Preparation of New Nitrogen-Bridged Heterocycles. 5.[1] Smooth Michael Additions of 2(3*H*)-Indolizinone Derivatives

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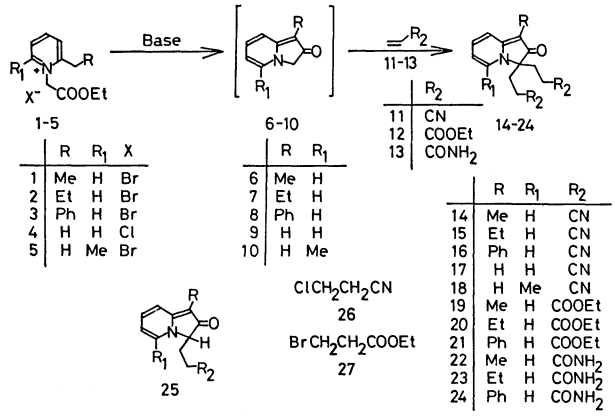
Michael additions of some 2(3*H*)-indolizinone derivatives to α,β-unsaturated nitriles, esters, and an amide gave the corresponding double Michael adducts, 3,3-disubstituted 2(3*H*)-indolizinones, in moderate to high yields, and those to methyl vinyl ketone afforded further condensed products, spiro[cyclohexane-1,3′(2′*H*)-indolizin]-2′-ones, instead of the expected 1:2 adducts. On the other hand, the reactions of the indolizinones with activated ethylenes having an appropriate leaving group at the β-position or with an acetylenic ester formed unstable 1:1 Michael adducts, which were converted to stable 2-acyloxy- or 2-alkoxy-3-vinylindolizine derivatives by the treatment with some acylating or alkylating agents in comparatively good yields.

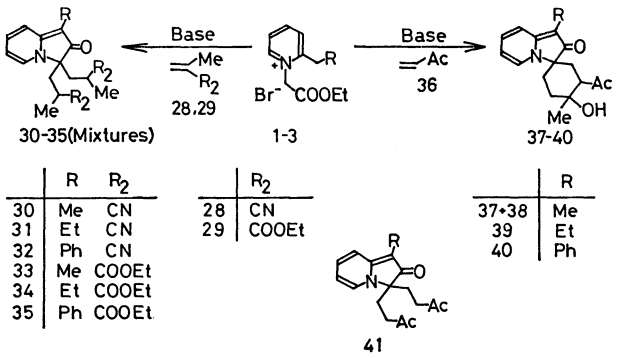
In our continuing investigation of the synthetic utilization of nitrogen-bridged heterocycles, we recently reported a facile preparative method of 2(3*H*)-indolizinone derivatives and their reactions with some alkylating and acylating agents.[1] The reactions of the indolizinones with these reagents are very useful for the preparations of simple 2-acyloxy- or 2-alkoxyindolizines and 3,3-dialkyl-2(3*H*)-indolizinones but not so for that of functionalized ones. Similarly, direct 3-vinylation of indolizines with activated ethoxymethylene compounds such as ethyl (ethoxymethylene)cyanoacetate and (ethoxymethylene)malononitrile was recently found by Masumura *et al.*[2] and by us,[3] but the application was largely restricted by the availability and thermal stability of the starting indolizines. In this paper we wish to report the one-pot and versatile syntheses of polyfunctionalized indolizine and indolizinone derivatives by way of Michael additions to 3-unsubstituted 2(3*H*)-indolizinones generated *in situ* from pyridinium salts.

Results and Discussion

Reactions of 2(3H)-Indolizinones with α,β-Unsaturated Nitriles, Esters, an Amide, and a Ketone. Since the high reactivity of the 3-methylene group in 2(3*H*)-indolizinone derivatives was proven well by the *C*-alkylation with various alkyl halides,[1] we focused next our attention on the functionalization of these indolizinones by taking advantage of their reactivity, especially the high nucleophilicity at the 3-position. As a model reaction for this purpose, Michael addition was examined under some alkaline conditions and proved to proceed successfully. For example, the reactions of 2(3*H*)-indolizinones **6**—**10**, generated *in situ* by the alkali treatment of the corresponding 1-(ethoxycarbonylmethyl)-2-methylpyridinium salts **1**—**5**, with excess acrylonitrile **11** gave yellow crystalline compounds, 3,3-bis(2-cyanoethyl)-2(3*H*)-indolizinone derivatives **14**—**18**, respectively, in various yields (0—95%) depending upon conditions used (See Table 1). Similarly, the reactions of **6**—**8** with excess ethyl acrylate **12**, and acrylamide **13** afforded the corresponding 1:2 adducts, 3,3-bis(2-ethoxycarbonylethyl)-**19**—**21** and 3,3-bis(2-carbamoylethyl)-2(3*H*)-indolizinones **22**—**24**, as products isolable each other. The products **14**, **16**, **19**, and **21** were the same with those



Scheme 1.



Scheme 2.

prepared by the reactions of **1** and **3** with 3-chloropropionitrile **26** and ethyl 3-bromopropionate **27** in the presence of alkali, respectively.[1] No 1:1 adduct such as **25**, however, could be detected in these reactions and even when equimolar amounts of olefins **11**—**13** were used.

On the other hand, the Michael additions of **6**—**8** to methacrylonitrile **28** and ethyl methacrylate **29** formed the mixtures **30**—**35** of each two stereoisomeric 1:2 adducts, respectively, which, though attempted separations were unsuccessful, were determined by the TLC and by the spectral inspection (See below). Interestingly, the reactions of **6**—**8** with methyl vinyl ketone **36** did not give the expected adduct **41** or a Robinson annelation product,[4] but afforded further condensed compounds, spiro[cyclohexane-1,3′(2′*H*)-indolizin]-2′-ones **37** and **38**, **39**, and **40** (Scheme 2).

Table 1. Some data of 3,3-disubstituted 2(3*H*)-indolizinones

Compd No.	Reactants		Yield/%[a]			Mp θ_m/°C	$\tilde{\nu}$/cm^{-1}(KBr)			Formula	Calcd(%)			Found(%)		
			A	B	C		C=O	(CN)			C	H	N	C	H	N
14	**1**	**11**	20		63	74— 75	1590	(2240)		$C_{15}H_{15}N_3O + H_2O$	66.40	6.32	15.49	66.44	6.16	15.60
15	**2**	**11**		54		138—140	1585	(2240)		$C_{16}H_{17}N_3O$	71.88	6.41	15.72	71.84	6.48	15.69
16	**3**	**11**	37		95	157—158	1605	(2240)		$C_{20}H_{17}N_3O$	76.17	5.43	13.33	75.91	5.44	13.37
17	**4**	**11**	0		19	167—169	1611	(2240)		$C_{14}H_{13}N_3O$	70.27	5.48	17.56	70.26	5.58	17.47
18	**5**	**11**		27		144—146	1600	(2245)		$C_{15}H_{15}N_3O$	71.12	5.97	16.59	71.16	6.11	16.65
19	**1**	**12**	0	75		128—130	Known compound[b]									
20	**2**	**12**		62		128—129	1734	1721	1600	$C_{20}H_{27}NO_5$	66.46	7.53	3.88	66.34	7.62	3.87
21	**3**	**12**	36	32		140—142	Known compound[b]									
22	**1**	**13**			84	260(decomp)	1663	1590		$C_{15}H_{19}N_3O_3$	62.26	6.62	14.52	62.45	6.64	14.32
23	**2**	**13**			76	223—225	1672	1578		$C_{16}H_{21}N_3O_3 + \frac{3}{2}H_2O$	58.16	7.32	12.72	58.09	7.44	12.67
24	**3**	**13**			91	190—193	1661	1595		$C_{20}H_{21}N_3O_3 + H_2O$	65.02	6.28	11.28	65.19	6.24	11.25
30	**1**	**28**	0	79		157—158	1595	(2240)		$C_{17}H_{19}N_3O + H_2O$	68.20	7.07	14.04	68.25	7.30	14.07
31	**2**	**28**			32	96— 97	1590	(2235)		$C_{18}H_{21}N_3O + \frac{1}{2}H_2O$	71.02	7.29	13.81	71.21	7.36	13.84
32	**3**	**28**	85			165—166	1600	(2240)		$C_{22}H_{21}N_3O$	76.94	6.16	12.24	76.95	6.20	12.31
33	**1**	**29**	0	52		116—118	1718	1592		$C_{21}H_{29}NO_5 + H_2O$	64.10	7.94	3.56	64.02	7.77	3.52
34	**2**	**29**			33	66— 67	1725	1600		$C_{22}H_{31}NO_5$	67.84	8.02	3.60	67.97	7.98	3.60
35	**3**	**29**	80			101—102	1724	1710	1604	$C_{26}H_{31}NO_5$	71.37	7.14	3.20	71.10	7.18	3.16
37[c]	**1**	**36**			52	182—184	1688	1594	d)	$C_{17}H_{21}NO_3$	71.05	7.37	4.87	70.78	7.46	4.84
38[e]	**1**	**36**			18	219—221	1690	1592	f)	$C_{17}H_{21}NO_3$	71.05	7.37	4.87	71.24	7.36	4.68
39[c]	**2**	**36**		48		164—166	1687	1588	g)	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	71.78	7.83	4.45
40[c]	**3**	**36**		46	92	212—214	1690	1592	h)	$C_{22}H_{23}NO_3$	75.62	6.63	4.01	75.59	6.66	4.00

a) Method A, Method B, and Method C. b) Ref. 1. c) High soluble substance. d) 3490 cm^{-1}(OH). e) Low soluble substance. f) 3170 cm^{-1}(OH). g) 3250 cm^{-1}(OH). h) 3500 cm^{-1}(OH).

In the above reactions of **6**—**10** with **11**—**13**, **28**, **29**, and **36** the method C using ethanolic sodium ethoxide as a base was found better than the method A (aq potassium hydroxide as a base) and B (anhydrous potassium carbonate) from the viewpoint of the yields of the corresponding products and the reaction time (See Table 1 and Experimental).

Structural elucidations of these double Michael adducts **14**—**24** and **30**—**35** and spiro compounds **37**—**40** were accomplished mainly by the physical and spectral means and in part by considering unequivocal syntheses of **14**, **16**, **19**, and **21**. In particular, the elementary analyses of all products were in good accord with the proposed compositions and the IR spectra showed without exceptions a largely shifted 2-keto absorption band characteristic of 2(3*H*)-indolizinone derivatives in the range of 1578—1611 cm^{-1}.[1,5] In addition, the saturated cyano bands (near 2240 cm^{-1}) in **14**—**18** and **30**—**32** or the saturated ester carbonyl bands (near 1730 cm^{-1}) in **19**—**21** and **33**—**35** also supported these structures. On the other hand, the IR spectra of **37**—**40** exhibited the carbonyl bands at comparatively low region (near 1690 cm^{-1}) and the hydroxyl absorption bands at 3170—3500 cm^{-1}, which suggested the presence of a hydrogen bonding between them. In the NMR spectra of these compounds **14**—**21**, **30**—**35**, and **37**—**40** the chemical shifts and the signal patterns (Table 2) due to the protons of the 2(3*H*)-indolizinone moiety were very similar to each others and also with those of authentic 3,3-dialkyl-2(3*H*)-indolizinone derivatives.[1] In addition, the fact that compounds **30**—**35** were mixtures of two stereoisomers (not *dl*-pair) was also indicated by the NMR spectral inspection: especially, the NMR spectra of **30**, **31**, and **33** showed clearly the proton signals due to the 1-methyl or 2-ethyl group of the minor product, together with the proton signals of the major compounds.[6] On the other hand, the NMR spectra of **37**—**40** were apparently different from those of initially expected 1:2 Michael adducts such as **41**. For example, the spectrum of **37** exhibited signals at δ 1.33 (3H, s), 2.28 (3H, s), 1.4—2.7 (6H, m), 4.11 (1H, q, J=12.0 and 4.0 Hz), and 4.03 (1H, s, disappeared with deuterium oxide) attributable to a methyl attached to an sp^3 carbon, only one acetyl, three methylenes, a methine, and a hydroxyl group, respectively, together with the signals due to the 2(3*H*)-indolizinone moiety. The NMR spectra of **39** and **40** were the almost same as that of **37**, while that of **38** was slightly different from them (Table 3). Apparently, the presences of the methyl group attached to an sp^3 carbon and the hydroxyl group showed that compounds **37**—**40** were formed by the condensation between the two 3-oxobutyl groups in primary 1:2 adduct **41**. Judging from above physical and spectral data, products **14**—**24** and **30**—**35** were concluded

TABLE 2. NMR DATA OF 3,3-DISUBSTITUTED 2(3*H*)-INDOLIZINONES

Compd[a,b] No.	C-5	C-6	C-7	C-8	C-1	R_2 and/or R_3				Methylene
14	7.57 br d	6.51 dt	7.43 br t	6.93 br d	1.78 s					1.8—2.7 m
15	7.56 br d	6.53 dt	7.46 br t	6.99 br d	1.07 c) t					1.8—2.6 m
16	d)	6.59 m	d)	d)	7.1—7.9 m					1.8—2.7 m
17	7.62 br d	6.62 dt	7.50 br t	7.05 br d	5.15 s					1.9—2.7 m
18	2.64 s	6.40 br d	7.42 q	6.93 dd	5.21 s					1.9—2.7 m
20	7.43 br d	6.30 dt	7.31 br t	6.86 br d	1.16 c) t	1.16 t	1.16 t	4.09 q	4.09 q	1.7—2.7 m
30[e,f]	7.67 br d	6.51 dt	7.47 br t	7.00 br d	1.81 s	1.21 d	1.31 d			1.7—3.1 m
31[e,g]	7.62 br d	6.50 dt	7.45 br t	7.00 br d	1.12 c) t	1.21 d	1.31 d			1.7—3.1 m
32	d)	6.83 m	d)	d)	7.1—7.9 m	1.25 d	1.39 d			1.7—3.1 m
33[e,h]	7.36 br d	6.24 dt	7.28 br t	6.77 br d	1.77 s	1.08 t	i, j)			1.7—2.9 m
34	7.31 br d	6.17 dt	7.27 br t	6.76 br d	i, c)	1.08 t	i, j)			1.7—2.7 m
35	d)	6.39 m	d)	d)	7.0—7.9 m	1.09 t	i, j)			1.7—3.0 m

a) The NMR data of compounds **19** and **21** were already described in Ref. 1, while those of **22—24** could not be measured owing to the low solubility. b) The coupling constants were as follows: $J_{5,6}=J_{6,7}=7.0$ Hz, $J_{7,8}=9.0$ Hz, $J_{6,8}=1.5$ Hz or 2.0 Hz, $J_{Et}=7.0$ Hz, and $J_{CHMe}=7.0$ Hz. c) Overlapped with the methylene protons. d) Overlapped with the phenyl protons. e) Major product. f) The 1-methyl signal of minor product appeared at δ 1.83 and the other signals were overlapped with those of major product. g) The methyl signal of the 1-ethyl group of minor product appeared at δ 1.11 and the other signals were overlapped with those of major product. h) The 1-methyl signal of minor product appeared at δ 1.80 and the other signals were overlapped with those of major product. i) Overlapped with the methyl protons in the ethoxycarbonyl groups. j) These methylene signals of the ethoxycarbonyl groups appeared at δ 3.5—4.4 as complex multiplets.

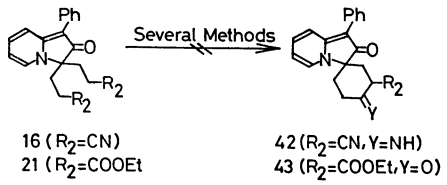
TABLE 3. NMR DATA OF SPIRO[CYCLOHEXANE-1,3′(2′*H*)-INDOLIZIN]-2′-ONES

Compd[a] No.	C-5	C-6	C-7	C-8	C-1	OH	C-Me	Ac	CHAc	Methylene
37[b]	7.56 br d	6.34 dt	7.34 br t	6.86 br d	1.77 s	4.03 s	1.33 s	2.28 s	4.11 q	1.4—2.7 m
38[c]	7.51 br d	6.38 dt	7.40 br t	6.84 br d	1.76 s	5.74 s	1.30 s	2.37 s	4.50 q	1.4—2.4 m
39[b]	7.55 br d	6.31 dt	7.31 br t	6.87 br d	1.08 d) t	4.02 s	1.33 s	2.28 s	4.10 q	1.4—2.4 m
40[b]	e)	6.50 m	e)	e)	7.1—7.9 m	4.04 s	1.36 s	2.28 s	4.15 q	1.4—2.7 m

a) The coupling constants were as follows: $J_{5,6}=J_{6,7}=7.0$ Hz, $J_{7,8}=9.0$ Hz, $J_{6,8}=1.5$ Hz, and $J_{CH_2CHAc}=12.0$ and 4.0 Hz. b) Substance with high solubility. c) Substance with low solubility. d) Overlapped with the methylene protons. e) Overlapped with the phenyl protons.

to be double Michael adducts of olefins **11—13**, **28**, and **29** to 2(3*H*)-indolizinones **6—10**, and **37—40** to be further condensed spiro[cyclohexane-1,3′(2′*H*)-indolizin]-2′-one derivatives. The stereochemistry of **30—35** and **37—40** were still uncertain, however.

The smooth formation of 3-spiroindolizinones **37—40**, perhaps *via* aldol reaction of the 1:2 adducts such as **41**, prompted us to investigate the possibility of similar cyclizations of other adducts. However, many attempts to obtain the corresponding spiro compounds



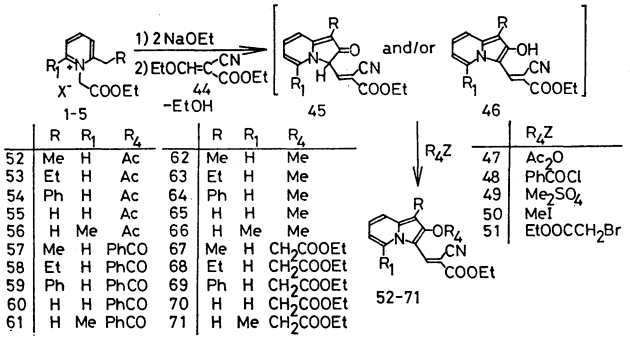
Scheme 3.

such as **42** and **43** from a nitrile **16** and an ester **21** were unsuccessful.[7]

Reactions of ***6*****—****10** *with Activated Ethylenes Possessing an Appropriate Leaving Group and an Acetylenic Ester.* In the *C*-alkylation and the Michael addition of 2(3*H*)-indolizinones such as **6**—**10**, the exclusive formation of the corresponding 3,3-disubstituted derivatives was always observed. However, in the reactions of **6** and **8**—**10** with active ethoxymethylene compounds, only 2*H*-pyrano[2,3-*b*]indolizin-2-one derivatives (formed *via* primary 1:1 Michael adducts between them) were isolated, though the yields were low.[1] The primary adducts could be detected with ease, by means of TLC, from the reaction mixtures at early stage of the addition of the ethoxymethylene compounds; however, they were very sensitive to air and a column chromatographic operation and thus they could not be isolated in pure form. In order to confirm the intermediacy of the labile adducts such as **45** and/or **46** shown in Scheme 4 and to find the method for the functionalization of these 2(3*H*)-indolizinones, their conversions to more stable derivatives, especially the replacements of the active proton at the 3-position in **45** and/or the hydroxyl proton in **46** with some acylating and alkylating agents, were attempted.

The reactions were performed stepwise as follows: 1) The treatment of pyridinium salt with two molar amounts of ethanolic sodium ethoxide (or methanolic sodium methoxide), 2) the addition of an equimolar amount of a vinylating agent, and 3) the addition of excess acylating or alkylating agent. For example, the reactions of salts **1**—**5**, ethyl (ethoxymethylene)-cyanoacetate **44**, and acetic anhydride **47** in the presence of alkali afforded yellow crystalline products, 2-acetoxy-3-vinylindolizine derivatives **52**—**56**, in 47—96% yields. Similar reactions in which benzoyl chloride **48**, dimethyl sulfate **49**, and ethyl bromoacetate **51** instead of **47** were used as an acylating or an alkylating agent gave the corresponding 2-benzoyloxy-**57**—**61**, 2-methoxy- **62**—**66**, and 2-(ethoxycarbonylmethoxy)-3-vinylindolizines **67**—**71**, respectively, as yellow or red crystals. The same 2-methoxy compounds **62** and **64** were also obtained by the reactions of **6** and **8** with **44** and methyl iodide **50**, but the yields were low (17 and 27%).

In order to establish the scope and limitation of this reaction, the uses of other ethoxymethylenes, a ketene dithioacetal, and an acetylenic ester as vinylating agents were investigated. For example, the

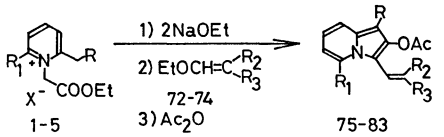


	R	R_1	R_4		R	R_1	R_4
52	Me	H	Ac	62	Me	H	Me
53	Et	H	Ac	63	Et	H	Me
54	Ph	H	Ac	64	Ph	H	Me
55	H	H	Ac	65	H	H	Me
56	H	Me	Ac	66	H	Me	Me
57	Me	H	PhCO	67	Me	H	CH_2COOEt
58	Et	H	PhCO	68	Et	H	CH_2COOEt
59	Ph	H	PhCO	69	Ph	H	CH_2COOEt
60	H	H	PhCO	70	H	H	CH_2COOEt
61	H	Me	PhCO	71	H	Me	CH_2COOEt

Scheme 4.

treatment of **6**—**10** or **6** and **8** with (ethoxymethylene)-malononitrile **72**, diethyl (ethoxymethylene)malonate **73**, and (ethoxymethylene)acetylacetone **74**, followed by the acetylation with acetic anhydride **47** gave the corresponding 2-acetoxy-3-vinylindolizine derivatives **75**—**83** in 32—91% yields (Scheme 5), while those of **6** and **8** with [bis(methylthio)methylene]malononitrile **84** and dimethyl acetylenedicarboxylate (DMAD) **87** afforded products **85**, **86**, **88**, and **89** in 75, 62, 70, and 60% yields, respectively (Scheme 6).

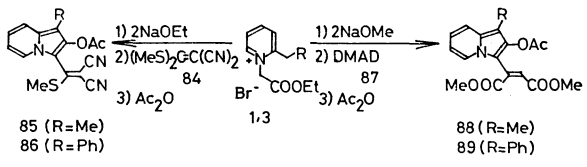
Structural assignments of these 2-(R_4-oxy)-3-vinylindolizine derivatives **52**—**71**, **75**—**83**, **85**, **86**, **88**, and **89** were achieved by their elementary analyses, spectral inspection, and partly on the basis of unequivocal syntheses. In particular, all of their elementary analyses were in good accord with the proposed compositions, and the IR spectra showed an α,β-unsaturated cyano band(s) at near 2200 cm^{-1} (**52**—**71**, **75**—**79**, **85**, and **86**) and/or an α,β-unsaturated carbonyl band(s) at 1653—1729 cm^{-1} (**52**—**71**, **80**—**83**, **88**, and **89**) attributable to the vinyl group introduced in these reactions (Table 4), but not the 2-keto carbonyl band at near 1600 cm^{-1} as seen in those of 2(3*H*)-indolizinones. The chemical shifts of the protons and alkyl protons on the indolizine ring in the NMR spectra of these products were much closer to those of aromatic indolizines rather than nonaromatic 2(3*H*)-indolizinones (Table 5). Furthermore, the chemical shifts (near δ 4.00) of the methyl protons in **62**—**66** and those (near δ 4.80) of the methylene protons in **67**—



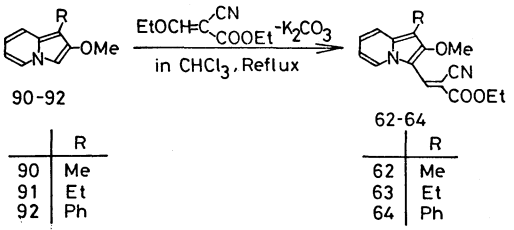
	R_2	R_3
72	CN	CN
73	COOEt	COOEt
74	Ac	Ac

	R	R_1	R_2	R_3
75	Me	H	CN	CN
76	Et	H	CN	CN
77	Ph	H	CN	CN
78	H	H	CN	CN
79	H	Me	CN	CN
80	Me	H	COOEt	COOEt
81	Ph	H	COOEt	COOEt
82	Me	H	Ac	Ac
83	Ph	H	Ac	Ac

Scheme 5.



Scheme 6.



	R
90	Me
91	Et
92	Ph

	R
62	Me
63	Et
64	Ph

Scheme 7.

TABLE 4. SOME DATA OF 3-VINYLINDOLIZINES

Compd No.	Reactants			Yield %	Mp θ_m/°C	$\tilde{\nu}$/cm^{-1} (KBr) C=O	(CN)	Formula	Calcd (%) C	H	N	Found(%) C	H	N
52	**1**	**44**	**47**	96	122—124	1768 1699	(2208)	$C_{17}H_{16}N_2O_4$	65.37	5.16	8.97	65.39	5.16	8.96
53	**2**	**44**	**47**	47	49— 51	1764 1700	(2204)	$C_{18}H_{18}N_2O_4$	66.25	5.56	8.58	66.33	5.49	8.56
54	**3**	**44**	**47**	89	153—154	1765 1686	(2205)	$C_{22}H_{18}N_2O_4$	70.58	4.85	7.48	70.48	4.88	7.19
55	**4**	**44**	**47**	93	112—113	1750 1695	(2200)	$C_{16}H_{14}N_2O_4$	64.42	4.73	9.39	64.37	4.76	9.41
56	**5**	**44**	**47**	94	165—167	1770 1700	(2212)	$C_{17}H_{16}N_2O_4$	65.37	5.16	8.97	65.52	5.14	8.84
57	**1**	**44**	**48**	60	136—138	1740 1690	(2202)	$C_{22}H_{18}N_2O_4$	70.58	4.85	7.48	70.67	4.77	7.46
58	**2**	**44**	**48**	57	98—100	1725 1695	(2195)	$C_{23}H_{20}N_2O_4$	71.12	5.19	7.21	71.15	5.19	7.22
59	**3**	**44**	**48**	48	181—183	1736 1702	(2200)	$C_{27}H_{20}N_2O_4$	74.30	4.62	6.42	74.39	4.63	6.32
60	**4**	**44**	**48**	24	115—117	1740 1681	(2195)	$C_{21}H_{16}N_2O_4$	69.99	4.48	7.77	70.04	4.40	7.80
61	**5**	**44**	**48**	52	161—163	1731 1702	(2208)	$C_{22}H_{18}N_2O_4$	70.58	4.85	7.48	70.32	4.79	7.42
62	**1**	**44**	**49**	80	106—108	1689	(2208)	$C_{16}H_{16}N_2O_3$	67.59	5.67	9.85	67.80	5.68	9.85
	1	**44**	**50**	17	106—108									
63	**2**	**44**	**49**	52	80— 83	1686	(2210)	$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39	68.44	6.15	9.33
64	**3**	**44**	**49**	57	88— 90	1695	(2192)	$C_{21}H_{18}N_2O_3$	72.82	5.24	8.09	72.75	5.33	8.04
	3	**44**	**50**	27	88— 90									
65	**4**	**44**	**49**	37	78— 81	1685	(2200)	$C_{15}H_{14}N_2O_3$	66.66	5.22	10.36	66.60	5.23	10.30
66	**5**	**44**	**49**	91	113—115	1690	(2201)	$C_{16}H_{14}N_2O_3$	67.59	5.67	9.85	67.35	5.65	9.78
67	**1**	**44**	**51**	62	123—125	1741 1691	(2206)	$C_{19}H_{20}N_2O_5$	64.04	5.66	7.86	64.20	5.59	7.77
68	**2**	**44**	**51**	55	99—101	1740 1690	(2205)	$C_{20}H_{22}N_2O_5$	64.85	5.99	7.56	64.77	6.00	7.51
69	**3**	**44**	**51**	70	121—124	1719 1703	(2200)	$C_{24}H_{22}N_2O_5$	68.89	5.30	6.69	68.90	5.31	6.67
70	**4**	**44**	**51**	28	96— 98	1737 1685	(2200)	$C_{18}H_{18}N_2O_5$	63.15	5.30	8.18	63.37	5.58	7.89
71	**5**	**44**	**51**	40	130—131	1732 1680	(2195)	$C_{19}H_{20}N_2O_5$	64.04	5.66	7.86	64.00	5.63	7.82
75	**1**	**72**	**47**	91	202—204	1755	(2210)	$C_{15}H_{11}N_3O_2$	67.92	4.18	15.84	67.87	4.14	15.93
76	**2**	**72**	**47**	54	201—203	1760	(2215)	$C_{16}H_{13}N_3O_2$	68.80	4.69	15.05	69.03	4.65	15.12
77	**3**	**72**	**47**	80	178—180	1771	(2218)	$C_{20}H_{13}N_3O_2$	73.38	4.00	12.84	73.35	4.07	12.81
78	**4**	**72**	**47**	57	200—202	1770	(2210 2198)	$C_{14}H_9N_3O_2$	66.93	3.61	16.73	66.84	3.69	16.73
79	**5**	**72**	**47**	89	176—178	1772	(2208)	$C_{15}H_{11}N_3O_2$	67.92	4.18	15.84	67.70	4.30	15.84
80	**1**	**73**	**47**	32	82— 83	1754 1716	1695	$C_{19}H_{21}NO_6$	63.50	5.89	3.90	63.54	5.93	3.85
81	**3**	**73**	**47**	38	118—120	1770 1715	1700	$C_{24}H_{23}NO_6$	68.40	5.50	3.33	68.48	5.74	3.03
82	**1**	**74**	**47**	74	142—144	1765 1653		$C_{17}H_{17}NO_4$	68.22	5.72	4.68	68.37	5.62	4.63
83	**3**	**74**	**47**	76	109—112	1773 1658		$C_{22}H_{19}NO_4+H_2O$	69.65	5.58	3.69	69.88	5.39	3.64
85	**1**	**84**	**47**	75	168—171	1762	(2200)	$C_{16}H_{13}N_3O_2S$	61.72	4.21	13.50	61.85	4.15	13.43
86	**3**	**84**	**47**	62	143—145	1759	(2206)	$C_{21}H_{15}N_3O_2S$	67.54	4.05	11.25	67.55	4.16	11.28
88	**1**	**87**	**47**	70	115—117	1760 1729	1693	$C_{17}H_{17}NO_6$	61.63	5.17	4.23	61.66	5.15	4.21
89	**3**	**87**	**47**	60	91— 94	1770 1722	1706	$C_{22}H_{19}NO_6$	67.17	4.87	3.56	67.21	4.87	3.52

71 derived from the alkylating agents **49**—**51** showed definitely that both groups were attached on an oxygen atom but not on the other atoms. Independent syntheses of 2-methoxy-3-vinylindolizines **62**—**64**, that is to say, the direct 3-vinylation of 2-methoxyindolizines **90**—**92** with **44** in the presence of alkali supported these proposed structures (Scheme 7). On the other hand, the configuration of the 3-vinyl moiety in **52**—**71** were concluded to be *trans* by the comparisons of the chemical shifts (δ 8.23—8.43) of the vinyl protons with those of similar 1-[8] and 3-vinylindolizines[2] and 3-vinylpyrazolo[1,5-*a*]pyridines,[9] but that in **88** and **89** were assigned tentatively to be *cis* by similar comparison of the vinyl proton signals at δ 6.18 and 6.30 with those at δ 6.48 and 6.80 in dimethyl maleate and dimethyl fumarate, respectively.

Reaction Mechanisms. Possible mechanisms for these reactions are summarized concisely in Scheme 8. Path a leading to compounds **14**—**24**, **30**—**35**, and **37**—**40** is the double Michael addition of electron-poor olefins **11**—**13**, **28**, **29**, and **36** to 3-unsubstituted 2(3*H*)-indolizinones **6**—**10** in the presence of alkali, and, in part, followed by the Aldol reaction of the primary 1:2 adducts such as **41**, and Path b leading to 2-(R_4-oxy)-3-vinylindolizines **52**—**71**, **75**—**83**, **85**, **86**, **88**, and **89** is the single Michael addition of vinylating agents **44**, **72**—**74**, **84**, and **87** to **6**—**10** and the elimination of one molecule of ethanol from **93**, followed by keto–enol isomerization and finally by the *O*-acylation or the *O*-alkylation of the resulting 3-vinyl-2-indolizinol **95**. Recently, the isolation of 2-indolizinol such as **95** in the reaction of 2,6-dimethylpyridinium salt **5** with a ketene dithioacetal was reported by Kobayashi *et al.*[10] The reason for the different behavior between the 1:1 and 1:2 Michael additions in these reactions was still uncertain, but the steric effect of the incoming olefins and the influence of the conjugation of the 3-vinyl group may be con-

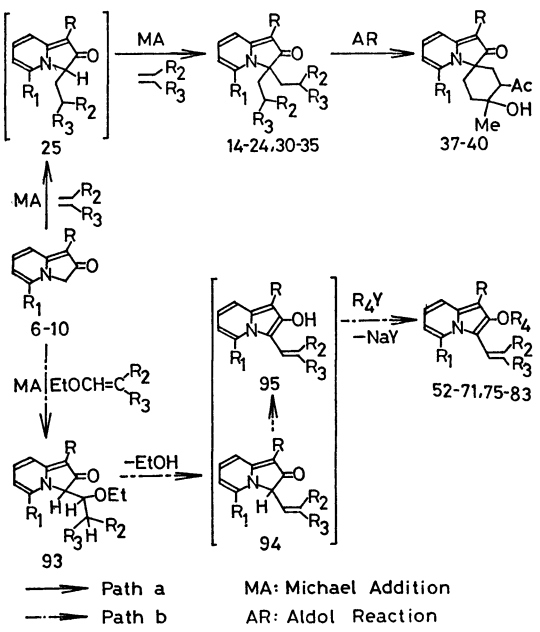
Table 5. NMR data of 3-vinylindolizines

Compd[a] No.	C-5	C-6	C-7	C-8	C-1	Vinyl R_2 and R_3				R_4
52	8.28 br d	6.88 dt	7.17 br t	7.47 br d	2.13 s	8.28 s	1.37 t	4.38 q		2.55 s
53	8.33 br d	6.91 dt	7.18 br t	7.52 br d	1.20 t 2.61 q	8.31 s	1.38 t	4.35 q		2.52 s
54	8.36 br d	6.96 dt	—b)—		7.0—7.8 m	8.39 s	1.37 t	4.34 q		2.34 s
55	8.30 br d	6.92 dt	7.19 br t	7.50 br d	6.82 s	8.38 s	1.40 t	4.38 q		2.50 s
56	2.88 s	6.67 br d	7.02 q	7.39 dd	6.82 s	8.77 s	1.40 t	4.38 q		2.51 s
57	b)	6.93 dt	b)	b)	2.18 s	8.30 s	1.33 t	4.30 q		7.0—8.5 m
58	b)	6.95 dt	b)	b)	1.19 t 2.66 q	8.31 s	1.30 t	4.29 q		7.1—8.6 m
59	b)	6.97 dt	b)	b)	7.1—7.9 m	8.37 s	1.38 t	4.28 q		7.1—8.5 m
60	b)	6.93 dt	b)	b)	6.83 s	8.40 s	1.36 t	4.33 q		7.1—8.6 m
61	2.83 s	6.62 br d	7.02 q	b)	6.77 s	8.75 s	1.33 t	4.30 q		7.3—8.5 m
62	8.29 br d	6.82 dt	7.13 br t	7.38 br d	2.30 s	8.23 s	1.38 t	4.33 q		4.07 s
63	8.38 br d	6.90 dt	7.18 br t	7.49 br d	1.25 t 2.80 q	8.31 s	1.38 t	4.35 q		4.08 s
64	8.37 br d	6.90 dt	b)	b)	7.0—7.7 m	8.37 s	1.40 t	4.37 q		3.77 s
65	8.33 br d	6.82 dt	7.13 br t	7.38 br d	6.08 s	8.27 s	1.37 t	4.33 q		4.00 s
66	2.82 s	6.59 br d	7.02 q	7.27 dd	6.13 s	8.68 s	1.38 t	4.32 q		4.03 s
67	8.40 br d	6.91 dt	7.20 br t	7.43 br d	2.29 s	8.41 s	1.38 t	4.37 q		4.86 c) s
68	8.42 br d	6.93 dt	7.20 br t	7.38 br d	1.25 t 2.80 q	8.43 s	1.30 t	4.38 q		4.82 d) q
69	8.46 br d	6.95 dt	b) br t	b) br d	7.0—7.7 m	8.53 s	1.39 t	4.37 q		4.53 e) s
70	8.42 br d	6.90 dt	7.20 br t	7.31 br d	6.03 s	8.38 s	1.38 t	4.38 q		4.81 f) s
71	2.84 s	6.63 br d	7.04 q	7.30 dd	6.06 s	8.78 s	1.37 t	4.33 q		4.85 g) s
75	8.23 br d	7.00 dt	7.27 br t	7.53 br d	2.15 s	7.57 s				2.52 s
76	8.27 br d	7.00 dt	7.28 br t	7.57 br d	1.19 t 2.61 q	7.57 s				2.51 s
77	8.29 br d	7.02 dt	b)	b)	7.1—7.8 m	7.67 s				2.32 s
78	8.25 br d	7.00 dt	7.28 br t	7.55 br d	6.90 s	7.63 s				2.50 s
79	2.85 s	6.75 br d	7.16 q	7.42 dd	6.88 s	8.08 s				2.48 s
80	8.08 br d	6.73 dt	7.00 br t	7.42 br d	2.12 s	7.98 s	1.23 t	1.33 t	4.33 q 4.35 q	2.35 s
81	8.11 br d	6.91 dt	b)	b)	7.0—7.8 m	8.00 s	1.29 t	1.34 t	4.32 q 4.37 q	2.17 s
82	8.12 br d	6.79 dt	7.07 br t	7.76 br d	2.13 s	7.97 s	2.30 s	2.37 s		2.37 s
83	8.19 br d	6.87 dt	b)	b)	7.0—7.8 m	8.01 s	2.13 s	2.36[h] s		2.43[i] s
85	8.39 br d	6.87 dt	7.10 br t	7.46 br d	2.18[j] s	2.20[k,l] s				2.41 s
86	8.40 br d	b)	b)	b)	6.7—7.8 m	2.29[l] s				2.29 s

TABLE 5. (Continued)

Compd[a] No.	C-5	C-6	C-7	C-8	C-1	Vinyl R_2 and R_3			R_4
88	8.30 br d	6.67 dt	6.91 br t	7.41 br d	2.08 s	6.18 s	3.75 s	3.90 s	2.30 s
89	8.37 br d	6.73 dt	6.97 br t	b) br d	7.1—7.8 m	6.30 s	3.80 s	3.94 s	2.19 s

a) The coupling constants were as follows: $J_{5,6}=J_{6,7}=7.0$ Hz, $J_{7,8}=9.0$ Hz, $J_{6,8}=1.5$ Hz, and $J_{Et}=7.0$ Hz. b) Overlapped with the phenyl protons. c) The ethoxycarbonyl signals appeared at δ 1.29 (t) and 4.27 (q). d) The ethoxycarbonyl signals appeared at δ 1.30 (t) and 4.28 (q). e) The ethoxycarbonyl signals appeared at δ 1.17 (t) and 4.10 (q). f) The ethoxycarbonyl signals appeared at δ 1.30 (t) and 4.29 (q). g) The ethoxycarbonyl signals appeared at δ 1.28 (t) and 4.28 (q). h) Or δ 2.43. i) Or δ 2.36. j) Or δ 2.20. k) Or δ 2.18. l) The methylthio protons.



Scheme 8.

sidered.

Since effective functionalization of indolizine nucleus, except the synthesis of cyclazine[11] and the route *via* 2-allylidene-1,2-dihydropyridine,[8] are scarcely found, our present reactions using the Michael additions of 3-unsubstituted 2(3*H*)-indolizinones may provide useful routes for the preparations of condensed indolizine series owing to the simplicity of the procedure and of easy availability of starting materials.

Experimental

Melting points were measured with a Yanagimoto MP-S3 micromelting point apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240 elemental analyzer. The 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.

Reactions of 2(3H)-Indolizinones ***6—10*** *with α,β-Unsaturated Nitriles, Esters, an Amide, and a Ketone. Method A*: To an ethanolic solution (60 ml) of 1-(ethoxycarbonylmethyl)-2-methylpyridinium salts (**1—5**, 5 mmol) and α,β-unsaturated compound (**11—13**, **28**, **29**, and **36**, 20 mmol) was added dropwise aqueous potassium hydroxide (5.5 mmol in 1 ml of water) with stirring at room temperature. After the addition the reaction mixture was stirred at the same temperature for about 2 h until the 2(3*H*)-indolizinone (**6—10**) formed *in situ* was disappeared (detected by TLC) and then filtered to remove insoluble substances. The filtrate was concentrated under reduced pressure, and the residue was separated by column chromatography (alumina) using ether and then chloroform as eluents. Recrystallization from chloroform–hexane gave yellow or orange crystals.

Method B: In similar procedure with Method A, anhydrous potassium carbonate (10 g) as a base was employed and the reactions required more prolonged times (12—24 h) than those in Method A.

Method C: As in Method B, ethanolic sodium ethoxide (5 mmol in 5 ml of ethanol) as a base was used and the reactions required the shortest times (1—2 h) among those in the three methods. On the other hand, the reactions of **6—8** with acrylamide **13** were carried out successfully at 60—70 °C for 1 h, since they were very slow at room temperature.

In the reactions of **6—8** with methacrylonitrile **28** and ethyl methacrylate **29**, the fact that these products **30—35** were mixtures of two stereoisomers (the individual isomers must be *dl*-pair or meso) was indicated by the TLC and also by the NMR spectra. However, our attempts to separate them were unsuccessful. In the reactions of **7** and **8** with methyl vinyl ketone **36** the low soluble products such as **37** could not be obtained. These results and spectral data are summarized in Tables 1—3.

Reactions of ***6*** *and* ***8*** *with 3-Chloropropionitrile* ***26*** *and Ethyl 3-Bromopropionate* ***27***. *General Method*: A mixture of pyridinium salt (**1** or **3**, 5 mmol) and halide (**26** or **27**, 20 mmol) was treated with ethanolic sodium ethoxide (10 mmol in 10 ml of ethanol) in ethanol (60 ml) with stirring at room temperature for 2 h. The resulting brown solution was filtered, and the filtrate was then concentrated at reduced pressure. The same work-ups of the residues as shown in Method A gave yellow crystalline compounds **14**, **16**, **19**, and **21** in 57, 76, 67, and 89% yields, respectively. These compounds **14**, **16**, **19**, and **21** coincided with those prepared above and also with authentic samples[1] in all respects.

Reactions of ***6—10*** *with Activated Ethylenes Possessing an Appropriate Leaving Group and an Acetylenic Ester. General Method*: Pyridinium salt (**1—5**, 3 mmol) dissolved completely in ethanol (50 ml) was heated with an ethanolic sodium ethoxide (6 mmol in 6 ml of ethanol) at 60—70 °C for 2—3 min and then an equimolar amount of vinylating agent (**44**, **72—74**, **84**, or **87**, 3 mmol) was added at once to the reaction mixture. After 1—2 min excess acylating or alkylating agent (**47—51**, 2 ml) was added and the resulting solution

was allowed to react for additional 30 min at the same temperature. The reaction mixture was filtered to remove insoluble inorganic substances and the filtrate was concentrated at reduced pressure. The residue was separated by column chromatography (alumina) using ether and then chloroform as eluents. Recrystallizations from ethanol or chloroform–hexane gave yellow (**52**—**56**, **62**—**71**, **75**—**83**, **88**, and **89**) or red needles (**57**—**61**, **85**, and **86**).

On the other hand, the reactions of **1** and **3** with dimethyl acetylenedicarboxylate **87** were performed in the presence of sodium methoxide as a base in methanol. These results and some data are summarized in Tables 4 and 5.

*Reactions of 2-Methoxyindolizines **90**—**92** with Ethoxymethylene Compound **44**.* *General Method*: A mixture of 2-methoxyindolizine (**90**—**92**, 1 mmol) and ethyl (ethoxymethylene)-cyanoacetate **44** (1 mmol) was heated under reflux in the presence of potassium carbonate (5 g) in chloroform (50 ml) for 3 d. The reaction mixture was filtered and the filtrate was concentrated at reduced pressure. The same work-ups of the residues as indicated in the syntheses of 3-vinylindolizines gave the corresponding 2-methoxy-3-vinylindolizine derivatives **62**—**64** in 81, 89, and 24% yields, respectively. These products **62**—**64** were in accord with those synthesized by the reactions of **6**—**8** with **44** and **49** or **50** in all respects.

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7) The alkaline conditions employed usually in Thorpe and Diechmann condensations were carried out (sodium ethoxide/benzene, potassium *t*-butoxide/toluene, sodium hydride/DMSO, and so on).
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