	CO_2Et
b	Et	H	H	H	CO_2Et
c	Pr	H	H	H	CO_2Et
d	Bu	H	H	H	CO_2Et
e	Me	H	Me	H	CO_2Et
f	Et	H	Me	H	CO_2Et
g	Pr	H	Me	H	CO_2Et
h	Bu	H	Me	H	CO_2Et
i	Et	Me	H	Me	CO_2Et
j	Pr	Me	H	Me	CO_2Et[a]
k	Bu	Me	H	Me	CO_2Et[a]

4+4'	R	R^1	R^2	R^3	R^4
l	Et	H	H	H	CN
m	Pr	H	H	H	CN
n	Bu	H	H	H	CN
o	Et	H	Me	H	CN
p	Pr	H	Me	H	CN
q	Bu	H	Me	H	CN
r	Et	Me	H	Me	CN
s	Pr	Me	H	Me	CN
t	Bu	Me	H	Me	CN

a) Only isomer 4.

Scheme 2.

much elaboration we found that these 2-(alkylamino)-indolizines **3a—t** are susceptible to the *N*-formylation reaction.

The reactions of indolizines **3a—i,l—t** with triethyl orthoformate and acetic anhydride in the presence of zinc chloride in refluxing DMF gave the corresponding 3-acetyl-2-(*N*-alkylformamido)indolizine derivatives as mixtures **4a—i,l—t**+**4′a—i,l—t**. In these reactions the formation of isomers **4a—i,l—t** were always predominant, but their separation by column chromatography was unsuccessful.[5] On the other hand, similar treatment of **3j,k** afforded only isomers **4j,k** (Scheme 2).

Although the elemental analyses for these products **4a—t**+**4′a—i,l—t** were in good accord with our pro-

posed compositions and the IR spectra showed also the absence of the amino absorption bands, the ^{1}H NMR spectra distinctly exhibited that these compounds except **4j**,**k** are *s-cis* and *s-trans* mixtures related to the *N*-alkylformamido group: each set of the formyl proton singlets appeared at δ=8.30—8.40 and 8.44—8.60, respectively (see Experimental). For example, the ^{1}H NMR spectra of **4a**+**4′a** had two sets of the signals (δ=8.30 and 8.47 (each 1H, s, CHO) and δ=3.38 and 3.26 (each 3H, s, *N*-CH_3, the ratio is 1:4)), together with other completely overlapped signals appearing at δ=1.37 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.46 (3H, s, $COCH_3$), 4.32 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.08 (1H, br t, J=7.0 and 7.0 Hz, 6-H), 7.50 (1H, br t, J=9.0 and 7.0 Hz, 7-H), 8.56 (1H, br d, J=9.0 Hz, 8-H), and 10.08 (1H, br d, J=7.0 Hz, 5-H). On the other hand, that of **4j** showed only proton signals at δ=0.86 (3H, br t, J=7.0 Hz, $NCH_2CH_2\underline{CH_3}$), 1.38 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 1.2—2.0 (2H, m, $NCH_2\underline{CH_2}CH_3$), 2.36 (3H, s, 6-$CH_3$), 2.52 (3H, s, $COCH_3$), 2.55 (3H, s, 8-CH_3), 4.1—4.6 (2H, m, $N\underline{CH_2}CH_2CH_3$), 7.08 (1H, br s, 7-H), 8.39 (1H, s, CHO), and 9.80 (1H, br s, 5-H), and no proton signals for its isomer **4′j** could be detected. From the consideration of the steric factors and the shielding effect of the indolizine ring on the formyl proton in these crowding molecules, we presumed the major isomers **4a**—**t** to be *s-trans* derivatives and the other **4′a**—**i**,**l**—**t** to be *s-cis* ones. This configurational assignment for **4a**—**t**+**4′a**—**i**,**l**—**t** was finally confirmed by a single crystal X-ray analysis for one compound. The crystal and structure analysis data for ethyl 3-acetyl-2-(*N*-butylformamido)-6,8-dimethylindolizine-1-carboxylate (**4k**) are listed in Table 1.[6] An ORTEP drawing[9] for **4k** is shown in Fig. 1. As might be expected, the 2-formamido moiety is nearly palnar and has a strong olefinic character (its N–C bond length is shortened to 1.350 Å and the carbonyl bond length is fairly extended to 1.245 Å). The 1-, 2-, and 3-positions in compound **4k** are naturally crowding (the dihedral angle between least-squares planes of the indolizine ring and the formamido group is 72°) and the configuration of the formamido group was *s-trans*.

Preparation of 1,4-Dihydropyrido[2,3-*b*]indolizin-4-one Derivatives. Since the thus obtained indolizines **4a**—**t**+**4′a**—**i**,**l**—**t** have an acetyl and a formamido group at the appropriate positions

Table 1. Crystal and Structure Analysis Data of Compounds **4k** and **7i**

Compound	**4k**	**7i**
Formula	$C_{20}H_{26}N_2O_4$	$C_{18}H_{20}N_2O_3$
Formula weight	358.44	312.37
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$; Z=2	$P2_1/n$; Z=4
Lattice parameter		
a/Å	13.137 (5)	11.527 (3)
b/Å	11.450 (5)	9.918 (2)
c/Å	12.027 (6)	14.680 (3)
α/°	45.21 (2)	90
β/°	51.20 (3)	107.31 (2)
γ/°	72.78 (3)	90
V/Å^3	965 (1)	1602.4 (7)
D_{calcd}/g cm^{-3}	1.233	1.295
Crystal size/mm^3	0.20×0.68×0.88	0.10×0.32×0.68
Diffractometer	Rigaku AFC5S	Rigaku AFC5S
Radiation	Mo$K\alpha$ (λ=0.71069 Å)	Mo$K\alpha$ (λ=0.71069 Å)
Monochrometer	Graphite	Graphite
Scan type	ω–2θ	ω–2θ
Scan speed	32° min^{-1} (in ω)	32° min^{-1} (in ω)
2θ max	55.0°	55.0°
Computer program	TEXSAN system[a)]	TEXSAN system[a)]
Structure solution	MITHRIL[b)]	MITHRIL[b)]
Hydrogen atom treatment	Calcd, not refined	Observed, isotropic
Refinement	Full-matrix, anisotropic	Full-matrix, anisotropic
Least-squares weight	$4F_o^2/\sigma^2(F_o^2)$	$4F_o^2/\sigma^2(F_o^2)$
No. of measurement ref.	Total: 4622 Unique: 4427	Total: 7721 Unique: 3896
No. of observations[c)]	2146	1461
No. of variables	236	289
Residuals R; R_w	0.069; 0.086	0.047; 0.051
Max shift/Error	0.01	0.22
$\Delta\rho_{max}$/e$^-$Å^{-3}; $\Delta\rho_{min}$/e$^-$Å^{-3}	0.70; −0.31	0.17; −0.15

a) See Ref. 7. b) Direct method, see Ref. 8. c) I>3.00$\sigma(I)$.

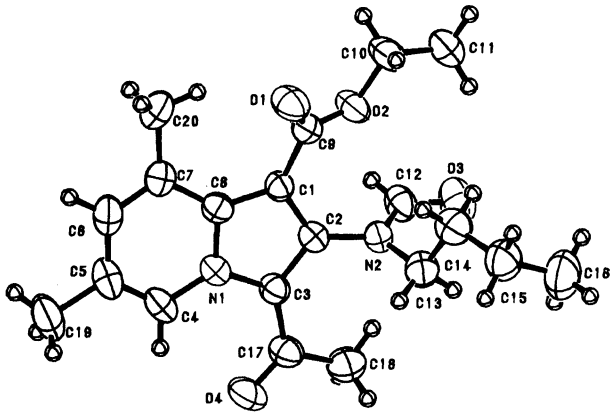


Fig. 1. ORTEP drawing of ethyl 3-acetyl-2-(*N*-butylformamido)-6,8-dimethylindolizine-1-carboxylate (**4k**) showing the atom labeling scheme and 50% probability thermal ellipsoids.

in the molecules, it was expected that the dehydration between their groups would provide the title compounds with ease. These 3-acetyl-2-(*N*-alkylformamido)indolizine derivatives **4a—i,l—t**+**4′a—i,l—t** were allowed to react in refluxing DMF in the presence of a strong base, such as potassium *t*-butoxide or sodium hydride, to provide the corresponding ethyl 1-alkyl-4-oxo-1,4-dihydropyrido[2,3-*b*]indolizin-10-carboxylates **7a—i** and 1-alkyl-4-oxo-1,4-dihydropyrido[2,3-*b*]indolizine-10-carbonitriles **7l—t** in 43—96% yields, respectively. On the other hand, similar treatment of indolizines **4j,k** did not produce any product such as **7j,k**. (Scheme 3) Though the reason why the expected **7j,k** could not be obtained is unclear, it might be owing to the severe crowding between the 1-, 2-, 3-, and 8-substituents in these molecules **4j,k**.[10]

The structures of products **7a—i,l—t** were decided by physical and spectral means: Their elemental analyses were in accord with our proposed compositions and their IR spectra showed characteristic absorption bands at 1608—1641 and 1665—1712 or 2202—2206 cm^{-1} attributable to a 4-pyridone carbonyl and an ester carbonyl or a cyano group, respectively. The ^1H NMR spectra (see Table 2) of **7a—i,l—t** had a characteristic AB quartet signals at δ=6.33—6.40 and 7.32—7.55 (its coupling constant is 8.0 Hz) and the absence of the acetyl group.

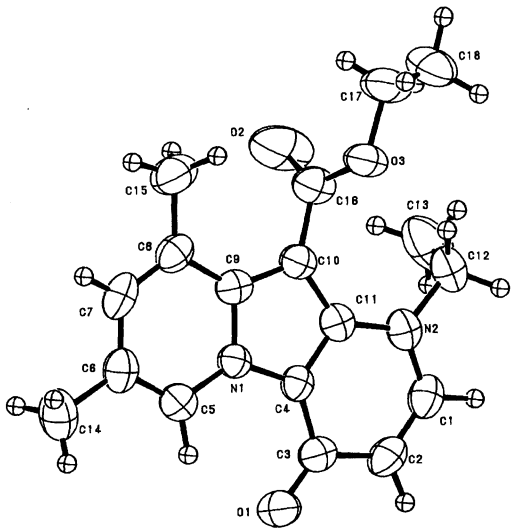
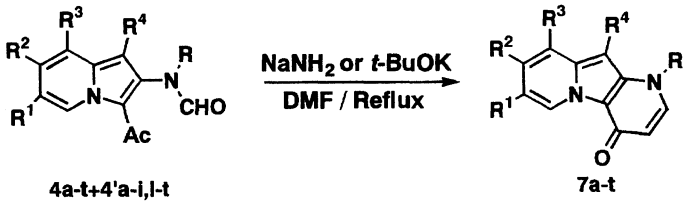


Fig. 2. ORTEP drawing of ethyl 1-ethyl-7,9-dimethyl-4-oxo-1,4-dihydropyrido[2,3-*b*]indolizine-10-carboxylate (**7i**) showing the atom labeling scheme and 50% probability thermal ellipsoids.



4a-t+4'a-i,l-t **7a-t**

7	R	R^1	R^2	R^3	R^4	7	R	R^1	R^2	R^3	R^4
a	Me	H	H	H	CO_2Et	l	Et	H	H	H	CN
b	Et	H	H	H	CO_2Et	m	Pr	H	H	H	CN
c	Pr	H	H	H	CO_2Et	n	Bu	H	H	H	CN
d	Bu	H	H	H	CO_2Et	o	Et	H	Me	H	CN
e	Me	H	Me	H	CO_2Et	p	Pr	H	Me	H	CN
f	Et	H	Me	H	CO_2Et	q	Bu	H	Me	H	CN
g	Pr	H	Me	H	CO_2Et	r	Et	Me	H	Me	CN
h	Bu	H	Me	H	CO_2Et	s	Pr	Me	H	Me	CN
i	Et	Me	H	Me	CO_2Et	t	Bu	Me	H	Me	CN
(j)	Pr	Me	H	Me	CO_2Et						
(K)	Bu	Me	H	Me	CO_2Et						

Scheme 3.

Table 2. ^{1}H NMR Spectral Data for 1,4-Dihydropyrido[2,3-*b*]indolizin-4-ones

Compd No.[a,b]	δ ($CDCl_3$)										
	C-2	C-3	C-6	C-7	C-8	C-9	R^4		N-R		
7a	7.37	6.40	10.26	7.02	7.45	8.28	4.47	1.48	4.12		
	d	d	br d	dt	br t	br d	q	t	s		
7b	7.43	6.39	10.22	6.96	7.47	8.29	4.47	1.49	4.69	1.40	
	d	d	br d	dt	br t	br d	q	t	q	t	
7c	7.41	6.38	10.24	6.96	7.41	8.26	4.46	1.49	4.65	1.3—2.2	0.88
	d	d	br d	dt	br t	br d	q	t	t	m	t
7d	7.41	6.38	10.22	6.96	7.47	8.26	4.48	1.49	4.69	1.0—2.0	0.90
	d	d	br d	dt	br t	br d	q	t	t	m	t
7e	7.36	6.38	10.15	6.85	2.50	8.08	4.48	1.50	4.12		
	d	d	d	dd	s	br s	q	t	s		
7f	7.38	6.38	10.09	6.80	2.49	8.04	4.46	1.50	4.68	1.40	
	d	d	d	dd	s	br s	q	t	q	t	
7g	7.38	6.36	10.13	6.81	2.49	8.03	4.47	1.49	4.63	1.3—2.2	0.88
	d	d	d	dd	s	br s	q	t	t	m	t
7h	7.38	6.36	10.14	6.80	2.48	8.01	4.46	1.49	4.65	1.0—2.0	0.89
	d	d	d	dd	s	br s	q	t	t	m	t
7i	7.34	6.32	9.90	2.34	6.98	2.47	4.44	1.44	4.24	1.41	
	d	d	br s	s	br s	s	q	t	q	t	
7l	7.44	6.39	10.13	7.04	7.56	7.81	—		4.39	1.57	
	d	d	br d	dt	br t	br d			q	t	
7m	7.44	6.36	10.10	7.06	7.57	7.85	—		4.33	1.3—2.2	1.01
	d	d	br d	dt	br t	br d			t	m	t
7n	7.38	6.36	10.04	7.02	7.51	7.78	—		4.37	1.0—2.0	1.00
	d	d	br d	dt	br t	br d			t	m	t
7o	7.42	6.36	9.95	6.91	2.56	7.55	—		4.46	1.58	
	d	d	d	dd	s	br s			q	t	
7p	7.55	6.39	10.03	6.93	2.56	7.63	—		4.34	1.3—2.2	1.09
	d	d	d	dd	s	br s			t	m	t
7q	7.34	6.33	9.87	6.86	2.51	7.51	—		4.33	1.0—2.0	1.00
	d	d	d	dd	s	br s			t	m	t
7r	7.36	6.36	9.84	2.38	7.10	2.81	—		4.47	1.59	
	d	d	br s	s	br s	s			q	t	
7s	7.36	6.34	9.86	2.38	7.12	2.81	—		4.36	1.3—2.2	1.06
	d	d	br s	s	br s	s			t	m	t
7t	7.32	6.33	9.81	2.37	7.10	2.80	—		4.38	1.0—2.0	0.98
	d	d	br s	s	br s	s			t	m	t

a) The coupling constants are as follows: $J_{2,3}$=8.0, $J_{6,7}=J_{7,8}$=7.0, $J_{8,9}$=9.0, $J_{7,9}$=2.0, J_{Et}=7.0 Hz.

Furthermore, the X-ray analysis for one compound completely proved these structures. The crystal and structure analysis data for ethyl 1-ethyl-7,9-dimethyl-4-oxo-1,4-dihydropyrido[2,3-*b*]indolizine-10-carboxylate (**7i**) are listed in Table 1.[6] An ORTEP drawing[9] for **7i** is shown in Fig. 2. The geometry of the indolizine ring in **7i** is very similar to that in **4k**. The 4-pyridone ring has a fairly aromatic character since this ring is almost planar and all bond lengths of the ring are in the range of 1.350—1.432 Å. Furthermore, the bond length (1.260 Å) for the carbonyl group of the 4-pyridone ring is still longer than that (1.245 Å for that in **4k**) of delocalized amide carbonyl groups.

Experimental

The melting points were measured with a Yanagimoto micromelting point apparatus and were not corrected. Microanalyses were done on a Perkin–Elmer 2400 elemental analyzer. The ^{1}H NMR spectra (60 MHz) were taken with Varian EM360A and Hitachi R-600 spectrometers in deuteriochloroform using tetramethylsilane as an internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO FT/IR-5300 infrared spectrophotometer.

Preparations of Acetyl[(*N*-alkyl)thiocarbamoyl]-(1-pyridinio)methylides. These acetyl[(*N*-alkyl)thiocarbamoyl](1-pyridinio)methylides **1a**—**k** were synthesized in 55—73% yields from the reactions of 1-acetonylpyridinium chloride (**8a**), 1-acetonyl-4-methylpyridinium chloride (**8b**), and 1-acetonyl-3,5-dimethylpyridinium chloride (**8c**) with methyl isothiocyanate (**9a**), ethyl isothiocyanate (**9b**), propyl isothiocyanate (**9c**), and butyl isothiocyanate (**9d**) in chloroform in the presence of excess potassium carbonate according to the procedure described earlier by us.[11] Some physical and spectral data for compounds **1a**—**k** are shown in Table 3.

Preparations of 3-Acetyl-2-(alkylamino)indolizine Derivatives. General Method. A chloroform solu-

Table 3. Some Data for (1-Pyridinio)methylides

Compd[a] No.	Reactants	Yield %	Mp θ_m/°C	ν(KBr)/cm^{-1} NH	CO	Formula[b]
1a	**8a+9a**	55	216—217[c]	3443	1618	$C_{10}H_{12}N_2OS$
1b	**8a+9b**	64	198—200	3409	1620	$C_{11}H_{14}N_2OS$
1c	**8a+9c**	65	188—190	3424	1620	$C_{12}H_{16}N_2OS$
1d	**8a+9d**	57	201—203	3439	1626	$C_{13}H_{18}N_2OS$
1e	**8b+9a**	73	216—217[c]	3437	1632	$C_{11}H_{14}N_2OS$
1f	**8b+9b**	71	212—214	3428	1632	$C_{12}H_{16}N_2OS$
1g	**8b+9c**	67	200—201	3428	1634	$C_{13}H_{18}N_2OS$
1h	**8b+9d**	60	207—208	3439	1640	$C_{14}H_{20}N_2OS$
1i	**8c+9b**	58	200—202	3436	1603	$C_{13}H_{18}N_2OS$
1j	**8c+9c**	61	183—184	3432	1601	$C_{14}H_{20}N_2OS$
1k	**8c+9d**	63	191—192	3451	1605	$C_{15}H_{22}N_2OS$

a) All compounds **1a**—**k** were obtained as orange needles. b) Satisfactory analyses for **1a**—**k** were obtained within ±0.30%. c) Deomp.

tion (10 ml) of (1-pyridinio)methylide (**1**, 2 mmol) and ethyl bromoacetate (**2a**, 2.4 mmol) or bromoacetonitrile (**2b**, 2.4 mmol) was kept at room temperature until the spot of the methylide in TLC monitoring had disappeared (about 12—24 h). The solution was concentrated under reduced pressure and the resulting pyridinium salt was washed three times with ether (each 20 ml) to remove excess alkylating agent. The salt was dissolved in chloroform (30 ml) and the solution was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (2.5 mmol) at 0 °C for 0.5 h and then with chloranil or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 2 mmol) at the same temperature for 12 h. The resulting solution was concentrated at reduced pressure and the residue was separated by column chromatography (alumina) using chloroform as an eluent. The combined chloroform layer was concentrated at reduced pressure and the crude crystals of 3-acetyl-2-(alkylamino)indolizines **3a**—**t** were recrystallized from ether to give pale yellow needles.

Chloranil was used as a dehydrogenating agent in the reactions of (1-pyridinio)-**1a**—**d** and (4-methyl-1-pyridinio)-methylides **1e**—**h** with **2a**,**b**, while the use of the same reagent in those of (3,5-dimethyl-1-pyridinio)methylides **1i**—**k** with **2a**,**b** did not give good results. So we used DDQ as a dehydrogenating agent in the latter.

Some physical and spectral data for compounds **3a**—**k** are shown in Table 4.

Preparations of 3-Acetyl-2-(*N*-alkylformamido)-indolizine Derivatives. General Method. A DMF solution (20 ml) of 1-acetyl-2-(alkylamino)indolizine (**3**, 2 mmol), triethyl orthoformate (2 ml), acetic anhydride (2

Table 4. Some Data for 3-Acetyl-2-(alkylamino)indolizine Derivatives

Compd[a] No.	Reactants	Yield %	Mp θ_m/°C	ν (KBr)/cm^{-1} NH	CO and/or CN		δ ($CDCl_3$)[b] Ac	5-H	Formula[c]
3a	**1a+2a**	34	59—60	3295	1657	1602	2.54	9.97	$C_{14}H_{16}N_2O_3$
3b	**1b+2a**	55	65—66	3290	1672	1602	2.57	9.99	$C_{15}H_{18}N_2O_3$
3c	**1c+2a**	30	86—87	3295	1669	1604	2.57	9.99	$C_{16}H_{20}N_2O_3$
3d	**1d+2a**	39	37—38	3308	1666	1602	2.55	9.98	$C_{17}H_{22}N_2O_3$
3e	**1e+2a**	15	83—85	3291	1666	1602	2.53	9.90	$C_{15}H_{18}N_2O_3$
3f	**1f+2a**	32	105—107	3296	1666	1610	2.55	9.98	$C_{16}H_{20}N_2O_3$
3g	**1g+2a**	24	73—74	3294	1664	1610	2.52	9.88	$C_{17}H_{22}N_2O_3$
3h	**1h+2a**	31	58—59	3290	1666	1608	2.54	9.90	$C_{18}H_{24}N_2O_3$
3i	**1i+2a**	35	65—66	3271	1684	1595	2.51	9.64	$C_{17}H_{22}N_2O_3$
3j	**1j+2a**	27	59—61	3271	1701	1628	2.52	9.62	$C_{18}H_{24}N_2O_3$
3k	**1k+2a**	33	49—50	3294	1662	1602	2.53	9.63	$C_{19}H_{26}N_2O_3$
3l	**1b+2b**	46	153—155	3270	2200	1595	2.50	8.70	$C_{13}H_{13}N_3O$
3m	**1c+2b**	60	151—153	3220	2205	1590	2.49	8.72	$C_{14}H_{15}N_3O$
3n	**1d+2b**	31	99—100	3281	2193	1628	2.49	8.67	$C_{15}H_{17}N_3O$
3o	**1f+2b**	52	177—178	3285	2203	1590	2.53	8.58	$C_{14}H_{15}N_3O$
3p	**1g+2b**	47	155—156	3290	2201	1589	2.62	8.62	$C_{15}H_{17}N_3O$
3q	**1h+2b**	19	124—125	3275	2196	1624	2.55	8.57	$C_{16}H_{19}N_3O$
3r	**1i+2b**	10	195—197	3271	2195	1595	2.53	8.44	$C_{15}H_{17}N_3O$
3s	**1j+2b**	13	131—133	3286	2198	1595	2.55	8.40	$C_{16}H_{19}N_3O$
3t	**1k+2b**	23	131—132	3271	2195	1621	2.50	8.36	$C_{17}H_{21}N_3O$

a) Compounds **3a**—**t** were obtained as pale yellow needles. b) The signals for the acetyl group and the 5-H appeared as a singlet and broad doublet, respectively. c) Satisfactory analyses for all compounds **3a**—**t** were obtained within ±0.34%.

ml), and zinc chloride (0.5 g) was heated under the reflux temperature for 2 h. The reaction mixture was concentrated at reduced pressure and the residue was separated by column chromatography on silica gel using chloroform. The combined chloroform layer involving products **4** and/or **4′** was concentrated under reduced pressure, and the crude product was recrystallized from ether.

All our attempts to separate these *s-trans* and *s-cis* mixtures **4a—i,l—t**+**4′a—i,l—t** by column chromatography were unsuccessful.

The reactions of 1-acetyl-2-(alkylamino)indolizines (**3**) with some alkylating agents, such as ethyl bromoacetate

Table 5. Some Data for 3-Acetyl-2-[(*N*-alkyl)formamido)]indolizine Derivatives

Compd[a] No.	React.	Yield %	Mp θ_m/°C	ν (KBr)/cm^{-1} CO and/or CN			δ ($CDCl_3$)[b] CHO[c]	CHO[d]	(4/4′)	Formula[e]
4a+4′a	**3a**	52	86—87	1697	1641		8.30	8.47	(4/1)	$C_{15}H_{16}N_2O_4$
4b+4′b	**3b**	86	91—93	1697	1637		8.34	8.50	(6/1)	$C_{16}H_{18}N_2O_4$
4c+4′c	**3c**	90	101—102	1691	1637		8.34	8.50	(6/1)	$C_{17}H_{20}N_2O_4$
4d+4′d	**3d**	61	95—96	1682	1635		8.31	8.46	(3/1)	$C_{18}H_{22}N_2O_4$
4e+4′e	**3e**	46	113—114	1691	1631		8.28	8.44	(7/1)	$C_{16}H_{18}N_2O_4$
4f+4′f	**3f**	58	63—64	1684	1635		8.33	8.49	(8/1)	$C_{17}H_{20}N_2O_4$[f]
4g+4′g	**3g**	55	103—105	1684	1618		8.28	8.45	(6/1)	$C_{18}H_{22}N_2O_4$
4h+4′h	**3h**	49	90—91	1680	1632		8.30	8.46	(8/1)	$C_{19}H_{24}N_2O_4$
4i+4′i	**3i**	81	94—95	1684	1618		8.38	8.48	(9/1)	$C_{18}H_{22}N_2O_4$
4j	**3j**	74	67—69	1680	1620		8.39		(1/0)	$C_{19}H_{24}N_2O_4$
4k	**3k**	59	64—66	1680	1632		8.39		(1/0)	$C_{20}H_{26}N_2O_4$
4l+4′l	**3l**	52	139—141	1691	1643	2218	8.37	8.60	(3/1)	$C_{14}H_{13}N_3O_2$
4m+4′m	**3m**	33	98—100	1688	1642	2218	8.40	8.60	(3/1)	$C_{15}H_{15}N_3O_2$
4n+4′n	**3n**	77	127—128	1682	1643	2218	8.34	8.52	(4/1)	$C_{16}H_{17}N_3O_2$
4o+4′o	**3o**	72	136—138	1682	1630	2220	8.30	8.46	(2/1)	$C_{15}H_{15}N_3O_2$
4p+4′p	**3p**	50	122—124	1689	1634	2218	8.36	8.53	(2/1)	$C_{16}H_{17}N_3O_2$
4q+4′q	**3q**	53	102—103	1689	1647	2216	8.26	8.44	(3/1)	$C_{17}H_{19}N_3O_2$
4r+4′r	**3r**	45	130—132	1697	1635	2216	8.34	8.54	(5/2)	$C_{16}H_{17}N_3O_2$
4s+4′s	**3s**	30	120—123	1688	1640	2218	8.34	8.51	(3/1)	$C_{17}H_{19}N_3O_2$
4t+4′t	**3t**	61	116—117	1698	1636	2216	8.33	8.51	(3/1)	$C_{18}H_{21}N_3O_2$

a) Compounds **3a—t** were obtained as pale yellow needles. b) The signals for the formyl proton appeared as a singlet. c) This value is for *s-trans* isomer **4**. d) This value is for *s-cis* isomer **4′**. e) Satisfactory analyses for all compounds **4a—t**+**4′a—t** were obtained within ±0.30%. f) Plus H_2O.

Table 6. Some Data for 1,4-Dihydropyrido[2,3-*b*]indolizin-2-one Derivatives

Compd[a] No.	Reactants	Yield %	Mp θ_m/°C	ν (KBr)/cm^{-1} CO		CN	Formula[b]
7a	**4a+4′a**	88	101—102	1697	1641		$C_{15}H_{14}N_2O_3$
7b	**4b+4′b**	96	111—112	1684	1635		$C_{16}H_{16}N_2O_3+H_2O$
7c	**4c+4′c**	90	120—121	1684	1636		$C_{17}H_{18}N_2O_3$
7d	**4d+4′d**	89	74—75	1682	1635		$C_{18}H_{20}N_2O_3+H_2O$
7e	**4e+4′e**	64	110—111	1689	1640		$C_{16}H_{16}N_2O_3+H_2O$
7f	**4f+4′f**	66	188—189	1691	1634		$C_{17}H_{18}N_2O_3$
7g	**4g+4′g**	62	126—127	1687	1626		$C_{18}H_{20}N_2O_3$
7h	**4h+4′h**	47	98—99	1665	1608		$C_{19}H_{22}N_2O_3$
7i	**4i+4′i**	85	170—171	1712	1616		$C_{18}H_{20}N_2O_3$
7j	**4j**	0					
7k	**4k**	0					
7l	**4l+4′l**	67	202—204	1620		2204	$C_{14}H_{11}N_3O+H_2O$
7m	**4m+4′m**	43	188—190	1618		2204	$C_{15}H_{13}N_3O$
7n	**4n+4′n**	92	202—203	1620		2204	$C_{16}H_{15}N_3O+H_2O$
7o	**4o+4′o**	66	188—189	1622		2204	$C_{15}H_{13}N_3O+H_2O$
7p	**4p+4′p**	36	205—207	1622		2204	$C_{16}H_{15}N_3O$
7q	**4q+4′q**	80	145—146	1626		2206	$C_{17}H_{17}N_3O+H_2O$
7r	**4r+4′r**	88	245—247	1620		2206	$C_{16}H_{15}N_3O$
7s	**4s+4′s**	52	270—272	1612		2202	$C_{17}H_{17}N_3O$
7t	**4t+4′t**	85	230—232	1624		2204	$C_{18}H_{19}N_3O+2H_2O$

a) Compounds **7a—i,l—t** were obtained as pale yellow needles. b) Satisfactory analyses for all compounds **7a—i,l—t** were obtained within ±0.35%.

(**2a**) and phenacyl bromide (**2c**), in the presence of a base were also unsuccessful.

Some data for compounds **4a**—**t**+**4′a**—**i**,**l**—**t** are shown in Table 5.

Preparations of 1,4-Dihydropyrido[2,3-*b*]indolizin-4-one Derivatives. General Method. A DMF solution of 3-acetyl-2-(***N***-alkylformamido)indolizine (**4**+**4′**, 1 mmol) and potassium *t*-butoxide or sodium amide (1.2 mmol) was heated under the reflux temperature for 8 h. The resulting solution was concentrated under reduced pressure and the residue was separated by column chromatography on silica gel using chloroform as an eluent.[12] The crude product was then recrystallized from ether–hexane.

In the case of dehydration of 3-acetyl-2-(*N*-alkylformamido)indolizine-1-carbonitriles **4l**—**t**+**4′l**—**t**, potassium *t*-butoxide as a basic catalyst had a sufficient effect, but it was insufficient in those with more crowding, like ethyl 3-acetyl-2-(*N*-alkylformamido)indolizine-1-carboxylates **4a**—**i**+**4′a**—**i**. In the latter cases sodium hydride was used as a base. However, ethyl 3-acetyl-6,8-dimethyl-2-(*N*-propylformamido)- **4j** and ethyl 3-acetyl-2-(*N*-butylformamido)-6,8-dimethylindolizine-1-carboxylate **4k** did not provide any products such as **7j**,**k** even under both alkaline conditions.

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

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3) This fact does not mean that the 2-alkylamino group in compounds **3a**—**k** forms a hydrogen-bonding with the 1-ethoxycarbonyl group rather than the 3-acetyl one. Judging from the chemical shifts (δ=9.8—10.1) for the 5-proton in ^{1}H NMR spectral data for 3-acetyl-2-(alkylthio)indolizine derivatives (see Refs. 2d, 2e, and 2f) and the severe steric hindrance in subsequent *N*-functionalization of compounds **3a**—**k**, the hydrogen-bonding in these compounds seems to be absent or very weak.

4) Though these reactions were examined toward other indolizines such as diethyl 2-(alkylamino)indolizine-1,3-dicarboxylates, the expected products could not be obtained at all.

5) These *s-trans* and *s-cis* products **4a**—**i**, **l**—**t** + **4′a**—**i**,**l**—**t** must be equilibrium mixtures, since each formation ratios are almostly invariable and the temperature-variable ^{1}H NMR spectrum (JEOL-FX-90Q spectrometer) of compound **4p**+**4p′** exhibited that two sets of proton signals collapse completely at over 90 °C to give only a set of proton signals.

6) Tables of the coordinates, bond lengths, bond and torsion angles, and $F_o - F_c$ tables for compounds **4k** and **7i** are deposited as Document No. 68065 at the Office of the Editor of Bull. Chem. Soc. Jpn.

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10) Since the large interaction between the 8-methyl group and the 1-ethoxycarbonyl group on the indolizine ring has been also observed (see Ref. 2d), 6,8-dimethylindolizine derivatives such as **4j**,**k** should be more crowding than the others.

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12) Though the reason is still unclear, alumina adsorbed very strongly these 1,4-dihydropyrido[2,3-*b*]indolizin-4-ones **7a**—**i**,**l**—**t** and the column separation using it did not provide good results.