69. *On the Ethylene Glycol Ketals of Sinomenine Derivatives*[1]

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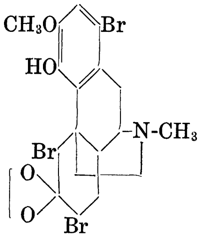
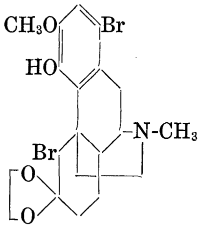
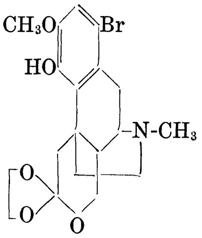
The very poor yield[2] in the preparation of (+)-1-bromocodeinone from (+)-1, 5, 7-tribromodihydrothebainone through ketal method, made it desirable to study the ketalisation of this tribromo substance with ethylene glycol more thoroughly. From the ketalised mixture we could isolate the following three ketals in nice crystals, namely the ethylene glycol ketal of (+)-1, 5, 7-tribromodihydrothebainone (I), of (+)-1, 5-dibromodihydrothebainone (II) and the 6 (?)-mono-ketal of 1-bromosinomeninone (III). The constitution of these three ketals was determined by elemental analyses as well as by the deketalisation and the followed treatment with caustic alkali. The ketals I and III gave 1-bromosinomeninone (IV) and the ketal II gave (+)-1-bromodihydrocodeinone (V).



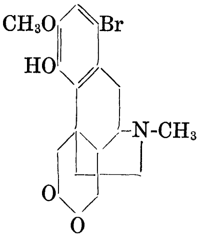
I



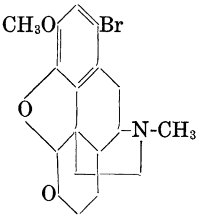
II



III



IV



V

The yield of these three ketals was not good. The mean value of twenty experiments, using 10 gr each of (+)-dihydrothebainone, was as follows:

1) ketalised part (I, II, and III) 30%,

2) unketalised part (which gave 1-bromosinomeninone (IV) on alkaline treatment) 30%,

3) inextractible and incrystallisable part 40%.

It was clear that the ketal II came from the insufficiency of bromination, but the calculated quantity of bromine made the brominated mixture more resinous and we were obliged to use a little less quantity of bromine in the bromination.

The ketals I and II have almost the same melting point and solubility in ordinary solvents and make an intimate mixture from which it was very difficult to separate each other. By five recrystallisations, we obtained a small quantity of the tribromo-ketal (I), which was pure enough for analysis. It melted at 185°. The bulk seemed to be the dibromo-ketal (II). This was no wonder, for the two bromine atoms on C (5) and C (7) seemed to exercise a stronger steric hindrance in ketalisation than the one bromine atom on C (5) in 1, 5-dibromodihydrothebainone. The ketalisation of the former was calculated to be 10% from the decomposition product, but the latter (1, 5-dibromodihydrothebainone) was ketalised actually more than 50%.

The pure dibromoketal (II) was isolated from this mixture by acetylation and the followed desacetylation. The ketal melted at 188°, and was the same with the dibromoketal prepared directly from (+)-1, 5-dibromodihydrothebainone.

It seemed to be probable that the ketal III, namely, 1-bromosinomeninone-6 (?)-ketal was formed from 1, 5, 7-tribromoketal (I) at the time of isolation from the ketalising mixture. If it were formed during the ketalisation, it would be further ketalised into the 1-bromosinomeninone diketal. Yet, the isolated 1, 5, 7-tribromoketal (I) was not turned into the 1-bromoketal (III) by the same treatment with caustic alkali as at the time of isolation.

The three ketals have peculiar character from the unketalised original substances, namely:

1) The ketal groups hinder to some degree the oxide ring closure between OH on C(4) and Br on C(5) through alkali. The oxide ring is closed by alkali at once in the ketal II, when it was deketalised.

2) They are all very sparingly soluble in caustic alkali.

3) The tribromoketal and dibromoketal give only faint ferric chloride reaction, but in the 1-monobromoketal the colouring is prominent. This may be due to the C(5)-standing bromine atom.

Experimental

(1) General procedure for the ketalisation.[3] Dihydrothebainone (10 gr) was tribrominated in glacial acetic acid. After the acetic acid was distilled off in vacuo, the residue was warmed with ethylene glycol (100 cc) and benzene (100 cc), sometimes with the addition of anhydrous sodium sulfate (70 gr). Benzene was slowly distilled off, being supplemented through a dropping funnel, until 1,000 cc or 1,500 cc of benzene was distilled in 10 or 15 hours. A longer distilling had a

rather bad effect on the yield.

To the residue, 33% caustic soda solution (33 cc) was added, the whole was warmed at 60° for two minutes, diluted with water (330 cc), and extracted with chloroform several times.

A main part of the ketals went into the chloroform, but a minor part remained as white crystals in water, which could easily be collected on filter. From the chloroform, the ketals crystallised out in white crystals on evaporation. These crystals were a mixture of three ketals, namely ketals I, II, and III. Ketals I and II had almost the same melting point (185 - 188°) and were very difficult to separate each other, but as the ketal III (m. p. 228°) was very soluble in chloroform and almost insoluble in ethyl acetate, it could be separated easily from the mixture.

(2) Ethylene glycol ketal of (+)-1, 5, 7-tribromodihydrothebainone. The mixture of the ketals I and II was five times recrystallised from ethyl acetate, until the m.p. became constant at 185°. The analysis showed that the substance was the ethylene glycol ketal of (+)-1, 5, 7-tribromodihydrothebainone. $[\alpha]^{12}_{D}=+37.0°$ (c 0.57, AcOEt). (Analysis. Calcd. for $C_{20}H_{24}O_4$ NBr_3: C, 41.26; H, 4.16; N, 2.41; Br, 41.18. Found: C, 41.07; H, 4.47; N, 2.29; Br, 41.61.)

The yield of the pure substance is scanty. For the large part remained intimately intermingled with the ethylene glycol ketal of (+)-1, 5-dibromodihydrothebainone, which was produced by the shortage of bromine. By hydrolysis of this mixture (m. p. 180 - 185°) (+)-1-bromosinomeninone and (+)-1-bromodihydrocodeinone were obtained in varying ratio in different lots. As the pure ketal of (+)-1, 5-dibromodihydrothebainone gave only the (+)-1-bromodihydrocodeinone, it was clear that the (+)-1-bromosinomeninone came from the 1, 5, 7-tribromoketal. Moreover, the acetylation of this ketal mixture gave the acetylated pure 1,5-dibromoketal, which was desacetylated into the ketal of 1, 5-dibromodihydrothebainone.

(3) Ethylene glycol ketal of (+)-1, 5-dibromodihydrothebainone (II). Preparation and isolation as given in general procedure. Crystals obtained from ethyl acetate were boiled with methanol to dissolve the attached impurities. Nice white prisms. M.p. 188°. Yield *ca.* 50%. Ferric chloride reaction pale green. $[\alpha]^{18}_{D}=+35.52°$ (c 1.064, AcOEt). (Analysis. Calcd. for $C_{20}H_{25}O_4NBr_2$ (503.24): C, 47.73; H, 5.01; N, 2.78; Br, 31.76. Found: C, 47.33; H, 4.80; N, 2.82; Br, 31.58.)

By warming with 5% hydrochloric acid and isolation from caustic alkaline solution, it gave only (+)-1-bromodihydrocodeinone (V).

Acetyl ester. Acetylation were carried out in ordinary way. M.p. 205°. Yield *ca.* 50%. $[\alpha]^{8}_{D}=+4.2°$ (c 1.648, chlf.). (Analysis. Calcd. for $C_{22}H_{27}O_5NBr_2$ (545.3): C, 48.46; H, 4.99; N, 2.57; Br, 29.31. Found:

C, 48.51; H, 5.24; N, 2.62; Br, 29.35.) By alkaline hydrolysis, it gave the original substance of m.p. 187°.

(4) 6(?)-Ethylene glycol ketal of (+)-1-bromosinomeninone (III). As this ketal is very sparingly soluble in ethyl acetate (*ca.* 0.5%), it can be separated from the other ketals very easily. M.p. 228°. Yield variable, but *ca.* 10% on an average. Ferric chloride reaction deep green. $[\alpha]_{D}^{16}=+110.3^{\circ}$ (c 1.117, chlf.). (Analysis. Calcd. for $C_{20}H_{24}O_5NBr$ (438.32): C, 54.80; H, 5.52; N, 3.19; Br, 18.23. Found: C, 55.07; H, 5.51; N, 3.09; Br, 18.86.) It gave only 1-bromosinomeninone on 5% HCl hydrolysis. Yield over 50%. By acetylation it gave a diacetate of m.p. 194°, perhaps the ketone group on C(7) being also acetylated into enolacetate. $[\alpha]_{D}^{9}=+24.6^{\circ}$ (c 1.136, chlf.). (Analysis. Calcd. for $C_{24}H_{28}O_7NBr$ (522.29): C, 55.18; H, 5.40; N, 2.68; Br, 15.30. Found: C, 55.16; H, 5.44; N, 2.61; Br, 15.22.) By alkaline hydrolysis the original 6-ketal was recovered from this diacetate.

(5) By further ketalisation this mono-ketal gave the same ethylene glycoldiketal of 1-bromosinomeninone which could be prepared directly from 1-bromosinomeninone. M.p. 138° (forming) from acetone. Also the mixed m.p. $[\alpha]_{D}^{18}=+66.96^{\circ}$ (c 1.135, chlf.). (Analysis. Calcd. for $C_{22}H_{28}O_6NBr+CH_3COCH_3$(540.45): C, 55.56; H, 6.34; N, 2.59; Br, 14.79. Found: C, 55.58; H, 6.37; N, 2.32; Br, 14.87.)

Properties of ethylene glycol ketals of some sinomenine derivatives, other than given in the above.

(1) Sinomenine and (2) sinomeninone (IV) gave the same diketal. Thus, the enolmethoxyl of sinomenine seems to have been hydrolysed in the ketalisation. The diketal from sinomenine melted at 207° (from methanol) and showed $[\alpha]_{D}^{20}=+60.4^{\circ}$ (c 1.38, chlf.). The diketal from sinomeninone melted at 207° (from methanol) and showed $[\alpha]_{D}^{16}=+59.7^{\circ}$ (c 0.517, chlf.). The mixed m.p. did not lower from the both sources. (Anal. Calc. for $C_{22}H_{29}O_6N$(403.46): C, 65.49; H, 7.25; N, 3.47; CH_3O (for one) 7.69. Found: C, 64.92; H, 7.34; N, 3.63; CH_3O, 7.33.)

(3) Dihydrosinomenine ketal methiodide. M.p. 247° (dec.) from ethanol. $[\alpha]_{D}^{18}=-6.4^{\circ}$ (c 0.484, H_2O). (Anal. Calc. for $C_{21}H_{29}O_5N\cdot CH_3I$ (517.39): C, 51.07; H, 6.23; N, 2.71; I, 24.53. Found: C, 50.83; H, 6.59; N, 2.67; I, 24.00.)

(4) (+)-Dihydrothebainone ketal methiodide. M.p. 263° (dec.) from ethanol. $[\alpha]_{D}^{14}=+15.3^{\circ}$ (c 0.872, H_2O). (Anal. Calc. for $C_{20}H_{27}O_4N\cdot CH_3I$ (487.37): C, 51.75; H, 6.25; N, 2.87; I, 26.04. Found: C, 51.94; H, 5.89; N, 2.90; I, 25.80.)

(5) (+)-1-Bromodihydrothebainone ketal. M.p. 115° (193° (dec.)). $[\alpha]_{D}^{18}=+52.0^{\circ}$ (c 0.923, chlf.). (Anal. Calc. for $C_{20}H_{26}O_4NBr$ (424.3): C, 56.61; H, 6.18; N, 3.30; Br, 18.83. Found: C, 56.89; H, 6.18; N, 2.93; Br, 18.41.) The acetate. M.p. 83° from ethanol. $[\alpha]_{D}^{18}=+25.8^{\circ}$ (c 1.549, chlf.). (Anal. Calc. for $C_{22}H_{28}O_5NBr$ (466.3): C, 56.65; H, 6.05; N, 3.00; Br, 17.14. Found: C, 56.10; H, 6.41; N, 2.84; Br, 16.96.)

(6) (+)-Dihydrocodeinone ketal. M.p. 174°. $[\alpha]_{D}^{10}=+172.6^{\circ}$ (c 1.857, chlf.). (Anal. Calc. for $C_{20}H_{25}O_4N$ (343.41): C, 69.95; H, 7.33; N, 4.08. Found: C, 70.77; H, 7.78; N, 3.98.)

(7) (+)-1-Bromodihydrocodeinone (V) ketal. M.p. 159° from acetone. $[\alpha]_{D}^{18}=+144.8^{\circ}$ (c 0.508, MeOH). (Anal. Calc. for $C_{20}H_{24}O_4NBr$ (422.32): C, 56.88; H, 5.73; N, 3.32; Br, 18.90. Found: C, 56.98; H, 5.63; N, 3.67; Br, 18.94.)

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References

1) The 76th Communication on Sinomenine.
2) K. Goto and I. Yamamoto: Proc. Japan Acad., **33**, 477 (1957).
3) Compare S. Bernstein et al.: J. A. C. S., **75**, 4830 (1953).