

**(12) STANDARD PATENT**  
**(19) AUSTRALIAN PATENT OFFICE**

(11) Application No. **AU 2009227521 B2**

(54) Title  
**A method for the preparation of fentanyl**

(51) International Patent Classification(s)  
**A01N 43/40** (2006.01) **A61K 31/445** (2006.01)

(21) Application No: **2009227521** (22) Date of Filing: **2009.03.09**

(87) WIPO No: **WO09/116084**

(30) Priority Data

(31)	Number	(32)	Date	(33)	Country
	<b>696/DEL/2008</b>		<b>2008.03.19</b>		<b>IN</b>

(43) Publication Date: **2009.09.24**

(44) Accepted Journal Date: **2015.03.12**

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pages 2011-2014  
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
24 September 2009 (24.09.2009)

PCT

(10) International Publication Number  
**WO 2009/116084 A3**

(51) International Patent Classification:  
*A01N 43/40* (2006.01) *A61K 31/445* (2006.01)

(21) International Application Number:  
PCT/IN2009/000159

(22) International Filing Date:  
9 March 2009 (09.03.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
696/DEL/2008 19 March 2008 (19.03.2008) IN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GI, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

**Published:**

— with international search report (Art. 21(3))

(88) Date of publication of the international search report:  
30 December 2009

(54) Title: A METHOD FOR THE PREPARATION OF FENTANYL

(57) Abstract: The invention provides a method for the preparation of fentanyl comprising: (a) reacting 4-piperidone hydrochloride (NPP) with aniline in presence of reducing environment to produce 4-anilinopiperidine (4-ANPP), (b) alkylating/reacting the 4-ANPP as obtained from step (a) with phenethyl halide under reflux conditions in highly alkaline medium to give 4-anilino-N-phenethylpiperidine, and (c) converting the said 4-anilino-N-phenethylpiperidine to fentanyl by reacting with propionyl chloride in presence of halogenated hydrocarbons then isolating fentanyl by solvent extraction and purified by crystallization from petroleum ether (60-80 °C).



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## A METHOD FOR THE PREPARATION OF FENTANYL.

## FIELD OF INVENTION:

This invention particularly relates a method that is simple, high yielding, cost effective, eco-friendly, environmentally safe, industrially feasible, does not require stringent process conditions, sophisticated infrastructure and specially skilled personnel.

## BACKGROUND OF THE INVENTION:

Fentanyl is a synthetic  $\mu$ -opioid receptor agonist with high lipid solubility. Fentanyl is generic name given to the chemical compound N-(1-phenethyl-4-piperidyl)propionanilide. It is well known narcotic analgesic used for both general as well as regional anesthesia and both during and or after surgery. It is 30 to 100 times more powerful than morphine and shows less emetic activity than morphine. Fentanyl citrate was first used as an intravenous anesthetic under the name 'Sublimaze' in 1960. It is also mydriatic and cholinergic in its action and found useful as analgesic particularly treating cancer pain. It has an analgesic potency 1000 times that of morphine. It has more than 12 different analogs.

Fentanyl was first synthesized in 1960 by Paul Janssen founder of **Janssen Pharmaceutica** involving reacting N-phenethylpiperidone with aniline to produce 4-anilino- N-phenethylpiperidone with yield of about 50-80% using **sodium borohydride** at room temperature followed by reacting with propionyl chloride in presence of pyridine wherein the **reaction is exothermic** and thus requires stringent process conditions. The fentanyl thus obtained with a yield over 90% is further purified by crystallization.

US patent no. 3,164,600 ('600) dated January 5, 1965 to Janssen in column 2 lines 45 to 70 and column 3, (Examples), discloses a process for the preparation of fentanyl that involves following five steps:

- (i) refluxing mixture of 1- benzyl-4-piperidone, aniline, toluene and 4 toluenesulfonic acid for 15 hrs to produce N-(1-benzyl-4-piperidylidene)aniline,

- (ii) reducing N-(1-benzyl-4-piperidylidene)aniline so obtained using lithium aluminium hydride in anhydrous ether to 1-benzyl-4-anilino piperidine in nitrogen atmosphere, then
- (iii) alkalizing by refluxing with propionic anhydride for 7 hrs to give N-(1-benzyl-4-piperidylidene)propionanilide,
- (iv) subjecting to debenzylation by employing hydrogenation over palladium on charcoal catalyst in ethanol to get N-(4-piperidyl)propionanilide, and finally
- (v) treating a mixture of N-(4-piperidyl)propionanilide, sodium carbonate and potassium iodide in hexone with the solution of  $\beta$  phenethylchloride in 4-methyl-2-pentanone and refluxed for 27 hrs to obtain fentanyl [N-(1-phenethyl-4-piperidyl)propionanilide].

The main disadvantage associated with this process is a multi-step, hence requires more time and over all appreciably reduced yield.

The other drawback is that it requires stringent operating conditions such as reflux temperature in all five steps thus making the process energy extensive, which in turn makes the process uneconomical.

The other drawback is that every process step makes use of organic solvent requiring removal of these solvents, which not only adds to the overall cost of the process but also makes the process environmentally unsound and unsafe.

Further steps (i), (ii), (iii), & (v) being moisture sensitive requires additional infrastructure and precautions, which is undesirable for large scale production.

Lithium aluminium hydride in step (ii) reacts violently with water and liberates hydrogen, which is likely to cause the material ignite. Thus, for large scale production, use of lithium aluminium hydride in step (ii) is undesirable from safety and environmental point of view.

Additionally, the diethyl ether used is highly inflammable low boiling organic solvent posing fire hazards that requires special fire safety measures particularly in up scaling of the process.

Similarly the palladium charcoal used in hydrogenation/debenzylation increases the cost of the process.

Further, the effluent stream of the subject process is likely to impair the environment.

In general the process as disclosed in '600 is energy extensive, cost extensive, time consuming, requires sophisticated infrastructure to maintain stringent operating conditions, requires specially trained skilled personnel, likely to impair ecosystem & environment and unfit for large scale production, i.e. industrially and commercially unviable.

Polish patent No. 72,416 describes a process for the preparation of fentanyl also comprises of following five steps:

- (i) condensation of 2-phenylethylamine with methyl or ethyl acrylate to get N,N-bis(2-carboxyethyl)-phenylethylamine,
- (ii) cyclising the said amine in presence of sodium methoxide (alkoxide) to give 1-(2-phenylethyl)piperidine-4-one,
- (iii) condensing the said 1-(2-phenylethyl)piperidine-4-one with aniline to give 1-(2-phenylethyl)piperidinylidene aniline, followed by
- (iv) reducing by employing lithium aluminium hydride and subsequently
- (v) acylating to procure fentanyl.

One of the main drawbacks associated with this process is employing moisture sensitive sodium methoxide and lithium aluminium hydride, the threats of which are described herein before.

Further, this process also involves five steps and thus inherits the drawbacks associated therewith.

In general, this process is also cost extensive, unsafe to environment, requires special operational conditions and thus unfeasible for industrial and commercial applications.

The Indian application No.2554/DEL/2004 to DRDO discloses a method comprising: (i) refluxing 4-piperidonehydrochloride monohydrate with phenethyl bromide in acetonitrile in presence of potassium carbonate and Tetra butyl Ammonium Bromide (TABAB) to give NPP (N- phenethyl-4-piperidone) (II) reacting NPP with aniline in presence of zinc and carboxylic acid preferably acetic acid to give ANPP, then reacting with propionyl chloride to get fentanyl. This process claims advantage over the prior art in (a) reducing number of steps from five to 3, (b) employing all readily available indigenous available reactants, and (c) eliminating employing moisture sensitive (sodium methoxide),

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fire hazard reagents (lithium metal hydride) and highly flammable low boiling solvent.

Though the process disclosed in the application is obviating drawbacks of the existing process to some extent, it suffers from the following drawbacks:

- ❖ The process is low yielding,
- ❖ Polymerization of 4-piperidone hydrochloride monohydrate reactant takes place in step (i), which results in increased load on effluent,
- ❖ Using organic solvent as a reaction medium and removal of organic solvent is necessary this adds to the cost as well as makes the process environmentally unsafe/unsound.
- ❖ Requirement of anhydrous conditions.

In view of this there is a need to provide simple, high yielding, cost effective, eco- friendly, environmentally safe, sound and beneficial, industrially feasible, that does not require stringent process conditions, sophisticated infrastructure and especially skilled personnel.

In one or more aspects, the present invention provides a method for the preparation of fentanyl obviating the draw backs of the existing processes.

In other aspects, the present invention provides a process having yield more than 60%.

In further aspects, the present invention provides a process that does not require organic solvent as the reaction medium thereby making the process cost effective as well as eco- friendly.

In yet other aspects, the present invention provides a process that avoids using hazardous reagents such as herein before disclosed thereby making the process environmentally safe, sound and beneficial.

In further aspects, the present invention provides an energy efficient process by reducing number of steps involved.

In other aspects, the present invention provides a process that does not require purification

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of intermediate.

In yet other aspects, the present invention provides a process wherein polymerization of the starting material is avoided thereby reducing the effluent load and making the process environment friendly environmentally sound and beneficial.

The novelty of the present invention resides in eliminating hazardous reagent such as sodium borohydride, sodium methoxide, lithium aluminium hydride, ether; using different starting material, avoiding polymerization of reagents, directing process in predetermined manner, eliminating using organic solvents.

Accordingly, the process of the present invention though uses N-phenethylpiperidone as one of the starting materials as disclosed by Janssen in 1960, differs from his process in avoiding employing sodium borohydride and eliminating exothermic reactions. This results in making process economical and environmentally safe.

The process of the present invention employs 4-piperidone hydrochloride monohydrate as starting material as against benzyl protected benzyl-4-piperidone being used in '600. Additionally, the hazardous reagents such as lithium aluminium hydride, inflammable low boiling solvents, high cost reagents such palladium charcoal and stringent process conditions being used in '600 are totally eliminated in the process of the subject application. Liberation of H ion required for reduction of imine formed through reaction of the starting material and aniline is regulated by avoiding escape of H from the reaction mass by replacing toluene and para toluene sulfonic acid (PTSA) by metal and aqueous carboxylic acid.

The process also differs from the one disclosed in Polish Patent as mentioned herein above, in not using sodium methoxide and lithium aluminium hydride in addition to reducing the number of steps from five to three.

The process of the present invention also has technical advancement over the Indian application No. 2554/DEL/2004. NPP when reacts with potassium carbonate gets converted

to free base and in this condition the amino and carbonyl groups of the reactant react and form polymer increasing load on effluent. Though the number of steps are three and starting material NPP is same in both these processes, the process of the present invention gives solution to overcome polymerization of NPP and proving the process environmentally sound, which is one of the major influencing factor. Additionally, elimination of organic solvents by aqueous medium reduces the cost of present invention substantially. The process of the present invention has overall cost reduction to the tune of 50%.

#### SUMMARY OF THE INVENTION:

Accordingly, the present invention provides a method for the preparation of fentanyl comprising:

- (a) reacting 4-piperidone hydrochloride with aniline in presence of reducing environment to produce 4-anilinopiperidine (AP),
- (b) alkylating/reacting the AP as obtained from step (a) with phenethyl halide under reflux conditions in highly alkaline medium to give 4-anilino-N-phenethylpiperidine, and
- (c) converting the said 4-anilino-N-phenethylpiperidine to fentanyl by reacting with propionyl chloride in presence of halogenated hydrocarbons then isolating fentanyl by solvent extraction and purified by crystallization from petroleum ether (60-80°C).

In one or more embodiments of the present invention, the reducing environment comprises metal and aqueous carboxylic acid preferably zinc or magnesium and aqueous acetic acid, more preferably zinc and 80 to 90% acetic acid.

According to other embodiments of this invention, the reaction in step (a) may initially be conducted at room temperature for 15 to 35 hrs preferably for 20 to 30 hrs followed by at an elevated temperature ranging from 50 to 90°C preferably at 65 to 80°C for 15 to 35 hrs preferably for 20 to 30 hrs.



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According to another embodiment of this invention the reaction in step (a) 4-piperidone hydrochloride and aniline may be used in 1:1 ratio.

According to yet other embodiment of this invention the reaction in step (a) is quenched with water preferably ice cold water and AP may be isolated by filtration followed by alkali neutralization.

According to yet another embodiment of this invention the reaction in step (b) phenethyl halide used may be chloride, bromide or iodide, preferably bromide.

According to yet another embodiment of this invention the reaction in step (b) the highly alkaline medium may have a pH above 14 and is provided by alkali metal hydroxide preferably sodium hydroxide.

According to yet another embodiment of this invention the reaction in step (b) may be proceeded optionally purifying AP.

According to still another embodiment of this invention the reaction in step (c) the halogenated hydrocarbons employed may be such as chloroform, dichloromethane, dichloroethane, tetrachloroethane, preferably dichloroethane.

According to yet another embodiment of this invention the reaction in step (c) 4 to 5 times propionyl chloride with respect to 4-anilino-N-phenethylpiperidine may be employed and added drop wise.

According to yet another embodiment of this invention the reaction in step (c) the solvent employed for solvent extraction may be halogenated hydrocarbons, preferably dichloromethane.

The invention is further illustrated by the following steps and non-limiting examples.

**Step I: Preparation of 4-anilinopiperidine:**

To a mixture of 0.5 to 5.0 parts(w/w) of 4-piperidone hydrochloride monohydrate preferably 1.00 to 3.00 parts (w/w) and 0.5 to 5.0 parts (w/w) of aniline preferably

1.0 to 2.0 parts (w/w), 1 to 20 parts (w/w) of zinc preferably 4 to 12 parts (w/w) and 5 to 100 parts (w/w) of 90% acetic acid preferably 20 to 50 parts (w/w) were added and stirred at room temperature for 15 to 35 hrs preferably 20 to 30 hrs and then at 50 to 90°C preferably at 65 to 80°C for 15 to 35 hrs preferably 20 to 30 hrs. After completion of the reaction, water was added to the reaction mixture and filtered. Crushed ice was added to the filtrate and was neutralized with excess of aqueous sodium hydroxide solution. The crude 4-anilinopiperidine was obtained by filtration. It was then recrystallized with acetone to give colorless needles of 4-anilinopiperidine, mp 105-06°C.

**Step II: Preparation of 4-anilino-N-phenethylpiperidine:**

In a round bottom flask, 1 to 5 parts (w/w) of 4-anilinopiperidine preferably 2 to 3 parts (w/w) prepared in step 1, 0.5 to 2.00 parts (w/w) of 100% aqueous sodium hydroxide solution preferably 1 to 3 parts (w/w) and 2 to 10 parts (w/w) of 2-phenethylbromide, preferably 4 to 6 parts (w/w) were taken. The reaction mixture was heated with stirring at 80 to 150°C preferably at 100 to 130°C for 2 to 10 hrs preferably 3 to 7 hrs. The reaction mixture was then poured in the ice cooled water and crude product 4-anilinophenethylpiperidine was obtained by filtration. The crude product was recrystallized with chloroform-petroleum ether (40-60°C) to give 4-anilino-N-phenethyl-piperidine, mp 98-100°C.

**Step III: Preparation of fentanyl (N-(1-phenethyl-4-piperidyl)propionanilide):**

A solution of 5.5 parts (w/w) of 4-anilino-N-phenethyl-piperidine preferably 1 to 3 parts in 5 to 15 parts (w/w) of dichloroethane preferably 8 to 12 parts was taken in a two neck round bottom flask fitted with a reflux condenser, pressure equalizing funnel and calcium chloride guard tube. To this stirred solution, 2 to 20 parts (w/w) of propionyl chloride preferably 5 to 15 parts was added drop wise through pressure equalizing funnel. After 2 to 6 hrs, preferably 4 to 5 hrs stirring at room temperature, the reaction mixture was washed with 20% sodium hydroxide solution. The washings were extracted with 2x50 to 80 parts preferably 65 to 70 parts dichloroethane. The combined organic phase was dried over sodium sulphate and concentrated to give fentanyl. The crude compound was recrystallised from petroleum ether (60 to 80°C) to give colourless crystals of pure fentanyl having mp 82 to 83°C.

**EXAMPLE 1:**

In a three neck round bottom flask equipped with mechanical stirrer and water condenser, 15.36 gm (0.10 moles) of 4-piperidone hydrochloride monohydrate and 20.95gm (0.255 moles) of aniline was added. To this mixture, 26.14 gm (0.40moles) of zinc and 120 gm (2.00 moles) of 90% acetic acid were added. The reaction mixture was stirred at room temperature for 12 hrs and at 50 to 70°C for 12 hrs. Water was then added to the reaction mixture and filtered. Crushed ice was added to the filtrate and was neutralized with excess of aqueous sodium hydroxide solution. The crude 4-anilinopiperidine was obtained by filtration.

In two neck round bottom flask equipped with condenser 17.6 gms (0.10 moles) of 4-anilinopiperidine obtained from step 1, and 50 ml of 100% sodium hydroxide was added. The reaction mixture was heated up to 120°C and 37 gms (0.2 moles) of 2-phenethyl bromide was then added. The reaction mixture was stirred for 2 hrs. After the completion of the reaction, the reaction mixture was poured in the ice cooled water. The crude product was obtained by filtration and recrystallised from petroleum ether (60 to 80°C) to give colourless crystals of 4-anilino-N-phenethyl piperidipure fentanyl N-(1-phenethyl-4-piperidyl)propionanilide).

In two neck round bottom flask equipped with condenser pressure equalizing funnel and calcium chloride guard tube, a solution of 28.0 (0.10 moles) of 4-anilino N-phenethyl piperidine prepared in step II, in 55 ml of dichloroethane was taken. To this solution, 9.25gm (0.10 moles) of propionyl chloride was added drop wise through pressure equalizing funnel with continuous stirring. After the completion of the addition, the mixture was further stirred for 5 hrs. After the completion of the reaction, the reaction mixture was washed with 20% sodium hydroxide solution. The aqueous phase was extracted with 2x50 ml of dichloromethane. The combined organic extract was dried over sodium sulphate and concentrated to give crude fentanyl. The crude product was recrystallised from petroleum ether (60 to 80°C) to give colourless crystals of pure fentanyl having mp 82 to 83°C.

#### EXAMPLE 2:

In a three neck round bottom flask equipped with mechanical stirrer and water condenser, 15.36 gm (0.10 moles) of 4-piperidone hydrochloride monohydrate and 9.3gm (0.10 moles) of aniline was added. To this mixture, 6.5 gm (0.10moles) of zinc and 0.6 gm (0.10 moles) of 90% acetic acid were added. The reaction mixture was stirred at room temperature for 24 hrs and at 50 to 70°C for 24 hrs. Water was

then added to the reaction mixture and filtered. Crushed ice was added to the filtrate and was neutralized with excess of aqueous sodium hydroxide solution. The crude 4-anilinopiperidine was obtained by filtration.

In two neck round bottom flask equipped with condenser 17.6 gms (0.10 moles) of 4-anilinopiperidine obtained from step 1, and 100 ml of 100% sodium hydroxide was added. The reaction mixture was heated up to 140°C and 18.5 gms (0.1 moles) of 2-phenethyl bromide was then added. The reaction mixture was stirred for 4 hrs. After the completion of the reaction, the reaction mixture was poured in the ice cooled water. The crude product was obtained by filtration and recrystallised from petroleum ether (60 to 80°C) to give colourless crystals of 4-anilino-N-phenethyl piperidipure fentanyl N-(1-phenethyl-4-piperidyl)propionanilide).

In two neck round bottom flask equipped with condenser pressure equalizing funnel and calcium chloride guard tube, a solution of 28.0 (0.10 moles) of 4-anilino\_N-phenethyl piperidine prepared in step II, in 100 ml of dichloroethane was taken. To this solution, 18.5gm (0.20 moles) of propionyl chloride was added drop wise through pressure equalizing funnel with continuous stirring. After the completion of the addition, the mixture was further stirred for 1 hrs. After the completion of the reaction, the reaction mixture was washed with 20% sodium hydroxide solution. The aqueous phase was extracted with 2x100 ml of dichloromethane. The combined organic extract was dried over sodium sulphate and concentrated to give crude fentanyl. The crude product was recrystallised from petroleum ether (60 to 80°C) to give colourless crystals of pure fentanyl having mp 82 to 83°C.

### EXAMPLE 3:

In a three neck round bottom flask equipped with mechanical stirrer and water condenser, 15.36 gm (0.10 moles) of 4-piperidone hydrochloride monohydrate and 16.43 gm (0.2 moles) of aniline was added. To this mixture, 130 gm (2.0moles) of zinc and 120 gm (2.00 moles) of 90% acetic acid were added. The reaction mixture was stirred at room temperature for 24 hrs and at 50 to 70°C for 24 hrs. Water was then added to the reaction mixture and filtered. Crushed ice was added to the filtrate and was neutralized with excess of aqueous sodium hydroxide solution. The crude 4-anilinopiperidine was obtained by filtration.

In two neck round bottom flask equipped with condenser 17.6 gms (0.10 moles) of 4-anilinopiperidine obtained from step 1, and 50 ml of 100% sodium hydroxide was

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added. The reaction mixture was heated up to 60°C and 27.75 gms (0.15 moles) of 2-phenethyl bromide was then added. The reaction mixture was stirred for 5 hrs. After the completion of the reaction, the reaction mixture was poured in the ice cooled water. The crude product was obtained by filtration and recrystallised from petroleum ether (60 to 80°C) to give colourless crystals of 4-anilino-N-phenethyl piperidipure fentanyl N-(1-phenethyl-4-piperidyl)propionanilide).

In two neck round bottom flask equipped with condenser pressure equalizing funnel and calcium chloride guard tube, a solution of 28.0 (0.10 moles) of 4-anilino-N-phenethyl piperidine prepared in step n, in 150 ml of dichloroethane was taken. To this solution, 9.25gm (0.10 moles) of propionyl chloride was added drop wise through pressure equalizing funnel with continuous stirring. After the completion of the addition, the mixture was further stirred for 10 hrs. After the completion of the reaction, the reaction mixture was washed with 20% sodium hydroxide solution. The aqueous phase was extracted with 2x100 ml of dichloromethane. The combined organic extract was dried over sodium sulphate and concentrated to give crude fentanyl. The crude product was recrystallised from petroleum ether (60 to 80°C) to give colourless crystals of pure fentanyl having mp 82 to 83°C.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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**THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:**

1. A method for the preparation of fentanyl comprising:
  - (a) reacting 4-piperidone hydrochloride with aniline in presence of reducing environment to produce 4-anilinopiperidine (AP),
  - (b) alkylating/reacting the AP as obtained from step (a) with phenethyl halide under reflux conditions in highly alkaline medium to give 4-anilino-N-phenethylpiperidine, and
  - (c) converting the said 4-anilino-N-phenethylpiperidine to fentanyl by reacting with propionyl chloride in presence of a halogenated hydrocarbon then isolating fentanyl by solvent extraction and purified by crystallization from petroleum ether (60-80°C).
2. A method as claimed in claim 1 wherein the reducing environment comprises metal and aqueous carboxylic acid.
3. A method as claimed in claim 2 wherein the reducing environment comprises zinc or magnesium and aqueous acetic acid.
4. A method as claimed in claim 1 wherein the reaction in step (a) is initially conducted at room temperature for a period of from 15 to 35 hrs followed by at an elevated temperature in the range of from 50 to 90°C for a period of from 15 to 35 hrs.
5. A method as claimed in claim 4, wherein the reaction in step (a) is initially conducted at room temperature for a period of from 20 to 30 hrs.
6. A method as claimed in claim 4 or claim 5, wherein following the initial period at room temperature, the reaction temperature in step (a) is elevated to a temperature in the range of from 65 to 80°C
7. A method as claimed in claim 6, wherein following the initial period at room temperature, the reaction temperature in step (a) is elevated for a period of from 20 to 30 hrs.

8. A method as claimed in any one of the preceding claims wherein in the reaction in step (a) 4-piperidone hydrochloride and aniline are used in a 1:1 ratio.
9. A method as claimed in claim 1 wherein the reaction in step (a) is quenched with water and 4-AP is isolated by filtration followed by alkali neutralization.
10. A method as claimed in any one of the preceding claims wherein in the reaction in step (b) the phenethyl halide is chloride, bromide or iodide.
11. A method as claimed in any one of the preceding claims wherein in the reaction in step (b) the highly alkaline medium has a pH around 14 and is provided by alkali metal hydroxide.
12. A method as claimed in claim 11 wherein alkali metal hydroxide in step (b) is sodium hydroxide.
13. A method as claimed in any one of the preceding claims wherein the AP is purified prior to reaction in step (b).
14. A method as claimed in any one of the preceding claims wherein in the reaction in step (c) the halogenated hydrocarbon is chloroform, dichloromethane, dichloroethane, tetrachloroethane.
15. A method as claimed in any one of the preceding claims wherein in the reaction in step (c) a 4 to 5 molar ratio of propionyl chloride with respect to 4-anilino-N-phenethylpiperidine is employed and added drop wise.
16. A method as claimed in any one of the preceding claims wherein in the reaction in step (c) the solvent employed for solvent extraction is a halogenated hydrocarbon.
17. A method as claimed in claim 16 wherein in the reaction in step (c) the solvent employed is dichloromethane.
18. A method for the preparation of fentanyl is substantially such as herein described

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reference to any one of the examples.