UDC 547.837

71. Yoshinobu Sato: The Synthesis of Lupine Alkaloids. II.[1] The Synthesis of 1-(α-Piperidyl)quinolizidine.

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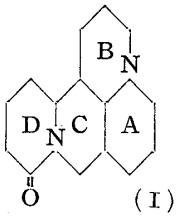
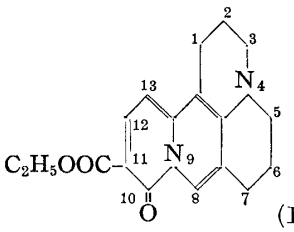
Studies on the structure of matrine, first isolated from the root of Japanese Sophora (*Sophora flavescenee*), were carried out by H. Kondo and his school and the structural formula (I)[2] was presented in 1936. Recently, Tsuda *et al.*[3] synthesized 11-ethoxycarbonyl-10-oxo-1,2,3,5,6,7-hexahydroquinolizo[1,8-*ab*]quinolizine (II), and this proved the structure of (I).

Another route of the synthesis of matrine was attempted; the formation of B- and C-rings by cyclization from the starting material having A- and D-rings.



(I)



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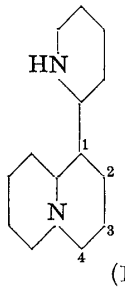
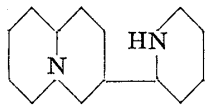


(III)



(IV)

As the preliminary step 1-(2-piperidyl)quinolizidine (III) was synthesized by three routes (Chart 1) from the same starting material, bis(2-pyridyl)methane (V),[4~6] obtained in 25% yield by boiling picolyllithium with 2-bromopyridine in ether. This compound lacks one carbon atom in matrine ring, which joins A- and B-rings to form C-ring and is an isomer of 3-(2-piperidyl)quinolizidine (IV).[7,8]

Bohlmann *et al.*[9] obtained 4-quinolizone compounds by condensing 2-picoline or ethyl 2-pyridylacetate with diethyl ethoxymethylmalonate in the presence of sodium amide in liquid ammonia. Bis(2-pyridyl)methane reacted very smoothly with diethyl ethoxymethylmalonate. The methylene group in bis(2-pyridyl)methane is very reactive due to the interaction of two pyridyl groups and 1-(2-pyridyl)-3-ethoxycarbonyl-4-quinolizone (VI) was easily obtained in a good yield only by heating bis(2-pyridyl)methane with diethyl ethoxymethylmalonate at 160~180°. The condensation of (V) with diethyl ethoxymethylmalonate in the presence of sodium amide in liquid ammonia gave the 4-quinolizone derivative in a poor yield and acid amide as a by-product. The infrared spectrum of (VI) exhibits the absorption bands for -COOR (1731 cm^{-1}), -CON< (1692 cm^{-1}), and pyridine ring (1636, 1593, and 1570 cm^{-1}), very analogous to those of structurally isomeric 1-ethoxycarbonyl-3-(2-pyridyl)-4-quinolizone (XII)[10] synthesized by Clemo, *et*

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1) Part I: This Bulletin, **2**, 190(1954).
2) K. Tsuda: Ber., **69**, 429(1936).
3) K. Tsuda, *et al.*: J. Org. Chem., **21**, 598(1956).
4) E. Leete, Léo Marion: Can. J. Chem., **30**, 563(1952).
5) N. Sperber, D. Papa, E. Schwenk, M. Sherlock: J. Am. Chem. Soc., **73**, 3856(1951).
6) After this method was devised, the next report appeared. C. Osuch, R. Levine: J. Am. Chem. Soc., **78**, 1723(1956).
7) K. Winterfeld, G. Wald, M. Rink: Ann., 588, 125(1954).
8) P. Knoth: Monatsh., **86**, 210(1955).
9) F. Bohlmann, N. Ottawa, R. Keller: Ann., 587, 162(1954); F. Bohlmann, A. English, J. Politt, H. Sander, W. Weise: Chem. Ber., 88, 1831(1955).
10) The infrared spectrum of this compound shows -COOR(1704 cm^{-1}), -CON<(1664 cm^{-1}), and pyridine ring (1638, 1590 and 1750 cm^{-1}).

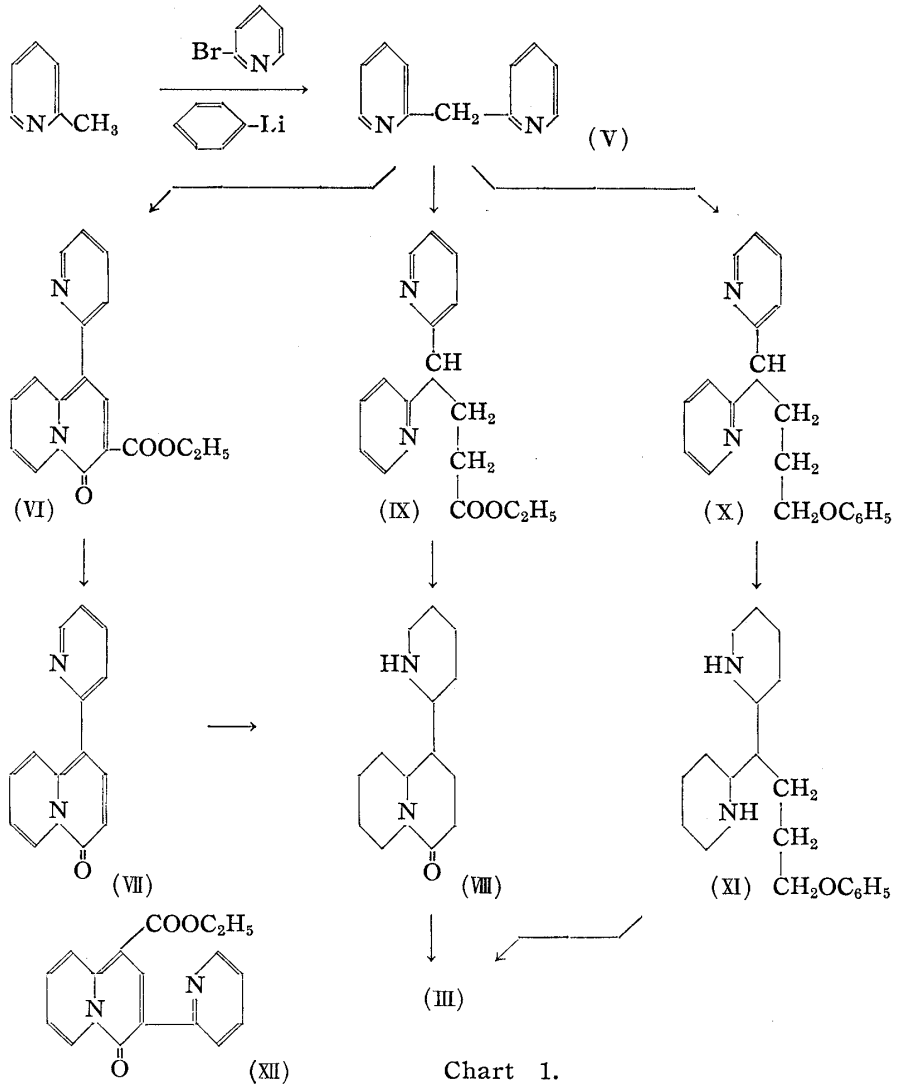

Chart 1.

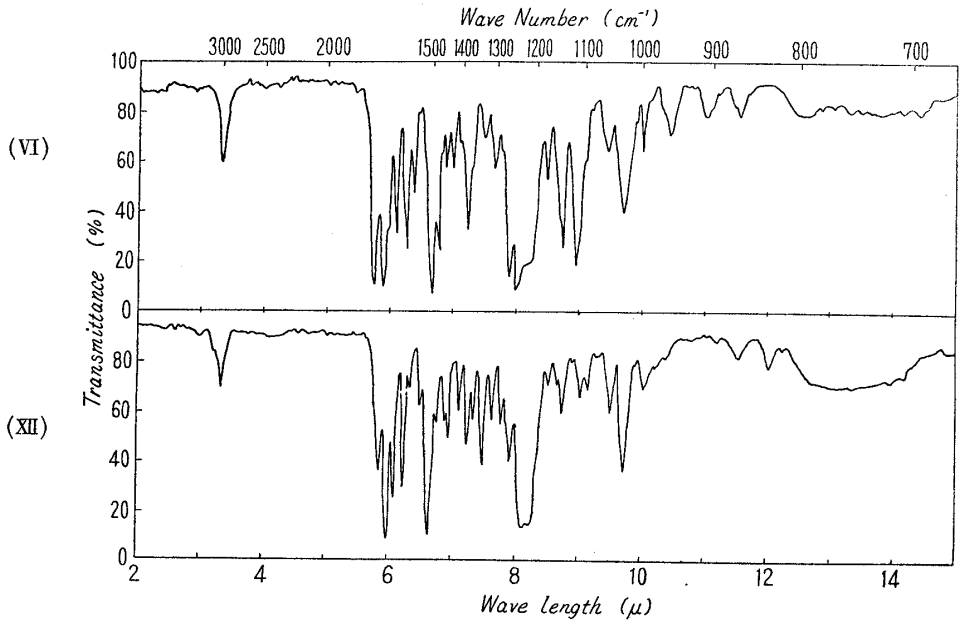

Fig. 1. Infrared Spectra of (VI) and (XII) (in $CHCl_3$)

al.[11] These two compounds have a strong fluorescence characteristic of quinolizine derivatives and the infrared spectra of these are shown in Fig. 1.

Decarboxylation of this compound (VI) by boiling in 5% hydrochloric acid afforded 1-(2-pyridyl)-4-quinolizone (VII) which shows a strong fluorescence and its infrared spectrum exhibited absorption bands for -CON<(1677^{-1} cm) and pyridine ring (1637, 1587, and 1565 cm^{-1}) but not for -COOR. This pyridyl-substituted quinolizone was catalytically hydrogenated over platinum oxide in glacial acetic acid to afford an oily base, 1-(2-piperidyl)-4-oxoquinolizidine (VIII). (VIII) shows no fluorescence and exhibits the infrared spectrum absorption bands for -CON<(1642 cm^{-1}) and >NH (3300 cm^{-1}) but not for pyridine ring.

This compound was also obtained by the next route. Bis(2-pyridyl)methane was condensed with ethyl 3-bromopropionate in the presence of phenyllithium and afforded an oily base, ethyl 4,4-bis(2-pyridyl)butyrate (IX). The oily base obtained by the catalytic hydrogenation of (IX) over platinum oxide in glacial acetic acid, followed by cyclization by heating at above 180° under reduced pressure for two hours, was proved to be identical with (VIII) by the mixed melting point of its picrolonate and the infrared spectra.

1-(2-Piperidyl)-4-oxoquinolizidine was reduced with lithium aluminum hydride in anhydrous ether and afforded an oily base, 1-(2-piperidyl)quinolizidine (III). The infrared spectrum of this compound has only the frequency for NH (3310 cm^{-1}). Two structural isomers are considered for this compound by whether the bond between quinolizidine and piperidine rings is axial or equatorial. Fractional recrystallization of the picrolonate of (III) afforded two kinds of crystals of m.p. 244° and 254°, the former being more soluble in methanol than the latter.

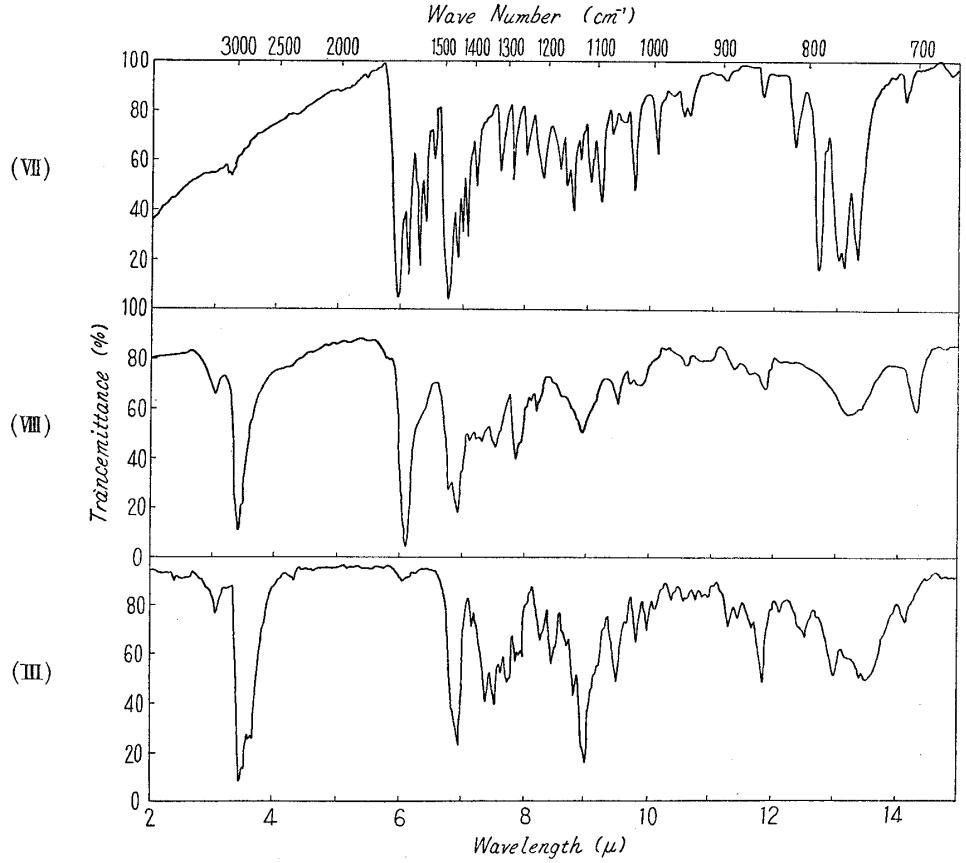

Fig. 2. Infrared Spectra of (VII), (VIII), and (III) (in $CHCl_3$)

11) G.R. Clemo, W. McG. Morgan, R. Raper: J. Chem. Soc., **1936**, 1025.

1-(2-Piperidyl)quinolizidine was also obtained by the following route. 3-Phenoxypropyl bromide was condensed with bis(2-pyridyl)methane in the presence of phenyllithium and quantitatively afforded 4,4-bis(2-pyridyl)butyl phenyl ether (X) as viscous oily base. The infrared spectrum of this compound exhibited the absorptions for ether linkage (1242 cm^{-1}) and pyridine and benzene rings (1600, 1590, 1570, and 1500 cm^{-1}). Catalytic hydrogenation of (X) over platinum oxide in 5% hydrochloric acid afforded the dipiperidyl compound (XI). The infrared spectrum of this compound showed absorptions for >NH (3300 cm^{-1}), ether linkage (1242 cm^{-1}), and a benzene ring (1603, 1590, and 1502 cm^{-1}). The ether linkage of this compound was cleaved by boiling in 48% hydrobromic acid and the product was cyclized with conc. potassium hydroxide to give (III). The infrared spectra of (VII), (VIII), and (III) are shown in Fig. 2.

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Experimental

Bis(2-pyridyl)methane (V)—A solution of 28 g. of 2-picoline in 50 cc. ether was added to a solution of PhLi in 200 cc. of ether, prepared from 4.2 g. Li and 47 g. bromobenzene. To this mixture, a solution of 47.4 g. of 2-bromopyridine in 50 cc. of ether was added gradually under cooling with ice and stirring. After 1 hr. the mixture was refluxed for 1 hr., cooled, and extracted with 200 cc. of 10% HCl. The acid solution was basified with K_2CO_3 and extracted with ether. The ether solution was dried over anhyd. Na_2SO_4 and the solvent was distilled off. The residue was distilled under reduced pressure. The fraction of $b.p_{0.3}$ 95~105° was obtained; 13.5 g.(21.6%). The picrate was obtained in ether solution, m.p. 202°(from EtOH). *Anal.* Calcd. for $C_{11}H_{10}N_2 \cdot 2C_6H_3O_7N_3$: C, 43.9; H, 2.54; N, 17.7. Found : C, 43.74; H, 2.72; N, 17.27.

1-(2-Pyridyl)-3-ethoxycarbonyl-4-quinolizone (VI)—1) A mixture of 17 g.(0.1 mole) of bis(2-pyridyl)methane and 21.0 g.(0.1 mole) of diethyl ethoxymethylmalonate was heated at 120~140° for 4 hrs. and at 180~190° for 3 hrs., during which the EtOH produced was distilled off. After the mixture was cool, petroleum ether was added and gave yellow prisms, m.p. 148~153°. Yield, 20 g. (70%). Recrystallization from a mixture of benzene and ether afforded yellow prisms, m.p. 153~155°. *Anal.* Calcd. for $C_{17}H_{14}O_3N_2$: C, 69.37; H, 4.80; N, 9.52. Found : C, 69.32; H, 5.10; N, 9.82.

2) A solution of 8.5 g.(0.05 mole) bis(2-pyridyl)methane in 50 cc. of ether was added to a suspension of $NaNH_2$(from 1.2 g. Na) in 100 cc. ether. To this mixture 10.8 g. of diethyl ethoxymethylmalonate was added dropwise with stirring and the mixture was refluxed for 3 hrs. After cool water was added and the ether layer was separated. The aq. solution was extracted with $CHCl_3$, the ether and $CHCl_3$ solutions were combined, dried, and the solvent distilled off. The residue, after distilling off the starting material *in vacuo*, was chromatographed on alumina as a benzene solution. Benzene eluate gave 1-(2-pyridyl)-3-ethoxycarbonyl-4-quinolizone, m.p. 153~155°. Yield, 0.69 g.(4.7%). The $CHCl_3$ eluate gave 1-(2-pyridyl)-3-carbamoyl-4-quinolizone, m.p. 283~285°. *Anal.* Calcd. for $C_{15}H_{11}O_2N_2$: C, 67.9; H, 4.18; N, 15.84. Found : C, 67.44; H, 4.22; N, 15.58.

1-(2-Pyridyl)-4-quinolizone (VII)—1-(2-Pyridyl)-3-ethoxycarbonyl-4-quinolizone (188 mg.) was refluxed with 20 cc. of 10% HCl for 10 hrs. The mixture was evaporated to dryness under a reduced pressure, the residue was dissolved in a small amount of water, basified with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4 and the solvent was distilled off to give yellow prisms, m.p. 143~144°(from EtOH and ether). Yield, 96 mg. *Anal.* Calcd. for $C_{14}H_{10}ON_2$: C, 75.65; H, 4.54; N, 12.61. Found : C, 75.87; H, 4.63; N, 12.32.

Ethyl 4,4-Bis(2-pyridyl)butyrate (IX)—A solution of 15 g. of bis(2-pyridyl)methane in 50 cc. of ether was added to PhLi solution in 100 cc. of ether, prepared from 1.25 g. Li and 14 g. bromobenzene. To this mixture a solution of 16.5 g. of ethyl 3-bromopropionate in 50 cc. of ether was added gradually with stirring. Then the mixture was refluxed for 3 hrs., water was added to decompose the Li complex, and then dil. HCl was added. The aq. layer was separated, basified with K_2CO_3, the liberated base was extracted with $CHCl_3$, and dried over anhyd. Na_2SO_4. The solvent was distilled off and the residue was distilled *in vacuo* to give a very viscous oil, $b.p_{0.06}$ 150~160°. Yield, 3.39 g. Dipicrate : m.p. 188~190° (from EtOH). *Anal.* Calcd. for $C_{16}H_{18}O_2N_2 \cdot 2C_6H_3O_7N_3$: C, 46.12; H, 3.33; N, 15.41. Found : C, 45.7; H, 3.21; N, 15.66.

1-(2-Piperidyl)-4-oxoquinolizidine (VIII)—1) 1-(2-Pyridyl)-4-quinolizone (1.5 g.) was hydrogenated over PtO_2 in glacial AcOH. The catalyst was filterd off and the solvent was evaporated to

dryness *in vacuo*. The residue was dissolved in a small amount of water and extracted with $CHCl_3$ after basifying with K_2CO_3. The extract was dried over anhyd. Na_2SO_4 and the solvent was distilled off. The residue (1.92 g.) was distilled under a reduced pressure to give a very viscous oil, b.p. 190~205°(bath temp.). Yield, 1.05 g. *Anal.* Calcd. for $C_{14}H_{24}ON_2$: C, 71.14; H, 10.24; N, 11.85. Found: C, 70.84; H, 10.24; N, 11.50. Picrolonate : m.p. 239~240° (decomp.)(from EtOH). *Anal.* Calcd. for $C_{14}H_{24}ON_2 \cdot C_{10}H_8O_5N_4$: C, 57.59; H, 6.44; N, 16.79. Found : C, 57.67; H, 6.24; N, 16.83.

2) Ethyl 4,4-bis(2-pyridyl)butyrate (3.3 g.) was hydrogenated over PtO_2 (0.5 g.) in glacial AcOH. The mixture was filtered and evaporated to dryness under a reduced pressure. The residue was dissolved in a small amount of water, basified with K_2CO_3, the liberated base was extracted with $CHCl_3$, the extract was dried over anhyd. Na_2SO_4, and the solvent was distilled off. The residue was heated at 200° under a reduced pressure (6~10 mm. Hg) for 2 hrs. and then distilled *in vacuo* to give a very viscous oil, $b.p_{0.004}$ 155~157°. Yield, 2.1 g.(73%). *Anal.* Calcd. for $C_{14}H_{24}ON_2$: C, 71.14; H, 10.24; N, 11.85. Found : C, 70.95; H, 9.93; N, 11.91.

4,4-Bis(2-pyridyl)butyl Phenyl Ether (X)—A solution of 34 g.(0.2 mole) of bis(2-pyridyl)methane in 100 cc. of ether was added gradually with stirring to a solution of PhLi in 200 cc. of ether, prepared from 2.8 g. Li and 31.4 g. bromobenzene. After stirring for 30 mins. 3-phenoxypropyl bromide in 100 cc. of ether was added, the mixture was stirred, and gently refluxed for 6 hrs. Water was added to decompose the Li complex and the ether layer was separated. The ether layer was extracted with 5% HCl, the acid layer was basified with K_2CO_3, and extracted with ether. The ether extract was dried over anhyd. Na_2SO_4 and the solvent was distilled off. The residual oil was distilled *in vacuo* to give a very viscous oil, $b.p_{0.002}$ 180~190°. Yield, 42.1 g.(69.2%).

4,4-Bis(2-piperidyl)butyl Phenyl Ether (XI)—2,2-Bis(2-pyridyl)butyl phenyl ether (11.8 g.) was hydrogenated over PtO_2 (1.0 g.) in 5% HCl (40 cc.). The catalyst was filtered off and concentrated *in vacuo*. The residue was basified with K_2CO_3, extracted with ether, the extract was dried over anhyd. Na_2SO_4, and the solvent was distilled off. The residue was distilled under a reduced pressure to give a very viscous oil, $b.p_{0.005}$ 172~180°. Yield, 8.5 g.

1-(2-Piperidyl)quinolizidine(lll)—1) 1-(2-Piperidyl)-4-Oxoquinolizidine (1.53 g.) was added to a solution of 1.0 g. of $LiAlH_4$ in 50 cc. of ether at room temperature and the mixture was gently refluxed for 5 hrs. To this mixture water was added to decompose the Li complex, the ether layer was separated, dried over anhyd. Na_2SO_4, and the solvent was distilled off. The residue was distilled under a reduced pressure to give an oil, $b.p_2$ 160~170°(bath temp.). Yield, 1.3 g. Picrolonate was obtained by adding an ether solution of picrolonic acid to 0.0638 g. of the base in ether. Yield, 0.2098 g. The crude picrolonate was digested with 40 cc. each of MeOH and filtered, and a total of 200 cc. of MeOH was needed to dissolve all the picrolonate completely. Each filtrate was concentrated and cooled. By this method two kinds of crystals were obtained; (a) m.p. 242~244° (decomp.), 0.0897 g., and (b) m.p. 253~254° (decomp.), 0.0716 g. (a) is more soluble in MeOH than (b). *Anal.* Calcd. for $C_{14}H_{26}N_2 \cdot 2C_{10}H_8O_5N_4$: C, 54.39; H, 5.64; N, 18.66. Found (Dipicrolonate of (a)) : C, 54.55; H, 5.97; N, 18.75. Found (Dipcrolonate (b)) : C, 54.37; H, 5.99; N, 18.64.

2) 4,4-Bis(2-piperidyl)butyl phenyl ether (4.7 g.) dissolved in 50 cc. of 48% HBr was left to stand over night and then refluxed for 5 hrs. After cool, the mixture was extracted with ether, the aqueous ayer was concentrated *in vacuo*, and treated with 30 cc. of 50% KOH. The mixture was extracted with ether, dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residue was distilled under a reduced pressure to give an oily base, $b.p_{0.03}$ 113~115°. Yield, 1.75 g. Dipicrolonate, m.p. 242~243°(decomp.). *Anal.* Calcd. for $C_{14}H_{16}N_2 \cdot 2C_{10}H_8O_5N_4$: C, 54.39; H, 5.64; N, 18.66. Found : C, 54.55; H, 5.97; N, 18.75.

Summary

1-(2-Piperidyl)quinolizidine was obtained from bis(2-pyridyl)methane by three routes. As an intermediate compound 1-(2-pyridyl)-3-ethoxycarbonyl-4-quinolizone, a structural isomer of 1-ethoxycarbonyl-3-(2-pyridyl)-4-quinolizone, was obtained in a good yield.

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