Oxidative cyclization of some 1-Aryl-5-(tetrazol-5-ylmethyl)pyrrolidin-2-ones and of a related piperidin-2-one. Preparation of fused tetracyclic tetrazolobenzodiazepinone derivatives

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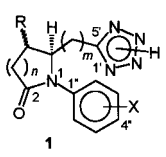
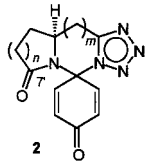
In contrast to compounds of type **1a**, compounds **1c–1i**, when treated with lead(IV) acetate or cerium(IV) ammonium nitrate, underwent oxidative cyclizations to afford the corresponding compounds of type **3** with both oxidants, while oxidation of compound **1p** afforded compound **2a** (*m* = *n* = 1).

Recently a series of compounds of type **1a** (**1**, *m*, *n* = 0, 1; X = 4″-OMe) were subjected to oxidation with cerium(IV) ammonium nitrate (CAN) in aqueous MeCN, and lead tetraacetate (LTA) in dry dioxane. *Different* oxidation products were obtained with the two oxidants: compounds of type **2a** (or their transformation products) with CAN[1, 2] and of type **3** (X = 3-OMe) with LTA,[3] respectively.



1



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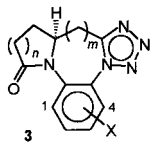
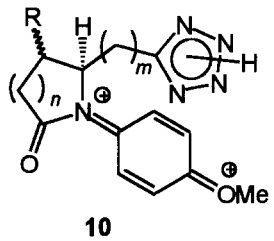


3

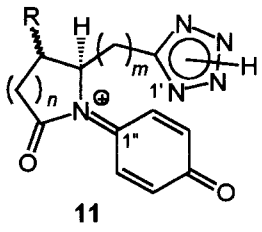
Compounds **1c**, **1d**, **1f**–**1h** (**1**, R = H; *m* = *n* = 1; X = H, 4″-Me, 3″-OMe, 4″-F and 4″-Cl) were now found to afford *identical* products, *víz*. the corresponding compounds **3** with both oxidants. Compound **1e**, (**1**, R = H; *m* = *n* = 1; X = 2″OMe), when treated with LTA, and compounds **1i** (**1**, R=H, *m* = *n* = l, x = 3″-OMe) and **1n** (**1**, R = H; *m* = 1, *n* = 2; X = 3″-OMe), when treated with CAN, also afforded compounds of type **3** (**1e** with loss of the methoxy group and **1i** yielding two isomers). Compounds **1k**, **1l** (**1**, R = H; *m* = *n* = 1; X = 2″-NO_2 and 4″-NO_2) and **1m** (**1**, R = H; *m* = 1, *n* = 2; X = 4″-Cl), due to the presence of the electron withdrawing substituents X, did not react with either of the two oxidants. Compound **1p** (**1**, R = H; *m* = *n* = 1; X = 4″-$NHCOCF_3$) afforded compound **2a** (*m* = *n* = 1) when oxidized with CAN.

The following explanation is suggested for the dissimilar behaviour of the 4″-methoxy (**1a**) and the other compounds of type **1**. The compounds **1a** are rapidly oxidized by both oxidants to the corresponding dications **10** which are prone to hydrolysis to the monocations **11**.[1, 2, 8] Since water is present in the CAN oxidations but not in the LTA oxidations closure of the fourth ring takes place at the dication and monocation stage, respectively, and leads to different products.

The *N*-aryl groups of compounds **1c**, **1d**, **1f**–**1i** and **1n** are less easy to oxidize than the *N*-(4-methoxyphenyl) group. Therefore these compounds may be assumed to undergo one, rather than two-electron oxidations. In contrast to the dications **10**, the resulting radical cations **13** are stable to hydrolysis (as would be also the corresponding dications). As a consequence, identical products will here be formed by oxidation with both oxidants *via* ring closure of the radical cations **13** with concomitant *N*-deprotonation, followed by oxidation of the resulting radicals **14a** to the corresponding cations **14b**. Deprotonation of the latter finally affords the corresponding compounds **3**.



10



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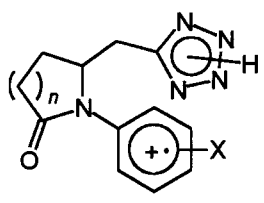
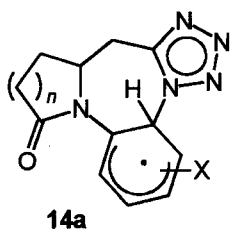
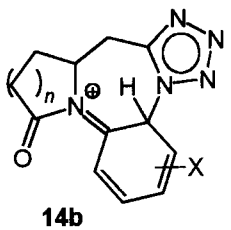


13



14a



14b

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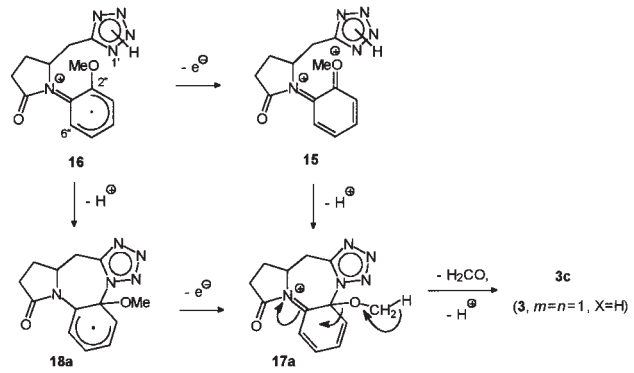
LTA oxidation of compound **1e** (**1**, R = H; *m* = *n* = 1; X = 2″-OMe) to afford, with loss of the 2″-methoxy group compound **3c** (**3**, *m* = *n* = 1, X = H) could involve, in principle, either dication **15** or radical cation **16** as the key intermediate. In the lactam *N*-substituent of both these species two sites, C-2″ and C-6″, are available for nucleophilic attack by N-1′. Attack at C-6″ would lead to the formation of compound **3e** (**3**, *m* = *n* = 1, X = 1-OMe) which has not been isolated, while attack at C-2″ should lead, with closure of the new ring taking place either at the radical cation or the dication stage to compound **3c** as shown below:



A possible explanation of the formation of compound **3c** rather than of **3e** in the LTA oxidation of compound **1e** came from its conformational study as well as that of its one (**16**) and two-electron oxidation products (**15**). The dihedral angles C2–N1–C1″–C2″ (α) in the most stable conformations of these species as well as rotational barriers (AM1 values) are shown in Table 1. While in the most stable conformation of **1e** and **15** the plane of the ring of the *N*-substituent and plane C2–N1–C1″ are not far from perpendicular, they are almost parallel in that of the one-electron oxidation product **16**, with C6″ being far and C2″ close to the tetrazole-ring, *i.e.* C2″ being preferentially attacked by the latter. If orientation in the ring closure step is indeed conformationally governed, this would mean that the oxidative ring closure takes place, also in the case of compound **1e**, at the radical cation stage.

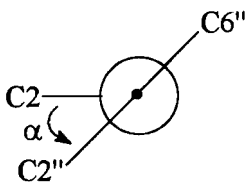


Table 1 The dihedral angles C2–N1–C1″–C2″ (α) and rotational barriers in the most stable conformations of compound **1e**, radical cation **16** and dication **15**

Species	α	Barriers (kJ/mol)
1e	80°	22.2
16	160°	56.9
15	65°	104.3

The formation of compound **2a** (*m* = *n* = *1*) on oxidation of compound **1p** (**1**, R = H; *m* = *n* = 1; X = 4″-NHCOCF$_3$) with CAN/aqueous acetonitrile may be rationalized by assuming successive formation of intermediate dication **19** and monocation **20** (the latter being an analogue of the monocations **11**). Ring closure and hydrolysis of **20** should then lead either *via* **11** (*m* = *n* = 1) or *via* **21** to compound **2a** (*m* = *n* = 1).

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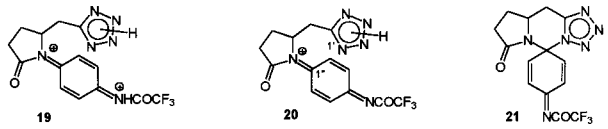

Techniques used: flash chromatography, IR, ^{1}H-NMR, MS, AM1 calculations

References: 9

Table 2a. Yields, melting points, molecular mass determinations or elemental analyses and IR spectra of compounds **6c**–**6i**, **6m** and **6n**

Table 2b. NMR spectra of compounds **6c**, **6d**, **6g**, **6m** and **6n**

Table 3a. Yields, melting points, molecular mass determinations or elemental analyses and IR spectra of compounds **7c**–**7i**, **7m**, **7n**, **8c**–**8i**, **8m**, **8n** and **9c**–**9q**

Table 3b. NMR spectra of some compounds **7**, **8**, and **9**

Table 4a. Yields, melting points, molecular mass determinations or elemental analyses and IR spectra of compounds **1c**–**1p**

Table 4b. NMR spectra of compounds **1c**–**1p**

Table 5a. Yields, melting points, molecular mass determinations or elemental analyses and IR spectra of compounds **3**

Table 5b. NMR spectra of compounds **3**

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