33. **Shojiro Uyeo* and Shigeru Kobayashi**:** Lycoris Alkaloids. XXIV[1]. Isolation and Characterization of Lycoremine.

(Pharmaceutical Institute, Medical Faculty, University of Osaka and University of Kyoto**)*

A number of alkaloids are contained in the bulb of *Lycoris radiata* Herb. Morishima[2] reported, in 1897, the isolation of two bases, lycorine and sekisanine[3]. Later, Kondo and collaborators[4] added seven new members to the series, and they designated them as lycorenine, lycoramine (pseudohomolycorine), homolycorine, pseudolycorine, base VIII (tazettine), base IX, and sekisanoline[5].

Through the kindness of Prof. H. Kondo in providing us with a quantity of crude materials and giving us his permission for their investigation, it became possible for us to undertake further studies of the lycoris alkaloids. The present paper describes the isolation and characterization of a new minor alkaloid.

In the separation of the known alkaloids from the crude material, according to the methods described previously in a series of papers[4], it was observed that there remained in the mother liquor a considerable amount of alkaloids. Since there has been no general procedure for the separation of this portion in the available literature, the authors decided to investigate the components with the hope of adding further members to this class of alkaloids.

Preliminary studies revealed that the residue, a viscous syrup, yielded no crystalline substance on treatment with a variety of solvents. Attempts have been made, therefore, to isolate individual constituents by means of the partial extraction method using dilute hydrochloric acid, whereby a moderately basic new alkaloid, m.p. 127～129°, was obtained. The authors have assigned the name lycoremine to this alkaloid. Later, it was found that the isolation of the base was particularly facilitated by processing through its hydrochloride, which is very slightly soluble in acetone. Analytical figures of the base and its salts support a molecular formula $C_{17}H_{21}O_3N$ for lycoremine. The Zeisel and the Herzig-Meyer determination reveal the presence of one O-methyl and one N-methyl group, respectively; but neither phenolic hydroxyl nor methylenedioxy group can be detected, the base being insoluble in aqueous alkali and giving neither the color reaction with ferric chloride nor Gaebel's reaction. Lycoremine shows no Liebermann's reaction for secondary amines and forms a methiodide, m.p. 289～291° (decomp.), with ease, a fact which suggests that it is a tertiary amine. The base reduces neither Fehling's solution nor Tollens' reagent. Attempts to prepare carbonyl derivatives have failed.

In accordance with these findings the base shows no carbonyl band in the $5\sim6\mu$ region of the infrared absorption spectrum. The ultraviolet absorption curve for the alkaloid shows a single maximum at 283 mμ ($\log \varepsilon=3.21$), suggesting the presence of a benzenoid

---

* Hotarugaike, Toyonaka, Osaka-fu (上尾庄次郎).

** Yoshida-konoe-cho, Sakyo-ku, Kyoto (小林茂).

[1] Part XXIII: Ann. Repts. ITSUU Lab. (Japan), 4, 73 (1953).

[2] Morishima: Arch. exptl. Path. Pharmakol., 1, 437 (1897).

[3] An attempt to isolate an alkaloid, the properties of which coincide closely with the data given for sekisanine, has so far been unsuccessful. Since we are no more possible to obtain the authentic specimen either of Morishima or of Kondo and Tomimura, confirmation by direct comparision has not been made, but it seems probable that sekisanine is identical with tazettine, as was suggested by Späth and Kahovec (Ber., 67, 1501 (1934)). The results of our experiments will be reported in detail at a later date.

[4] H. Kondo, *et al.*: J. Pharm. Soc. Japan, 47, 545 (1927), 49, 438 (1929), 52, 433 (1932), 53, 807 (1933).

[5] Since sekisanoline, a phenolic base, was described as amorphous, it was desirable to reinvestigate the phenolic fraction. The results obtained by us in recent years will be published later.

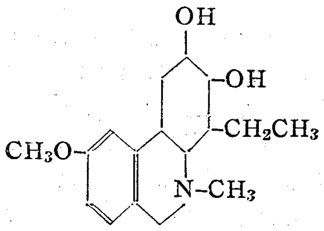
ring substituted with a methoxyl group. No evidence of the conjugation of a double bond with this benzene nucleus can be obtained.

Treatment of the alkaloid with acetic anhydride and anhydrous sodium acetate gives a crystalline monoacetate, m.p. 129~130.5°. This is an indication of the presence of one alcoholic hydroxyl group. In agreement with this fact the infrared spectrum exhibits OH absorption at 3.05μ. Of the three oxygen atoms of lycoremine, the nature of the two has thus been established, while the identification for the remaining one is still lacking.

Lycoremine absorbs one molar equivalent of hydrogen in the presence of palladized charcoal to give, as the main product, a base of m.p. 120~121°, the properties of which are in good agreement with those of lycoramine6), and a mixed melting point determination with an authentic specimen confirmed the identity conclusively. The close relationship between lycoremine and lycoramine has thus been established. The hydrogenation of lycoremine affords, besides lycoramine, in smaller amount an oily isomer with somewhat higher optical rotation than that of either lycoramine or lycoremine. Although this isomer has not been obtained pure because of the scantiness of material, it may be justified to suggest that the hydrogenation leads to the formation of a new asymmetric center, a fact which indicates that the double bond in lycoremine is of either a tri- or a tetra-substituted type.

Previously, the molecular formula $C_{17}H_{25}O_3N$ was assigned to lycoramine and the structure (I) was proposed6).

(I)



However, the analytical values given by the previous workers6) as well as those found by the present authors appear to show that lycoramine is represented precisely by $C_{17}H_{23}O_3N$ rather than by the formula with two more hydrogen atoms. Moreover, the presence of two secondary hydroxyl groups in the molecule, as is postulated in (I), may be improbable in view of the result obtained above (monoacetyllycoremine).

Therefore, the reinvestigation of the structure of lycoramine which seems desirable to the authors is in progress in their laboratory and the results will be reported in succeeding papers.

The authors wish to express their sincere thanks to Prof. H. Kondo for the donation of crude alkaloids and giving them valuable suggestions, to Prof. M. Tomita for helpful discussions, and to the Ministry of Education for a grant from the Scientific Research Fund. They are also indebted to Messrs. Hozumi and Imaeda, and to Miss Iwata for the microanalyses.

Experimental

General procedure for the isolation of the known alkaloids—The total alkaloidal fraction from *Lycoris radiata* in acidic aqueous solution was made alkaline with potassium carbonate and taken up in chloroform. Lycorine which was left alone as precipitate was filtered off. On standing the clear chloroform solution for some days, pseudolycorine deposited on the wall of the flask. The filtered solution was extracted with aqueous sodium hydroxide to remove phenolic bases including sekisanoline. The organic layer was then shaken with dilute hydrochloric acid, whereby all bases but homolycorine was taken up into the aqueous layer. The acid extract was then rendered alkaline and shaken with chloroform. Evaporation of the chloroform and addition of acetone to the residue gave a crystalline mixture, which was separated into lycorenine, tazettine, and the base IX by fractional crystallization from a variety of solvents. Addition of excess dilute perchloric acid to the filtrate precipitated lycoramine as its perchlorate, which was collected by filtration. The mother liquor was concentrated, diluted with water, rendered alkaline with sodium hydroxide and the liberated oil was taken up in chloroform. After removal of the solvent by distillation the residue was treated with various solvents but yielded no crystalline substance.

Isolation of lycoremine—Fifty-one g. of the above residue was dissolved in 340 cc. of chloroform and shaken with 100 cc. of 0.1*N* hydrochloric acid. The aqueous layer was separated and

---

6) Ber., 70, 2427 (1937).

the extraction of the chloroform solution was repeated using the same amount of hydrochloric acid each time until no more base could be extracted by the renewed portion of the acid. Each of the resulting aqueous solutions was rendered alkaline and extracted with chloroform. After drying, the solvent was removed by distillation to obtain 11 fractions. When each fraction was allowed to stand for some days after adding a few drops of acetone, it was observed that, from most of the fractions, there were separated crystalline precipitates, which were filtered off, and washed with a small amount of acetone. Purification of the crystals was accomplished by recrystallization from acetone and chromatography on alumina using chloroform as the solvent to give lycoremine and/or tazettine as shown in Table I. To each of the mother liquors from the precipitates was added a small excess of conc. hydrochloric acid, from which separated white crystalline lycoremine hydrochloride in an amount as given in Table I.

TABLE I

Fractions	1	2	3	4	5	6	7	8	9	10	11
pH of extracted solutions	6.8	6.4	6.2	6.2	6.0	5.6	5.0	1.6	<1.2	<1.2	<1.2
Yield of total bases	4.4 g.	4.2 g.	5.0 g.	3.8 g.	3.9 g.	6.3 g.	7.0 g.	4.0 g.	0.6 g.	0.4 g.	0.4 g.
Yield of crystals	—	—	—	0.15g.	0.55g.	0.82 g.	0.17g.	0.68g.	0.10g.	—	—
m.p. of crystals	—	—	—	110∼ 120°	97∼ 120°	126∼ 138°	116∼ 165°	204∼ 206°	200∼ 204°	—	—
Yield of lycoremine	—	—	—	—	—	0.38g.	0.09g.	—	—	—	—
Yield of tazettine	—	—	—	—	—	—	—	0.68g.	0.10g.	—	—
Yield of lycoremine-HCl	0.18g.	0.29g.	0.64g.	0.67g.	1.28g.	1.80g.	2.33g.	0.58g.	—	—	—

Lycoremine—Crude lycoremine was recrystallized from acetone several times to colorless prisms, m.p. 127∼129°, $[\alpha]_D^{32}$: -121.4° (c=0.9875 in abs. EtOH). It is readily soluble in methanol, ethanol, and chloroform, soluble in water, ether, benzene, and carbon tetrachloride, but practically insoluble in petroleum ether or aqueous sodium hydroxide. *Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87; CH_3O, 10.80; N–CH_3, 5.23. Found: C, 71.17, 71.14; H, 7.72, 7.55; N, 5.32, 5.10; CH_3O, 10.89, 10,91, 11.05; N–CH_3; 5.08, 5.01, 4.62.

Lycoremine hydrochloride was separated from the solution of lycoremine in methanol by the addition of conc. hydrochloric acid. Crystallization from methanol gave colorless prisms of m.p. 252.5∼253° (decomp.) which were soluble in hot methanol and in hot ethanol, but were almost insoluble in acetone, chloroform, and ether. *Anal.* Calcd. for $C_{17}H_{21}O_3N.HCl$: C, 63.05; H, 6.85; N, 4.32; Cl, 10.95. Found: C, 62.73; H, 6.83; N, 4.08; Cl, 11.04, 11.09.

Lycoremine perchlorate was precipitated from the methanolic solution with perchloric acid. Recrystallization from methanol afforded white needles of mp. 236∼237° (decomp.). *Anal.* Calcd. for $C_{17}H_{21}O_3N.HClO_4.H_2O$: C, 50.26; H, 5.96. Found: C, 50.27; H, 5.96. The hydrate did not lose water of crystallization when heated at 110° for 5 hours in vacuo.

Lycoremine acetate—A mixture of 0.2 g. of lycoremine dissolved in 1.4 cc. of acetic anhydride and 0.2 g. of anhydrous sodium acetate was heated on a water bath for 1.5 hours. After cooling, excess acetic anhydride was decomposed with 10 cc. of water and then the reaction mixture was made alkaline with potassium carbonate. The resulting precipitate was collected on a filter, washed with water, and dried on a clay plate to yield 0.22 g. of crystals melting at 124∼128°. Recrystallization from ether-petroleum ether gave crystals, m.p. 129∼130°. *Anal.* Calcd. for $C_{17}H_{20}O_3N(COCH_3)$: C, 69.28; H, 7.04; $COCH_3$, 13.07. Found; C, 69.56, 69.96; H, 6.80, 7.11; $COCH_3$, 13.61, 12.59.

Lycoremine methiodide—A solution of 0.5 g. of lycoremine in 2 cc. of methanol was heated with 2 g. of methyl iodide for 20 minutes. The reaction mixture was cooled and the white crystalline precipitate was collected on a filter. It consisted of 0.48 g. of methiodide which melted at 289∼291° (decomp.) after one recrystallization from methanol. *Anal.* Calcd. for $C_{17}H_{21}O_3N.CH_3I$: C, 50.35; H, 5.65; N, 3.26; I, 29.56. Found: C, 49.80, 50.08; H, 5.73, 5.83; N, 3.64; I, 29.65, 29.85.

Hydrogenation of lycoremine—A solution of 1 g. of lycoremine in 30 cc. of alcohol was hydrogenated at atmospheric pressure in the presence of 1 g. of 15% palladium-carbon catalyst. A total of 101 cc. of hydrogen was taken up in 3.5 hours. After removal of the catalyst, the filtrate was concentrated and the oily residue was converted to the perchlorate by the addition of 5% perchloric acid, obtaining 1.3 g. of white crystalline powder, which melted at 137° (decomp.) after one recrystallization from water. The melting point was not despressed on admixture with authentic lycoramine perchlorate.

An aqueous solution of the perchlorate was basified with excess sodium carbonate and extracted with ether. After drying and evaporating the ether, there remained 0.85 g. of a viscous oil, which was crystallized on trituration with acetone to give 0.48 g. of the free base as colorless plates, m.p. 120∼121°, $[\alpha]_D^{25}$: -97.4° (c=1.252 in 90% EtOH). This product did not depress the melting point of an authentic specimen of lycoramine. *Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01. Found: C, 70.67; H, 7.80.

The mother liquor from the lycoramine perchlorate was made alkaline and the liberated base was recovered with ether. After concentration of ethereal solution to dryness, a small amount of perchloric acid was added to the residue, and a small quantity of the solid material which separated out was filtered off. The mother liquor was treated as before and this procedure was repeated several times until no insoluble material was obtained by the addition of perchloric acid to the free base. Thus 0.05 g. of viscous oil, b.p$_{0.05}$ 190～200°, $[\alpha]_D^{24.5}$: −136.3° (c=0.375 in 90% EtOH), was obtained which could not be induced to crystallize by addition of a few seed crystals of lycoramine or lycoremine. *Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01. Found: C, 70.12; H, 8.40.

Summary

A new alkaloid, lycoremine, was isolated from *Lycoris radiata*. This compound can be represented by a formula $C_{17}H_{21}O_3N$ and contains one OCH_3, one $N\text{-}CH_3$, and one alcoholic hydroxyl group. Lycoremine was converted into lycoramine, $C_{17}H_{23}O_3N$, by hydrogenation from which the relationship between the two alkaloids was established.

(Received April 9, 1953)

---

34. Kyosuke Tsuda, Nobuo Ikekawa, Rinji Takasaki, and Yasumasa Yamakawa:

Studies on the Coal Tar Bases. III[1]. Synthesis of Dimethylpyridines.

(*Pharmaceutical Institute, Medical Faculty, University of Kyushu**)

Six possible isomers of lutidine have hitherto been found[2] from coal tar bases. All of these were obtained from coal tar bases of low temperature coking[3]. Ordinarily, 2,6-lutidine is distilled mixed with β- and γ-picoline from a fraction of b.p. 140～145°, and is separated by recrystallization of the hydrochloride or by the fractional distillation in vacuum of its N-oxide[4]. 2,4-, 2,5- and 2,3-Lutidine are distilled from a fraction of b.p. 157～163°, and these three bases are separated by recrystallization of their picrates but the yield of each base is small. It seemed that the best method to obtain 2,4-lutidine from coal tar was by a fractional distillation of its N-oxide[4]. 3,5-Lutidine is distilled from a fraction of b.p. 169～172°, and 3,4-lutidine from a fraction of b.p. 177～180° mixed with a certain amount of trimethylpyridine. In each case the base is separated by the recrystallization of the picrate.

All the lutidines, with the exception of 3,5-lutidine, have already been synthesized. 3,5-Lutidine was prepared in the present experiments, and 2,5-, and 2,3-lutidine by different methods from those given in literatures, which are described in the present paper.

3,5-Lutidine 3,5-Pyridinedicarboxylic acid (I)[5] was obtained by heating 2,3,5,6-pyridinetetracarboxylic acid[6], derived from 3,5-dicarbethoxy-2,6-dimethylpyridine[7], in glacial acetic acid. After esterification of the dicarboxylic acid of pyridine (I), ethyl ester (II) was reduced to the diol (III) with lithium aluminum hydride, and chlorinated to 3,5-dichloromethylpyridine (IV), m.p. 86～87°, with thionyl chloride. The dichloromethyl compound (IV) was converted readily to 3,5-dimethylpyridine (V), b.p. 171°, by reduction. It

---

* Hakata, Fukuoka (津田恭介, 池川信夫, 高崎林治, 山川泰正).

[1] Part II: This Bulletin, 1, 126 (1953).

[2] A. A. Morton: "The Chemistry of Heterocyclic Compounds". p. 206 (1946).

[3] This Bulletin, 1, 149 (1953).

[4] E. Ochiai, M. Ikehara, T. Kato, N. Ikekawa: J. Pharm. Soc. Japan, 71, 1385 (1951).

[5,6] A. Hartzsch, L. Weiss: Ber., 19, 284 (1886).

[7] Org. Syntheses, 14, 30 (1936).