STUDIES ON BIMOLECULAR ALKALOIDS. PART II.
REDUCTION OF DISINOMENINE AND Ψ-DISINOMENINE.

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In the preceding article,(1) the author, in cooperation with H. Sudzuki, reported the formation of disinomenine and ψ-disinomenine by the mild oxidation of sinomenine, and put forward the view that the isomerism of these two alkaloids might be due to the difference of the constitution of the third nucleus of phenanthrene, namely, to the difference of the linking position of the ethanamine group. It is of some interest, therefore, to see whether these two bimolecular alkaloids would give, on reduction, the same hydrogenated substance or not. The results of hydrogenation were the production of two different bimolecular substances, tetrahydro-disinomenine and tetrahydro-ψ-disinomenine, which are characterised by the following properties.

	Tetrahydro-disinomenine	Tetrahydro-ψ-disinomenine(2)
M. p. of free base	247°–252° (dec.)	271° (dec.)
M. p. of hydrochloride	>295°	not crystalline
Solubility of ,, ...	ca. 10%	∞
Form of ,, ...	hexagonal plates	——
M. p. of methiodide	275° (dec.)	285° (dec.)
M. p. of oxim	227°	242° (dec.)
M. p. of semicarbazone . . .	>290°	>290°
$[\alpha]_D$	+264°.41	+167°
Diazo reaction	50,000	25,000
$K_3Fe(CN)_6$ reaction	500,000	500,000
Formalin-sulphuric Acid . . .	weakly pink	faintly yellow

Tetrahydro-disinomenine and tetrahydro-ψ-disinomenine can also be obtained from dihydrosinomenine by mild oxidation with silver nitrate or potassium ferricyanide. And these two bases can easily be separated by alcohol, for tetrahydro-ψ-disinomenine is very difficultly soluble even in boiling alcohol. The tetrahydro-disinomenine can be purified through its hydrochloride, which crystallises well in hexagonal plates.

It is interesting to note that the colour reaction of disinomenine (pink) and ψ-disinomenine (brownish yellow) when dissolved in formaldehyde sulphuric acid is retained in the tetrahydro-derivatives in a diminished degree,

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(1) This Bulletin, **4** (1929), 107.

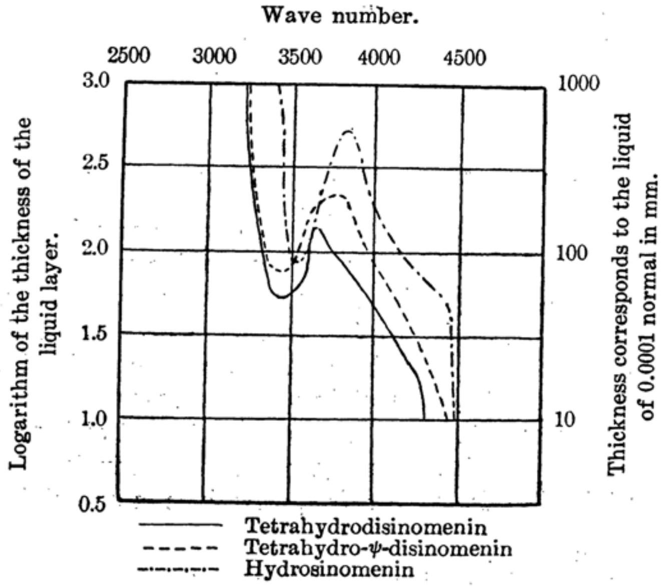
(2) Compare Kondo and Ochiai, *J. pharm. Soc. Japan*, **549** (1927), 124 (in German).

whilst that of hydrosinomenine (yellow, green, then blue with red fluorescence) is quite lost.

That in these two tetrahydro-derivatives, the original linking of two sinomenine molecules found in disinomenine and ψ-disinomenine, as was proved in Part I, must be remained untouched, is shown quite clearly from the decrease of the diazoreaction in these two alkaloids compared with sinomenine and hydrosinomenine. The fact that disinomenine and ψ-disinomenine give rise to two different tetrahydro-derivatives, seems to enforce the author's view regarding to the isomerism of the two alkaloids, given at the beginning of this article, since otherwise they might have given in all probability the identical tetrahydro-derivative in the same method of reduction. But, the final elucidation would be given only when these two alkaloid were decomposed into phenanthrene derivatives with side chain attaching to different position.

The mild oxidation and reduction of sinomenine are thus summarised in the following.

$$\begin{tikzcd}
\begin{array}{c}\text{Sinomenine}\\ C_{19}H_{23}NO_4\\ \text{m. p. } 159^\circ\ (-)\end{array} \arrow[r, "AgNO_3 \text{ or } K_3Fe(CN)_6"] \arrow[d, "PdCl_2+H_2"] & \begin{array}{ccc}\text{Disinomenine} & + & \psi\text{-disinomenine}\\ (C_{19}H_{22}NO_4)_2 & & (C_{19}H_{22}NO_4)_2\\ \text{m. p. } 222^\circ\ (+) & & \text{m. p. } 229^\circ\ (-)\end{array} \arrow[d, "PdCl_2+H_2"] \\
\begin{array}{c}\text{Hydro-}\\ \text{sinomenine}\\ C_{19}H_{25}NO_4\\ \text{m. p. } 202^\circ\ (+)\end{array} \arrow[r, "AgNO_3 \text{ or } K_3Fe(CN)_6"] & \begin{array}{ccc}\text{Tetrahydro-} & + & \text{Tetrahydro-}\\ \text{disinomenine} & & \psi\text{-disinomenine}\\ (C_{19}H_{24}NO_4)_2 & & (C_{19}H_{24}NO_4)_2\\ \text{dec. p. } 252^\circ\ (+) & & \text{dec. p. } 271^\circ\ (+)\end{array}
\end{tikzcd}$$



Absorption curves show very little difference in these two alkaloid, as seen from the annexed diagram.

The author expects to decompose these two alkaloids for the purpose of deciding the constitution.

Experimental.

Tetrahydro-disinomenine. Disinomenine hydrochloride (1.7 gr.) was shaken in an aqueous solution (100 c.c.) with 100 c.c. colloidal palladium (0.1 gr. + 0.1 gr. gummi arabic) in hydrogen atmosphere (absorbed, 125 c.c. in one hour.) Tetrahydro-derivative was isolated in a usual way and recrystallised from alcohol. Prisms of m. p. 252°; yield 1.1 gr. With naturally occurring disinomenine, the same result was obtained.

Anal. Found: C=68.75; H=7.69; N=4.68%. Calc. for $(C_{19}H_{24}NO_4)_2$: C=69.09; H=7.27; N=4.24%.

Mol. wt. Found (in glacial acetic acid): 714 (suspected to be associated slightly). Calc.: 660.

Methiodide: m. p. >275°. (Found: I=27.63%. Calc.: I=26.91%).

Oxim: m. p. 227°, dec. p. 245°. (Found: N=8.06%. Calc. for dioxim: N=8.11%).

Tetrahydro-ψ-disinomenine. ψ-Disinomenine (1.6 gr.) was reduced in the same way as above and 0.9 gr. tetrahydro-ψ-disinomenine was isolated. Long needles of dec. p. 271°. $[\alpha]_D^7 = +167°$. Difficultly soluble in ordinary organic solvents (0.13% in cold acetone; 1% in hot chloroform). The hydrochloride is not obtained in crystalline form.

Anal. Found: C=68.16; H=7.45; N=4.25%. Calc. for $(C_{19}H_{24}NO_4)_2$: C=69.09; H=7.27; N=4.24%.

Mol. wt. Found (in glacial acetic acid): 753 (a slight association is suspected). Calc.: 660.

Methiodide: m. p. 285° (dec.). (Found: I=28.23%. Calc.: I=26.90%).

Oxim: m. p. 242° (dec.). (Found: N=6.53%. Calc.: N=8.11%).

Linking of Dihydrosinomenine by Mild Oxidation.

With alkaline ferri-cyanide solution. To the solution of hydrosinomenine (9.5 gr. in 450 c.c. of 0.33% hydrochloric acid) potassium ferri-cyanide solution (9.5 gr. in 300 c.c. water) was added, followed by 150 c.c. of saturated soda solution. The bases were extracted with a large amount of chloroform and the residue of chloroform was boiled out with alcohol (60 c.c.). The insoluble part is tetrahydro-ψ-disinomenine (yield, 4.2 gr.; ca 45%). The soluble part was purified through its hydrochloride (yield, 1.2 gr.; ca 15%). The remainder was not crystallisable.

With silver nitrate. Hydrosinomenin (3 gr.) was dissolved in alcohol (50 c.c.) and water (200 c.c.) and was added with silver nitrate (1.5 gr.) in an aqueous solution (200 c.c.). After several minutes, the brine was added to the mixture (almost no precipitation) and then made alkaline with sodium carbonate solution. The treatment hereafter was carried out as in the preceding experiment. Yield: Tetrahydro-ψ-disinomenine (1.4 gr.; ca. 48%) and tetrahydro-disinomenine hydrochloride (1.0 gr.; ca. 30%).

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