SINOMENINE AND DISINOMENINE. XXI.

ON THE REACTION BETWEEN SINOMENINE AND FORMALDEHYDE.

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When sinomenine (III) is boiled for two hours with ten times its weight of formaline (40%), two new bases can be isolated from the reaction mixture. As the base A is difficultly soluble in methyl alcohol and water and the base B is very soluble in these two solvents, they can be easily separated each other. The properties of these two bases are given in the following table.

Table 1.

	The base A (5-oxymethyl-sinomenine, I)	Dihydro-5-oxymethyl-sinomenine	The base B (1, 5-dioxymethyl-sinomenine, IV)
Mol. formula.	$C_{20}H_{25}NO_5$	$C_{20}H_{27}NO_5$	$C_{21}H_{27}NO_6$
Yield	30%	55%	10%
Solvent for recryst	Methyl alc.	Methyl alc.	Chloroform or methyl alc.
M.p.	260° (dec.)	244°	242° (fr. Me-A) 252° (fr. Chloroform)
$[\alpha]_D$	−40.71°	+73.03°	−74.39°
No. of methoxyls	2	2	2
Mol. weight	Monomolecular	—	Monomolecular
M.p. of oxime (all amorphous)	240–245°	215–225°	200–215°
M.p. of iodomethylate	223° (fr. Me-A)	205-220° (dec.)	210° (280 dec.)
$FeCl_3$ reaction	Green	Green	Brown
Diazo-reaction	2,000,000 th*	2,000,000 th	20,000 th
$FeK_3(CN)_6$ reaction	Faint	Faint	Almost no.
$HCOH$-H_2SO_4 reaction	Green → Brown	Blue violet	Green

* The figures show the dilution, at which the reaction is still visible.

The constitution of the base A, which is called to be 5-oxymethyl-sinomenine, is deduced from the following considerations.

1. The base A gives the diazo coupling reaction and ferric chloride reaction in the same strength as with sinomenine. The phehol group (4) and its para-position (1) must, therefore, be intact.

2. The base A is laevo-rotatory and its reduction product, dihydro-5-oxymethyl-sinomenine, is dextro-rotatory. This relation is the same with that of sinomenine (−) to dihydro-sinomenine (+) or to sinomenine hydrate (+). This shows that in the base A the original double linking of sinomenine must be kept intact.

3. By the acetolysis at 180°, the base A gives a nitrogen free product $C_{23}H_{22}O_5$ and methyl-ethyl amine. This shows that the reaction with formaldehyde did not occur on the methyl-amino-ethyl side chain.

In these state of affairs, there remain only four carbon atoms, which can be suspected to be able to enter the reaction with formaldehyde, namely, C (5), C (9), C (10) and C (14). Among these C (14) must be excluded, since the hydrogen atom on it must be lost in the course of acetolysis. The choice must be then made on C (5) C (9) and C (10). Of these three, C (5) is naturally the most susceptible point, where formaldehyde can react.

The reactivity of a methylene group, vicinal to a ketonic group, against aldehyde is well-known and is of two kinds. First, it is the linking together of the two methylene groups by means of the carbon atom of the aldehyde, that is the formation of the substance of the type of methylene bis-aceto-acetic ester. In the present case, this supposition is quite excluded, since the base A as well as its decomposition product are monomolecular.

Secondly, it is the formation of the substance of the type of piperonylidene thebainone. Yet, this supposition does not reconcile with the results of the elemental analysis of the base A and of its decomposition product. Mereover, this type of reaction is known thitherto only with aromatic aldehydes, and not with the aliphatic.

The elemental analysis of the base A and of its decomposition product shows that the formaldehyde must have been introduced, in our case, as oxymethyl group. We have not many examples of this type of reaction in the literature, yet we can cite the case of methylol chinaldine(1) from chinaldine and formaldehyde in favor of our reasoning, although in the latter case, the reactivity of the methyl group is enhanced by the neighbouring $-C=N-$ group of the chinoline nucleus. The base A is called, accordingly, 5-oxymethyl-sinomenine.

By heating 5-oxymethyl-sinomenine with acetic anhydride in a sealed tube at 180° for fifteen hours, we obtained a nitrogen free substance $C_{23}H_{22}$

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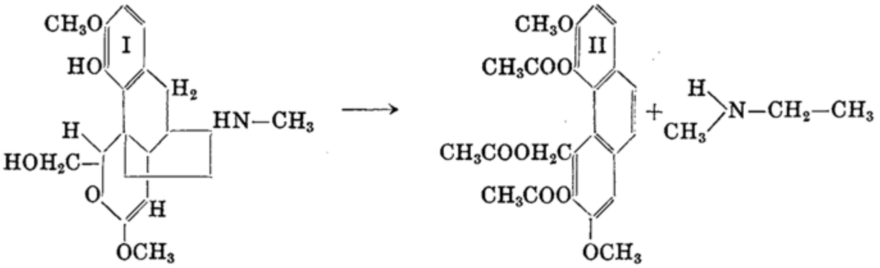
(1) Besthorn, *Ber.*, **39** (1906), 2329. Compare K. N. Welch, *J. Chem. Soc.*, **1930**, 257.

$O_8=C_{15}H_7(CH_3O)_2(CH_3COO)_3$ in 7% yield. The amine, splitted off, in this reaction, is also methyl-ethyl amine, as is the case with sinomenine(1).



By reducing 5-oxymethyl-sinomenine with Pd+H_2, we obtained dihydro-5-oxymethyl-sinomenine, whose properties are given in the third column of the Table 1. Yet, in an attempt to prepare this substance from dihydrosinomenine and formaline, the reaction products became syrupy.

The constitution of the base B, 1, 5-dioxymethyl-sinomenine (III) can be deduced from the following three facts.

1. Its molecular formula is $C_{21}H_{27}NO_6$.
2. It gives diazo coupling reaction very faintly (1:20,000th or thereabout). A second oxymethyl group must, therefore, have been introduced in the para-position to the phenol group.
3. By boiling pure 5-oxymethyl-sinomenine with formaline for one hour, 1,5-dioxymethyl-sinomenine was produced in a tolerably good yield.

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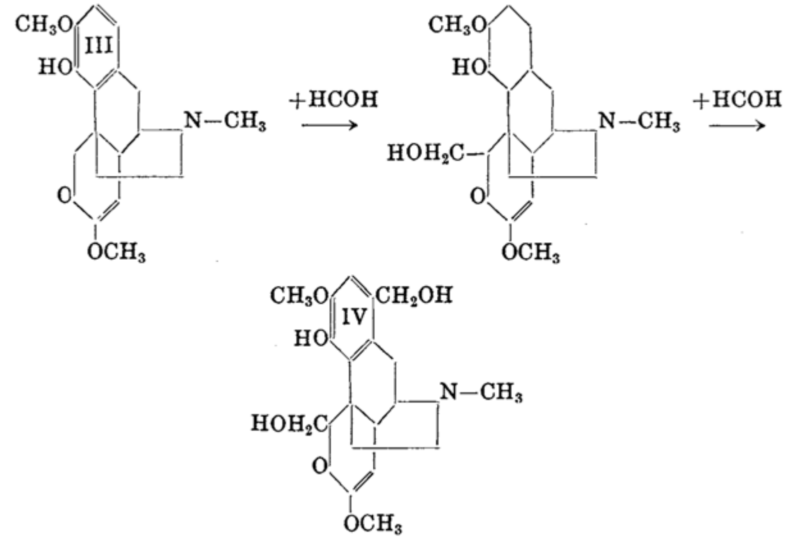

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(1) Goto, *J. of Agr. Chem. Soc. Japan*, **1** (1925), 50, 89.

Neither the acetolysis nor the reduction of 1,-5-dioxymethyl-sinomenine gave crystalline products.

Such introduction of oxymethyl group to the para- and ortho position of the phenol, had been studied already in 1894 by Manasse⁽¹⁾, who isolated saligenin and *p*-oxymethyl-phenol from the reaction mixture. He stated also that by the action of formaline on β-naphtol a dioxy-dinaphtyl-methan was produced. The studies in this line have been recently much advanced in relation to Bakelite.

Experimental Part.

1-Oxymethyl-sinomenine (1) and 1,5-Dioxymethyl-sinomenine (IV). When sinomenine (10 gr.) is boiled with formaline (50 c.c.; with the precipitate of oxymethylene), the base dissolves away slowly, changing the colour of the liquid into purple. After one hour, when the colour of the liquid turns brown, the boiling is discontinued and the mixture is diluted with water (100 c.c.). The reaction of the liquid is strongly alkaline. The bases are isolated from this mixture in the ordinary way. The raw yield is about 6 gr., i.e. 55% of the theoretical.

The raw product is recrystallised from boiling methyl alcohol (500 c.c.). 5-Oxymethyl-sinomenine crystallises out in stout prisms. Three recrystallisation is enough to obtain the substance in a pure state. M.p. 260° (dec.) The substance takes a purple colour at about 230°. Yield 3 gr. (ca. 30%). It does not react with Schiff's reagent.

The methyl alcoholic mother liquor is evaporated down, and the 5-oxymethyl-sinomenine is removed as far as possible. When long, hairy crystals of 1,5-dioxymethyl-sinomenine appear richly, it is evaporated to dryness and extracted with a little hot water. When the latter was shaken with chloroform or ether, the solvent as well as the aqueous layer is sometimes filled with the crystals of the substance. These crystals sinter at 95°, but melt at 252° (dec.) sharply. But, those crystals obtained by the evaporation of the solvents melt generally at 242°. Yield about 1 gr. (10%).

5-Oxymethyl-sinomenine was also isolated in a pure state from the cold mixture of sinomenine (1 gr.) and formaline (5 c.c.), after it was left stand for two weeks.

For the properties of 5-oxymethyl-sinomenine, see the first column of the Table 1.

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(1) *Ber.*, **27** (1894), 2411.

Anal. Found: C=66.43, 66.55; H=6.87, 7.00; N=3.86, 3.88; methoxyls=16.62, 17.01, 16.58%. $C_{20}H_{25}NO_5$=359 requires: C=66.85; H=6.96; N=3.90; methoxyls=17.22%.

Mol. weight, measured cryoscopically in acetic acid: (0.5692÷15.9052)×(39×0.379)×100=368; after Rast: (374÷4173)×(400÷9.53)×100=376.

Sp. rotatory power, in chloroform:

$$[\alpha]_D^{29} = -(0.78 \div 0.479) \times (50 \div 2) = -40.71^\circ$$

Oxime: amorph. decomposing between 240–245° (Found: N = 7.52%. Calc. for $C_{20}H_{21}N_2O_4$: N=7.48%).

Iodomethylate: long needles from methyl alcohol. M.P. 223° (dec.); m.p. 190–195° (from water). (Found: I=23.91%. Calc.: I=25.35%)

For the properties of 1,5-dioxymethyl-sinomenine, see the third column of the Table 1.

Anal: C=64.85; H=6.70; N=3.55; methoxyls=15.57, 16.01%. $C_{21}H_{27}NO_6$ = 389 requires: C=64.78; H=6.99; N=3.59; methoxyls=15.93%.

Mol. weight, measured after Rast:

$$(358 \div 3612) \times (400 \div 10.1) \times 100 = 392$$

Sp. rotatory power, measured in dilute methyl alcohol:

$$[\alpha]_D^{30} = -(2.77 \div 0.4654) \times (25 \div 2) = -74.39$$

Oxime: amorph. decomposing between 200-215°. Found: N=6.56%. Calc. for $C_{21}H_{28}N_2O_5$: N=6.93%.

Iodomethylate: crystallises out from methyl alcohol. M.p. 210°, but decomposes at 280–285°. Found: I=22.52%. Calc.: I=23.91%.

Decomposition of 5-Oxymethyl-sinomenine by Acetic Anhydride. 5-Oxymethyl-sinomenine is heated with 3–5 times its weight of acetic anhydride in a sealed tube for sixteen hours. The precipitate, formed by digesting the reaction mixture with much water, is dried and extracted with ether in a Soxleht's apparatus. The extracted substance is recrystallised first from methyl alcohol and then from glacial acetic acid. Long needles of pale yellow colour. M.p. 192–193°. Yield ca. 7%.

The above raw precipitate can be treated in the following away, also. It is dissolved in a small quantity of benzene and is added with petroleum ether in portions, until no precipitate is formed immediately after the addition. Then the mixture is filtered quickly and left stand. The needle crystals of the decomposition product appear after some time, and by its free evaporation some more is obtained.

This substance, presumably 5-acetoxy-methyl-diacetyl-sinomenol shows a green colour, when it is hydrolysed with alkali, but the hydrolysed solution does not give the sinomenol reaction(1). This might be due to the intervention of oxymethyl group in C (5).

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(1) This Bulletin, **4** (1929), 103.

Anal. Found: C=64.85; 64.66; H=5.09, 5.18; methoxyls=14.33%. $C_{23}H_{22}O_8$=426 requires: C=64.8, H=5.2; methoxyls=14.55%.

Mol. weight, measured after Rast:
$(201 \div 3536) \times (400 \div 5.48) \times 100 = 417.$

Nitrogenous Substance. The aqueous part, from which the above precipitate was removed, was evaporated down and distilled with much caustic soda. The overdistilled amine was caught in dilute hydrochloric acid. The hydrochloride of amine, thus obtained, was once purified through absolute alcohol. Very hygroscopic. Yield about 0.3 gr. from 10 gr. of 5-oxymethyl-sinomenine. The chloroaurate of this amine crystallises well from water and melts at 179–180°. The chloroplatinate crystallises from alcohol and decomposes at 224°. We have, here, clearly, methyl-ethyl-amine.

Dihydro-5-oxymethyl-sinomenine. 5-Oxymethyl-sinomenine (2 gr.) was shaken in dilute hydrochloric acid solution with $PdCl_2$ (0.1 gr.) and charcoal (1 gr.) in a hydrogen atmosphere. The sorption of hydrogen amounted to 175 c.c. in two hours (a little more than 1 mol.). Dihydro-5-oxymethyl-sinomenine crystallises out in short prisms from methyl alcohol and melts at 244°. Yield 1.1 gr. (55% of the theoretical.).

Anal. Found: C=66.80; H=7.76; N=3.91%. $C_{20}H_{27}NO_5$=361 requires: C=66.48; H=7.48; N=3.88%.

Sp. rotatory power, measured in methyl alcohol+chloroform.

$$[\alpha]_D^{29} = +(1.92 \div 0.3286) \times (25 \div 2) = +73.03$$

Oxime: amorph. decomposing at 215–225°. (Found: N = 7.34, 7.29%. Calc.: N=7.44%)

Iodomethylates: crystallisable from methyl alcohol. M.p. 205–220° (dec. from water). (Found: I=24.99%. Calc.: I=25.23%).

Transformation of 5-Oxymethyl-sinomenine into 1,5-Dioxymethyl-sinomenine. 5-Oxymethyl-sinomenine (1 gr.) was boiled with formaline (40%; 5 c.c.) for two hours. From the mixture of the bases, isolated in the way given above, we could isolate 1,5-dioxymethyl-sinomenine in ca. 10% yield. M.p. 242°. It gave only a brown colouration with ferric chloride in alcohol. Diazo-reaction was also strongly diminished (1 : 20,000th).

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