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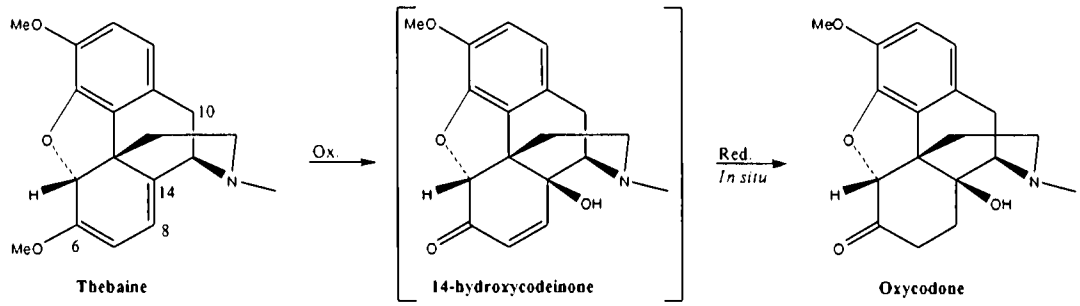
(54) Title: PREPARATION OF OXYCODONE

(57) Abstract: This invention relates to a pharmaceutical process, specifically for the preparation of oxycodone (II) from thebaine.

PREPARATION OF OXYCODONE

This invention relates to a pharmaceutical process, specifically for the preparation of oxycodone from thebaine.

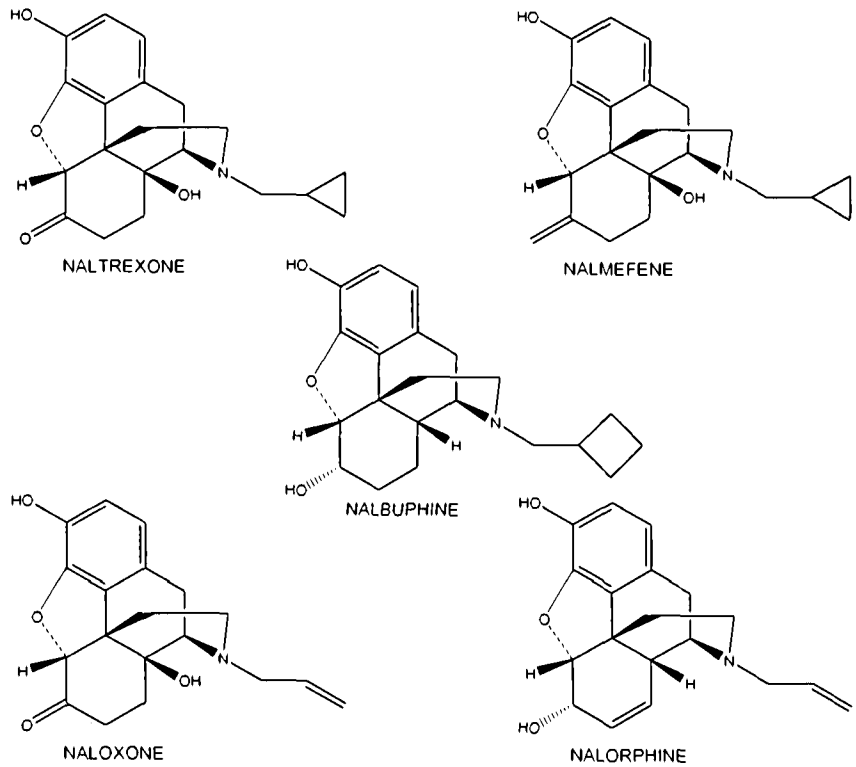
The following reaction sequence shows the conversion of thebaine to oxycodone via the intermediate 14-hydroxycodeinone.



Thebaine 14-hydroxycodeinone Oxycodone

In the oxidation step, the concomitant N-oxide of 14-hydroxycodeinone is also formed. However, this intermediate is reduced to the desired product during the subsequent reduction step.

Oxycodone and it's hydrochloride salt are analgesics and are useful intermediates for use in the production of other commercial and well known morphinans, including naltrexone and naloxone, which are shown below.



Oxycodone has been known for over 30 years and numerous reaction sequences are known for its preparation. Some known sequences for preparing oxycodone from thebaine are discussed below.

International Patent Application No PCT/SK2005/000014 (Zentiva, A.S.), discloses a method for the preparation of oxycodone from thebaine which is carried out in two steps. The first step is to react thebaine with hydrogen peroxide or peroxoacids in the presence of oxalic acid and another organic acid such as formic acid or acetic acid to produce 14-dihydroxycodeinone oxalate. 14-hydroxycodeinone is then isolated after addition of a base. The second step is to hydrogenate the 14-hydroxycodeinone with hydrogen in the presence of a catalyst to yield oxycodone. This international patent application describes a two-step process, each step being carried out in different solvents and in different vessels. It also describes the presence of oxalic acid being an essential element in the reaction.

US Patent No 6,262,266B (Boehringer Ingelheim Chemicals Inc) describes a method for the synthesis of oxycodone from codeine by first oxidising codeine to codeinone followed by protection of codeinone using an organo silyl compound to produce a dienol silyl ether derivative. The next step is an oxidation of the dienol silyl ether derivative of codeinone to produce 14-hydroxycodeinone, which in a further step is reduced by a catalytic hydrogen transfer method to produce oxycodone. The process described in US 6,262,266 is carried out in more than one step and each step is carried out in a different reaction vessel. Furthermore, US 6,262,266 teaches the necessity to use organo silyl compounds as protecting groups whereas this protecting step is not required by the present invention.

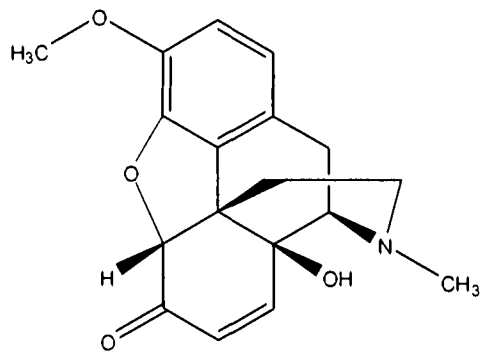
US Patent No 7,153,966 B (Johnson Matthey Public Limited) describes a method for the preparation of oxycodone from thebaine having low levels of impurities, such as 14-hydroxycodeinone. Two processes are exemplified in the patent. In the first process, formic acid and hydrogen peroxide is added to a solution of thebaine in water to produce 14-hydroxycodeinone. The 14-hydroxycodeinone is then transferred to a hydrogenation bottle, a palladium on carbon catalyst is added and hydrogen is passed through the mixture resulting in the production of oxycodone In the second process hydrogen peroxide is added to thebaine dissolved in formic acid. 14-hydroxycodeinone is isolated as a precipitate by the addition of ammonium hydroxide solution. The 14-hydroxycodeinone is then hydrogenated by passing hydrogen through a mixture of acetic acid and 14-hydroxycodeinone dissolved in water. Neither of the processes described are "one-step processes", performed in the same vessel without isolation and in the same solvent (e.g. acetic acid) from the beginning of the process to the end.

US Patent Application No. 10/892,578 (US 2005/0038251) (Francis *et al*) describes a small scale process for the preparation of oxycodone comprising the oxidation of thebaine to 14-hydroxycodeinone followed by reduction of the 14-hydroxycodeinone to oxycodone by hydrogenation. The processes described in this US application are not for large-scale preparation of

oxycodone or wherein the oxidation reaction is performed at a temperature of below 35°C as in the present invention.

US Patent Application No. 11/391,897 (US 2006/0173029) (Chapman *et al*) describes a small scale process for the preparation of oxycodone from thebaine in three steps. The first of the three steps is an oxidation reaction followed by two hydrogenation reactions via a 8,14-dihydroxy-7,8-dihydrocodeinone intermediate. This US patent application does not describe a process which can be performed on a large scale and can be carried out in one step, in the same solvent and without isolation of the intermediates.

Unfortunately, as can be seen from the above, known reaction sequences typically involve a number of steps (sometimes involving further protection steps) and have low overall yields. In addition, known reaction sequences often produce an undesired amount of a mutagenic by-product, 14-hydroxy-codeinone. Currently, the amount of 14-hydroxycodeinone allowed in the final product for administration is strictly regulated, varying from 10-150 ppm depending on the size of dosage administered to the patient.



14-hydroxycodeinone

It is desirable to find a method for producing oxycodone from thebaine which can be carried out in fewer steps, preferably in one step, and further preferably in the same "pot" and without the change of solvent.

It is also desirable to find a method for producing oxycodone from thebaine which does not involve the need to protect intermediates.

It is also desirable to find a method for producing oxycodone from thebaine which can be performed under ambient conditions.

Furthermore it is desirable to find a method which produces fewer impurities, such as the mutagenic 14-hydroxycodeinone and higher yields than current processes.

A skilled person in the pharmaceutical manufacturing industry would appreciate that scaling-up the amounts of reagents used in manufacturing processes from lab-sized scale does not always work. Many problems are involved in increasing the scale of industrial processes, such as, for example, inefficient heat transfer throughout vessels, inefficient mixing of reagents and lack of control when changing temperature. These difficulties may lead to, a reduction in overall yields and lower purities of the final products of large scale processes.

It is therefore also desirable to find a large scale method for processing oxycodone from thebaine which can be carried out in one step. Preferably the large scale method could be carried out in the same pot, without a change in solvent and would produce oxycodone in excellent yields. It would also be desirable to find a large scale method for producing oxycodone from thebaine in which the oxycodone product contains low levels of impurities.

There is provided a method for producing oxycodone from thebaine which overcomes many of the disadvantages of the prior art noted above.

The present invention provides a process for the large scale preparation of oxycodone from thebaine which comprises

(i) oxidation of thebaine to 14-hydroxycodeinone with a peroxide; and

(ii) reduction of 14-hydroxycodeinone with hydrogen, characterised in that:

(iii) the oxidation reaction is carried out on more than 50g of thebaine, and

(iv) both the oxidation and reduction reactions are carried out in acetic acid or propionic acid; and

(v) both the oxidation and reduction reactions are carried out in the same vessel without isolation of the 14-hydroxycodeinone; and

(vi) the oxidation reaction is performed at a temperature below 35°C.

It is a particular advantage of this process that it can be employed as a "one pot" process, that is both the oxidation and reduction reactions are carried out in the same vessel without change of solvent.

It is a further particular advantage that this process may be carried out on a large scale of 50g or more of thebaine, for example on 100g or more of thebaine, for example up to 250g or even more of thebaine.

The oxidation reaction is effected by addition of acetic acid or propionic acid in combination with the peroxide. The acetic acid or propionic acids act as solvents as well as peroxy acid precursors. The addition of acetic acid or propionic acid results in the formation of peracetic acid or perpropionic acid oxidation reagents *in-situ*. It has been found that acetic acid, preferably in the form of glacial acetic acid, results in a higher degree of conversion from thebaine to 14-hydroxycodeinone and N-oxides thereof than if propionic acid is used. For example, if glacial acetic acid is used, about 95% of the 14-hydroxycodeinone and its N-oxide is typically obtained. When propionic acid is used, conversions of greater than 90 % of 14-hydroxycodeinone and its N-oxide are typically obtained.

Suitably, the peroxide used in the oxidation reaction is hydrogen peroxide.

It was surprisingly noted during optimisation of the oxidation reaction that the use of formic acid (as taught in US Patent No 7,153, 966, GB939287 and US6090943) instead of acetic acid or propionic acid results in complete degradation of thebaine. The use of glacial acetic acid or propionic acid therefore leads to higher yields than if formic acid is used.

Furthermore, it has also been found that an acidified aqueous solution of potassium chromate (chromic acid) as the oxidation reagent did not result in an appropriate oxidation of thebaine.

Hydrogen peroxide may be added to the reaction mixture in more than one aliquot. For example it may be added in 2 or 3 aliquots.

The ratio of thebaine to carboxylic acid (acetic acid or propionic acid) and peroxide in the oxidation reaction effects the purity and yield of the oxidation products (14-hydroxycodienone and its N-oxide) as well as the reaction rate. The preferred ratio of thebaine to carboxylic acid to peroxide was found to be about 1g thebaine: 8ml carboxylic acid: 2ml peroxide, i.e. 1g thebaine: 8ml acetic acid: 2ml hydrogen peroxide. This ratio between the reagents resulted in the highest yield of intermediates obtained (about 95%, monitored by HPLC). When the ratio of thebaine to carboxylic acid was changed to 1g thebaine to 4ml carboxylic acid (i.e. acetic acid) and 2ml of peroxide (i.e. hydrogen peroxide), the yield of oxidation products is reduced to about 60%. Additionally, when the ratio of thebaine to carboxylic acid was changed to 1g thebaine to 16ml of carboxylic acid (i.e. acetic acid) and 2ml of peroxide (i.e. hydrogen peroxide), the yield of the oxidation products is reduced to about 93%, i.e. it had a negative effect on the impurity profile of the reaction.

The oxidation reaction may be performed at ambient temperature (i.e. between 15°C-30°C or preferably between 20°C-25°C). Suitably, the peroxide which is at a depressed temperature (i.e. about 0°C-5°C) is added

to the reaction mixture which is at an ambient temperature (i.e. between 15°C-30°C). By lowering the temperature, the overoxidation to e.g. the 8, 14-dihydroxycodeinone is suppressed, leading to an improved impurity profile. Typically this is achieved by cooling the reaction mixture towards the end of the oxidation step (i.e. to about 0°C-5°C) and halting the oxidation before all of the substrate has been consumed.

The oxidation reaction may take between 2 and 24 hours, 4 and 24 hours, 4 and 21 hours, 8 and 21 hours, 8 and 16 hours, 8 and 12 hours, 8 and 10 hours, 10 and 12 hours or 12 to 18 hours to complete. Suitably the reaction takes between 16-21 hours to complete at 23^0C.

The reduction reaction is carried out in the same vessel without isolation of the 14-hydroxycodeinone and its concomitant N-oxide.

The reduction reaction is effected by addition of a catalyst and hydrogen gas to the reaction mixture. Suitable catalysts include Palladium on carbon (Pd/C), platinum dioxide catalyst (PtO_2, e.g. PtO_2 type D) and Raney nickel. The preferred catalyst is palladium on carbon. The use of Pd/activated charcoal results in higher yields and less by-product formation than if PtO_2 or Raney nickel are used.

The hydrogen gas is added at a pressure of between 1-5 bar, 2-4 bar or about 3 bar. Preferably, hydrogen gas is added at a pressure of about 3 bar.

The reduction reaction is performed at a temperature between -5°C -30°C or -5°C-25°C. When conducted at a depressed temperature (i.e. -5^0C -5^0C), the reaction may take up to 100 hours to go to completion. Whereas at ambient temperature (i.e. 20^0C -25^0C), the reaction is complete after 30 hours.

By carrying out the oxidation and reduction reactions in the manner discussed above, it is possible to produce oxycodone free base in a large scale process from thebaine in one reaction vessel and without the change

of solvent. Furthermore both the oxidation and reduction reactions can be performed under ambient conditions, yielding, less impurities, such as the mutagenic 14-hydroxycodeinone. The final yields of oxycodone are typically in the range of 87-95 % with a purity of 93%. Further, recrystallisation of the isolated crude product results in a purity of oxycodone typically being greater than 98%. The overall yield of the process is normally in the range of 71-78 %.

The invention is illustrated by the examples below.

Example 1

A 2L reactor charged with glacial acetic acid (1L) was added fine grained thebaine (125 g) in one portion at ambient temperature. After ~60 min. a clear and pale yellow solution was obtained. The roomtemperated reaction mixture was quickly added (in one portion) an ice-cold 30% aqueous solution of H_2O_2 (250 ml). HPLC (Ph. Eur.) after 16 hours showed two main peaks, the expected product (73 %) and the N-oxide of 14-hydroxycodeinone (21 %) i.e. an reaction yield of ~94 %. About 2.5 % of the starting material was left unconsumed. The temperature was lowered to 10 °C before Pd/C (6 g) was added in one portion. The reactor was left for venting in about 1 hour before the temperature was raised to 23 °C and left for another hour. When the gas evolution had ceased the reactor was flushed with nitrogen 4 times before a H_2 pressure of ~45 psi (3 bars) was applied to the reactor. Reaction over-night showed a complete conversion of the intermediates to oxycodone as confirmed by HPLC (Ph. Eur.). The reaction mixture was filtered through a bed of celite following a removal of the solvent (750 ml) by reduced pressure. The removed solvent was replaced (by addition of 750 ml water) before quenching with 50 % NaOH (800 ml) to a heavy precipitation. The mixture was filtered, the filter cake was washed with water (1 L) and dried in a vacuum oven at 60 °C yielding oxycodone (free base) 110 g (87 %) with a purity of 93 % by HPLC (Ph. Eur.). 27 g of the isolated crude product was recrystallised by EtOH:H_2O 80:20 (made up of 400 ml rect. ethanol (EtOH:MeOH 95:5) and 100 ml

water) yielding oxycodone free base (22 g, 82 %) with a HPLC purity of >98 %.

Example 2

A 2L reactor charged with glacial acetic acid (0.64 L) was added fine grained thebaine (80 g) in one portion at 20 °C. After ~60 min. a clear and pale yellow solution was obtained. The roomtemperated reaction mixture was quickly added (in one portion) an ice-cold 30% aqueous solution of H_2O_2 (160 ml). After about 14 hours the temperature was increased to 23 °C. HPLC (Ph. Eur.) after a total reaction time of about 20 hours showed two main peaks giving a total reaction yield of ~90 % of 14-hydroxycodeinone and the concomitant N-oxide). 4 % of the starting material was left unconsumed. The reaction temperature was lowered to ~1 °C before Pd/C (6 g) was added in one portion. The reactor was left stirring for 21 h, was flushed with nitrogen 4 times before a H_2 pressure of ~3 bar was applied to the reaction vessel. Monitoring the reaction by HPLC (Ph. Eur) after 80 hours showed a complete conversion of the two main intermediates from the oxidation part of the process, to oxycodone. The reaction mixture was filtered through a bed of celite following a removal of the solvent (750 ml) by reduced pressure. The removed solvent was replaced (by addition of 750 ml water) before quenching with 50% NaOH (800 ml) to a heavy precipitation. The mixture was filtered, the filter cake was washed with water (1 L) and dried in a vacuum oven at 60 °C yielding 77.5 g (95 %) of crude oxycodone (free base) with a purity of 93% by the Ph. Eur. HPLC method.

Claims

1. A process for the large scale preparation of oxycodone from thebaine which comprises:-

(i) oxidation of thebaine to 14-hydroxycodeinone with a peroxide; and

(ii) reduction of 14-hydroxycodeinone with hydrogen, characterised in that:

(iii) the oxidation reaction is carried out on more than 50g of thebaine, and

(iv) both the oxidation and reduction reactions are carried out in acetic acid or propionic acid; and

(v) both the oxidation and reduction reactions are carried out in the same vessel without isolation of the 14-hydroxycodeinone; and

(vi) the oxidation reaction is performed at a temperature below 35°C.

2. A process as claimed in claim 1 wherein both the oxidation and reduction reactions are carried out in the same vessel without change of solvent.

3. A process as claimed in claim 1, wherein the oxidation reaction also produces intermediate N-oxides of 14-hydroxycodeinone, which are subsequently reduced in the reduction reaction.

4. A process as claimed in any of claims 1 to 3 wherein the oxidation reaction is effected by addition of acetic acid.

5. A process as claimed in claim 4 wherein the acetic acid is glacial acetic acid.

6. A process as claimed in any of claims 3 to 5 wherein the hydrogen peroxide is added in one or more aliquots.

7. A process as claimed in claim 6 wherein the hydrogen peroxide is added in 2 or 3 aliquots.

8. A process as claimed in claims 1 to 7 wherein the oxidation reaction is performed at 15°C to 30°C.

9. A process as claimed in claim 8 performed at 15°C to 30°C.

10. A process as claimed in any preceding claim wherein the peroxide is hydrogen peroxide.

11. A process as claimed in any of claims 1 to 10 wherein the reduction reaction is effected by addition of hydrogen gas and a catalyst, such as a palladium on carbon catalyst, a platinum dioxide catalyst or a Raney nickel catalyst.

12. A process as claimed in claim 11 wherein the catalyst is palladium on carbon (Pd/C).

13. A process as claimed in claims 7, 11 or 12 wherein the reduction reaction is performed between -5°C to 30°C.

14. A process as claimed in claim 13 performed at 0°C to 25°C.

15. A process as claimed in any of claims 11 to 14 wherein the hydrogen gas is added at a pressure of between 1 to 5 bar or 2 to 4 bar.

16. A process as claimed in claim 15 wherein the pressure is 3 bar.

17. A process as claimed in any preceding claim wherein the ratio of thebaine to peroxide and acetic or propionic acid is the same as 1g thebaine: 8mL acetic/propionic acid: 2mL peroxide.

18. A process as claimed in claim 17 wherein the peroxide is hydrogen peroxide and the acetic acid is glacial acetic acid.