UDC 547.83 .2.07

58. Tomishige Mizoguchi: Synthesis of 1-Azabicyclo[*x*, *y*, 0]alkanediones.*1

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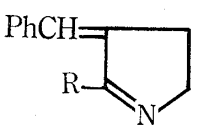
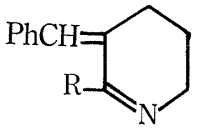
In the second[1] and the fourth paper[2] of this series were reported new syntheses of 2-substituted 3-benzylidene-1-pyrrolines (I) and 2-substituted 3-benzylidene-3,4,5,6-tetrahydropyridines (II).

Later the present writer succeeded in converting (I) into 1-acyl-2-substituted-3-pyrrolidinones (III), which may find wide application as an intermediate for synthesizing a variety of compounds, and as one of such examples the writer reported a new synthesis of nicotine, thus making synthesis of a series of tabacco bases by a new route feasible.

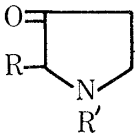
In this paper the writer wishes to describe a synthesis of a series of bicyclic compounds having nitrogen atom at a bridgehead, which may be represented by a general structure (IV).



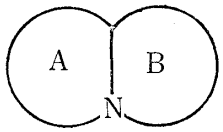
(I)
R=CH_3, Ph



(II)
R=CH_3, Ph, $CO_2C_2H_5$



(III)
R=CH_3, Ph, 3-pyridyl
R'=$COCH_3$, COPh



(IV)

Limiting the size of A-ring to 5- and 6-membered and that of B-ring to 5,6 and 7-membered ones there exist five kinds of combination, i.e. (5~5), (5~6), (5~7), (6~7), and (6~6), of which the corresponding dioxo-derivatives (XIa, b, c, e, f) were prepared (Chart 1). Though XIb (m=2. n=3) was readily obtained, the oppositely disposed isomeric dioxo-derivative (XId : m=3, n=2) could not be formed by the present method due to the reason mentioned later.

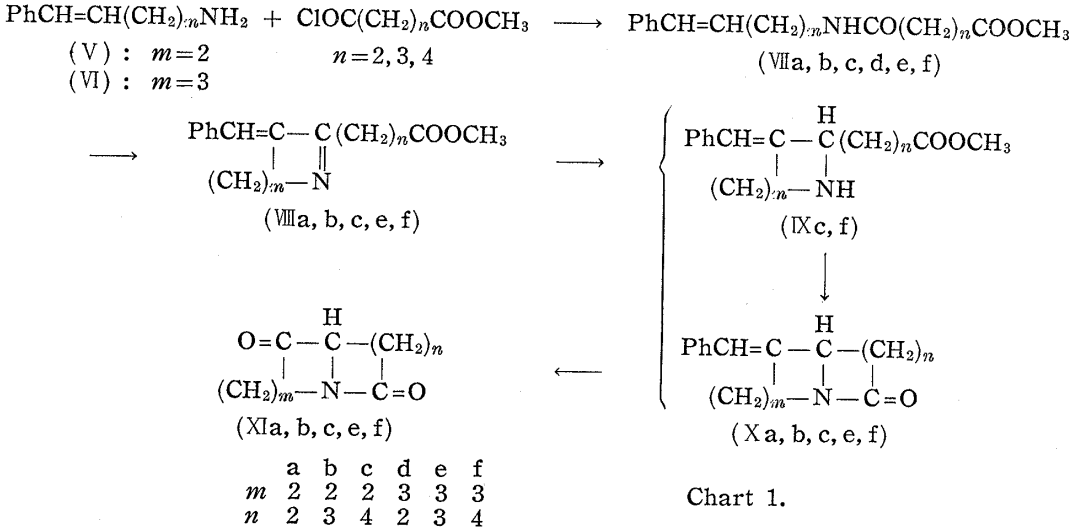


Chart 1.

*1 VI. Communication of "Extention of Bischler-Napieralski Reaction" by S. Sugasawa. Part V: T. Mizoguchi: This Bulletin, **9**, 818 (1961).

*2 Toda-machi, Kita-adachi-gun, Saitama-ken (溝口富茂).

1) S. Sugasawa, S. Ushioda: Tetrahedron, **5**, 48 (1959).

2) S. Sugasawa, T. Fujisawa: *Ibid.*, **7**, 185 (1959).

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The writer's first attempt to cyclize N-(4-phenyl-3- butenyl)- and N-(5-phenyl-4-pentenyl)-2-pyrrolidinone to produce the bicyclic compounds directly has failed under a variety of working conditions.

As an alternative route 4-phenyl-3-butenylamine (V)[1] and 5-phenyl-4-pentenylamine (VI)[2] were acylated with chloride of methyl hydrogen succinate, glutarate and adipate, yielding six kinds of ester amide (VIIa, b, c, d, e, f) (Table I). All these amides underwent smooth cyclization with phosphoryl chloride in boiling benzene[1,2] to furnish three 1-pyrrolines (VIIIa, b, c) and two 3,4,5,6-tetrahydropyridines (VIIIe, f) (Table II). Only the amide (VIId) could not be cyclized with phosphoryl chloride producing resinous product, from which nothing definite could be recovered. This failure may probably ascribed to the tendency of this amide to give succinimido-derivative with a loss of a molecule of methanol than to cyclize to pyrroline derivative with a loss of a molecule of water. The succinimido-derivative thus formed underwent further change giving rise to resinous product. Such is not without precedence as recorded by Sugasawa and Kobayashi,[3] who failed to cyclize methyl N-(3,4-dimethoxyphenethyl)succinamidate to methyl 6,7-dimethoxy-3,4-dihydro-1-isoquinolinepropionate.

That this cyclization method gives a better yield of the 5-membered pyrrolines than the corresponding 6-membered teterhydropyridines as mentioned before[1,2] was again confirmed in the present experiment as can be seen by comparing the cyclization results of (VIIa) and (VIId).

The five kinds of base thus prepared (VIIIa, b, c, e, f) were smoothly reduced by sodium borohydride in methanolic solution acidified properly with hydrochloric acid to afford the reduction products, of which those corresponding to (VIIIa, b, e) directly gave the lactams (Xa, b, e) with a loss of a molucule of methanol during work up, while the remaining ones were isolated as oily methyl 3-benzylidene-2-pyrrolidinevalerate (IXc) and 3-benzylidene-2-piperidinevalerate (IXf). The three formers were characterized as their crystalline picrate and their infrared absorption spectra also supported their structure as lactam derivative.

The ester (IXc) suffered a loss of a molecule of alcohol to furnish the lactam (Xc), when heated *in vacuo* 1 hour at 200° or distilled *in vacuo*, whereas the cyclization of (IXf) to yield the lactam (Xf) was not complete even after 5 hours' heating *in vacuo* at 200°. The latter which was separated from the survived base (IXf) by treating with dilute acetic acid, formed a yellow viscous syrup. As can be seen from the Table IV, the melting point of (Xc) is remarkably higher than that of others, but its structure was supported by infrared absorption data, analysis and molecular weight determination of it and its picrate.

The oxidative cleavage of the benzylidene group of these lactams was carried out with ozone as in the previous case*[1] and the dioxo-derivatives (XIa, b, c, e, f) were readily obtained as colorless viscous oil (Table V).

In conformity with their sutructure each manifested two infrared absorption bands to be assignable to ketone- and lactam-group and each gave the corresponding crystalline 2,4-dinitrophenylhydrazone, all of which analysed correctly.

For further confirmation of their structure (XIe) was converted to the known 1-quinolizidinone.

Thus 9,9-ethylenedioxy-4-quinolizidinone (XII) was prepared from (XIe) by the conventional method, which was directly reduced with litium aluminum hydride in ether. The reduction product (XIII) was a yellow mobile oil of b.p_5 100~104° (bath temperature) and was characterized as its crystalline methiodide.

3) K. Kobayashi : Yakugaku, **3**, 295 (1949).

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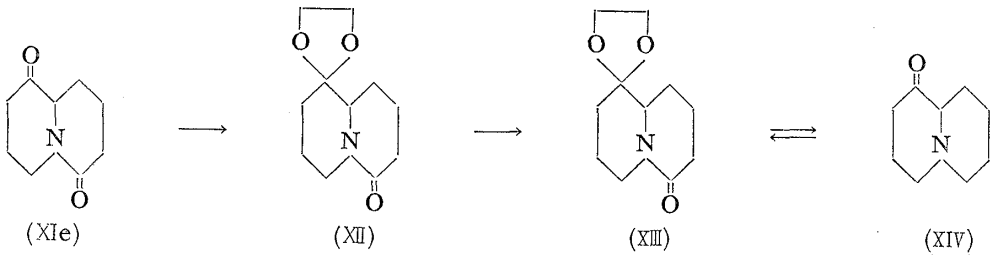

(XIe) (XII) (XIII) (XIV)

Chart 2.

When treated with dilute hydrochloric acid (XIII) gave 1-quinolizidinone (XIV) as a faint yellow mobile oil, b.p_3 80~85° (bath temperature). Its crystalline methiodide melted at 203~206°, whereas it should melt at 210° according to Clemo, *et al.*[4] Therefore the authentic specimen was prepared by the method of Clemo, which formed colorless prisms and melted at 206~209°, which was not depressed on admixture with the writer's product. Thus the both specimens were proved to be identical.

The compound (XIV) prepared according to Clemo's method was converted to the corresponding cyclic ethylene acetal derivative, whose methiodide melted alone at 254~255° and at 253~255° when admixed with the specimen of m.p. 252~253° (faintly reddens at 240°)

Table I. $PhCH{=}CH(CH_2)_mNHCO(CH_2)_nCOOCH_3$ (VII)

	m	*n*	Yield (%)	m.p. (°C)	Mol. formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR (Nujol) cm^{-1} amide	amide	amide	ester C=O	trans C=C
a	2	2	57.8	106~107	$C_{15}H_{19}O_3N$	68.94	7.33	5.36	68.92	7.18	5.24	3260	1645	1545	1730	971
b	2	3	37.7	76~78	$C_{16}H_{21}O_3N$	69.79	7.69	5.09	69.92	7.47	5.04	3270	1640	1545	1730	970
c	2	4	39.0	83.5~85	$C_{17}H_{23}O_3N$	70.56	8.01	4.84	70.92	8.00	4.85	3270	1640	1550	1730	970
d	3	2	72.7	69.5~70.5	$C_{16}H_{21}O_3N$	69.79	7.69	5.09	70.00	7.65	5.28	3280	1645	1550	1730	969
e	3	3	65.1	59~60	$C_{17}H_{23}O_3N$	70.56	8.01	4.84	70.77	7.97	4.98	3280	1640	1555	1740	969
f	3	4	64.0	59~60	$C_{18}H_{25}O_3N$	71.26	8.31	4.62	71.50	8.32	4.74	3280	1645	1555	1740	970

Table II. $PhCH{=}C(-(CH_2)_m-N)-C(=O)(CH_2)_nCOOCH_3$ (VIII)

	m	*n*	Yield (%)	m.p. (°C)	Picrate m.p. (°C)	Mol. formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	2	2	73	46~47[a]	172~173	$C_{21}H_{20}O_9N_4$	53.39	4.27	11.86	53.50	4.29	11.64
b	2	3	77	oil	163.5~164.5	$C_{22}H_{22}O_9N_4$	54.32	4.56	11.52	54.75	4.45	11.59
c	2	4	73.6	54~55[b]	140.5~141	$C_{23}H_{24}O_9N_4$	55.20	4.83	11.20	55.20	4.87	11.21
d	3	2	0	—	—	—	—	—	—	—	—	—
e	3	3	80.3	oil	175~176	$C_{23}H_{24}O_9N_4$	55.20	4.83	11.20	55.26	4.88	11.37
f	3	4	77.7	66~67[c]	144~145	$C_{24}H_{26}O_9N_4$	56.03	5.09	10.89	56.29	5.13	11.22

a) The crude base, m.p. 44~46°, was recrystallized from hexane to form colorless needles, which was analysed. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.04; H, 7.04; N, 5.76. Found : C, 73.63; H, 7.16; N, 5.83.

b) The crude base, m.p. 52~56°, was recrystallized from hexane to form colorless needles, which was analysed. *Anal.* Calcd. for $C_{17}H_{21}O_2N$: C, 75.24; H, 7.80; N, 5.16. Found : C, 75.03; H, 7.70; N, 5.44.

c) The crude base, m.p. 64~66°, was recrystallized from hexane to form colorless needles, which was analysed. *Anal.* Calcd. for $C_{18}H_{23}O_2N$: C, 75.76; H, 8.12; N, 4.91. Found : C, 75.92; H, 8.23; N, 4.95.

4) R. Clemo, R. Ramage : J. Chem. Soc., **1931**, 437.

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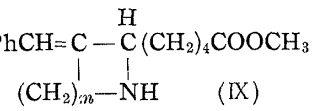
prepared by the writer's method. When infrared absorption bands of (XIII), (XIV) and (XIII) methiodide prepared by the both methods were compared each pair showed a slight difference around 1400 cm^{-1}, but they were identical in all other reeions.

This fact makes the writer to suppose that those prepared by the present method contain an insignificant ammount of contamination which could not be removed by the conventional methods of purification used in the present experiment.

TABLE III.

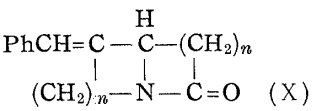


(IX)

	m	(VIII) (g.)	Yield (g.)	State	IR $\nu_{C=O}$* cm^{-1}	Picrate m.p. (°C)	Picrate Mol. formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
c	2	0.59	0.50	oil	1730	96～97	$C_{23}H_{26}O_9N_4$	54.97	5.22	11.15	54.93	5.26	11.49
f	3	0.50	0.47	oil	1740	119～120	$C_{24}H_{28}O_9N_4$	55.81	5.46	10.85	56.18	5.49	10.92

* capillary.

TABLE IV.

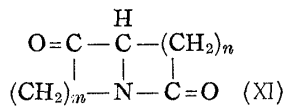


(X)

	m	n	(VIII) (g.)	Yield (g.)	State	IR $\nu_{C=O}$ cm^{-1}	Picrate Yield (%)	Picrate m.p. (°C)	Picrate Mol. formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	2	2	0.96	0.82	solid	1690[d]	84	98～99	$C_{20}H_{18}O_8N_4$	54.30	4.10	12.67	54.48	4.01	12.72
b	2	3	0.48	0.37	〃	1640[e]	77	145.5～146.5	$C_{21}H_{20}O_8N_4$	55.26	4.42	12.28	55.47	4.47	12.25
c	2	4	1.22[a]	1.06	m.p. 164.5～165.5[c]	1625[d]	72	110～112	$C_{22}H_{22}O_8N_4$	56.17	4.71	11.91	55.71	4.73	12.11
e	3	3	1.58	1.13	solid	1645[e]	69	95～97	$C_{22}H_{22}O_8N_4$	56.17	4.71	11.91	56.35	4.83	11.84
f	3	4	1.51[b]	1.12	syrup	1645[e]	77	102.5～104.5	$C_{23}H_{24}O_8N_4$	57.02	4.99	11.57	57.46	4.86	11.78

a) (IX)c. *b*) (IX)f. *c*) Anal.(experimental part). *d*) Nujol. *e*) capillary.

TABLE V.



(XI)

	m	n	(X)(mg.)	Concn. of O_3 (mg./min.)	Time (min.) (O_3 : mol.)	Yield (mg.)	b.p.(°C/mm.)[c]	IR[b] $\nu_{C=O}$ cm^{-1} ketone	IR[b] $\nu_{C=O}$ cm^{-1} lactam	2,4-Dinitrophenylhydrazone m.p. (°C)	2,4-Dinitrophenylhydrazone Mol. formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	2	2	693	5.92	33 (1.25)	323	122～124/3	1760	1700	188 (d.)[c]	$C_{13}H_{13}O_5N_5$	48.90	4.10	21.94	48.90	3.86	21.97
b	2	3	610	6.28	27 (1.32)	214	136～140/4	1755	1645	198 (d.)	$C_{14}H_{15}O_5N_5$	50.45	4.54	21.01	50.62	4.94	21.22
c	2	4	649	5.72	32 (1.42)	384	138～143/4	1750	1630	228 (d.)	$C_{15}H_{17}O_5N_5$	51.87	4.93	20.17	52.01	4.64	20.46
e	3	3	785	6.12	33 (1.29)	292	133～140/3	1725	1645	205 (d.)	$C_{15}H_{17}O_5N_5$	51.87	4.93	20.17	51.45	5.04	20.16
f	3	4	650	6.24	25 (1.25)	254	136～140/4	1720	1645	205～206(d.)	$C_{16}H_{19}O_5N_5$	53.18	5.30	19.38	53.59	5.74	19.16

a) bath temperature. *b*) capillary. *c*) decomposition.

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Experimental

Amides (VIIa,b,c,d,e,f)——These were obtained by acylating the amine (V or VI) (1～3 g.) dissolved in benzene with the equivalent amount of chloride of methyl hydrogen succinate, glutarate or adipate (dissolved in benzene) in the presence of 5% K_2CO_3 (1.1 equiv.) solution under the Schotten-Baumann condition and the product was recrystallized from benzene-hexane to form colorless needles or scales.

Details of (VIIa,b,c,d,e,f) are shown in Table I.

Cyclization of Amides (VIIa,b,c,d,e,f) to Bases (VIIIa,b,c,e,f)——A mixture of the amide (VII) (1 g.), benzene (6 cc.) and $POCl_3$ (5 cc.) was refluxed for 3 hr. After cool, benzene and excess of $POCl_3$ were removed *in vacuo*, leaving an orange residue, to which hexane was added and the whole was left standing for several hr. The supernatant hexane layer was decanted off and the residue was extracted repeatedly with 3.5% HCl solution under ice-cooling.

After being extracted once with Et_2O, the HCl solution was made alkaline with K_2CO_3 and extracted with Et_2O. The Et_2O solution was washed, dried and the Et_2O was removed to give crude cyclized base (VIII) as a yellow oil or crystals, which was characterized appropriately (Table II) and directly used for the next reaction.

Picrates : Yellow needles (from EtOH).

Details of (VIIIa,b,c,e,f) are described in Table II.

(VIId) could not be cyclized under the above condition. The reaction mixture darkened as soon as reflux started, from which none of basic product could be isolated.

Reduction of the Bases (VIIIa,b,c,e,f) by $NaBH_4$——The aforementioned base (VIII) (0.5～1.5 g.) was dissolved in MeOH (10～30 cc.) acidified with conc. HCl (1.1 mole), and to this solution was added $NaBH_4$ (2/5 wt. of used base (VIII)) in small portions during 7～10 min. under ice-cooling and stirring, and then stirring was continued for another 2 hr. at room temperature. MeOH was evaporated *in vacuo*, 2% NaOH solution was added to the residue and extracted with benzene. The benzene solution was washed with satd. NaCl solution, dried and the benzene was removed to give a yellow oily product.

By this procedure, (VIIIc,f) gave the corresponding esters (IXc,f) respectively, which were yellow oil, and characterized as their picrates.

Picrates : Yellow prisms (from benzene).

Detaits of (IXc,f) are shown in Table III.

In contrast to (VIIIc,f), (VIIIa,b,e) gave directly the corresponding lactams (Xa,b,e) as viscous oil. Although they solidified after being kept for several days in a refrigerator, they were used diretly for the next reaction as their purification were accompanied with difficulty.

Picrates : Yellow prisms (from benzene-hexane).

Details of (Xa,b,e) are shown in Table IV.

1-Aza-8-benzylidenebicyclo[5.3.0]decan-2-one (Xc)——i) The above mentioned ester (IXc) (0.30 g.) was distilled twice *in vacuo*, yielding a faint yellow oil of $b.p_3$ 178～181°(bath temperature), which immediately solidified. The product was recrystallized from benzene-hexane to give (Xc) (0.21 g.) as colorless needles, m.p. 163.5～164.5°, which was raised to 164.5～165.5° by further purification. *Anal.* Calcd. for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.80; mol. wt., 241.3. Found : C, 79.89; H, 7.97; N, 6.14; mol. wt. (Rast), 265.5.

Picrate : Yellow prisms (benzene-hexane).

ii) (IXc) (1.22 g.) was heated in an oil bath at 200～210°(bath temperature) *in vacuo* (15 mm. Hg) for 1 hr. After cool, the product was recrystallized from benzene-hexane to give (Xc) (0.85 g.) as colorless needles of m.p. 164～164.5°, which was identified with the one described above (i) by mixed melting point test and infrared spectra.

Details of (Xc) are shown in Table IV.

1-Aza-8-benzylidenebicyclo[5.4.0]undecan-2-one (Xf)——The above (IXf) (1.51 g.) was heated at 190～200°(bath temperature) (15 mm. Hg) for 5 hr., yielding a yellow syrup (1.37 g.), which was dissolved in benzene, washed with 10% AcOH solution and H_2O, dried and then benzene was removed. The yellow syrupy product (Xf) (1.12 g.) thus obtained was used for the next reaction without further purification.

Picrate : Yellow prisms (from benzene-hexane).

Details of (Xf) are shown in Table IV.

Ozone Oxidation of the Benzylidene Lactams (Xa,b,c,e,f)——Into a solution of (X) (0.6～0.8 g.) in AcOH (7.5～10 cc.) was bubbled O_2 stream (75 cc./min.) containing O_3 (5.4～5.9 wt. %) with ice-water cooling. After introducing 1.25～1.42 moles. of O_3, EtOH (the same vol. as AcOH) was added to this solution, and reduced catalytically over 10% Pd-C (1/10 wt. of (X)). The filtrate from the catalyst was evaporated *in vacuo* below 70°, leaving a brown syrup, which was dissolved in H_2O. After being extracted once with ether, the aq. solution was evaporated *in vacuo*. The residue was dissolved in benzene, dried over anhyd. Na_2SO_4 and benzene was removed. The remaining product was distilled to yield (XI) as a colorless oil.

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2,4-Dinitrophenylhydrazones : Yellow or orange fine needles (from EtOH or EtOH-H_2O).

Details of (XIa,b,c,e,f) are shown in Table V.

1,6-Quinolizidinedione Cyclic 1-(Ethylene Acetal) (XII)——A mixture of 1,6-quinolizidinedione (XIe) (0.103 g.) in benzene (ca. 40 cc.), ethylene glycol (0.113 g.) and *p*-toluene sulfonic acid (0.122 g.) was refluxed for 3 hr. in a flusk connected with a constant water separator. After cool, the benzene solution was dried over solid K_2CO_3 (over night) and benzene was removed leaving a yellow oil, which was purified by distillation to give (XII) (0.088 g. or 67.6%) as a faint yellow viscous oil of b.p_3 148～153°(bath temperature). IR $\nu_{max}^{cap\,liq.}$ cm^{-1} : 1710(VW, ester C=O), 1640(>NCO-), 1144, 1082(ethylenedioxy).

1-Quinolizidinone Cyclic Ethylene Acetel (XIII)——i) To a suspension of $LiAlH_4$ (0.20 g.) in dehyd. Et_2O (30 cc.) was added gradually a solution of the above oil (XII) (0.188 g.) in the same solvent (30 cc.) under ice-cooling and stirring, then stirring was continued under reflux for 4 hr. Working up as usual, a yellow oily product was obtained, which was purified by distillation to give (XIII) (0.133 g. or 76%) as a yellow mobile oil of b.p_5 100～104°(bath temperature). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2830, 2785, 2690 (*trans* quinolizidine), 1120, 1070 (ethylenedioxy).

Methiodide : Colorless fine needles (from MeOH-Et_2O), faintly reddened at *ca.* 240° and melted at 252～253°. *Anal.* Calcd. for $C_{12}H_{22}O_2NI$: C, 42.61; H, 6.56; N, 4.14. Found : C, 42.57; H, 6.27; N, N, 4.31.

ii) A mixture of 1-quinolizidinone (XIV) (0.110 g.) in benzene (ca. 40 cc.), ethylene glycol (0.12 g.) and *p*-toluene sulfonic acid (0.15 g.) was refluxed for 3.5 hr. and worked up as above (XII) to yield (XIII) (0.107 g. or 75.8%) as a faint yellow oil of b.$p_{14.5}$ 143～150°(bath temperature). IR ($CHCl_3$) spectrum was identical with (i) except a slight difference around 1400 cm^{-1}.

Methiodide : Colorless fine needles (from MeOH-Et_2O), m.p. 254～255°. *Anal.* Calcd. for $C_{12}H_{22}O_2NI$: C, 42.61; H, 6.56; N, 4.14. Found : C, 42.58; H, 6.58; N, 4.38. This was identified with the specimen described above (i) by mixed melting point test and infrared spectra, except the region around 1400 cm^{-1}.

1-Quinolizidinone (XIV)——A solution of the above (XIII) (0.112 g.) in 10% HCl (3 cc.) was warmed in a water bath for 2.5 hr. and then evaporated *in vacuo*. To the residue was added 33% NaOH solution and repeatedly extracted with Et_2O. The Et_2O solution was once washed with a small volume of satd. NaCl solution, dried and Et_2O was removed leaving a brown oil, which was distilled twice to give a faint yellow mobile oil (0.037 g. or 42.3%) of b.p_3 80～85°(bath temperature). RI $\nu_{max}^{CHCl_3}$ cm^{-1} : 2830, 2680 (*trans* quinolizidine), 1720 (C=O). The infrared chart was identical with the authentic one except the region around 1400 cm^{-1}.

Methiodide : MeI was added dropwise to the above oil, and the mixture was left standing at room temperature and the resulting solid product was recrystallized repeatedly from MeOH-Et_2O to from colorless prisms, m.p. 203～206°, which was identified with the authentic specimen (m.p. 206～209°) by mixed melting point test. *Anal.* Calcd. for $C_{10}H_{18}ONI$: N, 4.76. Found : N, 5.03.

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Summary

4-Phenyl-3-butenyl- and 5-phenyl-4-pentenyl-amine were acylated with chloride of methyl hydrogen succinate, glutarate and adipate yielding six kinds of ester amide (VIIa, b, c, d, e, f), all of which except (VIId) were cyclized with ease on being treated with $POCl_3$ in boiling benzene, giving three pyrrolines (VIIIa, b, c) and two hydropyridines (VIIIe, f). These were reduced and each were converted into the corresponding lactams (Xa, b, c, e, f), from which benzylidene group was removed by ozonization furnishing 5 kinds of title compounds (XIa, b, c, e, f). Their structures were supported by converting one (XIe) of them to the known 1-quinolizidinone, which was identified with the authentic specimen.

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