ELSEVIER

Dyes and Pigments, Vol. 39, No. 4, pp. 193–199, 1998

Printed in Great Britain
PII: S0143-7208(97)00052-1 0143-7208/98 $—see front matter

Synthesis of Naphthopyrones as Potential Monofunctional Photobiological Agents to DNA

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(Received 18 April 1997; accepted 23 May 1997)

ABSTRACT

Several naphthopyrones as monofunctional analogs of furocoumarins were synthesized starting from the corresponding hydroxynaphthopyrones. The structures of these new compounds were characterized and their absorption and fluorescence spectra were recorded. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: Naphthopyrones, monofunctional, photobiological.

INTRODUCTION

It is well known that coumarins enjoy wide application as laser dyes, fabric dyes, fluorescent labels and in the creation of photochromic materials. Naphthopyrones may be considered as coumarins with additional fused benzene rings, and can be expected to have photophysical and photobiological properties superior to those of coumarins due to their extended conjugation. In fact, naphthopyrones have been used as new types of laser dyes [1], anticarcinogenic agents [2], and thiol probes [3]. However, only a limited number of naphthopyrones are known.

Furocoumarins such as psoralens are well known to have very interesting and useful photosensitizing properties, and have been extensively utilized in many fields, such as in the treatment of hyperproliferative skin diseases. Our attempts have been focused on the development of their monofunctional analogs with improved photophysical and photobiological properties [4–9]. We report herein the synthesis of several naphthopyrones, in which the furan moiety of the furocoumarin is replaced by a benzene ring. In this structure only the pyrone photoreactive site is preserved, possibly leading to

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a true monofunctional photobiological agent. The diethylaminopropyloxy side chains bound to the naphthalene ring in compounds **3**, **7**, and **11** are aimed at granting higher water solubility and stronger binding to the polynucleotide through electrostatic interactions with the DNA phosphate groups.

RESULTS AND DISCUSSION

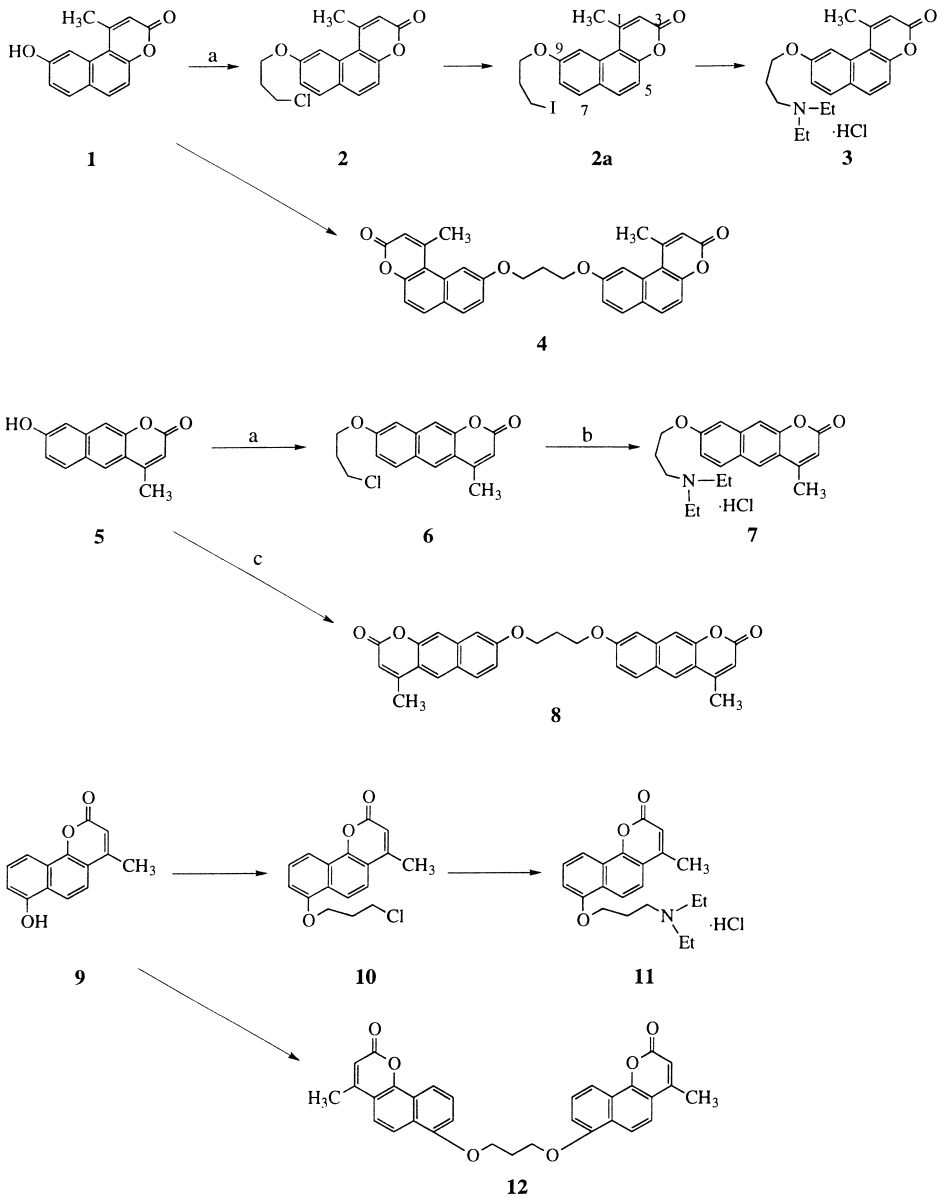
The synthetic methodology for the preparation of the naphthopyrones is displayed in Scheme 1. The starting materials, compounds **1** [9], **5** [9], **9** [7], were prepared from commercially available 2,7-naphthalenediol or 1,5-naphthalenediol by literature procedures. The condensation of compound **1** with 1,3-bromochloropropane (2 equivalent) to give the intermediate **2** in 78% yield. Interestingly, **2** crystallized from 95% ethanol as light yellow crystals, while **2** crystallized from methanol as colorless crystals. The molecular ion peak at *m/e* 304 (33.6) $[M+2], 302(100)[M]$ in MS, and the presence of proton resonances at δ 2.34 (m), 3.82 (t), 4.28 (t) ppm confirm the chloropropyloxy group in **2**. The displacement of **2** with sodium iodide gave the iodime analog **2a**, which reacted *in situ* with diethylamine to afford **3** in 53% yield. Compound **3** showed characteristic peaks at 1.23 (t), 3.17–3.47 (m), 9.21 (s, 1H, N^+-H) ppm in the ^{1}H NMR spectrum and 339 (4.0) [M-HCl] in the spectrum MS. Similarly, the naphthopyrones **6**, **7**, **10** and **11** were synthesized; and their structures were characterized by ^{1}H NMR, MS and elemental analysis. Our efforts have also been made on the synthesis of bisnaphthopyrones **4**, **8** and **12** which could be expected to serve as DNA bisintercalators through the reaction of the corresponding hydroxynaphthopyrones with 1,3-bromochloropropane (0.5 equivalent). Unfortunately, these three bisnaphthopyrones had extremely low solubilities in general solvents, even in DMSO. Such low solubilities did not allow further purification and studies on their properties.

UV-Vis and fluorescence spectra data of the naphthopyrones are shown in Table 1. All the naphthopyrones showed a bathochromic shift in their UV-Vis absorption relative to psoralen, and they absorbed somewhat more strongly in the UV-Vis region than psoralen. The absorption maxima increased in the order **6** < **2** < **10** and **7** < **3** < **11**. It is noteworthy that the Stoke's shifts of compounds **6** and **7** are larger than those of **2**, **3**, **10** and **11**.

EXPERIMENTAL

General

Melting points were taken on a digital melting point apparatus made in Shanghai and uncorrected. Mass spectra were recorded on a Hitachi M 80,



a: 1,3-bromochloropropane, K_2CO_3, acetone, reflux
b: 1) NaI, acetone, reflux; 2) $HNEt_2$, ethanol, reflux, hydrochloric acid
c: 1,3-bromochloropropane (0.5, equiv.), KI, K_2CO_3, acetone, reflux

Scheme 1.

TABLE 1
UV-Vis and Fluorescence Spectra Data of Naphthopyrones

Compd.	*UV$\lambda_{max,nm}$(logε)*	*Fl$\lambda_{max,nm}$*	*Stoke's shift (nm)*	*Ref.*
Psoralen	326[3.760]	445	119	10
2	363[3.9401]	442	79	
6	345[4.178]	465	120	
10	369[3.648]	447	78	
3	346[4.109]	431	85	
7	340[4.130]	460	120	
11	365[3.450]	441	76	

^{1}H NMR on a Bruker AM-300 (300 MHz) or DRX-400 (400 Hz) using TMS as internal standard. Combustion analysis for elemental composition was carried out on an Italy MOD. 1106 analyzer run by the analysis center of the East China University of Science and Technology. Absorption spectra were measured in absolute ethanol on a Shimadu UV-265 and fluorescence spectra on a Perkin Elmer LS 50. Commercial reagents and solvents were purchased from standard chemical suppliers.

1-Methyl-9- chloropropyloxy)naphtho[2,1-b]pyran-3-one(2)

*A typical synthetic procedure for **2**, **6** and **10**.*
A mixture of 1.068 g (4.73 mmol) of **1**, 1.530 g (9.68 mmol) of 1,3-bromochloropropane and 1.2 g (8.70 mmol) of K_2CO_3 in acetone was refluxed 17 h, cooled and filtered. After evaporation of the solvents, the residue was recrystallized from 95% ethanol to give 1.124 g of **2** as light yellow crystals in 78% yield. mp. 131.8–132.6°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (m, 2H, $ClCH_2\underline{CH_2}CH_2O$-), 2.94 (d, J=1.0Hz, 3H,1-CH_3), 3.82 (t, J=5.9 Hz, 2H, $Cl\underline{CH_2}CH_2O$-), 4.28 (t, J=5.9 Hz, 2H, $ClCH_2CH_2\underline{CH_2}O$-), 6.34 (d, J=1.0 Hz, 1H, 2-H), 7.21 (dd, J_{ax}=8.9 Hz, J_{ab}=2.4 Hz, 1H, 8-H), 7.32 (d, J=8.8 Hz, 1H, 5-H), 7.82 (d, J=8.9 Hz, 1H, 7-H), 7.89 (d, J=8.8 Hz, 1H, 6-H), 7.95 (d, J_{ba}=2.4 Hz, 1H, 10-H). MS (EI, 70eV) *m/e* (%) 304 (33.6) [M+2], 302 (100) [M], 274(23.4), 198(65.2), 197 (40.2). UV (ethanol) $\lambda_{max,nm}$, (1gε)=242 (4.688), 349 (4.068), 363 (3.940). FL (ethanol) λ_{max}=442 nm. Anal. calc. for $C_{17}H_{15}O_3Cl$: C 67.53, H 5.00; Found: C 67.50, H 5.01.

4-Methyl-8-(ω-chloropropyloxy)naphtho[2,3-b]pyran-2-one (6)

Yield 57%, mp. 168.3–168.5°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (t, 2H, $ClCH_2C\underline{CH_2}CH_2O$-), 2.53 (d, J=1.0 Hz, 3H, 4-CH_3), 3.81 (t, J=6.4 Hz, 2H, $Cl\underline{CH_2}CH_2CH_2O$-), 4.28 (t, J=5.8 Hz, 2H, $ClCH_2CH_2\underline{CH_2}O$-), 6.29 (s, 1H, 3-H), 7.15 (dd, J_{ax}=9.7 Hz, J_{ab}=2.3 Hz, 1H, 7-H), 7.16 (d, J_{ba}=2.3 Hz, 1H, 9-H), 7.59 (s, 1H, 10-H), 7.83 (d, J_{max}=9.7 Hz, 1H, 6-H), 8.01 (s, 1H,

5-H). MS (EI, 70eV) *m/e* (%) 304 (20.81) [M + 2], 302 (77.8) [M], 267 (6.2), 226 (100), 198(66.0), 169 (23.7), 115 (18.8). UV (ethanol) $\lambda_{max,nm}$ (lgε) = 277 (4.254), 286 (4.294), 345 (4.178). FL (ethanol) λ_{max} = 465 nm. Anal. calc. for $C_{17}H_{15}O_3Cl$: C 67.53, H 5.00; Found: C 67.497 H 4.98.

4-Methyl-7-(ω-chloropropyloxy)naphtho[1,2-b]pyran-2-one (10)

Yield 48%, mp. 170.7–171.0°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (t, 2H, $ClCH_2\underline{CH_2}CH_2O$-), 2.54 (d, J = 1.0 Hz, 3H, 4-CH_3), 3.88 (t, J = 6.3 Hz, 2H, $Cl\underline{CH_2}CH_2CH_2O$-), 4.34 (t, J = 5.8 Hz, 2H, $ClCH_2CH_2\underline{CH_2}O$-), 6.39 (d, J = 1.O Hz, 1H, 3-H), 7.02 (d, J = 7.8 Hz, 1H, 8-H), 7.56 (q, 2H, 9-H, 6-H), 8.11 (d, J = 8.8 Hz, 1H, 5-H), 8.16 (d, J = 8.4 Hz, 1H, 10-H). MS (EI, 70eV) *m/e* (%) 304 (27.6) [M + 2], 302 (78.5) [M], 226 (81.4), 198(100), 169 (45.2), 115 (44.2). UV (ethanol) $\lambda_{max,nm}$ (1gε) = 284 (4.481), 369 (3.648). FL (ethanol) λ_{max} = 447 nm. Anal. calc. for $C_{17}H_{15}O_3Cl$: C 67.53, H 5.00; Found: C 67.56, H 5.01.

1-Methyl-9-(ω-diethylaminopropyloxy)naphtho[2,1-b]pyran-3-one (3)

*Typical synthetic procedure for **3**, 7 and **11***
A mixture of 0.176 (0.58 mmol) of **2**, 0.12 g of sodium iodide in 40 ml of acetone was refluxed for 24 h. After evaporation of the solvent, to the residue was added 1.2 ml of diethylamine and 30 ml of anhydrous ethanol and the mixture stirred for 24 h at 70°C. After evaporation of solvent, the residue was dissolved in ethanol. After addition of 0.6 ml of conc. hydrochloric acid, filtration and recrystallization from ethanol, 0.115 g of **3** as yellow solid in 52.6% yield was obtained. mp. 208.6–210.6°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, J = 7.2 Hz, 6H, N-$CH_2\underline{CH_3}$, 2.20 (m, 2H, $ClCH_2\underline{CH_2}CH_2O$-), 2.96 (s, 3H, 1-$CH_3$), 3.17–3.47 (m, 6H, $CH_3\underline{CH_2NCH_2}CH_2CH_2O$-), 4.29 (t, J = 5.7 Hz, 2H, $ClCH_2CH_2\underline{CH_2}O$-), 6.50 (s, 1H, 2-H), 7.30 (dd, J_{ax} = 8.9 Hz, J_{ab} = 2.0 Hz, 1H, 8-H), 7.41 (d, J = 8.9 Hz, 1H, 5-H), 7.99 (d, J = 2.0 Hz, 1H, 10-H), 8.03 (d, J = 8.9 Hz, 1H, 7-H), 8.14 (d, J = 8.9 Hz, 1H, 6-H), 9.21 (s, 1H, N^+-H). MS (EI, 70 eV) *m/e* (%) 339 (4.0) [M-HCl], 324(2.6)[M-HCl-CH_3], 169 (6.6), 98 (5.8), 86 (100), 72 (17.7). UV (ethanol) $\lambda_{max,nm}$ (lgε) = 224 (3.812), 346 (4.109). FL (ethanol) λ_{max} = 431 nm. Anal. calc. for $C_{21}H_{26}O_3ClN$: C 67.10, H 6.97, N 3.73; Found: C 66.80, H 6.83, N 3.61.

4-Methyl-8-(ω-diethylaminopropyloxy)naphtho[2,3-b]pyran-2-one (7)

Yield: 58.6%, mp. 254.4–254.6°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 6H, N-$CH_2\underline{CH_3}$), 2.26 (t, 2H, $ClCH_2\underline{CH_2}CH_2O$-), 2.53 (s, 3H, 4-$CH_3$), 3.12–3.44 (m, 6H, $CH_3\underline{CH_2NCH_2}CH_2CH_2O$-), 4.24 (t, J = 5.8 Hz, 2H, $ClCH_2CH_2\underline{CH_2}O$-), 6.40 (s, 1H, 3-H), 7.21 (d, J = 9.1 Hz, 1H, 7-H), 7.42 (s,

1H, 9-H), 7.74 (s, 1H, 10-H), 8.03 (d, $J = 9.1$ Hz, 1H, 6-H), 8.36 (s, 1H, 5-H). MS (EI, 70 eV) *m*/*e* (%) 339 (4.8) [M-HCl], 324(2.7)[M-HCl-CH_3], 128 (8.9), 98 (12.3), 86 (100), 72 (21.6). UV (ethanol) $\lambda_{max,nm}$. (1gε) = 224 (4.218), 234 (4.250), 340 (4.130). FL (ethanol) $\lambda_{max} = 460$ nm. Anal. calc. for $C_{21}H_{26}O_3ClN$: C 67.10, H 6.97, N 3.73; Found: C 66.83, H 6.83, N 3.60.

4-Methyl-7-(ω-diethylaminopropyloxy)naphtho[1,2-b]pyran-2-one (11)

Yield: 61.1%, mp. 246.2–246.4°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.25 (t, $J = 7.2$ Hz, 6H, N-$CH_2\underline{CH_3}$), 2.28 (m, 2H, $ClCH_2\underline{CH_2}CH_2O$-), 2.55 (s, 3H, 4-$CH_3$), 3.24 (q, $J = 7.2$ Hz, 4H, $CH_3\underline{CH_2}N$), 3.36 (d, $J = 11.9$ Hz, 2H, -$OCH_2CH_2CH_2N$-), 4.32 (t, $J = 5.8$ Hz, 2H, $ClCH_2CH_2\underline{CH_2}O$-), 6.55 (s, 1H, 3-H), 7.23 (d, $J = 7.8$ Hz, 1H, 8-H), 7.66 (dd, $J = 7.8$ and 8.5 Hz, 1H, 9-H), 7.80 (d, $J = 9.0$ Hz, 1H, 6-H), 7.96 (d, $J = 8.5$ Hz, 1H, 10-H), 8.12 (d, $J = 9.0$ Hz, 1H, 5-H), 9.21 (s, 1H, N^+-H). MS (EI, 70 eV) *m*/*e* (%) 345 (0.4)[M-2CH_3], 339 (3.3) [M-HCl], 225(1.9), 197 (4.1), 169 (5.7), 128 (9.2), 114 (16.1), 86 (100), 72 (17.8). UV (ethanol) $\lambda_{max,nm}$ (lgε) = 282 (4.282), 365 (3.450). FL (ethanol) $\lambda_{max} = 441$ nm. Anal. calc. for $C_{21}H_{26}O_3ClN$: C 67.10, H 6.97, N 3.73; Found: C 66.80, H 6.8 1 , N 3.61.

Bisnaphthopyrone with trimethylene linkage (4)

*A typical procedure for preparation of **4**, **8** and **12***

A mixture of 1.004 g (4.44 mmol) of **1**, 0.355 g (2.25 mmol) of 1,3-bromochloropropane, 1 g of K_2CO_3 and 0.1 g of KI in acetone was refluxed for 3 days, cooled, filtered washed with acetone, aq 10% NaOH, water, and dried to give 0.641 g of **4**. MS (EI, 70eV) *m*/*e*(%) 492 (92.6)[M], 267(100), 239 (76.5), 217 (26.6), 169 (33.6).

Bisnaphthopyrone with trimethylene linkage (8)

MS (EI, 70 eV) *m*/*e*(%) 492 (50.4)[M], 267(73.7), 239 (36.0), 226 (50.2), 197(40.1).

Bisnaphthopyrone with trimethylene linkage (12)

MS (EI, 70 eV) *m*/*e* (%) 492 (54.8)[M], 267(100), 239 (60.9), 226 (23.3), 211(20.1), 197(19.7), 169 (31.5), 1 15 (18.1).

ACKNOWLEDGEMENTS

Financial support from National Natural Science Foundation of China and State Education Commission of China is greatly appreciated.

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