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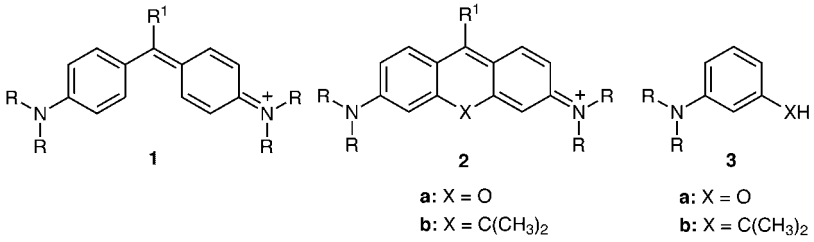
Alkylene-bridged *N,N,N′N′* – Tetrasubstituted Bis(2-amino-5-thiazolyl)methinium Salts— A New Class of Strongly Fluorescent Dyes**

Horst Hartmann* and Antje Noack

Owing to their strong fluorescence, pyronines **2a** ($R^1 = H$)[1] and rhodamines **2a** ($R^1 = Aryl$)[2] have found several practical applications, such as fluorescence and laser dyes,[3] or, if they are specifically functionalized, for example at the amino groups, as fluorescence markers for biological substrates and polymer characterization.[4] The fluorescence of the dyes **2a** is in sharp contrast to their unbridged di- and triarylmethane



dye analogues **1** which are nonfluorescent under normal conditions.[5] The fluorescence-enhancing effect of bridging by heteroatoms is associated, however, with a pronounced hypsochromism of the absorption of these dyes. Thus, the bridged di- and triarylmethane dyes **2a** absorb at about 550 nm. This is a nearly 50 nm shorter wavelength than the absorption wavelength of their unbridged analogous **1**.[6]

Whereas the fluorescence-enhancement is effected by the increasing rigidity of the molecular system and originates from a restriction or diminishing of the nonradiative deactivation processes[7] the hypsochromic effect originates from the incorporation of the lone pair of the bridging oxygen atom into the conjugation of the π system responsible for the color. This incorporation gives rise to a stabilization of the electronic ground state and, hence, to a widening of the gap between the ground and first excited state in the bridged compounds.[6]

In agreement with this postulate no hypsochromic effect is observed in going from the unbridged compounds **1** to the alkylene-bridged di- and triarylmethane dyes **2b** in which the bridging group has no lone pair. Therefore, these compounds absorb at nearly the same wavelength as their unbridged analogues **1**, but in contrast they exhibit, analogous to the oxygen-bridged compounds **2a**, a strong fluorescence.[8a] A practical application of the isopropylidene-bridged dyes **2b** has not been reported because the necessary educts for these compounds, the isopropylidene-substituted *N,N*-dialkylanilines **3b**, can only be prepared by a multistep reaction from commercially available precursors, making them far less

[*] Prof. Dr. H. Hartmann, Dr. A. Noack
Fachbereich Chemie der Fachhochschule Merseburg
Geusaer Strasse, 06217 Merseburg (Germany)
Fax: (+49) 3461-462192
E-mail: Horst.Hartmann@cui.fh-merseburg.de

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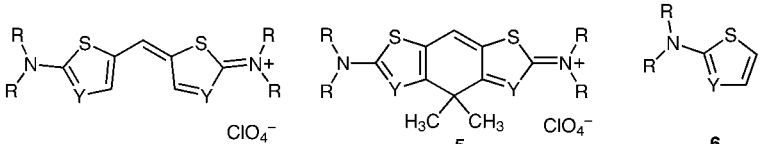
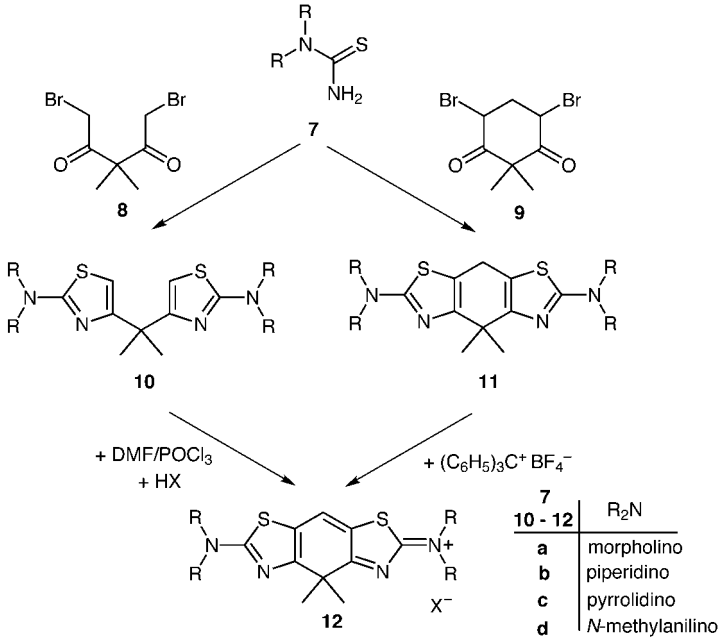
accessible than the educts **3a** for the oxygen-bridged compounds **2a**.[8b]

Recently it was demonstrated that some heterocyclic analogues of the di- and triarylmethane dyes **1**, such as the compounds **4**, exhibit similar spectroscopic properties to their carbocyclic parent compounds **1**.[9] Thus, the maxima of the longest-wavelength absorptions of the bis(2-dialkylamino-5-thienyl)methines **4a**[10] and bis(2-dialkylamino-5-thiazolyl)-methines **4b**[9, 11] are found at nearly the same wavelength as the maxima of their nonfluorescent parent compounds **1**.



This parallelism in the spectroscopic properties between the carbocyclic and heterocyclic methine dyes **1** and **4** inspired us to synthesize the alkylene-bridged analogues **5** of the bridged carbocyclic methine dyes **2** and to study their spectroscopic properties, especially their ability to fluorescence. In analogy to the synthesis of the unbridged compounds **4b** from the *N*,*N*-disubstituted 2-amino-thiazoles **6b**,[12] the first method studied for the synthesis of **5** was the reaction of *N*,*N*-disubstituted thioureas **7**[13] with the dibromo-substituted diketone **8**[14] (Scheme 1). This method gives the expected bisthiazoles **10**[15] which were subsequently transformed, by reaction with orthoformate esters and acetic anhydride in the presence of magnesium perchlorate[16] or, more preferably, by reaction with DMF and $POCl_3$ and addition of aqueous tetrafluoroboric or perchloric acid, into the bridged methine dyes **12**.



Scheme 1. Synthesis of the bis(2-amino-5-thiazolyl)methinium compound.

Although the desired products **12** could be obtained in this manner their yields were surprisingly low. The yields are reduced by the formation of by-products which probably result from an intermolecular condensation between two thiazole moieties of two educt molecules **10** which competes with the planed intramolecular condensation of the orthoformate esters with the two thiazole groups in **10**. Therefore, a second route for the preparation of **12** was designed. Instead of **8** the dibromo-cyclohexanedione **9** was chosen to react with **7**.[17] The compound **9** was prepared, analogously to compound **8**, by the bromination of its bromo-free precursor in glacial acetic acid.[18] The reaction of **9** with the appropriate *N*,*N*-disubstituted thiourea **7** in a molar ratio of 1:2 gave the tricyclic bisthiazole derivatives **11**.[19] These products were allowed to react in acetonitrile solution with trityl tetrafluoroborate affording the desired methine tetrafluoroborates **12** in satisfactory yields.

The structures of the isopropylidene-bridged methine dyes **12** were unambiguously confirmed by elemental analysis and NMR spectroscopy (Table 1). The dyes are deep blue and exhibit, as expected, a marked fluorescence. Figure 1 shows the absorption and emission spectrum of the morpholino-substituted compound **12a**. Like most dyes of this type this compound displays a narrow intense absorption band at about 620 nm.[20] Remarkably the position of this band is shifted to longer wavelength[21] than the longest-wavelength absorption band of the unbridged methine dye analogues **4b** (552 nm).[6] The fluorescence maxima from the isopropylidene-bridged methine dyes **12**, which are dependent on the polarity of solvents, are found at about 650 nm in toluene. The small Stokes shift observed is as

Table 1. Selected data for the bridged *N*,*N*,*N*′,*N*′,–tetrasubstituted bis(2-amino-5-thiazolyl)methinium tetrafluoroborates **12** (X = BF_4).[a,b]

12a: Yield 53% (method A)[c] and 51% (method B); m.p. 209–211 °C (CH_3CN/diethyl ether); ^{1}H NMR ([D$_6$]DMSO): δ = 1.65 (s, 6H, CH_3), 3.73 (t, 8H, NCH_2), 3.84 (t, 8H, OCH_2), 8.83 (s, 1H, CH); ^{13}C NMR ([D$_6$]DMSO): δ = 28.16, 45.74, 49.39, 65.18, 120.24, 139.89, 177.83, 181.36; UV/Vis absorption: λ_{max} = 616 nm, logε = 4.68; emission: λ_{max} = 654 nm, Φ = 56%

12b: Yield 49% (method A)[c] and 31% (method B); m.p. 203–205 °C (CH_3CN/diethyl ether); ^{1}H NMR ([D$_6$]DMSO): δ = 1.63 (s, 6H, CH_3), 1.70 (m, 12H, CH_2), 3.81 (m, 8H, NCH_2), 8.73 (s, 1H, CH); ^{13}C NMR ([D$_6$]DMSO): δ = 22.86, 24.91, 28.23, 45.58, 50.75, 119.74, 138.72, 176.95, 181.37; UV/Vis absorption: λ_{max} = 625 nm, logε = 4.62; emission: λ_{max} = 656 nm, Φ = 37%

12c: Yield 32% (method B); m.p. 160–162 °C (CH_3CN/diethyl ether); ^{1}H NMR ([D$_6$]DMSO): δ = 1.66 (s, 6H, CH_3), 2.09 (m, 8H, CH_2), 3.49 (m, 8H, NCH_2), 8.78 (s, 1H, CH); ^{13}C NMR ([D$_6$]DMSO): δ = 24.72, 28.24, 45.40, 51.07, 119.70, 139.91, 173.67, 180.89; UV/Vis absorpsion: λ_{max} = 616 nm, logε = 4.57; emission: λ_{max} = 649 nm, Φ = 21%

12d: Yield 38% (method B), m.p. 150–153 °C (CH_3CN/diethyl ether); ^{1}H NMR ([D$_6$]DMSO): δ = 1.71 (s, 6H, CH_3), 3.76 (s, 6H, NCH_3), 7.48–7.53 (m, 6H, CH), 7.64 (m, 4H, CH), 8.68 (s, 1H, CH); ^{13}C MMR ([D$_6$]DMSO): δ = 28.37, 42.15, 46.05, 121.65, 124.55, 125.73, 130.75, 143.65, 145.02, 172.44, 181.88; UV/Vis absorpsion: λ_{max} = 623 nm, logε = 4.64; emission: λ_{max} = 669 nm, Φ = 1%

[a] For the substitutents R_2N pattern, see Scheme 1. [b] Absorption data in dichloromethane, emission data in toluene; fluorescence quantum yield relative to rhodamine B(Φ = 86%). [c] Determined by ^{1}H NMR spectroscopy.

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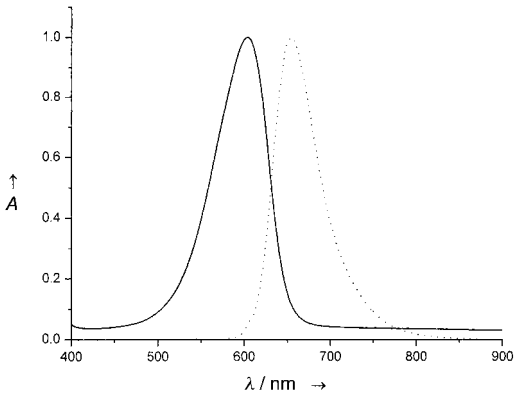

Figure 1. Absorption spectrum (——) and emission spectrum (····) of **12a**.

expected, and in accordance with the rigid structure of the dyes which prevents, or at least largely suppresses, a non-radiative deactivation of the excited state.

The reported route to strongly fluorescent bis(2-amino-5-thiazolyl)methinium salts **12** also indicates a simple way for preparing specially functionalized methine dyes which can be used, analogously to specially functionalized pyronine or rhodamine dyes **2a**,[4] as fluorescence markers for biological and polymeric substrates.

Experimental Section

Preparation of the isopropylidene-bridged *N,N,N′,N′*-tetrasubstituted bis(2-amino-5-thiazolyl)methinium salts **12**:

Method A: To a mixture of a 4-(2-(2-dialkylamino-4-thiazolyl)-2-propyl)-2-dialkylamino-thiazole **10** (0.01 mol) and DMF (20 mL) $POCl_3$ (0.02 mol, 3.0 g) was added dropwise under stirring at RT. After stirring for 3 h the reaction mixture was added dropwise, to a cooled solution of tetrafluoroboric acid (40%, 5 mL) in methanol (20 mL). The products precipitated after addition of diethyl ether (100 mL) and were isolated by filtration. As indicated by their ^{1}H NMR spectra the products in each case were a mixture of the corresponding dyes **12** and their dimers, from which the desired products could not be isolated, only identified by their characteristic ^{1}H NMR spectra and their intense fluorescence.

Method B: A mixture of a 2,6-bis(dialkylamino)-4,4-dimethyl-4,8-dihydrothiazolo[4,5-*f*]benzothiazole **11** (0.01 mol) and triphenylmethyl tetrafluoroborate (3.30 g, 0.01 mol) in acetonitrile (50 mL) was heated at reflux for 24 h. After cooling and reducing the volume to 5 mL diethyl ether (20 mL) was added to the reaction mixture and the precipitated **12** was isolated by filtration.

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[15] **10a**: Yield 82%; m.p. 140–143 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta =$ 1.60 (s, 6H, CH_3), 3.39 (t, 8H, NCH_2), 3.77 (t, 8H, OCH_2), 6.15 (s, 2H, CH); ^{13}C NMR ($CDCl_3$): $\delta = 27.87$, 41.93, 48.53, 66.18, 101.58, 160.27, 170.45. **10b**: yield 40%; m.p. 112–117 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 1.63$ (m, 18H, CH_3/CH_2), 3.41 (t, 8H, NCH_2), 6.10 (s, 2H, CH); ^{13}C NMR ($CDCl_3$): $\delta = 25.01$, 25.83, 28.68, 42.67, 50.24, 101.35, 161.08, 171.35.
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[17] Yield 61%; m.p. 83–85 °C (EtOH); ^{1}H NMR ($CDCl_3$): $\delta = 1.41$ (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.57 (q, 1H, CH_2), 3.18–3.33 (m, 2H, CH_2), 3.63 (dd, 1H, CH_2), 4.77 (t, 1H, CHBr), 4.98 (dd, 2H, CHBr).
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[19] **11a**: Yield 76%; m.p. 220–222 °C (toluene/MeOH); ^{1}H NMR ($CDCl_3$): $\delta = 1.49$ (s, 6H, CH_3), 3.41 (t, 8H, NCH_2), 3.78 (t, 8H, OCH_2), 3.82 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): $\delta = 23.33$, 28.16, 38.78, 48.57, 66.18, 111.60, 153.49, 169.76; **11b**: yield 66%; m.p. 275–277 °C (toluene); ^{1}H NMR ($CDCl_3$): $\delta = 1.53$ (s, 6H, CH_3), 1.65 (m, 12H, CH_2), 3.43 (m, 8H, CH_2), 3.81 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): $\delta =$ 24.06, 25.04, 25.78, 28.89, 39.44, 50.25, 111.44, 154.25, 170.66; **11c**: yield 79%; m.p. 250–252 °C (toluene); ^{1}H NMR ($CDCl_3$): $\delta = 1.59$ (s, 6H, CH_3), 2.01 (m, 8H, CH_2), 3.45 (t, 8H, CH_2), 3.83 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): $\delta = 24.20$, 26.33, 28.85, 39.56, 50.05, 110.52, 154.47, 166.67; **11d**: yield 66%; m.p. 153–154 °C (*n*-butanol); ^{1}H NMR ($CDCl_3$): $\delta = 1.64$ (s, 6H, CH_3), 3.56 (s, 6H, NCH_3), 3.72 (s, 2H, CH_2), 7.23 (m, 2H, CH), 7.42 (m, 8H, CH); ^{13}C NMR ($CDCl_3$): $\delta = 23.81$, 28.97, 39.41, 40.53, 112.16, 124.99, 126.28, 130.13, 147.36, 153.84, 168.57.
[20] The UV/Vis absorption and emission spectra were recorded with an MC 40 spectrometer (Zeiss) and Lambda 900 Spectrometer (Perkin-Elmer), respectively, the NMR spectra with a 300 MHz Spectrometer (Varian). The authors are indebted to Mrs. C. Koenig and Mrs. A. Schroeder for recording the NMR and UV/Vis absorption and emission data, respectively.
[21] The observed bathochromic shift can be explained if an S–S-interaction is assumed which gives rise to a pronounced hypsochromic effect in the color band of the unbridged dye **4b**; see: J. Fabian, H. Hartmann, K. Fabian, *Tetrahedron* **1973**, *29*, 2609–2619.

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