On 7-Hydroxy-dihydro-codeine, 7-Hydroxy-dihydro-thebainol and the corresponding (+)-Derivatives from Sinomenine.[1]

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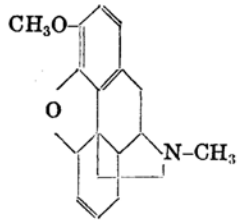
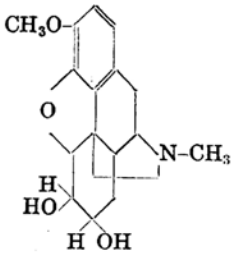
In the 47th communication on sinomenine[2], we have reported the formation of (+)-dihydro-codeine, (+)-dihydro-morphine and (+)-desoxycodeine-C from sinomenine. By mild oxidation of (+)-desoxy-codeine-C (I) with potassium permanganate[3], we obtained (+)-7-hydroxy-dihydro-codeine (II), which in turn could be racemised with (−)-7-hydroxy-dihydro-codeine, prepared from (−)-desoxy-codeine-C in the same way. The introduced two alcoholic groups have been demonstrated as dibenzoyl derivatives.

(1) The 50th Communication on Sinomenine.
(2) *Ann.*, **547** (1941), 194.
(3) Compare Cahn and Robinson, *J. Chem. Soc.*, **1926**, 908.

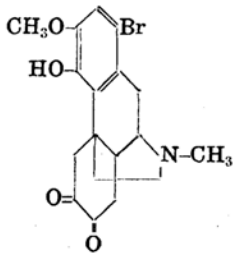


(I)

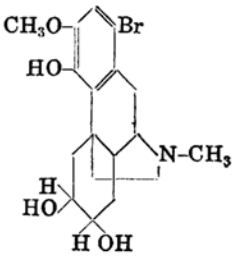


(II)

By reducing (+)-1-bromo-sinomeninone (III) with hydrogen gas in pyridine solution, using platin oxide as catalyst, the both ketonic groups were reduced and (+)-1-bromo-tetrahydro-sinomeninone (IV) was produced. By catalytic debromination of this substance in aqueous solution, we obtained terahydro-sinomeninone (V), namely (+)-7-hydroxydihydrothebainol in a good yield. The corresponding (−)-7-hydroxydihydro thebainol could be prepared from (−)-1-bromo-sinomeninone[4] in the same process and the both were racemised. The three hydroxygroups in these substances have been made clear by the formation of triacetyl-derivatives, in which, however, the sign of rotation has been inverted remarkably enough.



(III)



(IV)

(V) (Br = H, in IV)

The racemisation trials of the above three substances (II, IV and V) were also successfully carried out with their respective methiodides.

Experimental. (+)-7-*Hydroxy-dihydro-codeine* (II). (+)-Desoxy-codeine-C (I; 1.5 g.) was dissolved in a small quantity of 10% hydrochloric acid and made up to 150 c.c. with distilled water. The solution was made slightly alkaline with 10% potassium hydroxyde and kept at 0°C by cooling and adding ice to it. The solution was stirred mechanically and 1% potassium permanganate solution (61 c.c.; 10% more than the calculated quantity) was added in half an hour. After the solution was saturated with carbon dioxide, it was stirred 15 minutes more and then filtered. The filtrate was evaporated down to 40 c.c. and extracted with ether, which removes unchanged desoxy-codeine-C. The aqueous layer was then saturated with potassium carbonate and extracted with chloro-

(4) Schöpf, Pfeifer, Hirsch: *Ann.*, **492** (1932), 213;
Goto, Shishido, Takubo: *Ann.*, **497** (1932), 293.

form. When evaporated, the chloroform yielded 0.5 g. of white, crystalline powder. This was washed with alcohol and recrystallised from chloroform+ethanol (1:1). Colourless flat prisms, m.p. 225°. Insoluble in alcohol or in ordinary organic solvents. (Calc. for $C_{18}H_{23}O_4N \cdot \frac{1}{2}H_2O$ (326): C=66.26; H=7.36; N=4.29%. Found: C=66.44, 66.24, 66.41; H=7.32, 7.43, 7.31; N=4.34%). Spec. rotatory power. Subst.=0.1097 g.; Chloroform+ethanol (1:1) =10 c.c.; 1 dm-tube, $\alpha = +1.42°$. $[\alpha]_D^{21.5} = +129.4°$.

Methiodide. Prepared by heating the both components+methanol in a stoppered bottle at 100°C for 30 minutes. The elongated leaflets from methanol. m.p. 252°. Yield 80%. Spec. rotatory power: Subst.= 0.1012 g.; water=10 c.c.; 1 dm-tube. $\alpha = +0.91°$. $[\alpha]_D^{18.5} = +89.9°$

(−)-*7-Hydroxy-dihydro-codeine.* The preparation is same as above, except only from (−)-desoxy-codeine-C. m.p. 225°. (Found: C=66.77, 66.57; H=7.49, 7.53%). Spec. rotatory power: Subst.=0.1107 g.; ethanol +chloroform (1:1) =10 c.c.; 1 dm-tube. $\alpha = -1.42°$. $[\alpha]_D^{22} = -128.3°$.

Methiodide. The preparation is same as with (+)-substance. m.p. 252°. Spec. rotatory power: Subst.=0.1009 g.; water=10 c.c.; 1 dm-tube. $\alpha = -0.90°$. $[\alpha]_D^{18.5} = -89.2°$.

(d,l)-*7-Hydroxy-dihydro-codeine.* The above two solutions, used for the determination of spec. rotatory power, were combined and evaporated. The (d,l)-substance crystallised out at once. Prisms. m.p. 207°. $[\alpha]_D = \pm 0°$.

d,l-*Methiodide.* The above two solutions, used for determination of spec. rotatory power were combined and evaporated. The residue was recrystallised from methanol. m.p. 238°. Plates. $[\alpha]_D = \pm 0°$.

(−)-*Dibenzoyl-7-hydroxy-dihydro-codeine.* 7-Hydroxy-dihydro-codeine (0.1 g.) was dissolved in 1 c.c. pyridine and benzoylated by benzoyl-chloride (0.18 g.) at 0°C. By being kept on standing overnight, the dibenzoylated substance crystallised out from aqueous ammonium carbonate solution. Recrystallised from benzene, it forms colourless needles, melting at 128°. Yield 20%. (Calc. for $C_{32}H_{31}O_6N \cdot \frac{1}{2}H_2O$ (534): C=71.91; H=5.99, N=2.62%. Found: C=72.22; H=6.44; N=3.07%. Spec. rotatory power. Subst.=0.0485 g.; methanol=2.5 c.c.; 1 dm-tube. $\alpha = -3.18°$. $[\alpha]_D^{24.5} = -163.9°$.

Determination of benzoyl radicals. 0.0693 g. substance was hydrolysed by warm methanolic solution of potassium methylate, made acidic with phosphoric acid and steam-distilled. The distillate required 1.27 c.c. of 0.211 N NaOH, which corresponded to 0.0281 g. benzoyl, namely 40.5%. $C_{32}H_{31}NO_6$ (525) requires 40.0% benzoyl radical, calculated for two.

The simple titration gives nearly the same results, if we deduce the allowance for free dihydroxy-dihydro-codeine, using phenolphtaleine as indicator.

(+)-*1-Bromo-tetrahydro-sinomeninone* (IV). (+)-1-Bromo-sinomeninone (III 6.5 g.) in pyridine solution, added with platin oxide (0.3 g.), was reduced catalitically at 40°C., 2200 c.c. hydrogen were absorbed in 12 hours (calc. for 2H=740 c.c. at 10°). Pyridine was then removed in the diminished pressure and the residue was recrystallised from acetone. Yield ca. 5.5 g. This was dissolved in methanol (30 c.c.), added with chloroform (100 c.c.) and shaken with water. The trioxy-derivative

crystallised into almost colourless prisms in chloroform-layer. This was collected and washed with acetone (1.7 g.). The chloroform gives 1.8 g. substance after the evaporation. The combined yield was almost 50%. Flat prisms. m.p. 136°. (Calc. for $C_{18}H_{24}BrNO_4$(398): Br=20.10; N=3.52. Found: Br=20.79; N=3.27%). Spec. rotatory power. Subst.= 0.1212 g., ethanol=10 c.c.; 1 dm-tube. $\alpha=+0.33°$. $[\alpha]_D^{11}=+27.2°$.

Methiodide. Prepared in the usual way. Prisms. m.p. 277°. (from ethanol). Spec. rotatory power. Subst.=0.0718 g.; 50% Ethanol= 2.5 c.c.; 1 dm-tube. $\alpha=+0.22°$. $[\alpha]_D^{21}=+7.7°$.

(−)-1-*Bromo-tetrahydro-sinomeninone* (= 1-Bromo-7-hydroxy-dihydro-thebainol). The preparation is same as above. The pyridine solution gave the crystalls of the product, when left overnight. Yield 4.2 g. Recrystallised from acetone, it forms flat prisms, melting at 137°. Spec. rotatory power. Subst.=0.1206 g.; ethanol=10 c.c.; 1 dm-tube. $\alpha=-0.32°$. $[\alpha]_D^{15}=-26.5°$.

Methiodide. m.p. 277°. Spec. rotatory power. Subst.=0.0718 g.; 50% ethanol=2.5 c.c.; 1 dm-tube. $\alpha=-0.21°$. $[\alpha]_D^{21}=-7.3°$.

(d,l)-1-*Bromo-tetrahydro-sinomeninone.* (+) and (−) substances (0.1206 g. each) were mixed in ethanol solution and evaporated. *d,l*-Substance crystallised out from acetone into needles. It melts at 117°, solidifies on further heating and decomposes at 195°. $[\alpha]_D=\pm0°$.

(d,l)-1-*Bromo-tetrahydro-sinomeninone methiodide.* The preparation is as above. Recrystallised from ethanol. Prisms m.p. 286°. $[\alpha]_D=\pm0°$.

(+)-*Tetrahydro-sinomeninone* (Br.=H, in IV). (+)-1-Bromo-tetrahydro-sinomeninone (2.5 g.) was dissolved in 80 c.c. 1% hydrochloric acid, added with 0.2 g. palladium chloride and 2 g. charcoal, and shaken in hydrogen atmosphere at 40°C. 175 c.c. of hydrogen were absorbed in 15 minutes (calc. for 1 mol., 140 c.c. at 10°). The filtrate was made alkaline with sodium carbonate and the base was taken up in chloroform. The chloroform residue was recrystallised from acetone. Needles. m.p. 157°. However, the acetone residue (0.8 g.) on being acetylated gives the same triacetyl-derivative as the crystal itself. (Calc. for $C_{18}H_{25}NO_4$ (319): C=67.71, H=7.84, N=4.39%. Found: C=67.45, 67.80; H=7.77, 7.76%, N=4.24%). Spec. rotatory power. Subst.=0.1500; ethanol= 10 c.c.; 1 dm-tube. $\alpha=+0.36°$. $[\alpha]_D^{20}=+24.0°$.

Methiodide. Prisms. m.p. 290° (from ethanol). Spec. rotatory power. Subst.=0.0599 g.; 50% ethanol=2.5 c.c.; 1 dm-tube. $\alpha=+0.14°$. $[\alpha]_D^{19.5}=+5.8°$.

(−)-*Tetrahydro-sinomeninone* (=7-Hydroxy-dihydro-thebainol). Prepared in the same way as (+)-derivative. Yield 0.3 g. from 1.0 g. m.p. 157°. Spec. rotatory power. Subst.=0.1472 g.; ethanol=10 c.c.; 1 dm-tube. $\alpha=-0.35°$. $[\alpha]_D^{20}=-23.8°$.

Methiodide. m.p. 292°. Spec. rotatory power. Subst.=0.0599 g.; 50% ethanol=2.5 c.c.; 1 dm-tube. $\alpha=-0.13°$. $[\alpha]_D^{19.5}=-5.4°$.

(d,l)-*Tetrahydro-sinomeninone* (=d,l-7-*hydroxy-dihydro-thebainol*). The both optical antipodes (ca. 0.15 g. each) were mixed in ethanol and evaporated. The residue was recrystallised from acetone. Hexagonal prisms. m.p. 160°. $[\alpha]_D=\pm0°$.

(d,l)-*Tetrahydro-sinomeninone methiodide.* Prisms. m.p. 260°. $[\alpha]_D = \pm 0°$.

(+)-*Triacetyl-tetrahydro-sinomeninone.* (+)-Tetrahydro-sinomeninone (1 g.) was boiled with acetic anhydride (10 c.c.) and sodium acetate (1 g.) for 3 hours. After the acetic anhydride was removed in the diminished pressure, the residue was dissolved in a small quantity of methanol and poured in 2% acetic acid (100 c.c.). The filtrate was made alkaline with soda and extracted quickly with ether. When ether was evaporated, the triacetyl substance crystallised out in beautiful prisms. It was washed with little cold methanol. m.p. 197°. Yield 60%. (Calc. for $C_{24}H_{31}NO_7$ (445): C=64.72; H=6.97; N=3.15%. Found: C=64.54; H=6.83; N=3.26%.) Spec. rotatory power. Subst.=0.1493 g.; ethanol=10 c.c.; 1 dm-tube. $\alpha = -0.31°$. $[\alpha]_D^{13} = -20.8°$.

Methiodide. Prepared in the usual way. Angular plates. m.p. 290°. Spec. rotatory power. Subst.=0.0772 g.; 60% ethanol=10 c.c.; 1 dm-tube. $\alpha = -0.22°$. $[\alpha]_D^{21} = -29.5°$.

Determination of acetyl-radicals in the methiodide. 0.1319 g. methiodide was dissolved in the mixture of 5 c.c. of 0.31 N alcoholic caustic potash (=7.75 c.c. 0.2 N) and 5 c.c. of 0.2 N aqueous caustic potash, warmed for an hour on steam-bath and left 20 hours at room temperature. The hydrolysed solution was neutralised with 9.5 c.c. of 0.2 N sulphuric acid. Acetyl radicals corresponded to 3.25 c.c. of 0.2 N sulphuric acid, namely 21.1%. Calc. for three acetyls 22.00%.

(−)-*Triacetyl-tetrahydro-sinomeninone* (Triacetyl-7-hydroxy-dihydrothebainol). Preparation is same as above. m.p. 196°. Spec. rotatory power. Subst.=0.1478 g.; ethanol=10 c.c.; 1 dm-tube. $\alpha = +0.30°$. $[\alpha]_D^{14} = +20.3°$.

Methiodide. m.p. 292° from methanol. Spec. rotatory power. Subst. =0.0761 g.; 60% ethanol=10 c.c.; 1 dm-tube. $\alpha = +0.22°$. $[\alpha]_D^{21} = +28.9°$.

(d,l)-*Triacetyl-tetrahydro-sinomeninone.* The both optical antipodes were mixed in equal quantity in alcoholic solution and evaporated. It crystallises into prisms. m.p. 196°. $[\alpha]_D = \pm 0°$.

Methiodide. Flat prisms from ethanol. m.p. 292°. $[\alpha]_D = \pm 0°$.

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