In view of these data, it is considered that N-oxide group in pyridazine 1-oxide has a fixed polar effect, and the order of position reactivity in halogenopyridazine 1-oxides is 5>3>6>4.

The fact that property of pyridazine 1-oxides differ from the pyridine N-oxides will be elucidated by NMR studies.

The authors express their gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo for his kind advice, to Prof. T. Okamoto of the University of Tokyo for his kind guidance, and to Dr. T. Kariyone, the Director of this Institute, for his encouragement. They are also indebted to Dr. T. Oba and Mr. G. Kawabata for the measurement of infrared spectra, and to members of Central Analysis room of the University of Tokyo for the elemental analyses.

Summary

Reaction rates of 3-, 4-, 5-, and 6-chloropyridazine 1-oxides and other halogenopyridazine 1-oxides with piperidine and with sodium ethoxide were measured. The rates and derived parameters were compared. The rate order of position reactivity was 5>3>6>4.

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41. Shigenobu Okuda, Masafumi Yoshimoto, and Kyosuke Tsuda : Studies on Lupin Alkaloids. IV.*1 Total Syntheses of Optically Active Matrine and Allomatrine.

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(+)-Matrine (I) is the principal alkaloid of *Sophora flavescens*[1] and Mandel, *et al.* recently reported an elegant application of quinolizidine synthesis to the total synthesis of (±)-matrine.[2] However, they could not accomplish the optical resolution. Tsuda and co-workers reported on the synthesis of (±)-allomatridine (IV′) *via* two different procedures,[3,4] one of which consisted of the synthesis of octadehydromatrine (II). High pressure-high temperature hydrogenation of II with copper chromite catalyst afforded IV′, while hydrogenation at room temperature with platinum oxide gave rise to didehydromatrine (III), which was also cyclized reductively to IV′ on high pressure-high temperature hydrogenation with copper chromite.

This paper deals with the total syntheses of optically active (+)-matrine (I) and (+)-allomatrine (V)[5] from III, and describes reduction of III to the respective hexahydro

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*1 Part III. S. Okuda, H. Kataoka, K. Tsuda : This Bulletin, **13**, 491 (1965).

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1) *a*) N. Nagai, R. Tawara : J. Pharm. Soc. Japan, **9**, 54 (1889). *b*) F. Bohlmann, D. Rants, C. Arndt : Ber., **91**, 2189 (1958). *c*) Manske, Holmes : "The Alkaloids," Academic Press Inc., New York, Vol. III (1953), p. 178, Vol. VII (1960), p. 296.

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4) S. Okuda : Pharm. Bull. (Tokyo), **5**, 468 (1957).

5) *a*) E. Ochiai, S. Okuda, H. Minato : J. Pharm. Soc. Japan, **72**, 781 (1952). *b*) F. Rulko, N. F. Proskurnina : Zhur. Obshchei. Khim., **31**, 308 (1961).

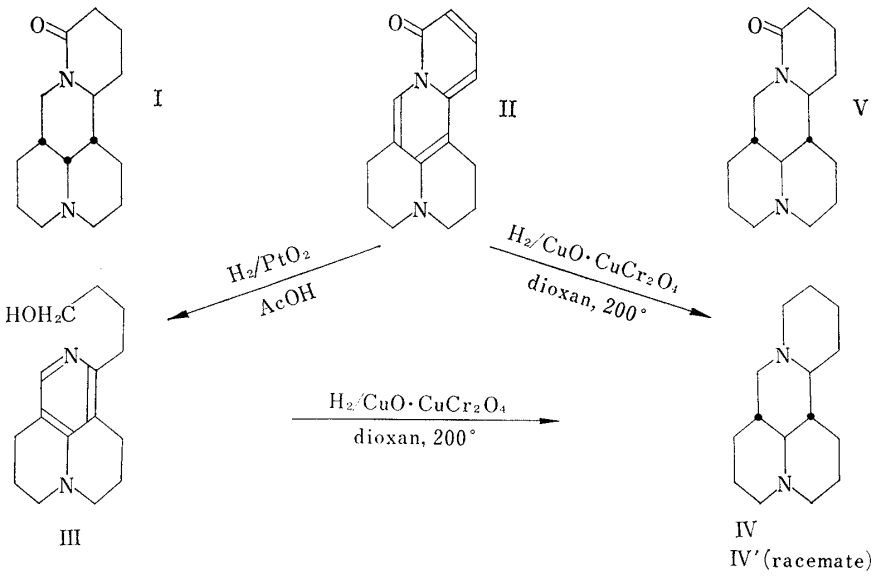

Chart 1.

derivatives Ⅵ′ and Ⅷ′, optical resolutions, oxidation to the corresponding amino acids and successive cyclization to I and V.

A treatment of Ⅲ with a large excess of sodium in refluxing absolute ethanol afforded (±)-allomatrinol (Ⅵ′) and (±)-matrinol (Ⅷ′) in 41% and 3.7% yields, respectively.

Isolation of Ⅵ′ was easily achieved by recrystallizing a mixture of the reaction products from acetone-ether to afford a pure speciman, m.p. 131°, which was optically resolved by means of dibenzoyl-(+)-tartaric acid. Two recrystallizations of the salt from ethanol gave pure dibenzoyl-(+)-tartaric acid salt of (+)-allomatrinol, m.p. 157° (decomp.), $[\alpha]_D^{13}$ −52.6°. Free amino alcohol from the above salt, m.p. 143.5°, $[\alpha]_D^{15}$ +41.1° is identical in all respects with the authentic (+)-allomatrinol (Ⅵ), m.p.143.5°, $[\alpha]_D^{15}$ +43.5°.

After removing a greater part of Ⅵ′ by means of recrystallization, the remnant was repeatedly chromatographed to give pure (±)-matrinol (Ⅷ′).

(±)-Matrinol fraction, eluted succeeding to the (±)-allomatrinol fraction from alumina column, exhibited the same Rf-value on the thin-layer chromatogram and a quite similar infrared spectrum in comparison with those of (+)-matrinol. Although all efforts to obtain a crystalline (±)-matrinol were unsuccessful, dibenzoyl-(+)-tartaric acid salt of N-benzoyl-(±)-matrinol (Ⅷ′) crystallized and the optical resolution of Ⅷ′ was performed *via* repeated recrystallizations of this salt from acetone. The salt, m.p. 135°, resulting after nine recrystallizations, gave rise to optically pure N-benzoate, m.p. 114~115°, $[\alpha]^{13.5}$: 226° (300 mμ), 127° (310 mμ), 48° (330 mμ), which was identical with the authentic N-benzoyl-(+)-matrinol, m.p. 115~116°, $[\alpha]^{13.5}$: 206° (300 mμ), 111° (310 mμ), 37° (330 mμ). Lithium aluminum hydride reduction of Ⅷ, followed by successive catalytic hydrogenation afforded (+)-matrinol (Ⅶ), m.p. 156.5°, $[\alpha]_D^{26}$ 17.1° in an almost quantitative yield.[6]

Both (+)-matrinol (Ⅶ) and (+)-allomatrinol (Ⅵ) were oxidized with chromium trioxide in 20% sulfuric acid into the corresponding amino acids, which were not isolated and immediately cyclized by heating in acetic anhydride. (+)-Matrine (I), m.p. 78~79°, $[\alpha]_D^{26}$ +37.9° and (+)-allomatrine, m.p. 103~104°, $[\alpha]_D^{26}$ +82.3°, thus obtained, were completely identical with authentic specimens and the yields were calculated to be 30% for I and 56% for V based on the alcohols.

6) E. Ochiai, H. Minato : This Bulletin, **9**, 92 (1961).

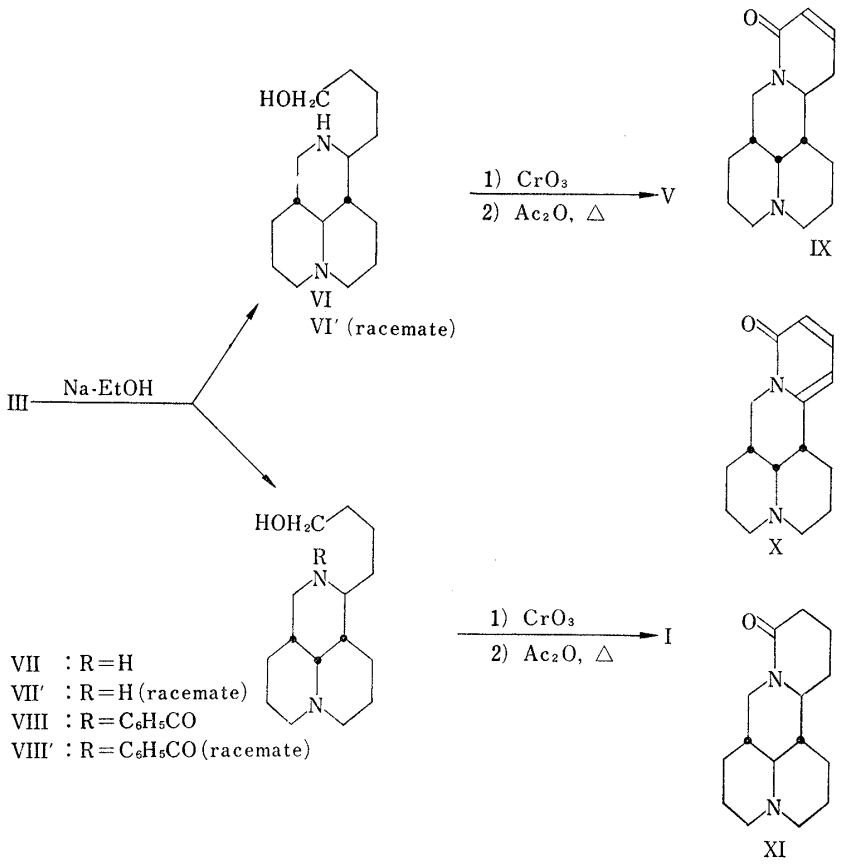

Chart 2.

The syntheses of (−)-sophocarpine (Ⅸ), (−)-sophoramine (Ⅹ), and (−)-isosophoramine(Ⅺ) from Ⅰ have been already achieved in this laboratory,[7] therefore, the present conversion of Ⅲ into Ⅰ also accomplishes the total syntheses of the above three alkaloids.

Experimental

All melting points were uncorrected. Infrared spectra were recorded through NaCl prism on Koken Infrared Spectrophotometer, Model DS301. Optical rotations in ultraviolet region were measured with an automatic recording ORD/UV-5 spectrophotometer of Nihon Bunko (Japan Spectroscopic Manufacturing Co., Ltd.) and $[\alpha]_D$ with a Yanagimoto Photo-Magnetic Polarimeter, Model OR-20.

Starting Material: Didehydromatrine (III)——According to the descriptions of Tsuda and coworkers,[3] octadehydromatrine (Ⅱ), m.p. 174~176°, was synthesized from (+)-matrine (Ⅰ) by dehydrogenation with Pd-asbestos at 300° and then it was converted into didehydromatrine (Ⅲ) *via* catalytic hydrogenation in acetic acid with PtO_2. Yield of Ⅲ, m.p. 105~106°, was 13.7% from Ⅰ.

Preparation of (±)-Allomatrinol (VI′) and (±)-Matrinol (VII′)——During the period of one hour, small pieces of Na (total 10.8 g.) were added to a solution of 1.84 g. of Ⅲ in 100 ml. of abs. EtOH and the mixture was refluxed for 6 hr. After cooling, 50 ml. of conc. HCl was added and EtOH was evaporated. The remnant was added with 50 ml. of H_2O, basified with K_2CO_3 and extracted with $CHCl_3$. After the $CHCl_3$ extract was dried over anhyd. Na_2SO_4, evaporation of $CHCl_3$ gave 1.8 g. of oil, which was triturated with acetone-ether. The crystals precipitated were recrystallized from the same solvent mixture to afford 600 mg. of (±)-allomatrinol, m.p. 131°. *Anal.* Calcd. for $C_{15}H_{28}ON_2$: C, 71.38; H, 11.18; N, 11.10. Found: C, 71.18; H, 11.16; N, 10.80. IR spectrum and Rf value (0.40) of TLC (Alumina G, $CHCl_3$-MeOH (10:1)) of this compound were identical with those authentic (+)-allomatrinol (Ⅵ).

An oil (1.2 g.) from the mother liquor of Ⅵ′ was chromatographed on 70 g. of Woelm alumina (grade 1) and the following fractions were obtained.

7) *a*) S. Okuda, H. Kamata, K. Tsuda, I. Murakoshi: Chem. Ind., **1962**, 1326. *b*) *Idem*: This Bulletin, **11**, 1349 (1963).

Fraction 1, eluted with ether containing 2~5% MeOH : a mixture of (±)-allomatrinol (VI′) and (±)-matrinol (VII′) 560 mg.

Fraction 2, eluted with ether containing 5% MeOH : almost pure (±)-matrinol, 90 mg., whose IR spectrum and Rf value (0.25) of TLC were quite similar to those of (+)-matrinol (VII).

Fraction 3, eluted with ether containing 10% MeOH : a mixture of (±)-matrinol and lower spots of TLC (not assigned), 300 mg.

Fraction 2 was dissolved in 10 ml. of benzene and to this 10 ml. of 10% NaOH was added. Under vigorous agitation, 0.5 g. of benzoylchloride was added and stirring was continued for 1.5 hr. The reaction mixture was worked up as usual and the resulting dibenzoyl derivative was partially hydrolyzed on heating with refluxing 10% KOH-EtOH for 1 hr. Monobenzoate, thus obtained after usual work up procedures, was purified through 4 g. Woelm alumina (grade 3) and 30 mg. of pure N-benzoyl-(±)-matrinol (VIII′), Rf (Alumina G, ether-benzene (1:1)); 0.2, Rf (Silica gel G, $CHCl_3$-MeOH (4:1)); 0.6, were obtained. Although this compound was not crystalline, the IR spectrum and Rf values were identical with those of an authentic N-benzoyl-(+)-matrinol (VIII). Recrystallization of fraction 1 from acetone-ether yielded another crop of allomatrinol, 170 mg. The mother liquor of fraction 1 and fraction 3 were combined and treated as in the case of fraction 2. N-benzoyl-(±)-matrinol (70 mg.) was isolated from a fraction eluted with benzene containing 5% ether. Yields : 770 mg. of (±)-allomatrinol and 100 mg. of N-benzoyl-(±)-matrinol, which correspond to 71 mg. of (±)-matrinol.

Preparation of (+)-Matrinol (VII) and N-Benzoyl-(+)-matrinol (VIII)——According to the procedures by Ochiai and Minato,[6] (+)-matrinol, m.p. 156.5°, $[\alpha]_D^{26}$ +17.1°(c=1.5, EtOH) was synthesized. *Anal.* Calcd. for $C_{15}H_{28}ON_2$: C, 71.38; H, 11.18; N, 11.10. Found : C, 71.44; H, 11.18; N, 10.91. To a solution of 400 mg. of (+)-matrinol in 10 ml. of benzene was added 10 ml. of 10% NaOH. Under vigorous agitation, 1.5 g. of benzoylchloride was added and stirring was continued for 1.5 hr. The reaction mixture was worked up as usual and the resulting dibenzoyl derivative was partially hydrolyzed on heating with a reflux in 10% KOH-EtOH for 1 hr. Monobenzoate, thus obtained after an usual work up, was purified through 20 g. of Woelm alumina (grade 3) and 240 mg. of N-benzoyl-(+)-matrinol, m.p. 116~117°, $[\alpha]^{13.5}$: 206°(300 mμ), 111°(310 mμ), 37°(330 mμ) : (c=0.10, EtOH), was obtained. *Anal.* Calcd. for $C_{22}H_{32}O_2N_2$: C, 74.12; H, 9.05; N, 7.86. Found : C, 74.12; H, 9.10; N, 7.88.

Preparation of (+)-Allomatrinol (VI)——The similar treatment of (+)-allomatrine as the preparation of (+)-matrinol from (+)-matrine gave (+)-allomatrinol, m.p. 143.5°, $[\alpha]_D^{15}$ +43.5°. *Anal.* Calcd. for $C_{15}H_{28}ON_2$: C, 71.38; H, 11.18; N, 11.10. Found : C, 71.55; H, 11.25; N, 11.37.

Optical Resolution of (±)-Allomatrinol (VI′)——To a solution of 600 mg. of VI′ in a small amount of MeOH, wan added a MeOH solution of dibenzoyl-(+)-tartaric acid (895 mg.). After acetone was added until the solution became slightly turbid, a seeding of very small crystals of dibenzoyl-(+)-tartaric acid salt of (+)-allomatrinol resulted in precipitation of crystalline material, 630 mg., m.p. 157°, $[\alpha]_D^{13}$ −52.6°(c=1.47, H_2O). Two recrystallizations from EtOH-MeOH gave 565 mg. of crystals, m.p. 157°, identical with the salt from authentic (+)-allomatrinol, m.p. 157.5°, $[\alpha]_D^{13}$ −52.4°(c=1.66, H_2O). Release of a base with K_2CO_3 from 500 mg. of this salt, followed by recrystallization from acetone, yielded 155 mg. of needles, m.p. 143.5°, $[\alpha]_D^{15}$ +41.1°(c=0.90, MeOH), $\nu_{max}^{CHCl_3}$ cm^{-1} : 3660, 3200 (NH and OH), 2800, 2720, 2640 (*trans*-quinolizidine); 1068 (C-O-). This compound was identical with an authentic(+)-allomatrinol (VI) by mixed melting point test, comparison of IR spectra and TLC. The mother liquor, separated from the first crop of dibenzoyl-(+)-tartaric acid salt of (+)-allomatrinol, was basified with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to dryness, the residue was recrystallized from acetone. Two recrystallizations afforded 150 mg. of (−)-allomatrinol, m.p. 143.0°, $[\alpha]_D^{15}$ −39.4°, whose IR spectra and TLC were completely identical with those of authentic (+)-isomer.

Optical Resolution of N-Benzoyl-(±)-matrinol——To an acetone solution of 165 mg. of N-benzoyl-(±)-matrinol (VIII′), an acetone solution of 175 mg. of dibenzoyl-(+)-tartaric acid was added and then fine crystals of dibenzoyl-(+)-tartaric acid salt of N-benzoyl-(+)-matrinol was seeded. Nine recrystallizations of 210 mg. of the precipitated material gave 50 mg. of a pure salt, m.p. 135°, $[\alpha]_D^{15}$ −33.2°(c=0.90, EtOH), which furnished 20 mg. of crystalline free N-benzoyl-(+)-matrinol. The crystals obtained by means of recrystallization from acetone-ether exhibited m.p. 114~115°, $[\alpha]^{13.5}$: 226°(300 mμ), 127°(310 mμ), 48°(330 mμ) : (c=0.10, EtOH), $\nu_{max}^{CHCl_3}$ cm^{-1} : 3450 (OH), 2785, 2717 (*trans*-quinolizidine), 1614 (CO). This compound was identical with an authentic N-benzoyl-(+)-matrinol by mixed melting point test and comparison of these physical data.

Preparation of (+)-Matrinol (VII) from N-Benzoyl-(+)-matrinol (VIII)——To a solution of 170 mg. of VIII in 20 ml. dry dioxane, 30 mg. of $LiAlH_4$ was added and refluxed for 4.5 hr. To the reaction mixture, 1 ml. of H_2O, 1 ml. of 10% NaOH and another 1 ml. of H_2O were added. The precipitated $Al(OH)_3$ was removed by filtration and the filtrate was dried over anhyd. Na_2SO_4. After removal of organic solvent, recrystallization of the residue (150 mg.) from acetone afforded 50 mg. of (+)-matrinol (VII), m.p. 156.5°, which was identified with an authentic specimen by mixed melting point test, comparison of IR spectra and TLC.

The remaining oil (100 mg.) from the mother liquor was submitted to catalytic hydrogenolysis in a mixture of 10 ml. of MeOH and 0.5 ml. of 1% HCl with 20 mg. of PtO_2 for 10 hr. After being worked up as usual, alumina chromatograph (3.0 g. of Woelm alumina, grade 3) afforded 25 mg. of starting material (Ⅷ) from the eluates with benzene containing 5% ether and 40 mg. of Ⅶ from the eluates with ether containing 5% MeOH. Total yields of Ⅶ was 90 mg., 88% based on the consumed Ⅷ.

Synthesis of (+)-Matrine (I) from (+)-Matrinol (VII)——To a solution of 100 mg. of Ⅶ in 5 ml. of 20% H_2SO_4, 60 mg. of CrO_3 was added. The reaction mixture was allowed to stand for 4 hr. at room temperature. After heating on a water bath for 5 min., 30 mg. of $NaHSO_3$ was added to decompose an excess reagent. The solution was basified with conc. aq. NH_3 and evaporated to dryness. The MeOH extract of the residue was evaporated and heated in 5 ml. of refluxing Ac_2O for 1 hr. After H_2O and a large excess of K_2CO_3 were added, the mixture was allowed to stand for a while and extracted with ether. The ether extract was dried over anhyd. Na_2SO_4, evaporated to give 50 mg. of oil, which was chromatographed on 2.5 g. Brockmann alumina. From the eluates with benzene and benzene-ether (9:1), 30 mg. of (+)-matrine, m.p. 78~79°, $[\alpha]_D^{26}$ +37.9° (c=1.69, H_2O), was obtained. This synthetic (+)-matrine was completely identical with an authentic (+)-matrine (I) in every respect.

Synthesis of (+)-allomatrine (V) from (+)-Allomatrinol (VI)——Similar treatments as in the above case were applied to the oxidation and the cyclization of a resulting amino acid. The cyclization product was purified on 4 g. of silica gel column and the eluates with ether containing 10~20% MeOH gave 55 mg. of (+)-allomatrine, m.p. 99~100°, which was recrystallized from ether-petroleum ether to yield crystals, m.p. 103~104°, $[\alpha]_D^{26}$ +82.3°(c=1.53, EtOH).

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Summary

Didehydromatrine (Ⅲ) was reduced to (±)-allomatrinol (Ⅵ′) and (±)-matrinol (Ⅶ′), and the latter of which was converted to N-benzoyl derivative (Ⅷ′). The optical resolution of Ⅵ′ and Ⅶ′ were carried out by means of dibenzoyl-(+)-tartaric acid. N-Benzoyl-(+)-matrinol (Ⅷ) was transformed to (+)-matrinol (Ⅶ) *via* hydrogenolysis. (+)-Matrinol (Ⅶ) and (+)-allomatrinol (Ⅵ) were derived into (+)-matrine (I) and (+)-allomatrine (V) by oxidation and successive cyclization.

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