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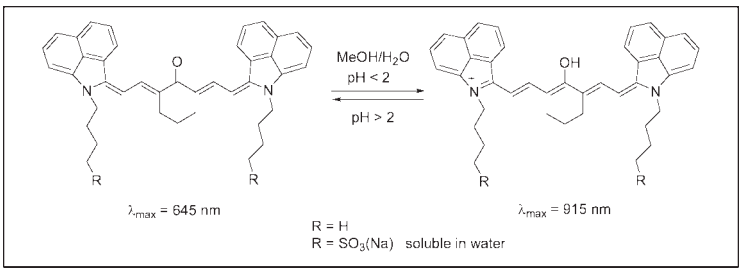

A number of benzo[*c,d*]indolium derivatives have been synthesized.

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INTRODUCTION

Cationic indolium and benzo-fused indolium moieties are common heterocyclic end units in cyanine and other polymethine dyes. As a general rule, the dyes containing benzo[*c,d*]indolium systems are more stable and show a batochromic shift in their electronic spectra in comparison with indolium, benzo[*e*]indolium, and benzo[*g*]indolium counterparts [1,2]. Synthesis of several 1-substituted 2-methylbenzo[*c,d*]indolium salts and examples of their use in the preparation of visible and near-infrared dyes are described in this report. We have concentrated on the chemistry of a hydrophobic *N*-butyl derivative **4** (Schemes 1 and 2) and its water-soluble analog **13** (Scheme 3). The common precursor to these compounds is readily available 1,8-naphtholactam (**1**) [3,4].

RESULTS AND DISCUSSION

One of the synthetic routes to *N*-alkylbenzo[*c,d*]indolium salts starting with **1** involves the intermediary of a derivative **2** [5,6]. Following the well-established chemistry, compound **2** was alkylated with *n*-butyl bromide and the resultant *N*-butyl derivative **3** was transformed to the desired iodide salt **4** by treatment with a mixture of acetic acid, hydrochloric acid, and potassium iodide. We found that it is not necessary to purify the intermediate product **3** as the synthesis of **4** proceeds in high yield with crude substrate **3**. The 2-methyl group in **4** is activated toward a reaction with a base such as pyridine to generate an intermediate anhydrobase or an enamine by proton abstraction (not shown). This intermediate product is nucleophilic and, as such, can undergo a reaction with the electrophilic Vilsmeier reagent derived from *N,N*-dimethylformamide and phosphorus oxychloride (Scheme 1).

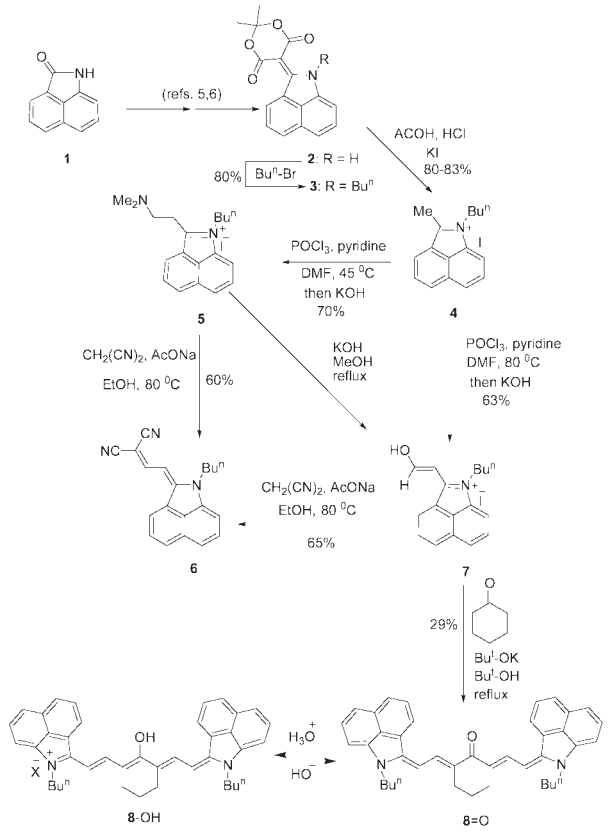
Interestingly, depending on conditions, two different products are formed, namely an enamine **5** or an unsaturated aldehyde **7**. The enamine **5** was independently transformed to the aldehyde **7** by treatment with potassium hydroxide in methanol under reflux conditions. Either compound **5** or **7**, can be efficiently condensed with malononitrile to give a visible dye **6**.

On the other hand, condensation of aldehyde **7** with cyclohexanone under basic conditions furnished a bis(aminodien)one **8═O** in low yield. This ketone is a visible dye (λ_{max} = 645 nm) in methanol under neutral or basic conditions. Under acidic conditions (pH < 2) dye **8═O** undergoes protonation at the carbonyl group with the formation of a hydroxy-substituted cyanine **8─OH** that absorbs in the near-infrared region (λ_{max} = 915 nm). The ketone/cyanine conversions are fully reversible, depending solely on pH conditions. Although the cyanine **8─OH** absorbs mainly in the invisible near-infrared region, it shows a residual absorption of low intensity in the visible region and is pink to the naked eye. The color change from deep dirty-green at basic or neutral pH to beautiful light-pink at low pH is quite dramatic. It should be noted that an attempted condensation of enamine **5** with cyclohexanone under conditions similar to those indicated above failed to produce dye **8═O**.

A different synthetic route to the dye system **8═O/8─OH** is presented in Scheme 2. We have previously used this approach for the synthesis of other pH-sensitive dyes [7].

In this two-step preparation the substrate **4** was treated with the Vilsmeier-Haack reagent **9** [8] in acetic anhydride in the presence of sodium acetate as a base

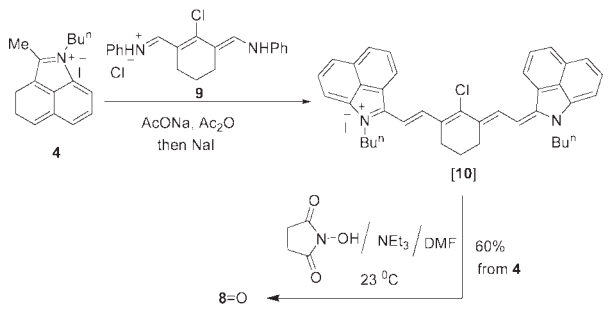
Scheme 1



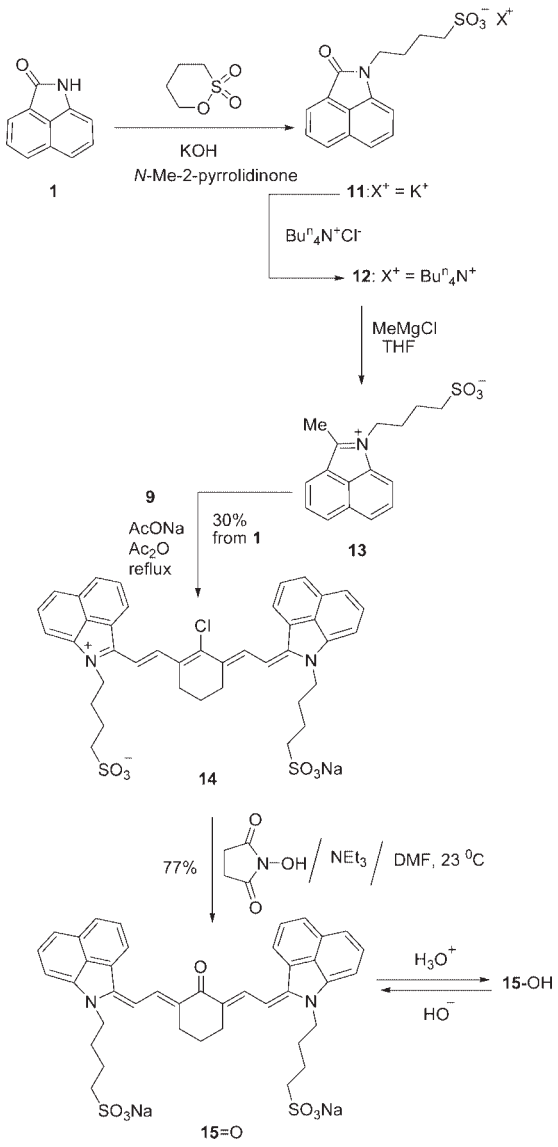
catalyst to furnish a chloro-substituted cyanine **10**, which then was transformed to **8=O** by the reaction with *N*-hydroxysuccinimide. The mechanism of this highly efficient transformation has been discussed previously [7]. This synthesis of **8=O** (Scheme 2) is more efficient and experimentally simpler than that shown in Scheme 1. Because of the high efficiency it was not necessary to purify the intermediate dye **10**. The final product **8=O** was obtained in an analytically pure form by using simple crystallization.

The synthesis of a water soluble pH-sensitive system **15=O/15—OH** is given in Scheme 3. The aqueous sol-

Scheme 2



Scheme 3



ubility is provided by the presence of sulfonate groups. As with other preparations discussed above, the starting material is 1,8-naphtholactam (**1**). Compound **1** was alkylated by the reaction with 1,4-butanesultone to give a sulfonatobutyl derivative **11**, the subsequent treatment of which with methylmagnesium chloride furnished the indolium product **13** [9]. The latter Grignard addition reaction gave compound **13** in low yield, which is due to low solubility of the potassium salt **11** in solvents suitable for organometallic reactions. This problem was overcome by transformation of the potassium salt **11** to a highly soluble tetrabutylammonium salt **12**. The reaction of **12** with methylmagnesium chloride in tetrahydrofuran furnished the desired product **13** in 85% yield. The subsequent construction of the dye system **15=O/15—OH** is similar to that of **8=O/8—OH**. The

difference is in the use of a sulfonatobutyl derivative **13** (Scheme 3) rather than a butyl derivative **4** (Scheme 2) for the condensation reaction with the Vilsmeier-Haack reagent **9**.

Since compounds **8** and **15** share the same chromophore, they show virtually identical spectral properties that depend on pH conditions. The transition ketone/cyanine for both **8** and **15** is characterized by $pK_a = 2$, as obtained by spectrophotometric titrations.

EXPERIMENTAL

1-Butyl-2-methylbenzo[*c,d*]indolium iodide, 4. Conversion of the commercial substrate **1** to 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)1*H*-benzo[*c,d*]indole (**2**), alkylation of **2** with *n*-butyl bromide to give **3**, and then the treatment of crude product **3** with a mixture of acetic acid, hydrochloric acid and potassium iodide to give the desired salt **4** were conducted by using general procedures for the preparation of similar derivatives [5,6]. After crystallization from ethanol/water (1:5), compound **4** was obtained in a total yield of 40% starting from **1**, mp > 300°C; ^{1}H NMR (deuteriochloroform): δ 0.95 (t, J = 7 Hz, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 3.20 (s, 3H), 4.17 (t, J = 7 Hz, 2H), 7.07 (d, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 7.87 (t, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 9.10 (d, J = 8 Hz, 1H). *Anal*. Calcd. for $C_{16}H_{18}IN$: C, 54.71; H, 5.17; N, 3.99. Found: C, 54.80; H, 5.13; N, 4.06.

1-Butyl-2-(2-dimethylaminovinyl)benzo[*c,d*]indolium iodide, 5. *N,N*-Dimethylformamide (1.0 mL) was cooled to 0°C and treated dropwise with phosphorus oxychloride (0.21 mL, 2.3 mmol) and then with a solution of salt **4** (0.35 g, 1.0 mmol) and pyridine (0.2 mL) in *N,N*-dimethylformamide (2.0 mL). The mixture was heated to 65°C for 40 min, then treated with an aqueous solution of potassium hydroxide (60%, 1 mL) and heated to 45°C for an additional 30 min. Extraction with dichloromethane (4 × 10 mL) followed by concentration of the extract and silica gel chromatography of the residue eluting with dichloromethane/methanol (19:1) gave 0.28 g (70%) of **5**; mp 182–183°C; ^{1}H NMR (deuteriochloroform): δ 0.95 (t, J = 8 Hz, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 3.47 (s, 3H), 3.86 (s, 3H), 4.17 (t, J = 8 Hz, 2H), 5.87 (d, J = 12 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 7.87 (t, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 8.96 (d, J = 12 Hz, 1H), 9.10 (d, J = 8 Hz, 1H); ms (esi): *m/z* 279 (M^+). *Anal*. Calcd. for $C_{19}H_{23}IN_2$: C, 56.17; H, 5.71; N, 6.89. Found: C, 56,05; H, 5.72; N, 6.83.

[2-(1-Butyl-1,2-dihydrobenzo[*c,d*]indol-2-ylidene)ethylidene]malononitrile, 6. A solution of salt **5** (63 mg, 0.15 mmol), malononitrile (15 mg, 0.22 mmol) and sodium acetate (16 mg, 0.20 mmol) in anhydrous ethanol (15 mL) was heated under reflux for 1 h. Silica gel chromatography eluting with hexanes/dichloromethane (5:1) gave 27 mg (60%) of **6**; mp 180–181°C; ^{1}H NMR (deuteriochloroform): δ 1.00 (t, J = 7 Hz, 3H), 1.46 (m, 2H), 1.80 (m, 2H), 4.01 (t, J = 7 Hz, 2H), 6.25 (d, J = 9 Hz, 1H), 6.99 (m, 1H), 7.52 (m, 2H), 7.74 (t, J = 8 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 8.32 (d, J = 9 Hz, 1H); ms (maldi) *m/z* 299 (M^+) and 300 ($M^+ + 1$); vis: λ_{max} in methanol, 519 nm and 556 nm. *Anal*. Calcd. For $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.22; H, 5.75; N, 13.91.

(1-Butyl-1,*2*-dihydrobenzo[*c,d*]indol-2-ylidene)acetaldehyde, 7. *N,N*-Dimethylformamide (1 mL) was stirred at 10°C and treated dropwise with phosphorus oxychloride (0.21 mL, 2.3 mmol) and then with a solution of **4** (1.9 g, 0.54 mmol) and pyridine (0.6 mL) in *N,N*-dimethylformamide (2 mL). The mixture was heated to 80°C for 40 min, then treated with an aqueous solution of potassium hydroxide (60%, 2.5 mL) and heated to 80°C for an additional 90 min. After cooling the mixture was extracted with dichloromethane (4 × 10 mL), the extracts were concentrated, and the residue was purified by silica gel chromatography eluting with dichloromethane/methanol (19:1) to furnish 1.6 g (65%) of **7**; mp 104–105°C; ^{1}H NMR (deuteriochloroform): δ 0.93 (t, J = 7 Hz, 3H), 1.39 (m, 2H), 1.66 (m, 2H), 4.00 (t, J = 7 Hz, 2H), 5.85 (d, J = 8 Hz, 1H), 7.12 (t, J = 8 Hz, 1H), 7.52 (m, 2H), 7.74 (t, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 8.60 (d, J = 8 Hz, 1H), 10.33 (d, J = 8 Hz, 1H); ms (esi): *m/z* 252 (M^+). *Anal*. Calcd. for $C_{17}H_{18}NO$: C, 80.92; H, 7.19; N, 5.55. Found: C, 81.05; H, 6.88; N, 5.56.

2,6-Bis[(1-ethyl-1,2-dihydrobenzo[*c,d*]indol-2-ylidene)ethylidene]cyclohexanone, 8=O. A solution of potassium *tert*-butoxide (116 mg, 1 mmol) in *tert*-butanol (15 mL) was stirred under a nitrogen atmosphere and treated with the aldehyde **7** (150 mL, 0.67 mmol) and cyclohexanone (0.34 μL, 0.33 mmol). The mixture was heated under reflux for 12 h, then cooled and quenched with water (1.0 mL). The resultant precipitate was collected by filtration, washed with water and cold methanol, and dried under reduced pressure at 23°C; yield 54 mg (29%); mp 188–190°C; ^{1}H NMR (deuteriochloroform): δ 1.00 (m, 6H), 1.48 (m, 4H), 1.80 (m, 4H), 1.99 (m, 2H), 2.79 (m, 4H), 3.88 (m, 4H), 6.06 (d, J = 13 Hz, 2H), 6.68 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 7.40 (t, J = 8 Hz, 2H), 7.65 (t, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 2H), 8.42 (d, J = 8 Hz, 2H), 8.77 (d, J = 8 Hz, 2H); vis: λ_{max} in methanol, 645 nm (ε 50800 M^{-1} cm^{-1}); nir: λ_{max} in methanol with one drop of concentrated hydrochloric acid (pH < 2, **8—OH**), 915 nm (ε 142000 M^{-1} cm^{-1}). *Anal*. Calcd. for $C_{40}H_{40}N_2O$: C, 85.06; H, 7.13; N, 4.96. Found: C, 85.33; H, 7.12; N, 4.95.

Alternative synthesis of 8=O. The Vilsmeier-Haack reagent **9** was obtained as reported previously [8]. Condensation of **9** with **4** was conducted in ethanol in the presence of sodium acetate by using a general procedure [10]. Crude product **10** was collected as a precipitate after treatment of the mixture with ether (nir: λ_{max} in methanol, 1025 nm) and used for the subsequent transformation to **8=O** without purification. Thus, crude dye **10**, obtained from 351 mg (1.0 mmol) of **4**, was dissolved in anhydrous *N,N*-dimethylformamide (15 mL), and this solution was treated with *N*-hydroxysuccinimide (0.33 g, 2.9 mmol) and triethylamine (0.5 mL) under a nitrogen atmosphere. The mixture was stirred at 23°C under nitrogen for 10 h and then diluted with ether (35 mL), which caused precipitation of **8=O**. The product was crystallized by dropwise dilution of a solution in methanol with *tert*-butyl methyl ether; yield 338 mg (60%) from **4**. The spectral characteristics of **8=O** thus obtained were virtually identical with those reported above.

1-(4-Sulfonatobutyl)-1,2-dihydrobenzo[*c,d*]indol-2-one, potassium salt, 11. This compound was obtained by the following modification of the published procedure [9] which did

not include any characterization of the product. A mixture of **1** (1.69 g, 10 mmol), powdered potassium hydroxide (1.12 g, 20 mmol), and *N*-methyl-2-pyrrolidone (5 mL) was stirred at 23°C for 15 min and then treated with 1,4-butanesultone (1.49 g, 11 mmol). The mixture was stirred at 80°C for an additional 10 h, then cooled and treated dropwise with acetone (25 mL), which caused crystallization of product **11**; yield 3.26 g (95%); mp 235–240°C; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 1.63 (t, J = 7 Hz, 2H), 1.78 (m, 2H), 2.45 (m, 2H), 3.90 (t, J = 7 Hz, 2H), 7.24 (d, J = 7 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.82 (t, J = 8 Hz, 1H), 8.06 (d, J = 8Hz, 1H), 8.20 (d, J = 8 Hz, 1H). *High-resolution ms* (esi, negative ion mode): calcd. for $C_{15}H_{14}NO_4S$, *m/z* 304.0643 (M^-); found *m/z* 304.0655.

1-(4-Sulfonatobutyl)-1,2-dihydrobenzo[*c,d*]indol-2-one, tetrabutylammonium salt, 12. This compound was obtained by the following modification of the published procedure [9] which did not include any characterization of the product. A mixture of salt **11** (3.0 g, 10 mmol) and tetrabutylammonium chloride (3.1 g, 11 mmol) in acetic acid (10 mL) was stirred at 90°C, treated dropwise with ethyl acetate, cooled, and filtered from the precipitate of potassium chloride. The filtrate was concentrated on a rotary evaporator and the oily residue was dissolved in dry toluene (50 mL). The azeotropic removal of traces of water by concentration on a rotary evaporator gave salt **12** (5.0 g, 93%) as a viscous oil; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 0.99 (t, J = 8 Hz, 12H), 1.43 (m, 8H), 1.65 (m, 8H), 1.95 (m, 4H), 2.90 (m, 2H), 3.27 (t, J = 8 Hz, 8H), 3.94 (t, J = 7 Hz), 6.98 (d, J = 7 Hz, 1H), 7.18 (d, J = 7 Hz, 1H), 7.25 (d, J = 7 Hz, 1H), 7.50 (m, 2H), 7.69 (t, J = 7 Hz, 1H), 8.02 (t, J = 7 Hz, 1H). *High-resolution ms* (esi, negative ion mode): calcd. for $C_{15}H_{14}NO_4S$ (M^-) , *m/z* 304.0643 ; found 304.0640.

1-(4-Sulfonatobutyl)-2-methylbenzo[*c,d*]indolium inner salt, 13. This compound was obtained by the following modification of the published procedure [9] which did not include any characterization of the product. Methylmagnesium chloride (3.0*M* solution in tetrahydrofuran, 15.0 mL, 45 mmol) was added dropwise to a stirred solution of salt **12** (5.46 g, 10 mmol) in anhydrous tetrahydrofuran under a nitrogen atmosphere. The mixture was stirred at 60°C for 1 h, then cooled, neutralized by dropwise addition of 3*M* hydrochloric acid, and consecutively diluted with ethanol (30 mL) and ether (30 mL). Cooling to 0°C for several hours resulted in crystallization of product **13**; yield 2.58 g (85%); mp 143–145°; ^{1}H NMR (deuterium oxide): δ 1.77 (t, J = 8 Hz, 2H), 2.03 (m, 2H), 2.84 (m, 2H), 3.01 (s, 3H), 4.50, (t, J = 8 Hz, 2H), 7.72 (t, J = 8 Hz, 1H), 7.84 (t, J = 8 Hz, 1H), 8.08 (m, 2H), 8.42 (d, J = 8 Hz, 1H), 8.50 (d, J = 8 Hz, 1H). *High-resolution ms* (maldi): calcd. for $C_{16}H_{18}NO_3S$ (M^+ + 1), *m/z* 304.1007; found *m/z* 304.1015.

Cyanine dye 14. A solution of inner salt **13** (303 mg, 1 mmol) Vilsmeier-Haack reagent **9** [8] (180 mg, 0.5 mmol), and sodium acetate (82 mg, 1 mmol) in acetic anhydride (20 mL) was heated under reflux for 8 h, then cooled and treated with ether (30 mL). The resultant precipitate of cyanine **14** was crystallized from methanol/ether; yield 115 mg (30%); mp > 300°C; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 1.82 (m, 14H), 2.83 (t, J = 7 Hz, 4H), 4.01 (t, J = 7 Hz, 4H), 6.20 (d, J = 13 Hz, 2H), 6.88 (d, J = 7 Hz, 2H), 7.29 (d, J = 7 Hz, 2H), 7.42 (t, J = 7 Hz, 2H), 7.73 (t, J = 7 Hz, 2H), 7.84 (d, J = 7 Hz, 2H), 8.04 (d, J = 7 Hz, 2H), 8.37 (d, J = 13 Hz, 2H); nir: λ_{max} in methanol, 1013 nm. *High-resolution ms* (esi, negative ion mode): calcd. for $C_{40}H_{38}{}^{35}ClN_2O_6S_2$ (M^-), *m/z* 741.1860; found *m/z* 741.1871.

2,6-Bis[2-[1-(sodium4-sulfonatobutyl)-1,2-dihydrobenzo-[*c,d*]indol-2-ylidene)]ethylidene]cyclohexanone, 15=O. Cyanine **14** was allowed to react with *N*-hydroxy-succinimide in the presence of triethylamine in *N,N*-dimethylformamide as described above for a similar transformation of **10** to **8=O**. Product **15=O** was precipitated by addition of ether and crystallized from methanol/ether; yield 115 mg starting with 150 mg of **14** (77%); mp > 300°C; ^{1}H NMR (deuterated dimethyl sulfoxide): δ 1.86 (m, 14H), 2.85 (t, J = 7 Hz, 4H), 4.02 (t, J = 7 Hz, 4H), 6.20 (d, J = 13 Hz, 2H), 6.90 (d, J = 7 Hz, 2H), 7.32 (d, J = 7 Hz, 2H), 7.45 (t, J = 7 Hz, 2H), 7.75 (t, J = 7 Hz, 2H), 7.87 (d, J = 7 Hz, 2H), 8.06 (d, J = 7 Hz, 2H), 8.42 (d, J = 7 Hz, 2H); vis: λ_{max} in methanol, 645 nm (ε 50800 M^{-1} cm^{-1}); nir: λ_{max} in methanol with one drop of concentrated hydrochloric acid (pH < 2, **15—OH**), 914 nm (ε 142000 M^{-1} cm^{-1}). *High-resolution ms* (maldi, negative ion mode): calcd. for $C_{40}H_{39}N_2O_7S_2$ (M^- + 1), *m/z* 723.2199; found *m/z* 723.2234.

REFERENCES AND NOTES

[1] Strekowski, L.; Lee, H.; Mason, J. C.; Say, M.; Patonay, G. J Heterocyclic Chem 2007, 475, 475.

[2] Strekowski, L., Ed. Heterocyclic Polymethine Dyes: Synthesis: Properties and Applications; Springer-Verlag: Berlin, 2008.

[3] Parker, R. J.; Smith, D. C. C. J Chem Soc (C) 1967, 2194.

[4] Elliger, C. A. Org Prep Proced Int 1985, 17, 419.

[5] Deligeorgiev, T. G.; Gadjev, N. I.; Drexhage, K. H. Dyes Pigments 1991, 15, 215.

[6] Lee, H.; Berezin, M. Y.; Henary, M.; Strekowski, L.; Achilefu, S. J Photochem Photobiol (A) 2008, 200, 438.

[7] Strekowski, L.; Mason, J. C.; Say, M.; Lee, H.; Gupta, R.; Hojjat, M. Heterocycl Commun 2005, 11, 129.

[8] Makin, S. M.; Boiko, L. I.; Shavrygina, O. A. Zh Org Khim 1977, 13, 1189.

[9] (a) Deroover, G. (Agfa-Gevaert N. V., Belgium), Eur. Pat. Appl. EP 1093 015 A1, 2001; (b) Deroover, G. Chem Abstr 2001, 134, 302961.

[10] Strekowski, L.; Gorecki, T.; Mason, J. C.; Lee, H.; Patonay, G. Heterocycl Commun 2001, 7, 117.