1 PERKIN

The synthesis of lactam analogues of fentanyl

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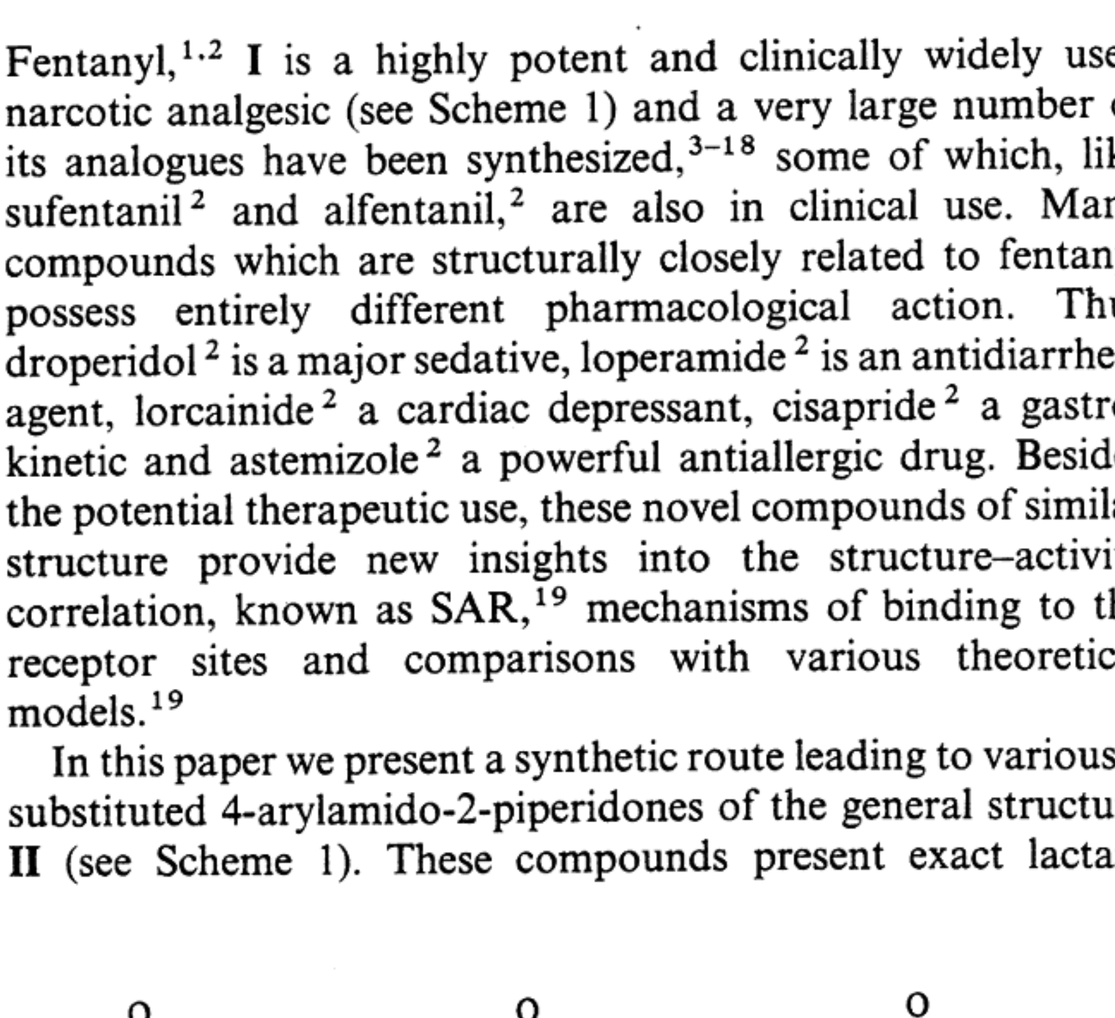
Fentanyl, sufentanil and alfentanil are clinically widely used anaesthetics and are structurally related to drugs with entirely different pharmacological activity such as droperidol, loperamide and lorcainide, *etc.* Therefore, in order to test their pharmacological activity, lactam analogues of fentanyl, a novel class of compounds, have been synthesized. In the first step, various primary amines have been selectively added to 1 equiv. of α,β-unsaturated esters, to afford the β-amino esters. *N*-Acylation of these intermediates with dimethyl malonate yields the amido esters, which have been further subjected to Dieckmann-type cyclization, to produce the corresponding 3-methoxycarbonylpiperidine-2,4-diones. The cyclization has been effected under phase-transfer conditions, utilizing potassium carbonate as base and 18-crown-6 as catalyst. This eliminates the need for strong and hazardous bases such as molten sodium or NaH. In the next step, acid hydrolysis and decarboxylation furnish the substituted piperidine-2,4-diones in good yields, as pure products. Alkylation of the *N*-phenethylpiperidine-2,4-dione with methyl iodide and potassium carbonate in DMSO gives the 3,3-dimethyl derivative. The alkylation procedure is also applicable to other alkylating agents. Reductive amination of the prepared piperidine-2,4-diones with aniline and $NaBH_3CN$ in buffered methanol gives the corresponding pure 4-anilino-2-piperidones. The lactam function can be readily reduced ($NaBH_4$–BF_3·Et_2O), as exemplified with the 3,3-dimethyl derivative, thus providing access to additional fentanyl analogues, not readily accessible by other routes. The synthesis is completed by *N*-acylation of the anilines with propionyl chloride using triethylamine as base. The prepared 4-propionanilido-2-piperidones and 4-propionanilidopiperidines are expected to provide useful structure–activity relationship data in the pharmacological studies.

Fentanyl,[1,2] **I** is a highly potent and clinically widely used narcotic analgesic (see Scheme 1) and a very large number of its analogues have been synthesized,[3–18] some of which, like sufentanil[2] and alfentanil,[2] are also in clinical use. Many compounds which are structurally closely related to fentanyl possess entirely different pharmacological action. Thus droperidol[2] is a major sedative, loperamide[2] is an antidiarrheal agent, lorcainide[2] a cardiac depressant, cisapride[2] a gastrokinetic and astemizole[2] a powerful antiallergic drug. Besides the potential therapeutic use, these novel compounds of similar structure provide new insights into the structure–activity correlation, known as SAR,[19] mechanisms of binding to the receptor sites and comparisons with various theoretical models.[19]

In this paper we present a synthetic route leading to variously substituted 4-arylamido-2-piperidones of the general structure **II** (see Scheme 1). These compounds present exact lactam analogues of fentanyl and to our knowledge have not been reported in the literature. Although neutral compounds, they can be readily administered as emulsions, using the fentanyl free base as a standard. The same general method also provides access to the substituted fentanyl analogues of the structure **III**, not readily accessible by other routes.

Examination of the target structures by retrosynthetic analysis,[20] revealed several possible synthetic approaches, mainly *via* *N*-alkylpiperidine-2,4-diones or, alternatively, *via* oxo or halogeno substituted pyridines. The latter method was rejected, since the appropriately substituted pyridines are often unavailable.

While a number of *N*-alkylpiperidine-2,4-diones are known, prepared by various multi-step routes,[21–38] they are often obtained in low overall yields. However, an unusual, Dieckmann-type condensation, described by a Japanese group,[35] was examined in detail in this research. The requisite amido esters **2a–d** were prepared as shown in Scheme 2 and Table 1. In the first step, primary amines (2-phenethylamine and cyclohexylamine) were selectively condensed with 1 mol equiv. of an α,β-unsaturated ester (methyl acrylate, methyl crotonate, methyl methacrylate, methyl hex-2-enoate, *etc.*) to give amino esters of the structure **1** in 75–85% yield, after vacuum distillation. This procedure required careful optimization. Although the bis adducts were occasionally side products with methyl acrylate, they could be minimized by running the reaction in more dilute solutions and/or at lower temperatures. The addition is efficiently catalysed by carboxylic acids. Methyl acrylate or methyl crotonate required no catalyst and the addition of 1 mol% of AcOH led to the bis adducts. In contrast, methyl methacrylate or methyl hex-2-enoate failed to react at all unless *ca.* 20 mol% of acetic acid was added. Four



I Fentanyl

II Lactam analogues of fentanyl

III Substituted analogues of fentanyl

Scheme 1

Table 1 Various cyclization–decarboxylation procedures attempted with the amido ester **2a**

Cyclization[a] method	Isolated intermediate	Method of hydrolysis/decarboxylation	Yield of the lactam **3a** (%)
Xylene–NaH or KH	Na or K-salt **2.1**	10% ox. acid[b]	33
Toluene–NaH	Na or K-salt **2.1**	10% ox. acid	40–45
Cyclohexane–NaH	Na or K-salt **2.1**	10% ox. acid	50–53
Toluene–K_2CO_3, 18-crown-6 (cat.)	Free acid **2.2**	10% ox. acid	75–80
NaH–THF	Decomp.	—	
Na-*tert*-pentoxide–toluene	Decomp.	—	

[a] All the cyclizations were conducted in boiling solvents. [b] Similar yields obtained with acetic acid, but neutralization was necessary before extraction.

representative examples of the prepared amino esters, **1a–d**, used in the subsequent steps, are given in Table 2. Some of these products, β-amino esters, may be alternatively obtained by condensing β-keto esters with amines followed by $NaBH_3CN$ reduction of the enamine formed.[39] Thus, when methyl acetoacetate was condensed with phenethylamine and then reduced, the amino ester **1c** was obtained in 93% overall yield. Since β-keto esters are readily prepared by acylation of the Meldrum's acid[40] or dilithium salt of ethyl hydrogen malonate,[41] this may provide access to a great variety of β-amino esters.

The second step involved *N*-acylation of the selected amino esters **1a–d** with dimethyl malonate or ethyl malonyl chloride.[35] Since the chloride had to be prepared separately[42] (*ca.* 40% overall yield) and the acylation required addition of triethylamine as a base, dimethyl malonate was preferred as the reagent. Also, it gave the purer products, **2a–d**, in *ca.* 90% yield. The reaction is moderately catalysed by DMAP,[43] (3–5 times rate increase, 10 mol%) but it does not proceed below *ca.* 100 °C. Occasionally, a small amount of a dimer (dimethyl malonate condensed with 2 mol equiv. of an amino ester, *ca.* 5%) is formed, however it can be rapidly removed by dry flash chromatography.[44] All four amido esters existed as pairs of rotatory isomers (*E* and *Z*) as revealed by ^{13}C NMR and ^1H NMR spectroscopy (at 20 °C) in a 1:2 ratio (see Table 3).

The original cyclization procedure, leading to *N*-alkyl-3-methoxycarbonylpiperidine-2,4-diones of the structure **2.2**, required powdered sodium in xylene.[35] The subsequent acetic acid hydrolysis and decarboxylation, furnished the corresponding *N*-alkylpiperidine-2,4-diones of the structure **3** in moderate overall yields. In this research, various bases and solvents were tested, using the amido ester **2a** as a model, in order to improve the yields and to simplify the cyclization step. Thus, bases such as NaH, KH, sodium or potassium *tert*-pentoxide in toluene or xylene, were examined, resulting only in low to modest yields of the product. More polar solvents like THF caused complete decomposition while less polar solvents like cyclohexane gave improved yields with NaH. In all instances the cyclization was carried out in boiling solvents, since at lower temperatures, various amounts of starting material were recovered. Surprisingly, even powdered KOH in DMSO (at 20 °C) led to a cyclization product, albeit in poor yield. When K_2CO_3 was used as a base (5–8 equiv.), a slow cyclization was observed in boiling toluene or xylene, while the addition of phase-transfer catalysts, 18-crown-6 or trioctyl(methyl)ammonium chloride (Aliquat 336) in 5–10 mol%, resulted in a dramatic rate acceleration, the cyclization being completed in a few hours. The crown ether was found to be more efficient and it was used in all further experiments. Since it was shown that phase-transfer catalysts probably cannot solubilize K_2CO_3[45] it is likely that the first step, deprotonation, takes place between the phases (solid–liquid). Hence, the slow step with strong bases is the cyclization, while with K_2CO_3 it is probably the deprotonation step. The results of this optimization are summarized in Table 1.

An attempt was made to replace the intermediate of the structure **2** with an acetamide, obtained by the acetylation of **1a** with acetic anhydride. However, when it was subjected to the cyclization conditions described above, only phenethylacetamide was isolated, indicating that β-elimination was the only reaction.

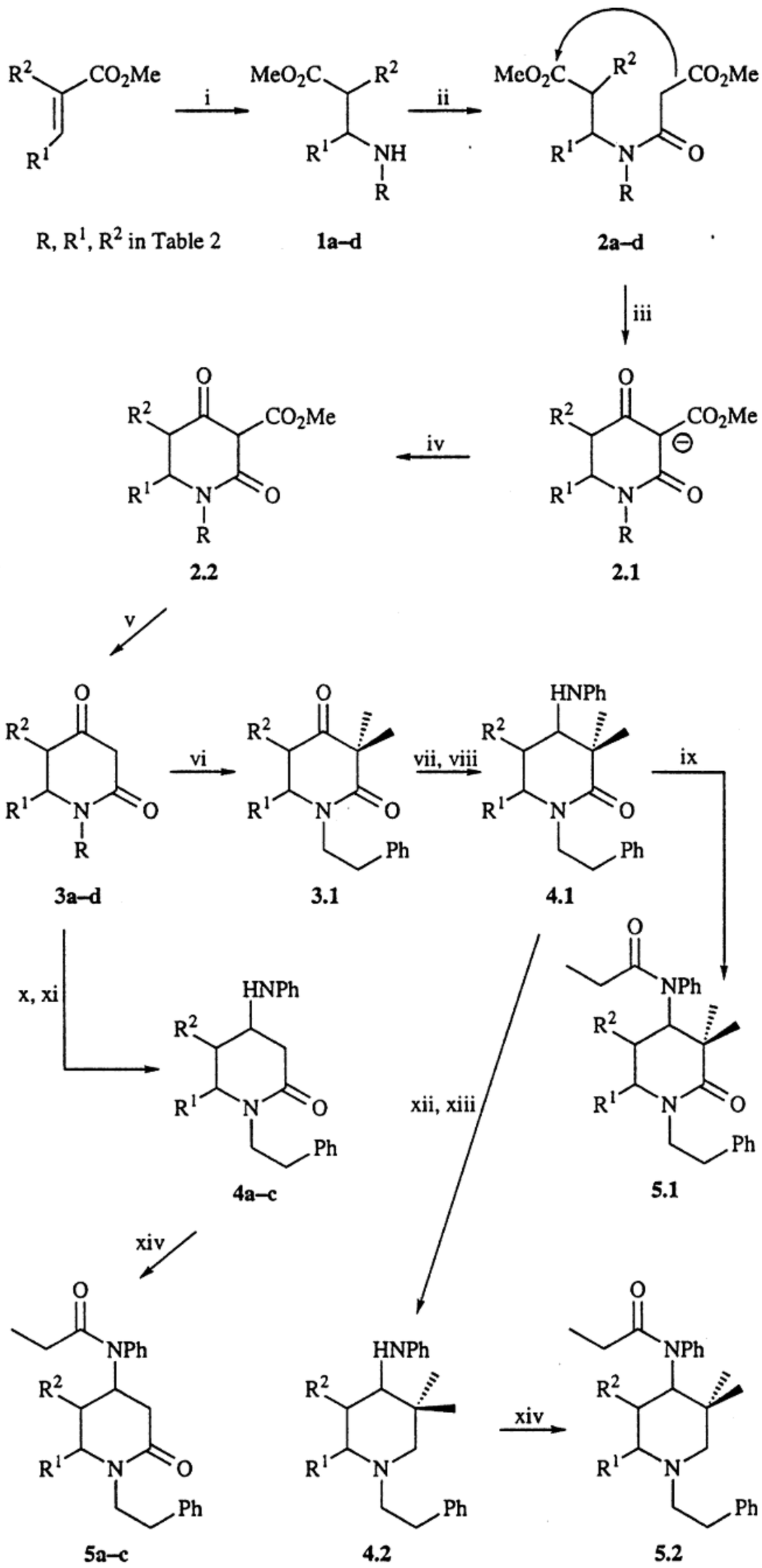
It is interesting to note that the enolate anion resulting from the amido ester **2**, although highly resonance stabilized, is still nucleophilic enough to be acylated by a relatively weak electrophile such as a methoxycarbonyl group. As with other Dieckman condensations, the reaction is probably reversible with the equilibrium shifted completely towards the highly stabilized product **2.1**.

Using the aforementioned phase-transfer conditions, the free acid **2.2** (estimated pK_a 4–6) was obtained after careful acid hydrolysis of the salt **2.1** (dil. HCl, 0 °C, 5 min), the spectra of which were satisfactory. Of the various conditions examined for acid hydrolysis–decarboxylation of the free acid **2.2** to the keto lactam **3**, boiling aqueous oxalic acid was found to afford almost quantitative yields.

The method used to prepare variously substituted *N*-alkylpiperidine-2,4-diones, **3**, described here is efficient, simple, inexpensive and suitable for large-scale preparations. It also eliminates the need for hazardous reagents like NaH or molten sodium. It should be noted that some *N*-alkylpiperidine-2,4-diones, such as methyprylon[25] and piperidione[27] possess pharmacological (mainly sedative) activity on their own and that a number of such novel compounds may be prepared by this procedure.

Since they are active methylene compounds, keto lactams of the structure **3** could react with various electrophiles under basic conditions.[46,47] To our knowledge, no alkylation of these substrates has been reported in the literature. The alkylation using bases such as NaH or Bu^tOK is complicated by enolate decomposition or *O*-alkylation, as observed in this research. However, the general procedure for cycloalkylation of active methylene compounds, described by a Russian group,[48] effected an efficient 3,3-dimethylation with methyl iodide and K_2CO_3 in DMSO. A small amount (*ca.* 5%) of *O*-alkylated product was removed by chromatography. The procedure is also applicable to other alkylating agents, like butyl iodide or 1,2-dibromoethane and it is currently being examined.

In the next stage, the keto lactams **3a–c** were subjected to the reductive amination with aniline (2.0 equiv.), using $NaBH_3CN$ as reducing agent in buffered methanol. Solid $NaH_2PO_4 \cdot H_2O$ was found to be an efficient buffer, with the reaction mixture kept at pH ~5. The best yields (85–90%), were obtained by stirring the mixture for 3–5 h without $NaBH_3CN$ added, in order to complete the formation of the enamine (according to TLC). Upon the addition of 1.2 equiv. of the reducing agent, the reduction was completed in 15–30 min as monitored by TLC. The standard work-up procedure involved acidification, basification, removal of the excess of aniline *in vacuo* and precipitation of the residue as the monooxalate salt. Alternatively, aniline also could be removed by addition of Et_2O, after basification, since the anilino lactams of the structure **4** are poorly soluble in this solvent. In the case of **3b**



Scheme 2 Synthesis of lactam analogues of fentanyl. *Reagents and conditions:* i, RNH_2, MeOH; ii, $CH_2(CO_2Me)_2$, PhMe, heat; iii, K_2CO_3PhMe, heat, 18-crown-6; iv, dil. HCl, 0 °C; v, $(CO_2H)_2$, H_2O, heat, $-CO_2$, MeOH; vi, MeI (2.2 equiv.), K_2CO_3, DMSO; vii, $PhNH_2$, xylene, heat; viii, $NaBH_3CN$, MeOH, pH 5; ix, EtCOCl, Et_3N, $(CH_2Cl)_2$, heat; x, $PhNH_2$, MeOH; xi, $NaBH_3CN$, MeOH, pH 5; xii, $NaBH_4$, $BF_3{\cdot}OEt_2$, diglyme, 0–80 °C; xiii, dil. HCl, reflux; xiv, EtCOCl, Et_3N.

and **3c**, two diastereoisomeric amines were formed, in the ratios 15:85 and 25:75, respectively, indicating a fair degree of stereoselectivity. Since they could not be discriminated by GC or TLC, their ratios were determined by ^1H NMR or ^{13}C NMR. Under the same conditions, 3,3-dimethyl keto lactam **3.1** failed to form an imine presumably because of steric restrictions and a two-step procedure was used instead. The imine, prepared first by condensing the reactants in xylene, was reduced with $NaBH_3CN$ in methanol at pH 5 (85% yield).

The synthesis was completed by acylation of the anilino lactams **4a–c** with propionyl chloride at 0–20 °C, in CH_2Cl_2 and using triethylamine as base. The corresponding propionanilides **5a–c** were obtained in nearly quantitative yields. Anilino lactam **4.1** reacted only slowly, and the acylation was effected in boiling dichloroethane. In the case of **5b** and **5c**, *cis*/*trans* mixtures were obtained, however it was possible to separate completely the more abundant (less polar) isomers by simple dry flash chromatography. The stereochemistry could not be determined from the available spectroscopic data.

The general synthetic procedure described here also permits the preparation of variously substituted, particularly 3,3-dialkylated, reduced analogues of fentanyl. Thus, for example, the reduction of 4-anilino lactam **4.1** with diborane,[49] generated *in situ* from $NaBH_4$ and $BF_3{\cdot}Et_2O$ in diglyme or THF afforded 84% of the diamine **4.2** as a single product. The 3,3-dimethylfentanyl, **5.2** was then prepared by propionylation, in analogy to **5.1**.

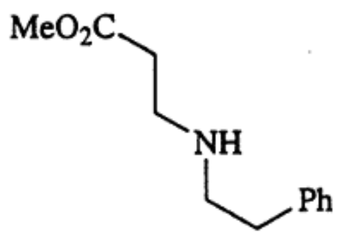
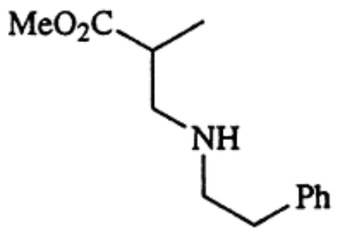
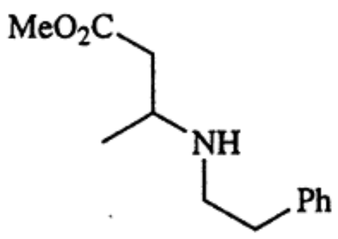
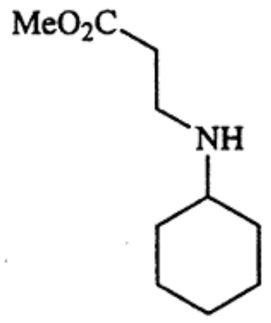
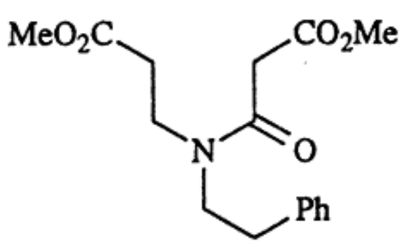
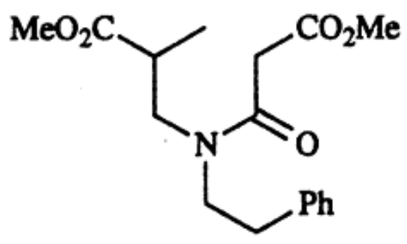
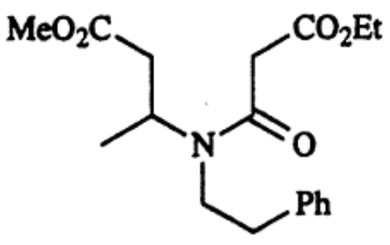
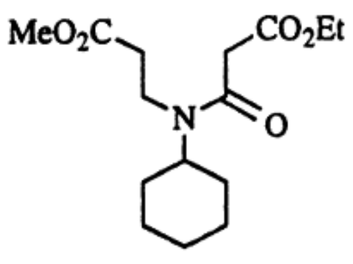
All of the prepared fentanyl analogues are currently being examined for their pharmacological activity.

The structures and purity of the prepared compounds were determined by instrumental methods: ^1H NMR, ^{13}C NMR, MS, IR and GC. All the compounds were homogeneous by GC and/or TLC and gave elemental microanalyses in agreement with the structures assigned (see Table 2). Spectral data are presented in Table 3.

Experimental

Melting points were taken with a Mel-Temp apparatus. IR spectra were recorded with a Perkin-Elmer FT IR 1725X spectrometer, ^1H NMR and ^{13}C NMR spectra with Bruker spectrometer at 250 and 60 MHz, respectively, with $CDCl_3$ as internal standard. Mass spectra were recorded with a Finigan-Math instrument, model 8230, using electron impact (70 eV) and chemical ionization (isobutane) techniques. Gas chromatograms were obtained with a capillary Varian instrument, model 3400, utilizing capillary non-polar column, DB-5. Reagent grade solvents were used and further purified as appropriate. Methylene dichloride and ethylene dichloride were distilled from P_2O_5, (20 g dm^{-3}), under N_2, in an apparatus protected with a P_2O_5 trap. Methanol was dried over molecular sieves 3 Å (100 g dm^{-3}, 24 h) and then distilled from metallic Mg (10 g dm^{-3}) under Ar. THF and diglyme were distilled first from powdered KOH (50 g dm^{-3}) under Ar, in an apparatus protected with a P_2O_5 trap and then refluxed over Na–benzophenone (3 g and 1 g dm^{-3}, respectively) until a stable deep blue colouration was obtained (1–2 h) and distilled again, immediately before use, under Ar. Toluene and xylene were dried azeotropically first and then distilled from NaH (60%; 5 g dm^{-3}) under Ar. Propionyl chloride was freshly distilled under Ar, in an apparatus provided with Vigreux column and protected with P_2O_5 trap. Aniline was purified by vacuum distillation (15 Torr), from zinc dust (10 g dm^{-3}). Phenylethylamine was vacuum distilled (15 Torr) prior to use. Light petroleum (bp 30–50 °C) and cyclohexane were distilled from conc. H_2SO_4 (50 g dm^{-3}), washed with 10% aq. NaOH and water and then dried over $CaCl_2$ and distilled from NaH (5 g dm^{-3}) under Ar. Sodium hydride was used as 60% dispersion in mineral oil. DMSO was first distilled at reduced pressure (15 Torr, first 10% discarded) and then stored over activated molecular sieves 4 Å, 50 g dm^{-3}. Molecular sieves were activated at 400 °C for 12 h and then transferred whilst hot into a can which was kept tightly closed. K_2CO_3 was dried at 240 °C for 12 h and then transferred whilst hot into a can which was kept tightly closed. Ethyl chloroformylacetate[42] and 18-crown-6[50] were prepared according to literature procedures. All chromatographic purifications were performed using a dry flash technique,[44] and silica gel 12–26 μm, 60 Å, ICN Biomedicals. Thin layer plates were prepared with silica HF_{254}, Merck, Darmstadt. Ar was extra pure grade, 5 ppm O_2, 3 ppm H_2O and was further dried over molecular sieves 4 Å. Other reagents were used as supplied, by Aldrich Chemical Co., Merck Darmstadt Chemical Co. and Fluka Chemical Co. Physical constants are given in Table 2, while all spectral data are in Table 3.

Table 2 Structures, physical constants and/or elemental microanalyses of the prepared compounds

No	Compd.	yield (%)	Bp/Torr or mp	Calc. (found)
1	 **1a**	83	122/0.5	-
2	 **1b**	75	113/0.1	-
3	 **1c**	81	117/0.4	-
4	 **1d**	84	89.05	-
5	 **2a**	90	Oil	-
6	 **2b**	92	Oil	-
7	 **2c**	89	Oil	-
8	 **2d**	95	Oil	-

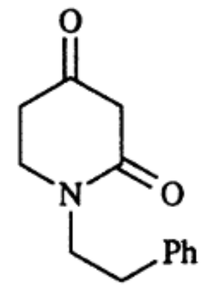
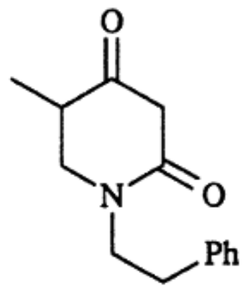
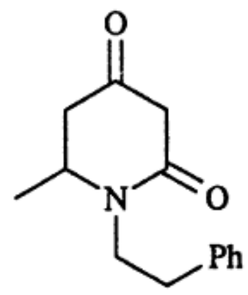
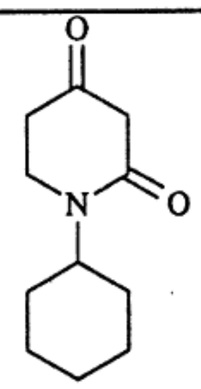
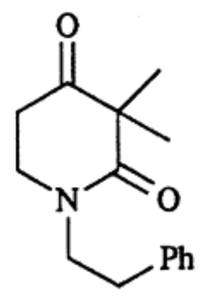
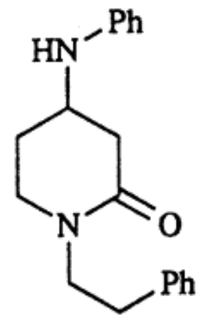
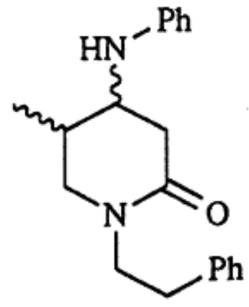
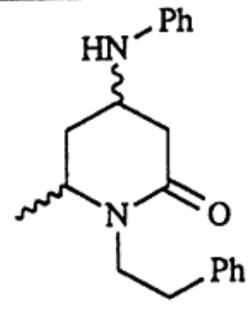
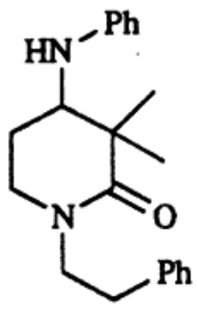
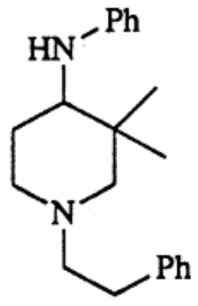
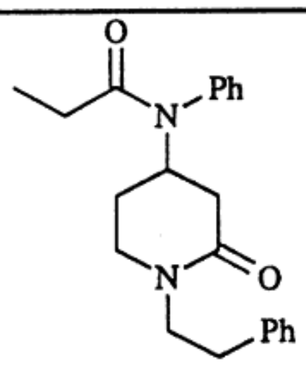
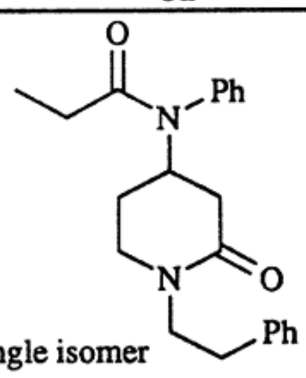
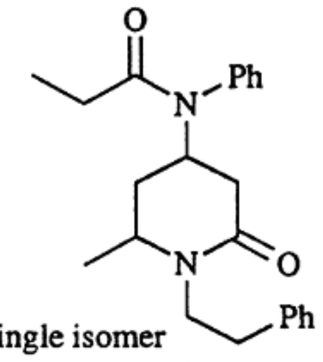
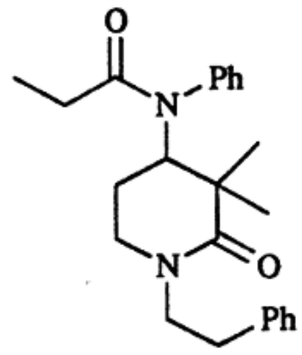
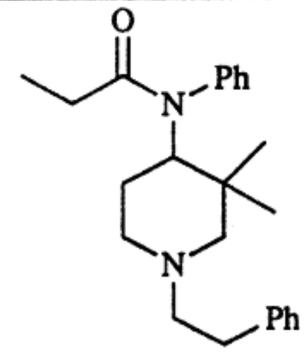
No	Compd.	yield (%)	Bp/Torr or mp	Calc. (found)
9	 **3a**	75–80	73	C 71.91 (C 71.27) H 6.91 (H 7.22) N 6.45 (N 6.69)
10	 **3b**	70–75	74.5	C 72.74 (C 72.36) H 7.35 (H 7.17) N 6.06 (N 6.43)
11	 **3c**	75	74	C 72.74 (C 72.40) H 7.35 (H 7.31) N 6.06 (N 6.27)
12	 **3d**	75	104–105	C 67.66 (C 67.42) H 8.77 (H 8.50) N 7.17 (N 7.42)
13	 **3.1**	80	71	C 73.48 (C 73.24) H 7.75 (H 7.77) N 5.71 (N 5.95)
14	 **4a**	90	109–110	C 77.56 (C 77.49) H 7.48 (H 7.54) N 9.52 (N 9.79)
15	 isomer ratio: 15:85 **4b**	86	158	C 77.93 (C 77.70) H 7.79 H 8.13 N 9.09 N 9.45
16	 isomer ratio: 25:75 **4c**	88	131-132	C 77.93 (C 77.60) H 7.79 H 8.16 N 9.09 N 9.46

Table 2 (*continued*)

No	Compd.	yield (%)	Bp/Torr or mp	Calc. (found)
17	 **4.1**	85	98.5	C 81.82 (C 81.51) H 9.08 (H 9.53) N 9.09 (N 9.52)
18	 **4.2**	84	oil	C 81.82 (C 81.51) H 9.08 (H 9.53) N 9.09 (N 9.52)
19	 **5a**	93	86	C 75.37 (C 75.43) H 7.42 (H 7.61) N 7.99 (N 8.15)
20	 single isomer **5b**	72*	137	C 75.84 (C 75.52) H 7.74 (H 8.09) N 7.69 (N 8.09)
21	 single isomer **5c**	65*	oil	C 75.84 (C 75.59) H 7.69 (H 8.03) N 7.69 (N 8.19)
22	 **5.1**	95	Oil	C 76.20 (C 75.85) H 7.93 (H 8.23) N 7.41 (N 7.80)
23	 **5.2**	90	Oil	C 79.13 (C 79.30) H 8.78 (H 8.86) N 7.69 (N 7.95)

* Yield of pure single isomer obtained after dry flash chromatography

Amino esters of structure **1** were prepared according to the typical procedure given for **1a**. In the case of **2b**, 20 mol% of AcOH was added, and neutralized prior to the work-up, with 50% K_2CO_3.

Methyl 3-[*N*-(phenethylamino)]propionate 1a

A three-necked, 250 cm^3 round-bottomed flask provided with a pressure-equalizing dropping funnel, thermometer and $CaCl_2$ drying tube was charged with MeOH (100 cm^3) and phenethylamine (24.24 g, 0.2 mol). The mixture was stirred magnetically and then cooled to 0–5 °C (ice-bath), while methyl acrylate (18.94 g, 0.22 mol) in MeOH (20 cm^3) was added dropwise over 1 h. The mixture was stirred at room temp. for 48 h, concentrated and vacuum distilled. After a small fore-run, pure **1a** distilled at 122 °C/0.5 Torr; yield: 34.4 g (83%); purity > 99% (GC).

Amido esters of the structure **2** were prepared according to the typical procedure given for **2a**. They also can be prepared according to the procedure given for **2d**.

Methyl 3-[*N*-phenethyl-*N*-(methoxycarbonylethanoyl)amino]-propionate 2a

A three-necked 250 cm^3 flask provided with a reflux condenser, thermometer and a pressure-equalizing dropping funnel, and protected with a $CaCl_2$ drying tube, was charged with dimethyl malonate (158.5 g, 1.2 mol) and heated to 160–170 °C with magnetic stirring. Compound **1a** (31.1 g, 0.15 mol) in dimethyl malonate (17 cm^3, 0.15 mol) was added dropwise over 1 h and the mixture heated at 160–170 °C with stirring for 1 h. The mixture was cooled to room temp., diluted with toluene (500 cm^3) and filtered through SiO_2 (400 g) under vacuum (dry flash chromatography). The column was washed with toluene (200 cm^3) and eluted with toluene–EtOAc (1 : 1). After concentration of the eluate, pure **2a** was obtained as a colourless oil (41.5 g, 90%) which was used directly in the next step.

Methyl 3-[*N*-cyclohexyl-*N*-(ethoxycarbonylethanoyl)amino]-propionate 2d

A two-necked round-bottomed flask provided with pressure-equalizing dropping funnel and a $CaCl_2$ drying tube was charged with methyl 3-(*N*-cyclohexylamino)propionate **1d** (18.5 g, 0.1 mol), triethylamine (11.11 g, 0.11 mol) and CH_2Cl_2 (150 cm^3). The mixture was cooled to 0 °C (ice-bath) and ethyl chloroformylacetate (16.55 g, 0.11 mol) was added dropwise over 30 min. Stirring was continued for 2 h after which the mixture was treated with 15% aqueous K_2CO_3 (100 cm^3), and stirring continued for 15 min. The contents were transferred to a separatory funnel and the organic layer was separated and washed with 10% HCl (100 cm^3). The solution was dried ($MgSO_4$), filtered and concentrated. The residual oil was dried *in vacuo* (50 °C, 0.1 Torr, 30 min); yield 28.4 g (95%).

***N*-Alkylpiperidine-2,4-diones 3**

These compounds were prepared according to the typical procedure given for **3a**. They also can be prepared according to the procedure given for **3d**.

Table 3 Spectroscopic data for the selected products synthesized

No.	Compd.	ν_{max}/cm^{-1}	$\delta_H(CDCl_3)$	$\delta_C(CDCl_3)$	*m/z* (%)
1	**1a**	3085, 3062, 3027, 2950, 2848, 1736, 1604, 1496, 1455, 1438, 1363, 1202, 1171, 1124, 751 and 701	1.74 (1 H, br s, NH), 2.51 (2 H, t, *J* 6.5, CH_2), 2.77–2.83 (2 H, m, CH_2), 2.90 (4 H, q, *J* 6.5, 2 CH_2), 3.70 (3 H, s, CH_3) and 7.20–7.39 (5 ArH, m)	33.90 (CH_2), 35.73 (CH_2), 44.33 (CH_2), 50.41 (CH_2), 50.81 (CH_3), 125.70 (ArCH), 127.70 (ArCH), 128.17 (ArCH), 128.20 (ArCH), 139.42 (ArC) and 172.32 (C=O)	208 (M + 1, 100)
2	**1b**	3085, 3062, 3027, 2953, 1736, 1604, 1496, 1455, 1438, 1377, 1300, 1254, 1196, 1174, 1079, 1008, 751 and 701	1.11 (3 H, d, *J* 6.4, CH_3), 1.71 (1 H, br s, NH), 2.40 (2 H, qd, J_1 6.6, J_2 15.2, CH_2), 2.76–2.97 (4 H, m, 2 CH_2), 3.13 (1 H, sext, *J* 6.4), 3.69 (3 H, s, CH_3) and 7.20–7.39 (5 ArH, m)	19.69 (CH_3), 35.78 (CH_2), 40.55 (CH_2), 47.60 (CH_2), 49.38 (CH), 50.61 (CH_3), 125.43 (ArCH), 127.72 (ArCH), 127.98 (ArCH), 139.28 (ArC) and 171.79 (C=O)	222 (M + 1, 0.12), 219 (M − 1, 0.4) and 130 (M − 91, 100)
3	**1c**	3333, 3062, 3027, 2972, 2937, 1736, 1604, 1542, 1496, 1455, 1436, 1362, 1258, 1201, 1172, 1126, 1085, 1031, 750 and 701	1.17 (3 H, d, *J* 7.0, CH_3), 1.69 (1 H, br s, NH), 2.61–2.70 (2 H, m), 2.73–2.82 (2 H, m), 2.85–2.92 (3 H, m), 3.71 (3 H, s, CH_3) and 7.17–7.35 (5 ArH, m)	14.16 (CH_3), 35.05 (CH_2), 38.90 (CH), 50.06 (CH), 50.28 (CH_3), 51.63 (CH_2), 125.21 (ArCH), 127.70 (ArCH), 127.81 (ArCH), 139.13 (ArC) and 174.81 (C=O)	222 (M + 1, 0.4) and 130 (M − 91, 100)
4	**2a**	3027, 2954, 1738, 1645, 1455, 1438, 1372, 1325, 1260, 1202, 1159, 1021, 754 and 703	2.53 (2 H, t, *J* 7.0, CH_2), 2.67 (2 H, t, *J* 6.9, CH_2), 2.87 (2 H, q, *J* 7.4, CH_2), 3.42–3.65 (m) 3.68 (s), 3.69 (s), 3.71 (s), 3.73 (s), 3.76 (s), 7.08–7.35 (5 ArH, m) (mixture of two rotatory isomers *Z*:*E* ~35:65)	31.60 (CH_2), 32.58 (CH_2), 32.97 (CH_2), 34.55 (CH_2), 39.93 (CH_2), 40.27 (CH_2), 41.87 (CH_2), 43.24 (CH_2), 43.92 (CH_2), 47.40 (CH_2), 50.39 (CH_2), 51.09, 51.34, 51.71, 51.75, 125.83 (ArCH), 126.30 (ArCH), 127.94 (ArCH), 128.23 (ArCH), 128.26 (ArCH), 137.28 (ArC), 138.37 (ArC), 165.64, 165.75 (C=O), 167.38 (C=O), 167.58 (C=O), 170.58 (C=O), 170.87 (C=O), 171.81 (C=O) (mixture of two rotatory isomers *Z*:*E* 35:65)	306 (M − 1, 3), 276 (6), 216 (14), 116 (100) and 104 (24)
5	**2b**		1.12 (3 H, t, *J* 7.0, CH_3), 2.72–2.87 (m), 2.94–3.09 (m), 3.12 (dd, J_1 1.2, J_2 4.4), 3.36–3.63 (m), 3.652 (s), 3.656 (s), 3.679 (s), 3.681 (s), 3.73 (s), 3.74 (s), 7.08–7.35 (5 ArH, m), 2.88 (2 H, t, *J* 8.0, CH_2), 3.30 (s), 3.33–3.44 (m) and 7.08–7.35 (5 ArH, m) (mixture of two rotatory isomers *Z* and *E*)	14.25 (CH_3), 14.39 (CH_3), 32.66 (CH_2), 34.19 (CH_2), 37.12 (CH), 38.15 (CH), 39.82 (CH_2) 40.08 (CH_2), 47.39 (CH_2), 48.22 (CH_2), 50.32 (CH_2), 50.74 (CH_2), 51.00 (CH_3), 51.27 (CH_3), 51.45 (CH_3), 125.63 (ArCH), 126.09 (ArCH), 127.76 (ArCH), 128.08 (ArCH), 137.17 (ArC), 138.29 (ArC), 165.57 (C=O), 165.73 (C=O), 167.20 (C=O), 167.40 (C=O), 174.19 (C=O), 174.86 (C=O) (mixture of two rotatory isomers *Z*:*E* ~37:63)	321 (M^+, 5), 290 (7), 230 (15), 130 (100), 105 (15) and 104 (24)
6	**2c**	3061, 3027, 2953, 1738, 1646, 1438, 1349, 1329, 1292, 1258, 1203, 1163, 1094, 1017, 754 and 702	1.25 (3 H, d, *J* 6.7, CH_3), 1.42 (3 H, d, *J* 6.9, CH_3), 2.42 (d, *J* 5.7), 2.48 (d, *J* 5.7), 2.59 (d, *J* 8.7), 2.66 (d, *J* 8.6), 2.72 (d, *J* 7.0), 3.47 (t, *J* 7.0), 3.59 (s), 3.65 (s), 3.68 (s), 3.69 (s), 3.74 (s), 3.76 (s), 3.78 (s), 3.82 (s), 4.30 (quint, *J* 7.12), 7.08–7.35 (5 ArH, m) (mixture of two rotatory isomers *Z*:*E* ~35:65)	17.66 (CH_3), 18.60 (CH_3), 34.12 (CH_2), 35.66 (CH_2), 38.04 (CH_2), 38.62 (CH_2), 40.85 (CH_2), 41.06 (CH_2), 43.05 (CH_2), 49.33 (CH_2), 49.91, 50.71, 50.88, 51.16, 51.54, 125.67 (ArCH), 126.16 (ArCH), 127.81 (ArCH), 127.98 (ArCH), 128.13 (ArCH), 137.30 (ArC), 138.81 (ArC), 165.47 (C=O), 167.36 (C=O), 167.67 (C=O), 170.43 (C=O), 171.26 (C=O) (mixture of two rotatory isomers *Z*:*E* ~35:65)	321 (M^+, 6), 290 (8), 230 (20), 130 (100), 105 (12) and 104 (14)
7	**3a**	2947, 1726, 1664, 1489, 1445, 1424, 1353, 1309, 1246, 1217, 1188, 757 and 706	2.42 (2 H, t, *J* 6.2, CH_2), 2.93 (2 H, t, *J* 7.1, CH_2), 3.32 (2 H, s, CH_2), 3.35 (2 H, t, *J* 6.1, CH_2), 3.75 (2 H, t, *J* 7.0, CH_2) and 7.19–7.35 (5 ArH, m)	34.09 (CH_2), 38.47 (CH_2), 44.35 (CH_2), 49.02 (CH_2), 49.45 (CH_2), 126.73 (ArCH), 128.72 (ArCH), 128.83 (ArCH), 138.70 (ArC), 166.11 (C=O, lactam) and 203.72 (C=O, keto)	217 (M^+, 50), 126 (88), 104 (33) and 42 (100)
8	**3b**	3059, 3027, 2932, 1726, 1651, 1454, 1366, 1309, 1170, 751 and 702	1.05 (3 H, d, *J* 6.8, CH_3), 2.40–2.55 (1 H, m), 2.92 (2 H, t, *J* 7.3, CH_2), 3.10–3.27 (2 H, m), 3.31 (2 H, d, *J* 3.3, CH_2), 3.63–3.84 (2 H, m) and 7.19–7.38 (5 ArH, m)	11.52 (CH_3), 33.67 (CH_2), 42.60 (CH), 47.27 (CH_2), 48.91 (CH_2), 50.74 (CH_2), 126.36 (ArCH), 128.36 (ArCH), 128.49 (ArCH), 138.32 (ArC), 166.00 (C=O) and 205.11 (C=O)	231 (M^+, 72), 140 (84), 105 (20) and 104 (100)
9	**3c**	3440, 3059, 3029, 2968, 2933, 1729, 1651, 1621, 1575, 1551, 1489, 1475, 1455, 1427, 1381, 1358, 1337, 1325, 1295, 1277, 1265, 1254, 1233, 1201, 749, 703, 613 and 505	1.17 (3 H, d, *J* 7.0, CH_3), 2.34 (1 H, dd, J_1 2.50, J_2 15.8), 2.51 (1 H, dd, J_1 6.0, J_2 15.8), 2.96 (2 H, hept, *J* 3.2), 3.09–3.20 (1 H, m), 3.29 (2 H, d, *J* 4.9, CH_2), 3.42 (1 H, quint, *J* 5.6) and 7.20–7.38 (m, 5 ArH)	19.84 (CH_2), 34.12 (CH_2), 45.61 (CH_2), 45.60 (CH_2), 48.15 (CH_2), 50.98 (CH), 126.58 (ArCH), 128.54 (ArCH), 128.73 (ArCH), 138.73 (ArC), 165.75 (C=O) and 203.69 (C=O)	231 (M^+, 62), 140 (100), 105 (20), 104 (91) and 98 (44)
10	**3.1**	3062, 3027, 2933, 1720, 1645, 1491, 1455, 1378, 1350, 1294, 1112, 749 and 702	1.30 (6 H, s, 2 CH_3), 2.51 (2 H, t, *J* 6.4, CH_2), 2.90 (2 H, t, *J* 7.0, CH_2), 3.25 (2 H, t, *J* 6.4, CH_2), 3.71 (2 H, t, *J* 7.2, CH_2) and 7.18–7.35 (5 ArH, m)	21.903 (2 CH_3), 32.962 (CH_2), 36.199 (CH_2), 42.361 (CH_2), 49.080 (CH_2), 51.740 (C), 125.862 (ArCH), 127.841 (ArCH), 128.166 (ArCH), 138.040 (ArC), 171.796 (C=O) and 208.254 (C=O)	245 (M^+, 23), 154 (60), 105 (24) and 104 (56)

Table 3 (*continued*)

11	**4a**	3331, 3060, 3026, 2920, 1626, 1601, 1530, 1497, 1453, 1344, 1321, 1306, 1269, 1249, 1129, 745, 698 and 502	1.67–1.78 (1 H, m), 2.01–2.15 (1 H, m), 2.31 (1 H, dd, J_1 7.8, J_2 17.3), 2.82 (dd, J_1 1.1, J_2 5.0), 2.92 (2 H, t, J 7.3), 3.14–3.20 (1 H, m), 3.52–3.75 (2 H, m), 6.59 (2 ArH, dd, J_1 1.0, J_2 8.7), 6.75 (1 ArH, tt, J_1 1.1, J_2 7.3) and 7.16–7.38 (7 ArH, m)	28.11 (CH_2), 33.17 (CH_2), 38.93 (CH_2), 45.15 (CH_2), 46.56 (CH), 48.63 (CH_2), 112.96 (ArCH), 117.44 (ArCH), 126.16 (ArCH), 128.24 (ArCH), 128.56 (ArCH), 129.07 (ArCH), 138.75 (ArC), 146.20 (ArC) and 167.67 (C=O)	294 (M^+, 100), 203 (58), 190 (22), 161 (21), 146 (20), 132 (91), 110 (21) and 105 (16)
12	**4b**	3324, 3024, 2925, 1617, 1602, 1524, 1502, 1373, 1315, 1277, 759, 743 and 694	0.93 (3 H, d, J 6.8, CH_3), 1.03 (3 H, d, J 6.7, CH_3), 1.69 (br s), 2.21–2.35 (m), 2.45 (dd, J_1 6.7, J_2 17.6), 2.67 (dd, J_1 5.4, J_2 17.6), 2.86–3.00 (m), 3.22 (dd, J_1 5.0, J_2 12.4), 3.41–3.67 (m), 3.72–3.83 (m), 6.55–6.64 (m), 6.67–6.80 (m), 7.09–7.39 (5 ArH, m) (mixture of *cis* and *trans* isomers ~15:85)	12.64 (CH_3), 15.52 (CH_3), 30.49 (CH), 33.13 (CH_2), 33.21 (CH_2), 33.88 (CH), 36.49 (CH_2), 37.98 (CH_2), 48.48 (CH_2), 48.63 (CH_2), 50.01 (CH), 51.51 (CH_2), 52.12 (CH), 52.46 (CH_2), 112.83 (ArCH), 113.09 (ArCH), 117.31 (ArCH), 117.45 (ArCH), 126.18 (ArCH), 126.22 (ArCH), 128.24 (ArCH), 128.29 (ArCH), 128.61 (ArCH), 129.07 (ArCH), 138.71 (ArC), 146.60 (ArC), 167.49 (C=O) and 168.01 (C=O) (mixture of *cis* and *trans* isomers ~15:85)	308 (M^+, 58), 217 (26), 146 (100) and 124 (22)
13	**4c**	3315, 3056, 3024, 2961, 1618, 1602, 1533, 1499, 1470, 1420, 1331, 1306, 1270, 752 and 698	1.22 (3 H, d, J 7.0, CH_3), 1.23 (3 H, d, J 7.0, CH_3), 1.20–1.45 (m), 1.59–1.77 (m), 2.19 (d, J 16.5), 2.23 (d, J 16.4), 2.30–2.41 (m), 2.72–3.11 (m), 3.82–3.94 (m), 4.03–4.14 (m), 6.55–6.64 (m, ArH), 6.67–6.80 (m, ArH), 7.09–7.39 (m, ArH) (mixture of *cis* and *trans* isomers ~25:75)	19.95 (CH_3), 21.52 (CH_3), 33.58 (CH_2), 33.81 (CH_2), 35.48 (CH_2), 38.42 (CH_2), 39.40 (CH_2), 39.79 (CH_2), 43.38 (CH), 45.02 (CH), 45.69 (CH), 46.71 (CH_2), 50.78 (CH), 51.06 (CH), 112.96 (ArCH), 113.05 (ArCH), 117.57 (ArCH), 126.18 (ArCH), 128.26 (ArCH), 128.61 (ArCH), 129.16 (ArCH), 138.94 (ArC), 139.00 (ArC), 146.17 (ArC), 146.26 (ArC), 167.89 (C=O) and 168.73 (C=O) (mixture of *cis* and *trans* isomers ~25:75)	308 (M^+, 100), 217 (72), 204 (24), 146 (40) and 132 (98)
14	**4.1**	3368, 3059, 3029, 2942, 1631, 1627, 1620, 1600, 1513, 1491, 1459, 1428, 1318, 1301, 1253, 1189, 749, 704 and 696	1.22 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 1.70 (1 H, br s), 1.73–1.82 (1 H, m), 1.95–2.08 (1 H, m), 2.91 (2 H, t, J 7.3, CH_2), 3.13 (2 H, t, J 6.3, CH_2), 3.38–3.72 (4 H, m), 6.58 (2 ArH, d, J 7.6), 6.72 (1 ArH, t, J 7.3) and 7.15–7.39 (7 ArH, m)	21.14 (CH_3), 23.8 (CH_2), 25.83 (CH_3), 32.96 (CH_2), 42.93 (CH), 45.20 (CH_2), 48.93 (CH_2), 55.77 (CH), 112.93 (ArCH), 117.28 (ArCH), 126.11 (ArCH), 128.14 (ArCH), 128.62 (ArCH), 129.06 (ArCH), 138.71 (ArC), 146.89 (ArC) and 174.33 (C=O)	322 (M^+, 80), 251 (12), 134 (26), 132 (100), 105 (18) and 104 (20)
15	**4.2**	3407, 3085, 3054, 3025, 2946, 1602, 1505, 1468, 1455, 1434, 1367, 1320, 1295, 1254, 1181, 1158, 1110, 748 and 695	0.99 (3 H, s, CH_3), 1.08 (3 H, s, CH_3), 1.57 (1 H, qd, J_1 4.1, J_2 11.4), 1.86–1.97 (2 H, m), 2.12 (1 H, td, J_1 2.8, J_2 11.5), 2.45–2.75 (4 H, m), 2.78–2.85 (2 H, m), 2.92–2.96 (1 H, m), 6.62–7.76 (3 ArH, m) and 7.08–7.18 (7 H, m)	19.89 (CH_3), 26.85 (CH_3), 28.95 (C), 33.66 (CH_2), 35.39 (CH_2), 53.74 (CH_2), 58.25 (CH), 60.29 (CH_2), 66.23 (CH_2), 113.05 (ArCH), 116.76 (ArCH), 125.82 (ArCH), 128.20 (ArCH), 128.68 (ArCH), 129.20 (ArCH), 140.58 (ArC) and 148.10 (ArC)	308 (M^+, 16), 218 (16), 217 (100), 174 (33) and 105 (16)
16	**5a**	3061, 3027, 2937, 1647, 1595, 1495, 1455, 1397, 1257, 748, 734 and 704	1.02 (3 H, t, J 7.4, CH_3), 1.49 (1 H, oct, J 6.6), 1.77–2.05 (1 H, m), 2.17 (1 H, dd, J_1 4.6, J_2 12.2), 2.62 (1 H, ddd, J_1 2.4, J_2 5.42, J_3 16.8), 2.81 (2 H, sext, J 3.5), 3.05 (1 H, ddd, J_1 2.1, J_2 5.6, J_3 12.2), 3.28 (1 H, td, J_1 4.2, J_2 12.1), 3.51 (2 H, oct, J 8.2), 4.95–5.09 (1 H, m) and 7.02–7.50 (10 ArH, m)	9.00 (CH_3), 27.86 (CH_2), 28.00 (CH_2), 32.90 (CH_2), 36.31 (CH_2), 45.93 (CH_2), 47.87 (CH), 48.48 (CH_2), 125.89 (ArCH), 127.98 (ArCH), 128.29 (ArCH), 128.32 (ArCH), 129.56 (ArCH), 130.00 (ArCH), 137.43 (ArC), 138.47 (ArC), 167.44 (C=O, lactam) and 173.06 (C=O, amide)	350 (25), 260 (12), 259 (86), 203 (18), 132 (46), 110 (100) and 105 (23)
17	**5b**	3065, 3028, 2969, 2939, 1657, 1636, 1594, 1494, 1453, 1424, 1374, 1352, 1313, 1290, 1274, 1249 and 703	0.98 (3 H, t, J 7.4, CH_3), 0.96 (3 H, d, J 7.0, CH_3), 1.84–2.04 (1 H, m), 2.29 (1 H, dd, J_1 9.4, J_2 17.5), 2.63 (3 H, qd, J_1 2.7, J_2 6.2), 2.83 (1 H, dd, J_1 5.6, J_2 12.3), 3.25–3.45 (3 H, m) and 4.99 (1 H, hept, J 3.2) (single isomer)	9.13 (CH_3), 12.51 (CH_3), 28.24 (CH_2), 30.63 (CH), 32.76 (CH_2), 34.40 (CH_2), 48.32 (CH_2), 51.89 (CH), 52.55 (CH_2), 125.90 (ArCH), 128.02 (ArCH), 128.26 (ArCH), 128.34 (ArCH), 128.89 (ArCH), 129.94 (ArCH), 138.45 (ArC), 139.18 (ArC), 166.91 (C=O, lactam) and 174.29 (C=O, amide) (single isomer)	364 (10), 274 (17), 273 (100), 217 (23), 204 (20), 132 (30), 124 (75) and 105 (18)
18	**5c**	3061, 3027, 2937, 1644, 1595, 1495, 1455, 1418, 1397, 1381, 1333, 1307, 1258, 1234, 1182, 1097, 1075, 1031, 750 and 704	1.02 (3 H, t, J 7.4, CH_3), 1.23 (3 H, d, J 6.3, CH_3), 1.36 (1 H, qd, J_d 1.6, J_q 12.6), 1.94 (2 H, qd, J_1 1.8, J_2 7.6), 2.12–2.19 (2 H, m), 2.55 (dd, J_1 3.1, J_2 4.9), 2.60–2.64 (m), 2.70 (dd, J_1 5.6, J_2 10.2), 2.67 (d, J 5.6), 2.92 (dd, J_1 5.7, J_2 10.4), 2.97 (dd, J_1 5.8, J_2 10.4), 3.35 (dd, J_1 5.7, J_2 10.2), 3.41 (dd, J_1 5.7, J_2 10.1), 3.52 (q, J 5.1), 3.73 (dd, J_1 5.6, J_2 10.4), 3.79 (dd, J_1 5.5, J_2 10.5), 5.00 (1 H, tdd, J_1 4.8, J_2 3.1, J_3 12.7, CH), 7.07–7.11 (2 ArH, m), 7.18–7.33 (5 ArH, m) and 7.42–7.50 (3 ArH, m) (single isomer)	9.10 (CH_3), 21.28 (CH_3), 28.15 (CH_2), 33.69 (CH_2), 36.98 (CH_2), 37.07 (CH_2), 44.72 (CH_2), 46.58 (CH), 50.77 (CH), 126.00 (ArCH), 128.13 (ArCH), 128.39 (ArCH), 128.45 (ArCH), 129.35 (ArCH), 129.66 (ArCH), 137.47 (ArC), 138.75 (ArC), 168.52 (C=O, amide) and 173.37 (C=O, lactam) (single isomer)	364 (M^+, 24), 274 (18), 273 (100), 217 (12), 216 (12), 146 (35), 124 (88), 105 (23) and 95 (24)
19	**5.1**	3062, 3027, 2975, 1658, 1637, 1595, 1494, 1455, 1428, 1399, 1384, 1363, 1258, 1225, 1186, 1153, 1091, 1028, 802, 749 and 703	1.0 (3 H, t, J 7.3, CH_3), 1.23 (3 H, s, CH_3), 1.34 (3 H, s, CH_3), 1.94 (2 H, q, J 7.4, CH_2), 2.12–2.34 (2 H, m), 2.56–2.80 (4 H, m, 2 CH_2), 2.90–2.99 (1 H, m), 3.50–3.61 (1 H, m), 5.01–5.12 (1 H, m) and 7.10–7.40 (10 ArH, m)	9.25 (CH_3), 21.53 (CH_3), 22.16 (CH), 22.78 (C), 26.91 (CH_3), 27.88 (CH_2), 32.55 (CH_2), 42.56 (CH_2), 44.87 (CH_2), 48.92 (CH_2), 125.69 (ArCH), 127.82 (ArCH), 128.01 (ArCH), 128.25 (ArCH), 128.39 (ArCH), 129.12 (ArCH), 138.64 (ArC), 140.25 (ArC), 174.05 (C=O) and 174.08 (C=O)	378 (M^+, 16), 288 (19), 287 (100), 231 (13), 230 (20), 132 (54) and 105 (16)

Table 3 (*continued*)

20	**5.2**	3061, 3026, 2936, 1660, 1595, 1495, 1454, 1365, 1323, 1250, 1209, 1125, 1084, 1055, 1030, 751, 705 and 506	0.70 (3 H, s, CH_3), 1.02 (3 H, t, J 7.4, CH_3), 1.07 (3 H, s, CH_3), 1.67 (1 H, dq, J_q 3.3, J_d 12.1), 1.88 (2 H, q, J 7.4, CH_2), 1.76–2.09 (2 H, m), 2.19 (1 H, td, J_d 2.6, J_t 11.2), 2.40–2.61 (3 H, m), 2.68–2.76 (2 H, m), 2.94–3.06 (m, 1 H), 4.79 (1 H, dd, J_1 3.8, J_2 12.6, CH) and 7.08–7.44 (10 ArH, m)	9.66 (CH_3), 20.86 (CH_3), 26.32 (CH_3), 28.01 (C), 28.41 (CH_2), 33.36 (CH_2), 36.60 (CH_2), 54.35 (CH_2), 59.36 (CH), 59.81 (CH_2), 68.50 (CH_2), 125.70 (ArCH), 127.88 (ArCH), 128.06 (ArCH), 128.53 (ArCH), 129.73 (ArCH), 131.60 (ArCH), 140.34 (ArC), 140.50 (ArC) and 174.78 (C=O)	363 (M − 1, 2), 274 (19) and 273 (100)

1-Phenethylpiperidine-2,4-dione 3a

A 500 cm^3 three-necked round-bottomed flask, equipped with mercury sealed mechanic stirrer, reflux condenser, pressure equalizing dropping funnel, heating mantle and protected with a $CaCl_2$ drying tube was charged with toluene (250 cm^3), K_2CO_3 (69.1 g, 0.50 mol) and 18-crown-6 (2.64 g, 0.01 mol). The mixture was stirred and heated to reflux, and **2a** (30.73 g, 0.1 mol) in toluene (50 cm^3) was added dropwise over a 1 h period. The stirring and heating were continued for 6 h, after which the mixture was cooled to 20 °C and, with continued stirring, diluted with water (150 cm^3). The toluene was separated and extracted with water (150 cm^3) after which the combined aqueous layer and extracts were cooled to 0 °C, stirred and slowly acidified to pH < 1 with 10% HCl (CO_2 evolution!). The mixture was extracted with CH_2Cl_2 (3 × 100 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated at 20–25 °C. The residue, the free acid **2.2**, was not purified since it decomposes easily and was homogenous by TLC; yield: 23.4 g (85%). The residue was transferred to a 500 cm^3 round-bottomed flask, charged with 200 cm^3 of 10% aqueous oxalic acid and the mixture stirred and heated to reflux for 4–5 h. After cooling to 20–25 °C the mixture was extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered and concentrated to give pure **3a** (>97% by GC and TLC); yield 16.7 g (90%). An analytical sample was prepared by chromatography using a cyclohexane–ethyl acetate gradient (95:5, 90:10, *etc.*).

1-Cyclohexylpiperidine-2,4-dione 3d

A three-necked, 500 cm^3 flask, equipped with a mercury sealed mechanical stirrer, reflux condenser, $CaCl_2$-drying tube and pressure-equalizing dropping funnel was charged with cyclohexane (200 cm^3) and NaH (60%; 4.4 g, 0.11 mol). The suspension was heated to reflux and a solution of the *N*-cyclohexylamido ester **2d** (14.95 g, 0.05 mol) in toluene (30 cm^3) was added dropwise over 1 h. Stirring and heating was continued for 4 h during which time hydrogen was evolved and a pale yellow precipitate was formed. The mixture was cooled to 20–25 °C, filtered with suction and the precipitate washed with cyclohexane (50 cm^3). It was then transfered to a flask with 10% aq. AcOH (400 cm). The mixture was stirred magnetically and heated to reflux (CO_2 evolution) for 4 h. After cooling to 20–25 °C the mixture was neutralized with $NaHCO_3$ (pH ~ 7) and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), filtered and concentrated to give the keto lactam **3d** (7.30 g, 75%).

1-Phenethyl-3,3-dimethylpiperidine-2,4-dione 3.1

A 100 cm^3 round-bottomed flask protected with a $CaCl_2$ drying tube was purged with Ar and charged with dry DMSO (50 cm^3), K_2CO_3 (13.82 g, 0.1 mol), MeI (10.63 g, 0.075 mol) and **3a** (5.43 g, 0.025 mol). The mixture was stirred magnetically for 24 h at 20–25 °C and then poured into water (200 cm^3) and extracted with CH_2Cl_2 (3 × 50 cm^3). The combined extracts were washed with water (100 cm^3) to remove DMSO, dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography (cyclohexane–ethyl acetate gradient 95:5, 90:10 *etc.*) to afford pure **3.1** (4.90 g, 80%).

The reductive amination of piperidine-2,4-diones **3a–c** was performed according to the typical procedure given for **4a**. For the piperidinedione **3.1**, the imine was formed separately and then reduced.

1-Phenethyl-4-anilino-2-piperidone 4a

A single-necked flask was charged with aniline (3.65 cm^3, 0.040 mol), $NaH_2PO_4 \cdot H_2O$ (10.0 g, 0.072 mol) and a solution of the piperidinedione **3a** (4.34 g, 0.020 mol) in MeOH (50 cm^3). The mixture was stirred magnetically at 20 °C for 3–4 h to give the enamine (TLC). When the reaction was complete, $NaBH_3CN$ (0.84 g, 0.0133 mol) was added and stirring continued for 30 min. When reduction was complete (monitored by TLC) 10% aq. HCl was added (H_2 evolution) to pH < 1, and stirring continued for 15 min. The mixture was concentrated, adjusted to pH > 11 (10% NaOH), with CH_2Cl_2 (2 × 50 cm^3), dried (K_2CO_3), filtered and the excess of aniline removed under reduced pressure (80–90 °C, 10 Torr). Alternatively, aniline can be removed by the addition of Et_2O, since the anilino lactams **4a–c** are poorly soluble in this solvent. The residue was pure **4a** (>97%, GC); yield 5.30 g (90%). It may be further purified by precipitation as the monooxalate salt from MeOH–Et_2O (1:9). An analytical sample was prepared by chromatography, using a cyclohexane–ethyl acetate gradient (95:5, 90:10, *etc.*).

1-Phenethyl-3,3-dimethyl-4-anilino-2-piperidone 4.1

A 100 cm^3 round-bottomed flask provided with Dean and Stark water separator and a $CaCl_2$ drying tube was charged with dry xylene (50 cm^3), aniline (3.72 g, 0.040 mol), $TsOH \cdot H_2O$ (0.18 g) and **3.1** (4.90 g, 0.020 mol). The mixture was stirred magnetically under reflux until the water separation was complete (3–4 h) and then cooled to 20–25 °C and concentrated. The residual mixture (imine and aniline) was dissolved in MeOH (50 cm^3), $NaH_2PO_4 \cdot H_2O$ (10 g, 0.072 mol) and $NaBH_3CN$ (0.84 g, 0.0133 mol) were added and the heterogenous mixture was stirred at 20–25 °C for 1–2 h. When the reaction was complete (monitored by IR and TLC) 10% aq. HCl was added slowly to the mixture (H_2 evolution) to pH < 1 after which it was stirred for 15 min and then concentrated at 20–25 °C. The residue was taken to pH > 11 with 10% aq. NaOH and extracted with CH_2Cl_2 (2 × 50 cm^3). The combined extracts were dried (K_2CO_3) after which the excess of aniline was distilled off at 15 Torr. The residue was pure **6** (>97% by GC); yield 5.48 g (85%). It may be further purified by precipitation as the monooxalate salt from MeOH–Et_2O (1:9). An analytical sample was prepared by chromatography using a cyclohexane–ethyl acetate gradient (95:5, 90:10, *etc.*).

Acylation of anilino lactams of the general structure **4**, was effected with propionyl chloride in CH_2Cl_2, at 20–25 °C, as given in the typical example for **5a**. In the case of **4.1** and **4.2** acylation was conducted in boiling ethylene dichloride.

1-Phenethyl-4-(*N*-propionylanilino)-2-piperidone 5a

A three-necked, 100 cm^3 flask, equipped with a thermometer, pressure-equalizing dropping funnel and a $CaCl_2$ drying tube was charged with CH_2Cl_2 (30 cm^3), triethylamine (3.04 g, 0.030 mol) and the anilino lactam **4a** (2.94 g, 0.01 mol). The mixture

was cooled to 0–5 °C (ice-bath) after which propionyl chloride (2.78 g, 0.030 mol) in CH_2Cl_2 (10 cm^3) was added dropwise. Stirring was continued for 5 h at 20–25 °C after which MeOH (20 cm^3), was added and stirring continued for 15 min. The mixture was concentrated, treated with 10% aq. NaOH (20 cm^3) and then extracted with CH_2Cl_2 (2 × 50 cm^3). The combined extracts were dried (K_2CO_3), filtered and evaporated. Chromatography (cyclohexane–ethyl acetate gradient) of the residue gave pure **5a**; yield: 3.25 g (93%).

1-Phenethyl-3,3-dimethyl-4-(*N*-propionylanilino)-2-piperidone 5.1

A three-necked round-bottomed flask fitted with a thermometer, pressure-equalizing dropping funnel, reflux condenser and $CaCl_2$ drying tube was purged with Ar and then charged with dry dichloroethane (30 cm^3), triethylamine (1.52 g, 0.015 mol) and **4.1** (3.22 g, 0.01 mol). The mixture was stirred magnetically while propionyl chloride (2.78 g, 0.03 mol) in dichloroethane (10 cm^3) was added dropwise to it. The mixture was stirred under reflux for 5 h, cooled to 20–25 °C, treated with MeOH (20 cm^3), stirred for 15 min and then concentrated at 25–35 °C. The residue was treated with 10% aq. NaOH (20 cm^3) and then extracted with CH_2Cl_2 (2 × 50 cm^3). The combined extracts were dried (anh. K_2CO_3) and evaporated to dryness. Chromatography (cyclohexane–ethyl acetate gradient) of the residue gave pure **5.1** (3.59 g, 95%).

1-Phenethyl-3,3-dimethyl-4-anilinopiperidine 4.2

A 100 cm^3 round-bottomed flask fitted with a thermometer, pressure-equalizing dropping funnel, reflux condenser and an oil bubbler was purged with Ar and then charged with diglyme (30 cm^3), $NaBH_4$ (1.0 g, 0.0264 mol) and **4.1** (3.22 g, 0.01 mol). The mixture was cooled to −5 °C (ice–salt bath) after which pure $BF_3{\cdot}Et_2O$ complex (3.90 g, 0.0275 mol) was added dropwise to it. After being stirred at 0–5 °C for 1 h, the mixture was heated at 80–90 °C for 1 h and then cooled to 20–25 °C and treated slowly with water (10 cm^3) followed by conc. HCl (20 cm^3). It was stirred and heated on a water-bath for 3 h and then cooled to 20–25 °C and evaporated to dryness at reduced pressure (10–15 Torr). The solid residue was made alkaline (10% aq. NaOH; to pH > 11) and then extracted with CH_2Cl_2 (2 × 50 cm^3). The combined extracts were dried (K_2CO_3) and evaporated to yield **5.2** (2.59 g, 84%). The product was used in the next step without purification. It may be precipitated as the dioxalate salt from MeOH–Et_2O (1:9). An analytical sample was prepared by chromatography (cyclohexane–ethyl acetate gradient).

1-Phenethyl-3,3-dimethyl-4-(*N*-propionylanilino)piperidine 5.2

A three-necked round-bottomed flask fitted with a thermometer, pressure-equalizing dropping funnel, reflux condenser and $CaCl_2$ drying tube was purged with Ar and then charged with dry dichloroethane (30 cm^3), triethylamine (1.52 g, 0.015 mol) and **4.2** (3.08 g, 0.01 mol). The mixture was stirred magnetically while propionyl chloride (2.78 g, 0.03 mol) in dichloroethane (10 cm^3) was added dropwise to it. The mixture was then stirred under reflux for 5 h, cooled to 20–25 °C, treated with MeOH (20 cm^3), stirred for 15 min and then concentrated at 25–35 °C. 10% Aqueous NaOH (40 cm^3) was added to the residue which was then extracted with CH_2Cl_2 (2 × 50 cm^3). The combined extracts were dried (K_2CO_3) and evaporated to dryness. The product was purified by precipitation as the monooxalate salt with anhydrous oxalic acid (1 g) in MeOH–Et_2O (1:9) followed by basification (10% aq. NaOH; pH > 11). The yield of pure **5.2** (pale yellow viscous oil) was 3.28 g (90%). An analytical sample was obtained by chromatography (cyclohexane–ethyl acetate gradient).

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