

**PREPARATION OF 4-(2-AMINOETHYL)-3,3-DIMETHYL-2-PIPERIDONE DERIVATIVES BY INTRAMOLECULAR REARRANGEMENT OF  $\alpha,\alpha$ -DIMETHYL-4-PIPERIDINEACETYL CHLORIDE**

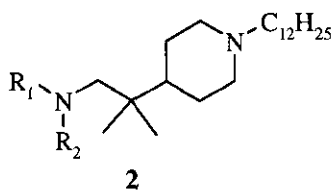
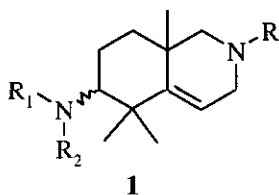
Jean L. Binet\*, Corinne Grandvincent, and Didier M. Thomas

Laboratoires Fournier S. A., 50 rue de Dijon, 21121 DAIX, France

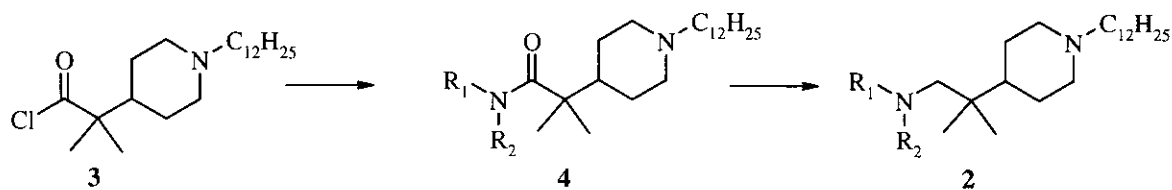
**Abstract-** Reaction of hindered amines with  $\alpha,\alpha$ -dimethyl-4-piperidineacetyl chloride provided 4-(2-aminoethyl)-3,3-dimethyl-2-piperidone derivatives by intramolecular rearrangement of the acid chloride.

**INTRODUCTION.**

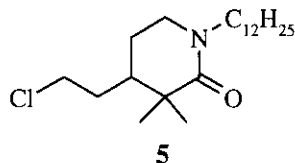
In an extension of our work<sup>1a</sup> on 8 $\alpha\beta$ -6-isoquinolineamine (1) as inhibitors of epoxysqualene cyclase, we prepared 4-piperidineethanamine derivatives<sup>1b</sup> having the general structure (2).



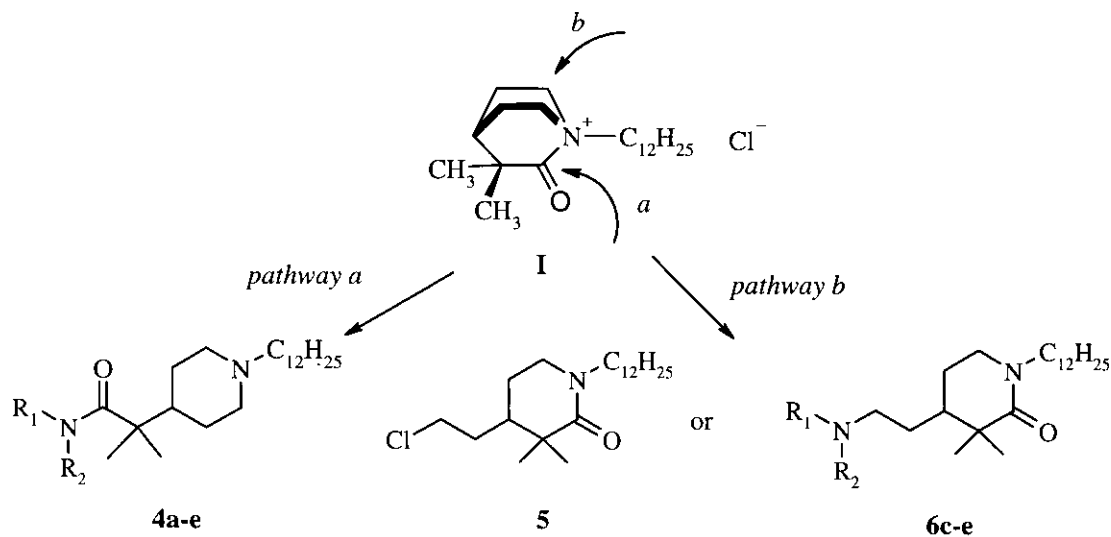
4-Piperidineethanamines (2) were obtained by condensation of amines  $R_1R_2NH$  with  $\alpha,\alpha$ -dimethyl-4-piperidineacetyl chloride (3) leading to amide compounds (4) which were subsequently reduced by  $LiAlH_4$  (Scheme 1).



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 ( $^1\text{H}$ ,  $^{13}\text{C}$  NMR, MS, IR, Elemental Analysis) as 4-(2-chloroethyl)-1-dodecyl-3,3-dimethyl-2-piperidone (**5**).



We speculated, as supported by the literature<sup>2-7</sup> that a rearrangement of 4-piperidineacetyl chloride (**3**)



- 4a**  $\text{R}_1 = \text{R}_2 = \text{H}$   
**4b**  $\text{R}_1 = \text{H}, \text{R}_2 = \text{CH}_3$   
**4c**  $\text{R}_1 = \text{R}_2 = \text{CH}_3$   
**4d**  $\text{R}_1 = \text{R}_2 = \text{C}_2\text{H}_5$   
**4e**  $\text{R}_1 = \text{CH}_3, \text{R}_2 = \text{Bn}$

- 6c**  $\text{R}_1 = \text{R}_2 = \text{CH}_3$   
**6d**  $\text{R}_1 = \text{R}_2 = \text{C}_2\text{H}_5$   
**6e**  $\text{R}_1 = \text{CH}_3, \text{R}_2 = \text{Bn}$

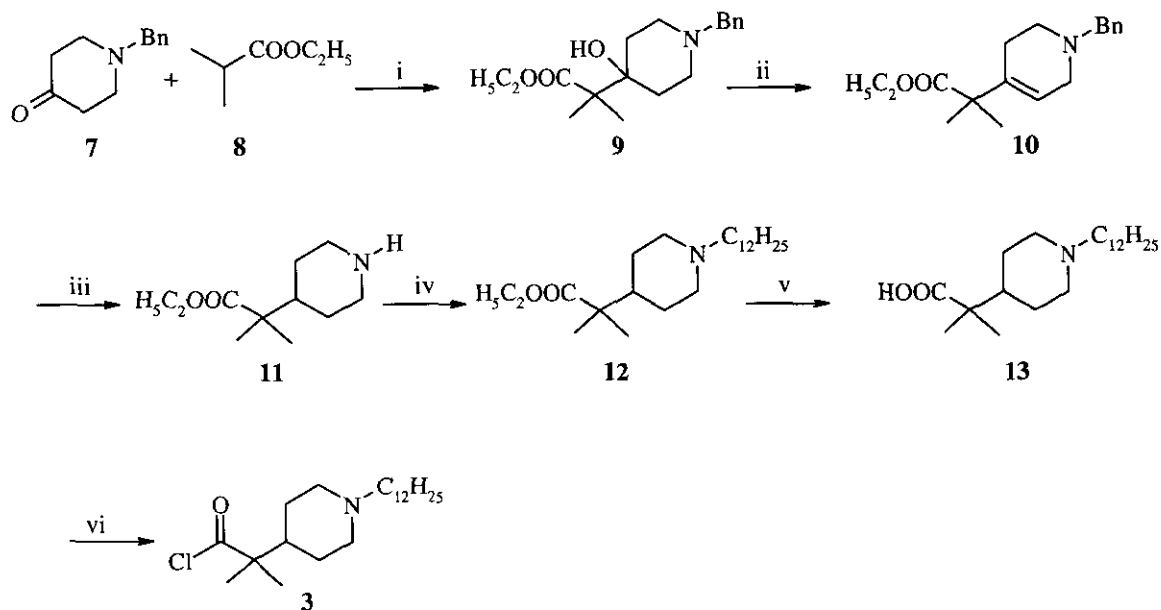
**Scheme 2**

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  $\text{SOCl}_2$  is described in Scheme 3.



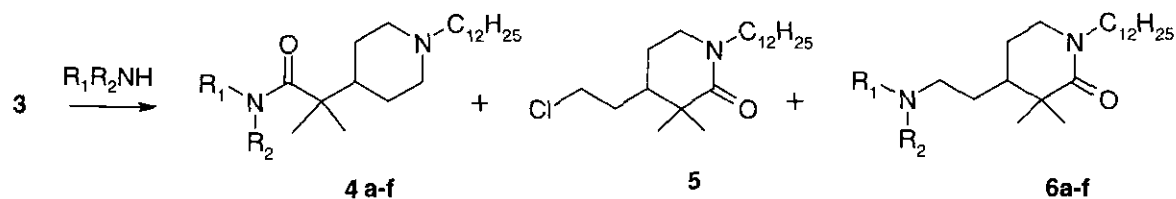
Reagents and conditions : i) LDA, THF,  $-50^{\circ}\text{C}$  ii)  $\text{SOCl}_2$ ,  $\text{CHCl}_3$ , cat DMF iii)  $\text{H}_2$ , 5% Pd/C,  $\text{CH}_3\text{OH}$ ,  $70^{\circ}\text{C}$  iv)  $\text{C}_{12}\text{H}_{25}\text{Br}$ ,  $\text{CH}_3\text{CN}$ ,  $\text{K}_2\text{CO}_3$ , NaI v) NaOH,  $\text{C}_2\text{H}_5\text{OH}$ ,  $\text{H}_2\text{O}$ , then 5N HCl vi)  $\text{SOCl}_2$ .

**Scheme 3**

Aldol condensation between 4-piperidone (**7**) and ester (**8**) in the presence of LDA led to 4-hydroxypiperidine<sup>8</sup> (**9**) which was subsequently dehydrated with  $\text{SOCl}_2$  in  $\text{CHCl}_3$  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  $\text{CH}_3\text{CN}$  gave **12** which was hydrolyzed with NaOH to yield the acid (**13**). Transformation of **13** into **3** was performed in  $\text{SOCl}_2$ .

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 <sub>1</sub> R <sub>2</sub> NH	yield % of product				
	4	5	6		
NH <sub>3</sub>	69	4a	0	0	6a
CH <sub>3</sub> NH <sub>2</sub>	72	4b	0	0	6b
(CH <sub>3</sub> ) <sub>2</sub> NH	56	4c	0	0	6c
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	22	4d	0	33	6d
Bn(CH <sub>3</sub> )NH	35	4e	0	23	6e
<i>i</i> Pr <sub>2</sub> NH	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<sub>1</sub> and R<sub>2</sub> 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<sub>3</sub> versus (CH<sub>3</sub>)<sub>2</sub>NH). 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.<sup>9</sup>

## EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer 782 spectrophotometer. <sup>1</sup>H and <sup>13</sup>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- $\alpha,\alpha$ -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<sub>2</sub> 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<sub>4</sub>Cl (400 mL) then extracted with ether. The organic layer was washed with brine, dried over MgSO<sub>4</sub> 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<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 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<sub>18</sub>H<sub>27</sub>NO<sub>3</sub>: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.23; H, 8.81; N, 4.96.

### 1,2,3,6-Tetrahydro- $\alpha,\alpha$ -dimethyl-1-phenylmethyl-4-pyridineacetic acid ethyl ester hydrochloride (**10**)

To a stirred solution of **9** (50 g, 0.164 mol) in  $\text{CHCl}_3$  (200 mL) and DMF (0.52 mL) was added dropwise  $\text{SOCl}_2$  (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  $\text{MgSO}_4$  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.  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ : 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).  $^1\text{H NMR}$  ( $\text{DMSO}-d_6 + \text{D}_2\text{O}$ )  $\delta$ : 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  $\text{C}_{18}\text{H}_{25}\text{NO}_2 \cdot \text{HCl}$ : C, 66.76; H, 8.09; N, 4.32. Found: C, 66.89; H, 8.10; N, 4.36.

#### **$\alpha,\alpha$ -Dimethyl-4-piperidineacetic acid ethyl ester (11)**

A solution of **10** (54.6 g, 0.169 mol) in  $\text{CH}_3\text{OH}$  (800 mL) was hydrogenated over 5% Pd/C (3 g) at 70°C under 80 bars  $\text{H}_2$  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  $\text{CH}_2\text{Cl}_2$ . The extracts were washed with brine, dried over  $\text{MgSO}_4$  and evaporated *in vacuo* to give **11** as a yellow oil (28.6 g, 85%). IR (neat) 3150, 1730  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 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  $\text{C}_{11}\text{H}_{21}\text{NO}_2 \cdot \text{HCl}$ : C, 56.04; H, 9.41; N, 5.94. Found: C, 56.48; H, 9.62; N, 5.96.

#### **$\alpha,\alpha$ -Dimethyl-1-dodecyl-4-piperidineacetic acid ethyl ester (12)**

A mixture of **11** (9.85 g, 0.05 mol),  $\text{K}_2\text{CO}_3$  (17.3 g, 0.125 mol), 1-bromododecane (14.9 mL, 0.062 mol) in  $\text{CH}_3\text{CN}$  (50 mL) was refluxed with stirring for 6 h. The reaction mixture was poured into water then extracted with  $\text{AcOC}_2\text{H}_5$ . The organic layer was washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on  $\text{SiO}_2$  with hexane- $\text{AcOC}_2\text{H}_5$

(9 : 1, v/v) as eluent to give **12** as an orange oil (6.7 g, 78%). IR (neat)  $1730\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 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:  $106^\circ\text{C}$  (ethyl alcohol-ether). Anal. Calcd for  $\text{C}_{23}\text{H}_{45}\text{NO}_2 \cdot \text{C}_4\text{H}_4\text{O}_4$ : C, 67.04; H, 10.21; N, 2.89. Found: C, 66.70; H, 10.11; N, 2.96.

### **$\alpha,\alpha$ -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  $192^\circ\text{C}$ . IR (KBr) 1700,  $2650\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 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  $\text{C}_{21}\text{H}_{41}\text{NO}_2 \cdot \text{HCl}$ : C, 67.07; H, 11.26; N, 3.73. Found: C, 67.02; H, 11.32; N, 3.85.

### **$\alpha,\alpha$ -Dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (3)**

**13** (17.9 g, 0.048 mol) was added by portion to  $\text{SOCl}_2$  (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,  $1930\text{ cm}^{-1}$ .

### **$\alpha,\alpha$ -Dimethyl-1-dodecyl-4-piperidineacetamide (4a)**

To a solution of **3** (8.6 g, 0.022 mol) in a mixture of toluene- $\text{CH}_2\text{Cl}_2$  (2 : 1, v/v, 100 mL) was carefully added liquid ammonia (80 mL) at  $-5^\circ\text{C}$ . After stirring for 72 h at rt, the reaction was quenched by water then extracted with  $\text{AcOC}_2\text{H}_5$ . The organic extracts were washed with water, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification of the residue by flash chromatography ( $\text{AcOC}_2\text{H}_5$ - $\text{CH}_3\text{OH}$ - $\text{NH}_4\text{OH}$ , 9 : 1 : 0.5, v/v) provided **4a** (5.2 g, 69%) as a colorless powder. mp  $123^\circ\text{C}$  (isopropyl ether). IR (KBr) 1630, 1650, 3220,  $3400\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 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*, $\alpha$ , $\alpha$ -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 ( $CDCl_3$ )  $\delta$ : 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*, $\alpha$ , $\alpha$ -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 ( $CDCl_3$ )  $\delta$ : 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  $C_{23}H_{46}N_2O \cdot C_4H_4O_4$ : C, 67.18; H, 10.44; N, 5.80. Found: C, 67.09; H, 10.46; N, 5.84.

#### 1-Dodecyl-*N,N*-diethyl- $\alpha$ , $\alpha$ -dimethyl-4-piperidineacetamide (**4d**) and 1-Dodecyl-4-[2-diethylamino)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 ( $CDCl_3$ )  $\delta$ : 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 ( $CDCl_3$ )  $\delta$ : 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 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).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 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  $\text{C}_{25}\text{H}_{50}\text{N}_2\text{O} \cdot \text{C}_2\text{H}_2\text{O}_4$ : 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- $\alpha,\alpha$ -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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 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 ( $\text{M}^+$ ).

**6e** IR (neat) 1640  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 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 ( $\text{M}^+$ ).

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

**4e** oxalate salt. mp: 125-130°C (ethyl alcohol). Anal. Calcd for  $\text{C}_{29}\text{H}_{50}\text{N}_2\text{O} \cdot \text{C}_2\text{H}_2\text{O}_4$ : 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  $\text{C}_{29}\text{H}_{50}\text{N}_2\text{O} \cdot \text{C}_2\text{H}_2\text{O}_4$ : 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  $\text{CHCl}_3$  (30 mL) was added dropwise at 0°C to a solution of **3** (18.7 g, 0.047 mol) in  $\text{CHCl}_3$  (100 mL). After stirring at rt for 3 days, the reaction mixture was quenched by 5N NaOH (50 mL) then extracted with  $\text{CH}_2\text{Cl}_2$  and the extracts were washed with brine and dried over  $\text{MgSO}_4$ . After evaporation of the solvent, the residue was chromatographed on  $\text{SiO}_2$

(toluene-isopropyl alcohol) to afford **5** (12.7 g, 75%). mp: 50°C (isopropyl ether). IR (KBr): 1640 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (CDCl<sub>3</sub>) 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<sup>+</sup>, <sup>35</sup>Cl) 357, 202 (M<sup>+</sup>-C<sub>11</sub>H<sub>23</sub>, <sup>35</sup>Cl). Anal. Calcd for C<sub>21</sub>H<sub>40</sub>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<sub>2</sub> (CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH, 9.5:0.5) to afford **6c** (1 g, 64%) as an oil. IR (neat) 1680 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>23</sub>H<sub>46</sub>N<sub>2</sub>O·C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>: C, 65.75; H, 10.59; N, 6.14. Found: C, 65.68; H, 10.43; N, 6.08.

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