General Procedure for the Benzylation of 3-Substituted Cyclohepta[b]pyrrol-8(1H)-one—A suspension of 3-substituted cyclohepta[b]pyrrol-8(1H)-one and one molar equivalent of *K* in dry toluene was refluxed for 4 hr. to give the corresponding potassium salt. To that mixture was added a slight excess of benzyl chloride. After stirring under reflux for 7~10 hr., the reaction mixture was poured into water. The separated organic layer was concentrated under reduced pressure and the residue was recrystallized from EtOH. Results are shown in Table II.

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Summary

In an effort to obtain active analgesic and anti-inflammatory agents, alkylation of cycloheptimidazolone and cyclohepta[b]pyrrolone was carried out. Benzylation of 4- and 6-hydroxycycloheptimidazol-2(1H)-one afforded 1-benzyl and 1,3-dibenzyl derivatives. Benzylation of cyclohepta[b]pyrrol-2(1H)-one afforded 1- and 3-benzyl derivatives. Benzylation of cyclohepta[b]pyrrole-2,8(1H,3H)-dione which is considered to be present in many tautomers afforded 3-benzyl, 3,3- and 1,3-dibenzyl, 1,3,3-tribenzyl and 1,3-dibenzyl-8-benzyloxy derivatives. By the alkylation of cycloheptimidazol-2(1H)-one and 3-substituted cyclohepta[b]pyrrol-8(1H)-one, a number of 1-alkyl derivatives were prepared. Among these products, 1-benzylcycloheptimidazol-2(1H)-one has been found to be the most active analgesic and anti-inflammatory agent.

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63. Shigenobu Okuda,*¹ Isamu Murakoshi,*² Hiromitsu Kamata,*¹ Yoshihiko Kashida,*³ Joju Haginiwa,*² and Kyosuke Tsuda*¹ :

Studies on Lupin Alkaloids. I. The Minor
Alkaloids of Japanese *Sophora flavescens*.

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In 1889, Nagai and his coworker¹⁾ isolated an alkaloid named matrine (I), m.p. 78°, $[\alpha]_D +39.1^\circ$ (H₂O), from a chinese drug "Kushin (a dry root of *Sophora flavescens*)."
Until recently very little was known regarding the minor alkaloids of this plant and only oxymatine (matrine N-oxide) (II) had been characterized.^{1,2)}

In 1958, Bohlmann³⁾ reported the isolation of (+)-matrine (I), (+)-oxymatine (II), (+)-sophoranol (III), (–)-anagyrine (IV), (–)-methylcytisine (V) and (–)-baptifoline (VI) from

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Fig. 1. Separation Procedure of the Alkaloids of *Sophora flavescens*

Chart 1.

European³⁾ *Sophora flavescens*. Previous to that time, Kashida, *et al.*⁴⁾ isolated (–)-anagyrine (III) and (–)-methylcytisine (V) from the unsaponifiable alkaloid fraction of Japanese *Sophora flavescens*.

Therefore it seemed necessary to confirm whether or not Japanese plant contains (+)-sophoranol (III) and (–)-baptifoline (VI) as in the case of the European species. As is known, the alkaloid content in plant can vary according to the season and the local. To obtain reliable data on the minor alkaloids of Japanese *Sophora flavescens* of known origin, the roots in the suburb of Chiba city were collected early in June of 1960 (Just before flowering). The separation procedures of alkaloids are outlined in Fig. 1.

Procedure A (alumina chromatography accompanied by saponification with 10% alcoholic potassium hydroxide) was simpler than procedure B (repeated alumina chromatography), since by saponification (+)-matrine (I), the only major component of the ether soluble saponifiable alkaloidal mixture, was removed as potassium matrinate which easily regenerates I by relactonization according to Nagai's description.⁵⁾ This procedure is suitable for the isolation of unsaponifiable (–)-anagyrine (IV), (–)-methylcytisine (V) and (–)-baptifoline (VI). However (–)-sophocarpine (VII) and (–)-sophoranol (III) could not be isolated *via* this method because the former was converted into the C₁₇-base, reported by Kashida,⁴⁾ and the latter was hydrolyzed into the product which could not be separated from matrinic acid. The C₁₇-base has now been shown to be an artifact produced from (–)-sophocarpine (VII) on a prolonged heating in 10% alcoholic potassium hydroxide. Namely this compound is (–)-13-ethylsophoramine (VIII).⁶⁾

Although procedure B is orthodox and rather tedious, this served for the isolation of (–)-sophocarpine (VII) and (+)-sophoranol (III). (–)-Sophocarpine (VII) was first eluted accompanied with (+)-matrine (I) and purified by fractional recrystallization of the hydroiodides from absolute alcohol. (+)-Sophocarpine was first isolated by Orekov from *Sophora alopecuroides* L.⁷⁾, and was demonstrated to be a monodehydromatrine since its catalytic hydrogenation gave quantitatively (+)-matrine (I) after the one mole hydrogen absorption.⁸⁾ However the position of double bond was not clarified. The spectral data (IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{–1}: 1670, 1608 (α,β -unsaturated lactam). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ): 260 (2500)) clearly indicate the existence of α,β -unsaturated lactam⁹⁾ in (–)-sophocarpine and VII was proposed as its structure.¹⁰⁾

The physical constants and yields of the alkaloids isolated in the present study are summarized in Table I.

To determine the purity of alumina chromatographic eluate, paper partition chromatography was very helpful and the following solvent systems were used for ascending development: A) butanol-ethanol-*N*/2 acetic acid=6:2:3, B) butanol-conc. hydrochloric acid-water=5:1:1, C) butanol-pyridine-water=4:3:7.*⁴ System A separated matrine (I), oxymatrine (II), anagyrine (IV), methylcytisine (V) and baptifoline (VI), but did not separate matrine (I), sophoranol (III) and sophocarpine (VII) from each other. System B separated matrine (I), oxymatrine (II), anagyrine (IV), methylcytisine (V) and

*⁴ The upper layer was used.

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TABLE I.

Alkaloids	Empirical formula	m.p. (°C)	$[\alpha]_D$	IR $\nu_{\text{CHCl}_3}^{\text{max}}$ cm^{-1}	UV λ_{max} $m\mu$ (ϵ) ^d	Yield ^e (%)
(+)-Matrine (I)	C ₁₅ H ₂₄ ON ₂	76	+ 39 ^b	2830, 2785 (<i>trans</i> -quinolizidine) 1617 (lactam C=O)		0.40
(+)-Oxymatrine (II)	C ₁₅ H ₂₄ O ₂ N ₂	207	+ 47 ^b	no <i>trans</i> -quinolizidine band 1616 (lactam C=O)		0.073
(+)-Sophoranol (III)	C ₁₅ H ₂₄ O ₂ N ₂	171	- 66 ^b	3400 (OH) 2815, 2768 (<i>trans</i> -quinolizidine) 1619 (lactam C=O)		0.035
(-)-Anagyrene (IV)	C ₁₅ H ₂₀ ON	oil	- 166 ^c	1653, 1567, 1548 (α -pyridone)	309 (8000) 233 (6800)	0.026
(-)-Methylcystisine (V)	C ₁₂ H ₁₆ ON ₂	136	- 228 ^b	1656, 1567, 1550 (α -pyridone)	309 (8000) 234 (6400)	0.010
(-)-Baptifoline (VI)	C ₁₅ H ₂₀ O ₂ N ₂	210	- 135 ^c	1650, 1565, 1550 (α -pyridone)	309 (8200) 233 (7000)	0.022
(-)-Sophocarpine (VII)	C ₁₅ H ₂₂ ON ₂	54 ^a	- 32 ^c	2825, 2780 (<i>trans</i> -quinolizidine) 1670, 1600 (α, ϵ -unsaturated lactam C=O) 817 (<i>cis</i> double bond conjugated with C=O)	260 (2500)	0.012
C ₁₇ -Base (VIII)	C ₁₇ H ₂₄ ON ₂	178	76 ^c	2840, 2790 (<i>trans</i> -quinolizidine) 1642, 1595, 1552 (α -pyridone)	309 (9500) 240 (5900)	

a) monohydrate
d) EtOH-solntion

b) H₂O-solution
e) calculated based on a dry root weight.

c) EtOH-solution

sophocarpine (VII), but did not separate oxymatrine (II) from sophoranol (III), and methylcystisine (V) from baptifoline (VI). However system C easily separated oxymatrine (II) from sophoranol (III), and methylcystisine (V) from baptifoline (VI). Therefore the combination of these systems was used to characterize all seven alkaloids from *Sophora flavescens* (cf. Table II).

TABLE II.

Alkaloid	Rf Value		
	System A	System B	System C
Oxymatrine	0.51	0.66	0.70
Matrine	0.48	0.74	
Sophocarpine	0.47	0.82	
Sophoranol	0.45	0.66	0.86
Anagyrene	0.40	0.45	
Methylcystisine	0.35	0.33	0.75
Baptifoline	0.32	0.35	0.80

Experimental^{*5}

Extraction of the Alkaloidal Fraction—The fine chips (5.3 kg.) of the dry roots of *Sophora flavescens*, collected in the suburb of Chiba city from 10th to 15th, June, 1960 (Just before flowering), were extracted seven times with CH₃OH at room temperature and then three times with CH₃OH at room temperature and then three times with the same solvent at 40~50°. The extracts were combined, concentrated to 2 L. and was added with 2 L. of CHCl₃. The tarish precipitate was removed and the organic layer was extracted

*5 All melting and boiling points are uncorrected. Unless otherwise noted, IR and UV were measured in CHCl₃ and EtOH respectively, and column chromatography was carried out utilizing neutral alumina (Woelm).

with dil. HCl solution. After removal of organic solvent *in vacuo*, the aqueous layer was made strongly alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and evaporated to give 55.7 g. of crude alkaloidal fraction.

Alkaloid Isolation—According to the usual work up procedure, 28.7 g. of the above alkaloidal fraction was dissolved in a small amount of $CHCl_3$ and added to 7~8 fold volume of ether. The precipitated oxymatrine fraction was purified *via* its picrate and 2.0 g. of pure (+)-oxymatrine (II), m.p. 207° (from acetone), were obtained. Evaporation of ether soluble fraction resulted in 18.24 g. of slightly brown oil, which was treated as follows.

Procedure A (Alumina chromatography accompanied with saponification by 10% alcoholic KOH)—Chromatography of 7.04 g. of the above mentioned ether soluble base was carried out on 120 g. of alumina furnishing two fractions: I (benzene-ether eluates), 4.77 g., PPC (paper partition chromatography) showed that this contained mainly (+)-matrine (I) and a small amount of (–)-anagyryne (IV) and (–)-methylcytisine (V); and II (ether- CH_3OH eluates), 2.07 g., PPC showed that this contained (+)-matrine (I) and (–)-baptifoline (VI).

Fraction-I was refluxed in 10% alcoholic KOH for 36 hr., EtOH was evaporated *in vacuo* and extracted with $CHCl_3$. The unsaponifiable base (1.19 g.) thus obtained and the similar unsaponifiable base from Fraction-II-1 (*vide infra*) were combined, and chromatographed on 50 g. of alumina. The C_{17} -base was eluted first with benzene and recrystallized from ether-petr. ether to give 0.17 g. of fine prisms, m.p. 178°, $[\alpha]_D^{25} -76^\circ$ (c=0.95, EtOH). *Anal.* Calcd. for $C_{17}H_{24}ON_2$: C, 74.96; H, 8.88; N, 10.29. Found: C, 75.20; H, 8.91; N, 10.19.

After elution of C_{17} -base, the alkaloids absorbed on alumina were removed with CH_3OH and the eluate was distilled *in vacuo*. From the fraction of b.p._{0.08} 160~180°, (–)-anagyryne (IV) was isolated *via* its perchlorate, 0.40 g. of needles (from EtOH), m.p. 315°, which was identified with the authentic (–)-anagyryne perchlorate by mixed melting point and comparison of IR (Nujol). The free base regenerated from the perchlorate was distilled *in vacuo* to afford a very pale yellow oil (bath temp. b.p._{0.008} 180°), $[\alpha]_D^{25} -166^\circ$ (c=1.12, EtOH), IR of which was superimposable with that of authentic sample.

From the mother liquor of (–)-anagyryne perchlorate, the free base was regenerated and converted into the picrate. Recrystallization of the picrate from EtOH gave 0.22 g. of yellow needles, m.p. 234°. The free alkaloid from the picrate was recrystallized from ether. Needles, m.p. 136°, $[\alpha]_D^{25} -228^\circ$ (c=1.3, H_2O), which was identified with an authentic specimen of (–)-methylcytisine by mixed melting point and comparison of IR.

Fraction-II was purified by alumina (35 g.) chromatography: Fraction-II-1 (ether eluates), 0.87 g., PPC showed that this contained mainly (+)-matrine. After refluxing with 10% alcoholic KOH, the unsaponifiable material (0.1 g.) was obtained and combined with the similar fraction from Fraction-I (*vide supra*). Fraction-II-2 ($CHCl_3$ eluates), 0.50 g. The eluates containing (–)-baptifoline (VI) were combined and recrystallized from benzene or acetone to give 0.23 g. of needles, m.p. 210°, $[\alpha]_D^{25} -135^\circ$ (c=1.1, EtOH), which was sent to Professor Bohlmann and identified with the authentic specimen of (–)-baptifoline (VI) by mixed melting point and comparison of IR. *Anal.* Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74. Found: C, 69.35; H, 7.61.

Consequently, the data can be summed up as follows: From 7.04 g. of ether soluble base, 0.29 g. of (–)-anagyryne (IV), 0.10 g. of (–)-methylcytisine (V), 0.23 g. of (–)-baptifoline (VI), 0.17 g. of C_{17} -base*⁶ and 4.35 g. of saponifiable alkaloids (mainly (+)-matrine (I)).

Procedure B (Repeated alumina chromatography)—Chromatography of 5.89 g. of ether soluble base (*vide supra*) was carried out on 100 g. of alumina offering Fraction-I (eluate with 1500 ml. of benzene), 1.69 g., and Fraction-II (exhaustive eluate with CH_3OH -ether (1:19)), 3.90 g. Fraction-I was dissolved in a small amount of abs. EtOH and redistilled HI was added under cooling with an ice-salt mixture to make slightly acidic with congo red. The precipitated needles were recrystallized from abs. EtOH to afford 0.16 g. of (–)-sophocarpine HI, fine needles, m.p. 276~278° (decomp.). *Anal.* Calcd. for $C_{15}H_{22}ON_2 \cdot HI$: C, 48.13; H, 6.15; N, 7.49. Found: C, 48.03; H, 6.16; N, 7.78.

Free base was recrystallized from petr. ether to afford fine prisms, m.p. 54°, $[\alpha]_D^{25} -32^\circ$ (c=1.0, EtOH), which was identified with the authentic sample of (–)-sophocarpine (VII) by mixed melting point and comparison of IR. *Anal.* Calcd. for $C_{15}H_{22}ON_2 \cdot H_2O$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.61; H, 9.10; N, 10.30. Picrate, yellow prisms, m.p. 157~159° (from EtOH). *Anal.* Calcd. for $C_{15}H_{22}ON_2 \cdot C_6H_3O_7N_3 \cdot \frac{1}{2}H_2O$: C, 52.06; H, 5.41; N, 14.46. Found: C, 52.28; H, 5.37; N, 14.63.

Fraction-II was rechromatographed on 150 g. of alumina, from which (+)-matrine (I), (–)-anagyryne (IV) and (–)-methylcytisine (V) were eluted with only benzene in this order. The matrine fraction and the base generated from the mother liquor of (–)-sophocarpine HI (*vide supra*) were combined and recrystallized from petr. ether to give (+)-matrine (I), m.p. 74~76° 3.52 g. Benzene containing 20~50% ether eluted a small amount of remaining (–)-methylcytisine (V) and then (+)-sophoranol (III). The sophoranol fraction were combined and recrystallized from acetone to afford 0.31 g. of long prisms, m.p.

*⁶ This corresponds to 0.15 g. of (–)-sophocarpine (VII).

171°, $[\alpha]_D^{25} +65^\circ$ ($c=1.2$, H_2O), which was identified with authentic (+)-sophoranol (III) prepared from (+)-matrine (I) by mixed melting point and comparison of IR. The eluates with ether- CH_3OH (1:10) gave a mixture of (–)-baptifoline (VI) and a small amount of remaining (+)-oxymatrine (II).

Consequently 3.52 g. of (+)-matrine (I), 0.31 g. of (+)-sophoranol (III) and 0.11 g. of (–)-sophocarpine (VII) were isolated from 5.89 g. of the ether soluble base.

Summarized Data of Alkaloids of *Sophora flavescens*—Putting the above mentioned data together, the following results were obtained. 5.3 kg. of dry root gave 55.7 g. of crude alkaloidal fraction from which were isolated :

21.2 g. of (+)-matrine (I)	0.52 g. of (–)-methylcytisine (V)
3.88 g. of (+)-oxymatrine (II)	1.16 g. of (–)-baptifoline (VI)
1.86 g. of (+)-sophoranol (III)	0.63 g. of (–)-sophocarpine (VII)
1.40 g. of (–)-anagyrene (IV)	

Preparation of C_{17} -base ((–)-13-Ethylsophoramine (VIII)) from (–)-Sophocarpine (VII)—Thirty four milligram of (–)-sophocarpine (VII) was dissolved in 2.5 ml. of 10% EtOH-KOH and refluxed for 27 hr. EtOH was evaporated *in vacuo* and the residue was extracted with ether. After drying on anhyd. Na_2SO_4 , ether was removed to give a semicrystalline base which was purified by alumina column. Six milligram of fine needles, m.p. 178°, which was identified with the sample of C_{17} -base obtained above by mixed melting point and comparison of IR.

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Summary

(+)-Matrine (I), (+)-oxymatrine (II), (+)-sophoranol (III), (–)-anagyrene (IV), (–)-methylcytisine (V), (–)-baptifoline (VI), and (–)-sophocarpine (VII) were isolated from the dry root of Japanese *Sophora flavescens*.

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64. Shigenobu Okuda,*¹ Hidesato Kataoka,*² and Kyosuke Tsuda*¹ : Studies on Lupin Alkaloids. II.*³ Absolute Configuration of Lupin Alkaloid. I.

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In 1953, Cookson¹⁾ assigned the absolute configuration of (–)-lupinine and (+)-epilupinine as formulas I and V respectively on the basis of his own data and the fact that (–)-4-methylnonane (IV), $[\alpha]_D^{18} -1.3^\circ$ (neat) derived from I by Karrer and his coworkers²⁾

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