Preparation of New Nitrogen-Bridged Heterocycles. 39.[1] One-Pot Synthesis of 2*H*-Pyrano[3,2-*a*]indolizin-2-one Derivatives

Akikazu Kakehi,* Suketaka Ito, and Ken Matsubara

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

(Received March 23, 1995)

Various ethyl 2-(3-cyanoallylidene)- or 2-[3-(ethoxycarbonyl)allylidene]-1,2-dihydropyridin-1-ylacetates were prepared from the reactions of 1-(1-ethoxycarbonylalkyl)-2-methylpyridinium halides with activated ethoxymethylidene compounds in the presence of a base. The treatment of these 2-allylidene-1,2-dihydropyridine derivatives with acetic acid at the reflux temperature gave directly the title compounds in low to moderate yields.

In previous papers we described that the reactions of some ethyl 2-allylidene-1,2-dihydropyridin-1-ylacetates, such as **A** (see Fig. 1), with acetic anhydride smoothly provided 2-acetoxy-1-vinylindolizine derivatives **B**;[2] the thus-obtained compounds **B** afforded 2*H*-pyrano[3,2-*a*]-indolizin-2-ones or 2-imines **C** in a treatment with concentrated sulfuric acid.[3] In an early mechanistic consideration of these reactions[3] we proposed the intervention of 1-vinylindolizin-2(3*H*)-one **D** or its enol isomer as a common intermediate for both products **B** and **C**, and the thermal cyclization process from **A** to **D**. However, our interest for exploring a more effective preparative method for 2*H*-pyrano[3,2-*a*]indolizin-2-one derivatives prompted us to reinvestigate these reactions; we noticed an alternative possibility that the transformation from **A** to **D** might be an acid-catalyzed cyclization process, due to the trace amount of acetic acid included in acetic anhydride or generated by the hydrolysis of the same reagent. We thus examined the behavior of these ethyl 2-allylidene-1,2-dihydropyridin-1-ylacetate derivatives in acetic acid, and, unexpectedly, found a new one-pot preparative method for 2*H*-pyrano[3,2-*a*]indolizin-2-one derivatives. In this paper we report on the preparation of various ethyl 2-allylidene-1,2-dihydropyridin-1-ylacetates from the corresponding pyridinium halides and activated ethoxymethylidene compounds, and their smooth transformations to 2*H*-pyrano[3,2-*a*]indolizin-2-one derivatives in refluxing acetic acid.

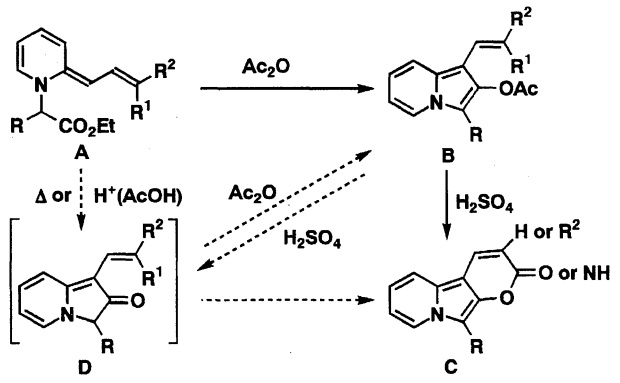
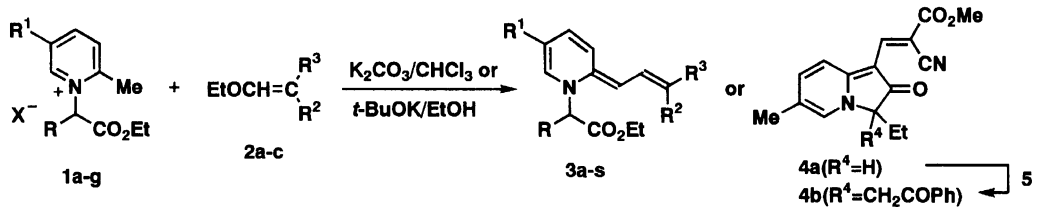


Fig. 1.

Results and Discussion

Preparations of 2-Allylidene-1,2-dihydropyridines. These ethyl 2-(3-cyanoallylidene)-1,2-dihydropyridin-1-ylacetate derivatives **3a—s** were prepared in variable yields from the reactions of 1-(1-ethoxycarbonylethyl)- (**1a—c**), 1-(1-ethoxycarbonylpropyl)-2-methylpyridinium bromides (**1d—f**), or 1-ethoxycarbonylmethyl-2-methylpyridinium chloride (**1g**) with activated ethoxymethylidene compounds, such as (ethoxymethylidene)malononitrile (**2a**), methyl 2-ethoxymethylidene-2-cyanoacetate (**2b**), and ethyl 2-ethoxymethylidene-2-cyanoacetate (**2c**) in the presence of a base (potassium carbonate or potassium *t*-butoxide) according to the literature.[2] Interestingly, 1-vinylindolizin-2(3*H*)-one derivative **4a** was obtained in 70% yield for once in the reaction of pyridinium salt **1e** with **2b**, though the reason for its formation was unclear because of a loss of the reproducibility (Scheme 1). Similarly, the reactions of salts **1a—f** and ethyl 2-(ethoxymethylidene)acetoacetate (**2d**) in the presence of potassium carbonate in chloroform gave the corresponding ethyl 2-(3-ethoxycarbonyl-4-oxo-2-pentenylidene)-1,2-dihydropyridin-1-ylacetates (**3t—y**) in 37—42% yields, while those in the presence of potassium *t*-butoxide in ethanol provided 3-acetyl-2*H*-pyrano[3,2-*a*]indolizin-2-one derivatives **6t—y** (see next section for structural



1	R	R^1	X
a	Me	H	Br
b	Me	Me	Br
c	Me	Et	Br
d	Et	H	Br
e	Et	Me	Br
f	Et	Et	Br
g	H	H	Cl

2	R^2	R^3
a	CN	CN
b	CN	CO_2Me
c	CN	CO_2Et

5: $BrCH_2COPh$

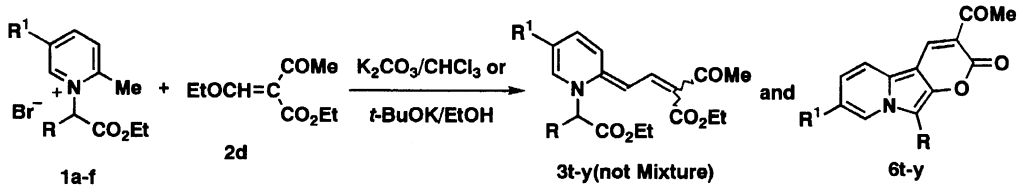
3	R	R^1	R^2	R^3
a	Me	H	CN	CN
b	Me	Me	CN	CN
c	Me	Et	CN	CN
d	Et	H	CN	CN
e	Et	Me	CN	CN
f	Et	Et	CN	CN
g	Me	H	CN	CO_2Me
h	Me	Me	CN	CO_2Me
i	Me	Et	CN	CO_2Me

3	R	R^1	R^2	R^3
j	Et	H	CN	CO_2Me
k	Et	Me	CN	CO_2Me
l	Et	Et	CN	CO_2Me
m	Me	H	CN	CO_2Et
n	Me	Me	CN	CO_2Et
o	Me	Et	CN	CO_2Et
p	Et	H	CN	CO_2Et
q	Et	Me	CN	CO_2Et
r	Et	Et	CN	CO_2Et
s	H	H	CN	CO_2Et

Scheme 1.

assignment) in low yield (3—6%) together with the expected 2-allylidene-1,2-dihydropyridines **3t**—**y** (7—29%) (Scheme 2).

The structures of products **3a**—**y** were determined by inspections of their physical and spectral data. The IR spectra showed characteristic absorption bands at 1658—1684, 1712—1744, and 2175—2199 cm^{-1} due to the α,β-unsaturated carbonyl, the saturated ester carbonyl, and the α,β-unsaturated cyano groups, respectively. The ^1H NMR spectra exhibited distinct AB-type signals (its coupling constant is 15.0 Hz) at δ=5.3—6.8 and 7.5—8.5, attributable to the two olefinic protons in the 2-allylidene moiety (see Table 2). Furthermore, the lower-shifted signal (δ=8.2—8.5) due to the 2(2)-proton in **3g**—**s** clearly showed the *E*-configuration for the terminal ethylene bond in the 2-allylidene moiety. However, the geometry of the 2-allylidene moiety in **3t**—**y** could not be determined because of similar anisotropic effects of these acyl groups. These IR and NMR spectral data for **3a**—**y** were very similar to those for 2-allylidene-1,2-dihydropyridine derivatives described earlier by us.[2,4] Compounds **3a**,**s** were in accord with authentic samples[2] in all respects. On the other hand, the structure of compound **4a** was determined by ^1H NMR and IR spectral inspections as well as by its reaction with phenacyl bromide (**5**). The ^1H NMR spectrum of **4a** showed proton signals at δ=0.78 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 2.28 (2H, m, J=7.0 and 4.0 Hz, $\underline{CH_2}CH_3$), 2.35 (3H, s, 6-Me), 3.86 (3H, s, OMe), 4.48 (1H, t, J=4.0 Hz, 3-H), 7.70 (1H, d, J=9.0 Hz, 7-H), 7.76 (1H, s, 5-H), 7.98 (1H, d, J=9.0 Hz, 8-H), and 8.16 (1H, s, vinyl-H),[5] and the IR spectra exhibited an α,β-unsaturated ester carbonyl (1709 cm^{-1}), the indolizin-2(3*H*)-one carbonyl (1668 cm^{-1}),[6] and an α,β-unsaturated cyano absorption band (2199 cm^{-1}), respectively. In particular, the presence of the 3-H signal [δ=4.48 (1H, t, J=4.0 Hz)]



3	R	R^1
t	Me	H
u	Me	Me
v	Me	Et
w	Et	H
x	Et	Me
y	Et	Et

6	R	R^1
t	Me	H
u	Me	Me
v	Me	Et
w	Et	H
x	Et	Me
y	Et	Et

Scheme 2.

coupled with the 3-ethyl group in the ^{1}H NMR spectrum and the lower-shifted carbonyl absorption band (1668 cm^{-1}) in the IR spectrum clearly indicated that this compound **4a** has an indolizin-2(3*H*)-one skeleton. As might be expected,[6] the reaction of this compound **4a** with a soft alkylating agent, such as **5**, in the presence of potassium *t*-butoxide provided only the corresponding *C*-alkylated product, 3-ethyl-3-phenacyl-1-vinyl-indolizin-2(3*H*)-one derivative **4b**,[5] in 96% yields (see Scheme 1).

Preparations of 2*H*-Pyrano[3,2-*a*]indolizin-2-ones. Although these 2-allylidene-1,2-dihydropyridines **3a**—**r**,**t**—**y** did not change in acetic acid at ordinary temperature (10—60 °C), we found that they smoothly collapsed in refluxing acetic acid to yield products **6a**—**r**,**t**—**y** with very strong fluorescence. When acetic acid solutions of 2-allylidene-1,2-dihydropyridine derivatives **3a**—**r**,**t**—**y** having a 1-(ethoxycarbonyl)ethyl or 1-(ethoxycarbonyl)propyl group at the 1-position were allowed to react at the reflux temperature for 2—3 h, the corresponding 2*H*-pyrano[3,2-*a*]indolizin-2-one derivatives **6a**—**r**,**t**—**y** were directly formed in 12—45% yields. A similar reaction of **3s** bearing an ethoxycarbonylmethyl group at the 1-position, however, provided only tarry materials, and no significant products, such as **6s**, could be obtained. The inaccessibility of 10-unsubstituted 2*H*-pyrano[3,2-*a*]indolizin-2-one (**6s**) can be attributed to the instability of this molecule under the reaction conditions employed here, because this 10-position in 2*H*-pyrano[3,2-*a*]indolizin-2-one corresponds to the 3-position of the indolizine skeleton with the highest electron density,[7] and the thermal instability of 3-unsubstituted indolizine derivatives is well known.[8] In the reaction of **3d** with acetic acid, the formation of 2,2-dicyanovinyl-2-ethoxy-3-ethylindolizine (**7**) was also detected (Scheme 3).

The elementary analyses for products **6a**—**r**,**t**—**y** were in good accord to our proposed compositions. The IR spectra of **6a**—**r**,**t**—**y** showed an α,β-unsaturated cyano and/or an α,β-unsaturated carbonyl, and the pyrone carbonyl absorption bands at 2193—2216, 1657—1689, and 1712—1751 cm^{-1}, respectively. Furthermore, the possibility of a 2*H*-pyrano[3,2-*a*]indolizin-2-imine structure (see structure **14** in Scheme 4 for Mechanisms) for compounds **6a**—**r** is completely excluded because no imino absorption band was exhibited in their IR spectra. Their ^{1}H NMR spectra (Table 1) clearly indicated all skeletal protons in the aromatic region (δ=7.06—8.04), and did not give any proton signal due to the methine and the ethoxycarbonyl groups in the 1-(ethoxycarbonyl)ethyl or the 1-(ethoxycarbonyl)propyl substituent. On the other hand, the structure of compound **7** was determined by the presences of an ethoxy proton signals at δ=1.43 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$) and 4.16 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$) as well as that of a vinyl proton singlet at δ=7.76 in the ^{1}H NMR spectrum. The chemical shifts and the signal patterns of this compound **7**, of course, were very similar to those for known 1-vinylindolizine derivatives.[2,8]

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

Compd	δ ($CDCl_3$)									
No.[a]	C-4	C-5	C-6	C-7		C-8	10-R		3-R[3]	
5a	8.44	b)	b)	b)		b)	2.52		—	
	s						s			
5b	8.40	7.76	7.23	2.50		7.85	2.48		—	
	s	d	br d	s		br s	s			
5c	8.35	7.78	7.27	1.32	2.75	7.88	2.48		—	
	s	d	br d	t	d	br s	s			
5d	8.34	b)	b)	b)		b)	1.35	3.00	—	
	s						t	q		
5e	8.36	7.71	7.22	2.45		7.90	1.33	3.01	—	
	s	d	br d	s		br s	t	q		
5f	8.37	7.75	7.26	1.32	2.75	7.91	1.32	2.99	—	
	s	d	br d	s	d	br s	t	q		
5g	8.96	7.82	7.32	7.08		8.04	2.55		3.94	
	s	d	br t	br t		d	s		s	
5h	8.95	7.74	7.23	2.41		7.85	2.41		3.88	
	s	d	br d	s		br s	s		s	
5i	9.00	7.79	7.19	1.27	2.72	7.87	2.43		3.86	
	s	d	br d	t	q	br s	s		s	
5j	8.92	7.80	7.30	7.06		8.09	1.33	3.00	3.89	
	s	d	br t	br t		d	t	q	s	
5k	8.83	7.68	7.14	2.41		7.83	1.31	2.96	3.90	
	s	d	br d	s		br s	t	q	s	
5l	8.84	7.71	7.17	1.30	2.72	7.83	1.30	2.97	3.89	
	s	d	br d	t	q	br s	t	q	s	
5m	8.93	7.83	7.30	7.07		8.02	2.49		1.39	4.37
	s	d	br t	br t		d	s		t	q
5n	8.94	7.73	7.15	2.39		7.82	2.42		1.35	4.33
	s	d	br d	s		br s	s		t	q
5o	8.95	7.76	7.18	1.29	2.71	7.83	2.42		1.36	4.34
	s	d	br d	t	q	br s	s		t	q
5p	8.87	7.78	7.30	7.08		8.07	1.30	2.99	1.38	4.34
	s	d	br t	br t		d	t	q	t	q
5q	8.84	7.70	7.13	2.40		7.82	1.31	2.98	1.38	4.35
	s	d	br d	s		br s	t	q	t	q
5r	8.87	7.75	7.17	1.32	2.71	7.83	1.32	3.00	1.34	4.36
	s	d	br d	t	q	br s	t	q	t	q
5t	8.92	7.81	7.35	7.11		8.02	2.54		2.70	
	s	d	br t	br t		d	s		s	
5u	8.87	7.73	7.20	2.46		7.80	2.50		2.69	
	s	d	br d	s		br s	s		s	
5v	8.91	7.74	7.22	1.34	2.79	7.81	2.51		2.70	
	s	d	br d	t	q	br s	s		s	
5w	8.91	7.82	7.33	7.09		8.08	1.37	3.02	2.69	
	s	d	br t	br t		d	t	q	s	
5x	8.90	7.75	7.18	2.46		7.85	1.37	3.03	2.70	
	s	d	br d	s		br s	t	q	s	
5y	8.88	7.75	7.21	1.33	2.74	7.83	1.36	3.02	2.69	
	s	d	br d	t	q	br s	t	q	s	

a) The main coupling constants are as follows: $J_{5,6}$=9.0, $J_{6,7}=J_{7,8}$=7.0 and J_{Et}=7.0 Hz. b) The chemical shifts for these protons could not be determined because of its low solubility in deuteriochloroform.

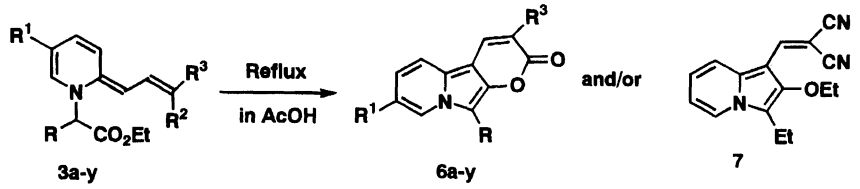
Reaction Mechanisms. Possible mechanisms for the transformation from 2-allylidene-1,2-dihydro-

Table 2. Some Data for 2-Allylidene-1,2-dihydropyridines **3**

Compd[a] No.	React.	Yield(%)[b] A	Yield(%)[b] B	Mp θ_m/°C	ν (KBr)/cm^{-1} CO		ν (KBr)/cm^{-1} CN		δ ($CDCl_3$)[c] CHR	2(1)-H	2(2)-H	Formula[d]
3a	**1a+2a**	72	—	147—149	1740		2176	2195	5.04	5.58	7.67	$C_{15}H_{15}N_3O_2$
3b	**1b+2a**	86	—	164—165	1739		2175	2195	5.01	5.52	7.61	$C_{16}H_{17}N_3O_2$
3c	**1c+2a**	80	—	145—148	1736		2175	2197	5.03	5.55	7.67	$C_{17}H_{19}N_3O_2$
3d	**1d+2a**	34	29	96—97	1742		2184		4.85	5.65	7.63	$C_{16}H_{17}N_3O_2$
3e	**1e+2a**	63	—	138—142	1744		2183		4.86	5.62	7.56	$C_{17}H_{19}N_3O_2$
3f	**1f+2a**	63	—	114—117	1742		2187		4.86	5.62	7.63	$C_{18}H_{21}N_3O_2$
3g	**1a+2b**	83	—	125—127	1732	1664	2195		5.04	5.59	8.31	$C_{16}H_{18}N_2O_4$
3h	**1b+2b**	97	—	183—185	1739	1665	2199		5.04	5.58	8.30	$C_{17}H_{20}N_2O_4$
3i	**1c+2b**	58	—	142—144	1740	1669	2197		5.05	5.56	8.32	$C_{18}H_{22}N_2O_4$
3j	**1d+2b**	51	62	e)	1741	1684	2191		4.85	5.63	8.22	e)
3k[f]	**1e+2b**	79	54	123—125	1732	1682	2183		4.85	5.65	8.23	$C_{18}H_{22}N_2O_4$
3l	**1f+2b**	48	86	72—74	1744	1682	2189		4.88	5.68	8.23	$C_{19}H_{24}N_2O_4$
3m	**1a+2c**	75	—	103—106	1740	1678	2193		5.02	5.61	8.30	Known compound[g]
3n	**1b+2c**	86	—	156—158	1740	1664	2191		5.01	5.57	8.27	$C_{18}H_{22}N_2O_4$
3o	**1c+2c**	96	—	117—119	1742	1665	2191		5.03	5.57	8.30	$C_{19}H_{24}N_2O_4$
3p	**1d+2c**	38	49	e)	1741	1668	2189		4.84	5.65	8.25	e)
3q	**1e+2c**	68	79	128—131	1739	1672	2178		4.88	5.65	8.29	$C_{19}H_{24}N_2O_4$
3r	**1f+2c**	20	43	83—85	1736	1684	2186		4.88	5.67	8.23	$C_{20}H_{26}N_2O_4$
3s	**1g+2c**	82	—	164—165	1742	1672	2184		4.58	5.35	8.23	Known compound[g]
3t[h]	**1a+2d**	37	26	e)	1717	1663			5.15	6.56	8.41	e)
3u[h]	**1b+2d**	41	29	135—137	1712	1663			5.17	6.64	8.40	$C_{19}H_{25}NO_5$
3v[h]	**1c+2d**	40	24	e)	1716	1662			5.17	6.67	8.42	e)
3w[h]	**1d+2d**	39	7	e)	1718	1660			4.93	6.58	8.31	e)
3x[h]	**1e+2d**	42	21	e)	1715	1658			5.00	6.70	8.34	e)
3y[h]	**1f+2d**	42	23	e)	1716	1662			5.01	6.79	8.34	e)

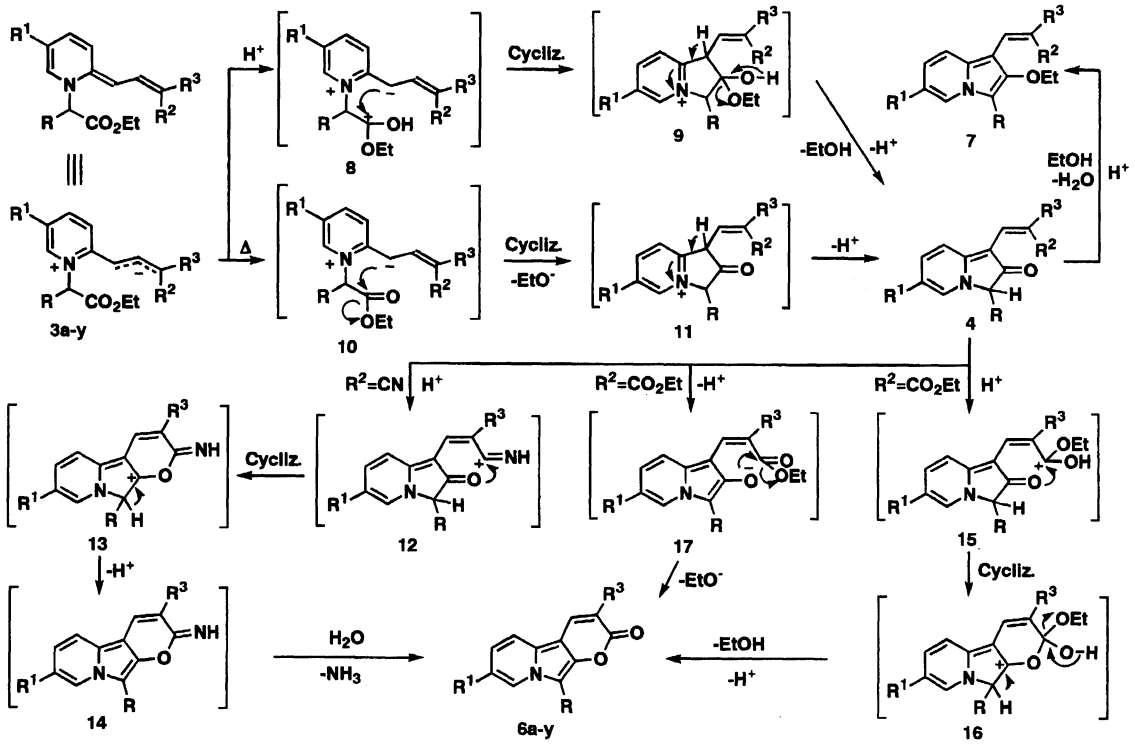
a) Compounds **3a**—**y** were obtained as red prisms. b) A: General method A. B: General method B. c) The signal pattern for the methine proton in **3a**—**r**, **t**—**y** is a quartet (R=Me) or a triplet (R=Et) whose coupling constant is 7.0 Hz. That for the 2(1) and 2(2)-protons on the 2-allylidene group is an AB quartet splitted with 15.0 Hz. d) Satisfactory elemental analyses (within ±0.3%) were obtained for **3a**—**i,k,l,n,o,q,r,u**. e) Pure sample for the analyses could not be obtained because of its thermal instability. f) For once, 1-vinylindolizin-2(3*H*)-one derivatives **4k** was obtained in 70% yield. g) See Ref. 2. h) In method B, 2*H*-pyrano[3,2-*a*]indolizin-2-ones **5t**—**y** were also formed in 6, 4, 5, 3, 4, and 6% yields, respectively.

pyridines **3** to 2*H*-pyrano[3,2-*a*]indolizin-2-ones **6** are shown in Scheme 4. In weak acidic media, such as acetic acid, it should be expected that the partial protonation on the ester carbonyl group in the 1-substituent of 2-allylidene-1,2-dihydropyridines **3** moderately enhances the electrophilicity at the carbonyl carbon atom; the interaction between this positive carbon and the localized negative 2(1)-carbon in the 2-allylidene group in the resulting intermediate **8** gives rise to cyclization to an adduct **9**. The eliminations of a proton and one molecule of ethanol from this adduct **9** may provide 1-vinylindolizin-2(3*H*)-one **4**; then, protonation of the cyano or the ester carbonyl group in the 1-vinyl substituent of **4** followed by a hard-hard interaction between the carbonium ion and the 2(3*H*)-indolizinone oxygen in the resulting intermediate **12** or **15** may lead to the tricyclic adduct, **13** or **16**. Finally, the deprotonation of **13** and the acid-catalyzed hydrolysis of the resulting 2*H*-pyrano[3,2-*a*]indolizin-2-imine (**14**), or the deprotonation and elimination of an ethanol molecule from **16**, should lead to 2*H*-pyrano[3,2-*a*]indolizin-2-one derivatives **6**—**r**,**t**—**y**. Furthermore, it is clear that the thermal route from **3** (via the intermediate **10** and then **11**) to intermediate **4** is also present, because both formations of 3-ethyl-1-vinylindolizin-2(3*H*)-one (**4a**) and 3-acetyl-2*H*-pyrano[3,2-*a*]indolizin-2-ones (**6t**—**y**) were actually observed, even under alkaline conditions. However, this thermal cyclization might not be the main process, compared with the loss of reproducibility for the formation of **4a** and the low yields for **6t**—**y**. On the other hand, the direct formation of **6t**—**y** under strong alkaline conditions (potassium *t*-butoxide) can be interpreted by considering the abstraction of the 3-proton from 3-alkyl-1-vinylindolizin-2(3*H*)-one (**4**) followed by an intramolecular nucleophilic attack of the resulting indolizin-2-olate ion **17** to the ester carbonyl carbon in the 1-vinyl substituent and the elimination of an ethoxide ion. The formation of 2-ethoxy-1-vinylindolizine **7** may be interpreted by an acid-catalyzed dehydration between indolizin-2(3*H*)-one **4** and an ethanol generated during this reaction. An alternative path in which the same product **7** was formed via the dehydration of a hemi-acetal intermediate **9** can be neglected because of the higher ability for the elimination of an ethoxy group over a hydroxyl group and of the precedent of acid-catalyzed ether formation between 3-vinylindolizin-2(3*H*)-one and methanol.[3]



6	R	R^1	R^3	6	R	R^1	R^3
a	Me	H	CN	m	Me	H	CO_2Et
b	Me	Me	CN	n	Me	Me	CO_2Et
c	Me	Et	CN	o	Me	Et	CO_2Et
d	Et	H	CN	p	Et	H	CO_2Et
e	Et	Me	CN	q	Et	Me	CO_2Et
f	Et	Et	CN	r	Et	Et	CO_2Et
g	Me	H	CO_2Me	(s)	H	H	CO_2Et
h	Me	Me	CO_2Me	t	Me	H	COMe
i	Me	Et	CO_2Me	u	Me	Me	COMe
j	Et	H	CO_2Me	v	Me	Et	COMe
k	Et	Me	CO_2Me	w	Et	H	COMe
l	Et	Et	CO_2Me	x	Et	Me	COMe
				y	Et	Et	COMe

Scheme 3.



Scheme 4.

Experimental

The melting points were measured with a Yanagimoto micromelting point apparatus and were not corrected. Microanalyses were carried out on a Perkin–Elmer 2400 elemental analyzer. The ^{1}H NMR spectra (60 MHz) were determined 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 Pyridinium Salts. 1-(Ethoxycarbonylmethyl)pyridinium halides **1a**—**g** were prepared in nearly quantitatively yields from the reactions of 2-methylpyridine, 2,5-dimethylpyridine, and 5-ethyl-2-methylpyridine with ethyl 2-bromopropionate, ethyl 2-bromobutyrate,

and ethyl chloroacetate in the absence of a solvent according to the procedure described earlier,[2] and were used for the next reactions without further purification.

Preparations of 2-Allylidene-1,2-dihydropyridines. General Method A: A chloroform solution (30 ml) of pyridinium salt (**1**, 3 mmol) and an ethoxymethylidene compound (**2**, 3 mmol) was treated with anhydrous potassium carbonate (5 g) under stirring at room temperature for 3 d. The resulting reaction mixture was filtered to remove insoluble inorganic substances; the filtrate was then concentrated at reduced pressure. The residue was separated by column chromatography on alumina using ether, and then chloroform as eluents. The combined chloroform layer, including the 2-allylidene-1,2-dihydropyridine derivative **3**, was concentrated at reduced pressure; the crude product was then recrystallized from chloroform–ether.

Method B: An ethanolic solution of pyridinium salt (**1**, 3 mmol) and an ethoxymethylidene compound (**2**, 3 mmol) was treated with potassium *t*-butoxide (3.5 mmol) at 60—80 °C in a water bath for 2—3 h. Similar work-ups to the resulting reaction mixture gave the corresponding 2-allylidene-1,2-dihydropyridines **3**.

In the reaction of salt **1e** with **2b**, 3-ethyl-1-vinylidolizin-2(3*H*)-one (**4a**) was obtained for once: **4a**, 70%, yellow needles, mp 182—185 °C, IR (KBr) 2199 (CN), and 1709 and 1668 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ=0.78 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 2.28 (2H, m, J=7.0 and 4.0 Hz, $\underline{CH_2}CH_3$), 2.35 (3H, s, 6-Me), 3.86 (3H, s, OMe), 4.48 (1H, t, J=4.0 Hz, 3-H), 7.70 (1H, d, J=9.0 Hz, 7-H), 7.76 (1H, s, 5-H), 7.98 (1H, d, J=9.0 Hz, 8-H), and 8.16 (1H, s, vinyl-H). Calcd for $C_{16}H_{16}N_2O_3$: C, 67.52; H, 5.85; N, 9.74%. Found: C, 67.59; H, 5.67; N, 9.85%. However, all our attempts toward its reappearance were unsuccessful.

In the reaction of salts **1a—f** with ethyl 2-(ethoxymethylidene)acetoacetate (**2d**) in the presence of potassium *t*-butoxide (Method B), 3-acetyl-2*H*-pyrano[3,2-*a*]indolizin-2-one derivatives **6t—y** were also obtained in 6, 4, 5, 3, 4, and 6% yields, respectively, together with the corresponding ethyl 2-[3-(ethoxycarbonyl)-4-oxo-2-pentenylidene]-1,2-dihydropyridin-1-ylacetates (**3t—y**). These results and some physical and spectral data are listed in Table 2.

Alkylation of 3-Ethyl-1-vinylindolizin-2(3*H*)-one (4a). Compound **4a** (0.284 g, 1 mmol) was allowed to react with phenacyl bromide (**5**, 0.199 g, 1 mmol) in the presence of potassium *t*-butoxide (1.5 mmol) in ethanol at 60—80 °C for 1 h. The resulting reaction mixture was concentrated at reduced pressure, and the residue was separated by colum chromatography on alumina using chloroform. The yellow-colored chloroform layers were combined and the solvent was removed off at reduced pressure. Recrystallization of the residue from chloroform–ether gave the 3-phenacyl derivatives **4b**, 96%, yellow needles, mp 241—243 °C, IR (KBr) 2201 (CN), and 1688 and 1638 cm^{-1} (CO), ^1H NMR ($CDCl_3$) δ=0.66 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 2.12 (2H, q, J=7.0 Hz, $\underline{CH_2}CH_3$), 2.30 (3H, s, 6-Me), 3.79 (2H, s, CH_2CO), 3.82 (3H, s, OMe), 7.2—8.1 (8H, m, Ph, 5-, 7-,

Table 3. Some Data for Pyrano[3,2-*a*]indolizines **6**

Compd[a] No.	React.	Yield %	Mp θ_m/°C	ν (KBr)/cm^{-1} CO	CN	Formula[b]
6a	**3a**	45	295—297	1721	2216	$C_{13}H_8N_2O_2+H_2O$
6b	**3b**	44	285—288	1717	2204	$C_{14}H_{10}N_2O_2$
6c	**3c**	31	247—250	1721	2216	$C_{15}H_{12}N_2O_2$
6d	**3d**	45[c]	225—228	1720	2193	$C_{14}H_{10}N_2O_2$
6e	**3e**	27	269—272	1723	2213	$C_{15}H_{12}N_2O_2$
6f	**3f**	12	230—233	1714	2211	$C_{16}H_{14}N_2O_2$
6g	**3g**	56	208—210	1735 1677		$C_{14}H_{11}NO_4$
6h	**3h**	38	246—249	1736 1688		$C_{15}H_{13}NO_4$
6i	**3i**	33	197—200	1732 1678		$C_{16}H_{15}NO_4$
6j	**3j**	33	181—184	1751 1682		$C_{15}H_{13}NO_4$
6k	**3k**	26	207—210	1751 1678		$C_{16}H_{15}NO_4$
6l	**3l**	43	176—179	1734 1686		$C_{17}H_{17}NO_4$
6m	**3m**	51	205—207	1736 1679		$C_{15}H_{13}NO_4$
6n	**3n**	41	241—244	1734 1678		$C_{16}H_{15}NO_4$
6o	**3o**	36	163—165	1738 1689		$C_{17}H_{17}NO_4$
6p	**3p**	37	155—158	1746 1680		$C_{16}H_{15}NO_4$
6q	**3q**	29	170—172	1736 1678		$C_{17}H_{17}NO_4$
6r	**3r**	32	130—131	1736 1684		$C_{18}H_{19}NO_4$
6s	**3s**	0				
6t	**3t**	23	210—212	1716 1663		$C_{14}H_{11}NO_3$
6u	**3u**	24	253—256	1717 1663		$C_{15}H_{13}NO_3$
6v	**3v**	31	209—213	1715 1663		$C_{16}H_{15}NO_3$
6w	**3w**	21	211—213	1716 1659		$C_{15}H_{13}NO_3$
6x	**3x**	25	232—235	1714 1657		$C_{16}H_{15}NO_3$
6y	**3y**	26	200—202	1712 1657		$C_{17}H_{17}NO_3$

a) Compounds **6a—c,g,h,j,k,m—p, s—u** were obtained as yellow needles, **6d,i, l,g,v,x** as brown prisms, and **6e,f** as orange needles. b) Satisfactory elementary analyses (within ±0.35%) for **6a—r,t—y** were obtained. c) Plus **7** (trace).

and 8-H), and 8.18 (1H, s, vinyl-H). Found: C, 71.65; H, 5.56; N, 6.89%. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96%.

Preparations of 2*H*-Pyrano[3,2-*a*]indolizin-2-ones. General Methods: An acetic acid solution (10 ml) of 2-allylidene-1,2-dihydropyridine (**3**, 1 mmol) was heated under reflux until the disappearance of **3** was confirmed by TLC monitoring (ca. 2—3 h). From the resulting solution acetic acid was completely removed at reduced pressure; the residue was separated by column chromatography on alumina using chloroform. After the chloroform layers were concentrated at reduced pressure, recrystallization from chloroform–ether gave the corresponding 2*H*-pyrano[3,2-*a*]indolizin-2-ones **6**.

In the reaction of 2-allylidene-1,2-dihydropyridine **3d** in acetic acid, the formation of a trace amount of 1-(2,2-dicyanovinyl)-2-ethoxy-3-ethylindolizine (**7**) was confirmed, together with that of 10-ethyl-2-oxo-2*H*-pyrano[3,2-*a*]-indolizine-3-carbonitrile (**6d**, 45%): **7**, trace, yellow needles, IR (KBr) 2210 cm^{-1} (CN), ^1H NMR ($CDCl_3$) δ=1.28 (3H, t, J=7.0 Hz, 3-$CH_2\underline{CH_3}$), 1.43 (3H, t, J=7.0 Hz, $OCH_2\underline{CH_3}$), 2.93 (2H, q, J=7.0 Hz, 3-$\underline{CH_2}CH_3$), 4.16 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.03 (1H, br t, J=7.0 and 7.0 Hz, 6-H), 7.37 (1H, br t, J=7.0 and 9.0 Hz, 7-H), 7.76 (1H, s, vinyl-H), 8.00 (1H, br d, J=7.0 Hz, 5-H), and 8.04 (1H, d, J=9.0 Hz, 8-H).[9)]

These results and some physical and spectral data are shown in Tables 1 and 3.

References

1) For part 38 of this series, see : A. Kakehi, S. Ito, and S. Fujita, *Bull. Chem. Soc. Jpn.*, **68**, 1473 (1995).

2) A. Kakehi, S. Ito, T. Maeda, R. Takeda, M. Nishimura, and T. Yamaguchi, *Chem. Lett.*, **1978**, 59; A. Kakehi, S. Ito, T. Maeda, R. Takeda, M. Nishimura, M. Tamashita, and T. Yamaguchi, *J. Org. Chem.*, **43**, 4837 (1978).

3) A. Kakehi, S. Ito, S. Murakami, and H. Sano, *Bull. Chem. Soc. Jpn.*, **57**, 548 (1984).

4) A. Kakehi, S. Ito, T. Funahashi, and N. Ogasawara, *Chem. Lett.*, **1975**, 919; A. Kakehi, S. Ito, T. Funahashi, and N. Ogasawara, *Bull. Chem. Soc. Jpn.*, **49**, 2250 (1976).

5) This low value (δ=8.16 or 8.18) for the vinyl proton in **4a**,**b** indicated clearly its *E*-configuration in the 1-vinly moiety.

6) A. Kakehi, S. Ito, K. Watanabe, M. Kitagawa, S. Takeuchi, and T. Hashimoto, *J. Org. Chem.*, **45**, 5100 (1980).

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

8) A. Kakehi, S. Ito, T. Ohizumi, and T. Maeda, *J. Org. Chem.*, **47**, 369 (1982).

9) The preparation of the analytical samples for this compounds **7** was not unsuccessful because of its low yield.