

SINOMENINE AND DISINOMENINE. XIX. ON REDUCTION
OF SINOMENINE AND DIHYDROSINOMENINE
WITH Na-AMALGAM.

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In the 11th report of this study,⁽¹⁾ one of the authors (K.G.), reported that he obtained by the reduction with Na-amalgam bis-[8, 8']-demethoxy-dihydrosinomenine [VII] from sinomenine and demethoxy-dihydrosinomenine (III; d-dihydrothebainone of Speyer) from dihydrosinomenine and by Clemmensen's method demethoxy-desoxo-dihydrosinomenine (VIII; d- β -tetrahydrodesoxy-codeine) from the both starting alkaloids. Recently, Ochiai and Hakozaiki⁽²⁾ repeated this reduction in several different ways and could this time obtain the demethoxy-dihydrosinomeninol [VI] in well crystallised form, melting at 138°. Thus they could endorse their former view,⁽³⁾ that the ketonic group of sinomenine could be reduced to the alcohol group by Na-amalgam.

Since in my first report on this problem, no mention was given in the latter point, I felt somewhat responsible to look for the alleged alcoholic base in the reduction products, and was fortunately enough to affirm the result, obtained by Kondo, Ochiai and Hakozaiki.

As is shown in details in the experimental part, the chief product of the reduction of dihydrosinomenine with Na-amalgam corresponding to 4H, is the mixed crystals (m.p. 149°) of demethylated ketonic and alcoholic

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

(2) *J. Pharm. Soc. Japan*, (1930), 53-59.

(3) *Ibid.*, (1926), 99-104.

bases. They are well defined, uniformly appearing crystals, but could not be resolved into the components by repeated recrystallisation from organic solvents, or by repeated dissolving in alkali and precipitating with carbonic acid gas. About one half of the mixed crystals could be transformed into the semicarbazone, and also into the iodomethylate of the demethoxy-dihydrosinomenine. Yet, the separation, as free bases, was perfectly impossible. Such cases are often met with as in aconitines, studied by Majima and co-workers⁽¹⁾ and in disinomenine and ψ -disinomenine of one of the authors.⁽²⁾

It is, therefore, better to reduce again these mixed crystals with Na-amalgam in order to obtain demethoxy-dihydrosinomeninol in a pure state. When the mixed crystals were treated with Na-amalgam corresponding to 3H or 6H in water, the alcoholic base was obtained in beautiful four-sided rhombic crystals from acetone. It sintered at 138°, melted at 142°, and decomposed at 143°. It formed no semicarbazone. Its rotatory power was $[\alpha]_D^{20} = +46.8^\circ$ and its iodomethylate decomposed at 280°. These properties well coincide with the description of Speyer and Siebert given to the dihydro-thebainone, of which our alcoholic base is regarded to be the optical antipode. The racemization was, however, not tried in this case, since Kondo and Ochiai reported four years ago that they could racemise successfully their iodomethylates.

The reason, why I did not obtain the above mentioned mixed crystals in the former study seems entirely due to the condition of Na-amalgam used at that time. Now, it was clearly settled that the best condition to obtain the demethoxy-dihydrosinomenine [III] in a pure state is to use the fresh Na-amalgam in an amount corresponding to 3H. Less than that, the demethylated ketonic base is contaminated by much unchanged dihydrosinomenine, whose separation presents always some difficulties.

In the course of this study, we could isolate a new alcoholic base (m.p. 162°) from that part of the reduction products of dihydrosinomenine, which is more soluble in the sodium carbonate solution containing much CO₂. The new alcoholic base has the formula C₁₉H₂₇NO₄, is monomolecular, retains two methoxys and does not form semicarbazone. Its properties are given in the second column of the Table 1. The yield was 1/5~1/10 of the above mentioned demethylated bases.

The formation of this new alcoholic base is quite intelligible from the constitutional formula of sinomenine [I] proposed by one of the authors (K.G.). According to it, sinomenine is an α , β -unsaturated ketonic base,

(1) Majima and Morio, *Ann.*, **476** (1929), 194.

(2) Goto, this Bulletin, **4** (1929), 129.

having an enol-methylether in the α -position. And the easy reduction of the methoxyl group by Na-amalgam is undoubtedly caused by the loosening (auflockende) action of the vicinal ketonic group. Now, in the course of the reduction, those molecules of dihydrosinomenine, whose ketonic group was first attacked and transformed into the alcohol, will lose this action on the methoxyl group, so that the methoxyl on C_{17} may be kept intact to the last. The new alcohol base will be called, therefore, dihydro-sinomeninol.

Table 1.

	Demethoxy-dihydro-sinomeninol (VI)	Dihydrosinomeninol (V)	Sinomeninol (IV)
Yield	12-30%	> 50%	> 30%
Mol. formula	$C_{18}H_{23}NO_3$	$C_{19}H_{27}NO_4$	$C_{19}H_{25}NO_4$
Solvents for recrystallisation	Acetone or ethyl acetate	Methyl alc. or benzene	Methyl alc., but not benzene
M.p.	{138° (sinters) 143° (dec.)}	{160° (sinters) 162° (dec.)}	{125° (sinter) 127° (dec.)}
$[\alpha]_D$	+46.8°	+1.93°	-23.7°
No. of Methoxyls	1	2	2
Formation of semicarbazone	No	No	No
M. p. of iodomethylate	280° (dec.)	249° (dec.)	272° (dec.)
$FeCl_3$ -reaction	Green	Green	Green
Diazo-reaction	2,000,000*	2,000,000	2,000,000
$FeK_3(CN)_6$ -reaction	500,000	500,000	500,000
Formaline-sulphuric acid reaction	Yellow $\rightarrow$ green $\rightarrow$ violet	Yellow $\rightarrow$ green $\rightarrow$ blue	Yellow $\rightarrow$ green $\rightarrow$ blue

* The figures show the dilution, at which the colour of the reactions is still visible.

The ratio of the reduction velocity of the ketone and the methoxyl groups in hydro-sinomenine may be calculated as about 10:1, on the basis of the yield of demethylated ketonic base and that of dihydro-sinomeninol. It is, therefore, very difficult to obtain the new base in a better yield by the alkaline reduction. We tried, accordingly, to reduce the ketonic group in acidic medium by Na-amalgam. As was seen in the catalytic reduction and in the Zn-amalgam reduction in the cold, sinomenine retains mostly its methoxyl group and the yield of hydrosinomenine amounts to the quantitative in the former case, and more than 50% in the latter. If we carry out

the reduction of hydrosinomenine quickly in an acidic medium, the yield of dihydrosinomeninol may be increased.

This is actually so. In reducing hydrosinomenine in a dilute acetic acid solution with Na-amalgam corresponding to 6H (considering the enormous loss of hydrogen) in half an hour, the yield of dihydrosinomeninol amounted to more than 50%. It melted at 162°, without depression even when admixed with that obtained in an alkaline reduction. All the other properties of both substances, originated from these two sources, coincided perfectly.

If the above supposition regarding to the formation of dihydrosinomeninol is correct, then sinomenine itself might be reduced to sinomeninol [IV], without losing its double linking as well as its enol-ether group. This is also actually the case. When sinomenine hydrochloride was reduced quickly in a dilute acetic acid solution as above described, a new base (m.p. 127°) was obtained in a yield about 30%. Its elemental analysis corresponds to $C_{19}H_{25}NO_4$ (thus isomeric with dihydrosinomenine), it has two methoxys, is monomolecular and does not form semicarbazone. The other properties are given in the third column of the Table 1.

The most striking properties of the sinomeninol are two. First, it is laevorotatory as sinomenine itself is. When the double linking of sinomenine was transformed into the single linking, the base invariably changes its direction of the rotation, no matter how this transformation was effected. Thus, sinomenine hydrate is dextrorotatory as dihydrosinomenine is. This unchanged direction of the rotation of sinomeninol speaks most fluently for the fact that the double linking of sinomenine was not attacked in the above reduction. But the decisive proof was given by the fact that sinomeninol could be reduced into dihydro-sinomeninol (m.p. 162°) by $Pd + H_2$. For, it is a known fact that the double linking of the phenanthrene alkaloid can be reduced catalytically,⁽¹⁾ whilst the reduction of a ketonic group goes on with much difficulty.⁽²⁾

The second property of sinomeninol, worthy of mention, is that it dissolves in caustic alkali without taking yellow colour. As was noticed first by R. Robinson,⁽³⁾ those substances, which have a ketone group and a double linking in conjugation, dissolves yellow in caustic alkali. In this point, sinomenine partakes the property of thebainone, only the difference being that sinomenine does not give the halochromy of thebainone against conc. mineral acids. This shows also that the position of the double linking

(1) Freund, *J. prakt. Chem.*, **101** (1921), 12.

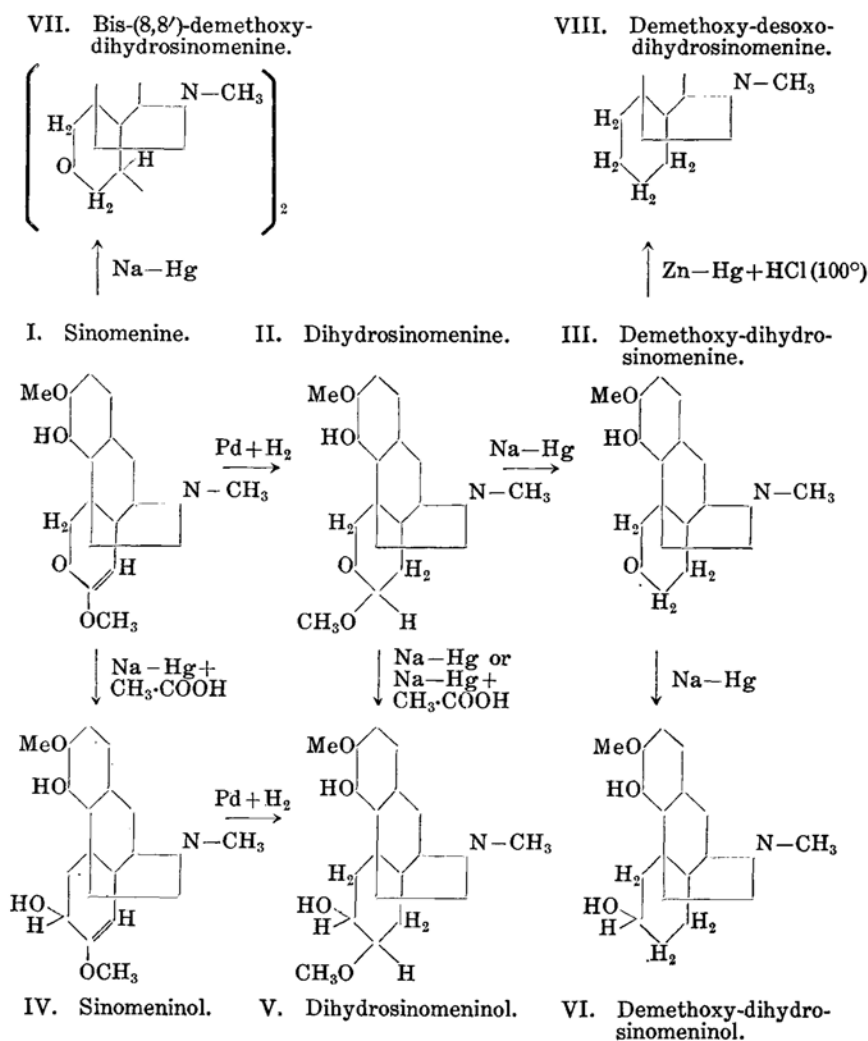
(2) Skita, *Ber.*, **54** (1921), 1562.

(3) Gulland and Robinson, *J. Chem. Soc.*, **123** (1923), 996.

may be reversed in thebainone and sinomenine. In this point, the recently proposed formula of thebainone by C. Schöpf⁽¹⁾ explains the property of thebainone as well as of sinomenine in some sense. Anyhow, the formation of sinomeninol and dihydro-sinomeninol gives one more proof that sinomenine must be an α, β -unsaturated, α -enolic ketone.

The relation of the bases, obtained hitherto by the reduction of sinomenine and dihydrosinomenine are given in the following Table 2.

Table 2.



(1) Schöpf, *Ann.*, **468** (1927), 158.

Conclusions. 1.—The best condition to obtain demethoxy-dihydrosinomenine (III) from dihydrosinomenine is to reduce the latter with Na-amalgam corresponding to 3H.

2.—In using Na-amalgam corresponding to 4H in the above reduction, the chief product is the mixed crystals of the demethylated ketonic and alcoholic bases (III+IV). As an accessory product, dihydrosinomeninol (V) is obtained.

3.—To prepare the demethoxy-dihydrosinomeninol in a pure state, it is better to reduce again the above mixed bases with much Na-amalgam.

4.—Dihydrosinomeninol is also produced by the Na-amalgam reduction of dihydrosinomenine in an acetic acid solution. The phenols C and D of Ochiai and Hakozaiki, which they think to be two new isomerides of the demethoxy-dihydrosinomenine, are probably one and the same substance and are nothing but our dihydrosinomeninol.

5.—By reducing sinomenine in an acetic acid solution sinomeninol (IV) is produced. This is identical with the phenol F of Ochiai and Hakozaiki. But they assigned to this base the dimeric formula $(C_{18}H_{24}NO_3)_2 \cdot H_2O$ and assumes it to be consisted of two molecules of an isomeric (?) demethoxy-dihydrosinomeninol.

Experimental.

Note on the Preparation of Dihydrosinomenine. Dihydrosinomenine can be prepared very easily from sinomenine by means of catalytic reduction with palladinised charcoal and hydrogen. The mixture, consisting of sinomenine hydrochloride (50 gr.) in 400 c.c. hot water, 0.3 gr. $PdCl_2$ in 40 c.c. dil. hydrochloric acid and charcoal (5 gr.), was shaken, while hot, vigorously with hand in a hydrogen atmosphere. The sorption of hydrogen amounts to 3600 c.c. (somewhat more than one molecule) in 15~30 minutes. Yield almost quantitative. M.p. 198° (from methyl alcohol).

The careful treatment of the methyl alcoholic mother liquor did not give other base than dihydrosinomenine.

Anal. Found: C=68.54; H=8.02; N=4.55. $C_{19}H_{25}NO_4$ requires: C=68.84; H=7.6; N=4.23%.

Sp. rotatory power, measured in chloroform: $[\alpha]_D^{25} = +193.58^\circ$; measured in dilute hydrochloric acid: $[\alpha]_D^{24} = +33.06^\circ$.

Oxim: m.p. 211° (dec.).

Semicarbazone: m.p. 209° (dec.) (Found: N=14.69%. Calculated for $C_{20}H_{28}O_5N_4$: N=14.43%.

Iodomethylate: m.p. 268° (dec.); solubility in water 0.34% (at room temperature).

Reduction of hydrosinomenine with Na-amalgam (corresponding to 4H). Hydrosinomenine (8 gr.) is suspended in 2% NaOH (80 c.c.) and is added with 5% Na-amalgam (50 gr.) After 24 hours, the aqueous part is diluted with water (80 c.c.) and supersaturated with CO₂. The pasty precipitate, first formed, changes gradually into rhombus plates, which are collected. The filtrate contains dihydrosinomeninol [IV].

The rhombus plates are again dissolved in 4% NaOH and precipitated with CO₂. This treatment is repeated once again. The united filtrate contains sometimes demethoxy-dihydrosinomenine [III].

The rhombus plates are finally recrystallised from acetone. When the substance crystallise out slowly, it forms stout prisms, but showing different faces more or less developed. M.p. 144° (dec. at 149°). These are the mixed crystals of demethylated ketonic and alcoholic bases [III+VI], and can not be easily resolved by recrystallisation.

From 1 gr. each of these crystals, 0.3 gr. and 0.4 gr. of semicarbazone was obtained.

From 1 gr. of these crystals, 0.5 gr. of demethoxy-dehydrosinomenine iodomethylate (m.p. 120°) is obtainable. The rest of the iodomethylate, which is more soluble in water, melts at 278°.

From these results, the mixed crystals must be consisted of almost equal parts of the two bases.

Methoxyls. Found: 10.68% (calc. for one: 10.23%)

Demethoxy-dihydrosinomeninol (VI). The above mentioned mixed crystals are again reduced with 5% Na-amalgam, corresponding to 8H. The precipitate formed by CO₂ is not rhombus plates this time, but remains pasty. This precipitate is purified through chloroform and recrystallised from acetone. It forms then nice rhombus plates, which softens at 138°, melts at 142° and decomposes at 143°. Yield about 50% (about 12.5% of dihydrosinomenine).

For the properties, see the first column of the Table 1.

Sp. rotatory power: 0.419 gr. subst. was dissolved into 10 c.c. methyl-alcohol. $\alpha = +0.98$; $d = 0.5$ dm. Therefore,

$$[\alpha]_D^{20} = (0.98 \div 0.419) \times (10 \div 0.5) = +46.8^\circ$$

It does not form semicarbazone; the starting material was recovered almost quantitatively in this trial.

Iodomethylate; long prisms from methyl alcohol. M.p. 280°. Very soluble in water, but recrystallisable from it.

Dihydrosinomeninol (V). (A) This base was isolated from sodium carbonate solution, from which the precipitate of the above described mixed bases was removed. Twice recrystallised from methyl alcohol, it forms nice

prisms and melts at 162° sharply, softening at 160° . Yield 4% and 6% each in two isolations.

(B) Hydrosinomenine (9.5 gr.) was dissolved in 6% acetic acid (50 c.c.) and added with 5% Na-amalgam (corresponding to 6H) in five portions, accompanied by the addition of glacial acetic acid to keep the solution always acidic (20 c.c. in total). The reduction finishes in 30 minutes. The base is isolated in the ordinary way, and recrystallised from methyl alcohol (60 c.c.). Yield 5 gr. (over 50% of the theoretical). M.p. 162° . The admixed m.p. with the prepate obtained in (A) shows no depression.

For the properties, see the second column of the Table 2.

Anal. Found: C=68.16; H=7.81; N=4.18; methoxyls=18.74%. $C_{19}H_{27}NO_4 = 333$ requires: C=68.46; H=8.11; N=4.21; methoxyls (2)=18.62%. The analysed substance was dried at $120^{\circ}\sim 130^{\circ}$.

Sp. rotatory power, measured in methyl alcohol: (A) the substance obtained by alkaline reduction.

$$[\alpha]_D^{20} = (0.07 \div 0.453) \times (25 \div 2) = +1.93^{\circ}$$

(B) the substance obtained by acidic reduction.

$$[\alpha]_D^{20} = (0.07 \div 0.499) \times (25 \div 2) = +1.75^{\circ}$$

Mol. Weight, measured after Rast. $(179 \div 1525) \times (400 \div 16.15) \times 100 = 291$.

The substance does not give semicarbazone, but the starting substance was recovered in a good yield in this trial.

Iodomethylate: Both the iodomethylates from the sources (A) and (B) can be obtained by mixing the bases with methyl iodide in methyl alcohol. They crystallise out in tetragonal or octagonal oblong plates, when the methyl alcohol is evaporated off. Recrystallised from water, it sinters at 218° , become waxy at 244° and decompose at 249° . (Found: J=26.88% Calc.: J=26.74%).

The specific rotatory power of the both iodomethylates are almost equal, when measured in aqueous solutions.

$$[\alpha]_D^{20} = - (0.35 \div 0.557) \times (10 \div 1) = -6.28 \quad (\text{from the source A})$$

$$[\alpha]_D^{20} = - (0.40 \div 0.594) \times (10 \div 1) = -6.73 \quad (\text{from the source B})$$

It is interesting to note, that both the iodomethylates are laevorotatory, in opposition to their free bases. Such inversion is often met with in amino-acids and in some of the alkaloids with carboxyl group.

In any way, the identity of the dihydrosinomeninols obtained by alkaline and acidic reductions seems to have been settled beyond doubt.

Sinomeninol (IV). 5% Na-amalgam (250 gr. corresponding to 10H) was put in a stout Erlenmeyer's flask, poured on with 100 c.c. of 20% sinomenine hydrochloride solution and added with glacial acetic acid in portions (50 c.c. in total), whilst the solution was cooled with ice-water from time to time. The reduction ends in 15 minutes. The isolated base is recrystallised twice from methyl alcohol. M. p. 127° (softening at 125°). Yield 5 gr. (over 30%).

For the properties, see the third column of the Table 1.

Anal. Found: C = 68.39, 68.73; H = 7.83, 7.81; N = 4.23; methoxyls = 18.59%. $C_{19}H_{25}NO_4=331$ requires: C=68.88; H=7.56; N=4.23; methoxyls (2)=18.73%.

Mol. weight, measured after Rast: $(150 \div 1632) \times (400 \div 11.6) \times 100 = 328$.

Sp. rotatory power, measured in chloroform: $[\alpha]_D^{25} = - (0.92 \div 0.39) \times (10 \div 1) = -23.7^\circ$

The base does not give semicarbazone, but the starting material is recovered in a good yield.

Iodomethylate: prepared in the methyl alcohol. Teragonal, oblong plates from methyl alcohol, but recrystallisable from water into long prisms. M.p. then 272° (dec.) (Found: I=26.88%. Calc.: I=26.74%).

Catalytic Reduction of Sinomeninol. Sinomeninol (1 gr.) was dissolved in dilute hydrochloric acid (110 c.c.), added with $PdCl_2$ (0.05 gr.) and charcoal (1 gr.) and shaken, while warm, in a hydrogen atmosphere. The sorption of hydrogen amounts to 97 c.c. (more than 2 H) in 40 minutes. The base, isolated in the ordinary way recrystallised from benzene, melted at 162°. Yield good. The admixture with the dihydrosinomeninol, obtained from dihydrosinomenine, does not lower the melting point.

Note. The constitution of sinactine (*l*-tetrahydro-*epi*-berberine⁽¹⁾) is to be regarded the 18th report of this study.

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(1) *J. Chem. Soc.*, (1930), 1234.