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Quinolizine Derivatives. VI.[1] Synthesis and Reaction of 1-Cyano-2-methylthio-4*H*-quinolizin-4-ones

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Reaction of α,α'-dimethylthiomethylene-2-pyridylacetonitrile (I) and active methylene compounds in dimethyl sulfoxide, in the presence of potassium carbonate, afforded 1-cyano-2-methylthio-4*H*-quinolizin-4-ones with the corresponding substituent in 3-position. Reaction of some of these 3-substituted compounds with benzylamine produced 2-benzylamino-1-cyano-4*H*-quinolizin-4-ones. Reduction of one of the 3-substituted compound over Raney nickel catalyst gave 1-cyano-3β-pyridyl-4*H*-quinolizin-4-one.

We have earlier synthesized α,α'-dimethylthiomethylene-2-pyridineacetonitrile (I) from 2-pyridineacetonitrile and reported that the methylthio group in I is substituted with amines and that the treatment of I with active methylene compounds like methyl cyanoacetate, in the presence of sodium methoxide, merely resulted the alcoholysis of I leading to methyl 2-pyridinecyanoacetate. However, direct fusion of 2-pyridineacetonitrile with methyl 1-cyano-2,2-dimethylthioacrylate at 110° afforded 1,3-dicyano-2-methylthio-4*H*-quinolizin-4-one (IIa).

In the present series of work, reaction of I with active methylene compounds was further examined and it was found that stirring of I with ethyl cyanoacetate in dehyd. dimethyl sulfoxide, in the presence of potassium carbonate, for 4 hr at room temperature afforded IIa in 61% yield. IIa obtained showed no depression of the melting point on admixture

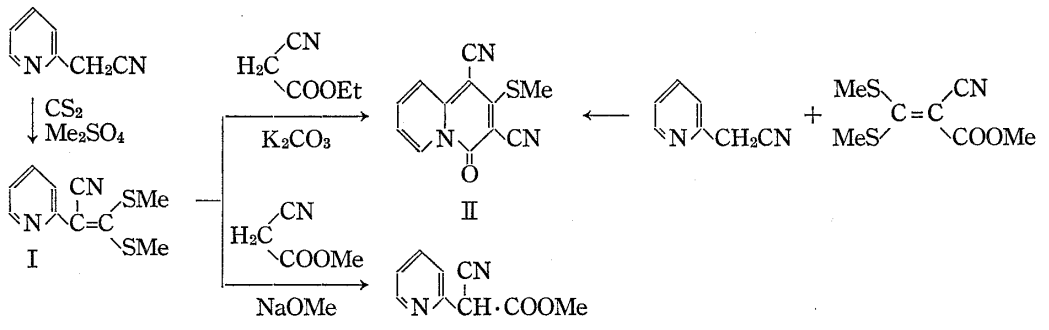

Chart 1

1) Part V: G. Kobayashi, Y. Matsuda, R. Natsuki, and M. Sone, *Chem. Pharm. Bull.* (Tokyo), **20**, 657 (1972).

2) Location: *1-14 Bunkyo-machi, Nagasaki, 852, Japan.*

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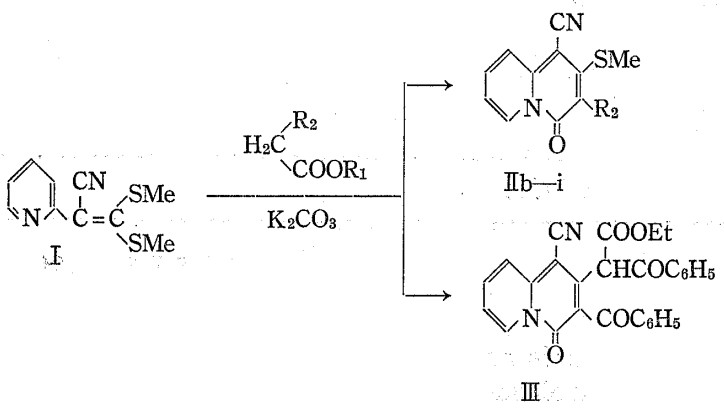
with the specimen obtained from I and methyl 1-cyano-2,2-dimethylthioacrylate, and their infrared (IR) and ultraviolet (UV) spectra were in complete agreement each other (*cf.* Chart 1).



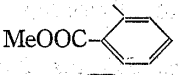
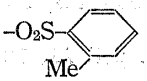
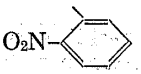
	R_1	R_2
a	-Et	-CN
b	-Et	$-COCH_3$
c	-Me	-COOMe
d	-Et	-COOEt
e	-Et	
f	-Et	$-COC_6H_5$
g	-Me	
h	-Et	
i	-Et	

Chart 2

The reaction of I and other active methylene compounds was carried out under the same conditions and the corresponding quinolizine compounds (IIb—i) were obtained in a comparatively good yield. The active methylene compounds used were ethyl acetoacetate, dimethyl malonate, diethyl malonate, ethyl 2-pyridineacetate, ethyl benzoylacetate, dimethyl homophthalate, ethyl *o*-tolenesulfonylacetate, and methyl *o*-nitrophenylacetate. The raction of I and ethyl benzoylacetate produced, besides the normal product (IIf), a compound (III) in which one more molecule of ethyl benzoylacetate had reacted with the methylthio group in the

Table I

No.	mp (°C)	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} mμ (log ε)
IIa	204—205	61	59.75	2.93	17.42	59.76	2.66	17.46	2193(CN) 1673(CO)	268.5(4.29) 288 (4.09) 313 (4.09) 357 (3.81) 416 (4.31)
IIb	178—179	45	60.46	3.90	10.85	60.82	4.12	10.17	2200(CN) 1700(CO) 1655(CO)	274 (4.19) 303 (4.00) 397 (4.17)
IIc	155	85	56.93	3.68	10.22	56.97	3.68	9.86	2250(CN) 1715(CO) 1650(CO)	273 (4.25) 300 (4.02) 395 (4.25)
IId	154—156	70	58.33	4.20	9.72	58.71	4.52	8.93	2250(CN) 1715(CO) 1650(CO)	273 (4.19) 300 (3.94) 396 (4.07)
IIe	175—176	50	65.52	3.78	14.33	65.22	3.97	14.38	2190(CN) 1650(CO)	276 (4.33) 303 (4.14) 396 (4.28)
IIf	177—179	40	67.50	3.78	8.75	67.14	3.32	8.02	2205(CN) 1705(CO) 1660(CO)	270 (4.33) 310 (3.96)[a] 398 (4.28)
IIg	168—170	50	65.14	4.03	8.00	65.03	4.07	7.60	2215(CN) 1720(CO) 1660(CO)	278 (4.26) 314 (4.00) 396 (4.21)
IIh	234—236	60	58.38	3.81	7.57	58.28	3.88	6.80	2200(CN) 1680(CO)	271 (4.26) 320 (4.12) 408 (4.36)
IIi	227—228	60	60.53	3.29	12.46	60.29	3.34	11.88	2200(CN) 1645(CO)	278 (4.36) 314 (4.14) 397 (4.26)
III	242	30	72.40	4.32	6.03	72.26	4.35	6.59	2225(CN) 1630—1660(CO)	270 [b] 403 [b]

a) shoulder *b*) Concentration was not measured due to insufficient solubility.

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Table II

No.	mp (°C)	Yield (%)	Analysis (%) Calcd. C	H	N	Found C	H	N	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} mμ (log ε)
IVa	185—187	80	68.46	4.54	12.61	68.19	4.40	12.34	3180(NH) 2195(CN) 1680(CO) 1655(CO)	260(4.59) 304(4.19) 396(3.98)
IVb	176—178	80	74.98	4.58	15.90	74.85	4.67	15.88	3180(NH) 2190(CN) 1650(CO)	268(4.60) 320(4.15) 390(4.03)
V	210—211	70	72.86	3.67	17.00	73.59	4.00	16.77	2200(CN) 1665(CO)	261(4.35) 415(4.33)

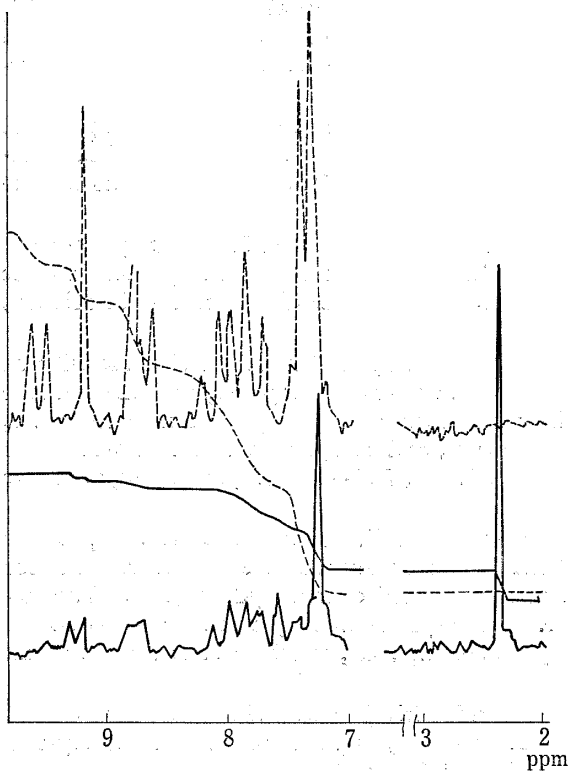
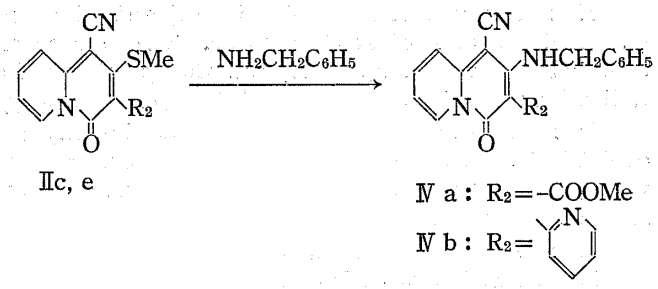


Fig. 1. Nuclear Magnetic Resonance Spectra of IIe and V ($CDCl_3$)

——: IIe ------: V



IIc, e

IV a : R_2=-COOMe

IV b : R_2=

Chart 3

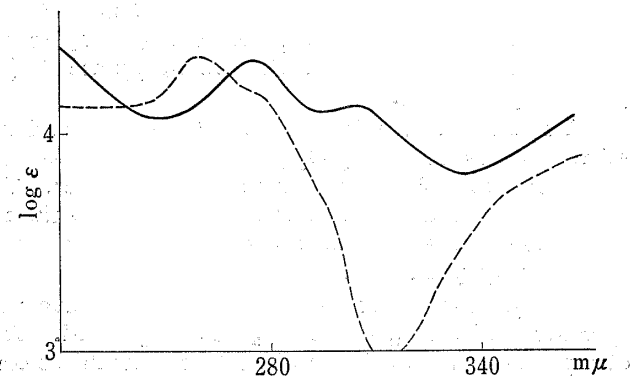


Fig. 2. Ultraviolet Spectra (EtOH) of IIe and V

——: IIe ------: V

2-position of IIf (*cf.* Chart 2 and Table I). These reactions indicated that quinolizin-4-one derivatives having variety of substituent in 3-position can be synthesized with comparative ease by this method.

We have also reported earlier[3] that the methylthio group in the 2-position of IIa was easily substituted with amines. Based on this knowledge, quinolizin-4-ones (IIc and IIe) with a different substituent in 3-position synthesized in the present series of work were reacted with benzylamine by refluxing in methanol and the corresponding 2-benzylamino compounds (IVa and IVb) were obtained in good yields (*cf.* Chart 3 and Table II).

3) G. Kobayashi, S. Furukawa, Y. Matsuda, and S. Matsunaga, *Yakugaku Zasshi*, **89**, 203 (1969).

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Catalytic reduction of IIe over Raney nickel resulted in the formation of a demethylthio compound, 1-cyano-3-pyridyl-4*H*-quinolizin-4-one (V). Nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$) of IIe exhibits a singlet of 3 methyl protons in methylthio group at 2.38 ppm and a multiplet of 8 aromatic protons at 7.29—9.3 ppm while that (in $CDCl_3$) of V exhibits a multiplet of 9 aromatic protons at 7.27—9.7 ppm. Therefore, the methylthio group at 2-position in IIe had been clearly liberated (*cf.* Table II, Fig. 1 and Fig. 2).

Further reduction of V to sparteine, a lupinus alkaloid, was attempted but a satisfactory result has not been obtained to date.

Experimental

Synthesis of 1-Cyano-2-methylthio-4*H*-quinolizin-4-ones (IIa—i, III)——IIa: A mixture of I (0.0025 mole) and ethyl cyanoacetate (0.0025 mole) in abs. Me_2SO, in the presence of K_2CO_3 (0.01 mole), was stirred at room temperature for 4 hr. The reaction mixture was poured into ice water, crystals formed were collected by suctional filtration, and recrystallized from methyl-cellosolve to crystals of mp 204—205° (*cf.* Table I).

IIb: A suspension of I (0.005 mole) and ethyl acetoacetate (0.005 mole) in abs. Me_2SO, with K_2CO_3 (0.02 mole) was stirred at 45° for 7 hr. The reaction mixture was poured into ice water, allowed to stand overnight in an ice box and crystals that precipitated out were collected by suctional filtration. Recrystallization from MeOH gave crystals of mp 178—179° (*cf.* Table I).

IIc: A mixture of I (0.0025 mole) and dimethyl malonate (0.0025 mole) in abs. Me_2SO, in the presence of K_2CO_3 (0.01 mole), was stirred for 6 hr at room temperature. The reaction mixture was poured into ice-water, and crystals that precipitated out were collected by suctional filtration. Recrystallization from MeOH gave crystals of mp 155° (*cf.* Table I).

IId: A mixture of I (0.0025 mole) and diethyl malonate (0.0025 mole) in abs. Me_2SO in presence of K_2CO_3 (0.01 mole), was stirred for 24 hr at room temperature. The reaction mixture was poured into ice water, and crystals formed were collected by suctional filtration. Recrystallization from MeOH afforded crystals of mp 154—156° (*cf.* Table I).

IIe: A mixture of ethyl 2-pyridineacetate (0.0025 mole) and K_2CO_3 (0.01 mole) in abs. Me_2SO was stirred at 70—80° for 1 hr. The compound (I, 0.0025 mole) was then added dropwise, and the mixture was stirred further for 8 hr at the same temperature. The reaction mixture was poured into ice-water, crystals that precipitated out were collected by suctional filtration, and recrystallized from iso-PrOH to crystals of mp 175—176°. NMR ($CDCl_3$) ppm: 2.38 (3H, singlet, SCH_3), 7.27—9.3 (8H, multiplet, aromatic proton) (*cf.* Table I).

IIf and III: A mixture of I (0.0025 mole) and ethyl benzoylacetate (0.0025 mole), in abs. Me_2SO was stirred in presence of K_2CO_3 (0.001 mole) at 85—90° for 15 hr. The reaction mixture was poured into ice water, and the solution was extracted with ether. The extract was dried over anhyd. Na_2SO_4. The solvent was evaporated, and MeOH was added to the residue. The crystals thereby formed were collected by suctional filtration and recrystallized from acetone to crystals of mp 242°, which did not contain S and should be compound III.

The aqueous layer left after ether extraction was reextracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated. The residue was recrystallized from MeOH to crystals of mp 177—179°, which contained S and should be compound IIf (*cf.* Table I).

IIg: A mixture of I (0.0025 mole) and dimethyl homophthalate (0.0025 mole) in abs. Me_2SO was stirred in presence of K_2CO_3 (0.01 mole) at 70—80° for 14 hr or heated in a boiling water bath for 5 hr. The reaction mixture was poured into ice-water and allowed to stand over night. The crystals that precipitated out were collected by suctional filtration. Recrystallization from MeOH gave a product of mp 168—170° (*cf.* Table I).

IIh: A mixture of I (0.0025 mole) and ethyl *o*-tolenesulfonylacetate (0.0025 mole), in presence of acetone (0.01 mole) added, was heated on a boiling water bath for 5 hr. The reaction mixture was poured into ice-water, and crystals that formed were collected by suctional filtration. Recrystallization form acetone gave a product of mp 234—236° (*cf.* Table I).

IIi: A mixture of I (0.0025 mole) and methyl *o*-nitrophenylacetate (0.0025 mole) in abs. Me_2SO, in presence of acetone (0.01 mole) added, was heated on a boiling water bath for 4.5 hr. The reaction mixture was poured into ice water, and crystals that formed were collected by suctional filtration. Recrystallization from acetone gave a product of mp 227—228° (*cf.* Table I).

2-Benzylamino-1-cyano-4*H*-quinolizin-4-ones (IVa, b)——IVa: A mixture of IIc (0.0025 mole) and benzylamine (0.00375 mole) in MeOH was refluxed for 35 hr, MeOH was evaporated, and the residue was recrystallized from MeOH to a product of mp 185—187° (*cf.* Table II).

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IVb: A mixture of IIe (0.0025 mole) and benzylamine (0.005 mole) was fused at 130—140° for 4 hr and MeOH was added to the cooled mixture by which the mixture crystallized. Recrystallization from MeOH gave a product of mp 176—178° (*cf.* Table II).

1-Cyano-3-pyridyl-4*H*-quinolizin-4-one (V)——A mixture of IIe (0.5 g) and Raney Ni (10 ml) in redistilled EtOH (70 ml) was refluxed for 5 hr, filtered, and the filtrate was concentrated under a reduced pressure. The crystals that precipitated out were collected, dissolved in benzene, and chromatographed over Al_2O_3. The fraction eluted with benzene was evaporated and the residue was recrystallized from benzene to a product of mp 210—211°. NMR ($CDCl_3$) ppm: δ 7.27—9.7 (9H, multiplet, aromatic proton) (*cf.* Table II).

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