Ring Closure Reactions of 4-Chloro-5-hydroxyalkylamino-6-nitro-3(2H)-pyridazinones:
Synthesis of Novel Pyridazino-Fused Ring Systems

Olivér Éliás a, László Károlyházy a, Géza Stájer b, Veronika Harmath c, Orsolya Barabás c and Péter Mátyus a

a Institute of Organic Chemistry, Semmelweis University, 1092 Budapest, Hőgyes Endre utca 7, Hungary
E-mail: oliver@szerves.sote.hu
b Institute of Pharmaceutical Chemistry, University of Szeged, 6720 Szeged, Eötvös utca 7, Hungary
c Department of Theoretical Chemistry, Eötvös Lóránd University, 1117 Budapest, Pázmány Péter sétány 1, Hungary

Received: 9 July 2000 / Uploaded: 27 July 2000

Abstract: Cyclization of the title compounds may occur in various ways (e.g., with the participation of C-6 or C-4 atom of the pyridazinone ring) to form differently fused pyridazino ring systems. The regiochemistry was found to be particularly dependent on the length of the side chain: from the hydroxyethylamino derivatives pyridazino[3,4-b]oxazines, and from hydroxypropylamino derivatives pyridazino[3,4-b]oxazepine and pyridazino[4,5-b]oxazepine systems were formed.

Keywords: 4-chloro-5-hydroxyalkylamino-6-nitro-3(2H)-pyridazinone; pyridazino[3,4-b] oxazepines; pyridazino[4,5-b]oxazepines.

Introduction

The 3(2H)-pyridazinones 1a, b, and 2a, b, possessing an N-benzyl-N-hydroxyethyl- or N-benzyl-N-hydroxypropylamino group as well as an ortho-chloro substituent, were shown to undergo ring closure reactions under basic conditions to afford pyridazino[4,5-b][1,4]oxazine and pyridazino[4,5-b] [1,5]oxazepine derivatives, 3 and 4, respectively (Scheme 1) [1, 2]. While various substituents at the pyridazinone ring and the hydroxalkylamino side chain have been found to be within the scope of these ring closure reactions, hydroxyalkylaminopyridazinones with a hydrogen atom at the amino or lactam nitrogen, could not be cyclized to oxazines or oxazepines [1, 3].

The 6-nitro derivative 6a was reported to undergo ring closure to form the [3,4-b] annelated pyridazino system, compound 7a [1]. Furthermore, we recently described that 6b could be cyclized to two differently fused ring systems, compounds 7b, and 9b. The former compound was formed by cyclization to C-6, in the same route as it was found for 7a, whereas formation of 9b could be interpreted by a Smiles rearrangement reaction (Scheme 2) [3]. These interesting results prompted us to study cyclization reactions of 4-chloro-5-hydroxyalkylamino-6-nitro derivatives devoting particular attention to the effects of substituents and length of the alkyl chain; and we decided to re-investigate the ring closure reactions of 6a, and 6b. We also thought that the presence of the chloro substituent in the annelated system of type 7, might provide an ease access to otherwise hardly available fused ring systems; in this paper, we report on the synthesis of a novel ortho- and peri-fused pyridazino ring system by utilizing 7b.
Results

First, compounds 6a-h were prepared from 4,5-dichloro-2-methyl-6-nitro-3(2H)-pyridazinone [4] with the respective aminoalcohols [5, 6] in refluxing ethanol. Separation of the 4-chloro-6-nitro derivatives from their 5-chloro-6-nitro regioisomers, which were also formed as minor products, could be generally achieved by column chromatography with the exception of 6b. In this case, fractional crystallization, and recrystallization were only successful to afford 6b in pure form. When 6b was treated with sodium ethoxide in refluxing ethanol, two bicyclic ring systems were indeed formed in a ratio of 7:1 as confirmed by $^1$H nmr analysis of the crude reaction mixture (clearly, two new sets of signals could be identified). These products could be isolated by column chromatography in 41% and 15% yields, respectively (the preparative yields were reproduced in independent experiments). The main product was easily assigned to the structure of 7b on the basis of spectral data and elementary analysis. Surprisingly enough, the constitution of the minor product could be identified as 8b, whereas the presence of its regioisomer 9b could be excluded; for comparison, 9b was also prepared from 5b. Compounds 7b, 8b, and 9b could be well distinguished by nmr data (Figure 1). Structures of 8b and 9b were unambiguously confirmed by single crystal X-ray analysis (Figure 2). On the basis of these experiments, formation of 9b in the ring closure reaction of 6b, as described earlier, can only be explained by the presence of 5b in the reaction mixture as an impurity of 6b, accordingly, no Smiles rearrangement occurred in the ring closure reaction of 6b.

With the expectation that the nitro group may enhance the cyclization tendency to C-6 and C-4, next, ring closure reactions of the hydroxyethylamino derivative 6c, and its homologs 6d and 6e, all possessing a hydrogen atom at the amino nitrogen, were investigated. In the first case, ring forming reaction smoothly occurred by treatment with one equivalent of sodium ethoxide, to afford the pyridazino[3,4-b]oxazine derivative 7c. The reaction of 6d led to the formations of the [3,4-b] annelated derivative 7d, and the 6-ethoxypyridazinone 10a. In the case of 6e, no ring closure could be detected, the respective 6-ethoxy compound 10b could only be isolated (Scheme 3). The remarkable difference found in cyclization behavior of these compounds is in agreement with the general tendency observed in forming 6-8 membered rings.

The ring closure reactions of alicyclic analogs of 6d, compounds 6f-h, afforded novel tricyclic ring systems 7f-h in yields. This type of annelation was confirmed by characteristic $^{13}$C nmr data [for pyridazine C-4, C-5, C-6, d 110.8, 141.7, 146.6 (7f); 111.5, 141.6, 146.3 (7g); 113.2, 140.3, 145.3 (7h) ppm, respectively].

To illustrate the reactivity and synthetic utility of the pyridazino[3,4-b]oxazepine system, next, dehalogenation was carried out by catalytic transfer hydrogenation to obtain 11. This compound was expected to react smoothly with electrophiles at C-6; accordingly, the aldehyde 12 could be obtained by Vilsmeier formylation in good yield.

Treatment of the aldehyde with Meldrum's acid in ethanol led to the formation of the novel ring system 14, via 13 (Scheme 4). The constitution of 14 was supported by spectral data, in particular, the chemical shifts of Ph-CH, and Ph-C [4.81 (1H, s); 66.5 ppm, respectively] were of diagnostic value.
Scheme 1

for 1-4. a: n = 0; b: n = 1

Reaction conditions, (i): NaOEt/EtOH, reflux.

Scheme 2

for 5-9. a: m = 0; b: m = 1

Reaction conditions, (i): NaOEt/EtOH, reflux.
Scheme 3

Reaction conditions, (i): NaOEt/EtOH, reflux
\[ \text{Reaction conditions, (i): HCOONH}_4, \text{Pd/C, EtOH, reflux} \]
\[ \text{P}_2\text{O}_5, \text{(CH}_3\text{)}_2\text{NCHO, 70 °C} \]
\[ \text{(iii): Meldrum's acid, EtOH, room temperature} \]

**Scheme 4**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ph-CH\textsubscript{2}- (\delta)</th>
<th>(C_a) (\delta)</th>
<th>(C_b)</th>
<th>(C_c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8b</td>
<td>4.16</td>
<td>149.4</td>
<td>130.6</td>
<td>147.7</td>
</tr>
<tr>
<td>9b</td>
<td>4.72</td>
<td>136.5</td>
<td>138.4</td>
<td>146.7</td>
</tr>
<tr>
<td>7b</td>
<td>4.63</td>
<td>121.5</td>
<td>146.7</td>
<td>151.4</td>
</tr>
</tbody>
</table>

**Figure 1.** Some characteristic NMR data of compounds 7b, 8b and 9b.
Figure 2. ORTEP drawings of compounds 8b and 9b.

References


Acknowledgements

Financial support of this work by OTKA (T-31910) is acknowledged. O.É. is grateful to Gedeon Richter Pharmaceutical Company for a fellowship.

All comments on this poster should be sent by e-mail to (mailto:ecsoc@listserv.arizona.edu) ecsoc@listserv.arizona.edu with A0040 as the message subject of your e-mail.