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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.
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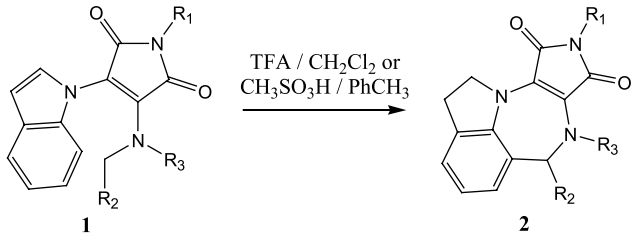
1. Introduction

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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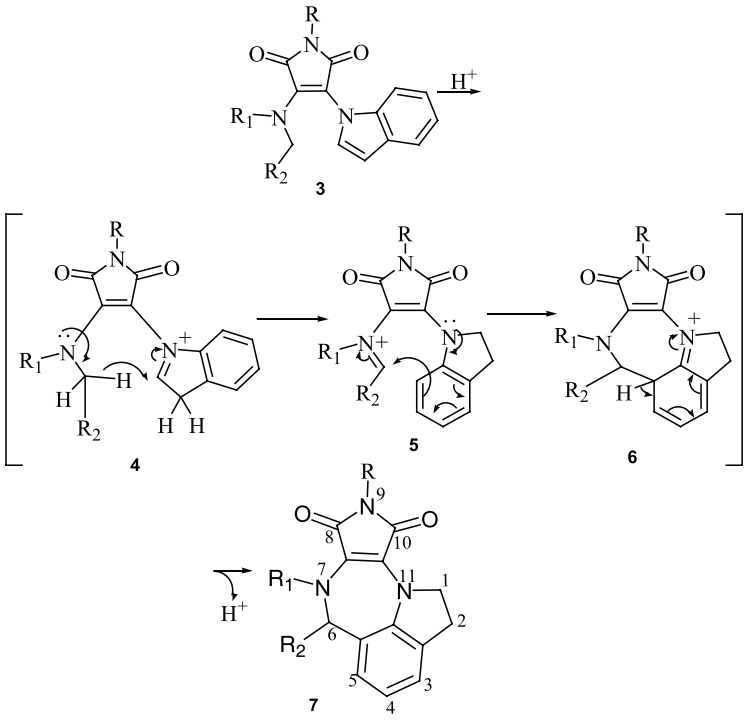

Figure 2.

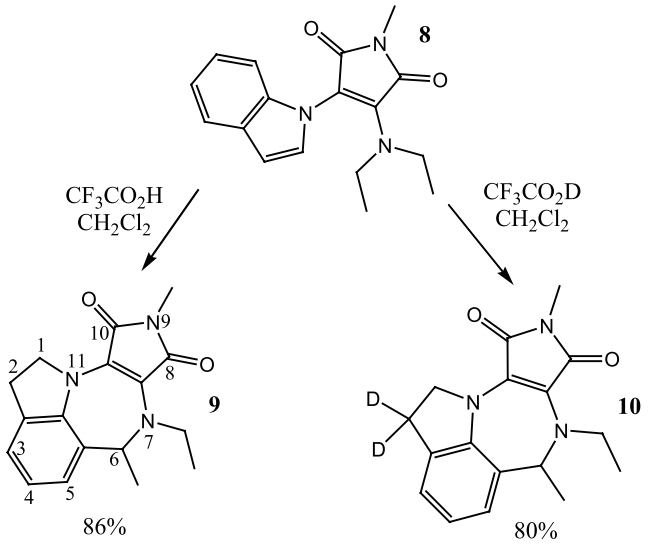

Figure 3.

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]

Table 1. The differences in NMR spectra of compounds **9** and **10**[a]

Compound **9**	Commentary	Compound **10**	Commentary
^{1}H NMR, δ, ppm			
3.1–3.25, 3H, m	C2–H_2 and one of the hydrogens of N7–CH_2 group	3.17, 1H, m	One of the hydrogens of N7–CH_2 group
4.43–4.49, 2H, m	C1–H_2	4.44, 2H, br s	C1–H_2
^{13}C NMR, δ, ppm			
28.2, s	*C*2	27.4–28.1, m	*C*2

[a] The spectra were registered in $CDCl_3$.

Table 2. Differences in NMR spectra of compounds **17** and **18**[a]

Compound **17**	Compound **18**	Commentary
^{1}H NMR		
1.42, 3H, d	Less intensive	C6–*C*H_3
4.45, 1H, q	4.34, 1H, t	C1–H_a
4.55, 1H, dt	Less intensive	C1–H_b
5.31, 1H, q	Less intensive	C6–*H*
^{13}C NMR		
20.3, s	21.1, m	C6–*C*H_3 (C6–*C*D_3)
48.3, s	50.2, m	*C*1
55.1, s	56.7, m	*C*6

[a] The spectra were registered in DMSO-d_6.

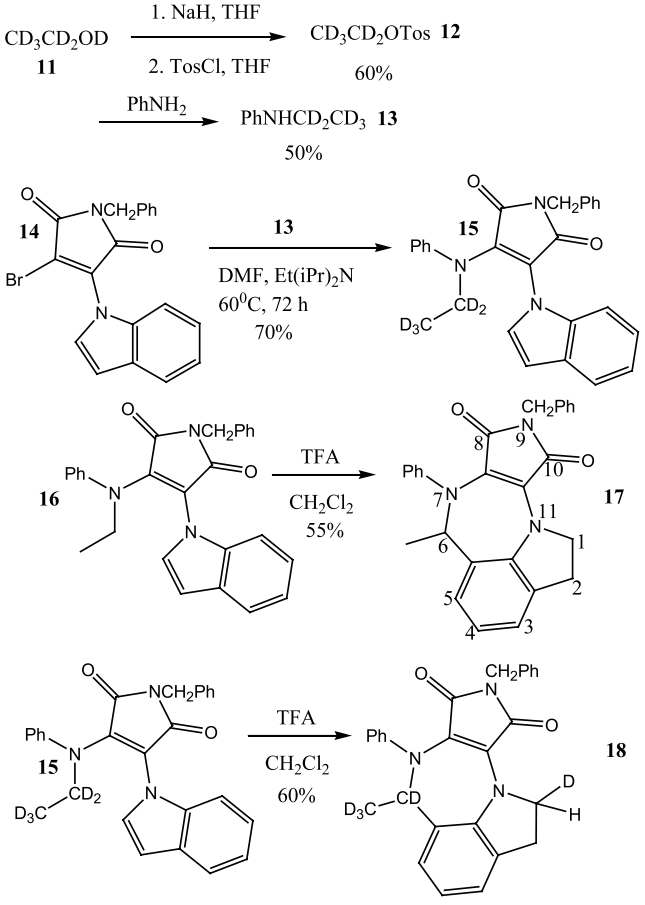

Figure 4.

3. Experimental

3.1. General

NMR spectra were recorded with Varian VXR-400 instrument at 400 MHz (^{1}H NMR) or at 75 MHz (^{13}C NMR) with internal references. Chemical shifts are given in ppm and coupling constants in Hz. Assignment of the signals was based on the decoupling experiments for ^{1}H NMR and APT-experiments for ^{13}C NMR spectra, the signals corresponding to the quaternary carbon atoms are marked (q). Electron impact mass-spectra (EI-MS) were obtained on an SAQ 710 Finnigan instrument at 70 eV (direct introduction, ion source temperature 150 °C). HRMS mass spectra were registered on a MAT 8430 Finnigan instrument with data operating system SS-300 (EI, 70 eV, direct introduction, ion source temperature 250 °C). Analytical TLC was performed on Kieselgel F254 plates (Merck) and column chromatography on Silica Gel Merck 60. Mps were determined on a Buchi SMP-20 apparatus and are uncorrected. Extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Solvents and reagents were obtained from commercial suppliers unless otherwise specified.

3.1.1. d_5-Ethyl tosylate (12). d_6-Ethanol (5.1 ml, 77.5 mmol) was added dropwise at 0 °C to the stirred suspension of NaH (2.4 g, 100 mmol) in THF (35 ml). The resulting suspension was stirred for 30 min at ambient temperature and treated with TosCl (19 g, 100 mmol) dissolved in THF (20 ml). The reaction mixture was stirred overnight, and the solvent was evaporated. The residue was dissolved in Et_2O–1 N HCl mixture (1:1, 100 ml). Organic phase was washed with $NaHCO_3$ solution (30 ml), water (30 ml), brine (30 ml) dried over Na_2SO_4 and evaporated. The residue was chromatographed (*n*-heptane–EtOAc, 20:1) to give **12** as an oil that crystallized upon standing at 0 °C for 7 days as colorless crystals (12.4 g, 61 mmol, 70%); mp 32–34 °C (*n*-heptane–EtOAc, 20:1); R_f 0.35 (*n*-heptane–EtOAc, 5:1); δ_H ($CDCl_3$) 2.4 (3H, s, PhCH_3), 7.3 (2H, d, Ph), 7.74 (2H, d, Ph); δ_C ($CDCl_3$) 13.2–13.9 (m, –CD_2*C*D_3), 21.4 (Ph*C*H_3) 65.7–66.1 (m, –CD_2CD_3), 127.6 (2C), 129.6 (2C), 133.0 (q), 144.5 (q) *m/z* (EI-MS) M^+ 205 (100), $M^+ - OCD_2CD_3$ 155 (85), 91 $M^+ - C_2D_5OSO_2$ (40%).

3.1.2. *N*-(d_5-Ethyl)aniline (13). The mixture of aniline (5 g, 54 mmol) and **12** (5.5 g, 27 mmol) was stirred at ambient temperature until no starting **12** could be detected by TLC. The reaction mixture was diluted with Et_2O (100 ml) and extracted with 2 N HCl (2×50 ml). The extracts were washed with $CHCl_3$ (50 ml), pH was adjusted to 12 with 2 N NaOH solution, and the amines were extracted with Et_2O

(2×75 ml). The extracts were dried over NaOH and evaporated. **13** was separated from the starting aniline by column chromatography (*n*-heptane→*n*-heptane–Et_3N, 20:1) to give **13** as a dark oil (2.3 g, 18.4 mmol, 50%); δ_H ($CDCl_3$) 3.5 (1H, br s, N*H*), 6.66 (3H, d, Ph), 6.76 (2H, t, Ph), 7.24 (3H,t, Ph); δ_C ($CDCl_3$) 13.6–14.1 (m, $-CD_2CD_3$), 37.1–37.5 (m, $-CD_2CD_3$), 112.5 (2C), 117.0, 129.0 (2C), 148.3 (q).

3.1.3. 2-Dideutero-1,2-dihydro-7-ethyl-6,9-dimethyl-6*H*-pyrrolo[3′,4′:2,3][1,4]diazepino[6,7,1-*hi*]indole-8,10-(7*H*,9*H*)-dione (10). A solution of 3-(diethylamino)-4-(1*H*-indol-1-yl)-1-methyl-1*H*-pyrrole-2,5-dione **8** (300 mg, 1 mmol) in CH_2Cl_2 (5 ml) was treated with CF_3CO_2D (1 ml). The reaction mixture was left to stir overnight and then poured into a mixture of EtOAc (50 ml) and aq $NaHCO_3$ (30 ml), the organic layer was separated, washed with aq $NaHCO_3$ (30 ml), water (30 ml), brine (30 ml) dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (*n*-heptane→*n*-heptane–acetone, 10:1) to give **10** as a dark violet solid (240 mg, 0.8 mmol, 80%); mp 80–82 °C (cyclohexane); R_f 0.41 (*n*-heptane–EtOAc, 3:1); *m*/*z* (EI HRMS) M^+ 299.1614 ($C_{17}H_{17}D_2N_3O_2$ requires 299.1601) (100), M^+-CH_3 284 (80), $M^+-NCH_2CH_3$ 256 (28), $M^+-C(O)NCH_3$ 241 (50%).

3.1.4. 1-Benzyl-3-[*N*-(d_5-ethyl)aniline]-4-(1*H*-indol-1-yl)-1*H*-pyrrole-2,5-dione (15). To the solution of 1-benzyl-3-bromo-4-(1*H*-indol-1-yl)-1*H*-pyrrole-2,5-dione **14** (1.1 g, 2.7 mmol) in DMF (10 ml) were added *N*-(d_5-ethyl)aniline (0.5 g, 3.9 mmol) and ethyldiisopropylamine (1 ml). The reaction mixture was stirred at 60 °C for 72 h and diluted with EtOAc (50 ml) and water (20 ml). The organic layer was separated and washed with 1 N HCl (2×10 ml), aq $NaHCO_3$ (10 ml), water (10 ml), brine (10 ml), dried and evaporated. The residue was purified by chromatography (*n*-heptane–EtOAc, 15:1) to give **15** as red crystals (0.8 g, 1.9 mmol, 70%); mp 112–114 °C (*n*-heptane–EtOAc); R_f 0.42 (*n*-heptane–EtOAc, 6:1); *m*/*z* (EI HRMS) M^+ 426.2087 ($C_{27}H_{18}D_5N_3O_2$ requires 426.2099) (100), M^+-CD_3 408 (11%).

3.1.5. 9-Benzyl-1,6-dideutero-2-hydro-6-(d_3-methyl)-7-phenyl-6*H*-pyrrolo[3′,4′:2,3][1,4]diazepino [6,7,1-*hi*]indole-8,10(7*H*,9*H*)-dione (18). To the stirred solution of **15** (200 mg, 0.48 mmol) in CH_2Cl_2 (20 ml) was added TFA (2 ml) and the mixture was left to stir for 8 h. The reaction mixture was diluted with EtOAc (60 ml) and washed with aq $NaHCO_3$ (3×20 ml), water (20 ml) and brine; dried and evaporated, the residue was chromatographed (*n*-heptane→*n*-heptane–acetone, 10:1) to give **18** as a dark violet solid (120 mg, 60%); mp 139–141 °C (cyclohexane), R_f 0.24 (*n*-heptane–EtOAc 6:1); *m*/*z* (EI HRMS) M^+ 426.2085 ($C_{27}H_{18}D_5N_3O_2$ requires 426.2099) (100%), *m*/*z* (EI-MS) M^+ 426 (100), M^+ (non-deuterated) 421 (15), M^+-CD_3 408 (30), M^+ (non-deuterated) $-CH_3$ 406 (9%).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.005

References and notes

1. Lakatosh, S. A.; Luzikov, Y. N.; Preobrazhenskaya, M. N. *Org. Biomol. Chem.* **2003**, *1*, 826–833.