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A New Synthesis of *dl*-Allomatridine

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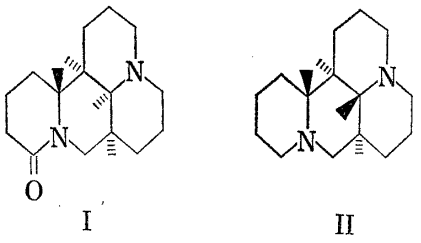
Ethyl 2-ω-cyanoethylamino-3-cyano-4-oxoquinolizine-1-carboxylate (VII) obtained from ethyl 2-methylthio-3-cyano-4-oxoquinolizine-1-carboxylate (V) as starting material for a new method of synthesis of *dl*-allomatridine(II).

Matrine, the principal alkaloid of Sophora flavencens Ait., has been shown to have the structure of I.[2] Matrine (I) has been changed to allomatridine (II) by reduction of high pressure hydrogenation with copper chromite or by zinc dust distillation.[3] The total synthesis of *dl*-allomatridine (II) were reported by Schöpf,[4] Tsuda[5] and Bohlmann group.[6] Previously we reported that the condensation of ethyl 2-pyridineacetate (III) with methyl 1-cyano 2,2-dimethylthio acrylate (IV) gave ethyl 2-methylthio-3-cyano 4-oxo quinolizine-1-carboxylate (V), and the reaction of V with β-aminopropionitrile (VI) yielded ethyl 2-ω-cyanoethylamino-3-cyano-4-oxoquinolizine-1-carboxylate (VII)[7] (see Chart 1).



I II

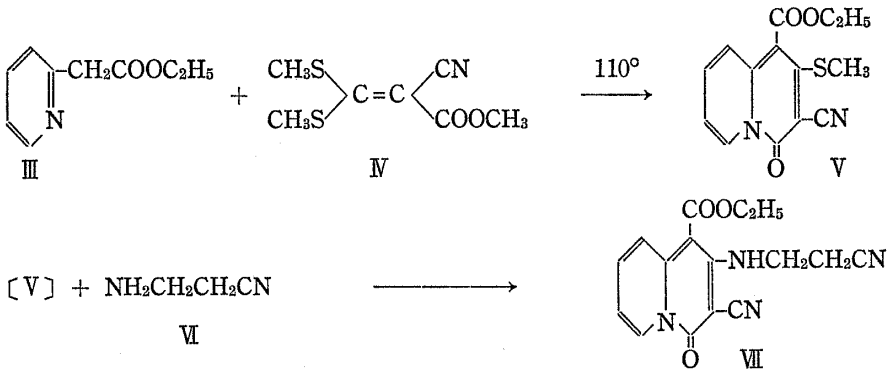


Chart 1

This report relates that we have developed the use of VII as starting material for a new method of synthesis of *dl*-allomatridine (II). Thorpe condensation of VII according to use of potassium *tert*-butylate as condensations reagent in abs. dimethylsulfoxide gave no cyclization product but gave ethyl 2-amino-3-cyano-4-oxoquinolizine-1-carboxylate (VIII), mp

1) Location: *1–14, Bunkyo-machi, Nagasaki.*
2) K. Tsuda and H. Mishima, *Chem. Pharm. Bull. (Tokyo)*, **5**, 285 (1957).
3) H. Kondo and T. Sato, *Yakugaku Zasshi*, **474**, 659. (1921).
4) C. Schöpf, H. Arm, B. Benz, and H. Krim, *Naturwissenschaften* **38**, 186 (1951).
5) *a*) K. Tsuda, S. Saeki, S. Imura, S. Okuda, Y. Sato, and H. Mishima, *J.Org. Chem.*, **21**, 598, 1481(1956).
   b) S. Okuda, *Pharm. Bull.* (Tokyo), **5**, 462, 468 (1957).
6) F. Bohlmann, E. Winterfeldt, and U. Friese, *Chem. Ber.*, **96**, 2251 (1963).
7) G. Kobayashi, S. Furukawa, Y. Matsuda, and S. Matsunaga, *Yakugaku Zasshi*, **89**, 203 (1969).

228.5—230°. Therefore, VII was heated with P.P.A at 95° to yield 1,6-dioxo-1,2,3,4-tetrahydropyrido[3,2-a]quinolizine-5-carboxamide (IX), mp 271—272°, and its infrared (IR) spectrum (KBr) exhibits absorption of carbonyl groups at 1660, 1650, 1640 cm^{-1}, which provided the evidence for this structure. Catalytic reduction of IX in glacial acetic acid with platinum oxide catalyst yielded 6-oxo-1,2,3,4,8,9,10,11-octahydropyrido[3,2-a]quinolizine-5-carboxamide (X), absorbing four molar equivalents of hydrogen. IR spectrum (KBr) of X exhibits absorption of carbonyl groups at 1660, 1637 cm^{-1}. Ultraviolet (UV) spectrum (EtOH) of X assigned that of tetrahydroquinolizine derivatives (see Fig. 1).

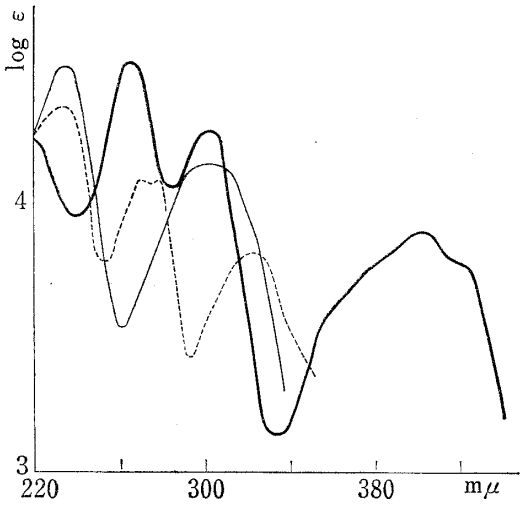


Fig. 1. Ultraviolet Spectrum (EtOH) of IX, X and XIII

—: IX, ——: X, -----: XIII

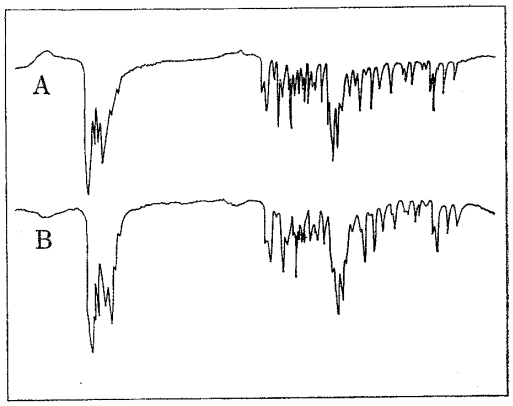


Fig. 2. Infrared Spectrum (KBr)

A: II (mp. 51—53°) in KBr
B: *dl*-allomatridine in KBr (S.Okuda)

X was heated with concentrated hydrobromic acid at 130° to yield 6-oxo-1,2,3,4,8,9,10,11-octahydropyrido[3,2-a]quinolizine (XI) which was decarboxylated, mp 255—256°, and its IR spectrum (KBr) exhibits of a carbonyl group at 1630 cm^{-1}, and its nuclear magnetic resonance (NMR) spectrum (CF_3COOH) exhibits a multiplet of 14 protons at 1.79—4.22 ppm and a singlet of one aromatic proton at 6.03 ppm. In order to synthesize the skeletal structure of matrine (I), XI and acrylonitrile were reacted with polyphosphoric acid to yield no four-condensed-ring product but to yield 4-β-carboxamidoethyl-6-oxo-1,2,3,8,9,10,11-hexahydropyrido[3,2-a]quinolizine (XII), mp 249—250°. IR spectrum (KBr) of XII exhibits absorption of carbonyl groups at 1670, 1630 cm^{-1}, and its NMR spectrum (CF_3COOH) exhibits a multipled of 18 protons at 1.80—4.30 ppm and a singlet of one aromatic proton at 6.35 ppm, which provided the evidence for this structure (XII). Next attempt was made to yield four-condensed-ring compound by reaction of XI and ethyl acrylate with polyphosphoric acid. The reaction product was white crystals of mp 168—169°, and its IR spectrum (KBr) exhibits absorption of carbonyl groups at 1675, 1630 cm^{-1}, and its UV spectrum (EtOH) was indicated in Fig. 1, and its NMR spectrum (CF_3COOH) does not exhibit a signal of aromatic proton at 6.35 ppm, which gave the evidence for the structure of 7,8-dioxo-1,2,3,5,6,7,10,11,12,13-decahydroquinolizino[1,9-a,b]quinolizine (XIII). Okuda reported that the high-pressure hydrogenation of 1,3,8-trioxo-1,2,3,5,6,7,10,11,12,13-decahydroquinolizino[1,9-a,b]quinolizine (XIV) in dioxane with copper chromite catalyst at high temperature afforded *dl*-allomatridine (II).[5b] Therefore, the final step in our work involved the reduction of XIII to *dl*-allomatridine (II). This transformation was accomplished by catalytic reduction of XIII with copper chromite in dioxane solvent, at 260° and 135 kg/cm^2 hydrogen pressure (at 14°). The *dl*-allomatridine (II) was identified by mixed melting point, infrared comparison and analysis (see Fig. 2) (see Chart 2)

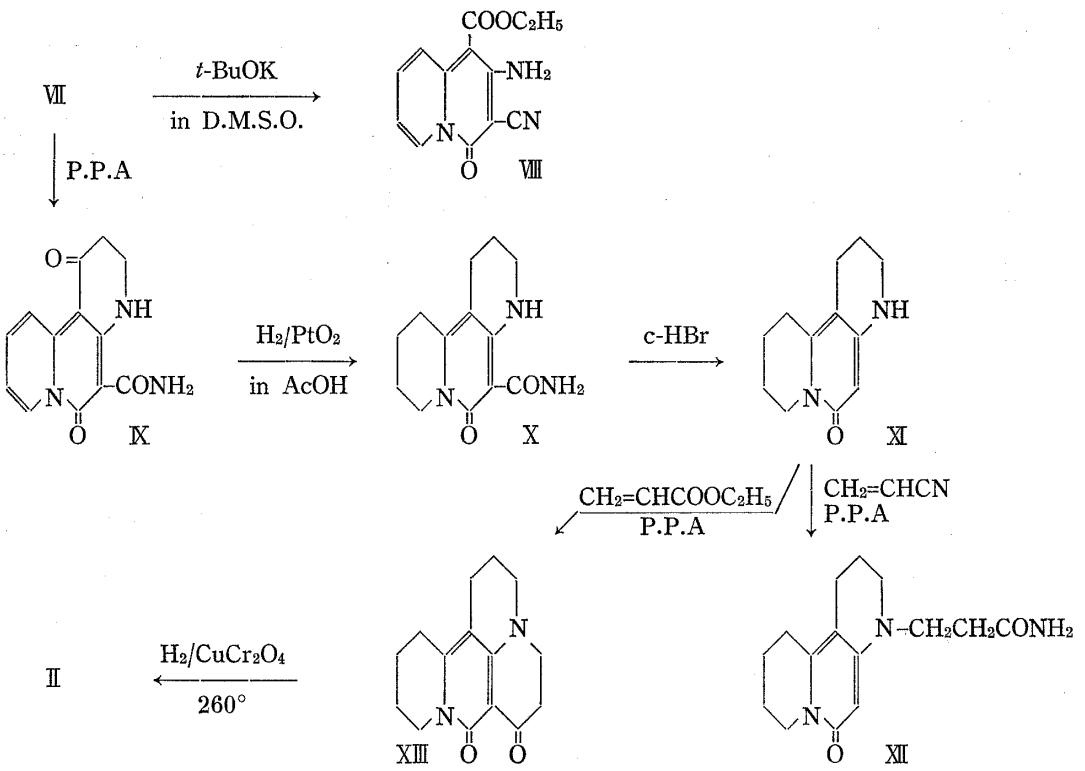


Chart 2

Experimental

Reaction of Ethyl 2-ω-Cyanoethylamino-3-cyano-4-oxoquinolizine-1-carboxylate (VII) with Potassium *tert*-Butylate——A suspension of 0.72 g of *t*-BuOK in 16 ml abs. dimethylsulfoxide was added to a solution of 2.0 g of VII dissolved in 12 ml abs dimethylsulfoxide at room temperature. The mixture was heated at 80° for 10 hr. After cooling, the mixture was poured into water and the precipitate were filtered and washed by water. The crystals were recrystallized from aceton. mp 228.5—230°. The crystals were identified by mixed melting point, infrared comparison, to ethyl 2-amino-3-cyano-4-oxoquinolizine-1-carboxylate (VIII).[7]

1,6-Dioxo-1,2,3,4-tetrahydropyrido[3,2-*a*]quinolizine-5-carboxamide (IX)——A solution of 2.0 g of VII dissolved in 30 ml polyphosphoric acid was heated at steam bath for 20 hr. After cooling, the mixture was poured over ice and the crystals separated were filtered and washed by water. The crystals were recrystallized from $CHCl_3$ mp 271—272°. Yield 70%. *Anal.* Calcd. for $C_{13}H_{11}O_3N_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.75; H, 4.40; N, 16.22. UV λ_{max}^{EtOH} mμ (log ε): 223 (4.14), 266 (4.50), 302 (4.24), 400 (3.90), 420 (3.77). IR δ_{max}^{KBr} cm^{-1}: 3345 (N–H), 1660, 1650, 1640 (C=O).

6-Oxo-1,2,3,4,8,9,10,11-octahydropyrido[3,2-*a*]quinolizine-5-carboxamide (X)——A solution of 3.0 g of IX dissolved 100 ml glacial AcOH was shaken in H_2 stream, with PtO_2 as catalyst. The reaction stopped after absorption of *ca.* 4 mole of H_2. The catalyst was filtered off, the solvent was evaporated from the filtrate, and the residue was washed by water and recrystallized from MeOH. mp 246—247°. Yield 80%. *Anal.* Calcd. for $C_{13}H_{17}O_2N_3$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.13; H, 7.06; N, 16.98. UV λ_{max}^{EtOH} mμ (log ε): 234 (4.51), 302 (4.13). IR δ_{max}^{KBr} cm^{-1}: 3300 (N–H), 1660, 1637 (C=O). NMR δ (in $CDCl_3$): 4.0—1.6 (14H, multiplet, $-CH_2-$).

6-Oxo-1,2,3,4,8,9,10,11-octahydropyrido[3,2-*a*]quinolizine (XI)——A solution of 2.0 g of X dissolved in 60 ml concentrated hydrobromic acid was heated at 130°. After cooling, the crystals separated were filtered and washed by AcOEt. The crystals were basified with 20% NaOH solution, and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and the solvent was evaporated. The residue was recrystallized from acetone–MeOH. mp 255—256°. Yield 64%. *Anal.* Calcd. for $C_{12}H_{16}ON_2$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.53; H, 8.18; N, 13.53. UV λ_{max}^{EtOH} mμ (log ε): 227 (4.45), 282 (3.96). IR δ_{max}^{KBr} cm^{-1}: 3238 (N–H), 1630 (C=O). NMR δ (in TFAc): 6.03 (1H, singlet, aromatic), 4.20—1.79 (14H, multiplet, $-CH_2-$).

4-β-Carboxamidoethyl-6-oxo-1,2,3,8,9,10,11-hexahydropyrido[3,2-*a*]quinolizine (XII)——A mixture of 0.5 g of XI, 0.1 g of acrylonitrile and 2 ml of polyphosphoric acid was heated at steam bath for 8 hrs. The mixture was poured into ice water and basified with Na_2CO_3, and extracted with $CHCl_3$. The extract was

dried over anhyd. Na_2SO_4 and the solvent was evaporated. The residue was recrystallized from acetone-MeOH. mp 249—250°. Yield 47%. *Anal.* Calcd. for $C_{15}H_{21}O_2N_3$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.63; H, 7.82; N, 15.05. UV λ_{max}^{EtOH} mμ (log ε): 233 (4.53), 283 (4.19). IR δ_{max}^{KBr} cm^{-1}: 3305 (N–H), 1670, 1630 (C=O). NMR δ (in TFAc): 6.35 (1H, singlet, aromatic), 4.3—1.8 (18H, multiplet, $-CH_2-$)

7,8-Dioxo-1,2,3,5,6,7,10,11,12,13-decahydroquinolizino[1,9-*a*,*b*]quinolizine (XIII)——A mixture of 0.5 g of XI, 0.5 g of ethyl acrylate and 5 ml of polyphosphoric acid was heated at steam bath for 7 hrs. The mixture was poured into ice–water and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and the solvent was evaporated. The residue was recrystallized from acetone–MeOH. mp 168—169°. Yield 42%. *Anal.* Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.34; H, 6.93; N, 10.45. UV λ_{max}^{EtOH} mμ (log ε): 235 (4.37), 270 (4.08), 277 (4.08), 322 (3.73). IR δ_{max}^{KBr} cm^{-1}: 1675, 1630 (C=O). NMR δ (in TFAc): 4.5—1.8 (18-H, multiplet, $-CH_2-$)

***dl*-Allomatridine (II)**——To a solution of 0.5 g XIII dissolved in 20 ml of dioxane was added 0.5 g copper chromite and the mixture was heated 7 hrs at 270° with initial hydrogen pressure of 130 kg/cm^2 (at 14°). The base obtained as a product was recrystallized from petroleum ether mp 51—53°. Yield 70%. *Anal.* Calcd. for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18; N, 11.95. Found: C, 76.92; H, 11.24; N, 12.12.

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