SINOMENINE AND DISINOMENINE.
PART XI. ON THE POSITION OF THE DOUBLE LINKING IN SINOMENINE.

By Kakuji GOTO and Hideo SUDZUKI.

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In Part X of this communication, the following three reasons were given in assigning C_7-C_8 position to the double linking of sinomenine.

1. The easy reducibleness of the double linking with nascent hydrogen.

2. The easy hydrolysis of the methoxylgroup, which situates on C_7, by the heating with dilute hydrochloric acid and the after-treatment with ammonia, viz., the formation of bis-[demethyl]-sinomenyliden.

3. The linking together of two sinomenine molecules by the reduction with Na-amalgam.

In the present paper, these three points, together with the formation of d-form of Speyer's dihydrothebainone, already mentioned, will be given in a detailed manner.

I.

When sinomenine is reduced with Na-amalgam in a dilute caustic soda solution, a substance $(C_{18}H_{22}NO_3)_2$ is formed in a 60% yield, besides a small quantity of a substance which is very similar to the desmethoxy-dihydrosinomenine. (See section II).

The substance $(C_{18}H_{22}NO_3)_2$ has a great tendency to crystallize and it forms beautiful prisms in the course of the evaporation of its chloroform solution. As is given in Table 1, it melts at 304°, and has a double molecular weight. It has only two methoxyls, thus one methoxyl group of each sinomenine molecule being reduced away. It retains the original keton group and forms a disemicarbazone. The ferric chloride reaction and diazoreaction are also retained in an undiminished degree.

Table 1.

$(C_{18}H_{22}NO_3)_2$	
Yield	ca. 60% (raw)
M. p.	304° (commonly 294°)
Crystal form	stout prisms
Mol. wt.	626 (calc. 600)
$[\alpha]_D$	−24.49°
M. p. of iodomethylate	>300°
M. p. semicarbazone	>300°
Methoxyls	two
$FeCl_3$-reaction	+in alcohol
Diazo-reaction	+in 2,500,000th dilution
$K_3Fe(CN)_6$-reaction	purple
Formaline-SO_4H_2	pure blue

As to the linking point of two sinomenine molecules in this substance, 1, 1′-position is excluded, since this substance gives diazoreaction in the same degree as sinomenine itself (disinomenine and ψ-disinomenine give the diazoreaction in a slightest degree).(1) The pinacone linking is also out of question, as the new substance forms a disemicarbazone and more especially, dihydrosinomenine does not give any double molecular substance by the reduction.

The formation of this double molecular compound can therefore only be explained by the parallelism with the reduction of the benzalacetone.

Harries and Muller(2) obtained, in 1902, a diphenyl-octadione by reducing benzal-acetone, and thus showed that α, ß-unsaturated ketone can be linked together by Na-amalgam reduction. The linking point was afterwards more thoroughly determined to be β-position to the ketone group with coumaline by Asahina and Shibata.(3)

From these considerations, it is most reasonable to assume that two melecules of sinomenine was linked together in the β—position to the keton group and that the double linking of the sinomenine must be conjugated to the keton group. This assumption is enforced through the fact that the double linking is reduced by the simple zinc dust and hydrochloric acid couple.

It is a difficult problem to determine whether the position of the ethanamine chain was dislocated or not by this reduction. Yet, the author

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(1) This Bulletin, **4** (1929), 129.

(2) *Ber.*, **35** (1902), 966.

(3) *J. Pharm. Soc. Japan*, (1918) p. 100 (in Japanese.)

feel to be justified to call this new double molecular substance "Bis-8,8'-demethoxy-dihydro-sinomenine".

II.

By the Na-amalgam reduction of dihydro-sinomenine, a monomolecular substance $C_{18}H_{23}NO_3$ was obtained in a yield about 65%. It crystallized in stout prisms from acetone. It has only one methoxyl group, retains the original keton group, and accordingly, it may be called demethoxy-dihydro-sinomenine.⑴ As is seen from the following table, it is an optical antipode of Speyer's *l*-dihydrothebainone in all probability. The racemisation was carried out with the iodomethylates of the both substances.

Table 2.

	Demethoxy-dihydrosinomenine (from hydrosinomenine)	Speyer's dihydrothebainone (from thebain)
Yield	ca. 65%	ca. 20%
M. p.	138°	151° (Speyer) 138° (Skita)
Crystall form	prisms	prisms
In alcohol	easily soluble	easily soluble
In acetone	less soluble	less soluble
Mol. wt.	385 (calc. 301)	——
$[\alpha]_D$ (free base)	+59.17°	-80.12° (Skita)
$[\alpha]_D$ (hydrochloride)	+48.88°	-50.71° (Speyer)
Methoxyl	one	——
M. p. of iodomethylate	120°	120°
M. p. of semicarbazone	235°	(226° (Speyer) (237° (Goto)
$FeCl_3$-reaction	+in alcohol	+in alcohol
Diazo-reaction	+in 2,500,000th dilution	+in 2,500,00th dilution
$K_3Fe(CN)_6$-reaction	+in 500,000th dilution	+in 500,000th dilution
Formaline-SO_4H_2	+Yellow → green	yellow → green

The specific rotatory power of the free base of demethoxy-dihydro-sinomenine is somewhat lower than that given by Skita, yet that of the hydrochloride coincides fairy well with the figure given by Speyer.

As regards the melting point of the semicarbazone of Speyer's dihydro-thebainone, it is generally believed to be at 226°⑵ Yet, the semicarbazone,

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(1) Reduction of an ether-group, which situates vicinally to a ketone, was also obtained by Wieland and Kotake in dihydro-des-N-methyl-dihydro-codeinon, *Ann.*, **444** (1925), 69.

(2) Gulland and Robinson. *J. Chem. Soc.*, **1923**, 1006.

which the author prepared from dihydro-thebainone and recrystallized from acetone melted at 237°, thus only two degrees higher than that of demethoxy-dihydrosinomenine. The mixed melting point of these two semicarbozone was at 235°.

III.

When sinomenine is reduced with zinc-amalgam in the hot, after the method of Clemmensen, it gives a substance of the composition $C_{18}H_{25}NO_2 + \frac{1}{2}H_2O$ in a yield about 20%. It melts at 148°, contains only one methoxyl group, but no keton group. The original phenol group seems to be intact, since it gives the strong ferric chloride reaction (in alcohol), the diazoreaction and ferri-cyanide reaction in an undiminished degree. This substance, which is to be called demethoxy-desoxo-dihydrosinomenine, is evidently the d-form of the ß-tetra-hydro-desoxy-codein, as is seen from the following table. This point was proved by the actual racemisation.

Table 3.

	Demethoxy-desoxo-dihydrosinomenine	β-Tetrahydrodesoxy-codein⑴
Yield	20%	——
M. p.	147~148°	147~148°
Cystall form	hexagonal plates	hexagonal plates
Mol. wt.	322 (calc. 287)	——
$[\alpha]_D^{19}$	+43.22°	weakly left
M. p. of iodomethylate	267°	263°
M. p. hydro-iodide	245°	240~241°
M. p. of hydrochloride	——	262
$FeCl_3$	+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 500,00th dilution
Formaline-H_2SO_4	yellow → purple	yellow purple

Hydrosinomenine gives also the same substance by the Clemmensen's reduction.

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(1) Frennd, *J. prakt. Chem.*, **101** (1921), 1.

IV.

If sinomenine is, as we insists, an enol-ether, it may be hydrolysed on its enol-ether group and give rise to a new ketone, as is the case with thebaine. This is actually so. When sinomenine was heated on a steam bath with 2N, 4N, 6N, 8N or fuming hydrochloric acid for two hours, and the base was set free with ammonia, then a new substance of melting point >312° was obtained in a yield about 10%. This substance contained only one methoxyl group and one ketone group against each molecule of sinomenine. But the measurement of the molecular weight showed clearly that it had a double molecular weight. We propose to call this substance "Bis-[demethyl]-sinomenyliden." The property of this substance is given in Table 4.

Table 4.

Yield	10%
M. p.	>312°
Crystall form	prisms
Mol. wt.	650 (calc. 602)
$[\alpha]_D$ (hydrochloride)	+335.52°
M. p. of iodomethylate	>300°
Methoxyls	two (one against each sinomenine molecule)
M. p. of monosemicarbazone	>300°
M. p. of dioxim	>300°
$FeCl_3$-reaction	brown (weak)
Diazo-reaction	+in 2,000,000th dilution
$FeK_3(CN)_6$-reaction	transitory
Formaline-H_2SO_4	yellow → green → bordeau

The condensation of the two molecules of demethyl-sinomenine may be interpreted in the following way. The hydrolysis of the enol-ether may cause a new ketone group to be introduced and the original double linking to be eliminated. The third nucleus of the phenanthrene takes, therefore, the aspect of diacetyl. As Pechmann(1) has proved in 1888, diacetyl or similarily constituted diketones undergo the condensation by the action of alkali, and give substituted chinones. The same condensation may occur with the demethoxylated sinomenine through ammonia. As to the positions of the condensation, we should like to assume C_6 (ketone group) and C_8

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(1) *Ber.*, **21** (1888), 1417.

(methylen group) of each sinomenine molecule, thus giving a chinone like constitution to the new substance.

One uncertainty about this assumption is that this condensed substance is colourless, even in solution. Yet the fact that it forms a monoxim by the ordinary treatment with hydroxylamine hydrochloride seems to favour the chinone constitution.

V.

Throughout the preceeding sections, the author maintained the view that sinomenine must be an α, ß-unsaturated ketone. If this is correct, the double linking of sinomenine must be reduced by hydrogen in status nascendi.

The reduction of sinomenine with Na-amalgam can also be cited in this favour, yet the action of Na-amalgam does not exclude the might-be catalytic action of quicksilver.

After long fruitless trials, the author succeeded at last in reducing sinomenine by zinc dust and hydrochloric acid in the cold. The yield of dihydrosinomenine was, however, scanty (=about 15% in the experiment of a small scale). The reason why such experiments did not succeed for a long time can be sought in the fact that sinomenine is less resistant against hot dilute acid. The heating sinomenine with zinc dust and acetic acid, for example, might lead invariably to the derivative of sinomenine-hydrate,(1) and not that of sinomenine.

By the way, it may be added here that sinomenine can be reduced by Clemmensen's zinc-amalgam and hydrochloric acid in the cold into dihydrosinomenine (yield 60%). Here neither the trace of bis-8,8′-demethoxy-dihydrosinomenine nor demethoxy-desoxo-dihydrosinomenine was met with. This method may be advantageously applied to those α, β-unsaturated ketones, which by the reduction with Na-amalgam invariably undergo condensation.

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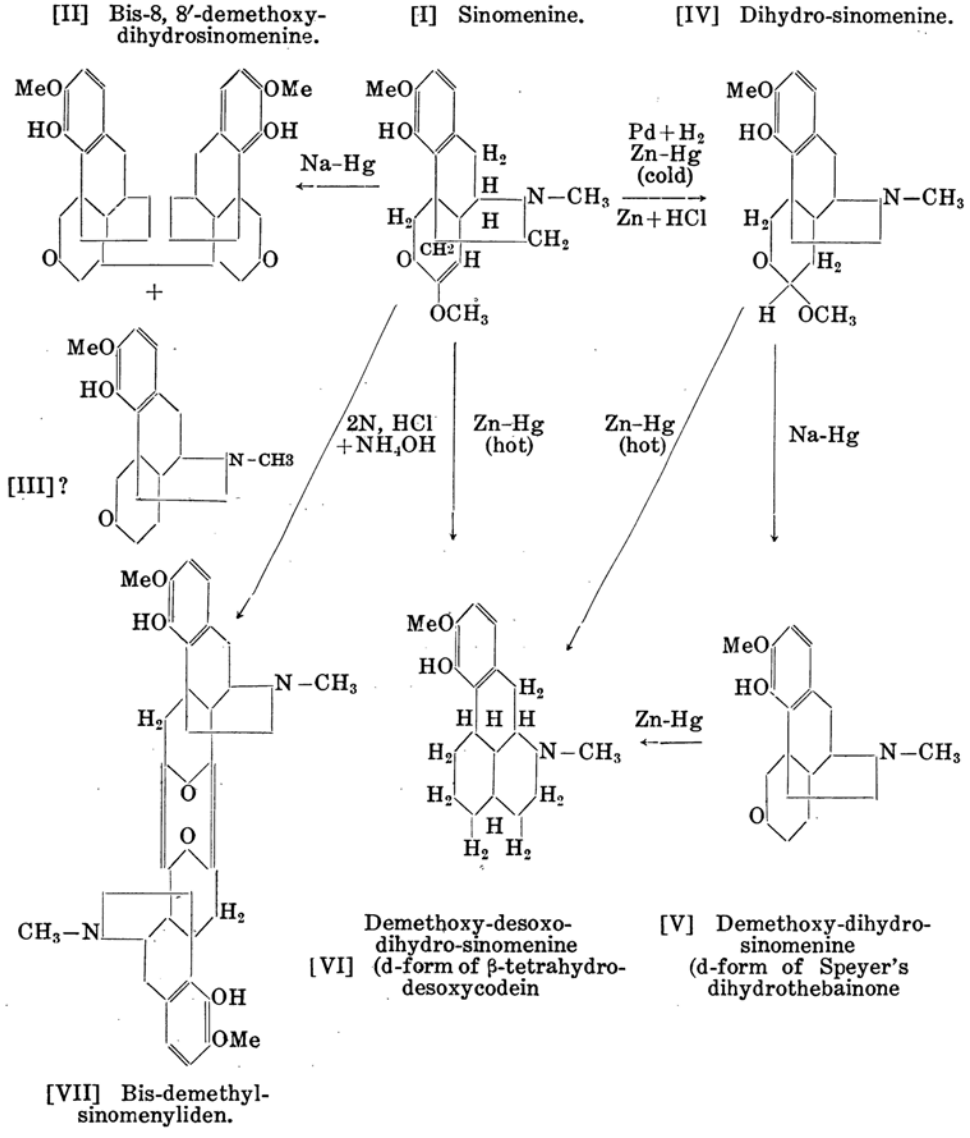
(1) Part XII of this communication, which will be published in the December number.
Note.—Reduction of sinomenine with sodium resp. zinc-amalgam was carried out by Kondo and Ochiai some time ago with totally different results. Compare, *Ann.*, **470** (1929), 224.

The above described transformation of sinomenine can be summarised in the following diagram.



Experimental.

Preparation and Properties of Bis-8, 8′-demethoxy-sinomenine. Sinomenine hydrochloride (5g.) is dissolved in 2% caustic soda (50 c.c.) and added with 40gr. 3% Na-amalgam (in four portions). Within 23 hours, the apueous part is saturated with carbon dioxide. The precipitate is collected and redissolved in chloroform. The crystalline residue, which remains on the evaporation of chloroform, is once boiled with a little acetone to remove impurities und recrystallised from a large quantity of alcohol. The pure substance crystallises in stout prisms, and melts at 304°. Yield about 1.5gr. (40%).

From the soluble part remaining in carbonic acid solution, a substance, melting at 134° was isolated. This seems to be very similar to the demethoxy-dihydro-sinomenine, which will be treated later.

As to the properties of bis-8,8′-demethoxy-hydrosinomenine, see the Table 1 in the theoretical part.

Anal. Found: C=70.95, 71.10, 71.94,; H=7.70, 7.77, 7.65; N=4.56%. Calc. for $(C_{18}H_{22}NO_3)_2=600$: C=72.00; H=7.33; N=4.66%.

Methoxyls Found: 11.37, 10.77. Calc. for one: 10.26%.

Mol. wt. Found (in glacial acetic acid): 650.

Sp. rotatory power: 0.8777gr. subst. was dissolved into 25 c.c. 1% hydrochloric acid solution. l=1 dm; $\alpha=-0.86$. $[\alpha]_D^{17}=-24.49°$

Semicarbazone: M. p. >300. (Found: N=14.07%. Calc. for disemicarbazone: N=15.68%).

Methiodide: M. p. >305°, needles. (Found: I=27.45%. Calc.: I=28.72%,)

Preparation and Properties of Demethoxy-dihydrosinomenine. The condition of the reduction is almost equal with the foregoing. The free base crystallises out from acetone slowly in prisms. It softens at 125° and melts at 138°. By drying at 100° over P_2O_5 in vacuum, it becomes syrupy. Yield: 3.9gr. from 6gr. of hydrosinomenine (65%).

The elimination of the methoxyl group seems to go on rather slowly and, even when a large quantity of Na-amalgam was used, the part, which crystallises afterwards, shows a little higher methoxyl number than calculated. The properties were given in Table 2.

Anal. Found: C=71.77; H=8.11; N=4.56%. Calc. for $C_{18}H_{23}NO_3=301$: C=71.76; H=7.64; N=4.65%. Methoxyl. Found: 10.91%. Calc. for one: 10.23%.

Mol. wt. Found (in glacial acetic acid): 358.

Sp. rotatory power. 1.0097gr. Subst. were dissolved into 25 c.c. alcoholic solution. l=1 dm. $\alpha=+2.39$, $[\alpha]_D^{19}=+59.17°$. 0.9718 gr. free base was dissolved into 25 c.c. 1% hydrochloric acid solution. l=1 dm. $\alpha=+1.90$, $[\alpha]_D^{19}=+48.88°$.

Semicarbazone. Prepared in the ordinary way, and recrystallised from acetone. M. p. 235°. (Found : N=15.66%. Calc : N=15.68%).

Methiodide : prisms collected in rosetts, (from water). M. p. 115° (Found : I=26.87%. Calc. : I=28.65%).

Racemisation of Demethoxy-dihydrosinomenine Iodomethylate with Dihydrothebainone Iodomethylate. Dihydrothebainone used in this experiment was prepared by the reduction of thebaine (10gr.) with Pd-H_2 and the sorption of hydrogen amounted to over two molecules (ca. 1600 c. c.). The mixture of the reduced bases was treated with 2% caustic soda solution (150 c. c.). The alkali soluble bases (yield : 2.8gr.) was tried to racemise with demethoxy-dihydrosinomenine, but, in contrary to the expectation, the crystalls obtained in this experiment turned the polarised light slightly left. The alkali soluble base thus seemed to have been still contaminated with dihydrothebainone.(1)

The alkali soluble part was, therefore, turned into its iodomethylate and the part, which directly crystallised out from methyl alcohol, was filtered away. The filtrate was evaporated and the residue crystallised from a little water. The fine crystalls thus obtained melted at 120°, viz. at the same point with the iodomethylate of desmethoxy-dihydrosinomenine. The specific rotatory power of the two iodomethylates is given below.

Demethoxy-dihydrosinomenine iodomethylate : $[\alpha]=+36.12°$ (0.3128 gr. subst, was dissolved into 10 c. c. water. $l=10$ cm., $\alpha=1.13$).

Dihydrothebainone iodomethylate : $[\alpha]=-34.36°$ (0.3148 gr. subst. was dissolved into 10 c. c. water. $l=5$ cm., $\alpha=0.54$).

To racemise the both iodomethylates, the above solutions were evaporated to a small bulk separately and mixed together in the hot. The beautiful prisms separated out instantly while hot, which melted at 231° sharply. The remarkable exaltation of the melting point might be due to the fact that recemic iodomethylate contained no crystal water. These crystalls did not rotate the polarised light.

0.5450 gr. subst. was dissolved into 10 c. c. water. $l=10$ cm., $\alpha=\pm 0$.

Preparation and Properties of Demethoxy-desoxo-dihydrosinomenine (d-form of β-Tetrahydro-desoxy-codein). Sinomenine hydrochloride (4 gr.) was added to the Clemmensen's zinc amalgam (prepared from 14gr. $HgCl_2$+ 7~10gr. Zn), poured on with hydrochloric acid (1 : 1 ; 10 c.c.) and heated on the steam bath for 6 hours. During the heating, the hydrochloric acid of the same concentration was added in small portions from time to time (the total amount 30 c.c.). After standing overnight, 25 c.c. of the filtrate

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(1) Skita, *Ber.*, **54** (1921), 1561. This is presumably the iodomethylate of dihydrothebaine.

were obtained, from which separated a syrupy precipitate when added with the same amount of water. The precipitate was dissolved in acetone (10 c.c.) and poured into chloroform (100 c. c.). The chloroform was washed thoroughly with ammonia to decompose the zinc double salts. The dried chloroform was evaporated and a little acetone was added to the residue. On cooling it with tap-water, the substance crystallised out in prisms. The yield was scanty (0.1gr. from the above treatment and 0.1gr. from the not precipitated part). M.p. 148°. With hydrosinomenine, the yield was somewhat better (30%).

The properties of this substance were given in Table 3. The big hexagonal plates (as were described by Freund) are obtainable when recrystallised from a large quantity of hot acetone.

Anal. Found: C=73.10, 73.42; H=8.38, 8.33; N=4.53. Calc. for $C_{18}H_{25}NO_2\frac{1}{2}H_2O$=296: C=72.97; H=8.73; N=4.72%.

Methoxyl. Found: 10.15, 10.16%. Calc. for one: 10.47%.

Mol. wt. Found (in glacial acetic acid): 322. Calc.: 296.

Sp. rotatory power. 0.7982gr. substance was dissolved into 25 c.c. alcoholic solution. l=1 dm., $\alpha=+1.38$. $[\alpha]_D=+43.22°$.

Methiodide: M. p. 267° (long needles from alcohol). Found: I=28.30 Calc.: I=29.59%.

Hydro-iodide, (prepared after Freund)(1): Long needles, m. p. 245°.

The substance does not make a semicarbazone.

Racemisation of Demethoxy-desoxo-dihydrosinomenine with β-Tetrahydrodesoxy-codeine. The β-tetradesoxy-codeine used in this experiment was prepared from codeine by the method of M. Freund.(1) It melted at 148°. As regards the colour reactions, see the right-hand column of Table 3.

For the racemisation, ca. 0.5 gr. of each substance was mixed in acetone solution. The crystalls (ca. 0.7gr.), which separated out instantly on cooling, were collected and redissolved in hot acetone. When acetone was evaporated down to ca. 6 c.c. in a cool place, ca. 0.3gr. substance was deposited in beautiful crystals. This was collected and examined on its rotatory power.

0.2949 gr. substance was dissolved into 10 c.c. chloroform. l=10 dm., $\alpha=\pm 0$.

The racemisation was thus complete. The racemic substance melted at 135° (from acetone). The iodomethylate prepared therefrom melted at 232° (from water).

Preparation and Properties of Bis-(demethyl)-sinomenyliden. Sinomenine hydrochloride (10gr.) is dissolved in 100 c.c. 2N hydrochloric acid, and heated on the steam bath for 2 hours. The base is set free with

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(1) *J. prakt. Chem.*, **101** (1921), 30.

ammonia and extracted with chloroform. The substance is easily crystalliable. M.p. >312°. Yield ca. 10%.⑴

For the properties of bis-[demethyl]-sinomenylinen. see Table 4.

Anal. Found : C=71.90, 71.43 ; H=6.95, 6.86 ; N=5.04%. Calc. for $(C_{18}H_{21}NO_3)_2$=598 : C=72.24 ; H=7.02 ; N=4.68%.

Methoxyls. Found : C=10.07, 10.08%. Calc. for two (one for each sinomenine molecule) 10.36%.

Mol. wt. Found (in glacial acetic acid) : 622.

Sp. rotatory power. 0.9694 gr. substance was dissolved into 25 c.c. 1% hydrochloric acid. l=1 dm., $\alpha=+13.01$, $[\alpha]_D^{17}=+335.52$

Methiodide: Very fine needles from water. M.p. 285° (?). Found : I=27.2% Calc. : I=28.78%.

Dioxim: M.p. >315° from chloroform. Found: N=8.66% Calc. for dioxim: N=8.91%.

Semicarbazone: M.p. >300°, prepared in the oridinary way. Found: N=7.29%. Calc. for disemicarbazone: N=14.96%.

Reduction of Sinomenine with Nascent Hydrogen. Sinomenine hydrochloride (1gr.) was dissolved in 30 c.c. 4% hydrochloric acid and added with 5gr. granular zinc. The mixture is cooled with water, and added with 10% hydrochloric acid from time to time (50 c.c. in total). Extracted in ordinary way and recrystallised from methyl alcohol, the reaction mixture gave 0.15gr. hydrosinomenine (m.p. 196° ; mixed melting point with that obtained by palladium-hydrogen reduction was 197°).

The mixture of sinomenine hydrochloride (4.5 gr.) zinc amalgam (ca. 10 gr.) and hydrochloric acid (1 : 1, ca 50 c.c.) was left overnight in a cool place. The filtrate gave no precipitate on the addition of water, but about 2.4 gr. hydro-sinomenine were isolated from it (m. p. 192°).

Hydrosinomenine, morphine and codein were not reduced in the above treatment. The reduction mixture of codeinone gave much precipitate with water, but it was not further studied.

Department of Chemotherapy
Kitasato Institute, Tokyo.

⑴ A better yield will be achieved when sinomenine hydrate is decompcsed by ammonia (see Part XII).