Preparation of New Nitrogen-bridged Heterocycles. A Facile Synthetic Method of Pyrano[2,3-*b*]indolizinone Derivatives

Akikazu KAKEHI,* Suketaka ITO, Kazunori NAKANISHI, Kozo WATANABE, and Masahiko KITAGAWA

Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380

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Pyrano[2,3-*b*]indolizinone derivatives were formed in 18—98% yields by the reactions of 3-[bis(alkylthio)-methylene]-2,3-dihydroindolizin-2-ones with various acetates in the presence of alkali. Dihydroindolizinones were readily obtained by the alkaline treatment of 1-[2,2-bis(alkylthio)-1-ethoxycarbonylvinyl]-2-ethylpyridinium iodides and -2-methylpyridinium iodides or by the *S*-alkylation of 3-[(alkylthio)mercaptomethylene]-1-phenyl-2,3-dihydroindolizin-2-ones with alkyliodides.

In a previous paper a report was given on the unexpected formation of 3-[bis(ethylthio)methylene]-1-methyl-2,3-dihydroindolizin-2-one in the reaction of 1-[1-ethoxycarbonyl-2,2-bis(ethylthio)vinyl]-2-ethylpyridinium iodide with alkali.[1] The compound is a quite new indolizine with an interesting structure: a) dihydroaromatic: b) enone and ketene dithioacetal: c) 2-methylene-1,2-dihydropyridine. We thus assumed that, if the structural contribution such as (C) (Fig. 1) for this 3-methylene-2,3-dihydroindolizin-2-one is present, the reaction of this molecule with a bifunctional reagent may lead to the condensed indolizine derivative. This was found to be the case, pyrano[2,3-*b*]indolizinone derivative being formed by the reaction with ethyl cyanoacetate under basic conditions. In this paper we wish to report the synthesis of some 3-methylene-2,3-dihydroindolizin-2-ones and their facile transformations into pyrano[2,3-*b*]indolizinone derivatives.

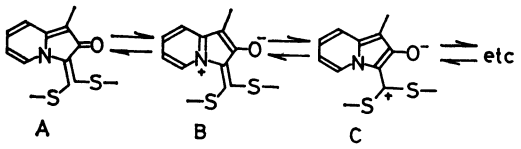


Fig. 1.

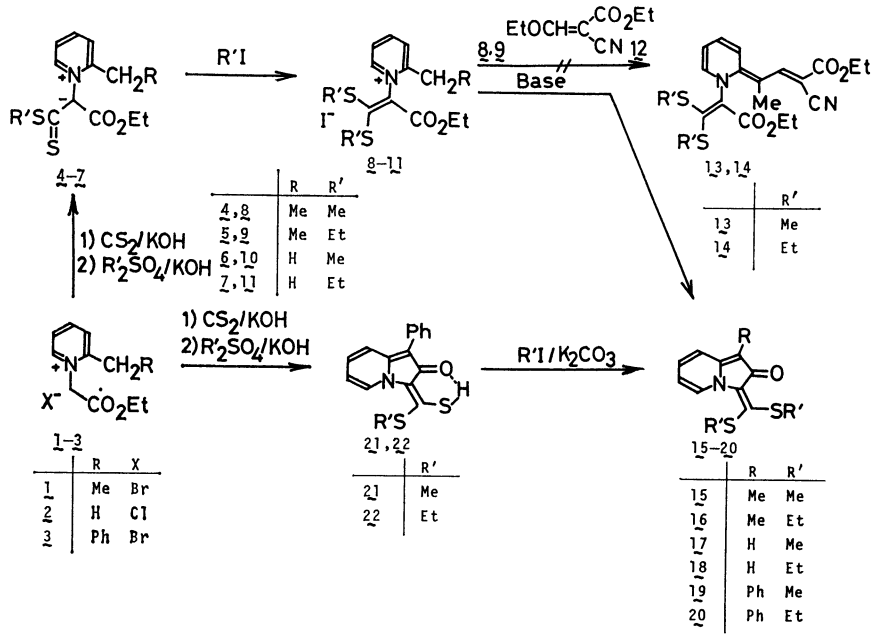
Results and Discussion

Preparation of 3-Methylene-2,3-dihydroindolizin-2-ones. The reactions of 1-[2,2-bis(alkylthio)-1-ethoxycarbonylvinyl]-2-ethylpyridinium iodides (**8** and **9**) and -2-methylpyridinium iodides (**10** and **11**), readily obtained from 1-(ethoxycarbonylmethyl)-2-ethylpyridinium bromide (**1**) and -2-methylpyridinium chloride (**2**) *via* the corresponding pyridinium ylides (**4**—**7**) (Scheme 1),[2] with alkali gave 3-[bis(alkylthio)methylene]-2,3-dihydroindolizin-2-one derivatives (**15**—**18**) as dark green prisms or oils in over 90% yields. In contrast with **10** and **11**,[3] alkaline treatment of 2-ethylpyridinium salts (**8** and **9**) in the presence of an activated ethoxymethylene compound such as ethyl (ethoxymethylene)cyanoacetate (**12**) afforded only 3-methylene-2,3-dihydroindolizin-2-ones (**15** and **16**) in comparable yields, and not the expected 2-allylidene-1,2-dihydropyridines (**13** and **14**). On the other hand, treatment of 2-benzyl-1-(ethoxycarbonylmethyl)pyridinium bromide (**3**) with carbon disulfide and then dialkyl sulfate in the presence of potassium hydroxide afforded 3-[(alkylthio)mercaptomethylene]-1-phenyl-2,3-dihydroindolizin-2-ones (**21** and **22**) as orange needles in 88 and 79% yields, respectively. *S*-Alkylation of the mercapto derivatives (**21** and **22**) with methyl and ethyl iodide in the presence of potassium carbonate in chloroform gave 3-[bis(alkylthio)methylene]-1-phenyl-2,3-dihydroindolizin-2-ones (**19** and **20**) in 96 and 91% yields, respectively.

The 3-methylene-2,3-dihydroindolizin-2-one derivatives (**15**, **16**, and **19**—**22**) were very stable under the usual conditions (below 80 °C), while the 1-unsubstituted derivatives (**17** and **18**) were considerably unstable even at room temperature and, in particular, very sensitive to column separation (alumina).

The structural assignment of the 2,3-dihydroindolizin-2-one derivatives (**15**—**22**) was accomplished mainly from physical and spectral data. For example, elementary analyses of the crystalline compounds (**15**, **19**, **21**, and **22**) were in good accord with the proposed structures. The IR spectra of **15**—**22** showed a strongly lowered carbonyl absorption near 1600 cm^{-1}, indicating the presence of the contribution of the polarized structure as observed in 2-methylene-1,2-dihydropyridine derivative,[4] and those of **21** and **22** exhibited also a weak mercapto absorption near 2500 cm^{-1} but no hydroxyl absorption over 3000 cm^{-1}. The IR spectra of **21** and **22** excluded the possibility of the 2-hydroxyindolizine structure. The NMR spectra (Table 1) of compounds **15**—**20**, and **21** and **22** are similar to each other, and the considerable low values of the skeletal protons in **15**—**20** in comparison with those of aromatic indolizines[5] strongly supported their dihydroindolizine structure. Furthermore, signals appearing at near δ 13 ppm in the NMR spectra of **21** and **22** should be due to the mercapto group hydrogen-bonding to the 2-carbonyl oxygen. The considerably high values of the chemical shifts of **21** and **22** as compared with those of **15**—**20** can be explained by the promoted aromatic character owing to the hydrogen-bonding.

Reactions of 3-Methylene-2,3-dihydroindolizin-2-ones with Various Acetates in the Presence of Alkali. In order to achieve transformation of these dihydroaromatic compounds (**15**—**20**) into condensed aromatic indolizine derivatives, we carried out their reactions with bifunctional reagents in the light of ketene dithioacetal chemistry.[6] We chose activated acetate derivatives, which can easily generate the nucleophilic carbanion under basic conditions and also have an electrophilic carbonyl carbon. When 3-methylene-2,3-dihydroindo-

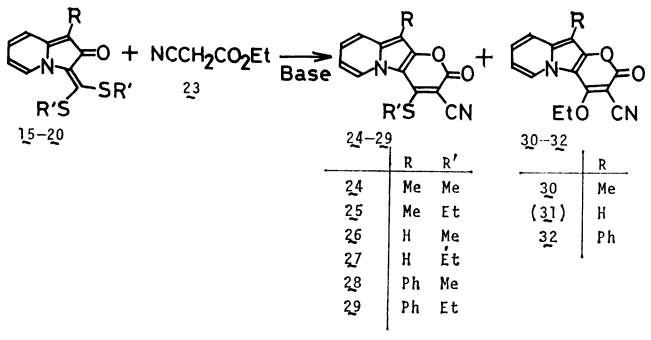


Scheme 1.

TABLE 1. NMR DATA OF 3-METHYLENE-2,3-DIHYDROINDOLIZIN-2-ONES

Compd no.	C-5	C-6	C-7	C-8	R	R′	R′(H)	Coupling constants
15	8.43 d	6.00 br t	6.5—7.0 m		1.79 s	2.37 s	2.63 s	$J_{5,6}=7.0$, $J_{6,7}=6.5$, $J_{6,8}=2.0$ Hz
16	8.59 d	5.93 dt	6.76 br t	6.53 br d	1.73 s	2.82 q 1.19 t	3.11 q 1.24 t	$J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=2.0$ Hz
17	8.55 d	6.13 br t	6.6—7.0 m		5.21 s	2.39 s	2.64 s	$J_{5,6}=7.0$, $J_{6,7}=6.5$, $J_{6,8}=2.0$ Hz
18	8.73 d	6.08 br t	6.6—7.1 m		5.17 s	2.90 q 1.24 t	3.20 q 1.27 t	$J_{5,6}=7.0$, $J_{6,7}=6.5$, $J_{6,8}=2.0$ Hz
19	8.60 d	6.15 dt	a)	a)	6.7—7.9 m	2.37 s	2.65 s	$J_{5,6}=J_{6,7}=7.0$, $J_{6,8}=1.5$ Hz
20	8.76 d	6.10 dt	b)	b)	6.7—7.8 m	2.91 q 1.24 t	3.23 q 1.28 t	$J_{5,6}=J_{6,7}=7.0$, $J_{6,8}=1.5$ Hz
21	9.40 d	6.82 dt	c)	c)	7.0—7.9 m	2.84 s	12.92[d] s	$J_{5,6}=J_{6,7}=7.0$, $J_{6,8}=1.5$ Hz
22	9.42 d	6.79 dt	c)	c)	7.0—7.9 m	3.51 q 1.44 t	12.93[d] s	$J_{5,6}=J_{6,7}=7.0$, $J_{6,8}=1.5$ Hz

a) Overlapped with phenyl signals appearing at δ 6.7—7.9. b) Overlapped with phenyl signals appearing at δ 6.7—7.8. c) Overlapped with phenyl signals appearing at δ 7.0—7.9. d) Proton of mercapto group.



Scheme 2.

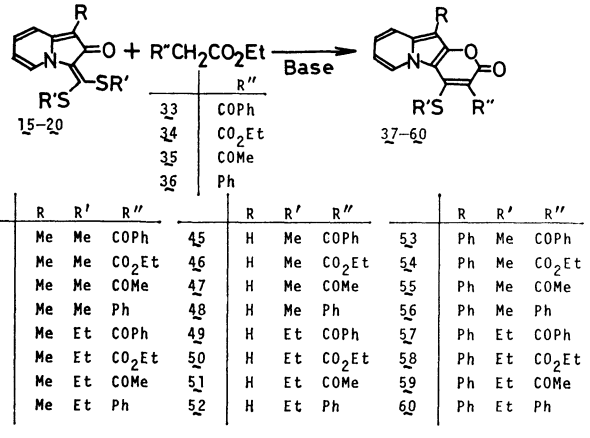
lizin-2-ones (**15**—**20**) were allowed to react with ethyl cyanoacetate (**23**) in benzene in the presence of triethylamine under reflux, smooth evolution of methanethiol or ethanethiol was observed, separation of the reaction solutions giving crystalline 4-alkylthio-3-cyano-2*H*-pyrano[2,3-*b*]indolizin-2-one derivatives (**24**—**29**). 4-Ethoxy derivatives **30** and **32** were also obtained in the reactions of **15** and **20** (Scheme 2). Furthermore, the respective replacement of the solvent and the base, benzene by ethanol and triethylamine by potassium *t*-butoxide, in the reactions of **15**, **16**, and **19** with **23** gave rise to increased formation of 4-ethoxypyranoindolizinones (**30** and **32**).

On the other hand, similar reactions of **15**—**20** with ethyl benzoylacetate (**33**), diethyl malonate (**34**), ethyl acetoacetate (**35**), and ethyl phenylacetate (**36**) in the presence of potassium *t*-butoxide gave only 4-alkylthio-2*H*-pyrano[2,3-*b*]indolizin-2-one derivatives (**37**—**60**) in 18—98% yields with the evolution of methanethiol or ethanethiol (Scheme 3). The use of triethylamine as a base in the above reactions did

Table 2. NMR data of pyrano[2,3-*b*]indolizinones

Compd no.[a]	C-6	C-7	C-8	C-9	C-10	C-3	C-4
24	9.45 d	——6.7—7.7m——			2.32 s	—	2.99 s
25	9.47 d	6.93 br t	7.33 br t	7.51 br d	2.27 s	—	3.50 q 1.41 t
26	9.46 d	——6.4—7.7m——			6.47 s	—	3.02 s
27	9.46 d	6.95 dt	7.32 br t	7.55 br d	6.39 s	—	3.53 q 1.41 t
28	9.43 d	6.99 dt	b)	b)	7.8—8.0m	—	3.01 s
29	9.59 d	6.97 dt	b)	b)	7.0—8.0m	—	3.53 q 1.46 t
30	8.78 d	c)	c)	c)	2.32 s	—	5.08 q 1.66 t
32	8.78 d	c)	c)	c)	7.2—8.0m	—	5.07 q 1.66 t
37	9.23 d	6.75 dt	7.08 br t	b)	2.30 s[d]	7.3—8.1m	2.33 s[e]
38	9.25 d	6.74 dt	7.09 br t	7.45 br d	2.28 s	4.40 q 1.39 t	2.52 s
39	9.28 d	6.82 dt	7.34 br t	7.49 br d	2.30 s	2.65 s	2.46 s
40	9.33 d	6.67 dt	6.97 br t	b)	2.32 s	7.1—7.6m	1.98 s
41	9.37 d	6.74 dt	7.08 br t	b)	2.34 s	7.3—8.1m	2.88 q 1.21 t
42	9.30 d	6.74 dt	7.08 br t	7.42 br d	2.28 s	4.41 q 1.40 t	2.97 q 1.31 t
43	9.36 d	6.78 dt	7.11 br t	7.45 br d	2.31 s	2.62 s	2.91 q 1.27 t
44	9.43 d	6.66 dt	6.98 br t	b)	2.35 s	7.2—7.6m	2.41 q 1.04 t
45	9.31 d	6.80 dt	7.10 br t	b)	6.38 s	7.3—8.1m	2.39 s
46	9.27 d	6.79 dt	7.10 bt t	7.47 br d	6.31 s	4.40 q 1.40 t	2.54 s
47	9.29 d	6.83 dt	7.15 br t	7.50 br d	6.36 s	2.66 s	2.49 s
48	9.41 d	6.70 dt	7.02 br t	b)	6.37 s	7.0—7.6m	2.03 s
49	9.43 d	6.88 dt	7.11 br t	b)	6.40 s	7.3—8.1m	2.89 q 1.21 t
50	9.51 d	6.88 dt	7.20 br t	7.58 br d	6.43 s	4.47 q 1.42 t	3.03 q 1.35 t
51	9.39 d	6.81 dt	7.13 br t	7.48 br d	6.32 s	2.61 s	2.92 q 1.29 t
52	9.50 d	6.70 dt	7.00 br t	b)	6.36 s	7.2—7.6m	2.42 q 1.05 t
53	9.38 d	6.80 dt	7.16 br t	b)	7.1—8.1m	7.1—8.1m	2.39 s
54	9.37 d	6.82 dt	7.13 br t	b)	7.2—7.9m	4.40 q 1.40 t	2.54 s
55	9.37 d	6.86 dt	b)	b)	7.0—8.0m	2.63 s	2.50 s
56	9.48 d	6.74 dt	7.04 br t	b)	7.2—7.9m	7.2—7.9m	2.03 s
57	9.55 d	6.85 dt	7.14 br t	b)	7.2—8.1m	7.2—8.1m	2.93 q 1.23 t
58	9.57 d	6.84 dt	b)	b)	7.0—8.0m	4.42 q 1.43 t	3.04 q 1.38 t
59	9.51 d	8.85 dt	b)	b)	7.0—8.0m	2.62 s	2.96 q 1.31 t
60	9.59 d	6.73 dt	7.05 br t	b)	7.1—8.0m	7.1—8.0m	2.43 q 1.07 t

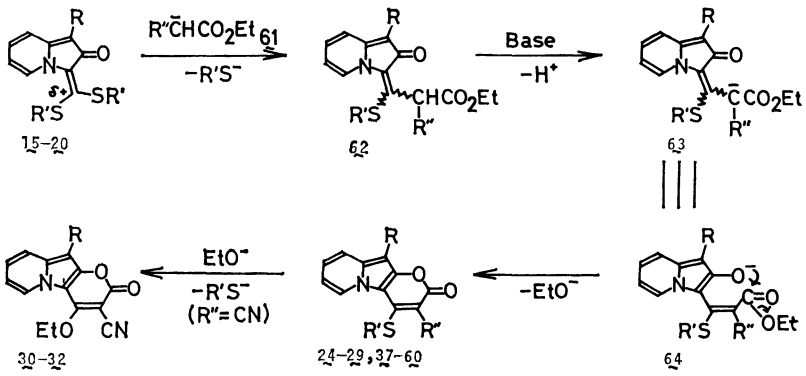
a) The coupling constants are as follows: $J_{6,7}=J_{7,8}=7.0$ Hz, $J_{8,9}=8.0$ Hz, $J_{7,9}=2.0$ Hz, and $J_{Et}=7.0$ Hz. b) Overlapped with phenyl proton signals. c) Overlapped with the C_7-, C_8-, and C_9-proton signals of the 4-alkylthiopyranoindolizinones (**24**, **25**, **28**, and **29**). d) Or 2.33. e) Or 2.30.



Scheme 3.

not give satisfactory results because of their diminished yields of pyranoindolizinones.

All the pyrano[2,3-*b*]indolizinones (**24**—**30**, **32**, and **37**—**60**) were very stable crystalline compounds with strong fluorescence. Elementary analyses of compounds **25**—**29** and **37**—**60** were in good accord with the postulated structures, the IR spectra always showing a strong absorption at 1670—1700 cm^{-1} due to the 2-pyrone carbonyl group (Table 4). As compared with 3-methylene-2,3-dihydroindolizin-2-ones (**15**—**22**), the NMR spectra of the pyranoindolizinones (**24**—**30**, **32**, and **37**—**60**) (Table 2) exhibited signals at a fairly low field attributable to the skeletal protons, whose values coincided with those of known aromatic indolizine derivatives.[5] For example, the NMR spectrum of **39** showed skeletal proton signals at δ 6.82 (1H, dt, J=7.0, 7.0, and 2.0 Hz, C_7–H), 7.34 (1H, br t, J=8.0 and 7.0 Hz, C_8–H), 7.49 (1H, br d, J=8.0 Hz, C_9–H), and 9.28 (1H, d, J=7.0 Hz, C_6–H), and methyl signals at δ 2.30 (3H, s, C_{10}–Me), 2.46 (3H, s, SMe), and 2.65 (3H, s, COMe), and the chemical shifts of the skeletal protons (δ 6.82—9.28) and of the C_{10}–Me protons (δ 2.30) were in line with those of 3-acylindolizines (δ 6.50—9.40)[3] and 1-methylindolizine (δ 2.27).[7] On the other hand, the NMR spectra of **30** and **32** were almost the same as those of 4-alkylthiopyrano[2,3-*b*]indolizin-2-ones (**24**—**29** and **37**—**60**)



Scheme 4.

TABLE 3. DATA OF 3-METHYLENE-2,3-DIHYDROINDOLIZIN-2-ONES

Compd no.	Precursor	Yield %	Mp/°C	ν_{CO}^{KBr}	ν_{SH}^{KBr}	Formula	Calcd (%) C	H	N	Found (%) C	H	N
15[a]	**8**	95	86—88	1600	—	$C_{12}H_{13}NOS_2$	57.34	5.21	5.57	57.37	5.21	5.54
16[b]	**9**	92	Oil	1600[c]	—							
17[b]	**10**	100[d]	Oil	1600[c]	—							
18[b]	**11**	100[d]	Oil	1600[c]	—							
19[a]	**21**	96	131—133	1595	—	$C_{17}H_{15}NOS_2$	65.14	4.82	4.47	65.36	4.85	4.50
20[b]	**22**	91	Oil	1600[c]	—							
21[e]	**3**	88	121—122	1572	2550	$C_{16}H_{13}NOS_2$	64.18	4.38	4.68	64.00	4.41	4.63
22[e]	**3**	79	119—121	1570	2510	$C_{17}H_{15}NOS_2$	65.14	4.82	4.47	65.02	4.83	4.46

a) Dark green prisms. b) Dark green oil. c) Neat. d) Crude yield. e) Orange needles.

except for the absence of the alkylthio signals and the presence of an ethoxyl signals (δ near 1.7 (3H, t, J=7.0 Hz) and near 5.1 (2H, q, J=7.0 Hz)). From the results and mechanistic consideration, the products **24**—**29** and **37**—**60**, and **30** and **32** were concluded to be 4-alkylthio-2*H*-pyrano[2,3-*b*]indolizin-2-one derivatives and the 4-ethoxy isomers, respectively.

Reaction Mechanism. The formation of pyranoindolizinones (**24**—**29** and **37**—**60**) is explained by the nucleophilic substitution with the carbanion (**61**), generated *in situ* by the treatment of acetates with base, at the 3-methylene position of 2,3-dihydroindolizin-2-ones (**15**—**20**), followed by the hydrogen abstraction from the resulting product (**62**) by a base catalyst and then the intramolecular nucleophilic cyclization of the anion (**64**) (*via* the primary carbanion (**63**)) with the elimination of an ethoxide ion. The fact that the primary substitution compound (**62**) was not isolated at all suggests a very fast progress of steps **62**→**63**→**64**→**24**—**29** and **37**—**60**. On the other hand, 4-ethoxypyranoindolizinones such as **30**—**32** should be formed *via* the nucleophilic substitution of 4-alkylthio-3-cyanopyranoindolizinones by the ethoxide ion generated *in situ* in these reaction systems, since, if similar substitution for 3-methylene-2,3-dihydroindolizin-2-ones (**15**—**20**) could occour initially, other 4-ethoxypyranoindolizinone derivatives should be formed together with **30** and **32**. In these reactions the reason for only the formation of 4-ethoxy-3-cyano-2*H*-pyrano[2,3-*b*]indolizin-2-ones (**30** and **32**) is not clear, but it may be related to the strong electron-withdrawing effect and the smaller hindrance of the cyano group. The mechanisms are summarized in Scheme 4.

Experimental

Melting points were measured with a Yanagimoto micro-melting point appratus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240 Elemental Analyzer. The NMR spectra were determined with a Varian EM360A NMR 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 Pyridinium Salts (**8**—**11**).* All the 1-[2,2-bis(alkylthio)-1-ethoxycarbonylvinyl]-2-ethylpyridinium iodides (**8** and **9**) and -2-methylpyridinium iodides (**10** and **11**)[2,3] were prepared from 1-(ethoxycarbonylmethyl)-2-ethylpyridinium bromide (**1**) and -2-methylpyridinium chloride (**2**) according to the procedure of Tominaga *et al.*[2] The results and some properties of new compounds (**4**, **5**, **8**, and **9**) are as follows: (**4**), 56%, yellow needles, mp 146—149 °C, Found: C, 54.86; H, 6.05; N, 4.90%. Calcd for $C_{13}H_{17}NO_2S_2$: C, 55.09; H, 6.05; N, 4.92%. (**5**), 38%, yellow needles, mp 103—106 °C, Found: C, 39.48; H, 4.78; N, 3.30%. Calcd for $C_{14}H_{20}NO_2S_2I$: C, 39.52; H, 4.74; N, 3.29%. (**8**), 91%, pale yellow prisms, mp 109—112 °C, Found: C, 56.61; H, 6.42; N, 4.63%. Calcd for $C_{14}H_{19}NO_2S_2$: C, 56.53; H, 6.44; N, 4.71%. (**9**), 86%, pale yellow prisms, mp 117—120 °C, Found: C, 42.36; H, 5.31; N, 3.22%. Calcd for $C_{16}H_{24}NO_2S_2I$: C, 42.38; H, 5.34; N, 3.09%.

*Preparation of 3-Methylene-2,3-dihydroindolizin-2-ones (**15**—**18**). General Method*: A chloroform solution (50 ml) of pyridinium salt (1 or 2 mmol) was treated with potassium carbonate (5 or 10 g) at room temperature until the TLC spot of the

Table 4. Data of pyrano[2,3-*b*]indolizinones

Compd no.	React.[a]		Base[b]	Yield %	Mp/°C	ν_{CO}^{KBr}	ν_{CN}^{KBr}	Formula	Calcd (%)			Found (%)		
									C	H	N	C	H	N
24	**15**	CA	TA	*ca* 75[c]				Mixture (**24**+**30**)						
25	**16**	CA	TA	73	266—268	1689	2200	$C_{15}H_{12}N_2O_2S$	63.36	4.25	9.85	63.49	4.18	9.75
26	**17**	CA	TA	37	265—267	1700	2215	$C_{13}H_8N_2O_2S$	60.92	3.15	10.93	61.08	3.31	10.62
27	**18**	CA	TA	71	211—214	1692	2200	$C_{14}H_{10}N_2O_2S$	62.20	3.73	10.36	62.33	3.68	10.33
28	**19**	CA	TA	*ca* 31[d]	164—167	1690	2200	$C_{19}H_{12}N_2O_2S$	68.66	3.64	8.43	68.81	3.63	8.14
29	**20**	CA	TA	74	223—226	1700	2200	$C_{20}H_{14}N_2O_2S$	69.34	4.07	8.09	69.14	4.25	8.11
37	**15**	BA	KB	98	175—177	1685		$C_{20}H_{15}NO_3S$	68.75	4.33	4.01	68.64	4.33	4.11
38	**15**	ML	KB	36	112—114	1688		$C_{16}H_{15}NO_4S$	60.55	4.76	4.41	60.59	4.73	4.69
39	**15**	AA	KB	54	158—160	1685		$C_{15}H_{13}NO_3S$	62.70	4.56	4.88	62.52	4.57	4.90
40	**15**	PA	KB	48	206—207	1684		$C_{19}H_{15}NO_2S$	71.00	4.70	4.36	71.05	4.66	4.35
41	**16**	BA	KB	91	159—162	1685	1674	$C_{21}H_{17}NO_3S$	69.40	4.72	3.85	69.06	4.72	3.83
42	**16**	ML	KB	62	140—143	1694	1725	$C_{17}H_{17}NO_4S$	61.61	5.17	4.23	61.33	5.18	4.27
43	**16**	AA	KB	60	122—125	1674	1700	$C_{16}H_{15}NO_3S$	63.76	5.02	4.65	63.49	5.05	4.59
44	**16**	PA	KB	46	156—159	1687		$C_{20}H_{17}NO_2S$	71.61	5.11	4.18	71.36	5.10	4.24
45	**17**	BA	KB	52	197—199	1670		$C_{19}H_{13}NO_3S$	68.04	3.91	4.18	68.02	3.94	4.15
46	**17**	ML	KB	41	123—125	1680	1700	$C_{15}H_{13}NO_4S$	59.39	4.32	4.62	59.67	4.32	4.68
47	**17**	AA	KB	45	103—105	1680	1668	$C_{14}H_{11}NO_3S$	61.52	4.06	5.13	61.23	4.02	5.10
48	**17**	PA	KB	18	160—161	1679		$C_{18}H_{13}NO_2S$	70.33	4.26	4.56	70.32	4.33	4.50
49	**18**	BA	KB	82	115—117	1691		$C_{20}H_{15}NO_3S$	68.75	4.33	4.01	68.75	4.34	3.99
50	**18**	ML	KB	56	121—124	1699	1730	$C_{16}H_{15}NO_4S$	60.55	4.76	4.41	60.34	4.71	4.26
51	**18**	AA	KB	60	114—116	1687	1704	$C_{15}H_{13}NO_3S$	62.70	4.56	4.88	62.55	4.64	4.87
52	**18**	PA	KB	38	136—138	1685		$C_{19}H_{15}NO_2S$	71.00	4.70	4.36	70.63	4.67	4.31
53	**19**	BA	KB	67	197—199	1680		$C_{25}H_{17}NO_3S$	72.97	4.16	3.40	72.85	4.14	3.13
54	**19**	ML	KB	50	123—125	1685	1715	$C_{21}H_{17}NO_4S$	66.47	4.52	3.69	66.76	4.53	3.48
55	**19**	AA	KB	47	124—127	1699		$C_{20}H_{15}NO_3S$	68.75	4.33	4.01	68.73	4.35	4.01
56	**19**	PA	KB	29	218—221	1682		$C_{24}H_{17}NO_2S$	75.17	4.47	3.65	74.89	4.51	3.56
57	**20**	BA	KB	61	186—188	1695		$C_{26}H_{19}NO_3S$	73.39	4.50	3.29	73.37	4.50	3.31
58	**20**	ML	KB	85	149—151	1692	1731	$C_{22}H_{19}NO_4S$	67.15	4.87	3.56	67.07	4.92	3.59
59	**20**	AA	KB	84	180—181	1689		$C_{21}H_{17}NO_3S$	69.40	4.72	3.85	69.27	4.67	4.03
60	**20**	PA	KB	80	188—191	1691		$C_{25}H_{19}NO_2S$	75.54	4.82	3.52	75.51	4.86	3.51

a) Abbreviations are as follows: CA; ethyl cyanoacetate. BA; ethyl benzoylacetate. ML; diethyl malonate. AA; ethyl acetoacetate. PA; ethyl phenylacetate. b) Abbreviations are as follows: TA; triethylamine. KB; potassium *t*-butoxide. c) Combined yield of compounds **24** and **30**. d) Combined yield with small amount of 4-ethoxypyranoindolizinone (**32**).

salt disappeared (*ca.* 10—15 h). Insoluble inorganic substances were removed from the reaction solution by filtration and the filtrate was concentrated at reduced pressure. The residues were separated by column chromatography (alumina) using ether–chloroform as an eluent in the cases of 1-methyl-3-methylene-2,3-dihydroindolizin-2-ones (**15** and **16**). However, the column separation of 1-unsubstituted 3-methylene-2,3-dihydroindolizin-2-ones (**17** and **18**) was unsuccessful because of their instability. The results and properties are given in Table 3.

*Preparation of 3-[(alkylthio)mercaptomethylene]-1-phenyl-2,3-dihydroindolizin-2-ones (**21** and **22**).* To an ethanol solution (100 ml) of 2-benzyl-1-(ethoxycarbonylmethyl)pyridinium bromide (**3**, 10 mmol) and carbon disulfide (1.1 g, 15 mmol) aq potassium hydroxide (KOH (2.8 g, 50 mmol) in 5 ml water) was added dropwise at room temperature. After the reaction mixture had been stirred for 1 h, ice water (200 ml) and then dialkyl sulfate (12 mmol) were added. The crude 3-[(alkylthio)mercaptomethylene]-1-phenyl-2,3-dihydroindolizin-2-one (**21** or **22**) precipitated was collected by filtration, dried, and recrystallized from chloroform. The results are summarized in Table 3.

*Preparation of 3-Methylene-2,3-dihydroindolizin-2-ones (**19** and **20**).* *General Method*: A chloroform solution (50 ml) of mercapto derivative (3 mmol) was treated with potassium carbonate (10 g) and methyl or ethyl iodide (4 mmol) at room temperature for 1—2 d, and the reaction mixture was filtered in order to remove insoluble substances. The filtrate was concentrated, and the residual oil was separated by column chromatography (alumina) using ether–chloroform as an eluent. The data are given in Table 3.

*Preparations of Pyrano[2,3-b]indolizinones (**24**—**30**, **32**, and **37**—**60**).* *Method A*: A benzene solution (30 ml) of 3-methylene-2,3-dihydroindolizin-2-one (1 mmol), ethyl cyanoacetate (**23**, 0.34 g, 3 mmol), and triethylamine (2 g) was allowed to react under reflux for 6—12 h. The reaction mixture was concentrated at reduced pressure, and the residual oil was separated by column chromatography (alumina). Recrystallization from chloroform–ether gave the corresponding 4-alkylthio-3-cyano-2*H*-pyrano[2,3-*b*]indolizin-2-ones (**24**—**29**) and the 4-ethoxy derivatives (**30** and **32**).

Method B: A benzene solution (30 ml) of 3-methylene-2,3-dihydroindolizin-2-one (1 mmol), the acetate (3—5 mmol), and potassium *t*-butoxide (1.5—2 mmol) was allowed to react under reflux until the TLC spot of 3-methylene-2,3-dihydroindolizin-2-one disappeared (3 h—3 d). The reaction mixture was then filtered in order to remove insoluble inorganic substances and the filtrate was concentrated at reduced pressure. The usual separation of the residual oils gave the corresponding 4-alkylthio-2*H*-pyrano[2,3-*b*]indolizin-2-one derivatives (**37**—**60**).

In the reactions of **15**, **16**, and **19** with **23**, the replacement of the solvent and base, benzene by ethanol and triethylamine by potassium *t*-butoxide, gave rise to increased formation of 4-ethoxypyranoindolizinones (**30** and **32**).

In the reactions with various acetates (**23** and **33**—**36**), 1-unsubstituted 3-methylene-2,3-dihydroindolizin-2-ones (**17** and **18**) were used without purification, the yields of pyranoindolizinones (**26**, **27**, and **45**—**52**) being estimated from the corresponding pyridinium salts (**10** and **11**).

The results and properties are summarized in Table 4.

References

1) A. Kakehi, S. Ito, K. Nakanishi, and M. Kitagawa, *Chem. Lett.*, **1979**, 297.

2) Y. Tominaga, Y. Miyake, H. Fujito, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **97**, 927 (1977).

3) A. Kakehi, S. Ito, T. Maeda, R. Takeda, M. Nishimura, M. Tamashima, and T. Yamaguchi, *J. Org. Chem.*, **43**, 4837 (1978).

4) T. Melton and D. G. Wibberley, *J. Chem. Soc., C*, **1967**, 983.

5) (a) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Tetrahedron*, **28**, 4947 (1972); (b) Y. Tamura, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2091; (c) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *ibid.*, **1973**, 2089; (d) A. Kakehi and S. Ito, *Bull. Chem. Soc. Jpn.*, **47**, 938 (1974); (e) Y. Tamura, Y. Sumida, S. Haruki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 575.

6) (a) T. Hatada, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 623 (1975); (b) Y. Tominaga, H. Fujito, K. Mizuyama, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.*, **25**, 1519 (1977); (c) Y. Tominaga, Y. Miyake, H. Fujito, K. Kurata, H. Awaya, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.*, **25**, 1528 (1977).

7) Unpublished data.