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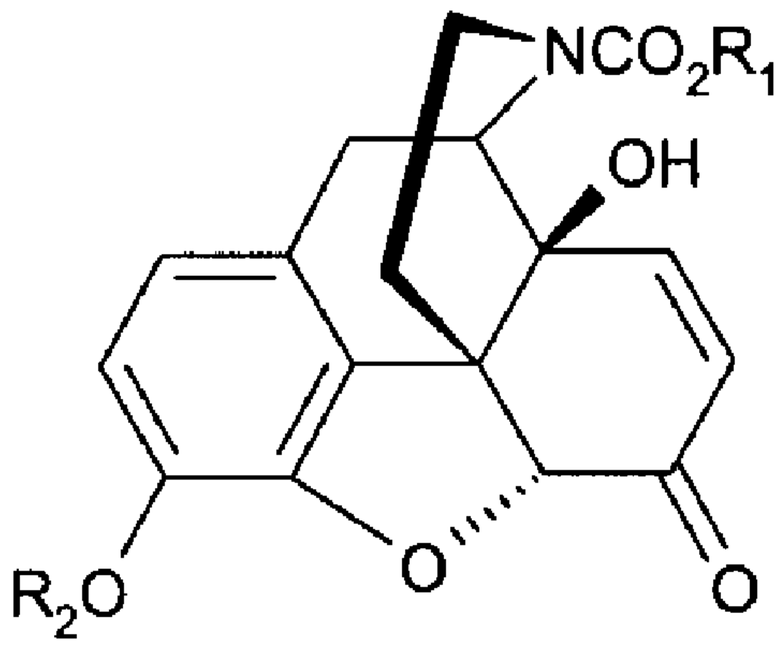
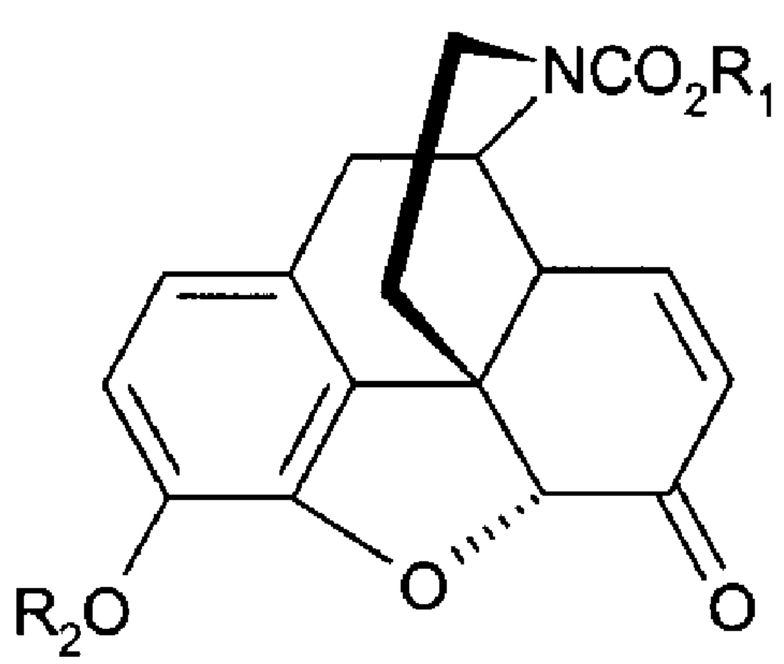
(54) Title: PROCESS FOR THE PREPARATION OF A 14-HYDROXYNORMORPHINONE DERIVATIVE



IV



III

(57) Abrégé/Abstract:
The present invention relates to process for the preparation of a 14-hydroxynormorphinone derivative of formula (IV) comprising reacting the compound of formula (III), with a cobalt (II) oxidant in the presence of a mild base and air or oxygen as the cooxidant; wherein R_1 is (1C-7C) alkyl optionally substituted with one or more chlorines, butenyl, vinyl, benzyl, phenyl or naphthyl; and R_2 is benzyl or benzyl substituted with one ore more (1C-6C) alkoxy group or benzyl substituted with one or more halogen. The process is very suitable in the production of noroxymorphone.

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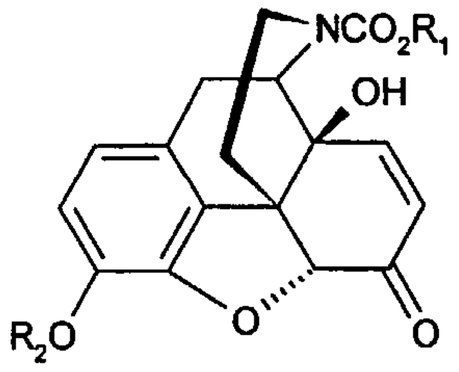

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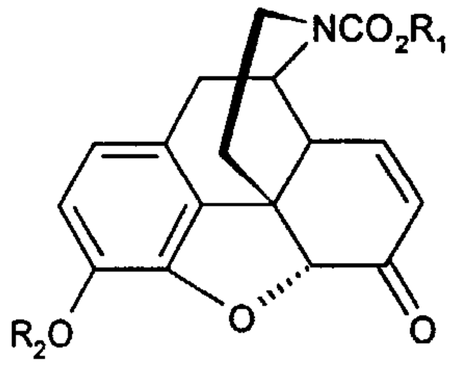


(III)

(57) Abstract: The present invention relates to process for the preparation of a 14-hydroxynormorphinone derivative of formula (IV) comprising reacting the compound of formula (III), with a cobalt (II) oxidant in the presence of a mild base and air or oxygen as the cooxidant; wherein R¿1? is (1C-7C) alkyl optionally substituted with one or more chlorines, butenyl, vinyl, benzyl, phenyl or naphthyl; and R¿2? is benzyl or benzyl substituted with one ore more (1C-6C) alkoxy group or benzyl substituted with one or more halogen. The process is very suitable in the production of noroxymorphone.

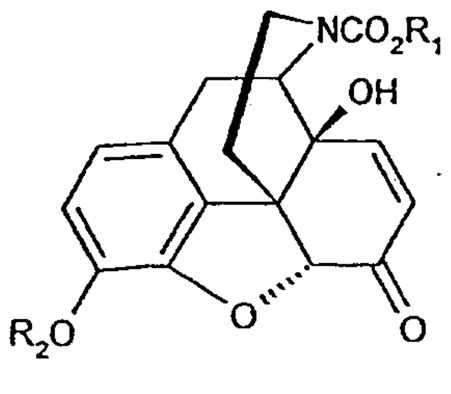
PROCESS FOR THE PREPARATION OF A 14-HYDROXYNORMORPHINONE DERIVATIVE

The invention relates to a process for the production of 14-hydroxynormorphinone derivatives, to a new synthetic route for producing noroxymorphone, as well as to new intermediates in said route.

Noroxymorphone is a key intermediate for the production of important medicinal opioids, such as naltrexone and naloxone. The common starting material for the production of these opioids is thebaine from which they are readily synthesized. However, thebaine has only a low natural abundance in poppy heads and opium. As the supply of thebaine is limited and the demand is increasing, many alternative approaches have been made for the preparation of 14-hydroxymorphine derivatives. See for example EP 0,158,476, US 5,922,876, and the references cited therein.

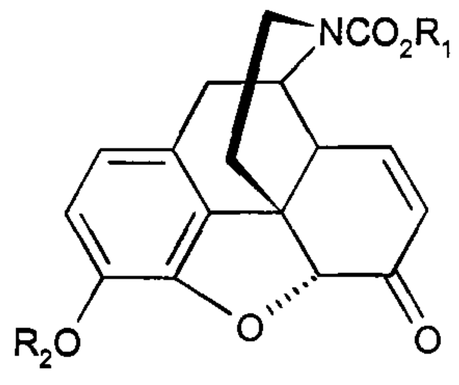
Further, in an attempt to remove the requirement for (the preparation of) thebaine, Coop et al. (Tetrahedron 55 (1999), 11429-11436; WO 00/66588) recently described an oxidative method for the production of 14-hydroxycodeinone in a yield of 51% from codeinone, using $Co(OAc)_3$ as the metallic oxidant in acetic acid at room temperature. Other oxidative conditions with metallic oxidants, such as $Co(OAc)_3$ under other conditions, $FeCl_3$, $Co(OAc)_2$ in combination with several cooxidants, RuO_4, $Mn(OAc)_3$, $Cu(OAc)_2$, and others, proved to be not very useful according to Coop.

Surprisingly, and in spite of the findings of Coop, it has now been found that in the production of 14-hydroxynormorphinone derivatives of formula IV from compounds of formula III cobalt (II) salts can be used as efficient oxidants when the reaction is performed in the presence of a mild base and oxygen or air is used as cooxidant. Therefore, the invention relates to a process for the preparation of a 14-hydroxynormorphinone derivative of formula IV



IV

comprising reacting the compound of formula **III**,

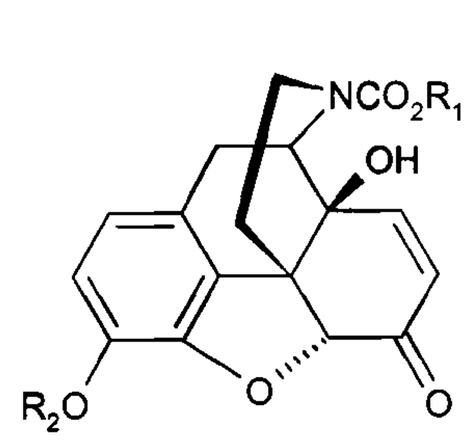


III

with a cobalt (II) oxidant in the presence of a mild base and air or oxygen as the cooxidant; wherein R_1 is (1-7C)alkyl optionally substituted with one or more chlorines (such as 1,1,1-trichloroethyl), butenyl, vinyl, benzyl, phenyl or naphthyl;

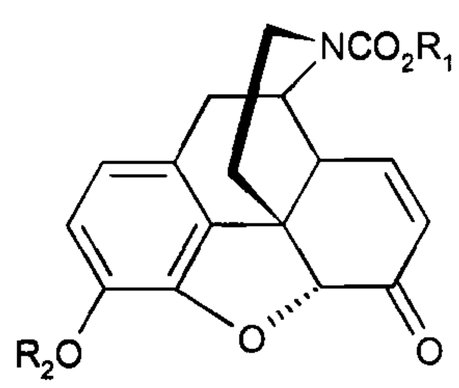
and R_2 is benzyl or benzyl substituted with one or more (1-6C)alkoxy group or benzyl substituted with one or more halogen.

According to one aspect of the present invention, there is provided a process for preparation of a 14-hydroxynormorphinone derivative of formula **IV**



IV

comprising reacting a compound of formula **III**,



III

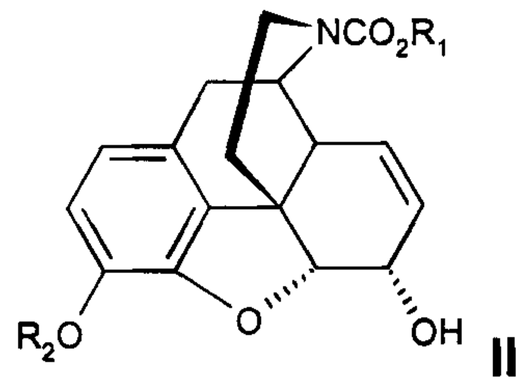
with a cobalt (II) oxidant in the presence of a mild base and air or oxygen as cooxidant;

wherein R_1 is (1C-7C)alkyl optionally substituted with one or more substituents wherein each substituent independently is chlorine, butenyl, vinyl, benzyl, phenyl or naphthyl;

and R_2 is benzyl, benzyl independently substituted with one or more (1C-6C)alkoxy group or benzyl independently substituted with one or more halogen.

According to another aspect of the present invention, there is provided a morphinone derivative wherein the derivative is the compound of the formula **III** as described herein.

According to still another aspect of the present invention, there is provided a process for preparation of a compound of formula **III**, wherein the compound of formula **III** is as described herein, the process comprising reactively contacting a morphine derivative of formula **II**



II

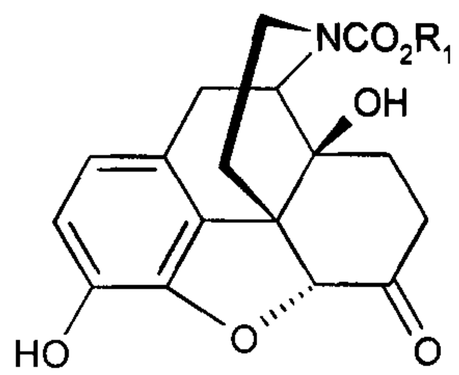
wherein R_1 and R_2 are as described herein, for the compound of formula **III**, with an oxidizing agent effective for oxidizing allylic hydroxy groups to form keto groups.

According to yet another aspect of the present invention, there is provided a process for production of noroxymorphone, comprising:

(a) a reaction step wherein a morphinone derivative of formula **III** as described herein is oxidized into a 14-hydroxynormorphinone derivative of formula **IV** as described herein,

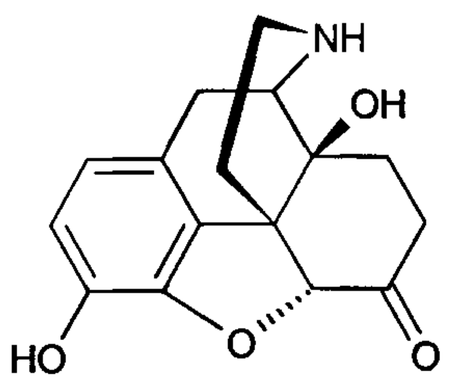
(b) deprotecting the 3-position and reducing the double bond at the 7,8-position of the 14-hydroxynormorphinone derivative of formula **IV** to form a 3,14-hydroxynormorphinone derivative of formula **V**,

2b



V

(c) wherein R_1 is as defined for the derivative of formula **IV**; and hydrolyzing the 3,14-hydroxynormorphinone derivative of formula **V** into noroxymorphone of formula **VI**,



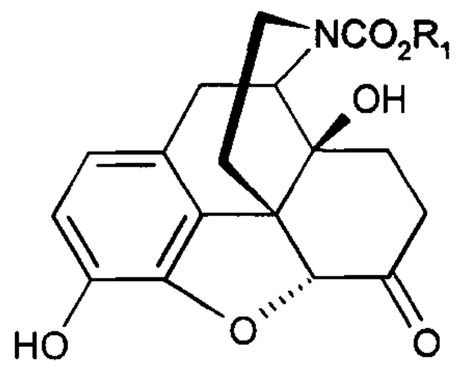
VI.

According to a further aspect of the present invention, there is provided a process for production of noroxymorphone, comprising:

(a) a reaction step comprising the oxidation of a compound of formula **II** as described herein to form a morphinone derivative of formula **III** as described herein,

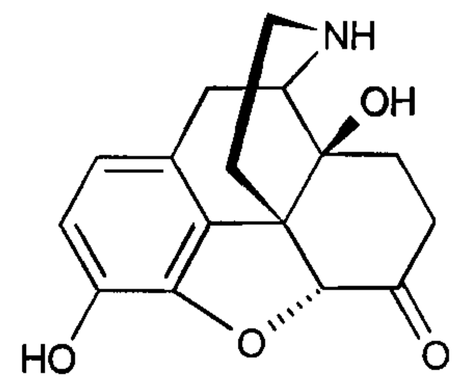
(b) a reaction step wherein a morphinone derivative of formula **III** as described herein is oxidized into a 14-hydroxynormorphinone derivative of formula **IV** as described herein,

(c) deprotecting the 3-position and reducing the double bond at the 7,8-position of the 14-hydroxynormorphinone derivative of formula **IV** to form a 3,14-hydroxynormorphinone derivative of formula **V**,



V

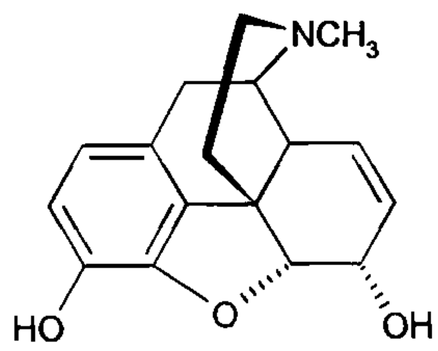
(d) wherein R_1 is as defined for the derivative of formula **IV**; and hydrolyzing the 3,14-hydroxynormorphinone derivative of formula **V** into noroxymorphone of formula **VI**,



VI.

According to yet a further aspect of the present invention, there is provided a process for production of noroxymorphone comprising

(a) converting morphine having the formula **I**



I

by reaction with a haloformate ester of the formula X-C(=O)OR_1, wherein R_1 is as described herein and X is a halogen,

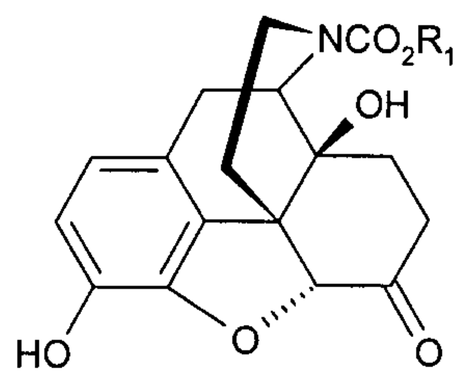
followed by a reaction with R_2-X, wherein X is a halogen and R_2 is as described herein, to form a morphine derivative of formula **II** as described herein;

(b) oxidizing the morphine of formula **II** to form a morphinone derivative of formula **III** according to the process as described herein;

(c) oxidizing the morphinone derivative of formula **III** to form a 14-hydroxynormorphinone derivative of formula **IV** according to the process as described herein;

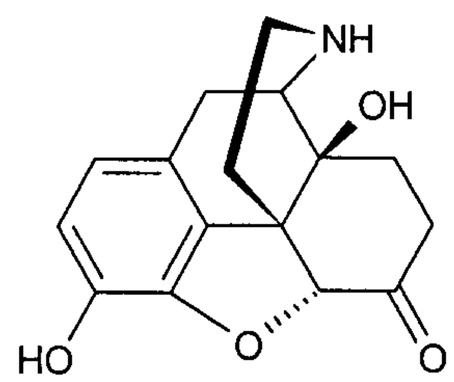
(d) deprotecting the 3-position and reducing the double bond at the 7,8-position of the 14-hydroxynormorphinone derivative of formula **IV** to form a 3,14-hydroxynormorphinone derivative of formula **V**,

2d



V;

(e) and hydrolyzing the 3,14-hydroxynormorphinone derivative of formula **V** into noroxymorphone of formula **VI**,



VI.

The oxidation process of the present invention is an efficient process with good yields, which are significantly improved when compared to the process described by Coop et al.

The cobalt (II) oxidant according to the present invention may be selected from a range of cobalt (II) salts, such as CoF_2, $CoCl_2$, $CoBr_2$, Co(II)sulfate, Co(II)nitrate, Co(II)acetate, Co(II)propionate, and the like, and mixtures thereof. The preferred oxidant in the process of this invention is $Co(OAc)_2$ and the preferred cooxidant is air. The reaction mixture of this oxidation process is a heterogeneous system; the oxidant dissolves only in minor amounts in the organic solvent that is used. The amount of cobalt (II) salts used is not very critical, as long as the system is heterogeneous, and a skilled person will know to choose sufficient amounts thereof. The cooxidant is introduced into the reaction mixture by bubbling it through the solution, while stirring.

A person skilled in the art is aware what type of base are meant with the term mild bases, however preferred bases are sodium acetate, potassium acetate, sodium phosphate and potassium phosphate. Most preferred is sodium acetate.

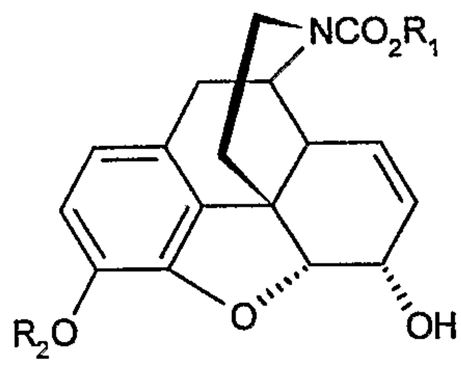
Preferably R_1 is (1-7C)alkyl, and most preferred is ethyl. For R_2 benzyl is most preferred. The oxidation process according to the present invention is performed

in an organic solvent well-suited for dissolution of this type of compounds, preferably (1-4C)alcohols or mixtures thereof. Preferred is ethanol.

The reaction temperature is usually higher than room temperature, and may be chosen dependent on the boiling point of the solvent used. However, the temperature may not be higher than about 100 °C in order to keep the oxygen sufficiently in solution.

In the terms (1-7C)alkyl, (1-6C)alkoxy and (1-4C)alcohols the alkyl group is a branched or unbranched alkyl group having 1 to 7, 1 to 6 or 1 to 4 carbon atoms, respectively, such as methyl, ethyl, isopropyl, t-butyl, heptyl and the like.

The compound of formula **III** may suitably prepared by methods well known in the art. Preferably, the process for the preparation of a compound of formula **III** comprises reactively contacting a morphine derivative of formula **II**



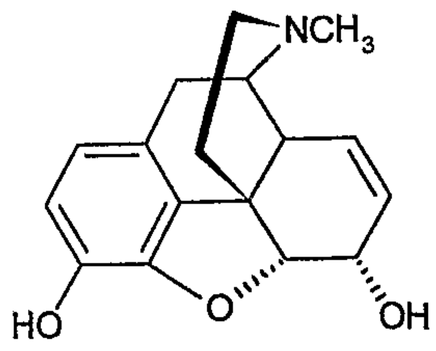
II

with an oxidizing agent effective for oxidizing allylic hydroxy groups to form keto groups, where a morphinone compound of the formula **III** is prepared. Preferably, the oxidizing agent is sodium dichromate. Preferably R_1 is ethyl. For R_2 benzyl is most preferred.

The new process of this invention may conveniently be used in the production of noroxymorphone. Therefore, another aspect of this invention is a process for the production of noroxymorphone, comprising a reaction step wherein a morphinone compound of formula **III** is oxidized into the 14-hydroxynormorphinone derivative of formula **IV**. In particular preferred is the process further comprising the oxidation of a morphine derivative of formula **II** into the compound of formula **III** as described above.

Especially preferred is a process for the production of noroxymorphone comprising the steps:

(a) converting morphine having the formula **I**



I

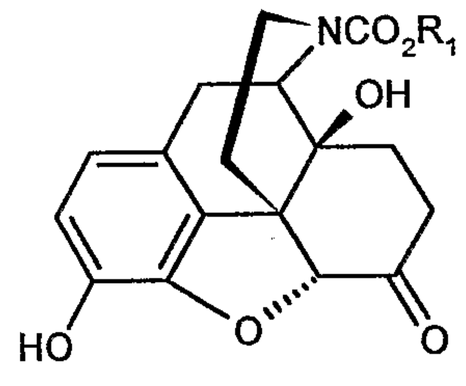
by reaction with a haloformate ester of the formula X-C(=O)OR_1, wherein R_1 is as previously defined and X is a halogen (F, Cl, Br or I, preferably Cl),

followed by a reaction with R_2-X, wherein X (preferably Cl) and R_2 are as previously defined, to form a morphine derivative of formula **II**;

(b) oxidizing the morphine of formula **II** to form a morphinone derivative of formula **III** according to the previously described process;

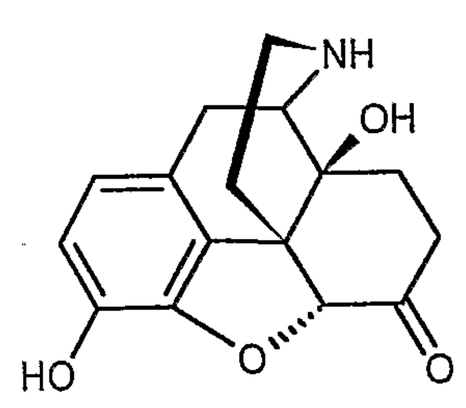
(c) oxidizing the morphinone derivative of formula **III** to form a 14-hydroxynormorphinone derivative of formula **IV** according to the previously described process;

(d) deprotecting the 3-position and (at the same time) reducing the double bond at the 7,8-position of the 14-hydroxynormorphinone derivative of formula **IV** to form a 3,14-hydroxynor-morphinone derivative of formula **V**, using methods well known in the art for such type of reaction, e.g. using hydrogen and palladium-carbon as a catalyst,



V;

(e) and hydrolyzing the 3,14-hydroxynormorphinone derivative of formula **V** into noroxymorphone of formula **VI**, using methods well known in the art for such type of hydrolysis, e.g. using sulfuric acid,



VI.

In the process for the production of noroxymorphone, the novel intermediates of formula **II**, **III** and **IV** form each another aspect of the present invention. The intermediates of formula **II**, **III**

and **IV** are in particular preferred wherein R_1 is ethyl. Also preferred are intermediates of formula **II, III** and **IV** wherein R_2 is benzyl. Most preferred are the intermediates of formula **II, III** and **IV** wherein R_1 is ethyl and R_2 is benzyl.

The invention is further illustrated by the following example.

EXAMPLE 1

The underlined numbers refer to the numbers of the structures of Scheme I. (Bn = benzyl).

(5α, 6α)-3-(benzyloxy)-7,8-didehydro-4,5-epoxy-6-hydroxymorphinan-17-carboxylic acid ethylester (2)

Morphine (1, 8 g) was dissolved in 80 ml of toluene and the solution was dried by azeotropic distillation of water. Sodium carbonate (15 g) and sodium hydrogen carbonate (6 g) were added and the solution was again dried by azeotropic distillation. Ethyl chloroformate (30 g) was slowly and in portions added over a period of approximately 4 h at 78°C. Completion of the reaction was checked with TLC. The excess of reagent and the salts were dissolved by addition of water. The layers were separated and the toluene layer was washed with water. The toluene solution was evaporated to dryness and the residue was dissolved in 70 ml of ethanol. The 3-carboxylic acid ethyl ester group was saponified by 6 g potassium hydroxide (dissolved in 18 ml of ethanol) and 5 g potassium carbonate at 55°C. The pH was checked (in a 1:1 dilution in water) and was >11. To this basic solution 5 g benzylchloride was added and the reaction was performed for 4 h at 75°C. The product was precipitated by the addition of water (70 ml), filtered, washed with water and dried. The yield of product (2) was 10 g. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29 (m, 3H), 1.92 (m, 2H), 2.52 (s, 1H), 2.72 (m, 2H), 2.85 (m, 1H), 3.01 (m, 1H), 4.01 (m, 1H), 4.17 (m, 3H), 4.87 (d, 1H), 4.89 (d, 1H), 5.09 (d, 1H), 5.18 (d, 1H), 5.29 (t, 1H), 5.72 (t, 1H), 6.53 (d, 1H), 6.75 (d, 1H), 7.37 (m, 5H).

(5α)-3-(benzyloxy)-7,8-didehydro-4,5-epoxy-6-oxomorphinan-17-carboxylic acid ethylester (3)

A solution of Jones reagent was prepared by dissolving 7,5 g sodium dichromate.$2H_2O$ in 22 ml water and 6 ml sulfuric acid. Compound (2) (7,5 g) was dissolved in 60 ml trichloro ethylene and

28 ml water was added. The pH was adjusted to 5 with sulfuric acid. The mixture was heated under reflux and the Jones reagens was slowly added over a period of 1 h. The oxidation was continued for another 1,5 h under reflux. The excess of oxidant was destroyed with 6 ml 2-propanol. The layers were separated and the organic layer was washed with 10% sodium hydrogen carbonate solution and water and dried with sodium sulfate. The solution was evaporated to dryness and the residue was dissolved in ethanol. Yield: ~ 9 g product (3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (m, 3H), 1.92 (m, 2H), 2.8 (m, 2H), 2.9 (m, 1H), 3.05 (m, 1H), 4.02 (m, 1H), 4.19 (m, 2H), 4.72 (s, 1H), 5.03 (m, 1H), 5.18 (s, 2H), 6.12 (dd, 1H), 6.57 (d, 1H), 6.64 (m, 1H), 6.74 (d, 1H), 7.34 (m, 5H).

(5α)-3-(benzyloxy)-7,8-didehydro-4,5-epoxy-14-hydroxy-6-oxomorphinan-17-carboxylic acid ethylester (4)

The solution of product (3) in ethanol (9 g in 135 ml) was heated to 60°C, 2,6 g cobalt (II) acetate and 0,5 g sodium acetate were added and air was bubbled through the solution under vigorous stirring. The reaction was followed with TLC. After completion of the reaction the solution was treated with charcoal (0,3 g) and filtered. The solution was distilled to volume and this concentrated solution (6,3 g (4) in 53 ml of ethanol) was transferred to the next step. ^{1}H NMR of 4 (360 MHz, CH_3OH-d4) δ 1.28 (m, 3H), 1.55 (m, 1H), 2.52 (m, 1H), 2.74 (m, 1H), 2.92 (m, 2H), 4.05 (m, 1H), 4.15 (m, 2H), 4.64 (m, 1H), 4.72 (s, 1H), 4.85 (m, 1H), 5.1 (s, 2H), 6.05 (d, 1H), 6.6 (d, 1H), 6.76 (d, 1H), 6.91 (m, 1H), 7.3 (m, 5H).

(5α)-4,5-epoxy-3,14-dihydroxy-6-oxomorphinan-17-carboxylic acid ethylester (5)

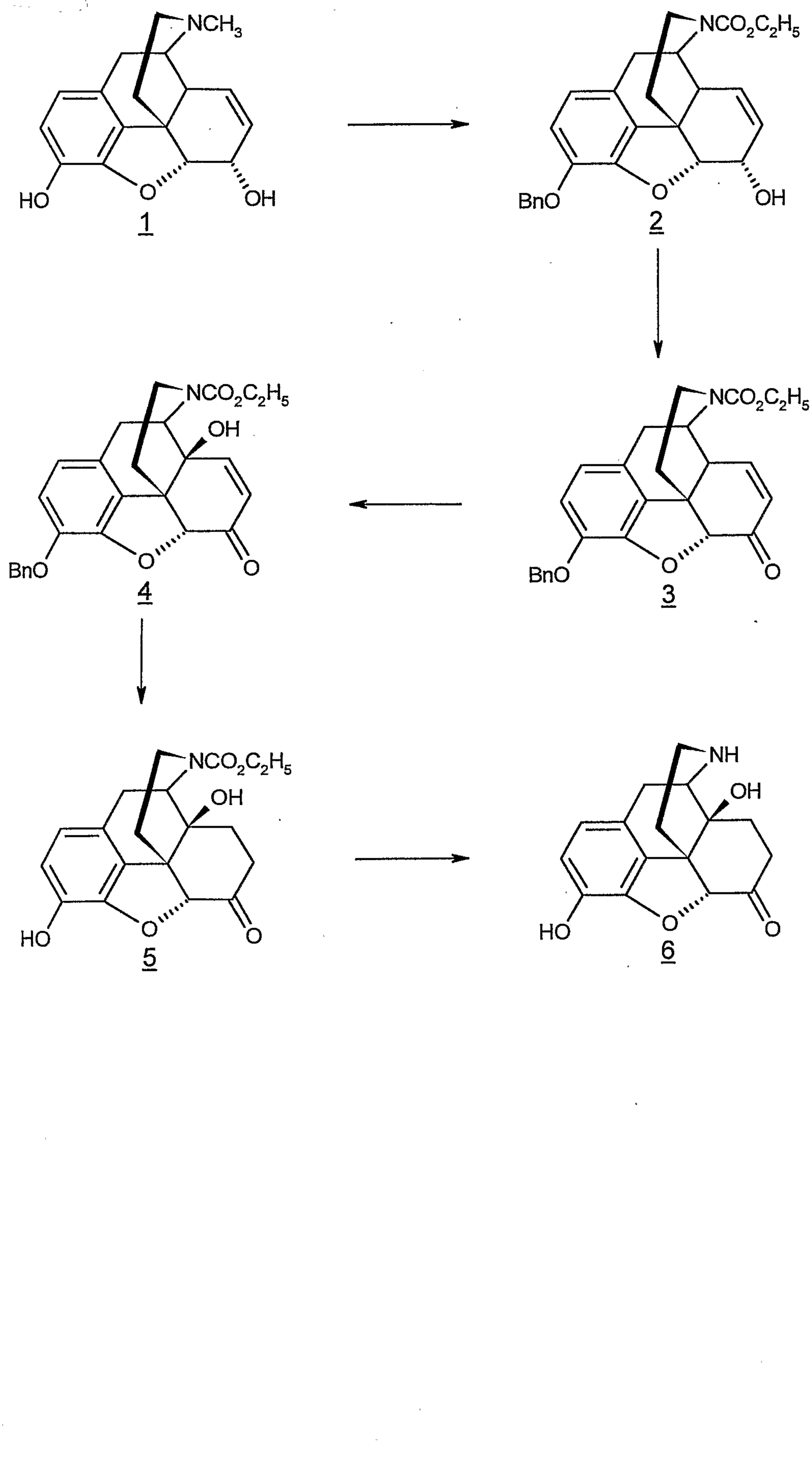
To the solution of the previous step 6 ml of acetic acid was added. The product (4) was reduced with hydrogen and palladium-carbon (5%) as a catalyst (0,9 g) at 20°C and normal pressure. After filtration and evaporation of ethanol 5,4 g of crude product (5) was obtained. The product was recrystallized from 2 parts (w/v) of ethyl acetate to obtain 4,7 g product (5).

(5α)-4,5-epoxy-3,14-dihydroxymorphinan-6-one (noroxymorphone) (6)

Product (5) (4,7 g) was dissolved in 28 ml of water and 5,6 ml of sulfuric acid and refluxed for approx. 24 h. The product was precipitated at pH = 9 by dilution with water and 4,6 g of crude product (6) was obtained after filtration and drying. The product was purified by dissolution in

ethanol, precipitation from this solvent at pH = 2, dissolution in water, charcoal treatment and precipitation at pH = 9. ^{1}H NMR (400 MHz, DMSO-d6) δ 1.17 (m, 1H), 1.41 (m, 1H), 1.72 (m, 1H), 2.07 (m, 1H), 2.29 (m, 1H), 2.36 (m, 1H), 2.62 (m, 1H), 3.9 (m, 4H), 4.68 (s, 1H), 6.52 (d, 1H), 6.56 (d, 1H).

SCHEME 1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OH
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NCO2C2H5
OH
BnO
O
O
4
NCO2C2H5
OH
HO
O
O
5
NH
OH
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O
O
6

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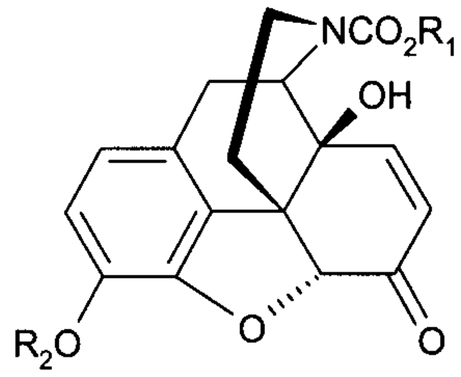
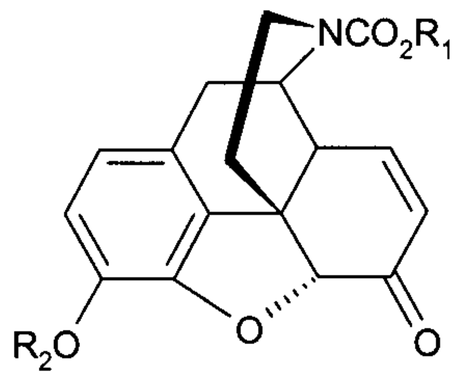
CLAIMS:

1. A process for preparation of a 14-hydroxynormorphinone derivative of formula **IV**



IV

comprising reacting a compound of formula **III**,



III

with a cobalt (II) oxidant in the presence of a mild base and air or oxygen as cooxidant;

wherein R_1 is (1C-7C)alkyl optionally substituted with one or more substituents wherein each substituent independently is chlorine, butenyl, vinyl, benzyl, phenyl or naphthyl;

and R_2 is benzyl, benzyl independently substituted with one or more (1C-6C)alkoxy group or benzyl independently substituted with one or more halogen.

2. The process of claim 1, wherein the cobalt (II) oxidant is $Co(OAc)_2$.

3. The process of claim 1 or 2, wherein the cooxidant is oxygen.

4. The process of claim 1 or 2, wherein the cooxidant is air.

5. The process of any one of claims 1 to 4, wherein the mild base is sodium acetate, potassium acetate, sodium phosphate or potassium phosphate.

6. The process of claim 5, wherein the mild base is sodium acetate.

7. The process of any one of claims 1 to 6, wherein R_1 is (1-7C)alkyl.

8. The process of claim 7, wherein R_1 is ethyl.

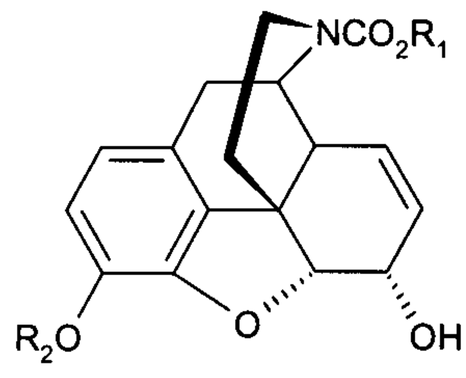
9. The process of any one of claims 1 to 8, wherein R_2 is benzyl.

10. A morphinone derivative wherein the derivative is the compound of the formula **III** as defined in claim 1.

11. The morphinone derivative of claim 10, wherein R_1 is ethyl.

12. The morphinone derivative of claim 10 or 11, wherein R_2 is benzyl.

13. A process for preparation of a compound of formula **III**, wherein the compound of formula **III** is as defined in claim 1, the process comprising reactively contacting a morphine derivative of formula **II**



II

wherein R_1 and R_2 are as defined in claim 1 for the compound of formula **III**, with an oxidizing agent effective for oxidizing allylic hydroxy groups to form keto groups.

14. The process of claim 13, wherein the oxidizing agent is sodium dichromate.

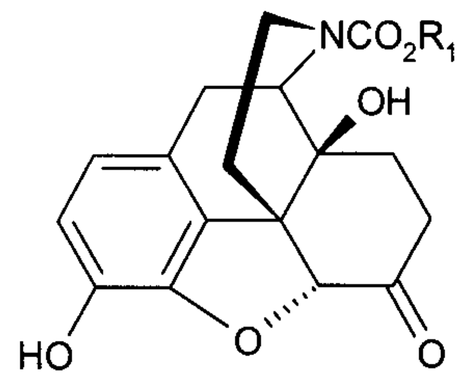
15. The process of claim 13 or 14, wherein R_1 is ethyl.

16. The process of any one of claims 13 to 15, wherein R_2 is benzyl.

17. A process for production of noroxymorphone, comprising:

(a) a reaction step wherein a morphinone derivative of formula **III** as defined in claim 1 is oxidized into a 14-hydroxynormorphinone derivative of formula **IV** as defined in claim 1,

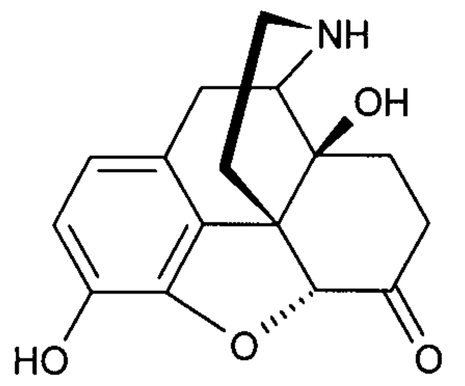
(b) deprotecting the 3-position and reducing the double bond at the 7,8-position of the 14-hydroxynormorphinone derivative of formula **IV** to form a 3,14-hydroxynormorphinone derivative of formula **V**,



V

wherein R_1 is as defined for the derivative of formula **IV**; and

(c) hydrolyzing the 3,14-hydroxynormorphinone derivative of formula **V** into noroxymorphone of formula **VI**,



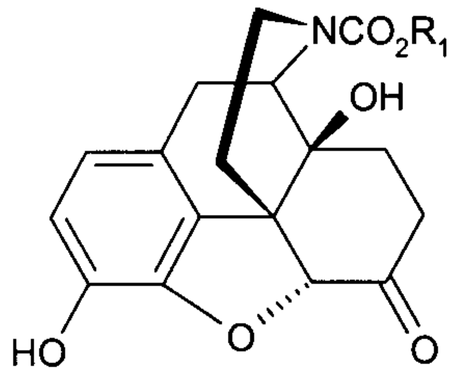
VI.

18. A process for production of noroxymorphone, comprising:

(a) a reaction step comprising the oxidation of a compound of formula **II** as defined in claim 13 to form a morphinone derivative of formula **III** as defined in claim 1,

(b) a reaction step wherein a morphinone derivative of formula **III** as defined in claim 1 is oxidized into a 14-hydroxynormorphinone derivative of formula **IV** as defined in claim 1,

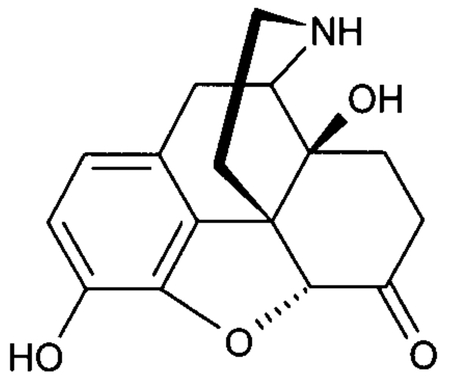
(c) deprotecting the 3-position and reducing the double bond at the 7,8-position of the 14-hydroxynormorphinone derivative of formula **IV** to form a 3,14-hydroxynormorphinone derivative of formula **V**,



V

wherein R_1 is as defined for the derivative of formula **IV**; and

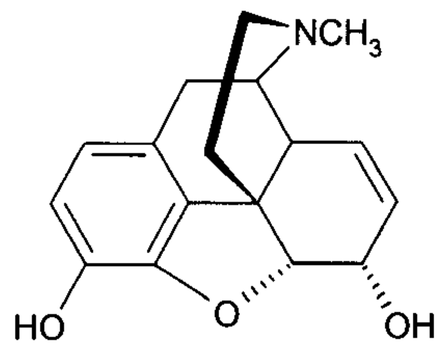
(d) hydrolyzing the 3,14-hydroxynormorphinone derivative of formula **V** into noroxymorphone of formula **VI**,



VI.

19. A process for production of noroxymorphone comprising

(a) converting morphine having the formula **I**



I

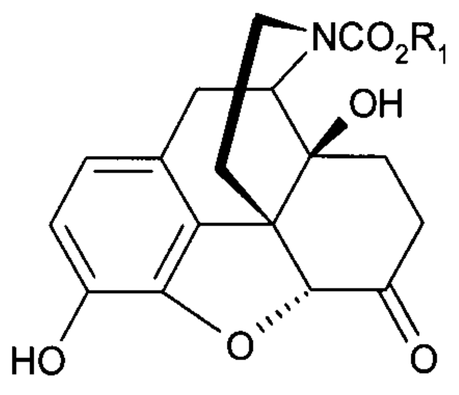
by reaction with a haloformate ester of the formula X-C(=O)OR_1, wherein R_1 is as defined in claim 1 and X is a halogen,

followed by a reaction with R_2-X, wherein X is a halogen and R_2 is as defined in claim 1, to form a morphine derivative of formula **II** as defined in claim 13;

(b) oxidizing the morphine of formula **II** to form a morphinone derivative of formula **III** according to the process as defined in claim 13;

(c) oxidizing the morphinone derivative of formula **III** to form a 14-hydroxynormorphinone derivative of formula **IV** according to the process as defined in claim 1;

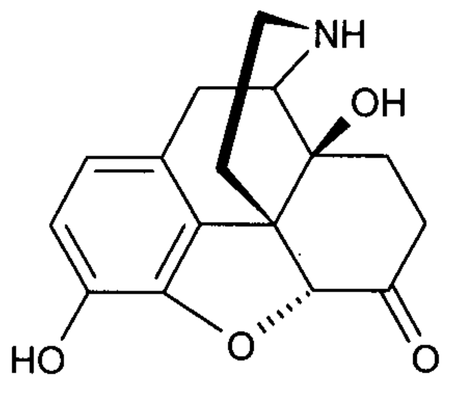
(d) deprotecting the 3-position and reducing the double bond at the 7,8-position of the 14-hydroxynormorphinone derivative of formula **IV** to form a 3,14-hydroxynormorphinone derivative of formula **V**,



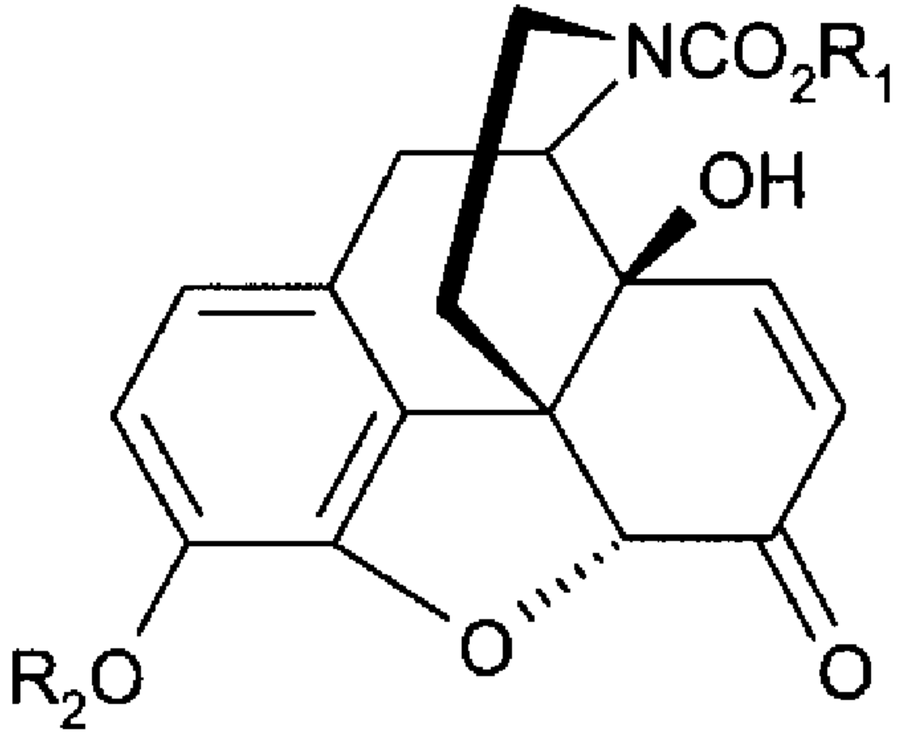
V

wherein R_1 is as defined in claim 1; and

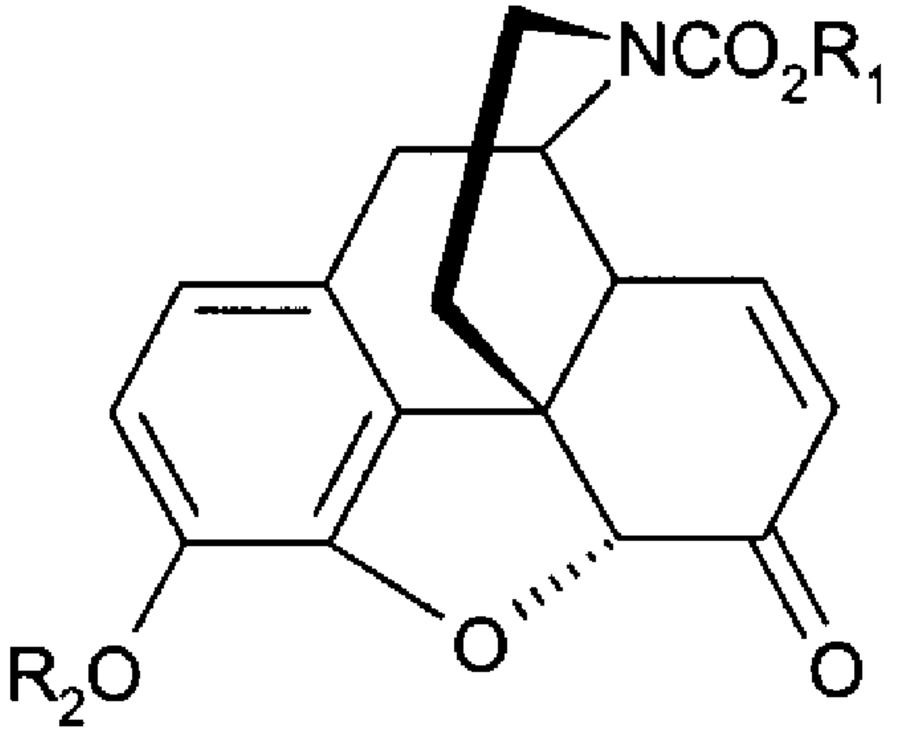
(e) hydrolyzing the 3,14-hydroxynormorphinone derivative of formula **V** into noroxymorphone of formula **VI**,



VI.



IV



III