SINOMENINE AND DISINOMENINE. PART XII.
ON SINOMENINE HYDRATE.

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In the last report, the formation of the bis-(demethyl)-sinomenyliden from sinomenine by the agency of a hot dilute hydrochloric acid and the treatment of ammonia was reported. In this paper, the mechanism of this transformation will be dealt with in a more detailed way.

When sinomenine was heated on a steam bath with dilute hydrochloric acid and the base was set free with sodium carbonate, no formation of the bis-(demethyl)-sinomenyliden was noticed, but a new substance of m.p. 139° was obtained in a yield more than 80%. If this new substance was dissolved in 1% hydrochloric acid, and was added with an equal quantity of ammonia (d=0.9), and left standing overnight, then bis-(demethyl)-sinomenyliden was obtained in a yield about 40%. This showed clearly that the hot dilute hydrochloric acid could only effect the transformation of sinomenine into the substance of m.p. 139° and that the concentrated ammonia could then convert the latter into bis-(demethyl)-sinomenyliden.

The elemental analysis proved that the substance of m.p. 139° was nothing but the sinomenine added with one molecule of water, which could not be removed by drying at 100° over P_2O_5 in vacuum. The water forms, thus, an integral part of the molecule. And the new substance is, therefore, called sinomenine hydrate. The properties of this new substance are compared with those of sinomenine in the following table.

Table 1.

	Sinomenine	Sinomenine hydrate
Yield	—	80%
Crystal form	prisms or hairy needles	prisms
Mol. formula	$C_{19}H_{23}NO_4$	$C_{19}H_{25}NO$
M.p.	159° (or 182°)	139° (or 160°)
Solubility in methyl alc.	33% (hot)	3.3% (hot)
$[\alpha]_D$	−73.9°	+40.8°

Table 1. (*Continued.*)

	Sinomenine	Sinomenine hydrate
Methoxyls	two	two
M.p. of oxim	264° (monoxim)	231° (dioxim)
D.p. of ICH_3	255°	264°
$FeCl_3$ reaction	very strong	strong in alc.
Diazo-reaction	+ in 2,000,000th dilution	+ in 2,000,000th dilution
$K_3Fe(CN)_6$-reaction	+ in 500,000th dilution	+ in 500,000th dilution
Formaline-H_2SO_4	yellow, green, blue	yellow, bordeau-red

As regards the position taken by the added water, C_7 is selected for OH and C_8 for H, from the following four reasons.

(1) Sinomenine hydrate dissolves in caustic alkali almost colourless. This shows the original double linking of sinomenine, which was conjugated to the ketone group, is quite saturated.

(2) In contrary to sinomenine, sinomenine hydrate does not give a bimolecular substance, when reduced with Na-amalgam, but gives the monomolecular substance given in (3). This shows also that the original double linking was quite lost.

(3) By reduction with $Pd+H_2$, sinomenine hydrate loses one methoxyl group, and gives two isomeric substances of the molecular formula $C_{18}H_{23}NO_3$.

(4) By the action of semicarbazide or hydroxylamine, sinomenine hydrate loses one methyl group and gives a disemicarbazone or a dioxime.

These behaviours of sinomenine hydrate are best explained by the constitutional formula (II), although it involves some remarkable features, which are not usual in the hitherto well-known facts, viz. the astonishing stability of this semi-acetal against acidic agents, and the easy hydrolysableness by the amino-radical of ammonia, semicarbazide and hydroxylamine, which remain to be explained by the future study.

When sinomenine hydrate was reduced with $Pd+H_2$, it gives two isomeric demethoxysinomenine hydrates, which are characterised by the properties given in the Table 2.

Table 2.

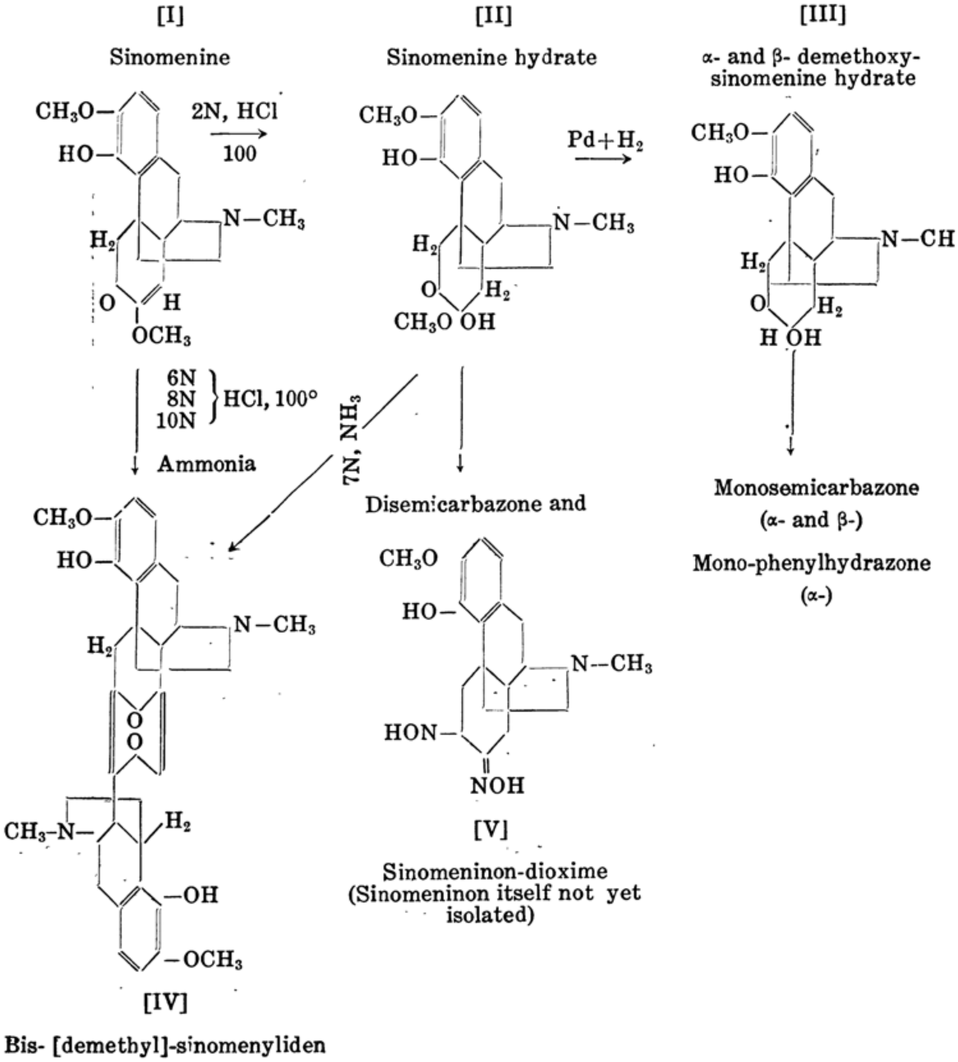
	α-Demethoxy-sinomenine hydrate	β-Demethoxy-sinomenine hydrate
Yield	45%	12.5%
Crystal form	stout prisms	hairy needles
M.p.	129°	65° (softens) 104° (melts)
Solubility in methyl alcohol	10% (hot)	3.3% (hot)
$[\alpha]_D$	+64.8°	+95.2°
Methoxyl	one	one
M.p. of oxim	170° (monoxim)	syrupy
D.p. of ICH_3	276°	289°
$FeCl_3$-reaction	+ in alcohol	+ in alcohol
Diazo-reaction	+ in 2,000,000th dilution	+ in 2,000,000th dilution
$K_3Fe(CN)_6$-reaction	+ in 500,000th dilution	+ in 500,000th dilution
Formaline-H_2SO_4	green, blue	green, blue

The reason, why these two isomeric substances are formed from sinomenine hydrate is not yet fully accounted for. The sinomenine hydrate may be an intimate mixture of two isomerides, which can only be separated by hydrogenation. This point needs further study.

The relation between sinomenine, sinomenine hydrate, α- and β-demethoxy-sinomenine hydrates, and bis-demethyl sinomenyliden are given in Table 3.

By simple heating of sinomenine hydrate, and α- and β-demethoxy-sinomenine hydrate for itself between 145°-155° for 10 minutes did not regain the sinomenine, nor gave demethoxy-sinomenine. Acetolysis of these three substances at 180° for 8 hours did not also give diacetyl-sinomenol resp. 3-methoxy-4, 6-diacetoxy-phenanthrene. The added water seems, therefore, to hinder the aromatisation of the nucleus.

Table 3.



Experimental.

Preparation of Sinomenine Hydrate. Sinomenine hydrochloride (10 gr.) is heated with 2N hydrochlcior acid (100 c.c.) on a steam-bath for two hours. After cooling, the base is precipitated with sodium carbonate, and extracted with chloroform in the ordinary way. The residue of chloroform is recrystallised from methyl alcohol. Prisms, isolated or collected in rosettes, m.p. 139°; yield over 80%. 4N, 6N, 8N, and 10N hydrochloric acid may be used in this hydration, but with different amount of the yield. Sulphuric acid (10%) can also effect this transformation, but the yield is far behind that obtained with hydrochloric acid.

The m.p. of this substance is raised slowly by repeated recrystallisation, but the above figure is commonly met with when measured soon after the isolation.

Anal. Found: C=65.74, 66.07; H=7.57, 7.37; N=3.91%. Calc. for $C_{19}H_{25}NO_5$: C=65.70; H=7.20; N=4.03%.

Mol. wt. Found (in glacial acetic acid): 289. Calc. for $C_{19}H_{25}NO_5$: 347.

Specific rotatory power. $[\alpha]_D^{26}=+40.8$ (0.9862 gr. subst. into 25 c.c. CCl_3H sol. l=2 dm.; $\alpha=+1.°61$).

Methoxyls. Found: 17.32, 16.82, 16.65, 16.24%, Calc. for two methoxyls: 17.86%.

Methiodide: dec. p. 264°. Found: I=27.18%. Calc. I=25.96%).

Disemicarbazone: prepared in the ordinary way, but not crystallisable. Purified by dissolving in a little methyl alcohol and precipitating with water, m.p. 191° (dec.)

Anal. Found: N=21.41, 20.71%. Calc. for $C_{20}H_{27}N_7O_5$: N=22.02%.

Methoxyls. Found: 6.36%. Calc. for one methoxyl: 6.96%.

Dioxim. Purified by dissolving in acetone and adding methyl alcohol to the residue of the acetone, m.p. 231° (dec.) Yield: 80%.

Anal. Found: N=11.35%. Calc. for $C_{19}H_{27}N_3O_5$: N=11.14%.

Methoxyls. Found: 8.85%. Calc. for one methoxyl: 8.22%.

Reduction of Sinomenine Hydrate by Na-amalgam. This reduction was carried out in the same way as was given in the last report.(1) The amalgam was very quickly consumed. Yield: 40%; m.p. 128°; admixture with α-demethoxy-sinomenine hydrate given below did not lower the m.p.

Methoxyl. Found: 9.72%. Calc. for one methoxyl in $C_{18}H_{23}NO_4$: 9.72%.

Preparation of α- and β-Demethoxy-sinomenine Hydrates. Sinomenine hydrate (10 gr.) was dissolved in 1% hydrochloric acid (100 c.c.), added with $PdCl_2$ (0.1 gr. in 50 c.c. H_2O) and gummi arabicum (0.1 gr. in 50 c.c.) and shaken in a hydrogen atmosphere. The absorption of hydrogen went on rather slowly. $PdCl_2$ and gummi arabicum were therefore added from time to time. After three or four hours, when 80% of the calculated quantity of the hydrogen was absorbed, the base was isolated in a usual way, and recrystallised from methyl alcohol. α- Compound crystallised out first in

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(1) This Bulletin, **4** (1929), 244.

stout prisms. The syrupy residue was again reduced in the above way and from this fraction, β- compound was chiefly obtained. Average yield: α-compound 45%; and β- compound 20%.

α- Demethoxy-sinomenine Hydrate. General properties were given in the Table 2. The melting point is raised slowly on keeping.

Anal. Crystal methyl alcohol. Found: 9.39%. Calc. for $C_{18}H_{23}NO_4$: $CH_3OH=9.64\%$. Found: $C=68.50$, 68.62; $H=6.99$, 7.32; $N=4.19\%$. Calc. for $C_{18}H_{23}NO_4$; $C=68.13$; $H=7.25$; $N=4.41\%$.

Methoxyl. Found: 9.53, 9.99%. Calc. for one methoxyl: 9.77%.

Mol. wt. Found (in glacial acetic acid): 343. Calc. for $C_{18}H_{23}NO_4$: 317.

Sp. rotatory power. 0.9799 gr. subst. was dissolved into 25 c.c. chloroform solution. $\alpha=+2.54°$; $d=1$ dm. $[\alpha]_D^{26°}=+64.8°$.

Oxim: prisms of m.p. 170° (dec.) Yield almost quantitative.

Anal. Found: $N=8.25\%$. Calc. for $C_{18}H_{24}N_2O_4$: $N=8.43\%$.

Methoxyl. Found: 9.12%. Calc. for one methoxyl: 9.33%.

Semicarbazone: m.p. 191° (dec.) ($N=14.70\%$. Calc. for $C_{18}H_{26}N_4O_4$: $N=14.97\%$).

Phenyl-hydrazone: hygroscopic, m.p. 140° (softening at 123°) ($N=10.31\%$. Calc. for $C_{24}H_{29}N_3O_3$: $N=10.31\%$).

Methiodide: m.p. 274∼276° (dec.). Yield almost quantivative. ($I=27.11\%$. Calc.: $I=27.65\%$).

β- Demethoxy-sinomenine Hydrate. See the Table 2 for general properties.

Anal. Crystal methyl alcohol. Found: $CH_3OH=9.24\%$. Calc.: 9.64%. Found: $C=68.56$; $H=7.22$; $N=4.35$. Calc. for $C_{18}H_{23}NO_4$: $C=68.13$; $H=7.25$; $N=4.41\%$.

Methoxyl. Found: 9.96%. Calc. for one methoxyl: 9.77%.

Mol. wt. Found (in glacial acetic acid): 346.5,

Sp. rotatory power: 0.3466 gr. subst. was dissolved into 10 c.c. chloroform solution. $\alpha=+3.30$; $d=1$ dm. $[\alpha]_D^{26°}=+95.2°$.

Methiodide: m.p. 280° (dec.) ($I=28.82\%$. Calc: $I=27.65\%$).

Semicarbazone: m.p. 206° (dec.) ($N=15.14\%$. Calc. for monosemicarbazone $C_{19}H_{26}N_4O_4$: $N=14.97\%$).

Oxim: not crystallisable, in contrary to the α-compound.

Preparation of Bis-(demethyl)-sinomenilyden from Sinomenine Hydrate. Sinomenine hydrate (1 gr.) was dissolved in 1% HCl (10 c.c.) and, after the addition of conc. ammonia (10 c.c.; $d=0.9$), left standing overnight. The precipitate was recrystallised from alcohol. Yield: 40%. m.p. >312°.

With sinomenine and dihydrosinomenine, only the original substances were recovered over 80% yield by this treatment.

By the way the crystallisable part isolated from the reduction product of the bis-demethyl-sinomenyliden by Pd + H_2, seems to be nothing but the unchanged starting material.

Anal. Found: C = 72.07; H = 6.94%. Calc. for unchanged bis-demethyl-sinomenilyden $(C_{18}H_{21}NO_3)_2$: C = 72.24; H = 7.02%.

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