SINOMENINE AND DISINOMENINE. PART X.[1] ON SYNTHESIS OF DIMETHYLSINOMENOL AND ON SINOMENOL-CHINONS.

By **Kakuji GOTO and Hideo SUDZUKI.**

Received June 21, 1929. Published July 28, 1929.

Sinomenol was first obtained by one of the authors (K.G.) from sinomenine by heating it with 66% potash at 180° for 1–2 hours. It was determined to be dioxy-dimethoxy-phenanthrene, from the analysis of the substance as well as of its derivatives. Moreover, dimethylsinomenol was obtained by the Hofmann's decomposition of sinomenine through caustic alkali and dimethyl-sulphate, diacetyl-sinomenol by the acetolysis, and dibenzoyl-sinomenol by the fusion with benzoyl-anhydride of sinomenine. As regards the relative position of the hydroxyl and methoxyl groups, K.G. assumed, from the colour reactions of sinomenol and of sinomenine, that sinomenol must be 3, 4– dimethoxy -5, 6– dioxy-phenanthrene. But, as was already cited, Kondo and Ochiai's synthesis of dimethylsinomenol after Pschorr's method proved that it is 3, 4, 6, 7–tetramethoxy-phenanthrene.

---

(1) This Bulletin, **4** (1929), 103. Part IX will be published later.

The present authors have repeated the synthesis of dimethylsinomenol and could verify Kondo and Ochiai's result. Considering the closely analogous colour reaction of sinomenol and 3-methoxy —4, 6— dioxy-phenanthrene against ammoniacal silver in acetone solution, sinomenol itself may be regarded to be 3, 7- dimethoxy —4, 6— dioxy-phenanthrene.

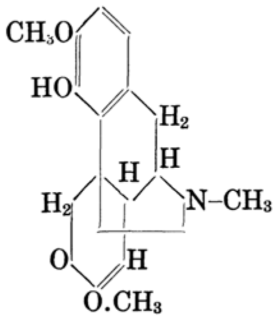
By way of this investigation, four chinons from sinomenol derivatives were prepared and ascertained as phenazines. These are summarized in the following table.

	M.p.	M.p. of phenazine
Sinomenol-chinon	259–263°	272°
Diacetyl- ,, ...	217–219°	255°
Diethyl- ,, ...	174°	188°
Dimethyl- ,, ...	266°	184°
Dibenzoyl- ,, ...	213°	254°

NOTE BY KAKUJI GOTO.

On the Revised Formula of Sinomenine. The synthesis of dimethylsinomenol necessitated to revise the provisional constitutional formula of sinomenine, which I advanced four years ago, chiefly on the ground of the colour reaction of sinomenine and sinomenol.

As sinomenine gives a strong diazo-reaction (sensitiveness 1:2,000,000), it is clear that the free phenol hydroxyl must lie in position 4. This position may be kept in sinomenol and hence the one methoxyl group in 3. The close analogy of the colour reaction of sinomenol and 3-methoxy -4, 6-dioxy-phenanthrene against ammoniacal silver in acetone solution leaves no doubt that the second phenol hydroxyl must lie in position 6 and hence the second methoxyl group in 7. This deduction is further supported by the fact that dihydro-sinomenine is transformed into d-form of Speyer's dihydro-thebainon by the reduction of Na-amalgam. From these reasons, as well as those, which will be enumerated afterwards, I should like to assign to the sinomenine $C_{19}H_{23}NO_4$ the following constitution.



This constitutional formula is somewhat similar to one which was proposed by Kondo and Ochiai two years ago, but there is a fundamental difference between them. For, in my formula, the double linkage is taken in C_7–C_8, regarding sinomenine to be an enol-ether and to the linking position of ethanamine chain C_{13} is selected decidedly.

The chief reasons, which let the author to assign C_7–C_8 position to the double linkage and C_{13} to the attaching point of the ethanamine group, will be explained in the following. The experimental data of the compounds here concerned will be published in the next communication.

(A) In contrary to the supposition of Kondo and Ochiai, sinomenine is not an optical antipode of a hypothetical 7-methoxy-thebainone.

1. Sinomenine dissolves yellow in dilute caustic alkali; this indicates that the double linking is conjugated with the ketone group. But, sinomenine does not give the halochromie with conc. hydrochloric acid. The double linking of sinomenine thus seems not to be in the same position with that of thebainone.

2. Sinomenine is far more easily decomposed by acetic anhydride than thebainone. This fact can not be explained, if we assume the same linking point of the ethanamine chain in sinomenine and in thebainone.

3. By boiling sinomenine with 66% alkali or by its acetolysis only the amine isolated hitherto was methyl-ethyl-amine, whereas ethanol-amine or its condensation product was met with in the same decomposition of thebainone. This fact also suggests that the constitution of the third nucleus in these two alkaloids is different.

(B) From the following three facts, the double linking of sinomenine is assumed to situate between C_7–C_8.

1. It was recently found that the double linking of sinomenine could be reduced with Zn-amalgam and hydrochloric acid or with Zinc and hydrochloric acid, both in the cold. The product is dihydro-sinomenine. This fact clearly indicates that sinomenine is an α, β-unsaturated ketone.

2. By the reduction with Na-amalgam, sinomenine gives a bimolecular substance, each molecule losing one methoxyl group at the same time. The linking of the two molecules of this kind was sometimes met with in α, β-unsaturated ketone, as Harries and Müller have first noticed. The linking point was determined to be β-position in relation to the ketone group in case of coumarine by Asahina and Fujita.(1)

---

(1) Asahina and Fujita, *J. Pharm. Soc. Japan*, No. 444 (1919), 97.

3. By heating sinomenine with 2N hydrochloric acid on a steam-bath for 2 hours and liberating the base with caustic ammonia, the author could isolate a bimolecular substance, which contained one methoxyl group less in each sinomenine molecule. The new ketone group, which must have been introduced by the hydrolysis of the enol-ether seems to cause the condensation of the two molecules of the substance newly formed, as is the case with diacetyl.*

(C) The C_{13} position for ethanamine chain was selected by the following reasons:

1. In the reaction, where sinomenol or its derivative is formed, the ethanamine chain of sinomenine is very easily removed. This fact indicates, as R. Robinson and Rucizka have often remarked, that the chain is attached to the tertiary carbon atom.

2. If sinomenine has thus two hydrogen atoms on C_5, then the ketone group in C_6 may enolise rather easily. Although the author can not yet prepare this substance with sinomenine itself, yet the desazoted substance, which was given on p. 168, Proc. Imp. Acad. 2 (1926) and afterwards proved to be bimolecular, is a tetramethoxy derivative, in spite of the fact that its side-chain is preserved.

3. Sinomenine seems to form a piperonyliden derivative, but the scanty yield and the difficulty of its purification makes the author to defer the investigation for future.

Experimental.

Synthesis of Dimethyl-sinomenol. This need not to be given in details, since it was carried out exactly in the same manner with Pschorr's original method. Only the melting point and yield of intermediates may be here summarily given.

(1) Acetvanillin (83%), m.p. 77°.
(2) Nitro-acetvanillin (78%), m.p. 85°.
(3) 2-Nitro-vanillin (65%), m.p. 138°.
(4) 2-Nitro-veratrumaldehyd (65%), m.p. 65°.
(5) Veratrumaldehyde (85%), m.p. 42°.

---

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

(1), (2), (3), (4), Pschorr and co-workers, *Ber.*, **32** (1899), 3407.

(5) Rosemund, *Ber.*, **43** (1910), 3415. Without heating.

(6) Azlacton of 3, 4-dimethoxy-phenylacetic acid (49%).

(7) 3, 4-Dimethoxy-phenyl-pyruvic acid (75%).

(8) Homoveratric acid (85%), m.p. 88°.

(9) 6-Br-veratrum-aldehyde (80%), m.p. 149°.

(10) Azlacton of 3, 4-dimethoxy-6-brom-phenyl-acetic acid (73%), m.p. 211°.

(11) 3, 4-Dimethoxy-6-bromphenyl-pyruvic acid (78%), m.p. 217°.

(12) 6-Brom-homoveratric Acid (90%), m.p. 113°.

(4) + (8) makes

(13) α-[3, 4-Dimethoxy-phenyl]-2-nitro-3, 4-dimethoxyl-cinnamic acid (48%), m.p. 193°.

(14) α-[3, 4-Dimethoxy-phenyl]-2-amino-3, 4-dimethoxy-cinnamic acid (86%), m.p. 146°.

For (15) and (16) see further down.

(17) 3, 4, 5, 6-Tetramethoxy-phenanthrene-9-carbonic acid (6%), m.p. 240°.

(18) α-[3, 4-Dimethoxy-6-bromphenyl]-2-nitro-3, 4-dimethoxy-cinnamic acid (45%), m.p. 216–218°.

(19) α-[3, 4-Dimethoxy-6-brom-phenyl]-2-amino-3, 4-dimethoxy-cinnamic acid (85%), m.p. 189°.

(20) 8-Brom-3, 4, 5, 6-tetramethoxyl-phenanthrene-9-carbonic acid (27%), m.p. 190°.

(15) 3, 4, 6, 7-Tetramethoxy-phenanthrene-9-carbonic acid (13%), m.p. 210°.

Anal. Found: C=67.05; H=5.21%. Calc. for $C_{19}H_{18}O_6$: C=66.66; H=5.26%.
Methoxyls. Found: 36.68%. Calc. for 4 CH_3O-: 36.25%.

Decarboxylation of this substance was carried out by heating it in a sealed tube with glacial acetic acid at 230° for 20 hours.

(16) 3, 4, 6, 7-Tetramethoxy-phenanthrene (24%), m.p. 123°—125°.

Admixture with the dimethylsinomenol originated from sinomenine did not lower the melting point.

Anal. Found: C=72.88; H=5.86%. Calc. for $C_{18}H_{18}O_4$: C=72.48; H=6.04%.
Methoxyls. Found: 41.79. Cal. for 4 methoxyls: 41.61%.

---

(6), (7), (9), (10), (11), Pschorr and co-workers, *Ann.*, **391** (1912), 33.

(8), (12), Perkins and co-workers, *J. Chem. Soc.*, 1925, 1693. Compare Kondo and Ochiai, *Ann.*, **470** (1929), 247.

Picrate. m.p. 124–125°. Admixture with dimethyl-sinomenol picrate (m.p. 124–128°) melted at 128°.

Anal. Found: N=7.88%. Calc. for $C_{24}H_{21}O_{11}N_3$: N=7.96%.

(21) 3, 4, 5, 6-Tetramethoxy-phenanthrene-9-carbonic acid. Prepared by reducing its 8-brom-derivative by Wohl's method.

Yield 50%. m.p. 240°. By decarboxylation, no crystalline substance was obtained.

Anal. Found: C=66.85; H=5.32%. Calc. for $C_{19}H_{18}O_6$: C=66.66; H=5.26%.
Methoxyls. Found: 36.87%. Calc. for $4CH_3O-$: 36.25%.

Sinomenol-chinon. Prepared by the hydrolysis of diacetyl-sinomenol-chinon in alcoholic solution with caustic soda in an atmosphere of hydrogen. Purified through ethyl-acetate. Brown needles of m.p. 259–263°. Yield scanty.

Anal. Found: C=63.97; H=3.99%. Calc. for $C_{16}H_{12}O_6$: C=64.00; H=4.00%.
Methoxyls. Found: 21.06%. Calc. for $2CH_3O-$: 20.66%.

This chinon gives the sinomenol reaction.

Sinomenol-chinon-phenazine. Prepared by ordinary method. m.p. 272.° Yield not very small.

Anal. Found: N=7.56%. Calc. for $C_{22}H_{16}O_4N_2$: N=7.52%.

Diacetyl-sinomenol-chinon. Prepared by the oxidation of diacetyl-sinomenol in glacial acetic acid by chromic acid. Purified through ethyl acetate. Orange red needles. Yield 10%. m.p. 217–219°.

Anal. Found: C=62.21; H=4.36%. Calc. for $C_{20}H_{16}O_8$: C=62.50; H=4.16%.
Methoxyls. Found: 16.06%. Cal. for $2\,CH_3O-$: 16.14%.

Diacetyl-sinomenol-chinon-phenazine. Yellow needles of m.p. 256°.

Anal. Found: N=5.83%. Calc. for $C_{20}H_{20}O_6N_2$: N=6.14%.

Diethyl-sinomenol-chinon. Prepared by the ethylation of the hydrolysed dibenzoyl-sinomenol-chinon with diethyl sulphate and caustic soda. Orange red needles of m.p. 174°. Yield 40%.

Anal. Found: C=67.76; H=5.59%. Calc. for $C_{20}H_{20}O_6$: C=67.41; H=5.61%.
Methoxyls. Found: 17.43%. Calc. for $2CH_3O-$: 17.41%.

Diethyl-sinomenol-chinon-phenazine. Yellow needles of m.p. 188°.

Anal. Found: N=6.06%. Calc. for $C_{20}H_{24}O_4N_2$: N=6.54%.

Dimethyl-sinomenol-chinon. Prepared in the same manner as diethyl sinomenol-chinon. Recrystallised from hot ethyl acetate, its forms beautiful red needles collected in rosettes.

Anal. Found: C=65.72; H=4.92%. Calc. for $C_{18}H_{16}O_6$: C=65.85; H=4.87%.
Methoxyls. Found: 37.31 %. Calc. for $4CH_3O-$: 37.80 %.

Dimethyl-sinomenol-chinon-phenazine. M.p. 184°; yellow needles.

Anal. Found: N=7.42 %. Calc. for $C_{24}H_{20}O_4N_2$: N=7.00%.

Dibenzoyl-sinomenol-chinon.(1) Prepared by the oxidation of dibenzoyl-sinomenol. Stout, cinnober red prism of m.p. 211°, yield 30%.

Anal. Found: C=75.48; H=5.27%. Calc. for $C_{30}H_{24}O_6$: C=75.00; H=5.00%.

Dibenzoyl-sinomenol-chinon-phenazine. Yellow needles of m.p. 254°, yield 70%.

Anal. Found: N=5.5 %. Calc. for $C_{36}H_{24}O_6N_2$: N=4.83%.

---

(1) See, *Journal of the Agricultural Chemical Society of Japan*, **1** (1925), No. 5.