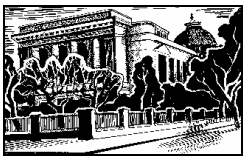

Directions of cyclization of 3,4-bis(indol-1-yl)maleimides substituted in indole nuclei depending from the position and nature of the substuents

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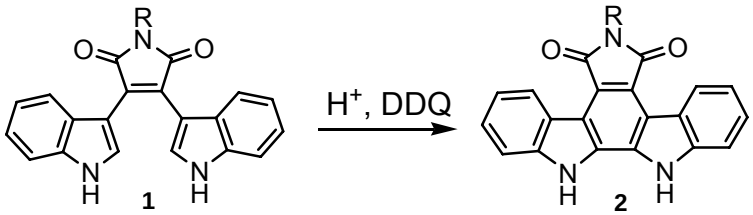
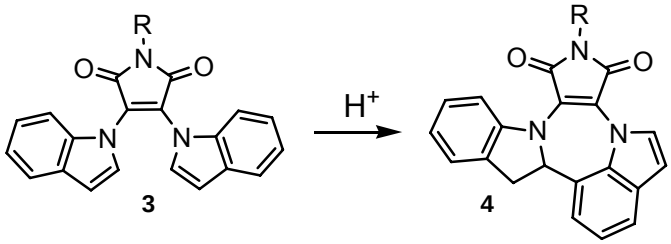
Introduction

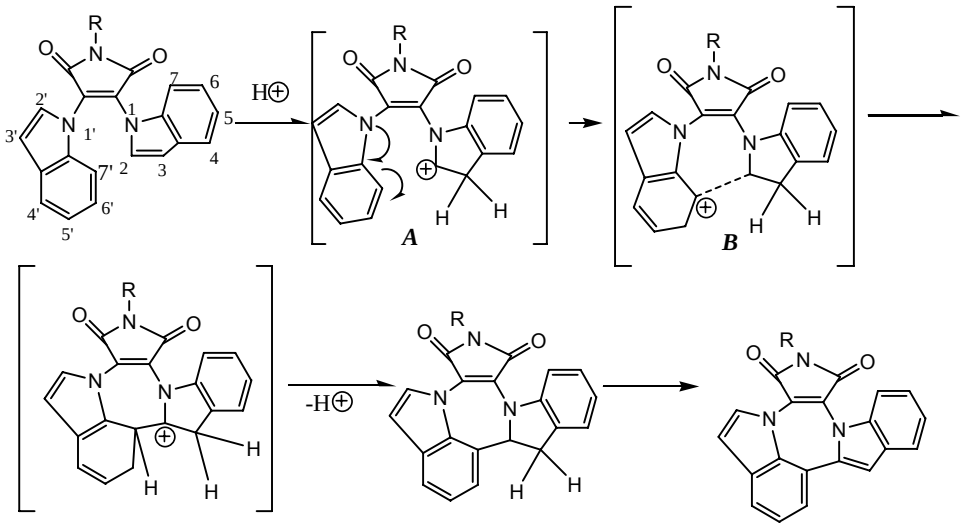
Bis(indol-3-yl)maleimides are of interest, as among their derivatives highly active inhibitors of proteinkinases were found. Bis(indol-3-yl)maleimides **1** form under the action of acids and DDQ maleimidoindolocarbazoles **2**.



Differently from **1**, bis(indol-1-yl)maleimides **3** form under the action of acids annelated diazepines[1, 4].



The reaction of cyclization proceeds *via* intermediate protonated (indoleninium) compound ***A*** and key intermediate ***B.***



Computation studies

The computations by DFT-method B3LYP/6-31G(d) confirmed the suggestion, that the direction of 2-7’ cyclization of 3,4-bis(indol-1-yl) maleimides (3) is mainly determined by geometrical parameters. According to the computations of structural parameters of all participants of this process, the geometrical configuration of the corresponding indoleninium cation (Fig. **1a**) is close to the configuration of the key intermediate (Fig.**1b**) for the 2-7’cyclization (the simulated approach to the helix type intermolecular electrophyle).

The investigation of energy of reagents, products, intermediates and the analysis of Energy Potential Surface by above quantum-chemical method shoved, that 2-7’ cyclization occurres without barrier activation. Indeed, this helix-type simulated intermediate (Fig.**1b**) corresponds to the global minimum on Energy Potential Surface.

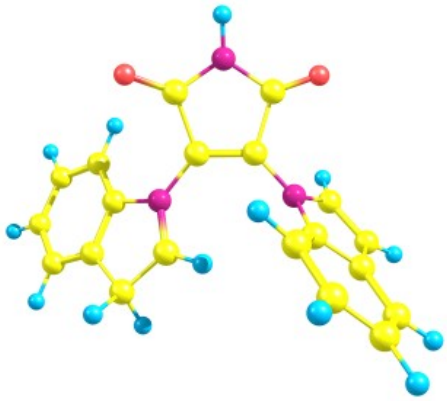


Fig. **1a**
Indoleninium cation

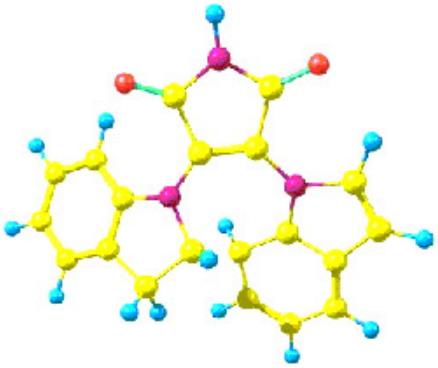
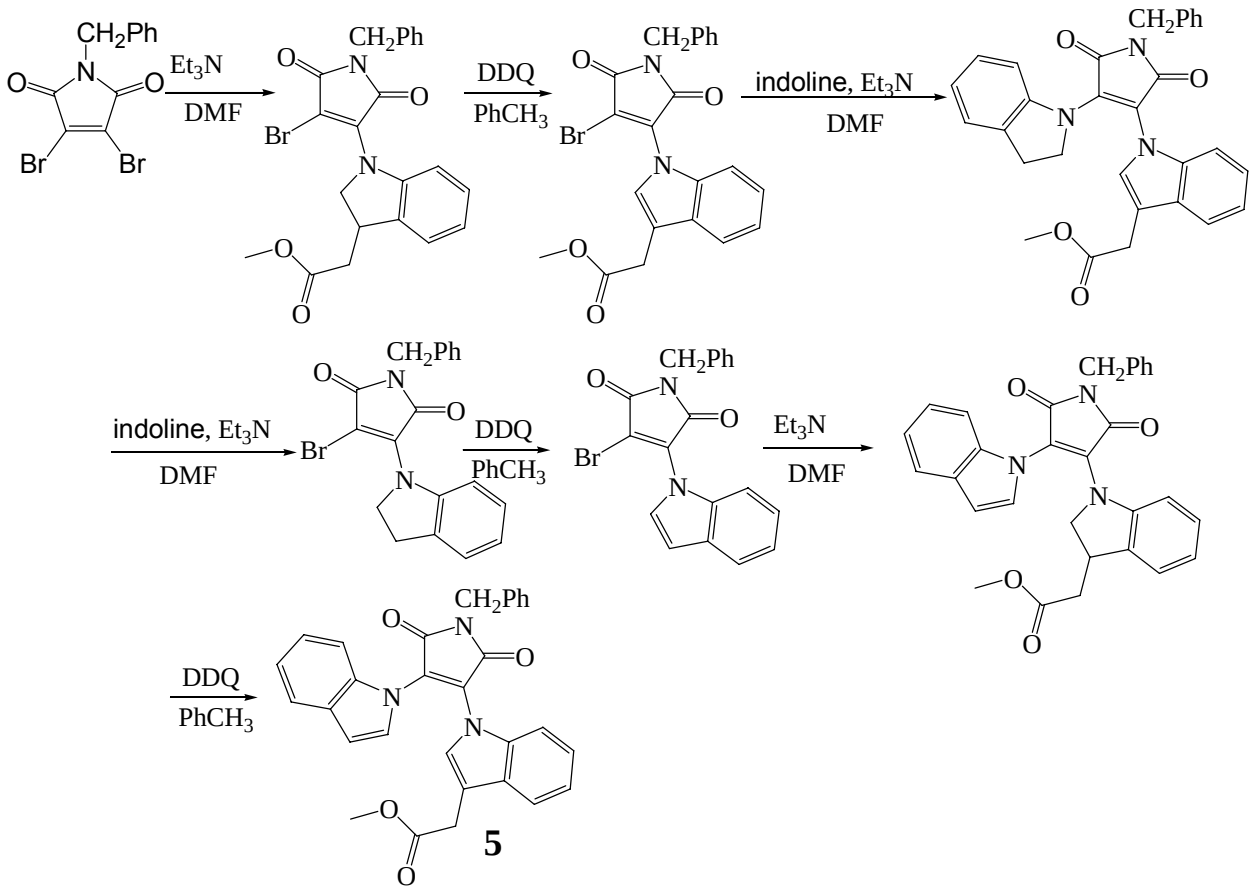


Fig. **1b**
Simulated helix-type intermediate

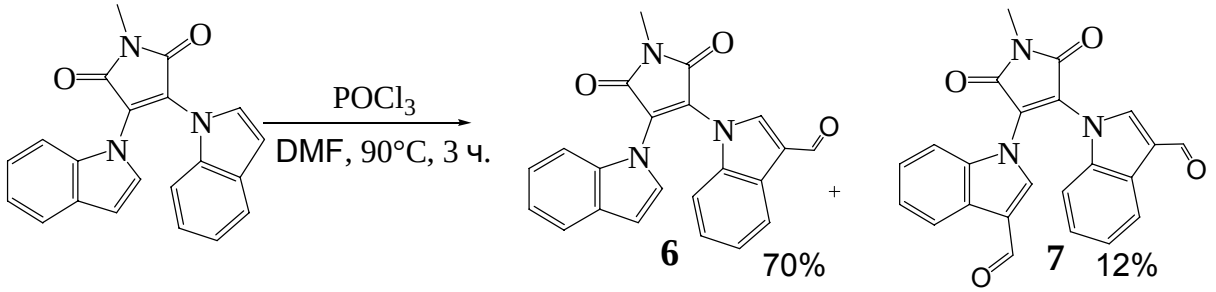
The aim of our research was to study the influence of substituents in indole ring of compound 3 on the derections of cyclization.

Results and Discussion

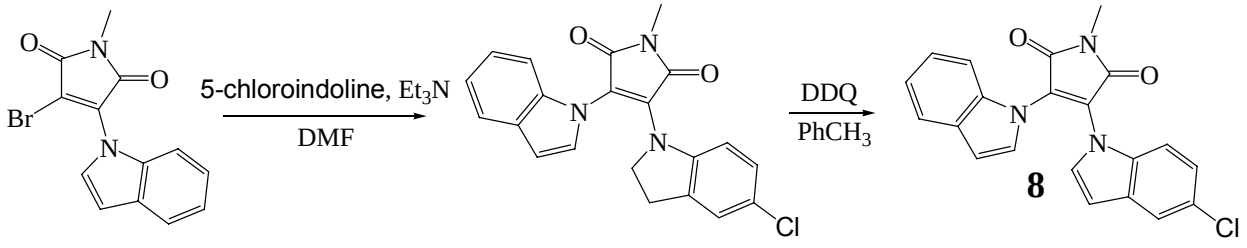
As starting compounds dibromomaleimides were used for the preparation of methyl 2-(1-(1-benzyl-4-(1H-indol-1-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-1H-indol-3-yl)acetate **5.**

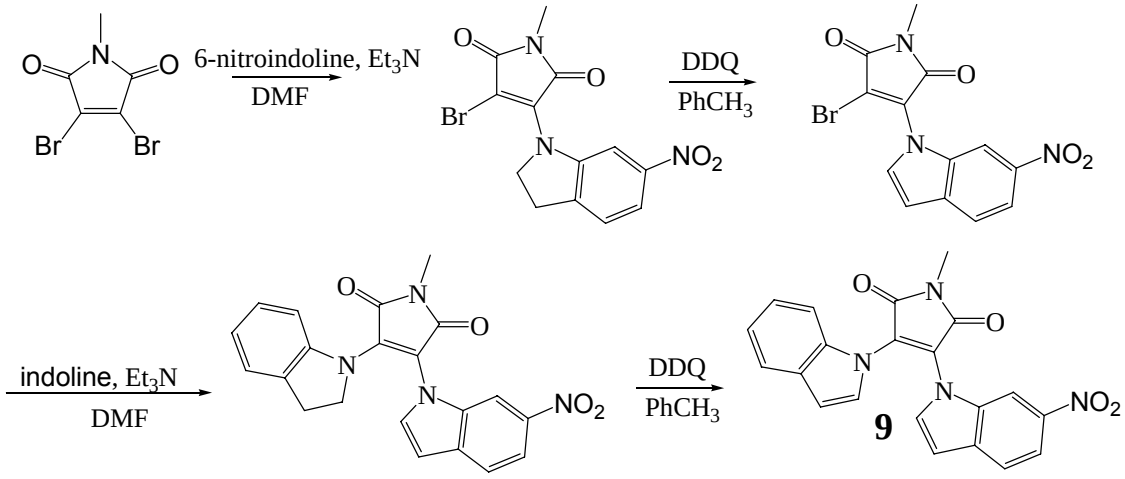


1-(4-(1H-indol-1-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-1H-indole-3-carbaldehyde **6** was obtained by formylation, a diformylated product **7** was also isolated

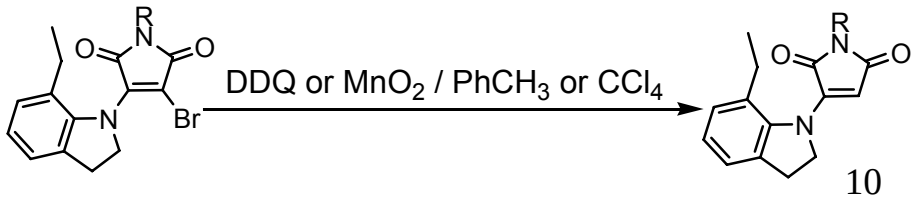


Synthesis of chloro- and nitro-substitubed bis(indol-1-il)maleimides (**8** and **9)** was performed starting from the corresponding substituted indolines.



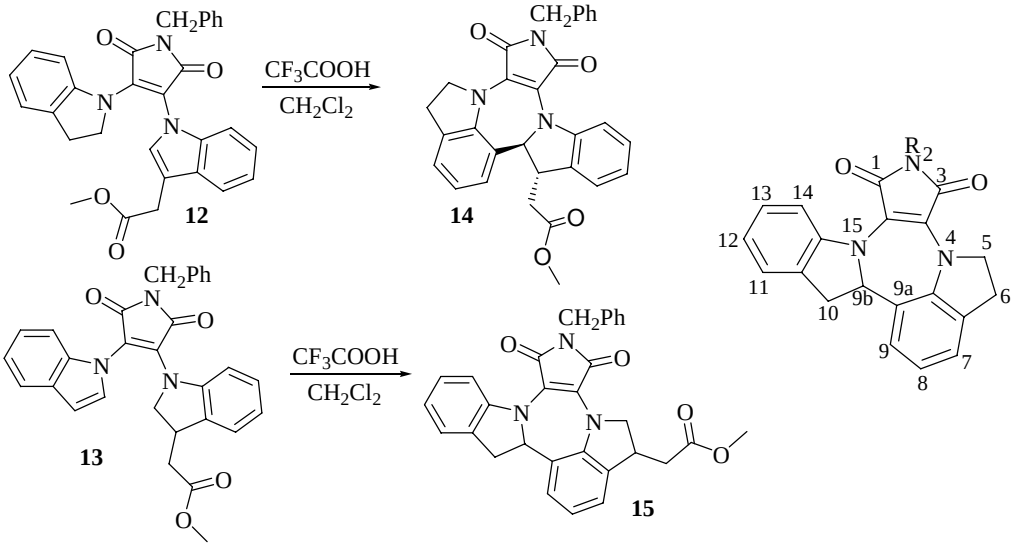


We failed to dehydrogenate 3-(2,3-dihydro-7-ethylindol-1-yl)-4-bromomaleimide **10**.

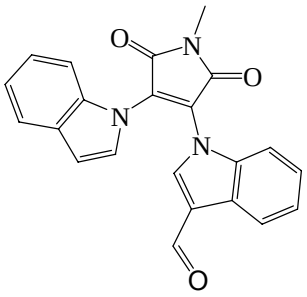


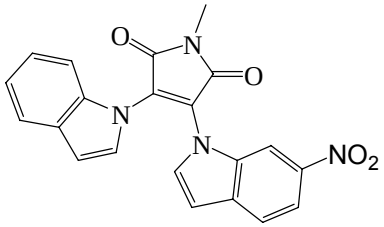
Cyclization compound **8** led to azepino-containg derivative **11.**

Cyclization of bis(indol-1-il)maleimides containing in position 3 of indole ring the CH_2COOEt fragment (**12, 13**) also produced annelated diazepines (**14, 15**).



We failed to cyclize the bis(indol-1-il)maleimides containing electrono-withdraing substituends:





Indeed, the quantum-chemical computation showed low electron density on the reaction center in 7’ position of NO_2-containing indole ring.

Conclusion

Cyclization of bis(indol1-yl)maleimides containing electronopositive substituents in pyrrole or benzene rings proceeds *via* formation of 2C-7’C bond and yields annelated azepino[1,4]derivatives