142. *Derivation of (+)-L-Sinomenine Methyl Ether from Thebaine*[1]

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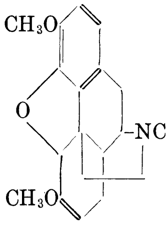
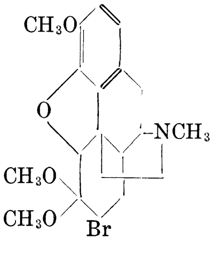
On the action of dimethyl sulfate and alkali on sinomeninone (III) and 1-bromosinomeninone one of us (K. G.) reported long ago.[2] The products were manifold according to the temperature and concentration of alkali. But the common feature in working in aqueous alkali was that the base was turned invariably into quaternary methyl methosulfate or its decomposition products. Among these, the most important product was 1-bromosinomenine methyl ether methylmethosulfate, isolated as methiodide. This reaction showed clearly that the ketone (7) could be converted into enol methoxyl quicker than the ketone (6). But the preparation of the product as a free base and without bromine was much more desirable.

Now the enol methylation of dihydrocodeinone with dimethyl sulfate and alkali in tert.-butanol gave at least 50% of enol methyl ether as free base.[3] We applied this method to (+)-sinomeninone and obtained sinomenine methyl ether (IV) in 2.5% yield.[4] (—)-L-Sinomeninone from thebaine gave the same result in the same treatment. The both sinomenine methyl ether hydrochlorides racemised well and the racemic free base melted at 158°.

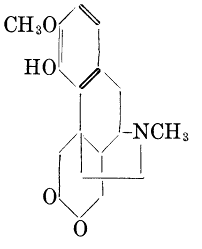
The starting material, (—)-L-sinomeninone was prepared in the following way.[5] Dihydrothebaine (I), prepared by the catalytic reduction of thebaine, was treated with N-bromosuccinimide in methanol. The (—)-L-7-bromodihydrocodeinone dimethyl ketal (II) was not isolated, but directly treated first with dilute hydrochloric acid, and then with caustic alkali. The (—)-L-sinomeninone (III) thus obtained showed the same physical constants with (+)-D-sinomeninone from sinomenine and racemised well with the latter.



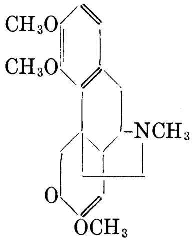
I



II



III



IV

Now, (−)-dihydrothebainone was first synthesized elementally by M. Gates⁽6⁾ and then by D. Ginsburg⁽7⁾ and could be easily converted into dihydrocodeinone⁽8⁾ or its enol methyl ether (dihydrothebaine). Accordingly, the conversion of (−)-dihydrothebaine into (+)-L-sinomenine methyl ether means the total synthesis of L-sinomenine methyl ether. And as the latter racemised well with the methyl ether of sinomenine, the present conversion can be regarded as an establishment of the constitution of sinomenine by synthetical way, although sinomenine itself was not yet synthesized.

Experimental

(1) (−)-L-Sinomeninone (III). A solution of (−)-L-dihydrothebaine (I; 2 gr) in methanol (30 cc), was added with N-bromosuccinimide (1.2 gr; 1 mol) and set aside for 1.5 hours at room temperature. The product was extracted with chloroform from the soda alkaline solution. And the residue of chloroform evaporation was hydrolysed with 2% hydrochloric acid (60 cc) at 75° for half an hour. To the cooled solution, 20% NaOH (30 cc) was added and the unhydrolysed part was removed with ether. The aqueous layer, after made alkaline with soda, was extracted with chloroform. The chloroform residue crystallised on addition of methanol. M. p. 139° (foaming). Yield 1 gr (50%). Ferric chloride reaction in methanol reddish brown (α-diketone). $[\alpha]_D^{12} = -43.0°$ (c 1.205, chlf.). (Analysis. Calcd. for $C_{18}H_{21}O_4N + CH_3OH$ (347.40): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.55; H, 7.28; N, 4.03).

d, l-Sinomeninone. *d, l*-Sinomeninone crystallised out from a methanolic solution of 80 mg each of (−)- and (+)-sinomeninone, when concentrated. M. p. 139° (foaming). $\alpha = \pm 0°$ (c 0.4, chlf.).

(2) *d, l*-7-Bromodihydrocodeinone dimethyl ketal (II). (+)-Substance from sinomenine.⁽3⁾ M. p. 117°. $[\alpha]_D^{10} = +164.5°$ (c 1.536, chlf.). (−)-Substance from thebaine. Isolation as given in Ref. 3). M. p. 117°. $[\alpha]_D^{14} = -163.2°$ (c 0.768, chlf.) (N. Calcd: 3.31%. Found: 3.64%).

A mixed solution of 50 mg each of (+)- and (−)-derivative was evaporated. The crystallised out *d, l*-substance melted at 164° (reddening). Prisms. $\alpha = \pm 0°$ (c 0.4, chlf.).

(3) (+)-L-Sinomenine methyl ether (IV). (−)-L-Sinomeninone (2 gr) was suspended in tert.-butanol (20 cc) and added to tert.-butanol (30 cc), dissolving 0.27 gr of sodium. To this clear solution, a tert.-butanolic (10 cc) solution of dimethyl sulfate (1.45 gr) was added under shaking in five portions. The addition of the same quantity of sodium tert.-butylate and tert.-butanolic solution of dimethyl sulfate was once more repeated. With shaking from time to time, the whole mixture was set aside for two hours. The temperature of reaction was kept at 30–35°.

Then the reaction mixture was made alkaline with ammonia and the bases were taken up in chloroform. The chloroform layer was washed with water and the residue of evaporation was digested with 10% NaOH and extracted with ether. The ethereal residue (0.4 gr) was dissolved in methanol (0.5 cc) and added with a few drops of 20% hydrochloric acid, when the hydrochloride of the (+)-L-sinomenine methyl ether crystallised out quickly. Raw yield 200 mg. After one recrystallisation from water (0.5 cc), the hydrochloride was pure. But the yield diminished to 50 mg. M. p. 254° (dec.). No ferric chloride reaction. $[\alpha]_D^{16}=+65.08°$ (c 0.630, H_2O). (Analysis. Calcd. for $C_{20}H_{25}O_4N \cdot HCl+H_2O$ (397.89): C, 60.37; H, 7.09; N, 3.52; Cl, 8.91. Found: C, 59.95; H, 7.13; N, 3.30; Cl, 8.56).

(4) (−)-D-Sinomenine methyl ether hydrochloride. (a) (+)-D-Sinomeninone was methylated just in the same way as above. The yield was also poor (2.5%). M. p. 254° (dec.). (b) Methylation of sinomenine was best effected by nitrosomethylurethane in methanol solution without the use of caustic alkali. The basicity of sinomenine was strong enough to decompose nitrosomethylurethane. After the development of nitrogen ended, hydrochloric acid was added to the reaction mixture and the hydrochloride of the methyl ether crystallised out beautifully. M. p. 254° (dec.). Also mixed m. p. with (a). $[\alpha]_D^{27}=-65.55°$ (c 0.557, H_2O).

Nitrosomethylurea was not decomposed by sinomenine in the cold.

d, l-Sinomenine methyl ether hydrochloride was obtained by the concentration of a methanolic solution of 20 mg each of (+)-L- and (−)-D-substance. Prisms. M. p. 241° (dec.). $\alpha=\pm 0°$ (c 0.3, H_2O).

(5) Free base of (+)-L-sinomenine methyl ether. The base was liberated from its hydrochloride with caustic soda in aqueous solution. The free base crystallised out from ether in beautiful long prisms. M. p. 178°. $[\alpha]_D^{19}=+69.0°$ (c 0.674, CH_3OH). These properties coincided well with those of (−)-D-sinomenine methyl ether, as follows. (−)-D-Sinomenine methyl ether. From (+)-D-sinomeninone. M. p. 178°, $[\alpha]_D^{21}=-69.3°$ (c 0.465, CH_3OH). From (−)-D-sinomenine. M. p. 178°, $[\alpha]_D^{21}=-68.5°$ (c 0.394, CH_3OH). (Analysis of the (+)-L-substance. Calcd. for $C_{20}H_{25}O_4N$ (343.41): C, 69.95; H, 7.33; N, 4.08. Found: C, 69.55; H, 7.12; N, 4.04).

d, l-Sinomenine methyl ether. M. p. 158°. $\alpha=\pm 0°$

We thank heartily Takeda Pharmaceutical Industries for microanalyses.

References

1) The 73rd Communication on Sinomenine.
We prefix those derivatives from morphine series with L and those from sinomenine with D, as the direction of rotation is reverted sometimes in them, although the absolute system of the both series is not yet known (K. Goto and I. Yamamoto: Proc. Japan Acad., **29**, 457 (1953). Cf. K. W. Bentley and H. M. E. Cardwell: J. Chem. Soc., **1955**, 3252).

2) K. Goto, T. Arai, and T. Odera: Bull. Chem. Soc. Japan, **18**, 116 (1943).

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4) The scanty yield in the preparation of sinomenine methyl ether may be due to the one mol of crystal methanol, contained in the sinomeninone, but the use of crystal methanol free sinomeninone did not raise the yield much.

5) C. Schöpf prepared (−)-L-1-bromosinomeninone by the action of caustic alkali on the tribrominated (−)-L-dihydrothebainone. But the debromination of this substance by the catalytic reduction leads always to the mixture of α- and β-dihydrosinomeninones, one of the ketone groups being reduced.

6) M. Gates and G. Tschudi: J. Am. Chem. Soc., **78**, 1380 (1955).

7) D. Elad and D. Ginsburg: J. Chem. Soc., **1954**, 3052.

8) C. Schöpf and H. Hirsch: Ann., **489**, 224 (1931).