SINOMENINE AND DISINOMENINE. PART XV. ON THE REDUCTION OF BROMO-SINOMENINE WITH NASCENT HYDROGEN.

By **Kakuji GOTO** and **Reikichi INABA.**

Received December 28, 1929. Published March 28, 1930.

In the XI communication,(1) one of the authors (K. G.) studied, in cooperation with H. Sudzuki, the reduction of sinomenine with nascent hydrogen and determined the following four facts.

1. Two molecules of sinomenine can be linked together with Na-amalgam reduction and give bis-8,8′-demethoxy-dihydrosinomenine.
2. Dihydrosinomenine gives by Na-amalgam reduction demethoxy-dihydrosinomenine, i.e., *d*-form of dihydrothebainone.
3. Sinomenine gives by Clemmensen's Zn-amalgam reduction in the hot demethoxy-desoxo-dihydrosinomenine, i. e., *d*-form of β-tetrahydro-desoxy-codeine.
4. The double linking of sinomenine can be reduced with nascent hydrogen, such as zinc and hydrochloric acid or Zn-amalgam and hydrochloric acid in the cold. The dihydrosinomenine thus obtained is identical with that produced by catalytic hydrogenation of sinomenine.

The research communicated in this report was carried out with the view to determine whether the bromo-sinomenine behaved in the same way as with sinomenine against these reducing agents. The results were completely affirmative as are shown in the following diagrams.

Properties of these substances may be summarised in the following table for convenience's sake.

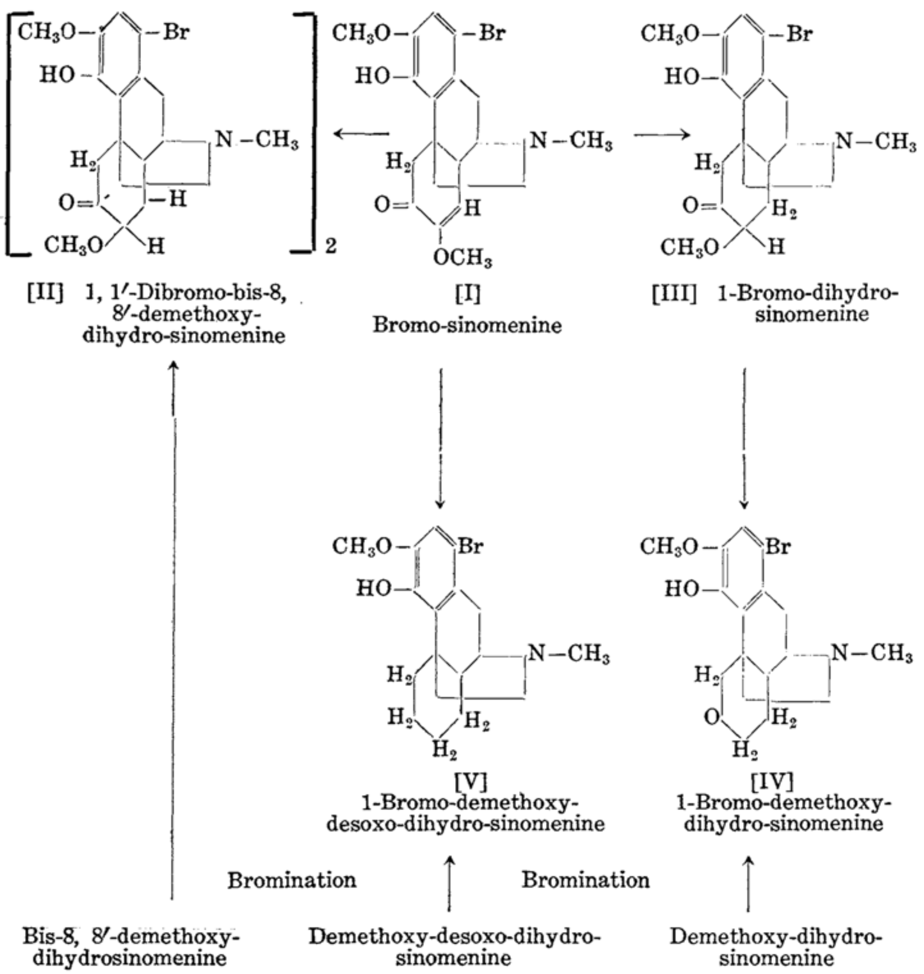
Table 1.

	1. 1′-Dibromo-bis-8,8′-demethoxy-dihydro-sinomenine	1-Bromo-demethoxy-dihydro-sinomenine	1-Bromo-demethoxy-desoxo-dihydro-sinomenine	Brominated β-tetrahydro-desoxycodeine
Yield	20%	40%	30%	50%
Crystal form	granular	prisms	prisms	prisms
M.p.	227°	119°	127°	127°
$[\alpha]_D$	+19.02°	+57.57°	+40.44°	-39.52°
M.p. of oxime	237° (dec.)	263°	—	—
M.p. of iodomethylate	253–255°	119° (sinters) 127° (dec.)	253–255°	—
$FeCl_3$-react. in alcohol	green	green	green	green
Diazo-reaction	400,000*	200,000	50,000	10,000
$FeK_3(CN)_6$-reaction	no	+only in 1,000th	no	no
Formaline-SO_4H_2	greenish blue	greenish blue	yellowish brown	yellowish brown

* The figures show the dilution, at which the colour is still visible.

---

(1) This Bulletin, **4** (1929), 244.



[II] 1, 1′-Dibromo-bis-8, 8′-demethoxy-dihydro-sinomenine

[I] Bromo-sinomenine

[III] 1-Bromo-dihydro-sinomenine

[V] 1-Bromo-demethoxy-desoxo-dihydro-sinomenine

[IV] 1-Bromo-demethoxy-dihydro-sinomenine

Bis-8, 8′-demethoxy-dihydrosinomenine

Demethoxy-desoxo-dihydro-sinomenine

Demethoxy-dihydro-sinomenine

By the reduction with Na-amalgam, bromo-sinomenine gave a substance of a bimolecular weight $(C_{18}H_{21}BrNO_3)_2$ in a yield about 20–40%, which melted at 227° and showed the properties given in the first column of the Table 1. Since the identical substance could be prepared by the bromination of bis-8,8′-demethoxy-dihydrosinomenine, it is clear that by the Na-amalgam reduction bromosinomenine is also linked together on its double linking. And from the same reasoning as was applied to the bis-8,8′-demethoxy-dihydro-sinomenine, it can be assumed that the linking point must be C_8 of each bromo-sinomenine molecule.

Secondly, bromo-dihydrosinomenine gave by the reduction with Na-amalgam, a substance $C_{18}H_{22}BrNO_3$ whose melting point was at 119°. Since the identical substance was also obtained by the direct bromination of demethoxy-dihydro-sinomenine, it is clear that the substance is nothing but brom-demethoxy-dihydro-sinomenine. Thus the action of Na-amalgam on bromo-dihydro-sinomenine is also the splitting off the methoxyl group, vicinal to the ketone, as was with dihydro-sinomenine.

Thirdly, by the Clemmensen's reduction of bromo-sinomenine, bromo-demethoxy-desoxo-sinomenine was obtained in 30% yield. The substance was checked by the bromination of demethoxy-desoxo-sinomenine, which gave the identical substance. The action of the zinc-amalgan and hydrochloric acid in the hot is, thus, the reduction of the double linking, the elimination of the methoxyl group and the reduction of the ketone to the methylene group. It is rather interesting to note that such complicated reactions could be effected in such a short lapse of time with tolerably good yield.

Moreover, the bromo-demethoxy-desoxo-dihydro-sinomenine ($[\alpha]_D = +40.44$) was racemised effectively with brominated β-tetrahydro-desoxy-codeine ($[\alpha]_D = -39.52$) prepared from codeine. This brings forward another evidence that the demethoxy-desoxo-dihydrosinomenine is the optical antipode of β-tetrahydro-desoxy-codeine. Hence, at least the three asymmetric carbon atoms C_{13}, C_{14} and C_9 of sinomenine must be arranged so as to form the image of the corresponding asymmetric carbon atoms of the reduced derivatives of codeine and thebaine.(1)

Fourthly and lastly, bromo-sinomenine was reduced with granular zinc and hydrochloric acid in the cold. Yield of bromo-dihydro-sinomenine was here about 30%.

Experimental.

1,1′-Dibromo-bis-8,8′-demethoxy-dihydro-sinomenine [II]. (1) Bromo-sinomenine (5 gr.) was reduced in 2% caustic soda solution (50 c.c.) with 5% Na-amalgam (30 gr.). After 72 hours, the aqueous part, diluted with water (150 c.c.), was saturated with carbonic acid gas. The precipitate was dissolved in chloroform. The residue of the evaporated chloroform crystallised out on addition of acetone. The yield of the raw material was 1.2 gr., viz. 34.3% of the theoretical. It was redissolved in dilute caustic soda, precipitated with CO_2 and again recrystallised from acetone. The substance has a nice appearance of crystals, but, on examination with microscope, it consisted from granules, showing no angles. It melted at 227° and darkened at 274°.

---

(1) Loc cit., p. 252.

(2) Bromination of bis-8,8′-demethoxy-dihydro-sinomenine (2 gr.) with bromine (1 gr.) in glacial acetic acid solution in the way already given, resulted in the same substance as above. The yield amounted to 70%. The melting point was at 227°, which was unaltered with the admixture of the substance obtained in the reaction (1).

As regards other properties of this substance, see the first column of the Table 1.

Anal. Found: C=56.77; H=5.56; N=3.42; Br=20.49, 20.61%. Calc. for $(C_{18}H_{23}BrNO_3)_2$=758: C=56.98; H=5.58; N=3.69; Br=21.08%.

Mol. wt. Found (in glacial acetic acid): 807. Calc.: 758.

Sp. rotatory power: 0.3549 gr. subst. was dissolved into 25 c.c. alcoholic solution. l=1 dm.; $\alpha=+0.27$; $[\alpha]_D^{13}=+19.02.^\circ$

Oxim: M.p. 237 (dec.) Found: N=7.09%. Calc. for $(C_{18}H_{24}BrNO_4)_2$: N=7.10%.

Iodomethylate: M.p. 253 ~ 255°. Yield 80%. Crystallises in stout prisms, when aqueous solution is very slowly cooled. Found: J=24.33%. Calc.: I=24.36%.

1-Bromo-demethoxy-dihydro-sinomenine [IV]. (1) Bromo-dihydro-sinomenine (5 gr.) was reduced in 2% caustic soda solution (60 c.c.) with 5% Na-amalgam. (36 gr. divided in two portions). After five days, when the alkaloid was completely dissolved, the aqueous part was treated as was given with 1.1′-dibromo-bis-8,8-demethoxy-dihydro-sinomenine. The reduced substance can be recrystallised from a small quantity of acetone. M.p. 119°. Yield 1.2 gr., viz. 35% of the theoretical.

(2) Bromination of demethoxy-dihydro-sinomenine, in the same way as was given above, resulted in the same 1-bromo-demethoxy-dihodro-sinomenine, which melted at 119°. The admixture of this substance with that obtained by the above reduction (1) did not lower the melting point. The yield was almost quantitative.

The properties of 1-bromo-demethoxy-dihydro-sinomenine are given in the second column of the Table 1.

Anal. Found: C=56.70; H=5.77; N=3.30; Br=20.97%. Calc. for $C_{18}H_{22}BrNO_3$: C=56.83; H=5.83; N=3.68; Br=21.02%.

Sp. rotatory power: 0.2866 gr. subst. was dissolved into 10 c.c. alcoholic solution. l=1 dm.; $\alpha=+1.65$. $[\alpha]_D^{13}=+57.57^\circ$.

Oxime: prepared in the ordinary way. Prisms, when precipitated with sodium carbonate from water. M.p. 263° (dec.) Found: N=6.98%. Calc.: N=7.08%

Iodomethylate: can be recrystallised from water very slowly. Fine prisms collected in globules, which sinter at 119° and decompose at 127°. Found: I=24.57%. Calc.: I=24.31%.

1-Bromo-demethoxy-desoxo-dihydro-sinomenine [V]. (1) Bromo-sinomenine hydrobromide (ca. 10 gr.) was added to Clemmensen's Zinc amalgam (a large quantity) and the mixture was first poured on with 20 c.c. hydrochloric acid (1:1). While the reaction mixture was heated in the boiling water bath for one and half hours, the fuming hydrochloric acid was added from time to time (30 c.c. in three portions).

The isolation took place as was given in the XI communication.(1) The bromo-demethoxy-desoxo-dihydro-sinomenine, thus obtained, can be recrystallised from acetone in prisms. M.p. 127°. Yield 2.2 gr. i.e. 30% of the theory.

(2) Bromination of demethoxy-desoxo-dihydro-sinomenine, in the way frequently cited, gave the above substance in 80% yield.

The mixed melting point of these two substances, prepared in the different way, remained unaltered (127°).

As regards the properties of this substance, see the third column of the Table 1.

Anal. Found: C=59.42; H=6.70; N=3.78; Br=21.08%. Calc. for $C_{18}H_{24}BrNO_2$: C=59.01; H=6.55; N=3.82; Br=21.83%.

Sp. rotatory power: 0.3066 gr. subst. was dissolved into 10 c.c. alcoholic solution. $l=5$ cm.; $\alpha=+0.62$. $[\alpha]_D^{12}=+40.44$.°

Racemisation of Bromo-demethoxy-desoxo-dihydro-sinomenine with Brominated β-Tetrahydro-desoxy-codeine. β-Tetrahydro-desoxy-codeine (0.5 gr.; m.p. 149°) was brominated in acetic acid (5 c.c.) with bromine (0.25 gr. in 5 c.c. acetic acid). The brominated substance melted at 127° and showed the properties given in the fourth column of the Table 1. Yield good. (Found: Br=21.94%. Calc. for $C_{18}H_{24}BrNO_2$: Br=21.83%).

Sp. rotatory power: 0.2935 gr. was dissolved into 10 c.c. alcoholic solution. $l=5$ cm.; $\alpha=-0.58$. $[\alpha]_D^{13}=-39.52$.°

Racemisation. The substances used in the above two estimations of the rotatory power were mixed together and, after evaporation of alcohol, recrystallised from a little acetone. Ca. 0.33 gr. of the substance was collected in this way. It sintered at 119° and decomposed at 122°. When 0.3213 gr. of this substance was dissolved into 10 c.c. alcoholic solution and examined on its rotatory power in the tube of 1 dm., it did not rotate the polarised light.

Reduction of Bromo-sinomenine with Zinc and Hydrochloric Acid [III]. Bromo-sinomenine (1 gr.) was suspended in 4% hydrochloric acid (30 c.c.) and reduced with granular zinc (5 gr.). At the interval of one hour, 10% HCl (10 c.c. each) was added five times. After 24 hours, the aqueous part was filtered and the reduced base was isolated in the ordinary way. As bromo-dihydro-sinomenine is very difficultly soluble in boiling

---

(1) This Bulletin, **4** (1929), 252.

ethyl alcohol, it could be purified easily. M.p. 236°. Admixture with bromohydro-sinomenine (m.p. 237°) prepared by the bromination of dihydrosinomenine did not alter the melting point.

Department of Chemotherapy,
Kitasato Institute, Tokyo.