The Aconite Alkaloids. XXIV. Oxidation of Miyaconitine and Miyaconitinone*

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Miyaconitine (I) $C_{23}H_{29}O_6N$ and miyaconitinone (II) $C_{23}H_{27}O_6N$ were isolated from *Aconitum miyabei*, Nakai, and the following extended formulae were given to them, respectively, in Part XVI[1].

$$C_{16}H_{20}\begin{cases}OCOCH_3\\OH\\(CO)_3\\N\text{-}C_2H_5\end{cases} \qquad C_{15}H_{19}\begin{cases}OCOCH_3\\(CO)_4\\N\text{-}C_2H_5\end{cases}$$

I II

Since these alkaloids were relatively unstable to oxidation with either potassium permanganate or nitric acid, no crystalline oxidation product could be isolated even by the best method[2] found for the aconite alkaloids by H. Suginome. But, when miyaconitinone was oxidized with potassium permanganate under milder conditions, oxomiyaconitinone (III) $C_{20}H_{20}O_6$ ($-CO-N-C_2H_5$) was obtained only in a small yield.

In Part XVI[1] it was shown that an α-diketone group exists in these two alkaloids, and it seemed that oxidation with hydrogen peroxide would be successful. But all attemps of oxidative ring opening under the vigorous conditions described, for instance, by Holleman[3] and by Boeseken[4], to open the ring of *o*-camphorquinone, were unsuccessful. The present author has established a milder method to oxidize *o*-camphorquinone almost quantitatively to camphoric acid and these alkaloids have been oxidized successfully to dibasic acids by this method.

Namely, oxidation of miyaconitine with dilute alkaline hydrogen peroxide gave a basic substance, oxymiyaconitine (IV) $C_{23}H_{29}O_7N$, and an acid, miyaconinic acid (V) $C_{21}H_{29}O_7N$. It was determined that miyaconinic acid retains the original ethylimino group but not the acetyl group. It was titrated as a monobasic acid and gave a monomethyl ester (VI) $C_{22}H_{31}O_7N$ by esterification with diazomethane, while the dimethyl ester (VII) $C_{23}H_{33}O_7N$ could be derived with dimethyl sulfate in a concentrated potassium hydroxide solution. Acetylation of the dimethyl ester afforded a diacetyl compound (VIII) $C_{27}H_{37}O_9N$. Miyaconinic acid as well as these derivatives could not be hydrogenated by the method[1] described as a method for comparison of miyaconitine with miyaconitinone. These experiments showed that miyaconitine was hydrolyzed and then oxidized at the α-diketone group to give a dibasic acid V and its transformations into the above-mentioned derivatives are represented by the following schema:

$$\text{I} \rightarrow C_{16}H_{20}\begin{cases}(OH)_2\\CO\\(COOH)_2\\N\text{-}C_2H_5\end{cases} \rightarrow C_{16}H_{20}\begin{cases}(OH)_2\\CO\\COOH\\COOCH_3\\N\text{-}C_2H_5\end{cases} \rightarrow$$

V VI

$$C_{16}H_{20}\begin{cases}(OH)_2\\CO\\(COOCH_3)_2\\N\text{-}C_2H_5\end{cases} \rightarrow C_{16}H_{20}\begin{cases}(OCOCH_3)_2\\CO\\(COOCH_3)_2\\N\text{-}C_2H_5\end{cases}$$

VII VIII

Oxidation of miyaconitinone by the same method gave miyaconinic acid and miyaconitinonic acid (IX) $C_{23}H_{29}O_8N$. The formation of miyaconinic acid from miyaconitinone is analogous to the alkaline hydrolysis of miyaconitine and miyaconitinone to miyaconine. Miyaconitinonic acid had an acetyl group and absorbed 1 mole of hydrogen, so that its relation to miyaconinic acid may be similar to the relation of miyaconitinone to miyaconine. Accordingly, formula IX is given to miyaconitinonic acid.

$$C_{15}H_{19}\begin{cases}OCOCH_3\\(CO)_2\\(COOH)_2\\N\text{-}C_2H_5\end{cases}$$

IX

* This constitutes a part of a series entitled "The Aconite Alkaloids" by H. Suginome. The report, "On Lucaconine" presented in *Proc. Japan Acad.*, **22**, 122(1946) will be called Part XXIII. Part XXII is H. Suginome and S. Umezawa, *J. Fac. Sci. Hokkaido Univ., Ser. III Chem.*, **4**, 44 (1950).

1) H. Suginome, S. Furusawa, Y. Chiba and S. Kakimoto, ibid., **4**, 1 (1950).

2) H. Suginome, ibid., **2**, 95 (1937): *Ann.*, **533**, 172 (1931).

3) M. A. F. Holleman, *Rec. trav. chim.*, **23**, 169 (1904).

4) M. J. Boeseken, ibid., **30**, 142 (1911).

Miyaconinone that had been obtained by acid hydrolysis of miyaconitinone was oxidized to miyaconinic acid. This relation also had the same resemblance as observed previously. Miyaconine was oxidized to isomiyaconinic acid (X) differing from miyaconinic acid in melting point, optical rotation and crystalline form, but possessing the same formula $C_{21}H_{29}O_7N$ and the same chemical properties.

When miyaconitinonic acid was treated with acetic anhydride or heated under a reduced pressure, carbon dioxide and water were split off, producing a weak base, anhydrodecarboxymiyaconitinonic acid (XI) $C_{22}H_{27}O_5N$. It absorbed 1 mole of hydrogen, and had still an acetyl group. It could be distilled in high vacuum and it corresponded to a base resulting from original miyaconitinone by loss of one carbonyl group. It would be the most useful substance for succeeding degradation to clarify the constitution of the original alkaloid. The same treatment of miyaconinic acid with acetic anhydride afforded a weak base, diacetyldecarboxymiyaconinic acid (XII) $C_{24}H_{33}O_7N$. From isomiyaconinic acid, diacetyldecarboxyisomiyaconinic acid (XIII) $C_{24}H_{33}O_7N$ was obtained.

These acids and derivatives were produced by opening of one ring containing the α-diketone group just as expected. Further, anhydrodecarboxy compound XI was derived by closing the ring and splitting off carbon dioxide and water.

As the acids were titrated as monobasic, the ring opening might have occurred in the neighborhood of the ethylimino group. Accordingly, it was expected that the ethylimino group would be changed in its chemical properties and attacked in the ordinary degradation process. But, methiodides of their esters returned readily with alkali to the original substances such as miyaconitine and miyaconitinone.

Experimental

Oxomiyaconitinone (III).—Two g. of miyaconitinone was added to a solution of 0.15 g. of potassium permanganate and 5 cc. of glacial acetic acid in 30 cc. of acetone and the solution was allowed to stand for 24 hr. After filtration to remove manganese dioxide, the solution was evaporated to dryness and the residue was dissolved in water. The crude oxomiyaconitinone was extracted from the aqueous solution with chloroform and recrystallized from ethanol. Yield, 0.2 g. White needles, m. p. 210°.

Anal. Found: C, 64.86; H, 6.10; (N)-C_2H_5, 7.49. Calcd. for $C_{21}H_{29}O_7N$-C_2H_5: C, 64.62; H, 5.90; (N)-C_2H_5, 6.80%.

A Modified Method for Preparation of Camphoric Acid.—To a mixture of 2.5 cc. of 3 percent hydrogen peroxide, 2.5 cc. of N potassium hydroxide solution and 5 cc. of water, 0.2 g. of *o*-camphorquinone was added and the mixture was shaken for 24 hr. The reaction mixture was acidified and concentrated to give 0.2 g. of camphoric acid. m. p. 186~187°. $[\alpha]_D^{10}$ +57.3° (acetone).

Anal. Found: C, 59.90; H, 7.99. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06%.

Oxidation of Miyaconitine with Hydrogen Peroxide.—*a*) *Oxymiyaconitine (IV).*—A suspension of 1.7 g. of powdered miyaconitine in a mixture of 8 cc. of 3 percent hydrogen peroxide, 10 cc. of N potassium hydroxide solution and 20 cc. of water, was shaken for 24 hr. The mixture of unchanged miyaconitine and oxymiyaconitine was collected and fractionally recrystallized from ethanol; 0.25 g. of oxymiyaconitine was obtained. m. p. 244~245° (decomp.). $[\alpha]_D^{9.5}$ +44.6° (N acetic acid).

Anal. Found: C, 64.33; H, 6.69. Calcd. for $C_{23}H_{29}O_7N$: C, 64.02; H, 6.78%.

b) *Miyaconinic acid (V).*—The basic filtrate from miyaconitine and oxymiyaconitine, was acidified with dilute hydrochloric acid and dried up under a reduced pressure. The residue was extracted with ethanol, the extract was evaporated to dryness and the residue was treated with dilute acetic acid. The crude acid thus obtained was dissolved in dilute ammonia water and reprecipitated with dilute acetic acid. Yield, 0.17 g. Needles, m. p. 295° (decomp.). $[\alpha]_D^{18}$ +17.7° (N ammonia). It contained 1 mole of water of crystallization.

Anal. Found: H_2O, 4.18. Calcd. for $C_{21}H_{29}O_7N$-H_2O: H_2O, 4.25. Found: C, 61.79; H, 6.96; N, 3.65; COOH*, 12.41. Calcd. for $C_{21}H_{29}O_7N$: C, 61.90; H, 7.18; H, 3.44; COOH, 11.08%.

c) *Monomethyl ester of miyaconinic acid (VI).*—To a suspension of 0.1 g. of miyaconinic acid in 25 cc. of ether, 0.1 g. of diazomethane was added and the mixture was allowed to stand for 24 hr. The precipitate was dissolved in dilute acetic acid and reprecipitated with dilute ammonia water. The precipitate was recrystallized from methanol. Yield, 0.1 g., m. p. 285° (decomp.). It contained 2 moles of water of crystallization.

Anal. Found: H_2O, 7.52. Calcd. for $C_{22}H_{31}O_7N \cdot 2H_2O$: H_2O, 7.88. Found: C, 62.73; H, 7.41; OCH_3, 7.76. Calcd. for $C_{22}H_{31}O_7N$: C, 62.69; H, 7.41; OCH_3 7.36%.

Its perchlorate melted at 210° with decomposition.

Anal. Found: Cl, 6.49. Calcd. for $C_{22}H_{31}O_7N \cdot HClO_4$: Cl, 6.80%.

Its methiodide melted at 271~272° with decomposition.

Anal. Found: C, 48.50; H, 5.51; I, 23.87. Calcd. for $C_{22}H_{31}O_7N \cdot CH_3I$: C, 48.90; H, 6.03; I, 23.53%.

d) *Dimethyl ester (VII).*—To a solution of 0.2 g. of miyaconinic acid in 1.3 cc. of 15 percent

* Titrated with 0.01 N potassium hydroxide (Indicator: Phenolphthalein).

potassium hydroxide solution, 1 cc. of dimethyl sulfate was added and the mixture was warmed at 60°. The reaction mixture was acidified with dilute sulfuric acid and filtered. The solution was alkalized with dilute ammonia water, producing 0.19 g. of the dimethyl ester. It melted at 296~297° with decomposition and formed a perchlorate and a methiodide.

Anal. Found: C, 63.58; H, 7.10; OCH_3, 14.08; (N)-C_2H_5, 7.18. Calcd. for $C_{23}H_{33}O_7N$: C, 63.41; H, 7.41; OCH_3, 14.24; (N)-C_2H_5, 6.67%. Found: Cl, 6.47. Calcd. for $C_{23}H_{33}O_7N\ HClO_4$; Cl, 6.62%.

e) Diacetyl dimethyl ester (VIII).—To a solution of 0.2 g. of dimethyl ester in 2 cc. of glacial acetic acid, 2 cc. of acetic anhydride and 2 cc. of pyridine were added. After 24 hr., the solvent was distilled off under a reduced pressure. The residue was dissolved in water, and dilute ammonia water was added to give 0.2 g. of diacetyl dimethyl ester. It was recrystallized from methanol. m. p. 167~168°.

Anal. Found: C, 62.65; H, 7.34; OCH_3, 11.12; (N)-C_2H_5, 5.43; $COCH_3$, 16.39. Calcd. for $C_{27}H_{37}O_9N$: C, 62.41; H, 7.18; OCH_3, 11.94; (N)-C_2H_5, 5.59; $COCH_3$, 16.57%.

Oxidation of Miyaconitinone. — Three g. of miyaconitinone was oxidized by the above-described method. After the separation of 0.32 g. of crude miyaconinic acid from the reaction mixture, chloroform was added to the filtrate and the mixture was stirred for several minutes. The semicrystalline product, presumably containing chloroform, was separated and warmed in water to remove the contained chloroform. From the concentrated solution, 0.17 g. of crude miyaconitinonic acid crystallized out in white needles. It was recrystallized from ethanol, m. p. 259° (decomp.). $[\alpha]_D^{10}$ −84.7° (N ammonia water).

Aanl. Found: C, 61.28; H, 6.57; COOH, 10.16; $COCH_3$, 9.83. Calcd. for $C_{23}H_{29}O_8N$: C, 61.73; H, 6.54; COOH, 10.05; $COCH_3$, 9.62%. 8.120 Mg. of sample absorbed 0.442 cc. of hydrogen (1.04 mol.).

Oxidation of Miyaconine. — Oxidation of 0.7 g. of miyaconine afforded 0.2 g. of isomiyaconinic acid. It melted at 268° with decomposition. White plates, $[\alpha]_D^{9.3}$ +27.3° (N ammonia water).

Anal. Found: H_2O, 4.55; C, 59.53; H, 7.06; COOH, 10.53. Calcd. for $C_{21}H_{29}O_7N \cdot H_2O$: H_2O, 4.25; C, 59.28; H, 7.35; COOH, 10.53%.

Oxidation of Miyaconinone. — From 0.45 g. of miyaconinone, 0.05 g. of miyaconinic acid was obtained, m. p. 295°.

Anal. Found: C, 62.69; H, 6.88. Calcd. for $C_{21}H_{29}O_7N$: C, 61.90; H, 7.18%.

Anhydrodecarboxymiyaconitinonic Acid (XI).—Miyaconitinonic acid (0.2 g.) was heated at 259° in a high vacuum for a few minutes. After cooling, the residue was recrystallized from ethanol to give anhydrodecarboxymiyaconitinonic acid. Yield, 0.13 g., m. p. 164~165°, $[\alpha]_D^{10}$ −117.0° (chloroform). XI was soluble in dilute hydrochloric acid, but almost insoluble in dilute acetic acid, and it was precipitated with ammonia water from the acidic solution. XI was also obtained from 0.1 g. of the original acid by heating with a mixture of 0.5 cc. of glacial acetic acid and 3 cc. of acetic anhydride for 1 hr., evaporating the solvent and adding water. XI was recrystallized from ethanol. Yield, 0.04 g.

Anal. Found: C, 67.43; H, 6.77; N, 3.74; $COCH_3$, 11.54. Calcd. for $C_{22}H_{27}O_6N$: C, 68.55; H, 7.06; N, 3.63; $COCH_3$, 11.09%. 8.533 Mg. of sample absorbed 0.442 cc. of hydrogen (1.15 mol.).

When this base was heated with 45 per cent ethanol for 2 hr., it was converted into a weak base, m. p. 194~195°, $[\alpha]_D^{10}$ −142.4° (chloroform). The latter base corresponded to decarboxymiyaconitinonic acid.

Anal. Found: C, 65.63; H, 6.94; $COCH_3$; 10.63. Calcd. for $C_{22}H_{29}O_6N$: C, 65.50; H, 7.25; $COCH_3$, 10.67%. 8.637 Mg. of sample absorbed 0.446 cc. of hydrogen (0.93 mol.).

Diacetyldecarboxymiyaconinic Acid (XII). —When 0.22 g. of miyaconinic acid was treated with acetic anhydride as mentioned above, 0.11 g. of diacetyldecarboxymiyaconinic acid was obtained in white prisms, m. p. 215~216°.

Anal. Found: C. 63.57; H, 6.39; $COCH_3$, 18.98. Calcd. for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.43; $COCH_3$, 19.68%.

Diacetyldecarboxyisomiyaconinic Acid (XIII).—From 0.1 g. of isomiyaconinic acid, 0.01 g. of diacetyldecarboxyisomiyaconinic acid was obtained in white needles, m. p. 200~202°.

Anal. Found: C, 63.73; H, 6.50; $COCH_3$, 19.80. Calcd. for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.43; $COCH_3$, 19.68%.

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