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Rearrangement of Pyrrolo[2,1-*c*][1,4]benzodiazepines into Cyclopenta[*b*][1,4]benzodiazepines Under Microwave or Conventional Heating Conditions.

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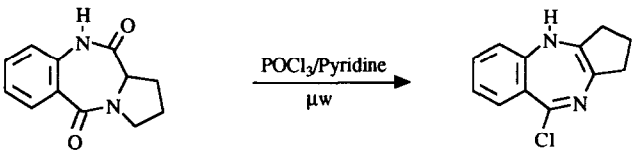
Abstract : Microwave or conventional heating of 2-hydroxy or 2-oxo-pyrrolo[2,1-*c*][1,4]benzodiazepine-diones in boiling phosphoryl chloride led to cyclopenta[*b*][1,4]benzodiazepines.

We recently described a new rearrangement of pyrrolo[2,1-*c*][1,4]benzodiazepines into cyclopenta[*b*][1,4]benzodiazepines (**Scheme 1**), that only occurred under microwave heating conditions[1] in boiling $POCl_3$.

Scheme 1



In the light of this preliminary result and taking into account the potentialities offered by this new tricyclic system in the field of medicinal chemistry, we investigated the behaviour of 2-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepine **1** and 2-oxopyrrolo[2,1-*c*][1,4]benzodiazepine **9** whose N10-C11 chloroimidates could not be prepared by reaction with phosphoryl chloride[2]. Indeed, when **1** was heated in $POCl_3$ in the presence of a catalytic amount of pyridine at 60-80°C, no reaction occurred. However, when the same reaction was conducted in boiling $POCl_3$, under normal or microwave heating conditions it produced in 45% yield a very complex mixture of rearranged or aromatized compounds[3] (**Scheme 2**) which we identified as the pyrrolobenzodiazepinedione **5**[4] and its chloroimidate **6**, the dihydropyrrolobenzodiazepine **2**, the dichlorotetrahydrocyclopentabenzodiazepine **3**, the cyclopentabenzodiazepine **7** and its chloroimidate **8**. The structures of all these compounds were confirmed by their analytical data (IR, ^1H NMR, ^{13}C NMR, MS and elemental analysis. See Table of Spectroscopic Data). The percentage of each compound depends on the experimental conditions and for example, in normal conditions the major products were found to be **6** and **7** accompanied with two minor products **2** and **3** and only trace amounts of **5** and **8**. Under microwave heating conditions **6** and **7** were the major products, **2**, **5** and **8** the minors and no trace of **3** was found. The structures were confirmed by unequivocal synthesis: treatment of **5** in boiling $POCl_3$ gave **6** (85%) and no rearrangement into **7** or **8** was observed.

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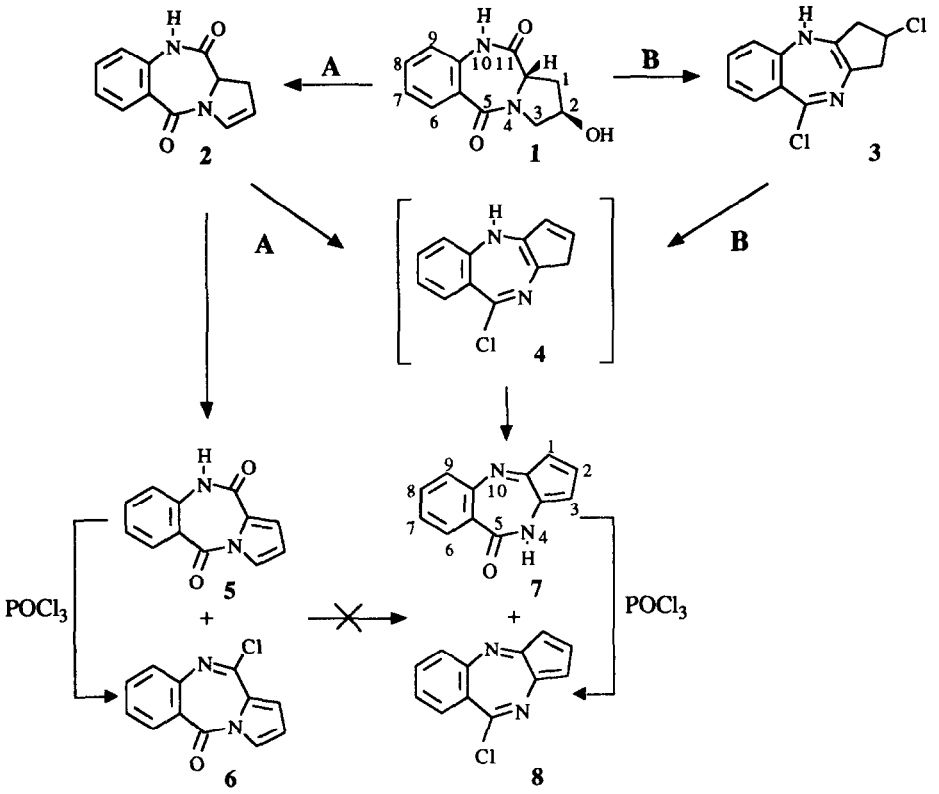
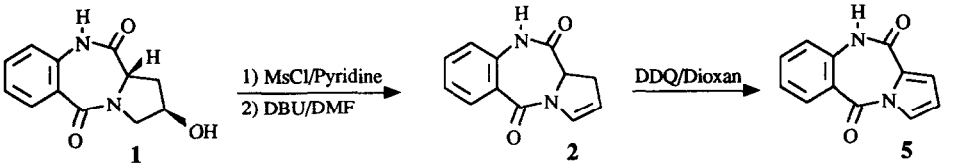
Scheme 2



Similar treatment of **7** gave **8** (90%). Compound **2** was synthesized in two steps from **1**, by initial treatment with mesyl chloride in pyridine[5] followed by an elimination reaction in boiling DMF in presence of DBU. Oxidation of **2** by DDQ in refluxing dioxan led to **5**. This synthesis of **5** is considerably more efficient than those previously described[6] (**Scheme 3**).

Scheme 3



In contrast to our observations in the unsubstituted series, two different competing reactions exist for **1**. They involve rearrangement and aromatization processes as described in **Scheme 2**. According to the pathway A, the reaction begins with a dehydration reaction leading to **2** which is then oxidized to give the aromatic pyrrolobenzodiazepines **5** and **6**, or is rearranged and then oxidized to give the aromatic cyclopentabenzodiazepines **7** and **8**, probably *via* the non-isolated dihydrocyclopentabenzodiazepine **4**. This pathway seems to be predominant under microwave heating conditions because no trace of **3** was found in these conditions. According to the pathway B, the first step of the reaction is the rearrangement of **1** giving **3** which

then leads to **4**. To confirm the pathway A, we treated **2** in boiling $POCl_3$/pyridine under microwave heating conditions. This reaction furnished a mixture of compounds **5**, **6**, **7** and **8**.

Scheme 4

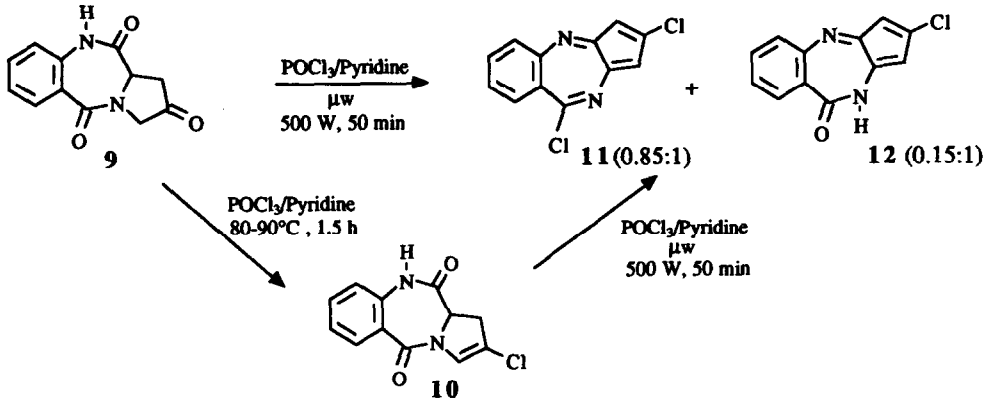


Table of Spectroscopic Data

N°	Mp (° C)	^{1}H NMR (400MHz, DMSO d_6)	^{13}C NMR (100MHz, DMSO d_6)	EI Mass Spectrum
2	230 (ethanol)	10.66, s, NH; 7.88, d, H-6; 7.61, dd, H-8; 7.33, dd, H-7; 7.23, d, H-9; 6.97, d, H-3; 5.53, d, H-2; 4.60, dd, H-11a; 3.44, d, 1H-1; 2.85, d, 1H-1	169.1; 161.6; 136.1; 132.5; 130.5; 127.2; 125.7; 124.2; 121.6; 112.7; 55.5; 30.3	214 ($M^{\cdot+}$, 100); 119 ($M^{\cdot+}$ - 95, 70)
3	200 (ether)	8.10, d, H-6; 7.89, s, NH; 7.69, d, H-9; 7.64, dd, H-7 or H-8; 7.47, dd, H-8 or H-7; 4.85, broad s, H-2; 3.74 and 3.54, 2d, 2H-3; 3.33 and 3.07, 2d, 2H-1	151.0; 147.7; 146.0; 129.6; 127.9; 124.7; 121.4; 117.1; 102.5; 51.0; 46.5; 33.7	256 ($M^{\cdot+}$ + 4, 13); 254 ($M^{\cdot+}$ +2, 64); 252 ($M^{\cdot+}$, 96)
6	160 (ethanol)	8.48, d, H-6; 8.34, dd, H-3; 7.89, dd, H-8; 7.69-7.63, m, H-7 and H-9; 7.49, dd, H-1; 6.88, dd, H-2	161.1; 142.2; 141.4; 135.4; 132.8; 132.6; 128.5; 128.1; 125.1; 124.7; 121.5; 114.6	232 ($M^{\cdot+}$ + 2, 35); 230 ($M^{\cdot+}$, 100); 195 ($M^{\cdot+}$ - Cl, 68)
7	> 260 (methanol)	11.89, s, NH; 9.06, d, H-1; 8.62, m, H-2 and H-3; 7.68, d, H-6; 7.59, dd, H-8; 7.40, d, H-9; 7.32, dd, H-7	160.8; 154.0; 150.5; 137.8; 135.7; 131.1; 123.9; 123.3; 122.3; 121.1; 118.8; 115.9	196 ($M^{\cdot+}$, 100); 168 ($M^{\cdot+}$ - CO, 27)
8	100 (ether)	9.30, dd, H-1; 9.02, dd, H-3; 8.77, dd, H-2; 8.08, d, H-6; 7.96-7.92, m, H-9 and H-8; 7.85, dd, H-7	154.6; 149.4; 148.8; 144.4; 135.1; 131.2; 128.2; 128.2; 124.6; 124.3; 123.6; 119.7	216 ($M^{\cdot+}$ + 2, 37); 214 ($M^{\cdot+}$, 100); 179 ($M^{\cdot+}$ - Cl, 85)
11	172 (ethanol)	9.09, d, H-1; 9.01, d, H-6; 8.67, d, H-3; 8.10, d, H-9; 7.78, m, H-8 and H-7	153.1; 149.7; 147.8; 145.1; 134.3; 132.0; 131.1; 129.7; 128.3; 125.4; 124.1; 120.6	252 ($M^{\cdot+}$ + 4, 11); 250 ($M^{\cdot+}$ + 2, 65); 248 ($M^{\cdot+}$, 100)
12	> 260 (ether)	11.64, s, NH; 9.08, d, H-1; 8.87, d, H-3; 8.12, d, H-6; 8.03, d, H-9; 7.84, dd, H-8; 7.62, dd, H-7	161.0; 152.8; 148.2; 144.3; 135.7; 131.7; 130.9; 130.1; 127.7; 124.3; 123.7; 120.1	232 ($M^{\cdot+}$ + 2, 23); 230 ($M^{\cdot+}$, 70)

In order to extend the scope of this rearrangement we studied the behaviour of the pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-trione **9**. Thus, when **9** was treated with boiling $POCl_3$ in the presence of a catalytic amount of pyridine at 80-90°C for 1.5 hour, only the 2-chloropyrrolo[2,1-*c*][1,4]benzodiazepine **10** was obtained, in agreement with a previous report[2]. Surprisingly when the reaction was conducted under microwave heating conditions[7], **9** rearranged and subsequently aromatized to give only the 2,5-dichlorocyclopenta[*b*][1,4]benzodiazepine **11** as a major product and its corresponding lactam **12** in a ratio 85/15 (^1H NMR) in 47% total yield. No trace of aromatized pyrrolobenzodiazepine was found (**Scheme 4**). Furthermore, the chloroalkene **10** is an intermediate of this rearrangement as was observed for **2**. Treatment of **10** in boiling $POCl_3$/pyridine under microwave heating conditions also gave a mixture of **11** and **12**.

In conclusion, the rearrangement of pyrrolo[2,1-*c*][1,4]benzodiazepines into cyclopenta[*b*][1,4]benzodiazepines seems to be quite general and can be applied to derivatives bearing a substituent in the 2 position or a C2-C3 double bond.

REFERENCES AND NOTES

1. Rault, S.; Gillard, A.C.; Foloppe, M.P.; Robba, M. *Tetrahedron Lett.*, **1995**, *36*, 6673-6674.
2. Kamal, A.; Thurston, D.E. *Tetrahedron Lett.*, **1989**, *30*, 6221-6222.
3. A typical experiment is as follows: a solution of **1** (10g, 43 mmoles) in $POCl_3$ (100 ml) and pyridine (2 ml) was heated at reflux in an oil bath for one hour. After elimination of $POCl_3$ under reduced pressure, the residue was taken up in water. The solid fraction was dissolved with diethyl ether to give 1.3g of a mixture of **5**, **6** and **8*** (5/80/15: ^1H NMR). **6** was isolated by crystallization from methanol and recrystallization from diethyl ether to give 1g of the pure product. The aqueous layer was then extracted with chloroform to give after evaporation 1.45g of a mixture of the compounds **2**, **5** and **7** (40/7/53: ^1H NMR). The aqueous layer was then basified with a 32% ammonia solution. The precipitate was filtered and gave after drying 1.6g of a mixture of **3** and **7** (20/80: ^1H NMR). By washing with cold methanol, 1g of **7** as insoluble material was isolated. After evaporation of the methanol, 0.3g of **3** crystallized from ether.
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6. Thurston, D.E.; Bose, D.S. *Chem. Reviews*, **1994**, *94*, 433-467.
7. A solution of **9** (6g, 26 mmoles) in $POCl_3$ (50 ml) and pyridine (2 ml) was heated with stirring under microwave application (500 W) for 50 minutes in a Normatron®[8] apparatus. After elimination of phosphoryl chloride under reduced pressure, the residue was taken up in water, basified (pH 11) with a 32% ammonia solution and extracted with diethyl ether. The organic layer was evaporated to give a mixture of **11** and **12**. By washing with cold methanol, a yellow solid was isolated. By crystallization from ethanol, 2.6g (40%) of **11** was obtained. After evaporation of the methanol, 0.4g (7%) of **12** crystallized from ether.
8. Rault, S.; Derobert, M. *Eur. Pat. Appl.* 0595084 A1. **1993**.

* Caution! Compounds **6**, **8** and **11** are severe irritants and must be handled only with gloves under a chemical fume hood.

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