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# NMR studies of the products of hydrolysis of 3-ethyl-2-methylbenzo[*d*]azol-3-ium iodides

Jivka Rashkova, Pavleta Tzvetkova, Svetlana Simova*, Lilia Viteva**, Tzveta Gospodova

*Institute of Organic Chemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev Str. Bl. 9, 1113 Sofia, Bulgaria*

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ABSTRACT

*N*-(2-Hydroxyphenyl)- and *N*-(2-mercaptophenyl)-*N*-ethylacetamides were found as the main reaction products of the hydrolysis of the corresponding 3-ethyl-2-methylbenzazol-3-ium iodides in boiling ethanol in the presence of piperidinium base; the same products were obtained in aq. DMSO. The thiol undergoes spontaneous or accelerated oxidative coupling to the corresponding disulfide and forms a methylene-bridged dimer in the presence of $CH_2Cl_2$. All amides displayed diastereotopicity of the *N*-methylene group protons due to restricted rotation around the *N–aryl* bond, which is *additional* to the normal restricted rotation around the N–CO amide bond. This hydrolysis might be of crucial importance in cyanine dye synthesis in which benzazolium salt precursors are used; the findings provide an explanation for the process of obtaining ramified compounds. Structural elucidation of all products was based on detailed NMR analysis. The revision of several dye structures has been proposed.



## 1. Introduction

*N*-Alkyl quaternary benzazole ammonium salts are important precursors in cyanine dye synthesis. In general, they are used as end group-forming synthons, which allows the introduction of specific substituents both in the heterocycle and at the quaternary nitrogen atom, thus contributing to the diversity of dye structure. Their intensive use is additionally due to the fact that either partial or complete incorporation of the polyene dye chain into a ring system significantly improves the thermal and/or photostability character of the dyes [1–12].

It has been recently reported, that some heterocyclic salts (benzoxazolium, -thiazolium and -selenazolium) undergo an unexpected reaction, promoted by the residual water in DMSO [13]. The species, obtained from benzoxazolium salts, have been described as hydroxylated benzoxazololes (see Scheme 1, conversion **1** ⇒ **2**). Their structures were corroborated by $^1$H NMR, $^{13}$C NMR and HR FAB-MS spectra. The presence of two geminal *N*-methylene non-equivalent protons (H, H′) has been cited as a characteristic proof for the presence of hydroxylated benzazole species. The authors suggest that under more rigorous conditions (elevated temperature, higher water content etc.) analogous conversion should also occur with benzothiazolium and benzoselenazolium salts. Numerous cyanine dyes, containing that structural fragment have been published [8,14,15].

The proposed structures of the hydroxylation products and derivatives thereof contradict recent results indicating that under analogous conditions 3-ethyl-2-methylbenzthiazolium iodide reacts with heterocycle ring opening [12]. The behaviour of quaternary benzthiazolium salts has been investigated by Metzner et al., in 1964, and only alkoxybenzothiazoles rather than their hydroxyl precursors were detected [16]. Cleavage of the benzthiazolium ring under different experimental conditions has been reported previously [17].

The present paper provides evidence that under basic conditions, as often used in dye synthesis, the interaction of 3-ethyl-2-methylbenzazolium iodides with water does not stop at the hydroxylated benzoazol compounds **2** (see Scheme 1). Cleavage of the heterocyclic ring yields the corresponding *N*-(2-hydroxyphenyl)- and *N*-(2-mercaptophenyl)-*N*-ethylacetamides. The compounds do exist in solution as mixtures of axially chiral conformers, recognized by the presence of geminal non-equivalent protons in the NMR spectra.

* Corresponding author. NMR Laboratory, Institute of Organic Chemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev Str. Bl. 9, 1113 Sofia, Bulgaria. Tel.: +359 2 9606 140; fax: +359 2 8700225.

** Corresponding author. Laboratory "Organic Synthesis and Stereochemistry", Institute of Organic Chemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev Str. Bl. 9, 1113 Sofia, Bulgaria. Tel.: +359 2 9606 114; fax: +359 2 8700225.

*E-mail addresses:* sds@orgchm.bas.bg (S. Simova), lilia@orgchm.bas.bg (L. Viteva).

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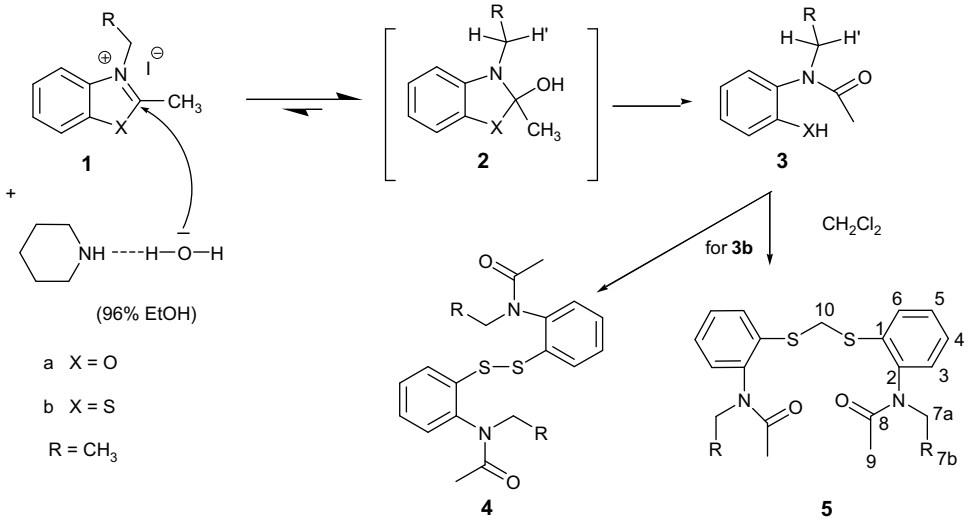



**Scheme 1.** Reaction products after hydrolysis of **1**.

## 2. Experimental

The 3-ethyl-2-methylbenzo[*d*]azol-3-ium iodides were prepared according to a literature procedure [18]. Thin layer chromatography (TLC) analysis of the reaction mixture and determination of the $R_f$ values of the products were performed on aluminum sheets pre-coated with silica gel 60 $F_{254}$ (Merck). Melting points were determined using Kofler apparatus and are uncorrected. Flash chromatography was carried out using Fluka Silica gel 60 (0.04–0.063 mm).

$^1$H (600.13 MHz), $^{13}$C (150.92 MHz) and $^{15}$N (60.82 MHz) spectra were acquired on an AVANCE AV600 II+ NMR spectrometer. Unless indicated all spectra were recorded in $CDCl_3$ at room temperature. TMS was used as an internal standard for the $^1$H and $^{13}$C spectra. Inverse detected $^{15}$N NMR chemical shifts are referenced to external liquid $NH_3$. Unambiguous assignment of the signals was made on the basis of the gradient enhanced versions of COSY, HSQC, HMBC, NOESY, 1D selective NOE and DOSY experiments [19].

### 2.1. Hydrolysis of 3-ethyl-2-methylbenzo[d]azol-3-ium iodides *1a* and *1b* to N-(2-hydroxyphenyl)- and N-(2-mercaptophenyl)-N-ethylacetamides *3a* and *3b*

A solution of 3-ethyl-2-methylbenzazolium iodide **1** (289 mg or 305 mg, 1 mmol), and piperidine (500 mg, 6 mmol) in 96% ethanol (150 mL) was heated under reflux. TLC analysis of the reaction mixture after 30 min demonstrated only traces of the starting salt. The solvent was removed in vacuum. The NMR investigation was carried out using pure **3a** and crude **3b**. Pure **3a** was isolated by column chromatography using methylene chloride/methanol = 30/1 as mobile phase. Yield 89%; white solid; m.p. 123–125 °C; $R_f$ = 0.19 (methylene chloride/methanol, 2/1).

The $^1$H NMR data for **3a** and **3b** are presented in Table 1. **3a** $^{13}$C NMR (150.92 MHz) – data in $CDCl_3$ and DMSO-$d_6$ in ppm (major *E* isomer): C-8 (172.34, *169.02*), C-1 (153,13, *153.15*), C-5 (129.75, *129.55*), C-3 (129.21, *128.72*), C-2 (128.61, *129.38*), C-4 (120.15, *119.33*), C-6 (117.67, *116.54*), C-7a (42.87, *41.66*), C-9 (22.35, *21.57*), C-7b (12.74, *12.51*).

The proton NMR spectrum of the crude product **3b** revealed that besides mercaptan (40.7%) it contains 6.1% of **4**, 2.4% of **1** and 50.8% pyperidine. $^{13}$C NMR (150.92 MHz) in ppm (major *E* isomer): C-8 (170.81), C-2 (139.44), C-1 (137.21), C-6 (131.45), C-5 (128.87), C-4 (128.00), C-3 (124.30), C-7a (41.54), C-9 (22.21), C-7b (12.45); $^{15}$N NMR (60.82 MHz) in ppm: 138.5.

### 2.2. Disulfide *4*

Compound **4** was isolated as the only reaction product in an attempt to purify the thiol **3b** by flash chromatography on silica gel. Thus, from the crude reaction mixture obtained from 1 mmol (305 mg) of benzthiazolium salt as described in Section 2.1 and using a mobile phase with a gradient of polarity from ether/hexane = 1/2 to ether/hexane = 3/1 disulfide **4**, 180 mg, 46% (corresponding to 92% of the monomeric form), were isolated as white solid; m.p. 97–99 °C; $R_f$ = 0.25 (ether/hexane, 3/1).

NMR data for **4**: $^1$H NMR (600.13 MHz) $\delta$ (observed multiplicity, assignment, detected marginal chemical shift difference in ppb between diastereoisomers): major *EE* isomers: 7.56 (ddd, H-6, 3), 7.35 (ddt, H-5, 2), 7.30 (dt, H-4), 7.15 (dd, H-3), 4.17 (dq, H-7a), 3.35 (ddq, H-7a′, 7), 1.87 (d, H-9, 4), 1.19 (dt, H-7b, 8); $^{13}$C NMR (150.92 MHz) in ppm: C-8 (170.23, 170.21), C-2 (139.74, 139.72), C-1

**Table 1**
$^1$H NMR shifts ($\delta$, ppm) and coupling constants (in Hz) of **3a** (pure) and **3b** (crude reaction mixture).

| Proton (multiplicity) | **3a** (major, *E*) | **3a** (minor, 4%, *Z*) | **3b** (major, *E*) | **3b** (minor, 5%, *Z*) |
|---|---|---|---|---|
| H-3 (dd) | 7.06 (*7.09*[a]) | 7.13 | 7.10 (7.12) | ov.[b] |
| | 7.7, 1.7 | 7.7, 1.6 | 7.8, 1.7 | |
| H-4 (ddd) | 6.91 (*6.84*) | 6.94 | 7.15 (*7.42*) | ov. |
| | 7.7, 7.5, 1.4 | 7.7, 7.6, 1.4 | 7.8, 7.5, 1.5 | |
| H-5 (ddd) | 7.27 (*7.18*) | 7.21 | 7.21 (*7.37*) | ov. |
| | 8.2, 7.5, 1.7 | 8.0, 7.6, 1.6 | 7.9, 7.5, 1.7 | |
| H-6 (dd) | 7.10 (*6.96*) | 7.09 | 7.49 (*7.89*) | ov. |
| | 8.2, 1.4 | 8.0, 1.4 | 7.9, 1.5 | |
| H-7a (dq) | 4.01 (*3.70*) | 3.79q | 4.10 (*4.15*) | 3.82 |
| | 13.5, 7.2 | 7.2 | 13.6, 7.3 | 14.7, 7.2 |
| H-7a′ (dq) | 3.46 (*3.37*) | 3.79q | 3.28 (*3.12*) | 3.60 |
| | 13.5, 7.2 | 7.2 | 13.6, 7.3 | 14.7, 7.2 |
| H-7b (t) | 1.12 (*0.97*) | 1.18 | 1.14 (0.96) | 1.03 |
| | 7.2 | 7.2 | 7.3 | 7.2 |
| H-9 (s) | 1.88 (*1.66*) | 2.37 | 1.83 (*1.59*) | 2.34 |
| OH | ~8.5 (~*10.5*) | ~7.3 | | |

[a] Chemical shifts in DMSO-$d_6$ are reported in brackets, indicating the considerable solvent dependence.
[b] ov. = overlapped signals.

(135.54), C-3 (129.82), C-5 (129.29), C-4 (127.78), C-6 (126.59, 126.58), C-7a (43.05, 43.01), C-9 (22.55), C-7b (13.13, 13.11); mixed *EZ* isomers: $^{1}$H NMR 7.71 (ddd, H-6, 9) and 7.50 (ddd, H-6′, 23), 7.35 (dt, H-5), 7.26 (dt, H-4), 7.12 (ddd, H-3, 2), 3.84 (ddq, H-7a, 8), 3.61 (dq, H-7a′), 2.34 (d, H-9, 2) and 1.83 (d, H-9′, 42), 1.26 (dt, H-7b, 7); $^{15}$N NMR (60.82 MHz) in ppm: 136.2; Anal. calcd for $C_{20}H_{24}N_2O_2S_2$: C 61.82, H 6.23, N 7.21, S 16.51; found C 61.52, H 6.47, N 7.51, S 16.73.

### 2.3. Bridged disulfide **5**

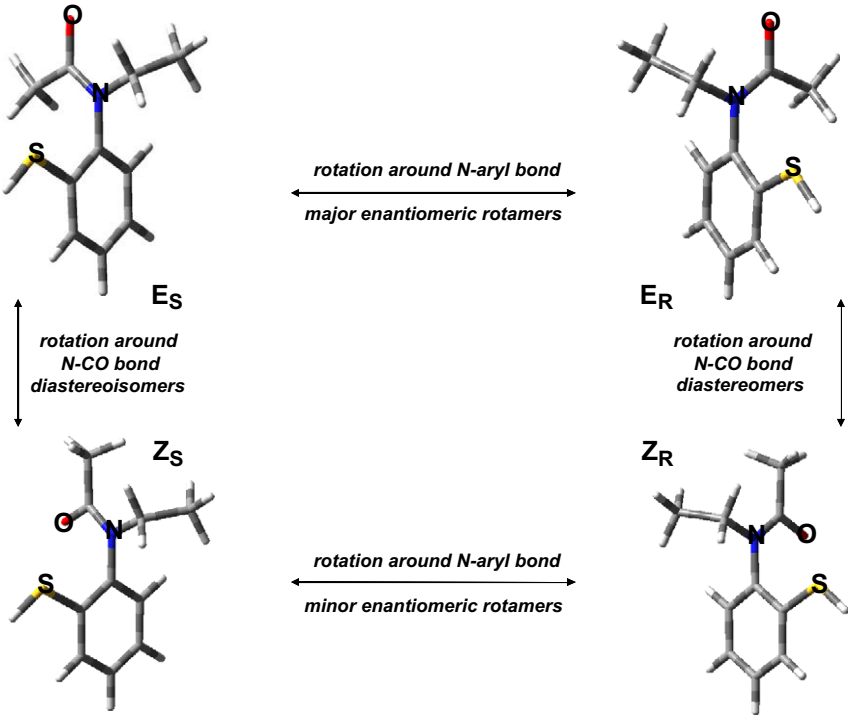
Compound **5** was obtained when dichloromethane was employed in the work-up procedure after hydrolysis. Thus, the crude reaction mixture from 1 mmol (305 mg) of benzthiazolium salt was extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic layers were dried over $Na_2SO_4$ and evaporated to dryness. TLC of the residue exhibited two main products with close $R_f$ values. Flash chromatography on silica gel, eluent methylene chloride/methanol = 100/1 afforded 55 mg of the less polar product as a viscous oil, which was identified as a bridged disulfide **5** and 120 mg of a more polar product, found to be identical with disulfide **4**.

NMR data for **5**: $^{1}$H NMR (600.13 MHz) $\delta$ major *EE* isomers (93%): 7.47 (dd, H-6), 7.42 (dt, H-5), 7.29 (dt, H-4), 7.16 (dt, H-3, 2), 4.47 (s, H-10), 4.06 (ddq, H-7a, 5), 3.14 (ddq, H-7a′, 15), 1.74 (d, H-9, 9), 1.09 (dt, H-7b, 3), $^{13}$C NMR (150.92 MHz) in ppm: C-8 (170.46), C-2 (139.79), C-1 (135.13, 135.11), C-3 (129.68), C-5 (128.98, 128.96), C-4 (127.16), C-6 (126.66, 126.64), C-7a (42.46, 42.44), C-10 (33.81), C-9 (22.28, 22.25), C-7b (12.97, 12.95); $^{15}$N NMR (60.82 MHz) 137.6; Anal. calcd for $C_{21}H_{26}N_2O_2S_2$: C 62.65, H 6.51, N 6.96, S 15.93; found C 62.31, H 6.77, N 7.29, S 16.25.

## 3. Results and discussion

Both 3-Ethyl-2-methylbenzo[*d*]azolium iodides (**1a** and **1b**) convert quantitatively after 30 min boiling in ethanol in the presence of piperidinium base into the new compounds **3a** and **3b**. The reaction could be easily followed by TLC. Their $^{1}$H and $^{13}$C NMR spectra correspond to *N*-(2-hydroxyphenyl)- and *N*-(2-mercaptophenyl)-*N*-ethylacetamides. Additionally, minor components could be revealed in the $^{1}$H NMR spectra in $CDCl_3$ and DMSO-$d_6$ (see Table 1). Detailed inspection of the proton and NOESY spectra enabled it to be established that in solution the compounds actually comprise four mutually converting species as shown in Scheme 2. Restricted rotation around the partially double N–CO bond gives rise to *E*/*Z* diastereoisomers, well known for amides (referred sometimes as *exo*–*endo* rotamers [20]). Additionally, the restricted rotation around the *N*–*aryl* bond (for aryl rings carrying at least one non-hydrogen *ortho*-substituent [21,22]) is responsible for the observed chemical shift non-equivalence of the diastereotopic methylene protons. Actually, the $E_S$ and $E_R$ (as well as $Z_R$ and $Z_S$) represent enantiomeric conformers that possess axial chirality (atropisomers). The NOESY spectra at several mixing times confirm that as usual for substituted acetanilides the major diastereoisomers of **3** possess *E*-configuration around the partially double N–CO bond with proximity between the methyl singlet and the aryl ring protons. The chemical shift difference between the non-equivalent methylene protons in the acetanilides with *Z*-configuration is smaller (∼0 for **3a**, ∼0.2 ppm for **3b**) as compared with 0.5–0.8 ppm for the corresponding protons in the structures with *E*-configuration. Analogous with previously reported studies [13] in wet DMSO **1a** and **1b** convert to acetanilides **3a** and **3b** [23].

Additional chemical evidence for the structure of acetanilide **3b** has been gained in the process of its purification. A small amount of the disulfide **4** has been detected in the crude reaction mixture, as well identified by the corresponding diffusion ordered (DOSY) NMR spectrum (see Fig. 1). The DOSY spectrum visualizes the resolution of monomeric–dimeric species and confirms the assignment of the higher molecular mass compound **4**.




**Scheme 2.** Isomeric **3** – schematic representation of the enantiomeric and diastereoisomeric conformers that result from the rotation around the *N*–*aryl* and N–CO bonds (blue: nitrogen, red: oxygen, yellow: sulphur). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

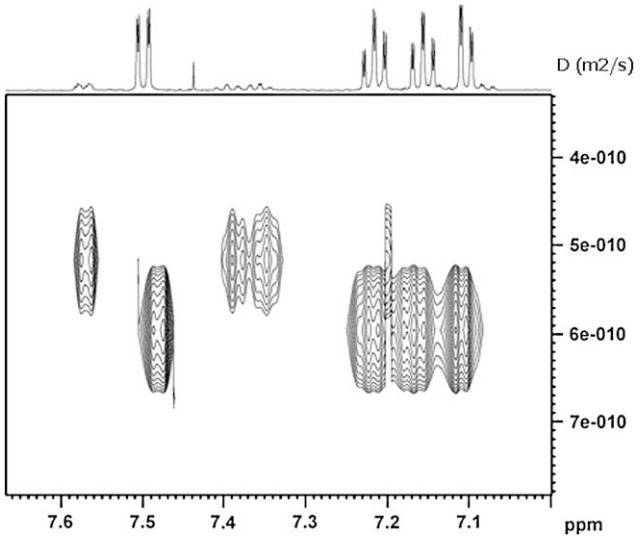



**Fig. 1.** DOSY spectra of the aromatic part of compounds **3** and **4**.

Our attempts to purify thiol **3b** using flash chromatography were unsuccessful. Disulfide was isolated as the only product, most probably due to acceleration of the oxidative coupling reaction on silica gel. Transformation of the thiol **3b** to dimer **4**, although not so fast, also proceeds spontaneously when the crude reaction mixture was allowed to stay in the open air. Compound **4** has been recently obtained as an unexpected product during attempts to oxidize **1b** to the corresponding S-oxides. The X-ray analysis proves its *EE* conformation in the solid state [24]. In solution disulfide **4** is a mixture of several racemic diastereoisomers due to the restricted rotation around the N–CO and around the *N–aryl* bonds in both parts of the molecules. The major isomers of the dimer **4** possess *E*-configuration around the partially restricted N–CO bonds and differ in the axial chirality of the two anilides ($E_{R^*}E_{R^*}$, $E_{R^*}E_{S^*}$, 95%). This is easily seen in the doubled multiplet structure (doublet of doublets of quartets, Fig. 2) of the high field methylene protons. Several doubled carbon chemical shift also reflect the tiny difference in the electronic structure of the two major diastereoisomers.

Additionally, two sets of proton signals for the four mixed minor isomers with *Z*-configuration ($E_{R^*}Z_{R^*}$, $E_{R^*}Z_{S^*}$, $Z_{R^*}E_{R^*}$, $Z_{R^*}E_{S^*}$ ~ 5%) are traced in the $^1$H and NOESY NMR spectra. Sufficiently well separated signals are detected only for the *ortho*-protons H-6,6′ and the methyl protons H-9,9′. The two diastereoisomers with *Z*-configuration ($Z_{R^*}Z_{R^*}$, $Z_{R^*}Z_{S^*}$) could not be unambiguously detected.

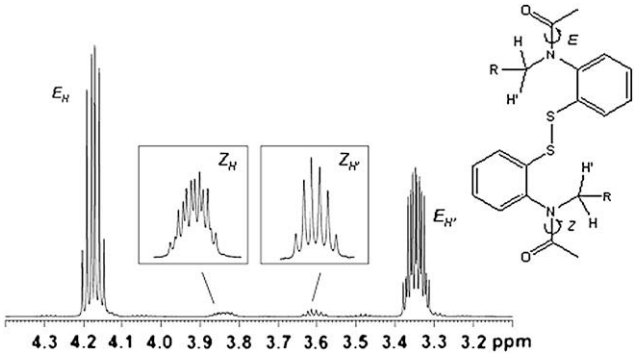



**Fig. 2.** Methylene part of the $^1$H NMR spectrum of **4**. The signals for the protons in the isomers with *Z*-configuration around the N–CO bond are zoomed for better visualization.

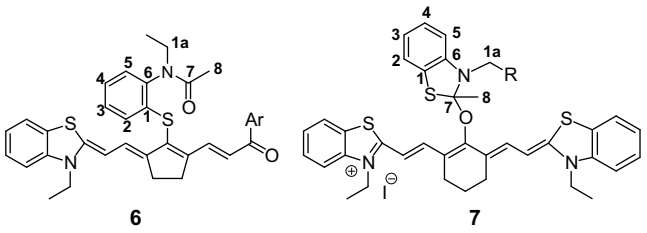
**Table 2**
$^1$H and $^{13}$C NMR shifts for the signals of the ramified part of **6** and **7** as described in the literature [8,12].[a]

| Position | $^1$H (**6**) ($CDCl_3$) | $^{13}$C (**6**) ($CDCl_3$) | $^{13}$C (**7**) (DMSO/$CDCl_3$ 1/1) | $^1$H (**7**) (DMSO/$CDCl_3$ 1/1) |
|---|---|---|---|---|
| 1 | – | 138.8 | 138.1 | – |
| 2 | 7.10 | 129.5 | 129.3 | 7.13 |
| 3 | to | 125.7 | 125.9 | to |
| 4 | 7.19 | 128.8 | 128.8 | 7.21 |
| 5 | 6.98 | 126.9 | 125.7 | 6.93 |
| 6 | – | 136.7 | 136.6 | – |
| 7 | – | 170.6 | 169.1 | – |
| 8 | 1.95 | 22.7 | 20.3 | 1.94 |
| 1a | 4.24/3.44 | 42.4 | 46.7 | 4.28/3.29 |

[a] Data for compound **5b** in [8] and **10a** in [12].

Confirmation for the formation of thiol **3b** is supported by our observation that if methylene chloride is applied in the work-up procedure, a significant quantity of a new product **5** containing a methylene bridge between the two sulfur atoms is formed via trapping of the transitional mercaptane **3b** by the solvent. Analogously to **4**, compound **5** is a mixture of several exchanging and two predominant diastereoisomers ($E_{R^*}E_{R^*}$, $E_{R^*}E_{S^*}$).

Employing a condensation reaction of 3-ethyl-2-methylbenzothiazolium iodide with a model heptamethine merocyanine in boiling pyridine we recently prepared the new nonamethine merocyanine dye **6** [12], whose structure was elucidated by X-ray crystallographic analysis. Additionally to the prolongation of the polymethine chain, ramification at the *meso*-position by replacement of a chlorine atom by a sulfur bridge resulting from the cleavage of the heterocyclic ring has been observed. The NMR spectroscopic data for **6** closely match those for compound **7** [8], published by Almeida et al. (see Table 2). The authors claim [14] that "the chlorine atom present in the exocyclic conjugated bridge incorporated in the polymethine chain of heptamethinecyanine dyes can be easily replaced by a substituted 2-methylbenzoazolium salt". Actually, the replacement proceeds only with the ring opened forms. This is evident by comparison of the NMR shifts for the substituent in the *meso*-position of compounds **6** and **7**, taking into account that the first structure is confirmed by X-ray analysis. Structure **7** is not compatible with the NMR data, because (i) an NMR shift of ~170 ppm for an $sp^3$-hybridized carbon atom is highly improbable [25]; (ii) NMR shifts below 120 ppm and 6.7 ppm should be expected for C-5 and H-5 in **7** because of their *ortho*-position to a highly electron-donating nitrogen atom contrary to an amide substituent that has a smaller shielding effect. It should be additionally noted, that the published data [8,12–15] indicate that replacement of the chlorine atom proceeds only if 2-methylbenzthiazolium or 2-methylbenzselenazolium salts, but not 2-methylbenzoxazolium salts are used (Scheme 3).




**Scheme 3.** A correct **6** and an erroneously elucidated structure **7** of ramified polymethine dyes.

## 4. Conclusion

Our investigations presented above demonstrate that the immediate products from the basic hydrolysis of the quaternary 3-ethyl-2-methylbenzazolium iodides are the corresponding *N*-aryl-*N*-alkylamides and not the *N*-alkylated dihydrobenzazol-2-ols. This finding manifests the instability of the initially formed hydroxylated intermediate and evidences that the actual agent which can accomplish nucleophilic replacement of a *meso*-chlorine atom in merocyanine dye synthesis is the respective substituted thiol.

Therefore, we think that the corresponding structures, published in this journal [8,15] as well as in [13,14] should be revised. The possibility of ring cleavage has to be taken into account in all cases where quaternized benzoazolium salts are used as reagents in the synthesis of cyanine dyes.

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## References

[1] Raue R. Methine dyes and pigments. In: Ulmann's encyclopedia of industrial chemistry. 5th ed., vol. A16. Weinheim: Wiley VCH; 1990. p. 487–534.
[2] Tyutulkov N, Fabian J, Mehlhorn A, Dietz F, Tadjer A. Polymethine dyes: structure and properties. Sofia: St. Kliment Ohridsky University Press; 1991.
[3] Bach G, Daehne S. Cyanine dyes and related compounds. In: Rodd's chemistry of carbon compounds, vol. IVb. Elsevier Science; 1997. p. 383–481 [chapter 15].
[4] Mishra A, Behera RK, Behera PK, Mishra BK, Behera GB. Chem Rev 2000;100:1973–2011.
[5] Lipowska M, Patonay G, Strekowski L. Synth Commun 1993;23:3087–94.
[6] Narayanan N, Patonay G, Strekowski L, Lipowska M. J Org Chem 1995;60:2391–5.
[7] Miltsov S, Encinas C, Alonso J. Tetrahedron Lett 2001;42:6129–31.
[8] Ramos S, Santos PF, Reis LV, Almeida P. Dyes Pigments 2002;53:143–52.
[9] Puyol M, Encinas C, Rivera L, Miltsov S, Alonso J. Sens Actuators 2006;B115:287–96.
[10] Encinas C, Miltsov S, Otazo E, Rivera L, Puyol M, Alonso J. Dyes Pigments 2006;71:28–36.
[11] Rivera L, Puyol M, Miltsov S, Alonso J. Anal Bioanal Chem 2007;387:2111–9.
[12] Viteva L, Gospodova Tz, Rashkova J, Abrahams I, Timtcheva I, Simova S, et al. Eur J Org Chem 2007:3102–14.
[13] Santos R, Fernandes LM, Boto RF, Simoes R, Almeida P. Tetrahedron Lett 2006;47:6723–5.
[14] Nunes MJ, Reis LV, Santos PF, Almeida P. Tetrahedron Lett 2007;48:5137–42.
[15] Pais IR, Nunes MJ, Reis LV, Santos PF, Almeida P. Dyes Pigments 2008;77:48–52.
[16] Metzer J, Larive H, Dennilauler R, Baralle R, Gaurat C. Bull Soc Chim Fr 1970;1:2868–78.
[17] (a) Chedekel MR, Sharp DE, Jeffery GA. Synth Commun 1980;10:167–73;
(b) Babudri F, Bartoli G, Ciminale F, Florio S. Tetrahedron Lett 1984;25:2047–50;
(c) Florio S, Epifani E, Ingrosso G. Tetrahedron 1984;4:4527–33;
(d) Babudri F, Florio S. Synthesis 1986;8:638–40;
(e) Aresta M, Nobile CF. J Chem Soc Dalton Trans 1976;13:1203–7.
[18] Hamer FM. J Chem Soc 1956:1480–98.
[19] Bruker pulse library programs: cosygpmfqf, hsqcedetgpsisp2.2, hmbcgplpndqf, noesygpphzs, selnogp and ledbpgp2s. 2007.
[20] Kim Y, Park Y, Park K. J Mol Struct 2006;783:61–5.
[21] (a) Mills W, Kelham R. J Chem Soc 1937:274–8;
(b) Shvo Y, Taylor E, Mislow K, Raban M. J Am Chem Soc 1967;89:4910–7;
(c) Kessler H, Rieker A. Liebigs Ann Chem 1967;708:57–68;
(d) Stewart W, Siddal III T. Chem Rev 1970;70:517–51.
[22] (a) Rodriguez J, Canoira L. J Chem Soc Perkin Trans 1994;2:1393–6;
(b) Rodriguez J, Canoira L, Calderon C, Martinez-Ripoll M, Blanco S. J Chem Soc Perkin Trans 1986;2:199–203;
(c) Rodriguez J, Canoira L, Temporano F. J Chem Soc Perkin Trans 1986;2:1193–6.
[23] The conversion of the salts in the corresponding acetamides proceeds in the NMR tube at a rate depending on the salt used (**1a** or **1b**), on the ratio of the concentration between starting material and water and on the temperature [see also [13]]. Starting from **1b** additional products are also formed. Detailed inspection of the NMR spectra did not give any evidence of the presence of hydroxylated products or ring-chain tautomerism.
[24] Reichardt C, Erfurt H-P, Harms K. Phosphorus, Sulfur Silicon Relat Elem 2003;178:1081–92.
[25] $^{13}C$ NMR chemical shifts for different ortho-esters are found in the region between 110 and 120 ppm, e.g. $CH_3C(OEt)_3$ at 114.2 ppm.