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(54) Title: IMPROVED METHOD OF MAKING SUFENTANIL

(57) Abstract: The present invention relates to a process for the preparation of piperidine derivatives including sufentanil and its pharmaceutically acceptable salts, such as it citrate salt

IMPROVED METHOD OF MAKING SUFENTANIL

FIELD OF THE INVENTION

[01] The present invention relates to a process for the preparation of piperidine derivatives including sufentanil and its pharmaceutically acceptable salts, such as its citrate salt.

BACKGROUND OF THE INVENTION

[02] Sufentanil is a piperidine derivative and is one member of a series of potent fentanyl analogues. Sufentanil is considered a powerful analgesic with an excellent safety margin as compared to other narcotic agents. Sufentanil has a high selectivity and affinity (approximately 10 times greater than fentanyl) for "mu" opiate receptors. Unlike fentanyl or morphine, sufentanil produces anesthesia with minimal side-effects. Sufentanil, when used in high doses with 100% oxygen in patients undergoing major surgical procedures has shown excellent cardiovascular stability, maintaining cardiac output and myocardial oxygen balance with minimal changes in heart rate.

[03] Because of its low cardiovascular toxicity, sufentanil has utility as a total intravenous anesthetic for major surgical procedures and finds particular utility for open heart surgery and major operations in patients with severe cardiovascular compromise.

[04] The chemical name for sufentanil is N-[4-(methoxymethyl)-1[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide. Sufentanil citrate is a white crystalline powder (molecular weight=578.68) that is very soluble in water and most common organic solvents.

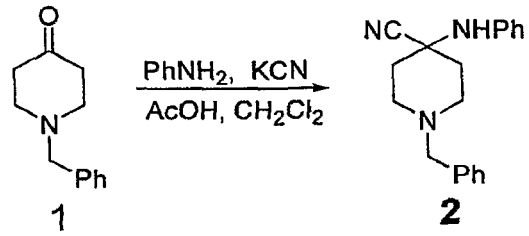
[05] Methods of synthesizing sufentanil and related derivatives are described in the following references: U.S. Pat. Nos. 3,998,834, 4,179,569 and 5,489,689; each of which is incorporated herein by reference in its entirety. There remains a need in the art for improved processes for producing piperidine derivatives including sufentanil.

DETAILED DESCRIPTION OF THE INVENTION

[06] The present invention provides a process for preparing piperidine derivatives and particularly sufentanil.

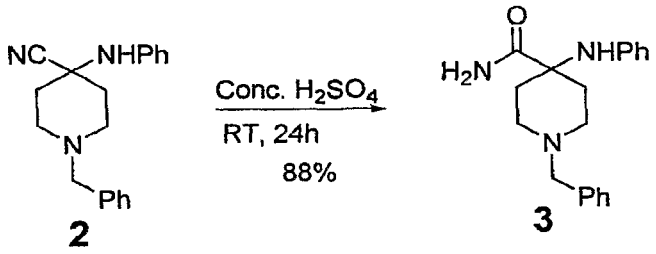
[07] A key feature of the present invention is that most of the intermediates are isolated in high yields and high purity avoiding the need for the imposition of expensive and time-consuming purification procedures.

[08] The multi-step synthesis is initiated with the commercially available 1-benzyl-4-piperidone (1). The piperidone is condensed with aniline and potassium cyanide in glacial acetic acid to the corresponding aniline (2) in very high yield.



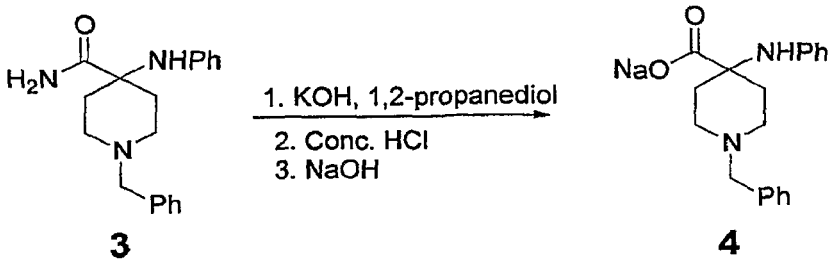
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[09] The nitrile (2) then is converted to an amide (3) by hydrolysis with concentrated sulfuric acid.



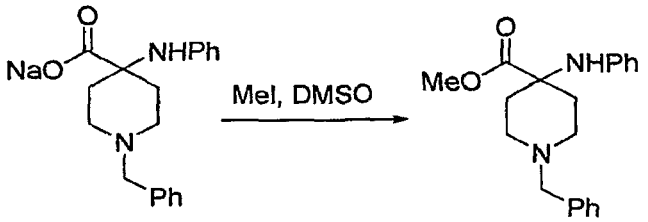
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[10] By subjecting the amide (3) to base hydrolysis, the corresponding carboxylic acid can be formed which then is isolated in high yield as the corresponding sodium salt (4).



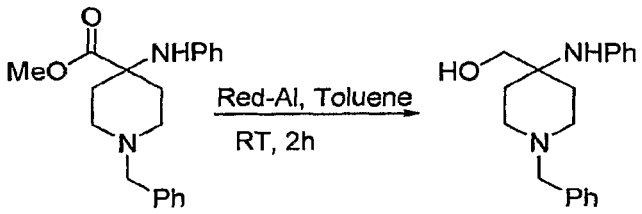
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[11] The sodium salt (4) is then converted to the methyl ester (5) in good yield by treating the salt with methyl iodide in dimethylsufoxide (DMSO).



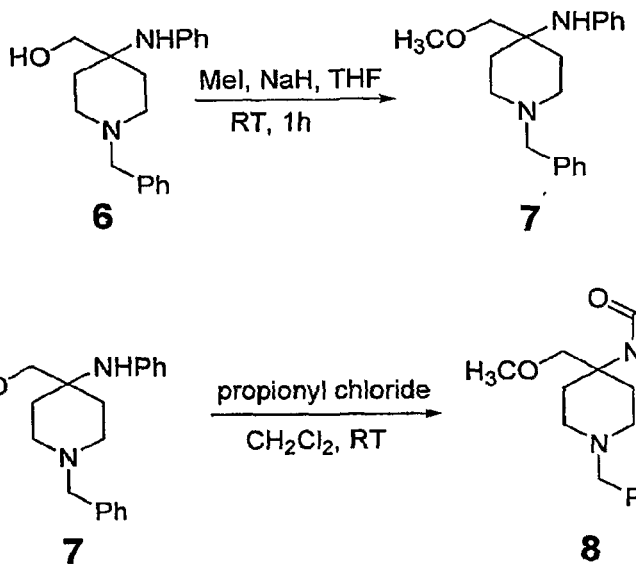
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[12] The ester (5) then is reduced to the related alcohol (6) with Red-Al under ambient conditions. The reaction is clean and fast.



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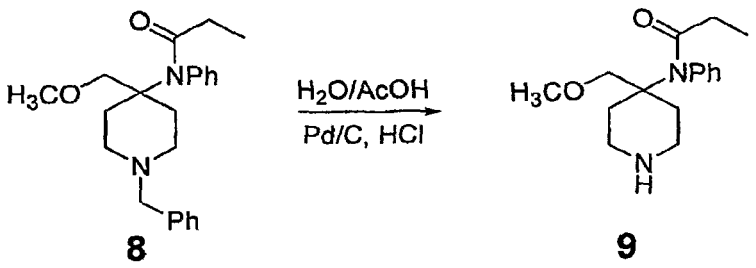
[13] The alcohol (6) is converted to the methyl ether (7) using methyl iodide and upon treatment with propionyl chloride, the ether yields a key intermediate (8), which is recovered as a pale yellow oil.



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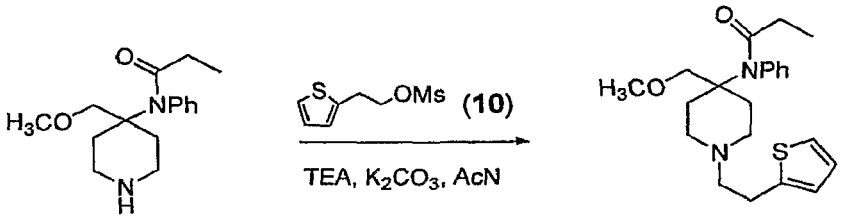
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[14] This key intermediate (8) then is debenzylated under classic conditions using palladium/carbon to produce the piperidine derivative (9) in high yield.



8 9

[15] A mesylate (10) is then coupled to the piperidine derivative (9) to yield sufentanil (11), which can be purified by re-crystallization.



9

11

SUFENTANIL

[16] The sufentanil can be isolated as an HCl salt and converted to a free base. Alternatively, the free base can be formed into the citrate salt, as described in the examples below. Obviously, the sufentanil also can be isolated by any suitable method.

[17] The invention is further illustrated by the following examples, which are not to be construed as limiting.

Example 1

[18] **Synthesis of 1-Benzyl-4-phenylaminopiperidine-4-carbonitrile**: A 22.0 L, 4-necked jacketed R.B flask was charged with 1-benzyl-4-piperidone (99%), 170.1 g (0.9 mol); aniline, 334.8 g (3.6 mol); KCN, 234 g (3.6 mol) and CH_2Cl_2 (dichloromethane) 2376 g (28.05 mol) and the suspension was stirred and cooled to 5 °C. Acetic acid, 1701 g (28.3 mol) was added dropwise over a period of about 3.5 hours keeping the internal temp at 5-8 °C. After the addition of acetic acid was complete, the reaction mixture was gradually warmed to 50 °C over a 1 hour period and then stirred at that temperature for 17 hours. The resulting suspension was then cooled to 20 °C. Crushed ice (5000 g) was then added into the reaction mixture and stirred. Thereafter, a 10N NaOH solution (1080 g) was slowly added to the reaction mixture over a period of 1.0 hour keeping the internal temperature below 20 °C. More dichloromethane (2000 mL) and distilled water (3000 mL) were added into to the reaction mixture. The organic phase was separated from the aqueous phase. The aqueous phase was extracted with additional dichlorometrhane (1 x 1000 mL) and the organic phases were combined. Solvent was removed from the combined organic phases using a Rotovap under reduced pressure. A light brown slurry was obtained at the end and was suspended in isopropanol (650 mL). The isopropanol was cooled in ice for 0.5 hour and the solids filtered. The solids were washed with more ice-cold IPA (200 mL) and then suctioned to dryness. The resulting white crystalline solid was air dried overnight to get 225 g of the target compound (86% yield based on piperidone).

Example 2

[19] **Synthesis of 1-Benzyl-4-phenylaminopiperidine-4-carboxylic acid amide:** A 2.0 L, 3-necked R.B flask was charged with 1288 g (13.1 mol) of conc. H_2SO_4. 100.0 g (0.34 mol) of the nitrile from Example 1 was added in small lots keeping the internal temp between 25-30 °C. After the addition of the nitrile was complete, stirring continued for about 20 hours. The reaction mixture was cooled in an ice-water bath for 15 min and then mixed with crushed ice (2.0 L) and stirred well. The reaction mixture was cooled in the ice bath for another 0.5 hour. A white solid was filtered from the chilled reaction mixture and the wet cake was dissolved in distilled water (1200 mL) to form a clear solution. The solution was stirred and 10 N NaOH solution (30% w/w) (250 mL, added as 50 mL portions) was added slowly and a white precipitate separated out. The so-formed suspension was cooled in an ice bath for 0.5 hour. The solids were filtered and the resulting filter case was washed with distillled water (2 x 150 mL). The white solid was dried in vacuum oven at 70 °C for 17 hours and a white amorphous powder (94.0 g, 88.6% yield) comprising the target compound was recovered.

Example 3

[20] **Synthesis of Sodium 1-Benzyl-4-phenylaminopiperidine-4-carboxylate:** A 3.0 L, 3-necked R.B. flask was charged with 200 g (0.65 mol) of the amide obtained in Example 2 followed by 145.0 g (2.58 mol) of KOH and 1036 g of 1,2-propane diol. The resulting suspension was stirred while heating under reflux for 27 hours. The reaction mixture was allowed to cool to room temperature. Distilled water (3000 mL) was added to the reaction mixture and then the mixture was cooled to 5 to 10 °C. Conc. HCl, 540 g (450 mL) was added slowly to reduce the pH to less than 1. Then, 30% sodium hydroxide solution (800 mL) was added slowly to raise the pH to 14, and an additional 700 mL of the 30% sodium hydroxide solution was added. The suspension of an off-white precipitate that was formed was cooled in ice-water over a period of 1 hour, with stirring. The solids were filtered using a buchner funnel, and the filtered solids were suctioned to

dryness. The partially wet cake was dissolved in distilled water (500 mL) at 60 °C. Isopropanol was added (1500 mL, added in 3 portions) and the resulting mixture was allowed to cool to RT and then was further cooled in ice-cold water for 1 hour. The off-white solid that formed was filtered and the solids were washed successively with an isopropanol-water solution (4:1, 500 mL) and then isopropanol (2 x 500 mL). The solids were suctioned to dryness and dried in a vacuum oven at 60 °C for two days to produce 132.0 g of the target compound. The above filtrate was concentrated to ¼th of total volume. The product was filtered and washed with isopropanol (100 mL). A second crop of solids (31.0 g) was obtained from the filtrate. Total yield of target compound was 163.0 g (76% yield).

Example 4

[21] **Synthesis of 1-Benzyl-4-phenylaminopiperidine-4-carboxylic acid methyl ester**: A 3.0 L, 3-necked R.B flask was charged with 120.0 g (0.36 mol) of the product of Example 3, followed by 1800 mL anhydrous DMSO. The resulting suspension was heated with stirring to 70-72 °C. After removing the heat source, 51.3 g (0.36 mol) of methyl iodide was added slowly. Towards the end of the addition of methyl iodide, the suspension became a very clear light yellow solution. After stirring the solution for 10 min, the reaction mixture was transferred to a 10.0 L extractor and diluted with distilled water (3600 mL) and hexanes (1800 mL). The organic layer was separated from the aqueous phase and the aqueous phase was extracted with more hexanes (900 mL). The organic phases were combined and washed with brine (1000 mL), dried over Na_2SO_4, and filtered. The solvent was then removed under a reduced pressure. White crystalline solid separated on removal of the solvent. Finally, the solids were dried under vacuum to produce 80.4 g (73% yield) of the target compound. Liquid chromatography showed 100% purity. ^{1}H NMR ($CDCl_3$): δ 7.8-7.1(m, 10H), 3.9(s,1H), 3.4(s, 3H), 3.5(s, 2H),2.6(m, 2H), 2.4(t, 2H), 2.2(dt, 2H), 2.0(m, 2H).

Example 5

[22] **Synthesis of 1-Benzyl-4-phenylamino-4-(hydroxymethyl) piperidine:** A 3.0 L, 4-necked R.B flask was charged with 84.0 g (0.26 mol) of the methyl ester produced in Example 4 followed by 420 mL of toluene under a nitrogen atmosphere. The mixture was stirred to obtain a colorless clear solution. 157.0 g (0.77 mol) of the Red-Al, vitride was added drop wise to the stirred solution over a period of 35 minutes. After the addition was complete, stirring continued at room temperature for and 100 minutes. Then, a 5% NaOH solution (175 mL) was added drop wise very slowly keeping the internal temperature in the range of 25-30 °C. The reaction mixture then was transferred to a separatory funnel and the bottom milky layer was separated. The organic layer was washed with brine (100 mL) and then dried over Na_2SO_4. The solution was filtered and toluene was removed under reduced pressure and the resulting oil was dried in vacuuo to get 82.1 g of viscous and light yellow oil (98%, corrected for residual solvents). Purity of Compound 6 was determined to be 99% by liquid chromatography. ^1H NMR ($CDCl_3$): δ 7.5-6.6(m, 10H), 3.6(s, 2H), 3.5(s, 2H), 2.6(m,3H), 2.3(t, 2H), 1.9(d, 2H), 1.6(dt, 2H).

Example 6

[23] **Synthesis of 1-Benzyl-4-phenylamino-4-methoxymethyl piperidine:** A 3.0 L, 4-necked R.B flask was charged with 12.2 g (0.3 mol) of NaH followed by THF (200 mL) under a N_2 atmosphere. While the resulting suspension was stirred, 75.5 g (0.25 mol) of the alcohol produced in Example 5 mixed with THF (180 mL) was added to the suspension over a period of 50 minutes. After the alcohol addition was complete, stirring was continued at room temperature for an additional 2.0 hours. 43.4 g (0.3 mol) of methyl iodide was added to the suspension over a period of 25 minutes. After the addition of the methyl iodide was complete, stirring continued at ambient temp for another 2.0 hours. More methyl iodide (3.65 g, 1.6 mL, 0.1 eq) was added and the reaction mixture was stirred for another hour. Distilled water (75 mL) was added slowly to the reaction mixture and a tan colored suspension formed. The suspension was diluted

with more distilled water (500 mL) and then the suspension was extracted with toluene (500 mL). The emulsion that formed was difficult to separate. The emulsion was filtered and a tan colored solid was separated. Then the organic phase was separated from the aqueous phase, which was extracted with more toluene (500 mL). The organic phases then were combined and washed with brine (250 mL). Solvent was removed from the organic phase under reduced pressure. Dichloromethane (50 mL) was added to the residue and evaporated. The process was repeated three times to obtain light brown-yellow oil. The oil was dried under vacuum at about 45 °C to produce 67.5 g of a light brown oil (80.5%, corrected for residual solvents). Purity of Compound 7 was determined to be 97.5% by liquid chromatography. ^{1}H NMR ($CDCl_3$): δ 7.6-6.7(m, 10H), 3.5(s, 2H), 3.3(d, 5H), 2.7-2.4(m, 4H), 1.9(d, 2H), 1.7(m, 2H)

Example 7

[24] **Synthesis of 1-Benzyl-4-[(1-oxopropyl)phenylamino]-4-methoxymethyl piperidine:** A 1.0 L, 3-necked R.B flask was charged with 31.35 g (0.10 mol) of the methyl ether of Example 6 (containing 6.5% residual solvent) followed by 220 mL of dichloromethane (CH_2Cl_2) to create a reaction mixture. Thereafter, 12.17 g (0.13 mol) of propionyl chloride was added drop wise to the reaction mixture over a period of 25 minutes keeping the internal temp below 26 °C. After the addition was complete, stirring of the reaction mixture continued at ambient temp. After stirring for an additional 3.0 hours (HPLC analysis showed 2.25 % SM), 1.3 g (0.012 mol) of triehylamine was added and the reaction mixture was stirred for 1 hour. Then, 100 mL of a 25 % potassium carbonate solution was slowly added to the reaction mixture. The reaction mixture was diluted with more distilled water (50 mL), and the organic phase was separated from the aqueous phase. The organic phase was washed with brine (100 mL). The residual solvent was removed on Rotovap under reduced pressure to yield a light yellow-brown oil. The product was dried under vacuum for two days to get 40.7 g of a crude product. The product purity was determined to be 94.5% by liquid chromotography. ^{1}H NMR

($CDCl_3$): δ 7.3(m, 10H), 4.1(s, 2H), 3.5(s, 2H), 3.4(s, 3H), 2.6(m, 2H), 2.1(m, 4H), 1.8(q, 2H), 1.7(dt, 2H), 0.9(t, 3H).

Example 8

[25] **Synthesis of 4-[(1-Oxopropyl)phenylamino]-4-methoxymethyl piperidine:** 18.9 g of the piperidine derivative produced in Example 7 was charged into a Parr hydrogenation bottle (500 mL), followed by a mixture of 72.0 mL of glacial acetic acid and 108 mL of distilled water, 21.0 mL of concentrated HCl and 1.89 g of wet Pd/C (10% wet). The hydrogenation bottle was flushed with hydrogen (3 times), and then stirred at 60 psi while warming the contents of the bottle to 50 °C over a period of 1 hour. Stirring of the reactor contents continued (at a bath temperature of 60 °C) at 60 psi for 20 hours. Then, the reaction mixture was cooled to room temperature and filtered using a short celite pad. Then, the solids were washed with 100 mL of distilled water. 200 g of crushed ice were added to the combined filtrates. 190 mL of a sodium hydroxide solution (30 % w/w, Fisher) was added to the aqueous mixture adjusting the pH to ~13. The aqueous mixture was transferred to a separatory funnel and extracted with dichloromethane (CH_2Cl_2) (1 x 500 mL, 1 x 250 mL, and 1 x 125 mL). The organic phases were combined and dried over Na_2SO_4. The organic phase was filtered and solvent was removed under reduced pressure at 30 °C to yield a light brown clear liquid. The liquid was dried under vacuum to get 14.0 g (98%) of crude product. LC analysis gave 92.7% purity. ^1H NMR ($CDCl_3$): δ 7.3(m, 10H), 4.1(s, 2H), 3.4(s, 3H), 2.9-2.6(m, 8H), 2.2(d, 2H), 1.8(q, 2H), 1.6(m, 2H), 0.9(t,3H).

Example 9

[26] **Synthesis of 2-(2-thienyl)ethanol methanesulfonate:** A solution of 20.0 g (0.16 mol) of 2-(2-thienyl)ethanol and 24 g (0.23 mol) of triethyl amine in 200 mL of methylene chloride was stirred at 10 °C and 24 g (0.21 mol) methanesulfonyl chloride was added to the solution over a period of 1.0 hour. Stirring was continued for about 16 hours, allowing the reaction mixture to warm to room temperature. The reaction mixture was

diluted with water (200 mL). The organic phase was separated, was washed with 5% sodium bicarbonate solution (2 x 100 mL), and the organic phase was dried over Na_2SO_4. The organic phase was filtered and the solvent was removed under reduced pressure. A light yellow orange oil was recovered and dried in vacuuo to get 30.0 g (93%) of the target product. ^1H NMR ($CDCl_3$): δ 7.2(m, 1H), 6.9(m, 2H), 4.4(t, 2H), 3.2(t, 2H), 2.9(s, 3H).

Example 10

[27] **Synthesis of N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide (SUFENTANIL):** A 500 mL, 2-necked R.B flask was charged with 13.5 g (0.05 mol) of the piperidine derivative of Example 8 followed by 10.1 g (0.05 mol) of the mesylate of Example 9. These ingredients were dissolved in 95 mL of HPLC grade acetonitrile. Then, 9.9 g (0.1 mol) of triethylamine, 1.68 g (0.012 mol) of potassium carbonate and 0.32 g (0.002 mol) of potassium iodide were added. The reaction mixture was warmed to 75 °C (reflux started) and stirred at that temperature. The reaction mixture was analyzed every hour by liquid chromatography to assess the progress of the reaction. After 5.0 hours, the reaction mixture was allowed to cool to room temperature. The reaction mixture was poured into 500 g of a crushed ice and stirred at 0 to 4 °C for 1h. Filtered the light yellow precipitate, and washed with an acetonitrile-water (1:4) mixture (2 x 50 mL). The precipitate was suctioned to dryness to get 16.0 g of a wet product. The purity was 88% by liquid chromatography. The crude product was then recrystallized from an isopropanol-water mixture (160 mL, 1:1) to get 9.0 g in first crop (98.8% purity by liquid chromatography analysis) and 1.3 g in a second crop (98.5% by liquid chromatography analysis).

Example 11

[28] **Sufentanil citrate**: the sufentanil obtained in Example 10 was converted to the citrate as follows. Sufentanil (9.81 g, 0.025 mol) was suspended in isopropanol (125 mL), and warmed to 40-45 °C with stirring to get a light yellow clear solution. To this solution a

solution of citric acid (4.87 g, 0.025 mol) in isopropyl alcohol (IPA) (34.0 mL) was added over a period of 5 minutes at a temperature of 45 °C to a clear solution. The resulting mixture was allowed to cool to room temperature. A white precipitate formed and was filtered. The white filter cake was washed with IPA (2 x 10 mL). The washed solids were air dried to get a white powder (14.9 g) of the target salt.

[29] The present invention has been described with reference to specific embodiments. However, this application is intended to cover those changes and substitutions that may be made by those skilled in the art without departing from the spirit and the scope of the invention. Unless otherwise specifically indicated, all percentages are by weight. Throughout the specification and in the claims the term "about" is intended to encompass + or – 5% and preferably is only about + or – 2%.

[30] CLAIMS

1. In a method of making sufentanil the improvement comprising:

(a) condensing 1-benzyl-4-piperidone with aniline and potassium cyanide in glacial acetic acid to form a corresponding nitrile

(b) hydrolyzing the nitrile to a corresponding amide

(c) base hydrolyzing the amide to a corresponding carboxylic acid and then forming a sodium salt

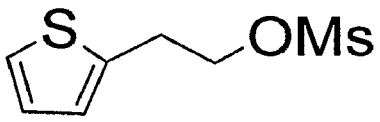
(d) treating the sodium salt with methyl iodide to from a methyl ester

(e) reducing the methyl ester to a corresponding alcohol with Red-Al

(f) forming a methyl ether from the alcohol using methyl iodide

(g) treating the methyl ether with propionyl chloride and then debenzylating the propionyl-treated material in the presence of palladium/carbon to produce a piperidine derivative, and

(h) coupling a mesylate of the following formula to the piperidine derivative to yield sufentanil:



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/015337

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D409/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 998 834 A (JANSSEN PAUL ADRIAAN JAN ET AL) 21 December 1976 (1976-12-21) cited in the application columns 29-30, lines 22-60 columns 39-40; example 1 columns 43-44; example V columns 71-72; example LXI	1
A	US 5 489 689 A (MATHEW JACOB [US]) 6 February 1996 (1996-02-06) cited in the application columns 5-14; examples 1-8	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Information on patent family members

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