[CONTRIBUTION FROM THE INSTITUTE OF APPLIED MICROBIOLOGY, UNIVERSITY OF TOKYO]

Studies on the Synthesis of Matrine. I. The Total Synthesis of Nordehydro-α-matrinidine and Dehydro-α-matrinidine

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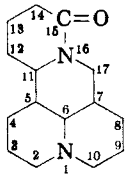
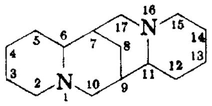
2-Methylperhydropyrido[3,4,5-*i,j*]quinolizine (9-methyl-9-azahexahydrojulolidine) obtained from 1-methyl-3,5-bis(β-ethoxycarbonylethyl)-4-piperidone in a good yield, was converted to 4,5,6,8,9,10-hexahydropyrido[3,4,5-*i,j*]quinolizine (9-azajulolidine) on dehydrogenation. This substance and its methyl derivative were identified respectively with nordehydro-α-matrinidine and dehydro-α-matrinidine, the decomposition products of matrine.

An alkaloid, matrine (I) was first isolated from the root of Japanese *Sophora flavescens* by N. Nagai[3] in 1889, and since then it has been isolated[4] also from various European species of Sophora plants. Studies on the structure of matrine were carried out by H. Kondo and his school[5] in Japan and the structural formula[6] was presented in 1936.

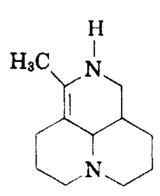
It is known that the structurally defined lupine alkaloids with 15 carbon atoms possess the ring system of either matrine or sparteine (II). Matrine and leontine[7] possess the former ring system and sparteine, α- and β- isosparteine, lupanine, α-isolupanine, anagyrine, thermopsine, and aphylline possess the latter system.



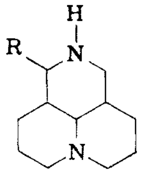
I[8]



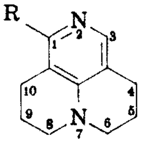
II[9]



III



IVa R = H
IVb R = CH₃



Va R = H
Vb R = CH₃

It is considered that a matrine ring would be formed when the C_9-C_{11} bond of sparteine ring is cleaved and then recyclized between C_5 and C_{11}.

The proof of this C_5-C_{11} bond in the matrine ring was made by ring cleavage with cyanogen bromide of the dihydro derivative of α-matrinidine (III),[10] one of the soda-lime distillation products of potassium matrinate. The secondary-secondary diamine formed by this ring cleavage lost ten hydrogen atoms on dehydrogenation to give a compound $C_{12}H_{14}N_2$, and this substance was oxidized to quinolinic acid.[11,12] From such results, it was concluded that $C_{12}H_{14}N_2$ would be a 1,6-naphthylidine derivative and that dihydro-α-matrinidine would then be 1-methylperhydropyrido [3,4,5-*i,j*] quinolizine (IVb).[13] It follows therefore, that the dehydro-α-matrinidine should have the structure of 1-methyl-4,5,6,8,9,10-hexahydropyrido [3,4,5-*i,j*]quinolizine (Vb).[13] These structures are also supported by the fact that Vb and its demethyl compound, *i.e.*, nordehydro-α-matrinidine (Va),[14] are optically inactive and that their ultraviolet

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(3) Nagai and Tawara, *J. Pharm. Soc. Japan*, 9, 54 (1889).

(4) Plugge, *Arch. Pharm.*, **233**, 441 (1895); Orekhov and Proskurnina, *Ber.*, **68**, 429 (1935); Orekhov, Proskurnina, and Konovalova, *Ber.*, **68**, 431 (1935); Briggs and Ricketts, *J. Chem. Soc.*, 1795 (1937); Briggs and Taylor, *J. Chem. Soc.*, 1206 (1938); Briggs and Russel, *J. Chem. Soc.*, 555 (1942); Briggs and Mangan, *J. Chem. Soc.*, 1889 (1948).

(5) Manske and Holmes, *The Alkaloids*, Vol. III, Academic Press Inc., New York, 1953, p. 178.

(6) Tsuda, *Ber.*, 69, 429 (1936), and *cf.* Footnote (5).

(7) Platanov and Kuzovkov, *J. Gen. Chem.* (*U.S.S.R.*), **26**, 283 (1956).

(8) The numbering of the matrine ring followed that of sparteine, for convenience.

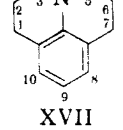
(9) This numbering follows that of Clemo, *J. Chem. Soc.*, 644 (1933).

(10) Oily substance which seems to be considerably pure. Infrared spectrum bands: $\rangle C{=}C\langle$ (1661 cm.$^{-1}$), bonded NH (3300 cm.$^{-1}$), free NH (3500 cm.$^{-1}$).

(11) Kondo, Ochiai, Tsuda, and Yoshida, *Ber.*, **68**, 570 (1935).

(12) K. Tsuda and K. Murakami, *Pharm. Soc. Japan*, **57**, 307 (1937) (Abstract in German).

(13) Ring Index name. A simpler, derived name for IVb and Vb would respectively be 8-methyl-9-azahexahydrojulolidine and 8-methyl-9-azajulolidine, based on the long used trivial name "julolidine" for XVII [*cf.* Reissert, *Ber.*, **28**, 841 (1891)]; Glass and Weissberger, *Org. Syntheses*, Coll. Vol. **3**, p. 504 (1954); Braunholtz and Mann. *J. Chem. Soc.*, 393 (1955), combined with the Ring Index numbering.



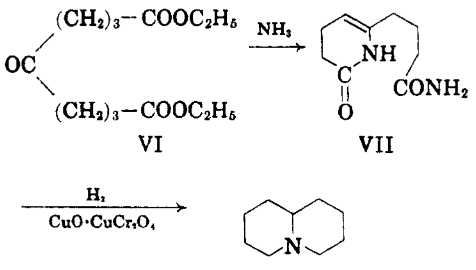
XVII

(14) Ochiai and Okuda, *Pharm. Bull.* (*Japan*), **1**, 266 (1953) (*Chem. Abstr.*, **49**, 8316 (1955)).

spectra exhibit specific absorption for 4-aminopyridine.[15]

The present communication deals with the syntheses of optically inactive Va and Vb of the α-matrinidine series. By the present determination of the structures of these compounds, the ring system of this series has been established and no longer leaves room for any doubt about the C_5–C_{11} bond in matrine. At the same time, the synthesis of Vb has opened a way for the synthesis of matrine or its stereoisomers.

The crystalline product, m.p. 256°, obtained from a mixture of diethyl 5-oxoazelate (VI)[16] and 28% ammonia water on standing at room temperature, gave analytical results corresponding to the molecular formula $C_9H_{14}N_2O_2$. From the ultraviolet absorption spectrum at 203 mμ (ϵ 13000) and infrared spectrum frequency bands for NH and NH_2 (3236 and 3086 cm.$^{-1}$), $-CONH_2$ and $-CONH-$ (1675 and 1638 cm.$^{-1}$), and for $>C{=}CH-$ (791 cm.$^{-1}$), this substance is found to be a Δ^5-piperidone compound (VII). This substance does not absorb hydrogen on catalytic hydrogenation at ordinary pressure but on high-pressure hydrogenation with copper chromite catalyst provides quinolizidine (VIII).[16,17] The formation of VII from VI resembles that of a Δ^5-piperidone from ammonia and 2-acetoglutarate.[18]



VI VII VIII

1 - Methyl - 3,5 - bis(β-ethoxycarbonylethyl)-4-piperidone (IXc) was prepared by the following process in order to carry out the same reaction. A Mannich reaction of ethyl 4-oxo-1,3,5,7-heptane tetracarboxylate,[16] formaldehyde, and methylamine hydrochloride afforded 1-methyl-3,5-diethoxycarbonyl-3,5-bis(β-ethoxycarbonylethyl)-4-piperidone (IXa) in 43% yield. Esterification of the dicarboxylic acid (IXb), obtained by heating IXa with hydrochloric acid, finally, afforded an ester (IXc), m.p. 45–46°.

On standing with ammonia water IXc, analogous to VI, was converted to (X),[19] m.p. 270° (decomp.), which possesses the molecular formula $C_{12}H_{19}N_3O_2$. The ultraviolet absorption maximum at 203 mμ (ϵ 13000) and the infrared spectrum exhibiting absorption bands for NH and NH_2 (3205 and 3086 cm.$^{-1}$) and for $-CONH_2$ and $-CONH-$ (1678 and 1661 cm.$^{-1}$) are essentially identical with those of VII. It is certain therefore that this substance possesses the structure represented by X. High-pressure hydrogenation of X with copper chromite catalyst affords a base, $C_{12}H_{22}N_2$, soluble in water, in over 80% yield calculated from IXc. This base is a tertiary-tertiary diamine with dissociation constants of pK_{b1} 4.39 and pK_{b2} 7.25, melts at 39–40°, and is hydroscopic. For purification of this base, it was converted to its monohydrate, m.p. 74–75°. The similarity in infrared absorption between this base and quinolizidine proves the fact that it is 2-methyl-perhydropyrido-[3,4,5-*i,j*] quinolizine (9-methyl-9-azahexahydrojulolidine) (XI).

On the other hand, the foregoing reaction sometimes failed to yield XI and only its 8-oxo compound (XII) would be formed, although the cause for such abnormal behavior is still uncertain. In such a case, a large amount of red cuprous oxide precipitated. The monohydrate of XII melts at 90–91° and exhibits infrared absorption bands at 1620 cm.$^{-1}$ (lactam carbonyl, $-CO-N{=}$). The base obtained by the lithium aluminum hydride reduction of XII does not coincide with XI. For example, when the reduction product is purified through its perchlorate and the liberated base is submitted to distillation, an oily substance is obtained. The analytical values of its picrolonate and chloroaurate give the same molecular formula as that of XI, but the mixed fusion with the corresponding salts of XI shows depression of the melting point. It is therefore assumed that the lithium aluminum hydride reduction product of XII is a stereoisomer[20] of XI.

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(15) Okuda, *Pharm. Bull.* (*Japan*), **4,** 257 (1956).

(16) Leonard and Goode, *J. Am. Chem. Soc.*, **72,** 5404 (1950).

(17) Winterfeld and Holschneider, *Ann.*, **499,** 109 (1932); Clemo, Ramage, and Raper, *J. Chem. Soc.*, 2959 (1932); Diels and Alder, *Ann.*, **505,** 103 (1933); Clemo, Metcalf, and Raper, *J. Chem. Soc.*, 1429 (1936); Boekelheide and Rothschild, *J. Am. Chem. Soc.*, **71,** 879 (1949), **69,** 3149 (1947); Doering and Weil, *J. Am. Chem. Soc.*, **69,** 2461 (1947).

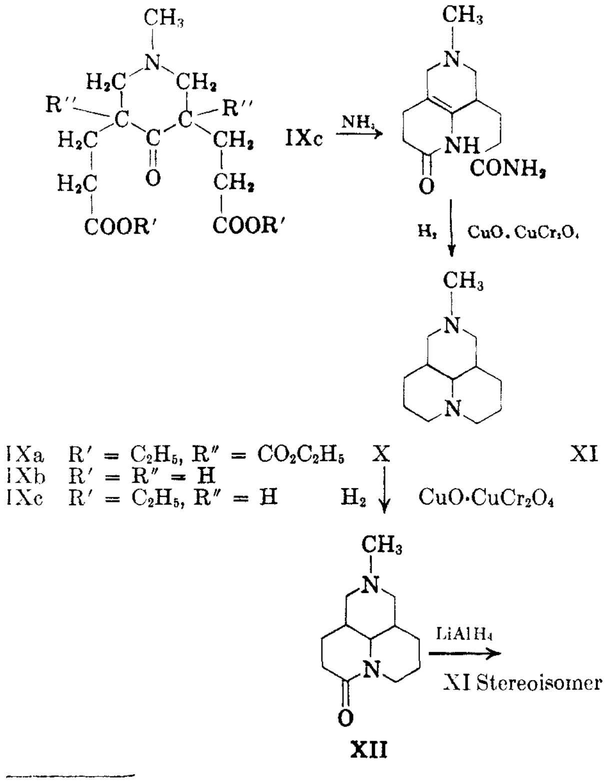
(18) Emery, *Amer. Chem. Jour.*, **13,** 352 (1891); Clemo and Welch, *J. Chem. Soc.*, **131,** 2624 (1928).

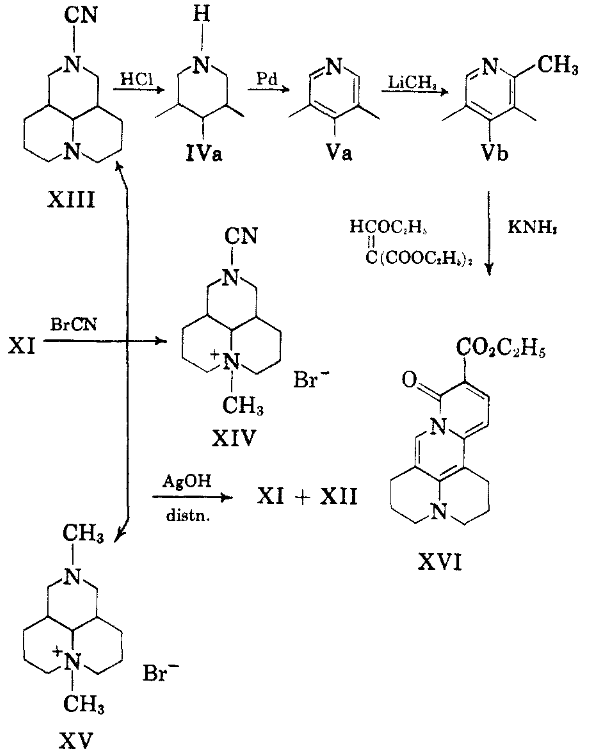
(19) X crystallizes from methanol only when the starting material used (IXc) is extremely pure. Normally, it is obtained as an amorphous solid but such solid can be used for conversion to XI.

(20) There are two kinds of meso compounds and one racemic compound as the stereoisomeric forms of XI. A crystalline salt suitable for the optical resolution of XI could not be found. Only one kind of crystalline dibenzoyl-*d*-tartrate of the N-cyanide (XIII) was obtained, but it affords an optically inactive free base and seemed to be a meso compound. XI (m.p. 39–40°) which seems to have the same configuration as XIII is also probably a meso compound, but nothing definite can be said at this stage. It is interesting to note that the high-pressure hydrogenation (catalyst, $CuO.CuCr_2O_4$) of 2,6-bis(β-ethoxycarbonylethyl)cyclohexanone oxime yields racemic hexahydrojulolidine [Leonard and Middleton, *J. Am. Chem. Soc.*, **74,** 5114 (1952)] while the hydrogenation of julolidine yields racemic hexahydro compound in amount larger than that of the meso hexahydro compound [Protiva and Prelog, *Helv. Chim. Acta*, **32,** 621 (1949)]. It is hoped that a more detailed report will be made on the conformation of XI after accumulation of more experimental data.

Reaction of XI with an equimolar amount of cyanogen bromide affords the N-cyanide (XIII) in 62% yield, with the formation of the methobromides of XI and XIII (XIV), (XV). These methobromides, when treated with silver oxide, respectively produced methohydroxides from which XI and XIII were regenerated by distillation under reduced pressure.[21]

The secondary amine (IVa), obtained from XIII by heating with hydrochloric acid, affords 4,5,6,8,9,10 - hexahydropyrido[3,4,5 - *i,j*]quinolizine (9 - azajulolidine) (Va) when heated with palladium asbestos at 250–270°. Va, its picrate, and its hydrobromide did not show any depression of the melting point on admixture respectively with the samples of nordehydro-α-matrinidine[22] derived from a natural source and its corresponding salts. The infrared spectrum of Va possesses absorption bands at 1588 and 1516 cm.$^{-1}$ (pyridine ring) and the ultraviolet spectrum of its hydrobromide and R_f value (0.62) on a paper chromatogram coincide respectively with those of the naturally derived compounds. Therefore, it was proved that the synthetic product was identical with nordehydro-α-matrinidine. When Va is heated with methyllithium in toluene, α-methylation of the pyridine ring[23] occurs and an oily Va is obtained. Mixed fusion and infrared spectra of picrates proved that Vb was identical with natural dehydro-α-matrinidine.





Condensation of Vb, with ethoxymethylenemalonic ester[24] in ether in the presence of sodium amide afforded an oily substance with a strong fluorescence, from which an orange yellow crystalline product, m.p. 194–195°, was obtained. The analytical values of this substance correspond exactly to those of XVI and the ultraviolet absorption maxima at 272, 284, and 409 mμ, and the infrared absorption bands at 1715 (ester carbonyl), 1661 (quinolizone carbonyl), 1642, 1585, 1536, 1515, 1451 (quinolizone double bond), and 1287 cm.$^{-1}$ (≡C–O–) indicate the presence of an α-ethoxycarbonylquinolizone ring.[24]

EXPERIMENTAL[25]

Δ⁶-6-(γ-Amidocarbonylpropyl)-2-piperidone (VII). A mixture of 15 g. of diethyl 5-oxoazelate[16] (VI) and 150 ml. of 28% ammonia water was allowed to stand for 5 days at room temperature, with occasional agitation. After distilling

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[21] Hofmann degradation of matrine or methyl N-methylmatrinate methiodide results in regeneration of the original base with liberation of methanol (Nagai and Kondo, *J. Pharm. Soc. Japan*, **23**, 993, 1109, 1211 (1903)).

[22] The data given in the reference literature of Footnote (14) are only for the picrate and hydrobromide of Va, and are not for the free amine. The nordehydro-α-matrinidine, m.p. 69–70°, was therefore prepared by the demethylation of dehydro-α-matrinidine, derived from matrine, by the method given in the literature 14.

[23] Ziegler and Zeiser, *Ber.*, **63**, 1847 (1930); Walters and McElvain, *Ber.*, **55**, 4626 (1933); Bohlmann, Englisch, Politt, Sanders, and Weise, *Ber.*, **88**, 1831 (1955).

[24] Bohlmann, Ottawa, and Keller, *Ann.*, **587**, 162 (1954); Bohlmann, Englisch, Politt, Sanders, and Weise, *Ber.*, **88**, 1831 (1955).

[25] All melting points and boiling points are uncorrected. Microanalyses were done by Mr. T. Onoe of the Takamine Research Laboratory, Sankyo Co., Ltd. Infrared spectra were measured as paraffin mulls on a Perkin-Elmer Model 21 double-beam recording spectrophotometer and were interpreted by Mr. H. Shindo of the Takamine Research Laboratory, Sankyo Co., Ltd.

off the ammonia water under reduced pressure, the residue was recrystallized from methanol to colorless plates, m.p. 255–256° (decomp.). Yield, 6 g. (57%).

Anal. Calc'd for $C_9H_{14}N_2O_2$: C, 59.34; H, 7.69; N, 15.38. Found: C, 59.13; H, 7.74; N, 15.58.

VII is insoluble in benzene, ether, and chloroform, sparingly soluble in ethanol, acetone, and ethyl acetate, and easily soluble in water and methanol. $\lambda_{max}^{H_2O}$ 203 mμ (ε 13000).

Quinolizidine (VIII). A mixture of 9.3 g. of VII, 5.3 g. of copper chromite, and 200 ml. of dioxane was shaken in hydrogen at 245° and 230 atmospheres for 1 hour. The catalyst was filtered off, dioxane was evaporated under reduced pressure, and the residue was dissolved in water. The solution was saturated with potassium carbonate and the base was taken up in ether. The ether residue was distilled to collect a fraction boiling at 184°. Yield, 3.5 g. (49%).

Picrate: Colorless plates, m.p. 197° (from acetone).

Anal. Calc'd for $C_9H_{17}N{\cdot}C_6H_3N_3O_7$: C, 48.91; H, 5.45; N, 15.21. Found: C, 49.23; H, 5.42; N, 15.55.

Chloroaurate: Yellow needles, m.p. 168° (from water).

The picrate and the chloroaurate here obtained showed no depression of the melting point on admixture with authentic samples prepared by the method given in the literature,[16] and the infrared spectra of these bases were in good agreement, exhibiting absorption bands at 1185, 1117, and 1095 cm.$^{-1}$ (tertiary nitrogen of $\mathrm{C{-}\underset{\substack{|\\ C}}{N}{-}C}$).[26]

1-Methyl-3,5-diethoxycarbonyl-3,5-bis(β-ethoxycarbonylethyl)-4-piperidone (IXa). A solution of 120 g. of ethyl 4-oxoheptane-1,3,5,7-tetracarboxylate, 51 g. of 30% aqueous formaldehyde, 25 g. of methylamine hydrochloride, and 33 g. of potassium hydrogen carbonate in 70% ethanol was allowed to stand at 23–25° for 4 days. The solvent was evaporated under reduced pressure at below 50°; the residue was dissolved in 10% hydrochloric acid, and insoluble material was removed by ether. The solution was neutralized with potassium carbonate, then basified, and the oily layer was taken up in ether. The ether layer was washed several times with water, dried over sodium sulfate, and ether was evaporated. The residue was distilled under reduced pressure to give IXa, b.p. 180°/0.1 mm. Yield, 57 g. (43%).

Meconate: Colorless plates, m.p. 149–150° (from ethanol).

Anal. Calc'd for $C_{22}H_{35}NO_9{\cdot}C_7H_4O_7$: C, 53.0; H, 5.90; N, 2.15. Found: C, 53.13; H, 5.99; N, 2.31.

1-Methyl-3,5-bis(β-ethoxycarbonylethyl)-4-piperidone (IXc). A solution of 11 g. of IXa in a mixture of 33 ml. of water and 87 ml. of 37% hydrochloric acid was refluxed for 25 hours. The crystalline residue, left after the evaporation of solvent under reduced pressure, gave the hydrochloride of IXb on washing with ethanol. Yield, 6.5 g. (90%). Recrystallization from ethanol gave colorless needles, m.p. 187–189°.

Anal. Calc'd for $C_{12}H_{19}NO_5{\cdot}HCl$: C, 49.06; H, 6.81; N, 4.70. Found: C, 48.86; H, 7.13; N, 4.91.

A solution of 6.5 g. of the hydrochloride of IXb in 75 ml. of anhydrous ethanol containing 0.7 ml. of sulfuric acid was refluxed for 25 hours. Ethanol was evaporated under reduced pressure, the residue was dissolved in 10% hydrochloric acid, and the solution was basified with potassium carbonate. This was extracted with ether, the ether layer was dried over sodium sulfate, and the solvent was removed. The residue was distilled under reduced pressure to yield 6 g. (90%) of IXc, b.p. 150–153°/0.1 mm. Recrystallization from petroleum ether afforded colorless prisms, m.p. 45–46°.

Anal. Calc'd for $C_{16}H_{27}NO_5$: C, 61.34; H, 8.62; N, 4.47. Found: C, 61.23; H, 8.62; N, 4.40. Infrared absorption: ν_{max} cm.$^{-1}$ 1731 (ester carbonyl), 1701 (ketone), 1183 ester $\equiv$C—O—).

Picrate: Yellow needles, m.p. 132° (from ethanol).

Anal. Calc'd for $C_{16}H_{27}NO_5{\cdot}C_6H_3N_3O_7$: C, 48.8; H, 5.5; N, 10.33. Found: C, 48.78; H, 5.69; N, 10.25.

Δ^9-6-Methyl-8-(β-aminocarbonylethyl)perhydro-1,6-naphthylid-2-one (X). A mixture of 19 g. of IXc and 190 ml. of 28% ammonia was agitated at room temperature until it was completely in solution and this was allowed to stand for one day. Ammonia water was distilled off under reduced pressure and the residue was dried at 120° for 30 minutes *in vacuo*. The amorphous solid (15 g.) was recrystallized from methanol to yield X as colorless plates, m.p. 269–270° (decomp.). It was insoluble in ether and easily soluble in water. $\lambda_{max}^{H_2O}$ 203 mμ (ε 13000).

Anal. Calc'd for $C_{12}H_{19}N_3O_2$: C, 60.75; H, 8.01; N, 17.72. Found: C, 61.12; H, 8.17; N, 17.93.

2-Methylperhydropyrido[3,4,5-i,j]quinolizine (XI). A mixture of 15 g. of amorphous X and 10 g. of copper chromite in 200 ml. of dioxane was submitted to hydrogenation at 250° and 225 atmospheres for 1 hour. The reaction product was 9.2 g. (84%) of XI, b.p. 70°/0.01 mm., m.p. 39–40°.

Anal. Calc'd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.34; N, 14.42. Found: C, 73.90; H, 11.00; N, 14.59.

On addition of a small amount of water, XI dissolved exothermically. The product which separated out of this aqueous solution was recrystallized from ether to colorless prisms, m.p. 74–75°. After drying *in vacuo* at 30°, this substance was distilled to afford the oily anhydride. This substance soon crystallized, m.p. 39–40°, but returned to the hydrate when left in air.

Chloroaurate: Yellow needles, m.p. 210–211° (from water).

Anal. Calc'd for $C_{12}H_{22}N_2{\cdot}2HCl{\cdot}2AuCl_3$: C, 16.55; H, 2.99; N, 3.29. Found: C, 16.38; H, 3.02; N, 2.99.

Dimethiodide: prisms, m.p. 286° (decomp.) (from ethanol).

Dipicrate: m.p. 277° (decomp.) (from acetone).

Dipicrolonate: yellow needles, m.p. 251° (decomp.) (from ethanol).

Dihydrochloride: needles, m.p. 293° (decomp.) (from ethanol).

Dihydrobromide: needles, m.p. 286° (decomp.) (from ethanol).

2-Methyl-8-oxoperhydropyrido[3,4,5-i,j]quinolizine (XII). A mixture of 28 g. of amorphous X, 6.5 g. of copper chromite, and 100 ml. of dioxane was hydrogenated at 110 atmospheres and 230–235° for 1 hour. A large amount of cuprous oxide precipitated out. The base obtained was distilled to yield 7 g. of an oil, b.p. 115–119°/0.5 mm., which later solidified and was recrystallized from ether to the monohydrate of XII, m.p. 90–91°.

Anal. Calc'd for $C_{12}H_{20}N_2O{\cdot}H_2O$: C, 63.7; H, 9.75; N, 12.4. Found: C, 63.95; H, 9.68; N, 12.15.

Picrate: m.p. 275° (decomp.).

Anal. Calc'd for $C_{12}H_{20}N_2O{\cdot}C_6H_3N_3O_7$: C, 49.43; H, 5.26; N, 16.01. Found: C, 49.35; H, 5.20; N, 16.35.

Chloroaurate: m.p. 215° (decomp.); *picrolonate:* m.p. 252° (decomp.).

Lithium aluminum hydride reduction of XII. After removal of the crystal-water of XII monohydrate by heating in benzene the anhydride (280 mg.) was obtained by distillation. It was dissolved in 10 ml. of a mixture of anhydrous ether and benzene (1:1) and this solution was added to a stirred solution of 102 mg. of lithium aluminum hydride in 50 ml. of ether. After refluxing for 3 hours, 4 ml. of water was added to the mixture and the ether layer was separated. The aqueous layer was basified with a solution of 3 g. of potassium hydroxide in 5 ml. of water and extracted with ether. The combined ether solution was dried, evaporated to dryness, and the residue was purified as the perchlorate from ethanol. The free base distilled at 140–150° (bath temp.) at 3 mm., tended to color, was soluble in water, and failed to undergo crystallization.

Chloroaurate: Yellow needles, m.p. 207–208° (decomp.) (from water).

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(26) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen & Co., Ltd. London (1954), p. 221.

Dipicrate: Yellow leaflets, m.p. 272° (from water).

Dihydrobromide: Amorphous.

Dipicrolonate: m.p. 237–239° (decomp.) (from ethanol).

Anal. Calc'd for $C_{12}H_{22}N_2 \cdot C_{20}H_{16}N_8O_{10}$: C, 53.00; H, 5.25; N, 19.38. Found: C, 53.20; H, 5.12; N, 19.74.

All of these chloroaurate, picrate, and picrolonate salts showed marked depression of the melting point on admixtures with the corresponding salts of XI and XII.

2-Cyanoperhydropyrido[3,4,5-i,j]quinolizine (XIII). The monohydrate of XI was dissolved in benzene and water was removed by distillation of the azeotropic mixture. The anhydrous residue was distilled under reduced pressure to afford the anhydrous XI and this was dissolved in 70 ml. of anhydrous ether. While cooling this solution in an ice-bath, an ether solution of 1.47 g. of cyanogen bromide was added in drops and a precipitate began to appear immediately. After allowing this mixture to stand overnight, the precipitated methobromide (XIV + XV) was collected by filtration. Yield, 1.5 g. Ether was evaporated from the filtrate and the residue was distilled under low pressure to yield 1.7 g. (63%) of a fraction of b.p. 140–150° (bath temp.)/0.05 mm., m.p. 48–52°. Recrystallization from petroleum benzine afforded colorless needles (XIII), m.p. 54–55°.

Anal. Calc'd for $C_{12}H_{19}N_3$: C, 70.24; H, 9.26; N, 20.45. Found: C, 70.42; H, 8.96; N, 20.43.

Picrate: Yellow prisms, m.p. 211° (from ethanol).

Anal. Calc'd for $C_{12}H_{19}N_3 \cdot C_6H_3N_3O_7$: C, 49.77; H, 5.06; N, 19.35. Found: C, 50.12; H, 4.77; N, 18.98.

A solution of 1.5 g. of the base methobromide (XIV + XV) in water was added to the suspension of freshly prepared silver oxide in water, the mixture was shaken, and water was distilled off under reduced pressure. The residue was distilled to yield 600 mg. of an oil, b.p. 100–150° (bath temp.)/0.1 mm. From this oil 300 mg. of a *picrate*, m.p. 275–277° (decomp.) (from ethanol) was obtained. This is sparingly soluble in ethanol and was identical with that of XI.

Another *picrate*, easily soluble in ethanol, was recrystallized from the same solvent to 400 mg. of crystals melting at 210–211°, identical with the picrate of XIII.

Optical resolution of XIII. XIII (450 mg.) and dibenzoyl-*d*-tartaric acid (810 mg.) were dissolved in ethanol, the solvent was evaporated, and the residue was dried after washing with ether, from which 1.1 g. of the hydrogen dibenzoyl-*d*-tartrate was obtained, m.p. 154–157°. Recrystallization from acetone was repeated to give a pure sample, m.p. 158–160°, $(\alpha)_D$: −48.0° ± 3° (*c*, 6.13 in methanol).

Anal. Calc'd for $C_{12}H_{19}N_3 \cdot C_{18}H_{14}O_8$: C, 63.94; H, 5.86; N, 7.46. Found: C, 63.88; H, 5.98; N, 7.23.

The base liberated from 500 mg. of this hydrogen tartrate gave 130 mg. of a crystalline product, m.p. 55–56°, undepressed on admixture with XIII. This base was optically inactive, $(\alpha)_D$ +0.15° ± 3° (*c*, 6.46 in methanol).

The hydrogen tartrate obtained from the acetone mother liquor also afforded an optically inactive base and thus the optical resolution could not be effected by this method.

Perhydropyrido[3,4,5-i,j]quinolizine (IVa). A solution of 1.7 g. of XIII in 20 ml. of 10% hydrochloric acid was refluxed for 4 hours, concentrated under reduced pressure, basified with potassium hydroxide, and the base was extracted with ether. After drying, ether was distilled off and the residue solidified readily into colorless prisms, m.p. 54–57°. Yield, 1.4 g. (92%). This substance formed plates, m.p. 57° (from petroleum ether), and was hygroscopic. The *dipicrate*, yellow needles m.p. 265° (decomp.) (from ethanol), was submitted for elemental analyses.

Anal. Calc'd for $C_{11}H_{20}N_2 \cdot 2C_6H_3N_3O_7$: C, 43.50; H, 3.90. Found: C, 43.48; H, 4.19.

p-Nitrobenzoate: White needles, m.p. 116° (from ether).

4,5,6,8,9,10-Hexahydropyrido[3,4,5-i,j]quinolizine (*nordehydro-α-matrinidine*) (Va). A mixture of 1.4 g. of IVa and 0.7 g. of 40% palladium asbestos was heated in a nitrogen atmosphere at 220–250° and 490 ml. (theoretical, 523 ml.) of hydrogen was generated in 40 minutes. The reaction product was distilled to yield 0.9 g. (68%) of a product, b.p. 160–180° (bath temp.)/0.1 mm., m.p. 62–66°. Recrystallization from petroleum benzine afforded leaflets, m.p. 30–31°, but when the substance was left in a desiccator or distilled, the melting point became 62–66°. This seems to be an example of polymorphism. The crystals melting at 62–66° were submitted to elemental analyses.

Anal. Calc'd for $C_{11}H_{14}N_2$: C, 75.86; H, 8.05; N, 16.10. Found: C, 75.53; H, 7.80; N, 15.99.

Hydrobromide: m.p. 275° (from acetone).

Anal. Calc'd for $C_{11}H_{14}N_2 \cdot HBr$: C, 51.80; H, 5.90. Found: C, 51.55; H, 5.95.

Ultraviolet absorption: $\lambda_{max}^{H_2O}$ (hydrobromide): 292 mμ (ε 16500).

Picrate: Yellow needles, m.p. 221–223° (from ethanol).

Anal. Calc'd for $C_{11}H_{14}N_2 \cdot C_6H_3N_3O_7$: C, 50.12; H, 4.22. Found: C, 50.47; H, 4.10.

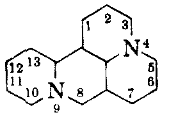
No depression of the melting points was observed on admixture of Va and its picrate with nordehydro-α-matrinidine[14] and its picrate. Paper chromatography of Va was carried out by the method of E. Ochiai and S. Okuda[14] and the R_f value of 0.62 was equal to that of nordehydro-α-matrinidine. The infrared spectra of the free bases were also identical.

1-Methyl-4,5,6,8,9,10-hexahydropyrido[3,4,5-i,j]quinolizine (Vb) (*Dehydro-α-matrinidine*). To an ether solution of methyllithium, prepared from 3 g. of methyl iodide and an excess of lithium by the method of Bohlmann, *et al.*,[23] 300 mg. of Va was added, followed by 10 ml. of toluene, and the ether was evaporated. This mixture was refluxed in an oil-bath for 6 hours, diluted with water, acidified with hydrochloric acid, and washed with ether. The aqueous layer was basified, and the liberated base was extracted with ether, directly converted to the hydrobromide, and recrystallized from acetone. The sparingly soluble hydrobromide of Va was collected and the hydrobromide in the mother liquor was converted to a picrate which was recrystallized from methanol. The sparingly soluble picrate of Va was further removed by filtration and the easily soluble *picrate of Vb* was finally obtained as yellow needles, m.p. 208–211°.

Anal. Calc'd for $C_{12}H_{16}N_2 \cdot C_6H_3N_3O_7$: C, 51.8; H, 4.56; N, 16.8. Found: C, 51.63; H, 4.92; N, 16.53.

The picrate of Vb showed no depression in the melting point on admixture with dehydro-α-matrinidine picrate. The infrared spectrum of Vb exhibits absorption bands for pyridine ring (1514, 1563, 1595 cm.$^{-1}$) and for tertiary nitrogen[26] (1134 and 1208 cm.$^{-1}$).

11-Ethoxycarbonyl-10-oxo-1,2,3,5,6,7-hexahydroquinolizo-[1,8-ab]quinolizine (XVI).[27] A solution of 18.8 g. (0.1 mole) of Vb[27,28] dissolved in 80 ml. of anhydrous ether was added dropwise into a liquid ammonia solution of sodium amide, prepared from 2.3 g. (0.1 mole) of metallic sodium and 150 ml. of liquid ammonia. To this solution 150 ml. of anhydrous ether was gradually added and ammonia was allowed to evaporate at room temperature. While stirring and cooling this solution 21.6 g. (0.1 mole) of diethyl ethoxymethylenemalonate dissolved in 80 ml. of anhydrous ether was added



XVII

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[27] Designated by the Ring Index system, in accordance with the numbering for XVII.

[28] Prepared by the palladium dehydrogenation of α-matrinidine (III).

during 1.5 hours. Stirring was continued for another 2 hours and an aqueous solution of ammonium chloride was added to destroy excess sodium amide. The aqueous layer was extracted four times each with 100 ml. of ether and the combined ether solution was dried over potassium carbonate. The solvent was evaporated and 13 g. of Vb was recovered by distillation at 130–145°/2 mm. The substance left after removal of Vb was dissolved in 30 ml. of benzene and chromatographed through a column containing 200 g. of alumina. After eluating the column with 1 l. of benzene a crystalline fraction (2 g.) was obtained.

The crystalline portion was recrystallized from ethyl acetate to give orange-yellow needles (XVI), m.p. 194–195°. Yield, 1.6 g. (5.2%). This substance is soluble in ether, benzene, methanol, and water and sparingly soluble in acetone and petroleum ether.

Anal. Calc'd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.54; N, 8.97. Found: C, 69.49; H, 6.43; N, 9.25.

Ultraviolet absorption: λ_{max}^{EtOH} mμ (ϵ): 272 (13200), 284 (13000), 409 (47000).

HONGO, TOKYO, JAPAN