Reaction of 1-Alkylpyridinium Salts Carrying a Methyl or an Amino Group at the 2- or 4-Position with Activated Ethoxymethylene Compounds in the Presence of Alkali

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It was found that various 1-alkyl-2-(**1a**—**d**) and 4-picolinium salts(**5a**,**b**) react smoothly with ethoxymethylene compounds(**2a**—**c**) activated by electron-withdrawing substituents in the presence of alkali to give the corresponding 1-alkyl-2-(**4a**—**i**) and 4-allylidenedihydropyridine derivatives(**6a**—**d**) in fairly good yields. 1-Methyl-2-(vinylimino)dihydropyridine(**8a**) and pyrimidine(**8b**) were obtained by the reactions of 1-methyl-2-aminopyridinium(**7a**) and pyrimidinium iodide(**7b**) with ethyl ethoxymethylenecyanoacetate(**2a**) under similar reaction conditions.

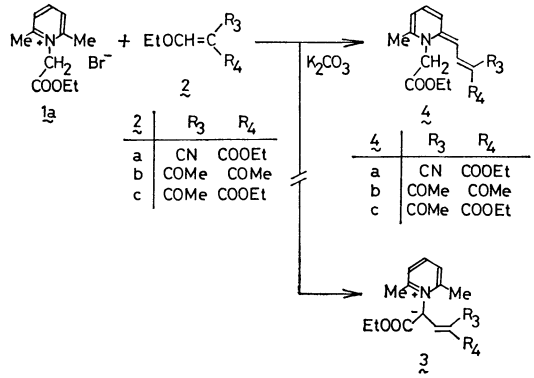
The reactions of 1-alkylpyridinium salts carrying a 2- or 4-methyl group with ethoxymethylene compounds in the presence of alkali afford the corresponding 2- or 4-allylidenedihydropyridine derivatives in fairly good yields rather than initially expected pyridinio-2-propen-1-ides.[1] The simplicity of the reaction procedure and the facile formation of allylidenedihydropyridines prompted us to extend the studies to aza-analogs, and we found that the reaction can be highly utilized for the preparation of this kind of compound.

This paper deals with the preparation of 2- or 4-allylidenedihydropyridines and the aza-analogs by the reactions of various 1-alkylpyridinium and pyrimidinium salts with activated ethoxymethylene compounds in the presence of an alkali.

Results and Discussion

*Reactions of 1-(Ethoxycarbonylmethyl)-2,6-lutidinium Bromide(**1a**) with Ethoxymethylene Compounds(**2a**—**c**).*
A mixture of 1-(ethoxycarbonylmethyl)-2,6-lutidinium bromide(**1a**) and ethyl ethoxymethylenecyanoacetate(**2a**) was treated with potassium carbonate in chloroform at room temperature to give a new crystalline compound(**4a**) in 57% yield. A similar treatment of salt(**1a**) with 3-ethoxymethylenepentane-2,4-dione(**2b**) and ethyl ethoxymethyleneacetoacetate(**2c**) afforded the corresponding products(**4b**,**c**) in 47 and 55% yields, respectively.

Although the structures of the compounds(**4a**—**c**) were expected to be 2,6-lutidino-2-propen-1-ides(**3a**—**c**) by their elemental analyses and by comparison with similar reaction examples reported by Tamura *et al.*,[2]



Scheme 1.

their spectral data were not compatible with the proposed structures: *e.g.*, the values (1735—1743 cm^{-1}) of each one carbonyl absorption in the IR spectra differ from those of the carbonyl group conjugated with carbon-carbon double bond or ylidic carbanion; the absence of one methyl group on the 2,6-lutidine ring and the presence of new olefinic AB-type protons in the NMR spectra (Table 1) show that these compounds (**4a**—**c**) are not 2,6-lutidino-2-propen-1-ides(**3a**—**c**), but the condensation products of ethoxymethylene compounds(**2a**—**c**) with a 2-methyl group on the 2,6-lutidine ring. The results are given below.

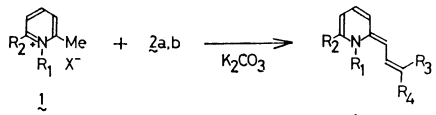
*Preparation of Other 1-Alkyl-2-(**4d**—**i**) and 4-Allylidenedihydropyridines(**6a**—**b**) and the Aza-analogs(**8a**—**b**).*
From the fact that the 1-ethoxycarbonylmethyl group in the pyridinium salt(**1a**) remains intact during the course of reaction, we attempted an extension of this reaction to other 1-alkylpyridinium salts.

As expected, 1-methyl-2-picolinium(**1b**), 1-methyl-2,6-lutidinium(**1c**), and 1-allyl-2-picolinium salts(**1d**) reacted smoothly with compounds(**2a**,**b**) in the presence of potassium carbonate to yield the corresponding 2-allylidenedihydropyridine derivatives(**4d**—**i**) in over 63% yields, the reactions with 1-methyl(**5a**) and 1-allyl-4-picolinium salts(**5b**) giving similarly the corresponding 4-allylidene derivatives(**6a**—**d**) in 85, 65, 80, and 56% yields, respectively. Vinyliminodihydropyridine derivatives(**8a**, **b**) were obtained in 87 and 58% yields by the reactions of compound(**2a**) with 1-methyl-2-aminopyridinium(**7a**) and pyrimidinium iodide(**7b**). The results are given in Schemes 2, 3 and 4. On the other hand, 1-methylpyridinium and 1-methyl-3-picolinium iodides did not react with ethoxymethylene compound(**2a**) under the same conditions, nor did pyridinium salts(**1a**, **b**) react with ethyl β-ethoxyatropate and ethyl β-bromomethacrylate.

Structural elucidation of the compounds(**4d**—**i**, **6a**—**d**, and **8a**, **b**) was achieved by means of elemental analyses (Table 3) and spectroscopic investigations. The chemical shifts of skeletal protons in the NMR spectra (Table 1) of these products are as a whole similar to each other and also to those of known allylidenedihydropyridines reported recently by Acheson and Woollard.[3]

Mechanism. The reactions should be initiated by proton abstraction from the 2-, 4-methyl or 2-amino group rather than the 1-methylene group in the corresponding pyridinium(**1a**—**d**, **5a**, **b**, and **7a**) and

pyrimidinium salt(**7b**) followed by the nucleophilic addition-elimination of the resulting dihydropyridine or dihydropyrimidine intermediates(**9** and **9'**) onto the β-carbon of ethoxymethylene compounds(**2a—c**), as shown in Scheme 5. A similar mechanism was proposed by Severin and Böhme.[4] In these reactions, the presence of an appropriate removing group in ethoxymethylene compounds and high electrophilicity are necessary, since the reactions between enamines and electrophilic olefins generally afford cyclobutane derivatives,[5] and ethyl β-ethoxyatropate and ethyl β-bromomethacrylate, which are activated by only one electron-withdrawing group, did not react with pyridinium salt under basic condition. Although there are some methods for the preparation of allylidene-



1	R_1	R_2	X
b	Me	H	I
c	Me	Me	I
d	$CH_2CH=CH_2$	H	Br

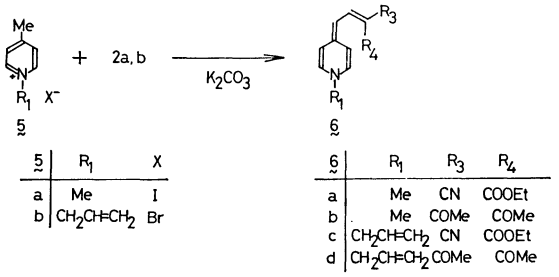
4	R_1	R_2	R_3	R_4
d	Me	H	CN	COOEt
e	Me	H	COMe	COMe
f	Me	Me	CN	COOEt
g	Me	Me	COMe	COMe
h	$CH_2CH=CH_2$	H	CN	COOEt
i	$CH_2CH=CH_2$	H	COMe	COMe

Scheme 2.

Table 1. NMR data of allylidene derivatives[6,7]

Compd No.	C-2	C-3	C-4	C-5	R_2	C-1'	C-2'	R_1[a]				R_3 and R_4[a]
4a	—	7.32 d	7.07 q	6.26 brd	2.38 s	5.37 d	8.07 d	4.67 s				
	$J_{3,4}=8.0$, $J_{4,5}=7.0$, $J_{1',2'}=13.0$											
4b	—	7.38 d	7.11 q	6.30 brd	2.34 s	6.84 d	7.78 d	4.70 s				2.34 s
	$J_{3,4}=8.0$, $J_{4,5}=7.0$, $J_{1',2'}=13.0$											
4c	—	7.46 d	7.05 q	6.25 brd	2.34 s	7.10 brd	8.15 brd	4.67 brs				2.40 s
	$J_{3,4}=8.0$, $J_{4,5}=7.0$, $J_{1',2'}=13.0$											
4d	—	7.0—7.4 m		6.31 brt	b)	5.38 d	7.99 d	3.54 s				
	$J=5.0$, 6.0, $J_{1',2'}=13.0$											
4e	—	7.42 drd	7.13 brt	4.31 brt	7.23 brd	6.94 d	7.75 d	3.57 s				2.34 s
	$J_{3,4}=8.0$, $J_{4,5}=6.0$, $J_{5,6}=7.0$, $J_{1',2'}=13.0$											
4f	—	7.31 d	7.10 q	6.31 brd	2.43 s	5.51 d	7.99 d	3.52 s				
	$J_{3,4}=8.0$, $J_{4,5}=7.0$, $J_{1',2'}=13.0$											
4g	—	7.60 d	7.30 q	6.52 brd	2.47 s	7.35 d	7.96 d	3.64 s				2.40 s
	$J_{3,4}=9.0$, $J_{4,5}=7.0$, $J_{1',2'}=13.0$											
4h	—	7.35 brd	7.12 brt	6.33 brt	7.22 brd	5.47 d	7.99 d	4.44 brd	5.15 drd	5.30 brd	5.75 m	
	$J_{3,4}=8.0$, $J_{4,5}=7.0$, $J_{5,6}=6.0$, $J_{1',2'}=13.0$, $J_{allyl}=5.0$, 10.0, 18.0											
4i	—	7.63 brd	7.33 brt	6.51 brt	7.42 brd	7.19 d	7.96 d	4.59 brd	5.33 brd	5.46 brd	6.00 m	2.41 s
	$J_{3,4}=8.0$, $J_{4,5}=7.0$, $J_{5,6}=6.0$, $J_{1',2'}=13.0$, $J_{allyl}=5.0$, 10.0, 17.0											
6a	6.91 d	6.82 br	—	6.36 br	6.91 d	5.56 d	7.85 d	3.51 s				
	$J_{2,3}=J_{5,6}=7.5$, $J_{1',2'}=13.0$											
6b	6.91 d	6.60 br	—	6.60 br	6.91 d	6.46 d	7.65 d	3.49 s				2.29 s
	$J_{2,3}=J_{5,6}=7.5$, $J_{1',2'}=13.0$											
6c	7.13 d	6.96 brd	—	6.47 brd	7.13 d	5.74 d	8.07 d	4.39 brd	5.31 brd	5.43 brd	5.98 m	
	$J_{2,3}=J_{5,6}=7.5$, $J_{1',2'}=13.0$, $J_{allyl}=5.0$, 10.0, 17.0											
6d	6.98 d	7.00 br	—	6.60 br	6.98 d	6.58 d	7.79 d	4.39 brd	5.23 brd	5.38 brd	5.90 m	2.36 s
	$J_{2,3}=J_{5,6}=7.5$, $J_{1',2'}=13.0$, $J_{allyl}=5.0$, 10.0, 17.0											
8a	—	7.55 brd	7.14 brt	6.62 brt	7.63 d	—	8.08 s	3.91 s				
	$J_{3,4}=9.0$, $J_{4,5}=7.5$, $J_{5,6}=6.5$											

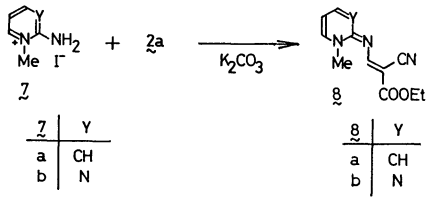
a) The chemical shifts of protons of ethoxycarbonyl groups are δ 4.0—4.5(2H, q) and 1.0—1.5(3H, t). b) Overlapped with C-3 and C-4 proton.



5	R_1	X
a	Me	I
b	$CH_2CH{=}CH_2$	Br

6	R_1	R_3	R_4
a	Me	CN	COOEt
b	Me	COMe	COMe
c	$CH_2CH{=}CH_2$	CN	COOEt
d	$CH_2CH{=}CH_2$	COMe	COMe

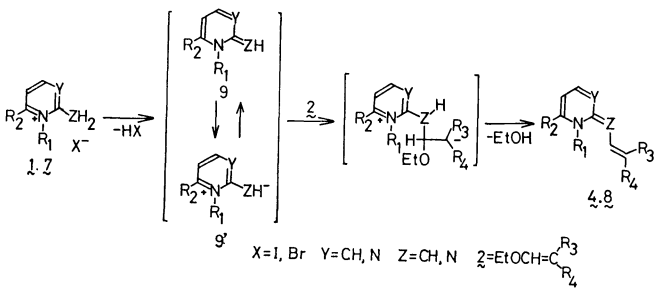
Scheme 3.



7	Y
a	CH
b	N

8	Y
a	CH
b	N

Scheme 4.



Scheme 5.

dihydropyridines, our method seems to be superior in simplicity of the reaction procedure and availability of the reactants to other methods.[3,4]

Experimental

Melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Microanalyses

TABLE 2. SOME DATA AND PROPERTIES OF ALLYLIDENEDIHYDROPYRIDINES AND THEIR AZA-ANALOGS

Compd No.	Materials No.		Solvent	Yield (%)	Mp (°C)	IR (cm^{-1})			
4a	**1a**	**2a**	$CHCl_3$	57	167—170	2210	1743	1525	
4b	**1a**	**2b**	$CHCl_3$	47	110—113		1735	1510	
4c	**1a**	**2c**	$CHCl_3$	55	113—115		1740	1652	1510
4d	**1b**	**2a**	$CHCl_3$	65	143—146	2190	1519		
4e	**1b**	**2b**	$CHCl_3$	65	222(dec)		1580	1500	
4f	**1c**	**2a**	$CHCl_3$	86	149(dec)	2190	1545		
4g	**1c**	**2b**	$CHCl_3$	63	175(dec)		1515		
4h	**1d**	**2a**	EtOH	82	155—158	2185	1510		
4i	**1d**	**2b**	$CHCl_3$	67	148—151		1583	1475	
6a	**5a**	**2a**	EtOH	85	206—207	2200	1655		
6b	**5a**	**2b**	EtOH	65	186—188		1640	1570	
6c	**5b**	**2a**	$CHCl_3$	80	149—151	2195	1645		
6d	**5b**	**2b**	$CHCl_3$	56	155—158		1578	1495	
8a	**7a**	**2a**	$CHCl_3$	87	116—117	2245	1493		
8b	**7b**	**2a**	$CHCl_3$	58	223—225	2210	1681	1450	

TABLE 3. APPEARANCE AND ANALYTICAL DATA

Compd No.	Appearance	Formula	Calcd %			Found %		
			C	H	N	C	H	N
4a	Orange Needles	$C_{17}H_{20}N_2O_4$	64.54	6.37	8.86	64.29	6.19	8.69
4b	Red Needles	$C_{17}H_{21}NO_4$	67.31	6.98	4.62	67.39	6.92	4.43
4c	Red Flakes	$C_{18}H_{23}NO_5$	64.85	6.95	4.20	64.66	6.76	4.10
4d	Orange Flakes	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	67.60	6.13	12.37
4e	Orange Needles	$C_{13}H_{15}NO_2$	71.86	6.96	6.45	71.72	7.01	6.50
4f	Orange Needles	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	68.89	6.55	11.35
4g	Orange Needles	a)	69.97	7.55	5.83	69.93	7.40	5.78
4h	Orange Needles	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93	70.25	6.26	10.77
4i	Red Needles	$C_{15}H_{17}NO_2$	74.05	7.04	5.76	74.22	7.07	5.51
6a	Red Flakes	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	67.81	6.09	12.17
6b	Red Needles	b)	66.36	7.28	5.95	66.25	7.41	5.99
6c	Red Flakes	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93	70.01	6.19	10.69
6d	Red Flakes	$C_{15}H_{17}NO_2$	74.05	7.04	5.76	73.79	7.02	5.63
8a	Yellow Needles	$C_{12}H_{13}N_3O_2$	62.32	5.67	18.17	62.30	5.73	18.43
8b	Orange Needles	$C_{11}H_{12}N_4O_2$	56.89	5.21	24.13	56.96	5.20	24.17

a) $C_{14}H_{17}NO_2 \cdot \frac{1}{2}H_2O$. b) $C_{13}H_{15}NO_2 \cdot H_2O$.

were carried out on a Perkin-Elmer 240 Elemental Analyzer. The NMR spectra were determined with a JEOL JNM-100 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO DS-301 spectrophotometer.

*Preparation of Pyridinium (**1a—d**, **5a**, **b**, and **7a**) and Pyrimidinium Salt(**7b**).* Pyridinium salts (**1a**—**d** and **5a**, **b**) were prepared by the treatment of alkylating agents such as ethyl bromoacetate, methyl iodide, and allyl bromide with the corresponding pyridine derivatives without solvent, and 2-aminopyridinium(**7a**) and pyrimidinium salt(**7b**) were obtained by the reactions of 2-aminopyridine and 2-aminopyrimidine with methyl iodide in chloroform. These salts were filtered off, washed several times with ether to remove unchanged materials and used for the reactions without further purification.

*Preparation of Allylidenedihydropyridines (**4a—i** and **6a—d**) and the Aza-analogs(**8a**, **b**).* *General Procedure*: A solution of salt(2.1 mmol) and ethoxymethylene compound(2 mmol) in 50 ml of chloroform or theanol was stirred with potassium carbonate(5 g) at room temperature for 3—4 days. The reaction mixture was then filtered to remove insoluble substances and the filtrate was concentrated *in vacuo*. The residue was separated by column chromatography(alumina) using chloroform as an eluent. Recrystallization from chloroform-hexane gave yellow to red colored crystalline products.

Although the compounds(**4a—i** and **6a—d**) were formed both in chloroform or ethanol, vinyliminodihydropyridine derivatives(**8a**, **b**) were obtained only in chloroform. The latter reactions in ethanol gave only polymeric substances. Neither 1-methylpyridinium nor 1-methyl-3-picolinium iodides which have no 2- or 4-methyl group on the pyridine ring react with ethyl ethoxymethylenecyanoacetate(**2a**); pyridinium salts(**1a**, **b**) also do not react with ethyl β-ethoxyatropate or ethyl β-bromomethacrylate.

The results and some properties are summarized in Tables 1, 2, and 3.

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6) Abbreviations of the spectral patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; dd, double doublets; m, multiplet.

7) The NMR spectrum of compound(**8b**) could not be taken because of its low solutility in deuteriochloroform.