The Aconite Alkaloids. XXXIII. On Lucidusculine. III***

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In the previous reports some derivatives of lucidusculine (I), $C_{24}H_{35}O_4N$, have been reported and the extended formula of compound I has been proposed[2,3].

Lately the author has investigated the behavior of compound I toward various oxidizing agents, and the previously proposed partial formula[2] is further extended.

Oxidation of compound I with 3% hydrogen peroxide gave lucidusculine *N*-oxide-a (II), $C_{24}H_{35}O_5N \cdot H_2O$, m. p. 191°C (decomp.) in a poor yield. From the procedure for its preparation, compound II seems to contain water of crystallization[4-7].

Further, in order to obtain an epoxide derivative of compound I, perbenzoic acid oxidation has been performed. This oxidation has not given the results expected in the cases of Senecio alkaloids[8] and atisine derivatives[9]. Compound I reacted with only one mole of perbenzoic acid under different conditions and an *N*-oxide, lucidusculine *N*-oxide-b (III), $C_{24}H_{35}O_5N \cdot 1/2H_2O_2$***, m. p. 200°C (decomp.), was yielded. This reaction proceeds similar to that of strychnine[10]. Compound III lost hydrogen peroxide of crystallization on standing for several months, being converted into lucidusculine *N*-oxide-c (IV), $C_{24}H_{35}O_5N$, m. p. 209°C**** (decomp.)[5]. Infrared spectrum of compound

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* This paper constitutes a part of a series entitled "The Aconite Alkaloids" by H. Suginome. Part XXX, cf. Foot Note 2). Part XXXII, cf. Foot Note 3).

** Part XXXII corresponds to part II of "On Lucidusculine". A preliminary note on part of the matter of this paper appeared in this Bulletin[1].

1) T. Amiya, This Bulletin, **30**, 677 (1957).

2) H. Suginome, T. Amiya and T. Shima, ibid., **32**, 824 (1959).

3) T. Amiya, ibid., **32**, 1133 (1959).

4) K. Bodendorf and B. Binder, *Arch. Pharm.*, **287**, 326 (1954).

5) D. W. Henry and E. Leete, *J. Am. Chem. Soc.*, **79**, 5254 (1957).

6) A. S. Bailey and R. Robinson, *J. Chem. Soc.*, **1948**, 703; R. H. F. Manske and H. L. Holmes, "The Alkaloids", Vol. II, Academic Press, Inc., Publishers, New York (1952), p. 522.

7) M. Oesterlin, *Ber.*, **76**, 224 (1943).

8) L. J. Dry, M. J. Koekemoer and F. L. Warren, *J. Chem. Soc.*, **1955**, 59.

9) C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.*, **170**, 515 (1947).

*** Compound III does not contain water of crystallization[1] but does contain hydrogen peroxide.

10) M. Kotake and T. Mitsuwa, *J. Chem. Soc. Japan*, **57**, 236 (1936); R. N. Chakravarti and R. Robinson, *J. Chem. Soc.*, **1947**, 78.

**** The previously reported d. p. is revised to this.

IV showed a band at 10.47μ characteristic of an *N*-oxide group[11,12]. Its ultraviolet absorption spectrum showed only end absorption.

Compound III was readily reduced with zinc dust and dilute sulfuric acid to compound I normally.

Oxidation of compound I with *N*-bromosuccinimide afforded dehydrolucidusculine (V), $C_{24}H_{33}O_4N$, m. p. 175~180°C, with loss of two hydrogens. Its infrared spectrum showed sharp bands at 10.15 and 11.34μ which were probably indicative of a cyclic ether[13,14]. Compound I lacks the bands corresponding to these (10.15 and 11.34μ) of compound V. It is, therefore, probable that the reaction proceeds as in the case of each delcosine[13] and delsoline[14] with formation of a cyclic carbinolamine internal ether between carbinolamine hydroxyl and one of the hydroxyls in compound I. This may be supported by the fact mentioned below that lucidusculine *N*-oxide was found to change to compound V. Its ultraviolet absorptions spectrum showed end absorption.

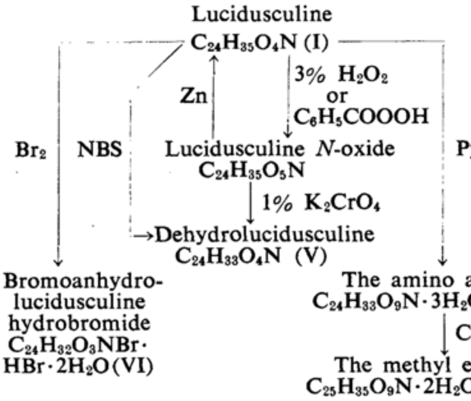
Strychnine *N*-oxide has been rearranged to a carbinolamine, pseudostrychnine[6]. Crow[15] mentioned the transformation of sparteine *N*-oxide to three possible carbinolamines. Therefore compound III was treated under the same conditions as in the case of the isomerization of strychnine *N*-oxide. Although an expected carbinolamine was not obtained, compound V was yielded. From these facts, it is supposed that an initially formed carbinolamine is changed to compound V with loss of one mole of water and with simultaneous formation of a carbinolamine internal ether.

In contrast to isoatisine[9], on bromination of compoud I no expected dibromo derivative was obtained. In this case a hydrobromide of a monobromo derivative, bromoanhydrolucidusculine hydrobromide (VI), $C_{24}H_{32}O_3NBr \cdot HBr \cdot 2H_2O$, m. p. 210°C (decomp.) was produced. Thus, the behavior of compound I on bromination is noted. Its infrared absorption spectrum showed the disappearance of a band which was characteristic of a terminal methylene group and corresponded to that (11.07μ)[16] of compound I[3]. From the observation of the molecular formula and its infrared spectrum, compound VI is perhaps yielded from an intermediate dibromo derivative, which is produced from compound I by the normal addition of one mole of bromine to a terminal methylene group, with simultaneous elimination of one mole each of water and hydrogen bromide. The ultraviolet absorption spectrum of compound VI does not correspond to that of a conjugated diene (Fig. 1). Although some interpretation of this observation might be presented, it will be left to a later occasion.

The oxidation of some of the aconite alkaloids, viz., atisine, isoatisine, kobusine and hypognavine with chromium trioxide-pyridine complex has been reported to give α,β-unsaturated ketone bases[19-21]. Furthermore, delpheline and lucaconine have been shown to be oxidized to lactams[22,23] by the same reagent.

On the other hand, the action of chromium trioxide-pyridine complex on compound I yielded an amino acid, $C_{24}H_{33}O_9N \cdot 3H_2O$, (VII), which showed no definite m. p. nor d. p., and gradually

TABLE I



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[11] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", 2nd. Ed., Methuen & Co., Ltd., London (1958), p. 308.

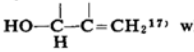
[12] R. H. Wiley and S. C. Slaymaker, *J. Am. Chem. Soc.*, 79, 2233 (1957).

[13] R. Anet, D. W. Clayton and Léo Marion, *Can. J. Chem.*, 35, 397 (1957).

[14] F. Sparatore, R. Greenhalgh and Léo Marion, *Tetrahedron*, 4, 157 (1958).

[15] See A. Albert, G. M. Badger and C. W. Shoppee, "Current Trends in Heterocyclic Chemistry", Butterworths Scientific Publications, London (1958), p. 116.

[16] From the observation of infrared spectra of luciculine[2,8] and isoluciculine[17], of two bands near wavelength 11μ the one at 11.02μ corresponds to that of the terminal methylene group of luciculine, whilst the other at 11.27μ[2,3] does not correspond. Normally, each of the compounds of the type $R_1R_2C=CH_2$[18] shows a band due to a terminal methylene group near this wavelength (11.27μ). This shift from the normal wavelength is explicable by the fact that luciculine includes an allyl alcohol moiety,


$HO-\underset{H}{\overset{|}{C}}-\overset{|}{C}=CH_2$[17] which contains a polar group in the α-carbon atom to the double bond[18]. Similarly, a band characteristic of a terminal methylene group of compound I is not that at 11.26μ[3] but that at 11.07μ. Furthermore, lucidusculine diacetate, luciculine methiodide, isomesoluciculine and bromolucidusculine cyanamide[3] show the bands attributable to the terminal methylene groups at 11.07, 10.98, 11.03 and 10.95μ in the infrared spectra, respectively.

[17] T. Amiya, This Bulletin, 32, 421 (1959).

[18] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", 2nd. Ed., Methuen & Co., Ltd., London (1958), p. 51.

[19] W. A. Jacobs and S. W. Pelletier, *J. Am. Chem. Soc.*, 76, 4496 (1954).

[20] T. Okamoto, *Chem. Pharm. Bull.*, 7, 44 (1959).

[21] S. Sakai, ibid., 7, 51 (1959).

[22] R. C. Cookson and M. E. Trevett, *Chem. & Ind.*, 1954 1324 ; *J. Chem. Soc.*, 1956, 2689.

[23] T. Amiya and T. Shima, This Bulletin, 31, 1083 (1958).

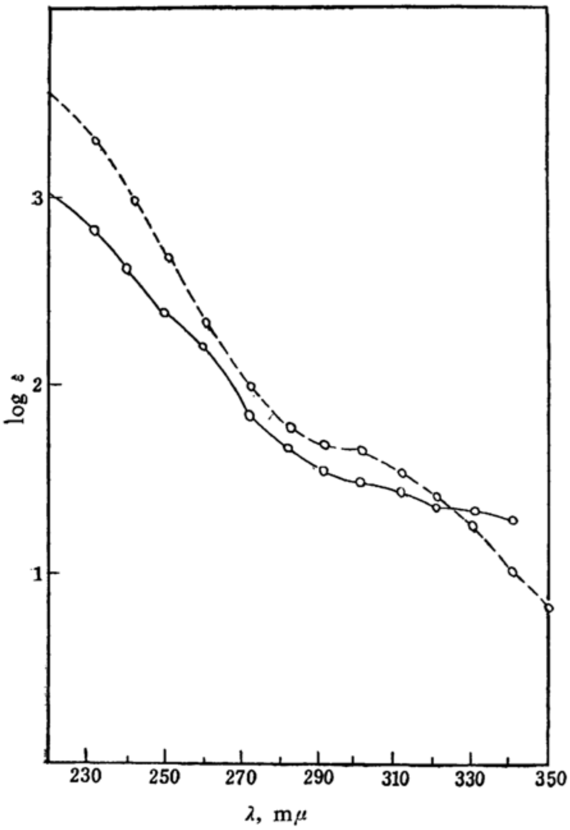


Fig. 1.

The amino acid (VII) --○--○--
Bromoanhydroluciduscu1ine
hydrobromide (VI) —○—○—

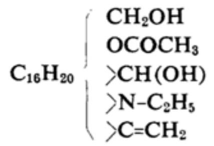
became black above 350°C. It is soluble in methanol and water but insoluble in ethanol and almost all other organic solvents. Although it showed no characteristic absorption maximum of a ketone carbonyl group in the ultraviolet spectrum (Fig. 1), its infrared spectrum showed a strong absorption near 5.85μ, indicating the presence of a ketone carbonyl group in a six-membered ring.

Methylation of compound VII with diazomethane gave a methyl ester (VIII), $C_{25}H_{35}O_9N \cdot 2H_2O$, which gradually swelled with decomposition near 288°C. The ultraviolet spectrum of compound VIII is similar to that of compound VII.

The oxidation of compound I with this milder reagent appears to convert the primary hydroxyl group to a carboxyl group as in the case of oxidation of a dodecahydrophenanthrene derivative[24], and probably the secondary one to the above mentioned ketone carbonyl group. Furthermore, the examination of the molecular formula, $C_{24}H_{33}O_9N \cdot 3H_2O$, and the infrared absorption spectrum of compound VII suggest that this oxidation reaction may cause formation of four new hydroxyl groups. Two of them seem to be introduced into the terminal methylene group as a vicinal glycol system. This is supported by the infrared absorption specteum of compound VII. The spectrum does not indicate a band due to a terminal methylene group near 11μ.

These results indicate that, of two hydroxyl groups in compound I, one is primary, and the other is secondary and is attached to a carbon atom in a six-membered ring.

Subsequently, the previously proposed partial formula[2] of I may be further summarized as[25],



$$C_{16}H_{20}\left\{\begin{array}{l} CH_2OH \\ OCOCH_3 \\ >CH(OH) \\ >N\text{-}C_2H_5 \\ >C{=}CH_2 \end{array}\right.$$

Lucidusculine (I)

Experimental

Lucidusculine *N*-Oxide-a (II).—Powdered lucidusculine (0.5 g.) was suspended in 50 cc. of about 3% hydrogen peroxide and stirred under warming. After one hour the base was dissolved, and the resulting solution was further stirred for 1.5 hr. without warming. The excessive hydrogen peroxide was then decomposed in contact with a small quantity of freshly prepared manganese dioxide. After removal of the manganese dioxide, the solution was further decolorized with active carbon. After removal of the active carbon by filtration, the solution was evaporated to dryness in vacuo, and the residue was crystallized from aqueous methanol. It was recrystallized from methanol. It showed m. p. 191°C (decomp.).

Found: C, 65.94; H, 8.37; H_2O, 3.31. Calcd. for $C_{24}H_{35}O_5N \cdot H_2O$: C, 66.18; H, 8.56; H_2O, 4.13%.

From the above described procedure, it is probable that the substance does not contain hydrogen peroxide but water of crystallization as strychnine *N*-oxide does[6,7].

Lucidusculine *N*-Oxide-b (III).—Lucidusculine (0.5 g.) dissolved in chloroform (10 cc.) was added to 12 cc. of chloroform solution of perbenzoic acid (about 4 mol. equiv.). The reaction mixture was allowed to stand in a refrigerator for 6 days, and then was evaporated to dryness. To the residue, ether, about 1 cc. of 2 N hydrochloric acid and a small quantity of water were simultaneously added and the mixture was shaken. The aqueous layer separated from ether layer was passed through a column 17 cm. by 2 sq. cm. of anion-exchange resin (Amberite IRA-400) and then the column was eluted with 100, 50 and 25 cc. of water one after the other. From the first fraction (100 cc.) of elute, the residue was obtained, which gave crystals, m. p. 193°C

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[24] G. I. Poos, W. F. Johns and L. H. Sarett, *J. Am. Chem. Soc.*, 77, 1026 (1955).

[25] The partial formula of I in a previous report[1] is revised to this.

(decomp.), on treatment with methanol. On recrystallization from methanol a material, m. p. 200°C (decomp.), $[\alpha]_D^{15}$ −101°, was obtained.

Found: C, 65.30, 65.52; H, 8.53, 8.68. Calcd. for $C_{24}H_{35}O_5N.{}^1/_2H_2O_2$: C, 66.32; H, 8.34%.

From the results described below it seems to contain hydrogen peroxide of crystallization. However, this material should be re-examined more precisely by iodometric titration.

Lucidusculine *N*-Oxide-c (IV).—To lucidusculine (1 g.) dissolved in 10 cc. of chloroform, were added 12 cc. of chloroform solution, containing excessive perbenzoic acid, and a few drops of water. After standing overnight, the chloroform was removed. The residue was digested with ether. To the ether-insoluble portion, 2 cc. of 2 N hydrochloric acid, water and chloroform were simultaneously added, and the mixture was shaken. The aqueous layer separated from chloroform layer was passed through the above mentioned column of anion-exchange resin and the column was eluted with water and then methanol. From the first fraction (80 cc. of aqueous elute), 0.7 g. of crystalline material, m. p. 198°C with decomposition was obtained. Subsequently, following fractions were discarded. It liberated iodine from acid solution of potassium iodide. From this fact, it seems to contain hydrogen peroxide of crystallization[4,7]. Recrystallization from methanol gave 0.2 g. of *N*-oxide-b which showed m. p. 205°C (decomp.)*. It was slightly soluble in chloroform and insoluble in ethyl acetate. The specimen several months old had lost hydrogen peroxide, and it showed no diminution of its weight by drying in vacuo at 100~110°C. It melted at 209°C with decomposition. The ultraviolet absorption spectrum of this compound in methanol showed end absorption and no maximum. The infrared absorption spectrum in Nujol showed the presence of hydroxyl groups (3.15 μ), an acetoxyl group (5.82 and 8.09 μ), an *N*-oxide group (10.47 μ) and a terminal methylene group (11.07 μ).

Found: C, 69.32; H, 8.27. Calcd. for $C_{24}H_{35}O_5N$: C, 69.03; H, 8.45%.

Reduction of Lucidusculine *N*-Oxide. — The *N*-oxide-b (0.15 g.) freshly prepared from lucidusculine by perbenzoic acid oxidation for 2 days was dissolved in 1.5 cc. of 10% sulfuric acid**. To this solution, a drop of cupper sulfate solution was added and then 0.15 g. of zinc powder was gradually added. After standing for 2.5 hr. the reaction mixture was filtered, made alkaline with aqueous ammonia and extracted with chloroform. After removal of the chloroform, the residue was crystallized from methanol. It melted at 169~173°C and showed no depression of the melting point on admixture with lucidusculine.

Oxidation of Lucidusculine with *N*-Bromosuccinimide [Dehydrolucidusculine (V)].—Lucidusculine (0.5 g.) and *N*-bromosuccinimide (0.23 g.) were dissolved in 250 cc. of benzene. After boiling for 3 hr., the formed precipitate was removed by filtration. The filtrate was evaporated to dryness in vacuo. The residue dissolved in chloroform was washed three times with sodium carbonate solution and then three times with water. After removal of the chloroform, the residue was redissolved in chloroform and chromatographed on alumina. The chromatogram was eluted with chloroform and acetone and then methanol. From the chloroform portion (15 cc.), 50 mg. of residue was obtained, which on recrystallization from methanol, melted at 175~180°C. From the acetone portion (30 cc.), impure lucidusculine was obtained. Accordingly, the methanol portion (15 cc.) was discarded. The ultraviolet absorption spectrum of this compound (m. p. 175~180°C) showed end absorption and no maximum. The infrared absorption spectrum in Nujol showed the presence of a hydroxyl group (3.08 μ), an acetoxyl group (5.76 and 8.09 μ), a terminal methylene group (10.75 μ) and a carbinolamine ether (10.15 and 11.34 μ).

Found: C, 71.51; H, 8.41. Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33%.

Dehydrolucidusculine (V) from Lucidusculine *N*-Oxide.—To 76 cc. of 1% K_2CrO_4 solution, was added lucidusculine *N*-oxide (200 mg.), which was the same sample as that used for the above described reduction. The material was heated on a water bath. The solution, which was transparent at first, became turbid in about thirty minutes. After heating for 1.5 hr., the separated material (50 mg.) was collected by filtration. It was dissolved in chloroform and the filtered solution was concentrated. On addition of methanol, a crystalline substance was obtained. On recrystallization from acetone, it melted at 173~177°C and showed no depression on admixture with sample obtained by the above described NBS oxidation.

Found: C, 72.38; H, 8.74***. Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33%.

Bromoanhydrolucidusculine Hydrobromide (VI).—To a solution of lucidusculine (0.5 g.) dissolved in 10 cc. of methanol, a freshly prepared 0.25 M solution of bromine in methanol was added dropwise. Excessive bromine was detected by potassium iodide starch paper. In total 8.5 cc. of reagent were added; after one hour, excessive bromine persisted (1 mol. 5.07 cc.). When the methanol solution was concentrated, it showed acid reaction to Congo red. It was evaporated to dryness in vacuo. The residue, on recrystallization from methanol, gave crystals, m. p. 210°C (decomp.). $[\alpha]_D^{18}$ −64.63°C (methanol). The ultraviolet absorption spectrum of this compound in methanol is graphed in Fig. 1. The infrared absorption spectrum in Nujol had no band attributable to a terminal methylene group; it showed the presence of a hydroxyl group (2.99 μ), an acetoxyl group (5.78 and 8.16 μ) and water (6.05 μ).

Found: C, 50.02; H, 6.74; Br, 29.70; H_2O, 5.5. Calcd. for $C_{24}H_{32}O_3NBr\cdot HBr\cdot 2H_2O$: C, 49.73; H, 6.43; Br, 27.57; H_2O, 6.2%.

The hydrobromide was soluble in water. The base, liberated from the hydrobromide with aqueous ammonia, could not have been obtained in a crystalline form on treatment with methanol.

The Amino Acid (VII).—A mixture of lucidusculine (1.8 g.) and chromium trioxide (2.4 g.) in

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* This material seems to be purer than the *N*-oxide-b which showed m. p. 200°C (decomp.).

** For hydrochloric acid[1], 10% sulfuric acid is substituted.

*** The figure, 8.75[1], was misprinted.

pyridine (48 cc.) that had been allowed to stand at room temperature overnight was filtered. The filtrate was evaporated to dryness in vacuo. The residue was treated with water saturated with sulfur dioxide. After standing overnight, the acid solution was made alkaline with saturated baryta water to precipitate chromic hydroxide. The alkaline solution from which the precipitate had been removed by filtration was made slightly acid by the addition of 10% sulfuric acid, and the precipitated barium sulfate was removed. The concentrated filtrate was neutralized with baryta water and was evaporated to dryness. The residue was treated with methanol and the undissolved barium sulfate was removed by filtration. The methanol solution was evaporated to dryness. To a solution of the residue (1.8 g.) dissolved in 9.5 cc. of methanol, 34 cc. of acetone was added. Then a yellow precipitate was formed. The transparent solution separated from the precipitate was concentrated to obtain a crystalline material; it weighed 1.4 g. It was dissolved in methanol (5.5 cc.). Upon the addition of 28 cc. of ethanol, 0.3 g. of a crystalline material was obtained. The mother liquor gave a second crop (0.3 g.) on recrystallization from methanol-ethanol.

The combined crystalline material (0.6 g.) was dissolved in 30 cc. of 70% methanol. The solution was passed through a column of 10 cc. of cation-exchange resin (Dowex 50) and eluted with the same solvent. The elute (280 cc.) was evaporated to dryness and yielded 540 mg. of crystalline residue. It was recrystallized from 70% methanol and gave 200 mg. of pure material. It was soluble in water and methanol but not in ethanol and other organic solvents. It showed no definite m. p. nor d. p. and gradually became black above 350°C. $[\alpha]_D^{16}$ $-26.22°$ (methanol). The ultraviolet absorption spectrum of this compond in methanol is graphed in Fig. 1. The infrared absorption spectrum in Nujol showed the presence of hydroxyl groups (2.92 μ), an acetoxyl group (5.78 and 8.11 μ), a ketone carbonyl group (5.85 μ), water (6.06 μ) and an ionized carboxyl group (6.19 μ).

Found: C, 54.22, 54.60; H, 7.88, 7.69; N, 3.05; H_2O, 10.11. Calcd. for $C_{24}H_{33}O_9N \cdot 3H_2O$[26]: C, 54.02; H, 7.36; N, 2.62; H_2O, 10.12%.

The Methyl Ester (VIII).—To the amino acid (0.25 g.) dissolved in methanol (12.5 cc.), a slight excess of ethereal solution of diazomethane was added. The reaction mixture was allowed to stand overnight and then was evaporated to dryness. The residue was dissolved in 1 N HCl and was precipitated by the addition of aqueous ammonia. The precipitate (0.1 g.) was crystallized from methanol-ethyl acetate and was further recrystallized from methanol. It showed no definite melting point nor definite d. p. and it swelled gradually with decomposition near 288°C. The ultraviolet absorption spectrum of this compound in methanol showed end absorption and no maximum.

Found: C, 57.01; H, 7.70; H_2O, 6.01. Calcd. for $C_{25}H_{35}O_9N \cdot 2H_2O$[26]: C, 56.69; H, 7.42; H_2O, 6.80%.

Summary

The alkaloid lucidusculine was oxidized by hydrogen peroxide and also by perbenzoic acid to lucidusculine *N*-oxide. The *N*-oxide could be converted back into the original base by reduction. Oxidation of the alkaloid with *N*-bromosuccinimide afforded dehydrolucidusculine which was also produced by transformation of lucidusculine *N*-oxide. Dehydrolucidusculine seems to be a cyclic carbinolamine internal ether. The action of bromine on the alkaloid was noticeable and gave bromoanhydrolucidusculine hydrobromide which was probably obtained from the intermediate dibromide with loss of one mole each of water and hydrogen bromide. Chromium trioxide-pyridine complex oxidized lucidusculine to an amino acid which, on methylation with diazomethane, gave a methyl ester. From these experimental results, the previously proposed partial formula of lucidusculine was further extended.

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[26] From the result of determination of water of crystallization the previously reported molecular formula[1] is revised to this.