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METHOD FOR PREPARING DIHYDROCODEINONE, DIHYDROMORPHINONE, AND CODEINONE

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10 Claims. (Cl. 260—285)

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This invention relates to the production of narcotics and more particularly to a process for the manufacture of morphine derivatives.

This application is a continuation-in-part of our copending application Serial No. 76,854, filed February 16, 1949, now abandoned.

Briefly this invention provides an effective method for the preparation of dihydrocodeinone from dihydrocodeine, of codeinone from codeine, and of dihydromorphinone from dihydromorphine by oxidation with a ketone in the presence of an aluminum alkoxide.

Among the objects of this invention are the provision of an improved process for the manufacture of morphine derivatives such as dihydrocodeinone, dihydromorphinone and codeinone; the provision of a process of the type set forth which employs readily available starting materials; provision of a process of the type referred to which gives good yields of dihydrocodeinone, dihydromorphinone or codeinone without simultaneous formation of substantial amounts of accompanying by-products; and the provision of a process of the type indicated which permits the recovery of unreacted starting material from the reaction mixture. Other objects will be in part apparent and in part pointed out hereinafter.

The invention accordingly comprises the steps and sequence of steps, and features of manipulation, which will be exemplified in the methods hereinafter described, and the scope of the application of which will be indicated in the following claims.

Dihydrocodeinone is a starting material in the manufacture of the valuable new analgesic drug metopon, and is itself an analgesic of considerable value for the alleviation of coughs, being more active than codeine in this respect. Until now, dihydrocodeinone has been obtained principally by the catalytic hydrogenation of the naturally occurring opium alkaloid thebaine, but supplies of this natural alkaloid are limited and a satisfactory and economical synthesis from a more readily obtainable starting material has not been available.

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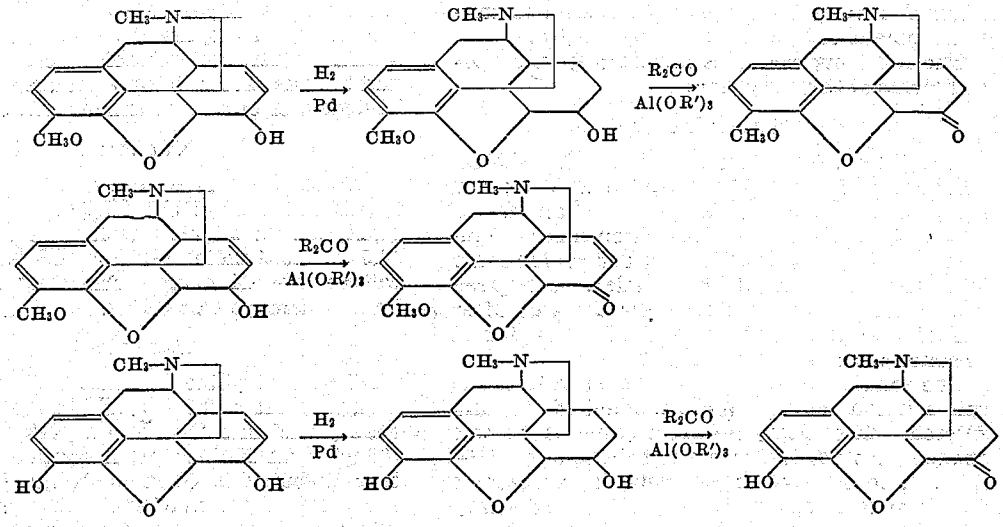
Codeine on the other hand is readily available and can be converted to dihydrocodeine almost quantitatively by catalytic hydrogenation, but the known methods for effecting the transformation of dihydrocodeine to dihydrocodeinone give very poor yields and the processes are beset with so many difficulties as to be impracticable.

Similar problems are encountered in the production of codeinone and dihydromorphinone. Although these are valuable pharmaceuticals a satisfactory method for the production of codeinone from codeine and dihydromorphinone from dihydromorphine has not been available.

We have discovered that if the oxidation of dihydrocodeine to dihydrocodeinone, of codeine to codeinone and of dihydromorphine to dihydromorphinone is effected by certain ketones in the presence of aluminum alkoxides, dihydrocodeine, codeine and dihydromorphine can be converted respectively to dihydrocodeinone, codeinone and dihydromorphinone in good yield. The unoxidized dihydrocodeine, codeine or dihydromorphine can be conveniently and substantially completely recovered, thus making the over-all conversion virtually complete.

The reactions are represented by the following equations;



where R and R' are organic residues.

For this reaction, a ketone having a sufficiently high oxidation potential is necessary but the ketone must not contain other functional groups which will destroy or condense with dihydrocodeinone, dihydrocodeine, codeine, codeinone, dihydromorphinone or dihydromorphine. Quinone, for example, possesses a very high oxidation potential, but, when it was used as the oxidizing agent in these reactions, the product was a dark insoluble substance from which no oxidized product could be isolated. It has been found that ketones of the following general formula are valuable in the process of this invention:

where R_1 is a radical selected from the group consisting of monocyclic hydrocarbon aryl and aralkyl derivatives and R_2 is radical selected from the group consisting of alkyl radicals and monocyclic hydrocarbon aryl and aralkyl radicals, one of which contains a substituent selected from the group consisting of alkoxy radicals and carbonyl oxygen on the alpha-carbon atom. Examples of such ketones are benzil, benzoin methyl ether, and alpha-methoxyacetophenone. Mixtures of such ketones may likewise be employed.

While many aluminum alkoxides will serve in this reaction, it is preferred that the alkoxides be derived from alcohols which are not themselves oxidized under the conditions of this reaction. Such alkoxides are the aluminum tertiary-alkoxides.

If the aluminum alkoxide is not freshly prepared or if an excess of it is used, it has been found that the unreacted dihydrocodeine is transformed to its stereoisomer, dihydroisocodeine, without affecting the quality or yield of the desired ketone. This does not affect the over-all conversion to dihydrocodeinone, since the isomer is oxidized under the same conditions as dihydrocodeine itself. If dihydrocodeine is reacted with an aluminum alkoxide without the ketone, it is substantially converted to dihydroisocodeine. This is a simple and convenient method for preparing the latter compound which heretofore could be prepared only by involved and difficult procedures. Dihydroisocodeine is an analgesic which, so far as is known, possesses properties generally quite similar to those of dihydrocodeine.

The reaction should be carried out in a suitable solvent. Any of the inert solvents, such as benzene, toluene or xylene, may be employed.

The following examples illustrate specific embodiments of this invention:

Example 1

In a 500 ml. flask were placed anhydrous dihydrocodeine (10 g.; 0.033 mole), benzil (21 g.; 0.10 mole) and dry toluene (250 ml.). Solvent (50 ml.) was distilled from the reaction mixture and to the bright yellow solution was added aluminum tertiary-butoxide (1 g.; 0.0040 mole). A deep red color developed almost immediately and after the solution had been refluxed for 18 hours it had assumed a dark brown coloration.

The solution was cooled, shaken with Rochelle salt solution (50 ml.) and filter aid (5 g.), and filtered. The clear, brown organic layer was shaken with 2% hydrochloric acid solution (100 ml.). The aqueous and toluene layers became yellow in color and a small quantity of a heavy dark brown oil separated. The dark oil and aqueous phase were drawn off into a second separatory funnel and treated with two 20 ml. portions of chloroform, which dissolved the oil and permitted complete separation of the acid layer. The aqueous layer was treated with one gram of decolorizing carbon and filtered. The clear yellow filtrate was cooled and stirred mechanically and sodium hydroxide solution was added dropwise. When a permanent turbidity appeared, sodium hydrosulfite (0.1 g.) was added to prevent discoloration and a seed crystal of dihydrocodeinone was added. Deposition of crystalline product began and the addition of sodium hydroxide was continued until the solution was strongly alkaline to phenolphthalein. The dense, finely crystalline precipitate, which proved to be crude dihydrocodeinone, was filtered off, washed with water and dried. The yield of material melting at 175°–190° C. was 3.63 g. (36%).

Example 2

In a 500 ml. flask were placed anhydrous dihydrocodeine (10 g.; 0.033 mole), the methyl ether of benzoin (45 g.; 0.2 mole) and dry toluene (250 ml.). Solvent (50 ml.) was distilled off and to the remaining solution was added aluminum tertiary-butoxide (4 g.; 0.016 mole). The solution assumed a red brown color almost at once, and was allowed to reflux for one hour.

The cooled solution was shaken with Rochelle salt solution (50 ml.) and filter aid (5 g.), and was filtered. The light yellow organic layer was separated from the filtrate and extracted with a total of 100 ml. of 2% hydrochloric acid. The acid extract was shaken with one 25 ml. portion of chloroform and two 50 ml. portions of ether, diluted to 200 ml. with water and cooled in an ice bath with mechanical stirring. The solution was slowly neutralized with sodium hydroxide, and when the first oily precipitate appeared was seeded with dihydrocodeinone. Crystallization set in and the addition of sodium hydroxide was continued until the solution was strongly alkaline. The white crystalline precipitate was filtered off, washed with water and dried. The yield of dihydrocodeinone melting at 185–194° C. was 6.10 g.

Extraction of the alkaline mother liquor with chloroform and evaporation of this extract to dryness yielded an additional 3.20 grams of crude dihydrocodeinone mixed with dihydrocodeine.

Example 3

Following the procedure described in Example 1, anhydrous dihydrocodeine (10 g.; 0.033 mole), α-methoxy acetophenone (15 g.; 0.1 mole), aluminum tertiary-butoxoide (1 g.; 0.004 mole) and toluene (200 ml.) were refluxed for 16 hours. The yield of dihydrocodeinone was 3.0 g.

Example 4

Following the procedure described in Example 1, anhydrous dihydrocodeine (10 g.; 0.033 mole), benzil (21 g.; 0.1 mole), aluminum isopropoxide (0.6 g.; 0.003 mole) and toluene (200 ml.) were refluxed for 44 hours. The yield of crude dihydrocodeinone was 0.93 g.

Example 5

Dihydromorphine hydrate (10 g.), benzoin methyl ether (22.5 g.) and toluene (250 ml.) were placed in a flask and a part of the toluene (80 ml.) was distilled off. A solution of aluminum tertiary-butoxide (4 g. in 30 ml. toluene) was added over a period of ten minutes and the mixture was then refluxed for sixteen hours. The cooled mixture was shaken with diluted hydro-

chloric acid (5 ml. concentrated acid and 70 ml. water) and the acid extract was washed with two successive 25-ml. portions of chloroform followed by two successive 25-ml. portions of ether. A 30% solution of potassium sodium tartrate (20 ml.) was added to the acid extract; the resulting solution was heated to expel ether and then made alkaline with ammonium hydroxide. When the sides of the container were scratched, a crystalline precipitate formed. This precipitate of crude dihydromorphinone was filtered off and dried, then dissolved in hot 90% alcohol (90 ml.) and an excess of oxalic acid was added. After the solution had cooled and the sides of the container had been scratched, a crystalline acid oxalate salt formed. This was filtered off and recrystallized from 90% alcohol. The purified salt was dissolved in water and converted to the free base with ammonium hydroxide. The purified dihydromorphinone weighed 1.7 g. It was compared with an authentic sample of dihydromorphinone and the two were found to be identical.

Example 6

The reaction described in the preceding example was repeated using 35 g. of benzil in place of benzoin methyl ether. The reaction mixture was refluxed for seventeen hours and pure dihydromorphinone was again recovered.

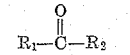
Many variations and modifications of this invention will be apparent to those skilled in the art. For example, the particular aluminum tertiary-alkoxide employed is not critical, aluminum tertiary-butoxide being preferred because of its availability.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As many changes could be made in the above methods without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

We claim:

1. The process for preparing a substance selected from the group consisting of dihydrocodeinone, dihydromorphinone and codeinone which comprises reacting the corresponding hydroxy compound selected from the group consisting of dihydrocodeine, dihydroisocodeine, codeine and dihydromorphine in the presence of an aluminum tertiary-alkoxide and a solvent, with a ketone having the general formula



in which R_1 is a radical selected from the group consisting of monocyclic hydrocarbon aryl and aralkyl radicals, and R_2 is a radical selected from the group consisting of alkyl radicals and monocyclic hydrocarbon aryl and aralkyl radicals, one of said radicals containing a substituent in the alpha position selected from the group consisting of alkoxy radicals and carbonyl oxygen.

2. The process for preparing dihydrocodeinone which comprises reacting dihydrocodeine with benzil in the presence of an aluminum tertiary-alkoxide and a solvent.

3. The process for preparing dihydrocodeinone which comprises reacting dihydrocodeine with benzoin methyl ether in the presence of an aluminum tertiary-alkoxide and a solvent.

4. The process for preparing dihydrocodeinone which comprises reacting dihydrocodeine with α-methoxyacetophenone in the presence of an aluminum tertiary-alkoxide and a solvent.

5. The method of preparing dihydrocodeinone which comprises reacting dihydrocodeine with benzil in the presence of aluminum tertiary-butoxide and toluene.

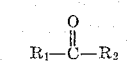
6. The method of preparing dihydrocodeinone which comprises reacting dihydrocodeine with benzoin methyl ether in the presence of aluminum tertiary-butoxide and toluene.

7. The process for preparing dihydromorphinone which comprises reacting dihydromorphine with benzil in the presence of an aluminum tertiary-alkoxide and a solvent.

8. The process for preparing dihydromorphinone which comprises reacting dihydromorphine with benzil in the presence of aluminum tertiary-butoxide and toluene.

9. The method of preparing dihydrocodeinone which comprises reacting dihydrocodeine with α-methoxyacetophenone in the presence of aluminum tertiary-butoxide and toluene.

10. The process for preparing dihydrocodeinone which comprises reacting dihydroiscodeine in the presence of an aluminum tertiary-alkoxide and a solvent, with a ketone having the general formula



in which R_1 is a radical selected from the group consisting of monocyclic hydrocarbon aryl and aralkyl radicals, and R_2 is a radical selected from the group consisting of alkyl radicals and monocyclic hydrocarbon aryl and aralkyl radicals, one of said radicals containing a substituent in the alpha position selected from the group consisting of alkoxy radicals and carbonyl oxygen.

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