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THE SYNTHESIS[1] OF CODEINE LABELED IN THE 3-METHOXY GROUP WITH C^{14}

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Of the opium alkaloids closely related to morphine in chemical structure, codeine is probably the most important because it possesses less addiction properties than morphine and is very widely used in clinical work.

In order to investigate the mechanism of analgesic reaction and addiction we have prepared this compound labeled with C^{14} in the 3-methoxyl group. It was felt that for pharmacological experiments labeling the molecule in the methoxyl carbon would be more useful than in the N-methyl group, since biological systems appear able to effect N-methyl exchanges.

A review of the literature (1) reveals that codeine has been prepared from morphine by methylation with a number of reagents such as methyl sulfate, diazomethane, and phenyltrimethylammonium ethoxide. Although some of these methods are practical even for industrial production, they were not readily adapted to the preparation of labeled codeine since the reagents were not available labeled with C^{14} or would result in an insufficient utilization of C^{14}.

The methylation of morphine with methyl iodide (which is available tagged with C^{14}) has been studied independently by Grimaux (2, 3) and by Hesse (4). Both workers reported an extremely small yield of codeine. This is due to the fact that in the morphine molecule there are three reactive groups capable of undergoing the methylation reaction, namely, the phenolic group, the tertiary amino group, and the allylic secondary alcohol group. An active methylation reagent like methyl iodide, when allowed to react with morphine in the presence of alkali, will methylate all three reactive groups, so that the final product may consist of a mixture of codeine, codeine methyl ether, and the methiodides of these alkaloids.

Since the reactive group in the morphine molecule that interferes most with the preparation of codeine is the tertiary amino group rather than the allylic secondary alcoholic group, it was believed that by decreasing the basicity of the tertiary amino group through oxide formation, that is, by using morphine-N-oxide instead of morphine for the methylation, the entering methyl group could be made to go almost exclusively to the phenolic group. The methylation of morphine-N-oxide with methyl sulfate and alkali and the reduction of the resulting codeine-N-oxide to codeine have been patented (5), although the use of methyl iodide in this protective methylation reaction does not seem to have been studied.

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In order to obtain the maximum yield based on methyl iodide, we desired to use pure morphine-N-oxide as the starting material. The direct oxidation of morphine with 30% hydrogen peroxide to the N-oxide by the method described in the literature (6, 7) was studied, and although the crude morphine-N-oxide could be obtained in good yield, the loss of material on recrystallization as the nitrate was excessive.

Therefore, the protective oxidation of Mannich (8) was adopted. Morphine was first converted to the mono-sodium derivative and then allowed to react with chloromethyl ether. The syrupy methoxymethyl ether of morphine thus obtained was oxidized with 30% hydrogen peroxide and the product, the methoxymethyl ether of morphine-N-oxide, was isolated as the crystalline acetone derivative, from which pure morphine-N-oxide was obtained after hydrolysis with dilute sulfuric acid and subsequent alkalinization with ammonia (9).

With this pure morphine-N-oxide as the starting material, methylation was carried out successfully with methyl-C^{14} iodide (10). The codeine-N-oxide thus obtained was immediately reduced by sulfur dioxide to codeine. After purification, the free base was converted to both codeine-C^{14} sulfate and codeine-C^{14} hydrochloride. These salts possess properties identical with the U.S.P. products described in the literature (11).

EXPERIMENTAL

Preparation of the methoxymethyl ether of morphine. The methoxymethyl ether of morphine was prepared by the method of Mannich (8) in a 63% yield of crude material.

Oxidation of the methoxymethyl ether of morphine. Crude methoxymethyl morphine was oxidized with hydrogen peroxide as described by Small (9). The yield of crystalline methoxymethyl morphine-N-oxide acetone compound, m.p. 98°, was 46% based on morphine.

Conversion of the methoxymethyl ether of morphine-N-oxide acetone compound to morphine-N-oxide. Methoxymethyl morphine-N-oxide acetone compound (37 g.) was stirred with 18.5 ml. of cold 25% sulfuric acid and the solution was allowed to stand at room temperature for 2½ hours. Then, 75 ml. of water was added and the acid solution was neutralized with concentrated ammonium hydroxide. White crystals formed readily. The mixture was allowed to stand in an ice-bath for one-half hour and the crystals were filtered off, washed with a little cold water and then with cold acetone, and dried in a desiccator. The yield was 25.3 g. (42.0% based on morphine) m.p. 271°.

Preparation of codeine (1). In a dry box 6.0 g. (20 moles) of pure morphine-N-oxide was dissolved in chilled sodium methoxide prepared from 0.46 g. (20 moles) of metallic sodium and 20 ml. of absolute methyl alcohol. The flask containing the brownish-orange solution was connected to a vacuum (12) manifold through the condenser and a stopcock and the solution was frozen with liquid nitrogen. Then, 2.22 g. (15.6 moles) of methyl iodide containing 5.1 mc. of C^{14} was distilled *in vacuo* into the reaction flask. The flask containing the frozen mixture was moved to a hood and the mixture refluxed on the steam-bath for four hours. After cooling, 5 ml. of water was added and sulfur dioxide was passed into the solution for one hour to reduce the codeine-N-oxide. To the flask containing the codeine, 30 ml. of water was added and the methyl alcohol was vacuum-distilled. Then, 10 ml. of 6 *N* sodium hydroxide was added to dissolve the morphine and the codeine was extracted with two 25-ml. and four 10-ml. protions of chloroform. The chloroform solution was washed with two 10-ml. aliquots of distilled water, dried with potassium carbonate, filtered, and evaporated to dryness.

Purification of codeine. The impure codeine was dissolved in the minimum amount of

benzene and petroleum ether (b.p. 30–60°) was added until no further increase in the yellowish-orange turbidity was observed; then the turbidity was removed by filtration. Excess petroleum ether was added to the filtrate to precipitate the codeine. The yellowish-orange turbidity was treated with benzene and petroleum ether once more. The turbidity appeared to be an impurity and was discarded. The benzene-petroleum ether solution was allowed to stand in an ice-box for complete precipitation. The precipitate was filtered off and the filtrate reworked for a second crop; m.p. of the codeine, 155°.

The codeine was dissolved in the minimum amount of absolute ethyl alcohol and hydrogen chloride gas was passed into the solution to convert the free base to the hydrochloride salt. The alcoholic solution of codeine hydrochloride was evaporated to dryness on a steam-bath and the residue was dissolved in the minimum amount of 95% ethyl alcohol and filtered. The filtrate was allowed to stand in an ice-box for one hour. The crystalline needles of codeine hydrochloride were collected by filtration, washed with cold absolute ethyl alcohol, and dried. The various fractions were thus purified. The combined yield was 3.65 g., which represents a 62.8% yield based on methyl iodide or 49.1% based on radioactive barium carbonate used to begin the synthesis. The specific activity of this material was 0.91 ± 0.02 μc/mg. while the calculated value was 0.88 ± 0.02 μc/mg.

Anal. Calc'd for $C_{18}H_{22}ClNO_3$: C, 64.37; H, 6.60; OCH_3, 9.23.
Found: C, 64.33; H, 6.55; OCH_3, 9.02.

As an additional check, two-dimensional paper chromatograms (13) were made of this product and radioautographs made of the paper. Only one radioactive spot was found, thus indicating the radiopurity of the product.

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SUMMARY

Codeine labeled in the 3-methoxy position with C^{14} has been prepared on a 20-mole scale in a yield of 63% based on methyl-C^{14} iodide.

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BIBLIOGRAPHY

(1) SMALL, *Chemistry of the Opium Alkaloids*, U. S. Government Printing Office, Washington, D. C., 1932, p. 175 ff.
(2) GRIMAUX, *Compt. rend.*, **92**, 1140, 1228 (1881); *Compt. rend.*, **93**, 67, 217, 591 (1881).
(3) GRIMAUX, *Phil. J. Trans.*, (3), **12**, 48 (1881).
(4) HESSE, *Ann.*, **222**, 203 (1883).
(5) MERCK, German Patent 418,391 (1923); *Frdl.*, **15**, 1515.
(6) FREUND AND SPEYER, *Ber.*, **43**, 3310 (1910).
(7) FREUND AND HERMINGHAUS, *Ber.*, **48**, 497 (1915).
(8) MANNICH, *Arch. Pharm.*, **254**, 358 (1916).
(9) SMALL, U.S. Patent 2,058,521, October 27, 1936; FARIS AND SMALL, *J. Org. Chem.*, **1**, 200 (1936).
(10) TOLBERT, *J. Am. Chem. Soc.*, **69**, 1529 (1947).
(11) *The Pharmacopoeia of the United States*, 12th edition, Mack Printing Company, Easton, Pennsylvania, 1942, pp. 138, 141.
(12) CALVIN, HEIDELBERGER, REID, TOLBERT, AND YANKWICH, *Isotopic Carbon*, John Wiley and Sons, Inc., New York, 1949.
(13) BENSON, BASSHAM, CALVIN, HAAS, GOODALE, AND STEPKA, *J. Am. Chem. Soc.*, in press.