SINOMENINE AND DISINOMENINE. PART XXVI. ON THE DECOMPOSITION OF SINOMENINE WITH DIMETHYL-SULPHATE.

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Received April 8th, 1931. Published May 28th, 1931.

In the XXV report of this study,⁽¹⁾ the Hofmann decomposition of sinomenine with the use of methyliodide and alkali was reported. In this communication, the same reactions were repeated with dimethylsulphate and alkali, and the results obtained partly ascertained those of the last report, but in regard to the nitrogen free substance, a new diphenanthryl derivative, different from the disinomenol, was obtained. These results are, for brevity's sake, summarized in the following way.

1. Sinomenine metho-sulphate [I] is best obtained by adding dimethylsulphate to the aqueous suspension of sinomenine and by precipitating the metho-sulphate by sodium carbonate solution. In this way, the yield is almost quantitative. The metho-sulphate shows the diazo-, $FeCl_3$, and

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(1) This Bulletin, **6** (1931), 79.

$FeK_3(CN)_6+CO_3Na_2$ reactions just as sinomenine hydrochloride itself and behaves against hot, dilute alkali in the same way as the iodomethylate does.

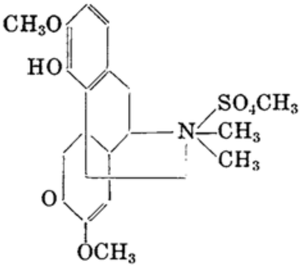
2. When sinomenine is methylated by dimethyl sulphate and caustic alkali at low temperature (cooling with ice-water), methyl-sinomenine metho-sulphate [II] is produced. The success of the reaction depends largely on the condition of the experiment, and the yield is very poor (15%). The trial to prepare this metho-sulphate from methyl-sinomenine in the way given [I] was unsuccessful.

3. The difficulty of the above reaction [2] lies chiefly in the easy opening of C_9–N linking of the metho-sulphate by the caustic alkali at the room temperature. In the latter condition, two kinds of methyl-sinomenine methine metho-sulphates, namely, the methyl-sinomenine-roseomethine-methosulphate and the methyl-sinomenine-violeo-methine-metho-sulphate [III] were isolated. Of these two, the former was more difficulty obtainable and in numerous experiments, it was obtained only twice (yield about 5%). The metho-sulphate of the methyl-sinomenine-violeomethine is, however, obtainable from sinomenine-achro-methine by dimethyl-sulphate and caustic soda at 0°C in a yield 60%.

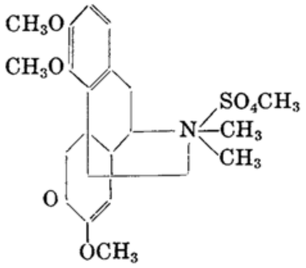
4. When the methyl-sinomenine-violeo-methine metho-sulphate is decomposed by boiling caustic soda (2–25%), a nitrogen-free substance ($C_{24}H_{30}O_8$; m.p. 310°) is produced. From the elemental analysis, the methoxyl content and the molecular weight determination, it must be a double molecular monomethyl-sinomenol. The linking point is supposed to be C_5, adjuscent to the free phenol group, which is newly formed from the original ketone group. The substance is named, therefore, 4,4′-dimethyl-bis-(5,5′)-sinomenol. This point was supported by the fact that the 4,4′, 6,6′-tetramethyl-bis-(5,5′)-sinomenol is quite different from the tetramethyl-disinomenol, obtained from sinomenine or disinomenine by the boiling 66% KOH and the followed methylation.

5. The above tetramethyl-bis-(5,5′)-sinomenol can be obtained directly from sinomenine by dimethyl-sulphate and alkali at the room temperature, if the reaction mixture is kept for a long time. This shows that the methyl-amino-ethyl-side chain of sinomenine is in a condition, which can be easily splitted off in the course of the aromatisation.

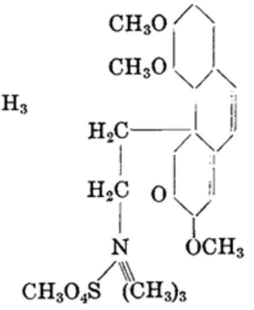
6. When the reaction mixture of sinomenine, dimethyl sulphate and caustic alkali is boiled, then the mixture of dimethyl-sinomenol and tetramethyl-bis-(5′5′)-sinomenol is obtained. This fact shows that there must be produced also the monomolecular 4-methyl-sinomenol, which perhaps on account of its low melting point could not be isolated in crystalline condition up to present.



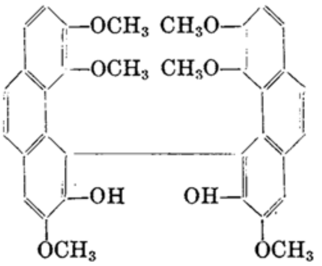
[I]



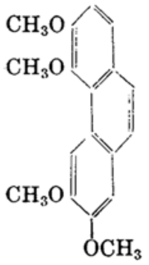
[II]



[III]



[IV]



[V]

7. By the present study, the following change in the nomenclature applied in the preliminary report appeared in *Proc. Imp. Acad.*, 2 (1926), 167 were necessitated.

The new nomenclature	To be abolished
1) Methyl-sinomenine-violeo-methine-metho-sulphate	1) α-Methyl-sinomenine-methine-methyl-sulphate
2) Methyl-sinomenine-roseo-methine-metho-sulphate	2) β-Methyl-sinomenine-methine-methyl-sulphate
3) 4, 4′-Dimethyl-bis-(5, 5′)-sinomenol	3) Trimethoxy-keto-vinyl-phenanthrene-tetrahydride
4) Tetramethyl-bis-(5, 5′)-sinomenol	4) α-Tetramethoxy-vinyl-phenanthrene-dihydride
5) Dimethyl-sinomenol	5) β-Tetramethoxy-vinyl-phenanthrene-dihydride m.p. 122°

Experimental.

1. **Sinomenine-methyl-methosulphate** [I]. Sinomenine hydrochloride (13.3 gr.) in an aqueous solution (80 c.c.) was added with anhydrous sodium carbonate (2 gr), and to this suspension of the free base, dimethyl sulphate

(9 c.c.) was added and well stirred. To the clear solution, which is produced in half an hour, a saturated sodium carbonate solution (40 c.c.) is added. After several hours, the precipitate is collected and recrystallized from ten parts of water. M.p. 265°C (decomposes). Yield quantitative. It gives no halochromy with conc. H_2SO_4 and HCl.

Anal. Found: C = 55.50; H = 6.23; N = 3.05; S = 7.06; CH_3O- = 20.53%.
$C_{21}H_{27}O_8NS$ requires C = 55.48; H = 6.58; N = 3.07; S = 7.03; CH_3O- = 20.39%.

2. **Methyl-sinomenine-methyl-metho-sulphate.** Sinomenine hydrochloride (10 gr) in an aqueous solution (70 c.c.) was added with anhydrous Na_2CO_3(1.5 gr in 20 c.c. water). This fine suspension of sinomenine was methylated with dimethyl sulphate (30 c.c.) and 33% NaOH (26 c.c.), given alterately in small portions, until the diazo-reaction disappeared. The reaction mixture was then extracted with chloroform sixteen times. By evaporating the dried chloroform, 1.5 gr. of the methyl-sinomenine methosulphate was obtained. It is hygroscopic, but recrystallisable from methanol into colourless prisms, melting at 245°. It gives no reaction for phenol group.

Anal. Found: CH_3O- = 25.89%. 4 CH_3O- in $C_{22}H_{29}O_8NS$ requires CH_3O- = 26.38%.

3. **Methyl-sinomenine-violeo-methine-methyl-metho-sulphate** [III].

(A) From sinomenine hydrochloride. The condition of the methylation is almost the same as (2), only the reagents being used in a somewhat larger quantity and the reaction mixture was warmed at 45° for some time. After six hours, the mixture was saturated with CO_2, added with Na_2CO_3 (saturated; 20 c.c.) and extracted with chloroform. The methosulphate is then precipitated from the chloroform solution (1 part) by ether (4 parts). Recrystallized from alcohol, it forms beautiful long prisms, which melts and decomposes at 204° sharply.

The substance is, however, better to be prepared from the sinomenine-achro-methine, as follows.

(B) Crude sinomenine-achro-methine (4.5 gr) is dissolved in 10% NaOH (15 c.c.) and set aside for 1.5 hours. (This treatment changes the achromethine into the violeo-methine). Then, the solution is methylated with dimethyl sulphate (15 c.c.) and 30% NaOH (15 c.c.) under ice-cooling. The reaction is completed by letting the mixture stand at the room temperature for three hours.

The yield is 2.5 gr, namely 60% of the theoretical.

The metho-sulphate dissolves deep blue in conc. H_2SO_4 and fuming HCl respectively.

Anal. Found: $C = 57.28$; $H = 6.87$; $N = 3.02$; $S = 6.69$; $CH_3O- = 25.15\%$. $C_{23}H_{33}O_8SN = 483$ requires $C = 57.14$; $H = 6.83$; $N = 3.02$; $S = 6.63$; $CH_3O-(4) = 25.67\%$.

Sp. rotatory power, measured in water,

$$[\alpha]_D^{13} = +(7.14 \div 0.1492) \times (10 \div 1) = +478^\circ$$

Sp. rotatory power, measured in chloroform,

$$[\alpha]_D^{20} = +(5.70 \div 0.245) \times (25 \div 1) = +581.6^\circ$$

4. **Methyl-sinomenine-roseo-methine-methyl-methosulphate.** Sinomenine (10 gr) was methylated with dimethyl-sulphate (50 c.c.) and 30% NaOH (68 c.c.) in an aqueous suspension (120 c.c.) The solution was nearly neutralized, added with saturated Na_2CO_3 solution (30 c.c.) and boiled for two hours. By extracting the cooled solution with chloroform, a reddish syrup (3.5 gr) was obtained from which on standing long separated first the crystals of methyl-sinomenine-violeo-methine-methyl-metho-sulphate. The alcoholic filtrate therefrom deposited, also on long standing, rhombic plates of the methyl-metho-sulphate of methyl sinomenine-roseo-methine. M.p. 178°. The substance dissolves deep red in conc. H_2SO_4 and in fuming HCl.

Anal. Found: $N = 2.99$; $CH_3O- = 24.38\%$. Calculated: $N = 2.99$; $CH_3O-(4) = 25.67\%$.

5. **4,4'-Dimethyl-bis-(5.5')-sinomenol** [IV]. Methyl-sinomenine-violeo-methine-methyl-metho-sulphate was boiled with ten times its weight of 2% NaOH for 20 minutes. The amine evolved was absorbed in dilute HCl. The aqueous part was extracted with chloroform, and the residue of the evaporation of the chloroform was recrystallised from glacial acetic acid or chloroform. It forms long colourless prisms, which melt at 310°. Yield ca. 20%. It dissolves in conc. H_2SO_4 brownish, and gives a green precipitate on diluting with water, but it does not show the sinomenol-reaction.

Anal. Found: $C = 71.96$; $H = 5.27$; $CH_3O- = 32.86\%$. $C_{34}H_{30}O_8 = 566$
Requires: $C = 72.05$; $H = 5.30$; $CH_3O-(6) = 32.68\%$.

Mol. Weight after Rast's,

$$M = (0.263 \div 2.478) \times 100 \times (400 \div 6.3) = 674.$$

The amine evolved was identified as trimethyl amine from the m.p. of its auri-chloride (m.p. 251°) and platini-chloride (m.p. 245°). It is clear that the trimethyl-amine is produced from the $CH_3{\cdot}CH_2{\cdot}N\,(CH_3)_3OH$ secondarily.

6. **4,4′-Dimethyl-6,6′-diacetyl-bis-(5,5′)-sinomenol.** 4,4′-Dimethyl-bis-(5,5′)-sinomenol [IV] gives this diacetylated substance, when boiled with acetic anhydride, added with Na-acetate for one hour. It is recrystallised from methanol in long prisms, m.p. 230°.

Anal. Found: C = 69.72, 69.85; H = 5.48, 5.52; CH_3O- = 28.63%. $C_{38}H_{34}O_{10}$ requires: C = 70.15; H = 5.23; $CH_3O-(6)$ = 28.61%.

7. **Tetramethoxy-bis-(5,5′)-sinomenol.** (A). Sinomenine HCl (20 gr) was methylated in an aqueous solution (100 c.c.) with dimethyl sulphate (53 c.c.) and 33% NaOH (79 c.c.) On standing this mixture for three weeks, a yellow crystalline substance was deposited on the bottom. The latter was dissolved in chloroform and precipitated with ethyl alcohol into long colourless prisms. M.p. 280°, but the substance recrystallised from acetone (1500 parts) melted at 283°C. Yield ca 2.2 gr. i.e. 13% of the theoretical.

(B). As the above preparation requires much time, it is better to boil the filtrate of the preparation, described in [3, B] with 33% NaOH (7 c.c.). As this filtrate contains some methyl-sinomenine-metho-sulphate and Na-CH_3-sulphate, so it gives tetramethyl-bis-(5,5′)-sinomenol in a tolerably good yield.

The substance is easily soluble in chloroform but very difficulty in alcohol, acetone (1:1 500) and ether. It dissolves in conc. H_2SO_4 brown and gives a green precipitate on diluting with water. Very resistent against $KMnO_4$. It has no rotatory power, showing that the sidechain must have been splitt off completely.

Anal. Found: C = 72.55, 72.34; H = 5.81, 6.18; CH_3O- = 41.64%. $C_{36}H_{34}O_8$ = 594 requires: C = 72.46; H = 5.79; $CH_3O-(8)$ = 41.75%.

Mol. Weight after Rast's,

$$M = (0.227 \div 2.142) \times 100 \times (400 \div 6.1) = 695.$$

Sp. rotatory power, measured in chloroform,

$$[\alpha]_D^{18} = (0 \div 0.1057) \times (10 \div 1) = 0.$$

8. In the preparation of 7, (A), we obtain a mixture of dimethyl-sinomenol and tetramethyl-bis-(5,5′)-sinomenol in different proportions,

when we boil the methylating mixture, using the dimethyl-sulphate and cautic alkali in different proportions. This shows that there must be the formation of the monomolecular 4-methyl-sinomenol in the above treatment, but the latter is not obtained in crystalline form yet. The substance, given in Proc. Imp. Acad. 2, (1926) 169, as β-tetramethoxy-vinyl-phenanthrene-dihydride (m.p. 122°), turned out to be nothing but dimethyl-sinomenol itself. The analysis made clear this point.

Anal. Found: C=72.38, 72.34; H=6.38, 6.18%. Calc. for $C_{18}H_{18}O_4$: C=72.45; H = 6.08%.

9. Dimethyl-sinomenol chinone. The alkaline filtrate from the preparation 7, (A), was diluted and oxidised with a dilute $KMnO_4$ solution, so long as the latter is still decolourised. Ether extracts therefrom a deep red substance (prisms) in a minute quantity. It melts at 266°C and forms a phenazine, which melts at 184°C. The mixed m.p. showed the substance is dimethyl-sinomenol-chinone, reported already in this Bulletin 4 (1929), 169.

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