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An optimized synthesis of a key pharmaceutical intermediate methyl 4-[(1-oxopropyl)phenylamino]piperidine-4-carboxylate

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Abstract: An efficient synthesis of methyl 4-[(1-oxopropyl)phenylamino]piperidine-4-carboxylate (**7**) has been developed, starting from 1-benzylpiperidin-4-one (**1**). The compound is a key intermediate in the synthesis of new generation, highly active narcotic analgesics, such as remifintanil, as well as the novel classes of fentanyl analogues. An optimized Strecker-type condensation of piperidone **1** with aniline and HCN yielded the anilino-nitrile **2** (≈90 %) which, upon selective hydrolysis with conc. H_2SO_4, gave the anilino-amide **3**. After vigorous basic hydrolysis of **3**, followed by acidification and successive treatment with $SOCl_2$ and MeOH, the anilino-ester **5** was obtained (40–45 %, in 3 steps). *N*-Acylation of **5** with propionyl chloride yielded the anilido-ester **6** (70–80 %). In the final step, the catalytic *N*-debenzylation of **6** was examined under various conditions and optimized to yield **7** in near quantitative yields.

Keywords: optimized Strecker reaction, functionalized piperidines, fentanyl-type central analgesics.

INTRODUCTION

Opioid agonists play a very significant role in contemporary clinical practice, both in short term and long term alleviation of pain, as well as in various fields of biomedical research.[1–3] Opioid antagonists too, have been widely used experimentally and to a limited extent clinically (mainly to treat opioid overdose). Among the three types of agonists, relatively specific for μ, κ and δ receptors respectively, μ agonists are the most significant therapeutically. These include structurally highly diverse compounds such as morphine,[4] meperidine,[4] methadone,[4] fentanyl,[4] etonitazene,[4] various peptides (CRF, dynorphin, endorphins, nociceptin)[4] and others.

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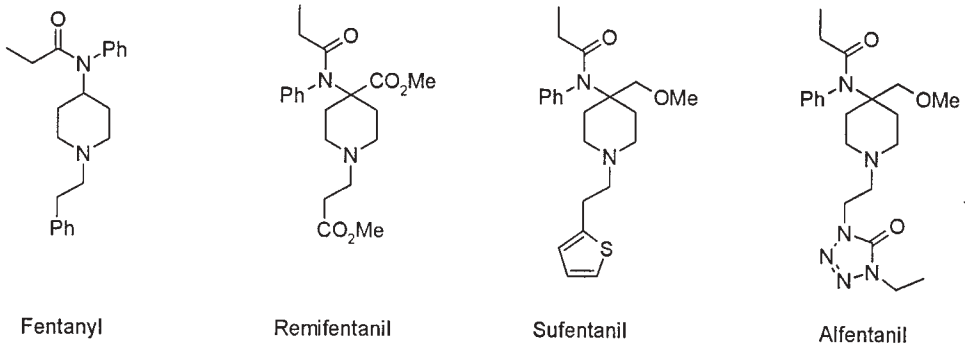
4-Anilido-piperidines[5] (fentanyl analogues) represent a particular class of μ agonists, characterized by very high analgesic potency, relatively short duration of action and good overall safety margin during surgical anesthesia. The clinically most useful drugs in this group, *i.e.*, fentanyl,[4] remifentanil,[4] sufentanil[4] and alfentanil,[4] are depicted in Scheme 1.



Scheme 1.

A very large number of fentanyl analogues have been synthesized in the past 30 years, with the aim of establishing a SAR (structure-activity relationship), to probe the receptor structure and to produce novel, clinically useful drugs with better pharmacological profile. The latter includes higher potency, higher receptor selectivity, less side effects such as respiratory depression and lower addiction potential.

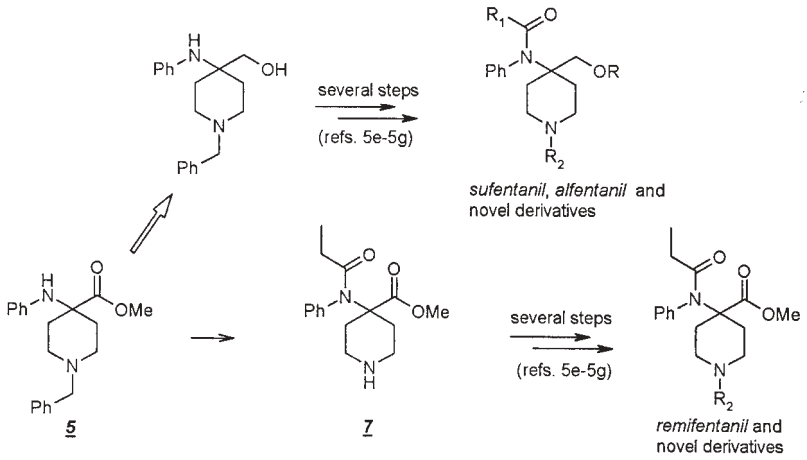
Initially, fentanyl and its analogues were used only in surgical anesthesia and to treat postoperative pain. In recent years, however, it also became a useful drug in controlling severe chronic pain, through transdermal patches (Duragesic®).[6] As fentanyl does not penetrate human skin readily, it would be useful, *inter alia*, to develop novel derivatives with better skin resorption.

In general, although the contemporary narcotic analgesics are highly useful and potent (some are more than 1000 times more potent than morphine), they still suffer from diverse and serious drawbacks. Hence, there is a constant need for a next generation of these drugs, with more acceptable pharmacological profiles.

RESULTS AND DISCUSSION

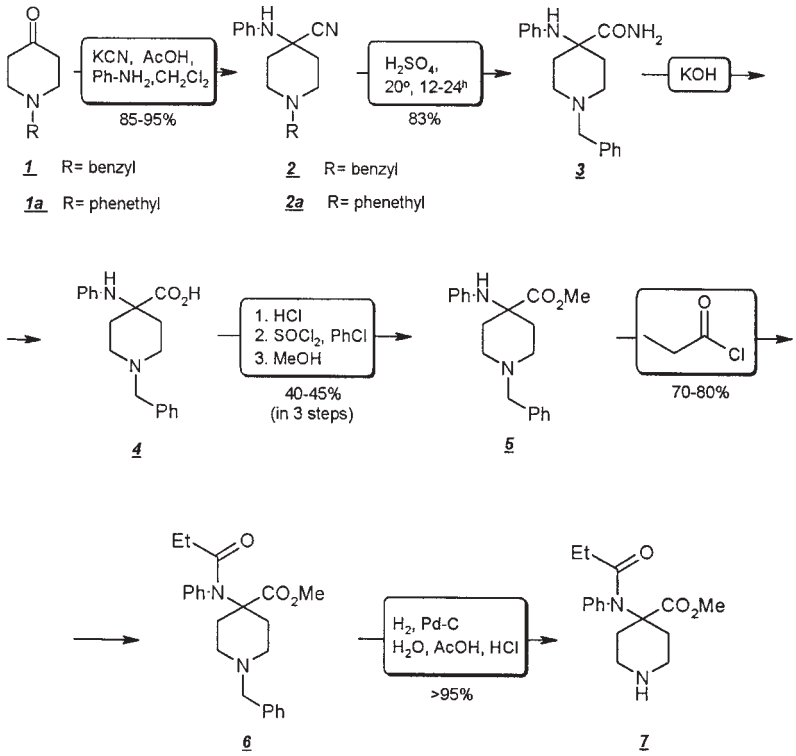
As part of our efforts to synthesize various novel derivatives of remifentanil, sufentanil and alfentanil, a substantially improved and modified synthesis of methyl 4-[(1-oxopropyl)phenylamino]piperidine-4-carboxylate (**7**) has been developed. Compound **7** and its precursor **5** are known[5e–5g] to be key intermediates in the synthesis of substituted fentanyl derivatives possessing groups such as 4-methoxycarbonyl, 4-methoxymethyl and others as outlined in Scheme 2. It also provides access to numerous other 4,4-disubstituted piperidine derivatives. The published syntheses of **7** suffer from low overall yields, tedious intermediate isolation and/or impure final product, as was evidenced in this research.

The synthesis presented herein is accomplished in 7 steps, starting from 1-benzyl piperidine-4-one (**1**), Scheme 3.



Scheme 2.

Piperidone **1** was condensed with aniline and HCN to yield the Strecker type anilino-nitrile **2**. Although this reaction has been the subject of numerous papers and patents, the yields and/or purity of the products, including **2**, have been quite variable and generally below 50 %. In this research the reaction conditions were optimized with respect to the solvent, reac-



Scheme 3.

tion temperature, molar ratio of the reactants and the acid catalyst. Initially, simple model ketones, such as cyclohexanone and 4-phenylbutan-2-one, were used for a rough estimate of the reaction parameters. This was followed by a detailed optimization on piperidone **1**, and piperidone **1a**. The optimal molar proportion of the reagents was found to be 4 eq. of KCN and 4 eq. of aniline per 1 eq. of ketone, with various solvents and acid catalysts. Lower proportions diminished the yields while higher proportions result in no further improvements.

Of the solvents tested (MeOH, EtOH, *i*-PrOH, pure AcOH, acetonitrile, CH_2Cl_2), the mixture CH_2Cl_2/AcOH (≈1:1) gave optimal results. The role of the CH_2Cl_2 is to dissolve the liberated HCN during the addition of AcOH at –5 to 0 ºC.

Although Strecker-type condensations are usually performed at 0–20 ºC, we found that subsequent heating at 45–50 ºC for 12–36 h was necessary to achieve nearly quantitative yields, possibly according to Scheme 4. A slight positive pressure of HCN was maintained in the apparatus using a mercury filled bubbler. In general, the amino-ketones (piperidones) were found to be much less reactive then the model ketones.

Although the reaction mechanism was not investigated in this research, it is known[7] that it involves cyanide ion addition to protonated imines, Scheme 4. Cyanohydrins are unlikely intermediates as they do not form carbocations readily. This is corroborated by the fact that sugar cyanohydrins (as well as other cyanohydrins) are hydrolyzed to α-hydroxy acids in dil. HCl (Kiliani-Fischer synthesis) without dehydration or chlorine substitution.[7–14] Similarly, acid-catalyzed esterification of α-hydroxy acids is easily accomplished with no dehydration.[15] To effect dehydration of cyanohydrins or α-hydroxy acids, likely *via* formation of carbocation intermediates, much more vigorous conditions are required. These include heating with $SOCl_2$[16] or H_2SO_4.[17] However, extensive decomposition was observed in the latter instance.

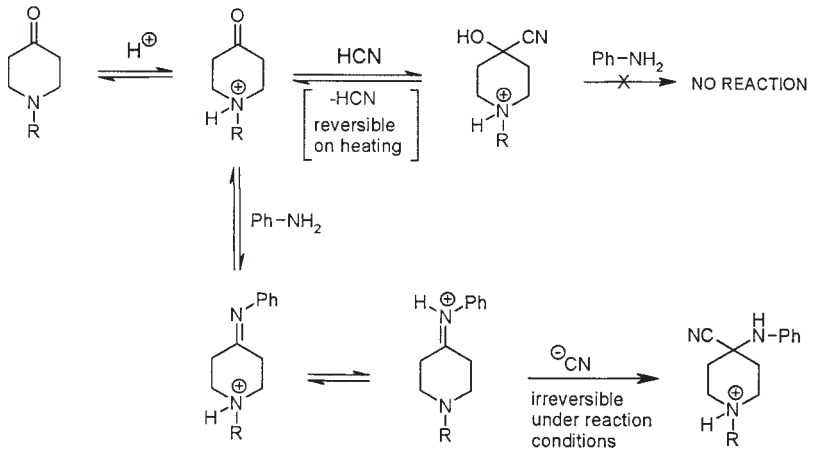
Since the cyanohydrins are actually formed in the course of the Strecker synthesis (as evidenced by tlc and instrumental methods), apparently the reverse reaction, HCN elimination, takes place upon heating, enabling the complete conversion of carbonyl compounds to amino-nitriles.

Among the examined acid catalysts, it was found that acetic acid, used as co-solvent with CH_2Cl_2, proved to be superior in terms of yields and purity. Other catalysts, *e.g.*, pure AcOH, TFA, HCl (aq.) TsOH, MsOH and AcOH/$ZnCl_2$, gave lower yields.

The procedure is equally applicable to 1-phenethyl-4-piperidone (**1a**) (≈90 % yield of the anilino-nitrile **2a**), however it fails completely with 3-methyl-1-phenethyl-piperidin-4-one, apparently due to steric factors. Some of the results are summarized in Table I.

In should be pointed out that the reaction protocol presented herein is applicable to a variety of ketones and also to some aliphatic amines such as benzylamine.

Numerous attempts to convert the anilino-nitrile **2** directly to the anilino-ester **5** (*via* a Pinner-type reaction[18,19]) failed. Thus reactions with MeOH/HCl, MeOH/HBr, MeOH/MsOH and MeOH/H_2SO_4 under various conditions, led exclusively to the starting piperidone **1**, due to the retro-Strecker process. The conversion was finally effected by modification of a known, three step procedure.



Scheme 4.

The anilino-nitrile **2** was selectively hydrolyzed to the corresponding anilino-amide **3** by dissolving in conc. H_2SO_4 and stirring for 24 h at 20 ºC. As the formed dihydrogensulphate salt of **3** is insoluble in the reaction medium, hydrolysis does not proceed further. The precipitated salt was first converted to the free base **3**, then subjected to vigorous basic hydrolysis (KOH, 1,2-propylene glycol, ≈200 ºC, 12 h, cat. 18-C-6) to yield the anilino-carboxylic acid **4** as the potassium salt. Various protocols to isolate this salt or the free acid **4** were examined, resulting only in very low yields. The problem was circumvented by acidification of the reaction mixture (conc. HCl, pH < 1), followed by solvent removal under reduced pressure. The resulting crude, solid, dihydrochloride of **4** was then heated with excess $SOCl_2$ in chlorobenzene (≈120 ºC, cat. DMF, 3–4 h) to form the acid chloride, followed by *in situ* treatment with excess methanol (at ≈20 ºC). After solvent removal and dry flash chromatography, the anilino-ester **5** was obtained in 40–45 % yield (for 3 steps).

TABLE I. Optimization of the Strecker-type condensation of piperidone **1**

Aniline/mol %	Solvent#	Acid	KCN/mol %	*t*/ºC	time / h	Isolated yield/%
120	MeOH	AcOH (2eq)	200	0–20	48	0–5
400	MeOH	AcOH (10 eq)	400	0–20	48	20–30
400	CH_2Cl_2	AcOH (30–50 eq)	400	0–20	48	45–55
400	AcOH	AcOH (50 eq)	400	0–20	48	45–55
400	AcOH	AcOH (50 eq)	400	0–20	7 days	≈60
400	CH_2Cl_2	AcOH (30–50 eq)	400	0–50	48	85–95

the use of molecular sieves 4A did not affect the yields substantially

The *N*-acylation of anilino-ester **5** was examined with various solvents and reagents. As a result of steric hidrance and low nucleophilicity of the aromatic amino group, the reaction is slow and often accompanied by decomposition. Various solvents and reagents were tested, usually resulting in lower yields or side products. Thus, with propionyl chlo-

ride in boiling CH_2Cl_2, the acylation practically did not proceed while in chlorobenzene (100–120 ºC) it resulted in massive decomposition. Similarly, the addition of pyridine or DMAP yielded numerous side products, while propionic anhydride at lower temperatures (< 100 ºC) was an ineffective acylating agent. In the boiling anhydride, however, gross decomposition occurred. Finally, acceptable yields and purity of the anilido-ester **6** were obtained using propionyl chloride (3 eq.), in boiling dichloroethane (80 ºC, 4–5 h) with the gradual addition of triethylamine (1 eq.). The product was isolated and recrystallized from methanol as the monooxalate salt (70–80 % yield of the pure free base).

In the final step of the synthesis, catalytic debenzylation of the anilido-ester **6** was examined using a Parr hydrogenation apparatus and varying amounts of 10 % Pd/C as catalyst. Initially, hydrogenolysis failed to proceed in the absence of acid. Thus, no appreciable reaction was observed in methanol, ethanol or ethyl acetate at 20–50 ºC (10 % Pd/C, 4–5 atm H_2, 2–12 h), possibly due to catalyst poisoning. Similarly, transfer hydrogenolysis with ammonium formate (at atmospheric pressure) yielded only negligible amounts of the desired product. The addition of acetic acid dramatically improved the yields and the reaction rate, however the obtained anilido-ester **7** was substantially contaminated with side products. A number of solvent systems were examined as summarized in Table II. Optimal yields, purity and reaction rate were achieved in a H_2O/AcOH mixture (3:2), in the presence of ≈5 eq. of HCl. Apparently, the purity of the product is substantially improved at low pH values, (< 1), in aqueous medium.

TABLE II. Optimization of the *N*-debenzylation procedure of the anilido-ester **6**

	Conditions: solvents; temp.; time; pressure	Catalyst 10 % Pd-C/wt. %	Isolated yield / %	Purity (GC; TLC; ^{1}H NMR)/%
1	HCO_2NH_4; MeOH; 24 h; 20 ºC; 1 atm	100	10–15	–
2	H_2·MeOH or EtOH or EtOAc; 5 h; 20–50 ºC; 4–5 atm	50–100	0	
3	H_2; MeOH/AcOH (99:1); 24 h; 20ºC; 3–4 atm	10	80–90	85
4	H_2; (EtOH or *i*-PrOH)/(AcOH(99:1); 24 h; 20 ºC; 3–4 atm	10	80–90	85–90
5.	H_2; AcOH(glac.); 4–6 h; 20 ºC; 3–4 atm	10	> 90	90
6.	H_2; AcOH /H_2O (4:6); ≈ 500 mol% HCl; 3–4 h; 20 ºC; 3–4 atm	10	» 95	96–98

All the synthesized compounds were fully characterized by instrumental methods, Table III, and the purity confirmed by capillary GC and tlc. (The data are given in the experimental section).

In conclusion, an efficient and optimized procedure for the synthesis of 4-[(1-oxopro-

pyl)phenylamino]piperidine-4-carboxylic acid methyl ester (**7**) has been developed. A useful protocol for a Strecker-type synthesis has been disclosed which is applicable to sterically unhindered ketones including piperidones. Finally, it was established that catalytic *N*-debenzylation of tertiary amines proceeds rapidly, selectively and quantitatively in aqueous medium, at pH < ≈ 1.

EXPERIMENTAL

All solvents and reagents used in the experiments were reagent grade and additionally purified and dried as appropriate. Molecular sieves (4A) were activated at 350 ºC (12 h), transferred to a steel container while hot and kept tightly closed. Methanol, *i*-PrOH, CH_2Cl_2 $(CH_2Cl)_2$, DMF, EtOAc, PhCl and hexane were dried over 4A sieves and distilled prior to use. Triethylamine was distilled from KOH. Propylene glycol was distilled (water aspirator vacuum) and the first 10 % of the distillate discarded. Aniline was distilled from Zn/HCl (water aspirator vaccum) and dried over 4A sieves. Acetic acid was fractionally distilled from $KMnO_4$. Thionyl chloride was distilled. Silica gel 60, ICN Pharmaceuticals, particle size 10–18 µm was used for dry flash chromatography. Other reagents were used as received.

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian Gemini spectrometer at 200 MHz and 50 MHz respectively, in $CDCl_3$, relative to Me_4Si. The IR spectra were recorded on a Perkin Elmer FTIR 1725X spectrometer. The mass spectra were obtained on a Math Finnegan instrument, model 8230, using iso-butane for chemical ionization. The gas chromatograms were recorded on a Varian 3400 instrument, using capillary columns DB-1 and DB-5. The thin layer plates were coated with Merck silica gel 60, HF254, 0.25 mm thickness.

*1-Benzyl-4-phenylaminopiperidine-4-carbonitrile (**2**)*

WARNING: HCN is an extremely lethal and volatile liquid/gas (b.p. ≈25 ºC). The reaction must be perfomed under a very efficient hood to prevent exposure to HCN. During the work-up procedure at least, it is mandatory to wear a gas-mask fitted with an appropriate filter. The residual solution, containing KCN must be slowly treated with a large excess of commercial sodium hypochlorite solution prior to disposal.

The apparatus consisted of a single necked, round bottomed flask (1L) equipped with a reflux condenser and pressure equalizing dropping funnel fitted atop the condenser. The funnel was capped with a rubber septum connected *via* a needle and tubing to a mercury filled bubbler. The flask was charged with piperidone **1** (0.10 mol; 18.9 g), aniline (0.40 mol; 37.2 g), solid KCN (0.40 mol; 26.0 g) and CH_2Cl_2 (200 mL). The mixture was cooled (≈5 ºC, ice-acetone bath) and stirred magnetically. The dropping funnel was charged with AcOH (3.0 mol; 180 mL) which was added dropwise, over an ≈3 h period, to the heterogeneous reaction mixture. The stirring was continued, and the mixture was heated (oil bath) at 45–50 ºC for 24 h. Some HCN evolved through the bubbler. After cooling to ≈20ºC, the contents were poured (hood, gas-mask) onto crushed ice (500 g), then partially neutralized (cold 25 % NaOH solution, 3.0 mol; 120 g). The neutralization was completed with K_2CO_3 (40 % solution , 1.0 mol; 138 g) to pH≈10. The layers separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 300 mL). The combined organic layers were concentrated (rotatory evaporator) and the liquid residue dissolved in *i*-PrOH (250 mL). After 48 h (at –10 ºC) the crystallized anilino-nitrile **2** was isolated by filtration, washed with *i*-PrOH (2 X 50 mL cooled at –20 ºC) and dried under reduced pressure. Yield: 26.2 g (90 %); white crystals. M.p. 105 ºC (lit.[5e] 105 ºC).

IR: 3405, 2954, 2227, 1602, 1511, 1459, 1319, 1283, 1267, 1174, 1158, 748, 698; ^{1}H-NMR: 1.92 (*td*, J_1 = 3.6, J_2 = 10.8, 2H), 2.29–2.53 (*m*, 4H), 2.79–2.85 (*m*. 2H), 3.56 (*s*, benz. CH_2), 3.64 (*s*, NH) 6.88–6.95 (*m*, $3H_{Ar}$) 7.20–7.33 (*m*, $7H_{Ar}$); ^{13}C-NMR: 36.09, 49.27, 59.06, 62.58, 117.78, 120.93, 127.26, 128.96, 129.00, 129.31, 134.02, 138.00, 143.29; MS: 292 (M+1, 80), 265 (50), 264 (M – HCN, 100).

*1-Phenethyl-4-phenylaminopiperidine-4-carbonitrile (**2a**)*

Compound **2a** was prepared by the same protocol as compound **2**, utilizing 1-phenethylpiperidin-4-one (**1a**) (20.3 g; 0.1 mol) and the same amounts of the other reagents and solvents. Yield: 28.1 g (92 %); white crystals. M.p. 118–119 ºC (lit.[5e] 120 ºC).

IR: 3375, 2964, 2235, 1605, 1527, 1499, 1346, 1324, 1106, 751, 704, 694; ^{1}H-NMR: 1.93 (*td*, J_1 = 3.0, J_2 = 13.2, 2H), 2.34–2.41 (*m*, 2H), 2.52 (*td*, J_1 = 2.2, J_2 = 13.0, 2H), 2.62–2.71 (*m*, 2H), 2.76–2.84 (*m*, 2H), 2.85–2.94 (*m*, 2H), 3.67 (*s*, NH), 6.85–7.0 (*m*, 3H_{Ar}), 7.15–7.38 (*m*, 7H_{Ar}); ^{13}C-NMR: 33.66, 36.05, 49.28, 53.00, 59.86, 117.74, 120.58, 120.92, 126.13, 128.41, 128.64, 129.30, 139.99, 143.25; MS: 597 (2M + 1, 0.4), 306 (M+1, 71), 278 (M – HCN, 100).

*1-Benzyl-4-phenylaminopiperidine-4-carboxylic acid amide (**3**)*

The nitrile **2** (25.0 g, 86 mmol) was dissolved in conc. H_2SO_4 (250 mL) at ≈20 ºC, in a single necked flask protected with a $CaCl_2$ trap. The mixture was stirred magnetically for 24 h, then the precipitated dihydrogensulphate salt of amide **3** was collected by filtration. The precipitate was dissolved in water (300 mL) and titrated with NaOH (25 % solution) to pH > 10. The separated free amide **3** was filtered off, washed with water and air dried. Yield: 22.1 g (83 %). An analytical sample was prepared by recrystallizing from *i*-PrOH. M.p. 167 ºC (lit.[5e] 167.5 ºC).

IR: 3445, 3355, 3058, 2959, 2810, 1678, 1605, 1519, 1499, 1473, 1443, 1365, 1342, 1326, 1308, 1266, 1196, 1185, 1169, 1154, 1113, 1063, 745, 734, 697; ^{1}H-NMR: 1.93 (*d*, *J* = 11.8, 2H), 2.11 (*t*, *J* = 13.4, 2H), 2.34 (*td*, J_1 = 2.6, J_2 = 12.0, 2H), 2.73–2.79 (*m*, 2H), 3.50 (benz. CH_2), 4.02 (NH), 5.30 ($CONH_2$), 6.63 (*dd*, J_1 = 0.8, J_2 = 8.8, 2H_{Ar}). 6.81 (*t*, *J* = 7.2, 1H_{Ar}), 7.15–7.32 (*m*, 7H_{Ar}); ^{13}C-NMR: 31.21, 48.65, 58.10, 62.85, 116.09, 119.15, 127.10, 128.23, 128.98, 129.14, 137.96, 143.67, 178.65; MS: 310; M+1 (100).

*1-Benzyl-4-phenylaminopiperidine-4-carboxylic acid methyl ester (**5**)*

A single necked flask equipped with a reflux condenser was charged with amide **3** (20.0 g, 65 mmol), solid 85 % KOH (260 mmol, 17.0 g), 18-crown-6-ether (5-mmol, 1.3 g) and 1,2-propylene glycol (150 mL). (Note: the ground glass joint must be protected by Teflon tape to prevent sticking). The mixture was stirred magnetically and heated (oil or air bath) to reflux for 24 h, then cooled to room temperature. Conc. HCl (≈40 mL) was added dropwise, with stirring, to pH < 1 (indicator paper). The solvent was evaporated (rotatory evaporator, oil bath, water aspirator) and the last traces removed with an oil pump. The solid residue, the dihydrochloride of anilino-acid **4** mixed with KCl, was transferred to a flask fitted with a reflux condenser and $CaCl_2$ trap, suspended in chlorobenzene (150 mL), followed by the addition of $SOCl_2$ (0.26 mol, 19.3 mL) and DMF (1.0 mL, 14 mmol). The mixture was stirred magnetically and heated at reflux for 5 h (SO_2 and HCl evolution) whereupon the color changed from tan to dark brown. After cooling to room temperature, MeOH (50 mL) was added slowly (vigorous gas evolution) and the stirring continued for 1 h. The heterogeneous mixture was concentrated (rotatory evaporator, oil bath), then treated with K_2CO_3 (25 % solution) to pH > 10. The mixture was extracted with toluene (3 X 100 mL), the combined extracts concentrated (rotatory evaporator) and the residue purified by dry flash chromatography (hexane/EtOAc, gradient 100/0 to 70/30). The pale yellow anilino-ester **5** was isolated as a viscous oil which crystallized upon standing. Yield: 8.6 g (41 %). M.p. 105 ºC (lit.[5e] 105 ºC).

IR: 3404, 3085, 3057, 3023, 2948, 2812, 1732, 1602, 1500, 1467, 1453, 1434, 1397, 1368, 1346, 1319, 1297, 1266, 1233, 1187, 1148, 1120, 1085, 1067, 1026, 1003, 746, 698. ^{1}H-NMR: 1.98–2.06 (*m*, 2H), 2.24 (*td*, J_1 = 3.4, J_2 = 13, 2H), 2.40 (*td*, J_1 = 2.6, J_2 = 10, 2H), 2.65 (*m*, 2H), 3.50 (CH_2 benz), 3.67 (CH_3), 3.86 (NH), 6.56 (*dd*, J_1 = 1.0, J_2 = 6.8, 2H_{Ar}), 6.74 (*t*, *J* = 7.2, 1H_{Ar}), 7.10–7.32 (*m*, 7H); ^{13}C-NMR:32.89, 48.85, 52.27, 58.19, 62.96, 115.23, 118.57, 127.05, 128.24, 129.11, 138.30, 144.93, 175.99; MS: 325 (M+1, 5), 324(M^+, 13), 231 (57), 172 (85), 91 (100).

*1-Benzyl-4-(N-phenylpropionylamino)piperidine-4-carboxylic acid methyl ester (**6**)*

To a flask fitted with a reflux condenser, pressure equalizing funnel and $CaCl_2$ trap were added anilino-ester **5** (8.0 g, 25 mmol), dichloroethane (50 mL) and propionyl chloride (75 mmol, 6.5 mL). The mixture was heated to reflux and stirred magnetically for 3 h, then Et_3N (25 mmol, 3.5 mL) was added gradually (over 1 h) and the stirring continued for 2 h. The mixture was cooled to 20 ºC, methanol (5 mL) was added and, after 1 h, the contents were poured into a 25 % K_2CO_3 solution (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (sieves 4A), filtered and concentrated. The residual oil was dissolved in *i*-PrOH (25 mL) and added gradually, with stir-

ring, to a solution of anh. oxalic acid (25 mmol, 2.25 g) in *i*-PrOH (25 mL). The solution was cooled (–20 ºC, 12 h), the precipitated oxalate salt collected by filtration and recrystallized from *i*-PrOH (50 mL). The free base was liberated by adding the solid oxalate salt into a 25 % K_2CO_3 solution (50 mL), extracted (2 × 50 mL CH_2Cl_2), dried (sieves 4A) and concentrated to afford **6**. Yield: 7.3 g (77 %) as a pale yellow oil.

IR: 3061, 3028, 2975, 2939, 2850, 1742, 1657, 1595, 1492, 1451, 1384, 1355, 1297, 1256, 1216, 1191, 1128, 1095, 1067, 742, 707; ^{1}H-NMR: 0.95 (J = 7.4, CH_3), 1.63 (td, J_d = 4.2, J_t = 13.0, 2H), 1.88 (q, J = 7.6, CH_2), 2.26 (d, J = 13.0, 2H), 2.42 (dd, J_1 = 2.2, J_2 = 11.4, 2H), 2.56–2.62 (m, 2H), 3.43 (s, benz. CH_2), 3.78 (s, CH_3), 7.13–7.43 (m, 10H_{Ar}); ^{13}C-NMR: 8.94, 28.84, 33.34, 49.58, 51.82, 62.62, 62.74, 125.12, 126.76, 127.96, 128.03, 128.45, 128.87, 129.11, 130.49, 138.14, 139.28, 173.88; MS: 381 (M+1, 100), 438 (M+58, 10).

4-[(1-oxopropyl)phenylamino]piperidine-4-carboxylic acid methyl ester (7)

Anilido-ester **6** (5.0 g, 13 mmol) was dissolved in H_2O/AcOH mixture (6:4, 50 mL) followed by the addition of conc. HCl (5.6 mL) and 10 % Pd/C (0.3 g). The mixture was transferred to a hydrogenation flask and fitted into a Parr hydrogenation apparatus. After hydrogen purging (3 times), shaking was continued for 4–5 h (20 ºC, ≈4 atm hydrogen pressure) whereupon a minimal drop in the pressure was observed. The reaction mixture was filtered, poured onto crashed ice (100 g) and titrated with 20 % NaOH solution to pH≈10 (indicator paper). The alternative workup involves concentration of the reaction mixture (rotatory evaporator) followed by neutralization (20 % NaOH solution to pH≈10). After extraction with CH_2Cl_2 (3 × 50 mL), the combined extracts were dried (anh. K_2CO_3), fitered and concentrated to afford pure anilido-ester **7** as a single product. Yield: 3.6 g (95 %); pale yellow oil.

IR: 3313, 3061, 2973, 2941, 2877, 1740, 1660, 1595, 1491, 1451, 1379, 1353, 1325, 1296, 1254, 1220, 1188, 1138, 1103, 1070, 999, 961, 757, 731, 708; ^{1}H-NMR: 0.96 (t, J = 7.6, CH_3), 1.41–1.56 (m, 2H), 1.86 (t, J = 7.4, CH_2), 1.96 (NH), 2.23–2.29 (m, 2H), 2.84 (dt, J_d = 12.2, J_t = 4.6, 2H), 2.97 (td, J_t = 13.0, J_d = 2.6, 2H), 3.81 (s, CH_3), 7.19–7.48 (m, 5H_{Ar}); ^{13}C-NMR: 9.07, 28.99, 34.40, 42.77, 52.06, 63.07, 128.65, 129.29, 130.58, 139.32, 173.89, 174.08; MS: 291 (M+1, 100), 348 (M+58, 15).

ИЗВОД

ОПТИМИЗОВАНА СИНТЕЗА ЗНАЧАЈНОГ ФАРМАЦЕУТСКОГ ИНТЕРМЕДИЈЕРА МЕТИЛ 4-[(1-ОКСОПРОПИЛ)ФЕНИЛАМИНО]ПИПЕРИДИН-4-КАРБОКСИЛАТА

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У овом раду развијена је ефикасна синтезаметил 4-(фенил-пропионил-амино)-пиперидин-4-карбоксилата (**7**), пролазећи од 1-бензил пиперидин-4-он-1 (**1**). Једињење **7** је кључни интермедијер у синтези нове генерације високо активних наркотичких аналгетика, као што је ремифентанил а такође и нових класа аналога фентанцла. У оптимизованој Стрецкер-овој кондензацији приперидона **1** са анилином и HCN, добијен је анилино-нитрил **2** (ї 90 % принос) чијом је селективном хидролизом помоћу конц. H_2SO_4 постао анилино-амид **3**. Интензивном базном хидролизом овог интермедијера, закишељавањем а затим сукцесивно реакцијом са $SOCl_2$ и MeOH, синтетисан је анилино-естар **5** (≈40–45 % принос у 3 фазе). *N*-ацеловањем анилино-естра **5** са пропионил хлоридом постао је анилидо-естар **6** (≈70–80 % принос). У последњом фази синтезе извршена је оптимизација каталитичког *N*-дебензиловања анилидо-естра **6** до финалног производа **7**, у приближно квантитативном приносу.

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