A Facile Method for Preparation of [$^2H_3$]-Sufentanil and Its Metabolites

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An improved process for the synthesis of sufentanil with an overall yield of 26% is described. The reactive and high yielding *N*-debenzylation of the piperidine intermediate 7 using a mixture of Pd/C and $Pd(OH)_2$ was applied to other drug intermediates affording free amines in short reaction times. The deuterium-labeled sufentanil and the metabolite desmethylsufentanil were synthesized applying the optimized process.

Key words controlled substance; *N*-debenzylation; desmethylsufentanil; *N*-benzylpiperidine; sufentanil

Sufentanil citrate, a piperidine derivative and a member of a series of potent fentanyl analogues (Fig. 1), is a powerful analgesic with an excellent safety margin as compared with other narcotic agents.[1—3] It is furthermore characterized by a high selectivity and affinity (approximately 10 times greater than fentanyl) for μ-opiate receptors. Sufentanil produces, unlike fentanyl or morphine, complete anesthesia with minimal side effects. When compared with fentanyl, its pharmacokinetic profile in man shows a smaller volume of distribution, resulting in a terminal half-life intermediate between alfentanil and fentanyl.[4,5] Furthermore, sufentanil suppresses most hormonal responses to surgical stimulation without producing significant cardiovascular depression. Additionally, sufentanil, like fentanyl, does not cause histamine release. Also, in low to moderate doses, sufentanil may have further advantages over other narcotic agents. When compared with meperidine, morphine, and fentanyl, in patients undergoing general surgery under balanced anesthesia, sufentanil provides stable cardiovascular parameters, low preoperative catecholamine plasma levels, very little need for additional inhalation supplementation, and a low incidence of postoperative respiratory depression. Because of its remarkably low cardiovascular toxicity, sufentanil citrate has been evaluated as a total intravenous anesthetic for major surgical procedures. It is primarily used for open heart surgery and major operations in patients with severe cardiovascular compromise.[6]

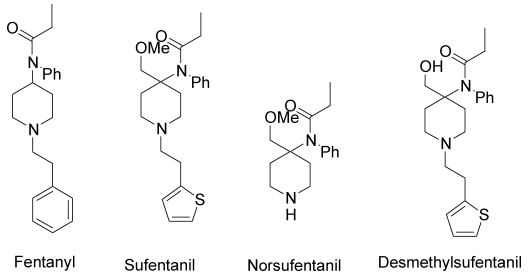
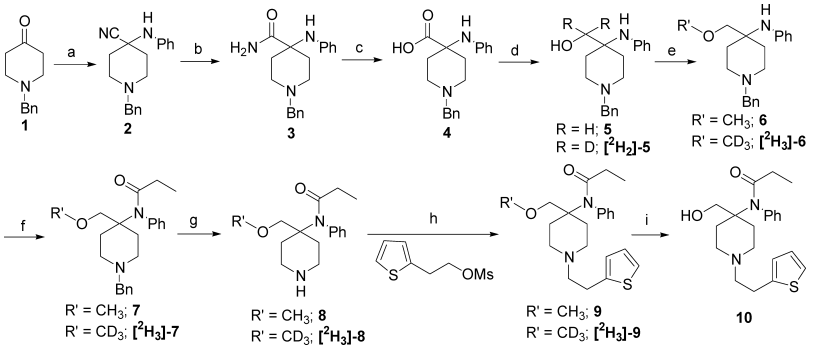


Fig. 1. Structures of Fentanil Analogues

The original synthesis of sufentanil from *N*-benzyl piperidone reported by Janssen and Van Daele involves 10 steps with an overall yield of 2%.[7] Subsequent modifications of the original method with minimum number of steps improved the overall yield to 15%.[8,9] Despite poor overall yield, Janssen's method is the convenient commercial route adopted till date for the synthesis of sufentanil and related fentanyl drugs. An improved process that can enhance the overall yield and overcome the main problems associated with the commercial route is therefore desirable. This paper describes high-yielding direct reduction of amino acid intermediate **4** and mild debenzylation of **7** as key improvements in the original process leading to an overall yield of 26%.

Results and Discussion

Convenient Synthesis of Sufentanil and Its Metabolites The improved process adopted for the synthesis of sufentanil free base is shown in Chart 1. Strecker reaction of *N*-benzylpiperidone **1** with aniline and KCN in aqueous acetic acid formed the cyanoamine **2** in high yield.[10] Hydrolysis of the nitrile group to amide **3** was achieved in using H_2O_2/



(a) aniline, KCN, AcOH, 88%; (b) 30% H_2O_2, K_2CO_3, DMSO, overnight, 85%; (c) KOH, ethylene glycol, reflux, 86%; (d) $LiAlH_4$ or $LiAlD_4$, THF, reflux, overnight, 82%; (e) NaH, 50 °C, 2 h, MeI or CD_3I, 83%; (f) propionyl chloride, CH_2Cl_2, 86%; (g) Pd/C, $Pd(OH)_2$/C, MeOH, H_2, 50 psi, 92%; (h) K_2CO_3, KI, Et_3N, CH_3CN, reflux, 80%; (i) BBr_3, CH_2Cl_2, −78 °C, 15 min, rt, 3 h, 93%.

Chart 1. Synthesis of Sufentanil

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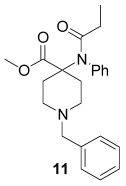
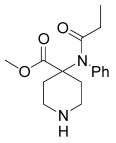
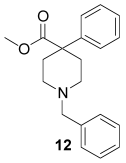
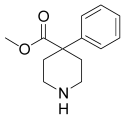
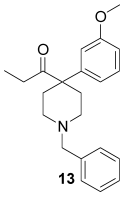
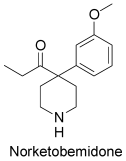
K_2CO_3/dimethyl sulfoxide (DMSO).[11] The method is more convenient than the sulfuric acid method, which requires more acid and subsequently difficult workup. Base hydrolysis of amide using KOH in ethylene glycol at reflux for 3 h afforded the corresponding amino acid **4**. The low-soluble amino acid was isolated in high purity by filtration of the neutralized reaction mixture and washing repeatedly with water, aqueous acetone, and dichloromethane respectively. The direct reduction of the amino acid **4** to amino alcohol **5** was reported inefficient by different methods and most of the reported protocols convert **4** to corresponding ester followed by reduction to alcohol.[12] This two-step reduction process either consumes longer reaction time for esterification[13] or gives lower overall yield.[14] In contrast, amino acid **4** underwent facile reduction to the corresponding amino alcohol **5** in good yield and high purity with $LiAlH_4$ in refluxing THF. The reduction of carboxylic acid group was demonstrated with $LiAlD_4$ affording deuterium-labeled amino alcohol [$^2H_2$]-**5**. Selective methylation of alcohol **5** was low yielding (around 25% isolated yield) with unwashed 60% NaH in mineral oil. However, repeatedly washed (with pentane and THF) and dried reagent afforded the product **6** in good purity in 83% isolated yield. The amine **6** was converted to amide **7** by reacting with propionyl chloride. The pre-final process of debenzylation proved troublesome. Debenzylation of **7** was reported using Pd/C at high pressure of hydrogen and elevated temperatures either in alcohol or aqueous acid as solvents.[15,16] Other methods of debenzylation either employ Pearlman's catalyst[12,17] at high pressure (55—60 psi) and elevated temperature (50 °C) or converting the benzyl group to carbamate followed by hydrolysis.[18—20] Attempted catalytic transfer hydrogenation as well as hydrogenation of **7** with 10% Pd/C (10 to 25 wt% loading) at 50—60 psi hydrogen atmosphere at ambient temperature did not show any product formation in different solvents. The intermediates **5** and **6** under similar conditions were sluggish and no debenzylated product was observed. The use of 20% $Pd(OH)_2$/C (10 wt% loading) in the place of Pd/C indicated the formation of product. The reaction at 50 psi was however very slow and most of the starting material remained unconsumed even after 15 h of reaction. The reaction was then attempted with a mixture of 10% by weight of 10% Pd/C and 10% by weight of 20% $Pd(OH)_2$/C. Surprisingly, the reaction was very fast and afforded the debenzylated product **8** in very high purity in 12 h without the need of any external heating. The higher scale reaction (6 g) displayed consistent reactivity affording the norsufentanil **8** in 92% isolated yield. Final alkylation using the mesylate of 2-(thienyl)ethanol and triethylamine in acetonitrile formed sufentanil **9** as a white solid in 80% yield. All the reactions in the process remarkably proceed with yields >80%. Similarly facile reduction of acid **4** and debenzylation of **7** in high yields improved the overall yield of sufentanil to 26%.

New Debenzylation Condition The new debenzylation condition was examined for bioactive molecules **11**,[15] **12**,[21] and **13**[22] containing similar *N*-benzylpiperidine intermediates. The results obtained are shown in Table 1. In all cases the combined Pd/C–$Pd(OH)_2$ catalyst was found more effective compared with individual catalysts. We supposed that formation of high activity of the palladium catalyst takes place on palladium(II) hydroxide in the process of deposition–precipitation and chemical bonding such as Pd–O–Pd may be formed in the interface of palladium particles and the $Pd(OH)_2$ during the process of debenzylation. We may infer that the high activity of the palladium catalyst prepared by deposition–precipitation is caused by the strong interaction between palladium particles and the $Pd(OH)_2$.[23]

Table 1. Debenzylation of *N*-Benzylpiperidines Using a Mixture of Pd/C and $Pd(OH)_2$/C

Entry	Substrate	Time (h)	Product[a]	Yield (%)[b]
1	 **11**	10	 Norcarfentanil **11a**	85
2	 **12**	6	 Norpethidine **12a**	88
3	 **13**	8	 Norketobemidone **13a**	93

a) The amines were subsequently alkylated to final drugs: **11a** was benzylated back to **11**; **12a** was converted to diphenoxylate; **13a** was converted to ketobemidone. *b*) Isolated yield.

Synthesis of [$^2H_3$]-Sufentanil and Its Metabolites The optimized procedure was extended for the synthesis of deuterium-labeled sufentanil[24,25] by employing [$^2H_3$]-methyl iodide. In case of more deuterium incorporation into the molecule, [$^2H_2$]-**5** can be reacted further in similar fashion to form [$^2H_5$]-**9**. The optimized procedure was also utilized for the synthesis of metabolites of sufentanil.[26,27] The inactive *N*-dealkylated metabolite **8** (norsufentanil) was formed as an intermediate during the synthesis. On the other hand, the bioactive *O*-demethylated metabolite **10** (desmethylsufentanil) was formed in 93% by reacting sufentanil with BBr_3 at −78 °C (Chart 1).

Conclusion

In this study, we established facile preparation of sufentanil and its metabolites with 26% overall yield and succeeded in preparation of their deuterium-labeled products. The new debenzylation condition, the combined Pd/C–$Pd(OH)_2$ catalyst was found more effective compared with individual catalysts.

Experimental

THF was distilled from sodium-benzophenone under argon and CH_2Cl_2 was distilled from CaH_2. ^{1}H-NMR spectra were obtained at 400 MHz, and ^{13}C-NMR spectra were obtained at 100.6 MHz using a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26, 77.0 ppm). Infrared spectra were recorded using a JASCO FT/IR 410 spectrometer. Gas chromatography-mass spectrometry was performed using Agilent 7890/5975C MSD on DB 35MS capillary column. The following GC condition was used for all the compounds. Carrier gas, helium; pressure, 16.089 psi; injection temperature (split mode), 300 °C; oven temperature

program, 200 °C for 1 min and ramped at 20 °C/min to 250 °C for 10—40 min. Preparation of **11**, **12**, and **13** followed the previously published procedure; the ^{1}H- and ^{13}C-NMR data were consistent with those published.

1-Benzyl-4-phenylamino-4-piperidinecarbonitrile (2) 1-Benzyl-4-piperidone (9.0 ml, 48.6 mmol), aniline (5.0 ml, 53.5 mmol), and glacial acetic acid (10.8 ml) were weighed in a 250 ml round bottom flask. While the mixture was stirring at 0 °C, an aqueous solution of KCN was prepared by dissolving KCN (3.65 g, 56.0 mmol) in water (12.5 ml). The KCN solution was placed in an addition funnel, and slowly added to the reaction mixture over 30 min. The addition funnel was replaced with a ground glass stopper, and the reaction mixture was stirred at rt for 18 h. During this time a copious precipitate formed. The reaction mixture was poured onto a mixture of ice (50 g) and concentrated aqueous NH_4OH (50 ml). The mixture was extracted with CH_2C1_2 (3×50 ml). The combined organic extracts were washed with water (10 ml), dried over $MgSO_4$, and solvent removed in vacuum. The resulting oily solid was triturated with Et_2O (20 ml). A white crystalline solid was collected by vacuum filtration (12.50 g, 88% yield). mp 146—148 °C; GC, t_R=8.5 min. MS (EI, 70 eV): *m/z* (%): 263.1 (M^+-28, 26), 172.1 (28), 144.1 (34), 91.1 (100), 77.1 (30). IR (KBr): 3405, 2813, 2758, 1602, 1496, 1313, 1114, 1098, 1024, 699 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27—7.17 (m, 7H), 6.87—6.83 (m, 3H), 3.60 (s, 1H), 3.49 (s, 2H), 2.76—2.73 (b, 2H), 2.43—2.37 (t, *J*=10.4 Hz, 2H), 2.29—2.25 (d, *J*=10.8 Hz, 2H), 1.86 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$), δ: 143.4, 138.1, 129.3, 129.0, 128.4, 127.3, 120.9, 120.8, 117.8, 62.7, 52.5, 49.3, 36.1.

4-Anilino-1-(2-phenylethyl)piperidine-4-carboxamide (3) Potassium carbonate (854 mg, 6.2 mmol) was added to a solution of 1-benzyl-4-phenylamino-4-piperidinecarbonitrile **2** (12.00 g, 41.2 mmol) in DMSO (72 ml) at room temperature. Hydrogen peroxide (30 wt%, 10.1 ml, 99.0 mmol) was slowly added using an addition funnel to the slurry, and the mixture was left overnight while stirring. After completion of the reaction, water (430 ml) was added and crystals were isolated by filtration. It was washed with water and vacuum-dried to produce 10.80 g (85%) of white solid. mp 191—193 °C; GC, t_R=35.4 min. MS (EI, 70 eV): *m/z* (%): 309.0 (M^+, 7), 265.1 (38), 216.1 (30), 172.1 (45), 146.0 (29), 120.1 (20), 91.1 (100), 77.1 (10). IR (KBr): 3447, 3354, 2809, 2757, 1669, 1605, 1499, 1307, 1168, 1024, 744, 696 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30—7.23 (m, 5H), 7.20—7.17 (t, *J*=8.2 Hz, 2H), 6.9 (b, 1H), 6.82—6.78 (t, *J*=7.4 Hz, 1H), 6.64—6.62 (d, *J*=7.8 Hz, 2H), 5.65 (b, 1H), 4.03 (s, 1H), 3.48 (s, 2H), 2.76—2.72 (d, *J*=12.2 Hz, 2H), 2.36—2.29 (t, *J*=12.3 Hz, 2H), 2.13—2.06 (t, *J*=12.1 Hz, 2H), 1.92 (d, *J*=12.2 Hz, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 178.7, 143.7, 138.3, 129.2, 129.0, 128.3, 127.1, 119.2, 116.2, 63.0, 58.3, 48.7, 31.3.

1-Benzyl-4-phenylaminopiperidine-4-carboxylic Acid (4) Solid KOH (6.34 g, 113.3 mmol) was weighed in a 100 ml single neck flask equipped with a reflux condenser. Ethylene glycol (40 ml) was added and the contents were heated around 100 °C to form a clear solution. The flask was cooled to room temperature and 4-anilino-1-(2-phenylethyl)piperidine-4-carboxamide **3** (10.00 g, 32.4 mmol) was added immediately. The clear solution formed after brief heating was refluxed (210 °C) for 3 h. The flask was cooled to room temperature and poured onto ice and stirred for 10 min. Conc. HCl was added dropwise, with stirring, to pH *ca.* 6—7 (indicator paper). More amount of pale yellow solid formed was allowed to stand at 0 °C for 1 h then vacuum filtered. The solid was slurry washed with excess water and then with 30% aqueous acetone. The resulting white solid (8.60 g, 86%) was collected and vacuum dried to remove final traces of solvents. mp 243—245 °C. IR (KBr): 3330, 3058, 2174, 1600, 1499, 1380, 1329, 1073, 806, 746, 699 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3SOCD_3) δ: 7.27—7.21 (m, 5H), 7.0—6.99 (t, *J*=7.5 Hz, 2H), 6.55—6.48 (m, 3H), 3.46 (s, 2H), 2.51—2.49 (m, 2H), 2.38—2.33 (t, *J*=9.4 Hz, 2H), 2.03—1.91 (m, 4H). ^{13}C-NMR (100.6 MHz, CD_3SOCD_3) δ: 177.5, 146.9, 138.7, 129.3, 129.0, 128.6, 127.4, 116.4, 114.2, 62.5, 57.4, 48.9, 32.6.

1-Benzyl-4-phenylamino-4-(hydroxymethyl)piperidine (5) $LiAlH_4$ (1.88 g, 49.4 mmol) was weighed into an oven dried two-necked flask with a condenser under argon atmosphere. The flask was cooled to 0 °C with ice-salt bath and THF (160 ml) was carefully added to form slurry. After 10 min, solid 1-benzyl-4-phenylaminopiperidine-4-carboxylic acid **4** (8.00 g, 24.7 mmol) was added portionwise over a period of 30 min and stirred further at the same temperature for 30 min. It was then warmed to room temperature and refluxed for a period of 16 h. After completion of the reaction, the flask was cooled to 0 °C, and carefully quenched with moist THF. The reaction mixture was filtered over celite and washed with more of EtOAc (3×25 ml). The organic washings were combined and concentrated under reduced pressure to afford product as a pale orange viscous liquid sufficiently pure for further reactions (6.30 g, 82%). For the synthesis of [$^2H_2$]-**5**, the reaction was performed as described above using $LiAlD_4$. GC, t_R=18.2 min. MS (EI, 70 eV): *m/z* (%): 296.1 (M^+, 1), 266.1 (22), 203.1 (12), 186.1 (14), 172.1 (93), 146.1 (22), 120.1 (12), 91.1 (100), 77.1 (9). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28—7.21 (m, 5H), 7.16—7.12 (t, *J*=7.4 Hz, 2H), 6.81—6.78 (t, *J*=6.4 Hz, 1H), 6.75—6.73 (d, *J*=8.5 Hz, 2H), 3.58 (s, 2H), 3.46 (s, 2H), 2.56—2.53 (b, 2H), 2.24 (t, *J*=6.9 Hz, 2H), 1.89—1.86 (d, *J*=13.9 Hz, 2H), 1.66—1.63 (t, *J*=6.9 Hz, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 162.6, 145.2, 138.2, 129.2, 128.3, 127.1, 119.8, 118.5, 67.3, 63.3, 55.7, 49.1, 36.5, 32.7, 31.5.

Data for [$^2H_2$]-**5**: GC, t_R=17.6 min. MS (EI, 70 eV): *m/z* (%): 298.1 (M^+, 1), 266.1 (19), 205.1 (10), 188.1 (14), 172.1 (88), 146.1 (22), 120.1 (12), 91.1 (100), 77.1 (9). IR (KBr): 3421, 2925, 2231, 2067, 1600, 1497, 1265, 1097, 746, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36—7.28 (m, 5H), 7.22—7.18 (t, *J*=7.8 Hz, 2H), 6.88—6.84 (t, *J*=7.3 Hz, 1H), 6.80—6.78 (d, *J*=8.0 Hz, 2H), 3.53 (s, 2H), 3.28 (b, 1H), 2.56—2.60—2.40 (m, 2H), 2.36—2.30 (m, 2H), 1.94—1.91 (m, 2H), 1.73—1.64 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 145.5, 138.2, 129.3, 129.2, 128.3, 127.2, 119.7, 118.5, 66.3, 63.3, 55.5, 49.1, 32.5.

1-Benzyl-4-phenylamino-4-(methoxymethyl)piperidine (6) THF (50 ml) was added at ambient temperature to NaH (60%, washed three times with hexane and vacuum dried, 1.39 g, 34.6 mmol) weighed in an oven-dried 250 ml two neck flask under argon. The flask was cooled to 0 °C and 1-benzyl-4-phenylamino-4-(hydroxymethyl)-piperidine **5** (5.00 g, 16.9 mmol) in THF (25 ml) was added dropwise and the slurry was gradually warmed to 50 °C and stirred for 2 h. The flask was again cooled to 0 °C in an ice-bath and methyl iodide (1.10 ml, 17.7 mmol) was added slowly over a period of 15—30 min. After warming to room temperature, the contents were stirred for further 2 h during which a large amount of white precipitate was formed. After the completion of the reaction, water (50 ml) was added and extracted with CH_2Cl_2 (3×30 ml). The combined organic extracts were washed with brine, filtered, dried over Na_2SO_4 and concentrated in vacuum to afford a crude product which was purified by column chromatography on basic alumina using EtOAc–hexane as a mobile phase to afford product as a colorless liquid (4.35 g, 83%). For the synthesis of [$^2H_3$]-**6**, the reaction was performed as described above using CD_3I. GC, t_R=12.7 min. MS (EI, 70 eV): *m/z* (%): 310.2 (M^+, 6), 265.1 (36), 217.2 (17), 186.1 (38), 172.1 (87), 146.1 (34), 120.1 (21), 91.1 (100), 77.1 (7). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.29—7.18 (m, 5H), 7.13—7.09 (t, *J*=7.3 Hz, 2H), 6.79—6.75 (t, *J*=7.6 Hz, 3H), 3.47 (s, 2H), 3.28 (s, 2H), 3.25 (s, 3H), 2.54—2.39 (m, 4H), 1.89—1.65 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 146.0, 138.5, 129.2, 128.9, 128.3, 127.0, 119.8, 63.3, 59.2, 55.2, 49.2, 32.8.

Data for [$^2H_3$]-**6**: GC, t_R=12.2 min. MS (EI, 70 eV): *m/z* (%): 313.2 (M^+, 4), 268.1 (27), 220.2 (18), 186.1 (35), 172.1 (81), 146.1 (30), 120.1 (19), 91.1 (100), 77.0 (8). IR (KBr): 3736, 2930, 2352, 2235, 2069, 1613, 1458, 1267, 1124, 741 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38—7.22 (m, 5H), 7.22—7.19 (m, 2H), 6.86—6.84 (m, 3H), 3.55 (s, 2H), 3.37 (s, 2H), 2.63—2.60 (m, 2H), 2.53—2.48 (m, 2H), 1.98—1.95 (m, 2H), 1.82—1.75 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 146.1, 138.6, 129.2, 128.9, 128.3, 127.0, 119.7, 63.3, 58.0 (m), 55.2, 49.2, 32.9.

1-Benzyl-4-[(*N*-(1-oxopropyl)-*N*-phenylamino]-4-(methoxymethyl)-piperidine (7) Triethylamine (2.33 ml, 16.8 mmol) was added to a solution of 1-benzyl-4-phenylamino-4-(methoxymethyl)-piperidine **6** (4.00 g, 12.9 mmol) in CH_2Cl_2 (28 ml) at room temperature. The flask was cooled to 0 °C in an ice-bath followed by dropwise addition of propionyl chloride (1.46 ml, 16.8 mmol) over 15 min. The contents were stirred at the same temperature for 1 h and at rt for 5 h. After the completion of the reaction, water was added and extracted with CH_2Cl_2 (2×30 ml). The organic extracts were dried and concentrated to yield 1-benzyl-4-[(*N*-(1-oxopropyl)-*N*-phenylamino]-4-(methoxymethyl)-piperidine **7** as a colorless liquid (4.05 g, 86%) sufficiently pure for the further reactions. [$^2H_3$]-**6** was reacted in a similar fashion to afford [$^2H_3$]-**7**. GC, t_R=20.2 min. MS (EI, 70 eV): *m/z* (%): 366.2 (M^+, 1), 351.2 (1), 321.2 (8), 309.2 (8), 245.2 (11), 218.2 (81), 186.1 (24), 172.1 (52), 146.1 (17), 126.1 (52), 91.1 (100). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34—7.32 (m, 3H), 7.31—7.23 (m, 7H), 4.07 (s, 2H), 3.46 (s, 2H), 3.43 (s, 3H), 2.60—2.57 (m, 2H), 2.22—2.12 (m, 4H), 1.86—1.81 (q, *J*=7.4 Hz, 2H), 1.73—1.67 (m, 2H), 0.98—0.94 (t, *J*=7.4 Hz, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 174.5, 141.3, 138.1, 131.3, 129.1, 128.5, 128.1, 127.7, 127.0, 70.6, 63.0, 61.6, 59.2, 50.1, 33.1, 30.7, 9.5.

Data for [$^2H_3$]-**7**: GC, t_R=19.2 min. MS (EI, 70 eV): *m/z* (%): 312.1 (7), 245.1 (9), 221.2 (59), 202.0 (9), 186.1 (18), 172.1 (47), 146.1 (13), 129.1 (42), 91.1 (100). IR (KBr): 3736, 2927, 2347, 2065, 1656, 1375, 1130, 702 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32—7.30 (m, 3H), 7.29—7.20 (m, 7H), 4.04 (s, 2H), 3.43 (s, 2H), 2.57—2.54 (m, 2H), 2.20—2.13 (m,

4H), 1.83—1.80 (q, J=7.4 Hz, 2H), 1.71—1.65 (m, 2H), 0.95—0.91 (t, J=7.4 Hz, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 174.6, 141.3, 138.0, 131.3, 129.2, 128.5, 128.2, 127.7, 127.0, 70.5, 63.0, 61.6, 58.0 (m), 50.0, 33.1, 30.7, 9.5.

2-(Thiophen-2-yl)ethyl Methanesulfonate To a solution of 2-(thiophen-2-yl)ethanol (3.00 g, 23.7 mmol) in CH_2Cl_2 (45 ml) in a 250 ml flask was added triethylamine (3.63 ml, 26.0 mmol) and the clear solution was stirred at room temperature for 30 min. It was then cooled to 0—5 °C with ice-salt bath and methanesulfonyl chloride (1.92 ml, 24.9 mmol) was added dropwise in 10 min. The resulting white slurry was then allowed to warm to room temperature. After completion of the reaction (TLC, 1 h), $NaHCO_3$ solution (30 ml) was added and the organic layer was separated. The aqueous layer was extracted again with CH_2Cl_2 (25 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 2-(thiophen-2-yl)ethyl methanesulfonate as a colorless liquid (4.53 g, 94%). IR (KBr): 3650, 2938, 1353, 1169, 959, 903, 799, 704 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.20—7.19 (dd, J=5.1, 1.2 Hz, 1H), 6.97—6.95 (dd, J=5.1, 3.5 Hz, 1H), 6.92—6.91 (m, 1H), 4.44—4.40 (t, J=6.6 Hz, 2H), 3.29—3.26 (t, J=6.6 Hz, 2H), 2.92 (s, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 138.2, 127.1, 126.3, 124.6, 69.8, 37.4, 29.8.

Norsufentanil (8) A mixture of 10% Pd/C (500 mg, 10 wt%) and 20% $Pd(OH)_2$/C (500 mg, 10 wt%) were weighed in a Parr glass vessel and carefully wet with methanol. A solution of **7** (5.30 g, 14.8 mmol) in methanol (32 ml) was added and then flushed three times with hydrogen gas. The vessel was finally charged with hydrogen gas (60 psi) and shaken mechanically for 12 h. After completion of the reaction (TLC, 12 h), the reaction mixture was filtered through a pad of celite and washed with excess methanol (2×30 ml). The filtrate was concentrated under reduced pressure to afford the product as a colorless liquid (3.68 g, 92%) which was immediately used for the final step. The same procedure was followed for debenzylation of **11**, **12** and **13**. [$^2H_3$]-**7** was reacted in a similar fashion to afford [$^2H_3$]-**8**.

Sufentanil (9) To a solution of norsufentanil **8** (4.28 g, 15.5 mmol) in acetonitrile (45 ml) in a 100 ml two-neck flask with a condenser were added K_2CO_3 (214 mg, 1.6 mmol), 2-(thiophen-2-yl)ethyl methanesulfonate (3.51 g, 17.1 mmol) and KI (77 mg, 0.47 mmol). Et_3N (4.32 ml, 31.0 mmol) was added to the slurry at room temperature and the contents were heated under reflux overnight. After completion of the reaction, the flask was cooled and the solvent was pumped off under reduced pressure. Water was added and the mixture was extracted with EtOAc (3×20 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude product as a colorless liquid. Purification by a short path column chromatography on alumina using EtOAc–hexane as a mobile phase afforded pure product **9** which crystallized on cooling in an ice-bath to colorless solid (4.80 g, 80%). [$^2H_3$]-**8** was reacted in a similar fashion to afford [$^2H_3$]-**9**. mp 103—104 °C; GC, t_R=28.2 min. MS (EI, 70 eV): m/z (%): 384.2 (1), 357.2 (1), 341.2 (1), 289.1 (100), 187.1 (2), 158.1 (4), 140.1 (23), 110.1 (11), 93.1 (24). IR (KBr): 3082, 2982, 2920, 2809, 2728, 1655, 1488, 1358, 1251, 1117, 774, 702 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30—7.23 (m, 5H), 7.05—7.03 (dd, J=5.1, 1.1 Hz, 1H), 6.85—6.82 (dd, J=5.1, 3.4 Hz, 1H), 6.73—6.72 (dd, J=3.4, 0.6 Hz, 1H), 4.03 (s, 2H), 3.38 (s, 3H), 2.92—2.88 (t, J=7.4 Hz, 2H), 2.64—2.61 (m, 2H), 2.55—2.52 (t, J=7.4 Hz, 2H), 2.20—2.15 (m, 4H), 1.81—1.76 (q, J=7.3 Hz, 2H), 1.71—1.65 (m, 2H), 0.91—0.87 (t, J=7.3 Hz, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 174.6, 142.7, 141.2, 131.3, 128.6, 127.8, 126.6, 124.6, 123.4, 70.3, 61.5, 60.1, 59.2, 50.2, 33.2, 30.7, 27.8, 9.5.

Data for [$^2H_3$]-**9**: mp 103—104 °C; GC, t_R=27.5 min. MS (EI, 70 eV): m/z (%): 387.2 (1), 341.2 (1), 292.1 (100), 187.1 (2), 158.1 (3), 143.1 (20), 111.1 (12), 93.1 (10). IR (KBr): 2934, 2811, 2351, 2181, 2052, 1647, 1594, 1491, 1374, 1250, 1130, 703 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34—7.26 (m, 5H), 7.10—7.09 (dd, J=4.4, 0.6 Hz, 1H), 6.90—6.88 (dd, J=5.1, 3.5 Hz, 1H), 6.78—6.77 (m, 1H), 4.06 (s, 2H), 2.97—2.93 (t, J=7.5 Hz, 2H), 2.69—2.65 (m, 2H), 2.61—2.57 (t, J=7.6 Hz, 2H), 2.26—2.18 (m, 4H), 1.85—1.80 (q, J=7.4 Hz, 2H), 1.74—1.71 (m, 2H), 0.95—0.91 (t, J=7.4 Hz, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 174.7, 142.7, 141.2, 131.3, 128.6, 127.8, 126.6, 124.6, 123.4, 70.4, 61.5, 60.0, 58.0 (m, very weak signal), 50.1, 33.1, 30.7, 27.8, 9.5.

Desmethylsufentanil (10) Sufentanil **9** (100 mg, 0.26 mmol) was dissolved in dry CH_2Cl_2 (2 ml) in a two-neck flask under argon atmosphere. The reaction mixture was cooled to −78 °C and BBr_3 (0.26 ml, 1.0 M solution) was added dropwise for a period of 15 min. The contents were further stirred at the same temperature for 15 min and warmed to room temperature and stirred 3 h. After the completion of the reaction, water was added followed by 2 N NaOH solution and extracted with CH_2Cl_2 (2×5 ml). The combined organic extracts were dried and concentrated to afford pure product **10** as colorless solid (90 mg, 93%). mp 120—122 °C. IR (KBr): 3160, 2923, 2826, 2345, 2065, 1655, 1594, 1486, 1373, 1250, 1057, 769, 705, 692 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.42—7.37 (m, 3H), 7.16—7.14 (m, 2H), 7.11—7.10 (dd, J=5.1, 1.1 Hz, 1H), 6.91—6.89 (dd, J=5.1, 3.4 Hz, 1H), 6.79—6.78 (d, J=2.8 Hz, 1H), 5.17 (b, 1H), 4.04—4.03 (d, J=3.8 Hz, 2H), 2.98—2.94 (t, J=7.4 Hz, 2H), 2.81—2.78 (m, 2H), 2.63—2.60 (t, J=8.2 Hz, 2H), 2.30—2.24 (t, J=11.7 Hz, 2H), 2.07—2.04 (dd, J=13.1, 1.8 Hz, 2H), 1.91—1.86 (q, J=7.4 Hz, 2H), 1.65—1.60 (dt, J=12.2, 2.6 Hz, 2H), 0.94—0.98 (t, J=7.4 Hz, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 176.7, 142.5, 140.5, 130.2, 129.3, 128.5, 126.6, 124.6, 123.5, 66.7, 63.77, 59.8, 50.4, 32.7, 30.6, 27.8, 9.6.

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