51. On 7-Demethoxysinomenine[1]

By Kakuji GOTO, M.J.A., and Izuru YAMAMOTO
Department of Chemistry, Kitasato Institute, Tokyo, Japan

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Sinomenine (I) is laevorotatory. But when its double bond between C (7)~C (8) is reduced, it becomes invariably dextrorotatory. These dextrorotating derivatives are always the optical antipodes of morphine derivatives, if in the latter series the corresponding compounds exist[2]. From this fact, therefore, the laevorotation of sinomenine seems to be caused by its double linking between C (7)~C (8).

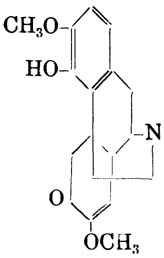
In 1931, C. Schöpf[3] prepared true thebainone (II) from thebaine and maintained that it was different from the sulphur free ketone of Pschorr. L. Small[4] and one of us (K.G.[5]) proved that the both products were one and the same. We ascertained, moreover, that the both products rotated the plane of polarization to left in the same degree. Therefore, if we could prepare 7-demethoxysinomenine, it must turn the plane of polarization to right, in spite of the fact that in this product the double linking is kept in the original place. It is worth-while to ascertain this deduction by experiment.

To prepare 7-demethoxysinomenine from (+)-dihydrothebainone (III) and its derivatives, several methods were tried, but all remained fruitless[6]. Recently the use of 2, 4-dinitrophenylhydrazine was introduced to prepare α, β-unsaturated ketone from α-halogen ketone, especially in steroid chemistry. Taking use of this method, M. Gates reported that he could prepare (−)-morphine synthetically[7]. We followed his method and could go so far to 7-demethoxysinomeninol (V), but met difficulty in oxidizing the latter to the expected ketone by Oppenauer's method. Moreover, the yield was scanty in every step of this method.

We returned then to dihydrosinomeninone (IV; (+)-7-hydroxydihydrothebainone). We prepared first its 2,4-dinitrophenylhydrazone and treated the latter with phosphorus pentachloride to replace its α-hydroxyl group with chlorine. By liberating the hydrochloride of the reacted base with ammonia and extracting with chloroform, we obtained the dinitrophenylhydrazone of the unsaturated ketone and by its cleavage 7-demethoxysinomenine (II). Its nature was proved by converting it into some corresponding derivatives of (−) true thebainone.

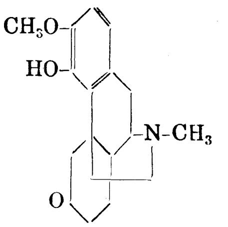
7-Demethoxysinomenine is dextrorotatory, as expected and racemized well with true thebainone. Consequently we can conclude that in the laevorotation of sinomenine the C (7)-situated enolmethoxyl must play an important rôle. 7-Demethoxysinomenine gives thus a good example that the direction of rotation is determined, not only by each optical centre, but also by a factor which is not in direct relation with these optical centres.

The yield of 7-demethoxysinomenine from sinomenine is ca. 5 per cent and the method is open to much improvement, to which we will proceed later.



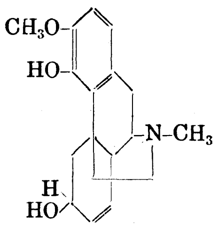
I. Sinomenine

II. 7-Demethoxy-sinomenine (H in 7)



III. 7-Demethoxy-dihydrosinomenine

IV. α-Dihydro-sinomeninone (OH in 7)



V. 7-Demethoxy-sinomeninol

Experimental

7-Demethoxysinomenine (II; (+)-Thebainone)

α-Dihydrosinomeninone (IV; 2gr. 1 mol.) was dissolved in glacial acetic acid (20cc.), added with 2,4-dinitrophenylhydrazine (1.25gr. 1 mol.) and heated on wire gauze. After dissolving of the latter, the liquid was kept at 100–105° for two minutes. Then the flask was stoppered tightly, cooled with water and set aside for one hour at room temperature. The content was then diluted with water, made alkaline with ammonia and extracted with chloroform. The chloroform layer, after washing with water and dehydration, was evaporated down to 30cc.

This chloroform solution was then poured into ice cooled chloroform (30cc.), containing PCl_5 (5gr.) in 20min., during which much yellow precipitate was formed. After standing 2 hours at room temperature, the now brown precipitate was filtered away and the chloroform was washed with ammonia and water, concentrated and passed through a column of alumina. The chloroform eluate was evaporated and the residue was crystallized from benzene. The 2,4-dinitrophenylhydrazone of 7-demethoxysinomenine thus obtained is long prism and melts at 138° with foaming. Yield 600mg. (ca. 20%). $[\alpha]_D^{17} = +1373°$ (c 0.800, chlf.). $\lambda_{max}^{chlf.}$ 381 mμ, log ε 4.45, (Anal. Calcd. for $C_{24}H_{25}O_6N_5$ (479.5): N, 14.61. Found: N, 14.12).[8]

Cleavage. The above phenylhydrazone (5 gr. recrystallized from benzene) was boiled with acetone (175 cc.) and conc. HCl (7 cc.) for 3 hours and half on a steam bath. Acetone was distilled away i.v., the residue was added with 10% HCl and shaken with chloroform repeatedly to remove phenylhydrazones. The aqueous layer was then made alkaline with sodium carbonate and the (+)-thebainone was extracted with chloroform. The residue of chloroform was crystallized from benzene. Tables. Two recrystallizations brought up the m.p. to 146–148°. $[\alpha]_D^{15}=+45.7^\circ$ (c 1.629, alc.). (Anal. Calcd. for $C_{18}H_{21}O_3N\ 1/2H_2O$ (308.4): C, 70.09; H, 7.17; N, 4.54; CH_3O, 10.06. Found: C, 69.92; H, 7.36; N, 4.56; CH_3O, 10.10).

Methiodide. Recrystallized from 96% alc. M.p. 246° (dec. uncorr.). (Anal. Calcd. for $C_{19}H_{24}O_3NI$ (441.3): I, 28.76. Found: I, 28.65).

Oxime hydrochloride. Crystallized out at once, when 7-demethoxysinomenine is heated with the equimolecular solution of $HONH_2 \cdot HCl$. Short prisms from water. M.p. 290° (dec.). (Anal. Calcd. for $C_{18}H_{22}O_3N_2 \cdot HCl$ (350.7): N, 7.99. Found: N, 7.69).

d, l-Thebainone

60 mg. each of (−) and (+)-thebainone were racemized in dissolving in acetone. The racemic base crystallized out in tables. M.p. 194°. Recrystallization did not alter the m.p. $\alpha=0$ (c 1.00, chlf.).

1-Bromo-7-demethoxysinomenine (der. from III)

7-Demethoxydihydrosinomenine (III; 2 gr.) was dibrominated in glacial acetic acid (20 cc.). To this solution, 2,4-dinitrophenylhydrazine (1.45 gr.) was added and the mixture was heated as described in the foregoing section, only under the current of carbon dioxide. After cooling, the acetic acid was removed by distillation i.v., the residue was made alkaline with dil. ammonia and extracted with chloroform. From the chloroform residue, 2,4-dinitrophenylhydrazone of 1-bromo-7-demethoxysinomenine crystallized out in prisms. Yield 940 mg. (29%). M.p. 203°, after several recrystallization from chloroform plus ethyl acetate, $[\alpha]_D^{24}=+1336^\circ$ (c 0.27. chlf.). $\lambda_{max}^{chlf.}$ 379 mμ, log ε 4.41. (Anal. Calcd. for $C_{24}H_{24}O_6N_5$ Br: N, 12.54. Found: N, 12.65).

Cleavage. The above hydrazone (10 g.) was cleaved in acetone by HCl as described with (+)-thebainone. To the residue of the distillation of acetone, water (150 cc.) and chloroform (150 cc.) were added and shaken vigorously. The dinitrophenylhydrazones were filtered off and the aqueous layer was shaken with chloroform several times to remove the hydrochloride of uncleaved base. The cleaved base was precipitated from aqueous layer by sodium carbonate and extracted with chloroform. Prisms from acetone. Yield 25%. M.p. 196°. $[\alpha]_D^{11}=$

+83.2° (c 1.681, chlf.). (Anal. Calcd. for $C_{18}H_{20}O_3NBr$: Br, 21.16. Found: Br, 21.20).

The same 1-bromo substance can be obtained by the bromination of 7-demethoxysinomenine in glacial acetic acid. Short prisms. M.p. 196°. Also the mixed m.p. with the above substance unaltered.

7-Demethoxysinomeninol (V)

(A) 1-Bromo-7-demethoxysinomenine (Formula derived from II; 0.2gr.) was reduced with $LiAlH_4$ (0.2gr.) in boiling tetrahydrofurane (20cc.) for 4 hours. The base, extracted in ordinary way, crystallized out from chloroform residue, when added with acetone. Prisms. M.p. 181°, after recrystallization from acetone. Beilstein test negative. $[\alpha]_D^6 = -90.3°$ (c 0.895, chlf.)9). (Anal. Calcd. for $C_{18}H_{23}O_3N$ (301.4): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.80; H, 7.35; N, 4.82).

(B) The same 7-demethoxysinomeninol was obtained from 7-demethoxysinomenine (II) by $LiAlH_4$ reduction in ether. M.p. 181° from acetone. The mixed m.p. with the substance from (A) unaltered.

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References

1) The 63rd. Comm. on Sinomenine.
2) K. Goto and T. Takebe: Proc. Imp. Acad., **9**, 390 (1933).
3) C. Schöpf and H. Hirsch: Ann., **489**, 224 (1931).
4) L. F. Small and D. E. Morris: J. A. C. S., **54**, 2122 (1932).
5) K. Goto and H. Ogawa: Ann., **511**, 202 (1934).
6) K. Goto and M. Michi: Acta Phytochim., 183, 187 (1944).
7) M. Gates and G. Tschudi: J. A. C. S., **74**, 1109 (1952).
8) On (−) derivative, see M. Gates and R. Helg: J. A. C. S., **75**, 379 (1953). Here we may take the opportunity to thank Prof. Marshall Gates, who was kind enough to have sent the detailed condition of his experiments to one of the authors (I. Y.).
9) From this fact, it may be assumed that if true thebainone-(−) from thebaine is reduced by the same method, the thebainol thus obtained must turn the plane of polarization to right.