The Aconite Alkaloids. XXX*. On Lucidusculine

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Lucidusculine, $C_{24}H_{35}O_4N$, was previously isolated from the roots of *Aconitum lucidusculum* Nakai by R. Majima and S. Morio[1,2], and studied by H. Suginome and his collaborators[3-5]. Lucidusculine is a monoacetate of a trihydric amino alcohol, luciculine, $C_{22}H_{33}O_3N\cdot H_2O$[2,5], which was obtained by hydrolysis of the former. The presence of an *N*-ethyl group was confirmed by the formation of mesoluciculine, $C_{21}H_{31}O_3N\cdot H_2O$[5], on Hofmann degradation of luciculine. Further, as lucidusculine absorbed one mole of hydrogen on catalytic hydrogenation, it was assumed that the base has one double bond[4].

On the basis of the above results, the partial structure of lucidusculine was previously represented as:

$$C_{20}H_{25}\left\{\begin{array}{l}(OH)_2\\ OCOCH_3\\ >N\text{-}C_2H_5\\ 1\,F\end{array}\right.$$

Luciculine shows absorption peaks in the infrared spectrum at 6.09 and 11.27 μ and lucidusculine diacetate[4] shows peaks at 6.08 and 11.32 μ. Nevertheless, dihydrolucidusculine diacetate shows no peak near the above-mentioned region[6]. These data suggest the presence of a terminal methylene group in each of luciculine and lucidusculine diacetate, which is also supported by the isolation of formaldehyde as the dimedone complex in ozonolysis experiment with lucidusculine and lucidusculine diacetate. Further, mesoluciculine gave 0.45 mol. of acetic acid on Kuhn-Roth oxidation, while dihydromesoluciculine[7] yielded 0.92 mol. of acetic acid on the same oxidation. The difference (0.47 mol.) can be explained by the following scheme:

$$\underset{\text{Mesoluciculine}}{>C=CH_2}\ \xrightarrow{H_2}\ \underset{\text{Dihydromesoluciculine}}{>CH-CH_3}$$

From these results and the biogenesis of the aconite alkaloids[8], the formula of

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* The report, "Aconite Alkaloids. On Pyrolytic Products of Aconitine, Oxonitine, and their Derivatives", printed in This Bulletin, 31, 658 (1958), constitutes Part XXXI. Part XXIX: H. Suginome, S. Imato, S. Yamada and N. Katsui, This Bulletin, 23, 819 (1959).

[1] R. Majima and S. Morio, *Proc. Imp. Acad. Tokyo*, **7**, 351 (1931).

[2] R. Majima and S. Morio, *Ber.*, **65**, 559 (1932).

[3] H. Suginome and F. Shimanouchi, *Ann.*, **545**, 222 (1940).

[4] H. Suginome, S. Kakimoto and J. Sonoda, *J. Fac. Sci., Hokkaido Univ., Ser. III. Chem.*, **4**, 25 (1950).

[5] H. Suginome and S. Umezawa, ibid., 44.

[6] T. Amiya, unpublished work.

[7] H. Suginome and S. Umezawa, *J. Fac. Sci., Hokkaido Univ., Ser., III. Chem.*, **4**, Supplement, 74 (1952).

[8] R. H. F. Manske, H. L. Holmes, "The Alkaloids", Vol. IV, Academic Press, Inc., New York (1954), p. 280.

lucidusculine may be extended further as follows:

$$C_{18}H_{23}\left\{\begin{array}{l}(OH)_2\\ OCOCH_3\\ >N-C_2H_5\\ >C=CH_2\end{array}\right.$$

Lucidusculine is assumed to have a hexacyclic structure based on the skeletal formula $C_{19}H_{29}N$[3].

Amiya and Nagaoka previously isolated lucidusculine and jesaconitine from the roots of *Aconitum* species from Shoya, Hidaka in Hokkaido[9]. Extraction with ethanol and the following treatment were done in the same way as in the case of other aconite roots[10], and these two alkaloids were isolated from the water-insoluble portion. Now, quantitative separation of these alkaloids from mother-roots and from daughter-roots of the above-mentioned *Aconitum* plants by Ochiai's chromatographic method[11] was tried. As a model experiment, aconitine, jesaconitine and lucidusculine were dissolved in chloroform which was saturated with concentrated ammonia water[12], the solution was passed through a column of alumina, and the column was eluted with chloroform-ammonia water, followed by acetone and then methanol. The residue from the chloroform-ammonia water elute was found to be composed of aconitine and jesaconitine and that from the acetone elute was composed of lucidusculine only. Thus, the same procedure was applied to the above-mentioned water-insoluble portions with results as follows:

Weights of dried roots	Water-insoluble portions	Crystalline alkaloids	
Mother-roots	4.4 g.	Jesaconitine	0.4 g.
4.5 kg.		Lucidusculine	0.2 g.
Daughter-roots	20.5 g.	Jesaconitine	1.4 g.
4.5 kg.		Lucidusculine	0.8 g.

Experimental

Ozonolysis of Lucidusculine.—Lucidusculine (95 mg.) was ozonized in 20 ml. of chloroform-acetic acid (1 : 1 by volume) at $-25\sim-35$°C with three moles of ozone. The solution was hydrogenated with 5% palladium-carbon for 15 min. After removal of the palladium-carbon, dimedone (75 mg.) was added to the solution. After standing overnight, the solvents were completely evaporated in vacuo. To the residue, 10% sodium hydroxide solution (5 ml.) was added. When the solution was washed with chloroform and acidified with hydrochloric acid, the crystalline dimedone-formaldehyde complex was separated. It was extracted with chloroform and the chloroform solution was evaporated in vacuo to give a crystalline residue. Recrystallization from ethanol yielded 10 mg. of the dimedone-formaldehyde complex, which melted at 190°C and showed no depression of the melting point on admixture with an authentic specimen.

Ozonolysis of Lucidusculine Diacetate.—Lucidusculine diacetate (350 mg.) was ozonized and treated in the same way. Thus, 65 mg. of the dimedone-formaldehyde complex was obtained.

Kuhn-Roth Oxidation.—Mesoluciculine and dihydromesoluciculine were oxidized by L. G. Ginger's method[13]. The results were as follows:

Mesoluciculine: *Anal.* Found: (C)-CH_3, 1.84 (0.45 mol.). Calcd. for $C_{21}H_{31}O_3N\cdot H_2O$: 1 (C)-$CH_3$, 4.13%.

Dihydromesoluciculine: *Anal.* Found: (C)-CH_3, 3.71 (0.92 mol.). Calcd. for $C_{21}H_{33}O_3N\cdot 1.5H_2O$: 1 (C)-$CH_3$, 4.01%.

Model Experiment of Separation.—Lucidusculine, aconitine and jesaconitine (100 mg. each) were dissolved in 10 ml. of chloroform-ammonia water, the solution was passed through a column (1.4 cm. in diameter) of 90 g. of alumina, and the column was eluted with 280 ml. of chloroform-ammonia water, 100 ml. of acetone and 100 ml. of methanol in succession. The chloroform-ammonia water elute gave 200 mg. of a residue. The solution of the residue (0.661 mg.) in methanol (10 ml.) gave an ultraviolet absorption spectrum, λ 220 mμ (E 0.69)[14], λ_{max} 232 mμ (E 0.91), λ_{min} 245 mμ (E 0.78) and λ_{max} 259 mμ (E 1.10). The solution of 0.323 mg. of aconitine and 0.323 mg. of jesaconitine in 10 ml. of methanol showed an identical ultraviolet spectrum[15]. The acetone elute gave 100 mg. of lucidusculine melting at 170°C alone and on admixture with an authentic specimen.

Isolation of Alkaloids.—The dried roots were divided into mother-roots and daughter-roots.

Isolation of alkaloids from mother-roots.—The mother-roots (4.5 kg.) were ground and percolated with ethanol. The percolate was treated as in the case of other aconite roots[10]. The water-insoluble portion (4.4 g.) was dissolved in 10 ml. of chloroform-ammonia water and the solution was passed through a column (1.4 cm. in diameter) of 90 g. of alumina, and the column was

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[9] T. Amiya and I. Nagaoka, Read before the 5th Annual Meeting of the Chemical Society of Japan, held in Tokyo, April, 1952, and the 6th Annual Meeting of the Chemical Society of Japan, held in Kyoto, April, 1953. The plants were collected by I. Nagaoka and the late T. Ichihashi in Sepetember, 1944.

[10] H. Suginome, S. Furusawa, Y. Chiba and S. Kakimoto, *J. Fac. Sci., Hokkaido Univ., Ser. III. Chem.*, **4**, 1 (1950).

[11] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani and S. Hung, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **72**, 816 (1952).

[12] This solvent is designated as "chloroform-ammonia water".

[13] L. G. Ginger, *J. Biol. Chem.*, **156**, 453 (1944).

[14] $E=\log_{10} I_0/I$.

[15] A. E. Gillam, E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry", Edward Arnold Publishers, Ltd., London, (1954), p. 185; E. Ochiai, T. Okamoto and S. Sakai, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **75**, 545 (1955).

eluted with 280 ml. of chloroform-ammonia water, next with 100 ml. of acetone and then with 70ml. of methanol. The basic substance was obtained from the entire amount of the chloroform-ammonia water elute. It was purified as perchlorate by recrystallization from ethanol and 0.5 g. of pure perchlorate was obtained, m. p. 220~230°C (decomp.). The base (0.670 mg.) liberated from the perchlorate by means of ammonia water was dissolved in 10 ml. of methanol. The solution showed ultraviolet absorption, λ 220 mμ (E 0.55), $\lambda_{\min}$ 225 mμ (E 0.44) and $\lambda_{\max}$ 259 mμ (E 1.44). The solution of 0.130 mg. of aconitine and 0.540 mg. of jesaconitine in 10 ml. of methanol showed an identical ultraviolet spectrum. The spectral observations and the experiments mentioned below indicate that jesaconitine is contained in the material in an amount of about 80%15,16).

The remaining portion of the free base was extracted with ether in a Soxhlet extractor for 3 hr.; and the extracted base was transformed into the perchlorate. The salt yielded 0.1 g. of the salt of "jesaconitine-rich base" upon recrystallization from ethanol. The purified salt had m. p. 230°C (decomp.), $[\alpha]_D^{25}$ $-12.6°$ (methanol). The jesaconitine-rich base (0.673 mg.) prepared from the above salt was dissolved in 10 ml. of methanol. The solution showed ultraviolet absorption, λ 220 mμ (E 0.50), $\lambda_{\min}$ 225 mμ (E 0.32) and $\lambda_{\max}$ 259 mμ (E 1.79). The solution of 0.060 mg. of aconitine and 0.615 mg. of jesaconitine in 10 ml. of methanol showed an identical ultraviolet spectrum. The salt of the jesaconitine-rich base was analyzed.

Anal. Found: C, 53.72; H, 6.44; N, 2.06. Calcd. for $C_{35}H_{49}O_{12}N\cdot HClO_4$17): C, 54.15; H, 6.49; N, 1.80%.

After evaporation of the acetone elute in vacuo, the residue yielded 0.2 g. of lucidusculine by recrystallization from ethanol, m. p. 170°C with no depression on admixture with an authentic specimen.

Isolation of alkaloids from daughter-roots.— The water-insoluble portion (20.5 g.) from 4.5 kg. of the daughter-roots was treated in the same way as in the case of the mother-roots. The basic substance was obtained from the entire portion of the chloroform-ammonia water elute. The perchlorate of the base was recrystallized from ethanol. The free base liberated from the perchlorate was neutralized with 0.77 N hydrobromic acid. The solution of the resulting hydrobromide gave 0.08 g. of a crystalline material on standing18). The free base (0.665 mg.) prepared from the hydrobromide was dissolved in 10 ml. of methanol. The solution showed ultraviolet absorption, $\lambda_{\max}$ 232 mμ (E 0.90), $\lambda_{\min}$ 245 mμ (E 0.71) and $\lambda_{\max}$ 259 mμ (E 1.03). The solution of 0.356 mg. of aconitine and 0.309 mg. of jesaconitine in 10 ml. of methanol gave an identical ultraviolet spectrum.

The mother liquor from the hydrobromide was treated with ammonia water, yielding 1.7 g. of the free base. The solution of the free base (0.667 mg.) in 10 ml. of methanol showed ultraviolet absorption, λ 220 mμ (E 0.55), $\lambda_{\min}$ 225 mμ (E 0.44) and $\lambda_{\max}$ 259 mμ (E 1.53). The solution of 0.120 mg. of aconitine and 0.545 mg. of jesaconitine in 10 ml. of methanol showed an identical ultraviolet spectrum.

The spectral observations and the experiments described below indicate that jesaconitine was contained in an amount of about 80%.

The remaining portion of the above free base was extracted with ether in a Soxhlet extractor for 3 hr.; and the extracted base was transformed into the perchlorate. The crude perchlorate yielded 0.2 g. of the perchlorate of a jesaconitine-rich base upon recrystallization from ethanol. The purified perchlorate had m. p. 230°C (decomp.), $[\alpha]_D^{25}$ -14.8°C (methanol). The solution of jesaconitine-rich base (0.673 mg.), prepared from a part of the perchlorate, in 10 ml. of methanol showed ultraviolet absorption, λ 220 mμ (E 0.50), $\lambda_{\min}$ 225 mμ (E 0.32) and $\lambda_{\max}$ 259 mμ (E 1.79). The solution of 0.060 mg. of aconitine and 0.615 mg. of jesaconitine showed an identical ultaviolet spectrum. The purified perchlorate was analyzed.

Anal. Found: C, 53.92; H, 6.50; N, 1.91. Calcd. for $C_{35}H_{49}O_{12}N\cdot HClO_4$: C, 54.15; H, 6.49; N, 1.80%.

Hydrolysis of the ether-insoluble portion (1.1 g.) of the above base gave 50 mg. of anisic acid and 300 mg. of aconine hydrochloride, which melted at 176°C and was analyzed.

Anal. Found. C, 52.65; H, 8.16; N, 2.43. Calcd. for $C_{25}H_{41}O_9N\cdot HCl\cdot 2H_2O$: C, 52.48; H, 8.04; N, 2.45%.

The acetone elute gave 0.8 g. of lucidusculine as in the case of the mother-roots, m. p. 170°C with no depression on admixture with an authentic specimen.

Summary

1. In lucidusculine the presence of a double bond had previously been assumed. Further, on the basis of observations of the infrared spectra of luciculine, lucidusculine diacetate and dihydrolucidusculine diacetate, the presence of a terminal methylene group in lucidusculine was suggested.

Kuhn-Roth oxidation of mesoluciculine and of dihydromesoluciculine and ozonolysis of lucidusculine and of lucidusculine diacetate supported the suggested presence of a terminal methylene group. These results and the biogenesis of the aconite

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16) On account of the the existence of the benzoyl ester of an alkaloidal amino alcohol, aconitine was assumed to be present.

17) If the salt is composed of 1 mol. of jesaconitine and 1/10 mol. of aconitine, the calculated values are: C, 54.19; H, 6.44%.

18) The benzoyl ester of an alkaloidal amino alcohol may be aconitine; this seems to be supported by the fact that the crystalline hydrobromide of the ester alkaloid is slighthly soluble in water.

alkaloids show that the double bond in lucidusculine belongs to a terminal methylene group.

2. The roots of *Aconitum* species from Shoya, Hidaka in Hokkaido, were divided into mother-roots and daughter-roots; the water-insoluble basic portions were obtained from both; lucidusculine and jesaconitine were isolated by the chromatographic method.

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