13. *On Some Derivatives of Metathebainone*[1]

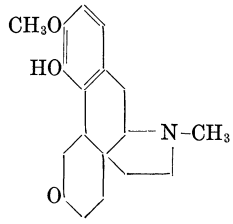
By Kakuji GOTO, M.J.A., and Izuru YAMAMOTO
Department of Chemistry, Kitasato Institute, Tokyo, Japan
(Comm. Jan. 12, 1961)

The authors have prepared (+)-morphine from (+)-dihydrocodeinone by two methods, viz. 2,4-dinitrophenylhydrazine method of M. Gates and α-bromodimethylketal method of L. Small.[2] The authors now applied those two methods to (−)-dihydrometathebainone to see whether it gave metamorphine or not. (−)-Dihydrometathebainone behaved, however, somewhat differently and the authors could not attain the expected results. Since this difference seems to be due to the different attaching point of ethanamine chain in these two substances, it may be worth while to record the experiments in some detail.

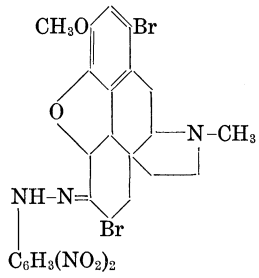
When dihydrometathebainone (I) was treated with 3 mols of bromine and then added with 2,4-dinitrophenylhydrazine in acetic acid, a bulky precipitate was formed on neutralizing hydrobromic acid with sodium acetate. The precipitate was boiled for 30 minutes with pyridine and a dinitrophenylhydrazone of m.p. 263° (dec.) was obtained in crystalline form. This crystal, when decomposed with acetone-hydrochloric acid, gave crystal of m.p. 199°, which is deduced to be 1-bromo-7-hydroxydihydrometacodeinone (III) from its properties, namely insolubility in caustic alkali, negative ferric chloride reaction and infrared absorption (non-conjugated ketone (5.85 μ) and hydroxyl (2.93 μ)). The substance of m.p. 199° was then reduced with $LiAlH_4$ in tetrahydrofuran into a bromine free substance of m.p. 201°. This substance seemed to be 7-hydroxydihydrometacodeine (IV) from its properties. The above 2,4-dinitrophenylhydrazone of m.p. 263° was therefore undoubtedly that of 1,7-dibromodihydrometacodeinone (II).

The stability of this 2,4-dinitrophenylhydrazone against boiling pyridine is remarkable compared with that of tribromodihydrothebainone, whose bromine atom on C(7) is easily eliminated in the formation of a double bond by this treatment. Moreover, in the derivatives of dihydrometacodeinone the arrangement oxide ring(C(4)-C(5))-ketone(C(6))-hydroxyl(C(7)) is stable, while in dihydrocodeinone derivatives this sequence rearranges invariably into hydroxyl(C(4)) and two vicinal ketone groups(C(6) and C(7)).

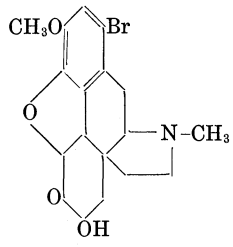
Beside these, there are some more minute differences in the behaviour of dihydrocodeinone and dihydrometacodeinone against same reagents, but they will be dealt with in the experimental.



I

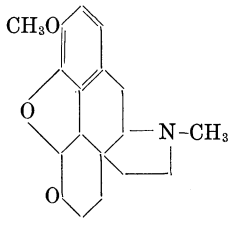


II



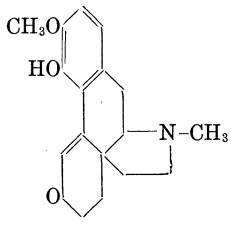
III

IV $\left(\rangle CO = \rangle C\langle^{OH}_{H},\ Br=H\right)$

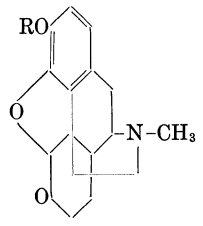


V

VI $\left(\rangle CO = \rangle C\langle^{OH}_{H}\right)$



VII



IX

X$\left(R=CH_3,\ \rangle O = OH,\ H\right)$

VIII $\left(\rangle CO = -OCH_3,\ \Delta^{6,7}\right)$

Experimental

(1) 2,4-Dinitrophenylhydrazone of 1,7-dibromodihydrometacodeinone (II). Dihydrometathebainone hydrochloride (2.5 gr) was dissolved in glacial acetic acid (25 cc) and tribrominated with acetic acid solution (40 cc) of bromine (3.6 gr). After standing half an hour, 2,4-dinitrophenylhydrazine (1.63 gr) and fused sodium acetate (2 gr) were added to the solution and the whole was warmed at 30° for an hour, when a bulky orange precipitate was formed. The acetic acid was then driven off at 60° i.v. and the residue was refluxed with pyridine (25 cc) for 30 minutes. The residue from pyridine was dissolved in chloroform and the chloroform was washed with 5% caustic soda and then with water. The residue of the chloroform evaporation crystallized out from ethyl acetate and was purified from chloroform-ethyl acetate. Orange red prisms. M.p. 263° (dec.). $[\alpha]_D^{17}=+393.3°$ (c 0.787, chlf.). $\lambda_{max}^{chlf.}$ 370 mμ. (Anal. Calcd. for $C_{24}H_{23}O_6N_5Br_2$ (637.30): C, 45.23; H, 3.64; N, 10.99; Br, 25.08. Found: C, 45.10; H, 3.73; N, 10.95; Br, 25.02.)

(2) 1-Bromo-7-hydroxydihydrometacodeinone (III). The above hydrazone (1.0 gr) was cleaved in acetone (30 cc) with conc. hydrochloric acid (3 cc) by warming at 50° for 20 hours. After driving off the large part of acetone, the remaining liquid was poured into

50 cc of 2% hydrochloric acid. The filtered solution was made alkaline and extracted with ether. The ethereal solution was washed with 5% caustic soda and then the base was removed from ether to 5% hydrochloric acid. From the latter, the base was again set free and extracted with ether. The ethereal residue crystallized out in colourless prisms. Yield 0.23 gr (37%). M.p. 199° (dec.) from ethyl acetate. No ferric chloride reaction. Insoluble in dil. caustic soda. With conc. H_2SO_4 it gives faint yellow colour at first, but the colour changes deep red on standing. Infrared absorption reveals non-conjugated ketone (5.85 μ) and hydroxyl (2.93 μ). $[\alpha]_D^{19} = -67.6°$ (c 0.991, chlf.). (Anal. Calcd. for $C_{18}H_{20}O_4NBr$: C, 54.83; H, 5.11; N, 3.55; Br, 20.27. Found: C, 54.99; H, 5.02; N, 3.47; Br, 19.91.)

(3) 7-Hydroxydihydrometacodeine (IV). The above base (III; 0.4 gr) was reduced with $LiAlH_4$ (0.6 gr) in tetrahydrofuran solution (40 cc) by boiling for 18 hours. After driving off the solvent, the unused $LiAlH_4$ was decomposed by ethyl acetate, and the precipitate was dissolved in 10% HCl (15 cc) and poured into 20% NaOH (15 cc) containing 3 gr of Rochelle salt. The base was then extracted from this solution with chloroform several times. The residue of chloroform evaporation crystallized from acetone, and was purified from chloroform-ethyl acetate. M.p. 201°, colourless prisms. Yield 0.25 gr (60%). Beilstein reaction negative. Mixed m.p. with starting material (III; m.p. 199°) lowered to 175° (dec.). $[\alpha]_D^{22} = -227.2°$ (c 0.323, chlf.). (Anal. Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 67.82; H, 7.02; N, 4.61.) Infrared absorption reveals hydroxyl (3.0 μ) but no carbonyl band.

(4) Dihydrometacodeine (VI). To the methanolic suspension (50 cc) of dihydrometacodeinone (2 gr), $NaBH_4$ (1.2 gr) was added in 15 minutes and set aside for two hours at room temperature. The solution was made strongly alkaline with 20% caustic soda (40 cc) and extracted with chloroform three times. The chloroform was washed with water and driven off. The residue was recrystallized from ethyl acetate three times. M.p. 125° (foaming; sintering from 116°). Yield 80%. No ferric chloride reaction. $[\alpha]_D^{30} = -100.7°$ (c 1.894, chlf.). Infrared, no carbonyl band, but hydroxyl (2.82 μ). (Anal. Calcd. for $C_{18}H_{23}O_3N$ (301.37): C, 71.73; H, 7.69; N, 4.65. Found: C, 70.98; H, 7.77; N, 4.65.) No crystalline methiodide. Acetyl dihydrometacodeine is also amorphous, but on addition of methyl iodide to it, methiodide was obtained in crystals. M.p. 243° (dec.) from ethanol. (Anal. Calcd. for $C_{20}H_{25}O_4N \cdot CH_3J$ (485.35): J, 26.2%. Found: J, 25.7%.)

(5) Dihydrometacodeinone enol methyl ether (VIII). In the *ter.*-butanolic solution (12 cc) of metallic sodium (0.083 gr), dihydrometacodeinone (1.0 gr) was dissolved. To this solution, a mixture of dimethyl

sulfate (0.42 gr) and *ter.*-butanol (2 cc) was added in twenty minutes. After standing for one hour, the whole was warmed on a steam bath further for one hour and then the large part of *ter.*-butanol was evaporated. To the residual liquid, water (33 cc) and ammonia (2 cc) were added and shaken with chloroform three times. When the residue of chloroform evaporation was treated with methanol, a small quantity (0.1 gr) of the starting material was recovered. The main part was dried up and in Al_2O_3-chloroform system chromatographically separated. From the first run of elution chloroform, 0.4 gr of the enol ether was obtained. M.p. 90–91° from ether. Colourless prisms. Yield 0.33 gr (30%). (Anal. Calcd. for $C_{19}H_{23}O_3N$ (313.38): C, 72.82; H, 7.40; N, 4.47; CH_3O–, 19.86. Found: C, 72.83; H, 7.22; N, 4.50; CH_3O–, 19.20.) This substance gave no crystalline $BrOCH_3$ adduct on its enol double bond.

(6) Metathebainone (VII) from dihydrometacodeinone (V). Dihydrometacodeinone (0.25 gr) was heated with pyridine hydrochloride (3 gr) at 173–180° for seven minutes. The reacting mixture was made alkaline and extracted with chloroform. The chloroform residue gave metathebainone, m.p. 116° (foaming). Yield 58%. Ferric chloride reaction green. Mixed m.p. with metathebainone of authentic preparation remained unaltered.

(7) (+)-Dihydromorphinone (IX, R=H). (+)-Dihydrocodeinone (0.5 gr) was demethylated by heating with pyridine hydrochloride at 210–220° for five minutes. The base, isolated in ordinary way, showed to be (+)-dihydromorphinone. M.p. 266° (dec.) from methanol. Prisms. Yield 0.28 gr. $[\alpha]_D^{20}=+206.1°$ (c 1.053, chlf.). (Anal. Calcd. for $C_{17}H_{19}O_3N$ (285.3): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.65; H, 7.28; N, 4.79.)

Oxime. Prepared in ordinary way. M.p. 235° (dec.) from methanol. (Anal. Calcd. for $C_{17}H_{20}O_3N_2$: N, 9.33. Found: N, 9.28.)

The above properties coincided well with those of (−)-dihydromorphinone except the direction of optical rotation.

(8) (+)-Dihydroisocodeine (X). Reduction of (+)-dihydrocodeinone to (+)-dihydrocodeine with $NaBH_4$[3] was re-examined and the formation of (+)-dihydroisocodeine was ascertained. The both (+)-dihydrocodeines were successfully separated by the aid of column chromatography.[4]

(+)-Dihydrocodeinone (1.5 gr) was dissolved in methanol (30 cc) and added with $NaBH_4$ (0.8 gr) in 7 minutes. After two hours, the methanol was evaporated down to the half of its volume at 70° i.v. and added with 20% NaOH (7 cc) and warmed at 80° for 1.5 minutes. The alkaline solution was diluted with water (40 cc) and extracted with chloroform three times. Evaporation of the chloroform left a thick syrup (1.5 gr). The syrup was dissolved in chloroform (15 cc) again and poured on an alumina-column (50 gr Al_2O_3, 25 cm high) and

was eluted with chloroform into 37 fractions, each consisting 6 cc chloroform. The main part of (+)-dihydrocodeine came out in fractions 7–17, crystallized rather quickly, and melted at 89° (sintering at 86°). M.p. of the crystal water free substance was 110°. Yield 0.44 gr. Added with those of the other fractions, total yield 0.81 gr (54%). Picrate, m.p. 209°. Methiodide, m.p. 257°. The mixed m.p. with (+)-dihydrocodeine, prepared by the catalytic reduction of (+)-dihydrocodeinone was unaltered. The same is true of the picrate and the methiodide.

(+)-Dihydroisocodeine (X). The alumina-column, eluted out with chloroform, was treated with 5% H_2SO_4 (100 cc), and the acidic eluate was made alkaline with caustic soda and extracted with chloroform. The residue of the chloroform was crystallized from ethanol. M.p. 200° (after two recrystallization from ethanol). Yield 0.36 gr (24%). $[\alpha]_D^{10}=+139.1°$ (c 1.08, EtOH). (Anal. Calcd. for $C_{18}H_{23}O_3N$ (301.31): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.95; H, 7.47; N, 4.48.)

Methiodide. M.p. 273° (dec.). (Anal. J. Calcd: 28.63. Found: 28.43.)

Acetyl derivative. M.p. 166°. $[\alpha]_D^{10}=+124.8°$ (c 1.200, EtOH). (Anal. Calcd. for $C_{20}H_{25}O_4N$ (343.41): N, 4.08. Found: 4.00.)

These melting points coincide well with those of (−)-dihydroisocodeine and its corresponding derivatives.

The authors thank heartily the Takeda Pharmaceutical Industries for their kind micro-analyses.

References

1) The 77th Communication on Sinomenine.
2) K. Goto and I. Yamamoto: Proc. Japan Acad., **30**, 769 (1954); **33**, 477 (1957); cf. **34**, 60 (1958).
3) K. Goto and I. Yamamoto: Bull. Agr. Chem. Soc. Japan, **19**, 110 (1955).
4) Cf. M. M. Baizer, A. Loter, K. S. Ellner, and D. R. Satriana: J. Org. Chem., **16**, 543 (1951).