3(β)-6(α)-dihydroxycholic acid (m. p. 191–192°). In conjunction with work soon to be published by James S. Moffatt this establishes the configuration of the C_6-hydroxyl group in hyodesoxycholic acid.

2. Methyl 3(α)-acetoxy-6(β)-hydroxycholanate previously reported as obtained by reduction of methyl 3(α)-acetoxy-6-ketocholanate has been reoxidized to the starting ketone thus confirming the cholanic acid structure of this compound.

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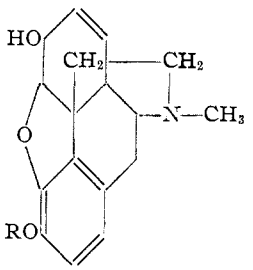
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SASKATCHEWAN]

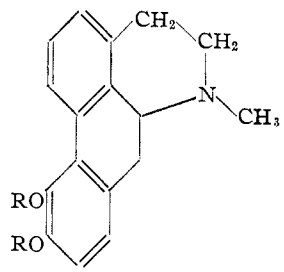
A Possible Route to the Location of the Nitrogen Atom in Morphine. I

BY H. L. HOLMES[1] AND C. C. LEE[2]

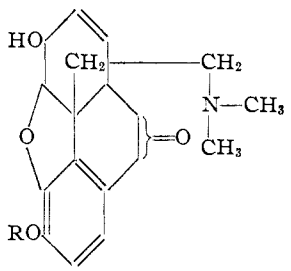
Although twenty years have elapsed since the proposal of an adequate structure for morphine I (R = H)[3] no evidence has been presented to definitely locate both the carbon and nitrogen ends of the ethanamine chain. The conversion of morphine to apomorphine, II (R = H), and the synthesis of apomorphine dimethyl ether, II (R = CH_3),[4,5] might be construed as evidence for the location of the nitrogen atom at C_9 of the hydrophenanthrene nucleus. However, in the light of the conversion of thebaine to thebenine, there is no reason to suppose that the nitrogen end of the ethanamine chain, like the carbon end, has not suffered a change. It was the oxidation of codeine, I (R = CH_3) to hydroxycodeine[6] followed by characterization of its methine (III) as a ketone[7,8] and identification of its acetolysis product as a 9- or 10- acetoxy derivative of acetylmethylmorphol (IV) that unequivocally located the nitrogen at C_9 or C_{10}.



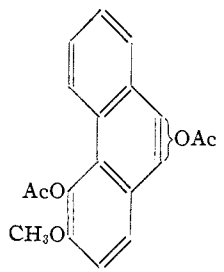
R = H or CH_3
I



R = H or CH_3
II



III



IV

It is to be seen that if the nitrogen atom were related to the contiguous hydroxyl of hydroxycodeine then location of the hydroxyl group would definitely establish the position of the nitrogen atom in the morphine molecule. In relating the nitrogen atom to the hydroxyl group only three possibilities need be considered: (a) are the nitrogen atom and the hydroxyl attached to the same carbon atom, (b) are the nitrogen atom and hydroxyl attached to different carbon atoms and (c) is hydroxycodeine an intermediate product (an amine oxide) that is readily isomerized to a product falling into one of the above categories.[9] In the event that hydroxycodeine is of type "a" then like hydroxystrychnine and cotarnine it should exhibit properties diagnostic for a carbinolamine. Furthermore, since the structure about the nitrogen atom of codeine exhibits a close similarity to that about N^b of strychnine[10] then it might be expected that hydroxycodeine would result by a method similar to that for the preparation of hydroxystrychnine.[11] This has not been realized. The yield of hydroxycodeine has been improved to 15% by the controlled oxidation of codeine with chromic acid.[12] The melting point of this base is largely dependent upon the type of apparatus used and upon the rate of heating and it has been found more satisfactory to characterize this base by its rotation in chloroform solution ($[\alpha]^{22}D$ −115 ± 1°). The chloroplatinate, methiodide and picrate have also been prepared.

A control experiment with strychnine, run simultaneously with the attempted oxidation of codeine, gave hydroxystrychnine which was characterized by conversion to its methyl and ethyl ethers by solution in the respective alcohols. Hydroxycodeine, under similar conditions, failed to give an ether. Extension of the analogy with hydroxystrychnine failed, for unlike this base,[13]

(1) Associate Professor of Chemistry.

(2) This work, which has been sponsored by a grant from the National Research Council of Canada, has been presented in a thesis to the College of Engineering in partial fulfilment of the requirements for the degree of Bachelor of Science in Chemical Engineering.

(3) Gulland and Robinson, *Mem. Proc. Manchester Lit. & Phil. Soc.*, **69**, 79 (1925).

(4) Pschorr and Avenarius, *Ber.*, **62**, 321 (1929).

(5) Späth and Hromatka, *ibid.*, **62**, 325 (1929).

(6) Ach and Knorr, *ibid.*, **36**, 3067 (1903).

(7) Pschorr and Einbeck, *ibid.*, **40**, 1980 (1907).

(8) Knorr and Hörlein, 2042 (1907).

(9) Pinner and Wolffenstein, *ibid.*, **25**, 1428 (1892).

(10) Holmes, Openshaw and Robinson, *J. Chem. Soc.*, 908 (1946).

(11) Leuchs, *Ber.*, **70**, 1543 (1937).

(12) Knorr and Schneider, *ibid.*, **39**, 1414 (1906).

(13) Leuchs, Flammersfeld, Villain and Schöne, *ibid.*, **76**, 1065 (1943).

hydroxycodeine was recovered unchanged after heating with an acetic acid solution of malonic acid. Finally, if hydroxycodeine is a carbinolamine then, like cotarnine,[14] it should condense with acetone when heated with an aqueous solution of sodium carbonate. This objective was not attained. Hydroxycodeine does not appear to be an amine oxide for it was not reduced to codeine by sulfurous acid. Failure of the diagnostic carbinolamine and amine oxide reactions in the case of hydroxycodeine would suggest that the hydroxyl is beta to the nitrogen atom. Extension of the study of this compound to the diagnostic reactions for β-ethanolamines is planned for the near future.

Two projected methods for the location of the hydroxyl group of hydroxycodeine are under way. The most direct route involves the methylation of the diphenol from IV followed by the synthesis of the two possible trimethoxyphenanthrenes. The alternate scheme involves the addition of two moles of methylmagnesium iodide to III, followed by dehydration, acetolysis and methylation to a 9- or 10-methyldimethylmorphol. The synthesis of one of these phenanthrene derivatives appears in the following paper.

Experimental Part

Hydroxycodeine.[6] **A.**—A vigorously stirred solution of 15.0 g. of codeine (m. p. 154–155°) in 80 g. of concentrated sulfuric acid and 160 g. of water was oxidized at 5° by the dropwise addition of a solution of 4.2 g. of chromic anhydride in dilute sulfuric acid (5.0 g. of sulfuric acid and 10.0 g. of water). Fifteen minutes were required for the addition of the oxidant and stirring was continued an additional thirty minutes. Solid sodium carbonate was added in small portions until the reaction mixture was only slightly acid to litmus. The separation of sodium sulfate makes the reaction mixture very viscous at this point. The sodium sulfate was collected on a Büchner funnel and washed with a little water. The combined filtrates were made strongly basic with 75 cc. of 20% sodium hydroxide solution and extracted many times with chloroform. The yellow chloroform extract was washed with water and dried over sodium sulfate. After removal of the solvent (last traces under vacuum) the brown oil which remained was dissolved in 200 cc. of hot benzene. When cold, 0.1 g. of an amorphous product separated which melted above 300°. Removal of the amorphous material and concentration of the benzene solution to 75 cc. gave 2.3 g. (15%) of hydroxycodeine which melted at 186°. Two crystallizations from benzene gave rosets of yellow leaflets melting at 205–206° (uncor.). This product, in agreement with that prepared by Knorr, gave a carmine red color with concentrated sulfuric acid. The specific rotation of a solution of 0.1257 g. of hydroxycodeine in 12.93 cc. of chloroform was $[\alpha]^{22}D$ −115 ± 1° (l = 1). The recovered hydroxycodeine melted at 205–206°.

Further concentration of the benzene solution gave 2.5 g. of yellow crystals which melted at 154–160° and may be mostly unchanged codeine.

B.—A solution of 4.0 g. of acetylcodeine (m. p. 132–133° (cor.)) in dilute sulfuric acid (11 cc. of concentrated sulfuric acid and 41 cc. of water) was oxidized with a solution of 0.75 g. of chromic anhydride in 5 cc. of water as described above. A yellow powder (0.45 g.) melting at 181° was recovered which, after several crystallizations from benzene, melted alone and on admixture with an authentic sample at 202–204° (uncor.).

(14) Liebermann and Kropf, *ibid.*, **37**, 211 (1904).

Derivatives of **Hydroxycodeine**.—The picrate of hydroxycodeine crystallizes from an aqueous solution of picric acid in yellow micro-plates and melts at 166°.

A quantitative yield of the methiodide was obtained by refluxing 0.1 g. of hydroxycodeine with 4 cc. of methyl iodide and 2 cc. of absolute methanol for twenty hours. The methiodide separated in sheaves of elongated plates and melted at 240–250° with decomposition.

The chloroplatinate, which crystallized from dilute hydrochloric acid as green micro-hexagonal crystals, showed no definite melting point, however, decomposition set in about 225°.

Hydroxystrychnine.—Strychnine (10.0 g.) was oxidized to hydroxystrychnine by the method of Leuchs.[11] By this method 0.7 g. of hydroxystrychnine methyl ether (m. p. 160–162°) was obtained which, when hydrolyzed (2.4 cc. of hot 1 N hydrochloric acid), gave 0.4 g. of material melting at 231–232.5° (cor.).

The above product was isomerized to the hydroxystrychnine of Warnat[15] by solution in 1 N hydrochloric acid and precipitating with boiling 1 N ammonium hydroxide, m. p. 258–261°. Leuchs[11] reports a melting point of 263° with previous softening at 258°. The methyl ether and the ethyl ether melted, respectively, at 196° (Warnat[15] reports m. p. 198–200°) and 229° (uncor.).

Hydroxybrucine was prepared by the oxidation of brucine by the method of Leuchs and Tessmar.[16] The hydroxybrucine was found to melt at 265° (uncor.), while the above authors report a melting point of 268° for this base. Attempts to prepare hydroxycodeine by the above two methods failed, and the codeine was quantitatively recovered.

Carbinolamine Reactions on Hydroxycodeine.—1. Hydroxycodeine was refluxed for one hour with absolute methanol. After removal of the solvent and crystallization of the residue from benzene only hydroxycodeine (m. p. 205–206° (uncor.)) was recovered.

2. A solution of 0.06 g. of hydroxycodeine in 0.5 cc. of glacial acetic acid was heated for one hour on the steam-bath with 0.05 g. of malonic acid. The reaction mixture was made strongly alkaline with sodium hydroxide and repeatedly extracted with chloroform. Almost a quantitative recovery of hydroxycodeine was obtained upon removal of the chloroform.

3. A solution of 0.10 g. of hydroxycodeine in 1 cc. of acetone was allowed to stand at room temperature with 1 or 2 drops of a saturated aqueous solution of sodium carbonate. The acetone was removed and the residue extracted in chloroform. Removal of the solvent and crystallization from benzene afforded only hydroxycodeine.

Attempts to reduce hydroxycodeine with sulfurous acid and to dehydrate it by sublimation under high vacuum failed.

Acknowledgments.—A generous quantity of codeine was received from Merck and Company Limited of Canada. This gift is gratefully acknowledged.

Summary

A projected scheme, involving the use of hydroxycodeine, has been outlined for definitely locating the nitrogen atom in the morphine alkaloids. A procedure, leading to an improvement in the yield of hydroxycodeine, has been described. The application of various reactions to hydroxycodeine which are diagnostic for carbinolamines and amine oxides has led to the conclusion that these systems are not present in hydroxycodeine.

SASKATOON, SASKATCHEWAN RECEIVED MARCH 5, 1947

(15) Warnat, *Helv. Chim. Acta*, **14**, 997 (1931).

(16) Leuchs and Tessmar, *Ber.*, **70**, 2369 (1937).