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

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Abstract- Reaction of hindered amines with $\alpha,\alpha$-dimethyl-4-piperidoneacetyl 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 8aß-6-isoquinolineamine (1) as inhibitors of epoxysqualene cyclase, we prepared 4-piperidineethanamine derivatives$^{1b}$ 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 (\(^{1}H, ^{13}C\) NMR, MS, IR, Elemental Analysis) as 4-(2-chloroethyl)-1-dodecyl-3,3-dimethyl-2-piperidone (5).

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

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

We report herein details of the reaction of \(\text{3}\) with various amines.

**RESULTS AND DISCUSSION.**

The synthesis of the acid \((\text{13})\) giving rise to the acid chloride \((\text{3})\) by refluxing in \(\text{SOCl}_2\) is described in Scheme 3.

\[
\begin{array}{c}
\text{7} \quad \text{8} \\
\text{H}_2\text{C}_2\text{OOC} \quad \text{H}_2\text{C}_2\text{OOC} \\
\text{Bn} \quad \text{Bn} \\
\text{9} \quad \text{10} \\
\text{11} \quad \text{12} \quad \text{13} \\
\end{array}
\]

Reagents and conditions: i) LDA, THF, \(-50^\circ\text{C}\) ii) \(\text{SOCl}_2\), \(\text{CHCl}_3\), cat DMF iii) \(\text{H}_2\), 5% \(\text{Pd/C}\), \(\text{CH}_3\text{OH}\), 70°C iv) \(\text{C}_1\text{H}_2\text{Br}\), \(\text{CH}_3\text{CN}\), \(\text{K}_2\text{CO}_3\), \(\text{NaI}\) v) \(\text{NaOH}\), \(\text{C}_2\text{H}_5\text{OH}\), \(\text{H}_2\text{O}\), then 5N \(\text{HCl}\) vi) \(\text{SOCl}_2\).

Scheme 3

Aldol condensation between 4-piperidone \((\text{7})\) and ester \((\text{8})\) in the presence of LDA led to 4-hydroxy-piperidine\(^8\) \((\text{9})\) which was subsequently dehydrated with \(\text{SOCl}_2\) in \(\text{CHCl}_3\) to give \(\text{10}\). Hydrogenation of the double bond and hydrogenolysis of the benzyl group of \(\text{10}\) proceeded in one step with 5% \(\text{Pd/C}\) as catalyst to afford \(\text{11}\). Alkylation of \(\text{11}\) with 1-bromododecane in \(\text{CH}_3\text{CN}\) gave \(\text{12}\) which was hydrolyzed with \(\text{NaOH}\) to yield the acid \((\text{13})\). Transformation of \(\text{13}\) into \(\text{3}\) 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.

<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;NH</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₃</td>
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<td>0</td>
</tr>
<tr>
<td>CH₃NH₂</td>
<td>72</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(CH₃)₂NH</td>
<td>56</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(C₂H₅)₂NH</td>
<td>22</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Bn(CH₃)NH</td>
<td>35</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>iPr₂NH</td>
<td>0</td>
<td>50</td>
<td>0</td>
</tr>
</tbody>
</table>

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 R₁ and R₂ 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. NH₃ versus (CH₃)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. 1H and 13C 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 N2 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 NH4Cl (400 mL) then extracted with ether. The organic layer was washed with brine, dried over MgSO4 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; 1H NMR (CDCl3) 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 C18H27NO3: 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 CHCl₃ (200 mL) and DMF (0.52 mL) was added dropwise SOCl₂ (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 MgSO₄ 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 (38.9 g, 74%). mp 208°C. ¹H NMR (DMSO-d₆) 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). ¹H NMR (DMSO-d₆ + D₂O) 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 C₁₈H₂₅N₂.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 CH₃OH (800 mL) was hydrogenated over 5% Pd/C (3 g) at 70°C under 80 bars H₂ 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 CH₂Cl₂. The extracts were washed with brine, dried over MgSO₄ and evaporated in vacuo to give 11 as a yellow oil (28.6 g, 85%). IR (neat) 3150, 1730 cm⁻¹; ¹H NMR (CDCl₃) 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).


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

A mixture of 11 (9.85 g, 0.05 mol), K₂CO₃ (17.3 g, 0.125 mol), 1-bromododecane (14.9 mL, 0.062 mol) in CH₃CN (50 mL) was refluxed with stirring for 6 h. The reaction mixture was poured into water then extracted with AcOCl₃H₅. The organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The resulting residue was subjected to column chromatography on SiO₂ with hexane-AcOCl₃H₅.
(9 : 1, v/v) as eluent to give 12 as an orange oil (6.7 g, 78%). IR (neat) 1730 cm\(^{-1}\); \(^1\)H NMR (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°C (ethyl alcohol-ether). Anal. Calcd for C\(_{23}\)H\(_{45}\)NO\(_2\), C\(_4\)H\(_4\)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%). IR (KBr) 1700, 2650 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 0.88 (t, \(J=6.4\) Hz, 3H), 1.18 (s, 6H), 1.27 (m, 18H), 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\(_{23}\)H\(_{45}\)NO\(_2\). 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 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\(^{-1}\).

\(\alpha,\alpha\)-Dimethyl-1-dodecyl-4-piperidineacetaamide (4a)

To a solution of 3 (8.6 g, 0.022 mol) in a mixture of toluene-CH\(_2\)Cl\(_2\) (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 AcOCC\(_2\)H. The organic extracts were washed with water, dried over MgSO\(_4\) and concentrated in vacuo. Purification of the residue by flash chromatography (AcOCC\(_2\)H-CH\(_2\)OH-NH\(_4\)OH, 9 : 1 : 0.5, v/v/v) provided 4a (5.2 g, 69%) as a colorless powder. mp 123°C (isopropyl ether). IR (KBr) 1630, 1650, 3220, 3400 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 0.88 (t, \(J=6.4\) Hz, 3H), 1.13 (s, 6H), 1.25-1.60 (m,
1-Dodecyl-N,N,N,N-tetramethyl-4-piperidineacetamide (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 (CDCl₃) 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 C₂₃H₄₆N₂O. C₄H₄O₄: 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-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 CHCl₃ (300 mL). The reaction mixture was stirred at 0°C for 3 days, then the reaction was quenched by 1N NaOH and extracted with AcO₂C₂H₅. The extracts were washed with brine, dried over MgSO₄ and concentrated in vacuo to give a red oily residue which was chromatographed on SiO₂ (CH₂Cl₂: CH₃OH, 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 (CDCl₃) 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). ¹³C NMR (CDCl₃) 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 C₂₅H₅₀N₂O: C, 76.09; H, 12.77; N, 7.10 Found: C, 76.25; H, 12.55; N, 7.25.
6d IR (neat) 1640 cm\(^{-1}\); \(^1\)H NMR (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). \(^13\)C NMR (CDCl\(_3\)) \(\delta\): 175.4, 51.3, 47.6, 46.8, 46.7, 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\(_{23}\)H\(_{30}\)N\(_2\)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-[(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\(^{-1}\); \(^1\)H NMR (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 (El) m/z 442 (M\(^+\)).

6e IR (neat) 1640 cm\(^{-1}\); \(^1\)H NMR (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 (El) m/z 442 (M\(^+\)).

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


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\(_2\)Cl\(_2\) 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\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 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\(_3\)) \(\delta\): 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 (El) m/z: \((M^+ , 35\)Cl \) 357, 202 \((M^+ -C\(_1\)H\(_2\), Cl\)\). Anal. Calcd for C\(_{21}\)H\(_{40}\)NOCI: 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\(_2\)Cl\(_2\) : CH\(_3\)OH, 9.5 : 0.5) to afford \(6c\) (1 g, 64%) as an oil. IR (neat) 1680 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 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\(_2\)O\(_2\): C, 65.75; H, 10.59; N, 6.14. Found: C, 65.68; H, 10.43; N, 6.08.

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REFERENCES


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