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October 19, 1949

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F. N. Chang**, J. F. Oneto, Peter P. T. Sah, B. M. Tolbert and H. Rapoport

Medical School, Division of Pharmacology and Experimental Therapeutics and College of Pharmacy, University of California, San Francisco, and Radiation Laboratory and Department of Chemistry, University of California, Berkeley

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ABSTRACT

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

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** Present address: Department of Pharmacology, Washington University Medical School, St. Louis, Missouri

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Medical School, Division of Pharmacology and Experimental Therapeutics and College of Pharmacy, University of California, San Francisco, and Radiation Laboratory and Department of Chemistry, University of California, Berkeley

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-methoxy group. It was felt that for pharmacological experiments labeling the molecule in the methoxy 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 dimethyl sulfate, diazomethane and phenyltrimethyl ammonium 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}.

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** Present address: Department of Pharmacology, Washington University Medical School, St. Louis, Missouri.

(1) Small, "Chemistry of the Opium Alkaloids," p.175f (1932), U. S. Government Printing Office, Washington D. C.

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 such that the final product consists 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 dimethyl 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.

In order to obtain 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)

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(2) Grimaux, Compt. rend., 92, 1140 1228 (1881); 93, 67, 217, 591 (1881).
(3) Grimaux, Phil. J. Trans., (3), 12, 48 (1881).
(4) Hesse, Ann., 222, 203 (1883).
(5) Merck, D.R.P. 418391 (1928); Friedl, 15, 1515.
(6) Freund and Speyer, Ber., 43, 3310 (1910).
(7) Freund and Herminghaus, Ber., 48, 497 (1915).

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 Methoxymethyl Ether of Morphine: - Clean metallic sodium (4.6 g., 200 mmole) was added to 120 ml. of ethyl alcohol in a round-bottomed flask equipped with reflux condenser. When the reaction was completed, 56 ml. of water was added and then 57 g. (182 mmole) of pulverized morphine was dissolved portion wise. (The alkoxide solution was placed in an ice bath before adding the morphine). To the resulting clear solution, still chilled, 240 ml. of ethyl ether was added with stirring. After allowing the mixture to stand in the ice bath, the precipitate

(8) Mannich, Arch. Pharm., 254, 358 (1916).
(9) Small, U.S. Patent 2058521, October 27, 1936.
(10) Tolbert, J. Am. Chem. Soc., 69, 1529 (1947).
(11) The Pharmacopoeia of the United States, pp 138, 141 (1942), 12th edition, Mack Printing Company, Easton, Pennsylvania.

was filtered with suction, washed twice with 160 ml. of 50% ethyl alcohol-50% ethyl ether mixture, then once with 160 ml. of ethyl ether and sucked to dryness. The product was dried at reduced pressure over calcium chloride for 42 hours. The yield was quantitative, m.p. 126-128°.

The sodium morphinate was suspended in 140 ml. of dry chloroform in a 500 ml. three-necked flask equipped with a stirrer, dropping funnel and condenser, all protected with calcium chloride tubes. The mixture was chilled in an ice bath and 15 ml. of chloromethyl ether in 28 ml. of dry chloroform was added dropwise with stirring which was continued for 45 minutes after the chloromethyl ether had been added. An insoluble slurry layer formed which was removed with suction filtration and washed with dry chloroform. The filtrate and washings were dried over potassium carbonate and filtered again.

The solvent was removed from the dried filtrate under reduced pressure in a 40° water bath. The yield of the methoxymethyl ether of morphine was 42.3 g. (63.2% based on morphine).

Oxidation of Methoxymethyl Ether of Morphine: - To a 500 ml. round-bottomed flask equipped with a reflux condenser was added the morphine methoxymethyl ether and 24.5 ml. of 30% hydrogen peroxide. The mixture was warmed gradually and refluxed for 30 minutes in a water bath not warmer than 50°. Excess hydrogen peroxide and water were then removed under reduced pressure in a water bath at 40-50° to leave a glassy residue in the flask. Hot acetone (254 ml.) was added and the flask heated with vigorous stirring until a clear solution formed. The mixture was chilled in an ice bath for 30 minutes and the crystals of morphine ether-N-oxide acetone filtered off, washed with cold acetone and dried in a desiccator over calcium chloride for 48 hours. The white crystalline material weighed 37 g. Yield, 45.8% based on morphine, m.p. 98°.

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 2-1/2 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 mmoles) of pure morphine-N-oxide was dissolved in chilled sodium methoxide prepared from 0.46 g. (20 mmole) of metallic sodium and 20 ml. of absolute methyl alcohol. The flask containing the brownish orange solution was connected to a vacuum manifold (12) through the condenser and a stopcock and the solution frozen with liquid nitrogen. Then, 2.22 g. (15.6 mmoles) of methyl iodide containing 5.1 mc. of C^{14} (10) 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 vacuum distilled. Then, 10 ml. of 6N sodium hydroxide was added to dissolve the morphine and the codeine was extracted with two 25 ml. and four 10 ml. portions of chloroform. The chloroform solution was washed with two 10 ml. aliquots of distilled water, dried with anhydrous potassium carbonate, filtered and evaporated to dryness.

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(12) Calvin, Heidelberger, Reid, Tolbert and Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, 1949.

Purification of Codeine: - The impure codeine was dissolved in a minimum amount of benzene and petroleum ether (b.p. 30-60°) added until no further increase in yellowish-orange turbidity was observed, and the turbidity was removed by filtration. Excess petroleum ether was then 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 a minimum amount of absolute ethyl alcohol and hydrogen chloride gas 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 dissolved in a 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.

After 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 the 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.

Calcd. for $C_{18}H_{22}NO_3Cl$: 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.

(13) Benson, Bassham, Calvin, Haas, Goodale and Stepka, J. Am. Chem. Soc., in press.

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Summary

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