AN EASY ACCESS TO THE EXOCYCLIC LACTAMS ANALOGOUS OF THE CENTRAL NERVOUS SYSTEM ACTIVE TRICYCLIC NITROXAPINE, MIANSERINE AND CHLOTHIAPINE AGENTS USING N-ACYLIMINIUM CHEMISTRY

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Abstract – The conformationally restrained dibenzothia(oxa)zepines and dibenzazepines 4-6 analogous to the antidepressant Sintamil® were prepared easily by \(\pi\)-cationic cyclization of the \(N\)-acyliminium ions 9A-C precursors with neat trifluoroacetic acid in three step-sequence starting from available amines and anhydrides. The regioselectivity in the reduction of imides especially in the cyclization step was also discussed.

INTRODUCTION
Dibenzothia(oxa)zepines are important and widely used scaffolds in medicinal chemistry. For example, Methiapine (1a) and Clothiapine (1b) are reported as anti-psychoneurotics\(^\text{1}\) and their oxygenated derivatives Defanyl\(^\text{®}\) (2a),\(^\text{2}\) Sintamil\(^\text{®}\) (2c)\(^\text{3}\) and Loxpine (2b)\(^\text{4}\) are also efficient as antidepressants and antipsychotics, respectively. In addition, other analogous have also shown remarkable activities as a non-nucleoside type inhibitors of wild type HIV-1 replication.\(^\text{5}\) The dibenzothiazepine Seroguel related to products 1a,b, exerts and increasing 5-HT\(_2\) affinity relative to the so popular Clozapine and possibly a lower potential for causing agranulocytosis,\(^\text{6}\) constitutes also another interesting example. Also, dibenzodiazepines Perlapine (3a) and Mianserine (3b), as the carbon-analogous of the latter structures, were used for their hypnotic and sedative properties and for the treatment of depressions associated or not with the anxiety. As a consequence, new methods enabling the efficient preparation of libraries based on these scaffolds should be useful for lead generation of various drug discovery programs.
RESULTS AND DISCUSSION

In our group we are interested in the development of simple approaches towards aza-heterocyclic systems containing benzo(thia and oxa)azepines moieties with promising pharmaceutical activities. Our objective herein was to construct the conformationally restrained products 4-6 analogous to Sintamil® (2c) and the use of N-acyliminium chemistry to provide these targets in an efficient and concise manner seemed to be a valuable strategy. In fact, in association with our recent reports using N-acyliminium cyclization in tandem with Grignard reaction and heterocyclization processes, we reasoned that a suitably substituted N-acyliminium precursor of type 1 could allow a facile approach to the title targets 4-6 (Scheme 1).

First, the synthesis of the required N-acyliminium ions precursors of type 10 was accomplished by a two-step sequence as outlined in Scheme 2. The N-alkylated imides 9 as starting materials are not commercially available but were prepared easily according to known procedures from anhydrides 7A-C and amines 8a-d by thermal amino-anhydride condensation in refluxing acetic acid for 48 h (40-99%). Reduction of imides 9Aa (X=O) and 9Ab (X=S) was performed with a large excess of NaBH₄ (3-6 equiv.) in dry EtOH at 0 °C for a short time (1 h). Under these conditions, only the opened alcohol-amides 10A(a,b)U were isolated in excellent yields (Table 1). Interestingly, the reaction profile was inverted giving the expected hydroxyl-lactams 10A(a,b)V when Zn(BH₄)₂ was used instead of NaBH₄ under
conditions ii (Scheme 2). The yields were however lower (61 and 66\%, respectively) than those obtained for 10A(a,b)U under conditions i. Further, all attempts of reduction of imides 9B(a,b) to access hydroxyl-lactams 10B(a,b) by using conditions i but at 0-5 °C failed since only succinimide derivatives 9A(a,b) were isolated in high yields average 90\% in both cases. The regioselective reduction of one function of the imides 9B(a-d) was ultimately accomplished under mild conditions with NaBH₄ in MeOH at 0 °C for 1-2 h (monitored by TLC using a silica gel plate and cyclohexane/AcOEt as the eluting mixture) in the presence of CeCl₃.7H₂O (40-99\% yield). By using the same protocol, the imides 9C(a-d) provided only α-hydroxy-lactams 10C(a-d) in yields ranging from 40 to 83\%. In all cases no opened alcohol-amides were detected in the crude reaction mixture but we observe the formation of two regioisomers in 9:1 (10CaU,V; 60\% yield) and 8:2 (10CdU,V; 40\% yield) ratios in favor of 10C(a,d)V in which the hydroxyl function is near the methyl group at C4-position of the 1,5-dihydropyrrol-2-one nuclei. These results are in accordance with those published by us and others for related structures.

**Scheme 2.** Scheme leading to α-hydroxy-lactams 10 precursors of the tetracyclic systems.

![Scheme 2](image)

**Table 1.** Imides 10 and corresponding α-hydroxy-lactams 10.

<table>
<thead>
<tr>
<th>Product</th>
<th>Imide 9A Yield (%)</th>
<th>Alcool-amide 10AU Yield (%)</th>
<th>Hydroxy-lactam 10AV Yield (%)</th>
<th>Imide 9B Yield (%)</th>
<th>Hydroxy-lactam 10B Yield (%)</th>
<th>Imide 9C Yield (%)</th>
<th>Hydroxy-lactams 10CU Yield (%)</th>
<th>Hydroxy-lactams 10CV Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a (X=O)</td>
<td>93</td>
<td>89 (0)</td>
<td>0 (61)</td>
<td>61</td>
<td>81</td>
<td>93</td>
<td>68</td>
<td>(80/20)</td>
</tr>
<tr>
<td>b (X=S)</td>
<td>95</td>
<td>93 (0)</td>
<td>0 (66)</td>
<td>64</td>
<td>69</td>
<td>90</td>
<td>47</td>
<td>(100/0)</td>
</tr>
<tr>
<td>c (X=S)</td>
<td>-a</td>
<td>-a</td>
<td>-a</td>
<td>58</td>
<td>47</td>
<td>40</td>
<td>83</td>
<td>(100/0)</td>
</tr>
<tr>
<td>d (X=CH₂)</td>
<td>-a</td>
<td>-a</td>
<td>-a</td>
<td>65</td>
<td>74</td>
<td>99</td>
<td>40</td>
<td>(90/10)</td>
</tr>
</tbody>
</table>

* The reaction was not performed in this case. Conditions i lead only to alcohol-amides 10A(a,b)U while conditions ii provided exclusively α-hydroxy-lactams 10A(a,b)V. The ratio of products was determined by ¹H NMR spectroscopy. Yields of the reaction are in % and the ratios are given in parentheses.
Having established earlier the capacity of trifluoroacetic acid to promote the capture of an \( N \)-acyliminium ion in an intramolecular manner with an array of nucleophiles,\(^7\)\(^8\) \( \alpha \)-phenyoxy(thio)-\( N \)-phenylamidals and \( \alpha \)-benzyl-\( N \)-phenylamidals of type 10 (Scheme 3) were subjected to this general \( \pi \)-cyclization protocol (neat TFA, room temperature).\(^13\) Under these conditions, \( \alpha \)-hydroxy-lactams 10A,B provided a cyclized lactams 4a,b\(^14\) and 5a-d\(^15\) with the intermediacy of species I (Scheme 1). In the tetracyclic system 5a-d, the double bond of the dihydropyrrole ring is in conjugation with the benzene ring in accordance with our own earlier observations.\(^11\) Interestingly, under same conditions a mixture of 10C(a-d)U and 10C(a-d)V led to the expected products 6U and 6V in moderate to very good yields (Table 2). These products, which in case of 6(a,b)U\(^16\) and 6(a,b)V were separable easily by flush chromatography on silica gel column, were obtained in yields ranging from 46 to 84% (Table 2). The structure of these products as well as all reported in this paper was supported by NMR (\(^1\)H, \(^{13}\)C, Dept) spectroscopic analysis. In fact, the NMR studies demonstrate that lactams 6(a,c,d)U appeared in less conjugated form (proved by the presence of an angular proton in the \(^1\)H NMR spectra) except in the case of 6bU (form L) while lactams 6(a,b)V exist only in the more conjugated form as mentioned above for the corresponding lactams 5a-d.

Scheme 3. \( \pi \)-Cyclization of \( \alpha \)-hydroxy-lactams 10 into the tetracyclic systems 4-6.

\[
\begin{align*}
\text{10A(a,b)V} & \quad \text{TFA, ta} \quad \text{12 h} \\
\text{10B(a-d)} & \quad \text{TFA, ta} \quad \text{12 h} \\
\text{10C(a-d)U} & \quad \text{TFA, ta} \quad \text{12 h} \\
\text{10C(a-d)V} & \quad \text{TFA, ta} \quad \text{12 h}
\end{align*}
\]

Table 2. Yields and melting points of the tetracyclic systems 4-6.

<table>
<thead>
<tr>
<th>Product index</th>
<th>Cyclic product 4 Yield (%), mp (°C)</th>
<th>Cyclic product 5 Yield (%), mp (°C)</th>
<th>Cyclic product 6U Yield (%), mp (°C)</th>
<th>Cyclic product 6V Yield (%), mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a ) (X=O)</td>
<td>84 , 127</td>
<td>64 , 115</td>
<td>65(^b) , 159</td>
<td>65(^b) , 172</td>
</tr>
<tr>
<td>( b ) (X=S)</td>
<td>87 , 144</td>
<td>57 , 207</td>
<td>84(^c) , 207</td>
<td>84(^c) , 170</td>
</tr>
<tr>
<td>( c ) (X=S)</td>
<td>-(^a)</td>
<td>66 , 172</td>
<td>71 , 129</td>
<td>-(^d)</td>
</tr>
<tr>
<td>( d ) (X=CH(_2))</td>
<td>-(^a)</td>
<td>45 , 181</td>
<td>46 , 155</td>
<td>-(^d)</td>
</tr>
</tbody>
</table>

\(^a\) No reaction was performed in this case. \(^b\) The separable regioisomers were obtained in 9/1 ratio in favor of 6aU. \(^c\) The separable regioisomers were obtained in 8/2 ratio in favor of 6bU. \(^d\) Products not obtained.
In summary, we have developed efficient and versatile method for the synthesis of conformationally constrained 4-6 analogous to the antidepressant Sintamil® in three step-sequence starting from easily available substrates. The key step of this sequence was the trifluoroacetic acid-catalyzed intramolecular \( \pi \)-cationic cyclization and significant structural variation via the heteroelement (X=O, S, CH\(_2\)) as an \( N \)-acyliminium source was also realized.

**ACKNOWLEDGEMENTS**

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**REFERENCES AND NOTES**


13. General procedure for cyclization of hydroxy-lactams 10. Neat TFA (10 mL) was added to a stirred solution of the hydroxyl-lactam (10, 10 mmol), obtained by standard borohydride reduction of the imide 9 as indicated above in the text. After 4–12 h of reaction at rt whilst stirring, the reaction mixture was diluted with water (45 mL) and neutralized on cooling with 5% NaOH aqueous solution. The solution was extracted twice with CH₂Cl₂ (25 mL) and separated. The organic layer was washed with water, brine, separated, dried with MgSO₄, and the solvents evaporated in vacuo. The resulting crude residue was purified by chromatography [SiO₂, AcOEt/cyclohexane (4:1)] and recrystallized from the indicated solvents to give the expected tricyclic product.

14. Selected data for 1,2,3,13b-tetrahydropyrrolo[1,2-d]dibenzo[b,f][1,4]oxazepin-3-one (4a). This compound was isolated as a white solid in 84% yield after recrystallization from Et₂O and melted at 127 °C; IR (KBr) ν 1711 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.22-2.44 (m, 1H, H₇pyrrolidine), 2.47-2.71 (m, 3H, H₇pyrrolidine), 5.28-5.39 (m, 1H, CH), 7.07-7.28 (m, 7H, H aromatic), 7.72 (d, 1H, J=8.3 Hz, H aromatic); ¹³C-NMR (CDCl₃) δ 27.1 (CH₂), 31.3 (CH₂), 60.4 (CH), 121.8 (CH), 125.0 (CH), 125.1 (CH), 125.2 (CH), 126.6 (CH), 127.0 (CH), 127.6 (CH), 129.5 (CH), 130.4 (Cq), 130.9 (Cq), 151.6 (Cq), 155.7 (Cq), 174.1 (CO); MS (EI, 70 ev) m/z: 251 (M+); Anal. Calcd for C₁₆H₁₃NO₂ (251.28): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.31; H, 5.09; N, 5.48.

15. Selected data for 1,2-dihydropyrrolo[1,2-d]dibenzo[b,f][1,4]oxazepin-3-one (5a). This product was isolated as a white solid in 64% yield after recrystallization from Et₂O/cyclohexane and melted at 115 °C; IR (KBr) ν 1712 cm⁻¹; ¹H-NMR (CDCl₃) δ 3.40 (s, 2H, CH₂-C=), 5.60 (s, 1H, CH=C), 7.13-7.42 (m, 6H, H aromatic), 7.52 (d, 1H, J=7.6 Hz, H aromatic), 7.87 (d, 1H, J=7.6 Hz, H aromatic); ¹³C-NMR (CDCl₃) δ 37.5 (CH₂), 102.3 (CH=), 121.0 (CH), 121.8 (CH), 125.5 (CH), 125.6 (CH), 125.7 (CH), 127.0 (Cq), 127.3 (CH), 128.6 (CH), 129.0 (Cq), 131.2 (CH), 142.5 (Cq), 151.5 (Cq), 156.6 (Cq), 176.1 (CO); MS (EI, 70 ev) m/z: 249 (M+); Anal. Calcd for C₁₆H₁₁NO₂ (249.27): C, 77.10; H, 4.45; N, 5.62. Found: C, 76.92; H, 4.30; N, 5.48.

16. Selected data for 1-methyl-3,13b-dihydropyrrolo[1,2-d]dibenzo[b,f][1,4]oxazepin-3-one (6Ua). This product was isolated as a white solid in 65% yield after recrystallization from Et₂O/hexane and melted at 159 °C; IR (KBr) ν 1687 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.07 (d, 3H, J=1.3 Hz, CH₃(CH₃)), 6.11 (q, 1H, J=1.3 Hz, CH(CH₃)), 6.96-7.17 (q, 4H, H aromatic+CH=C), 7.20-7.35 (m, 4H, H aromatic), 8.85 (d, 1H, J=7.6 Hz, H aromatic); ¹³C-NMR (CDCl₃) δ 11.6 (CH₃), 60.7 (CH), 120.7 (CH), 121.3 (CH), 122.0 (CH), 125.0 (CH), 125.2 (CH), 125.3 (CH), 126.8 (CH), 129.5 (Cq), 130.6 (CH), 131.2 (Cq), 137.5 (CH), 137.7 (Cq), 146.1 (Cq), 156.6 (Cq), 169.9 (CO); MS (EI, 70 ev) m/z: 263 (M+); Anal. Calcd for C₁₇H₁₃NO₂ (263.29): C, 77.55; H, 4.98; N, 5.32. Found: C, 77.33; H, 4.76; N, 5.16.