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A METHOD FOR PREPARING CODEINONE

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### Authors

Rapoport, Henry  
Reist, Helen N.

### Publication Date

1954-08-27

UCRL 2683  
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UCRL-2683  
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Contract No. W-7405-eng-48

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Henry Rapoport and Helen N. Reist

August 27, 1954

Berkeley, California

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Department of Chemistry and Radiation Laboratory  
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ABSTRACT

A new and superior method has been found for preparing codeinone by silver carbonate oxidation of codeine.

## A METHOD FOR PREPARING CODEINONE

Henry Rapoport and Helen N. Reist

Department of Chemistry and Radiation Laboratory  
University of California, Berkeley

August 27, 1954

In the course of preparing various glycosides of codeine<sup>1</sup> for biological investigations, the consistently poor yields induced us to examine the reaction in greater detail. The procedure being employed was the usual treatment of a benzene solution of an alcohol (codeine) with an acetylglycosyl bromide in the presence of silver carbonate. As the reaction proceeded, there was a pronounced frothing and the silver carbonate became black. Analysis of the benzene-insoluble material at the conclusion of the reaction established the presence of considerable free silver, indicating that an unexpected oxidation had occurred. That it was the codeine being oxidized was demonstrated by an experiment in which the acetylglycosyl bromide was omitted and from which codeinone was isolated in fair yield.

A study was then made of various factors in this reaction and their effect on the yield of codeinone. The quantity of silver carbonate, the mode of addition of silver carbonate and codeine, and the time of reflux were all varied, and conditions were found which resulted in a 75% yield of codeinone. These consisted of simply heating under reflux a solution of codeine in benzene with 500 mole per cent of silver carbonate. Although the chromic acid oxidation of codeine to codeinone has been much improved recently<sup>2</sup> and an excellent Oppenauer oxidation procedure is now available,<sup>3</sup> the simplicity and very good yield of the present silver carbonate method make it an attractive alternative method for preparing codeinone.

A search of the literature revealed no such previous application of silver carbonate, although silver oxide in anhydrous ether has been used in the preparation of quinones<sup>4, 5</sup> and silver salts (and silver hydroxide) have served for various oxidations.<sup>5</sup> In seeking possible extensions and limitations of this silver carbonate procedure, the reactions with dihydrocodeine and

neopine were tried. No reaction took place with dihydrocodeine and it was recovered quantitatively. With neopine definite blackening of the silver carbonate occurred but the only isolable product was neopine in an 18% recovery.

### Experimental

Preparation of Silver Carbonate. - The yellow precipitate of silver carbonate formed when 300 ml. of an aqueous solution containing 25.6 g. of sodium bicarbonate was added to 580 ml. of 10% aqueous silver nitrate was washed by decantation six times with 1.5 l. portions of distilled water and four times with 700 ml. portions of methanol. It was then transferred to and washed on a suction filter funnel using a total of 2 l. of absolute ether. After being sucked dry on the funnel for about 20 min., the product was stored in vacuo over magnesium perchlorate in the dark. When first prepared, the silver carbonate is yellow, but on storage the color gradually changes to yellow-green and finally brown. This seems to have no adverse effect on its ability to oxidize codeine, and preparations over a month old have been used successfully.

Anal. Calcd. for  $\text{Ag}_2\text{CO}_3$ : Ag, 78.2; C, 4.4.

Found: Ag, 78.1; C, 4.4.

Codeinone. - After 25 ml. was distilled from a solution of 6 g. (0.02 mole) of codeine in 125 ml. of benzene, 27.6 g. (0.1 mole) of silver carbonate was added and the mixture was heated under reflux with rapid stirring in a nitrogen atmosphere for one hour during which an additional 10 ml. of solvent was removed by distillation. The hot mixture was then filtered, the insoluble portion was digested with two 50 ml. portions of benzene, and the combined filtrate and digests were concentrated at the water pump until crystals began to appear. These were removed by filtration after cooling, and the filtrate was further concentrated. In this manner, two crops were obtained, for a total of 4.5 g. (75% yield), melting at 179-182° to a characteristic red melt. On recrystallization from benzene using decolorizing carbon, 4.0 g. of practically colorless codeinone resulted, m.p. 181-182°;  $[\alpha]_D^{21}$  - 208° (c, 1.0, 95% ethanol) (Reported<sup>2</sup> m.p. 181.5-182.5°;  $[\alpha]_D^{20}$  - 205° (c, 0.8, 99% alcohol.)

Codeinone oxime hydrochloride was prepared and melted at 257-260° with decomposition (reported<sup>2</sup> m.p. 258°).

On reduction with sodium borohydride, codeinone was converted to codeine, <sup>6</sup> m. p. 156-157°.

The work described in this paper was sponsored by the U. S. Atomic Energy Commission.

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