The Aconite Alkaloids. XXVIII.[1] *The Isolation of a New Alkaloid, Sachaconitine, from Aconitum Miyabei, Nakai*

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In a previous paper of this series[2], it was reported that two alkaloids, miyaconitine, $C_{23}H_{29}O_6N$, and miyaconitinone, $C_{23}H_{27}O_6N$, had been isolated from the roots of Aconitum Miyabei, Nakai. The present paper describes the isolation and the characterization of a new alkaloid, sachaconitine, which was obtained, in addition to the above-mentioned alkaloids, from the same material.

In the isolation of miyaconitine and miyaconitinone[2], they were crystallized from fraction III[3] and their mother liquors still contained appreciable amounts of basic substances.

The amorphous base obtained from the mother liquors was dissolved in 1 N-acetic acid and 10 % aqueous sodium carbonate was added to the solution. The precipitate was filtered off, and the filtrate was extracted with ether. The extracted base was then converted into the perchlorate. The crystalline perchlorate is easily soluble in alcohol and in hot water. From alcohol it crystallized in needles, m. p. 188~189°C, $[\alpha]_D$ $-23.72°$ and from water its trihydrate crystallized in prisms, m. p. 180~185°C after softening at 100°C.

The composition, $C_{23}H_{37}O_4N \cdot HClO_4$, compares favorably with the analytical results; the formula was ascertained by analyses of acid oxalate, m. p. 182~183°C, aurichloride, m. p. 198~199°C, free base, m. p. 129~130°C, $[\alpha]_D$ $-13.08°$, and the diacetyl derivative, m. p. 114~116°C, $[\alpha]_D$ $-10.87°$.

It appears that this alkaloid has not yet been described, and the name "sachaconitine" was given to the new alkaloid. The analyses do not discriminate between H_{37} and H_{39} in the composition. Though the analytical result of diacetyl sachaconitine favors the latter, the formula with H_{37} seems more probable since it brings sachaconitine into line with other aconite alkaloids for reasons described below.

The base is stable against alkali and acid and thus contains no ester group. Acetylation of the base with acetyl chloride yielded a diacetyl compound which gave the original base on saponification. The presence of two methoxyl groups was confirmed by the Micro-Zeizel methoxyl determination. Hence the base contains two hydroxyl and two methoxyl groups.

The base gave ethyl iodide in the Herzig-Mayer *N*-alkyl determination and acetaldehyde on oxidation with permanganate, similarly to other aconite alkaloids containing an *N*-ethyl group, for example, lycoctonine[4-6], delpheline[7], and aconitine[8]. Coockson and Trevett[7] and Abubakirov and Yunusov[9] succeeded in confirming the presence of a simple *N*-alkyl group by converting de-ethyl derivatives (nor-componds) into the corresponding alkaloids. It appears, therefore, that the new alkaloid also contains a simple *N*-ethyl group.

On the other hand, it has been reported[10] that atisine with an oxazolidine ring[11] gave also ethyl iodide in the *N*-alkyl determination by the same method. But sachaconitine contains two methoxyl and two hydroxyl groups, and no more oxygen atoms to make such a ring.

The base was not hydrogenated with platinum oxide in acidic solution. The ultraviolet spectrum of the base showed only end absorption (Fig. 1) quite similarly

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1) Part XXVII, S. Furusawa, This Bulletin, **32**, 399 (1959).

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

3) Fraction I is the part readily precipitable with aqueous ammonia. The mother liquor from fraction I is shaken with chloroform and then the resulting chloroform extract is treated with 1N-hydrochloric acid. Then the material obtained from chloroform solution is called fraction II and the part precipitated with ammonia from the acidic solution is called fraction III.

4) H. Suginome and K. Ohno, *J. Fac. Sci., Hokkaido Univ., Ser. III. Chem.*, **4**, 36 (1950).

5) M. S. Rabinovich and R. A. Konovalova, *J. Gen. Chem.* (*U. S. S. R.*), **19**, 1387 (1949).

6) J. A. Goodson, *J. Chem. Soc.*, **1945**, 145.

7) R. C. Cookson and M. E. Trevett, ibid., **1956**, 2689.

8) R. Majima and K. Tamura, *Ann.*, **526**, 116 (1936).

9) N. K. Abubakirov and S. Yu. Yunusov, *J. Gen. Chem. U. S. S. R.* **27**, 733 (1954).

9) C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.*, **170**, 515 (1947); **174**, 1001 (1948).

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

to lycoctonine[12] possessing no unsaturation.

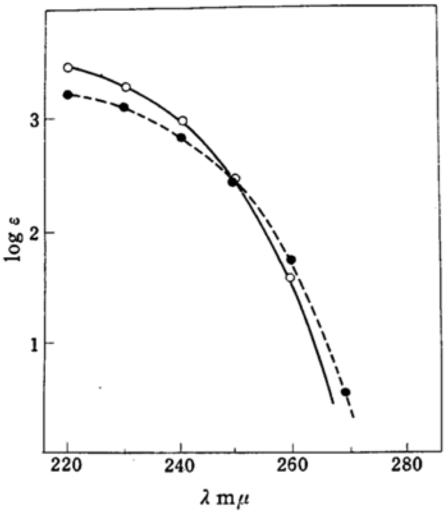

Fig. 1

Sachaconitine —○—○—
Lycoctonine ---●---●---

The above results relate the formula $C_{23}H_{37}O_4N$ of sachaconitine to other aconite alkaloids possessing the $C_{19}H_{29}N$ skeleton which is believed to be the fundamental base as pointed out by Suginome and Ohno[4], by Stern[13] and by Edwards and Marion[12]. Accordingly the formula can be extended as follows:

$$C_{19}H_{24}\left\{\begin{array}{l}(OCH_3)_2\\(OH)_2\\N{-}C_2H_5\end{array}\right.$$

The three alkaloids, miyaconitine, miyaconitinone and sachaconitine, were thus isolated from fraction III; they had no toxicity. In general, toxic bases containing an acyl and an aroyl group in aconite roots have been obtained from fraction I[3].

In attempts to isolate a crystalline substance from the amorphous base from the same roots, the fourth alkaloid, $C_{33}H_{45}O_9N$, m. p. 167~168°C, $[\alpha]_D$ +20.1° was isolated from fraction I. It agrees with delphinine in the composition but not in physical constants. Thus the name "base D" was assigned tentatively to this alkaloid. The investigation concerning the identification of "base D" with delphinine will be reported in a later paper.

Experimental

Isolation of Sachaconitine Perchlorate.—The residue of evaporation of the mother liquors from crystallization of miyaconitine and miyaconitinone perchlorate was converted into the free base by the usual method of treatment with chloroform and alkali. Amorphous basic material (14 g.) thus obtained was neutralized with 10% acetic acid and diluted with water. To the diluted solution 30% aqueous sodium carbonate was added until no more precipitate was produced. The precipitate was filtered off, but not examined.

The filtrate was subjected to continuous extraction with ether. Miyaconitinone remaining in the crude material separated out in prisms in 1 hr. Without removing it, extraction was continued further for 40 hr.

The extract, after being separated from miyaconitinone and dried over anhydrous sodium sulfate, was evaporated under reduced pressure to yield 7.5 g. of an amorphous material. This material was again neutralized with 0.1 N-hydrochloric acid and to the resulting solution 30% aqueous sodium perchlorate was added in small portions. On addition of the perchlorate the solution first became turbid but soon turned clear on stirring with further portions of the perchlorate solution. When turbidity was no longer noticed, the resulting solution was warmed on a steam bath until it became clear, treated with charcoal and filtered while hot. The perchlorate of the base separated as an oil on cooling the solution. The aqueous layer was decanted off and the oil was allowed to stand at room temperature overnight to give a gum containing some crystals which could not be separated. The gum was dissolved in a small amount of methanol and the solution was diluted with water until faint cloudiness remained. Concentration of the solution at room temperature gave 5 g. of crude sachaconitine perchlorate.

Sachaconitine perchlorate is easily soluble in alcohol and in hot water, and slightly soluble in cold water. From alcohol it crystallized in needles, m. p. 188~189°C, $[\alpha]_D^{20}$ −23.72° (C, 1.79 in alc.), and from water the trihydrate crystallized in plates, m. p. 188~189°C after softening at 100°C. The trihydrate gave the same m. p. and $[\alpha]_D$ after being dried over P_2O_5 under reduced pressure.

Anal. Found (anhydrous): C, 56.06; H, 7.70; N, 2.47; Cl, 7.34. Calcd. for $C_{23}H_{37}O_4N \cdot HClO_4$: C, 56.09; H, 7.72; N, 2.84; Cl, 7.21. Calcd. for $C_{23}H_{39}O_4N \cdot HClO_4$: C, 55.91; H, 8.16; N, 2.84; Cl, 7.18. Found (trihydrate): H_2O, 9.88. Calcd. for $C_{23}H_{37}O_4N \cdot HClO_4 \cdot 3H_2O$: H_2O, 9.89%.

Sachatonitine.—The solution of the perchlorate in water was warmed to 50~60°C, and basified with aqueous sodium carbonate. The free base separated out as a resin, which soon solidified on cooling. Colorless plates from alcohol, m. p. 129~130°C, $[\alpha]_D^{20}$ −13.08° (C, 2.35 in 95% alc.).

Anal. Found: C, 70.35; H, 9.39; N, 3.59%. Calcd. for $C_{23}H_{37}O_4N$: C, 70.58; H, 9.46; N, 3.55%. Calcd. for $C_{23}H_{39}O_4N$: C, 70.19; H, 9.99; N, 3.56%.

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[12] O. E. Edwards and Leo Marion, *Can. J. Chem.*, **30**, 627 (1952).

[13] E. S. Stern, "The Aconitum and Delphinium Alkaloids" in "The Alkaloids", Vol. IV, edited by R. H. F. Manske and H. L. Holmes, Academic Press Inc., New York (1954), p. 275.

The ultraviolet spectrum of the base showed only end absorption (Fig. 1).

The base was subjected to the Micro-Zeizel methoxyl, and the Herzig-Meyer *N*-alkyl determinations.

Anal. Found: CH_3O-, 15.91; C_2H_5-, 7.02. Calcd. for $C_{19}H_{26}O_2(OCH_3)_2 \cdot N \cdot C_2H_5$: CH_3O-, 15.85; C_2H_5-, 7.42%. Calcd. for $C_{19}H_{23}O_2(OCH_3)_2 \cdot N \cdot C_2H_5$: CH_3O-, 15.77; C_2H_5-, 7.38%.

The base (100 mg.) was submitted to the conventional Herzig-Meyer *N*-alkyl determination; the gases which evolved during pyrolysis of the hydroiodide were passed into a cold solution of trimethylamine in alcohol. The ethanol-soluble salt, ethyltrimethyl-ammonium iodide, was obtained from the trimethylamine solution.

Anal. Found: I, 59.27. Calcd. for $C_5H_{14}NI$: I, 59.04%.

The base absorbed no hydrogen in the presence of PtO_2 in acetic acid solution.

A solution of sachaconitine in 1N-potassium hydroxide in 50% aqueous methanol was refluxed on a steam bath for 30 min. From the resulting reaction mixture no acidic substance was detected, but unchanged sachaconitine was recovered.

Estimation of Acetaldehyde.—To a cold solution of 400 mg. of sachaconitine in 3 cc. of 1N-sulfuric acid, 15 cc. of 2% aqueous potassium permanganate was added dropwise in the course of 3 hr. After standing overnight, the manganese dioxide was filtered off and washed twice with water. The combined filterate and washings were distilled into a receiver containing 50 cc. of a slightly alkaline solution of 280 mg. of dimedone. Acidification with hydrochloric acid gave 73 mg. of acetaldehyde-dimedone, m. p. 139~140°C. It showed no depression of the melting point on admixture with an authentic specimen.

Sachaconitine Aurichloride. — The compound, prepared from the base and auric chloride, crystallized from a mixture of acetone and ether in prisms, m. p. 197~198°C (decomp.).

Anal. Found: Au, 26.88. Calcd. for $C_{23}H_{37}O_4N \cdot AuCl_3 \cdot HCl$: Au, 26.96%. Calcd. for $C_{23}H_{39}O_4N \cdot AuCl_3 \cdot HCl$: Au, 26.88%.

Sachaconitine Acid Oxalate.—The compound, prepared from the base and oxalic acid, crystallized from absolute alcohol in needles, m. p. 182~183°C, $[\alpha]_D^{20}$ −29.71° (C, 0.69 in 70% alc.)

Anal. Found: C, 61.70; H, 8.16. Calcd. for $C_{23}H_{37}O_4N \cdot C_2H_2O_4$: C, 62.35; H, 8.16. Calcd. for $C_{23}H_{39}O_4N \cdot C_2H_2O_4$: C, 62.09; H, 8.55%.

Sachaconitine Hydrochloride.—Dried hydrogen chloride was passed into a solution of the base in anhydrous acetone to produce a white precipitate. Reprecipitation by adding acetone to a very concentrated alcoholic solution of the precipitate gave sachaconitine hydrochloride in colorless needles, m. p. 203~204°C, $[\alpha]_D^{20}$ −30.43° (C, 0.78 in 95% alc.). No satisfactory analytical data have been found because of the extremely hygroscopic property of this compound.

Diacetylsachaconitine.—The base (1 g.) was treated with 4 g. of acetyl chloride in a sealed tube at room temperature for 5 days. The excess of the reagent was distilled off under reduced pressure and water was added. The aqueous solution was basified and extracted with chloroform. The residual product, obtained by evaporation of the chloroform, was crystallized from aqueous alcohol to give 400 mg. of plates, m. p. 114~116°C, $[\alpha]_D^{20}$ −10.87° (C, 1.70 in 95% alc.).

Anal. Found: C, 68.03, H, 8.92, N, 3.12. Calcd. for $C_{22}H_{35}O_2N \cdot (OCOCH_3)_2$: C, 68.18; H, 8.69; N, 2.95%. Calcd. for $C_{23}H_{37}O_2N \cdot (OCOCH_3)_2$: C, 67.89; H, 9.07; N, 2.93%.

On saponifying diacetylsachaconitine with alkali sachaconitine was regenerated.

Isolation of "Base D". — Fraction 1[3] (10 g.) was refluxed with 100 cc. of ether for 30 min. on a steam bath and the ether insoluble residue was again refluxed with 50 cc. of fresh ether. Complete removal of the solvent from the combined extracts gave 8 g. of amorphous yellow powder, which was neutralized with 1N-acetic acid and diluted to 100 cc. with water. To the resulting solution powdered sodium bicarbonate was added in small portions until no further precipitation was noticed. After being left to stand for 30 min., the resinous precipitate (Ia) was filtered off. From the filtrate a precipitate (Ib) was obtained on adding 50 cc. of 20% aqueous sodium carbonate, and another (Ic) on adding ammonia. No crystallizable alkaloids were obtaind from Ia and Ic. The fractional precipitation of Ib with sodium bicarbonate and carbonate was repeated twice; then 5 g. of powder precipitating with sodium carbonate was obtained. This material was dissolved in alcohol and the solvent was allowed to evaporate at room temperature, because heating of the solution caused crystallization with difficulty. Thus 2.5 g. of the crystalline "base D" was deposited from the alcoholic solution.

"Base D" is readily soluble in alcohol, chloroform and ether and insoluble in petroleum ether. It was recrystallized from a mixture of ether and petroleum ether in needles, m. p. 167~168°C, $[\alpha]_D^{20}$ +20.10° (C, 2.05 in 95% alc.).

Anal. Found: C, 66.13; H, 7.54; N, 2.23. Calcd. for $C_{33}H_{45}O_9N$: C, 66.09; H, 7.56; N, 2.34%.

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