A Facile Method for Preparation of \( ^{2}\)H3-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 \( \mu \)-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)

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. Streeker 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% \( H_2O_2 / \) K2CO3, DMSO, overnight, 85%; (c) KOH, ethylene glycol, reflux, 86%; (d) LiAlH4 or LiAlD4, THF, reflux, overnight, 82%; (e) NaH, 50 °C, 2 h, MeI or CD3I, 83%; (f) propionyl chloride, CH2Cl2, 86%; (g) Pd/C, Pd(OH)2/C, MeOH, H2, 50 psi, 92%; (h) K2CO3, KI, Et3N, CH3CN, reflux, 80%; (i) BBr3, CH2Cl2, /H11002 78 °C, 15 min, rt, 3 h, 93%.

Chart 1. Synthesis of Sufentanil

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K₂CO₃/dimethyl sulfoxide (DMSO). 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. This two-step reduction process either consumes longer reaction time for esterification or gives lower overall yield. In contrast, amino acid 4 underwent facile reduction to the corresponding amino alcohol 5 in good yield and high purity with LiAlD₄ in reflowing THF. The reduction of carboxylic acid group was demonstrated with LiAlH₄ affording deuterium-labeled amino alcohol [²H₅]-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 debenzylolation 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. Other methods of debenzylolation either employ Pearlman’s catalyst at high pressure (55—60 psi) and elevated temperature (50 °C) or converting the benzyl group to carbamate followed by hydrolysis. 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 debenzylolated 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 debenzylolated 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 debenzylolation 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 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.

### Synthesis of [²H₅]-Sufentanil and Its Metabolites

The optimized procedure was extended for the synthesis of deuterium-labeled sufentanil by employing [²H₅]-methyl iodide. In case of more deuterium incorporation into the molecule, [²H₅]-5 can be reacted further in similar fashion to form [²H₅]-9. The optimized procedure was also utilized for the synthesis of metabolites of sufentanil. The inactive O-dealkylated metabolite (norsufentanil) was formed as an intermediate during the synthesis. On the other hand, the bioactive O-demethylated metabolite (desmethylsufentanil) was formed in 93% by reacting sufentanil with BBr₃ 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 CH₂Cl₂ was distilled from CaH₂. ¹H-NMR spectra were obtained at 400 MHz, and ¹³C-NMR spectra were obtained at 100.6 MHz using a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to CDCl₃ (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...

### Table 1. Debrenylation of N-Benzylpiperidines Using a Mixture of Pd/C and Pd(OH)₂/C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>[12]</td>
<td>6</td>
<td>Norpethidine 12a</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>[13]</td>
<td>8</td>
<td>Norketobemidone 13a</td>
<td>93</td>
</tr>
</tbody>
</table>

*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.
program, 200°C for 1 min and ramped to 20°C/min to 250°C for 10—
40 min. Preparation of 11, 12, and 13 followed the previously published pro-
cedure; the 1H- and 13C-NMR data were consistent with those published.
1-Benzyl-4-phenylamino-4-piperidinecarbonitrile (2) 1-Benzyl-4-
phenylpiperidin-4-ylamine (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). While the mixture was slowly added using an addition funnel to the slurry, and the mixture was left at room temperature. Hydrogen peroxide (30 wt%, 10.1 ml, 99.0 mmol) was added and crystals were isolated by filtration. It was washed with water and was recrystallized and vacuum dried to remove final traces of solvents. mp 243—245°C.

The reaction mixture was poured onto a mixture of acetic acid (10.8 ml) and 50% aqueous NH4OH (50 ml). The mixture was ex-
plosive precipitate formed. The reaction mixture was poured onto a mixture of KCN (3.65 g, 56.0 mmol) in water (12.5 ml). The KCN solu-

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The resulting oily solid was triturated with Et2O (20 ml). A white crys-
talline solid was collected by vacuum filtration (12.50 g, 88% yield), mp 146—148°C; 1H-NMR (CDCl3): d 2.56—2.53 (b, 2H), 2.24 (t, J = 12.2 Hz, 2H), 2.03—1.91 (m, 4H). 13C-NMR (100.6 MHz, CDCl3): δ 7.30—7.23 (m, 5H), 7.20—7.17 (t, J = 7.4 Hz, 2H), 6.85—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). 11C-NMR (100.6 MHz, CDCl3): δ 145.5, 138.2, 129.3, 129.2, 128.3, 127.3, 119.2, 118.5, 66.3, 63.5, 55.4, 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-(methoxymethyl)piperidine (5) (8.86 g, 32.5 mmol) was added and cooled to 0°C, and carefully quenched with moist THF. The reaction mixture was allowed to stand at 0°C for 1 h then was added dropwise, with stirring, to pH 7. The mixture was cooled to 0°C, and carefully quenched with moist THF. The reaction mixture was diluted 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 carefully quenched with moist THF. The reaction mixture was decanted and vacuum dried to remove final traces of solvents. mp 243—245°C.

The reaction mixture was poured onto a mixture of acetic acid (10.8 ml) and 50% aqueous NH4OH (50 ml). The mixture was ex-
plosive precipitate formed. The reaction mixture was poured onto a mixture of KCN (3.65 g, 56.0 mmol) in water (12.5 ml). The KCN solu-

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tion was added and crystals were isolated by filtration. It was washed with water and was recrystallized and vacuum dried to remove final traces of solvents. mp 243—245°C.
4H), 1.83—1.80 (q, 6H), 1.71—1.65 (m, 2H), 0.95—0.91 (t, J = 7.4 Hz, 3H). 13C-NMR (100.6 MHz, CDCl3) δ: 174.6, 141.1, 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)-ethyl methanesulfonate (3.00 g, 23.7 mmol) in CH2Cl2 (45 ml) in a 250 ml flask under argon atmosphere. The solution was cooled and the solvent was pumped off under reduced pressure. Water 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 reaction mixture was filtered through a pad of celite and washed with excess methanol. A solution of 5% Pd/C (500 mg, 10 wt%) was weighed in a Parr glass vessel and carefully wet with methanol. A solution of 2-(thiophen-2-yl)ethanol (3.00 g, 23.7 mmol) in CH2Cl2 (45 ml) in a 250 ml flask was added and the mixture was extracted with EtOAc (32 ml) cooled and the solvent was pumped off under reduced pressure. 2N NaOH solution and extracted with CH2Cl2 (25 ml). The combined organic extracts were dried over MgSO4, filtered and concentrated under reduced pressure to afford colorless liquid (4.80 g, 80%). [2H3]-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 norsufentanil (8) (5.30 g, 14.8 mmol) in methanol (30 ml). The filtrate was concentrated under reduced pressure to afford [2H3]-desmethylsufentanil (9).

References