Studies on Sinomenine.

Part LXVIII. (+)-*Codeinone from Sinomenine.*

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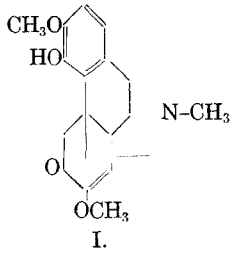
Received March 11, 1955

A short survey of sinomenine investigation is given in the theoretical part, principally on the transformation of sinomenine derivatives, hitherto almost unnoticed in morphine derivatives. In experimental, the preparation of (+)-codeinone from sinomenine, reduction of 1-bromocodeinone and similar compounds with $SnCl_2$+HCl, and the use of $NaBH_4$ on the reduction of the ketonic group in sinomenine derivatives are described.

Theoretical (K. G.)

Sinomenine (I) is the principal alkaloid of *Sinomenium acutum Rehd et Wils.* (Menispermaceae), a native climbing plant of south Japan. Its constitution was elucidated by the study of H. Kondo and E. Ochiai[1] on one side and of K. Goto[2] on the other, though its synthesis[3] was not yet realized. From sinomenine the following optical antipodes of morphine group were prepared and many of them[4] were well racemized with those corresponding substances derived from thebaine and codeine.



I.

(1) (+)-Dihydrothebainone
(2) (+)-Dihydrothebainol
(3) (+)-Tetrahydrodesoxycodeine
(4) (+)-7-Oxy-dihydrothebainol
(5) (+)-1-Bromosinomeninone
(6) (+)-α-Dihydrosinomeninone[4a]
(7) (+)-β-Dihydrosinomeninone
(8) (+)-Tetrahydrosinomeninone
(9) (+)-and (−)-7-Oxy-dihydrocodeine
(10) (+)-Desoxycodeine-D
(11) (+)-Dihydrocodeinone
(12) (+)-Dihydrocodeine[4b]
(13) (+)-Dihydromorphine[4b]
(14) (+)-Codeine
(15) (+)-Codeinone
(16) (+)-Morphine

The work to prepare (+)-meta-thebainone, (+)-thebenine and (+)-morphothebaine is now going on in the author's laboratory.

1) H. Kondo and E. Ochiai: *Ann.* **470**, 224 (1929) and others papers in *J. pharm. Soc. Japan* (1929-1930).

2) 68th communications up to present, many of which are cited in this synopsis.

3) Robert Robinson: *Madrid Lecture.*

4) In some cases, the preparation of (−)-substance was renounced, on account of the shortage of materials.

4a) K. Goto and Y. Shibasaki: *Ann.*, **503**, 277 (1933).

4b) K. Goto and Tatsuo Arai: *Ann.*, **547**, 194 (1941).

As the detailed description of the determination of the constitution of sinomenine was reported in our former papers, here we wish to limit ourselves to survey the principal results obtained in our research and those reactions which were not hitherto observed by the other workers in morphine group.

From Sinomenine to (+)-Morphine

Since the establishment of the fact that sinomenine is an optical antipode of morphine group, our main object of the study was to derive (+)-morphine from sinomenine and to study its physiological properties.

The elemental synthesis of (−)-morphine was accomplished by Gates and his co-workers[5] in 1952, but it did not daunt our long cherished project. As our former trials to reach (+)-morphine from several sides (including from (+)-dihydrothebainone) were all fruitless, we took up Gates's method, which used 2,4-dinitrophenylhydrazine to fix the ketone group of the brominated dihydrothebainone. Our method[6] modified that of Gates in several minor points and was shown in the following diagram.

Sinomenine $\xrightarrow{\text{Cat. red.}}$ Dihydrosinomenine $\xrightarrow{Na\text{-}Hg}$ (+)-Dihydrothebainone $\xrightarrow{+3Br_2}$ 1,5,7-Tribromo-(+)-dihydrothebainone ⟶ 2,4-dinitrophenylhydrazone $\xrightarrow[\text{and cleavage}]{\text{Pyridine (heat)}}$ 1-Bromo-(+)-codeinone $\xrightarrow{LiAlH_4}$ (+)-Codeine $\xrightarrow{\text{Pyridine-HCl}}$ (+)-Morphine

Or alternatively,

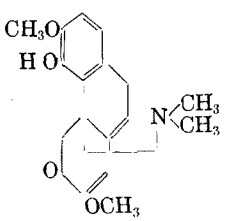
(+)-Dihydrothebainone $\xrightarrow[\text{Alkali}]{+2Br_2}$ (+)-1-Bromo-dihydrocodeinone $\xrightarrow{+Br_2}$ 1,7-Dibromo-(+)-dihydrocodeinone ⟶ 2,4-dinitrophenylhydrazone $\xrightarrow[\text{and cleavage}]{\text{Pyridine(heat)}}$ (+)-1-Bromo-codeinone

The over-all yield of (+)-morphine from sinomenine was 0.2% at best. A better method must be devised to prepare enough material in order to proceed to its pharmaceutical study.

Three Sinomenine-methines[7]

Sinomenine gives three kinds of methine, viz., color reaction with conc. H_2SO_4

(1) Sinomenine achromethine (II) almost colourless
(2) „ roseomethine (III) red
(3) „ violeomethine (IV) deep blue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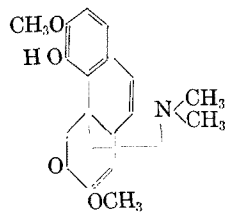
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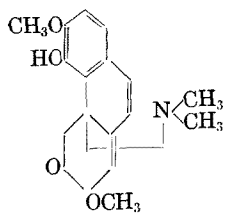

IV.

Achromethine is formed, when sinomenine methiodide is boiled with the calculated quantity of 2% NaOH for one minuite. A longer boiling turns it into roseomethine. As achromethine takes no colouration with conc. H_2SO_4, the author assumes its double bond to be in $C_9 \sim C_{14}$. Achromethine is turned on long keeping into roseomethine, whose second double bond is supposed to be between $C_9 \sim C_{10}$, because of its red colour reaction with conc. H_2SO_4. Keeping achromethine in

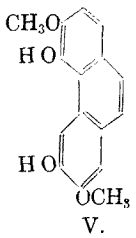
5) M. Gates and G. Tschudi: *J. Am. Chem. Soc.*, **74**, 1109 (1952).

6) K. Goto and I. Yamamoto: *Proc. Japan Acad.*, **30**, 769 (1954).

7) K. Goto and H. Shishido: *Bull. Chem. Soc. Japan*, **6** 76 (1931).

10% KOH overnight turns it into violeomethine, perhaps the two double bonds being at $\Delta^{8,14}$ and $\Delta^{9,10}$.

As to the colouration of substances with conc. H_2SO_4, there are studies of Schöpf[8] on meta-thebainone and of Kuhn[9] on diphenyl-polyene. Author's experience shows also that all des-N-methyl-bases of sinomenine derivatives give red colouration with conc. H_2SO_4, but their dihydrodes-N-methyl-bases do not. Well known red colouration of thebenine with conc. HCl disappears[10], when it is hydrogenated on its $\Delta^{9,10}$. Those derivatives of sinomenine, whose conjugated double bonds are assumed to be also conjugated with benzene nucleus take blue colour with conc. H_2SO_4.

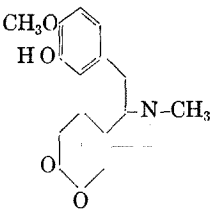


V.

Sinomenine or its methiodide is decomposed into sinomenol, namely, 3,7-dimethoxy-4,6-dioxy-phenanthrene (V), by boiling with 66% caustic soda for one hour[11]. The liberated amine is methyl-ethyl- resp. dimethyl-ethyl-amine.

Sinomeninone and Sinomeninic acid

Sinomenine is easily hydrolyzed on its enol-methoxyl and gives sinomeninone (VI)[12]. Sinomeninone, an α-diketone, is again easily oxidized by 30% H_2O_2 into sinomeninic acid[13], in which hydrolyzed ring (III) of sinomenine is opened. By catalytic reduction with $PdCl_2$, sinomeninone gives α- and β-dihydrosinomeninones, α- being 6-keto-7-ol (VIII) derivative and β- being 7-keto-6-ol (IX) substance. This relation was well established by the hydrolysis of sinomeninol (X), which was obtained by $LiAlH_4$ reduction of sinomenine and gave exclusively β-dihydrosinomeninone[14]. On the contrary, the both ketone groups were reduced by PtO_2 as catalyst and tetrahydrosinomeninone was formed. By boiling tetrahydrosinomeninone with 55% sulphuric acid, a new (+)-dihydrothebainone was isolated, which was totally



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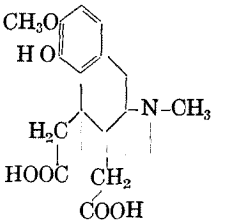

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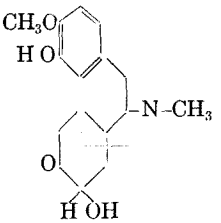

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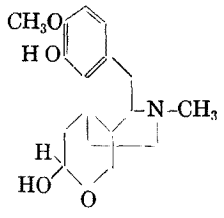

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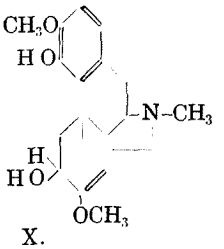


X.

different from the known (+)-dihydrothebainone and we regarded it as (+)-

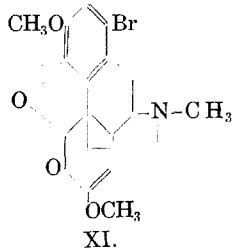
8) C. Schöpf and Borkowsky: *Ann.*, **458**, 148 (1927).
9) R. Kuhn: *Helv. Chim. Acta.*, **13**, 64 (1930).
10) K. Goto, H. Shishido and K. Takubo: *Ann.*, **497**, 295 (1932).
11) K. Goto, H. Sudzuki: *Bull. Chem. Soc. Japan.*, **4**, 163 (1929).
12) K. Goto and H. Sudzuki: *Bull. Chem. Soc. Japan.*, **4**, 271 (1929).
13) K. Goto, K. Takubo and S. Mitsui: *Ann.*, **494**, 1 (1932)
14) K. Goto, I. Yamamoto: *Proc. Japan Acad.*, **29**, 513 (1954).

dihydrothebainone-7[15].

Sinomeninic acid, its derivatives and (−)-tetrahydrosinomeninone were also obtained from (−)-1-bromosinomeninone and were racemized with corresponding (+)-derivatives.

1-Bromosinomeneine

This substance was prepared by the bromination of sinomenine with two molecules of bromine. By elemental analysis, it was proved that it contained only one atom of bromine and at the same time three hydrogen atoms less than sinomenine[16]. While the author was reserving a decision on its constitution, C. Schöpf succeeded to close the oxide ring in (−)-dihydrothebainone by bromination and suggested that the 1-bromosinomeneine must have the oxide ring closed. The author, hereupon, took out, by its decomposition with dimethyl sulphate and alkali, a morphenol (XVII) derivative, instead of morphol derivative and verified Schöpf's suggestion[17]. 1-Bromosinomeneine, as an optical antipode of hypothetical 1-bromo-7-methoxy-(−)-codeinone, shows many peculiar characters,



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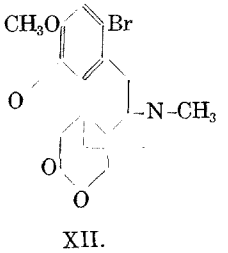
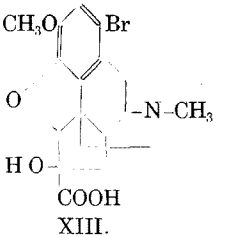


XII.

some of which will be reported here shortly.

Sinomenilic acid; Naphtindene alkaloids

1-Bromosinomeneine is also hydrolyzed into 1-bromosinomeneine ketone (XII)[17] in the same treatment as with sinomenine. But this epoxy-6,7-diketone undergoes very easily benzilic acid transformation, when it comes in contact with cold, dilute caustic alkali. The here obtained 1-bromosinomenilic acid loses formic acid by cold fuming sulphuric acid and is transformed into 1-bromosinomenilone[18]. The debrominated substance is a new type of alkaloids, which has a naphtindene skeletone[19]. The oxide ring of sino-



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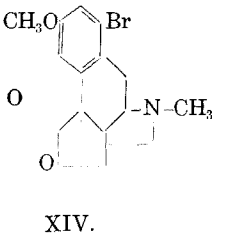

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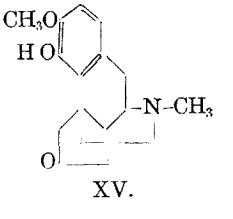


XV.

menilone is opened by sodium amalgam and gives dihydrosinomenilone (XV), which in turn was decomposed by Hofmann's method into a thebenone analogue. But, this nitrogen free substance, in the way of preparation, loses one molecule of water from its two molecules and is condensed into anhydro-bis-sinomelone, which was strongly laevorotatory.

The ketone oxygen of dihydrosinomenilone was replaced by two chlorine atoms and then by two hydrogen atoms. The obtained dihydrosinomenilane is also

15) K. Goto and K. Michi: *Bull. Chem. Soc. Japan*, **22**, 262 (1949)

16) K. Goto and T. Nambo: *Bull. Chem. Soc. Japan*, **5**, 165 (1930).

17) K. Goto, K. Takubo and S. Mitsui: *Ann.*, **489**, 86 (1931).

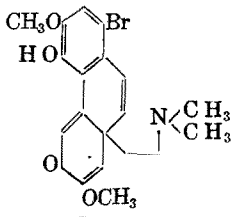
18) K. Goto, H. Shishido and K. Takubo: *Ann.*, **495**, 122 (1932).

19) K. Goto and K. Takubo: *Ann.*, **499**, 169 (1932).

decomposed into sinomelane and dihydro-sinomelane (monomolecular)[20].

des-N-Methyl-1-bromo-dehydro-meta-sinomenine

The second remarkable disintegration of 1-bromosinomeneine was found in its methiodide[21]. When the latter was treated with cold, 0.2% caustic soda, it was transformed momentaneously into des-N-methyl-1-bromo-dehydro-meta-sinomenine (XVI). When we carried out this reaction with 10% NaOH at 100°, we obtained a cinnabar red Na-salt of the oxy-quinone. This des-N-methyl-base was decomposed by boiling caustic soda solution into 1-bromosinomenol, namely 1-bromo-4,6-dioxy-3,7-dimethoxy-phenanthrene quantitatively. This shows that the ethanamine chain must be attached to C_{13} or C_{14} in this substance. In the oxy-quinone formula this side chain could not stand at C_{13}, and we assumed its location at C_{14}. This easy disintegration reminded us of Knorr's observation that methiodide of codeine was too labile to be recrystallized from water[22].



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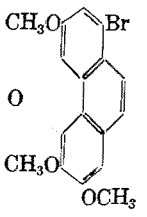

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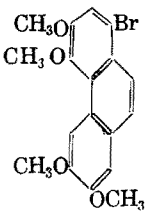


XVIIa.

This disintegration explains clearly the fact that in the Hofmann decomposition of 1-bromosinomeneine with dimethylsulphate and caustic soda, we sometimes obtained morphenol (XVII) and sometimes morphol (XVIIa). If the above transformation happened before the decomposition we obtained only morphol derivative, but when the ketone group at C_6 was first transformed into enol-methoxyl, then the oxide ring would be kept intact and we obtained morphenol derivative.

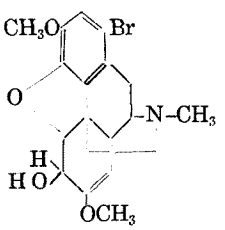
The last fact induced us to try Hofmann decomposition of sinomenine derivatives with dimethyl sulphate and alkali at lower temperature (70°). We obtained 1-bromosinomenol dimethyl ether from 1-bromosinomenine in a good yield, but sinomenine itself gave bimolecular phenanthrene, which was different from the known disinomenol dimethyl ether, perhaps two molecules having been linked together at C_5, in an ortho position to a newly formed phenol group. This linking of oxy-phenanthrene in para or ortho position by warming with dilute caustic alkali, seems to be a general reaction. Pure sinomenine gives in the alkalysis with 66% NaOH, a small quantity of disinomenol. Acetyl thebaol gives bis-1,1'-dithebaol in 45% yield, when warmed with 10% alkali on a water bath while stronger alkali (50% KOH) had no similar effect on it[23].

1-Bromosinomeneine alcohol

By Meerwein-Pondorf reduction of 1-bromosinomeneine, we obtained 1-bromosinomeneine alcohol (XVIII)[24]. The fact that in the latter substance the

20) K. Goto and H. Shishido: *Ann.*, **507**, 296 (1933).
21) K. Goto, T. Arai and T. Odera: *Bull. Chem. Soc. Japan*, **17**, 393 (1942).
22) Ach, Knorr: *Ber.*, **36**, 3067 (1903).
23) K. Goto, T. Arai and T. Odera: *Bull. Chem. Soc. Japan*, **18**, 116 (1943).

original ketone group was reduced to a secondary alcohol was proved by the reformation of the 1-bromosinomeneine through its oxidation by CrO_3 or $KMnO_4$ and by Oppenauer's method. One very remarkable property of this alcohol is that, when it comes in contact with cold dilute hydrochloric acid, it is transformed into 1-bromosinomeninone (XIX) in a few minutes. This may be explained by the hydrolysis of enol methoxyl, α-ketol-transformation and then opening of the oxide ring. We often experienced that, in the alkaloids of sinomenine type with a ketone group on C_6, an oxide ring and a hydroxyl or methoxyl on C_7 can not co-exist, and they are converged into one ketone group on C_7. Thus, dihydrosinomenine can not close the oxide ring by dibromination, but gives 1-bromosinomeninone. This fact is rather contrasted with the stability of 1-bromosinomeneine ketone, 7-oxy-dihydrocodeine and 7,8-dioxy-dihydrocodeine. Anyhow, the above mentioned transformation is very remarkable, because such a complex reaction is accomplished by such a mild reagent so rapidly.



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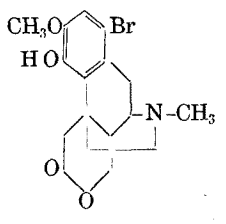
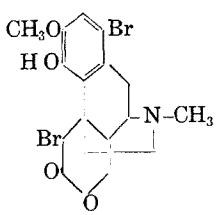


XIX.

Acetolysis of 1-Bromosinomeneine ketone

By boiling with acetic anhydride, 1-bromosinomeneine ketone or 1,5-dibromosinomeninone (XX) is decomposed into 1-bromo-3-methoxy-4,6,7-triacetoxy-phenanthrene and diacetyl-1-bromo-dehydrosinomeninone[24a] (XXI). The latter substance was isolated as methiodide (the free base was not crystallizable). This methiodide was decomposed into des-N-methy-1-bromo-dehydrosinomeninone by mild treatment with caustic alkali. This des-N-methyl-base contains only one optical centre at C_{13} and is strongly dextrorotatory, $[\alpha]_D = +283.9°$. By the treatment of the diacetyl methiodide with dimethyl sulphate, alkali and potassium iodide, we obtained methiodide of des-N-methyl-1-bromo-dehydro-sinomeninone dimethyl ether. This substance, as well as des-N-methyl-1-bromo-dehydrosinomeninone, gave deep blue colour with conc. sulphuric acid. This colour reaction seems to be characteristic in sinomenine derivatives when two double bonds are conjugated to the benzene nucleus. We assume, therefore, a new double bond, which was introduced by fission of the oxide ring, was shifted to $C_{8\sim14}$. If this assumption is true, it is noteworthy that such a shifting occurred over the ethanamine chain. It is only explicable by assuming an intermediate three or



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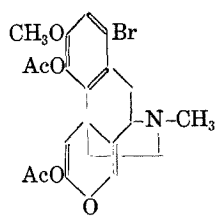
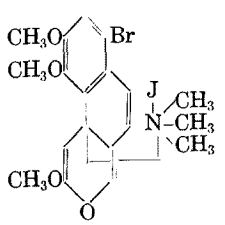


XXI.



XXII.

24) K. Goto, T. Arai and T. Kono: *Bull. Chem. Soc. Japan*, **23** 17 (1950).

24a) K. Goto, R. Mori and T. Arai: *Bull. Chem. Soc. Japan* **17**, 439 (1942).

four membered ring formation. The above methiodide of des-N-methyl-dimethyl ether gave by acetolysis a good yield of 1-bromo-7-acetoxy-3,4,6-trimethyl-phenanthrene.

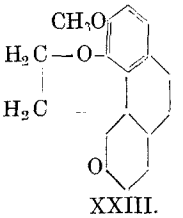
The reaction, here explained, was carried out also with (−)-1,5-dibromo-sinomeninone from thebaine. All the corresponding derivatives were racemized with those from sinomenine.

(−)-Thebenone; a new proposal

Thebenone (XXIII) was first prepared by Wieland and Kotake[25] by the Hofmann decomposition of (−)-dihydrothebainone. We have prepared five thebenones from sinomenine derivatives as shown in Table I.

Table I.

	(+)-2H-thebainone[26]	2H-sinomenine[27]	(+)-4H-des-oxycodeine[28]	(+)-1-Br-2H-thebainone[29]	Sinomeninone-furazane[28]
Base	+ 59°	+194°	+ 43°	+ 79°	+136°
des-N-base	− 55°	− 84°	− 65°	− 8°	+ 50°
2H-des-N-base	+ 68°	+ 2°	+ 78°	+ 61°	+ 22°
Dehydrothebenone	−207°	−286°	−178°	−186°	−485°
Thebenone	− 79°	−148°	− 3°	− 23°	−120°



XXIII.

It is noteworthy that the optical rotation changes its sign stepwise from base to thebenone. Thebenone from sinomenine (+) is laevorotatory, while thebenone from thebaine (−) is dextrorotatory. Here some confusion on the original substance occurrs, if we simply designate them as (+) or (−)-thebenone. We propose therefore in the study of sinomenine or morphine, we should prefix D to the derivatives of sinomenine and L to those of morphine group in necessary case. Thus if we designate thebenone from sinomenine as D-thebenone (−) and that from thebaine as L-thebenone (+), there could be no confusion. Further examples will be furnished later.

This nomenclature was already adopted in cases of amino acids and monosaccharides. We hope this proposition would be taken into consideration by organic chemical circles.

(+)-True Thebainone

Sinomenine is laevorotatory. But when its double bond is reduced, it becomes invariably dextrorotatory. These dextrorotating derivatives are always the optical antipodes of morphine derivatives, if in the latter series the corresponding compounds exist. From this fact, it is beyond doubt that the skeleton of sinomenine is the optical antipode of that of morphine group. The laevorotation of sinomenine seemed therefore to be caused by its double linking[30].

In 1931, C. Schöpf[30] prepared true thebainone (XXIV) from thebaine. L. Small[31] and K. Goto[32] found that it was laevorotatory. This showed that if we

25) H. Wieland and M. Kotake: *Ann.*, **444** 88 (1925).

26) K. Goto, R. Inaba and H. Shishido: *Ann.*, **485**, 247 (1931).

27) K. Goto and H. Shishido: *Bull. Chem. Soc. Japan*, **6**, 231 (1931).

28) K. Goto and S. Mitsui: *Bull. Chem. Soc. Japan*, **6**, 197, (1931).

29) K. Goto, H. Ogawa and J. Saito: *Bull. Chem. Soc. Japan*, **10**, 481 (1935).

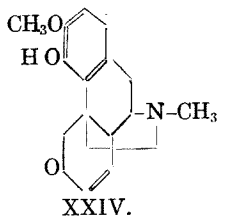
30) C. Schöpf and H. Hirsch: *Ann.*, **489**, 244 (1931).

31) L. Small and D.E. Morris: *J. Am. Chem. Soc.*, **54**, 2122 (1932).

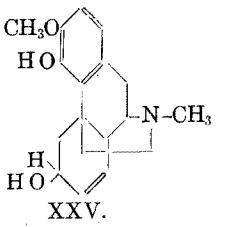
32) K. Goto and H. Ogawa: *Ann.*, **511**, 202 (1934).

could prepare 7-demethoxysinomenine, it must turn the plane of polarization to right. K. Goto and I. Yamamoto[33] prepared recently 7-demethoxysinomenine from α-dihydrosinomeninone and found that it was dextrorotatory and well racemized with Schöpf's true thebainone. The laevorotation of sinomenine seems, thus, not to be caused by double linking, but caused by the enol-methoxyl attached to the double bond. Such action of methoxyl which stands in β- or γ-position to the optical centre, on the invertion of optical rotation is, we think, rather noteworthy.

We can add one more instance, hitherto to have been met with, in which sinomenine derivative showed laevorotation. The 7-demethoxysinomeninol (XXV) which was prepared by $LiAlH_4$ reduction of 7-demethoxysinomenine[34] showed laevorotation, and racemized with (+)-thebainol from true thebainone. Here the rotation is inverted in morphine and sinomenine group. This is one of the reasons in our proposal to prefix their names with L- or D- in necessary cases.



XXIV.



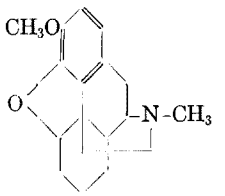
XXV.

Two new ring closures

(1) When α-dihydrosinomeninone (VIII) was boiled with 50% sulphuric acid at 130° for one hour, we obtained (+)-dihydrocodeinone in 50% yield[35]. Dihydrosinomenine behaved also perfectly in the same way. This remarkable reaction may be explained by the anionotropy of hydroxyl group, which stands in α-position to ketone. If we assume the ketone group enolized, then this anionotropy is similar to the geraniol-linalool transformation. R. Robinson explained the codeine-pseudocodeine transformation on the same basis[36].

β-Dihydrosinomeninone gave (+)-dihydrocodeinone also in the same way. In this reaction α-ketol transformation must preceed the anionotropy.

XXVI.



(2) When (+)-dihydrothebainol was treated in the same way, the oxide ring was also closed and we obtained (+)-dihydrodesoxycodeine-D (XXVI). This reaction seems to have been brought about by the introduction of a double bond between $C_5 \sim C_6$ and then the addition of phenol group to this double linking.

Bimolecular alkaloids of Disinomenine type

Disinomenine (XXVII) was first isolated by the spontaneous decomposition of the gold chloride double salt of sinomenine hydrochloride and afterwards from the plant itself. The alkaloid is bimolecular and the linking position is assumed to be in 1,1′, because of the strong decrease of the diazo-reaction of sinomenine, which is still noticeable in 2,000,000th dilution with diazobenzene sulphonic acid. Other alkaloids of sinomenine type (OH in 4, H in 1) can be linked together in the same way with mild oxidizing agents, such as

33) K. Goto and I. Yamamoto: *Proc. Japan Acad.*, **29**, 210 (1953).

34) K. Goto and I. Yamamoto: *ibid.*, **29**, 457 (1953).

35) K. Goto and K. Michi: *Acta Phytochimica* (**1949**) 183, 187.

36) Gulland and Robinson: J. Chem. Soc., 123, 980 (1923).

gold chloride, silver nitrate, ferric chloride, potassium ferri-cyanide and alkali, dilute permanganate and dilute hydrogen peroxide. The linking was tried with the following seven alkaloids and we obtained always a pair of the bimolecular alkaloids. The relation of these alkaloids are shown by arrows in Table II.[37]

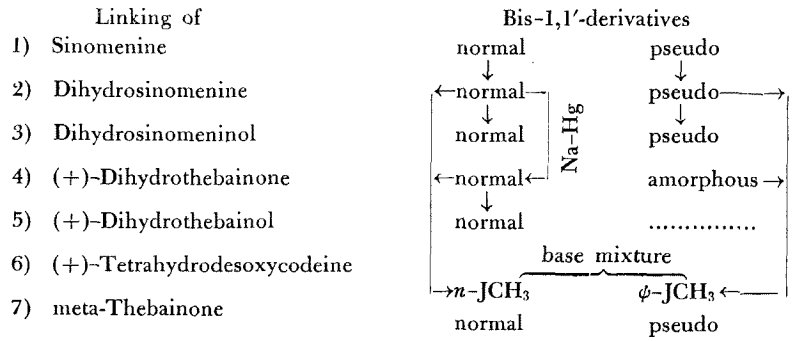
and in the other case *en dos*. In other words, the two alkaloids are only different in the way of overlapping of the ethanamine chains (I and II).

A———·····B A·····———B

I II

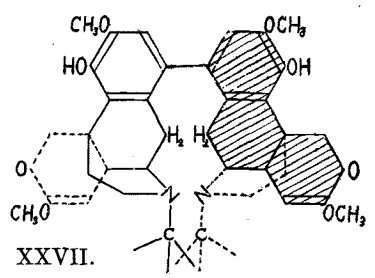
But when the formula I wants to become II, one of the component must

Table II.



Note 1) Short, vertical arrows show catalytic reduction.
2) Long arrows on both sides indicate Clemmensen reduction.
3) Normal series forms crystallizable hydrochloride, but pseudo series does not.
4) Bis-1,1′-sinomenine, whose hydrochloride is crystalline, is natural and we call this series normal.

As to the cause of the existence of these pairs, we came now to the assumption that it is a similar, but a particular case of the stereoisomerism of the substituted diphenyls. Only the difference is that in this case the hindering facter of free rotation is the ethanamine chains, instead of ortho substituents of diphenyl nucleus. In linking of these alkaloids, two molecules can be linked together in two ways, namely in one case *en face*



XXVII.

rotate ca. 360 degrees (in extreme case) and we imagine that this farreaching free rotation is greatly hindered by some reason hitherto unknown. This assumption seems to have been proved partly by the Hofmann decomposition. *n*- and *φ*-bis-1,1′-(+)-tetrahydrodesoxycodeine gave the same bis-1,1′-des-N-methyl-base, the same bis-1,1′-dehydrothebenane and the same bis-1,1′-thebenane. The identity of respective derivatives from both sources was proved by the m.p., specific rotatory power and ultraviolet absorption. The same was true of the bis-1,1′-dihydrosinomenine.

Bis-1,1′-sinomenines and bis-1,1′-metathebainones[38] are not fitted for this decomposition, as they gave the same bimolecular phenanthrene respectively. But the fact that only one form is

37) K. Goto, I. Yamamoto and S. Mastumoto: *Proc., Japan Acad.*, **30**, 883 (1954); *Bull. Agr. Chem. Soc. Japan*, **19**, 1 (1955).

38) K. Goto and Z. Kitasato: *Ann.* **481**, 81 (1930).

hitherto known in pseudomorphine seems to be of value in our argument. If it is linked together in 2,2 -position as we assume, the overlapping difference of ethanamine chains can not occurr.

Experimental (I. Y.)

(1) 2,4-Dinitrophenylhydrazone of (+)-1-bromocodeinone.

(+)-Dihydrothebainone (2 g.) was brominated (3.2 g. Br_2; 3 mol.) in glacial acetic acid (20 cc). To this solution, dinitrophenylhydrazine (1.44 g; 1.1 mol.) was added. After the latter dissolved, fused sodium acetate (1.1 g; 2 mol.) was added to fix free hydrogen bromide. The whole was then incubated at 28° for 20 hours and the acetic acid was removed i.v. at 50°. Seven lots of the residue were united and boiled with 140 cc of pyridine for 30 min. (bath temp. 130-140°). Pyridine was distilled i.v. and the residue was taken up in much chloroform. The chloroform was washed many times with 10% NaOH, and the remaining pyridine was removed by washing with 10% HCl. The dinitrophenylhydrazone remained in chloroform in this operation. The chloroform was washed with soda, dried and concentrated and passed through a column of Al_2O_3. The elution was done also with chloroform. From the residue of chloroform evaporation, the required dinitrophenylhydrazone crystallized out on addition of ethyl acetate. Yield 47% of theory.

(2) (+)-Codeinone. As Oppenauer's oxidation of (+)-codeine into (+)-codeinone failed[39], we returned to the original method of Knorr (*Ber.*, **36**, 3067 (1903)). Yield 0.1 gr. from 0.8 gr. (+)-codeine. M.p. 185° after two recrystallizations from ether. $[\alpha]_D^{14}=+206.0°$ (c 0.334, alc.). (*Anal.* Calcd. for $C_{18}H_{19}O_3N$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.49; H, 6.15; N, 4.79).

(3) d,l-Codeinone. 0.013 gr. each of (−)- and (+)-codeinone (m.p. 185° in both substances) were dissolved in ethyl acetate+ether and the residue of the evaporation of the solvent was twice recrystallized from acetone. M.p. 175°, $\alpha=\pm 0°$ (c 0.2, alc.).

(4) Reduction of 1-bromosinomenine derivatives with $SnCl_2$ and HCl.

Through reducing with stannous chloride and hydrochloric acid, (+)-1-bromocodeinone gave unexpectedly (+)-dihydrothebainone, instead of (+)-1-bromometathebainone. The reduction of nuclear halogen atom, which stands in ortho or para position to phenol group, was already reported by H. Burton (*J. Chem. Soc.*, **1945**, 280). But the influence of the bromine atom in (1) of bromo codeinone on the molecule as a whole is rather surprising.

We tried the same reduction with seven other 1-bromosinomenine derivatives and obtained similar results, as shown in Table III.

(5) Reduction of the ketonic group of sinomenine derivatives with $NaBH_4$. We tried the reduction with following seven substances and the results are summarized in Table IV.

Table III.

	Starting meterial (all (+))	Reduced substance obtained	Yield
1)	1-Bromocodeinone	Dihydrothebainone	30%
2)	1-Bromodihydrothebainone	,,	53%
3)	Tribromodihydrothebainone	,,	33%
4)	1-Bromosinomeneine	β-Dihydrosinomeninone	34%
5)	Sinomenine	,,	57%
6)	1-Bromosinomeninone	,,	31%

1) It was rather curious that we isolated only β-form and not α-form. It was proved that α-form was transformed into β-form by hot hydrobromic acid but the change was not complete (K. Goto and Y. Shibazaki: *Ann.*, **503**, 281 (1933). 2) Efficacy of $SnCl_2$ used in these experiments was proved by transforming (−)-codeinone into (−)-meta-thebainone (Yield ca. 30%).

39) However, Findlay and Small: *J. Am. Chem. Soc.* **73**, 4001 (1951).

Table IV.

	Starting Material (+)	Reduced Substance	Yield (%)	Alternative method
1)	Dihydrocodeinone	(+)-Dihydrocodeine	80	Cat. reduction with PtO_2+ H_2 in MeOH or Pyridine
2)	Bromosinomeneine	Bromosinomeneine alcohol	70	Meerwein-Pondorf's reduction
3)	Sinomenine	Sinomeninol	40	$LiAlH_4$ in 4H-furane
4)	Dihydrosinomenine	Dihydrosinomeninol	70	Cat. red. with PtO_2+H_2 or Na-Hg reduction
5)	Dihydrothebainone	Dihydrothebainol	70	Na-Hg reduction
6)	Sinomeninone	Tetrahydrosinomeninone	60	Cat. red. with. PtO_2+H_2
7)	Bromosinomeneine-ketone	a new substance of m.p. 165° (Yield 60%), which is free from ferric chloride reaction, resistant to 10% NaOH, but is transformed into Bromosinomeninone by 10%HCl. This substance is perhaps 1-bromo-4,5-epoxy-6-hydroxy-7-keto derivative.		

The general procedure of these experiments is as follows. The starting material is dissolved or suspended in 20 times methanol, and is added with excess of $NaBH_4$. Evolution of hydrogen is accompanied. After 2 hours ca. 2/3 of the methanol is evaporated and the base is isolated from the caustic alkaline solution (in case of non-phenolic base) or from the soda alkaline solution.

Note: The experimental part and a part of the theoretical of this paper were read by K. G. in the XIVth International Congress of Pure and Applied Chemistry, Zurich, July, 1955.