[Chem. Pharm. Bull. 25(7)1519—1527(1977)]

UDC 547.821.3.04 : 547.239.2.04

Heterocyclic Ketenethioacetal Derivatives. IX.[1] Reactions of 1-[2,2-Bis(methylthio)vinyl]pyridinium Iodides with Active Methylene Compounds

Yoshinori Tominaga, Hiroshi Fujito, Kazumichi Mizuyama, Yoshiro Matsuda, and Goro Kobayashi

Faculty of Pharmaceutical Sciences, Nagasaki University[2]

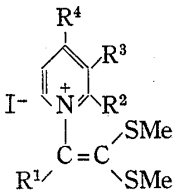
(Received August 27, 1976)

The reaction of 1-[2,2-bis(methylthio)vinyl]pyridinium iodide derivatives (**1a—k**) with active methylene compounds in the presence of a base in ethanol, dimethylformamide, or dimethyl sulfoxide gave pyridinium allylide, indolizine, and N-[2,2-bis(methylthio)-vinyl]-N-(6,6-disubstituted 1,3,5-hexatrienyl)amine derivatives.

Keywords——substitution of ketenethioacetal active methylene; reaction of methylthiovinylpyridine; pyridinium allylide; ring opening pyridinium salt; indolizine ketenethioacetal

It is well known that ketenethioacetals are attacked by nucleophilic reagents with replacement of either one or two methylthio groups attached to the same carbon atom by such groups as amines or active methylene compounds.[1,3] In our previous paper, we reported that the reaction of heterocyclic ketenethioacetal derivatives, containing an aromatic quaternary nitrogen as an electron-attracting group, *e.g.*, 1-methyl-2-[2,2-bis(methylthio)vinyl]pyridinium iodide, *etc.*, with nucleophilic reagents such as amines and active methylene compounds gave the corresponding substituted products.[4]

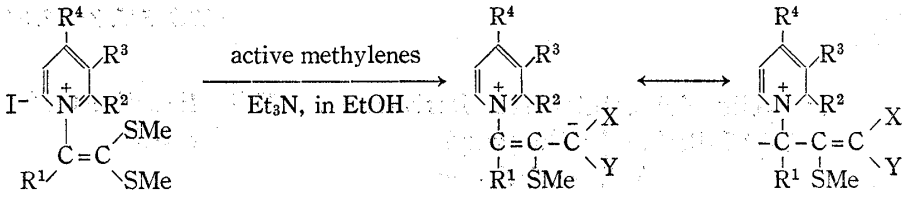
In this paper, we report the reaction of 1-[2,2-bis(methylthio)vinyl]pyridinium iodides (**1a—k**) (Chart 1), which were prepared by the method of Kröhnke,[1,5] with active methylene compounds in the presence of a base.



	R^1	R^2	R^3	R^4
1a	H	H	H	H
1b	COPh	H	H	H
1c	COPh	Me	H	H
1d	COPh	H	Me	H
1e	COPh	H	H	Me
1f	COPh	Me	H	Me
1g	COOEt	H	H	H
1h	COOEt	Me	H	H
1i	COOEt	H	Me	H
1j	COOEt	H	H	Me
1k	$CONH_2$	H	H	H

Chart 1

1) Part VIII: Y. Tominaga, Y. Miyake, H. Fujito, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, "in press."
2) Location: *1–14, Bunkyo-machi, Nagasaki, 852, Japan.*
3) *a*) S. Harry, B. Bernd, and G. Karl, *Z. Chem.*, **13**, 294 (1973) [*Chem. Abstr.*, **80**, 3361 (1974)]; *b*) S. Ueno, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 2624 (1974); *c*) H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 13 (1975); *d*) Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 378 (1975); *e*) T. Hatada, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 623 (1975); *f*) Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 980 (1975); *g*) Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 1073 (1975); *h*) R.R. Rastogi, H. Ila, and H. Junjapa, *J. Chem. Soc. Chem. Commun.*, **1975**, 645; *i*) R. Neidlein and H. Reuter, *Synthesis*, **1971**, 540; *j*) H. Braeuniger and J. French, *Chem. Abstr.*, **82**, 86287*b* (1973).
4) *a*) R. Gompper, B. Wetzel, and W. Elser, *Tetrahedron Lett.*, **1968**, 5519; *b*) K. Mizuyama, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **94**, 702 (1974); *c*) K. Mizuyama, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **95**, 290 (1975).
5) *a*) F. Kröhnke and K. Gerlach, *Chem. Ber.*, **95**, 1108 (1962); *b*) F. Kröhnke and W. Zecher, *Chem. Ber.*, **95**, 1128 (1962).

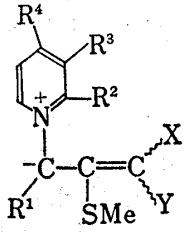


1b, e, g, h, i, j **2a—h** **2′**

	R^1	R^2	R^3	R^4	x	Y
2a	COPh	H	H	H	CN	CN
2b	COPh	H	H	H	CN	COOMe
2c	COPh	H	H	Me	CN	CN
2d	COOEt	H	H	H	CN	CN
2e	COOEt	Me	H	H	CN	CN
2f	COOEt	H	Me	H	CN	CN
2g	COOEt	H	H	Me	CN	CN
2h	COPh	Me	H	Me	CN	CN

Chart 2

TABLE I.



No.	R^1	R^2	R^3	R^4	X	Y	Yield (%)	mp (°C)	Appearance	Formula
2a	COPh	H	H	H	CN	CN	61	192	Orange plates	$C_{18}H_{13}N_3OS$
2b	COPh	H	H	H	CN	COOOMe	45	222	Red columns	$C_{19}H_{16}N_2O_3S$
2c	COPh	H	H	Me	CN	CN	67	219	Orange needles	$C_{19}H_{15}N_3OS$
2d	COOEt	H	H	H	CN	CN	91	172	Orange needles	$C_{14}H_{13}N_3O_2S$
2e	COOEt	Me	H	H	CN	CN	73	166	Orange columns	$C_{15}H_{15}N_3O_2S$
2f	COOEt	H	Me	H	CN	CN	93	193	Orange needles	$C_{15}H_{15}N_3O_2S$
2g	COOEt	H	H	Me	CN	CN	62	214	Orange leaflets	$C_{15}H_{15}N_3O_2S$
2h	COPh	Me	H	Me	CN	CN	36	214	Orange needles	$C_{20}H_{17}N_3OS$

No.	Analysis(%) Calcd. (Found) C	H	N	S	IR ν(KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)
2a	67.68 (67.62)	4.10 (4.04)	13.16 (13.08)	10.04 (9.99)	2180(CN), 1585(C=O)	262(4.11), 324(3.76), 408(4.28)
2b	64.75 (64.76)	4.58 (4.66)	7.95 (7.56)	9.10 (9.12)	2180(CN), 1660(C=O)	262(4.09), 332(3.77), 427(4.16)
2c	68.44 (68.08)	4.54 (4.58)	12.60 (12.28)	9.62 (9.06)	2160(CN), 1590(C=O)	254(4.24), 324(3.72), 410(4.38)
2d	58.52 (58.25)	4.56 (4.55)	14.63 (14.57)	11.16 (11.21)	2170(CN), 1674(C=O)	264(3.69), 362(4.16)
2e	59.78 (59.69)	5.02 (4.91)	13.94 (13.69)	10.64 (10.46)	2160(CN), 1674(C=O)	270(3.92), 362(4.37)
2f	59.78 (59.70)	5.02 (5.02)	13.94 (13.94)	10.64 (10.64)	2160, 2170(CN), 1672(C=O)	270(3.75), 362(4.28)
2g	59.78 (59.67)	5.02 (4.94)	13.94 (13.63)	10.64 (10.47)	2200(CN), 1590(C=O)	270(4.08), 400(4.20)
2h	69.14 (69.01)	4.94 (4.93)	12.09 (11.81)	9.23 (9.11)	2160, 2180(CN), 1630(C=O)	263(4.17), 405(4.30)

The reaction of **1b** and **1g** with active methylene compounds (malononitrile, methyl cyanoacetate) in the presence of triethylamine as a base in ethanol gave the corresponding substituted products (**2a**—**c**) of ketenethioacetal in good yields together with violet-colored products in 1% yield.[6] Compounds (**2a**—**c**) were found to be the pyridinium allylides[7] which were useful as synthetic intermediates for indolizine derivatives. In a similar manner, the reaction of **1e**, **h**, **i**, and **j**, which have a methyl group on the pyridine ring, with malononitrile gave the N-allylides (**2d**—**g**) and very small amount of violet-colored products. However, **1a** did not react with active methylene compounds (malononitrile, methyl cyanoacetate) under a similar condition. One of the reason for it can be regarded as the low reactivity of methylthio groups in **1a** since there is only one pyridinium cation as the withdrawing groups. On the other hand, we have previously reported that the ketenethioacetals, 2- or 4-[1-substituted 2,2-bis(methylthio)vinyl]pyridinium salts, react with active methylene compounds to form the replacement products of methylthio group of ketenethioacetals in good yields.[4a,b]

The reaction of **1g** with phenylsulfonylacetonitrile under a similar condition gave an indolizine derivative, 1-cyano-3-ethoxycarbonyl-2-methylthioindolizine (**4a**) in 48% yield, which was identified with an authentic sample prepared by the reaction of 2-[1-cyano-2,2-bis(methylthio)vinyl]pyridine with ethyl bromoacetate in the presence of triethylamine.[8] Similarly, the reaction of 1-[1-ethoxycarbonyl-2,2-bis(methylthio)vinyl]-3-methylpyridinium iodide (**1i**) with phenylsulfonylacetonitrile afforded 1-cyano-3-ethoxycarbonyl-8-methyl-2-methylthioindolizine(**4b**) in 55% yield. The mechanism of this reaction is outlined in Chart 3.

Next, the reaction of lg with nitromethane was examined, but a crystalline compound was not obtained. However, the reaction of **1i** with nitromethane gave colorless crystals, mp 87°, in 73% yield. Elemental analysis and mass spectroscopy (M^+ 249) of this compound agreed with $C_{13}H_{15}NO_2S$. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) of this compound showed signals due to ethoxy protons as a triplet at δ 1.44 and as a quartet at δ 4.40, methylthio protons as a singlet at δ2.46 (3H), an aromatic proton as a singlet at δ 6.22 (1H), and three aromatic protons on the pyridine ring at δ 9.30 (doublet, J=7 Hz), 6.83 (doublet, J=7 Hz), and 6.63 (triplet, J=7, 7 Hz). Its ultraviolet (UV) spectrum revealed absorption maxima at 237 nm (logε 4.18), 274 nm (logε 4.63), and 340 nm (logε 3.94), which are similar to those of 4a, and its infrared (IR) spectrum showed the absorption of a carbonyl group of ethyl ester at 1670 cm^{-1}. From these spectroscopic data and elemental analysis, this compound was found to be a cyclized product, 3-ethoxycarbonyl-8-methyl-2-methylthioindolizine (**5**), which would be formed by the 1,5-cyclization and elimination of nitrous acid as shown in Chart 3. Kröhnke and his coworkers also reported similar results that N-phenacyl-N-acetonylcycliminium salts underwent cyclization with nitromethane in a basic medium.[9]

The reaction of 1-[1-benzoyl-2,2-bis(methylthio)vinyl]-2-methylpyridinium iodode (**1c**) with malononitrile did not give the N-allylides but afforded a product, mp 161°, as red needles. Elemental analysis and mass spectroscopy agreed with $C_{19}H_{13}N_3S$ (mol. wt., 315.23). The NMR spectrum of this compound revealed a sharp singlet due to methyl protons at δ

6) Y. Tominaga, K. Mizuyama, Y. Miyake, H. Fujito, Y. Matsuda, and G. Kobayashi, *Heterocycles*, **3**, 793 (1975).

7) *a*) F. Kröhnke and D. Morler, *Ann. Chem.*, **744**, 65 (1971); *b*) D.I. Schütze and F. Kröhnke, *Ann. Chem.*, **765**, 20 (1972); *c*) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Tetrahedron*, **28**, 4947 (1972); *d*) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *J. Chem. Soc. Perkin I*, **1973**, 2089; *e*) Y. Tamura, Y. Sumida, and M. Ikeda, *J. Chem. Soc. Perkin I*, **1973**, 2091; *f*) Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *J. Chem. Soc. Perkin I*, **1973**, 2580.

8) C. Maseda, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **94**, 839 (1974).

9) W. Kiel and F. Kröhnke, *Chem. Ber.*, **105**, 3709 (1972).

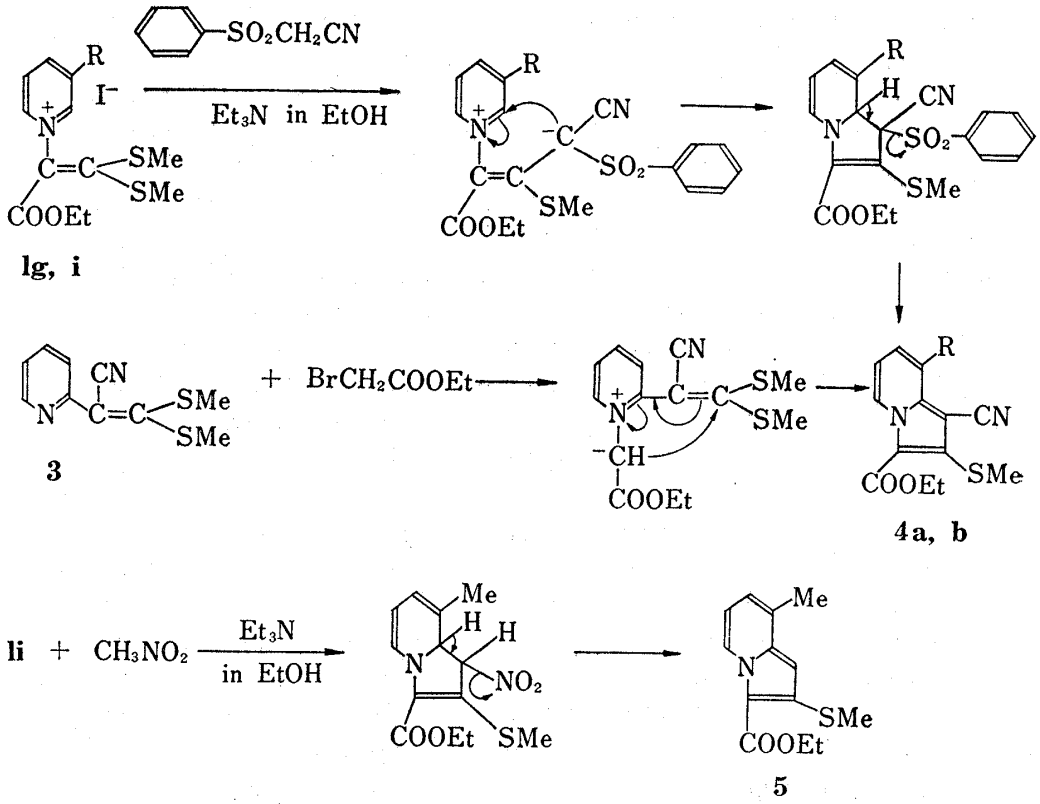


Chart 3

2.17 (3H, SCH_3) and a singlet at δ 6.90 (1H) due to an aromatic proton. Its IR spectrum showed an absorption at 2210 cm^{-1} due to a cyano group and its UV spectrum revealed maxima at 246 nm (logε 4.46), 330 nm (logε 3.99), and 475 nm (logε 3.98). From these spectral data and elemental analysis, this compound was assigned as 3-(2,2-dicyano-1-methylthio)vinyl-2-phenylindolizine (**6a**). Similarly, the reaction of **1c** with phenylsulfonylacetonitrile afforded indolizine derivative (**6a**). However, 1-[1-benzoyl-2,2-bis(methylthio)vinyl]-2,4-dimethylpyridinium iodide (**1f**) reacted with malononitrile in a similar manner to give two products, N-allylide (**2h**) and indolizine derivative (**6c**), in 36% and 46% yields, respectively. The reaction of **1c** with methyl cyanoacetate gave an oily product which further reacted with

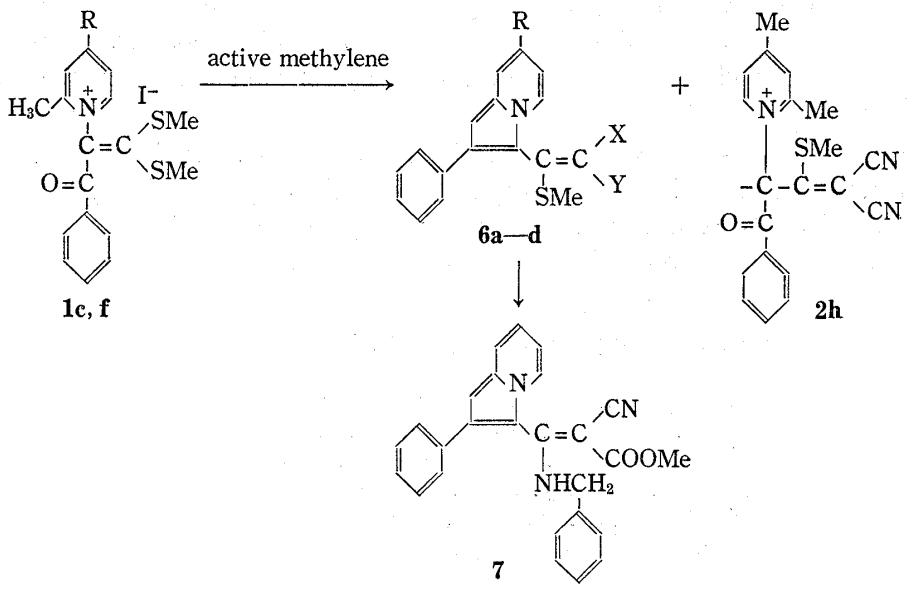
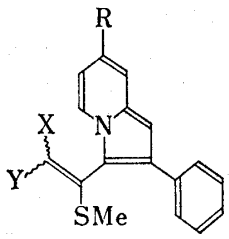


Chart 4

TABLE II.



No.	R	X	Y	Yield (%)	mp (°C)	Crystal form	Formula	Analysis (%) Calcd. (Found) C	H	H	S	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm(log ε)
6a	H	CN	CN	48	161	Red prisms	$C_{19}H_{13}N_3S$	72.37 (72.41)	4.16 (3.89)	13.33 (13.23)	10.95 (10.03)	2200(CN)	245(4.43) 330(3.99) 474(3.98)
6b	H	CN	SO_2-Ph	74	168	Orange needles	$C_{18}H_{14}N_2O_2S_2$	66.95 (66.45)	4.22 (4.13)	6.50 (6.34)	14.89 (14.71)	2190(CN)	250(4.52) 325(4.09) 470(3.89)
6c	Me	CN	CN	61	193	Red plates	$C_{20}H_{15}N_3S$	72.92 (72.49)	4.60 (4.49)	12.75 (13.37)	9.73 (9.52)	2200(CN)	247(4.60) 330(4.09) 483(4.08)
7	H	CN	COO-Me	68	191	Colorless needles	$C_{26}H_{21}N_3O_2$	76.64 (76.83)	5.20 (5.06)	10.31 (10.19)		2190(CN) 3200(NH) 1675(CO)	248(4.61) 300(4.32) 370(3.66)

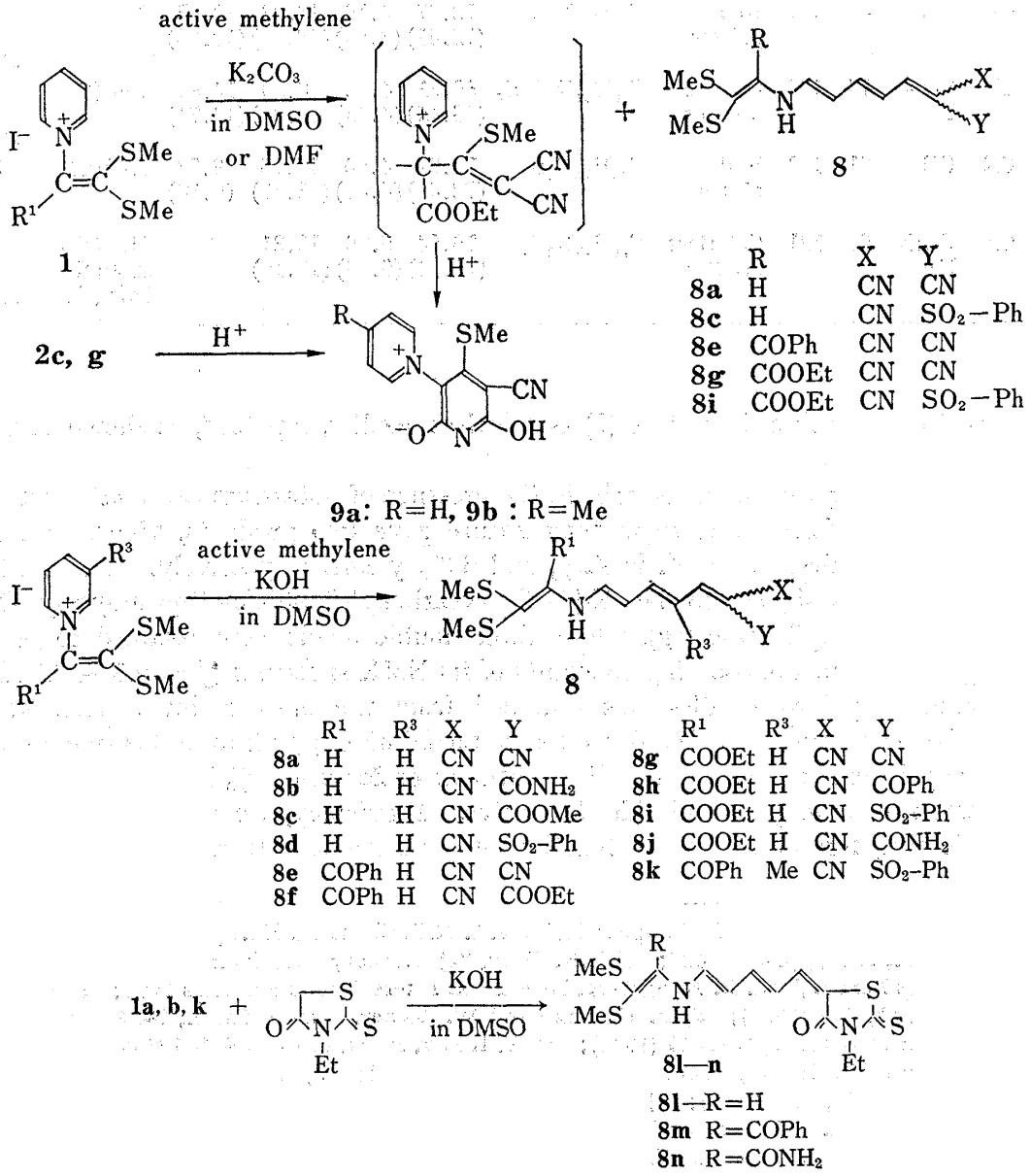
benzylamine to give-amino derivative (**7**) as colorless needles, mp 191°, as shown in Chart 4 and Table II.

The reaction of **1g** with malononitrile in the presence of potassium carbonate in dimethyl sulfoxide or dimethylformide at room temperature gave two products, violet needles, mp 164°, and yellow needles, mp 330°, in 42% and 36% yields, respectively. The product of violet needles was assigned to be N-[1-ethoxycarbonyl-2,2-bis(methylthio)vinyl]-N-(6,6-dicyano-1,3,5-hexatrienyl)amine (**8g**), whose three double bonds were assumed to be in all-trans arrangement from the coupling constants of its NMR spectrum (J=10.5—13.5 Hz).[6,10] The compound of yellow needles was obtained from the mother liquor after standing overnight. Its structure was found to be glutaconimide pyridinium betaine (**9a**) from elemental analysis and spectral data. The treatment of **2c** with 10% hydrochloric acid solution also gave the same glutaconimide derivative. Previously, we had reported a similar glutaconimide ring formation by the reaction of ketenethioacetal with active methylene

10) *a*) H.S. Mosher, in "Heterocyclic Compounds," Vol. 1. R.C. Elderfield Ed., John Wiley and Sons, Inc., New York, N.Y., 1950, pp. 424—432; *b*) E.N. Shaw, "Quaternary Pyridinium Compounds in Pyridine and Derivatives Part II," ed. E. Klingsberg, New York, Interscience Publishers 1961; *c*) F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953); *d*) F. Kröhnke and W. Zecher, *Angew. Chem.*, **74**, 811 (1962); *e*) F. Kröhnke, *Angew. Chem.*, **75**, 181, 317 (1963); *f*) W. König, *Prakt. Chem.*, **69**, 105 (1904); *g*) Th. Zinke, G. Heuser, and W. Moller, *Ann. Chem.*, **333**, 296 (1904); *h*) M.S. Moss and H.J. Pylanoe, *Nature* (London), **210**, 940 (1966); *i*) G.W. Fisher, *Buch. Z. Chemi.*, **8**, 379 (1968), [*Chem. Abstr.*, **70**, 11041*k* (1964)]; *j*) H. Aklbrecht and F. Kröhnke, *Ann. Chem.*, **701**, 126 (1967); *k*) A.F. Vompe and N.F. Turitsyne, *Zh. Obsch. Khim.*, **27**, 3282 (1957) [*Chem. Abstr.*, **52**, 9112*d* (1958)]; *l*) Th. Zinke and W. Wurker, *Ann. Chem.*, **338**, 107 (1905); *idem*, *ibid.*, **341**, 365 (1905); *m*) G.W. Fisher, *Chem. Ber.*, **103**, 3489 (1970); *n*) Y. Tamura, N. Tsujimoto, and M. Mano, *Chem. Pharm. Bull.* (Tokyo), **19**, 130 (1971); *o*) J.C. Powers, *J. Org. Chem.*, **30**, 2534 (1965); *p*) J. Schnekenburg and D. Heber, *Chem. Ber.*, **107**, 3405 (1974); *q*) F.T. Boyle and R. Hull, *J. Chem. Soc. Perkin I*, **1974**, 1541; *r*) R.D. Chambers, W. Keneth, R. Musgrave, and P.G. Urben, *Chem. Ind.*, **18**, 89 (1975); *s*) Y. Tominaga, K. Mizuyama, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 1670 (1974); *t*) K. Utimoto, N. Sasaki, M. Obayashi, and H. Nozaki, *Tetrahedron*, **32**, 769 (1976).

compounds.[11] In a similar manner, the reaction of ketenethioacetal derivatives (**1a—c**) with active methylene compounds (malononitrile, phenylsulfonylacetonitrile) afforded the ring-opened products (**8a, d, e, i**) with yith yields given in Table III. The reaction of **1j** with malononitrile gave glutaconimide pyridinium betaine (**9b**) and ring opened product which could not be purified further.

When potassium hydroxide was used instead of triethylamine or potassium carbonate in dimethyl sulfoxide, ketenethioacetals reacted easily with active methylene compounds (malononitrile, methyl cyanoacetate, cyanoacetamide, phenylsulfonylacetonitrile, 3-ethylrhodanine) to form only the corresponding ring-opened products in excellent yields as the ring opening reactions of pyridinium salts are well known.[10] Data were summarized in



	R	X	Y
8a	H	CN	CN
8c	H	CN	SO_2–Ph
8e	COPh	CN	CN
8g	COOEt	CN	CN
8i	COOEt	CN	SO_2–Ph

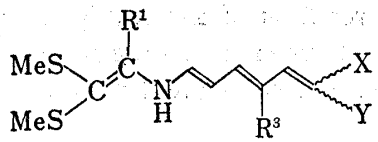
	R^1	R^3	X	Y
8a	H	H	CN	CN
8b	H	H	CN	$CONH_2$
8c	H	H	CN	COOMe
8d	H	H	CN	SO_2-Ph
8e	COPh	H	CN	CN
8f	COPh	H	CN	COOEt
8g	COOEt	H	CN	CN
8h	COOEt	H	CN	COPh
8i	COOEt	H	CN	SO_2-Ph
8j	COOEt	H	CN	$CONH_2$
8k	COPh	Me	CN	SO_2-Ph

Chart 5

11) *a*) R. Kuwayama and S. Kataoka, *Yakugaku Zasshi*, **85**, 387 (1965); *b*) G. Kobayashi, Y. Matsuda, R. Natsuki, and Y. Tominaga, *Yakugaku Zasshi*, **92**, 1468 (1972); *c*) Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **93**, 1523 (1973); *d*) S. Kisaki, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 2246 (1974).

Table III. There are a few reports of the ring opening reaction of pyridinium salts with active methylenes.[12] In these reports, the reaction of N-alkoxy pyridinium salts with

TABLE III.



No.	R^1	R^3	X	Y	Base (yield %)	mp (°C)	Appearance	Formula
8a	H	H	CN	CN	A (95) B (93)	155	Violet needles	$C_{12}H_{13}N_3S_2$
8b	H	H	CN	$CONH_2$	A (87)	172	Violet needles	$C_{12}H_{15}N_3OS_2$
8c	H	H	CN	COOMe	A (45)	160	Violet needles	$C_{13}H_{16}N_2O_2S_2$
8d	H	H	CN	SO_2-Ph	A (99) B (94)	165	Violet needles	$C_{17}H_{18}N_2O_2S_3$
8e	COPh	H	CN	CN	A (93) B (66) C (0.4)	233	Violet needles	$C_{19}H_{17}N_3OS_2$
8f	COPh	H	CN	COOEt	A (45)	169	Violet needles	$C_{21}H_{22}N_2O_3S_2$
8g	COOEt	H	CN	CN	A (67) B (37) C (1)	164	Violet needles	$C_{15}H_{19}N_3O_2S_2$
8h	COOEt	H	CN	COPh	A (65)	180	Violet crystals	$C_{21}H_{22}N_2O_3S_2$
8i	COOEt	H	CN	SO_2-Ph	A (84) B (67)	161	Red leaflets	$C_{20}H_{22}N_2O_4S_3$
8j	COOEt	H	CN	$CONH_2$	A (87)	165	Violet crystals	$C_{15}H_{19}N_3O_3S_2$
8k	COPh	Me	CN	SO_2-Ph	A (63)	197	Violet prisms	$C_{25}H_{24}N_2O_3S_3$

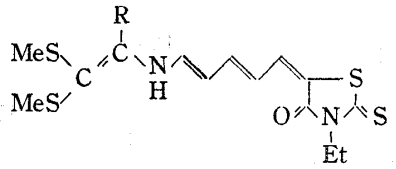
No.	Analysis (%) Calcd. (Found)				IR ν(KBr) cm^{-1}				UV λ_{max}^{EtOH} nm (10gε)
	C	H	N	S	ν NH	ν CN	νCO	ν C=C	
8a	54.72 (54.37)	4.99 (4.90)	15.45 (15.70)	24.35 (23.88)	3240	2180		1625	500(4.72)
8b	51.22 (51.16)	5.37 (5.40)	14.93 (15.03)	22.79 (22.82)	3440 3240 3120	2190	1670	1635	473(4.52)
8c	52.68 (52.51)	5.44 (5.67)	9.45 (9.61)	21.63 (21.49)	3220	2205	1700	1630	493(4.58)
8d	53.94 (53.79)	4.79 (4.82)	7.40 (7.34)	25.41 (25.27)	3210	2190		1630	500(4.94)
8e	62.10 (62.38)	4.66 (4.92)	11.44 (10.75)	17.45 (16.73)	3210	2200		1615	525(4.95)
8f	60.84 (60.71)	5.35 (5.49)	6.76 (6.63)	15.47 (15.45)	3210	2200	1700 1660	1625	254(4.01) 476(4.72)
8g	53.39 (53.43)	5.68 (5.52)	12.45 (12.45)	19.00 (19.41)	3200	2180 2190	1715	1620	487(4.59)
8h	60.84 (61.22)	5.35 (5.42)	6.76 (6.59)	15.47 (14.81)	3200	2190	1720	1630	520(4.81)
8i	53.31 (53.12)	4.92 (4.58)	6.22 (6.05)	21.35 (21.33)	3280	2190	1713	1630	485(4.92)
8j	50.97 (51.08)	5.42 (5.52)	11.89 (11.75)	18.15 (17.96)	3440 3240 2140	2190	1725 1675	1630	460(4.82)
8k	60.45 (60.05)	4.87 (4.77)	5.64 (5.44)	19.37 (19.29)	3260	2180	1660	1620	490(4.68)

a) A; KOH, B; K_2CO_3, C; Et_3N.

12) *a*) P. Pfeiffer and E. Enders, *Chem. Ber.*, **84**, 313 (1904); *b*) N.I. Fisher and F.M. Hamer, *J. Chem. Soc.*, **1933**, 189; *c*) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, p. 307; *d*) K. Hafner, *Angew. Chem.*, **67**, 302 (1955); *e*) K. Hafner, *Angew. Chem.*, **70**, 421 (1958); *f*) K. Hafner and H. Kaiser, *Ann. Chem.*, **618**, 140 (1958).

nitromethane in the presence of sodium methoxide gave ring-opened compound, which was determined to have all-trans double bond system from analysis of the NMR spectrum,[12c] although the ring opening reaction of 2-methylpyridine derivatives with active methylenes would be different from the above ring opening reactions. These reactions and the structures of products will be discussed in a subsequent paper.

Table IV.



No.	R	Yield (%)	mp (°C)	Appearance	Formula
8l	H	84	172	Violet needles	$C_{14}H_{18}N_2OS_4$
8m	COPh	72	158	Violet crystals	$C_{21}H_{22}N_2O_2S_4$
8n	$CONH_2$	92	300	Violet crystals	$C_{15}H_{19}N_3O_2S_4$

No.	Analysis (%) Calcd. (Found) C	H	N	S	IR ν(KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)
8l	46.89 (46.78)	5.06 (4.98)	7.81 (7.54)	35.77 (35.36)	3300(NH), 1680(C=O)	530(4.80)
8m	54.51 (55.07)	4.79 (5.04)	6.06 (5.82)	27.72 (27.69)	3300(NH), 1670, 1630(C=O)	550(4.84)
8n	44.86 (45.27)	4.77 (4.59)	10.46 (10.03)	31.94 (31.73)	1660, 1630(C=O)	520(4.79)

Experimental

All melting points were determined in a capillary tube and are uncorrected. IR spectra were recorded in KBr pellets on a Nihon-Bunko IRA-2 spectrometer, UV absorption spectra were determined on a Hitachi EP-S2 spectrometer in 95% EtOH, and NMR spectra were obtained using a JNM-PS-100 (100 MHz) spectrometer with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were recorded on a JEOL JMS-01SG doublefocus mass spectrometer using direct sample insertion into ion source in all cases.

Synthesis of N-Allylides (2a—h)——To a solution of 0.01 mol of ketenethioacetal derivative (**1b, e, g, h, i, j**) and 0.012—0.02 mol of active methylene compound (malononitrile or methyl cyanoacetate) in EtOH (80 ml), Et_3N (10 ml) was added and the mixture was refluxed on a boiling water bath for 2—4 hr. When Et_3N was added, the mixture turned reddish brown. After evaporation of the solvent, the reddish oil was chromatographed over Al_2O_3 with benzene–EtOH (10: 1) to give N-allylide in a good yield and with EtOH to give violet product in about 1% yield. The results are shown in Table I.

1-Cyano-3-ethoxycarbonyl-2-methylthioindolizines (4a, b)——To a solution of 0.01 mol of ketenethioacetal (**1g, i**) and phenylsulfonylacetonitrile (1.82 g) in EtOH (80 ml), Et_3N (10 ml) was added and the mixture was refluxed on a boiling water bath for 5 hr. The solvent was evaporated under a reduced pressure, the residue was poured into 100 ml of ice-water, the brown solid was separated by decantation, and 5 ml of EtOH was then added into this solid to give crystalline products, which were recrystallized from EtOH to give **4a**, mp 139° and **4b**, mp 120°, as colorless needles in 48 and 58% yields, respectively. **4a** was identified with an authentic sample.[8] **4b**: *Anal.* Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.48; H, 5.13; N, 10.20. IR ν (KBr) cm^{-1}: 2200 (CN), 1672 (C=O of ester group). UV λ_{max}^{EtOH} nm (log ε): 235 (4.53), 272 (4.72), 280 (4.71), 330 (3.94).

3-Ethoxycarbonyl-8-methyl-2-methylthioindolizine (5)——To a solution of **1i** (2.05 g) and $MeNO_2$ (0.65 g) in EtOH (50 ml), Et_3N (2 ml) was added and the mixture was refluxed on a boiling water bath for 5 hr. After removal of the solvent, the residue was poured into 100 ml of ice-water. The precipitate was separated by decantation and recrystallized from EtOH to give colorless needles (**5**), mp 87°, in 57% yield. *Anal.* Calcd. for $C_{13}H_{15}NO_2S$; C, 62.64; H, 6.07; N, 5.62. Found: C, 62.54; H, 5.99; N, 5.51. IR ν (KBr) cm^{-1}:

1670, 1407, 1380, 1245, 1235, 1090. UV λ_{max}^{EtOH} nm (log ε): 237 (4.18), 274 (4.63), 340 (3.90), 354 (3.94). NMR ($CDCl_3$) δ: 1.45 (3H, triplet, CH_2–$\underline{CH_3}$), 2.42 (3H, singlet, 8-CH_3), 4.52 (3H, singlet, SCH_3), 6.22 (1H, singlet, 1-H), 6.63 (1H, triplet, 6-H), 6.81 (1H, doublet, J=7 Hz, 7-H), 9.30 (1H, doublet, J=7 Hz, 5-H).

Synthesis of 2-Phenyl-3-(1-methylthiovinyl)indolizines (6a—c)——To a solution of 0.01 mol of ketenethioacetal (**1c, f**) and 0.012 mol of active methylene compound (malononitrile or phenylsulfonylacetonitrile) in EtOH (100 ml), Et_3N (10 ml) was added and the mixture was refluxed on a boiling water bath for 3 hr. After evaporation of the solvent, the residue was chromatographed over Al_2O_3 with benzene–EtOH (5: 1) to give 3-vinylindolizine derivative (**6a, b, c**), which was recrystallized from MeOH. When compound (**1f**) was treated with malononitrile, two products N-allylide (**2h**), mp 214°, and indolizine derivative (**6c**), mp 193°, in 35 and 46% yields, respectively. These products were easily separated by fractional crystallization from MeOH. These results are shown in Table II.

3-(1-Benzylamino-2-cyano-2-methoxycarbonyl)vinyl-2-phenylindolizine (7)——To a solution of **1c** (2.2 g) and methyl cyanoacetate (0.6 g) in EtOH (50 ml), Et_3N (6 ml) was added and the mixture was refluxed on a boiling water bath for 3 hr. After evaporation of the solvent, the residue was chromatographed over Al_2O_3 with benzene–MeOH (5: 1) to give a reddish oil, which was dissolved in 50 ml of MeOH and then benzylamine was added to the solution. The mixture was refluxed on a boiling water bath for 1 hr. After the solvent was evaporated, 100 ml of ice-water was added to its residue. This solution was acidified with 10% HCl solution and the resulting precipitate was collected by filtration. This precipitate was recrystallized from MeOH to give colorless needles (7), mp 191°, in 65% yield. *anal.* Calcd. for $C_{26}H_{21}N_3O_2$: C, 76.64, H, 5.20; N, 10.31. Found: C, 76.83; H, 5.06; N, 10.19. IR ν (KBr) cm^{-1}: 3200 (NH), 2200 (CN), 1674 (C=O). UV λ_{max}^{EtOH} nm (log ε): 248 (4.61), 300 (4.32).

Reaction of Ig with Malononitrile in the Presence of K_2CO_3——To a solution of Ig (2.05 g) and malononitrile (1 g) in Me_2SO or dimethylformamide (30 ml), K_2CO_3 (2 g) was added and the mixture was stirred at room temperature for 4 hr, by which the mixture turned violet. The violet reaction mixture was poured into 200 ml of ice-water and acidified with 10% HCl solution. The precipitate formed was collected by filtration, washed with water, and recrystallized from EtOH to give N-[1-ethoxycarbonyl-2,2-bis(methylthio)-vinyl]-N-(6,6-dicyano-1,3,5-hexatrienyl)amine (**8g**), mp 164°, in 42% yield. The filtrate was allowed to stand overnight at room temperature to give pyridinium betaine of glutaconimide derivative (**9a**) as yellow needles, mp 330°, in 36% yield, which was recrystallized from EtOH. *Anal.* Calcd. for $C_{12}H_9N_3O_2S$: C, 55.60; H, 3.50; N, 16.21. Found: C, 55.67; H, 3.15; N, 16.26. IR λ (KBr) cm^{-1}: 3190, 3450 (OH or NH). UV λ_{max}^{EtOH} nm 250, 340. NMR ($(CD_3)_2SO$) δ: 2.28 (3H, singlet, SCH_3).

Reaction of 1a, b, g with Active Methylene Compound in the Presence of K_2CO_3——To a solution of 0.01 mol of ketenethioacetal (**1a, b, g**) and 0.012 mol of active methylene compound (malononitrile, phenylsulfonylacetonitrile) in Me_2SO (50 ml), K_2CO_3 (4 g) was added and the mixture was stirred at room temperature for 4 hr. The violet reaction mixture was poured into 500 ml of ice-water and acidified with 10% HCl solution. The precipitate was collected by filtration, washed with water, and recrystallized from EtOH to give ring-opened product. Analytical data are shown in Table III and IV.

Treatment of 2c and 2g with Acidic Solution——A solution of **2c** or **2g** (1 g) in 10% HCl solution (50 ml) was allowed to stand overnight. The yellow precipitate that formed was collected by filtration, washed with water, and recrystallized from EtOH to give glutaconimide derivatives (**9a, b**) in 70—80% yield. **9b**: yellow needles, mp 300°. *Anal.* Calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.14; H, 4.06; N, 15.38; S, 11.71. Found: C, 57.08; H, 4.32; N, 15.21; S, 11.70. IR ν(KBr) cm^{-1}: 3070 (NH or OH), 2200 (CN), 1620—1640 (C=O, broad). UV λ_{max}^{EtOH} nm: 250, 344. NMR (CF_3COOH) δ: 2.68 (3H, singlet, SCH_3), 2.81 (3H, singlet, 4-CH_3), 7.98 (2H, doublet, J=5 Hz, 3 and 5-H), 8.50 (2h, doublet, J=5 Hz, 2 and 6-H).

Ring-opening Reaction of 1 with Active Methylene Compound in the Presence of Powdered KOH——To a solution of 0.01 mol of ketenethioacetal (**1a, b, g, i**) and 0.01 mol of active methylene compound (malononitrile, methyl cyanoacetate, phenylsulfonylacetonitrile, or 3-ethylrhodanine), powdered KOH (2 g) was added and the mixture was stirred at room temperature for 3—5 hr. The reaction mixture was poured into 500 ml of ice-water and acidified with 10% HCl solution. The precipitate was collected by filtration, washed with water, and recrystallized from EtOH or MeOH to give ring-opened product in a good yield. Analytical data are shown in Table III and IV.

Acknowledgement The authors are very grateful to Mrs. H. Mazume for microanalyses, to Mr. M. Owatari for the measurement of IR and UV spectra, to Mr. H. Inata for NMR spectra, and to Mr. H. Yamaguchi for mass spectra, all of this university.