SINOMENINE AND DISINOMENINE. XXV.
ON THREE DIFFERENT SINOMENINE-METHINES.

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In the previous note, published in 1926,(1) one of the authors (K.G.) reported preliminarily on the three different products of sinomenine [I], produced by the Hofmann decomposition. Now that the constitution of sinomenine is fairly well established,(2) we undertook the investigation again and could trace the relation of these three methines, the results of which will be published here with some necessary supplements and corrections to the former note.

When sinomenine iodomethylate was boiled with 2% NaOH (2 mol) for one minute, there is formed an iodine free substance, $C_{20}H_{25}NO_4$, of m.p. 179°. To this substance, formerly the name N-methyl-anhydro-sinomeninium-base and the constitution [II] had been given chiefly from the following three reasons.

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(1) *Proc. Imp. Acad.*, **2** (1926), 167.
(2) In the XXIV report of this study, (*Ann.*, **485** (1931), 247), the results are partly summarized.

1. The extreme easy formation of this substance, compared with the other two methines.

2. The characteristic unstableness of this substance, which does not allow the recrystallization even from alcohol. This might indicate the splitting off of the double linking between $C_{(9)}$ and N.

3. Very weak halochromy with conc. H_2SO_4. All the methines of morphine and codeine are known to give strong colouration with this reagent.

Yet, the fact that the hydroiodide of this substance is totally different from the starting material was very singular, although this fact was not mentioned in that short note.

Now, we prepared the hydroiodide and iodomethylate of this substance carefully and found that these two salts give the same weak halochromy with conc. H_2SO_4. In addition to this, the fact that the iodomethylate of this substance is transformed into the iodomethylate of the secoud methine by cold 10% NaOH, which give an intense blue halochromy with H_2SO_4, reminded us of the transformation of α-methyl-morphi-methine into β-methyl-morphi-methine by alcoholic alkali. We are, therefore, inclined now to give this substance the methine constitution [III] and call it sinomenine-achro-methine.

As its iodomethylate, the sinomenine-achro-methine itself can be transformed into the methine, which gives an intense blue colour with conc. H_2SO_4. This methine was called α-sinomenine-methine in the previous note, but we wish to call it now sinomenine-violeo-methine, in order to avoid confusion with the prefixes of the six methyl-morphi-methines, since the relation of each sinomenine methine to the corresponding methyl-morphi-methine is not exactly determined. We believe, however, that the sinomenine-violeo-methine corresponds to the β-methyl-morphi-methine from the reasons, which will be given later.

From sinomenine iodomethylate, another methine, which gives a strong red halochromy against conc. H_2SO_4, is obtainable. At first, this methine was obtained by boiling sinomenine iodomethylate with 5% NaOH (5 mol) for a short time. In this treatment this methine is produced side by side with the violeo-methine, the yield of the both methines being extremely small (5—7%). Now, it was found that the crude sinomenine-achro-methine, recrystallized from alcohol and kept for years, transforms itself partly into this methine. That in this transformation, the sodium bicarbonate, which might be attached to the crude methine, may be the cause, was proved by the experiment that the iodomethylate of the achro-methine could be turned into that of this methine by boiling in methyl-alcohol, added with a bit of sodium bicarbonate. This third methine was called β-sinomenine-methine in the previous note, but we propose now the new name sinomenine-roseo-methine for it. The iodomethylate of this roseo-methine was transformed, then, into that of violeo-methine by cold 10% NaOH.

The relation of these three sinomenine-methines is given in the Table 1 and their properties are summarized in the Table 2.

Table 1.

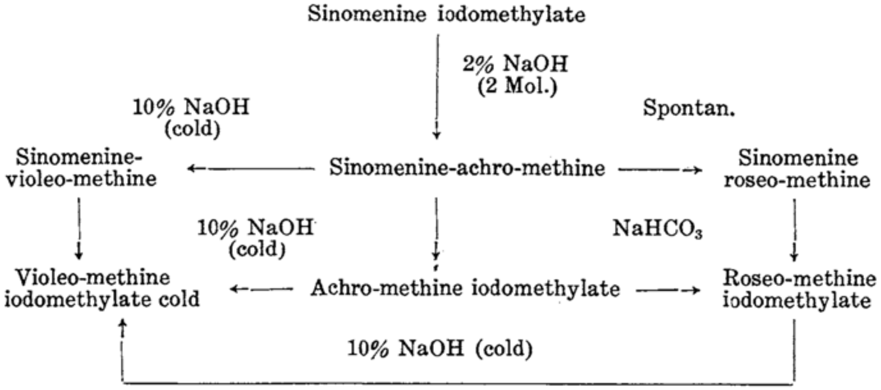

Table 2.

Substance Former names*	Sinomenine-achro-methine N-methyl-anhydro-sinomeniniumbase	Sinomenine-roseo-methine β-Sinomenine methine	Sinomenine-violeo-methine α-Sinomenine methine
M. p.	179°	163°**	172°—173°
Sol. in ether	easier soluble	difficultly sol.	almost not
$[\alpha]_D$	+72.58°	+135.70	+434.78°
Diazo-reaction	2,000,000th	100,000th	2,000,000th
Conc. H_2SO_4	faintly yellow	carmin red	deep blue
Fuming HCl	lyra	yellowish red	deep blue
M.p. of iodomethylate	212° (fr. water)	277° (fr. methanol)	209° (from water)
$[\alpha]_D$	−33.00°	−48.26°	+373.36°

The above three reactions are same with their corresponding free bases.

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* *Proc. Imp. Acad.*, **2** (1926), 167.

** M.p. 263° in the above note is clearly a misprint.

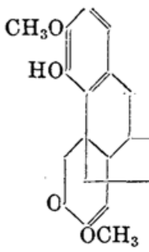
As regards the constitution of these three methines, we will now provisionally give the following explanation. In these three methines, no dislocation of the attaching groups and the linking point of dimethyl-amino-ethyl group seems to have occurred. For, the achro-methine and the violeo-methine (iodomethylate) could be very easily decomposed into sinomenol by the same methods as with the sinomenine itself. Though the roseo-methine has not been decomposed, the same argument could be applied to it, since its iodomethylate could be transformed into that of the violeo-methine. The cause of the difference in these three methines then may be due to the displacement of the double linkings, as Knorr and Robinson suspected to be the case in methyl-morphi-methines.

Now, we feel it is almost doubtless that the sinomenine-violeo-methine corresponds to the β-methyl-morphi-methine from the following considerations.

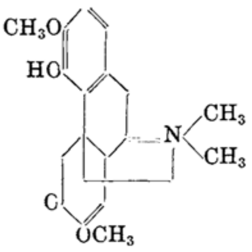
1) Its mode of formation (cold 10% NaOH).
2) Its high specific rotatory power.
3) Its intense blue halochromy with conc. H_2SO_4 and with fuming HCl.

R. Robinson,(1) based on the study of neopine, gave to the β-methyl-morphi-methine the constitution [VI]. This constitution seems to explain partly its high specific rotatory power as well as its intense halochromy. If this conception is not errornous, the sinomenine-violeo-methine may possess the constitution [V].(2)

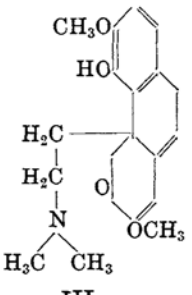
The question, which of the remaining two sinomenine-methines corresponds to the α-methyl-morphi-methine is difficult to say. But, from (1) its



I.



II.*



III.

* Partly modified, with necessary corrections.

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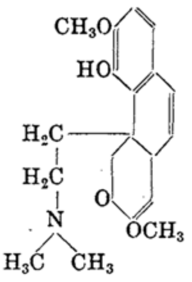
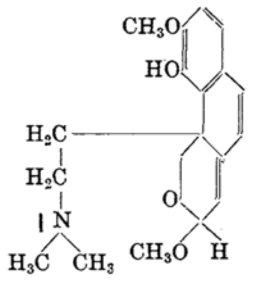
(1) R. Robinson, J. C. Smith, *J. Chem. Soc.*, **1926**, 903; compare also E. Speyer, Koulen, *Liebig's Annalen*, **438** (1924), 34, and R. S. Cahn, *J. Chem. Soc.*, **1926**, 2562.

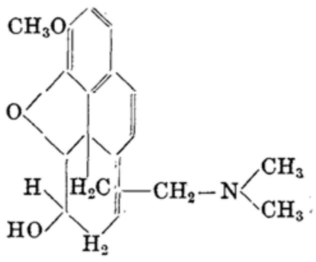
(2) An objection to this explanation may be the transposition of the double linking from α, β- to β, γ-position relating to the ketone group. But, after the text-book of Meyer-Jacobson (2. Edition, I, 1, p. 947), such a transposition is not without examples in unsaturated acids.



IV.



V.



VI.

very easy formation and (2) its very weak halochromy aganinst conc. H_2SO_4, we wish to give the constitution [III] to the sinomenine-achro-methine, taking the new double linking between C (9) and C (14). It is remarkable that all the derivatives of sinomenine, which have not the double linking in C (7) and C (8), stand stronger against the Hofmann decomposition. The iodomethylates of dihydro-sinomenine, of its demethoxy- and demethoxy-desoxo-derivatives are opend successfully in their C (9) and N-linking by boiling with 16.6% KOH over thirty minutes. This shows that the double linking in C (7) and C (8) makes easy the opening of the ring. If so, why should not the new double linking conjugate to the old one and enter between C (9) and C (14)? If we assume the double linking in C (9) and C (10) in the habitual way, the easy formation of the achro-methine could not be explained.

The position C (9) and C (14) is also convenient to explain the extremely weak halochromy of the substance. All the other methines of sinomenine series, which are produced by boiling 16.6% KOH or 25% NaOH over thirty minutes, give strong yellowish red or red halochromy against conc. H_2SO_4. This property is partaken by other hydrated phenanthrenes, which have a double linking in α, β-position to the not hydrated benzene nucleus, say, meta-thebainone(1) and benzylidene-*d*-thebenone.(2)

It may not be unreasonable to seek, therefore, the cause of the very weak halochromy of the achro-methine in the different position of the double linking from that of all the other methines.

As to the roseo-methine, we wish to give the constitution [IV] to it. The rearrangement of a β, γ-double linking to the benzene nucleus into the α, β-position by the action of alkali is well known in eugenol and allylbenzene. Whether this arrangement could be effected by a so mild reagent as $NaHCO_3$ is a question. Yet, seeing that the yield in this rearrangement

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(1) C. Schöpf, H. Perrey, *Liebig's Annalen*, **483** (1930), 170.

(2) H. Wieland, M. Kotake, *Liebig's Annalen*, **444** (1925), 90.

is far less than the quantitative and that the roseo-methine gives an intense red halochromy as almost all the other methines, we propose this explanation for the present.

It seems to us that there must be some means, by which the above hypothesis can be verified or not. For example, the reductive method, which was so useful in determining the C (7)—C (8) position of the double linking in sinomenine, may be applied to the above three methines. Yet, all the preliminary experiments, carried out for the purpose, gave very unpromissing results, and we are forced to be satisfied with the above hypothetical explanations for the present. But the question whether the stage of sinomenine-achro-methine is passed or to be isolated in future in the methines, derived from morphine or condeine remains to be an interesting problem.

Experimental.

1. **Sinomenin-achro-methine**, [III]. Sinomenine iodomethylate (2 gr.) is boiled with 2% NaOH (20 c.c.; 2 mol) for one minute. The brownish coloured liquid is quickly cooled with water and saturated with CO_2 gas.

The reddish brown precipitate is then washed with hot water and dried on a porous plate. It is already crystalline. The raw yield amounts to 80% of the theoretical.

The purification is best effected through its sodium salt. When the crude product was poured on with ice-cold 10% NaOH, there is formed almost colourless phenolate of the substance. The latter is quickly collected on a glass-filter, washed with alkali and then redissolved in water. When the aqueous solution is again saturated with CO_2 gas, the achro-methine crystallises out in faintly brownish⁽¹⁾ flat prisms. One more recrystallization from much ether turns the substance into long prisms. They are still faintly coloured. This seems to be due to some impurity, which is quickly formed by the decomposition of the achro-methine itself. M.p. 179° (sintering at 173°). Its halochromy in conc. H_2SO_4 is very faintly yellow (almost colourless), so it is named sinomenine-achro-methine.

The properties of this methine is given in the first column of the Table 1.

Anal. Found: C=69.80, 70.10; H=7.05, 7.32; N=4.18; Methoxyl=18.15%.
$C_{20}H_{25}NO_4$=343 requires: C=69.97; H=7.28; N=4.08; Methoxyl=18.07%.
Sp. rotatory power, in chloroform: $[\alpha]_D^{16} = +(0.43 \div 0.1481) \times (25 \div 1) = +72.58°$.

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(1) This brownish red substance seems to be produced by a partial decomposition of the achro-methine and gives a deep green halochromy with conc. H_2SO_4. The achro-methine seems to be turned into this substance at its melting point, but the substance itself could not be yet obtained in a crystalline form.

Hydro-iodide: long prisms, m.p. is very unsharp, but lies at 115~118° (sintering at 80°). Halochromy in conc. H_2SO_4 or in fuming HCl is the same with the free methine. (Found: I=27.18. $C_{20}H_{25}NO_4 \cdot HI$ requires I=26.96%) Hydro-chloride and hydrobromide is too hygroscopic for the analysis.

Iodomethylate: is prepared in methyl-alcohol without heating. It melts at 212° with decomposition. Halochromy is same as above.

Anal. Found: C=51.93, 51.98; H=5.76, 5.98; N=2.99; Methoxyl=12.48; I=26.09%. $C_{21}H_{28}NO_4I$=484.9 requires: C=51.96; H=5.77; N=2.89; Methoxyl=12.78; I=26.17%.

Sp. rotatory power, measured in water: $[\alpha]_D^{17}=(-0.11\div0.3333)\times(50\div0.5)=-33.00°$

Oxime: prepared in the ordinary way at room temperature. Recrystallisable from methylalcohol and ether into prisms collected in rosettes. Decomposes at 204~205° (losing water at 120°). (Found: N=7.79%. Calc. for the monoxime: N=7.82%).

Decomposition of the achro-methine with 66% KOH resp. with benzoyl-anhydride gave the same sinomenol resp. dibenzoyl-sinomenol as with sinomenine itself, the yield also being almost equal with the latter. The amine, evolved in the potash fusion, was also dimethyl-ethyl-amine. (The auri-chloride decomposed at 220° and the platini-chloride decomposed at 239°).

2. Sinomenine-roseo-methine. [IV]. The free base of this substance is formed, when the sinomenine iodo-methylate is decomposed with 5% NaOH (5 mol). But from the crude achro-methine, recrystallized from alcohol and kept for years, it was accidentally isolated in ca. 10% yield. The change might have been effected through the sodium bicarbonate, attached to the crystalls. This point was made clear with their iodomethylates. (See later on).

It is yellowish, melts at 163° and gives an intense red (carmin) halochromy in conc. H_2SO_4 and an yellowish red in fuming HCl. It is, therefore, called sinomenine-roseo-methine.

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

Anal. Found: C=69.78; H=7.16; N=4.10; CH_3O-=18.24%. $C_{20}H_{25}NO_4$=343 requires: C=69.97; H=7.28; N=4.08; CH_3O-=18.07%.

Sp. rotatory power, measured in chloroform:

$$[\alpha]_D^{16}=(+1.03\div0.0759)\times(10\div1)=+135.70°$$

Iodomethylate. It was first noticed that the iodomethylate of the crude achro-methine, when prepared by boiling in methyl-alcohol, contains sometimes the iodomethylate of the roseo-methine. Therefore, in order to transform the iodomethylate of the achro-methine into that of the roseo-methine, the former was boiled in ten times its weight of methyl alcohol with a bit of sodium bicarbonate for one hour and was set aside, after being filtered from the bicarbonate. On the next day, the crystalls deposited on the bottom was collected and recrystallized from methyl alcohol. It forms yellow long prisms, which melt and decompose at 276°. Admixture with the iodomethylate obtained in 1926, did not lower the melting point. Halochromy is the same with the free roseo-methine.

Anal. Found: $C=52.05$; $H=5.88$; $N=2.84$; $CH_3O=12.42$; $I=26.05\%$.
$C_{21}H_{28}NO_4I=484.9$ requires: $C=51.96$; $H=5.77$; $N=2.89$; $CH_3O=12.78$; $I=26.17\%$

Sp. rotatory power, measured in water: $[\alpha]_D^{17}=(-0.25\div0.1295)\times(25\div1)=-48.26°$

To prove the point, that the sodium bicarbonate effect this change, the pure achro-methine iodo-methylate was boiled in methyl alcohol without the addition of $HNaCO_3$. It was found that the iodomethylate, chrystallized out from the solution gave only the faintly yellow halochromy and melted also at 212°.

The yield of the roseo-methine was not good and the decomposition trial was not carried out with it. But the fact that it stands between the achro- and violeo-methines was proved by turning its iodomethylates into that of the violeo-methine by the action of cold 10% NaOH.

The only anormality of this methine is in the very diminished diazo-reaction, compared with the other sinomenine derivatives with the free C(1). We hope to clear away this question by a further study in a near future.

3. **Sinomenine-violeo-methine.** [V]. It was noticed, at the beginning of the study of sinomenine, that the action of boiling caustic alkali turns sinomenine into the substance which gives an intense bluish halochromy with conc. H_2SO_4. The substance, which is the cause of this colour, as well as its iodomethylate were isolated six years ago. This time, it was obtained from the achromethine and the relation was clearly settled.

When the achro-methine (1 gr.) is kept overnight in 10% NaOH (8 c.c.) and methyl-alcohol (4 c.c.) and then saturated with CO_2 gas, a precipitate is formed in the ice-cooled solution. This is collected and crystallized from chloroform by the addition of much ether. Yield about 20%, but, as will be described later, the change is almost the theoretical with the iodomethylate. It forms flat prisms and melts at 172~173°. It gives an intense blue halochromy with conc. H_2SO_4 as well as with fuming HCl. Hence the name sinomenine-violeo-methine is given.

The properties of this substance is given in the third column of the Table 1.

Anal. Found: $C=70.03, 69.32$; $H=7.25, 7.20$; $N=4.23$; $CH_3O{-}=18.19\%$.
$C_{20}H_{25}NO_4=343$ requires $C=69.97$; $H=7.28$; $N=4.08$; $CH_3O{-}=18.07\%$
Sp. rotatory power, measured in chloroform:

$$[\alpha]_D^{17}=(+0.19\div0.2185)\times(250\div0.5)=+434.78^\circ$$

The iodomethylate is formed from that of the achro-methine in an almost theoretical yield by the action of the cold 10% NaOH (5 times). The change seems to be complete in a few hours, judged from the halochromy, but the mixture is better to be left stand overnight for the precaution. It is well cooled with ice and saturated with CO_2 gas. As this substance is most difficultly soluble in water of the three, it crystallises out almost completely. It is colourless prisms collected in a form of a fun. M.p. 209° (dec., from water). Halochromy is the same as the free methine.

Anal. Found: $C=51.84, 51.85, 51.60$; $H=6.01, 6.11, 6.20$; $N=2.99$; $CH_3O=12.64$; $I=26.29\%$. $C_{21}H_{28}NO_4I=484.9$ requires: $C=51.96$; $H=5.77$; $N=2.89$; $CH_3O=12.78$; $I=26.17\%$.

Sp. rotatory power, measured in water: $[\alpha]_D^{17}=(+0.30\div0.1607)\times(100\div0.5)=+373.36^\circ$

The violeo-methine iodomethylate is already decomposed into sinomenol by boiling 3.3% NaOH for an hour (m.p. 172°). The use of 20% NaOH in this decomposition turns the greater part of sinomenol into disinomenol. This easy splitting off of the side chain is undoubtedly due to the strong tendency to aromatize of the nuclei II and III of the hydrated phenanthrene, since it contains a ketone group, which can enolize in presence of alkali. This is the reason why we must effect the transformation of the achro-methine into the violeo-methine in the cold.

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