United States Patent Office

3,320,262

Patented May 16, 1967

3,320,262

14 HYDROXY MORPHINE AND CODEINE CARBOXYMETHYLOXIMES

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No Drawing. Filed Sept. 22, 1964, Ser. No. 398,426

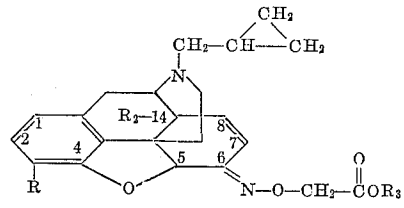
12 Claims. (Cl. 260—285)

The present invention deals with new morphine and codeine derivatives. More particularly, it deals with carboxymethyloximes of N-cyclopropymethyl substituted morphine and codeine compounds and their esters.

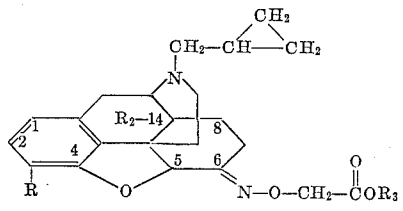
The novel compounds of the present invention are derived by a series of reaction steps which additionally provide new intermediate compounds as well.

The new N-cyclopropylmethyl-carboxymethyloximes and their esters of the present invention are characterized by the following generic formulae and include morphine and codeine derivatives:

(I)



(I-*a*)



wherein R is selected from the group consisting of methoxy and hydroxy, and R_2 is selected from the group consisting of hydrogen and hydroxy, and wherein R_3 is selected from the group consisting of H, CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $CH_2{=}CHCH_2$ and $C_6H_5CH_2$.

The aforesaid compounds can be in combined form such as hydrochlorides, sulphates, and other acid salts; however when R_3 is H, basic salts are utilizable.

When used for pharmaceutical application, they can be combined with a pharmaceutically acceptable inert carrier of the type known in the art to be suitable for morphine and codeine derivatives, such as distilled water, milksugar, starch, etc. and these resulting pharmaceutical compositions can be taken parenterally, orally or rectally. Such compositions contain a major proportion of pharmaceutical carrier and a minor amount of compounds (I) or (I-*a*), the percentage of the active compound (I) or (I-*a*) generally falling within the range of 0.1 to 20% of the total pharmaceutical composition.

Compounds of generic Formula I and I-*a* offer improved analgesic and antitussive effects. They may be employed for the relief of pain and cough in the same manner as morphine and codeine compounds in general. Evidence indicates that the present compounds may have low physical dependency and offer distinct advantages over morphine and codeine and their other derivatives.

The following are specific examples of the compounds of Formula I:

N-cyclopropylmethyl-nor-14-hydroxycodeinone-6-carboxymethyloxime

N-cyclopropylmethyl-nor-codeinone-6-carboxymethyloxime

N-cyclopropylmethyl-nor-14-hydroxymorphinone-6-carboxymethyloxime

N-cyclopropylmethyl-nor-morphinone-6-carboxymethyloxime methylester

The following are specific examples of the compounds of Formula I-*a*:

N-cyclopropylmethyl-nor-14-hydroxydihydrocodeinone-6-carboxymethyloxime

N-cyclopropylmethyl-nor-14-hydroxydihydrocodeinone-6-carboxymethyloxime methylester

N-cyclopropylmethyl-nor-dihydrocodeinone-6-carboxymethyloxime methylester

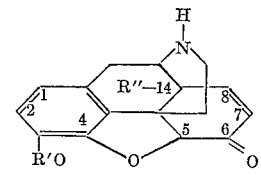
N-cyclopropylmethyl-nor-14-hydroxydihydromorphinone-6-carboxymethyloxime methylester

N-cyclopropylmethyl-nor-dihydromorphinone-6-carboxymethyloxime methylester

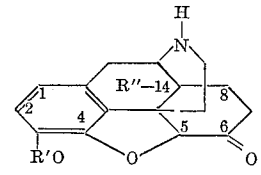
Although we have illustrated some compositions as being carboxymethyloximes and some as their methylesters, these compositions may well be methyl-esters, ethyl-esters, propyl-esters, allyl-esters, and benzyl-esters, as well as the free carboxymethyloximes.

The carboxymethyloximes of the 6 ketone derivatives of morphine and codeine and their esters as set forth in generic Formulae I and I-*a* are prepared by a series of reaction stages as follows:

(II)



(II-*a*)



wherein R′ is selected from the group consisting of hydrogen and methyl and R″ selected from the group consisting of hydrogen and hydroxyl.

(1) A compound having the structure II or II-*a* is reacted with cyclopropylmethylhalide and sodium bicarbonate in an appropriate solvent to produce the resultant N-cyclopropylmethyl compound.

In such initial reaction stage a solvent such as absolute ethanol, N-propyl alcohol or dioxane may be employed as the solvent. Reaction times and temperatures are sufficient to cause reaction between the cyclopropylmethylhalide group and the nitrogen atom of II or II-*a* to form the resultant N-cyclopropylmethyl derivative. In general, temperatures of the order of 25° C. to 100° C., particularly 50° to 90° are employed, with reaction period of ½ to 28 or more hours; the optimum time is a few hours.

Other bicarbonates, or other bases can be used as for example potassium carbonate, sodium carbonate, potassium bicarbonate and, generally, weak inorganic bases.

The resultant N-cyclopropylmethyl compounds may be recovered via any of the variety of conventional techniques, such as addition of water and extraction with a suitable organic solvent, such as chloroform, which may thereafter be evaporated to yield a N-cyclopropylmethyl-morphine or codeine derivative. Alternately, the reaction

mixture may be filtered and the solvent simply evaporated, to yield as a residue the desired intermediate product.

(2) The acid salt of carboxymethoxylamine is dissolved in the appropriate alcohol and heated for 1 to 24 hours at a temperature of 50° to 100° C., depending upon the alcohol used, to yield the desired ester of the carboxymethoxylamine. The products are obtained by removing the excess alcohol under vacuum and partitioning the residue between chloroform and dilute sodium hydroxide solution. The chloroform is then dried and evaporated to leave the desired product as the residue. This may then be converted to the acid salt by treatment with the appropriate acid.

(3) The resultant N-cyclopropylmethyl compound of step (1) is then reacted with the esterified carboxymethoxylamine of step (2) in aqueous dioxane containing sodium bicarbonate for 3 to 8 hours which is a sufficient time to produce the corresponding carboxymethyloxime ester derivatives of the N-cyclopropylmethyl compound.

Alternatively, the methyl esters can be produced as follows:

(4) The N-cyclopropylmethyl compound of step (1) is reacted with carboxymethoxylamine or its acid salts in an aqueous ethanol solvent additionally containing potassium or sodium hydroxide for a period of from 2 to 6 hours to produce the corresponding carboxymethyloxime derivative.

In general, about equal molar quantities of the product of step (1) are reacted with the carboxymethoxylamine or its acid salts. In general about 0.4 to 1.0 gram of carboxymethoxylamine or its acid salts are utilized per gram of intermediate, with the amount of base required being one equivalent of N-cyclopropylmethyl intermediate reacted. The amount of alcohol utilized is sufficient to insure solution of the resultant product and control of the reaction temperature.

In general temperatures of the order of 50° C. to 95° C. can be utilized together with suitable reaction periods of 2 to 6 hours to form the corresponding carboxymethyloxime. The product can be obtained by cooling to cause its crystallization, generally in combination with concentrating the reaction mixture after the reaction has been completed by the use of vacuum evaporation.

(5) The resulting N-cyclopropylmethylcarboxymethyloxime-codeine or morphine derivative formed in step (4) is then further reacted with an excess of ethereal diazomethane to give methyl esters of the carboxymethyloximes.

This reaction can take place by allowing the compounds to stand at room temperature in a suitable solvent such as ethanol. Room temperature conditions of under two hours, e.g. 10 minutes to an hour, have been found to be suitable. Reaction temperature may vary from 10° C. to 30° C. and the reaction period from 5 minutes upwards to 3 hours, preferably 15 to 20 minutes.

However, the resulting product may be recovered from the reaction medium by conventional techniques such as vacuum distillation or steam bath evaporation of the solvent, and recrystallization of the residue from a suitable solvent such as ethanol, chloroform, or the like.

The various aspects and modifications of the present invention will be made more clearly apparent by reference to the following description and accompanying examples. In these examples each series of reactions used in forming the esters of carboxymethyloximes of the 6-ketone derivatives of N-cyclopropylmethyl-nor-morphine and N-cyclopropylmethyl-nor-codeine, are designated by Roman letters.

The above is a preferred procedure for the preparation of the carboxymethyloximes and their esters, however, modifications in this procedure such as time, temperature and solvents may be adopted for the production of the said carboxymethyloximes and their esters.

There are listed below five examples of appropriate series of reactions utilizable in producing the compositions of the various groupings additionally delineated.

(I) N - CYCLOPROPYLMETHYL - NOR - 14 - HYDROXYDIHYDROMORPHINONE - 6 - CARBOXYMETHYLOXIME BENZYLESTER

Example 1.—N-cyclopropylmethyl-nor-14-hydroxydihydromorphinone

5 grams N-nor-14-hydroxydihydromorphinone was dissolved in 200 cc. of absolute ethanol, and 3 grams of sodium bicarbonate was added, after which 3 g. of cyclopropylmethylbromide were added dropwise with stirring. After the addition was complete the mixture was heated at 60° C. for 14 hours. Filtration was followed by evaporation of solvent and the residue was recrystallized from ethanol to give the product.

Example 2.—Carboxymethoxylamine benzylester

5 grams of carboxymethoxylaminesulfate is suspended in 75 cc. of benzyl alcohol and heated with stirring at 60° C. (under nitrogen) for 6 hours. The excess benzyl alcohol is then removed under vacuum on a steam bath, and the residue is partitioned between 100 cc. of chloroform and 75 cc. of 5% aqueous sodium hydroxide. The chloroform layer is dried over sodium sulfate and evaporated to leave as the residue the benzylester of carboxymethoxylamine.

Example 3.—N-cyclopropylmethyl-nor-14 - hydroxydihydromorphinone-6-carboxymethyloxime benzylester

To a solution of 5 g. of N-cyclopropylmethyl-nor-14-hydroxydihydromorphinone in 100 ml. of aqueous ethanol containing 0.5 g. sodium bicarbonate was added 3 grams of carboxymethoxylamine benzylester. The mixture was kept at 60° C. for 6 hours, and the solution was concentrated to ⅓ of the volume in vacuo and the product crystallized on cooling.

(II) N - CYCLOPROPYLMETHYL - NOR - CODEINONE - 6 - CARBOXYMETHYLOXIME ALLYLESTER

Example 4.—N-cyclopropylmethyl-nor-codeinone

To a solution of 6 g. of nor-codeinone in 66 cc. of propyl alochol was added 3 grams of cyclopropylmethyl chloride and 3 grams of sodium bicarbonate, the resulting suspension was heated at 60° C. for 6 hours. The solvent was removed under reduced pressure and the residue taken up in 100 ml. of chloroform. The chloroform layer was washed with water and extracted with 100 ml. of dilute sulfuric acid. The acid solution was made to pH 10 with sodium carbonate and then extracted with three times 75 cc. of chloroform. The chloroform was dried over sodium sulfate and evaporated. The residue represented the desired product.

Example 5.—Carboxymethoxylamine allylester

5 grams of carboxymethoxylamine hydrochloride was suspended in 100 cc. of allyl alcohol and stirred under nitrogen at 40° C. for 10 hours. The alcohol was removed in vacuo at 30° C. and the residue was taken up in 100 cc. of methylene chloride and 75 cc. of 5% sodium hydroxide. The organic layer was dried and evaporated to leave the allyl ester of carboxymethoxylamine.

Example 6.—N-cyclopropylmethyl-nor-codeinone-6-carboxymethyloxime allylester

To a solution of 5 grams of N-cyclopropylmethyl-nor-codeinone in 100 cc. of dioxane containing ½ g. of sodium bicarbonate was added 3.5 gr. of carboxymethoxylamine allylester. The mixture was stirred at 50° C. for 8 hours and the solution concentrated to ⅓ of its volume in vacuo. On addition of 25 cc. of water and cooling the product crystallized.

(III) N - CYCLOPROPYLMETHYL - NOR - 14 - HYDROXYCODEINONE - 6 - CARBOXYMETHYLOXIME PROPYLESTER

Example 7.—N-cyclopropylmethyl-nor-14-hydroxycodeinone

A 10 gram sample of nor-14-hydroxycodeinone was dissolved in 100 ml. of dioxane and 6 g. of sodium bicarbonate was added. To the stirred suspension a solution of 6 g. cyclopropylmethylbromide in 50 ml. of dioxane was added dropwise. The mixture was then stirred and heated at 75° C. for 16 hours. It was then filtered and the dioxane was removed in vacuo. The residue crystallized from ethylacetate to yield the product.

Example 8.—Carboxymethoxylamine propylester hydrochloride

5 grams of carboxymethoxylamine p-toluene sulfonate is dissolved in 100 cc. of N-propyl alcohol and stirred at 70° C. for 8 hours. The alcohol is removed in vacuo at 40° C. and the residue is taken up in cold dilute sodium hydroxide solution and the precipitate filtered off. The precipitate which represents the desired product is dissolved in an exact equivalent of dilute hydrochloric acid. The water is then removed at 20° C. in vacuo and the residue of the carboxymethoxylamine propylester hydrochloride salt is obtained.

Example 9.—N-cyclopropylmethyl-nor-14-hydroxycodeinone-6-carboxymethyloxime propylester

To a solution of 6 gr. of carboxylmethoxylamine propylester hydrochloride in 50 cc. of one normal potassium hydroxide was added a solution of 8 g. of N-cyclopropylmethyl-nor-14-hydroxycodeinone and 150 ml. of ethanol. The mixture was heated at 65° C. for 10 hours and then concentrated to ¼ of the volume in vacuo. 50 cc. of water were then added and on cooling the product crystallized.

(IV) N - CYCLOPROPYLMETHYL - NOR - DIHYDROMORPHINONE - 6 - CARBOXYMETHYLOXIME ETHYLESTER

Example 10.—N-cyclopropylmethyl-nor-dihydromorphinone

A 10 gram sample of nor-dihydromorphinone was dissolved in 100 ml. of n-propyl alcohol and 6 g. sodium bicarbonate was added. To the stirred suspension a solution of 6 g. cyclopropylmethyl bromide in 50 ml. of n-propyl alcohol was added dropwise. The mixture was then stirred and heated at 75° C. for 16 hours. It was then filtered and the n-propanol was removed in vacuo. The residue crystallized from ethyl-acetate to yield the product.

Example 11.—Carboxymethoxylamine ethylester

10 grams of carboxymethylamine hydrochloride is dissolved in 75 cc. of ethyl alcohol and heated at reflux for 9 hours. The ethyl alcohol is removed in vacuo and the residue is treated with cold 1-normal sodium solution hydroxide and the resultant suspension extracted with 100 cc. of chloroform. The chloroform is dried and evaporated to give the desired product.

Example 12.—N-cyclopropylmethyl-nor-dihydromorphinone-6-carboxymethyloxime ethylester

To a solution of 6 grams of N-cycloproylmethyl-nordihydromorphinone in 100 ml. of ethanol containing 1 gram of sodium bicarbonate is added 3½ grams of carboxymethoxylamine ethyl ester. The solution is stirred

under nitrogen at 60° C. for 15 hours. It is then concentrated to ¼ of the volume and 20 cc. of water is added. The product crystallizes on cooling.

(V) N - CYCLOPROPYLMETHYL - NOR - 14 - HYDROXYDIHYDROCODEINONE - 6 - CARBOXYMETHYLOXIME METHYL ESTER

Example 13.—N-cyclopropylmethyl-nor-14-hydroxydihydrocodeinone

To a solution of 10 grams of nor-14-hydroxydihydrocodeinone in 150 cc. absolute ethanol was added 5 grams of cyclopropylmethylbromide and 5 grams of sodium bicarbonate. The resulting suspension was refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was taken up in 200 ml. chloroform, which was washed with water. The chloroform was then extracted with 2×100 ml. of dilute hydrochloric acid. The acid solution was treated with charcoal, filtered and made to pH 9.5 with concentrated ammonia. The basic solution was then extracted with 3×100 cc. chloroform and the chloroform was dried over Na_2SO_4 and evaporated. The residue was recrystallized from ethanol to give the product.

Example 14.—N-cyclopropylmethyl-nor-14-hydroxydihydrocodeinone-6-carboxymethyloxime

To a solution of 10 grams of N-cyclopropylmethyl-nor-14-hydroxydihydrocodeinone in 100 ml. of ethanol was added 8 grams of carboxymethoxylamine hydrochloride and 35 ml. of 2 N KOH solution. The mixture was refluxed at 72° C. for 8 hours and the volume was concentrated to ⅓ under reduced pressure. The product crystallized on cooling, and could be recrystallized from dilute ethanol.

Example 15.—N - cyclopropylmethyl - nor - 14 - hydroxydihydrocodeinone-6-carboxymethyloxime methyl ester

A solution of N-cyclopropylmethyl-nor-14-hydroxydihydrocodeinone-6-carboxymethyloxime in ethanol was treated with an ethereal diazomethane solution until the yellow color persisted. After standing at room temperature for 1 hour, the solvents were removed by evaporation on a steam bath and the residue was recrystallized from ethanol to give the product.

A representative compound of the present invention, namely, N-cyclopropylmethyl-nor - 14 - hydroxydihydrocodeinone - 6 - carboxymethyloxime methylester was found to have alagesic effect when tested by the hotplate method equivalent to and ED_{50} of 16.2 mg. per kg. bodyweight in mice subcutaneously.

It was employed also in a series of tests with monkeys to determine its physical dependency characteristics and duration of drug action. These tests were performed in the following manner:

Monkeys, physically dependent on 3 mg./kg. morphine sulfate g6h, were withdrawn until abstinence signs of intermediate severity were present (12 to 14 hours). N-cyclopropylmethyl - nor - 14 - hydroxydihydrocodeinone - 6 - carboxymethyloxime methyester was injected at this time in the dosage units indicated below; the monkeys were graded just prior to injection and at intervals of ½, 1, 2, 3, 4, 5, and 6 hours after injection. Grades were based on withdrawal intensity of opiate-like depression and side effects.

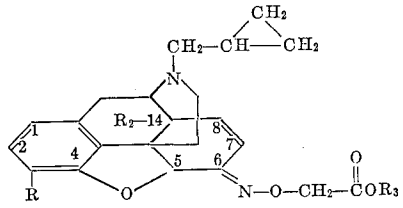
It was found that at dosages of 1 and 2 mg./kg. of body weight, partial suppression of symptoms was obtained. The duration of action was about 4 hours and the physical dependency of the drug was indicated to be low.

Various modifications may be made to and within the present invention.

Having described the present invention, that which is sought to be protected is set forth in the following claims.

What is claimed is:

1. Carboxymethyloxime compound of the formula:



wherein R is selected from the group consisting of hydroxy and methoxy, and R_2 is selected from the group consisting of hydrogen or hydroxy, and wherein R_3 is selected from the group consisting of H, CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $CH_2{=}CH{-}CH_2$ and $C_6H_5CH_2$.

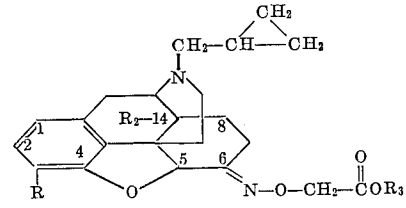
2. N-cyclopropylmethyl-norcodeinone - 6 - carboxymethyloxime.

3. N-cyclopropylmethyl - nor - morphinone - 6 - carboxyloxime.

4. N-cyclopropylmethyl - nor - 14 - hydroxycodeinone-6-carboxymethyloxime.

5. N-cyclopropylmethyl - nor - codeinone - 6-carboxymethyloxime methylester.

6. Carboxymethyloxime compound of the formula:



wherein R is selected from the group consisting of hydroxy and methoxy, and R_2 is selected from the group

consisting of hydrogen or hydroxy, and wherein R_3 is selected from the group consisting of H, CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $CH{=}CH{-}CH_2$ and $C_6H_5CH_2$.

7. N-cyclopropylmethyl - nor - 14 - hydroxydihydrocodeinone-6-carboxymethyloxime.

8. N-cyclopropylmethyl - nor - dihydrocodeinone-6-carboxymethyloxime methylester.

9. N-cyclopropylmethyl - nor - 14 - hydroxydihydrocodeinone-6-carboxymethyloxime methylester.

10. N-cyclopropylmethyl - nor - 14 - hydroxydihydromorphinone-6-carboxymethyloxime methylester.

11. The carboxymethyloxime compounds of claim 1 wherein R_2 is hydrogen.

12. The carboxymethyloxime compounds of claim 6 wherein R_2 is hydrogen.

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