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Synthesis and Photooxygenation of 2,3,6-Trimethylfuro[2,3-b][1]naphtho[4a,7a-e,f]pyrida-5,7-dione, A Potential Chemiluminescent Probe for Singlet Oxygen

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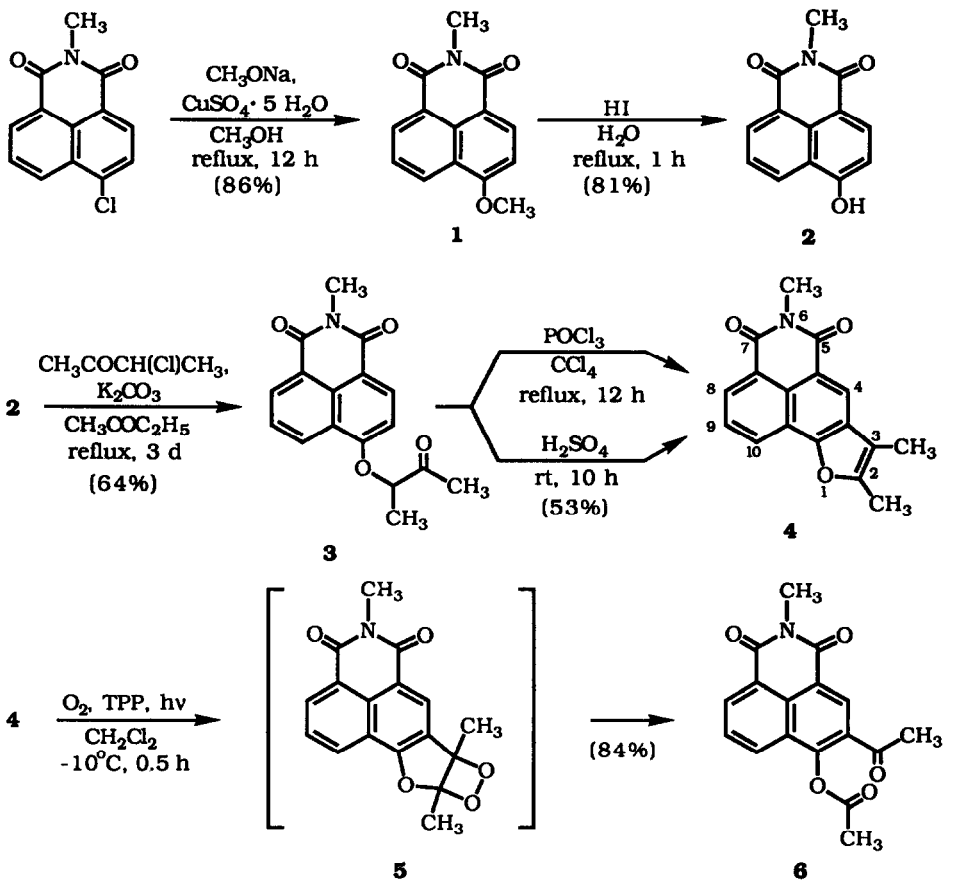
Abstract: As potential chemiluminescent probe for singlet oxygen, the furonaphthalimide **4** was synthesized in five steps (ca. 25% overall yield), by starting from commercially available 4-chloro-1,8-naphthalic anhydride; its photooxygenation at -10°C gave the cleavage product **6** of the intermediary dioxetane **5**, which is thermally too labile for isolation and could not be detected even by low temperature NMR spectroscopy. The new 1,8-naphthalimide derivatives **3**, **4** and **6** were fully characterized and their absorption and fluorescence spectral properties were determined.

1,8-Naphthalimide derivatives exhibit strong fluorescence emission and serve for this reason as fluorescence probes, e. g. for hypoxic cells in solid tumors [1, 2], as solar energy collecting materials [3], as electrooptically sensitive materials [4], and for laser activity [5, 6]. For our photobiological work [7] we required dioxetanes with an efficient fluorophor as a chemiluminescent probe. We report herein the synthesis of 2,3,6-trimethylfuro[2,3-b][1]naphtho[4a,7a-e,f]pyrida-5,7-dione (**4**), a potential chemiluminescent probe for singlet oxygen, its absorption and fluorescence spectral properties, and photooxygenation.

The synthesis of furonaphthalimide **4** is displayed in Scheme 1. 4-Chloro-N-methyl-1,8-naphthalimide was prepared by imidation of the commercially available 4-chloro-1,8-naphthalic anhydride according to the reported procedure [8] and methoxylated in the presence of cupric ion as catalyst to afford the 1,8-naphthalimide **1** in 86% yield. Demethylation of **1** with aqueous HI at reflux gave the naphthol derivative **2** in 81% yield. The latter was converted with 3-chloro-2-butanone to the ether derivative **3** in

64% yield, which possesses in the ^{13}C NMR spectrum a characteristic peak at δ 208.0 (s) for the ketone group and the imide carbon atoms are located at δ 164.1 (s) and 164.8 (s). The cyclization of **3** under acidic conditions gave exclusively the hitherto unknown furonaphthalimide **4**. Cyclization at the *peri* position to the corresponding pyran, as observed in the Pschorr cyclization[10] of 4-(2-aminophenylthio)-1,8-naphthalimide, did not take place. The structure of **4** was

Scheme 1



conformed by the presence of the characteristic resonances at δ 152.5 and 112.3 for the C-2 and C-3 of the furan ring.

Tetraphenylporphine (TPP)-sensitized photooxygenation of furonaphthalimide **4** in

methylene chloride at -10 °C gave exclusively the decomposition product **6** of dioxetane **5**. The dioxetane was thermally too labile even at low temperature for spectral observation. The decomposition product **6** showed two new carbonyl peaks at δ 169.2 (s) and 197.2 (s) in the ^{13}C NMR spectrum for the acetoxy and acetyl groups.

The UV-VIS and fluorescence spectral properties of the naphthalimide derivatives prepared herein were determined and are given along with other spectral data in the Experimental Section. Compared to the simple 1,8-naphthalimide **1**, the furonaphthalimide **4** displays the expected large bathochromic shift in the absorption and fluorescence spectra, a result of the extended conjugation with the furan ring; however, surprising is the fact that the fluorescence quantum yields of the furonaphthalimide **4** and its photooxygenation cleavage product **6** are significantly lower than that of the 1,8-naphthalimide **1**.

The facts that the furonaphthalimide **4** reacts readily with singlet oxygen even at subambient temperatures (-10°C) and the 1,8-naphthalimide **6**, which is the chemienergized species in the cleavage of the intermediary dioxetane **5**, is a fluorophor, make the naphthalimide **4** a potential chemiluminescent probe for singlet oxygen in chemical and biological oxidations. However, the fluorescence efficiency of 1,4-naphthalimide **6** should be improved by appropriate structural variations of the furonaphthalimide **4**, and thus make the latter more useful particularly for biological processes.

Experimental Section

Melting points were taken on a Reichart Thermovar Kofler apparatus.- Infrared spectra: Perkin Elmer 1420 ratio recording infrared spectrometer.- Absorbtion spectra: Hitachi U-3200 spectrophotometer in benzene-free absolute ethanol; the accuracy of the peak wavelengths was ±1 nm and the error in the extinction coefficients was ±5 %.- Fluorescence spectra: Perkin Elmer LS 50 luminescence spectrometer; the fluorescence quantum yields were determined relative to quinine sulfate in sulfuric acid as standard (ϕ^{fl} = 0.54) by using published procedures [10]; the error was about ± 10 %.- ^{1}H and ^{13}C NMR spectra: Bruker AC 250 (250 MHz) spectrometer with $CDCl_3$ or TMS as internal standard.- Combustion analyses for elemental composition: Carlo Erba 1106 analyser run by the Microanalytical Division of the Institute of Inorganic Chemistry, University of Würzburg.- Thin layer chromatography (TLC): Polygram SIL/G/UV 254 (40x80 mm) from Macherey and Nagel Co.- Column chromatography: silica gel (60-230 mesh) from Woelm or silylated silica gel 60 from Merck.- For the removal of the solvent, a rotary evaporator (20 °C/20-15 Torr) was used. Commercial reagents and solvents were purchased from

standard chemical suppliers and purified to match the reported physical and spectral data.

The starting material 4-chloro-N-methyl-1,8-naphthalimide was prepared from 4-chloro-1,8-naphthalic anhydride according to the reported procedure [8].

4-Methoxy-N-methyl-1,8-naphthalimide [11] (**1**).

A mixture of 4.00 g (16.3 mmol) of 4-chloro-N-methyl-1,8-naphthalimide, 7.00 g (130 mmol) of CH_3ONa, and 0.500 g (2.00 mmol) of $CuSO_4 \cdot 5H_2O$ were refluxed in 50 ml of CH_3OH for 12 h. After the removal of the solvent and washing of the residue with water (100 ml), **1** was obtained as yellow needles in 86 % yield, m.p. 195-198°C (lit. [11] 197-201 °C). UV (ethanol): λ_{max}(lg ε) = 217 nm (4.117), 240 (4.480), 362 (4.150); Fluorescence (EtOH): λ^{fl} = 444nm; ϕ^{fl} = 0.81 ± 0.08.

4-Hydroxy-N-methyl-1,8-naphthalimide [11] (**2**).

A mixture of 4.00 g (16.6 mmol) of **1** and 100 ml of concentrated HI (57 %) was refluxed for 3 h. After cooling and filtration, yellow needles of **2** were obtained in 81 % yield, m.p. 300-303 °C (lit. [11] 303.5-305.5 °C). ^{1}H NMR ($CDCl_3$): δ = 3.33 (s, 3H, N-CH_3), 7.12 (d, J = 8.1 Hz, 1H, 3-H), 7.12 (dd, J_{XA} = 7.5 Hz, J_{XB} = 8.3 Hz, 1H, 6-H), 8.29 (d, J = 8.1 Hz, 1H, 3-H), 7.72 (dd, J_{XA} = 7.5, J_{XB} = 8.3 Hz, 1H, 6-H), 8.29 (d, J = 8.1 Hz, 1H, 2-H), 8.41 (d, J_{AX} = 7.5 Hz, 1H, 5-H), 8.48 (d, J = 8.3 Hz, 1H, 7-H), 11.82 (s, 1H, OH); UV (ethanol): λ_{max} (lg ε) = 250 nm (4.417), 382 (4.033).

2-Methyl-6-(2'-oxobutan-3'-yl-naphtho[3a,9a-c,d]pyrida-1,3-dione (**3**).

3.00 g (13.2 mmol) of **2**, 1.50 ml (14.8 mmol) of 3-chloro-2-butanone, and 2.10 g (15.2 mmol) of K_2CO_3 in 40 ml of 2-butanone were refluxed for 3 d. After removal of the solvent, the residue was extracted with ether (3 x 80 ml), the ether solution was washed with water (3 x 10 ml), and dried over anhydrous $MgSO_4$ to afford after removal of the solvent 2.50 g (64 %) of the crude product as yellow needles, m.p. 147-148 °C (ethyl acetate). IR (KBr): ν = 3080 cm^{-1}, 2900, 1715 (NC=O), 1705 (C=O), 1665, 1600, 1515, 1465, 1415, 1405, 1365, 1290, 1270, 1235, 1100, 1055; ^{1}H NMR ($CDCl_3$) : δ = 1.66 (d, J = 8.0 Hz, 3H, 4'- CH_3), 2.20 (s, 3H , 1'-CH_3), 3.48 (s, 3H, N-CH_3), 4.99 (q, J = 8.0 Hz, 1H, 3'-H), 6.80 (d, J = 10.0 Hz, 1H, 5-H), 7.70 (dd, J_{XA} = 9.0 Hz, J_{XB} = 10.0 Hz, 1H, 8-H), 8.44 (d, J_{AX} = 9.0 Hz, 1H, 7-H), 8.58 (d, J = 10.0 Hz, 1H, 4-H), 8.59 (d, J_{BX} = 10.0 Hz, 1H, 9-H); ^{13}C NMR ($CDCl_3$): δ = 17.8 (q, 4'-CH_3), 25.2 (q, 1'-CH_3), 27.3 (q, N-CH_3), 80.2 (d, C-3), 106.8 (d, C-5), 116.3 (s, C-6a), 122.7 (s, C-3b), 123.8 (s, C-9a), 126.7 (d, C-8), 128.8 (d, C-7), 129.7 (s, C-3a),

132.2 (d, C-4), 133.5 (d, C-9), 158.6 (s, C-6), 164.1 (s, C-3), 164.8 (s, C-1), 208.0 (s, C-2'); UV (ethanol): λ_{max} (lg ε) = 203 nm (4.356), 217 (4.386), 240 (4.667), 361 (4.341); Found: C, 68.55; H, 5.14; N, 4.67. $C_{17}H_{15}O_4N$ requires C, 68.88; H, 5.09; N, 4.71.

2,3,6-Trimethylfuro[2,3-b][1]naphtho[4a,7a-e,f]pyrida-5,7-dione (**4**).
Method A: 0.800 g (2.70 mmol) of **3** was added to 20 ml of $POCl_3$ and the mixture was refluxed for 12 h. After cooling and addition of 200 ml of ice/water, the reaction mixture was extracted with ether (3 x 100 ml), washed with water (2 x 10 ml), and dried over $MgSO_4$. The solvent was removed and column chromatography of the residue on silica gel with a 1:2 mixture of ethyl acetate/petroleum ether (30 - 70 °C) as eluant gave 0.160 g (21 %) of **4** as yellow needles, m.p. 215-216 °C (ethyl acetate).
Method B: 200 mg (0.670 mmol) of **3** and 10 ml of concentrated H_2SO_4 (98 %) were stirred for 10 h at room temperature. The work-up procedure was the same as for Method A and 100 mg (53 %) of **4** was obtained.
IR (KBr): ν = 2900 cm^{-1}, 1695 (C=O), 1660, 1460, 1390, 1350, 1285, 1090, 780; ^1H NMR ($CDCl_3$): δ = 2.22 (d, J = 0.8 Hz, 3H, 3-CH_3), 2.46 (d, J = 0.8 Hz, 3H, 2-CH_3), 3.49 (s, 3H, N-CH_3), 7.68 (dd, J_{XA} = 6.0 Hz, J_{XB} = 5.0 Hz, 1H, 9-H), 8.42 (dd, J_{AX} = 6.0 Hz, J_{AB} = 1.1 Hz, 1H, 10-H), 8.45 (dd, J_{BX} = 5.0 Hz, J_{BA} = 1.1 Hz, 1H, 8-H), 8.57 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$): δ = 8.4 (q, 3-CH_3) 12.4 (q, 2-CH_3), 27.5 (q, N-CH_3), 112.3 (s, C-3), 117.5 (s, C-3a), 119.0 (s, 10a), 123.2 (s, C-4b), 125.2 (d, C-9), 125.8 (s, C-7a), 126.4 (d, C-10), 127.0 (d, C-8), 127.1(s, C-4a), 129.5 (s, C-4), 152.5 (s, C-2 or C10b), 152.7 (s, C-10b or C-2), 165.0 (s, C-7), 165.1 (s, C-5); UV (ethanol): λ_{max} (lg ε) = 235 nm (4.657), 275 (4.635), 347 (4.338), 390 (4.208); Fluorescence (EtOH): λ^{fl} = 472 nm, ϕ^{fl} = 0.10 ± 0.01; Found: C, 73.47; H, 4.82; N, 4.61. $C_{17}H_{13}O_3N$ requires C, 73.11; H, 4.69; N, 5.02.

2-Methyl-6-acetoxy-5-acetyl-naphto[3a,9a-c,d]pyrida-1,3-dione (**6**).
A solution of 0.300 g (1.10 mmol) of **4** in 50 ml of CH_2Cl_2, which contained 5 mg of tetraphenylporphine (TPP) as sensitizer, was irradiated externally with a 150-W sodium lamp (Philips G/98/2 SON 150w) at -10 °C for 0.5 h, while a gentle stream of dry oxygen gas was continuously passed through the reaction mixture. After the removal of the solvent, the residue was chromatographed on silica gel by using a 1:1 mixture of ether/petroleum ether (30 - 50 °C) and 0.280 g (84 %) of **6** was obtained as yellow needles, m. p. 162-163 °C (ether). IR (KBr): ν = 2950 cm^{-1}, 1770 (OC=O), 1750 (C=O), 1700 (N-C=O), 1655, 1590, 1410, 1360, 1330, 1210, 1180, 1140; ^1H NMR ($CDCl_3$): δ = 2.48 [s, 3H, -OC(O)CH_3], 2.68 [s, 3H, -C(O)CH_3)], 3.49 (s, 3H,

N-CH_3), 7.65 (dd, J_{XA}= 8.5 Hz, J_{XB}=7.3 Hz, 1H, 8-H), 8.30 (dd, J_{AX}= 8.5 Hz, J_{AB}= 1.1 Hz, 1H, 7-H), 8.61 (dd, J_{BX}=7.3 Hz, J_{BA}=1.1 Hz, 1H, 9-H), 8.87 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$): δ = 21.5 [q, -OC(O)CH_3], 21.6 (q, N-CH_3), 29.9 [q, -C(O)CH_3], 120.6 (s, C-6a), 122.3 (s, C-3b), 122.5 (s, C-9a), 128.6 (d, C-8), 129.4 (s, C-3a) 129.8 (d, C-7), 131.5 (d, C-9), 133.8 (d, C-4), 150.3 (s, C-5), 150.5 (s, C-6), 163.5 (s, C-1) 164.1 (s, C-3), 169.2 (s, -OC=O), 197.2 (s, C=O); UV (ethanol): λ_{max} (lg ε) = 242 nm (4.640), 254 (4.625), 339 (3.951), 421 (3.640); Fluorescence (EtOH): λ^{fl}= 520 nm, ϕ^{fl}= 0.17 ± 0.012; Found: C, 65.57; H, 4.45; N, 4.54. $C_{17}H_{13}O_5$ requires C, 65.59; H, 4.21; N, 4.50.

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