BuOH–AcOH–H_2O (5:1:4) for about 20 hours. The paper was dried in air, portions corresponding to the products were cut out, and eluted descendingly with $N/4$ ammonium hydroxide. Each of these metabolites was hydrolyzed with hydrochloric acid and determined by the colorimetric method using the Ehrlich's reagent as sulfadiazine. The content was calculated from a calibration curve prepared beforehand.

The amount excreted 48 hours after oral administration of 2 g. of sulfadiazine was 1620 mg., calculated as sulfadiazine, including 862 mg. of sulfadiazine, 730 mg. of N^4-acetylsulfadiazine, 11 mg. of sulfadiazine-N^4-glucuronide, 14 mg. of sulfadiazine-N^4-sulfonate, and 5 mg. of sulfanilamide, calculated as sulfadiazine respectively.

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94. Ichiro Matsuo, Kazuro Sugimoto,*1 and Sadao Ohki*2 : Synthesis of Quinolizine Derivatives. XVI.*3 Synthesis of 3-(Subst.-benzyl)quinolizidine.

(*The Technical Research and Development Institute, Japan Defence Agency, Medical Department Self Defence Force,*1 *and Tokyo College of Pharmacy*2)

The sulfate of sparteine, one of the alkaloids isolated from *Cytisus scoparius* and *Lupinus luteus* has been widely used as an uterus contracting agent, bnt its action was considered to be not strong enough for the practical use. Therefore, in order to find out more active substances than sparteine with stronger activity, the authors attempted to synthesize scores of quinolizidine derivatives and their pharmacological actions were discussed.[1)]

In this paper since sparteine was considered to be composed of two quinolizidine nucleus, syntheses of simple quinolizidine derivatives such as 3-(*p*-subst.-benzyl)quinolizidine were described to examine the contracting activity.

Among the compounds synthesized, 3-phenyl-, 3-butyl- and 3-amyl-quinolizidines were found to show several folds of activity to sparteine sulfate, when tested by the Magnus method with the extracted intestinal canal from guinea pigs. However, the test results of these compounds *in vivo* was not always parallel to that by the Magnus method and a big question was raised upon the practical efficacy. Based upon these facts, preparation of quinolizidine series of stronger activity with less accessory reactions, were attempted with great expectation.

This report deals with the discovery of one promissing compound with stronger activity, even by the test *in vivo*.

In a previous paper,[1)] 3-subst.-quinolizidine was found to show the probable chemical structures to cause the action. Among the 3-subst. compounds synthesized, 3-(subst.-benzyl)-derivative (I) was found to show a remarkable action, and especially

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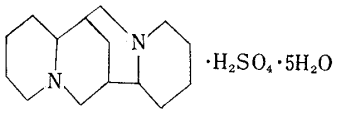
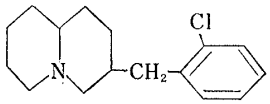
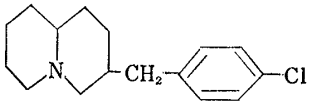
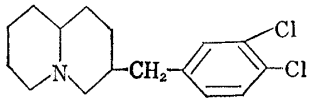
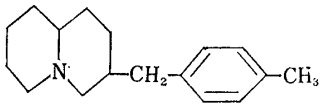
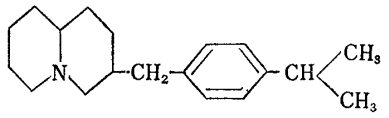
*3 Part XIV : This Bulletin, **14**, 147 (1966). Part XV : Yakugaku Zasshi, submitted for publication.
1) Part XIII : This Bulletin, **10**, 1250 (1962).

3-(*p*-chlorobenzyl)quinolizidine (Ib) was recognized to be the strongest (Table I).

Table I. Pharmacological Test

Compound No.	Structure	Uterus contracting action: Magnus Rabbit 10^{-6} g./ml.	Uterus contracting action: *in vivo* Rabbit 0.5~2.0 mg./kg.	Blood pressure: Rabbit 0.5~2.0 mg./kg.
—		+	++	slightly down
Ia		+	+	〃
Ib		+++	+++	very slightly down
Ic		++	++	slightly down
Id		++	++	〃
Ie		++	++	〃

Pharmacological tests were made with the sulfate of samples using rabbit. Strength of the action was compared with sparteine sulfate.

Clinical data reveal that Ib possesses several folds of activity to sparteine in contracting uterus both *in vitro* and *in vivo*, being accompanied with about one third of accessory reactions.

Intermediate pharmacological tests were already reported.*[4]

In this paper, synthesis of Ia~e was described. The synthetic processes by the two methods (1) and (2), were shown in Charts 1 and 2 below, respectively. Ia~e were prepared by the method (1), shown in Chart 1 and also Ib was synthesized by the method (2), shown in Chart 2. The compounds (Ia~e) contain two kinds of diastereomer and the ratio of the mixture of the isomer was studied by the different synthetic methods, described bellow.

The method (1) shown in Chart 1 is the one corresponding to the method reported on 3-alkyl-, aralkylquinolizidine synthesis.[2,3] 3-Ethoxycarbonyl-4-quinolizidinone (Ⅱ)[2] was led to its sodium salt with sodium metal in anhydrous toluene and it was heated with benzylchloride derivatives to give 3-ethoxycarbonyl-3-(subst.-benzyl)-4-quinolizidinone (Ⅲ), which was hydrolyzed in ethanolic alkaline solution and 3-(subst.-benzyl)-4-quinolizidinone*[5] (Ⅴ) was obtained, following to decarboxylation (Table Ⅱ).

*[4] R. Nagashima, N. Takano, A. Shioya : Presented at the 30th Kanto Divisional Meeting, Pharmacological Society of Japan, June 13, 1964; S. Mizuno, K. Saito, A. Ohta : Presented at the 32th Kanto Meeting, The Japanese Obstetrical and Gynecological Society, May 30, 1965.

*[5] A special investigation on the two possible diastereomers was not carried out.

2) S. Ohki, Y. Noike : Yakugaku Zasshi, **72**, 490 (1952); S. Ohki, I. Matsuo : This Bulletin, **7**, 892 (1959).

3) I. Matsuo : Yakugaku Zasshi, **81**, 1083 (1961).

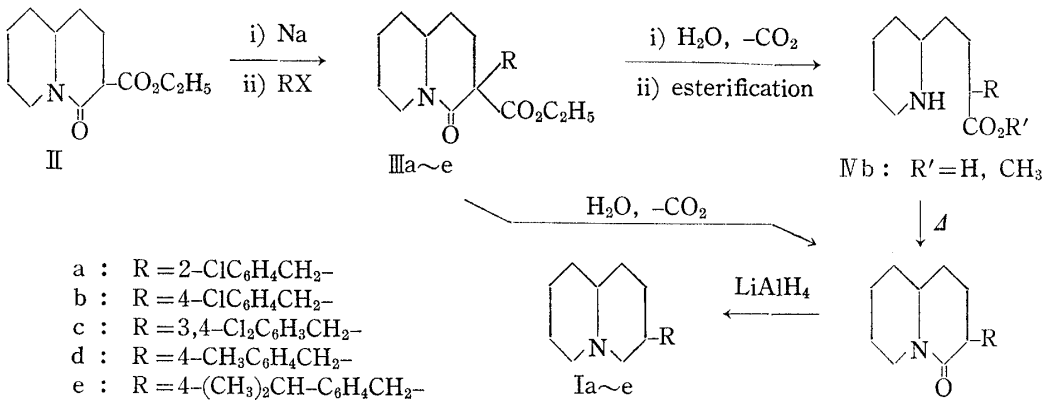


Chart 1.

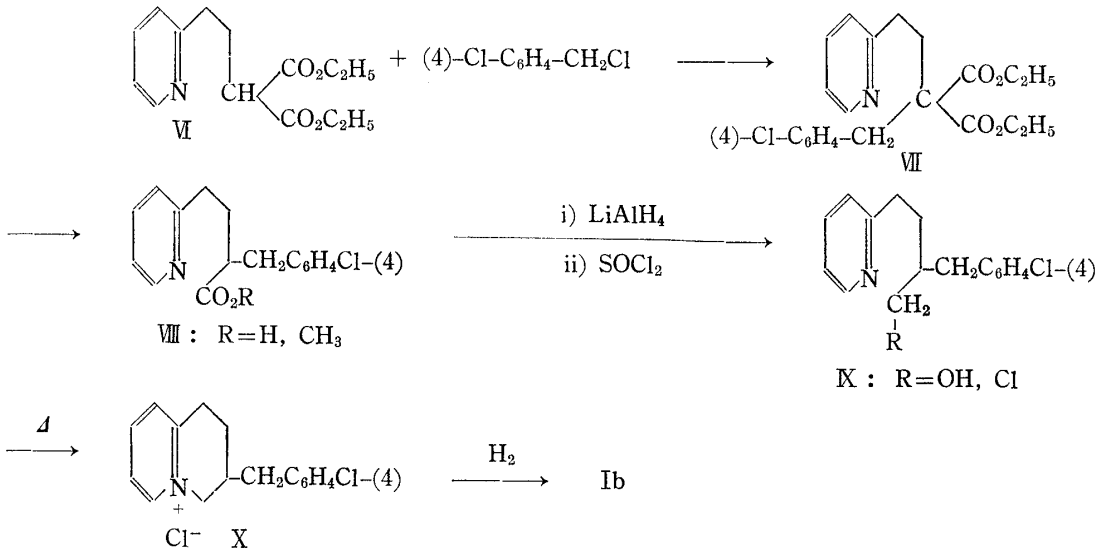


Chart 2.

Another synthetic method of Vb was studied seperately from Ⅲ to Ⅴ through Ⅳ but any superior yield to the method Ⅲ to Ⅴ has not been observed.

Reduction of Ⅴ with lithium aluminum hydride afforded 3-(subst.-benzyl)quinolizidine (Ⅰ) (Table Ⅲ).

Free base of Ia~e showed generally wide range of melting point and boiling point, which suggested that there exists a mixture of two diastereomers. As to Ib, a separation was attempted as described later.

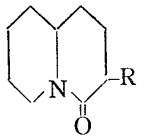
Their sulfate were used for the pharmacological test and no special attention was paid on the stereoisomer.

As the pharmacological action of Ib was remarkable, another method (2) of synthesis was comparatively examined.

Diethyl (4-chlorobenzyl)[2-(2-pyridyl)ethyl]malonate (Ⅶ) was prepared by the reaction of sodium salt of diethyl [2-(2-pyridyl)ethyl]malonate (Ⅵ)[4] and *p*-chlorobenzyl chloride in anhydrous toluene. After it was hydrolysed by heating with 20% hydrochloric acid, followed by decarboxylation, 2-(*p*-chlorobenzyl)-4-(2-pyridyl)butyric acid (Ⅷ : R=H) was synthesized. The overall yield from Ⅵ to Ⅷ (R=H) was 57.7%. Esterification afforded butyric acid methyl ester (Ⅷ : $R=CH_3$), the yellow color of which was changed into red immediately during the distillation and it was gradually resinified when kept standing. This was reduced with lithium aluminum hydride in tetrahydrofuran into butanol (Ⅸ : R=OH). The oily substance gave its picrate, m.p.

4) S. Ohki, K. Yamakawa : This Bulletin, **1**, 260 (1953).

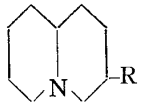
TABLE II.



Compound No.	R	Formula	Appearance	b.p. °C/mm. Hg (m.p. °C)	Recryst. solv.	Yield from II (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Va	2-Cl-C_6H_4-CH_2-	$C_{16}H_{20}ONCl$	colorless plates	210/6 (100～106)	acetone-ether	58.2	69.12	7.25	—	69.08	7.39	—
Vb	4-Cl-C_6H_4-CH_2-	〃	〃	215～225/6 (111～113)	ether	61.8	69.12	7.25	—	69.21	7.47	—
Vc	3,4-Cl_2-C_6H_3-CH_2-	$C_{16}H_{19}ONCl_2$	〃	(94～97)	〃	53.5	61.59	6.14	4.49	62.08	6.37	4.66
Vd	4-CH_3-C_6H_4-CH_2-	$C_{17}H_{23}ON$	faint greenish oil	165～168/4	——	53.7	—	—	5.45	—	—	5.55
Ve	4-$(CH_3)_2CH$-C_6H_4-CH_2-	$C_{19}H_{27}ON$	yellow orange oil	chromatographed with ether	——	50.0	—	—	—	—	—	—

IR (CONH): Va 1630 (KBr), Vb 1620 (KBr), Vc 1617 (KBr), Vd 1640 (liq.)

TABLE III.

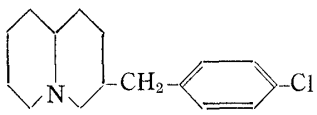


Compound No.	R	Formula free base or derivatives	Appearance	b.p. °C/mm. Hg (m.p. °C)	Recryst. solv.	Yield from V (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	2-Cl-C_6H_4-CH_2-	free base $C_{16}H_{22}NCl$	colorless oil	147～155/4	——	80	73.06	8.43	—	72.98	8.60	—
		HCl-salt $C_{16}H_{23}NCl_2$	colorless powder	(238～239)	EtOH-AcOEt	—	64.05	7.73	—	64.01	7.73	—
Ib	4-Cl-C_6H_4-CH_2-	free base $C_{16}H_{22}NCl$	colorless plates	186～192/6.5 (40～55)	MeOH-H_2O or acetone-H_2O	80～85	73.06	8.43	5.31	72.85	8.41	4.97
		methiodide $C_{17}H_{25}NClI$	colorless powder	(187～191)	EtOH-ether	—	50.29	6.21	3.54	50.70	6.24	3.98
		phenolphthalinate $C_{36}H_{38}O_4NCl$	〃	(159～162)	H_2O-ether	—	74.03	6.56	2.39	73.79	6.88	2.21
		tartarate $C_{20}H_{28}O_6NCl \cdot H_2O$	〃	(115～118)	H_2O-acetone	—	55.60	7.00	3.24	55.80	6.96	3.03
		HCl-salt $C_{16}H_{23}NCl_2$	〃	(181～182)	acetone-*n*-hexane	—	64.05	7.73	—	63.69	7.71	—
Ic	3,4-Cl_2-C_6H_3-CH_2-	free base $C_{16}H_{21}NCl_2$	faint yellow oil	185～192/4	——	60	64.48	7.10	—	64.05	6.97	—
		picrate $C_{22}H_{24}O_7N_4Cl_2$	yellow plates	(166～168)	AcOH-EtOH	—	50.14	4.59	—	50.45	4.70	—
		HCl-salt $C_{16}H_{22}NCl_2$	colorless powder	(158～162)	AcOEt-petr. ether	—	57.36	6.62	—	57.39	6.87	—
Id	4-CH_3-C_6H_4-CH_2-	free base $C_{17}H_{25}N$	faint greenish oil	165～168/4 (49～56)	——	86.2	—	—	5.75	—	—	5.54
		methiodide $C_{18}H_{28}NI$	colorless plates	(196～198)	EtOH-AcOEt	—	56.01	7.31	3.63	55.94	7.27	3.23
Ie	4-$(CH_3)_2CH$-C_6H_4-CH_2-	free base $C_{19}H_{29}N$	faint greenish oil	160～170/5	——	70	—	—	5.16	—	—	4.81
		methiodide $C_{20}H_{32}NI$	faint yellowish powder	(145～147)	acetone	—	58.02	7.79	3.38	57.99	7.73	3.22

125~127°. Ester (Ⅷ : R=CH_3) are apt to be strongly resinified and butyric acid (Ⅷ : R =H) was used for the reduction similarly to the method with lithium aluminum hydride in tetrahydrofuran into butanol (Ⅸ : R=OH) in 70.4% yield. The direct reduction method of carboxylic acid was found to be superior to the others. Chlorination of (Ⅸ : R=OH) with thionyl chloride produced butyl chloride (Ⅸ : R′=Cl) in 74.4 % yield, which was later cyclized to 3-(*p*-chlorobenzyl)-1,2,3,4-tetrahydroquinolizinium chloride (X) by heating, in 77.5% yield. Catalytic reduction of X afforded the expected Ib in 78.6% yield with platinic oxide and in 70.0% with Raney nickel. Therefore, the method (1) was found to be superior to the method (2) In the synthesis of Ib.

Nextly, a separation of diastereomer of Ib in Ia~e series was attempted. The distillation of Ib, obtained by both the methods (1) and (2), it was crystallized to a substance m.p. 40~55°, from which only one sort of crystal, m.p. 73°, (picrate, m.p. 198~199°) were separated, after repeated recrystallizations.

It was difficult to obtain the other isomer in pure state and the separation was tried as a form of picrate because the separation was found to be difficult as a free base. Picrate was deposited in ethanolic solution by an addition of a little excess of picric acid and collected. It was supposed to be a mixture of the two kinds of isomers of showing the melting point in the range 168~189°. The filtrate was concentrated and the picrates produced were separated, showing m.p. 156~163°. They are then separated into two kinds of picrate : one of them show m.p. 156~157° and is comparatively soluble in warm ethanol and the other shows the compound of m.p. 198~199°, which is hardly soluble in ethanol but soluble in warm acetic acid. The latter picrate, m.p. 198~199° was found to be identical with the picrate, (m.p. 198~199°) derived from the compound of free base, m.p. 73° described above. From the former picrate, m.p. 156~157° free base of m.p. 60° was obtained. In Table Ⅳ, the details are summarized.

Table Ⅳ. Isomers of 

Isomers	Free base or derivatives	Formula	Appearance	m.p. (°C)	Recryst. solv.	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
A	free base	$C_{16}H_{22}NCl$	colorless plates	73	MeOH-H_2O or acetone-H_2O	73.06	8.43	5.33	72.86	8.36	5.43
	picrate	$C_{22}H_{25}O_7N_4Cl$	yellow prisms	198~199	AcOH	53.64	5.07	11.37	53.56	5.18	11.55
	methiodide	$C_{17}H_{25}NClI$	colorless plates	209~211	EtOH-ether	50.29	6.21	3.54	50.57	6.53	3.20
B	free base	$C_{16}H_{22}NCl$	colorless plates	60	MeOH-H_2O or acetone-H_2O	73.06	8.43	5.33	72.86	8.34	5.43
	picrate	$C_{22}H_{25}O_7N_4Cl$	yellow plates	155~157	EtOH	53.64	5.07	11.37	53.97	5.12	11.51
	methiodide	$C_{17}H_{25}NClI$	colorless plates	205~207	EtOH-ether	50.29	6.21	3.54	50.42	6.42	3.36

Both compounds of m.p. 73° and m.p. 60° showed the IR absorption of *trans*-quinolizidine ring at 2700~2800 cm^{-1} [5] and they corresponded to either 3-equatorial (*p*-chlorobenzyl)-*trans*-quinolizidine or 3-axial (*p*-chlorobenzyl)-*trans*-quinolizidine.

According to the method shown in the Chart 1, both picrates of Ib, m.p. 198~199°

5) F. Bohlmann : Angew. Chem., **69**, 645 (1957).

and m.p. 156~157° were obtained in the ratio of about 5:1 (total amount of which corresponds to 57.6% of separable pure picrates) and the method (2) showed the ratio of about 1:5 (or 1:6.5) (total amount of which corresponds to either 48.0 or 52.6% of separable pure picrates). The accuracy of these ratios could not be expected because of the poor total yield and of the complicated separation method of picrate, depending on the solubility, but it may be considered to give one of the materials for the determination of steric structure. According to the usual separation method of two isomers, separations as either a free base or picrate were attempted. However, the separation of the two isomers of different melting point needs so much complicated operation and the respective yield was so poor that gas chromatographic separation was attempted. On the other hand, measurements of nuclear magnetic resonance (NMR) and dipole moment on each isomer, obtained by one of the methods were made. The conformation of the isomers are studied and the details will be reported in the sucussive paper.

Experimental

3-(*p*-Chlorobenzyl)quinolizidine (Ib) was mainly described as an example (Table II and III).

Synthesis According to the Method (1)

3-(*p*-Chlorobenzyl)-4-quinolizidinone (Vb)——Method A : 70.0 g. of 3-ethoxycarbonyl-4-quinolizidinone[1] was dissolved in 500 ml. of anhydrous toluene, and it was refluxed with 7.0 g. of sodium powder to give Na-salt. To this 50.0 g. of 4-chlorobenzyl chloride was added and refluxed for 12 hr. After cooling, water was added to remove the produced NaCl in the reaction and the water layer was separated. The toluene layer was separated, after being dehydrated with Na_2SO_4. Evaporation of toluene gave crude oily substance, 3-(*p*-chlorobenzyl)-3-ethoxycarbonyl-4-quinolizidinone (IIIb), which was saponified by refluxing in 1500 ml. of 20% alcoholic KOH (1.8 moles of KOH) for about 8 hr. After the evaporation of EtOH, the residual water solution, in order to remove the unsaponified substance was extracted with a shake of ether. The remaining water layer was acidified with acetic acid and then extracted with benzene, followed by the desiccation over Na_2SO_4. After evaporating benzene, the residue was heated at 150~170° for one hour to decarboxylation. Glutenous substance after decarboxylation was dissolved in 200 ml. of benzene, washed with 10% NaOH to remove undecarboxylated substance and water, dehydrated with Na_2SO_4 and benzene was evaporated and finally it was distilled *in vacuo*, $b.p_6$ 210~215°, yielding 32.5 g. (61.8%), which was crystallized in colorless plates, m.p. 111~113°, recrystallized from ether.

Method B : (i) 2-(*p*-Chlorobenzyl)-4-(2-piperidyl)butyric acid hydrochloride (VIb) : A mixture of 27.0 g. of IIIb the crude benzene solution of IIIb, after evaporation of toluene, was purified through alumina chromatography developed by benzene and 300 ml. of 20% HCl was refluxed for 8 hr. and the concentration of the reaction solution *in vacuo* gave glutinous substance, which was solidified. Recrystallization from acetone-ether gave colorless plates, m.p. 207° in 70% yield. *Anal.* Calcd. for $C_{16}H_{22}O_2NCl \cdot HCl$: C, 57.88; H, 6.68; N, 4.22. Found : C, 57.80; H, 6.70; N, 4.31. IR cm^{-1} : 1730 (-COOH). (ii) IVb (R'=H)→IVb (R'=CH_3) : 11.0 g. of hydrochloride of IVb (R'=H) was dissolved in 100 ml. of anhydrous MeOH and refluxed for 6 hr. on a water bath, after dry HCl gas was saturated. MeOH was removed and the residue was recrystallized from acetone-ether to give 8.3 g. of hygroscopic colorless plates, m.p. 93~94°. *Anal.* Calcd. for $C_{17}H_{24}O_2NCl \cdot HCl$: C, 58.95; H, 7.22; N, 4.04. Found : C, 59.07; H, 7.33; N, 4.05. IR cm^{-1} : 1625 (-$COOCH_3$). (iii) IVb (R'=CH_3)→Vb : 8.0 g. of IVb (R'=CH_3) hydrochloride was dissolved in water, basified with K_2CO_3 paste and the oily substance was extracted with benzene and washed with water. After evaporation of benzene, it was further heated at about 130° for dealcoholation. After a gradual rise of oil temperature up to 230°, it was switched to the vacuum distillation to give 4.9 g. of viscous pale yellow oil, $b.p_6$ 213~223° which was crystallized in colorless plates, m.p. 110~112° in 66.2% yield. A mixed melting point on admixture with the compound obtained by the Method A showed no depression.

3-(*p*-Chlorobenzyl)quinolizidine (Ib)——8.7 g. of Vb was reduced by refluxing for 8 hr. with 1.2 g. of $LiAlH_4$ in either tetrahydrofuran or ether. After kept standing overnight, it was decomposed with ice-water and extracted with benzene, being desiccated over K_2CO_3. Evaporation of benzene gave pale yellow viscous oil, $b.p_{6.5}$ 186~192°, 6.2 g. in 74.4% yield. It was crystallized on keep standing. Recrystallization from a MeOH-H_2O mixture gave colorless plates, m.p. 40~55°, a mixture of two racemates being separated later.

Synthesis by the Method (2)

2-(*p*-Chlorobenzyl)-4-(2-pyridyl)butyric Acid (VIII : R=H)——(i) Diethyl (*p*-chlorobenzyl)[2-(2-pyridyl)-ethyl]malonate (VI) : 80 g. of diethyl [2-(2-pyridyl)ethyl]malonate (VI) was dissolved in 350 ml. of anhydrous toluene, to this was added 6.9 g. of sodium metal and they were refluxed for 10 hr. by agitation to give clear red sodium salt solution (VI). To this 50.0 g. of *p*-chlorobenzyl chloride in 200 ml. of anhydrous toluene was added dropwise and they were further reacted for 12 hr. at 110°. After cooling, a little amount of water

was added to remove the produced NaCl in the reaction and toluene was separated, followed by the concentration, giving crude red glutinous substance Ⅶ. (ii) Ⅶ→Ⅷ : Ⅶ was dissolved in 500 ml. of 20% HCl and it was saponified by refluxing for 12 hr., followed by decarboxylation. The residual glutinous substance after evaporation *in vacuo*, was dissolved in 50% KOH under cooling and neutral substances was removed by extracting with benzene. The alkaline solution was acidified with AcOH and extracted with benzene, which was followed by washing with water and dehydrating with Na_2SC_4. After removing impurities by passing through permutite column, benzene was evaporated to give crude Ⅷ, which was recrystallized from acetone to afford 50.0 g. of colorless plates, m.p. 112~113° in 57.7% yield. *Anal.* Calcd. for $C_{16}H_{16}O_2NCl$: C, 66.26; H, 5.56; N, 4.83. Found : C, 66.28; H, 5.74; N, 4.70. IR cm^{-1}: 1740 (COOH).

Methyl Ester (VIII : R=CH_3)——The glutinous substance (Ⅷ : R=H)·HCl, obtained by heating Ⅶ with HCl was dissolved in MeOH and it was refluxed on a water bath for 8 hr. after dry HCl gas was saturated under ice cooling. After being concentrated *in vacuo*, it was alkalified with K_2CO_3 paste and extracted with benzene, which was then washed with water, followed by desiccation over Na_2SO_4. After evaporating benzene, distillation gave yellow oil, $b.p_{5\sim5.5}$ 185~192°, which turned red coloration in the contact with air. It showes stronger tendency of later resinification. Yield 78%. IR cm^{-1} : 1732 ($COOCH_3$). Picrate : greenish yellow crystals, m.p. 85°(from EtOH). *Anal.* Calcd. for $C_{17}H_{18}O_3NCl\cdot C_6H_3O_6N_3$: C, 51.98; H, 3.98; N, 10.39. Found : C, 52.18; H, 4.24; N, 10.51.

2-(*p*-Chlorobenzyl)-4-(2-pyridyl)-1-butanol (IX : R=OH)——(a) 14.5 g. of acid (Ⅷ : R=H) was dissolved in 100 ml. of dehydrated tetrahydrofuran and it was added dropwise to the suspension of 2 g. of $LiAlH_4$ in the same solvent with agitation under cooling with water. After 5 hr. reflux on a water bath, it was kept standing overnight. After the reaction mixture was decomposed with water, it was extracted with 150 ml. of benzene which was then washed with water and desiccated over Na_2SO_4. Distillation gave 9.7 g. of faint yellow oil, $b.p_5$ 197~205° in 70.4% yield. (b) 9.5 g. of methyl ester (Ⅷ : R=CH_3) was dissolved in 100 ml. of anhydrous tetrahydrofuran and it was added to the 30 ml. of $LiAlH_4$ suspension in the same solvent dropwise under ice cooling, stirred for 5 hr. and kept standing overnight in N_2 stream. It was decomposed with water, extracted with benzene and treated similarly to (a), giving 5 g. in 58.2% yield. Picrate : faint greenish yellow plates, m.p. 125~127° (from EtOH). *Anal.* Calcd. for $C_{16}H_{18}ONCl\cdot C_6H_3O_7N_3$: C, 52.27; H, 4.19; N, 11.11. Found : C, 52.14; H, 4.34; N, 10.89.

Chloride (IX : R=Cl)——9.5 g. of the alcohol (Ⅸ : R=OH) was dissolved in 80 ml. of dehydrated $CHCl_3$ and to this 28 ml. of $SOCl_2$ was added dropwise under cooling. It was refluxed for 3 hr. on a water bath and kept standing overnight. Evaporation of $CHCl_3$ *in vacuo* gave hydrochloride, colorless plates, m.p. 163~164° in 68% yield, recrystallized from acetone. *Anal.* Calcd. for $C_{16}H_{17}NCl_2\cdot HCl$: C, 58.05; H, 5.48; N, 4.23. Found : C, 57.85; H, 5.54; N, 4.50.

3-(*p*-Chlorobenzyl)-1,2,3,4-tetrahydroquinolizinium Chloride (X)——The hydrochloride of the chloride (Ⅸ : R=Cl) obtained above was dissolved in a small amount of water, alkalified with $KHCO_3$ and it was extracted with anhydrous toluene, followed by washing with water and desiccation over $CaCl_2$. After 5 hr. reflux of the toluene solution, glutinous substance was precipitated. It was kept standing overnight, the supernatant was removed by decantation, the residue was washed with anhydrous petroleum ether and recrystallization from MeOH-acetone gave colorless plates, being, very hygroscopic, m.p. 77~78° in 77.5% yield. *Anal.* Calcd. for $C_{16}H_{17}NCl_2\cdot 1\frac{1}{2}H_2O$: C, 59.81; H, 6.23; N, 4.36. Found : C, 59.56; H, 6.35; N, 4.34.

Synthesis of Ib by the Reduction of quinolizinium Chloride (X)——(a) 1.0 g. of X was dissolved in 30 ml. of dehydrated EtOH, and it was treated with catalytic reduction under atmospheric temperature and pressure, in the presence of 0.3 g. of PtO_2. After the separation of catalyst, the filtrate was evaporated and it was dissolved in a small amount of water, which was alkalified with K_2CO_3 paste. It was extracted with benzene, washed with water and desiccated over Na_2SO_4. Distillation gave 0.7 g. of colorless viscous oil, $b.p_{4.5}$ 155~165° in 78.6% yield. (b) 1.1 g. of X was dissolved in 30 ml. of anhydrous EtOH, to this 30 mg. of AcONa and 0.5 g. of Raney Ni were added. It was reduced catalytically at 10 initial atomic pressure at room temperature, 28~32°. After the separation from the catalyst, the filtrate was concentrated, alkalified with K_2CO_3 paste and extracted with benzene. A similar treatment gave oily substance in 70% yield. The IR spectra of both compounds obtained according to the (a) and (b) method are quite identical. The substance is a mixture of stereoisomers.

Separation of Stereoisomer of Ib (Table IV)——Separation of picrate : 1.8 g. of Ib prepared according to the method (1) was dissolved in 100 ml. of EtOH and to this 1.8 g. of picric acid was added and warmed for a while. It was kept standing to cool for crystallization. Crystals are deposited by rubbing the wall of the flask at about 30° of interior temperature was separated to give 2.2 g. of picrate, m.p. 168~189°. The filtrate was concentrated to half the volume and kept standing, giving 0.5 g. of picrate, m.p. 156~163°. Total yield of picrate was 82%. Recrystallization of the former crystal, m.p. 168~189° from AcOH gave 1.6 g. of crystal, m.p. 198~199°. Recrystallization of the crystal, m.p. 156~163° from EtOH gave 0.3 g. of crystal, m.p. 156~157°. Pure picrate was yielded in 57.6% and the ratio by weight $\frac{\text{m.p. 198~199°}}{\text{m.p. 156~157°}}=\frac{5}{1}$

(This ratio varies a little with the operation process). According to the method (2), when Ib was reduced with PtO_2, the ratio was : $\frac{\text{m.p. } 198\sim199^\circ}{\text{m.p. } 156\sim157^\circ}=\frac{1}{5}$ (total yield of picrate is 48.0%) and in the case with Raney Ni, the ratio was $\frac{1}{6.5}$ (total yield is 52.6%).

Free base : Picrate was suspended in 10% KOH solution and then it was extracted with benzene, which was washed with water and desiccated over Na_2SO_4. Evaporation of benzene gave free base in 88.2~90% yield.

Methiodide : A reflux with CH_3I in MeOH for one hour prepared methiodide in quantitative yield.

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Summary

Some kinds of simple quinolizidine derivatives were recently found to possess sparteine-like uterus contracting action and this time the new substance with stronger contracting action has been found. Among 3-(subst.-benzyl)-quinolizidine derivatives, 3-(4-chlorobenzyl)-quinolizidine (Ib) was found to be the strongest. Ib showed several folds of activity to sparteine sulfate both *in vitro* and *in vivo* and the toxicity was found to be about one third of it.

The synthesis of Ib was carried out according to the two method (1) and (2), the former synthetic process being found to be beneficial.

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95. Fumio Yoneda, Takayuki Ohtaka, and Yoshihiro Nitta : Pyridazine Derivatives. X.*1 10*H*-Benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine and 5*H*-Benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine.

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In an earlier communication[1] the reaction of 4-(2-amino-phenylthio)-3,6-dichloropyridazine with hydrochloric acid has been shown to give 3-chloro-5*H*-benzo[*b*]pyridazino[4,3-*e*][1,4]thiazine (3,4-diazaphenothiazine type) as well as 3-chloro-10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4]thiazine (1,2-diazaphenothiazine type) originally claimed.[2] This novel entry into 3,4-diazaphenothiazine system prompted us to look more closely into synthetic methods for these preparations and also to investigate the mechanism of these reactions by a molecular orbital method. In the present paper we report the details of some of our investigations.

Treatment of 3,4,6-trichloropyridazine with 2-aminothiophenol in methanolic potassium hydroxide solution yielded 4-(2-aminophenylthio)-3,6-dichloropyridazine (I). In this case, proof of the structure of I was obtained from the fact that the condensation of 4-bromo-3,6-dichloropyridazine (II) with 2-aminothiophenol gave the same

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*1 Part IX : Yakugaku Zasshi, in press.

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