[Chem. Pharm. Bull. 20(4) 657—663 (1972)]

UDC 547.834.2.057 : 547.833.04

Studies of Quinolizine Derivatives. V.[1] Synthesis of 3-Cyano-2-methylthio-4-oxo-6,7-dihydrobenzo [*a*] quinolizines and Their Reactions

GORO KOBAYASHI, YOSHIRO MATSUDA, REIKO NATSUKI
and MASAKATSU SONE

Pharmaceutical Faculty, University of Nagasaki[2]

(Received March 1, 1970)

Reaction of 3,4-dihydroisoquinolineacetonitrile (I) and methyl 1-cyano-2,2-dimethylthioacrylate (II) gave 3-cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (III). III reacted with various amines to form 1,3-dicyano-2-amino-4-oxo-6,7-dihydrobenzo-[*a*]quinolizines (IVa—g). III also reacted with active methylene compounds to form 1,3-dicyano-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (V—IX).

In the reaction of 1,3-dicyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (IIIa) and 2-amino-1,3-dicyano-4-oxo-6,7-dihydrobenzo[*a*]quinolizine (IVd) with concentrated sulfuric acid, the cyano group in 1-position was found to be easily liberated and that in 3-position was converted into a carboxamide group.

Reduction of 1,3-dicyano-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (IIIa,b, IVa, Vb) with sodium borohydride in ethanol or N,N-dimethylformamide gave 1,3-dicyano-4-oxo-1,6,7,11b-tetrahydro-9,10-dimetoxybenzo[*a*]quinolizines (XI, XIIa,b, XIII) by the reduction of quinolizine skeleton.

The previous papers of this series,[1,3-5] showed that the reaction of 2-pyridineacetonitriles (I) and methyl 1-cyano-2,2-dimethylthioacrylate (II) gave 3-cyano-2-methylthio-4*H*-quinolizin-4-ones (III), their reaction were examined, and that *dl*-allomatridine was synthesised from III. We applied this knowledge to 3,4-dihydroisoquinolineacetonitriles, obtained 3-cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (III), and examined their reaction.

Synthesis of 3-Cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (IIIa—d)

Condensation of 3,4-dihydroisoquinolineacetonitriles (Ia, c) with methyl 1-cyano-2,2-dimethylthioacrylate (II) gave 1,3-dicyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (II a, c) by melting at 130°.

Condensation of ethyl 3,4-dihydroisoquinoline-1-acetates (Ib, d) with II gave 3-cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (IIIb, d), the ethoxycarbonyl group in 1-position of which appeared to be liberated by a molten state at 100°. Nuclear magnetic resonance (NMR) spectrum (in CF_3COOH) of IIIa exhibits a multiplet of 4 aromatic protons at 7.3—8.4 ppm while that (in CF_3COOH) of IIIb exhibits a multiplet of 5 aromatic protons at 7.2—8.0 ppm. Therefore, the ethoxycarbonyl group at 1-position in IIIb had been clearly liberated (Chart 1 and Table I).

Reaction of 3-Cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines with Amines

Replacement of methylthio group with an amino group by the reaction of 3-cyano-2-methylthio-4*H*-quinolizin-4-one derivatives with an amino compound has been reported[3] and this method was applied to the reaction of 3-cyano-2-methylthio-4-oxo-6,7-dihydrobenzo-[*a*]quinolizines (IIIa—c) with amines. The aminated compounds (IVa—g) were obtained in

---

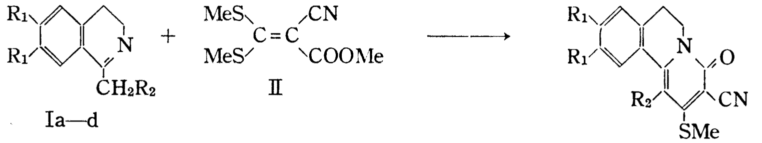
[1] Part IV: G. Kobayashi, Y. Matsuda, and R. Natsuki, *Yakugaku Zasshi*, **91**, 1275 (1971).

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

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

[4] G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki and S. Matsunaga, *Yakugaku Zasshi*, **90**, 127 (1970).

[5] G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki and S. Matsunaga, *Chem. Pharm. Bull.* (Tokyo), **18**, 124 (1970).



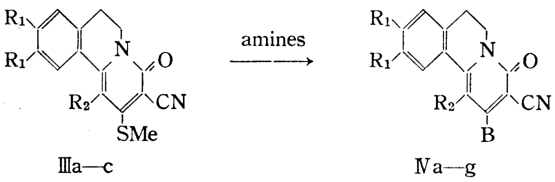
Ia—d II IIIa—d

Ia : R_1=H R_2=CN
Ib : R_1=H R_2=COOEt
Ic : R_1=OMe R_2=CN
Id : R_1=OMe R_2=COOEt

IIIa : R_1=H R_2=CN
IIIb : R_1=H R_2=H
IIIc : R_1=OMe R_2=CN
IIId : R_1=OMe R_2=H

Chart 1

a satisfactory yield from IIIa—c by reaction with amines (benzylamine, cycohexylamine, morpholine, ammonium acetate, piperidine) by melting or by refluxing in ethanol (Chart 2 and Table II).



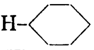
	R_1	R_2	B
IVa	: H	CN	-$NHCH_2C_6H_5$
IVb	: H	CN	-NH-
IVc	: H	CN	
IVd	: H	CN	-NH_2
IVe	: H	CN	
IVf	: H	H	-$NHCH_2C_6H_5$
IVg	: H_3CO	CN	-$NHCH_2C_6H_5$

Chart 2

Reaction of 1,3-Dicyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (IIIa, c) with Active Methylene Compounds

It had been found previously[1] that the reactions of 3-cyano-2-methylthio-4*H*-quinolizin-4-one derivatives with active methylene compounds resulted in replacement of the methylthio

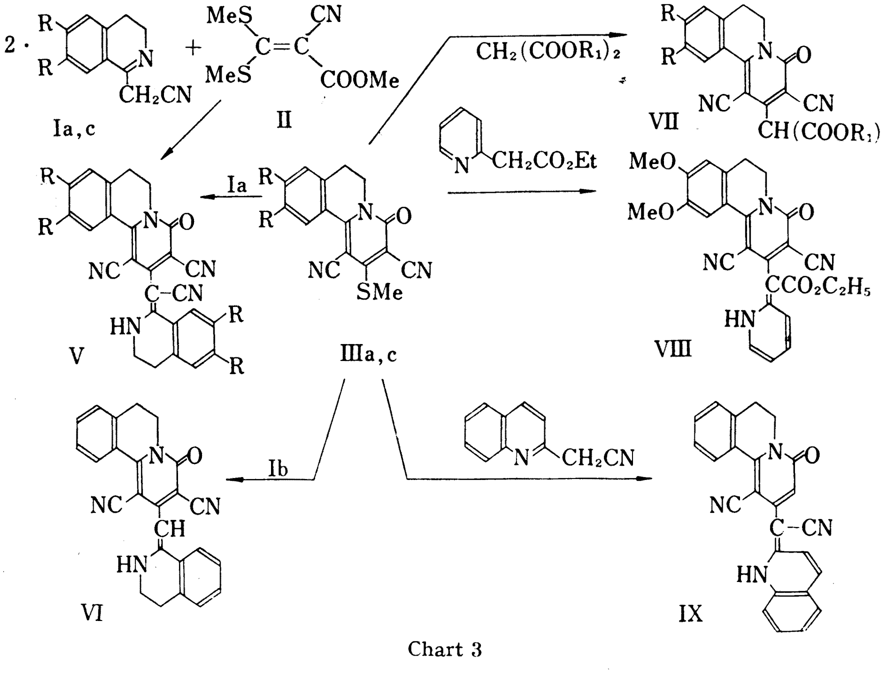


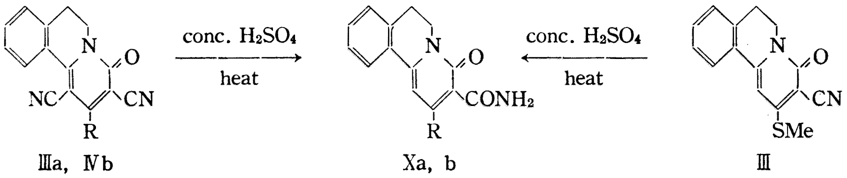
Chart 3

group with active methylene group when stirred with potassium carbonate in absolute dimethyl sulfoxide at room temperature. We applied this condition to the reaction of IIIa—c with 3,4-dihydroisoquinolineacetonitriles (IIIa—c), methyl malonate, ethyl malonate, or ethyl 2-pyridineacetate as active methylene compound. This replacement reaction of IIIa and IIIc with 3,4-dihydroisoquinolineacetonitrile (Ia) in the presence of sodium hydride in N,N-dimethylformamide gave Va and Vb. Va and Vb were also obtained on heating 2 moles of Ia and Ic with 1 mole of II, in the presence of potassium carbonate in N,N-dimethylformamide on a boiling water bath.

This replacement reaction of IIIa with Ib gave VI which appeared to be a decarboxylated compound. The reaction of IIIa and IIIc with other active methylene compounds (malonates, ethyl 2-pyridineacetate, 2-quinolineacetonitrile) gave VII, VIII, and IX in a similar manner (Chart 3).

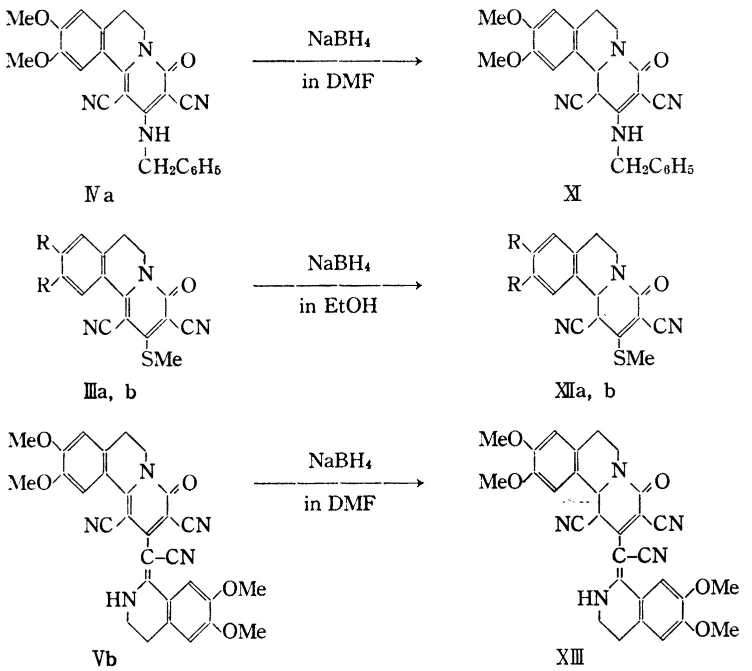
Reaction of 1,3-Dicyano-4-oxo-6,7-dihydrobenzo[*a*]quinolizines with Concentrated Sulfuric Acid

The reaction of the compound IIa with concentrated sulfuric acid gave Xa in which the cyano group in 1-position appeared to be liberated and the cyano group in 3-position was changed to carboxamide by hydrolysis. Elimination of the cyano group in 1-position was evident from the reaction of IIIb without a cyano group in 1-position with concentrated sulfuric acid which gave Xa. The NMR spectrum (in CF_3COOH) of IIIa exhibited absorption



IIIa, IVb Xa, b III

Chart 4



IVa XI IIIa, b XIIa, b Vb XIII

Chart 5

for four aromatic protons (7.4—8.4 ppm; 4H, multiplet), while that of Xa showed the presence of five aromatic protons (7.5—8.1 ppm, 5H, multiplet), indicating the presence of aromatic protons in 1-position of Xa. This reaction also occurred in IVd having an amino group in 2-position (Chart 4).

Reduction of Quinolizine Skeleton with Sodium Borohydride

Reduction of ethyl 2-amino-3-cyano-4-oxo-4H-quinolizine-1-carboxylate derivatives with sodium borohydride was found to give ethyl 2-amino-3-cyano-4-oxo-1,6,7,8,9,10-hexahydro-4*H*-quinolizine-1-carboxylate derivatives.[4] Miyadera, *et al.*[6] reported that the reduction of benzo[*b*]quinolizinium bromide with sodium borohydride gave three kinds of reduction products, benzo[*b*]quinolizidine, 3,6,11,11a-tetrahydro-4*H*-benzo[*b*]quinolizine, and 1,6,11,11a-tetrahydro-4*H*-benzoquinolizine, while Yamada, *et al.*[7] examined the reaction of cyanopyridines or cyanoquinolines with sodium borohydride for the reduction of cyano group or pyridine skeleton. It had been proved that IV was converted to XI by reduction with sodium borohydride in N,N-dimethylformamide at room temperature without reduction of the cyano group.

This reduction occurred in a similar manner in the case of IIIa, IIIb, and Vd. (Chart 5).

Compounds VI and VII, and their reduction product XIII, having the emetine skeleton are very useful for the synthesis of compounds analogous to emetine.

Experimental

Synthesis of 3-Cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizine Derivatives (IIIa—d)——IIIa,c: A mixture of 0.005 mole of Ia or Ic and 0.005 mole of II was heated in an oil bath at 130—140° for 6 hr and crystals separated out during this time. The crystals were collected and recrystallized from acetone–MeOH (IIIa) or from $CHCl_3$–MeOH (IIIc).

IIIb,d: (a) A mixture of 0.005 mole of Ib or Ic, 0.005 mole of II, and 0.01 mole of K_2CO_3 in 10 ml absolution N,N-dimethylformamide (DMF) was heated in a boiling water bath for 6 hr, the solvent was

TABLE I

III	mp (°C)	Yield (%)	Analysis (%)						NMR (CF_3COOH) ppm	IR (KBr) cm^{-1}	UV λ_{max} mμ (log ε)
			Calcd.			Found					
			C	H	N	C	H	N			
a	221—222	80	65.52	3.78	14.33	65.69	3.85	13.11	SCH_3 3.0 (s) aromatic 4H 7.3—8.4 (m)	$\nu_{C=O}$ 1660 $\nu_{C\equiv N}$ 2210	226 (3.92) 276 (3.80) 374 (3.86)
b	240—244	60	67.15	4.51	10.44	66.94	4.45	10.26	SCH_3 2.78 (s) aromatic 5H 7.2—8.0 (m)	$\nu_{C=O}$ 1630 $\nu_{C\equiv N}$ 2210	245 (4.22) 262 (4.43) 289 (3.78) 368 (4.47)
c	250—252	80	61.19	4.28	11.89	61.44	4.23	11.33	—	$\nu_{C=O}$ 1640 $\nu_{C\equiv N}$ 2220	257[a] 290[a] 402[a]
d	273—274	70	62.19	4.91	8.53	61.78	4.79	7.61	SCH_3 2.77 (s) 2-OCH_3 4.05 (s) aromatic 2H 7.0 (d) H 7.45 (s)	$\nu_{C=O}$ 1640 $\nu_{C\equiv N}$ 2220	247[a] 268[a] 320[a] 388[b]

a) Concentration is unknown because of being insoluble.
b) shoulder

---

6) T. Miyadera and R. Tachikawa, *Tetrahedron*, **25**, 5189 (1969).

7) S. Yamada, Y. Kikugawa, I. Saito, M. Kuramoto and H. Watanabe, Abstract of Papers, *2nd Congress of Heterocyclic Chemistry*, 54 (1969).

evaporated *in vacuo*, and water was added to the residual solution. The crystals that precipitated out were collected and recrystallized from acetone–petro. benzine.

(b) A mixture of 0.005 mole of Ib or Ic and 0.005 mole of II was heated in an oil bath at 120° for 4 hr. The crystals separated out during this time. The crystals were collected and recrystallized from acetone–petro. benzine (Table I).

Reaction of 3-Cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines (IIIa—c) and Amines——IVa—c, e—g: A mixture of 0.3 g of IIIa—c and 0.5 ml of an amines was refluxed in EtOH for 5 hr. After removal of EtOH, the residue was washed with petro. benzine and recrystallized from MeOH–$CHCl_3$, benzene, or acetone (Table II).

IVd: A mixture of 0.4 g of IIIa and 8 g of $AcONH_4$ was heated in an oil bath at 145° for 3 hr. After water was added to the reaction mixture, the resulting precipitate was collected, washed with water, and sucked dry. The crystals were recrystallized from MeOH–$CHCl_3$ (Table II).

TABLE II

IV	mp (°C)	Yield (%)	Analysis (%) Calcd. C	H	N	Found C	H	N	IR (KBr) cm^{-1}	UV λ_{max} mμ (log ε)
a	217	80	74.98	4.58	15.90	75.11	4.60	15.57	$\nu_{C=O}$ 1650 $\nu_{C\equiv N}$ 2200 ν_{N-H} 3320	256 (4.66) 340 (4.18)
b	206—207	70	73.23	5.85	16.27	73.37	6.07	16.01	$\nu_{C=O}$ 1630 $\nu_{C\equiv N}$ 2200 ν_{N-H} 3355	255 (4.65) 289 (3.20) 340 (4.05)
c	260—261	75	68.66	4.85	16.86	68.29	5.26	16.36	$\nu_{C=O}$ 1640 $\nu_{C=N}$ 2210	242$^{a)}$ 280$^{b)}$ 306$^{b)}$ 360
d	>300	60	68.69	3.84	21.37	68.76	3.74	20.63	$\nu_{C=O}$ 1650 $\nu_{C\equiv N}$ 2210 ν_{N-H} 3300 3400 3480	252 (3.65) 275 (4.07) 296 (4.23) 314 (4.30) 324 (4.31)
e	239—240	75	72.70	5.49	16.96	72.59	5.73	16.78	$\nu_{C=O}$ 1630 1655 $\nu_{C\equiv N}$ 2210	270$^{b)}$(4.48) 282 (4.49) 355 (4.23)
f	232—233	80	77.04	5.23	12.84	77.12	5.58	12.18	$\nu_{C=O}$ 1620 $\nu_{C=N}$ 2200 ν_{N-H} 3400	226 (4.47) 334 (4.26)
g	210—211	75	69.89	4.89	13.59	69.31	4.86	13.51	$\nu_{C=O}$ 1660 $\nu_{C\equiv N}$ 2200 ν_{N-H} 3426	247 (4.78) 292 (3.97) 363 (4.34)

a) Concentration is unknown because of being insoluble.
b) shoulder

Reaction of 3-Cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizines and Active Methylene Compounds——Va, b: (a) A mixture of 0.35 g of IIIa and 0.50 g of Ia or Ic was added under stirring in 0.1 g of NaH suspended in 10 ml of DMF. The reaction mixture was heated on a boiling water bath for 8 hr, the solvent was evaporated *in vacuo*, and ice-water was added to the residue. This was extracted with $CHCl_3$ and the solvent was evaporated. The residue was recrystallized from $CHCl_3$–MeOH (Table III).

(b) A mixture of 1.7 g of Ia or Ic, 1.0 g of II, and 1 g of K_2CO_3 in 10 ml of DMF was heated on a boiling water bath. After DMF was evaporated *in vacuo*, water was added to the residue. The resulting precipitate was collected, washed with water, and sucked dry. The residue was recrystallized from MeOH–$CHCl_3$ (Table III).

VI: A mixture of 0.3 g of IIIa, 0.2 g of Ib, and 0.9 g of K_2CO_3 in 10 ml of abs. DMF was heated on a boiling water bath for 11 hr. After DMF was evaporated *in vacuo*, ice-water was added to the residue. The resulting precipitate was collected, washed with H_2O, and sucked dry. The residue was recrystallized from benzene–acetone (Table III).

VIIa, b: A mixture of 0.25 g of IIIc and 0.1 g of dimethyl or diethyl malonate added to a suspension of 0.1 g of NaH in 10 ml of DMF with stirring was heated on a boiling water bath for 7 hr. After DMF was evaporated *in vacuo*, ice-water was added to the residue, and the solution was acidified with 10% HCl. The resulting precipitate was collected, washed with water, and the dried precipitate was recrystallized from acetone (Table III).

Table III

	mp (°C)	Yield (%)	Analysis (%)						NMR (CF_3COOH) ppm	IR (KBr) cm^{-1}	UV λ_{max} mμ (log ε)
			Calcd.			Found					
			C	H	N	C	H	N			
Va	288—290	70	75.16	4.12	16.86	75.00	4.20	16.34	4H 3 —3.4 (m) 4H 4.15—4.5 (m) aromatic 8H 7.5 —8.5 (m)	$\nu_{C=O}$ 1660 $\nu_{C\equiv N}$ 2208 ν_{N-H} 3350	275[a)] 352 380
Vb	>300	80	67.28	4.71	13.08	66.46	4.73	11.98	4H 3.1 —3.5 (m) $4OCH_3$ 4.15 (s) 4H 4.3 —4.7 (m) aromatic 2H 7.12 (m) 2H 8.0 —8.2 (m)	$\nu_{C=O}$ 1650 $\nu_{C\equiv N}$ 2200 ν_{N-H} 3340	274[a)] 320 380
VI	275—277	75	76.90	4.65	14.35	77.29	5.19	13.36	5H 3 —3.5 (m) 4H 4.2 —4.5 (m) aromatic 8H 7.3 —8.5 (m)	—	231[a)] 300 356 376 396
VIIa	R_1: Et 151—152	80	65.18	4.72	10.37	65.26	4.94	9.70	$-CH_3$ 1.47 (q) $-CH_2-$ 4.5 (q) -CH< 5.58 (q)	$\nu_{C=O}$ 1645 1715 $\nu_{C\equiv N}$ 2180	231 (4.43) 273 (4.29) 376 (4.37)
VIIb	R_1: Me 233—235	75	60.41	4.38	9.61	60.23	4.40	9.22	$2-OCH_3$ 3.86 (s) $2-OCH_3$ 3.95 (s) -CH< 5.2 (s)	$\nu_{C=O}$ 1665 1750 $\nu_{C\equiv N}$ 2225	300[a)] 400
VIII	245—248	70	66.37	4.71	11.91	66.41	4.68	11.40	—	$\nu_{C=O}$ 1650 1685 $\nu_{C\equiv N}$ 2200 ν_{N-H} 3305	250[a)] 325 377 453 470
IX	>300	70	75.54	3.63	16.99	75.10	3.56	16.10	aromatic 10H 7.6—9.5 2H 4.3—4.9 2H 3.1—3.6	$\nu_{C=O}$ 1665 $\nu_{C\equiv O}$ 2205 2220 ν_{N-H} 3320	264[a)] 311 370 472 495

a) Concentration is unknown because of being insoluble.

Table IV

X	mp (°C)	Yield (%)	Analysis (%)						NMR (CF_3COOH) ppm	IR (KBr) cm^{-1}	UV λ_{max} mμ (log ε)
			Calcd.			Found					
			C	H	N	C	H	N			
a	248—249	60	62.93	4.93	9.79	62.38	5.14	9.31	SCH_3 3.2 aromatic 5H 7.5—8.1	$\nu_{C=O}$ 1650 ν_{N-H} 3345	231.5 (4.12) 259 (4.26) 360 (4.22)
b	>300	75	65.87	5.13	16.46	65.37	5.29	15.19	—	$\nu_{C=O}$ 1645 ν_{N-H} 3240 3400	225 (4.47) 236[a)] (4.44) 327 (4.25)

a) shoulder

VIII: A mixture of 0.2 g of IIIc, 0.25 g of ethyl 2-pyridineacetate, and 0.3 g of K_2CO_3 in 10 ml of DMF was stirred at room temperature for 2 hr. The reaction mixture was added into ice-water and the resulting precipitate was filtered. The dried crystals were recrystallized from MeOH–$CHCl_3$ (Table III).

IX: A mixture of 0.2 g of IIIa, 0.2 g of 2-quinolineacetonitrile and 0.2 g of K_2CO_3 in 10 ml of DMF was stirred at room temperature for 1.5 hr. The reaction mixture was added to ice-water and the resulting precipitate was collected, dried, and recrystallized from MeOH–$CHCl_3$ (Table III).

Reaction of 3-Cyano-4-oxo-6,7-dihydrobenzo[*a*]quinolizine Derivatives (IIIa, IIIb, IVd) and conc. H_2SO_4 (Xa, b)——A mixture of 0.2 g of IIIa, IIIb or IVd and 4 ml of conc. H_2SO_4 was heated on a boiling water bath for 1.5 hr. The reaction mixture was poured into ice-water and the resulting precipitate was collected, washed with water, dried, and recrystallized from MeOH (Table IV).

1,3-Dicyano-2-benzylamino-4-oxo-1,6,7,11b-tetrahydro-9,10-dimethoxybenzo[*a*]quinolizine (XI)——A solution of IVa (0.2 g) in DMF (5 ml) was added under stirring in a solution of $NaBH_4$ (0.1 g) in DMF (10 ml). Stirring was continued at room temp. for 3 hr. The solution was acidified with AcOH, the solvent was evaporated *in vacuo*, Na_2CO_3 solution was added to the residue, and the resulting precipitate was collected and recrystallized from MeOH–$CHCl_3$ (Table V).

Reduction of IIIa,c (XIIa,b)——A solution of IIIa or IIIc (0.25 g) in EtOH (2.0 ml) was added under stirring to ice-cooled solution of $NaBH_4$ (0.25 g) in EtOH (10 ml) during 5 min. After being stirred for 7 hr, the resulting mixture was treated as described for XI. The crude crystals were recrystallized from MeOH (Table V).

Table V

	mp (°C)	Yield (%)	Analysis (%) Calcd. C	H	N	Found C	H	N	NMR (CF_3COOH) ppm	IR (KBr) cm^{-1}	UV λ_{max} mμ (log ε)
XI	>260	70	69.55	5.35	13.52	69.60	5.39	12.66	1-H 6.9 11b-H 6.22	$\nu_{C=O}$ 1645 (s) $\nu_{C\equiv N}$ 2210 ν_{N-H} 3320	290 (4.28)
XIIa	220	65	65.08	4.44	14.23	64.93	4.49	14.17	SMe 2.95 1-H 5.35 11b-H 4.85	$\nu_{C=O}$ 1645 $\nu_{C\equiv N}$ 2200	277 (3.92) 318 (3.80) 370 (3.86)
XIIb	223—225	60	60.84	4.82	11.83	60.70	4.51	11.96	SMe 2.96 2-0-Me 4.05 1-H 5.35 11b-H 4.85	$\nu_{C=O}$ 1660 $\nu_{C\equiv N}$ 2210	257.5 (4.30) 290 (4.14) 400 (4.31)
XIII	>300	45	67.63	5.06	13.03	66.51	4.91	12.24	—	$\nu_{C=O}$ 1650 $\nu_{C\equiv N}$ 2200	248[a] 364

[a] Concentration is unknown because of being insoluble.

Reduction of Vb (XIII)——(a): A solution of Vb (0.2 g) in DMF (10 ml) was added under stirring to ice-cooled solution of $NaBH_4$ (0.2 g) in DMF (10 ml) during 5 min. After stirring for 5 hr, the resulting mixture was treated as described for XI. The residue was recrystallized from MeOH–$CHCl_3$.

(b): A mixture of 0.1 g of XIIb, 0.1 g of Ic, and 0.1 g of K_2CO_3 in 10 ml of DMF was heated on a boiling water bath for 5 hr. The reaction mixture was poured into ice-water, the solution was acidified with 10% HCl, and the resulting precipitate was recrystallized from MeOH–$CHCl_3$ (Table V).

Acknowledgement The authors thanks are due to Mrs. H. Mazume of this faculty for microanalysis, to Mr. M. Owatari for UV and IR spectra and to Miss K. Ota for NMR spectra.