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Synthesis of New Pyrrolo[2,1-*b*]Quinazolinones by Original Rearrangement of Pyrrolo[2,1-*c*][1,4]Benzodiazepines.

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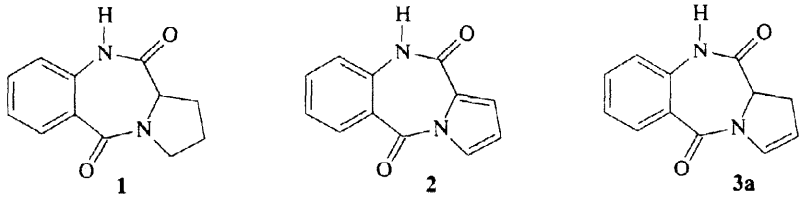
Abstract: 1,10,11,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones **3a-d** in concentrated hydrochloric acid rearranged into the new 2,3,4,4a-tetrahydropyrrolo[2,1-*b*]quinazolin-9(1H)-one 1-carboxylic acids **4a-d** in a very good yield.

Within the framework of a study on the synthesis of new rearrangements of pyrrolo[2,1-*c*][1,4] benzodiazepines[1,2], we were interested in the stability of benzodiazepines **1-3a** (**Scheme 1**) in acidic medium and we now report our results bringing to the fore the formation of a new quinazolinone **4**.

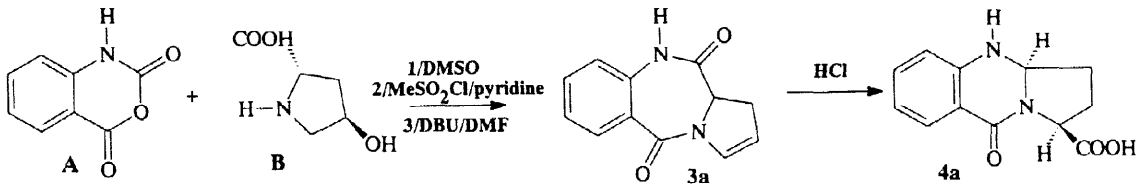
Scheme 1



1 **2** **3a**

If we did not observe any structural modification of compounds **1** and **2** during their treatment in acidic medium, benzodiazepine **3a** has for it shown a different behaviour. Indeed, after heating a few minutes in concentrated hydrochloric acid, **3a** leads to the unexpected formation of a 2,3,4,4a-tetrahydropyrrolo [2,1-*b*]quinazolin-9(1H)-one 1-carboxylic acid **4a** in 80% yield of pure product. This simple and efficient synthesis (total yield 36%) is carried out in four steps by the condensation of isatoïc anhydride **A** and the trans-4-hydroxy-L-proline **B** (**Scheme 2**).

Scheme 2



A **B** **3a** **4a**

The analysis of the spectroscopic characteristics (IR, NMR, mass, elementary analysis) allowed the characterization of the compound **4a**[3] and the highlighting of only one isomer in the mixture. The X-rays analysis (**Figure 1**) of an analogous compound **5aa** confirmed its structure of quinazolinone: it is about a *cis* structure and the reaction is diastereoselective.

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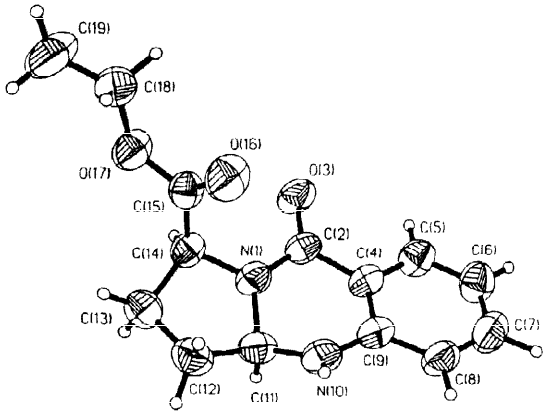
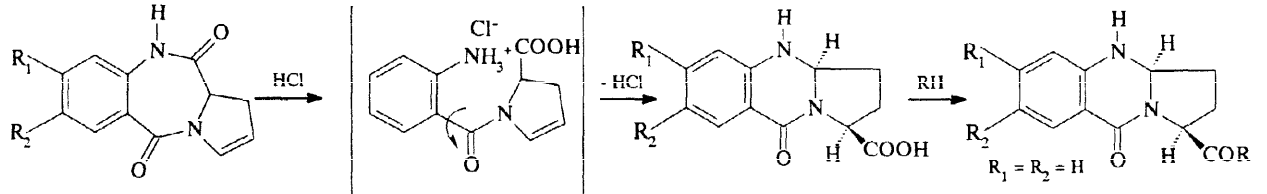
Figure 1: ORTEP diagram of compound **5aa**



The mechanism of formation of **4a** could be explained by the following pathway: contrary to the corresponding tetrahydrobenzodiazepines, **3a** would open in acidic medium on the level of the lactam N10-C11 bond to lead to a non isolated amino acid which would be rearranged in quinazolinone **4a** (**Scheme 3**).

Scheme 3



3a $R_1 = R_2 = H$
3b $R_1 = H$ $R_2 = Cl$
3c $R_1 = Cl$ $R_2 = H$
3d $R_1 = H$ $R_2 = CH_3$

3'a

4a $R_1 = R_2 = H$ **80%**
4b $R_1 = H$ $R_2 = Cl$ **70%**
4c $R_1 = Cl$ $R_2 = H$ **75%**
4d $R_1 = H$ $R_2 = CH_3$ **70%**

5aa R = OEt **80%**
5ab R = OMe **80%**
5ac R = $NHCH_2CH(Me)_2$ **50%**
5ad R = $NHCH_2C_6H_5$ **60%**

In order to generalize this new rearrangement, we submitted other tetrahydropyrrolo [2,1-*c*][1,4]benzodiazepines **3b-d** differently substituted on the aromatic nucleus to the same conditions. The corresponding quinazolinones **4b-d** were obtained with excellent yields (**Scheme 3**). The acid **4a** was then carried out in standard conditions to give new esters **5aa-5ab** and carboxamides **5ac-5ad** of quinazolinones as reported in **Scheme 3**.

To our knowledge, there is actually no report in the literature for such a rearrangement. However, the structural analogy of these quinazolinones **4** with a natural alkaloid, the vasicinone, known to exhibit interesting pharmacological properties as bronchodilator[4] or anticholinesterasic[5], makes of these compounds new potent scaffolds in medicinal chemistry.

REFERENCES AND NOTES

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3. The experiment is as follows: compound **3a** (2g, 8.6mmoles) in concentrated hydrochloric acid (5 mL) was heated in an oil bath (60°C) for thirty minutes. After elimination of HCl under reduced pressure, the residue was taken up in a saturated aqueous solution of sodium bicarbonate. The aqueous layer was then reacidified by HCl and the precipitate collected by filtration. The obtained product was dried to give 1.6g (80%) of **4a** as a pure white powder: Mp: 260°C; IR (KBr) 3230, 1710, 1640 cm^{-1}; ^1H NMR (DMSO-d6) δ 1.95 (2H, m, CH_2), 2.23 (2H, m, CH_2), 4.31 (1H, d, H-C-COOH), 4.95 (1H, dd, H-C-NH), 6.73 (2H, d+t, H_{arom}), 6.98 (1H, broad s, NH), 7.26 (2H, t, H_{arom}), 7.57 (2H, d, H_{arom}), 12.60 (1H, broad s, COOH); ^{13}C NMR (DMSO-d6) δ 26.5, 31.1, 56.6, 69.8, 114.8, 116.5, 117.8, 127.4, 133, 149.1, 161.2, 172.8; MS (m/z) 232 (M^+); Anal. *Calcd* for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. *Found* C, 61.66; H, 5.28; N, 11.98.
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