39. *On the Acetolysis of (+)-1, 5, 7-Tribromodihydrothebainone and (+)-1, 7-Dibromodihydrocodeinone*[*]

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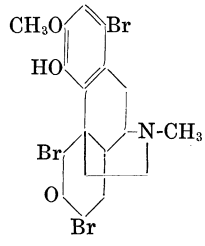
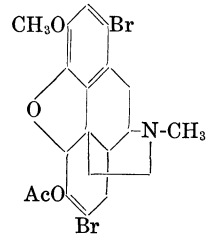
I. On the acetolysis of (+)-1, 5, 7-tribromodihydrothebainone

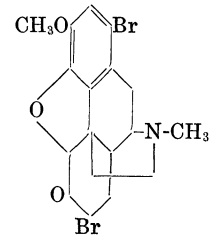
This experiment was carried out to see how behaves (+)-1, 5, 7-tribromodihydrothebainone (I) on mild acetolysis, namely whether it gives (+)-1-bromocodeinone by this treatment or not. The result was that it gave solely an enol acetate of (+)-1, 7-dibromodihydrocodeinone (II) and no trace of phenanthrene was detected. The oxide ring closure of the starting substance (I) by boiling with acetic anhydride was rather unexpected from our former experience,[2] but seemed to be not unnatural, if the C(5)-standing bromine atom was replaced by acetoxy radical in this procedure.



I



II



III

Moreover, the formation of the same (+)-1, 7-dibromodihydrocodeinone enol acetate from (+)-1, 7-dibromodihydrocodeinone (III) makes the oxide ring closure doubtless. It is, however, uncertain that the enol double bond lies in $\Delta^{5,6}$ or $\Delta^{6,7}$. The $\Delta^{6,7}$ is more preferable from the experience with dihydrocodeinone enol methylether. Here lies the double bond between $\Delta^{6,7}$ without doubt.

The above consideration is supported also by its transformation. (+)-1, 7-Dihydrocodeinone enol acetate gave with caustic alkali very easily (+)-1-bromosinomeninone, as (+)-1, 7-dibromodihydrocodeinone (III) did. By catalytic reduction in an acidic medium, it gave (+)-dihydrocodeinone itself, but when the reduction was carried out in the presence of sodium bicarbonate to neutralise the acid to be produced, we obtained (+)-dihydrocodeinone enol acetate in 10% yield.

These investigations are of some interest in view of the fact that the different sinomenine derivatives behaved very differently in boiling with acetic anhydride according to slight differences in their constitution.

[*] The 75th Communication on Sinomenine.

These relations are shown in the following list.

	Substance	Transformed products	Ref.
I	Dihydrocodeinone	Simple enol acetate	See Experimental.
II	1-Bromodihydrocodeinone	,,	
III	1, 5, 7-Tribromodihydro-thebainone	1, 7-Dibromodihydro-codeinone enol acetate	
IV	1, 7-Dibromodihydrocodeinone	,,	
V	1-Bromosinomeneine ketone[2]	1-Bromodehydro-sinomeninone diacetate	2) K. Goto et al.: B.C.S.J., **17**, 439 (1942).
VI	1, 5-Dibromosinomeninone	1-Bromo-3-methoxy-4, 6, 7-triacetoxy-phenanthrene	
VII	Sinomeninone[3]	3-Methoxy-4, 6-diacetoxy-phenanthrene (or its 1-Br-der.)	3) C. Schöpf et al.: Ann., **492**, 213 (1932). K. Goto et al.: Ann., **497**, 289 (1932).
VIII	1-Bromosinomeninone	Isothebenine triacetate (or its 1-Br-der.)	

Experimental

(1) (+)-Dihydrocodeinone enol acetate. Preparation as usual. M.p. 155°. (Anal. Calc. for $C_{20}H_{23}O_4N$ (341.39): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.44; H, 6.54; N, 4.08.)

d, l-Dihydrocodeinone enol acetate. M.p. 165°. $\alpha = \pm 0°$ (c 0.4, chlf.).

(2) (+)-1-Bromodihydrocodeinone enol acetate. Preparation as usual. M.p. 162°. (Anal. Calc. for $C_{20}H_{22}O_4NBr$ (420.30): C, 57.15; H, 5.28; N, 3.33; Br, 19.01. Found: C, 57.46; H, 5.49; N, 3.14; Br, 18.53.)

d, l-1-Bromodihydrocodeinone enol acetate. M.p. 176°. $\alpha = \pm 0°$ (c 0.8, chlf.).

(3) (+)-1, 7-Dibromodihydrocodeinone enol acetate (II) (a) From (+)-dihydrothebainone. (+)-Dihydrothebainone (5 gr) was brominated with 3 mols Br_2 in glacial acetic acid (50 cc). After distillation of acetic acid, the residue was boiled with acetic anhydride (20 gr), and fused sodium acetate (2 gr) for 3.5 hours. The anhydride was then distilled off i.v. and the residue suspended in 10 cc methanol, was poured into 100 cc 3% acetic acid. The precipitate was collected and washed with methanol (50 cc). Once recrystallised from water, the colourless product of m.p. 265° was obtained. Yield 2.5 gr (25%). This was found to be the hydrobromide of the substance (II).

(b) The same hydrobromide can be obtained from (+)-1-bromodihydrocodeinone. (+)-1-Bromodihydrocodeinone hydrobromide was monobrominated and boiled with acetic anhydride as in (a). Yield of the substance of m.p. 265° was more than 10%. From the filtrate, some quantity of the free base was obtained.

$[\alpha]_D^{20} = +208.5°$ (c 0.92, chlf.). λ_{max}^{MeOH} 292 mμ. Its spectrum represents an ordinary form. (Anal. Calc. for $C_{20}H_{21}O_4NBr_2 \cdot HBr = 580.13$: C, 41.40; H, 3.82; N, 2.41; Br, 41.33 (of which mobile Br, 13.78). Found:

C, 42.69; H, 4.17; N, 2.62; Br, 42.24 (mobile Br 13.57).)

Hydrolysis. The hydrobromide (II; 100 mg) was dissolved in methanol (5 gr), added with 33% caustic soda (6 drops) and set aside overnight. From this, 1-bromosinomeninone (m.p. 228°, also the mixed m.p.) was obtained almost quantitatively.

The free base is liberated from the hydrobromide with sodium carbonate, or obtained directly from the above acetic acid filtrate. M.p. 255°. Very soluble in methanol. It gives no ferric chloride reaction but Beilstein reaction is positive. $[\alpha]_D^{25}=+229.8°$ (c 1.848, chlf.). (Anal. Calc. for $C_{20}H_{21}O_4NBr_2=499.2$: C, 48.09; H, 4.21; N, 2.81; Br, 32.01. Found: C, 48.39; H, 4.42; N, 3.20; Br, 31.93.)

It regenerates the hydrobromide with HBr.

(−)-L-1, 7-Dibromodihydrocodeinone enol acetate. Preparation from (−)-L-tribromodihydrothebainone as with (+)-derivative. M.p. of the hydrobromide 265°. $[\alpha]_D^{18}=-210.2°$ (c 0.820, chlf.).

The free base melted at 255°. (Anal. Found: C, 48.21; H, 4.29; N, 2.81; Br, 31.89. Calc. as above.)

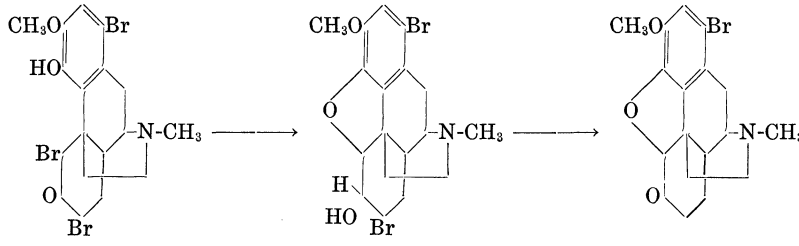
d, l-1, 7-Dibromodihydrocodeinone enol acetate hydrobromide. M.p. 265° from methanol. $\alpha=\pm 0$ (c 0.7, chlf.). The free racemic body obtained from the above racemic hydrobromide melted at 200° (from ether). $\alpha=\pm 0°$ (c 0.7, chlf.).

Catalytic reduction of the hydrobromide of (II). (a) In acidic medium. The reduction mixture consisted of 0.5 gr the hydrobromide of m.p. 265°, 50 mg $PdCl_2$, 140 cc methanol and 1 cc 10% HCl. The calculated quantity of H_2 was absorbed in 30 min. The isolated base crystallised well from acetone. M.p. 191–195°. It gave neither Beilstein nor ferric chloride reaction. Mixed with (+)-dihydrocodeinone of m.p. 196°, it melted at 195°. (b) In sodium bicarbonate alkaline medium. The catalytic reduction was carried out in a similar manner as above, only 300 mg sodium bicarbonate took place of 1 cc 10% HCl. From 1 gr the hydrobromide 100 mg of dihydrocodeinone enol acetate (m.p. 150°) was obtained. Neither Beilstein reaction nor ferric chloride reaction. Mixed m.p. with the enol acetate of m.p. 155° remained 150°. From uncrystallisable part, after hydrolysis, some (+)-dihydrocodeine was isolated.

II. On the transformation of (+)-1, 7-dibromodihydrocodeine

In the previous experiments it was shown that the ketone group of (+)-1, 5, 7-tribromodihydrothebainone hindered the introduction of a double linking by the elimination of α-standing bromine atom. It is, therefore, reasonable to suspect that if the ketone group was reduced to a secondary alcohol beforehand, this introduction might be realized with some ease. We prepared (+)-1, 5-dibromodihydrocodeine and ex-

amined its behaviour against acidic as well as basic reagents. But, the substance gave exclusively (+)-1-bromodihydrocodeinone in these treatments. The results are summarised in the following table.



I II III

	Method of treating	Result (Percentage shows the yield of 1-bromodihydrocodeinone.)
(1)	CH_3ONa (10%), 28°, 1.5 h	Quantitative (m.p. 205°)
(2)	Pyridine, 135–140°, 1/2 h	80% (m.p. 205°)
(3)	Acetic anhydride, 95°, 2 h	Amorphous, but gives 1-bromodihydrocodeinone on hydrolysis (m.p. 206°)
(4)	$CH_3 \cdot COOAg + CH_3 \cdot COOH$, 100°, 1 h	>70% (m.p. 206°)
(5)	$PO_4HNa_2 + PO_4H_3$, 100°, 1 h	Unchanged (>80% recovered)
(6)	2.5% HCl, boiling, 1/2 h	>75% (m.p. 205°)
(7)	C_6H_5COCl + pyridine, 100°, 2 h	Unchanged
(8)	Na-glycolate, 150°, 13 h	No crystalline substance
(9)	Conc. ammonia at room temp.	Unchanged

The convergence of a vicinal bromohydrine to a ketone group is a common phenomenon, but it is remarkable that in this case bromohydrine-7, 6 converged to the C(6)-keto group, while in (+)-7-hydroxydihydrothebainol the two secondary alcohol groups converged to the C(7)-keto group, giving (+)-dihydrothebainone-7.[1] This difference must have been caused by the influence of the oxide ring.

The (+)-1, 7-dibromodihydrocodeine was prepared in two ways, either by $NaBH_4$ reduction of (+)-1, 5, 7-tribromodihydrothebainone or by the monobromination of (+)-1-bromodihydrocodeinone and the followed reduction. As it is shown in the experimental part, here was obtained one and the same (+)-1, 7-dibromodihydrocodeine. It is therefore clear that in the former method the oxide ring must have been closed during the reduction or the extraction from alkaline medium.

Experimental

(1) (+)-1, 7-Dibromodihydrocodeine (II). (a) From 1, 5, 7-tribromodihydrothebainone. (+)-Dihydrothebainone (4 gr) was tribrominated in acetic acid. The acetic acid was evaporated i.v. and driven off by repeated evaporation with methanol. The residue was dissolved in

1) K. Goto and K. Michi: Bull. Chem. Soc. Japan, **22**, 262 (1949).

methanol (40 cc) and reduced with $NaBH_4$ (2 gr). After standing two hours, the product was extracted with chloroform from soda alkaline solution. 1, 7-Dibromodihydrocodeine crystallised out from chloroform in short prisms. It sinters from 168° and melts at 230° with forming. Yield 2.8 gr (46%).

(b) From 1-bromodihydrocodeinone. 1-Bromodihydrocodeinone hydrobromide (2.4 gr = 2 gr free base) was monobrominated in acetic acid. After evaporation of acetic acid as in (a), the residue was reduced in methanol (35 cc) with $NaBH_4$ (0.5 gr). Yield 1.4 gr (72%). M.p. 230° (dec.) sintering at 170°. The mixed m.p. of (a) and (b) unaltered.

$[\alpha]_D^{30} = +138.4°$ (c 1.819, chlf.). The substance shows no ferric chloride reaction, and is insoluble in caustic alkali. (Anal. Calc. for $C_{18}H_{21}O_3NBr_2$: C, 47.08; H, 4.61; N, 3.05; Br, 34.81. Found: C, 47.32; H, 4.49; N, 3.14; Br, 35.05.)

The hydrochloride and the hydrolysis. When the above bromohydrin (0.5 gr) was heated with 2.5% HCl (20 cc) on a water bath and cooled, the hydrochloride of the bromohydrin crystallised out in beautiful prisms. M.p. 260° (sharp, dec.). (Anal. Calc.: Cl, 7.15. Found: Cl, 6.87.) From the filtrate, after boiling 30 min, (+)-1-bromodihydrocodeinone was obtained in a quantitative yield. M.p. 205°.

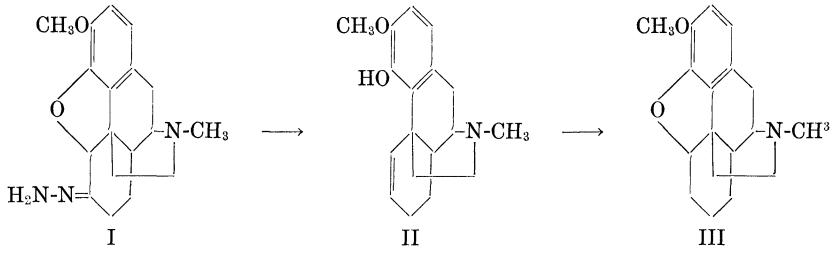
Methiodide. Prepared in ordinary way. Short prisms. M.p. 179° (sharp, dec.). (Anal. Calc.: I, 21.11. Found: I, 20.76.)

(2) (−)-L-1, 7-Dibromodihydrocodeine. Preparation as with (+)-D-substance. M.p. 230°. $[\alpha]_D^{17} = -135.7°$ (c 1.105, chlf.). (Anal. Calc. as above. Found: C, 46.91; H, 4.70; N, 2.64; Br, 35.05.)

d, l-1, 7-Dibromodihydrocodeine. M.p. 183° (from methanol). $\alpha = \pm 0°$ (c 2.0, chlf.).

III. Miscellaneous

(1) (+)-Desoxydihydrocodeine-C. After L. Small,[2] we have prepared (+)-desoxydihydrocodeine-C from (+)-dihydrocodeinone by boiling the latter with NH_2-NH_2, NaOH, and glycol at 130°. The product was then boiled with 50% sulfuric acid for 1 hour and turned into (+)-desoxydihydrocodeine-D (III).

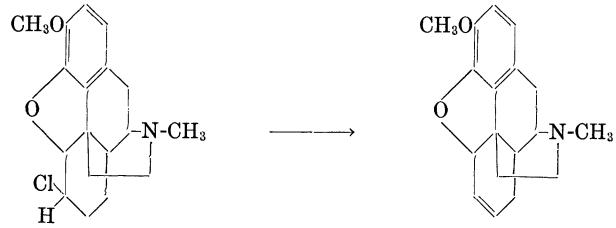


2) L. Small: J. Org. Chem., **17**, 1540 (1952). There recorded $[\alpha]_D^{20} = -4.0°$

This transformation proved our view that in the transformation of dihydrothebainol into desoxydihydrocodeine-D by boiling with 50% sulfuric acid the intermediate product must be desoxydihydrocodeine-C, as advocated in Acta Phytochimica, 15, 187 (1949).

(+)-Desoxydihydrocodeine-C (II) crystallised from acetone with 2 mols of the solvent and melts at 112°. $[\alpha]_D^{29} = +1.7°$ (c 1.508, abs. alc.). (Anal. Calc. for $C_{18}H_{23}O_2N$ (285.37): C, 75.75; H, 8.12; N, 4.91. Found: C, 75.42; H, 8.13; N, 4.69.)

(2) A simpler method to prepare (+)-desoxycodeine-C (V) from (+)-dihydrochlorocodide. In this preparation, boiling of the latter with Na dissolved in glycol at 140° for 1.4 hours in an open vessel can well replace the method, in which the chlorocodide is treated with $Na+CH_3OH$ in a closed tube in the same way. Yield, twice repeated, more than 50%.



IV V

(3) (+)-Dihydrocodeinone from sinomenine *par un coup*. Sinomenine hydrochloride (1 gr) was dissolved in syrupy phosphoric acid (10 cc) and added with stannous chloride (2.5 gr). The whole was then warmed first at 100° in an oil bath for half an hour (hydrolysis of enol methoxyl and reduction of one ketone group) and then at 135° for one and half hours (transformation of (+)-dihydrosinomeninone into (+)-dihydrocodeinone).[3] The extraction and purification of the latter as usual. M.p. 194° (also the mixed m.p.). Yield 65%.

50% sulfuric acid can replace the phosphoric acid, only in this case a larger amount of $SnCl_2+2H_2O$ (10 gr) and a shorter boiling (1 hour) are necessary.

But, for the preparation of a large amount, boiling of dihydrosinomenine with 50% sulfuric acid is more convenient.

The authors' sincere thanks are due to the Takeda Pharmaceutical Industries for the micro-analyses.

3) K. Goto and I. Yamamoto: Bull. Agr. Chem. Soc. Japan, **19**, 119 (19)55.