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Studies on Azasteroids and Related Compounds. III.[1] On the Cyclodehydration of Cyclic Ketone and β-Aminoester

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With additional identification of two products (V) and (VI) from the reaction between β-aminoester (I) and 2-tetralone, and with results of the reactions hitherto investigated, we proposed the whole aspect of the reaction between β-aminoester and cyclic ketone, as possibly yielding at least nine products. And as the extension to 14-azasteroid syntheses, it was examined the reactions between ethyl 2-pyrrolidine- and 2-piperidine-acetates with 3,4-dihydro-6-methoxy-1*H*-naphthalen-2-one to afford 1,2,3,5,6,11,12,12a-octahydro-8-methoxynaphth[2,1-*e*]indolizin-11-one (XVIIIa) and 1,2,3,4,6,7,13,13a-octahydro 9-methoxy-12*H*-naphtho[1,2-*c*]quinolizin-12-one (XVIIIb) as expected, besides two other products in each case.

Additional identification of two new products from the cyclodehydration between methyl 2-methyl-3-methylaminopropionate (I) and 2-tetralone enabled us to depict the whole aspect of the reaction between cyclic ketone and β-aminoester.

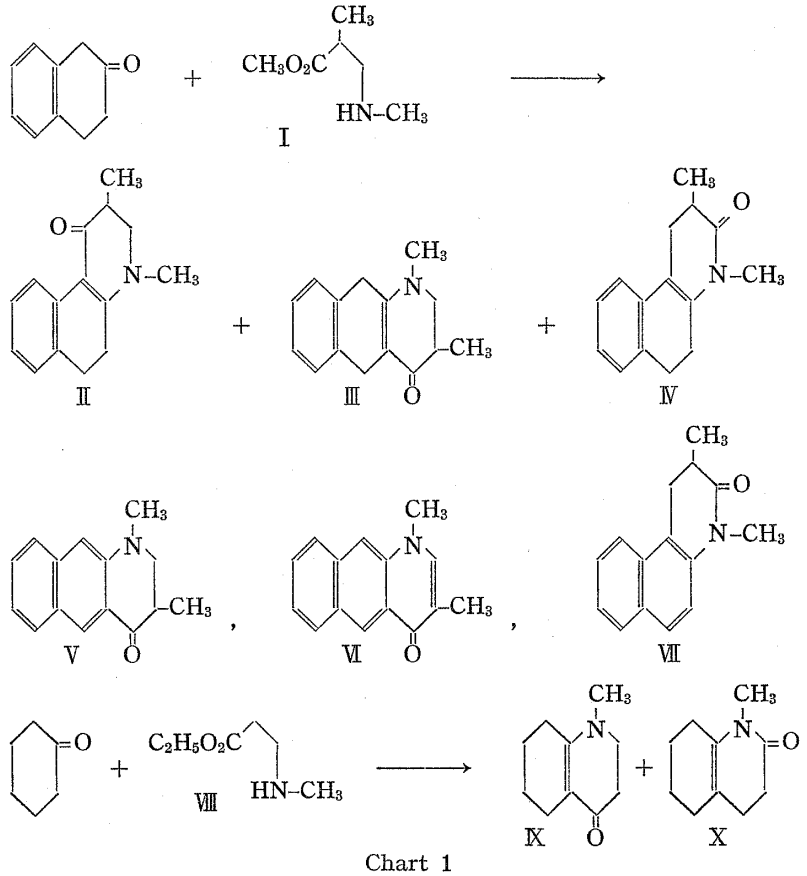

Chart 1

1) Part II: Z. Horii, K. Morikawa and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1472 (1968).
2) Location: *Toneyama, Toyonaka, Osaka.*

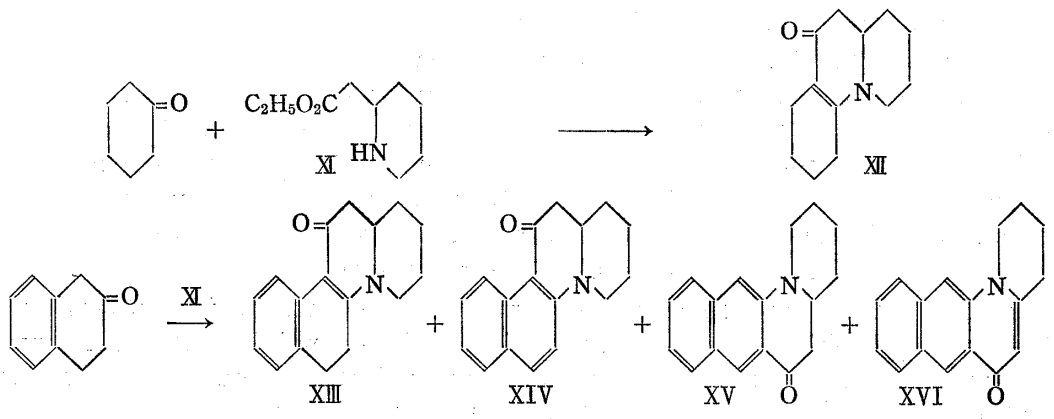

Chart 2

Previously, Horii and coworkers[3] have isolated three products (II), (III) and (IV) from the reaction of I with 2–tetralone, and two products (IX) and (X) from the reaction of ethyl 2–methylaminopropionate (VIII) with cyclohexanone. It has also been reported[4] that the reaction of ethyl 2–piperidineacetate (XI) with cyclohexanone or 2–tetralone gave the compound (XII) or the compounds (XIII), (XIV), (XV) and (XVI), respectively.

Upon consideration of the results obtained so far, one can readily expect that the compounds like V and VI or VII might be present or formed in the reaction of I with 2–tetralone. Thus, we repeated the same reaction between β–aminoester (I) and 2–tetralone under the same reaction condition as previously described.[3] Two new compounds, 2,3–dihydro–1,3–dimethylbenzo[*g*]quinolin–4(1*H*)–one (V) and 1,3–dimethylbenzo[*g*]quinolin–4(1*H*)–ne (VI) were isolated besides three previously described products. However, despite the detailed study of the mother liquor of the reaction mixture, we could not detect 1,2–dihydro–2,4–dimethylbenzo[*f*]quinolin–3(4*H*)–ne (VII), which was alternatively prepared from IV by dehydrogenation with chloranil in xylene in 75.5% yield, or with palladium on charcoal in toluene in 32.4% yield.

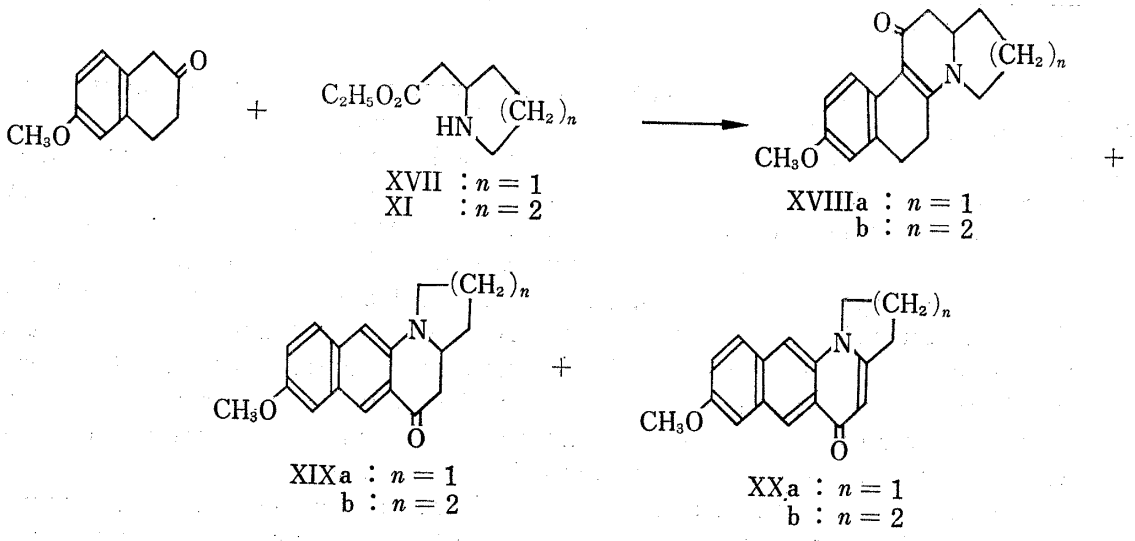

Chart 3

3) Z. Horii, C. Iwata, I. Ninomiya, N. Imamura, M. Ito and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **12**, 1405 (1964).
4) Z. Horii, K. Morikawa, Y. Tamura and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **14**, 1399 (1966).

The structures of V, VI and VII were assigned by their infrared and nuclear (IR) magnetic resonance (NMR) spectra. The compound (V) had bands at 1682, 1632 and 1603 cm^{-1} in its infrared spectrum, which appeared similarly in that of the compound (XV).[4] The infrared spectrum of the compound (VI) showed three peaks at 1640, 1628, 1615, 1582 and 1558 cm^{-1} and was well resembled with that of the compound (XVI).[4] The compound (VII) had only one charac- teristic band at 1655 cm^{-1} attributable for the lactam grouping in the infrared spectrum and its NMR spectrum exhibited signals due to six protons in the aromatic region, and three protons of C-methyl group as doublet centered at 8.7 τ.

In extending these cyclodehydration reactions to the azasteroid syntheses, we have treated ethyl 2-pyrrolidineacetate (XVII) and ethyl 2-piperidineacetate (XI) with 3,4-dihydro-6-methoxy-1*H*-naphthalen-2-one and obtained three products in each case, as shown in Chart 3, of which 1,2,3,5,6,11,12,12a,-octahydro-8-methoxynaphth[2,1-*e*]indolizin-11-one (XVIIIa)[5] and 1,2,3,4,6,7,13,13a-octahydro-9-methoxy-12*H*-naphtho[1,2-*c*]quinolizin 12-one (XVIIIb) have the 14-azasteroidal skeletons and structures of these products were assigned from their infrared spectra as shown in Table I.

Table I

Compound No.	Appearance	mp (°C)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	NMR τ (signals for aromatic protons)
V	orange crystal	77.5— 78.5	1682(s), 1632(vs), 1603(s)	——
VI	pale yellow needle	200 —201	1640(m), 1628(sh), 1615(s), 1582(vs), 1558(m)	——
XVIIIa	slightly yellow needle	212 —213[a]	1606(s, broad), 1548(vs), 1501(m)	——
XIXa	reddish orange needle	190.5—191.5[b]	1675(s), 1620(w), 1603(vs)	——
XXa	fine yellow needle	246 —247	1625(s), 1599(s), 1584(w),	1564(m)
XVIIIb	almost colorless needle	140 —141	1613(s, broad), 1524(vs), 1502(s)	1.73(d) 3.24(m)
XIVb	orange crystal	144 —145	1675(s), 1631(w), 1600(vs)	1.60(s) 2.85(m)
XXb	pale yellow needle	225 —226	1621(s), 1590(s), 1566(m)	1.25(s) 2.60(m)

a) lit.[5] 210.5—212° *b*) lit.[5] 191.5—192.5°

From the results of these reactions, we can now summarize the reaction between cyclic ketone and β-aminoester, and show the reaction processes as in Fig. 1.

In the cyclodehydration reaction between a cyclic ketone and an β-aminoester, one can obtain at least nine products (**1**–**9**), as shown in Fig. 1. As for the reaction mechanism, cyclic ketone would react with an β-aminoester at a boiling temperature of the solvent such as benzene, toluene or xylene in the presence of *p*-toluenesulfonic acid to give the enaminoesters (**10**) and (**11**), which then cyclize upon heating in the same solvent or in ethylene glycol to give the vinylogous lactams (**1**) and (**4**), respectively. As the route to **2** and **3**, dehydrogenation of the enaminoester (**10**) to the compound (**12**) followed by cyclization to **2** and then possibly **3** is preferred because **1** was resistant to dehydrogenation[4] and we could not detect **3** in any of these reactions examined. On the other hand, the another vinylogous lactam (**4**) is susceptible to dehydrogenation to give the compounds (**5**) and then (**6**).

The formation of the enaminolactam (**7**) is considered as follows. When the enaminoester (**10**) is thermally unstable, the decomposition of **10** could occur to give acrylate and **13** which recombine by the Michael type condensation to the enaminoester (**14**), followed by

5) While preparing this manuscript, H.O. Huisman, *et al.*, *Tetrahedron Letters*, **1967**, 3529, reported briefly identical syntheses of XVIIIa and XIXa, but their chemical properties were little informed.

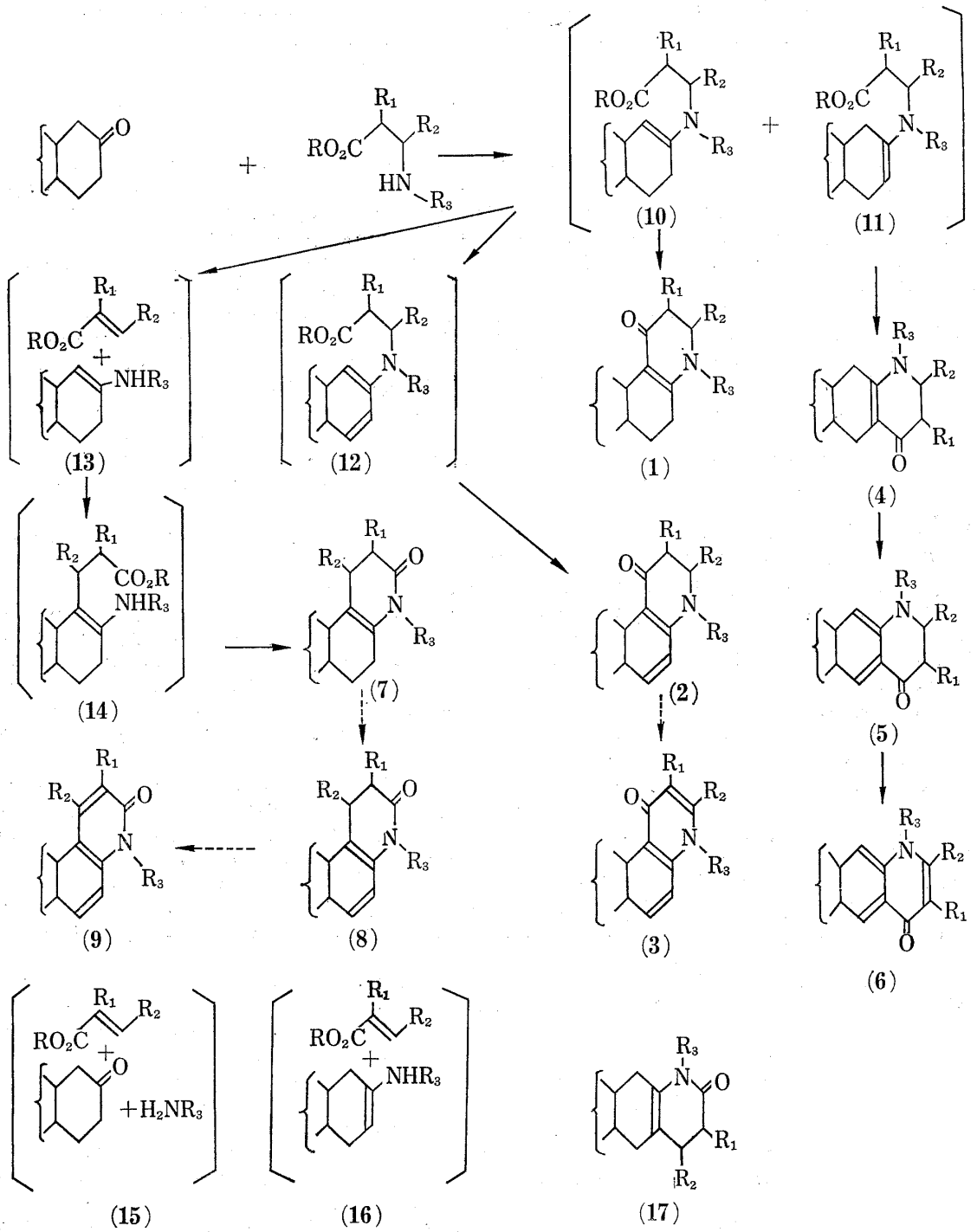

Fig. 1

spontaneous cyclization to the enaminolactam (**7**), which might be susceptible to dehydrogenation to the lactams (**8**) and then (**9**), although we failed to isolate either **8** or **9**.

As for the another possible course to the enaminolactam (**7**), it can be assumed that the *β*-aminoester itself would be decomposed to **15**, which then affords the enaminolactam (**7**) *via* the inetermediary (**13**) and (**14**). However, from the facts that the formation of the enaminoester (**10**) was confirmed from the infrared spectrum of the reaction mixture and that the enaminolactam (**7**) was the main product in the cyclodehydration reaction concurrent with such decomposition, the reaction course *via* **15** could be negligible.

And though, as shown in Fig. 1, the decomposition of the enaminoester (**11**) to **16** could be considered, neither **11** nor **17** was isolated from these reactions.

Experimental[6]

Ethyl 2-pyrrolidineacetate (XVII)[7] was prepared by hydrogenation of ethyl 2-pyrroleacetate with 5% Rh on alumina in AcOH with the initial pressure of hydrogen at 9.7 atm. at 25°, bp 108° (25 mmHg).

Repeated Reaction of Methyl 2-Methyl-3-methylaminopropionate (I) with 2-Tetralone——The reaction between I and 2-tetralone was repeated just as described in the previous paper,[3,8] and the reaction mixture obtained from 12 g of I and 13.2 g of 2-tetralone, was chromatographed on 200 g of alumina. After isolating three reported products (II, III and IV), two new products (V and VI) were obtained as follows.

The fractions, exhibiting three characteristic absorptions of the same intensities in 1570—1650 cm^{-1} region, were collected and rechromatographed on alumina to give 30 mg of orange crystal, mp 77.5—78.5°, upon recrystallization from petr. ether, 2,3-dihydro-1,3-dimethylbenzo[*g*]quinoline-4(1*H*)-one (V). *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.75; H, 6.57; N, 6.23.

The last fractions, having the similar pattern of IR absorption with that of XVI, were collected and rechromatographed on alumina to afford 300 mg of greenish-yellow crystal, which was recrystallized from benzene–petr. ether to pale yellow crystal, 1,3-dimethylbenzo[*g*]quinoline-4(1*H*)-one (VI), mp 200—201°. *Anal.* Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.75; H, 5.89; N, 6.17. IR spectrum of VI was quite similar to that of XVI.[4]

Picrate, yellow crystal, recrystallized from EtOH, mp 205—206°(decomp.). *Anal.* Calcd. for $C_{21}H_{16}O_8N_4$: C, 55.75; H, 3.57; N, 12.37. Found: C, 55.53; H, 3.43; N, 12.45.

Dehydrogenation of 1,2,5,6-Tetrahydro-2,4-dimethylbenzo[*f*]quinoline-3(4*H*)-one (IV)——a) With Chloranil in Xylene: A solution of 530 mg (2.34 mmoles) of IV and 550 mg (2.23 mmoles) of chloranil in 60ml of xylene was heated under reflux for 4 hr. After cooling, the reaction mixture was washed with 10% NaOH and then with H_2O, and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 480 mg of almost colorless crystalline solid, mp 103—108°, which was recrystallized from aq. EtOH to give 400 mg (75.5%) of colorless plates, 1,2-dihydro-2,4-dimethylbenzo[*f*]quinolin-3(4*H*)-one (VII), mp 112—115°. *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.79; H, 6.55; N, 6.03. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655. NMR $\tau_{max}^{CDCl_3}$: 8.7 (d. $-CH-CH_3$).

b) With 10% Pd-C in Toluene : A mixture of 620 mg of IV and 250 mg of 10% Pd-C in 40 ml of dry toluene was heated under reflux for 3.5 hr. After cooling, the catalyst was filtered off, and the filtrate was condensed *in vacuo* to dryness to afford 560 mg of almost colorless solid, which was crystallized from EtOH to give 280 mg of colorless crystal, mp 146—162°, the structure of which was not thouroghly investigated. The ethanolic mother liquor was evaporated *in vacuo* to afforde colorless solid, mp 103—112°, recrystallization of this residue from aq. EtOH gave 200 mg (32.4%) of colorless plate, mp 112—115°, which was identical with VII obtained in a), on comparison of their IR spectra and mixed melting point determination. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655.

Reaction of Ethyl 2-Piperidineacetate with 3,4-Dihydro-6-methoxy-1*H*-naphthalene-2-one——A solution of 5.0 g (0.03 mole) of ethyl 2-piperidineacetate and 5.3 g (0.03 mole) of 3,4-dihydro-6-methoxy-1*H*-naphthalene-2-one in 200 ml of dry xylene containing 200 mg of *p*-TsOH was heated under reflux in N_2 stream with Dean-Stark water separator in order to remove water as it formed for 30 hr. After evaporation of xylene, 150 ml of ethylene glycol was added and the resulting solution was heated under vigorous reflux for 5 hr. After cooling, an equal amount of H_2O was added, and the mixture was extracted with benzene. The benzene extract was washed well with H_2O, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a brown viscous oil which was submitted to alumina column chromatography. The first fraction eluted by benzene gave 1.70 g (20%) of orange crystal, 1,2,3,4,4a,5-hexahydro-9-methoxy-6*H*-naphtho[2,3-*c*]quinolizin-6-one (XIXb), recrystallized from *n*-hexane, mp 144—145°. *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.95; H, 6.70; N, 4.82. UV λ_{max}^{EtOH} mμ (log ε): 265 (4.66) and 450 (3.95). $\lambda_{max}^{EtOH\text{-}HCl}$ mμ (log ε): 264 (4.65) and 450 (3.84).

The second fraction eluted by 1:1 mixture of benzene–chloroform afforded 1.71 g (20%) of almost colorless needle, 1,2,3,4,6,7,13,13a-octahydro-9-methoxy-12*H*-naphtho[1,2-*c*]quinolizin-12-one (XVIIIb), mp 140—141°, upon recrystallization from benzene–chloroform. *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.06; H, 7.47; N, 4.94. Found: C, 76.29; H, 7.25; N, 4.69. UV λ_{max}^{EtOH} mμ (log ε): 275 (4.11) and 368 (3.86). $\lambda_{max}^{EtOH\text{-}HCl}$ mμ (log ε): 264 (4.24) and 380 (3.59).

The third elution by chloroform gave 0.68 g (8%) of pale yellow needle, 1,2,3,4,-tetrahydro-9-methoxy-6*H*-naphtho[2,3-*c*]quinolizin-6-one (XXb), mp 225—226°, upon recrystallization from benzene–*n*-hexane.

6) Melting points are uncorrected.
7) G.R. Clemo and T.A. Melrose, *J. Chem. Soc.*, **1942**, 424.
8) Z. Horii, C. Iwata, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **10**, 940 (1962).

Anal. Calcd. for $C_{18}H_{17}O_2N$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.10; H, 6.02; N, 4.98. UV λ_{max}^{EtOH} mμ (log ε): 212 (4.58), 252 (4.62), 268 (4.86) and 273 (4.90). $\lambda_{max}^{EtOH-HCl}$ mμ (log ε): 235 (4.62) and 277 (4.88).

Dehydrogenation of 1,2,3,4,4a,5-Hexahydro-9-methoxy-6*H*-naphtho[2,3-*c*]quinolizin-6-one (XIXb) to XXb——A mixture of 200 mg of XIXb and 100 mg of 10% Pd–C in 10 ml of freshly distilled tetraline was heated under reflux for 2 hr over a gauze. After removing catalyst and solvent, a brown pasty residue was chromatographed on 20 g of alumina with benzene and chloroform as eluents. After recovering 10 mg of the starting material from the fraction by 1: 1 mixture of benzene–chloroform, the fraction eluted by chloroform gave 130 mg (65%) of pale yellow needle, mp 225—226°, recrystallized from benzene–*n*–hexane, which was not depressed on admixture with the sample of XXb obtained above and their IR spectra were identical in all region. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1621 (s), 1590 (s) and 1566 (m).

Reaction of Ethyl 2-Pyrrolidineacetate with 3,4-Dihydro-6-methoxy-1*H*-naphthalene-2-one——A mixture of 2.2 g of ethyl 2–pyrrolidineacetate and 2.5 g of 3,4–dihydro–6–methoxy–1*H*–naphthalene–2–one in 150 ml of xylene in the presence of small amount of *p*–TsOH was treated as above and the resulting reaction products were chromatographed on 120 g of alumina.

The first elution by benzene afforded, upon recrystallization from benzene and *n*–hexane, 690 mg (18%) of reddish orange needle, mp 190.5—191.5, 1,2,3,3a,4,5–hexahydro–8–methoxynaphth[2,3–*e*]indolizin–5–one (XIXa). *Anal.* Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.30; H, 6.31; N, 5.32.

After eluting out a fraction containing trace of strongly fluorescent material, which showed IR absorptions at 1605 (broad) and 1535 cm^{-1}, the fraction eluted by 1: 1 mixture of benzene–chloroform gave 570 mg (15%) of slightly yellow needle, 1,2,3,5,6,11,12,12a,–octahydro–8–methoxynaphth[2,1–*e*]indolizin–11–one (XVIIIa), mp 212—213°, upon recrystallization from chloroform–petr. ether. *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.49; H, 6.94; N, 5.20.

The fraction eluted by chloroform gave, upon recrystallization from chloroform–petr. ether, *ca.* 5 mg of fine yellow neelde, mp 246—247°, which could be assumed to be 1,2,3,5–tetrahydro–8–methoxynaphth[2,3–*e*]–indolizin–5–one (XXa) from its infrared spectrum shown in Table I and from the analogy of these reactions, although we could not have analysis due to insufficient amount.