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Synthesis of 3H-1,8,9-trimethylthieno[3′,2′:6,7]naphtho [2,1-b]pyran-3-one with Potential Photobiological Activity

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ABSTRACT

3H-1,8,9-Trimethylthieno[3′,2′:6,7]naphtho[2,1-b]pyran-3-one, a potential photobiological agent, was synthesized in six steps starting from commercially available 2,7-naphthalenediol. The key step involved is a Newman–Kwart rearrangement of naphthopyrone **2**. *The structures of* **6** *and its precursors were fully characterized and their absorption and fluorescence spectra recorded.* © *1998 Elsevier Science Ltd*

Keywords: photobiological agent, 3H-1,8,9-trimethylthieno[3′,2′:6,7]-naphtho[2,1-b]pyran-3-one, furonaphthopyrones.

INTRODUCTION

It is well known that Furocoumarim type dyes such as psoralens exibit very strong photobiological activities to DNA [1], and for this reason they are used extensively in the photochemotherapy (PUVA-therapy) of hyperproliferatives skin diseases [2–5], as photochemical reagents for the investigation of nucleic acid structure and function [6, 7], and as light-activated pesticides [8]. More recently, they have also been utilized in the treatment of human immunodeficiency disease (AIDS) [9–11]. However, some undesirable side effects are present such as a persistant erythema [12], genotoxicity [13], and a possible risk of skin cancer [14], which may be attributed to furocoumarin

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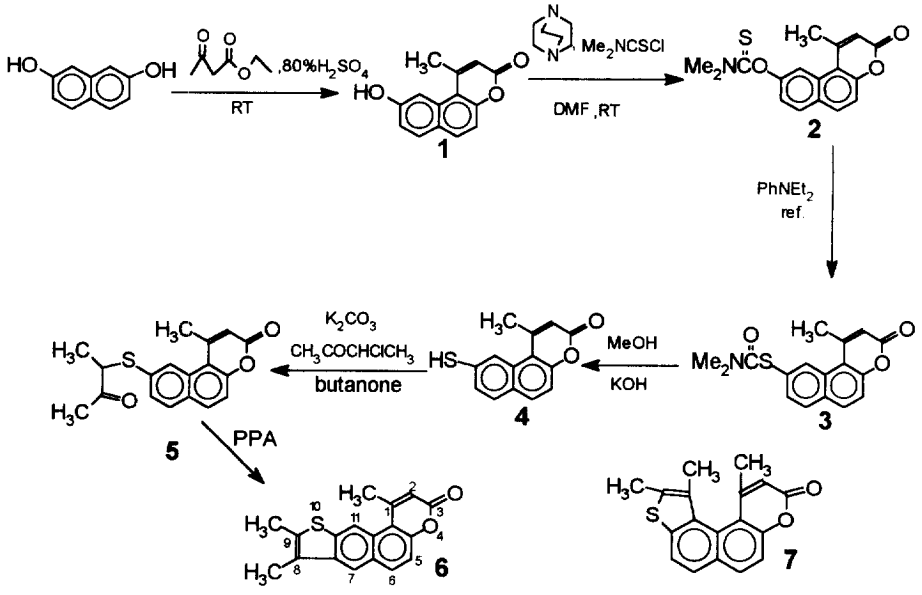
interstrand cross-links with DNA rather than to monofunctional adducts [15], and some research strategies have emerged with the aim of diminishing these side effects [16–22]. Our attempts have been focused on the synthesis, crystal structure and DNA intercalation of furonaphthopyrones and their sulphur analogues, which were expected to decrease the toxicity and to have photophysical and photobiological properties superior to furocoumarins by incorporating an additional benzene ring between the active double bonds of the α-pyrone and the furan moities [23–27]. The differences of photobiological and mutagenic activities between psoralens and angelicins [28,29] indicate that the geometries of the active double bonds of α-pyrone and the furon moities play a crucial role in their properties. We report here the synthesis of theinonaphthopyrone **6** with new skeleton structure and potentially interesting photobiological features.

RESULTS AND DISCUSSION

The synthetic methodology for the preparation of the thienonaphthyopyrone **6** is displayed in Scheme 1. The naphthopyrone **1** was readily prepared by our improved procedure [30], in which 2,7-naphthalenediol was condensed with ethyl acetoacetate in 80% H_2SO_4. The naphthopyrone **1** was treated with dimethylthiocarbamoyl chloride in the presence of 1,4-diazabicycolo[2.2.2]octane



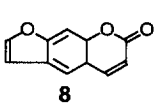
Scheme 1.

to give **2** in 95% yield. The molecular ion peak at *m/e* 313, 88 in MS, and the presence of proton resonances at δ 3.44, 3.52 ppm confirm the dimethylthiocarbamoyl group in **2**. The preparation of **3** was based on the Newman–Kwart rearrangement [31] of **2**. The naphthopyrone **2** was refluxed in *N*, *N*-diethylaniline for 14 h to afford **3** in 70% isolated yeild, and the starting naphthypyrone **2** was completely finished, which indicated that the Newman–Kwart rearrangement **2** proceeded faster than that of its analogue [26]. The naphthopyrone **3** showed characteristic peaks at δ 3.07 (*s*, *br*, NCH_3), 3.16 (*s*, *br*, NCH_3) ppm, *m/e* 313 (42) [M^+], 72(100) [Me_2NCO^+] in MS. The naphthopyrone **3** was readily hydrolyzed to **4** in 79% yield; its structure was confirmed by the proton peak at 3.72 ppm for SH in ^1H NMR and the molecular ion peak at 242 (100) in MS. The reaction of **4** with 3-chloro-2-butanone in butanone in the presence of K_2CO_3 gave **5** in 49% isolated yield. The presence of the proton resonances at δ 1.50 (*d*, $J = 7.1$ Hz, 3H, $4CH_3$), 2.32 (*s*, 1'-CH_3), 3.29 (*q*, $J = 7.1$ Hz, 1H, 3'H) ppm for 4'-H, 1'-H, 3'-H confirm the presence of the ether group in **5**. The cyclization of **5** in polyphosphoric acid exclusively gave the thienonaphthopyrone **6** in 71% yield without the isomoer **7**, which probably resulted from the instability of **7** at room temperature [32]. The structure of **6** was fully characterised by ^1H NMR, MS and the elemental analysis.

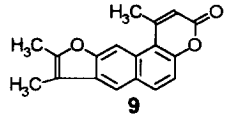
Compared with compounds **8** and **9** (as shown in Table 1), the thienonaphthopyrone **6** showed a bathocromic shaft in the UV-Vis absorption and flouresence maxima; and it absorbs somewhat more strongly in the UV-Vis region than the furocoumarin **8**. These spectral properties of the theinonaphthopyrone **6** are advantageous for the photobinding to DNA, provided that these heteroarenes also exhibit intercalation.

TABLE 1
UV-Vis and Flourescence Spectra Data of the Thienonaphthopyrone **6**, the Furocoumarin **8** and the Furonaphthoprone **9**

Compound	*UV* λ_{max} *(nm) (log* ε*)*	*FL* λ_{max} *(nm)*	*Stoke's shift (nm)*	*Ref.*
6	383[3.892]	486	103	
8	326[3.760]	445	119	33
9	346[4.112]	431	85	30



8



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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, ^{1}H NMR on a Bruker AM-300 (300 MHz) 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 Shimadlu UV-265 and fluorescence spectra on a Perkin Elmer LS 50. Commercial reagents and solvents were purchased from standard chemical supplier.

Synthesis of 9-(*N*,*N*-dimethylthiocarbomoyloxy)-l-methylnaphtho[2,1-b] pyran-3-one (2)

A mixture of 2.246 g (9.94 mmol) of **1**, 2.6 g (20 mmol) of dimethylthiocarbamoyl chloride, 2.4 g (20 mmol) of 1,4-diazabicyclo[2.2.2]octane in 40 ml anhydrous DMF was stirred at room temperature for 15 h, and poured on 200 g crushed ice. After filtration, the solid was washed with 10% HCl, water and treated with cold methanol, and recrystallized from methanol to give 2.936 g of **2** as light yellow needles in 94% yield, melting point 236.6–236.7°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ2.92 (s, 3H, l-CH_3), 3.44(s, 3H, NCH_3), 3.52 (s, 3H, NCH_3), 6.38 (s, lH, 2-H), 7.32 (dd, J_{AX} = 8.8 HZ, J_{AB} = 2.0 Hz, lH, 8-H), 7.47 (d, J = 8.9 Hz, lH, 5-H,), 7.94 (d, J_{XA} = 8.8 Hz, IH, 7-H), 7.99 (d, J = 8.9 Hz, lH, 6-H), 8.29 (d, J_{BA} = 2.0 Hz, lH, 10-H). MS(EI 70eV) *m/z* (%): 313(28.8) [M^+], 88(100), 72(90.3). UV (ethanol) $\lambda_{max,nm}$ ($\log\varepsilon$) = 327(3.920), 346(3.914); FL(ethanol) λ_{max} = 430 nm. Analysis calculated for $C_{17}H_{15}NO_3S$ (%): C 65.16, H 4.82, N 4.47; Found: C 64.98, H 4.74, N 4.47.

Synthesis of 9-(*N*,*N*-dimethylcarbamoylthio)-1-methylnaphtho[2,1-b]pyran-1-one (3)

3.78 g (12.1 mmol) of **2** was dissolved in 80 ml of *N*, *N*-diethylaniline and the reaction mixture was refluxed under a nitrogen atmosphere for 14 h, cooled and poured into 300 ml of 10% HCI; The precipitate was filtered, washed free of acid, treated with cold methanol, and recrystalized from methanol to afford 2.650 g of **3** in 70.1% yield. mp 216.7–217.0°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.96 (s, 3H, 1-CH_3), 3.07 (s, br, 3H, NCH_3), 3.16 (s, br, 3H, NCH_3), 6.40 (s, lH, 2-H), 7.51 (d, J = 8.9 Hz, lH, 5-H), 7.63 (dd, J_{AX} = 8.4 Hz,

J_{AB} = 1.2 Hz, 1H, 8-H), 7.92 (d, J = 8.4 Hz, 1H, 7-H), 7.99 (d, J = 8.9 Hz, 1H, 6-H), 8.81 (s, 1H, 10-H). MS(EI 70 eV) m/z (%): 313 (42.4)[M^+], 72 (100) [Me_2NCO^+]. UV(ethanol) $\lambda_{max,nm}$ (log ε) = 321(4.169), 350(4.179), 366(4.080); FL (ethanol) λ_{max} = 416 nm. Analysis calculated for $C_{17}H_{15}NO_3S$ (%): C 65.16, H 4.82, N 4.47; Found: C 65.06, H 4.84, N 4.38.

Synthesis of 9-mercapto-1-methylnaphtho[2,1-b]pyran-3-one (4)

A mixture of 0.494 g (1.58 mmol) of **3**, 0.3 g of KOH in 20 ml of methanol was refluxed under a nitrogen atmosphere for 12 h, cooled and poured into 60 ml 10% HCl. The precipitate was filtered, washed free of acid, dried and recrystalized from methanol to afford 0.268 g of **4** in 70% yield. mp 157.2–157.9°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.91 (s, 3H, 1-CH_3), 3.72 (s, 1H, SH), 6.37 (s, 1H, 2-H), 7.40 (d, J = 9.0 Hz, 1H, 5-H), 7.41 (dd, J_{AX} = 8.5 Hz, J_{AB} = 1.6 Hz, 1H, 8-H), 7.77 (d, J_{XA} = 8.5 Hz 1H, 7-H), 7.89 (d, J = 9.0 Hz, 1H, 6-H), 8.47 (s, 1H, 10-H). MS(EI 70 eV) m/z (%): 242(100)[M^+], 214(52.2)[M^+-CO], 181(45.9). UV (ethanol) $\lambda_{max.nm}$ (log ε) = 350(4.052), 364(3.930)(sh); FL(ethanol) λ_{max} = 422 nm. Analysis calculated for $C_{14}H_{10}O_2S$ (%): C 69.40, H 4.16; Found: C 69.20, H 4.19.

Synthesis of 9-[(2'-oxobutan-3'-yl)thio]-1-methylnaphtho[2,1-b]pyran-3-one (5)

A mixture of 0.5 g (2.1 mmol) of **4**, 0.35 g of anhydrous potassium carbonate and 0.5 ml of 3-chloro-2-butanone in 40 ml of butanone was refluxed for 4 h cooled, poured into 250 ml ice water, filtered, and the residue washed with 10% NaOH and water. After recrystallization from methanol, 0.315 g of **5** in 49% yield was obtained. mp 127.4–127.7°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50 (d, J = 7.1 Hz, 3H, 4'-CH_3), 2.32 (s, 3H, 1'-CH_3), 2.94 (s, 3H, 1-CH_3), 3.92 (q, J = 7.1 Hz, 1H, 3'-H), 6.40 (d, J = 0.7 Hz, 1H, 2-H), 7.46 (d, J = 8.8 Hz, 1H, 5-H), 7.49 (dd, J_{AX} = 9.0 Hz, J_{AB} = 1.5 Hz, 1H, 8-H), 7.83 (d, J = 8.8 Hz, 1H, 6-H), 7.93 (d, J_{XA} = 9.0 Hz, 1H, 7-H), 8.55(s, 1H, 10-H). MS (EI 70 eV) m/z (%): 315(73.9), 313(100), 312(75.1), 269(64.8). UV (ethanol) $\lambda_{max,\ nm}$ (log ε) = 334(4.057)(sh), 350(4.114), 366(3.990); FL(ethanol) λ_{max} = 451 nm. Analysis calculated for $C_{18}H_{16}O_3S$ (%): C 69.21, H 4.16; Found: C 69.08, H 5.14.

Synthesis of 3H-1,8,9-Trimethylthieno[3',2':6,7]naphtho[2,1-b]pyran-3-one (6)

A mixture of 0.151 g (0.48 mmol) of **5** and 5.5 ml of polyphosphoric acid was stirred for 5 h at 105°C under a nitrogen atmosphere, cooled and poured into 100 ml ice water. The precipitate was filtered, washed free of acid, dried and recrystallized from ethyl acetate to give **6** in 71% yield; melting point 253.0–253.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.37 (s, 3H, 8-CH_3), 2.54 (s,

3H, 9-CH_3), 2.90 (s, 3H, 1-CH_3), 6.32 (s, lH, 2-H), 7.35 (d, $J=9.0$ Hz, lH, 5-H), 7.96 (s, lH, 7-H), 7.99 (d, $J=9.0$ Hz, lH, 6-H), 8.80 (s, lH, 11-H). UV (ethanol) $\lambda_{max,nm}$ ($\log\varepsilon$) = 290(4.298), 310(4.286), 383(3.892); FL(ethanol) λ_{max} = 486 nm. MS(EI 70 eV) *m/z* (%): 295 (21.2) [$M^+ + 1$], 294 (100) [M^+], 266 (45.1), 251(19.2). Analysis calculated for $C_{18}H_{14}O_2S$ (%): C 73.44, H 4.79; Found: C 73.39, H 4.78.

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