171°, $[\alpha]_D^{25}$ +65°(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 whidh were isolated :

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

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.

The authors express their deep gratitiude to Emeritus Professor (Tokyo University) E. Ochiai for his continuous interest throughout the course of this work. They are also indebted to Professor N. F. Proskurnina, S. Ordzhonikidze All-Union Chem. Pharm. Research Inst., Moscow, for the kind supply of (−)-sophocarpine and Professor F. Bohlmann, Technical University of Berlin, for his cordial cooperation. Thanks are also due to Misses H. Yamanouchi, K. Hayashi ank K. Arimoto in the Institute of Applied Microbiology, Tokyo University, for Microanalyses and infrared spectra.

Summary

(+)-Matrine (I), (+)-oxymatry (II), (+)-sophoranol (III), (−)-anagyrine (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.

(Institute of Applied Microbiology, University of Tokyo[*1]
and Kowa Chemical Laboratories, Kowa Co., Ltd.[*2])

In 1953, Cookson[1] 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° (neat) derived from I by Karrer and his coworkers[2]

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[*2] 3-399, Shimotakaido, Suginami-ku, Tokyo (片岡英達).

[*3] Part I. S. Okuda, I. Murakoshi, H. Kamata, Y. Kashida, J. Haginiwa, K. Tsuda : This Bulletin, **13**, 482 (1965).

1) R. C. Cookson : Chem. & Ind. (London), **1953**, 337.

2) P. Karrer, F. Canal, K. Zohner, R. Widmer : Helv. Chim. Acta, **11**, 1062 (1928).

had the same sign of optical rotation as (−)-4-methylnonane, $[\alpha]_D$ −1.7°, of known absolute configuration.*4

At that time, Karrer degraded I by successive Hofmann degradations and hydrogenations in order to clarify the skeletal structure and little care was taken to obtain optically pure 4-methylnonane for absolute configuration studies. Accordingly Karrer's 4-methylnonane had a smaller rotational value than that of the hydrocarbon of known absolute configuration.

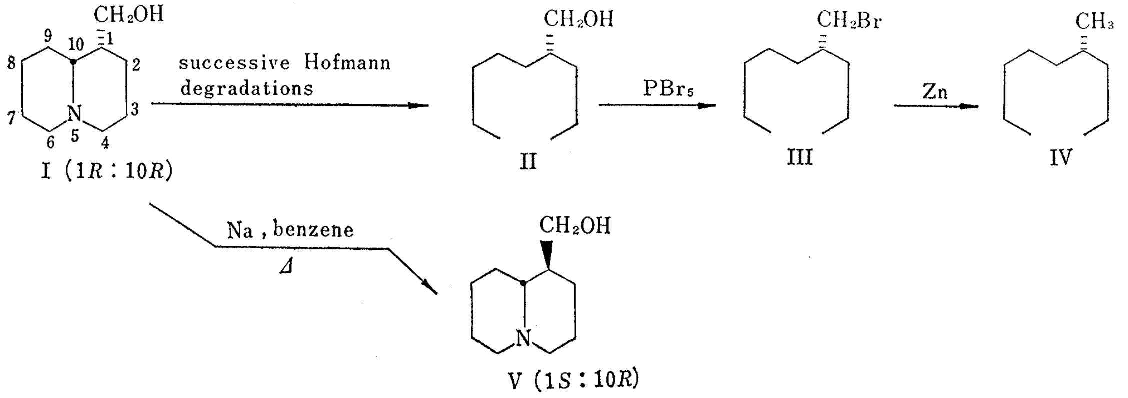
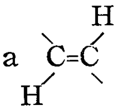
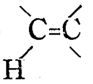


Chart 1.

The present investigation was undertaken to reexamine the degradation products of I in advance of absolute configuration studies of other lupin alkaloids interrelatable to I. To obtain (−)-4-methylnonane of the highest possible optical purity, the isolation of the optically active ten-membered ring methine (VI) was attempted at the first Hofmann degradation stage, since the dihydromethine (IX) would not be affected at asymmetric center during subsequent Hofmann degradations.

Isolation of VI was achieved by utilizing the basicty differences of the methines (VI, VII, and VIII). The methine base, more easily extractable with pottasium biphosphate solution, showed a  $\mathrm{HC{=}CH}$ type absorption (1641, 960 cm^{-1}) in the infrared spectrum and not that corresponding to  $\mathrm{C{=}CH}$, whereas the less basic methine (probably a mixture of VII and VIII) exhibited a terminal vinyl type absorption at 1610, 990, and 910 cm^{-1}. Therefore the former is VI and the stronger basicity of this methine (*pKa* 9.19), as compared to the other methine mixture (*pKa* 8.7), is probably due to the trans-1,2,3,4,5,8,9,10-octahydroazecine structure. Purification of VI by chromatography on alumina afforded a colorless oil of $[\alpha]_D^{27}$ +12.2°, methiodide derivative m.p. 227~228°. Hydrogenation of VI followed by methiodation or *vi'ce ver'sa* gave the methiodide of IX, m.p. 202~203° (decomp.), whose characteristics coincided with those of Karrer's unclarified crystalline methiodide, m.p. 202~203°. Accordingly a large amount of the methiodide was prepared following Karrer's procedures and identified with the methiodide of IX. Repeated crystallization of this compound afforded a sample, m.p. 202~203° (decomp.), $[\alpha]_{370}^{30}$ −2.2°. The specimen of $[\alpha]_{370}^{30}$ −1.8° (presumed to contain at least 9% of the optical antipode) was used for the following Hofmann degradation and the resulting methine

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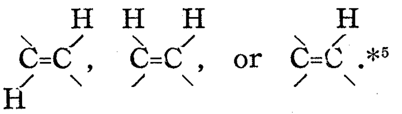
*4 This was synthesized by Levene, *et al.* (P. A. Levene, R. E. Marker : J. Biol. Chem., **91**, 1794 (1931)). However its absolute configuration had not been shown chemically until Freudenberg, *et al.* (K. Freudenberg, W. Hohmann : Ann., **584**, 54 (1953)) derived (+)-methylhexane from (−)-shikimic acid of known absolute configuration.

base showed terminal vinyl absorption at 1640, 995, and 907 cm^{-1} in the infrared spectrum but not those corresponding to



$\underset{H}{C}{=}\overset{H}{C}$, $\overset{H}{C}{=}\overset{H}{C}$, or $C{=}\overset{H}{C}$.[*5]

After hydrogenation of this methine base the last Hofmann degradation followed by hydrogenation was carried out without any purification of the intermediates, since no racemization could occur during these steps. Alcohol II, thus obtained, was tosylated and treated with lithium aluminum hydride. The final product was purified by distillation after exhaustive washing with conc. sulfuric acid to remove the ether[*6] byproduced during the second and third Hofmann degradations. Since 4-methylnonane (IV) thus purified, $b.p_{760}$ 162°, *d* 0.740, retention time of gas chromatogram 3.8 min.,[*7] showed $[\alpha]_D$ −1.33°, it can be said that if the methiodiode of $[\alpha]_{370}$ −2.2° is used, the rotation value of IV would be increased to −1.6°.

On the other hand, IV resulting from the VI deleted fraction of the first Hofmann degradation product has the same physical constants except its higher optical rotation value ($[\alpha]_D$ −1.55°)[*8] as those of IV derived *via* VI.

Consequently, the absolute configuration of (−)-lupinine and (+)-epilupinine are reconfirmed to be represented by formulas I and V respectively.

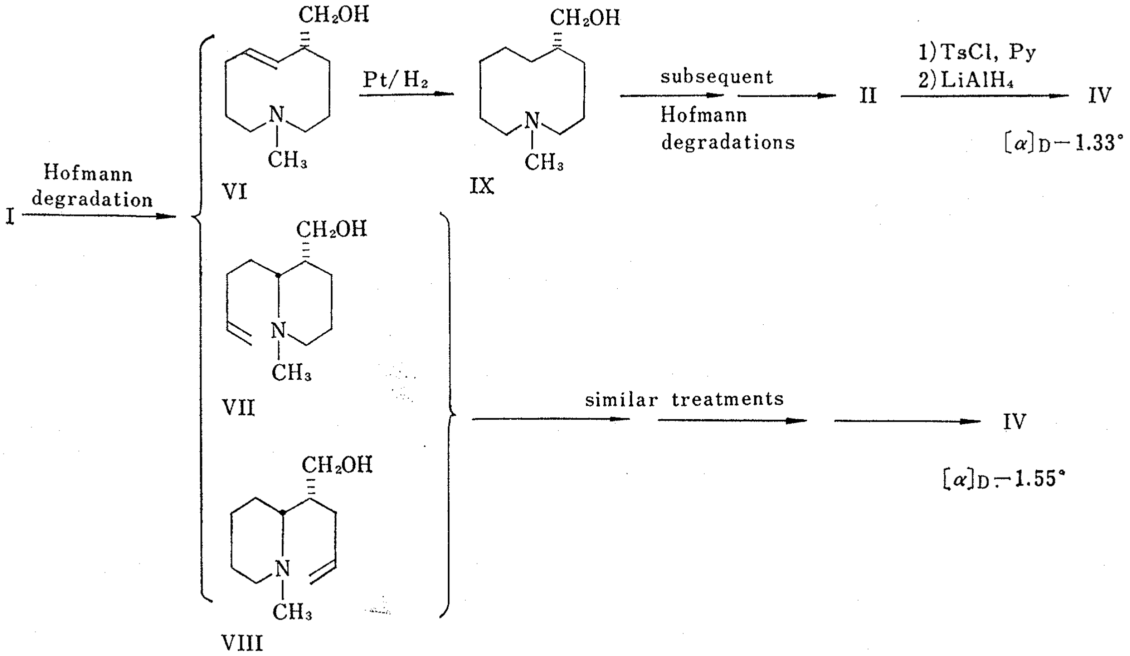


Chart 2.

Experimental

Ascending method was adopted in all paper partition chromatography, with No. 51A paper of Toyo Roshi Co. and a solvent system of BuOH-0.5*N* AcOH-EtOH=6:3:2, and the spots were visualized with H_2PtCl_6-KI. All melting points and boiling point are uncorrected. Capillary method was used for the IR spectra of liquid compounds, unless otherwise noted.

[*5] This fact also is additional support for the ten-membered ring structure of VI and IX.

[*6] IR spectrum of the ether recovered from conc. sulfuric acid extract showed C-O-C absorption at 1097 cm^{-1} (capillary) and a microanalysis of this compound also indicated the presence of oxygen. However, further investigation was not done because of lack of material.

[*7] Only one single sharp peak was observed.

[*8] This higher value, as compared to the former case, shows that the second and third Hofmann degradation effected less racemization.

Isolation of VI from the Products of the First Hofmann Degradation of I——The degradation of I (92 g.) was carried out according to Karrer's description and colorless oily mixture (92 g.) was obtained. b.p_1 95~115°. IR $\nu_{\max}$ cm^{-1}: 3410, 2800~2700, 1665, 1642, 995, 962, 907. This mixture was fractionated to three parts by virtue of basicity and solubility differences of the components, that is, a solution of the mixture in benzene was shaken with 1.0 equivalent KH_2PO_4 saturated water. The benzene layer gave fraction A. The water layer was basified with NaOH, extracted with benzene, and the benzene layer was washed with water. This benzene layer gave C. Benzene extract from the water washing basified with NaOH afforded B.

A) 42 g. oil, IR $\nu_{\max}$ cm^{-1}: 1642, 995, 907 ($-CH=CH_2$), Rf 0.54 (brown), *pKa* 8.70 (25°, 50% EtOH), methiodide: liquid.

B) 13 g. semicrystalls, IR resembles to that of I, Rf 0.4 (gray), *pKa* 9.49 (20°, 50% EtOH), methiodide: m.p. 295° (identical with $I-CH_3I$).

C) 37 g. oil, IR $\nu_{\max}$ cm^{-1}: 1665 (weak), 962 $\left(\mathrm{H{-}\overset{|}{C}{=}\underset{|}{C}{-}H}\right)$, Rf 0.4 (greenish blue), *pKa* 9.19 (25°, 50% EtOH). Methiodide: m.p. 226~228°. Al_2O_3 (Brockmann, 25 g.) column chromatography of fraction C (1.0 g.) with petr. ether-benzene elution afforded a colorless oil IV (0.6 g.), $[\alpha]_D^{27}$ +12.2° (c=5.9, EtOH). VI-CH_3I m.p. 227~228°, $[\alpha]_D^{24}$ −28° (c=3, H_2O), *Anal.* Calcd. for $C_{12}H_{24}ONI$: C, 44.31; H, 7.44; N, 4.31. Found: C, 44.45; H, 7.49; N, 4.17.

Preparation of IX-Methiodide——a) Catalytic hydrogenation of VI in MeOH with PtO_2 gave a dextro rotatory oil IX. Rf 0.44 (greenish-blue). IX-CH_3I m.p. 202~203°, *Anal.* Calcd. for $C_{12}H_{26}ONI$: C, 44.04; H, 8.01; N, 4.28. Found: C, 44.19; H, 8.11; N, 4.16.

2) Methiodide of IX was obtained also by catalytic hydrogenation of VI-CH_3I in MeOH with PtO_2.

3) A large scale preparation of IX-CH_3I was carried as follows, methine base mixture (30 g.) of the first Hofmann degradation products was dissolved in dil. HCl, being adjusted to pH 5, hydrogenated catalytically with PtO_2 (H_2 consumption was 90% of theoretical amount), filtered, and after being made alkaline extracted with ether. Evaporation of ether gave an oil. This was dissolved in EtOH, on which an excess of CH_3I was added gradually. When the exothermic reaction was ceased, a large amount of acetone was added to complete the crystallization of methiodide. I-CH_3I; 2.7 g. of m.p. 295°. IX-CH_3I; m.p. 200~203°, 12 g., Yield 22.5%, $[\alpha]_{370}^{30}$ −1.8° (c=5, MeOH). Repeated crystallization improved these values to m.p. 202~203°, $[\alpha]_{370}^{30}$ −2.2°.

The Second Degradation and Hydrogenation——Water suspension of IX-CH_3I (20 g.) and Ag_2O freshly prepared from $AgNO_3$ (13 g.) was stirred for 2 hr. at room temperature, filtered, concentrated, and heated up to 180° *in vacuo* (water pump), epuipping a distillating apparatus. Redistillation of the distillate gave a pale yellow liquid (10.7 g.). b.p_2 106~118°, IR $\nu_{\max}$ cm^{-1}: 1640, 995, 907 ($-CH=CH_2$). The liquid was hydrogenated with PtO_2 by the same method as described before, to afford a colorless oil (11 g.), b.p_{18} 154~157°, Rf 0.6 (red brown).

The Third Degradation and Hydrogenation——Treatment of the amine (11 g.) obtained above with an excess of CH_3I in MeOH gave an oily methiodide, which was converted to a methohydroxide with Ag_2O. The Hofmann degradation was performed in a rather large flask equipped with distillating attachments and traps containing dil. HCl, when effervescence of $N(CH_3)_3$ was ceased after gradual heating up to 150° under atmospheric pressure, the residue in the flask and the oil in traps were taken out into ether. Basic substances were removed by washing with dil. HCl from the ether layer. A colorless oil with strong paraffinlike odor was obtained as neutral products. Yield 5.45 g. of b.p_{13} 85~105°, IR $\nu_{\max}$ cm^{-1}: 1640, 990, 908 ($-CH=CH_2$). This unsaturated alcohol (5.35 g.) was hydrogenated with PtO_2 catalyst in EtOH, filtered and distilled into two fractions. b.p_{13} 85~90° colorless light liquid 0.32 g. IR $\nu_{\max}$ cm^{-1}: 1113, 1097 (−O−), OH absorption band was negligiblly small. b.p_{13} 90~106° liquid (II) 4.43 g. IR $\nu_{\max}$ cm^{-1}: 3420; $\nu_{\max}^{\mathrm{CHCl_3}}$: 3630, 3465 (OH). $[\alpha]_D^{10}$ +0.6° (neat).

(−)-4-Methylnonane (IV)——The saturated hydroxy compound (II) of b.p_{13} 90~106° (4.3 g.) was mixed with TsCl (8 g.) and pyridine (40 ml.) at −10°. The mixture was kept standing one night at 5~10°, poured onto a large amunt of water and ether, and shaken adequately. The ether layer was washed with water, dil. AcOH, and with $NaHCO_3$ solution. Ether was removed under 35° to give a colorless liquid (8.5 g.). IR $\nu_{\max}$ cm^{-1}: 1603, 1356, 1187, 1176 ($-SO_3-$), no OH band. The oil was treated with $LiAlH_4$ in ether in usual way to afford a liquid (3.7 g.), b.p_{760} 160~170°. Its IR $\nu_{\max}$ cm^{-1}: 1113, 1097 shows the contamination of ether compounds. To remove the ether compounds, byproduced mainly during the third Hofmann degradation, *via* an oxonium salt, the fraction of b.p. 160~170° was exhaustively shaken with conc. H_2SO_4 for 15 hr. at room temperature, washed with water and NaOH solution, dried over anhyd. K_2CO_3. The distillation afforded a colorless benzine like oil (2.4 g.) (IV) b.p_{760} 162°. IR $\nu_{\max}$ cm^{-1}: 2950, 2925, 2870, 1464, 1376, $[\alpha]_D^{10}$ −1.33°, *d* 0.740. *Anal.* Calcd. for $C_{10}H_{22}$: C, 84.41; H, 15.59. Found: C, 84.50; H, 15.42. Thus obtained oil shows a single sharp peak of retenntion time 3.8 min. on gas chromatogram of silicon D.C. 550 on celite 545 (80~100 mesh) 5 mm. × 2 m. stainless steel, column temp. 142°, He 46 ml./min. 0.2 kg./cm².

Degradation of the IX Deleted Mixture——The IX deleted methine base mixture of the first Hofmann degradation was treated according to the same procedures as in the case of IX. IR spectrum of the second degradation product shows more intense absorption at 967 cm^{-1} $\left(\text{H}-\overset{|}{\text{C}}=\underset{|}{\text{C}}-\text{H}\right)$, than those at 993, 907 cm^{-1} (-CH=CH$_2$), whereas the corresponding product derived *via* IX showed no absorption band due to trans disubstituted ethylene. The third degradation gave neutral products, which showed no IR absorption band attributable to trans disubstituted ethylene group. The final compound (IV) was obtained in overall yield of about 19% from (−)-lupinine (I) and is identical with (−)-4-methylnonane derived *via* IX on IR and gas chromatogram but has larger optical rotation value, $[\alpha]_D^{10}$ −1.55°, *d* 0.740.

Summary

Hofmann degradation of (−)-lupinine was reinvestigated to obtain (−)-4-methylnonane of the highest possible optical purity and Cookson's assignments of the absolute configurations of (−)-lupinine and (+)-epilupinine were reconfirmed.

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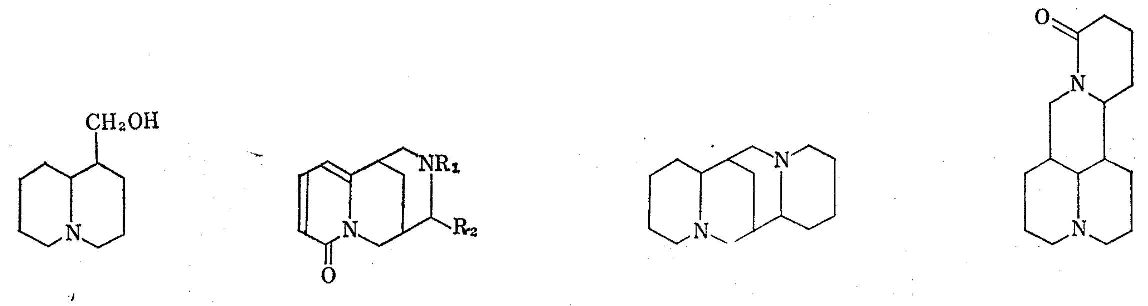
65. Shigenobu Okuda,[*1] Hidesato Kataoka,[*2] and Kyosuke Tsuda[*1] : Studies on Lupin Alkaloids. III. Absolute Configurations of Lupin Alkaloids. II.[*3,*4]

(*Institute of Applied Microbiology, University of Tokyo*[*1] *and Kowa Chemical Laboratories, Kowa Co., Ltd.*[*2])

Over sixty lupin alkaloids have been isolated from various plants of Leguminosae, Berberidaceae, and Chenopodiaceae and the structures of about three fourths are now known. The great majority of lupin alkaloids contain the quinolizidine ring and are generally classified into the following four types:



lupinine−type cytisine−type sparteine−type matrine−type

Chart 1.

These four types of alkaloids are biogenetically related each other and the various types often occur together in one plant. Therefore studies on the absolute configurations of lupin alkaloids are interesting not only chemically but also biogenetically.

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[*3] Part II: This Bulletin, **13**, 487 (1965).

[*4] Preliminary communications. S. Okuda, H. Kataoka, K. Tsuda: Chem. & Ind. (London), **1961**, 1115, 1751.