117. Transformation of 1-Bromosinomenine into (+)-Morphine¹⁾

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1-Bromosinomenine (II) is easily obtainable by the dibromination of sinomenine (I). It is to be regarded as the optical antipode of a hypothetical 1-bromo-7-methoxycodeinone. Therefore, if we could replace its 7-methoxyl group by hydrogen, we would have (+)-1-bromocodeinone (III) from sinomenine.

This transformation was realised through its 2,4-dinitrophenylhydrazone in a somewhat roundabout way. When the hydrazone²⁾ of 1-bromosinomenine was hydrolysed on its 7-enolmethoxyl, it gave the 6-hydrazone of 1-bromosinomenine ketone (IV). The latter was reduced very mildly, to avoid the reduction of the hydrazone group, with NaBH₄. We obtained thus the hydrazone of 1-bromo-7-hydroxy-dihydrocodeinone (V),³⁾ which could not exist as a free ketone base.

The hydroxyl group was then replaced by chlorine atom with phosphorus pentachloride in chloroform. The here obtained 1-bromo-7-chloro-(+)-dihydrocodeinone-2,4-dinitrophenylhydrazone (VI) was not isolated in crystalline form, but was heated at once with pyridine at 135° for 30 min. We obtained the expected 2,4-dinitrophenylhydrazone of 1-bromo-(+)-codeinone in 70% yield.

Its property was exactly the same with that of the substance prepared from 1,7-dibromo-(+)-dihydrocodeinone, as follows.

	From 1-bromo-sinomenine	From 1, 7-dibromo-(+)-dihydrocodeinone
M.p.	224° dec.	224° dec.
[α] _D	+1927°	+1937°
Ultraviolet absorption	378 mμ	380 mμ

The hydrazone thus obtained was cleaved into (+)-1-bromocodeinone, reduced then by LiAlH₄ into (+)-codeine and lastly demethylated into (+)-morphine. These three substances coincided respectively well with those obtained from 1,7-dibromo-(+)-dihydrocodeinone, only with the yield almost quintupled. The bottleneck was always in the cleavage of the hydrazone of 1-bromocodeinone (average 25%). This wants a further study.

1) The 70th Comm. on Sinomenine.

2) Abbreviated from 2, 4-dinitrophenylhydrazone.

3) See experimental for details.

Our hearty thank is due to Shionogi Pharmaceutical Co. for delivering us freely the rhizome of *Sinomenium acutum* and to Sankyo Pharmaceutical Co. for carrying out the microanalyses.

Note. Here we may add that the ketal method, reported in Proc. Japan Acad., 32, 45 (1956), seems to have no practical value. After one year's ardent research, we could not improve its exceedingly poor yield. On the ketal derivatives of sinomenine and allied substances, we wish to report somewhere shortly.

Experimental

(1) 2,4-Dinitrophenylhydrazone of 1-bromosinomenine. 1-Bromosinomenine (II, 0.5 gr) and 2,4-dinitrophenylhydrazine (0.25 gr) were warmed in acetic acid (5 cc) at 50° for 30 min. The hydrazone was extracted by chloroform from soda-alkaline solution. Yellowish red prisms from acetone. M.p. 210° (immersed in a bath warmed at 205°. At the slow heating, no sharp m.p. was observed).

$\lambda_{\text{max}}^{\text{chlf.}}$, 379 m μ (log ϵ 4.47). $[\alpha]_{\text{D}}^{18} = +1502.8^\circ$ (c 0.78, chlf.). (Analysis. Calcd. for C₂₅H₂₄O₇N₅Br: N, 11.94. Found: N, 11.77).

(2) Hydrolysis of the above hydrazone on its 7-enolmethoxyl was accomplished by refluxing it (0.3 gr) in acetone (30 cc) and 20% HCl (1.5 cc) for two hours. 1-Bromosinomenine ketone-6-hydrazone (IV), recrystallised from acetone melted at 160° with decomposition. $\lambda_{\text{max}}^{\text{chlf.}}$, 396 m μ (log ϵ 4.38), $[\alpha]_{\text{D}}^{20} = +800.8^\circ$ (c 0.247, chlf.). (Analysis. Calcd. for C₂₄H₂₂O₇N₅Br (572.37): N, 12.24%; CH₃O, 5.42%. Found: N,

12.18%; CH₃O, 5.32%).

(3) Reduction of 1-bromosinomeneine ketone-6-(2,4-dinitrophenyl)-hydrazone. 2 gr of the hydrazone was dissolved in ethyl acetate (45 cc), ice-cooled and added with methanolic suspension (10 cc) of NaBH₄ (50 mg) in one lot. After five min. 10 cc of 10% hydrochloric acid was added and the whole was left stand for ten min. again. The ethyl acetate layer was washed twice with soda, once with water, dried, and evaporated. When benzene was added to the residue, the alcoholic base crystallised out after sometime. M.p. 165° (with foaming). Yield 1.6 gr (80%). The m.p. is raised to 206° (dec.) by the recrystallisation from ethyl acetate, but the yield is scanty. (Analysis. Calcd. for C₂₄H₂₄O₇N₅Br (574.38): C, 50.18; H, 4.21; N, 12.19; Br, 13.91. Found: C, 50.34; H, 4.47; N, 12.36; Br, 13.86). From this analysis and the following transformation, it is doubtless that we have here the hydrazone of a 1-bromo-7-hydroxy-(+)-dihydrocodeinone, but this hydrazone (m.p. 206°) is not the same with the hydrazone,⁴⁾ obtained from 1,7-dibromodihydrocodeinone on treating it with 2,4-dinitrophenylhydrazine. The property of these two hydrazones is compared in the following.

	From 1-bromo- sinomeneine	From 1, 7-dibromo- (+)-dihydrocodeinone
M.p.	165° (foams) 206° dec.	212°
[α] _D (chlf.)	+409.4° (22°, c 0.936)	+1022.5° (28°, c 1.274)
λ _{max} ^{chlf.}	365 mμ	365 mμ
Boiling with pyridine	To introduce double bond, the hydroxyl must be first replaced by Cl.	Double bond is introduced.

Whether these differences come from the direction of the hydrazone group (syn- or anti-) or from the diastereoisomerism of the secondary alcohol or from the combined causes is not known at present.

Cleavage. By cleaving this hydrazone (m.p. 165°, 0.15 gr) with acetone (20 cc) and conc. HCl (2 cc) at 60° for 1.5 hours, we obtained 80 mg of 1-bromosinomeninone (m.p. 228°, also the mixed m.p.). This proved that the ketone group at C(7) of the hydrazone was reduced to

alcohol, for it is our long experience that the system $\begin{array}{c} \text{H} \\ | \\ \text{---C---C---C---} \\ | \quad | \quad | \\ \text{O} \quad \text{O} \quad \text{OH} \end{array}$

can not exist in sinomenine derivatives, but converges invariably into a phenol and a diketone $\begin{array}{c} \text{---C---C---C---} \\ | \quad | \quad | \\ \text{OH} \quad \text{H}_2\text{O} \quad \text{O} \quad \text{O} \end{array}$.

4) Marshall Gates, from the result of the elementary analysis (J. A. C. S., **78**, 1385 (1956)), first pointed out that in this hydrazone the bromine atom on C(7) was already hydrolysed away. Our recent analysis coincided well with his result (Anal. Found: C, 50.26; H, 4.09; N, 11.34; Br, 14.06. Calcd. loc. cit.).

Treating this hydrazone (VI) with conc. ammonia regenerated the hydrazone of the starting 1-bromo-7-hydroxy-(+)-dihydrocodeinone (V), in contrary to the hydrazone of 7-chloro-(+)-dihydrothebainone.⁵⁾

(4) 2,4-Dinitrophenylhydrazone of 1-bromo-(+)-codeinone. 2 gr of the substance of m.p. 165° (foaming), dissolved in 40 cc of chloroform, was added to the fine suspension of PCl₅ (4 gr) in chloroform (60 cc) under ice-cooling. By shaking gently, the pentachloride dissolved, leaving a homogeneous yellow solution. After standing one hour, the chloroform solution was washed thrice with ice-water, once with soda solution, dried, and evaporated.

The residue was heated with pyridine (20 cc) at 140° (bath temp.) for 30 min. Pyridine was then driven away i.v. and the residue was dissolved in chloroform (40 cc). The chloroform solution was washed once with 5% caustic soda and twice with 5% hydrochloric acid to remove phenolic substance and pyridine. The chloroform solution, after washed once with soda, was evaporated and the residue was treated with ethyl acetate, when the 2,4-dinitrophenylhydrazone of (+)-1-bromocodeinone crystallised out in prisms at once. M.p. 220°. Yield 1.25 gr. Twice recrystallised from ethyl acetate, the m.p. was raised to 224°. $\lambda_{\text{max}}^{\text{chlf.}}$: 378 m μ (log ϵ 4.52). $[\alpha]_{\text{D}}^{20} = +1927^\circ$ (c 0.642, chlf.).

(5) Transformation into (+)-codeine and (+)-morphine. On these transformations, we have already reported.⁶⁾ Only the cleavage was carried out this time by immersing the cleaving flasks in a water bath at 50° for 20 hours (and two overnights at room temp.), by which the yield of (+)-1-bromocodeinone was raised to 25%.

	From 1-Br-sinomenine	From 1,7-dibromo- dihydrocodeinone	Mixed m.p.
(+)-1-Br-codeinone	204°	204°	204°
(+)-Codeine	158°; $[\alpha]_{\text{D}} + 137.4^\circ$	157°; $[\alpha]_{\text{D}} + 137.4^\circ$	157°
(+)-Morphine	246°	245°	245°

In general, the manipulation up to the hydrazone of 1-bromocodeinone is far easier in this method than in 1,7-dibromodihydrocodeinone method. It is, however, only applicable to sinomenine itself.

5) Proc. Japan Acad., **29**, 211 (1953).

6) Proc. Japan Acad., **30**, 769 (1954).