Studies on Tertiary Amine Oxides. LIX,1) A New Total Synthesis of dl-Allomatridine

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1,1-Ethylendioxy-9-(2-pyridyl)quinolizidine (1) was converted to N-ethoxycarbonyl-pyridinium salt (3) via monohydrobromide (2) by successive treatment with ammonium bromide and ethyl bromoacetate. The reaction of 3 with hydrochloric acid was markedly affected with the concentration of the acid. Thus, when 3 was heated with 15—20% hydrochloric acid, ring closure took place accompanied by hydrolysis of the ketal and ester groups and also decarboxylation to give 17-hydroxy compound (4). Heating with triethylamine gave dehydrated pyridinium salt (5) which was reduced with sodium borohydride and then catalytically to dl-allomatridine (6).

On the other hand, heating 3 with 5—10% hydrochloric acid gave a carboxylic acid (9) which was also transformed into 6 through an ester (10) and a ring closure product (11) as shown in Chart 2. The action of 30% acid on 3 followed by the similar treatments afforded 1-hydroxy-9-(2-pyridyl)quinolizidine (7).

Transformation of 1 to 17-hydroxyallomatridine (8) was further achieved successively by hydrolysis to 1-oxo compound (12), formation of its cyanohydrin (13) and hydrogenation over Raney nickel.

Keywords—lupine alkaloid; 1-substituted 9-(2-pyridyl)quinolizidine; 17-hydroxyallomatridine; pyridinium salt; hydrolytic ring closure; reductive ring closure

As an extension of our study on the reaction of acyl-adduct of aromatic N-oxide with enamine,3) we have examined the reaction using 1(10)-dehydroquinolizidine as a heterocyclic enamine and found that 1-(2-pyridyl)quinolizidine (A) was formed from the reaction with N-benzoxyloxypyridinium chloride after treatment of the reaction mixture with sodium borohydride.4) Further, with an aim to open a new route to matrine type alkaloids, reactions of

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\begin{align*}
\text{N}^+ \text{Cl}^- + \text{OCOPh} & \xrightarrow{1) \text{CH}_2\text{Cl}_2, \text{R.T.}} \xrightarrow{2) \text{NaBH}_4, \text{EtOH}} \text{N} \xrightarrow{\text{Z}} \text{Cl} \\
\text{N} & \xrightarrow{\text{N}} \text{N} \\
\text{CH}_3 & \xrightarrow{\text{C}} \text{OH} & \text{OH} & \xrightarrow{\text{C'}} \text{OH} \\
\text{Cl} & \xrightarrow{\text{Ph}} \text{phenyl}
\end{align*}
\]

2) Location: Maidashi, Higashi-ku, Fukuoka.
1-substituted and 1,1-disubstituted 9-dehydroquinolizidines were carried out under the same conditions, and 9-(2-pyridyl)quinolizidine derivatives, e.g., B, C and 1, were obtained.\(^5\)

During the course of these studies, the synthesis of 17-hydroxy base (C') by the Hofmann-Leffler reaction of N-chloro-piperidyl compound (C) obtained from 1-hydroxy-1-methyl-9-(2-pyridyl)quinolizidine (C) was tried under various conditions, but all attempts failed as described in a previous paper.\(^5\) However we succeeded in the synthesis of d,l-allomatrine by the reaction sequence starting from 1,1-ethylenedioxy-9-(2-pyridyl)quinolizidine (I)\(^5\) as shown in Chart 1. We now wish to describe this and related studies, although several groups have already reported on the synthesis of this base artificially derived from matrine, the principal alkaloid of Sophora flavescens.\(^6\)

When a solution of 1 and an equivalent of ammonium bromide in aqueous ethanol was heated at 60\(^\circ\)C, an evolution of ammonia was apparently noticed and a product (2) was formed which could be conceivable to be monohydrobromide of 1 from the deformed Bohlmann bands in its infrared (IR) spectrum. However no data other than IR spectrum was obtained because it was highly hygroscopic.

Subsequently, the reaction of 2 with ethyl bromoacetate was carried out in order to prepare N-ethoxy carbonylmethylpyridinium salt (3). While no reaction occurred when 2 was treated at room temperature with ethyl bromoacetate in anhydrous ethanol, the reaction at reflux for 40 hours gave a colorless crystalline product (3). Since it was also highly hygroscopic and rapidly changed to an oil in the air, its purification by recrystallization was not successfully effected. However it formed a dipicrate \(\text{C}_{30}\text{H}_{20}\text{O}_{4}\text{N}_{2}\cdot\text{C}_{12}\text{H}_{15}\text{O}_{14}\text{N}_{4}\cdot1/2\text{C}_{2}\text{H}_{5}\text{COCH}_{3}\) yellow needles, mp 223—224\(^\circ\), when treated with sodium picrate in aqueous solution followed by recrystallization of precipitates from a mixture of ethanol and acetone. The IR spectrum of the crude 3 displayed an ester carbonyl band at 1755 cm\(^{-1}\) and a band due to pyridinium moiety at 1625 cm\(^{-1}\), and the nuclear magnetic resonance (NMR) spectrum showed a three-proton triplet \(J=7.0\) Hz, \(-\text{COCH}_{2}\text{CH}_{3}\)), a four-proton broad singlet \(-\text{OCH}_{2}\text{CH}_{2}\text{O}-\), a two-proton quartet \(J=7.0\) Hz, \(-\text{COCH}_{2}\text{CH}_{3}\)) and a four-proton multiplet \(\text{C}_{5}\text{H}_{5}-\text{C}_{6}\text{H}_{5}\text{C}_{6}-\text{C}_{6}\text{H}-\text{H}\) of the pyridinium ring) at \(\tau 8.80, 6.00—5.50, 4.40\) and 2.25—1.10, respectively. Thus 3 was reasonably assigned 1,1-ethylenedioxy-9-[2-(N-ethoxy carbonylmethyl)pyridinium]yl-5H]-quinolizidinium dibromide.

Next, hydrolysis of 3 with hydrochloric acid was examined in some detail and it was found that the reaction was markedly affected by the concentration of the acid.

Heating 3 with 15—20\% hydrochloric acid for 5 hours produced 17-hydroxy compound (4) which could be conceivably formed by hydrolyses of the ketal and ester groups and consecutive ring closure accompanied by decarboxylation. While 4 formed brownish crystals when thoroughly dried over calcium chloride in a desiccator, purification by recrystallization failed again because of its highly hygroscopic property. The structure assignment of 4 was based on the fact the crude 4 lacked carbonyl band in the IR spectrum and no signals due to ethyl and ethylene protons were observed in the NMR spectrum and also on the reactions described below.

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After various preliminary experiments, we succeeded in transformation of 4 into dl-allomatridine by the following reaction sequence. An anhydrous ethanol solution of the crude 4 and 4 molar excess of triethylamine was refluxed for 5 hours and the reaction mixture was consecutively treated with excess sodium borohydride with ice-cooling. To the residue obtained on evaporation of the solvent and excess triethylamine under reduced pressure was added water, and the resulted solution was extracted with ether to give a very unstable yellow oil. Since it was markedly prone to resiniification, it was converted into its hydrochloride by passing hydrogen chloride gas in its ether solution and this salt was hydrogenated over platinum oxide in anhydrous ethanol. Separation by chromatography on a silica gel column with petr. ether, ether and methanol to afford two products, 6 and 7.

Product 6 was a light yellow oil and formed a dipicate with the empirical formula C_{13}H_{26}N_2·C_{12}H_6O_{14}N_3, yellow needles, mp 262—263°. The melting point of this dipirate agreed with that of d-allomatridine obtained from naturally occurring d-matrine and no depression was observed on the admixture. Furthermore, the IR spectra of both dipirates were practically identical and the free bases showed practically the same IR spectrum, the same Rf value in TLC and the same Rf value in gas chromatography. Thus product 6 was identified as dl-allomatridine; the overall yield of 6 from 1 was only 1—1.5%.

\[ \begin{array}{ccc}
\text{N} & \text{Z} & \text{N} \\
\text{NH}, \text{Br, 60°, EtOH} & \text{BrCH}_{2}\text{COOEt} & \text{CH}_{2}\text{COOEt} \\
\text{1} & \text{2} & \text{3} \\
\end{array} \]

\[ \begin{array}{ccc}
\text{15—20% HCl, heat} & \text{NEt}_{3} & \text{EtOH} \\
\text{4} & \text{5} & \\
\text{2Cl}^- & \\
\end{array} \]

\[ \begin{array}{ccc}
\text{1) NaBH}_4, \text{EtOH} & \text{2) H}_2/\text{PtO}_2 & \text{1) NaBH}_4, \text{EtOH} \\
\text{8} & \text{6} & \text{OH} \\
\text{7} & \text{N} & \\
\end{array} \]

\[ \begin{array}{c}
\text{: Z = O} \\
\text{Chart 1} \\
\end{array} \]

7) H. Kondo and T. Sato, Yakugaku Zasshi, 474, 659 (1921).
Product 7, colorless granular crystals, mp 135°, was proved identical with 1-hydroxy-9-(2-pyridyl)quinolizidine by direct comparison with a sample prepared by sodium borohydride reduction of 1-oxo-9-(2-pyridyl)quinolizidine (12) (Chart 3).

The formation of 6 from 4 likely proceeded via 8-dehydro compound 5. This was verified by the following experiment. When 4 was successively reduced with excess sodium borohydride in anhydrous ethanol and hydrogenated over platinum oxide omitting the initial treatment with triethylamine, 17-hydroxyallomatridine (8) was obtained instead of 6. Compound 8 was isolated as a light yellow oil and gave a dipicrate, C_{15}H_{26}ON_{2}.C_{12}H_{14}O_{4}N_{6}, yellow needles, mp 221—223°, which was proved identical with the dipicrate of a sample prepared by another route from a cyanohydrin derivative 13 mentioned later. This result apparently indicates that triethylamine behaved as a dehydrating agent and converted 4 into 5.

The detailed features of reduction of 5 were not necessarily clear, but the direct hydrogenation over platinum oxide was found to give rather unsatisfactory result; apparently the two-step reduction is more favorable for the transformation of 5 into 6.

On the other hand, heating 3 with 5—10% hydrochloric acid for 5 hours caused hydrolyses of the ketal and ester groups but not decarboxylation to give a carboxylic acid (9). Compound 9 was obtained again as highly hygroscopic brownish crystals and could not be purified by recrystallization, but its IR absorption at 1710 cm⁻¹ (C=O) as well as the NMR spectrum which lacked signals due to ethyl and ethylenedioxy protons but showed a two-proton multiplet at δ 4.5—4.3 (2N-C₆H₄) were consisted with the assigned structure. Further 9 was successfully transformed into its ethyl ester (10) by treatment at room temperature overnight with anhydrous ethanol saturated with hydrogen chloride. The IR spectrum of 10 displayed two carbonyl bands at 1745 (ester) and 1715 cm⁻¹ (ketone), and its NMR spectrum showed ethyl protons at δ 8.70 (3H, t) and 5.62 (2H, q), pyridinium methylene protons at δ 4.50—4.20 (2H, m) and four protons at C₅ C₆ of pyridinium ring at δ 2.51—1.00 (4H, m).

When 10 was treated successively with triethylamine, sodium borohydride and hydrogen over platinum oxide in the similar manner with the above-mentioned reaction of 4, 8-ethoxy-carbonyl-17-hydroxyallomatridine (11) was obtained in place of 6 together with 7.

Compound 11 is a light yellow viscous oil, bp 200—250° (1 mmHg) (bath temp.), and formed a dipicrate, C_{15}H_{30}O_{2}N_{2}.C_{12}H_{14}O_{4}N_{6}, yellow needles, mp 233—234°. The mass spectrum of the free 11 liberated from the purified dipicrate showed the parent peak at m/e 322 and the following characteristic peaks at m/e 304 (M⁺—H₂O), 275 (M⁺—H₂O-C₅H₅), 249 (M⁺—CO₂C₂H₅) and 231 (M⁺—H₂O—CO₂C₂H₅). Its IR spectrum exhibited a hydroxy band, Bohmann bands and ester carbonyl band at 3560, 2975—2975 and 1735 cm⁻¹, respectively, and the NMR spectrum showed ethyl protons at δ 8.75 (3H, t) and 5.75 (2H, q) and a hydroxy proton exchangeable with D₂O at δ 6.14 (1H, b.s.). These observations agreed with assigned structure. The yield of 11 as dipicrate was about 2.5% calculated from 1.

The synthesis of dl-allomatridine 6 from 11 was also successfully achieved on heating with concentrated hydrochloric acid in a sealed tube for 5 hours followed by reduction with sodium borohydride in ethanol.

It was further found that when 3 was heated with 30% hydrochloric acid followed by treatment with triethylamine, sodium borohydride and hydrogen over platinum oxide in the same way, 1-hydroxy-9-(2-pyridyl)quinolizidine 7 was obtained as the sole product in 10% yield, no 6 being detected. This result indicates that not only hydrolyses of the ketal and ester groups but also extrusion of ethoxycarbonylmethyl group occurred in the first step, and may account for the formation of 7 in the above-mentioned cases using hydrochloric acid of somewhat lower concentrations.

These reactions are shown in Chart 2.

Finally, another route from 1 to 6 formulated in Chart 3 was investigated. A solution of 1 in 15—20% hydrochloric acid was refluxed for 5 hours to give 1-oxo-9-(2-pyridyl)quinolizidine (12) as a brownish oil, bp 180—200° (0.5 mmHg) (bath temp.) in 84% yield. Although
12 was fairly unstable and prone to resinification on standing, its structure was reasonably assignable from an IR absorption at 1725 cm\(^{-1}\), analytical values of dipicrate (C\(_{14}\)H\(_{16}\)ON\(_2\)· C\(_{12}\)H\(_6\)O\(_{14}\)N\(_8\)) and the following conversions to 7 and the crystalline cyanohydrin (13).

Reduction of 12 with sodium borohydride in ethanol smoothly afforded 1-hydroxy-9-(2-pyridyl)quinolizidine 7 in a good yield of 70\%. A solutions of 12 and excess acetone cyanohydrin in dichloromethane was stirred at room temperature for 48 hours to give 13, colorless pills, mp 170—172\(^{\circ}\) in 52% yield. Its molecular formula was established as C\(_{19}\)H\(_{18}\)ON\(_3\) from the mass spectrum (M\(^+\), m/e 257) and elemental analysis. Its IR spectrum indicated the presence of pyridine ring (1600 cm\(^{-1}\)) and the NMR spectrum showed a one-proton singlet, a three-proton and a one-proton multiplets at \(\tau\) 6.99, 2.18—3.00 and 1.45—1.60 which were reasonably assigned to a hydroxy proton, C\(_3^7\), C\(_4^7\) and C\(_6\)-protons of the pyridine ring, and its C\(_8\)-proton, respectively.

Compound 13 was hydrogenated in dioxane over Raney nickel at an initial hydrogen pressure of 100 atm. at 190\(^{\circ}\) to give 17-hydroxyallomatrine (8) colorless pills, mp 125—128\(^{\circ}\) in 84\% yield. Its analytical values and the parent peak of the mass spectrum (M\(^+\), m/e 249) agreed with the molecular formula C\(_{19}\)H\(_{19}\)ON\(_2\); it formed a dipicrate, C\(_{15}\)H\(_{20}\)ON\(_2\)·C\(_{12}\)H\(_6\)O\(_{14}\)N\(_8\), yellow needles, mp 221—223\(^{\circ}\). The IR spectrum of 8 exhibited a hydroxy band at 3550 cm\(^{-1}\) and its NMR spectrum showed a one-proton singlet exchangeable with D\(_2\)O at \(\tau\) 6.88.

Although these observations evidently support the assigned structure of 8, it is quite curious that 17-hydroxy base 8 was obtained instead of \(dL\)-allomatrine 6 itself under such rather drastic conditions. The transformation of 8 by dehydration and reduction into 6 is
not accomplished yet because of lack the sample of 8; such a study is now under way in our laboratory.

Bohllmann, et al. have reported that 17-hydroxymatridine and 17-hydroxyallomatridine (8') are formed when matrine or allomatrine is dehydrogenated with mercuric acetate followed by reduction of perchlorate of dehydrogenation product with lithium aluminum hydride as shown above.9

Compound 8' melts at 78° and apparently differs from our 17-hydroxyallomatridine (8) (mp 125—128°). Taking account of the reaction sequence, the position of hydroxy group in 8 is probably correct. Bohllmann, et al.8 have assigned the structures of their hydroxy bases only by IR spectroscopy. Further work is also in progress to elucidate the reason for these contradictory results.

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\begin{align*}
&\text{CH}_2\text{C}_6\text{H}_4\text{OH} \\
&\text{CH}_2\text{C}_6\text{H}_4\text{CN} \\
&\text{H}_2 \\
&\text{Raney Ni} \\
&\text{NaBH}_4 \\
&\text{EtOH} \\
&\text{12} \\
&\text{13} \\
&\text{7} \\
&\text{8}
\end{align*}
\]

\text{Chart 3}

**Preparation of 1,1-Ethyleneidioxyl-9-[2-(N-ethoxycarbonylmethyl)pyridinium]yl-5H-quinolizinidinium Dibromide (3) from 1,1-Ethyleneidioxyl-9-(pyridyl)quinolizinidinium (1)— **A solution of 1 (0.5 g, 0.002 mole) and \(\text{NH}_2\text{Br} \) (0.025 g, 0.0023 mole) in \(\text{EtOH-}\text{H}_2\text{O} \) (1: 1 v/v, 100 ml) was heated at 60° for 3 hr to generate \(\text{NH}_3\) gas. The reaction mixture was evaporated in vacuo to give monohydrobromide of 1 (2) as colorless crystals which were too hygroscopic to be purified by recrystallization. It contained bromide ion and showed the deformed Bohllmann bands in its IR spectrum.

A solution of 2 thus obtained and ethyl bromoacetate (2 g, 5 equiv.) in anhyd. \(\text{EtOH} \) (10 ml) was refluxed for 40 hr. Evaporation of \(\text{EtOH} \) followed by washing excess ethyl bromoacetate with ether afforded pyridinium salt (3) as colorless crystals which were also too hygroscopic to be purified by recrystallization. IR \text{v}_{\text{max}} \text{cm}^{-1}: 1755 \text{ (ester C=O)}, 1625 \text{ (C=N)}. \text{NMR} \text{ (D}_2\text{O)}: 8.80 \text{ (3H, t, } J = 7.0 \text{ Hz, } \text{CO}_2\text{CH}_2\text{CH}_3\text{)}, 6.00—5.50 \text{ (4H, m, } \text{OCH}_2\text{CH}_2\text{O—)}, 4.40 \text{ (2H, q, } J = 7.0 \text{ Hz, } \text{CO}_2\text{CH}_2\text{CH}_3\text{)}, 2.25—1.10 \text{ (4H, m, C}_2\text{H}_5\text{, C}_2\text{H}_5\text{, C}_2\text{H}_5\text{, and C}_2\text{H}_5\text{ of pyridinium ring)}. \text{ Sodium picrate was added to an aqueous solution of the crude 3 to give 0.3 g (17%) of dipicrate, yellow needles, mp 223—224° (\text{EtOH-}\text{CH}_2\text{COCH}_3). Anal. Calcd. for C_{29}H_{29}O_4N_2·C_{12}H_4O_1N_4·1/2CH_3COCH_3: C, 46.37; H, 4.27; N, 12.94. Found: C, 46.69; H, 4.16; N, 13.03.**

**Synthesis of dl-Allomatridine (6) from 3—**A 20% HCl solution of 3 prepared from 1 (1 g) was refluxed for 5 hr. The reaction mixture was evaporated in vacuo and dried thoroughly over CaCl_2 in a desiccator to give brownish crystals (4), however it was highly hygroscopic and could not be purified by recrystallization. Its IR spectrum lacked carbonyl band, and no signals due to ethyl (−COOC_2H_5) or ethylene protons (−OCH_2−CH_2−) were observed in the NMR spectrum.

A solution of 4 and \(\text{NEt}_3 \) (2 g, 4.5 equiv.) in anhyd. \(\text{EtOH} \) (100 ml) was refluxed for 5 hr (the formation of 5), and the cooled mixture was consecutively stirred with \(\text{NaBH}_4 \) (1.5 g) with ice-cooling. The solvent and excess \(\text{NEt}_3 \) was evaporated in vacuo, water was added to the residue which was extracted with ether, and the extract was dried over MgSO_4. Dry HCl was passed in the extract, the extract was evaporated and the resi-

9) All melting and boiling points are uncorrected. IR spectra were recorded on JASCO DS-301, IR-S, and IR-E spectrophotometers, NMR spectra were measured with JNM C-60H spectrophotometer at 60 MHz using TMS as internal reference.
due was taken up in H$_2$O$_2$, shaken with AgCl (1 g) for 30 min to remove Br$^-$. The filtrate was neutralized with 10% NaOH, extracted with ether and HCl gas was again passed in the ether extract. The ether was evaporated and a solution of the residue in EtOH (50 ml) was hydrogenated over PtO$_2$ (60 mg) at ordinary temperature and pressure. After filtration of the catalyst, the filtrate was evaporated, neutralized with 10% NaOH and extracted with ether. The extract residue was chromatographed on a silica gel column to afford a trace of unidentified product (mass spectrum m/e: 278 [M$^+$]), 6 and 7, from the fractions successively eluted with petr. ether–ether (1:1), ether–MeOH (100:1) and ether–MeOH (20:1), respectively.

Product 6: 6-Allomatromidine, a light yellow oil, 20 mg. Its IR spectrum, Rf value in TLC and t$_R$ value in gas chromatography were practically identical with those of 6-allomatromidine obtained from naturally occurring 6-matrinine. Dipirerate: yellow needles, mp 282–283$^\circ$ (acetone). Anal. Calcd. for C$_{22}$H$_{22}$N$_2$C$_6$H$_{14}$O$_7$N$_2$: C, 46.8; H, 4.65; N, 15.54. Found: C, 47.20; H, 4.68; N, 15.20. It was proved identical with an authentic sample of the diplorite of 6-allomatromidine by admixture and the comparison of their IR spectra.

Product 7: 1-Hydroxy-9-(2-pyridyl)quinolizidine; dipirerate, 20 mg. The identity was confirmed by direct comparison with a sample prepared from 1-oxo-9-(2-pyridyl)quinolizidine (12) as described later.

Transformation of 3 to 17-Hydroxyallomatromatrine (8) via 4 —— Pyridinium salt 3 prepared from 1 (0.5 g, 0.002 mole) and NH$_4$Br (0.025 g, 0.0023 mole) was heated with 20% HCl (20 ml), and treated successively with NaB$_4$H$_4$ (0.8 g) and hydrogen over PtO$_2$ (0.04 g) in the similar way as the foregoing experiment except for treatment with NEt$_3$. The product was chromatographed on a silica gel column with ether–MeOH (20:1) to give 0.22 g of 17-hydroxyallomatromatrine (8) as a light yellow oil. Dipirerate: yellow needles, mp 221–223$^\circ$ (acetone). Anal. Calcd. for C$_{18}$H$_{22}$NO$_2$C$_6$H$_{14}$O$_4$N$_4$: C, 45.76; H, 4.52; N, 15.82. Found: C, 45.80; H, 4.09; N, 15.67. Its identity was established by admixture of the dipirerate with authentic sample mentioned later.

Transformation of 3 to 8-Ethoxycarbonyl-17-hydroxyallomatromatrine (11) —— A 7% HCl (30 ml) solution of 3 prepared from 1 (1 g) was refluxed for 5 hr to give brown crystals (9) which was too hygroscopic to be purified by recrystallization. IR $\nu$ max cm$^{-1}$: 1710 (C=O). NMR $\tau$ (D$_2$O): 4.5–4.3 (2H, m, $\gamma$N–CH$_2$); no signal due to $\alpha$-C$_{12}$H$_7$ or $\gamma$-C$_{12}$H$_7$ was noticed.

An anhyd. EtOH (100 ml) solution of the crude 9 was saturated with dried HCl gas and kept for 24 hr to give ethyl ester (10) as brown crystals which were again highly hygroscopic. IR $\nu$ max cm$^{-1}$: 1745 (ester C=O), 1715 (C=O). NMR $\tau$ (D$_2$O): 8.70 (3H, $t$, $J$ = 7.0 Hz, COOHCH$_2$H), 5.82 (2H, q, $J$ = 7.0 Hz, COOCH$_2$H), 4.50–4.20 (2H, m, $\gamma$N–CH$_2$), 2.15–1.00 (4H, protons of pyridinium ring).

An anhyd. EtOH (100 ml) solution of 10 and NEt$_3$ (2 g, ca. 4.5 equiv.) was refluxed for 5 hr, and the cooled reaction mixture was treated with NaB$_4$H$_4$ (1.5 g), HCl gas and then hydrogenated in anhyd. EtOH (50 ml) over PtO$_2$ (0.06 g) in the same way as the conversion of 3 to 6. A mixture of products was chromatographed on a silica gel column to afford a trace of unidentified product [Mass Spectrum m/e: 278 (M$^+$)], 11 and 7, from the fractions successively eluted with petr. ether–ether (1:1), ether–MeOH (100:1) and ether–MeOH (20:1), respectively.

Product 11: 8-Ethoxycarbonyl-17-hydroxyallomatromatrine, a light yellow oil, bp 200–220$^\circ$ (1 mmHg) (bath temp.), 2.5% as the dipirerate. IR $\nu$ max cm$^{-1}$: 3550 (OH), 2950–2795 (Bohlmann bands), 1735 (ester C=O). NMR $\tau$ (CDCl$_3$): 8.75 (3H, $t$, $J$ = 7.0 Hz, COOCH$_2$H$_2$), 6.14 (1H, m, OH), 5.75 (2H, q, $J$ = 7.0 Hz, COOCH$_2$H$_2$). Mass Spectrum m/e: 322 (M$^+$), 304 (M$^+$–H$_2$O), 276 (M$^+$–H$_2$O–C$_2$H$_4$), 249 (M$^+$–COOHCH$_2$), 231 (M$^+$–H$_2$O–COOHCH$_2$). Dipirerate: yellow needles, mp 233–234$^\circ$ (EtOH–acetone). Anal. Calcd. for C$_{18}$H$_{22}$NO$_2$C$_6$H$_{14}$O$_4$N$_4$: C, 46.15; H, 4.62; N, 14.36. Found: C, 46.25; H, 4.76; N, 14.22.

Product 7: 1-Hydroxy-9-(2-pyridyl)quinolizidine, 0.05%, 2 g. The identity was confirmed by direct comparison with a sample prepared from 12.

Synthesis of 6 from 11 —— A 35% HCl (30 ml) solution of 11 (0.2 g) was heated in a sealed tube at 250–260$^\circ$ for 5 hr. The residue obtained by evaporation of HCl was neutralized with 10% Na$_2$CO$_3$ and extracted with ether. Dry HCl gas was passed in the ether solution, ether was evaporated and the residue was treated with NaB$_4$H$_4$ (0.1 g) in anhyd. EtOH (50 ml) to give a minute amount of an oil. This product gave 5 mg of a dipirerate, yellow needles, mp 262–263$^\circ$, which was proved identical with the dipirerate of 6-allomatromatrine 6.

Formation of 1-Hydroxy-9-(2-pyridyl)quinolizidine (7) from 3 —— A solution of pyridinium salt 3 prepared from 1 (0.5 g, 0.002 mole) in 30% HCl (10 ml) was refluxed for 10 hr. The reaction mixture was successively submitted to treatment with NEt$_3$, NaB$_4$H$_4$ reduction and hydrogenation over PtO$_2$ in the same way with the case of synthesis of 6 from 3 to give 0.045 g (10%) of 7. Dipirerate: mp 220–221$^\circ$. It was proved identical with a sample prepared from 12 by the admixture of their dipirerates.

1-Oxo-9-(2-pyridyl)quinolizidine (12) —— A solution of 1 (0.1 g) in 20% HCl (30 ml) was refluxed for 3 hr. The cooled solution was neutralized with 10% NaOH and extracted with ether to give 0.07 g (84%) of 12, a brown oil, bp 180–200$^\circ$ (0.5 mmHg) (bath temp.). IR $\nu$ max cm$^{-1}$: 1725 (C=O). Dipirerate: yellow needles, mp 195–196.5$^\circ$ (acetone). Anal. Calcd. for C$_{18}$H$_{17}$NO$_2$C$_6$H$_{14}$O$_4$N$_4$: C, 45.35; H, 3.49; N, 16.28. Found: C, 45.74; H, 3.68; N, 16.03.

1-Hydroxy-9-(2-pyridyl)quinolizidine (7) —— A solution of 12 (0.07 g) was treated at room temperature with NaB$_4$H$_4$ (0.06 g) for 12 hr to give 0.05 g (70%) of 7, colorless granules, mp 135$^\circ$ (hexane), bp 200$^\circ$ (0.007 mmHg) (bath temp.). Anal. Calcd. for C$_{18}$H$_{17}$NO$_2$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.20; H, 8.50.
N, 11.98. IR ν_{max} cm^{-1}: 3550 (OH), 1605 (pyridine). NMR ν (CDCl₃): 3.00—2.20 (3H, m, C₆-H of pyridine), 1.55—1.35 (1H, m, C₆-H of pyridine). Mass Spectrum m/e: 282 (M⁺). Dipicrate: yellow needles, mp 220—221° (EtOH-acetone). Anal. Calcd. for C_{14}H_{26}O_{3}N_{2}: C, 45.22; H, 3.77; N, 16.23. Found: C, 45.36; H, 3.86; N, 16.24.

1-Cyano-1-hydroxy-9-(2-pyridyl)quinolinizine (13) — A solution of 12 (0.23 g, 0.001 mole) and acetone cyanohydrin (0.34 g, 0.04 mole) in CH₃Cl₂ (10 ml) was stirred at room temperature for 48 hr to give 0.132 g (52%) of 13, colorless pills, mp 170—172° (isopropyl ether-EtOH). IR ν_{max} cm^{-1}: 1600 (pyridine). NMR ν (CDCl₃): 6.99 (1H, s, OH), 3.00—2.18 (3H, m, C₆-H of pyridine), 1.60—1.45 (1H, m, C₆-H of pyridine ring). Mass Spectrum m/e: 257 (M⁺). Anal. Calcd. for C_{18}H_{24}O_{3}N₂: C, 70.00; H, 7.44; N, 16.33. Found: C, 69.64; H, 7.68; N, 15.98.

Synthesis of 17-Hydroxyallomatrine (8) from 13 — A solution of 13 (0.13 g, 0.0005 mole) in dioxane (20 ml) was hydrogenated over Raney Ni (0.03 g) at an initial hydrogen pressure of 100 atm at 190° to give 0.041 g (34%) of 8, colorless pills, mp 125—128° (isopropyl ether-ether). IR ν_{max} cm^{-1}: 3350 (OH). NMR ν (CDCl₃): 6.83 (1H, s, OH). Mass Spectrum m/e: 250 (M⁺). Anal. Calcd. for C_{13}H_{18}O₃N₂: C, 71.95; H, 10.45; N, 11.19. Found: C, 71.65; H, 10.59; N, 10.88. Dipicrate: yellow needles, mp 222—223° (acetone). Anal. Calcd. for C_{13}H_{18}O₃N₂: C, 45.76; H, 4.52; N, 15.82. Found: C, 45.89; H, 4.09; N, 15.67.

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