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40. Shigeru Sako*1 and Takanobu Itai: Kinetics of the Nucleophilic Displacement Reactions of Halogenopyridazine 1-Oxides.

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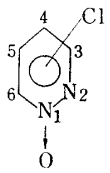
In the previous paper, nucleophilic displacement of chlorine atoms in chloropyridazine 1-oxides was investigated and following results were obtained. 3-Chlorine of 3,6-dichloropyridazine 1-oxide was more reactive than 6-chlorine,[1] but the difference of reactivity between 3- and 6-chlorine in monochloropyridazine 1-oxides was indefinite,[2] and 4-chloro-3,6-dimethylpyridazine 1-oxide was less active than 5-chloro-3,6-dimethylpyridazine 1-oxide.[3] These results are opposed to the reactivity predicted from the property of pyridine N-oxides and quinoline N-oxides.



The present work was undertaken to determine quantitatively the effects of N-oxide group and ring nitrogen on the rate of displacement of halogen atoms of halogenopyridazine 1-oxides. The reaction of 3-, 4-, 5-, and 6-chloropyridazine 1-oxides, 4- and 5-chloro-3,6-dimethylpyridazine 1-oxides, and 3- and 4-bromopyridazine 1-oxides with piperidine, and the reaction of 3- and 4-chloropyridazine 1-oxides with sodium ethoxide were investigated.

On the kinetic study of the displacement of halogen atoms in 4-halogenoquinoline 1-oxides by piperidine, Okamoto, Hayatsu and Baba[4] used a large excess of piperidine to avoid the effect of acid catalysis. Present procedure followed to that of Okamoto, *et al.*

Experimental

Reactants and Products

Table I.

Pyridazine 1-oxide	m.p. (°C)	Procedure
3-Chloro-	94.5~ 95.5	5)
4-Chloro-	119.5~121	6)
5-Chloro-	119 ~120.5	7)
6-Chloro-	156 ~157	2)
4-Chloro-3,6-dimethyl-	132 ~133	3)
5-Chloro-3,6-dimethyl-	126 ~127	3)
3-Bromo-	122 ~123	7)
4-Bromo-	124 ~125.5	7)

Piperidine——Commercial piperidine was dehydrated with KOH and dehydrated piperidine was refluxed with Na for several hours. The piperidine was then distilled, and the fraction, b.p. 105.5~106.0°, was collected, refluxed again with Na and redistilled. The purified piperidine was further distilled.

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1) S. Sako: This Bulletin, **10**, 956 (1962).
2) *Idem*: *Ibid.*, **11**, 261 (1963).
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4) T. Okamoto, H. Hayatsu, Y. Baba: This Bulletin, 8, 892 (1960).
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Sodium Ethoxide——Sodium ethoxide solutions were prepared by dissolving clean sodium in EtOH purified as described below, and standardized acidimetrically.

Piperidinopyridazine N-Oxides (General Procedure)——A mixture of chloropyridazine 1-oxide, an excess of piperidine and EtOH was heated in a sealed tube on a boiling water bath. After adding $NaHCO_3$ to the mixture, the solvent was evaporated under reduced pressure. The residue was extracted with hot benzene, and the benzene was evaporated to dryness. The extract was recrystallized from benzene or petr. benzin to colorless prisms or needles. 4-Chloro-3,6-dimethylpyridazine 1-oxide was reacted with piperidine at 140~145°. The properties and analytical data of the compounds are summarized in Table II and III, respectively.

Table II.

Pyridazine 1-oxide	Solvents of recrystallization	Crystalline forms	m.p. (°C)
3-Piperidino-	benzene-petr. benzin	needles	83~ 84
4-Piperidino-	benzene	prisms	146~147
5-Piperidino-	〃	〃	151~152
6-Piperidino-	petr. benzin	needles	101~102
4-Piperidino-3,6-dimethyl-	〃	〃	72~ 73
5-Piperidino-3,6-dimethyl-	benzene	prisms	130~131

Table III.

Pyridazine 1-oxide		Calcd. (%)			Found (%)		
		C	H	N	C	H	N
3-Piperidino-	$C_9H_{13}ON_3$	60.31	7.31	23.45	60.93	7.65	22.88
4-Piperidino-	〃	60.31	7.31	23.45	59.84	7.64	22.99
5-Piperidino-	〃	60.31	7.31	23.45	60.20	7.21	23.46
6-Piperidino-	〃	60.31	7.31	23.45	60.18	7.47	23.49
4-Piperidino-3,6-dimethyl-	$C_{11}H_{17}ON_3$	63.74	8.27	20.27	63.29	8.47	19.77
5-Piperidino-3,6-dimethyl-	〃	63.74	8.27	20.27	64.09	8.17	20.16

4-Ethoxypyridazine 1-Oxide——A mixture of 4-chloropyridazine 1-oxide and EtOH solution of excess EtONa was allowed to stand at room temperature. After adding a small amount of water to the mixture, the solution was extracted with $CHCl_3$, which was dried over anhyd. Na_2SO_4 and evaporated to dryness. The extract was recrystallized from benzene to colorless needles, m.p. 91~92°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.61; H, 5.79; N, 20.30.

3-Ethoxypyridazine 1-Oxide——A mixture of 3-chloropyridazine 1-oxide and EtOH solution of excess EtONa was treated as described above. The extract was recrystallized from ligroin-benzene to colorless prisms, m.p. 74~75°, which were identical with authentic 3-ethoxypyridazine 1-oxide[8] by mixed melting point determination and comparison of their IR spectra.

Solvent——EtOH was dried with Na and redistilled.

Ultraviolet Spectra of the Reactants and Products——In Fig. 1, UV spectra of these reactants and products in 0.5*N* H_2SO_4(50% EtOH-H_2O) are shown, but 6-chloropyridazine 1-oxide and 6-piperidinopyridazine 1-oxide were measured in ethanolic 0.5*N* H_2SO_4.

Typical Rate Measurement by the Spectroscopic Method——The procedure was modified from the method of Okamoto[4] used for the reaction of halogenoquinoline 1-oxide with piperidine. 3-Chloropyridazine 1-oxide and piperidine were separately dissolved in EtOH at the concentration of $1.0020\times10^{-2}M$ and 0.4306*M*, respectively. A flask containing the former solution and a flask containing the latter solution were immersed into a thermostat adjusted to $30\pm0.1°$. When the solutions were brought to the thermostat temperature, the solution of the chloro-compound (10 ml.) was pippeted into a flask (placed in the thermostat) with a glass stopper, and the same volume of the solution of piperidine were mixed (concentration of the 3-chloropyridazine 1-oxide, $5.010\times10^{-3}M$; piperidine, 0.2153*M*). This time was recorded as zero time. One ml. of the reaction solution was pippeted into a flask containing 1.0 ml. of 1*N* H_2SO_4 at definite intervals. This was diluted accurately with 0.5*N* H_2SO_4(prepared by mixing equal volumes of 1*N* H_2SO_4 and EtOH) to make its optical density at 374 mμ between 0.1 and 0.6.

8) T. Itai, S. Sako: This Bulletin, **10**, 989 (1962).

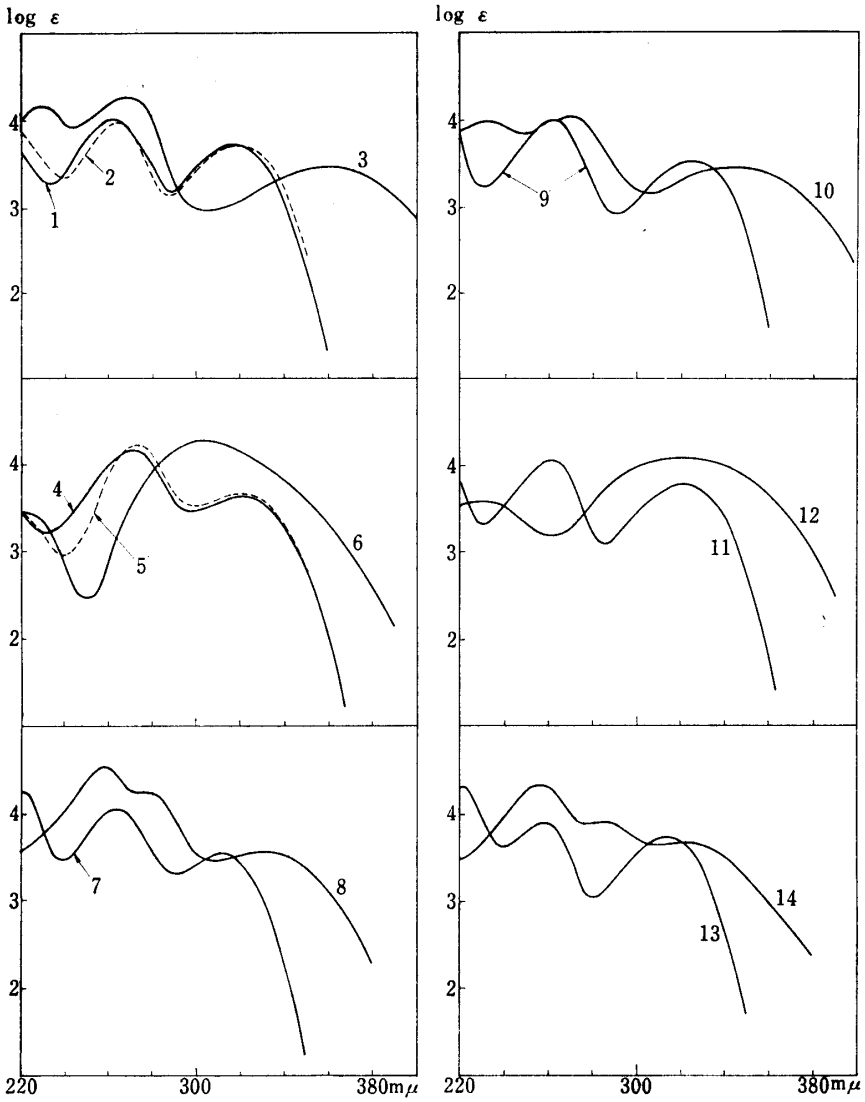

Fig. 1. Ultraviolet Spectra of the Reactants and Products in 0.5*N* Sulfuric Acid (50% EtOH–H_2O, but EtOH is used for 9 and 10)

1: 3-chloropyridazine 1-oxide
2: 3-bromopyridazine 1-oxide
3: 3-piperidinopyridazine 1-oxide
4: 4-chloropyridazine 1-oxide
5: 4-bromopyridazine 1-oxide
6: 4-piperidinopyridazine 1-oxide
7: 5-chloropyridazine 1-oxide
8: 5-piperidinopyridazine 1-oxide
9: 6-chloropyridazine 1-oxide
10: 6-piperidinopyridazine 1-oxide
11: 4-chloro-3,6-dimethylpyridazine 1-oxide
12: 4-piperidino-3,6-dimethylpyridazine 1-oxide
13: 5-chloro-3,6-dimethylpyridazine 1-oxide
14: 5-piperidino-3,6-dimethylpyridazine 1-oxide

The other piperidino-compounds were measured at the wave length shown in Table IV. For the reaction solution of 6-chloropyridazine 1-oxide, 0.5*N* H_2SO_4 in EtOH was used in place of 0.5*N* H_2SO_4 in 50% EtOH. The reactions at above 60° were studied by the method of sealed ampules. 4-Chloro-3,6-dimethylpyridazine 1-oxide was reacted in a thermostat at 130±2°.

Table IV. Wave Lengths Used in Measurement

Pyridazine 1-oxide	mμ	Pyridazine 1-oxide	mμ
3-Piperidino-	374	6-Piperidino-	380
4-Piperidino-	374	4-Piperidino-3,6-dimethyl-	372
5-Piperidino-	362	5-Piperidino-3,6-dimethyl-	362

Rate constant was calculated from the equation $\log a-\log(a-x)=k_1t/2.303$, $k_2=k_1/b$ (where a and b are the initial concentrations of a halogeno compound and piperidine, respectively, and x is the concentration of the product at time t). Fig. 2 shows the plots of $\log(a-x)$ *vs.* t, and the plots were linear. The slope of the line was determined by the method of least squares, and the pseudo first order rate constant k_1 was obtained as 7.860×10^{-5} sec^{-1}. This first order rate constant was divided by the concentration of piperidine to give the second-order rate constant k_2, as 3.65×10^{-4}L. mole^{-1} sec^{-1}.

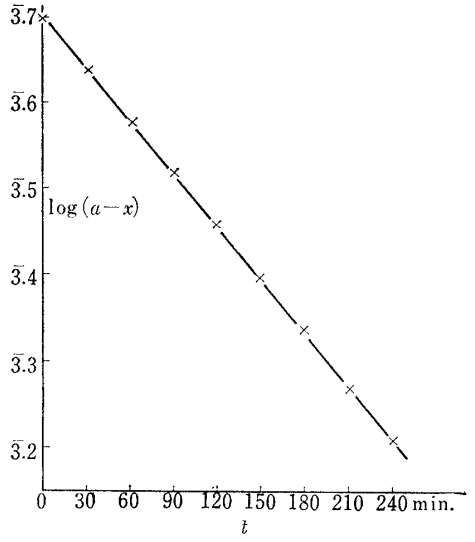

Fig. 2. The Plots of $\log(a-z)$ *vs.* Time for the Reaction of 3-Chloropyridazine 1-Oxide

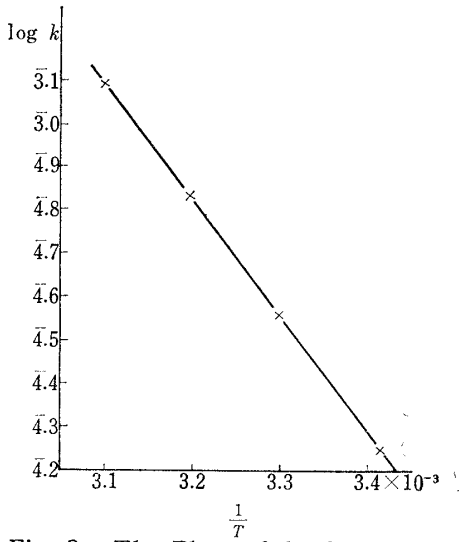

Fig. 3. The Plots of $\log k$ *vs.* $1/T$ for the Reaction of 3-Chloropyridazine 1-Oxide

Activation energy, E_a, was calculated from the expression : $\log k=\log A-E_a/2.303RT$. In Fig. 3, the plots of $\log k$ *vs.* $1/T$ are shown. E_a was obtained from the slopes of this line (by the method of least squares). From this expression, rate constant at 50° was also calculated.

The entropy of activation, $\Delta S^{\neq}$, at 50° was calculated from the following equation : $\Delta S^{\neq}=2.303R\cdot\left(\log\frac{hk}{kT}+\frac{E_a}{2.303RT}\right)$. The value of $k_2^{50°}$, E_a, and $\Delta S^{\neq}$ were 1.26×10^{-3}L. mole^{-1} sec^{-1}, 12.2 kcal. mole^{-1}, and -34 cal. deg.$^{-1}$ mole^{-1}(e. u.), respectively.

In the reaction of 6-chloropyridazine 1-oxide, produced 6-piperidinopyridazine 1-oxide was somewhat unstable, but the kinetic data by the spectroscopic method coincided with those by the titration technique. UV spectra of the reaction solutions of the other chloro compounds at time t_∞ were identical with that of corresponding piperidino compound showed in Fig. 1.

Typical Rate Measurement by the Titration Technique——An ethanolic solution (100 ml.), $4.92\times10^{-2}M$ with respect to 4-chloropyridazine 1-oxide and $0.1262M$ with respect to EtONa, was prepared and 10 ml. aliquot was pippeted into flasks with glass stoppers at thermostat temperature ($20\pm0.1°$). The flasks were taken out successively from the thermostat at definite intervals. Soon after being removed, the reaction solution in the flask was poured into a separatory funnel which contained 15 ml. of $0.05N$ $AgNO_3$, 4 ml. of 60% HNO_3 and 10 ml. of benzene. The flask was washed with four 5 ml. portions of H_2O and washings were also added to the funnel. The funnel was shaken thoroughly, the water layer was separated and the benzene layer was washed with 20 ml. of H_2O. The H_2O layer and H_2O washings were combined and, after adding $NH_4Fe(SO_4)_2$ reagent, the solution was titrated with $0.05N$ NH_4SCN (Volhard method). Thus the amounts of liberated chloride ion were determined.

Table V. Reaction of 4-Chloropyridazine 1-Oxide with Sodium Ethoxide in Ethanol at 20°

Time (min.)	0	10	20	30	50
$\times10^{-2}M$	1.02	1.69	2.37	2.77	3.41
$\log\frac{a(b-x)}{b(a-x)}$	0.06446	0.12024	0.19507	0.25188	0.37621

$a=4.92\times10^{-2}M$, $b=0.1262M$ $k_2=3.13\times10^{-2}$L. mole^{-1} sec^{-1}.

Rate constant was calculated from the expression : $k_2=\frac{2.303}{t(b-a)}\cdot\log\frac{a(b-x)}{b(a-x)}$ (where a and b are initial concentration of the chloro compound and EtONa, respectively, and x is the concentration of the product at t). Detail values are given in Table V.

The rate constant at 50°, energy of activation, and entropy of activation were calculated as described above.

Results and Discussion

Experimental second-order rate constants are summarized in Table VI and VII. From these data, rate constants at 50°, energies of activation Ea, and entropies of activation $\Delta S^{\neq}$ were calculated, and results were assembled in Table VIII and IX.

Concerning the reactivity of pyridine 1-oxide and quinoline 1-oxide at substitution reactions, the following facts had been known. 4-Position of pyridine 1-oxide is reactive

Table VI. Experimental Rate Constants for the Reaction of Halogenopyridazine 1-Oxides with Piperidine in Ethanol

Pyridazine 1-oxide	$k\times10^5$ L. mole^{-1} sec^{-1}			
	20°	30°	40°	50°
3-Chloro-	18.0, 17.1	36.5	68.4, 69.1	124
4-Chloro-	0.878, 0.885	1.88	3.64, 3.76	7.05
5-Chloro-	43.0, 39.3	84.6	155, 163	284
6-Chloro-	4.89, 4.92	10.7	20.0, 20.5, 19.7	39.7
3-Bromo-		53.3	103	186
4-Bromo-		1.82	3.85	7.20
	120°	130°	140°	
4-Chloro-3,6-dimethyl-	1.43	2.01	2.81	
	50°	60°	70°	
5-Chloro-3,6-dimethyl-	3.21	5.27	9.34	

Table VII. Experimental Rate Constants for the Reaction of Chloropyridazine 1-Oxides with Sodium Ethoxide in Ethanol

Pyridazine 1-oxide	$k\times10^3$ L. mole^{-1} sec^{-1}			
	2°	12°	20°	30°
3-Chloro-	2.49	7.69	21.3	
4-Chloro-		1.20	3.13	9.55

Table VIII. Summary of Kinetic Data for the Reactions of Halogenopyridazine 1-Oxide with Piperidine[a)]

Pyridazine 1-oxide	$k_2^{50°}\times10^5$ L. mole^{-1} sec^{-1}	Ea kcal. mole^{-1}	$\Delta S^{\neq}$ cal. deg^{-1} mole^{-1}
5-Chloro-	288	12.1	−33
3-Chloro-	126	12.2	−34
6-Chloro-	39.4	13.0	−34
4-Chloro-	7.08	13.0	−37
3-Bromo-	187	12.2	−33
4-Bromo-	7.34	13.4	−36
5-Chloro-3,6-dimethyl-	3.15	11.7	−43
4-Chloro-3,6-dimethyl-	0.0694	10.9	−53

Table IX. Kinetics Data for the Reactions of Chloropyridazine 1-Oxides with Sodium Ethoxide[a]

Pyridazine 1-oxide	$k_2^{50°} \times 10^2$ L. mole^{-1} sec^{-1}	*Ea* kcal.	$\Delta S^{\neq}$ e. u.
3-Chloro-	42.8	19.1	−1.3
4-Chloro-	7.22	19.7	−2.9

a) The errors of *k*, *Ea*, and $\Delta S^{\neq}$ are within ±5%, ±1 kcal., and ±3 e.u., respectively.

in both nucleophilic and electrophilic substitutions,[9] the order of reactivity in each position is 4>2>3 for the electrophilic substitution and 4, 2>3 for the nucleophilic substitution.[10,11] 4-Position of quinoline 1-oxide is also reactive to both substitutions.[9] In the reaction with piperidine (in 95% ethanol), 4-chloroquinoline 1-oxide reacted 28 times faster than 4-chloroquinoline at 100°.[4] Kinetic data of the reactions chloropyridines and their N-oxides with sodium methoxide in methanol were reported by Liveris and Miller.[12] The rate order of position reactivity of these compounds was 4>2>3. The order of *Ea* was 4<2<3. Chloropyridine N-oxide was more reactive than chloropyridine.

From the property of pyridine 1-oxide and quinoline 1-oxide, high reactivity of 4-position of pyridazine 1-oxide to the nucleophilic substitution was anticipated, but, as shown in Table VIII and IX, the opposite results were given. In the reaction of chloropyridazine 1-oxides with piperidine in ethanolic solution, the rate order of position reactivity was 5>3>6>4, and a ratio of rate was 41:18:5.6:1 at 50°. *Ea* are slightly decreased and $\Delta S^{\neq}$ are slightly increased according as increase of reaction rate.

5-Chloro-3,6-dimethylpyridazine 1-oxide was more reactive than 4-chloro-3,6-dimethylpyridazine 1-oxide, and the rate ratio was 45:1.

The reactivity of 3- and 4-halogenopyridazine 1-oxides was further investigated. 3-Bromopyridazine 1-oxide reacted with piperidine 25.5 times faster than 4-bromopyridazine 1-oxide. In the reaction with sodium ethoxide in ethanol, the rate ratio of 3-chloropyridazine 1-oxide to 4-chloropyridazine 1-oxide was 5.9:1 (Table IX).

These data show that 3-position of pyridazine 1-oxide is always more reactive than 4-position to the nucleophilic substitution. *Ea* of 3-position was slightly smaller than that of 4-position, and $\Delta S^{\neq}$ of 3-position was slightly larger than that of 4-position in all cases.

Liveris and Miller[12] gave σ values of ring nitrogen and N-oxide group in pyridine and its N-oxide on the basis of the data for the reaction of chloropyridines and their N-oxides with sodium methoxide. $\sigma^*(p)$ and $\sigma^*(m)$ for N-oxide group are 1.674 and 1.225, respectively. $\sigma^*(p)$ and $\sigma^*(m)$ for ring nitrogen are 1.165 and 0.596, respectively. These values show that N-oxide group has a very high Hammett substiuent constant and its polar effect is larger than that of nitrogen in base.

As the variation of $\Delta S^{\neq}$ value of 3-, 4-, 5-, and 6-chloropyridazine 1-oxide, except for 4- and 5-chloro-3,6-dimethylpyridazine 1-oxides, was small, it is considered that the strength of polar effect of the N-oxide group and ring nitrogen is indicated by the reaction rate or energy of activation, therefore, in the nucleophilic substitution, polar effect of N-oxide group in pyridazine 1-oxide is smaller than that of ring nitrogen unlike the cases of pyridine 1-oxide and quinoline 1-oxide.

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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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