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New photochromes equipped with positively charged ammonium fragments

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Quaternization of N-heterocycle-fused chromenes with iodomethane and of triethylamine with 3-bromopropyl-substituted spironaphthoxazine affords new ammonium-equipped photochromes.

Photochromic benzo- and naphthopyrans are promising for reversible photocontrol of DNA intercalation. In the initial state, these compounds are colourless. Nonplanarity of their molecules is maintained by the presence of two phenyl substituents in the pyran moiety. One may expect that before irradiation, due to spatial hindrances, no noticeable interaction with DNA should occur.1-7 Upon irradiation, the photochrome molecule is transformed into a planar open form which seems capable of inserting between DNA base pairs. For small aromatic compounds, the presence of positive charge in a molecule is required to provide interaction with DNA, which is important for designing new chemotherapeutic agents and health safe DNA labels.8

A goal of this study was a synthesis of new positively charged photochromic compounds capable of photocontrolled DNA intercalation. We were aiming to obtain quaternary ammonium salts from N-heterocycle-fused chromenes 1-5 (Scheme 1) and from 3-bromopropyl-containing spironaphthoxazine 8 (Scheme 2).

Known^{9–11} heterocyclic chromenes 1-5 were prepared by titanium tetraethoxide-assisted condensation of the corresponding phenolic derivatives with β , β -diphenylacrolein in fair to good yields (see Scheme 1). For their N-quarternization, iodomethane was used. The reaction was carried out in excess of MeI in a closed ampoule at ~60 °C. In cases of reactants 2, 3 and 5, the target salts were not obtained. The N-atom in compounds 2-5 possesses lower basicity compared to that of compound 1. This fact explains the fair yield of product 6 and moderate yield of product 7. In case of chromenes 2, 3 and 5, one can suppose that steric hindrance can also hamper the N-methylation. The structure of chromene 4 was confirmed by X-ray analysis[‡] (Figure 1 and Online Supplementary Materials).

Spironaphthoxazine salt 9 was prepared in three steps (see Scheme 2).[†] Its key precursor 8 was synthesized from 2,3,3trimethylindoline and 1,3-dibromopropane (cf. ref. 1) through obtaining quaternary indoline salt 10 along with cyclic side product 11. Heterocyclization of compound 10 with 1-nitrosonaphthalen-2-ol gave the spiro derivative 8 in only 10% yield. Final reaction of compound 8 with triethylamine afforded the target salt 9 in 38% yield.

[†] General procedure for the synthesis of 6, 7. In a thick-walled glass tube equipped with a threaded teflon stopper, 0.158 mmol of 1 or 4 and 2 ml of iodomethane were mixed. The solution obtained was stirred at 60 °C for 3 h. Then, the solvent was removed; and the residue was treated with diethyl ether to yield salt 6 or 7 as yellow solids.

9-Methyl-3,3-diphenyl-3H-pyrano[2,3-h]isoquinolinium iodide 6: yield 87%, mp 218-222°C. ¹H NMR (CDCl₃) δ: 4.80 (s, 3 H, NMe), 6.56 (d, 1H, H-2, J 10.1 Hz), 7.20-7.48 (m, 10H), 7.71 (d, 1H, J 8.9 Hz), 7.83 (d, 1H, J 8.9 Hz), 7.97-8.17 (m, 3H), 10.97 (s, 1H, H-10). Found (%): C, 63.52; H, 4.28. Calc. for C25H20INO (%): C, 62.90; H, 4.22.



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Figure 1 Molecular structure of chromene 4.

Salts **6**, **7** and **9** are well soluble in polar organic solvents and water. Optical investigation showed that compound **6** is fluorescent ($\lambda_{\text{max}}^{\text{fl}}$ 395 nm in MeCN, λ^{ex} 313 nm), and does not exhibit photochromism (see Figure S1 in Online Suplementary Materials). In contrast, benzoxazole derivative **7** exhibits good photochromic properties (colorability upon cessation of radiation) in polar acetonitrile and methanol (Figure 2),[§] which is unusual for chromenes.¹² The values of the bleaching rate constant *k* is $1.02 \times 10^{-3} \text{ s}^{-1}$, the half bleaching time $\tau_{1/2}$ is 680 s. Spironaphthoxazine **9** demonstrates the photochromic properties; however, the stability of the open form in aqueous solutions at

1,2,4-Trimethyl-6,6-diphenyl-6H-chromeno[6,7-d]oxazolium iodide 7: yield 36%, mp 245–247 °C. ¹H NMR (CDCl₃) δ : 2.45 (s, 3 H, 4-Me), 3.29 (s, 3 H, 2-Me), 4.25 (s, 3 H, 1-Me), 6.34 (d, 1 H, H-7, J 10.0 Hz), 6.82 (d, 1 H, H-8, J 10.0 Hz), 7.24–7.47 (m, 11 H). ¹³C NMR (63 MHz, CDCl₃) δ : 8.88, 22.30, 36.46, 82.77, 114.02, 114.27, 122.14, 122.89, 123.41, 126.38, 126.76, 126.81, 127.41, 127.49, 128.16, 145.30, 151.19, 151.76, 173.22, 181.68. Found (%): C, 60.92; H, 4.53. Calc. for $C_{25}H_{22}INO_2$ (%): C, 60.62; H, 4.48.

{3-[3,3-Dimethylspiro(indoline-2,3'-[3H]naphtho[2,1-b][1,4]oxazin)-1-yl]propyl}triethylammonium bromide 9. Spironaphthoxazine 8 (0.053 g, 0.122 mmol) [prepared from 1-(3-bromopropyl)-2,3,3-trimethyl-3H-indolium iodide¹] and freshly distilled triethylamine (0.123 g, 1.22 mmol) were dissolved in 5 ml of dry acetonitrile. The solution was stirred at 60 °C for 24 h. Then, the solvent was removed under reduced pressure and the residue was treated with diethyl ether to afford 0.025 g (38%) of salt 9 as creamy-beige solid, mp 218–220 °C. ¹H NMR (DMSO- d_6) δ : 1.08 (t, 9 H, 3 CH₂Me, J 7.1 Hz), 1.26 (s, 3 H, Me), 1.30 (s, 3 H, Me), 1.75-1.88 (m, 1H, CH₂), 1.98-2.11 (m, 1H, CH₂), 3.10-3.27 (m, 10H), 6.81 (d, 1H, J 7.8 Hz), 6.86 (dd, 1H, J 7.4 Hz), 7.10-7.22 (m, 3H), 7.43 (dd, 1H, J 7.6 Hz), 7.60 (dd, 1H, J 7.6 Hz), 7.82 (d, 1H, J 8.9 Hz), 7.86 (d, 1H, J 8.2 Hz), 7.97 (s, 1H), 8.49 (d, 1H, J 8.4 Hz). ¹³C NMR (150 MHz, DMSO-d₆) δ : 7.02, 20.55, 20.68, 25.12, 40.80, 51.73, 52.11, 53.72, 98.68, 106.90, 106.92, 116.63, 119.63, 120.97, 121.72, 122.00, 124.17, 127.15, 127.78, 127.82, 128.89, 130.12, 130.30, 135.21, 143.17, 146.14, 151.69. Found (%): C, 67.32; H, 7.20. Calc. for C30H38BrN3O (%): C, 67.16; H, 7.14.

^{*} *Crystal data for* **4**. Crystals of C₂₄H₁₉NO₂ (*M* = 353.4) are monoclinic, *P*2₁/*n*, *a* = 8.5061(2), *b* = 16.8993(4) and *c* = 13.7042(3) Å, β = 107.827°, *V* = 1875.35(7) Å³, *Z* = 4, *d*_{calc} = 1.252 g cm⁻³, μ = 0.079 mm⁻¹, *F*(000) = = 744. Observed reflections 17678, independent reflections 4679, *R*_{int} = 0.11.

Crystals suitable for X-ray diffraction were grown up by slow evaporation of solution in CH₂Cl₂. X-ray diffraction experiments were carried out with a Bruker APEX II CCD area detector, using graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å, ω -scans). Reflection intensities were integrated using SAINT software and absorption correction was applied semi-empirically using SADABS program. The structures were solved by direct method and refined by the full-matrix least-squares against F^2 in anisotropic approximation for non-hydrogen atoms.

CCDC 1042670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

[§] Electronic absorption spectra were recorded on Varian Cary 50 and Avantes AvaSpec-2048 spectrophotometers. Spectra of coloured forms were obtained when samples in the spectrometer cell were simultaneously exposed to continuous irradiation, generated by mercury high pressure lamp (120 W) or xenone–mercury high pressure lamp (1000 W). Fluorescence spectra were recorded on a FluoroLog-3-221 spectrofluorimeter.



Figure 2 Absorption spectra of compound 7 in methanol ($C = 66.5 \,\mu$ mol dm⁻³, 20 °C) prior to (solid line) and after 1 min of irradiation by monochromatic light with $\lambda = 315 \,\text{nm}$ (dashed line).

20 °C was low. Nevertheless, based on photochromic characteristics both **7** and **9** photochromes can be considered as appropriate candidates for testing as photoswitchable intercalators for DNA.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.09.018.

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