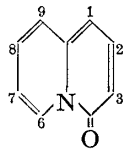
UDC 547.94 : 547.834.2

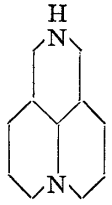
48. **Yoshinobu Sato**: Syntheses of Allied Compounds of Lupine Alkaloids. III.[1] Synthesis of 3,6-Dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine.[2]

(*Takamine Laboratory, Sankyo Co., Ltd.**)

Attempts were made to synthesize perhydropyrido[3,4,5-*i*,*j*]quinolizine (II) (9-aza-hexahydrojulolidine), the perhydro compound of nordehydro-*α*-matrinidine obtained from matrine, from a derivative of 4-oxo-4*H*-quinolizine (I) possessing substituents in 1- and 9-positions, and an important intermediate in this synthesis, 3,6-dioxo-1*H*,3*H*,6*H*-pyrano-[3,4,5-*i*,*j*]quinolizine (XXI), the δ-lactone compound of 4-oxo-4*H*-quinolizine, was obtained in the present series of work. This paper describes the stepwise synthesis of (XXI).



(I)



(II)

Ethyl 2-methylnicotinate (III), obtained by the condensation of acrolein and ethyl 3-aminocrotonate,[3] failed to undergo further condensation with diethyl ethoxymethylenemalonate to form the 4-oxo-4*H*-quinolizine ring and, therefore, attempt was made to obtain the quinolizine compound from 3-methoxymethyl-2-cyanomethylpyridine (XI) and ethyl 3-methoxymethyl-2-pyridylacetate (XII) through the route shown in Chart 1. 2-Methyl-3-pyridinemethanol (IV), obtained by reduction of (III) with lithium aluminum hydride in ether, was treated with thionyl chloride in benzene and the chloro compound (V) so obtained was reacted with sodium methoxide or benzyloxide, affording 3-methoxymethyl- (VI) or 3-benzyloxymethyl-2-methylpyridine (VI′).

G. Kobayashi and others,[4] and Boekelheide, *et al.*[5] had obtained 2-pyridinemethanol

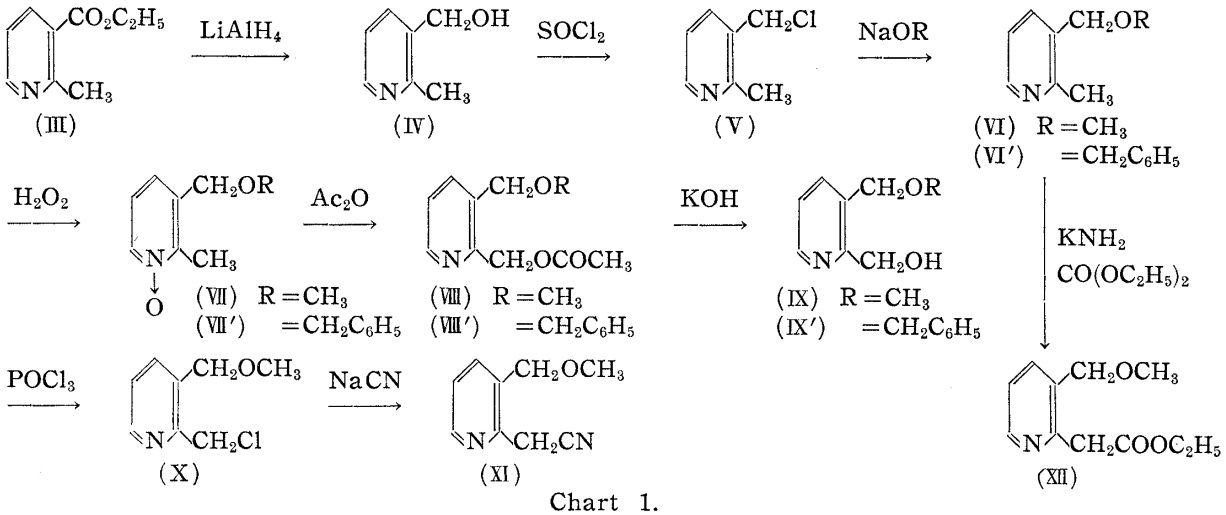


Chart 1.

* Nishi-shinagawa, Shinagawa-ku, Tokyo (佐藤義信).

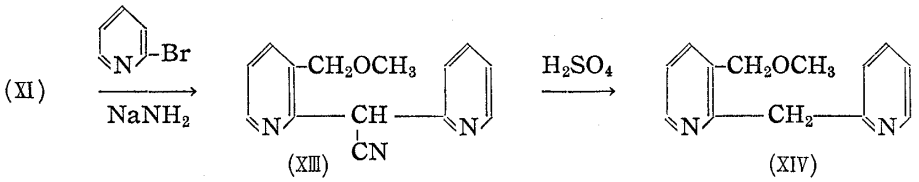
1) Part II : This Bulletin, **5**, 412(1957).
2) A brief report of this work was published as a Communication to the Editor in This Bulletin, **6**, 222(1958).
3) K. Tsuda, Y. Sato, N. Ikekawa, H. Mishima : J. Org. Chem., **21**, 800(1956).
4) G. Kobayashi, S. Furukawa : This Bulletin, **1**, 347(1953).
5) V. Boekelheide, W. J. Linn : J. Am. Chem. Soc., **76**, 1286(1954).

acetate by heating 2-picoline 1-oxide with acetic anhydride and this procedure was applied to the foregoing (VI) and (VI'), from which 3-methoxymethyl- (VIII) and 3-benzyloxymethyl-2-pyridinemethanol acetate (VIII') were respectively obtained.

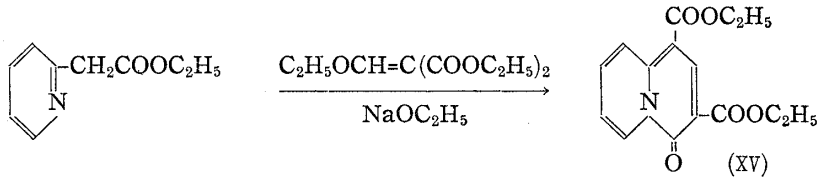
Boekelheide and others obtained 2-pyridinemethanol by saponification of 2-pyridinemethanol acetate with boiling in conc. hydrochloric acid but its yield was less than 50%. In the present work, the corresponding alcohols were obtained by boiling (VII) and (VIII') with potassium hydroxide in ethanol, in a high yield of 78% and 60%, respectively affording 3-methoxymethyl- (IX) and 3-benzyloxymethyl-2-pyridinemethanol (IX').

Treatment of the alcohol compound (IX) with phosphoryl chloride in benzene gave the chloro compound (X) which was refluxed in methanol with sodium cyanide to form 2-cyanomethyl-3-methoxymethylpyridine. Condensation of 2-methyl-3-methoxymethylpyridine (VI) with diethyl carbonate in ether, in the presence of potassium amide, afforded ethyl 3-methoxymethyl-2-pyridylacetate (XII).

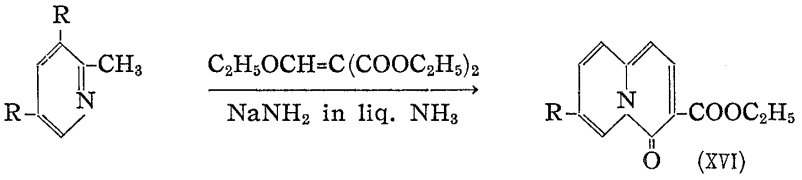
Condensation of (XI) with 2-bromopyridine in ether, in the presence of sodium amide gave 2-(2-pyridyl)-2-(3-methoxymethyl-2-pyridyl)acetonitrile (XIII) which, on boiling in 70% sulfuric acid, underwent decarboxylation and saponification to form 2-(2-pyridyl)-2-(3-methoxymethylpyridyl)methane (XIV).



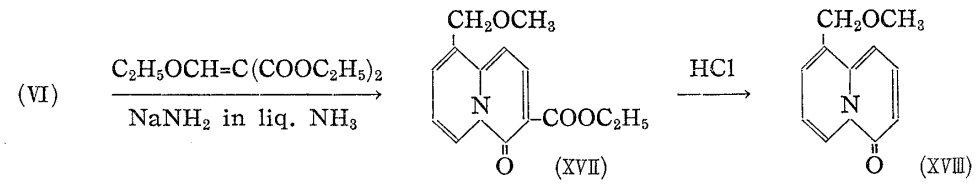
Boekelheide and others[6] obtained 1,3-bis(ethoxycarbonyl)-4-oxo-4*H*-quinolizine (XV) by condensation of ethyl 2-pyridylacetate and diethyl ethoxymethylenemalonate in the presence of sodium alkoxide.



Bohlmann and others[7] prepared several kinds of 4-oxo-4*H*-quinolizine derivative by condensation of ethyl 2-pyridylacetate possessing substituents in the ring with diethyl ethoxymethylenemalonate, and (XVI), also by condensation of 2-picoline itself and also its derivatives possessing substituents in the ring with diethyl ethoxymethylenemalonate in liquid ammonia, in the presence of sodium amide.



Following the method of Bohlmann, *et al.*, 3-ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XVII) was obtained from (VI).



6) V. Boekelheide, J. P. Lodge, Jr. : J. Am. Chem. Soc., **73**, 3681(1951).
7) F. Bohlmann, A. English, J. Politt, H. Sander, W. Weise : Ber., 88, 1831(1955).

In the case of ring-substituted 2-pyridylacetonitrile or ethyl 2-pyridylacetate compounds, simply boiling (XI) or (XII) with diethyl ethoxymethylenemalonate easily afforded 1-cyano-3-ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XIX) or 1,3-bis(ethoxycarbonyl)-9-methoxymethyl-4-oxo-4*H*-quinolizine (XXII).

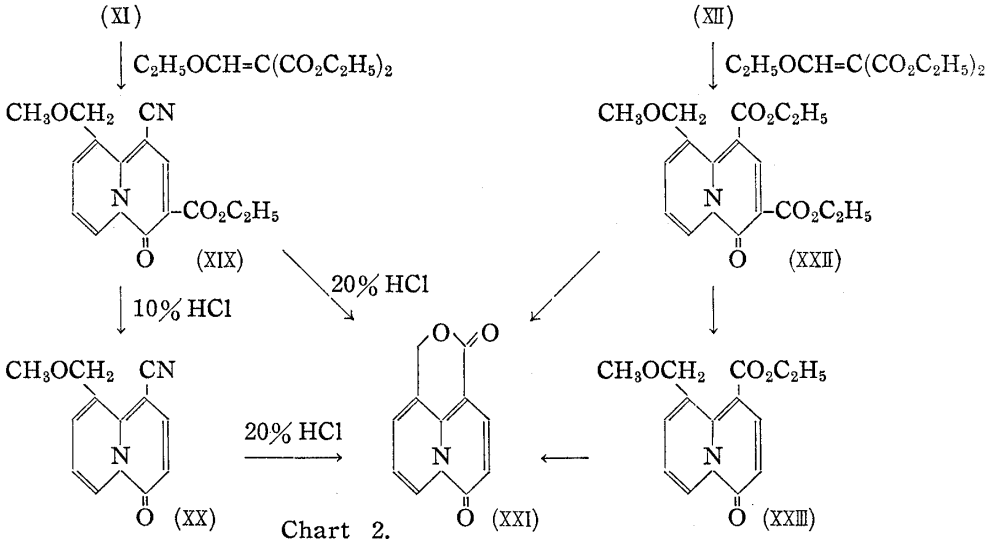


Chart 2.

On boiling with 15% hydrochloric acid, 3-ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XVII) underwent facile saponification and decarboxylation to form 9-methoxymethyl-4-oxo-4*H*-quinolizine (XVIII). On the other hand, saponification of 1,3-bis(ethoxycarbonyl)-4-oxo-4*H*-quinolizine by hydrochloric acid had been found by Boekelheide and others[6] to afford 1-ethoxycarbonyl-4-oxo-4*H*-quinolizine, the ethoxycarbonyl group in 3-position being preferentially removed over that in 1-position. Similarly, boiling of (XIX) with 10% hydrochloric acid effected preferential saponification and decarboxylation of the ethoxycarbonyl group in its 3-position to form 1-cyano-9-methoxymethyl-4-oxo-4*H*-quinolizine (XX). In this case, however, a higher concentration of the acid or prolonged heating resulted in the formation of a by-product as yellow crystals (A) of m.p. 254°. While boiling of (XIX) with 10% hydrochloric acid for 3 hours afforded (XX) alone, heating with 20% hydrochloric acid for 5 hours gave (A) alone. The reaction of (XXII) progressed under a more milder condition than that of (XIX) to give 1-ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XXIII) and (A).

This by-product (A) had a strong fluorescence characteristic of 4-oxo-4*H*-quinolizine and its analytical values agreed with the composition for $C_{11}H_7O_3N$. Its infrared spectrum, similar to those of (XIX) and (XX), exhibited absorption for -CON< at 1684 cm^{-1}, as well as that of δ-lactone -C=O at 1724 cm^{-1}. While the infrared spectrum of (XX) exhibited absorptions for ether linkage at 1088 cm^{-1} and -C≡N at 2195 cm^{-1}, that of (A) does not have any absorptions in the region of 1150~1060 cm^{-1} for ether linkage and for -CN. Therefore, it is concluded that this substance (A) is a δ-lactone compoud, i.e. 3,6-dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine (XXI).

In general, the methoxymethylene group bonded directly to pyridine or quinolizine ring is not saponified on boiling with 20% hydrochloric acid.[8] The fact that (XXII)

8) a) (VIII) was saponified by conc. hydrochloric acid to give (IX) but did not undergo cleavage of the ether bond. b) 2-Methyl-3-hydroxy-4-methoxymethyl-5-aminomethylpyridine, when heated in a sealed tube with 2.5*N* hydrochloric acid at 180°, undergoes cleavage of the ether bond to form 2-methyl-3-hydroxy-4-hydroxymethyl-5-aminomethylpyridine (cf. S. A. Harris, D. Heyl, K. Folkers : J. Am. Chem. Soc., **66**, 2088(1944)). c) Reduction of 7,9-bis(methoxymethyl)-4-oxo-4*H*-quinolizine affords 7,9-bis(methoxymethyl)-4-oxoquinolizidine without change of methoxymethyl group. The latter undergoes ether cleavage when heated with 48% hydrobromic acid at 120° in a sealed tube (cf. F. Bohlmann : Ber., **89**, 792(1956)).

forms (XXIII) under far milder condition than (XIX) is probably due to a more facile saponification of the ethoxycarbonyl group than cyano group. This, in turn, indicates that a compound with methoxymethylene group is less likely to be saponified than that with cyano group under the same condition. Therefore, in the case of (XIX) or (XXII), saponification of cyano or ethoxycarbonyl group in 1-position to a carboxyl is accompanied by concurrent elimination of methanol from that and methoxymethyl group in 9-position to form the δ-lactone compound(XXI). Such formation of a lactone from methyl ether and carboxyl groups is without example but it is assumed that the 4-oxo-4*H*-quinolizine compound, which had formed the δ-lactone, easily forms a six-membered lactone ring because the two bonds at 1- and 9-positions in this compound are situated on the plane determining 1-, 9-, and 10-positions (more generally, the quinolizine plane).

The writer expresses his deep gratitude to Prof. K. Tsuda of the Institute of Applied Microbiology, University of Tokyo, for his kind and helpful guidances and to Mr. M. Matsui, Director of this Laboratory, for encouragement. He is indebted to Mr. Eiji Ohki for his technical cooperation in part of this experiment, to Misses T. Furukawa and H. Otsuka, and Mr. T. Onoe for microanalyses, and to Messrs. H. Shindo, O. Amakasu, and N. Higosaki for spectral measurements.

Experimental

2-Methyl-3-hydroxymethylpyridine (IV)—A solution of 109 g.(0.645 mole) of ethyl 2-methylnicotinate (III) in 100 cc. of dehyd. Et_2O was added gradually to a suspension of 21 g. of $LiAlH_4$ in dehyd. Et_2O under chilling and stirring. After the addition was complete, the mixture was stirred at room temperature for 1 hr. and then boiled under reflux for 3 hr. Moist Et_2O was added to decompose the complex salt, Et_2O layer was dried over anhyd. Na_2SO_4, and the solvent was distilled off. The residual oil was distilled under reduced pressure to give a pale yellow oil, $b.p_5$ 125~127°. Yield, 67 g. (84.2%). On standing, the oil crystallized, m.p. 46~47°. *Anal.* Calcd. for C_7H_9ON : C, 68.27; H, 7.37; N, 11.37. Found : C, 68.03; H, 7.11; N, 11.73. U.V. λ_{max}^{EtOH} mμ(log ε) : 264(3.55), 270(3.45).

Picrate : Yellow crystals, m.p. 166~168°(from EtOH). *Anal.* Calcd. for $C_{13}H_{12}O_8N_4$: C, 44.32; H, 3.43; N, 15.91. Found : C, 43.81; H, 3.21; N, 16.21.

2-Methyl-3-methoxymethylpyridine (VI)—To a solution of 113 g.(0.92 mole) of 2-methyl-3-hydroxymethylpyridine (IV) in 500 cc. of dehyd. benzene, 120 g.(1 mole) of $SOCl_2$ was added under chilling with ice and stirring. After the addition was complete, the mixture was stirred at room temperature for 1 hr. The mixture was concentrated under a reduced pressure to give the hydrochloride of 2-methyl-3-chloromethylpyridine (V).

A solution of the above hydrochloride of (V) in 200 cc. of MeOH was added to a solution of MeONa (prepared from 46 g. of Na) in 1 L. of MeOH. After the addition was complete, the mixture was boiled under reflux for 3 hr., the precipitated NaCl was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was dissolved in a small amount of water and then extracted with $CHCl_3$. $CHCl_3$ layer was dried, the solvent was distilled off, and the residual oil was distilled under a reduced pressure to give a pale yellow oil, $b.p_{30}$ 107~110°. Yield, 87.4 g.(69.3%). *Anal.* Calcd. for $C_8H_{11}ON$: C, 70.04; H, 8.08; N, 10.21. Found : C, 69.76; H, 8.34; N, 10.20. U.V. λ_{max}^{EtOH} mμ(log ε): 263.5(3.56), 269.5(3.49).

Picrate : m.p. 140~141° (from EtOH). *Anal.* Calcd. for $C_{14}H_{14}O_8N_4$: C, 45.90; H, 3.85; N, 15.30. Found : C, 45.61; H, 3.80; N, 15.50.

2-Methyl-3-benzyloxymethylpyridine (VI′)—65 g.(0.58 mole) of 2-methyl-3-hydroxymethylpyridine (IV) was converted to the Cl compound (V) in the manner previously described for the prepartion of (VI). A solution of Cl compoud in 100 cc. of benzyl alcohol was treated with a solution of sodium benzyloxide (prepared from 13 g. of Na) in 200 cc. benzyl alcohol. The mixture was treated in a usual manner to give a yellow oil, $b.p_2$ 145~150°. Yield, 38.5 g.(38%). *Anal.* Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09; N, 6.57. Found : C, 76.56; H, 7.30; N, 6.67.

Picrate : m.p. 175~177° (from EtOH). *Anal.* Calcd. for $C_{20}H_{18}O_8N_4$: C, 54.30; H, 4.10; N, 12.67. Found : C, 54.30; H, 4.09; N, 12.86.

2-Methyl-3-methoxymethylpyridine 1-Oxide (VII)—A mixture containg 23.0 g.(0.167 mole) of 2-methyl-3-methoxymethylpyridne (VI), 100 cc. of glacial AcOH, and 17 cc. of 30% H_2O_2 solution was heated at 70~80° for 3 hr. Additional 12 cc. of 30% H_2O_2 solution was then added and the resulting mixture was heated at 70~80° for another 9 hr. The mixture was then concentrated to a volume of 15 cc., an equal volume of water was added, and the solution was again concentrated to 15 cc. The residue was taken up in 50 cc. of $CHCl_3$ and shaken with an aqueous paste of K_2CO_3 until no further CO_2 evolved. The $CHCl_3$ layer was then separated, dried, and concentrated under a reduced pressure. The residual oil was distilled to give 23.0 g.(87.5%) of a colorless oil, $b.p_2$ 135~138°, which crystallized on standing, m.p. 55~60°. U.V. λ_{max}^{EtOH} mμ(log ε) : 216.5(4.53), 259.5(4.28).

Picrate : Yellow crystals, m.p. 92~95° (from EtOH). *Anal.* Calcd. for $C_{14}H_{14}O_9N_4$: C, 43.98; H, 3.69; N, 14.66. Found : C, 43.62; H, 4.03; N, 15.17.

2-Methyl-3-benzyloxymethylpyridine 1-Oxide (VII′)—A sample of 21.3 g.(0.1 mole) of (VI′) was treated as previously described for the preparation of (VII) to give a viscous oil, b.$p_{0.02\sim0.05}$ 170~180°. Yield, 17.4 g.(76%).

Picrate : m.p. 104~106° (from EtOH). *Anal.* Calcd. for $C_{20}H_{18}O_9N_4$: C, 52.40; H, 3.96; N, 12.22. Found : C, 52.48, H, 4.47; N, 12.15.

3-Methoxymethyl-2-pyridinemethanol Acetate (VIII)—To 63.0 g. of gently boiling Ac_2O, 42.4 g. (0.277 mole) of (VII) was added dropwise. When the addition was complete, the solution was boiled under reflux for 15 min. and then distilled directly under reduced pressure, from which 45 g.(95%) of a pale yellow oil, b.p_5 135~138°, was collected. U.V. λ_{max}^{EtOH} mμ(log ε) : 262.5(3.50), 267.5(3.45).

Picrate : Yellow crystals, m.p. 132~133° (from EtOH). *Anal.* Calcd. for $C_{16}H_{16}O_{10}N_4$: C, 45.29; H, 3.80; N, 13.21. Found : C, 45.73; H, 4.07; N, 13.32.

3-Benzyloxymethyl-2-pyridinemethanol Acetate (VIII′)—A sample of 17.4 g.(0.076 mole) of (VII′) was treated with 30 g. of Ac_2O in the manner described for the preparation of (VIII), and 13.6 g.(65.5%) of yellow oil, b.p_3 160~170°, was obtained. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found : C, 70.75; H, 6.67; N, 6.09.

Picrate : Yellow crystals, m.p. 170~172° (from EtOH). *Anal.* Calcd. for $C_{22}H_{20}O_{10}N_4$: C, 52.80; H, 4.03; N, 11.20. Found : C, 52.42; H, 4.36; N, 11.47.

3-Methoxymethyl-2-pyridinemethanol (IX)—A solution of 6.5 g. of (VIII) and 5 g. of KOH in 50 cc. of EtOH was boiled under reflux for 6 hr. The solution was evaporated to dryness under a reduced pressure, the residue was dissolved in a small amount of water, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried, the solvent was distilled off, and the residue was distilled. There was collected 4 g.(78.5%) of pale yellow oil, b.$p_{0.05}$ 120~125°. U. V. λ_{max}^{EtOH} mμ(log ε) : 262(3.52), 267.5(3.43).

Picrate : Yellow crystals, m.p. 127~128° (from EtOH). *Anal.* Calcd. for $C_{14}H_{14}O_9N_4$: C, 43.98; H, 3.69; N, 14.66. Found : C, 43.80; H, 3.89; N, 15.03.

3-Benzyloxymethyl-2-pyridinemethanol(IX′)—A sample of 13.6 g. (0.05 mole) of (VIII′) was hydrolyzed with 10 g. of KOH in 100 cc. of EtOH in the manner described for the preparation of (IX), and 7.5 g. (58.5%) of viscous yellow oil, b.$p_{0.005}$ 140~150°, was obtained. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found : C, 73.18; H, 6.58; N, 6.08.

Picrate : Yellow crystals, m.p. 162~164° (from EtOH). *Anal.* Calcd. for $C_{20}H_{18}O_9N_4$: C, 52.40; H, 3.96; N, 12.22. Found : C, 52.64; H, 4.18; N, 12.32.

2-Chloromethyl-3-methoxymethylpyridine (X)—To a solution of 7.5 g.(0.049 mole) of (IX) in 50 cc. of AcOEt, 10 g. of $POCl_3$ was added gradually under agitation and chilling with ice. When the addition was complete, the solution was agitated at room temperature for 3 hr., the mixture was concentrated under a reduced pressure, the residue was treated with ice and water, and made alkaline with K_2CO_3. The liberated base was extracted with Et_2O, Et_2O layer was dried over anhyd. Na_2SO_4, and the solvent was distilled off. The residual oil gave the picrate, m.p. 112~114.5°, of 2-chloromethyl-3-methoxymethylpyridine after recrystallization from EtOH. *Anal.* Calcd. for $C_{14}H_{13}O_8N_4Cl$: C, 41.95; H, 3.20; N, 13.98. Found : C, 42.21; H, 348; N, 14.21

2-Cyanomethyl-3-methoxymethylpyridine (XI)—A solution of (X), obtained from 26.7 g.(0.174 mole) of 3-methoxymethyl-2-pyridinemethanol, in 100 cc. of EtOH was added gradually during about 5 hr. to a solution of 30 g. of NaCN in 15 cc. of water and 400 cc. of EtOH. When the addition was complete, the solution was boiled under reflux for 10 hr. When cool, the precipitated NaCl was filtered off and the solution was concentrated under a reduced pressure. The residue was dissolved in a small amount of water and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residual oil was distilled under a reduced pressure to give a pale yellow oil, b.$p_{0.05}$ 110~115°. Yield, 24.5 g.(83.5%). U. V. λ_{max}^{EtOH} mμ(log ε) : 261(3.47), 267(3.63).

Picrate : Yellow crystals, m.p. 146~148° (from EtOH). *Anal.* Calcd. for $C_{15}H_{13}O_8N_5$: C, 46.04; H, 3.35; N, 17.90. Found : C, 46.23; H, 3.67; N, 17.69.

2-(2-Pyridyl)-2-(3-methoxymethyl-2-pyridyl)acetonitrile (XIII)—14.6 g. (0.0895 mole) of (XI) was added during 1 hr. to a suspension of $NaNH_2$ (prepared from 4.6 g. of Na) in 500 cc. of dehyd. Et_2O. To this mixture, 15.8 g.(0.1 mole) of 2-bromopyridine was added gradually and the whole was stirred for 3 hr. at room temperature. After the addition of NH_4Cl to destroy the unreacted $NaNH_2$, water was added and aqueous layer was separated. Aqueous layer was acidified with HCl and extracted with Et_2O. Aqueous layer was made basic with KOH and extracted with Et_2O. Et_2O layer was dried, the solvent was distilled off, and the residual oil was distilled under a reduced pressure to collect unreacted 2-cyanomethyl-3-methoxymethylpyridine. The distillation residue was dissolved in benzene and chromatographed over Al_2O_3 to give reddish yellow crystals, m.p. 79~80° (from Et_2O-petr. ether). Yield, 2.198 g.(15.9%). *Anal.* Clacd. for $C_{14}H_{13}ON_3$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.03; H, 5.67; N, 17.88.

Picrate : Yellow crystals, m.p. 132~134° (from EtOH). *Anal.* Calcd. for $C_{20}H_{16}O_8N_6$: C, 51.28;

H, 3.44; N, 17.94. Found : C, 51.38; H, 3.68; N, 17.76.

(3-Methoxymethyl-2-pyridyl)-2-pyridylmethane (XIV)—A mixture of 0.843 g. of (XIII) and 20 cc. of 70% H_2SO_4 was boiled for 4 hr. After cool, the mixture was basified with KOH and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and the solvent was distilled off. The residual oil gave the dipicrate of (3-methoxymethyl-2-pyridyl)-2-pyridylmethane, m.p. 168~170° (from EtOH). *Anal.* Calcd. for $C_{25}H_{20}O_{15}N_8$: C, 44.7; H, 2.98; N, 16.66. Found : C, 44.56; H, 2.70; N, 16.93.

3-Ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XVII)—13.7 g.(0.1 mole) of (VI) was added gradually with stirring to a solution of $NaNH_2$ (prepared from 4.4 g. of Na) in 100 cc. of liquid NH_3, and then to this mixture a solution of 21.6 g.(0.1 mole) of diethyl ethoxymethylenemalonate in 100 cc. of Et_2O was added with stirring. The stirring was continued for 30 min., 150 cc. of Et_2O was added, and NH_3 was evaporated. The Et_2O layer was separated and the residue was extracted with $CHCl_3$. The combined Et_2O layer and $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and the solvent was distilled off. The residue was dissolved in benzene and petr. ether was added to give yellow crystals, m.p. 109~110° (from EtOH). Yield, 2.5 g. *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found : C, 64.38; H, 5.76; N, 5.41. U.V. λ_{max}^{EtOH} mμ(log ε) : 257.5(4.01), 266(3.96), 408(4.26). I.R. $\nu_{max}^{CHCl_3}$ cm^{-1} : 1724(ester C=O), 1681(-CON<), 1096(ether).

9-Methoxymethyl-4-oxo-4*H*-quinolizine (XVIII)—0.546 g. of (XVII) was boiled under reflux for 5 hr. with 35 cc. of 10% HCl. When cool, the solution was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and the solvent was distilled off. There was obtained 0.3409 g. of yellow crystals, m.p. 59~61° (from EtOH). *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found : C, 70.13; H, 5.98; N, 7.31. U.V. λ_{max}^{EtOH} mμ(log ε) : 248.5(4.12), 256 (4.02), 371(4.15), 383(4.17). I.R. $\nu_{max}^{CHCl_3}$ cm^{-1} : 1661(-CON<), 1089(ether).

1-Cyano-3-ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XIX)—A mixture of (XI) (30 g., 0.185 mole) and diethyl ethoxymethylenemalonate (52 g., 0.24 mole) was boiled under reflux for 2 hr., and heated at 190~200° for 3 hr., during which the EtOH produced was distilled off. When the mixture was cool, petr. ether was added to give yellow crystals, m.p. 156~158° (from EtOH). Yield, 21.1 g.(40%). *Anal.* Calcd. for $C_{15}H_{14}O_4N_2$: C, 61.31; H, 5.15; N, 10.21. Found : C, 61.07; H, 5.28; N, 9.90. U.V. λ_{max}^{MeOH} mμ(log ε) : 258.5(4.17), 266.5(4.21), 346(3.96), 4.06(4.28). I.R. $\nu_{max}^{CHCl_3}$ cm^{-1} : 2227 (CN), 1745(ester C=O), 1712(CON<), 1105(ether).

Ethyl (3-Methoxymethyl-2-pyridyl)acetate (XII)[9]—To a solution of KNH_2 (prepared from 1.8 g. of K) in 100 cc. of liq. NH_3, 6 g. of (VI) was added. After the addition was complete, 100 cc. of dehyd. Et_2O was added and NH_3 was evaporated. 5.5 g. of $CO(OEt)_2$ was added to the mixture and boiled under reflux for 2 hr. An aqueous solution of NH_4Cl was added and Et_2O layer was separated. The Et_2O layer was extracted with 10% HCl. The aqueous solution was basified with K_2CO_3 and extracted with Et_2O. The Et_2O layer was dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residue was distilled under a reduced pressure to give a yellow oil, $b.p_5$ 150~152°. Yield, 2 g. *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69. Found : C, 63.16; H, 7.18; N, 6.88.

1,3-Bis(ethoxycarbonyl)-9-methoxymethyl-4-oxo-4*H*-quinolizine (XXII)—A mixture of (XII) (0.674 g.) and diethyl ethoxymethylenemalonate (0.869 g.) was boiled under reflux (200°) for 8 hr. The benzene solution of the reaction mixture was chromatographed over 30 g. of Al_2O_3 to give yellow crystals, m.p. 75~77° (from Et_2O). Yield, 0.41 g. *Anal.* Calcd. for $C_{17}H_{19}O_6N$: C, 61.12; H, 5.7; N, 4.22. Found : C, 61.22; H, 6.12; N, 4.02. U.V. λ_{max}^{EtOH} mμ(log ε) : 263(4.16); 350(3.93); 4.08(4.24). I.R. $\nu_{max}^{CHCl_3}$ cm^{-1} : 1724(ether C=O), 1700(-CON<), 1100, 1110(ether).

1-Cyano-9-methoxymethyl-4-oxo-4*H*-quinolizine (XX)—A mixture of 3.16 g. of 1-cyano-3-ethoxycarbonyl-4-oxo-4*H*-quinolizine (XIX) and 200 cc. of 10% HCl was boiled under reflux for 5 hr. The mixture was allowed to stand over night and the precipitated yellow amorphous crystals were collected (1.8147 g.). Aqueous layer was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and the solvent was distilled off. The residual yellow crystals (0.9905 g.) and the previously collected crystats were combined and recrystallized from a mixture of MeOH and AcOEt, m.p. 150~151°. Yield, 1.8520 g.(75.5%). *Anal.* Calcd. for $C_{12}H_{10}O_2N_2$: C, 67.28; H, 4.71; N, 13.08. Found : C, 67.09; H, 5.05; N, 12.73. U.V. λ_{max}^{MeOH} mμ(log ε) : 259(4.13), 272.5(4.08), 380(4.20). I.R. $\nu_{max}^{CHCl_3}$ cm^{-1} : 2195(CN), 1675(-CON<), 1088(ether).

3,6-Dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine (XXI)—i) From 1-Cyano-3-ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XIX) : 17 g.(0.062 mole) of (XIX) was boiled under reflux with 1500 cc. of 20% HCl for 5 hrs. After the mixture was cooled, K_2CO_3 was added to make the mixture weakly acidic. After the precipitated inorganic salt was filtered off, the mixture was extracted with $CHCl_3$, the $CHCl_3$ layer was dried, and the solvent was distilled off. The residual crystals were recrystallized from EtOH to 9 g.(56%) of yellow crystals, m.p. 252~254°. *Anal.* Calcd. for $C_{11}H_7O_3N$: C, 65.67; H, 3.51; N, 6.96. Found : C, 65.96; H, 3.70; N, 6.91. U.V. λ_{max}^{MeOH} mμ(log ε) : 254(3.84), 260.5(3.87), 288.5(3.89), 355(4.18). I.R. ν_{max}^{KBr} cm^{-1} : 1724(lactone), 1684(-CON<).

9) This experiment was carried out by Mr. Eiji Ohki of the Institute of Applied Microbiology, University of Tokyo.

ii) From 1-Cyano-9-methoxymethyl-4-oxo-4*H*-quinolizine (XX) : 0.9129 g. of (XX) was boiled under reflux for 5 hr. with 80 cc. of 20% HCl. The mixture was neutralized with K_2CO_3 and extracted with $CHCl_3$. From the $CHCl_3$ layer 0.537 g.(62.5%) of yellow crystals, m.p. 252~254° (from EtOH), was obtained.

1-Ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine (XXIII)—1.3 g. of 1,3-bis(ethoxycarbonyl)-9-methoxymethyl-4-oxo-4*H*-quinolizine (XXII) was boiled under reflux for 1 hr. with 75 cc. of 18% HCl. After the mixture was cooled, K_2CO_3 was added and neutralized solution was extracted with $CHCl_3$. The $CHCl_3$ layer was dried, the solvent was distilled off, and the residual crystals were recrystallized to give 0.0611 g. of yellow crystals, m.p. 252~254° (from EtOH). This showed no depression on admixture with the crystals of m.p. 252~254° obtained from (XIX) or (XX).

From the alcoholic filtrate left after separation of above crystals of m.p. 252~254°, yellow crystals, m.p. 82~84°, were obtained; yield, 0.09 g. *Anal.* Calcd. for $C_{14}H_{15}O_4N$: N, 5.36. Found : N, 5.24. U.V. λ_{max}^{EtOH} mμ(log ε) : 260(4.14), 381(4.16). I.R. ν_{max}^{KBr} cm^{-1} : 1712(ester C=O), 1680(-CON<).

Summary

2-Cyanomethyl-3-methoxymethylpyridine and ethyl (3-methoxymethyl-2-pyridyl)acetate were prepared from ethyl 2-methylnicotinate. Condensation of these compounds with diethyl ethoxymethylenemalonate afforded 1,3-bis(ethoxycarbonyl)-9-methoxymethyl-4-oxo-4*H*-quinolizine and 1-cyano-3-ethoxycarbonyl-9-methoxymethyl-4-oxo-4*H*-quinolizine. The ethoxycarbonyl group in these compounds was saponified and further decarboxylated on being heated with hydrochloric acid. A more drastic condition easily afforded 3,6-dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine.

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49. Yoshinobu Sato : Syntheses of Allied Compounds of Lupine Alkaloids. IV.[1] Synthesis and Hydrogenation of 4-Oxo-4*H*-quinolizine Derivatives.

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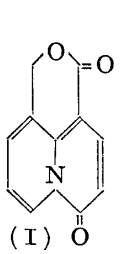
Experiments were carried out to prepare 2-methylperhydropyrido[3,4,5-*i*,*j*]quinolizine (II) (9-methyl-9-azahexahydrojulolidine), an intermediate obtained during synthesis of matrine by Tsuda and others,[2] from 3,6-dioxo-1*H*,3*H*,6*H*-pyrano[3,4,5-*i*,*j*]quinolizine (I) whose synthesis was described in the preceding report.[1]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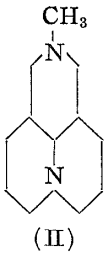
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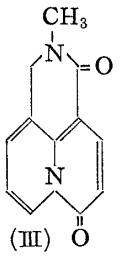
(III)

On heating (I) with excess of methylamine in a sealed tube at 80~100°, yellow crystals, m.p. 259°, are obtained. This substance shows fluorescence like (I) and its infrared spectrum exhibits a new additional absorption for a lactam but not that for hydroxyl or C=O in δ-lactone. Therefore, this compound must be 3,6-dioxo-2-methyl-2,3-dihydro-1*H*,6*H*-pyrido[3,4,5-*i*,*j*]quinolizine (III).

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1) Part III : This Bulletin, **7**, 241(1959); *ibid.*, **6**, 222(1958).

2) K. Tsuda, *et al.* : J. Org. Chem., **21**, 1481(1956).