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Diazepines[1,4] annelated with indoline and maleimide from 3-(di)alkylamino-4-(indol-1-yl)maleimides: mechanism of rearrangement and cyclization

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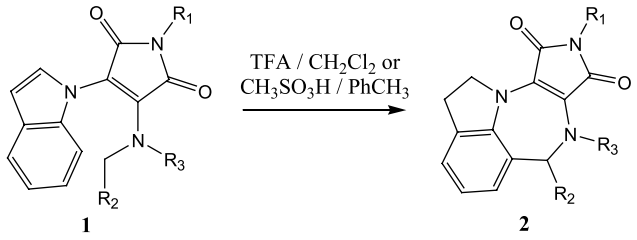
Abstract—The mechanism of cyclization of 3-(di)alkylamino-4-(indol-1-yl)maleimides to diazepine[1,4] derivatives was elucidated using deuterium labeled precursors.

1. Introduction

In our previous paper[1] we have described an unusual cyclization of 3-(di)alkylamino-4-(indol-1-yl)maleimides (**1**) by protic acids leading to the diazepines[1,4] with annelated indoline and maleimide nuclei (**2**) (Fig. 1).



1 **2**

Figure 1.

We assumed that the cyclization proceeds via three steps (Fig. 2): (1) protonation of the indole nucleus at position 3 (**4**); (2) hydride shift from the carbon atom adjacent to the nitrogen atom to position 2 of the protonated indole nucleus. This shift leads to the formation of indoline and iminium ion moieties (**5**); (3) electrophilic attack of the iminium ion at position 7 of the indoline nucleus resulting in protonated diazepine derivative **6**. Presented herein are the results of the experiments performed to test this hypothesis.

2. Results and discussion

Treatment of 3-diethylamino-4-(indol-1-yl)-1-methylmaleimide **8** with TFA in CH_2Cl_2 gave diazepine derivative **9**.[1] Similarly, the dideuterated product **10** was obtained in 80% yield when CF_3CO_2D was used (Fig. 3).

The ^1H and ^{13}C NMR spectra of compounds **9** and **10** were compared (Table 1).

The ^1H NMR spectrum of **10** was more straightforward than that obtained for **9**. Instead of a three hydrogen multiplet in the range δ 3.1–3.25 the single hydrogen multiplet at δ 3.17 was present. The latter was coupled with three hydrogen triplet at δ 1.08. This fact allows us to identify this signal as one of the hydrogens of the methylene group attached to N7. The signals corresponding to the hydrogens at C2 (position-3 of the indoline subfragment) were absent. The signal corresponding to the hydrogens at C1 (position-2 of indoline subfragment) at δ 4.44 was a broad singlet instead of complex multiplet at δ 4.43–4.49 in the spectrum of **9**. The other parameters of ^1H NMR spectra of **9** and **10** were similar. In the ^{13}C NMR spectrum of **9** the singlet signal of C2 atom at δ 28.2 was present; in contrast, in the ^{13}C NMR spectrum of **10** a multiplet (a doublet of triplets $J=30.5$, 19.8 Hz) at δ 27.4–28.1 was detectable. Thus, we conclude that the product of cyclization of indolylmaleimide **8** by CF_3CO_2D (compound **10**) has two deuterium atoms at position 2 (position 3 of indoline subfragment). This finding supports the hypothesis that the first step of cyclization is the protonation of the indole nucleus at position 3.

We next set out to find the source of hydrogen at C1 in the

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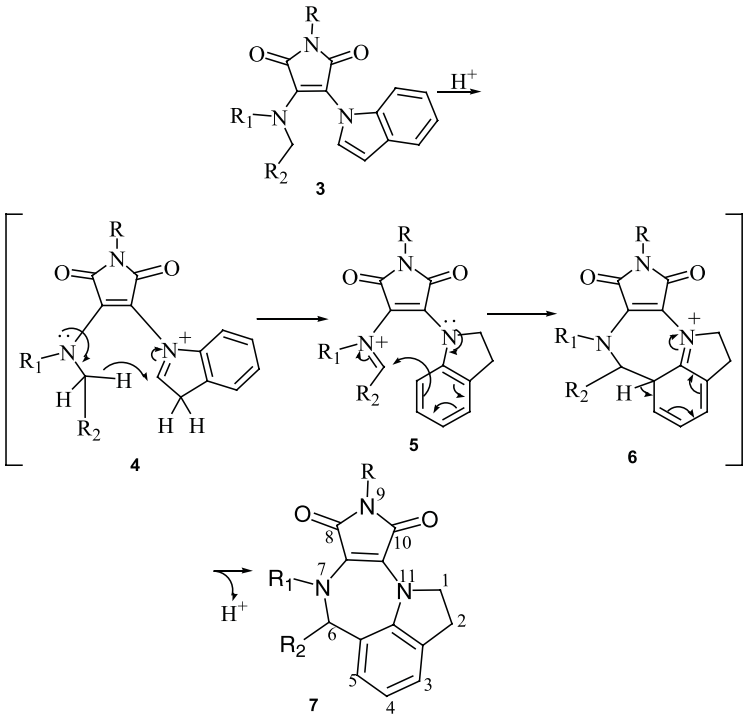

Figure 2.

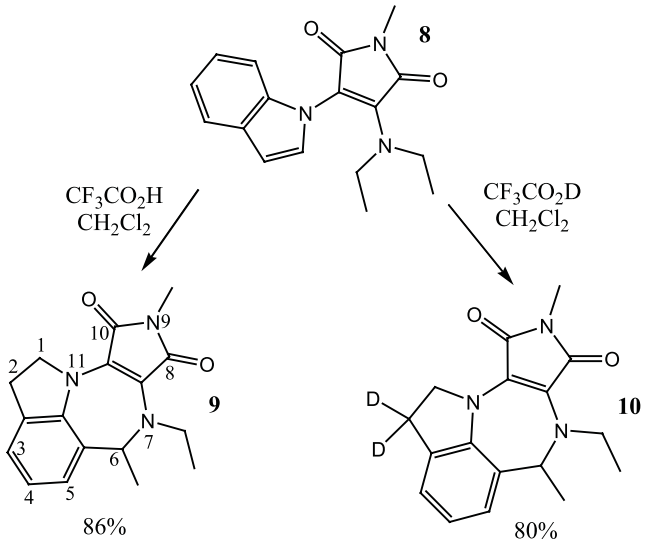

Figure 3.

cyclization products **2**. 1-Benzyl-3-[(d_5-ethyl)anilino]-4-(1*H*-indol-1-yl)-1*H*-pyrrole-2,5-dione **15** was used as a model compound in this experiment. Sodium d_5-ethylate prepared from d_6-ethanol **11** and NaH in THF was treated with TosCl to give d_5-ethyl tosylate **12**. *N*-(d_5-Ethyl)aniline **13** was obtained by the reaction of **12** with an excess of aniline. The reaction of **13** with 3-bromo-4-(indole-1-yl)maleimide **14** in DMF in the presence of Huenig base yielded **15**. According to the EI-MS spectrum and ^{1}H NMR data of **15** the percentage of deuterium incorporation was 97%. The signals corresponding to the carbon atoms of the ethyl group of non-deuterated **15** were observed in the ^{13}C NMR spectrum as low intensity singlets at δ 13.7 and 46.6. Thus the percentage of deuterium incorporation in **12**, **13**, and **14** can be evaluated as more than 97%.

The synthesis of indolinodiazepine derivative **17** from indolomaleimide **16** was described previously.[1] Indolomaleimide **15** was treated with TFA in CH_2Cl_2 and the cyclization product **18** was isolated as described for compound **17**.[1] The ^{1}H and ^{13}C NMR spectra of **18** were compared with the spectra of non-deuterated indolinodiazepine **17** (Table 2) and demonstrate that compound **18** contains as an admixture about 15% of non-deuterated compound **17**. ^{1}H NMR spectra of compounds **17** and **18** were very close. However, in ^{1}H NMR spectrum of **18** the signals of an admixture of **17** [hydrogen atom at C6 (one hydrogen quadruplet at δ 5.31), methyl group at C6 (three hydrogen doublet at δ 1.42) and one of the signals corresponding to hydrogens at C1 (doublet of triplets at δ 4.55)] were observed with the relative intensity of 15%; and the signal of another C1–H hydrogen at δ 4.35 was a triplet whereas in compound **17** it was a quadruplet. In the ^{13}C NMR spectrum of **18** C6–*C*H$_3$ methyl carbon signal, as well as the signals of C6 and C1, were observed as multiplets at δ 21.1, 50.2, and 56.7 instead of singlets at δ 20.3, 48.3 and 55.1, respectively. The signals of carbon atoms of non-deuterated product were also detectable as low intensity singlets at δ 22.3, 50.5 and 57.1. EI-MS data show that compound **18** contains the admixtures of the corresponding tetra-deutero derivative (~25%) and non-deutero compound **17** (~13%) (Fig. 4).

Altogether, our data demonstrate that, in the cyclization of compound **15**, the deuterium atom migrates from the position adjacent to nitrogen of *N*-(d_5-ethyl)aniline residue to position-2 of the indole nucleus. This model confirms the mechanism of the cyclization process suggested in our previous study.[1]