Notes

UDC 615.783.1-012

Michihiro Yamada : A New Synthetic Method of Codeine from Thebaine.

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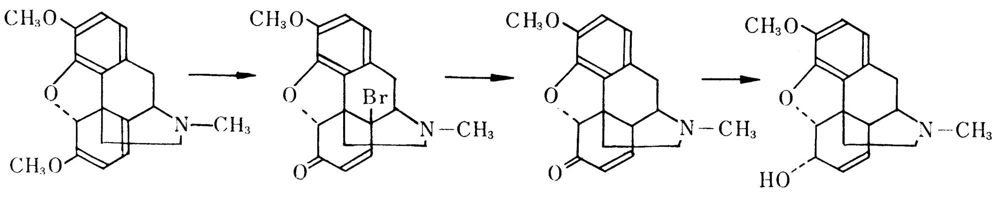
Thebaine (I), one of the main alkaloids of opium, is not available for medical use, because it does not show any useful pharmacological activities, such as analgetic, anesthetic, sedative and antitussive actions. Moreover, it has rather strong toxicity, such as spastic action. It has been utilized only for the starting material of Eucodal (=14-hydroxydihydrocodeinone).

The auther has been making research on exploitation of thebaine and established a new synthetic method of codeine (IV), increasing its demand as antitussive agent recently.

Hitherto, two different methods for preparing codeinone (III), which is the intermediate of codeine, from thebaine, have been reported.

According to the first method,[1] thebaine is hydrolyzed to codeinone under the acidic condition, and the other one,[2] 14-bromocodeinone (II), prepared from thebaine, is reduced to codeinone with iron-powder and dilute sulfuric acid. However, both methods give codeinone in very low yield and are not suitable for the practical production.



(I) (II) (III) (IV)

In this paper, the author intends to report a new synthetic method of codeinone in good yield by the reduction of 14-bromocodeinone with zinc-dust and glacial acetic acid.

This compound was identified as codeinone, obtained by oxidation of codeine with chromic acid[4] or silver carbonate,[5] by mixed melting point and infrared and ultra-

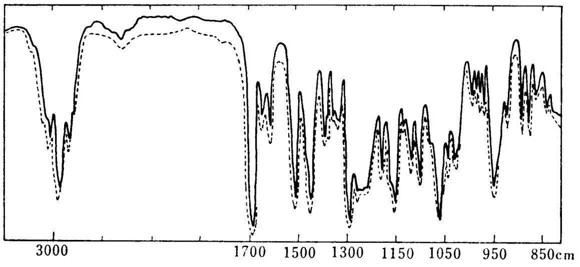


Fig. 1. Infrared Spectra of Codeinone (in $CHCl_3$)

—— Prepared from codeine by oxidation with Ag_2CO_3

------ Prepared from 14-bromocodeinone by reduction with Zn-dust

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1) L. Knorr, H. Hörlein : Ber., **39**, 1409 (1906); C. Schöpf, H. Hirsch : Ann., **489**, 224 (1931).

2) M. Freund : Ber., **39**, 844 (1906).

3) H. Conroy : J. Am. Chem. Soc., **77**, 5960 (1955).

4) S.P. Findlay, L.F. Small : *Ibid.*, **72**, 3247 (1950).

5) H. Ropoport, H.N. Reist : *Ibid.*, **77**, 490 (1955).

violet spectra. Furthermore, it quantitatively gave codeine by reduction with sodium borohydride.

Experimental

14-Bromocodeinone (II)——Thebaine (62.2 g.) was treated with N-bromosuccinimide in 2 : 1 (by volume) Me_2CO-H_2O mixture under the condition of Conroy's report,[3] and then gave 14-bromocodeinone, yellow crystals. The yield, after drying at 60°, was 54.0 g. (71.8%).

Codeinone (III)——To a solution of 14-bromocodeinone (15 g., 0.04 mol.) in 40 ml. of AcOH, Zn-dust (3.12 g., 0.04 × 1.2 mol.), activated by dil. HCl, was added in small portions with stirring during 15 min., maintaining at 15～17° by external cooling. After addition, the mixture was stirred for 3.5 hr. at room temperature (20～22°) and then poured into 250 ml. of ice-water. This mixture was filtered to remove a trace of unreacted Zn-dust and the filtrate was made alkaline with conc. NH_4OH, extracted with three 150 ml. portions of $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in 50 ml. of benzene and to this solution, 400 ml. of petr. ether was added. After the separation of solid, the filtrate was concentrated *in vacuo*. The residue was crystallized, m.p. 163～166°. After recrystallization from AcOEt, it showed m.p. 181～182°, undepression on admixture with authentic sample[4,5] and IR spectra of the two samples were identical. The total yield was 3.55 g. (30.0%). *Anal.* Calcd. for $C_{18}H_{19}NO_3$: C, 72.73; H, 6.40; N, 4.71. Found : C, 73.14; H, 6.39; N, 5.02.

Codeine (IV)——To the solution of codeinone (4.0 g.) in 20 ml. of MeOH, $NaBH_4$ (10 g.) in 240 ml. of MeOH was added, and allowed to stand at room temperature (20～25°) for 1.5 hr., then concentrated under reduced pressure to about 1/3 volume, and diluted with 200 ml. of 10% NaOH. The solution was heated on the steam-bath until boiling, diluted with 300 ml. of H_2O and extracted with four 100 ml. portions of $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and the solvent was removed by distillation *in vacuo*. The residue was crystallized, m.p. 149～152°. After recrystallization from benzene, it showed m.p. 154～156°, undepressed on admixture with natural codeine and IR and UV spectra of both samples were identical. The yield was 3.7 g. (91.8%).

The author expresses his gratitude to Prof. K. Tsuda of Tokyo University, to Mr. M. Matsui, the Director of this Laboratory, and to Dr. I. Iwai, the Chief of the Section, for their kind guidance in this work. He is also indebted to Mr. H. Higuchi and N. Higosaki for measurement of infrared and ultraviolet spectra, and to Mr. T. Onoe, Misses T. Furukawa and H. Ohtsuka for elemental analyses.

Summary

Treatment of 14-bromocodeinone, prepared from thebaine, with zinc-dust in glacial acetic acid gave codeinone, m.p. 181～182°. Codeinone was quantitatively reduced to codeine with sodium borohydride.

(Received May 22, 1961)

UDC 582.682.581.19 : 615.783.1

Katsuaki Matsui, Saburo Akagi, and Fukutaro Ugai : Chemical Constituents of the Alkaloid-free Fraction from Opium.

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The alkaloid-free press-cake, which obtained from opium in the usual manner, was extracted with methanol and the extract was evaporated under a reduced pressure.

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