degradation product shows more intense absorption at 967 cm^{-1} $\left(H-\overset{|}{C}=\underset{|}{C}-H\right)$, 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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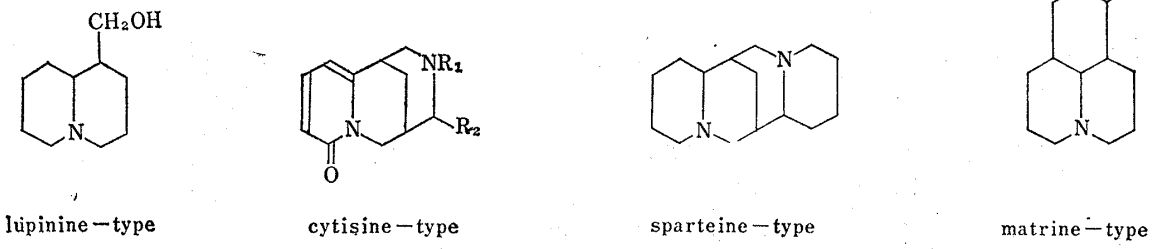
65. Shigenobu Okuda,*1 Hidesato Kataoka,*2 and Kyosuke Tsuda*1 : Studies on Lupin Alkaloids. III. Absolute Configurations of Lupin Alkaloids. II.*3,*4

(*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.

*1 Mukogaoka-yayoicho, Bunkyo-ku, Tokyo (奥田重信，津田恭介).
*2 3-399, Shimotakaido, Suginami-ku, Tokyo (片岡英達).
*3 Part Ⅱ : This Bulletin, **13**, 487 (1965).
*4 Preliminary communications. S. Okuda, H. Kataoka, K. Tsuda : Chem. & Ind. (London), **1961**, 1115, 1751.

Among them (−)-lupinine (Ⅷ) and (+)-epilupinine (Ⅸ) are known to be (1*R*:5*R*:10*R*)- and (1*S*:5*R*:10*R*)-1-quinolizidinemethanol respectively,[1] as reconfirmed in a preceeding paper.*[3] However the absolute configurations of other three types remained for further investigation. The present paper is concerned with the absolute configurations of sparteine- and cytisine-type alkaloids. The sparteine-type, largest group of the above four, comprises over 20 kinds of C-15 alkaloids and has been the object of extensive chemical studies. Cytisine-type is structurally the intermediate between lupinine- and sparteine-type and the biogenesis of this type is especially interesting. Elucidation of the absolute configurations of the above two types has been performed by the chemical interrelation between (+)-epilupinine (Ⅸ) and (−)-anagyrine (Ⅰ), which was chosen as the representative of sparteine type, and then between (−)-anagyrine (Ⅰ) and (−)-cytisine (Ⅻ).

Ing reported the preparation of dilactam (Ⅲ) from (−)-anagyrne (Ⅰ) *via* ozonization of anagyramide (Ⅱ).[2] The latter was presumed to be 17-oxoanagyrine because sparteine, having the same B,C,D-ring structure as (−)-anagyrine (Ⅰ), was known to be oxidized into 17-oxosparteine.[3] Ozonization of the pyridone ring (ring A) in Ⅱ gave rise to another piperidone ring (ring B) and consequently the resulting dilactam was expected to be 1,2,3,8,9,10,11,11*a*-octahydro-1,5-methano-4*H*-pyrido[1,2-*a*][1,5]diazocine-4,6(5*H*)-dione (Ⅲ). If it is in reality, it might be reasonably assumed that a selective hydrolysis of external lactam at C_4-position would afford a monolactam of α-dicarboxylic acid (Ⅳ). The latter would be easily decarboxylated to the lupinine type derivative of known absolute configuration. This plan has been successfully accomplished as described below.

According to the description of Ing,[2] dilactam (Ⅲ), m.p. 258°, $[\alpha]_D^{20}$ +21.2° (EtOH), was prepared from (−)-anagyrine (Ⅰ), $[\alpha]_D^{20}$ −165.6° (EtOH), isolated from Japanese *Sophora flavescens*.[4] The infrared spectrum of this dilactam exhibited lactam absorptions at 1640 and 1680 cm^{-1}. The former absorption corresponded to the more hindered

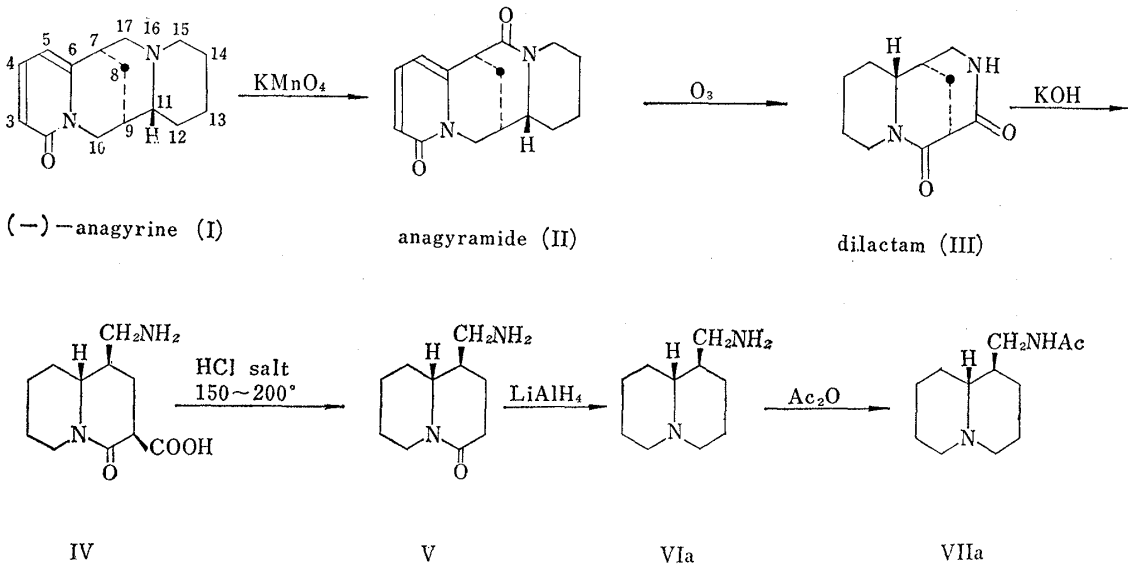


Chart 2.

1) R. C. Cookson: Chem. & Ind. (London), **1953**, 337.
2) H. R. Ing: J. Chem. Soc., **1933**, 504.
3) G. R. Clemo, R. Raper: *Ibid.*, **1933**, 644; G. R. Clemo, W. McG. Morgan, R. Raper: *Ibid.*, **1936**, 1025.
4) S. Okuda, I. Murakoshi, H. Kamata, Y. Kashida, J. Haginiwa, K. Tsuda: This Bulletin, **12**, 482 (1964).

internal lactam at C_6-position and the latter to the less hindered external one at C_4-position. A partial hydrolysis of III with one mole equivalent of potassium hydroxide in aqueous ethanol gave mainly the expected monolactam acid (IV) which was converted into the hydrochloride and without purification heated to about 200° for decarboxylation. After rapid evolution of carbon dioxide ceased, the resulting aminolactam (V) was purified by vacuum distillation to afford a very hygroscopic viscous oil, b.p_4 175~177°, $[\alpha]_D^{18}$ −51.2° (EtOH), in 80% overall yield from III. Lithium aluminum hydride reduction of aminolactam (V) in tetrahydrofuran furnished (+)-aminomethylquinolizidine (VIa), b.p_4 ca. 100° (bath temperature), $[\alpha]_D^{19}$ +55° (EtOH), which gave a dipicrate, m.p. 229°, and a monoacetate (VIIa), m.p. 147~148°, $[\alpha]_D^{20}$ +56.4° (EtOH).

In order to confirm whether the above (+)-1-aminomethylquinolizidine (VIa) belongs to 1*R*- or 1*S*-series, (1*R*:5*R*:10*R*)-1-aminomethylquinolilidine (VIb) was synthesized from (+)-epilupinine (IX). (+)-Epilupinine (IX), m.p. 78°, $[\alpha]_D^{10}$ +37° (EtOH), was prepared in 60% yield from (−)-lupinine (VIII), m.p. 70~71°, $[\alpha]_D^{10}$ −21° (EtOH), by the modified epimerization procedure with sodium dispersion*5 and tosylated in pyridine. Even under conditions maintaining the temperature of reaction and work up below 20°, the tosylate (X), m.p. 71~72°, $[\alpha]_D^{10}$ +18.5° (EtOH), was obtained in yield somewhat under 50% and accompanied ay a considerable amount of 1-chloromethylquinolizidine, b.p_{10} 110°, $[\alpha]_D^{16}$ +51.2° (EtOH), which might be produced by S_N 2 type reaction of X with hydrogen chloride generated during the tosylation. In fact the yield of this chloride was raised to over 90% when the tosylation was carried out at 100° for 1 hour, and furthermore a treatment of X with pyridine and hydrogen chloride at 90° for 1 hour provided this compound in 80% yield. Then (1*S*:5*R*:10*R*)-1-chloromethylquinolizidine (XI) was prepared from (+)-epilupinine (IX) by chlorination with thionyl chloride and identified with the above chloride. Synthesis of (1*R*:5*R*:10*R*)-1-aminomethylquinolizidine (VIb), b.p_5 94~98°, $[\alpha]_D^{19}$ +54.7° (EtOH), was effected by amination of X with ethanolic ammonia at 135° for 15 hours, and by treatment of XI with ethanolic ammonia at 160~170° for 20 hours or with potassium phthalimide in dimethylformamide at 150~155° for 20 hours.

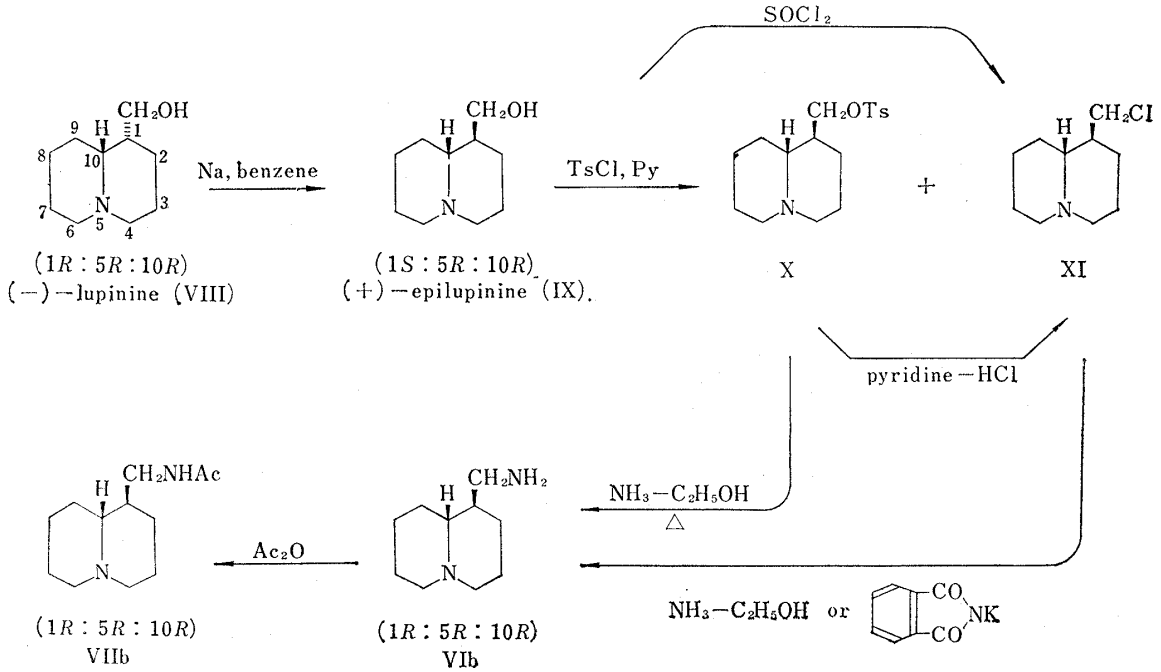


Chart 3.

*5 Although sodium wire was used in literature (cf. C. Schöpf, E. Schmidt, W. Braun : Chem. Ber., **64**, 63 (1931)), sodium dispersion was employed in the present study to improve the yield of IX.

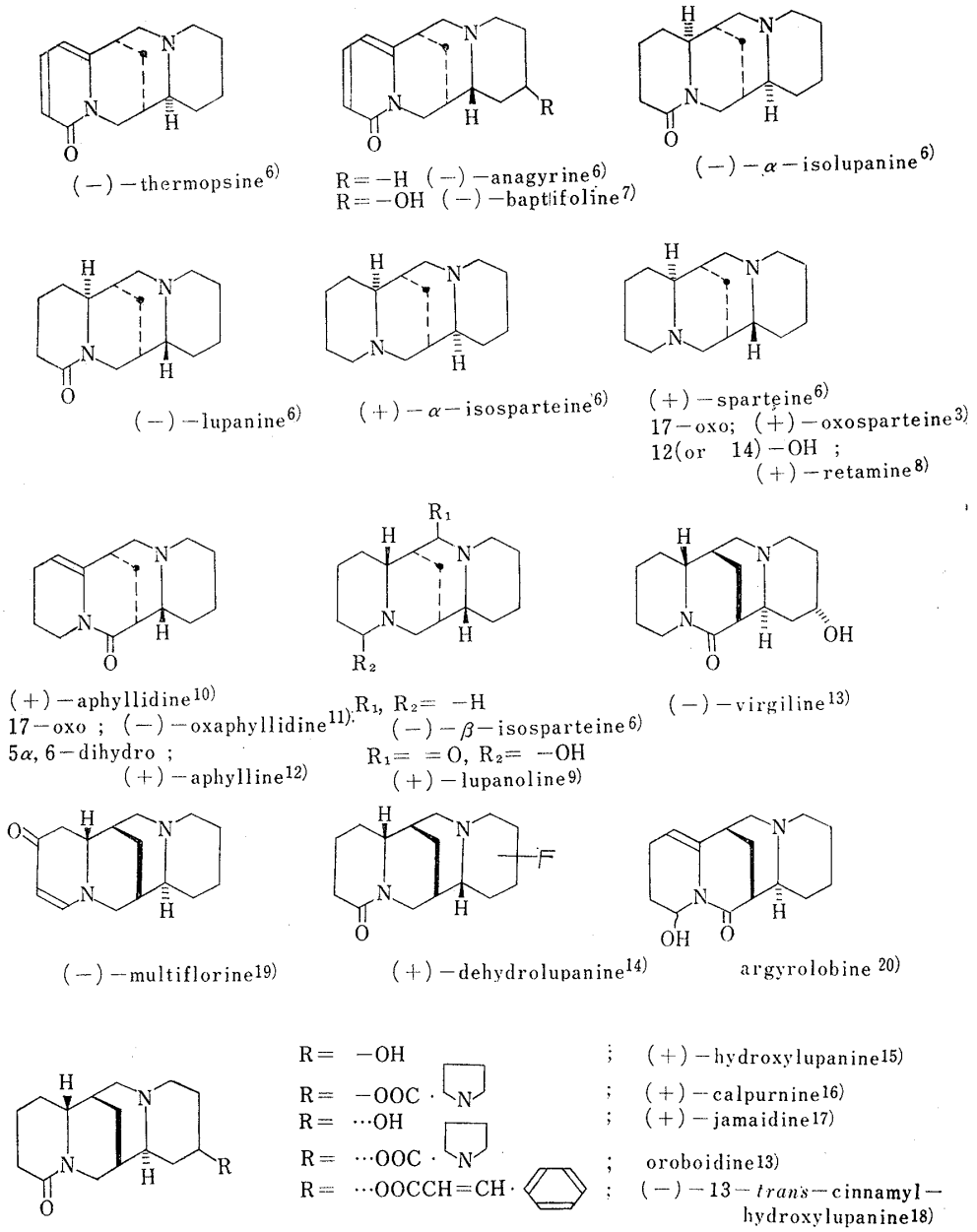


Chart 4.

6) L. Marion, N. J. Leonard : Can. J. Chem., **29**, 355 (1951).
7) M. Martin-Smith, L. Marion : *Ibid.*, **35**, 37 (1957).
8) F. Bohlmann, E. Winterfeld : Chem. Ber., **95**, 2365 (1962).
9) B. P. Moore, L. Marion : Can. J. Chem., **31**, 187 (1953).
10) A. S. Sadykov, R. N. Nurridinov : Doklady Akad. Nauk S. S. S. R., **102**, 755 (1955).
11) *Idem* : Doklady Akad. Nauk Uzbek S. S. R., **1957**, 15.
12) O. E. Edwards, F. H. Clarke, B. Douglas : Can. J. Chem., **32**, 235 (1954); F. Galinovsky, E. Jarisch : Monatsh. Chem., **84**, 199 (1953).
13) G. C. Gerrans, J. H. Mason : Chem. & Ind. (London), **1963**, 1433.
14) M. Rink, H. Schäfer : Arch. Pharm., **287**, 290 (1954).
15) F. Galinovsky, M. Pöhm : Monatsh. Chem., **80**, 864 (1949).
16) A. Goosen : J. Chem. Soc., **1963**, 3067.
17) H. A. Lloyd, E. C. Horning : J. Org. Chem., **25**, 1959 (1960).
18) M. Wiewiorowsky, M. D. Bratek : Bull. Acad. Polon. Sci. Biol., **10**, 349 (1962).
19) W. D. Crow : Aust. J. Chem., **12**, 474 (1959).
20) Y. Tsuda, L. Marion : Can. J. Chem., **42**, 764 (1964).

It was deduced that (+)-1-aminomethylquinolizidine (Ⅵa) derived from (−)-anagyrine (I) was completely identical with (1*R*:5*R*:10*R*)-1-aminomethylquinolizidine (Ⅵb) prepared from (+)-epilupinine (Ⅸ), by mixed melting point test and comparison of infrared spectra and $[\alpha]_D$ values of the acetates (Ⅶa, b) and dipicrates. Accordingly the absolute configurations of C_9 and C_{11} in (−)-anagyrine (I) are same as C_1 and C_{10} in (+)-epilupinine (Ⅸ) respectively, since those were not affected during the interrelation sequence mentioned above.

Thus the absolute configurations of (−)-anagyrine (I) and the related alkaloids are assigned as shown in Chart 4 and the present result agrees with Brewster's prediction[5] regarding the absolute configuration of sparteine-type alkaloids based on dissymmetry rule.

Thus the absolute configurations of lupinine- and sparteine-type are clarified and the next target is the chemical interrelation between these and cytisine-type for the purpose of elucidating the absolute configuration of the latter.*[6]

Dilactam (Ⅲ) utilized in the course of above investigation has the same gross skeleton as (−)-cytisine (Ⅻ) except that A ring in the former is a saturated piperidine moiety and on the other hand that in latter is α-pyridone. It is known that the exhaustive catalytic hydrogenation of (−)-cytisine (Ⅻ) gave tetrahydrodeoxycytisine (XIII)[21] having *trans*-quinolizidine structure since hydrogenation took place from the less hindered side. On the other hand it is expected that lithium aluminum hydride reduction of dilactam (Ⅲ) will give (1*R*:5*S*:7*S*:11*aR*)-1,2,3,4,5,6,9,10,11,11*a*-decahydro-1,5-methano-8*H*-pyrido-[1,2-*a*][1,5]diazocine (XV)*[4] containing *cis*-quinolizidine, which could be transformed into the more stable epimer of *trans*-quinolizidine type by dehydrogenation involving the hydrogen at C_{11a}-position followed by catalytic hydrogenation. The expected epimerization product should be tetrahydrodeoxycytisine (XIII) itself or an antipode. According to this plan the chemical interrelation between (−)-anagyrine (I) and (−)-cytisine (Ⅻ) was carried out as follows.

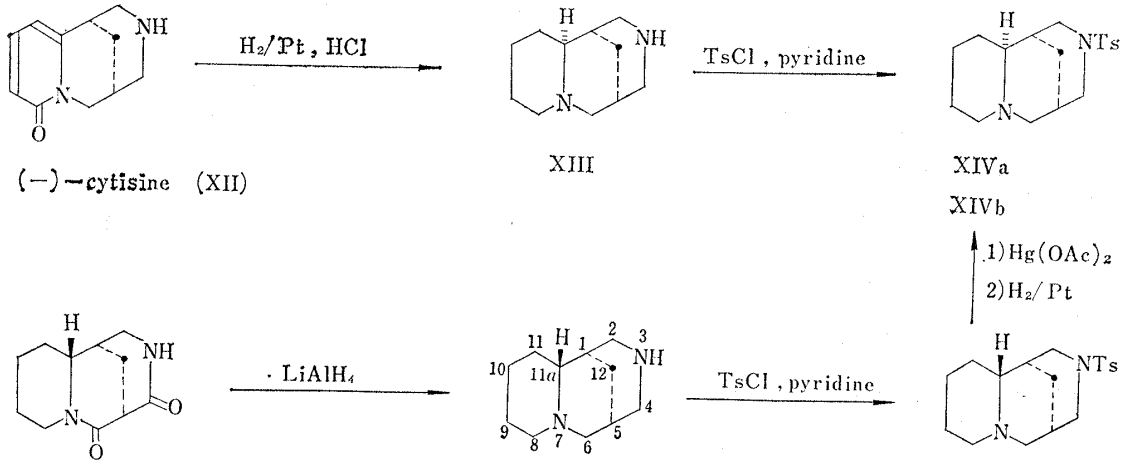


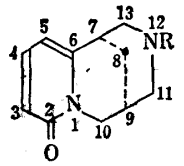
Chart 5.

*[6] Marion, *et al.* reported the interrelation between (−)-angustifoline into (−)-sparteine (cf. L. Marion, M. Wiewiorowski, M. D. Bratek : Tetrahedron Letters, No. 19, 1 (1960)). On the other hand Bohlmann, *et al.* carried out the conversion of natural cytisine into angustifoline and epi-baptifoline. However the optical activities of the latter two compounds were not described and the absolute configuration of (−)-cytisine was not unambiguous (cf. F. Bohlmann, E. Winterfeldt, H. Overwien, H. Pagel : Ber., **95**, 944 (1962)).

5) J. H. Brewster : Tetrahedron, **13**, 106 (1961).
21) F. Galinovsky, E. Stern : Chem. Ber., **77**, 132 (1944).

Lithium aluminum hydride reduction of dilactam (Ⅲ) in tetrahydrofuran furnished (1*R*:5*S*:7*S*:11*aR*)-1,2,3,4,5,6,9,10,11,11*a*-decahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocine (XV) in 65% yield after purification *via* styphnate, m.p. 213°, and tosylated in pyridine and tosyl chloride. The resulting tosylate (XVI), m.p. 174°, $[\alpha]_D^{27}$ −11° (benzene), whose infrared spectrum exhibited no *trans*-quinolizidine absorption, was epimerized by dehydrogenation with mercuric acetate in aqueous acetic acid, succesively followed by catalytic hydrogenation with platinum oxide. The epimeric tosylate (XIV), m.p. 144°, $[\alpha]_D^{25}$ +10° (benzene), was obtained in a moderate yield and the infrared spectrum showed *trans*-quinolizidine bands at 2810, 2760, and 2735 cm^{-1}, indicating the inversion of C_{11a}-hydrogen.

On the other hand (−)-cytisine (Ⅻ) was exhaustively hydrogenated with platinum oxide in dilute aqueos hydrochloric acid according to the description of Galinovsky,[6] and the resulting tetrahydrodeoxycytisine (XIII) was tosylated. The tosylate thus obtained (XIVa), m.p. 144°, $[\alpha]_D^{32}$ +9.8° (benzene), was proved completely identical with the above epimeric tosylate (XIVb) by mixed melting point test and comparison of their infrared spectra and $[\alpha]_D$ values. Since the absolute configurations of C_7 and C_9 of (−)-cytisine (Ⅻ) and those of dilactam (Ⅲ) are unquestionably retained through the interrelation experiments described above, the absolute configurations of C_7 and C_9 an the former are same as the corresponding ones in (−)-anagyrine (I) respectively. Consequently the absolute configurations of (−)-cytisine (Ⅻ) and related alkaloids are established as indicated in Chart 6.



(7*R*:9*S*)

R=−H
(−)-cytisine
R=−CH_3
(−)-methylcytisine
R=−$(CH_2)_2$·CH=CH_2
(−)-rhombifoline

Chart 6.

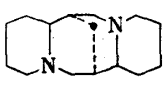
Among the four types of lupin alkaloids, the absolute configurations of lupinine-, sparteine-, and cytisine-type are now clarified and an interest-

Table I.

No.	Source	Sparteine	Lupanine	Other alkaloid
1	*Ammodendrone conollyi* Bge.	+		(−)-anagyrine, conolline, ammodendrine
2	*Baptisia versicolor* Lodd.	+	−	(−)-anagyrine
3	*Cytisus caucasicus* Hort.	+		〃
4	*Cytisus ratisbonnensis* Schaeff	−	+	
5	*Lupinus caudatus* Kellog.	−	+	(−)-*α*-isosparteine, (+)-*α*-isolupanine, (+)-thermopsine, (−)-anagyrine[a]
6	*Lupinus Laxus* Rydb.	−	+	
7	*Lupinus pusillus* Pursh.	+	−	(−)-*β*-isosparteine, (−)-anagyrine
8	*Lupinus sericeus* Pursh.	−	+	(−)-*β*-isosparteine,[a] (+)-*α*-isolupanine
9	*Lupinus wyethi* S. Wats.	−	+	(+)-hydroxylupanine
10	*Lupinus arboreus* Sims.	−	±	
11	*Lupinus barbiger* S. Wats.	−	+	
12	*Leontice eversmanni* Bge.	+	−	(−)-leontidine, (±)-leontine, (−)-methylcytisine

a) In these exceptional cases, (−)-anagyrine or (−)-*β*-isosparteine occur together with their antipodal series.

(+)−sparteine series : (+)-sparteine, (−)-lupanine, (−)-anagyrine, (−)-*α*-isolupanine, (−)-thermopsine, (−)-*β*-isosparteine



(−)−sparteine series : (−)-sparteine, (+)-lupanine, (−)-*α*-isosparteine, (+)-*α*-isolupanine, (+)-thermopsine

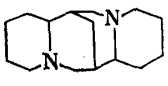
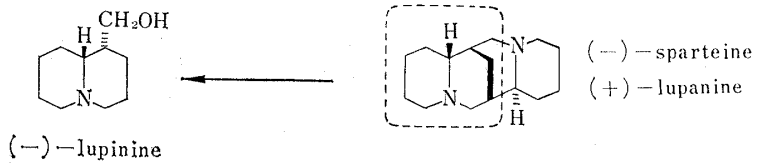


Table II.

No.	Source	Lupinine	Epi-lup.	Sparteine	Lupanine
1	*Lupinus luteus* L.	—		—	
2	*Lupinus niger* Pharm.	—		—	
3	*Lupinus pilosus* L. or Walt.		+		+



(−)−lupinine

(−)−sparteine
(+)−lupanine

Table III.

No.	Source	Anag.	Therm.	Cyt.	Me-cyt.	Spar.	Other alkaloid
1	*Anagyris foetida* Lour.	—		—	—	+	
2	*Baptisia australis* (L.) R. Br.			—	—	+	P-2
3	*Baptisia minor* Lehm.	—		—	—	+	(−)-baptifoline[a]
4	*Baptisia perfoliata* (L.) R. Br.	—		—	—	+	(−)-baptifoline,[a] P-2
5	*Genista aethnensis* D. C.			—		—	(+)-retamine[a]
6	*Genista monosperma* Lam.	—		—	—	+	(+)-oxosparteine[a]
7	*Retama sphaerocarpa* Boiss.			—		±	(+)-retamine[a]
8	*Spartium junceum* Lam.	—		—	—	—[b]	
9	*Thermopsis lanceolata* R. Br.	—	—	—	—	+	
10	*Thermopsis rhombifolia* (Nutt) Richards.	—	—	—	—		(+)-rhombifoline

a) These alkaloids belong to the (+)-sparteine series.
b) In this case, (−)-spartein was found together with (−)-cytisine series.

(−)−cytisine series (+)−sparteine series

ing relationship was observed between the natural distribution of these type alkaloids and their absolute configurations.

1) (+)-Sparteine series and (−)-sparteine series generally do not occur together as shown in Table I.

2) (−)-Lupinine (Ⅷ) or (+)-epilupinine (Ⅸ) is found together with (−)-sparteine series, in which the part surrounded by a dotted line in Table Ⅱ corresponds to the absolute configuration of (−)-lupinine.

3) (−)-Cytisine series are accompanied by (−)-sparteine series in which the absolute configuration of methylene bridge is the same as that of (−)-cytisine (cf. Table Ⅲ).

The absolute configurations of the matrine-type alkaloids have not been determined. When the absolute configurations of matrine type alkaloids, the last of above four groups, has been elucidated,*7 it is to be expected that the relationship between the natural occurrence of lupin alkaloids which contain the quinolizidine ring and their absolute configurations can be correlated biogenetically.

*7 The absolute configuration of (+)-matrine has been proposed by S. Okuda, *et al.* (cf. Abstract of IUPAC-Symposium on the chemistry of Natural Products, April, 1964 (Kyoto, Japan), p. 88) and the details will be discussed in a forthcoming paper.

Experimental

Ascending method was adogted in all paper partition chromatography (PPC) with No. 51A paper of Toyo Roshi, a solvent system of BuOH, 0.5*N* AcOH, EtOH=6:3:2, and the spots were sprayed with H_2PtCl_6-KI or Dragendorff's reagent. All melting points and boiling points are uncorrected.

Anagyramide (II)——$KMnO_4$ (10 g.) saturated aqueous solution was added gradually to (−)-anagyrine (I) (10 g.) in H_2O (50 ml.) with vigorous stirring, keeping the temperature between 5~10°. It required about 1 hr. to accomplish the addition and violet color of $KMnO_4$ lasted over 2 min. at the end period. The stirring was continued more 30 min. and the solution was filtered with celite. The colorless filtrate was neutralized with dil. HCl, concentrated to dryness and extracted with $CHCl_3$. Evaporation of $CHCl_3$ afforded crude crystals, 8.65 g. (82%), m.p. 119~202°. Recrystallization from benzene gave II, m.p. 201~202°. PPC: Rf 0.76. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (lactam), 1645, 1580, 1545 (α-pyridone).

Dilactam (III)——O_3 in O_2 was passed into solution of II (8 g.) in $CHCl_3$ (40 ml.) under ice-salt cooling for 3 hr., $NaHSO_3$ (10 g.) in water (30 ml.) was added immediately after the ozonization and shaken for 1 hr. The $CHCl_3$ solution was dried over K_2CO_3. Crude crystals were obtained after removing $CHCl_3$, m.p. 235~245°, 4.9 g., recrystallization of which from MeOH-AcOEt provided III, 3.8 g., m.p. 258°, $[\alpha]_D^{20}$ +21.2° (EtOH), yield 59%. PPC: Rf 0.65. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 3240 (NH), 1680, 1640 (lactam CO).

Amino-lactam (V)——To a solution of III (0.855 g.) in EtOH (10 ml.), KOH (0.25 g. in H_2O (2 ml.) was added under ice cooling. Then the homogeneous solution was heated on boiling water bath for 30 min. (on removing EtOH, no precipitate appeared), made slightly acidic with 10% HCl (2.8 ml.) and evaporated to dryness. Hydrochloride of IV thus obtained was heated to 210° (bath temperature) for 30 min., CO_2 evolution commenced around 150°. The residual brown oil was basified with aqueous K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over K_2CO_3 and the solvent was removed. Distillation afforded 0.6 g. (yield 80%) of a very hygroscopic viscous oil V, b.p_4 175~177°. $[\alpha]_D^{18}$ −51.2° (c=3.65, EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3367, 3200 (NH), 1620 (lactam CO). PPC: Rf 0.41. Picrolonate, m.p. 220° (decomp.). *Anal.* Calcd. for $C_{10}H_{18}ON_2 \cdot C_{10}H_8O_5N_4$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.51; H, 6.05; N, 18.41.

(+)-1-Aminomethylquinolizidine (VIa)——A mixture of V (0.4 g.) and $LiAlH_4$ (0.3 g.) in tetrahydrofuran (5 ml.) was refluxed 1 hr., tetrahydrofuran was removed *in vacuo*, and to the residue was added ether followed by H_2O. After separation of the organic layer and drying over K_2CO_3, the solvent was removed. The resulting oil was distilled to provide a colorless dextro rotatory oil (VIa), 0.25 g. yield 74%. b.p_4 ca. 100° (bath temperature). $[\alpha]_D^{19}$ +55° (c=5.2, EtOH). This substance is too unstable in the air forming an ether insoluble crystalline carbonate (needles) to examine their physical constants accurately. PPC: Rf 0.1~0.2. Dipicrate, m.p. 229°. *Anal.* Calcd. for $C_{10}H_{10}N_2 \cdot (C_6H_3O_7N_3)_2$: C, 42.17; H, 4.18. Found: C, 42.46; H, 4.27.

(+)-1-Acetamidomethylquinolizidine (VIIa)——A mixture of VIa (0.2 g.) and Ac_2O (2 ml.) was heated on a water bath for 20 min., AcOH and excess of Ac_2O were removed *in vacuo*, the residue was basified with K_2CO_3 and extracted with ether. Evaporation of ether left brown crystals, which were recrystallized from AcOEt using active charcoal to give colorless needles (VIIa), 0.16 g. m.p. 147~148°. $[\alpha]_D^{20}$ +56.4° (c=0.71, EtOH). PPC: Rf 0.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435 (NH), 2805, 2760 (*trans*-quinolizidine), 1667 (amide I), 1515 (amide II). *Anal.* Calcd. for $C_{12}H_{22}ON_2$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.85; H, 10.49; N, 13.41.

(+)-Epilupinine (IX)——A mixture of (−)-lupinine (VIII) (4 g.), Na dispersion (0.2 g.), anhydrous benzene (30 ml.) was heated at 120~130° (bath temperature) for 4 days. To the brown colored reaction mixture was added some H_2O to decompose the sodium alkoxide. The benzene layer was taken, dried over K_2CO_3, benzene was removed leaving an oil, which was dissolved into a small quantity of ether, agitation of the solution induced precipitation of crystals, recrystallization of which from ether gave IX, 2.4 g. yield 60%. colorless rods, m.p. 77~78°. $[\alpha]_D^{10}$ +37.0° (c=3.38, EtOH). PPC: Rf 0.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3625 (free OH), 2820, 2760 (*trans*-quinolizidine), the free OH band is more intense as compared to that of VIII indicating less hydrogen bonding than in VIII.

This epimerization was undertaken several times and following facts were observed: NaH is also as effective as Na dispersion, a bath temperature below 110° is insufficient, while much higher temperature decreases the yield and addition of more Na or of benzophenone as catalyst does not accelerate the epimerization remarkably.

(+)-Epilupinine *p*-Toluenesulfonatate (X)——(+)-Epilupinine (IX) (1.0 g.), TsCl (1.9 g.), anhydrous pyridine (5 ml.) were mixed under cooling with ice-salt, after standing 2 days at room temperature (ca. 20°) pyridine was removed *in vacuo* at room temperature. The residue was dissolved in dil. HCl, washed with ether, basified and extracted ether. Evaporation of ether afforded a semicrystalline mass which was recrystallized from petr. ether to give X (0.55 g. of rods). m.p. 71~72°. $[\alpha]_D^{10}$ +18.5° (c=5.4, EtOH). PPC: Rf 0.72. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2825, 2770 (*trans*-quinolizidine), 1601, 1358, 1175 (-SO_3-). *Anal.* Calcd. for $C_{17}H_{25}O_3NS$: C, 63.12; H, 7.82; N, 4.55. Picrate, m.p. 170~171° (EtOH-ether).

An additional crop of X (0.28 g.) was obtained by liquid column chromatography of the mother liquors (ca. 1 g. solute) with Al_2O_3 (35 g., Brockmann) and ether. In this chromatography, 1-chloromethylquinolizidine (XI) (0.47 g.) was isolated as a forerun from the column. When the tosylation mixture was heated at 100° for 1 hr., the yield of XI reached 91%, and heating a mixture of X, pyridine-HCl and pyridine at 90° for 1 hr. provided XI in 80% yield. The chlorocompound obtained above is identical with that derived from IX by treatment with $SOCl_2$ in usual way. XI is a colorless liquid, $b.p_{10}$ 110°. $[\alpha]_D^{16}$ +51.2° (c=4.6, EtOH). Picrate, m.p. 154°. XI-HCl, m.p. 228°. $[\alpha]_D^{20}$ +29.6° (c=3.2, EtOH). *Anal.* Calcd. for $C_{10}H_{18}NCl$: C, 53.37; H, 8.54; N, 6.25; Cl, 31.63. Found: C, 53.25; H, 8.49; N, 6.12; Cl, 31.44.

(+)-(1*R*:5*R*:10*R*)-1-Aminomethylquinolizidine (VIb) and VIIb——a) The tosylate (X) (0.15 g.) in NH_3 saturated EtOH (6 ml.) was heated in a sealed tube at 135° for 15 hr., evaporated to dryness, basified with K_2CO_3, extracted with ether to give an oil obtained above was heated with Ac_2O (4 ml.) on a water bath 1 hr. and excess Ac_2O was removed. Neutralization with K_2CO_3 and extraction with ether afforded colorless needles (VIIb), m.p. 147~148°. The IR is entirely identical with that of VIIa derived from I. $[\alpha]_D^{20}$ +56.7° (c=0.74, EtOH). *Anal.* Calcd. for $C_{12}H_{22}ON_2$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.31; H, 10.62; N, 13.52. PPC: Rf 0.45.

b) 1-Chloromethylquinolizidine (XI) (0.1 g.) in NH_3 saturated EtOH (3 ml.) was heated in a sealed tube at 160~170° for 20 hr. (heating at 135° for 1 hr. was insufficient) and treated in the same way as described before to give an oil, from which a picrate of m.p. 229° and an acetate m.p. 147~148° were derived. These are respectively identical with those obtained in the procedure a) by mixed melting point test and their IR spectra.

c) A mixture of XI (1.7 g.), potassium phthalimide (1.9 g.), dimethylformamide (4 ml.) was heated at 95~100° for 1 hr. and 150~155° for for 2 hr. and KCl was filtered from the hot dark brown reaction mixture. But there was no precipitation of an organic compound on cooling. Evaporation of the solvent left an oil (2.7 g.), to which 6*N* HCl (40 ml.) was added. After refluxing 1 night, cooling, filtering, and evaporating to dryness, the residue was dissolved into a small quantity of H_2O. The aqueous solution was made strongly basic with KOH, and extracu afforded a colorless liquid VIb (1.1 g.), $b.p_5$ 94~98°. $[\alpha]_D^{19}$ +54.7° (c=5.52, EtOH).

(+)-Tetrahydrodeoxycytisine (XIII)——According to the description of Galinovsky, (−)-cytisine (XII) (263 mg.) was catalytically hydrogenated with PtO_2 in dil. HCl solution at atmospheric pressure for 15 hr. and Pt was filtered. The filtrate was concentrated to dryness to yield crude crystals (XIII-2HCl) of m.p. 260°, from which impure free base XIII was obtained as a liquid purifiable *vin* itr styphnate m.p. 225~228° or its picrate m.p. 231~232° (decomp.). PPC: Rf 0.63. IR $\nu_{max}^{capil.}$ cm^{-1}: 3340 (NH), 2800, 2760 (*trans*-quinolizidine). *Anal.* Calcd. for $C_{11}H_{20}O_8N_2 \cdot (C_6H_3O_8N_3)_2$ (XIII-styphnate): C, 41.20; H, 3.91; N, 16.71. Found: C, 41.25; H, 3.99; N, 17.26.

(+)-Tetrahydrodeoxycytisine *p*-Toluenesulfonate (XIVa)——A mixture of XIII (prepared fron 51 mg. of XIII-2HCl), TsCl (76 mg.) and anhydrous pyridine (1 ml.) was kept standing for over night. After remolval of pyridine on a boiling water bath, the residue was dissolved in 10% HCl solution washed with ether, made basic with NaOH, and extracted with ether. Impure crystals (XIII, 50 mg.) were obtained and purified by passing through a column of neutral Al_2O_3 with benzene-ether. Recrystallization from benzene-petr. ether solution provided colorless rods. m.p. 144°. $[\alpha]_D^{32}$ +9.8° (c=2.05, benzene). PPC: Rf 0.64 (blue). *Anal.* Calcd. for $C_{18}H_{26}O_2N_2S$: C, 64.84; H, 8.03; N, 8.29. Found: C, 64.63; H, 7.84; N, 8.38. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2810, 2760, 2735 (*trans*-quinolizidine), 1597 (phenyl), 1330, 1162 (-SO_2N-).

(1*R*:5*S*:7*S*:11a*R*)-1,2,3,4,5,6,9,10,11,12a-Decahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocine (XV)——Dilactam (III) (2 g.) of m.p. 258°, $[\alpha]_D^{20}$ +21.2° (EtOH), prepared from I was added to $LiAlH_4$ (4 g.) in tetrahydrofuran (50 ml.) and refluxed for 8 hr. After the solvent was removed *in vacuo* the reaction mixture was decomposed with moist ether. To the ether layer dried over anhydrous Na_2SO_4, was added gradually a solution of styphnic acid (1 g.) in MeOH with stirring. Recrystallization of the precipitate from MeOH-AcOEt furnished XV-styphnate (1.9 g., yield 65%) as yellow needles, m.p. 213°. *Anal.* Calcd. for $(C_{11}H_{20}N_2)_2 \cdot C_6H_3O_8N_3$: C, 55.52; H, 7.16; N, 16.19. Found: C, 55.66; H, 7.16; N, 16.12. By decomposing XV-styphnate in usual way, the pure free base (XV) could be obtained as a colorless oil which is distillable but hygroscopic and slightly unstable in the air. PPC: Rf 0.45. IR $\nu_{max}^{capil.}$: 3340 cm^{-1} (NH), no *trans*-quinolizidine band is observed.

XV *p*-Toluenesulfonate (XVI)——Tosylation of XV prepared from its styphnate (0.1 g.), by the same method as described before in the case of XIV, gave crystalline (XVI, 54 mg.), colorless rods of m.p. 174°. $[\alpha]_D^{27}$ −11° (c=4.0, benzene). PPC: Rf 0.66 (brown). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2822, 2770 (weak), 1600 (phenyl), 1332, 1164 (-SO_2N-). *Anal.* Calcd. for $C_{18}H_{26}O_2N_2S$: C, 64.63; H, 7.84; N, 8.38. Found: C, 64.99; H, 7.99; N, 8.27.

(+)-(1*R*:5*R*:7*R*:11a*S*)-3-*p*-Toluenesulfonyl-1,2,3,4,5,6,9,10,11,11a-decahydro-1,5-methano-8*H*-pyrido-[1,2-*a*][1,5]diazocine (XIVb)——A solution of XVI (0.3 g.) and $Hg(CAc)_2$ (1 g.) in 5% AcOH (30 ml.) was heated on a boiling water bath for 4 hr., cooled and filtered. The precipitated HgOAc was 0.33 g., 70% of theoretical. Excess mercury was precipitated by H_2S from the filtrate after acidified with dil. HCl. The filtrate was concentrated to a pale brown oil to remove H_2S completely, which was dissolved again in dil.

AcOH, treated with charcoal and shaken with Adams' platinum catalyst (ca. 1 g.) to eliminate all traces of H_2S. The H_2S free filtrate was hydrogenated with another catalyst, PtO_2 (1 g.), at atmospheric pressure for 2 hr. After consuming 15 ml. of H_2, the catalyst was filtered and the filtrate was concentrated *in vacuo* at about 50° to a small quantity, made basic with NaOH and extracted with ether. Evaporation of ether yielded a pale brown oil (0.265 g.) which gradually solidified. This mixture was dissolved in benzene and placed on Al_2O_3 (10 g., Brockmann), eluted with benzene to give a crystalline mixture (0.167 g., m.p. 130~142°), which was rechromatographed on Al_2O_3 (12 g.) with benzene. The first fraction was identified as the starting material (XVI), and the middle fractions are still mixtures of XIVb and XVI judging from their IR spectra. Crystals of m.p. 138~142° were collected from the last fractions and recrystallized from benzene-petr. ether to give colorless rods (XIVb), m.p. 144° (29 mg.). $[\alpha]_D^{25}$ +10° (c=1.2, benzene). *Anal.* Calcd. for $C_{18}H_{26}O_2N_2S$: C, 64.63; H, 7.84; N, 8.38. Found: C, 64.82; H, 7.95; N, 8.26. The IR spectrum in $CHCl_3$ and PPC are completely identical with those of XIVa, and no melting point depression was observed on admixture with XIVa. At least more than one third of this epimerization product was estimated to be XIVb by its IR, but a good separation of XIVb from XVI with Al_2O_3 column seemed to be so difficult that XIVb could not be obtained in good yield.

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Summary

The chemical interrelations between (+)-epilupinine (IX) and (−)-anagyrine (I), and then between I and (−)-cytisine (XII) were carried out. Consequently the absolute configurations of (−)-anagyrine (I), (−)-cytisine (XII) and related alkaloids were clarified.

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66. Fumio Yoneda, Takuyuki Miyamae und Yoshihiro Nitta: Synthese der 1,2,3,4-Tetrahydrochinolin-derivate.

(*Forschungslaboratorium, Chugai Pharmaz. A. G.*[*1])

Das seit einigen Jahren als neues Antihistaminikum in die Therapie eingeführte 1-*p*-Chlorbenzyl-2-(1-pyrrolidinylmethyl)benzimidazol (Allercur) (I) unterscheidet sich strukturell vom früheren Antihistaminikum Antergan (II) nur durch den Ringschluss durch ein Heteroatom Stickstoff.

In Betrachtung der chemischen Ähnlichkeit zum I, synthetisierten wir diesmal 1,2,3,4-Tetrahydrochinolin-derivate (III), die durch den Ersatz eines Stickstoffs vom I durch eine Äthylenbrücke aufgebaut sind und es wurde geprüft, ob die Äthylenbrücke-substitution die Antihistamin-Wirkung im Vergleich zu I wesentlich verändert.

Im nachfolgenden berichten wir über die Erkenntnisse, die wir in Versuchen hierüber gewonnen haben.

Als Ausgangsmaterial wurde 2-Chlormethylchinolin (IV) benutzt. IV kann nach dem Kobayashi'schen Verfahren[1] bei der Chlorierung vom aus Chinaldin-N-oxyd übergeführten 2-Chinolin methanol mit Thionylchlorid hergestellt werden.

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*1 Takataminami-cho, Toshima-ku, Tokio (米田文郎, 宮前卓之, 新田義博).

1) G. Kobayashi: Yakugaku-Zasshi, **74**, 791 (1954).