PREPARATION OF 4-(2-AMINOETHYL)-3,3-DIMETHYL-2-PIPERIDONE DERIVATIVES BY INTRAMOLECULAR REARRANGEMENT OF α,α-DIMETHYL-4-PIPERIDINEACETYL CHLORIDE

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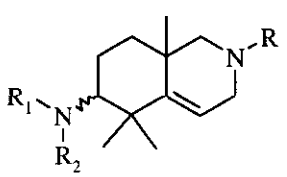
Abstract- Reaction of hindered amines with α,α-dimethyl-4-piperidineacetyl chloride provided 4-(2-aminoethyl)-3,3-dimethyl-2-piperidone derivatives by intramolecular rearrangement of the acid chloride.

INTRODUCTION.

In an extension of our work[1a] on 8aβ-6-isoquinolineamine (**1**) as inhibitors of epoxysqualene cyclase, we prepared 4-piperidineethanamine derivatives[1b] having the general structure (**2**).



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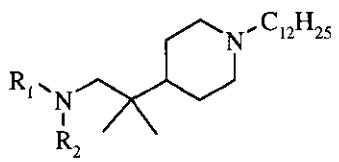

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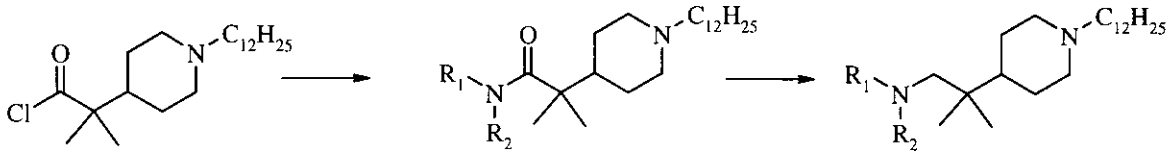
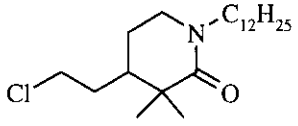
4-Piperidineethanamines (**2**) were obtained by condensation of amines R_1R_2NH with α,α-dimethyl-4-piperidineacetyl chloride (**3**) leading to amide compounds (**4**) which were subsequently reduced by $LiAlH_4$ (Scheme 1).



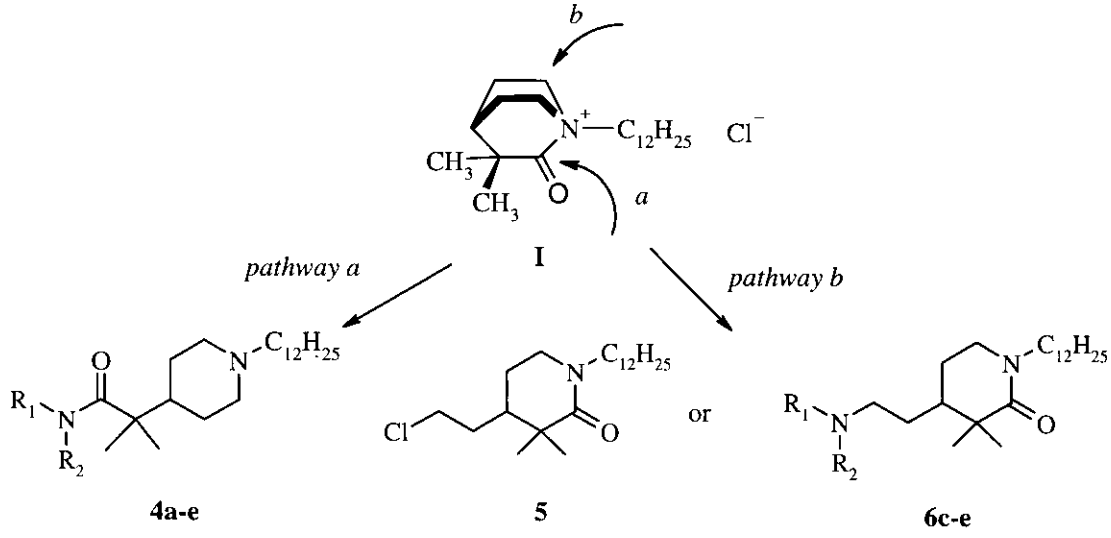
Scheme 1

However, use of diisopropylamine in the reaction sequence did not lead to the expected amide (**4**); instead, a nonbasic, chlorine-containing substance was obtained in a 50% yield; this unexpected compound was identified (^{1}H, ^{13}C NMR, MS, IR, Elemental Analysis) as 4-(2-chloroethyl)-1-dodecyl-3,3-dimethyl-2-piperidone (**5**).



5

We speculated, as supported by the literature[2-7] that a rearrangement of 4-piperidineacetyl chloride (**3**)



4a-e **5** **6c-e**

4a $R_1 = R_2 = H$
4b $R_1 = H$, $R_2 = CH_3$
4c $R_1 = R_2 = CH_3$
4d $R_1 = R_2 = C_2H_5$
4e $R_1 = CH_3$, $R_2 = Bn$

6c $R_1 = R_2 = CH_3$
6d $R_1 = R_2 = C_2H_5$
6e $R_1 = CH_3$, $R_2 = Bn$

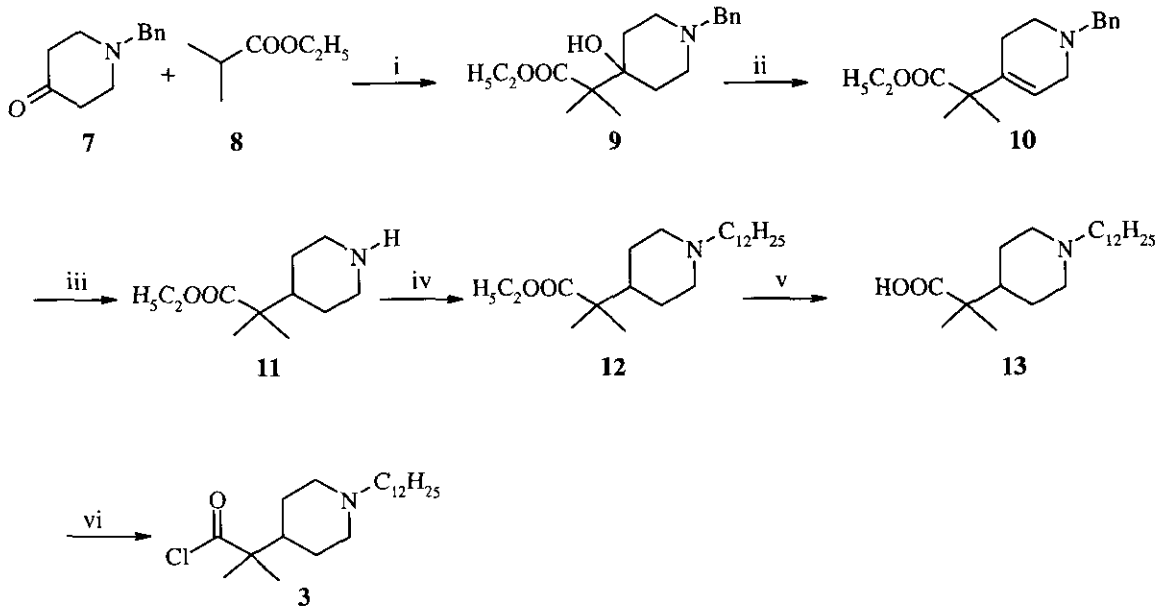
Scheme 2

as a free base had transpired, *via* the bicyclic ammonium intermediate (**I**) in which the acid chloride has internally acylated the amino group. Two modes of cleavage (*a* and *b*) are available from **I** giving rise to the expected compounds (**4**) or to the rearranged products (**5**) or (**6**) (Scheme 2).

We report herein details of the reaction of **3** with various amines.

RESULTS AND DISCUSSION.

The synthesis of the acid (**13**) giving rise to the acid chloride (**3**) by refluxing in $SOCl_2$ is described in Scheme 3.



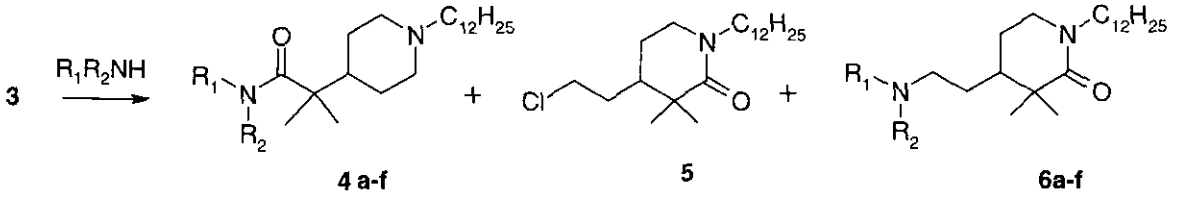
Reagents and conditions : i) LDA, THF, -50°C ii) $SOCl_2$, $CHCl_3$, cat DMF iii) H_2, 5% Pd/C, CH_3OH, 70°C iv) $C_{12}H_{25}Br$, CH_3CN, K_2CO_3, NaI v) NaOH, C_2H_5OH, H_2O, then 5N HCl vi) $SOCl_2$.

Scheme 3

Aldol condensation between 4-piperidone (**7**) and ester (**8**) in the presence of LDA led to 4-hydroxy-piperidine[8] (**9**) which was subsequently dehydrated with $SOCl_2$ in $CHCl_3$ to give **10** . Hydrogenation of the double bond and hydrogenolysis of the benzyl group of **10** proceeded in one step with 5% Pd/C as catalyst to afford **11** . Alkylation of **11** with 1-bromododecane in CH_3CN gave **12** which was hydrolyzed with NaOH to yield the acid (**13**). Transformation of **13** into **3** was performed in $SOCl_2$.

The resulting acid chloride (**3**) reacted with various amines and the results of this reaction are summarized in Table 1.

Table 1 : Reaction of 3 with various amines.



R_1R_2NH	yield % of product 4		5	6	
NH_3	69	**4a**	0	0	**6a**
CH_3NH_2	72	**4b**	0	0	**6b**
$(CH_3)_2NH$	56	**4c**	0	0	**6c**
$(C_2H_5)_2NH$	22	**4d**	0	33	**6d**
$Bn(CH_3)NH$	35	**4e**	0	23	**6e**
$i Pr_2NH$	0	**4f**	50	0	**6f**

As described above, rearrangement did not occur with amines such as ammonia, methylamine or dimethylamine. Reaction of **3** with diethylamine or *N*-methylbenzylamine afforded respectively a mixture of **4d-e** and **6d-e** whereas diisopropylamine exclusively led to the chloro derivative (**5**).

This product proved to be useful, giving access to rearranged compounds (**6a-c**) bearing small R_1 and R_2 groups. For example, **6c** was obtained in 69% yield reacting **5** with an excess of dimethylamine in a sealed vessel at 130°C.

These results seem to indicate that the regioselectivity of the reaction is mainly controlled by steric parameters. Indeed, small nucleophiles reacted exclusively according to pathway *a* whatever their nucleophilicity (e.g. NH_3 versus $(CH_3)_2NH$). Bigger amines partly reacted according to pathway *a*. However, these rather hindered nucleophiles reacted also according to pathway *b* which involves attack of

the sterically more accessible methylene site of the molecule. Finally, the bulky diisopropylamine cannot react, and the only isolated compound (**5**) resulted from the nucleophilic attack of the chloride anion *via* the sterically less hindered route *b*. This last reaction is reminiscent of *N*-dealkylation procedures using chloroformate reagents.[9]

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer 782 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC300 spectrometer using tetramethylsilane as internal reference. MS spectra were measured with a Nermag Model R30-10 spectrometer. Structural assignments for all new compounds are consistent with their spectra. Elemental analyses were performed on a Perkin-Elmer 240C apparatus.

4-Hydroxy-α,α-dimethyl-1-phenylmethyl-4-piperidineacetic acid ethyl ester (9)

A solution of diisopropylamine (152.8 mL, 1.09 mol) in dry THF (100 mL) was stirred at -50°C in an atmosphere of N_2 and a 2.5M solution in hexane (400 mL, 1 mol) of nBuLi was added dropwise. The mixture was stirred at -50°C for 45 min and then 2-methylpropanoic acid ethyl ester (121.8 mL, 0.909 mol) in THF (100 mL) was added dropwise and stirring was continued for a further 1 h. A solution of 1-phenylmethyl-4-piperidone (120.5 mL, 0.68 mol) in THF (100 mL) was added dropwise at -50°C, then the reaction mixture was warmed at rt overnight. The reaction was quenched by adding saturated aqueous NH_4Cl (400 mL) then extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to leave an oil. Distillation under reduced pressure of the oily product afforded (**9**) (172.3 g, 83%) as an orange oil. bp 150-156°C / 0.45 mm Hg. IR (neat) : 3500, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.23 (s, 6H), 1.27 (t, *J*=7.1 Hz, 3H), 1.43 (m, 2H), 1.78 (dt, *J*=4.39, 12.9 Hz, 2H), 2.37 (dt, *J*=2.39, 12.99 Hz, 2H), 2.69 (m, 2H), 3.48 (s, 1H), 3.52 (s, 2H), 4.16 (q, *J*=7.1 Hz, 2H), 7.22-7.33 (m, 5H).). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.23; H, 8.81; N, 4.96.

1,2,3,6-Tetrahydro-α,α-dimethyl-1-phenylmethyl-4-pyridineacetic acid ethyl ester hydrochloride (10)

To a stirred solution of **9** (50 g, 0.164 mol) in $CHCl_3$ (200 mL) and DMF (0.52 mL) was added dropwise $SOCl_2$ (24 mL, 0.33 mol). The reaction mixture was stirred under reflux for 8 h, then the solution was evaporated *in vacuo*. The resulting residue was made alkaline with 10N NaOH (20 mL) and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* . Hydrochloride salt was prepared in isopropyl alcohol solution by adding HCl gas to afford **10** as a white powder, which was recrystallized from isopropyl alcohol (38.9g, 74%). mp 208°C. ^{1}H NMR (DMSO-d_6) δ: 1.16 (t, *J*=7.1 Hz, 3H), 1.24 (s, 6H), 2.17 (m, 2H), 3.02-3.57 (complex m, 4H), 4.05 (q, *J*=7.1 Hz, 2H), 4.27 (m, 2H), 5.54 (m, 1H), 7.44 (m, 3H), 7.58 (m, 2H), 10.90 (br s, 1H). ^{1}H NMR (DMSO-d_6 + D_2O) δ: 1.10 (t, *J*=7.1 Hz, 3H), 1.19 (s, 6H), 2.21 (m, 2H), 3.14 (m, 2H), 3.50 (m, 2H), 4.00 (q, *J*=7.1 Hz, 2H), 4.17 (s, 2H), 5.50 (m, 1H), 7.42 (s, 5H). Anal. Calcd for $C_{18}H_{25}NO_2$. HCl: C, 66.76; H, 8.09 ; N, 4.32. Found: C, 66.89; H, 8.10; N, 4.36.

α,α-Dimethyl-4-piperidineacetic acid ethyl ester (11)

A solution of **10** (54.6 g, 0.169 mol) in CH_3OH (800 mL) was hydrogenated over 5% Pd/C (3 g) at 70°C under 80 bars H_2 pressure. After completion of the reaction, the mixture was filtered, and the filtrate was evaporated *in vacuo*. The solid residue was quenched with 10N NaOH then extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give **11** as a yellow oil (28.6 g , 85%). IR (neat) 3150, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.10 (s, 6H), 1.25 (m, 5H), 1.52 (m, 3H), 1.69 (m, 1H), 2.58 (dt, *J*=2.5, 12.2 Hz, 2H), 3.11 (m, 2H), 4.12 (q, *J*=7.1 Hz, 2H).

A sample of the free base was converted into its hydrochloride salt in ether. mp: 190°C (isopropyl alcohol). Anal. Calcd for $C_{11}H_{21}NO_2$. HCl: C, 56.04; H, 9.41; N, 5.94. Found: C, 56.48; H, 9.62; N, 5.96.

α,α-Dimethyl-1-dodecyl-4-piperidineacetic acid ethyl ester (12)

A mixture of **11** (9.85 g, 0.05 mol), K_2CO_3 (17.3 g, 0.125 mol), 1-bromododecane (14.9 mL, 0.062 mol) in CH_3CN (50 mL) was refluxed with stirring for 6 h. The reaction mixture was poured into water then extracted with $AcOC_2H_5$. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on SiO_2 with hexane-$AcOC_2H_5$

(9 : 1, v/v) as eluent to give **12** as an orange oil (6.7 g, 78%). IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.11 (s, 6H), 1.22-1.60 (m, 28H), 1.85 (dt, *J*=2.0, 11.7 Hz, 2H), 2.27 (m, 2H), 2.98 (m, 2H), 4.12 (q, *J*=7.1 Hz, 2H).

The free base was converted into its fumarate salt. mp: 106°C (ethyl alcohol-ether). Anal. Calcd for $C_{23}H_{45}NO_2$. $C_4H_4O_4$: C, 67.04; H, 10.21; N, 2.89. Found: C, 66.70; H, 10.11; N, 2.96.

α,α-Dimethyl-1-dodecyl-4-piperidineacetic acid hydrochloride (13)

NaOH pellets (24.6 g, 0.614 mol) were added to a solution of **12** (22.5 g, 0.061 mol) in 50% EtOH (210 mL), then the resulting mixture was refluxed with stirring for 3 days. The solution was poured with cooling into 5N HCl (200 mL), the resulting precipitate was filtrated and washed with ether. Recrystallization from 80% EtOH gave **13** as a white solid. (17.8 g, 77%). mp 192°C. IR (KBr) 1700, 2650 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.18 (s, 6H), 1.27 (m, 18H), 1.82 (m, 5H), 2.12 (m, 2H), 2.70 (m, 2H), 2.94 (m, 2H), 3.64 (m, 2H), 9.25 (br s, 1H), 11.50 (br s, 1H). Anal. Calcd for $C_{21}H_{41}NO_2$. HCl: C, 67.07; H, 11.26; N, 3.73. Found: C, 67.02; H, 11.32; N, 3.85.

α,α-Dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (3)

13 (17.9 g, 0.048 mol) was added by portion to $SOCl_2$ (100 mL, 1.37 mol), then the mixture was refluxed for 7.5 h. The solution was evaporated *in vacuo* to afford **3** which was used in the following reactions without purification. IR (KBr) 1470, 1780, 1805, 1930 cm^{-1}.

α,α-Dimethyl-1-dodecyl-4-piperidineacetamide (4a)

To a solution of **3** (8.6 g, 0.022 mol) in a mixture of toluene-CH_2Cl_2 (2 : 1, v/v, 100 mL) was carefully added liquid ammonia (80 mL) at -5°C. After stirring for 72 h at rt, the reaction was quenched by water then extracted with $AcOC_2H_5$. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography ($AcOC_2H_5$-CH_3OH-NH_4OH, 9 :1 : 0.5, v/v) provided **4a** (5.2 g, 69%) as a colorless powder. mp 123°C (isopropyl ether). IR (KBr) 1630, 1650, 3220, 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.13 (s, 6H), 1.25-1.60 (m,

25H), 1.87 (t, *J*=11.2 Hz, 2H), 2.27 (m, 2H), 2.99 (m, 2H), 5.47 (br s, 1H), 5.63 (br s, 1H). Anal. Calcd for $C_{21}H_{42}N_2O$: C, 74.49; H, 12.51; N, 8.28 Found: C, 74.25; H, 12.55; N, 8.25.

1-Dodecyl-*N*,α,α-trimethyl-4-piperidineacetamide (4b)

The same procedure as above, using methylamine instead of ammonia, gave **4b** (72%) . mp 78°C (isopropyl ether). IR (neat) 1640, 3330 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.11 (s, 6H), 1.25-1.54 (m, 24H), 1.67 (m, 1H), 1.90 (m, 2H), 2.30 (m, 2H), 2.80 (d, *J*=4.1 Hz, 3H), 3.01 (m, 2H), 5.67 (m, 1H). Anal. Calcd for $C_{22}H_{44}N_2O$: C, 74.94; H, 12.58; N, 7.94 Found: C, 74.55; H, 12.55; N, 8.15.

1-Dodecyl-*N*,*N*,α,α-tetramethyl-4-piperidineacetamide fumarate (4c)

The same procedure as described for **4a** was performed, using dimethylamine instead of ammonia to give **4c** as a free base. mp: 49°C. IR (neat) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.21 (s, 6H), 1.25-1.33 (m, 18H), 1.47 (m, 6H), 1.68-1.88 (m, 3H), 2.27 (m, 2H), 3.01 (m, 8H).

The free base was converted into its fumarate salt. mp: 190°C (ethyl alcohol- ether). Anal. Calcd for $C_{23}H_{46}N_2O$. $C_4H_4O_4$: C, 67.18; H, 10.44; N, 5.80. Found: C, 67.09; H, 10.46; N, 5.84.

1-Dodecyl-*N*,*N*-diethyl-α,α-dimethyl-4-piperidineacetamide (4d) and 1-Dodecyl-4-[2-diethyl-amino)ethyl]-3,3-dimethyl-2-piperidone (6d)

Diethylamine (40 mL, 0.55 mol) was added dropwise at 0°C to a solution of **3** (18 g, 0.045 mol) in $CHCl_3$ (300 mL). The reaction mixture was stirred at 0°C for 3 days, then the reaction was quenched by 1N NaOH and extracted with $AcOC_2H_5$. The extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a red oily residue which was chromatographed on SiO_2 (CH_2Cl_2 : CH_3OH, 94 : 6, v/v) to give **4d** (4 g , 22%). mp < 50°C. Further elution afforded **6d** (6 g , 33%) as an oil.

(4d) IR (neat) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.14 (t, *J*=7 Hz, 6H), 1.20 (s, 6H), 1.25 (m, 18H), 1.51 (m, 6H), 1.66 (m, 1H), 1.86 (m, 2H), 2.30 (m, 2H), 3.03 (m, 2H), 3.40 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 175.9, 59.1, 54.6, 45.6, 43.2, 41.8, 31.9, 29.7, 29.64, 29.62, 29.59, 29.36, 27.7, 27.1, 26.9, 23.4, 22.7, 14.1. Anal. Calcd for $C_{25}H_{50}N_2O$: C, 76.09; H, 12.77; N, 7.10 Found: C, 76.25; H, 12.55; N, 7.25.

6d IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.08 (s, 3H), 1.11 (t, *J*=7.2 Hz, 6H), 1.24-1.34 (m, 22H), 1.45-1.89 (m, 6H), 2.50-2.72 (m, 6H), 3.23-3.32 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 175.4, 51.3, 47.6, 46.8, 46.7, 42.2, 41.1, 31.9, 29.64, 29.63, 29.59, 29.4, 29.3, 27.0, 26.9, 26.5, 25.6, 24.0, 22.7, 21.4, 14.1, 11.0.

6d as free base was converted into its oxalate salt. mp: 83°C (acetone). Anal. Calcd for $C_{25}H_{50}N_2O.C_2H_2O_4$: C, 66.90; H, 10.81; N, 5.78. Found: C, 67.24; H, 11.03; N, 5.81.

1-Dodecyl-*N*-methyl-*N*-phenylmethyl-α,α-dimethyl-4-piperidineacetamide (4e) and 1-Dodecyl-4-[2-[(*N*-methyl-*N*-phenylmethyl)amino]ethyl]-3,3-dimethyl-2-piperidone (6e)

The title compounds were prepared as above from **3**, using *N*-methylbenzylamine instead of diethylamine to afford **4e** as an oil (23%) and **6e** (36%) as an amorphous compound.

4e IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.25 (m, 24H), 1.51 (m, 6H), 1.80 (m, 3H), 2.27 (m, 2H), 2.99 (m, 5H), 4.65 (s, 2H), 7.2-7.36 (m, 5H). MS (EI) m/z 442 (M^+).

6e IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.06 (s, 3H), 1.25 (m, 22H), 1.49-1.78 (m, 6H), 2.21 (s, 3H), 2.32-2.44 (m, 2H), 3.20 (m, 2H), 3.28 (t, 2H), 3.39 (d, *J*=13 Hz, 1H), 3.57 (d, *J*=13 Hz, 1H), 7.23-7.35 (m, 5H). MS (EI) m/z 442 (M^+).

4e and **6e** were converted into their oxalate salts.

4e oxalate salt. mp: 125-130°C (ethyl alcohol). Anal. Calcd for $C_{29}H_{50}N_2O.C_2H_2O_4$: C, 69.88; H, 9.84; N, 5.26. Found: C, 69.32; H, 9.95; N, 5.31.

6e oxalate salt. mp: 125°C (acetone). Anal. Calcd for $C_{29}H_{50}N_2O.C_2H_2O_4$: C, 69.88; H, 9.84; N, 5.26. Found: C, 69.72; H, 9.97; N, 5.44.

1-Dodecyl-4-(2-chloroethyl)-3,3-dimethyl-2-piperidone (5)

A solution of diisopropylamine (20 mL, 0.14 mol) in $CHCl_3$ (30 mL) was added dropwise at 0°C to a solution of **3** (18.7 g, 0.047 mol) in $CHCl_3$ (100 mL). After stirring at rt for 3 days, the reaction mixture was quenched by 5N NaOH (50 mL) then extracted with CH_2Cl_2 and the extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on SiO_2

(toluene -isopropyl alcohol) to afford **5** (12.7 g, 75%). mp: 50°C (isopropyl ether). IR (KBr) : 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.07 (s, 3H), 1.25 (m, 21H), 1.49-1.69 (m, 4H), 1.75-1.99 (m, 3H), 3.22-3.33 (m, 4H), 3.48-3.57 (m, 1H), 3.64-3.72 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 175.10, 47.68, 46.55, 43.30, 41.83, 40.05, 32.82, 31.91, 29.63, 29.57, 29.39, 29.34, 26.95, 26.89, 25.49, 23.33, 22.68, 21.38, 14.11. MS (EI) m/z : (M^+ ,^{35}Cl) 357, 202 (M^+-$C_{11}H_{23}$, ^{35}Cl). Anal. Calcd for $C_{21}H_{40}NOCl$: C, 70.45; H, 11.26; N, 3.91. Found: C, 70.45; H, 11.63; N, 4.04.

1-Dodecyl-4-(2-dimethylaminoethyl)-3,3-dimethyl-2-piperidone (6c)

A solution of **5** (1.5 g, 4.2 mmol) and dimethylamine (15 mL, 0.23 mol) in methyl isobutyl ketone (50 mL) was heated at 160°C in a pressure bottle for 10 h. After evaporation of the solvent, the residue was purified by flash chromatography on SiO_2 (CH_2Cl_2 : CH_3OH, 9.5 : 0.5) to afford **6c** (1 g, 64%) as an oil. IR (neat) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.88 (t, *J*=6.4 Hz, 3H), 1.08 (s, 3H), 1.25 (m, 22H), 1.49-1.72 (m, 5H), 1.84-1.90 (m, 1H), 2.24 (s, 6H), 2.28-2.34 (m, 2H), 3.2-3.32 (m, 4H)

(**6c**) was converted into its oxalate salt. mp: 116°C (isopropyl alcohol). Anal. Calcd for $C_{23}H_{46}N_2O.C_2H_2O_4$: C, 65.75; H, 10.59; N, 6.14. Found: C, 65.68; H, 10.43; N, 6.08.

ACKNOWLEDGMENTS

The authors wish to thank C. Duprat for the synthetic work and G.Martin-Gousset for NMR spectral data. We thank Ph. Durand and P. Renaut for many hints and remarks on the manuscript.

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Received, 1st March, 1999