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Mesomeric betaines constructed of quinolinium cations and carboxylate anions separated by thiophene-ethynyl spacers as fluorescent dipoles

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ABSTRACT

4- and 5-((1-Methylquinolinium-3-yl)ethynyl)thiophene-2-carboxylates were prepared starting from 3-ethynylquinoline which was subjected to a Sonogashira-Hagihara coupling with ethyl 4- and 5-bromothiophenecarboxylates, respectively. Methylation to give the corresponding quinolinium salts, saponification under basic conditions, acidification to give the carboxylic acids, and basification finally yielded the title compounds. Calculations of the frontier orbital profiles confirm the classification of these mesomeric betaines as cross-conjugated systems, as the HOMO is essentially located in the carboxylate group which is connected to the spacer by a nodal position. Fluorescence spectroscopic investigations were performed.

1. Introduction

Since the discovery of the first heterocyclic mesomeric betaine in 1882 by Emil Fischer[1] and its structure elucidation decades later[2–4] this substance class has developed to versatile starting materials for heterocycle synthesis,[5–9] polymers and new materials,[10–13] natural product chemistry,[14] solvatochromic dyes,[15] and the preparation of pharmacologically active compounds.[16–19] Very recently, mesomeric betaines have been recognized and applied as starting materials for the generation of N-heterocyclic carbenes[20] or of their anionic derivatives[20,21] which form by deprotonation[22–24] or tautomerization.[25–31] Due to the fact that mesomeric betaines can exclusively be represented by dipolar resonance forms which delocalize the negative and the positive charges within a common π-electron system, this substance class has been the subject of controversial discussions - probably initiated by *Katritzky* as early as 1955[32] - concerning their adequate Lewis structures in combination with suitable mesomeric forms. Classifications have been published in 1985[33] and 2013.[34] The latter bases on a matrix-connectivity analysis and led to the recognition of five classes and nine sub-classes of heterocyclic mesomeric betaines. Quinolinium-3-carboxylate **1** (benzo-trigonelline, 3QB), which has been studied with respect to hydrogen bond formation,[35,36] hydrate formation[37] as well as biological activities,[38,39] belongs to the class of cross-conjugated mesomeric betaines (CCMB) (Scheme 1).[40] As shown in representation **I** the negative charge is restricted to an odd, alternant fragment and the positive charge is restricted to another odd, alternant fragment which are linked via inactive (unstarred) positions through a union bond ("*u*"). Concerning the anionic fragment, the inactive position corresponds to a nodal position of the HOMO which induces a π-electronic charge separation in the ground-state. This is characteristic of CCMBs.

Mesomeric betaines possessing triple bonds are seldom. Hetarenium rings substituted by acetylide groups form a class of compounds with interesting properties, as resonance forms of allenylidenes have to be taken into consideration which are either neutral compounds (*c.f.* **2**)[41] or betaines (*c.f.* **3**) (Scheme 2).[40] Imidazolium-2-acetylides have been reported as well.[42]

The mesomeric betaine **4** constructed of a quinolinium cation and *ortho*-benzoate separated by an ethyne-diyl spacer proved to be unstable, as a strong hydrogen bond causes a considerably bent *transoid* triple bond which is very susceptible toward attack by

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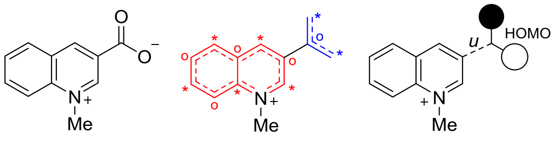
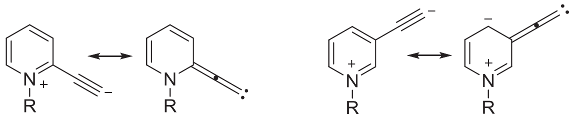


1 **I** **II**

Scheme 1. Quinolinium-3-carboxylate is a cross-conjugated heterocyclic mesomeric betaine.



2 **3**

Scheme 2. Heterocyclic mesomeric betaines with acetylide structure increments.

water and rearrangement to 2-(quinolinium-3-yl)-indenide **5**[43] (Scheme 3).

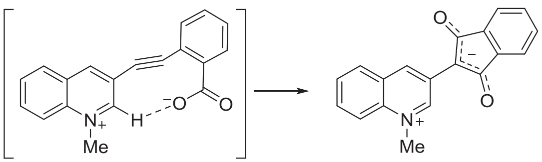
We describe here the syntheses and properties of a combination of the cross-conjugated heterocyclic mesomeric betaines and thiophene rings substituted by ethynyl groups. We formally separated the quinolinium rings of quinolinium-3-carboxylates from their carboxylate group by spacers which consisted of ethynylthiophenes to prepare new representatives of heterocyclic mesomeric betaines.

2. Results and discussion

The target molecules were prepared in four steps starting from 3-ethynylquinoline **5** and the corresponding bromothiophenes **6a,b**. First, the starting material **5** was subjected to a Sonogashira-Hagihara coupling (Scheme 4). This protocol delivered the acetylenes **7a,b** in moderate to very good yields. We then tested a series of methylation reactions of the acetylenes **7a,b** for the preparation of the corresponding salts **8a,b**.

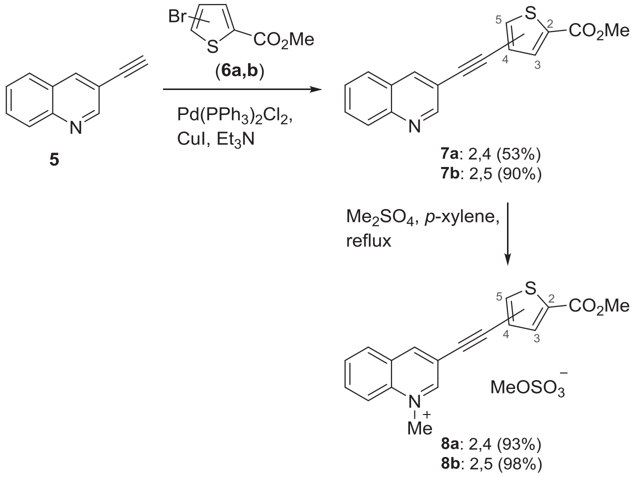
Methyl iodide in a solvent mixture of acetone, methanol, and acetonitrile gave only low yields of the corresponding iodide even after very long reaction times at reflux temperature. Stoichiometric amounts of methyl triflate at temperatures between 0 and 20 °C in dichloromethane were found to give slightly lower yields of the quinolinium salts **8a,b** (as triflates) in comparison to the methylation with dimethylsulfate in *p*-xylene under reflux conditions. The salts were then obtained as methylsulfates in excellent yields and proved to be hygroscopic compounds. The methylsulfate anions can be detected at approximately 3.36 ppm and 52.7 ppm (for the 2,5- and 2,4- substitution pattern, respectively) in the ^{1}H and ^{13}C NMR spectra, respectively.

Then we tested conditions for the ester hydrolysis of the salts **8a,b**. Acid-catalyzed hydrolysis did not provide any evidence for the formation of the desired saponified products although we tested various acids in different concentrations. Presumably a proton-catalyzed reaction of the triple bond takes place under these conditions. We finally were successful on employing ten equivalents of sodium hydroxide in a methanol-water mixture, followed by the addition of aqueous HCl to form the acids **9a,b** in good to excellent yields, from which the desired mesomeric betaines **10a,b** were formed after addition of triethylamine in good yields (Scheme 5).



4 **5**

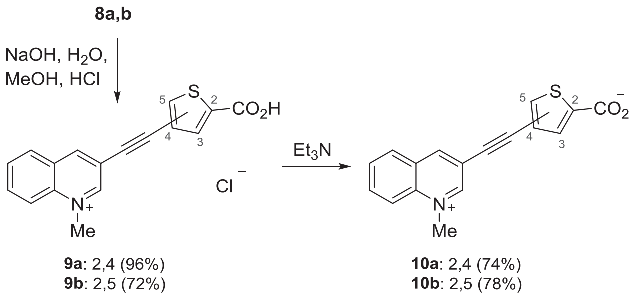
Scheme 3. Heterocyclic mesomeric betaines with ortho-benzoate moieties are unstable.



Scheme 4. Synthesis of the quinolinium salts.

The chemical shift differences on betaine formation from the acids proved to be very small. Thus, the resonance frequencies of the quinolinium rings change only by 0.07–0.15 ppm on betaine formation. This is in accord with the following measurement which we performed as comparison. 4-Methylbenzoic acid was deprotonated to its corresponding anion with 1,8-bis(*N*,*N*-dimethylamino) naphthalene in DMSO-d_6 (Scheme 6). While the proton of the protonated base occurred characteristically at $\delta = 21$ ppm the chemical shift differences on formation of the benzoate have similar values as found for the conversion of **9a,b** to **10a,b**.

Usually mesomeric betaines display considerably different frontier orbital profiles in comparison to their covalent neutral precursors. Indeed, DFT calculations show that the highest occupied molecular orbital (HOMO) as well as the lowest unoccupied molecular orbital (LUMO) of the ester **7a** are distributed all over the π-conjugated system. By contrast, the calculated frontier orbitals of the target betaine **10a** confirmed the classification as cross-conjugated heterocyclic mesomeric betaines (CCMB), as the highest occupied molecular orbitals (HOMOs) are essentially located in the carboxylate group, whereas the LUMO is essentially located in the quinolinium ring (Fig. 1). The same is true for **7b** and **10b**. On conversion of **7a** to **10a** the permanent dipole moment increases from 1.89 D to 29.20 D. Likewise, the permanent dipole moments of **7b** and **10b** were calculated to be 1.96 D and 29.27 D, respectively.



Scheme 5. Synthesis of the title compounds.