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# An expedient route to aromatic pyrrolo[2,1-*c*][1,4]benzodiazepines and a study of their reactivity

Frédéric Fabis, Jana Sopkova-de Oliveira Santos, Sandrine Fouchet-Jolivet and Sylvain Rault*

*Centre d'Etudes et de Recherche sur le Médicament de Normandie, UFR des Sciences Pharmaceutiques, Université de Caen, 5 rue Vaubénard, 14032 Caen Cedex, France*

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**Abstract**—2-Hydroxypyrrolo[2,1-*c*][1,4]benzodiazepines were aromatised in refluxing thionyl chloride into 11-chloropyrrolo[2,1-*c*]-[1,4]benzodiazepines in high yield. This aromatic system is doubly reactive towards nucleophiles leading to rearranged products such as iminobenzoxazines and quinazolines. © 2001 Elsevier Science Ltd. All rights reserved.

In the course of our work aiming to develop new heterocyclic systems usable in the field of medicinal chemistry, we have already described several rearrangements in the pyrrolo[2,1-*c*][1,4]benzodiazepine series.[1–3] We also shown that heating of 2-hydroxypyrrolo[2,1-*c*]-[1,4]benzodiazepine **1a** in $POCl_3$ in the presence of pyridine led to a complex mixture of rearranged and aromatic products from which we could isolate the aromatic 11-chloropyrrolo[2,1-*c*][1,4]benzodiazepine **2a** (Fig. 1).[4]

We were very interested in **2a** because its chloroimine moiety in the $N_{10}$–$C_{11}$ position is similar, in our mind, to the imine or carbinolamine equivalent found in a group of antitumor antibiotics such as anthramycin, tomaymycin, DC-81, neothramycins A and B and chicamycin.[5] In these structures, the $N_{10}$–$C_{11}$ imine moiety and the *S* configuration at the chiral $C_{11a}$ position are required for DNA interaction.[6] This interaction proceeds via the formation of an aminal covalent bond between the exocyclic C2-amino group of a guanine and the N10–C11 imine functionality (Fig. 2); however, the pyrrolo[2,1-*c*][1,4]benzodiazepine system in which the pyrrole ring is fully unsaturated was reported as having little interest from a biological standpoint owing to the unreactivity of the imine double bond toward nucleophiles[5] (Fig. 3).

Compound **2a** became interesting because the chlorine atom on $C_{11}$ could reinforce its electrophilic character and enhance its ability to react with nucleophiles, whilst on the other hand it could also act as a scaffold for the preparation of numerous tricyclic derivatives which would have structures closely related to antipsychotic drugs. So we investigated the efficient synthesis of **2a** by the use of thionyl chloride in the presence of one equivalent of pyridine (reflux, 2 h), which led directly to the aromatic structure **2a** (70% yield, Scheme 1). The reaction was generalised to the easily available 2-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepines differently substituted on the benzene ring **1b**–**d**[7,8] (**2b**, 65%; **2c**, 70%; **2d**, 62%; Scheme 1). Moreover, we were able to determine the crystallographic data of **2a**.[9]

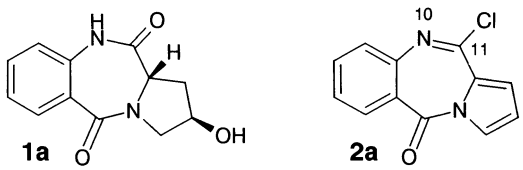


**Figure 1.**

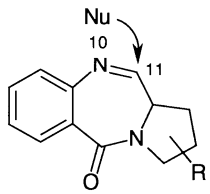


**Figure 2.**

*Keywords*: pyrrolo[2,1-*c*][1,4]benzodiazepine; aromatisation; thionyl chloride; iminobenzoxazine; quinazoline.

* Corresponding author. Tel.: 33-2-31934169; fax: 33-2-31931188; e-mail: rault@pharmacie.unicaen.fr


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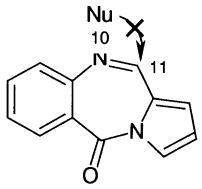
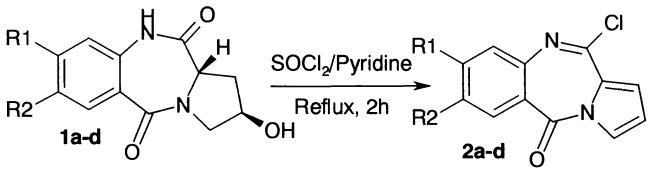



**Figure 3.**




a : $R_1$=$R_2$=H
b : $R_1$=H, $R_2$=Cl
c : $R_1$=H, $R_2$=$CH_3$
d : $R_1$=$R_2$=methylene dioxy

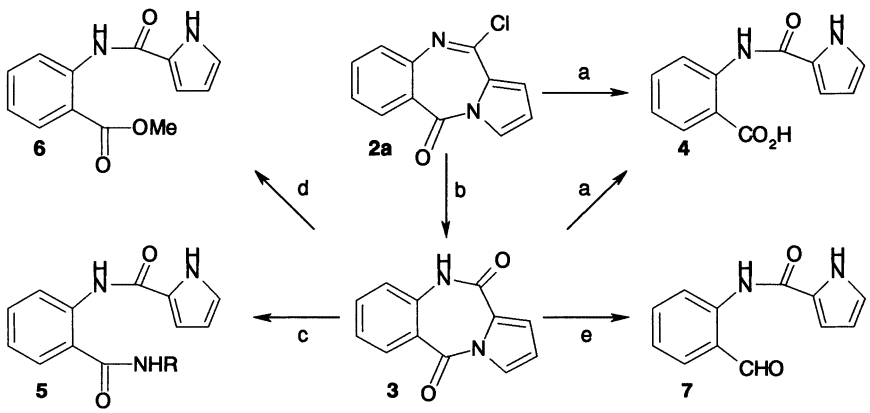
**Scheme 1.**

Exposed to air moisture for several days, compound **2a** hydrolysed to give the dilactam **3**. The synthesis of **3** was reported before by Carey from condensation of isatoic anhydride and the potassium salt of pyrrole in 24% yield.[10] We first tried to hydrolyse the imidoyl chloride moiety of **2a** under basic conditions (KOH 2N, acetone). After acidification we obtained the acid **4**[11] in 95% yield (Scheme 2). However, in acidic conditions (HCl 6N) **2a** seemed to be much more stable and the hydrolysis of the imidoyl chloride succeeded to give the dilactam **3** in 86% yield (Scheme 2). Compound **2a** appeared to be very sensitive to nucleophilic attack at the $N_{10}$–$C_{11}$ chloroimine moiety as we expected, but also in an unexpected way at the carbonyl–pyrrole bond. To confirm this reactivity, we exposed the dilactam **3** to different nucleophiles. As for **2a**, **3** opened under alkaline conditions to give the anthranilic derivative **4** (Scheme 2). The reaction of **3** with ammonia, methylamine or sodium methoxide led, respectively, to anthranilamides **5** and methyl anthranilate **6** (Scheme 2). This particular reactivity confirms the results of Carey who reported the opening of the diazepine ring of **3** by treatment with lithium aluminium hydride to form the aldehyde **7**[10] (Scheme 2).

The reaction of **2a** with amines appeared to be more complex since rearranged products were obtained. Ammonia led to an anthranilonitrile derivative **8**, methylamine to the 4-methyliminobenzoxazine **9**, hydrazine to the 3-aminoquinazolin-4-one **10**[11] and dimethylamine to the disubstituted product **11** (Scheme 3).

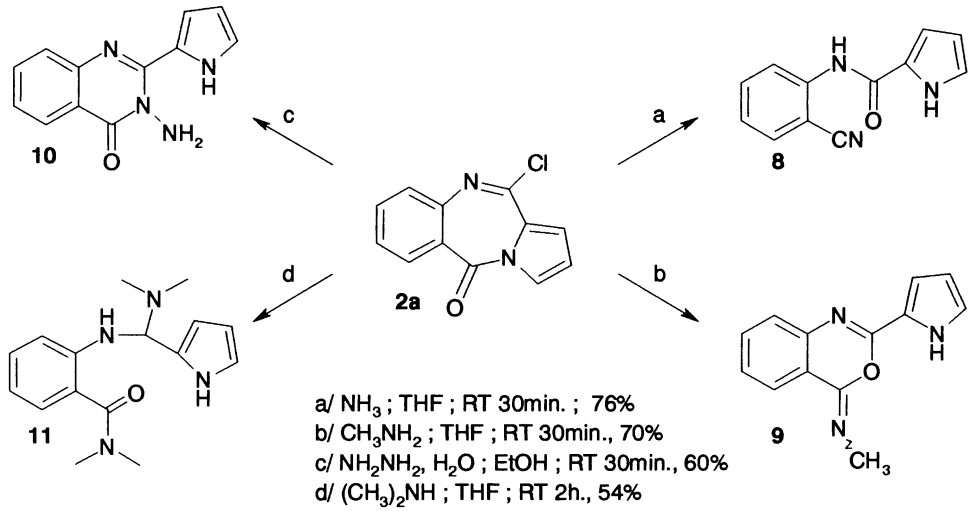
These structures are the evidence of a double reactivity of the aromatic pyrrolo[2,1-*c*][1,4]benzodiazepine **2a** at both the $N_4$–$C_5$ carbonylpyrrole bond and the $N_{10}$–$C_{11}$ chloroimine moiety. This original and readily available method to synthesise aromatic pyrrolo[2,1-*c*]-[1,4]benzodiazepines will permit us to study further the reactivity of this system and the results will be published in due course.

Typical experimental procedure for aromatisation: to a solution of 22 mmol (1.75 ml) of pyridine in 150 ml of thionyl chloride, 22 mmol (5 g) of 2-hydroxypyrrolobenzodiazepine **1a** were added portionwise. The solution was then refluxed for 2 h and thionyl chloride was evaporated under reduced pressure. The residue was triturated in crushed ice and the resulting solid was filtrated and washed with water and a saturated sodium hydrogencarbonate solution. The solid was then dissolved in boiling cyclohexane, treated with charcoal and filtered. The chloroimine **2a** crystallised as a yellow solid on cooling.




a/ acetone, KOH 2N, 50°C, 15min., 95%
b/ HCl 6N, 80°C, 1h, 86%
c/ $RNH_2$, THF, RT, 1h : R=H, 95%[11] ; R=$CH_3$, 75%
d/ $CH_3ONa$, $CH_3OH$, RT, 93%
e/ $LiAlH_4$[10]

**Scheme 2.**




**Scheme 3.**

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