On the Reduction of 1-Bromo-sinomeneine*

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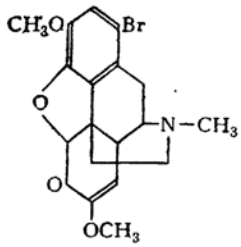
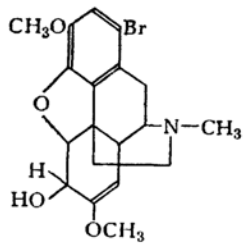
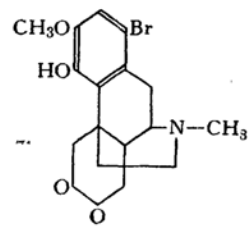
By the catalytic reduction of 1-bromo-sinomeneine (I) in weakly acidic solution, as well as by the sodium-amalgam reduction, its oxide ring is invariably opened and we obtain a mixture of alkali-soluble bases, which is almost inseparable into pure components. However, by the reduction with aluminium isopropylate we obtained a base of m. p. 171°C, to which we give the constitution II and which we will call 1-bromo-sinomeneine-alcohol from the following reasons:



I



II



III

(1) The base of m. p. 171°C is insoluble in 2% caustic soda and gives no ferric chloride reaction.

(2) By benzoylation, it gives a monobenzoyl derivative, but it is not reacted by diazomethane.

(3) It contains two original methoxyl groups, one of which is exceedingly hydrolysable with dilute acid (enol methoxyl).

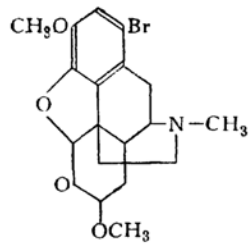
(4) It gives 1-bromo-diacetyl-sinomenol, namely, 1-bromo-3, 7-dimethoxy-4, 6-diacetoxy-phenanthrene, on acetolysis.

The substance of m. p. 171° may be, therefore, an optical antipode of hypothetical 1-bromo-7-methoxy-codeine, for it contains the morphine skeleton and all its functional groups, but superfluous bromine and enol-methoxyl at the same time.

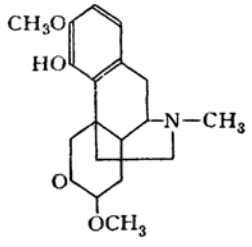
A very remarkable property of this substance is the ease, with which it is converted into 1-bromo-sinomeninone (III). For instance, when the substance of m. p. 171° was dissolved in 2% hydrochloric acid at room temperature and when the solution was immediately made alkaline with sodium carbonate, we obtained 1-bromo-sinomeninone in 64% yield. It seems that the mere dissolution of the substance in a dilute mineral acid effects this deep-seated transformation.

Now, we find several cases of hydrolytical opening of oxide-ring in the chemistry of the morphine group as in the molecular rearrangement of thebaine into thebenine or of morphine into apomorphine. In both cases, a stronger acid (14% or fuming) and a higher temperature (100° or 130°) are necessary. Only in the conversion of β-chlorcodide into β-ethyl-thiocodide, the opening of oxide-ring is effected by 5/2 N caustic soda at the boiling temperature (after Small).

The above-mentioned property of this substance led us to some confusion at the earlier stage of investigation. We supposed at first the substance of m. p. 171° had the constitution IV, namely 1-bromo-dihydrosinomeneine, on the ground that the substance of this constitution could never be obtained by the bromination of



IV (hypothetical)



V

dihydrosinomenine (V), but we always got 1-bromo-sinomeninone (III) instead.[1] We suspected that this might have been due to the easy decomposition of preformed IV into the more stable III.

If it is the case, then the substance of m. p. 171° formed by the reduction, may be decomposed into III by a slight shock, namely by the dilute hydrochloric acid. It may be strange that the ketonic group remains intact, while the double linkage is reduced by Meerwein-Pondorf's method. But Lund[2] gives an instance where ketonic group and α, β-double bond were reduced simultaneously.

In this respect, we applied the above reduction method to sinomenine and 1-bromo-sinomenine, with the results that both these substances were very difficultly reduced on their ketonic group. We recovered some unchanged

* Studies on Sinomenine, Part LXII. Parts LIX and LX, Acta Phytochimica. XV, 183, 187 (1949)

(1) *Ann.*, **489**, 94 (1931)
(2) **Ber., 70,** 1520 (1937)

substances, but could not isolate reduced bases in crystalline state.

Catalytic reduction of 1-bromo-sinomeneine in pyridine solution, using PtO_2 as catalyst, was more fruitful. It gave the substance of m. p. 171° and 1-bromo-dihydrosinomenine, each in a 10-20% yield. This indicates that in some molecules the ketonic group only and in others the double bond as well as the oxide-ring are reduced. However, in sinomenine and 1-bromo-sinomenine the reduction goes on in a somewhat different way. For, we obtained from the former dihydrosinomenine and dihydrosinomeninol, and from the latter, 1-bromo-dihydrosinomenine. Thus the oxide-ring seems to play an important part in the catalytic reduction as well as in the Meerwein-Pondorf's reduction.

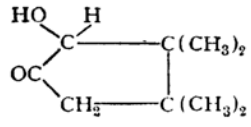
The production of the substance of m. p. 171° in the above catalytic reduction seems to have decided the constitution of this substance in favor of formula II. But the last decision was given by the reformation of 1-bromo-sinomeneine by the oxidation of the substance of m. p. 171° by Pshorr's method. The latter gave on the oxidation with chromic acid as well as with potassium permanganate, the starting material, 1-bromo-sinomeneine, in tolerable yield, viz. 40% resp. 20%.

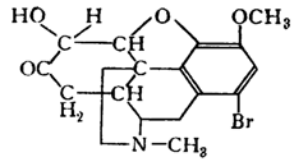
The constitution being thus settled, a problem still remains, why then 1-bromo-sinomeneine alcohol is so unstable towards dilute mineral acid. We do not think that the $C_{(7)}$-situated ketonic group is so efficient as to make the oxide-ring open by such mild treatment. For, we prepare 1-bromo-sinomeneine-ketone by heating 1-bromo-sinomeneine in 10% hydrochloric acid solution for one hour at 100°.[3] The fission of oxide-ring may be, therefore, brought about perhaps by one of the following causes.

(1) The $C_{(6)}$-situated alcohol group may cooperate with $C_{(7)}$-situated ketonic group to open the oxide-ring. The newly introduced alcoholic group may converge to one ketonic group in $C_{(6)}$ to be able to conjugate the ketonic group in $C_{(7)}$. The drawback of this supposition is that we have no similarly constituted morphine alkaloids, and therefore have met with no analogical transformation.

(2) The second theory is based on α-ketol-rearrangement and recurs to the above hypothetical 1-bromo-dihydrosinomeneine (IV). If the $C_{(6)}$-alcoholic and $C_{(7)}$-ketonic group, produced by the hydrolysis of the enol methoxyl, interchanged the position by α-ketol-rearrangement, then the supposed very unstable base IV might be produced, and this may be instantly transformed into 1-bromo-sinomeninone, owing to its supposed unstability.

This transformation, caused by such mild reagent, might at first seem very strange, but the investigation of Ingold and Shoppee[4] on the tautomerism of 1-hydroxy-2, 2, 3, 3-tetramethyl-cyclopentanone-5 seems to throw some light on the above view.





Naturally, there may be some deep difference in the behaviour of 5-membered and 6-membered rings, yet the similarity of the constitution of these two substance is more than apparent. If, by the α-ketol rearrangement, the $C_{(6)}$-ketonic and $C_{(7)}$-alcoholic base is produced from 1-bromo-sinomeneine-alcohol even in a minute quantity and transformed into more stable 1-bromo-sinomeninone, then the reaction, as it is not reversible, may largely proceed in this direction.

The fact that we always obtain 7-hydroxy-derivative only in the catalytic reduction of sinomeninone, an α-diketone, may indicate that the equilibrium is strongly in favor of 7-hydroxy-6-keto-derivative than the reversed one.

Experimental

(1) Preparation of 1-bromo-sinomeneine alcohol

A. With aluminium isopropylate The apparatus was constructed after H. Lund.[2] One and half gram of aluminium-isopropylate was dissolved in 20 cc. isopropyl alcohol and 2g. of 1-bromo-sinomeneine was added. The reduction was carried out on a steam bath and was complete after two or three hours, during which 50 cc. isopropyl alcohol were added in drops. Then the solvent was distilled over and the residue was treated with 11% cold caustic soda solution so as to dissolve the aluminium hydroxide almost completely. The alkaline solution was then shaken with ether four times. When the dried ether was distilled away, 1-bromo-sinomeneine alcohol crystallized out in stout prisms. The crystallisation can be accelerated with addition of alcohol. M. p. 171°. Yield 40-60%. Recrystallization from methanol, alcohol or acetone did not raise the melting point. The substance showed no coloring with ferric chloride in methanol solution.

Analysis Found: C, 56.17; H, 5.422; N, 3.374; CH_3O, 14.93%. Calc. for $C_{19}H_{22}O_4NBr$ (408): C, 55.88; H, 5.39; N, 3.431; CH_3O, 15.20%. Sp. rotation. 0.2055g. subst. was dissolved into 10 c.c. methanol.

$\alpha = +1.10°$ $[\alpha]_D^{19} = 1.10/2.055 \times 100 = +53.530°$.
Mol. weight after Rast. Camphor, 3.274, 3.834, 3.460 mg.; subst., 0.195, 0.336, 0.358 mg. $\Delta = 6.0°$, 8.5°, 10.6°
Mol. weight = 379, 412, 390

(3) This Bulletin, **5**, 165 (1930)
(4) Shoppee, *J. Chem. Soc.*, **1928**, 1667

Methiodide Prepared in methanol solution and recrystallized from water. M. p. 232-233°. Analysis. Found; C, 43.52; H, 4.504; I, 23.01%. Calc. for $C_{20}H_{25}O_4NBrI$: C, 43.64; H, 4.54; I, 23.08%

Once, when the methanol solution was boiled, we obtained the methiodide of 1-bromo-sinomeninone (m. p. 245-246°), instead of that of the original substance. This might be due to the liberation of hydroiodic acid during the reaction. (compare (2))

Monobenzoylester 0.5g. of 1-bromo-sinomeneine alcohol was dissolved in 1 cc. pyridine and benzoyl chloride (1 mol) was added under cooling. The mixture was then set aside overnight and the benzoylated substance was precipitated with water. The precipitate was then collected and recrystallized from the mixture of alcohol and acetone. M. p. 194.5° The yield was ca. 70%. The analysis coincides well with the calculation for monobenzoyl-compound. (Found: C, 61.15; H, 4.89%. Calc. for $C_{26}H_{23}O_5NBr$: C, 60.94; H, 5.08%)

The ester was hydrolysed to the original substance (m. p. 171°), when boiled with sodium carbonate in pyridine.

B. Reduction of 1-bromo-sinomeneine with PtO_2+H_2 in pyridine solution One gram of 1-bromo-sinomeneine was dissolved in 20 cc. of pyridine and 0.05g. PtO_2 was added. In shaking the flask in the hydrogen atomosphere at 1 atm. and 26-27°, ca. 100 cc. hydrogen was absorbed in three hours and the reaction came almost to a standstill. As the pyridine alone had absorbed ca. 40 cc. hydrogen in a blank test, the net volume of hydrogen absorbed amounted to 56.5 cc. (at N. T. P.), corresponding to one molecular equivalent (calc. 55 cc.). The platinum black was then filtered off and the solution was concentrated in vacuum. The residue was dissolved in 5% acetic acid and filtered quickly. The filtrate was made alkaline with 11% caustic soda solution and was shaken four times with ether. The treatment of the ethereal residue was done as described under (A), and 1-bromo-sinomeneine alcohol (m. p. 171°) was obtained in 10-20% yield The m. p. was unaltered by admixture with the specimen prepared by the aluminium isopropylate method.

When the above mentioned caustic soda solution was saturated with carbon dioxide and extracted with chloroform, a substance which melts at 216° was obtained. The melting point was, however, raised to 235°, when recrystallized from chloroform and alcohol. The yield was 10-20%.

It gave a green color with ferric chloride and formed a semicarbazone of m. p 250-256° and methiodide of m. p. 224° (dec.). These facts indicate that we have here 1-bromo-dihydrosinomenine.[5]

(2) Rearrangement of 1-bromo-sinomeneine alcohol into 1-bromo-sinomeninone

This was effected under various concentration of hydrochloric acid with varying yields. The best yield was described in the theoretical part. Dilute acetic acid seems to effect this change very slowly, or not at all. (compare (4)).

(3) Acetolysis of 1-Bromo-sinomineine alcohol

0.7g. of the substance was boiled with 0.7g. of sodium acetate and 7cc. of acetic anhydride for eight hours. After the solution was concentrated to a syrup in vacuum, a quantity of water was added, the precipitate was collected (ca. 0.7g.) and recrystallized from glacial acetic acid. M. p. 186° (also, the mixed melting point with 1-bromo-diacetyl-sinomenol of different origin).

Analysis. Found: C, 55.71; H, 3.921; CH_3O, 13.90%. Calc. for $C_{20}H_{17}O_6Br$: C, 55.43; H, 3.92; CH_3O, 14.31%.

(4) Catalytic reduction of 1-bromo-sinomeneine-alcohol

By the catalytic reduction of 1-bromo-sinomeneine alcohol with Pd-SO_4Ba as catalyst in a weakly acidic (hydrochloric or acetic) solution, we obtained (a) sinomeninone, when only one mol of hydrogen was absorbed, and (b) α- and β-dihydrosinomeninones, when two mols of hydrogen was utilized. Sinomeninone was identified with its melting point (151°, when dried over P_2O_5 in vacuo at 100°), with melting point of the iodomethylate (M. p. 265°), with elemental analysis, with methoxyl determination (two, one from crystal methanol) as well as with its decomposition into 3-methoxyl-4, 6-acetoxyl-phenanthrene. It is clear that the weak acidity of the solution first converted the substance into bromo-sinomeninone and the debromination followed.

α- and β-Dihydrosinomeninone are only the further reduction product of the sinomeninone. The remarkable fact here is that the 2% acetic acid effected the conversion of the substance into the 1-bromo-sinomeninone in this case. Seeing that the time elapsed in this reduction amounted to more than 24 hours and that the debromnation necessarily gave rise to some hydrobromic acid, the above change does not seem to be exceptional.

(5) Reduction of some other sinomenine derivatives with aluminium isopropylate

The experimental condition was the same as was given in ((1) A). The results are summarized as follows:

(i) Sinomenine (4g.) Starting material was recovered more than 50%. No other crystalline substance was isolated from mother liquor.

(ii) 1-Bromosinomenine hydrochloride (6g.) Starting substance was recovered in 10%, besides a small amount of a substance of m. p. 216°, which was not further examined.

(iii) (+)-1-Bromo-dihydro-codeinone (4.4g.) Four grams of non-phenolic base (m. p. 188°) was obtained, but not investigated further.

(iv) 1-Bromo-sinomeninone Reduction took seven hours. Ether took up almost nothing from the caustic alkali solution. Chloroform extraction from soda alkaline solution, gave 2.3g. of mixed bases. Acetylation of this mixture gave a minute quantity of a substance of m. p. 184°. This melting point coincides with that of triacetate of 1-bromo-tetrahydro-sinomeninone prepared for comparision.[6] The mixed melting point was also unaltered. This proves that in 1-bromo-sinomeninone, its both ketonic groups were reduced by aluminium isopropylate in a small degree.

(5) This Bulletin, **4**, 197 (1929)

(6) K. Goto and T. Arai, This Bulletin, **17**, 116 (1942)

(6) Catalytic reduction of sinomenine and 1-bromo-sinomenine with PtO_2+H_2 in pyridine solution

Conducted as given in ((1) B).

(i) Sinomenine (1g.) was reduced with PtO_2 (0.2g.) in 20cc. pyridine. Temperature 25-26°. It took 2-5 hours to absorb 120cc. hydrogen (calc. 136cc. for $2H_2$). Yield: dihydro-sinomeninol (F. 160-162°) in 60%.(7)

(ii) When only 0.05g. PtO_2 was used in the same experiment, one mol of hydrogen was absorbed in three hours. Yield: dihydro-sinomenine (m. p. 198°) in 50-60%. Also, it was identified as oxime (m. p. 212-213°).

(iii) 1-Bromo-sinomenine (1g.) was reduced in the same condition as in (ii). One mol of hydrogen was absorbed in three hours. Yield: 1-bromo-dihydro-sinomenine (m. p. 235°) in 20-30%. Its semicarbazone showed the correct melting point 248-250°.

The reduction seems thus largely to depend upon the quantity of the catalyst used. When the catalyst was used in a small quantity, the reduction stopped after the hydrogenation of the double linkage, while in larger quantity the ketonic group is reduced to alcoholic also. This is a direct contradiction to the reduction of 1-bromo-sinomeneine, in which the ketonic group is reduced in prior to the double linkage. This may be due to the influence of the oxide-ring. We have already met with the similar phenomenon in the aluminium isopropylate reduction (compare (5)).

(7) Oxidation of 1-bromo-sinomeneine alcohol to 1-bromo-sinomeneine

A. With CrO_3. 0.1g. CrO_3 was dissolved in 10 cc. of acetone. One third of this solution was dropped slowly into 10cc. of acetone solution containing 0.2g. of 1-bromo-sinomeneine alcohol, at room temperature. The brown precipitate was filtered off and the filtrate was concentrated until crystals separated. The crystals (m. p. 180-200°) were dissolved in chloroform and the solution was washed with dilute caustic soda. To the concentrated chloroform solution, a large quantity of alcohol was added to make 1-bromo-sinomeneine crystallize out M. p. 214°, also admixture with 1-bromo-sinomeneine prepared by bromination method. Yield 40%. Analysis. Found: C, 55.86; H, 5.13; N, 3.20%. Calc. for $C_{19}H_{20}O_4NBr$: C, 56.11; H, 4.93; N, 3.45%.

B. With $KMnO_4$ 1-Bromo-sinomeneine alcohol (0.2g.) was dissolved in acetone (10cc.) and $KMnO_4$ (0.08g.) was added little by little during 1.5 hours. MnO_2 was filtered off, and the solution was concentrated. Dilute caustic soda was added and 1-bromo-sinomeneine was extracted three times with chloroform. The purification was carried out as above, but the melting point was somewhat lower (210°). The base was therefore turned into its methiodide, which showed the correct melting point 211° (also the mixed melting point). Yield of the base 20%.

The 1-bromo-sinomeneine alcohol was not, however, acted by H_2O_2 in acetic acid or by NaOBr in a mild condition.

Our thanks are due to Miss Yoshiko Suzuki of our laboratory (Agricultural Department), who helped us in carrying out some of the micro-analyses in this work.

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Agricultural Department, the University of Tokyo and the Kitasato Institute.

(7) K. Goto and S. Mitsui, This Bulletin, 5, 282 (1930)