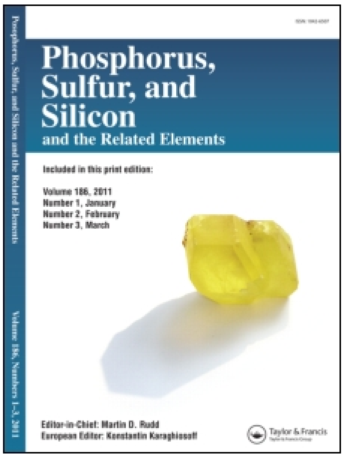

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SYNTHESIS OF 2H-4,8-DIMETHYLTHIENO[2′,3′:5,6]NAPHTHO[1,2-b]PYRAN-2-ONE WITH POTENTIAL PHOTOBIOLOGICAL ACTIVITY TO DNA

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2H-4,8-Dimethylthieno[2′,3′:5,6]naphtho[1,2-b]pyran-2-one (**7**), a potential photobiological agent, was synthesized in six steps starting from commercially available 1,5-naphthalenediol. A Newman-Kwart rearrangement of naphthopyrone **2** and an unusual S-Claisen rearrangement of naphthopyrone **5** are the key steps. The structures of **7** and its precursors were fully characterized.

Key words: Naphthopyrone, thienonaphthopyrone, Newman-Kwart rearrangement, photobiological agent, S-Claisen rearrangement, DNA.

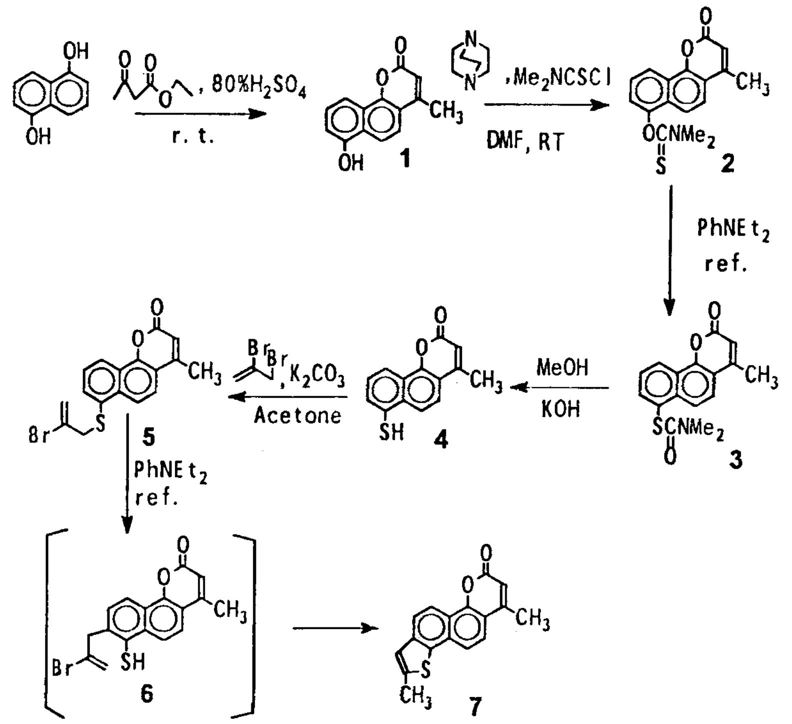
INTRODUCTION

Furocoumarins such as psoralens exhibit very strong photobiological activities to DNA,[1] and for this reason they are extensively used in the photochemotherapy (PUVA-therapy) of hyperproliferatives skin diseases such as psoriasis, micosis fungoides, vitiligo and T-cell lymphoma,[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 are also utilized in the treatment of human immunodeficiency disease (AIDS).[9–11] However, some undesirable side effects are present such as a persistent erythema,[12] genotoxicity,[13] and a possible risk of skin cancer,[14] which may be attributed to furocoumarin interstrand crosslinks with DNA rather than to monofunctional adducts,[15] and some research strategies have immerged with the aim of diminishing these side effects.[16–22] In the course of our work concerning access to new monofunctional analogous of psoralens, we recently described the synthesis, crystal structure and DNA intercalation of furonaphthopyrones, which were expected to decrease the toxicity, and have photophysical and photobiological properties superior to furocoumarins by incorporating an additional benzene ring between active double bonds of the α-pyrone and the furan moieties.[23–25] Since the replacement of the endocyclic oxygen atoms by sulfur can improve the singlet oxygen quantum yield and photobiological properties of psoralens,[26–28] we herein report the synthesis of thienonaphthopyrone **7**, which may be a monofunctional and more effective photobiological agent to DNA.

RESULTS AND DISCUSSION

The synthetic methodology for the preparation of the thienonaphthopyrone is displayed in Scheme I. The naphthopyrone **1** was readily prepared by our improved

SCHEME I



procedure, in which the 1,5-naphthalenediol condensed with ethyl acetoacetate in 80% H_2SO_4 instead of conc. H_2SO_4 and the purification was also much simpler than that previously reported.[23] The naphthopyrone **2** was synthesized in two ways. The naphthopyrone **1** was treated with dimethylthiocarbamoyl chloride in the presence of sodium hydride to give **2** in 44% yield, while **2** was obtained in 66% yield when 1,4-diazabicyclo[2.2.2] octane was used as base. Obviously, method B was much more efficient and concise than method A for the use of different base. The absence of HO group absorption in the IR, the molecular ion peak at m/e 313 in MS, and the presence of proton resonances at δ 3.49 (d, J = 2.4 Hz), 3.57 (d, J = 2.2 Hz) ppm confirm the dimethylthiocarbamoyl group in **2**. The preparation of **3** was based on the Newman-Kwart rearrangement[29,30] of **2**. The naphthopyrone **2** was refluxed in diphenyl ether for 1.5 h to give **2** in low yield, and the IR showed that decomposition occurred, while **2** was refluxed in N,N-diethylaniline for 18 hours to afford **3** in higher yield and the reaction was relatively slow, the starting naphthopyrone **2** still being detectable by TLC after 48 hours. The naphthopyrone **3** showed characteristic peaks at δ 3.05 (s, br, NCH_3), 3.26 (s, br, NCH_3) ppm, 1732, 1666 cm^{-1} in IR, and m/e 72 (100) [Me_2NCO^+] in MS. The naphthopyrone **3** was hydrolyzed to **4**, whose structure was confirmed by ^1H NMR, IR, MS. Because **4** was unstable and easily become black in the air, its elemental analysis data was not satisfactory and the hydrolysis reaction was performed under the nitrogen atmosphere. The reaction of **4** with 2,3-dibromopropene in acetone in the presence of K_2CO_3 gave **5** in 51.5%

isolated yield. The presence of the proton resonances at δ 5.34 (d, J = 1.9 Hz), 5.44 (t, J = 0.9 Hz) ppm for 3′-H confirm the presence of the bromoallyl group in **5**. **5** was refluxed in N,N-diethylaniline to give **7** in ca. 40%. The use of nitrogen atmosphere in the reaction is very important and prevents the formation of tars due to the oxidation reactions. The chemical shift at δ 7.16 (s) for 9-H of the furan ring and the molecular fragment peaks at m/e 280 (100), 252 (84.5) are in good agreement with the structure of **7**. According to the result of the related mechanistic studies,[31] **7** was probably produced by the dehydrobromination of the intermediate **6** formed via a S-Claisen rearrangement reaction of **5** as shown in Scheme I.

EXPERIMENTAL

Melting points were taken on a digital melting point apparatus made in Shanghai and uncorrected. Infrared spectra were recorded on a Magna-IR 550, mass spectra 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. Commercial reagents and solvents were purchased from standard chemical supplier and used without further purification, 2,3-dibromopropene was prepared by literature.[32]

Synthesis of 4-methyl-7-hydroxynaphtho[1,2-b]pyran-2-one (**1**)[23]: **1** was prepared by following improved procedure: To a mixture of 2.0 g (12.5 mmol) of 1,5-naphthalenediol and 4 ml of ethyl acetoacetate was added 15 ml of 80% (v/v) H_2SO_4 below 10°C. The reaction mixture was stirred for 24 h at room temperature, and poured into 200 ml of ice water. After filtration, the filter cake was washed with a small amount of acetone, dried and dissolved in aqueous 10% NaOH solution, which was acidified with 10% HCl and dried to give 2.46 g (87%) of **1** as yellow solid. The TLC (petroleum ether:ethyl acetate = 1:1) of product **1** show only one spot.

Synthesis of 7-(N,N-dimethylthiocarbomoyloxy)-4-methylnaphtho[1,2-b]pyran-2-one (**2**): *Method A*: To a solution of 1.500 g (6.64 mol) of **1** in 15 ml of dry DMF was added 0.255 g (10.62 mmol) of sodium hydride, and stirred. After the evolution of hydrogen had ceased, 0.954 g (7.72 mmol) of dimethylthiocarbamoyl chloride was added to the solution. The reaction solution was stirred for 1 h at 60°C, and poured into 75 ml of cool water to afford crude product of **2** as yellow solid, which was purified by recrystallization from 95% ethanol to give 0.917 of **2** in 44% yield.

Method B: A mixture of 1.460 g (6.46 mmol) of **1**, 1.601 g (13.0 mmol) of dimethylthiocarbamoyl chloride, 1.448 g (12.9 mmol) of 1,4-diazabicyclo[2.2.2]octane in 20 ml anhydrous DMF was stirred at room temperature for 2 h, and poured on 100 g crushed ice. After filtration, the solid was washed with 10% HCl, water and treated with cold methanol, and recrystallized from methanol to give 1.330 g of **2** as light yellow needles in 66% yield. mp 241.6–242.0°C; ^{1}H NMR (acetone-d_6): δ 2.59 (d, J = 1.1 Hz, 3H, 4-CH_3), 3.49 (d, J = 2.4 Hz, 3H, NCH_3), 3.57 (d, J = 2.2 Hz, 3H, NCH_3), 6.45 (d, J = 1.1 Hz, 1H, 3-H), 7.42 (dd, J_{AX} = 7.6 Hz, J_{AB} = 1.0 Hz, 1H, 8-H), 7.71–7.78 (m, 3H, 5-H, 6-H, 9-H), 8.40 (d, J_{BX} = 8.6 Hz, 1H, 10-H). MS (EI 70 eV) m/z (%): 315 (3.75) [M^+ + 2], 313 (20.9) [M^+], 225 (1.01), 89 (100), 72 (58.1). IR (KBr): ν = 2970, 2940, 1732 (C=O), 1622, 1540, 1510, 1476, 1400, 1290, 1238, 1226, 1180, 1134, 996, 952, 862, 818, 770 cm^{-1}. Anal. calcd. for $C_{17}H_{15}NO_3S$ (%): C 65.16, H 4.82, N 4.47; Found: C 65.25, H 4.88, N 4.34.

Synthesis of 7-(N,N-dimethylcarbamoylthio)-4-methylnaphtho[1,2-b]pyran-2-one (**3**): 4.2 g (13.4 mmol) of **2** was dissolved in 40 ml of N,N-diethylaniline and the reaction mixture was refluxed under the nitrogen atmosphere for 18 h, cooled and poured into 400 ml of 10% HCl; The precipitate was filtered, washed free of acid, treated with cold methanol to afford 3.954 g of **3** in 94.1% yield. Recrystallization from methanol to give analytical sample as yellow needles. mp 186.3–187.0°C. ^{1}H NMR (acetone-d_6): δ 2.60 (d, J = 1.1 Hz, 3H, 4-CH_3), 3.05 (s, br, 3H, NCH_3), 3.26 (s, br, 3H, NCH_3), 6.45 (d, J = 1.1 Hz, 1H, 3-H), 7.73 (dd, J_{AX} = 7.1 Hz, J_{BX} = 7.3 Hz, 1H, 9-H), 7.85 (d, J = 9.2 Hz, 1H, 6-H), 7.94 (dd, J_{AX} = 7.1 Hz, J_{AB} = 1.1 Hz, 1H, 8-H), 8.2 (d, J = 9.2 Hz, 1H, 5-H), 8.59 (dd, J_{BX} = 7.3 Hz, J_{AB} = 1.1 Hz, 1H, 10-H). MS (EI 70 eV) m/z (%): 315 (2.2) [M^+ + 2], 314 (5.8) [M^+ + 1], 313 (26.9) [M^+], 241 (6.8) [M^+-Me_2NCO], 72 (100) [Me_2NCO^+]. IR (KBr): ν = 3067, 2932, 1732, 1666, 1604, 1558, 1496, 1465, 1361, 1259, 1105, 943, 906, 844, 806, 761 cm^{-1}. Anal. calcd. for $C_{17}H_{15}NO_3S$ (%): C 65.16, H 4.82, N 4.47; Found: C 65.32, H 4.82, N 4.38.

Synthesis of 7-mercapto-4-methylnaphtho[1,2-b]pyran-2-one (**4**): A mixture of 1.33 g (4.25 mmol) of **3**, 0.734 g (13 mmol) of KOH in 40 ml of methanol was refluxed under nitrogen atmosphere for 24 h. The solvent was removed in vacuum and 20 ml of water was added to the residue, and the mixture was extracted with either (3 × 30 ml). The aqueous solution was acidified with conc. HCl to pH = 1 to give a crude product of **4**, which was washed, dried and recrystallized from methanol to afford 0.812 g of **4** in 78.9% yield. mp 276–280°C. ^{1}H NMR (acetone-d_6): δ 2.59 (d, J = 1.1 Hz, 3H, 4-CH$_3$), 6.46 (d, J = 1.1 Hz, 1H, 3-H), 7.58 (dd, J_{AX} = 7.3 Hz, J_{BX} = 8.5 Hz, 1H, 9-H), 7.85 (d, J_{AX} = 7.3 Hz, 1H, 8-H), 7.91 (d, J = 9.1 Hz, 1H, 6-H), 8.03 (d, J = 9.1 Hz, 1H, 5-H), 8.34 (d, J_{BX} = 8.5 Hz, 1H, 10-H). MS (EI 70 eV) m/z (%): 243 (4.7) [M$^+$ + 1], 242 (20.1) [M$^+$], 214 (10.0) [M$^+$-CO]. IR (KBr): ν = 1726, 1620, 1606, 1560, 1480, 1380, 1160, 1140, 1090, 1035, 880, 810, 780 cm^{-1}.

Synthesis of 7-[(2-bromoallyl)thio]-4-methylnaphtho[1,2-b]pyran-2-one (**5**): A mixture of 0.781 g (3.22 mmol) of **4**, 0.65 g of anhydrous potassium carbonate and 1.23 g (6.15 mmol) of freshly distilled **2**, 3-dibromopropene in 40 ml acetone was refluxed for 15 h. Inorganic salts were filtered from the cooled solution and washed with acetone. Evaporation of the combined filtrate under reduced pressure left a brownish residue. After recrystallization from methanol, 0.601 g of **5** in 51.5% yield was obtained as yellow needles. mp 143.0–143.6°C. ^{1}H NMR (acetone-d_6): δ 2.55 (d, J = 1.0 Hz, 3H, 4-CH$_3$), 3.84 (s, 2H, —SCH$_2$—), 5.34 (d, J = 1.9 Hz, 1H, =CH), 5.44 (t, J = 0.9 Hz, 1H, =CH), 6.41 (d, J = 1.0 Hz, 1H, 3-H), 7.57 (dd, J_{AX} = 7.4 Hz, J_{BX} = 8.3 Hz, 1H, 9-H), 7.70 (d, J = 9.1 Hz, 1H, 6-H), 7.79 (dd, J_{AX} = 7.4 Hz, J_{AB} = 0.9 Hz, 1H, 8-H), 8.37 (d, J = 9.1 Hz, 1H, 5-H), 8.54 (d, J_{BX} = 8.3 Hz, 1H, 10-H). MS (EI 70 eV) m/z (%): 363 (27.0) [M$^+$ + 2], 361 (27.3) [M$^+$], 362 (96.5), 360 (92.1), 281 (100) [M$^+$-Br], 241 (98.2). IR (KBr): ν = 1724, 1624, 1602, 1558, 1501, 1464, 1373, 1319, 1200, 1167, 1142, 1111, 1099, 941, 908, 873, 852, 838, 823, 808, 759, 594 cm^{-1}. Anal. calcd. for $C_{17}H_{15}BrO_2S$ (%): C 56.52, H 3.66; Found: C 56.72, H 3.70.

Synthesis of 4,8-dimethylthieno[2',3':5,6]naphtho[1,2-b]pyran-2-one (**7**): A mixture of 0.330 g (0.91 mmol) of **5** and 15 ml of freshly distilled N,N-diethylaniline was refluxed for 24 h under a nitrogen atmosphere. The reaction solution was cooled and poured into 50 ml of 10% HCl. The precipitate was filtered, washed free of acid and dried. The crude product was subject to TLC using a mixture of ethyl acetate and petroleum ether as eluent to give **5**, yield 40% (in ca). ^{1}H NMR (CDCl$_3$): δ 2.54 (s, 3H, 8-CH$_3$), 2.69 (s, 3H, 4-CH$_3$), 6.36 (s, 1H, 3-H), 7.16 (s, 1H, 9-H), 7.67 (d, J = 8.7 Hz, 1H, 11-H), 7.83 (d, J = 8.8 Hz, 1H, 6-H), 7.87 (d, J = 8.8 Hz, 1H, 5-H), 8.43 (d, J = 8.7 Hz, 1H, 10-H). MS (EI 70 eV) m/z (%): 281 (22.2) [M$^+$ + 1], 280 (100) [M$^+$], 252 (84.5) [M$^+$ − CO]. 223 (14.6), 208 (17.9). Anal. calcd. for $C_{17}H_{13}O_2S$ (%): C 72.86, H 4.64. Found: C 72.67, H 4.60.

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