[Chem. Pharm. Bull. 25(1) 79—86 (1977)]

UDC 547.821'546.21.04 : 547.834.2.04

Studies on Tertiary Amine Oxides. LIX.[1] A New Total Synthesis of *dl*-Allomatridine

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(Received May 12, 1976)

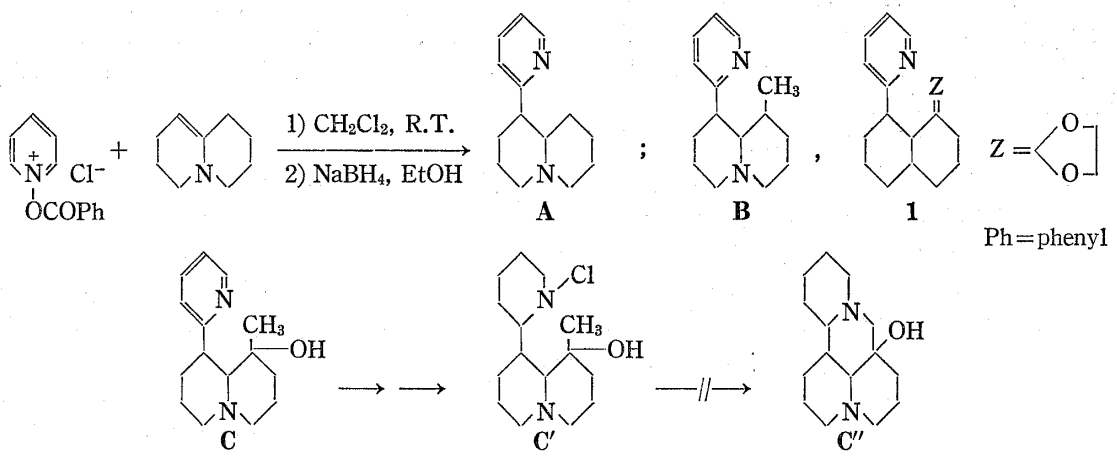
1,1-Ethylenedioxy-9-(2-pyridyl)quinolizidine (**1**) was converted to N-ethoxycarbonylpyridinium salt (**3**) *via* monohydrobromide (**2**) by successive treatment with ammonium bromide and ethyl bromoacetate. The reaction of **3** with hydrochloric acid was markedly affected with the concentration 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

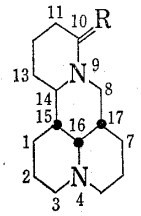
As an extension of our study on the reaction of acyl-adduct of aromatic N-oxide with enamine,[3] we have examined the reaction using 1(10)-dehydroquinolizidine as a heterocyclic enamine and found that 1-(2-pyridyl)quinolizidine (**A**) was formed from the reaction with N-benzoyloxypyridinium chloride 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



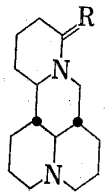
1) Part LVIII: S. Saeki, A. Yamashita, Y. Morinaka, and M. Hamana, *Chem. Pharm. Bull.* (Tokyo), **24**, 2509 (1976).
2) Location: *Maidashi, Higashi-ku, Fukuoka.*
3) *a*) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **13**, 912 (1965); *b*) *Idem, ibid.*, **14**, 762 (1966); *c*) *Idem, ibid.*, **15**, 474 (1967); *d*) *Idem, Yakugaku Zasshi*, **89**, 641 (1969); *e*) M. Nakanishi, M. Yatabe, and M. Hamana, *Heterocycles*, **3**, 287 (1975).
4) S. Saeki, A. Yamashita, Y. Matsukura, and M. Hamana, *Chem. Pharm. Bull.* (Tokyo), **22**, 2341 (1974).

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.[1,5]

During the course of these studies, the synthesis of 17-hydroxy base (**C**″) by the Hofmann-Leffler reaction of N-chloropiperidyl 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 *dl*-allomatridine by the reaction sequence starting from 1,1-ethylenedioxy-9-(2-pyridyl)quinolizidine (**1**)[1] 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]



R=O matrine
R=H_2 matridine



R=O allomatrine
R=H_2 allomatridine

When a solution of **1** and an equivalent of ammonium bromide in aqueous ethanol was heated at 60°, 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-ethoxycarbonylmethylpyridinium 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 $C_{20}H_{29}O_4N_2 \cdot C_{12}H_5O_{14}N_6 \cdot 1/2CH_3COCH_3$, yellow needles, mp 223—224°, 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, $-CO_2CH_2C\underline{H}_3$), a four-proton broad singlet ($-OC\underline{H}_2C\underline{H}_2O-$), a two-proton quartet (J=7.0 Hz, $-CO_2C\underline{H}_2CH_3$) and a four-proton multiplet (C_3-, C_4-, C_5- and C_6-H of the pyridinium ring) at τ 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-ethoxycarbonylmethyl)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 that 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.

5) S. Saeki, A. Yamashita, Y. Morinaka, and M. Hamana, *Yakugaku Zasshi*, **96**, 456 (1976).
6) *a*) C. Schöpf, H. Arm, B. Benz, and H. Krim, *Naturwissenschaften*, **38**, 186 (1951); *b*) K. Tsuda, S. Saeki, S. Imura, S. Okuda, Y. Sato, and H. Mishima, *J. Org. Chem.*, **21**, 598 and 1481 (1956); *c*) S. Okuda, *Pharm. Bull.* (Tokyo), **5**, 462 and 468 (1957); *d*) F. Bohlmann, E. Winterfeldt, and U. Friese, *Chem. Ber.*, **96**, 2251 (1963); *e*) G. Kobayashi, S. Furukawa, Y. Matsuda, R. Natsuki, and S. Matsunaga, *Chem. Pharm. Bull.* (Tokyo), **18**, 124 (1970).

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 resinification, 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 dipicrate with the empirical formula $C_{15}H_{26}N_2 \cdot C_{12}H_6O_{14}N_3$, yellow needles, mp 262—263°. The melting point of this dipicrate agreeded with that of *d*-allomatridine[7] obtained from naturally occurring *d*-matrine and no depression was observed on the admixture. Furthermore, the IR spectra of both dipicrates were practically identical and the free bases showed practically the same IR spectrum, the same *Rf* value in TLC and the same *Rt* value in gas chromatography. Thus product **6** was identified as *dl*-allomatridine; the overall yield of **6** from **1** was only 1—1.5%.

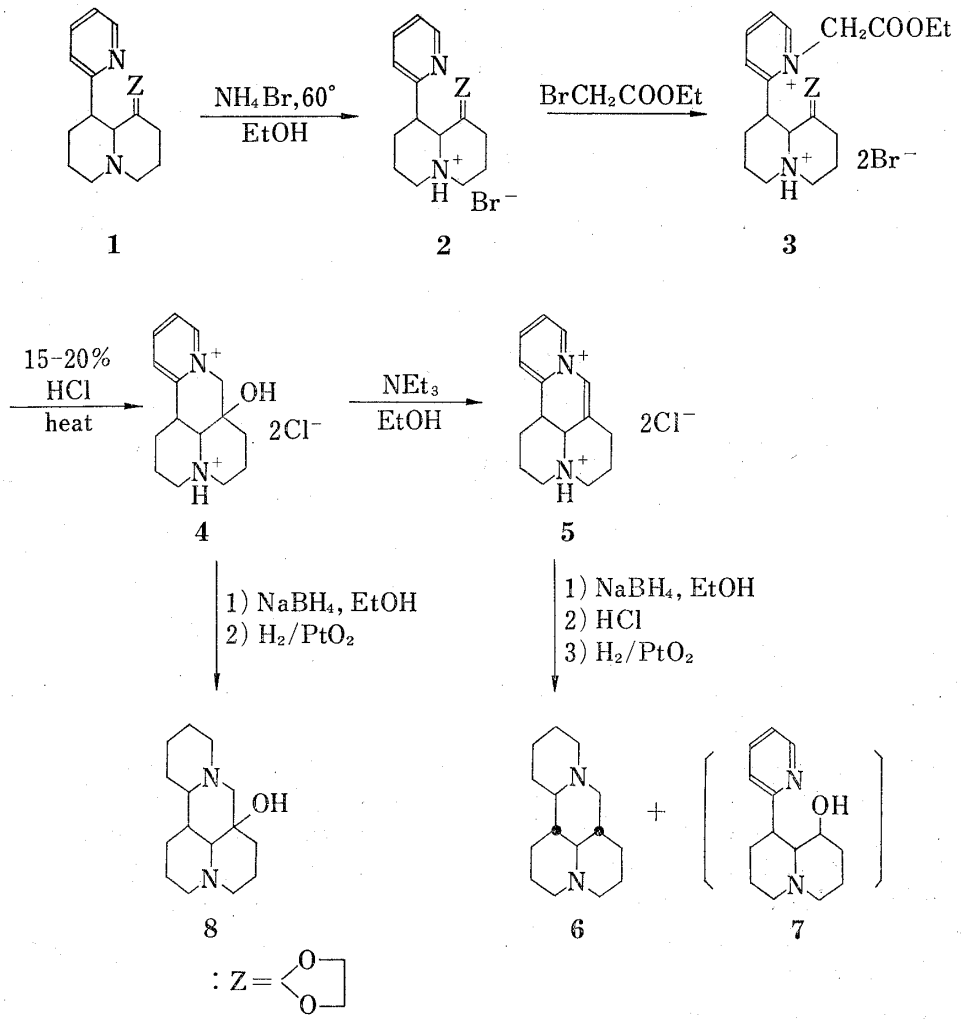


Chart 1

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, $C_{15}H_{26}ON_2 \cdot C_{12}H_6O_{14}N_6$, 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 neccessarily 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 τ 4.5—4.3 ($\overset{+}{\text{N}}$–$\underline{\text{C}}\text{H}_2$–) 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 τ 8.70 (3H, t) and 5.62 (2H, q), pyridinium methylene protons at τ 4.50—4.20 (2H, m) and four protons at C_3–C_6 of pyridinium ring at τ 2.15—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-ethoxycarbonyl-17-hydroxyallomatridine (**11**) was obtained in place of **6** together with **7**.

Compound **11** is a light yellow viscous oil, bp 200—220° (1 mmHg) (bath temp.), and formed a dipicrate, $C_{18}H_{30}O_3N_2 \cdot C_{12}H_6O_{14}N_6$, 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 ($M^+ - H_2O$), 275 ($M^+ - H_2O - C_2H_5$), 249 ($M^+ - CO_2C_2H_5$) and 231 ($M^+ - H_2O - CO_2C_2H_5$). Its IR spectrum exhibited a hydroxy band, Bohlmann bands and ester carbonyl band at 3550, 2975—2795 and 1735 cm^{-1}, respectively, and the NMR spectrum showed ethyl protons at τ 8.75 (3H, t) and 5.75 (2H, q) and a hydroxy proton exchangeable with D_2O at τ 6.14 (1H, b.s.). These observations agreeded 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

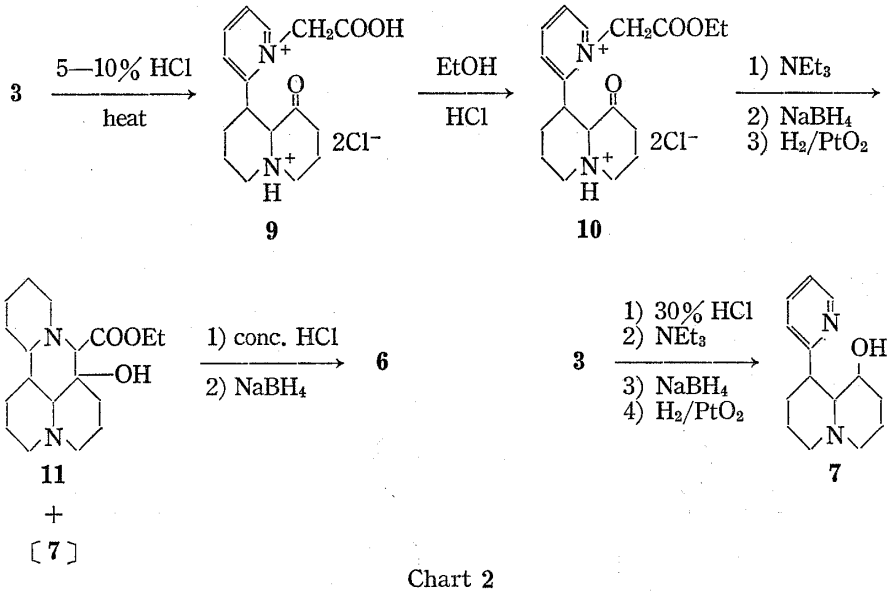


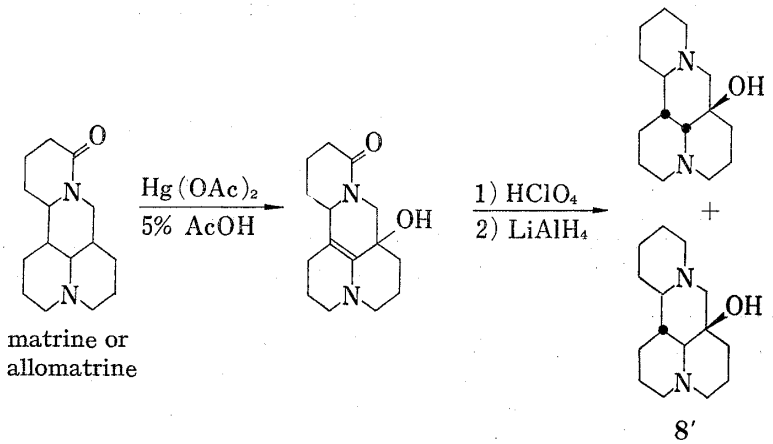
Chart 2

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 ($C_{14}H_{18}ON_2 \cdot C_{12}H_6O_{14}N_6$) 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 pillars, mp 170—172° in 52% yield. Its molecular formula was established as $C_{15}H_{19}ON_3$ 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 τ 6.99, 2.18—3.00 and 1.45—1.60 which were reasonably assinged to a hydroxy proton, C_3-, C_4- and C_5-protons of the pyridine ring, and its C_6-proton, respectively.

Compound **13** was hydrogenated in dioxane over Raney nickel at an initial hydrogen pressure of 100 atm. at 190° to give 17-hydroxyallomatridine (**8**) colorless pillars, mp 125—128° in 34% yield. Its analytical values and the parent peak of the mass spectrum (M^+, *m/e* 249) agreeded with the molecular formula $C_{15}H_{26}ON_2$; it formed a dipicrate, $C_{15}H_{26}ON_2 \cdot C_{12}H_6O_{14}N_6$, yellow needles, mp 221—223°. The IR spectrum of **8** exhibited a hydroxy band at 3350 cm^{-1} and its NMR spectrum showed a one-proton singlet exchangeable with D_2O at τ 6.83.

Although these observations evidently support the assigned structure of **8**, it is quite curious that 17-hydroxy base **8** was obtained instead of *dl*-allomatridine **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.

Bohlmann, *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.[8]

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. Bohlmann, *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.

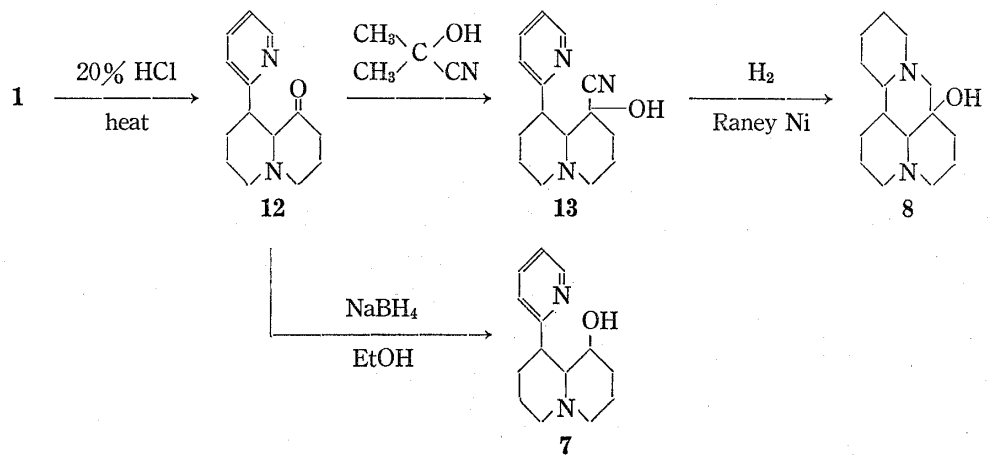


Chart 3

Experimental[9]

Preparation of 1,1-Ethylenedioxy-9-[2-(N-ethoxycarbonylmethyl)pyridinium]yl-5H-quinolizidinium Dibromide (3) from 1,1-Ethylenedioxy-9-(pyridyl)quinolizidine (1)——A solution of **1** (0.5 g, 0.002 mole) and NH_4Br (0.025 g, 0.0023 mole) in EtOH–H_2O (1 : 1 v/v, 100 ml) was heated at 60° for 3 hr to generate 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 Bohlmann bands in its IR spectrum.

A solution of **2** thus obtained and ethyl bromoacetate (2 g, 5 equiv.) in anhyd. EtOH (10 ml) was refluxed for 40 hr. Evaporation of 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 ν_{max}^{Nujol} cm^{-1}: 1755 (ester C=O), 1625 (C=N). NMR τ (D_2O): 8.80 (3H, t, J=7.0 Hz, $-CO_2CH_2\underline{CH_3}$), 6.00—5.50 (4H, m, $-O\underline{CH_2}\underline{CH_2}O-$), 4.40 (2H, q, J=7.0 Hz, $-CO_2\underline{CH_2}CH_3$), 2.25—1.10 (4H, m, C_3–, C_4–, C_5–, and C_6–H of pyridinium ring). 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° (EtOH–CH_3COCH_3). *Anal.* Calcd. for $C_{20}H_{29}O_4N_2 \cdot C_{12}H_5O_{14}N_6 \cdot 1/2CH_3COCH_3$: 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 ($-COOC_2\underline{H_5}$) or ethylene protons ($-OC\underline{H_2}-C\underline{H_2}O-$) were observed in the NMR spectrum.

A solution of **4** and NEt_3 (2 g, 4.5 equiv.) in anhyd. EtOH (100 ml) was refluxed for 5 hr (the formation of **5**), and the cooled mixture was consecutively stirred with $NaBH_4$ (1.5 g) with ice-cooling. The solvent and excess 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-

8) F. Bohlmann, W. Weise, D. Rahtz, and C. Arndt, *Chem. Ber.*, **91**, 2176 (1958).
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_2O, shaken with AgCl (1 g) for 30 min to remove Br^- as AgBr and filtered. 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**: *dl*-Allomatridine, 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 *d*-allomatridine[7] obtained from naturally occurring *d*-matrine. Dipicrate: yellow needles, mp 262—263° (acetone). *Anal.* Calcd. for $C_{15}H_{26}N_2 \cdot C_{12}H_6O_{14}N_2 \cdot 1/2CH_3COCH_3$: C, 47.44; H, 4.85; N, 15.54. Found: C, 47.20; H, 4.68; N, 15.26. It was proved identical with an authentic sample of the dipicrate of *d*-allomatridine[7] by admixture and the comparison of their IR spectra.

Product **7**: 1-Hydroxy-9-(2-pyridyl)quinolizidine; dipicrate, 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-Hydroxyallomatridine (8) *via* 4——Pyridinium salt **3** prepared from **1** (0.5 g, 0.002 mole) and NH_4Br (0.025 g, 0.0023 mole) was heated with 20% HCl (20 ml), and treated successively with $NaBH_4$ (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 0.02 g of 17-hydroxyallomatridine (**8**) as a light yellow oil. Dipicrate: yellow needles, mp 221—223° (acetone). *Anal.* Calcd. for $C_{15}H_{19}ON_2 \cdot C_{12}H_6O_{14}N_6$: C, 45.76; H, 4.52; N, 15.82. Found: C, 45.89; H, 4.09; N, 15.67. Its identity was established by admixture of the dipicrate with authentic sample mentioned later.

Transformation of 3 to 8-Ethoxycarbonyl-17-hydroxyallomatridine (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 ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR τ (D_2O): 4.5—4.3 (2H, m, $\overset{+}{\rangle}N-CH_2-$); no signal due to $-C_2H_5$ or $-CH_2CH_2-$ 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 ν_{max}^{Nujol} cm^{-1}: 1745 (ester C=O), 1715 (C=O). NMR τ (D_2O): 8.70 (3H, t, J=7.0 Hz, $-COOCH_2C\underline{H}_3$), 5.62 (2H, q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$), 4.50—4.20 (2H, m, $\overset{+}{\rangle}N-C\underline{H}_2-$), 2.15—1.00 (4H, protons of pyridinium ring).

An anhyd. EtOH (100 ml) solution of the crude **10** and NEt_3 (2 g, *ca.* 4.5 equiv.) was refluxed for 5 hr, and the cooled reaction mixture was treated with $NaBH_4$ (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-hydroxyallomatridine, a light yellow oil, bp 200—220° (1 mmHg) (bath temp.), 2.5% as the dipicrate. IR ν_{max}^{neat} cm^{-1}: 3550 (OH), 2950—2795 (Bohlmann bands), 1735 (ester C=O). NMR τ ($CDCl_3$): 8.75 (3H, t, J=7.0 Hz, $-COOCH_2C\underline{H}_3$), 6.14 (1H, m, OH), 5.75 (2H, q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$). Mass Spectrum *m/e*: 322 (M^+), 304 (M^+-H_2O), 276 ($M^+-H_2O-C_2H_5$), 249 ($M^+-COOC_2H_5$), 231 ($M^+-H_2O-COOC_2H_5$). Dipicrate: yellow needles, mp 233—234° (EtOH–acetone). *Anal.* Calcd. for $C_{18}H_{30}O_3N_2 \cdot C_{12}H_6O_{14}N_6$: 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 g, 2%. 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° for 5 hr. The residue obtained by evaporation of HCl was neutralized with 10% Na_2CO_3 and extracted with ether. Dry HCl gas was passed in the ether solution, ether was evaporated and the residue was treated with $NaBH_4$ (0.1 g) in anhyd. EtOH (50 ml) to give a minute amount of an oil. This product gave 5 mg of a dipicrate, yellow needles, mp 262—263°, which was proved identical with the dipicrate of *dl*-allomatridine **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, $NaBH_4$ 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**. Dipicrate: mp 220—221°. It was proved identical with a sample prepared from **12** by the admixture of their dipicrates.

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° (0.5 mmHg) (bath temp.). IR ν_{max}^{neat} cm^{-1}: 1725 (C=O). Dipicrate: yellow needles, mp 195—196.5° (acetone). *Anal.* Calcd. for $C_{14}H_{18}ON_2 \cdot C_{12}H_6O_{14}N_6$: 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 $NaBH_4$ (0.05 g) for 12 hr to give 0.05 g (70%) of **7**, colorless granules, mp 135° (hexane), bp 200° (0.007 mmHg) (bath temp.). *Anal.* Calcd. for $C_{14}H_{20}ON_2$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.20; H, 8.50;

N, 11.98. IR ν_{max}^{Nujol} cm^{-1}: 3550 (OH), 1605 (pyridine). NMR τ ($CDCl_3$): 3.00—2.20 (3H, m, C_3–, C_4–, C_5–H of pyridine), 1.55—1.35 (1H, m, C_6–H of pyridine). Mass Spectrum *m/e*: 232 (M^+). Dipicrate: yellow needles, mp 220—221° (EtOH–acetone). *Anal.* Calcd. for $C_{14}H_{20}ON_2 \cdot C_{12}H_6O_{14}N_6$: 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)quinolizidine (13)——A solution of **12** (0.23 g, 0.001 mole) and acetone cyanohydrin (0.34 g, 0.04 mole) in CH_2Cl_2 (10 ml) was stirred a room temperature for 48 hr to give 0.132 g (52%) of **13**, colorless pillars, mp 170—172° (isopropyl ether–EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1600 (pyridine). NMR τ ($CDCl_3$): 6.99 (1H, s, OH), 3.00—2.18 (3H, m, C_3–, C_4–, C_5–H of pyridine), 1.60—1.45 (1H, m, C_6–H of pyridine ring). Mass Spectrum *m/e*: 257 (M^+). *Anal.* Calcd. for $C_{15}H_{19}ON_3$: C, 70.00; H, 7.44; N, 16.33. Found: C, 69.64; H, 7.68; N, 15.98.

Synthesis of 17-Hydroxyallomatridine (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 pillars, mp 125—128° (isopropyl ether–ether). IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH). NMR τ ($CDCl_3$): 6.83 (1H, s, OH). Mass Spectrum *m/e*: 250 (M^+). *Anal.* Calcd. for $C_{15}H_{26}ON_2$: 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 $C_{15}H_{19}ON_2 \cdot C_{12}H_6O_{14}N_6$: C, 45.76; H, 4.52; N, 15.82. Found: C, 45.89; H, 4.09; N, 15.67.

Acknowledgement The authors are grateful to Prof. S. Okuda, Institute of Applied Microbiology, University of Tokyo, and Prof. S. Fukushima, Shizuoka College of Pharmacy, for their generous gift of *d*-allomatridine.