162. (+)-Codeine and (+)-Morphine from Sinomenine[1]

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The former trials to obtain (+)-codeine (I) from (+)-1,5,7-tribromodihydrothebainone (II) were fruitless, on account of the instability of the latter against caustic alkali. It gave always 1-bromosinomeninone (III) by the treatment with this reagent. The action of pyridine on (II) or (IV) was the formation of an yellow pyridinium bromide, which was very resistant to cleavage. Mattox-Kendall's method[2] to use 2,4-dinitrophenylhydrazine seemed to be the only promising method for our purpose and we made actually some preliminary experiments in this direction.

At this moment, Marshall Gates et al.[3] reported a total synthesis of (−)-morphine, using Mattox-Kendall's method in the later stage. We resolved to follow Gates's method to reach (+)-codeine quickly, although Prof. Gates very kindly warned us in his private letter on difficult points in his experiment. We followed first exactly his prescription and found that his warning was very true. We have, therefore, modified his method in three directions. First, we started with (+)-1,7-dibromodihydrocodeinone (IV), instead of (+)-1,5,7-tribromodihydrothebainone (II), as in the former, the oxide ring is already closed. From IV, 2,4-dinitrophenylhydrazone was made at room temperature. Secondly, this hydrazone was then dehydrobrominated by boiling with pyridine at 140° (bath temp.). Here the yield was about 67 per cent. Thirdly, the cleavage of the 2,4-dinitrophenylhydrazone of 1-bromo-D-codeinone thus obtained, was carried out, not by boiling with acetone and conc. HCl, but by leaving the mixture in a thermostat of 40° for 48 hours. The reduction of 1-bromo-D-codeinone was carried out by boiling with $LiAlH_4$ in tetrahydrofurane. The over-all yield of (+)-codeine was about 1% from sinomenine.

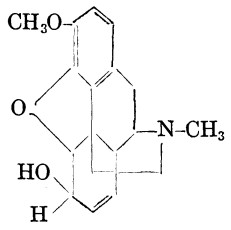
(+)-Codeine thus obtained, crystallized out from ether in colourless, long, stout prisms, melted at 158°, showed specific rotation $[\alpha]_D^{25} = +137.4°$ and well racemized with natural (−)-codeine. Its methiodide melted at 267° and racemized also with the (−)-methiodide. The m.p. of the racemic free base and methiodide were 143° and 246° respectively.

(+)-Codeine was demethylated on its methoxyl by Prey's pyridine hydrochloride method. The yield was only 20%. The obtained (+)-

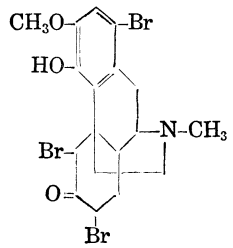
D-morphine melted at 248~249° (incorr.) with decomposition and showed the specific rotation $[\alpha]_D^{24} = +132°$ and well racemized with (−)-morphine. The racemic morphine melted at 232~233° (incorr.). The over-all yield of (+)-morphine from sinomenine is thus *ca.* 0.15 %.

Although our procedure might have not contributed much to the improvement of the yield, yet the reaction at each step in our modification is easily controllable and gives always a steady result. We hope that more detailed investigation may bring the elevation of the over-all yield in future.

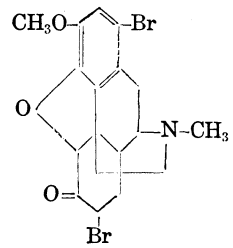
Lastly, it is noteworthy that, while the ketone-adjacent bromine atom at C(7) of tribromodihydrothebainone is not easily removed by boiling with pyridine, the same bromine atom is very easily lost as hydrobromide by the same treatment, when the ketone is turned into its 2,4-dinitrophenylhydrazone. The Mattox-Kendall's electronic explanation seems to have been justified at least in this case.



I. Codeine



II. 1,5,7-Tribromo-dihydrothebainone



IV. 1,7-Dibromo-dihydrocodeinone

V. Morphine (OH in 3)

III. 1-Bromosinomeninone (H_2 in 5, O in 7)

Experimental

1-Bromo-D-codeinone

2,4-Dinitrophenylhydrazone of 1,7-dibromodihydro-D-codeinone. 1-Bromodihydro-D-codeinone-HBr (2.4 gr) was dissolved in glacial acetic acid (30 cc) and brominated with bromine (0.84 gr, 1 mol. in 40 cc glacial acetic acid).[4] To this solution 2,4-dinitrophenylhydrazine (1.14 gr, 1.1 mol.) was added and warmed at 45° for 3 min., until dissolved. The excess of HBr was fixed by the addition of fused Na-acetate (0.43 gr, 1 mol.) and the solution was left stand overnight at room temperature. The diluted acetic acid solution was made alkaline with sodium carbonate and shaken with chloroform several times. When the chloroform was dried and evaporated and was added with a little ethyl acetate, the dinitrophenylhydrazone crystallized out in reddish yellow prisms in an almost pure state. M.p.

204° (recryst. from chloroform+ethyl acetate). $[\alpha]_D^{28} = +1022.5°$ (c 1.274, chlf.). $\lambda_{max.}^{chlf.}$ 365 mμ. Yield 1.87 gr (56%). (Anal. Calcd. for $C_{24}H_{22}N_5O_6Br_2$: N, 10.99. Found: N, 11.34).

2,4-Dinitrophenylhydrazone of 1-bromo-D-codeinone. The above phenylhydrazone (700 mgr) was dissolved in pyridine (14 cc) and refluxed at 140° (bath temp.) for 30 min. The cooled solution was added with chloroform (50 cc) and washed with 10% hydrochloric acid three times (30 cc each). The dinitrophenylhydrazone remained in chloroform in this treatment. The chloroform, after washed with sodium carbonate solution and dried, was evaporated. From the residue, the required substance crystallized out in yellow prisms upon the addition of ethyl acetate. M.p. 221°. But, once recrystallized from chloroform+ethyl acetate, m.p. was raised to 224°. Yield 400 mg (67 %). $[\alpha]_D^9 = +1937°$ (c 0.804, chlf.). $\lambda_{max.}^{chlf.}$ 380 mμ, log ε 4.51. (Anal. Calcd. for $C_{24}H_{20}O_5N_6Br$: N, 12.60. Found: N, 12.28).

Cleavage. The above phenylhydrazone of 1-bromo-D-codeinone (7.7 gr) was dissolved in acetone (260 cc), added with conc. HCl (26 cc) and incubated at 40° for 48 hours. About three fourth of acetone was then distilled away from the bath of 45°. The residue was poured into 2 % HCl (400 cc) at 40°. The clear aqueous solution, freed from resinous precipitate, was made alkaline with sodium carbonate and the base was taken up in ether. From the ethereal solution, after washed with caustic soda, the base was again extracted with 5 % HCl. The freed base from this acidic extract crystallized out in prisms from ether. Yield 870 mg. M.p. 199°.

The resinous precipitate was again cleaved in the same way and gave 140 mg of 1-bromo-D-codeinone of m.p. 195°. The third cleavage was useless (yield 5 mg). The total yield of crude product was 1015 mg (20 %).

The 1-bromo-D-codeinone, recrystallized from ethyl acetate, melted at 202~205° (incorr.) with decomposition. Gave no ferric chloride reaction. Showed $[\alpha]_D^{20} = +166°$ (c 0.695, chlf.). (Anal. Calcd. for $C_{18}H_{18}NO_3Br$: C, 57.44; H, 4.78; N, 3.70. Found: C, 57.44; H, 4.63; N, 3.88).

(+)-Codeine

1-Bromo-D-codeinone (1.89 gr) were dissolved in tetrahydrofurane (50 cc) and refluxed with $LiAlH_4$ (1 gr) for 7 hours and 30 minutes on a steam bath. After distillation of tetrahydrofurane, the residue was covered with chloroform (50 cc) and dissolved in 5 % hydrochloric acid (20 cc). To this acidic solution, 10 % caustic soda was added again, until almost all mineral matters were dissolved. The base was taken up in chloroform and the chloroform residue was turned

into hydrochloride. Yield 0.62 gr, from which 0.37 gr (*ca.* 24.5 %) free (+)-codeine was obtained as colourless prisms. M.p. 147°. Beilstein and ferric chloride reaction negative. $[\alpha]_D^{25} = +137.4°$ (c 0.7429, alc.). (Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.24; H, 7.02; N, 4.68. Found: C, 72.49; H, 6.96; N, 4.58).

Methiodide. Prepared in ordinary way. M.p. 267° (dec.). $[\alpha]_D^{27} = +80.7°$ (c 0.3816, 94% alc.). (Anal. Calcd. for $C_{18}H_{21}O_3N \cdot CH_3I$: N, 3.17. Found: N, 3.10).

d,l-Codeine

35 mg each of (−)- and (+)-codeine were dissolved in ether and mixed. On evaporation of ether *ca.* 60 mg racemic codeine were collected. M.p. 143°. $\alpha = \pm 0$.

d,l-Codeine methiodide. The racemic methiodide prepared from the equal quantity of (−)- and (+)-codeine methiodide melted at 246° (from ethanol) with decomposition.

(+)-Morphine

A mixture of (+)-codeine (300 mg) and pyridine hydrochloride (3 gr) was heated in an oil bath at 175° (internal temperature of the test tube) for 10 min., under the current of dry CO_2. The isolation of (+)-morphine, a phenolic base, was carried out in an ordinary way. Recrystallized from methanol and ether, it formed prisms and melted at 247～248° (incorr.). Yield 45 mg (23%, deducting unchanged (+)-codeine, which amounted to 120mg as hydrobromide).

Ferric chloride reaction positive. $[\alpha]_D^{24} = +132.1°$ (c 0.383, methanol). (Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.33; H, 6.53; N, 4.86).

d,l-Morphine

18 mg each of (−)- and (+)-morphine were mixed well in methanol+ether solution and evaporated. The crystallized base melted 232～233° and showed no rotatory power.

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Recently, we have boiled 2,4-dinitrophenylhydrazone of 1,5,7-tribromo-(+)-dihydrothebainone with pyridine in the same way as described before. The yield of 2,4-dinitrophenylhydrazone of 1-bromo-(+)-codeinone was 35%. This means the over-all yield of (+)-morphine doubled. Details will be published in the next communication.

References

1) The 66th Comm. on Sinomenine.
2) V. Mattox and E. Kendall: J. A. C. S., **70**, 882 (1948); **72**, 2290 (1950).
3) M. Gates and G. Tschudi: J. A. C. S., **74**, 1109 (1952).
4) The bromine atom enters C (7). This is proved by its almost quantitative transformation into 1-bromosinomeninone (III), when treated with caustic alkali.