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

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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(2*H*)-pyridazinone; pyridazino[3,4-*b*] oxazepines; pyridazino[4,5-*b*]oxazepines.

Introduction

The 3(2*H*)-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**.

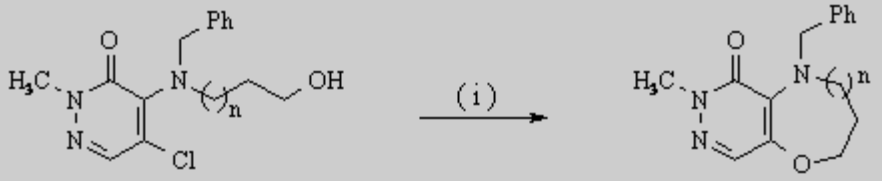
Results

First, compounds **6a**-**h** were prepared from 4,5-dichloro-2-methyl-6-nitro-3(2*H*)-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**.

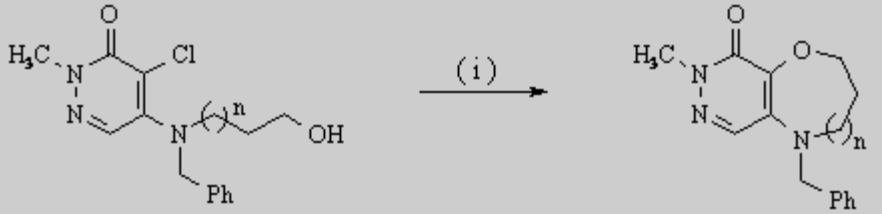
With the expectation that the nitro group may enhance the cyclization tendency to *C*-6 and *C*-4, next, ring closure reactions of the hydroxyethylamino derivative **6c**, and its homologs **6d** and **6e**, all possessing a hydrogen atom at the amino nitrogen, were investigated. In the first case, ring 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-C*H*, and Ph-*C* [4.81 (1H, s); 66.5 ppm, respectively] were of diagnostic value.



1a,b **3a,b**

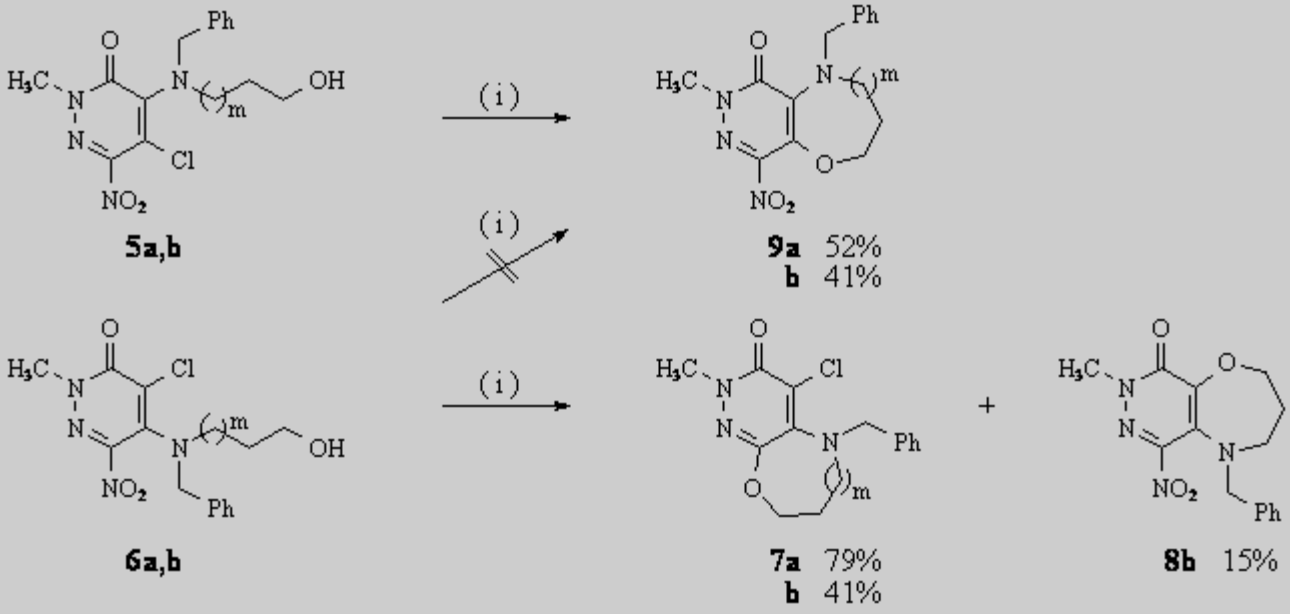


2a,b **4a,b**

for **1**-**4**, **a**: n = 0; **b**: n = 1

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

Scheme 1



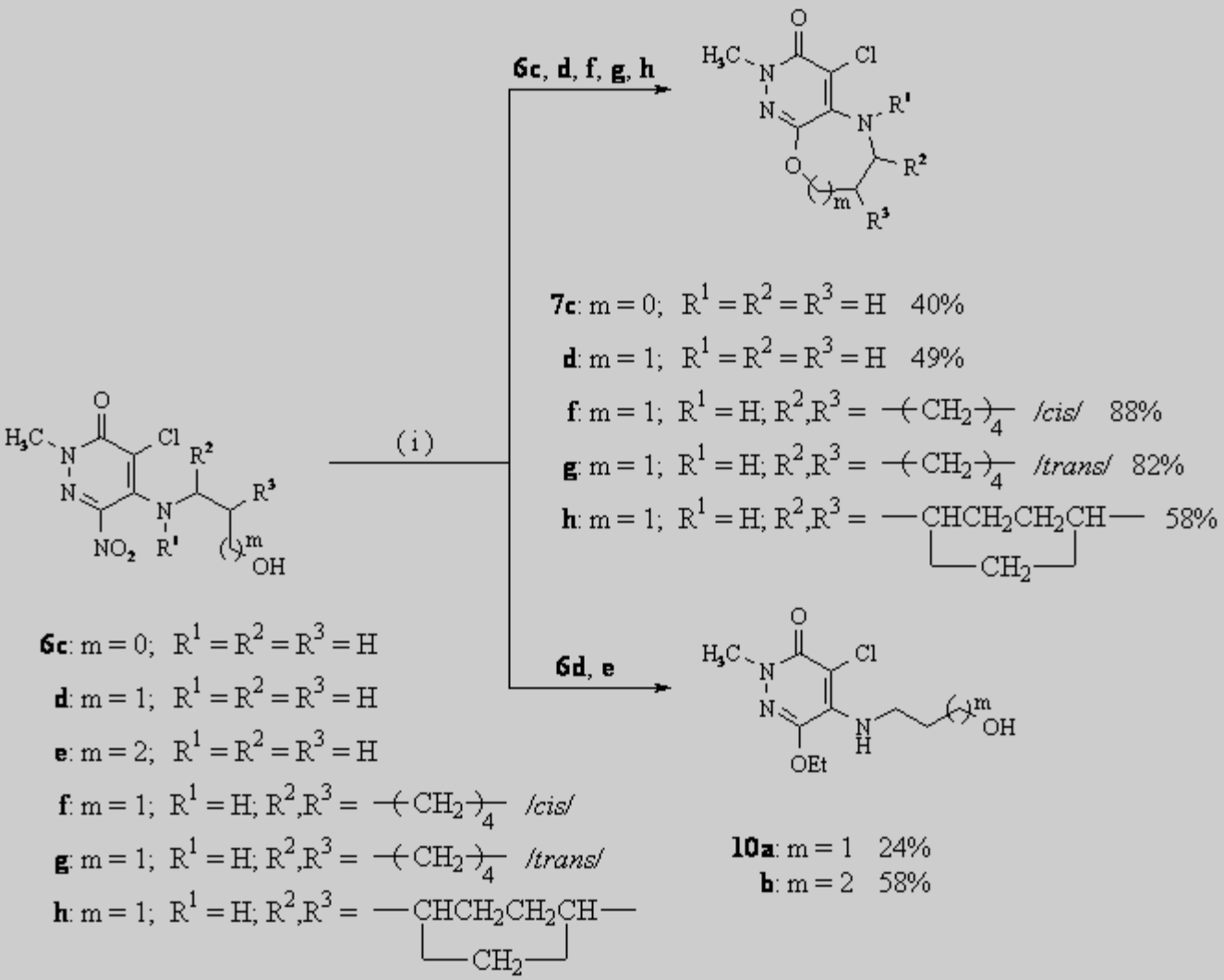
5a,b **9a** 52%
b 41%

6a,b **7a** 79%
b 41%
8b 15%

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

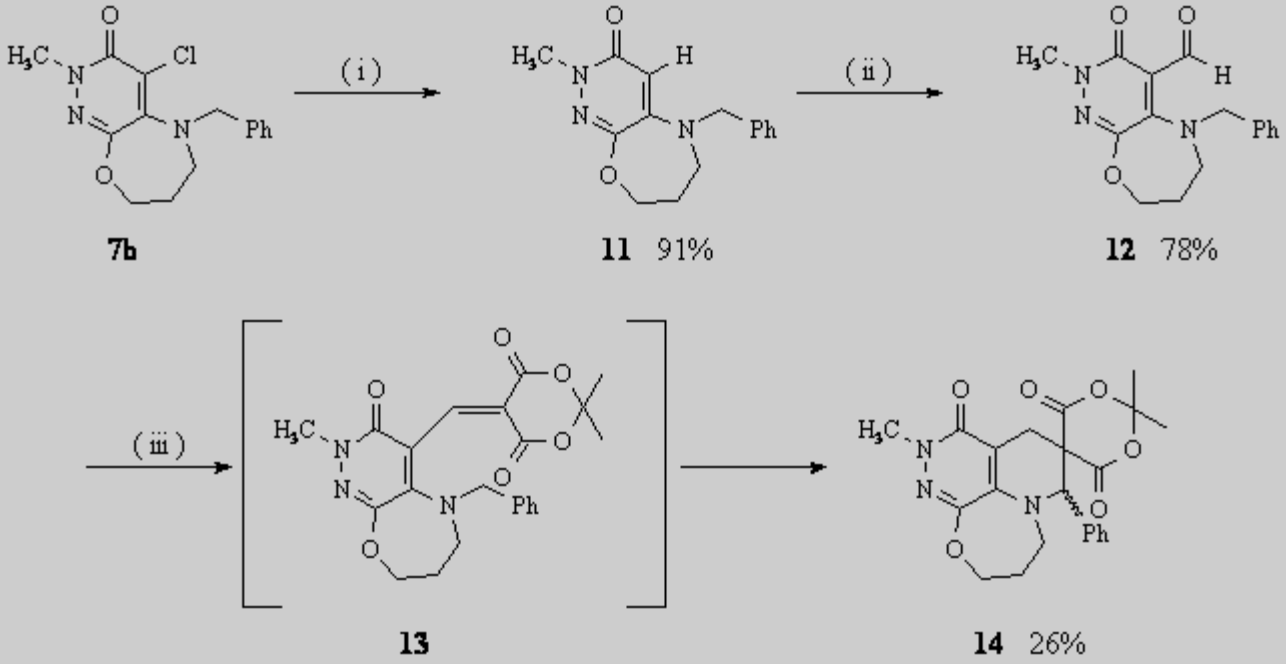
Reaction conditions, (i): NaOEt/EtOH, reflux.

Scheme 2



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

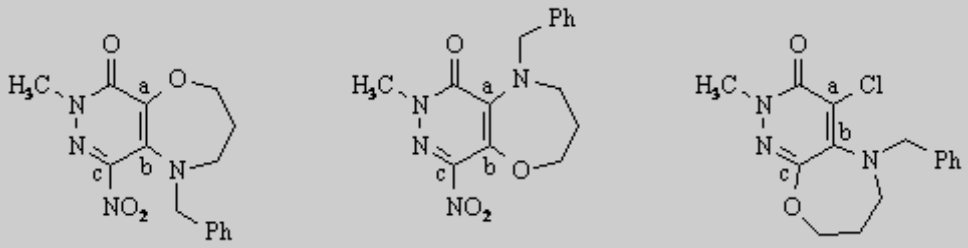
Scheme 3



Reaction conditions, (i): $HCOONH_4$, Pd/C, EtOH, reflux (ii):$POCl_3$, $(CH_3)_2NCHO$, 70 °C

(iii): Meldrum's acid, EtOH, room temperature

Scheme 4



8b **9b** **7b**

δ Ph-CH_2-	4.16	4.72	4.63
δ C_a	149.4	136.5	121.5
C_b	130.6	138.4	146.7
C_c	147.7	146.7	151.4

Figure 1. Some characteristic nmr data of compounds **7b**, **8b** and **9b**.

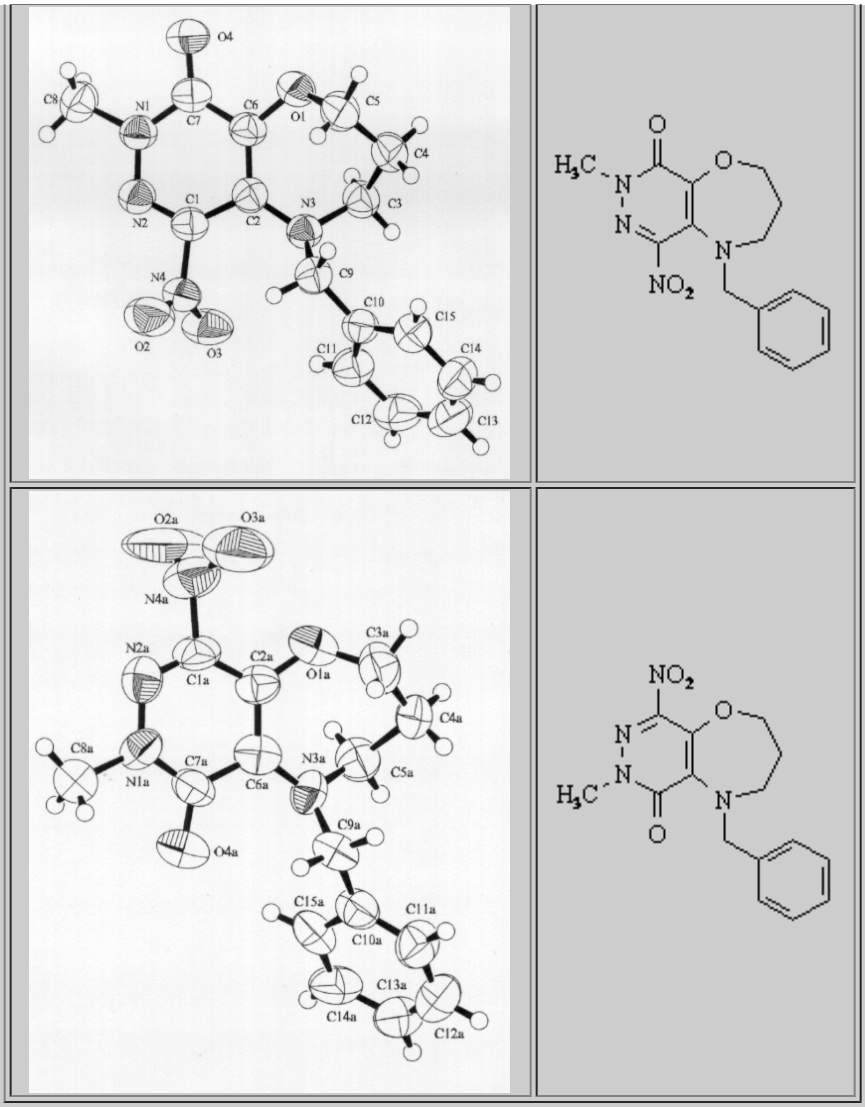


Figure 2. ORTEP drawings of compounds **8b** and **9b**.

References

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Acknowledgements

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