SINOMENINE AND DISINOMENINE. PART XVI.

ON ISOBROMO-SINOMENINE (OR BROMO-SINOMENEINE).

By **Kakuji GOTO** and **Taro NAMBO.**

Received April 22, 1930. Published May 28, 1930.

Isobromo-sinomenine is always produced in minor, but varying quantities when sinomenine hydrochloride is brominated in glacial acetic acid. The properties of the chief product, bromo-sinomenine, had been greatly elucidated by the studies, published in the former three papers.(1) This communication deals with the formation and the transformation of isobromo-sinomenine.

The properties of bromo-sinomenine and isobromo-sinomenine was contrasted in the Table 1 of the 13th communication of this study. The most striking differences are, for convenience's sake, here again pointed out.

	Bromo-sinomenine	Isobromo-sinomenine
Specific rotation	−	+
$FeCl_3$ reaction	Strong as with sinomenine	Very weak
$FeK_3(CN)_6$ reaction	Strong as with sinomenine	No
M.p. of bromo-sinomeninone derived from them	227°C.	197°C.

The research had been made first on the following two assumptions, which were, however, quickly to be given up by the reasons annexed to them.

1. Bromo-sinomenine might have been hydrated on its double linking by the action of hydrobromic acid gas generated in the process of bromination. Isobromo-sinomenine might be, therefore, bromo-sinomenine hydrate.(2) But, this assumption collided with the fact that isobromo-sinomeninone, derived from isobromo-sinomenine, was quite different from bromo-sinomeninone produced from bromo-sinomenine.

2. Isobromo-sinomenine might be acetylated bromo-sinomenine, the acetylation being effected by the catalysis of hydrobromic acid gas in the

---

(1) K. Goto and T. Nakamura, this Bulletin, **4** (1929), 195; K. Goto and T. Nambo, ibid., **5** (1930), 73; K. Goto and R. Inaba, ibid., **5** (1930), 93.

(2) Compare sinomenine hydrate, this Bulletin, **4** (1929), 271.

glacial acetic acid. The elementary composition of isobromo-sinomenine resp. isobromo-sinomeninone and supposed acetylated bromo-sinomenine resp. bromo-sinomeninone is very similar, and the elemental analysis alone could not decide this problem.

Yet, with all effort we could not prove the acetyl radical by the hydrolysis, the attempted transformation of bromo-sinomenine or its ketone into isobromo-sinomenine or its ketone and the transformation vice versa could not be realised. Moreover, the fact that the bromination of sinomenine in propionic acid (Kahlbaum) afforded also isobromo-sinomenine at last decided the case in the negative sense.

Then we came to suspect the oxidative action of bromine. In the course of bromination, we always notice the formation of red syruppy substance, which is dissolved later and whose quantity is increased according to the velocity of the addition of bromine. If this syruppy substance is a perbromide of brominated sinomenine, then the sinomenine molecule will be oxidised, when the perbromide is decomposed. This supposition agrees well with the elemental analysis of isobromo-sinomenine and of its ketone. If isobromo-sinomenine contains two atoms of hydrogen less than bromo-sinomenine, it is no wonder that isobromo-sinomeninone is totally different from ordinary bromo-sinomeninone.

Hereupon, sinomenine was brominated with 2 mol. of bromine and the isobromo-sinomenine was obtained in 40% yield in three experiments. As is seen from the example of nicotine perbromide,(1) sinomenine perbromide has probably the formula $C_{19}H_{22}Br\ NO_4.\ BrH.\ Br_2$, and the number of hydrogen atoms taken away at the decomposition of this perbromide would be two.

From these facts and arguments, the names isobromo-sinomenine and isobromo-sinomeninone would be inappropriate, and the authors wish to replace them by bromo-sinomeneine and bromo-sinomeneine ketone.(2) But the points, from which these two atoms of hydrogen were taken away, can not be decided at present.

When the brominating mixture (bromine 2 atoms) was left stand for a long time, bromo-sinomenine disappears slowly and bromo-sinomeninone appears in its place. Thus from the mixture left stand for a weak, bromo-sinomeninone was isolated in 40% yield. Thus, the hydrobromic acid gas generated in glacial acetic acid, at the concentration of 1/2~1/3 normality, could effect the hydrolysis of the enolic methoxyl of sinomenine at ordinary

---

(1) Pinner, *Ber.*, **26** (1893), 292; M. Freund, *Ber.*, **39** (1906), 847.

(2) The name bromo-dehydro-sinomenine would be preferable, but the name dehydro-sinomenine was given to the other substance.

temperature. Sinomenine hydrochloride was also transformed into its hydrate by the same treatment, the necessary hydrochloric acid gas being liberated from acetyl chloride.

Experimental.

Bromo-sinomenine. Sinomenine hydrochloride (10 gr.), dissolved in glacial acetic acid (50 c.c.), is slowly added with bromine (5 gr.; 1 mol.) in glacial acetic acid solution (25 c.c.) at 15°C. When the precipitate of the perbromide was dissappeared, the bases are isolated in the ordinary way. The yield of the bromo-sinomenine (m.p. 153°) is 80% and that of isobromo-sinomenine varies 2~20%.

Anal. of bromosinomenine. Found: C=55.38, 56.09; H=5.71, 5.71; N=3.27; Br=19.91; CH_3O-=14.86%. $C_{19}H_{22}NO_4Br$=408 requires C=55.82; H=5.39; N=3.52; Br=19.61; CH_3O-=15.19%.

Mol. wt. Found (in glacial acetic acid): 425, 443.

Sp. rotatory power: $[\alpha]_D^6 = (-0.354\times10)\div(0.3989\times1.0) = -8.87°$ in chloroform.

Hydrochloride (with 3 aq.): m.p. 116°. (Solubility in water 0.66%).

Hydrobromide: m.p. 232° (from methyl alcohol). Solubility in water 0.632%.

The both show beautiful silky lustre, when suspended in water.

Oxime: Dec. p. 211° (softening at 168°) Found: N=6.35%. Calc. for $C_{19}H_{23}N_2O_4Br$: N=6.62%.

Iodomethylate: m.p. 80°. Found: I=39.37, 30.12, 31.46%. Calc.: 23.08%. These extremely high values of iodine perhaps show the mobility of bromine atom against $AgNO_3+HNO_3$ at the ordinary temperature.

Isobromo-sinomenine (or Bromo-sinomeneine). Bromination is effected in the same way as above, only 2 mols. of bromine being used. Yield about 40%. The base is recrystallisable in long prisms from 100 parts of boiling alcohol. M.p. 217°.

Anal. Found: C=56.44, 55.97, 55.94; H=5.29, 4.91, 5.35; N=3.57; Br=19.30, 18.73; CH_3O-=15.29%. $C_{19}H_{20}BrNO_4$=408 requires C=56.16; H=4.92; N=3.45; Br=19.71; CH_3O-=15.27%.

Mol. wt. Found (in glacial acetic acid): 406, 414.

Sp. rotatory power: $[\alpha]_D^9 = (+3.23\times10)\div(0.3890\times10) = -83.03$ in chloroform.

Hydrochloride: m.p. 231° (dec.) Solubility in water 2.96%.

Hydrobromide: m.p. 229°. Solubility in water 0.84%.

Oxime: m.p. 162°; hydrochloride m.p.>280°, softening at 236°. Found: N=6.04%. $C_{19}H_{20}BrN_2O_4.HCl$ requires N=6.12%.

Iodomethylate: m.p. 211–212°. Found: I=22.03%. Calc.: I=23.77%.

Isobromo-sinomeninone (or Bromo-sinomeneine Ketone). Prepared by heating isobromo-sinomenine (5 gr.) in 2n.HCl (25 c.c.) at 100° for one hour. Fine needles, melting at 198°. Very soluble in methyl alcohol, but recrystallisable from chloroform.

Anal. Found: C=55.01, 54.88, 55.23; H=4.98, 5.18, 4.94; N=3.27; Br=20.68; CH_3O—=7.93, 8.03%. $C_{18}H_{18}NO_4Br$ requires C=55.01; H=4.59; N=3.55; Br=20.30; CH_3O—=7.87%.

Sp. rotatory power: $[\alpha]_D^9 = (1.60 \times 10.0) \div (0.2666 \times 0.5) = +119.89°$.

Dioxime: m.p. 173.5° (dec.); hydrochloride, m.p. 212°, softening at 208°. Found: N=9.12%. $C_{18}H_{20}N_3O_4$ Br. HCl=458 requires N=9.12%.

Iodomethylate: m.p. 195° (dec.), softening at 190°. Found: I=22.03%. Calc.: 23.69%.

Bromo-sinomeninone. Brominating mixture as was described with bromo-sinomenine was left stand for some weeks, from which at several intervals brominated bases were isolated. The chief product was bromo-sinomeninone, melting at 227°. The yield was tolerably good, when the isolation was carried out after one week's standing.

Anal. Found: C=55.19, H=5.10, Br=20.24, CH_3O—=8.02%. Calc. for $C_{18}H_{20}NO_4Br$: C=54.82, H=5.07, Br=20.30; CH_3O—=7.86%.

Oxime: m.p. 189°. Found: N=9.47%. Calc.: N=9.90%.

Iodomethylate: m.p. 246° (mixed m.p. with that prepared in ordinary way 245°).

These results show clearly that bromo-sinomenine is transformed into bromo-sinomeninone in the brominating mixture. Moreover, the bromo-sinomenine itself was transformed into the bromo-sinomeninone in glacial acetic acid at ordinary temperature by the hydrobromic acid at the concentration as was attained in the bromination.

Sinomenine Hydrate. From the following mixtures, which were prepared to imitate the contents of hydrobromic acid gas in the brominating mixture, sinomenine hydrate was isolated in the annexed yield.

1. When the mixture was composed of sinomenine (free) 33 gr., glacial acetic acid 50 c.c., hydrobromic acid (48%) 20 c.c. and acetic anhydride (to destroy water) 50 c.c. the yield of sinomenine hydrate was: 4.5% after 24 hours, 15% after 48 hours and 45% after 2 weeks.
2. When the hydrobromic acid was replaced by acetyl-chloride, (sinomenine hydrochloride 40 gr., glacial acetic acid 100 c.c., acetyl anhydride 10 c.c. and acetyl chloride 7.8 gr.), the yield of sinomenine hydrate was 10% after 48 hours, but much better after 2 or 3 weeks.

The sinomenine hydrate was identified by the following properties.

M.p. 157° (twice recrystallised from ethyl alcohol.)(1)

---

(1) When sinomenine hydrate was isolated from the 2 n. HCl, it melts generally at 138° thereabout. Recrystallisation elevates the melting point slowly and 157° is the most reliable, though it may not be the highest.

Anal. Found: $C=65.68$; $H=7.29$; $N=4.03$; $CH_3O-=17.72\%$. Calc. for $C_{19}H_{25}NO_5$: $C=65.70$; $H=7.20$; $N=4.03$; $CH_3O-=17.86\%$.

Sp. rotatory power: $[\alpha]_D^7=+41.85$. Oxime: m.p. 231°.

Iodomethylate: Melting and decomposing into yellow bubbles at 192–195°. (The dec. point 264° formerly given was regretfully based on some accidental error. The new dec. point 192–195° was checked by three different preparations, obtained from different lots of sinomenine hydrate). Found: $I=24.56\%$. Calc.: $I=25.97\%$.

Department of Chemoterapy,
Kitasato Institute, Tokyo.