REACTION OF 4-ARYL-2,3-DIHYDRO-2-PHENYL-1H-1,5-BENZODIAZEPINES WITH 2-CHLOROACETYL CHLORIDE. SYNTHESIS OF N-ACYL- AND AZETO[1,2-a]-1,5-BENZODIAZEPINES

Braulio Insuasty,* Jairo Quiroga,* Rodrigo Abonia,* Henry Insuasty, Rodrigo Abonia, Henry Escobar, Emilso Diaz and Manuel Nogueras
jaquir@univalle.edu.co

*aGrupo de Investigacion en Compuestos Heterociclicos, Departamento de Quimica, Universidad del Valle, A.A. 25360 Cali, Colombia. bDepartamento de Quimica, Universidad de Narino, A. A. 1175, Pasto, Colombia. cDepartamento de Quimica Inorganica y Organica, Universidad de Jaen, 23071 Jaen, Spain

Abstract: It was found that 2-chloroacetyl chloride 7 reacts primarily over the NH-group at position 1 of 1,5-benzodiazepines 6a-e in dry benzene at room temperature in the presence of TEA to render the N-acetyl derivatives 8a-e in good yields. Subsequently, cycloaddition reaction of compounds 8a-e with 7 in dry benzene-TEA lead to the formation of the new azeto[1,2-a][1,5]benzodiazepines 9a-e in moderate yields, involving the imino (C=N) moiety at position 4. The structure of compounds 8a-e and 9a-e was assigned by 1H and 13C NMR spectra and 2D experiments.

Introduction

The importance of β-lactam derivatives in medicinal chemistry has been clearly demonstrated.1 Owing to their high efficacy and extremely safe toxicological profile; they are the agents of choice in the current therapeutic index for bacterial infections. Tremendous efforts have been made for the synthesis and structural modification of the β-lactam nucleus to increase antimicrobial activity and pharmacokinetic performance.

Apart from their clinical use, recent reports on the use of β-lactams for purposes other than antibiotic ones are gaining attention. This four-member cyclic amide has been extensively used for the synthesis of several biological active heterocyclic compounds: the anti-tumor drug paclitaxel (Taxol™) can be prepared by coupling of naturally occurring baccatin and an appropriately substituted hydroxy β-lactam.2 Additionally, it has been established that certain β-lactams have cholesterol-lowering properties.3

On the other hand, some 1,5-benzodiazepines are compounds showing high bioactivity as neoplasm inhibitors4 (for example, benzodiazepine 1) and as antiepileptic agents5 (for example, clobazan 2) (Figure-1). Now we are interested in the synthesis of new acylated and tricyclic benzodiazepine derivatives because it has been found that adding a chain or another ring to the previous system it could improve the biological activity for those compounds.6

Figure-1 : Some 1, 5-benzodiazepines with biological activity
Recently, our research group\textsuperscript{7} reported the selective synthesis of the 1,5-benzodiazepine derivatives 3, 4 and 5 (Figure-2) from the reaction of \( \beta \)-(N,N-dimethylamino)propiophenones and \textit{ortho}-phenylenediamine. Continuing with these findings we decided to prepare new N-acylated derivatives 8a-e and tricyclic \( \beta \)-lactams 9a-e through N-acylation and cycloaddition reactions of 4-aryl-2,3-dihydro-2-phenyl-1\( H \)-1,5-benzodiazepines 6a-e with 2-chloroacetyl chloride 7.

\textbf{Results and Discussions}

The starting benzodiazepines 6a-e were obtained following a procedure similar to reported by Pozarentzi and co-workers,\textsuperscript{8} from the reaction of \textit{o}-phenylenediamine and chalcones in the presence of catalytic amounts of acetic acid, under microwave irradiation.

Subsequently, the benzodiazepines 6a-e were subjected to reaction with the acyl chloride 7 in dry benzene and TEA at room temperature, affording the N-(2-chloroacetyl)-1,5-benzodiazepine derivatives 8a-e in good yields (66-95\%) (Scheme-1, Table-1).
Table-1: N-Acyl 1,5-benzodiazepine derivatives 8a-e and Azeto[1,2-a][1,5]benzodiazepines 9a-e

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Ar</th>
<th>m.p., °C</th>
<th>Yield, %</th>
<th>Time, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>C₆H₄</td>
<td>176</td>
<td>90</td>
<td>3</td>
</tr>
<tr>
<td>8b</td>
<td>4-CH₃C₆H₄</td>
<td>142</td>
<td>91</td>
<td>1</td>
</tr>
<tr>
<td>8c</td>
<td>4-ClC₆H₄</td>
<td>149</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>8d</td>
<td>4-BrC₆H₄</td>
<td>153</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>8e</td>
<td>4-O₂NC₆H₄</td>
<td>148</td>
<td>95</td>
<td>3</td>
</tr>
<tr>
<td>9a</td>
<td>C₆H₄</td>
<td>261</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>9b</td>
<td>4-CH₃C₆H₄</td>
<td>221</td>
<td>41</td>
<td>8</td>
</tr>
<tr>
<td>9c</td>
<td>4-ClC₆H₄</td>
<td>245</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>9d</td>
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<tr>
<td>9e</td>
<td>4-O₂NC₆H₄</td>
<td>235</td>
<td>35</td>
<td>8</td>
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</tbody>
</table>

In the same way, a prolonged treatment of compounds 8a-e with an excess of acetyl chloride 7 in refluxing dry benzene-TEA media led to the new azeto[1,2-a]-1,5-benzodiazepines 9a-e in moderate yields (35-52 %) (Scheme-1, Table-1).

The structure of compounds 8a-e and 9a-e were assigned by IR, 'H and 13C NMR and two-dimensional experiments and confirmed by mass spectrometry.

In the IR spectra of compounds 8a-e a characteristic band for the C=N group is observed at 1604-1587 cm⁻¹ along with a band at 1664-1650 cm⁻¹ assigned to the C=O stretching vibration of the side chain. In consequence the typical band of the starting materials 6a-e assignable to the N-H stretching is not present. Compounds 9a-e did not exhibit absorptions for the C=N group, but they show two bands at 1772-1762 cm⁻¹ and 1679-1650 cm⁻¹ assigned to the two C=O groups of β-lactam and the amide moities respectively, which indicate the incorporation of a second molecule of acetyl chloride 7.

The most characteristic 'H NMR signals for compounds 8a-e corresponds to the CH₂-CH fragment of the diazepine ring which appears as a AMX spin system and show three sets of signals at δ = 2.87 - 2.74 (t, 1H, HA), 3.58 - 3.47 (dd, 1H, HM) and 6.25 - 6.15 (dd, 1H, HX) with coupling constants JAM = 13 Hz, JAX = 14 Hz and JMX = 5 Hz. Two doublets at δ = 3.77 and 4.16 assigned to H-L also are observed for these compounds. The 13C NMR spectra of compounds 8a-e show a typical signal for the amide C=O group at δ = 165.8 - 165.5 ppm, which confirm the formation of the expected N-acyl systems. Additionally, these structures were confirmed by X-ray diffraction of compound 8a.

The 'H NMR spectra of compounds 9a-e show also the pattern for the fragment CH₂-CH of the diazepine ring, the characteristic signals for H-11 in the side chain on N-1 and a singlet at δ = 5.75 - 5.61 assigned to the 2-H of the β-lactam ring which appears relatively shifted to downfield by the effect of the vicinal electron-withdrawing chloride and carbonyl groups.
All carbon atoms and the remaining protons were assigned on the basis of DEPT and two-dimensional experiments (COSY, HSQC, HMBC and NOESY).

In the HMBC spectra of compounds 9a-e were observed three-bond correlations between C-3 and H-2 and between C-2 and H_M as well as two-bond correlations between C-1 and H-2 and between C-2a and H-2, which helped us to corroborate the formation of the four-member ring (β-lactam). Additionally, the NOESY spectra shows a spatial correlation between H_A and 2-H which is only possible if the cycloaddition of 7 over the C=N moiety of 8a-e has proceeded.

According to the results and in agreement with earlier reports\textsuperscript{7,10,11,13} we suggest the following sequence of steps for the formation of products 8a-e and 9a-e. Compounds 8 and 9 could be formed through intermediates as shown in Scheme 2. In the first reaction (N-acylation), TEA was added to the solution of 6a-e in benzene before adding the acyl chloride 7 with the purpose not only to neutralize the hydrogen chloride formed during the process but also to activate the NH group of 6 toward nucleophilic attack, because is well known\textsuperscript{9} on its lesser reactivity than a typical NH group. In the second reaction (cycloaddition) the TEA helps to trap the HCl formed and also to remove one of the two α-hydrogen atoms from the acyliminium intermediate 10 to form the enolate intermediate 11, whose subsequent cyclization generates the fused azete ring in compounds 9a-e.
Experimental
All melting points were determined on a Buchi melting-point apparatus and are uncorrected. NMR spectra were recorded on a Bruker DPX 300 (300 MHz and 75.5 MHz for $^1$H and $^{13}$C, respectively), DMSO-$d_6$ as solvent, TMS as internal standard. IR spectra were recorded on an ATI-MATTSON FT spectrophotometer for samples in KBr discs. Mass spectra were run on a Hewlett Packard 5989-B spectrometer (El, 70 eV). The elemental analysis has been obtained using a LECO CHNS-900 equipment.

General procedure for the synthesis of 4-Aryl-1-(chloroacetyl)-2,3-dihydro-2-phenyl-1H-1,5-benzodiazepines 8a-e.
A solution of 2-chloroacetyl chloride 7 (1 mmol) in dry benzene (5 mL) was added dropwise at room temperature to a solution of the corresponding benzodiazepine 6a-e (1 mmol) and TEA (excess) in dry benzene (20 mL). The reaction mixture was stirred for 1-5 h at room temperature and monitored by TLC. Solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel and chloroform as eluent.

1-(Chloroacetyl)-2,3-dihydro-2,4-diphenyl-1H-1,5-benzodiazepine 8a:
Pale yellow crystals, yield 90%; m.p. 176 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ = 2.80 (t, 1H, $H_2$), 3.53 (dd, 1H, $H_3$), 3.76 (d, 1H, 11'-H), 4.18 (d, 1H, 11-H), 6.18 (dd, 1H, $H_2$, 1H, $H_3$), 7.24-7.59 (m, 9H, Aromat. H), 7.56 (d, 2H, $H_{ar}$, Ar), 8.17 (d, 2H, $H_{ar}$, Ar); $^{13}$C NMR (DMSO-$d_6$): $\delta$ = 34.2 (C-3), 42.4 (C-11), 67.0 (C-2), 128.2 (C-9a), 136.9 (C, Ar), 139.8 (C, Ph), 147.3 (C-5a), 156.6 (C-10), 170.1 (C-4); [125.2, 125.8, 126.3, 127.4, 127.7, 28.4, 128.7, 129.9, 131.4 (aromat. C)], MS (70 eV): m/z (%) = 376/374 (M+, 36/68), 339 (45), 337 (55), 297 (87), 194 (100), 191 (51).
Anal. Calcd. for C$_{23}$H$_{18}$BrClN$_2$O: C, 60.88; H, 4.00; N, 6.17. Found: C, 60.82; H, 4.05; N, 6.12.

4-(4-Bromophenyl)-1-(chloroacetyl)-2,3-dihydro-2-phenyl-1H-1,5-benzodiazepine 8d:
Pale yellow crystals, yield 70%; m.p. 153 °C; $^1$H NMR (DMSO-$d_6$): $\delta$ = 2.79 (t, 1H, $H_2$), 3.50 (dd, 1H, $H_3$), 3.75 (d, 1H, 11'-H), 4.16 (d, 1H, 11-H), 6.18 (dd, 1H, $H_2$, 1H, $H_3$), 7.25-7.57 (m, 9H, Aromat. H), 7.73 (d, 2H, $H_{ar}$, Ar), 8.12 (d, 2H, $H_{ar}$, Ar); $^{13}$C NMR (DMSO-$d_6$): $\delta$ = 34.1 (C-3), 42.5 (C-11), 67.1 (C-2), 125.3 (C$_p$ Ar), 128.3 (C-9a), 136.1 (C Ar), 139.7 (C, Ph), 147.1 (C-5a), 156.7 (C-10), 169.4 (C-4); [125.3, 126.0, 126.4, 127.8, 128.4, 129.6, 129.9, 130.1, 131.8 (aromat. C)], MS (70 eV): m/z (%) = 456/454/452 (M+, 26/51/44), 417 (45), 405 (62), 403 (64), 377 (57), 375 (61), 349 (20), 272 (38), 270 (49), 77 (100).
Anal. Calcd. for C$_{23}$H$_{18}$BrClN$_2$O: C, 60.88; H, 4.00; N, 6.17. Found: C, 60.82; H, 4.05; N, 6.12.
1-(Chloroacetyl)-2,3-dihydro-4-(4-nitrophenyl)-2-phenyl-1H-1,5-benzodiazepine 8e: Pale yellow crystals, yield 95%; m.p. 148 °C; ¹H NMR (DMSO-δδ): δ = 2.87 (t, 1H, H₆), 3.58 (dd, 1H, H₅), 3.77 (d, 1H, H₅), 4.16 (d, 1H, Hₓ), 6.25 (dd, 1H, Hₓ), 7.30-7.61 (m, 9H, aromat. H), 8.35 (d, 2H, Hₖ Ar), 8.43 (d, 2H, Hₗ Ar); ¹³C NMR (DMSO-δδ): δ = 34.4 (C-3), 42.5 (C-11), 67.2 (C-2), 128.3 (C-9a), 139.7 (C, de B), 142.6 (Cₚ of ring A), 146.9 (C, of ring A), 149.0 (C-5a), 165.8 (C-10), 169.1 (C-4), [123.9, 125.5, 126.5, 126.6, 127.9, 128.5, 128.9, 130.0, 130.2, (aromat. C)]; MS (70 eV): m/z (%) = 421/419 (M⁺, 13/43), 384 (32), 382 (17), 370 (96), 342 (73), 315 (27), 236 (43), 77 (100).


General procedure for synthesis of 2a-aryl-2-chloro-5-(chloroacetyl)-4-phenyl-2a,3,4,5-tetrahydroazeto[1,2-a]-1,5-benzodiazepin-1-ones 9a-e.

A solution of the corresponding compound 8a-e (1 mmol) and 2-chloroacetyl chloride 7 (2 mmol) in dry benzene (10 mL) was heated for 7-10 h to reflux and monitored by TLC. Once the starting materials were mixed, a solution of TEA (excess) in dry benzene (5 mL) was slowly added during the two first hours of reaction. After solvent was removed, the residue was purified by column chromatography on silica gel with a mixture of ethyl acetate/hexanes (1:5) as eluent.

2-Chloro-5-(chloroacetyl)-2a,4-diphenyl-2a,3,4,5-tetrahydroazeto[1,2-a]-1,5-benzodiazepin-1-one 9a: White crystals, yield 43%; m.p. 261 °C; ¹H NMR (DMSO-δδ): δ = 3.01 (dd,1H, H₆), 3.47 (d, 1H, 11'-H), 3.59 (dd, 1H, H₅), 3.97 (d, 1H, H₅), 5.65 (s, 1H, 2-H), 5.76 (dd,1H, Hₓ), 6.87-8.37 (m, 14H, aromat. H); ¹³C NMR (DMSO-δδ): δ = 36.0 (C-3), 42.7 (C-11), 56.1 (C-4), 65.3 (C-2), 70.5 (C-2a), 124.1 (C-5a), 134.4 (C-9a), 137.2 (C, Ar), 138.5 (C, Ph), 162.5 (C-1), 165.5 (C-10), [119.3, 124.6, 125.3, 126.3, 127.2, 127.7, 127.9, 128.3, 128.5, 128.7, 130.1, 132.1, (aromat. C)]; MS (70 eV): m/z (%) = 454/452/450 (M⁺, 5/22/40), 415 (100), 413 (43), 380 (13), 379 (45), 325 (14), 321 (50), 297 (26), 270 (21), 221 (46), 194 (44).


2-Chloro-5-(chloroacetyl)-2a-(4-methylphenyl)-4-phenyl-2a,3,4,5-tetrahydroazeto[1,2-a]-1,5-benzodiazepin-1-one 9b: White crystals, yield 41%; m.p. 221 °C; ¹H NMR (DMSO-δδ): δ = 2.31 (s, 3H, CH₃), 2.98 (dd,1H, H₆), 3.44 (d, 1H, 11'-H), 3.55 (d, 1H, 11-H), 3.95 (d, 1H, 11-H), 5.61 (s, 1H, 2-H), 5.77 (dd,1H, Hₓ), 6.86-8.36 (m, 13H, aromat. H); ¹³C NMR (DMSO-δδ): δ = 20.8 (CH₃), 36.1 (C-3), 42.7 (C-11), 56.1 (C-4), 65.5 (C-2), 70.4 (C-2a), 124.2 (C-5a), 134.2 (C, Ar), 134.3 (C-9a), 136.8 (C, Ph), 138.6 (C, Ph), 162.6 (C-1), 165.5 (C-10), [119.3, 124.5, 125.3, 126.2, 127.2, 127.7, 128.3, 129.1, 129.3, 130.0, 132.1, (aromat. C)]; MS (70 eV): m/z (%) = 468/466/464 (M⁺, 5/22/40), 429 (100), 428 (43), 393 (45), 335 (50), 311 (26), 284 (21), 235 (46), 223 (28), 219 (33), 208 (44).

Anal. Calcd. for C₂₆H₂₂Cl₂N₂O₂: C, 67.10; H, 4.76; N, 6.02. Found: C, 67.06; H, 4.71; N, 6.11.

2-Chloro-5-(chloroacetyl)-2a-(4-chlorophenyl)-4-phenyl-2a,3,4,5-tetrahydroazeto[1,2-a]-1,5-benzodiazepin-1-one 9c: White crystals, yield 50%; m.p. 245 °C; ¹H NMR (DMSO-δδ): δ = 3.03 (dd,1H, H₆), 3.53 (d, 1H, 11'-H), 3.60 (dd, 1H, H₅), 4.02 (d, 1H, 11-H), 5.66 (s, 1H, 2-H), 5.78 (dd,1H, Hₓ), 6.87-8.35 (m, 13H, aromat. H); ¹³C NMR (DMSO-δδ): δ = 35.8 (C-3), 43.0 (C-11), 55.9 (C-4), 65.3 (C-2), 70.2 (C-2a), 124.0 (C-5a), 132.6 (C, Ar), 134.2 (C-9a), 136.4 (C, Ph), 162.4 (C-1), 165.6 (C-10), [119.4, 124.7, 127.2, 127.6, 127.7, 128.3, 128.5, 128.8, 130.1, 132.1, (aromat. C)]; MS (70 eV): m/z (%) = 488/486/484 (M⁺, 4/11/12), 451 (13), 449 (20), 373 (17), 371 (16),239 (15), 223 (20), 228 (23), 195 (19), 77 (100).

Anal. Calcd. for C₂₃H₁₉Cl₂N₂O₂: C, 61.81; H, 3.94; N, 5.77. Found: C, 61.77; H, 3.92; N, 5.72.
2a-(4-Bromophenyl)-2-chloro-5-(chloroacetyl)-4-phenyl-2a,3,4,5-tetrahydroazeto[1,2-a]-1,5-benzodiazepin-1-one 9d: White crystals, yield 52%; m.p. H NMR (DMSO-<i>d</i><sub>6</sub>): δ = 3.02 (dd, 1H, H<sub>A</sub>), 3.53 (d, 1H, 1 l'-H), 3.59 (dd, 1H, H<sub>M</sub>), 4.02 (d, 1H, 11-H), 5.65 (s, 1H, 2-H), 5.78 (dd, 1H, H<sub>x</sub>), 6.88-8.35 (m, 13H, aromat. H); 13C NMR (DMSO-<i>d</i><sub>6</sub>): δ = 35.7 (C-3), 43.0 (C-11), 55.9 (C-4), 65.2 (C-2), 70.2 (C-2a), 121.3 (C, Ar), 124.0 (C-5a), 134.2 (C-9a), 136.8 (C, Ar), 138.3 (C, Ph), 162.3 (C-1), 165.6 (C-10), [119.4, 124.7, 127.2, 127.8, 127.9, 128.3, 128.6, 130.1, 131.3, 131.8, 132.1, (aromat. C)]; MS (70 eV): m/z (%) = 530 (M<sup>+</sup> + 3), 495 (6), 417 (7), 375 (4), 301 (4), 274 (9), 193 (10), 77 (100).
Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>BrCl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 56.63; H, 3.61; N, 5.28. Found: C, 56.67; H, 3.31; N, 5.25.

2-Chloro-5-(chloroacetyl)-2a-(4-nitrophenyl)-4-phenyl-2a,3,4,5-tetrahydroazeto[1,2-a]-1,5-benzodiazepin-1-one 9e: White crystals, yield 35%; m.p. 235 °C; H NMR (DMSO-<i>d</i><sub>6</sub>): δ = 3.14 (dd, 1H, H<sub>A</sub>), 3.60 (d, 1H, 1 l'-H), 3.72 (dd, 1H, H<sub>M</sub>), 4.07 (d, 1H, 11-H), 5.75 (s, 1H, 2-H), 5.80 (dd, 1H, H<sub>x</sub>), 6.88-8.39 (m, 13H, aromat. H); 13C NMR (DMSO-<i>d</i><sub>6</sub>): δ = 35.7 (C-3), 43.1 (C-11), 55.7 (C-4), 64.9 (C-2), 70.2 (C-2a), 123.8 (C-5a), 137.9 (C, Ph), 145.0 (C, Ar), 146.8 (C<sub>p</sub> Ar), 161.9 (C-1), 165.6 (C-10), [119.5, 123.6, 123.9, 124.7, 127.0, 127.2, 127.4, 127.8, 128.0, 128.3, 130.2, 132.1, (aromat. C)]; MS (70 eV): m/z (%) = 499/497/495 (M<sup>+</sup> + 2) 1/15, 479 (17), 478 (60), 404 (18), 402 (46), 342 (13), 77 (100).
Anal. Calcd. for C<sub>25</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 60.50; H, 3.86; N, 8.47. Found: C, 60.54; H, 3.92; N, 8.41.

Conclusion

In conclusion, we have synthesized new N-acyl and azeto[1,2-a]-1,5-benzodiazepine derivatives under mild reaction conditions in moderate to good yields. This methodology could be extended to other diazepines containing free amino and/or imino groups including to those bearing heteroaromatic rings instead of the usual benzene ring.

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References


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