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Synthesis of Furonaphthalimides as Novel DNA Intercalators

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ABSTRACT

Two new furonaphthalimides have been synthesized, and their absorption and fluorescence spectra recorded. The possibilities of these furonaphthalimides being utilized as novel intercalating DNA cleavers is discussed.

1 INTRODUCTION

1,8-Naphthalimide derivatives exhibit strong fluorescence,[1–4] and for this reason they have versatile applications in many fields, e.g. for hypoxic cells in solid tumours,[5,6] as solar energy collectors, as electro-optically sensitive materials,[7,8] for laser activity,[9,10] and as fluorescent brightening agents for polymeric materials.[11] More recently, 1,8-naphthalimide derivatives have been studied as DNA intercalators,[12–14] photo-induced DNA cleavers[15–17] and chemiluminescent probes for singlet oxygen.[18] We report here the synthesis of two new furonaphthalimides with more efficient DNA-binding activities compared with previously reported *N*-methyl analogues.[13,14]

2 RESULTS AND DISCUSSION

The synthetic methodology for the preparation of the furonaphthalimides is shown in Scheme 1. The starting material, 4-hydroxy-1,8-naphthalic anhydride **1**, was prepared from acenaphthene in three steps. Compound **2** was obtained in 57% yield through the condensation of compound **1** with 3-chloro-

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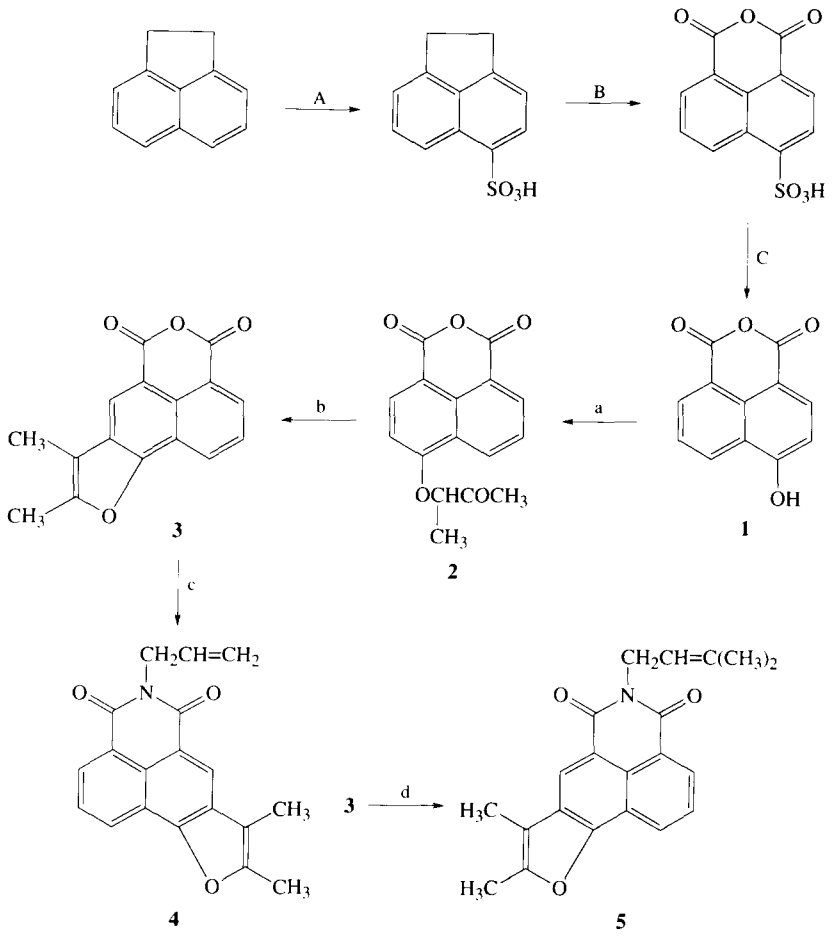


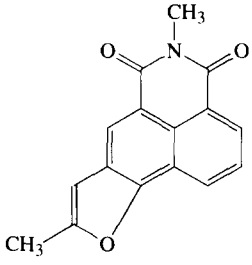
A: $ClSO_3H$, CH_2Cl_2, 0–5 °C
B: (i) $K_2Cr_2O_7$, CH_3CO_2H, 90–120 °C, 5 h; (ii) aq. HCl
C: KOH, 200–300 °C, 45 min; (ii) aq. HCl
a: $CH_3CHClCOCH_3$, $CH_3COCH_2CH_3$, K_2CO_3, ref. 3d
b: PPA, 120 °C, 4.5 h
c: CH_3OH, $CH_2{=}CHCH_2NH_2$, ref. 6h
d: CH_3CH_2OH, $Me_2C{=}CHCH_2NH_2$, ref. 4h

Scheme 1

2-butanone; the IR spectrum confirmed the absence of an OH group and the ^1H NMR spectrum showed peaks at δ =1·71 (d,J=7·1 Hz), 2·32 (s) and 5·32 (q,J=7·1 Hz) corresponding to the 2'-oxobuta-3'-yl group. The cyclization of compound **2** in the presence of polyphosphoric acid (PPA) gave the intermediate compound **3** in 44% yield. The furonaphthalimides **4** and **5** were readily obtained in high yield by the condensation of compound **3** with the appropriate amine, and their structures were fully characterized. Compounds **4** and **5** showed a hypsochromic shift in their UV-absorption

TABLE 1
UV and Fluorescence Spectra Data of Furonaphthalimides

Compound number	*UV* λ_{max} *(log* ϵ*)*	*FL* $\lambda_{max}(\phi)$	*Ref.*
4	343(3·86)	484·6(0·105)	
5	345(4·01)	482·5(0·099)	
6	371·8(3·74)	446·2(0·11)	14
7	390·0(4·21)	471·8(0·10)	18



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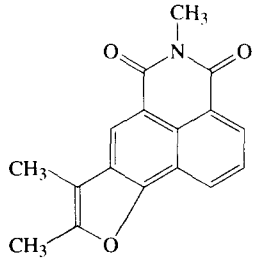

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maxima, and a bathochromic shift in their fluorescence maxima, relative to compounds **6** and **7** (as shown in Table 1).

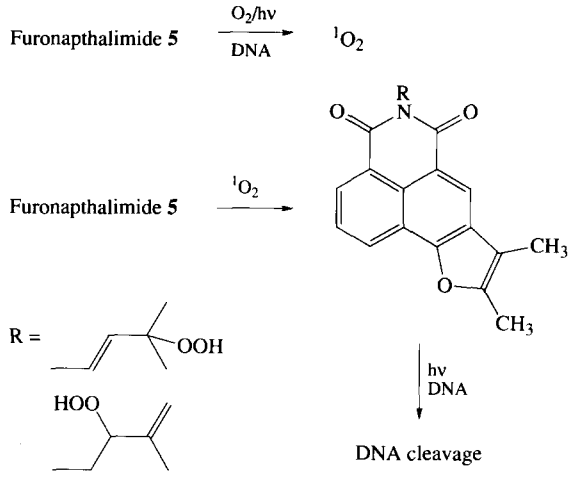
The evaluation of the DNA-intercalating activities of the furonaphthalimides **4** and **6** by a fluorescence quenching technique[19] shows that compound **4** intercalates with DNA more efficiently than compound **6**, which indicates that allylic substituents play an important role in DNA intercalations. Further biological studies of compounds **4** and **5** are being carried out.

Compared with compounds **6** and **7**, the furonaphthalimides **4** and **5** have two advantages; namely (1) allylic substituents on the N-atom can promote the DNA-intercalating efficiency; (2) since the [2+2] photoaddition of the furan site of some photosensitizers (for instance, furocoumarins) and DNA-ajacent pyrimidine bases generates $^1O_2$,[20] it is plausible that furonanphthalimide hydroperoxides are produced *in situ* when compound **5** is treated with DNA under irradiation conditions (Scheme 2).[21] Thus, a novel intercalating DNA cleaver might be obtained.[22]

3 EXPERIMENTAL

3.1 General

Melting points were taken on a digital melting point apparatus made in Shanghai. Infrared spectra were recorded on a IR-7650 made in Shanghai, mass spectra on a Hitachi M 80, ^{1}H NMR on a Brucker Wp-100sy (100 MHz)



Scheme 2

or on a Brucker AM-300 (300 MHz) using $CDCl_3$ or TMS as internal standard. Combustion analysis for elemental composition was carried out on an Italy MOD.1106 analyser. Absorption spectra were measured in absolute ethanol on a Shimadzu UV-265 and fluorescence spectra on a Perkin Elmer LS 50 using quinine sulphate in sulphuric acid as quantum yield standard.

3.2 Synthesis of 4-[(2'-oxobutan-3'-yl)oxy]-1,8-naphthalic anhydride(2)

A mixture of 4-hydroxy-1,8-naphthalic anhydride **1** (2 g), 3-chloro-2-butanone (2ml), K_2CO_3 (2 g), and butanone (60 ml) was refluxed for 3 days; after removal of solvent, 10% hydrochloric acid was added and the resulting precipitate was filtered, washed with water and a little butanone, and dried to give compound **2** in 57% yield. An analytical sample was obtained by column chromatography using a mixture of petroleum ether and ethyl acetate as eluent. M.p. 180–181°C. IR(KBr): 1770, 1730(br), 1595, 1580, 1405, 1265, 1020, 770, 755, 675 cm^{-1}. ^1H NMR (CD_3COCD_3): δ = 1·71, 3H, d, J = 7·1 Hz, 4'-CH_3, 2·32, 3H, s, 1'-CH_3, 5·32, 1H, J = 7·1 Hz, 3'-CH, 7·11, 1H, 5-H, d, J = 7·8 Hz, 7.84, 1H, 8-H, dd, J_{XA} = 7·2 Hz, J_{XB} = 8·6 Hz, 8·49, 1H, 7-H, d, J_{AX} = 7·2 Hz, 8·57, 1H, 4-H, d, J=7·8, Hz, 8·77, 1H, 9-H, d, J_{BX} = 8·6 Hz.

MS(El 70eV): m/e(%) 284(40·8)[M^+], 215(51·5), 197(84·5)[M^+-$OCH(CH_3)COCH_3$], 170(100). $C_{16}H_{12}O_5$: Calcd,C,67·60, H,4·25. Found,C,67·86, H,4·38.

3.3 Synthesis of 2,3-dimethylfuro[2,3-b][1]naphtho[4a,7a-e,f]pyran-5,7-dione(3)

A mixture of compound **2** (1.2 g) and polyphosphoric acid (30 ml) was stirred for 4·5 h at 120°C; the reaction mixture was poured into ice water

and the resulting precipitate was filtered and washed with water. The filter cake was dissolved in acetone and chromatographed using a mixture of petroleum ether and ethyl acetate as eluent to give **3** as yellow needles in 44% yield, m.p. 214–216°C.
IR(KBr): 2920, 2860, 1770, 1730, 1580, 1465, 1300, 1030, 1015, 760 cm^{-1}. ^1H NMR(CF_3COOD): δ =1·84, 3H, s, 3-CH_3, 2·08, 3H, s, 2-CH_3, 7·42, 1H, 9-H, dd, J_{XA} = 9·5 Hz, 8·18, 1H, 10-H, d, J_{AX} = 9·5 Hz, 8·32, 1H, 8-H, d, J_{BX} = 7·9 Hz, 8·37, 1H, 4-H, s. MS(EI 70eV): m/e(%) 267(17·9)[M^+ + 1], 265(100)[M^+-1], 222(95·9)M^+-CO]. $C_{16}H_{10}O_4$: Calcd, C,72·18, H, 3·78. Found, C,72·03, H,3·70.

3.4 Synthesis of 6-allyl-2,3-dimethylfuro[2,3-b][1]naphtho[4a,7a-e,f] pyrida-5,7-dione(4)

A mixture of compound **3** (0·5 g), allylamine (1 ml), and methanol (50 ml) was refluxed for 6 h. After removal of solvent and recrystallization from ethanol, yellow needles of **4** were obtained in 87% yield.; m.p. 172–174°C.

IR(KBr): 2915, 2845, 1690, 1660, 1635, 1620, 1585, 1570, 1455, 1370, 1265, 1220, 1170, 780, 690 cm^{-1}. ^1H NMR(CD_3COCD_3): δ=2·33, 3H, s, 3-CH_3, 2·57, 3H, s, 2-CH_3, 4·76, 2H, d, J = 4·8 Hz, N-CH_2, 5·24, 2H, m = CH_2, 5·86–6·24, 1H, m, 2'-CH=, 7·90, 1H, 9-H, dd, J_{XA} = 8·6 Hz, J_{XB} =7·1 Hz, 8·48, 1H, 10-H, d, J_{AX} =8·6 Hz, 8·53, 1H, 8-H, d, J_{BX} =7·1 Hz, 8·56, 1H, 4-H, s.

UV (ethanol): λ_{max} (log ϵ)=207 nm (4·23), 233(4·39), 272(4·40), 343 (3·86); Fluorescence (ethanol): λ^{fl}=484·6 nm, ϕ^{fl}=0·105. MS(El 70eV): m/e(%) 306(12·7)[M^+ + 1], 305(55·0)[M^+], 290(100)[M^+-CH_3]. $C_{19}H_{15}NO_3$: Calcd, C,74·74, H,4·95, N,4·59. Found, C,74·78, H,4·95, N,4·61.

3.5 Synthesis of 2,3-dimethyl-6-(3',3'-dimethylallyl)furo[2,3-b][1]naphtho[4a, 7a-e,f] pyrida-5,7-dione(5)

A mixture of compound **3** (60 mg) and 3,3-dimethylallylamine (0·113 g) in 10 ml of ethanol was refluxed for 4 h. After cooling, filtering and drying, the yellow coloured **5** was obtained in 80% yield; m.p. 177·5–177·8°C (ethanol).

IR(KBr): 2960, 2910, 2850, 1690, 1650, 1640, 1620, 1590, 1570, 1455, 1365, 1350, 1320, 1260, 1225, 1160, 850, 800, 790 cm^{-1}.

^1H NMR (CD_3COCD_3): δ = 1·71, 3H, s, 3'-CH_3, 1·90, 3H, s, 3'-CH_3, 2·37, 3H, s, 3-CH_3, 2·58, 3H, s, 2-CH_3, 4·76, 2H, d, J = 7·0 Hz, N-CH_2, 5·35, 1H, t, J = 7·0 Hz, 2'-CH=, 7·94, 1H, 9-H, dd, J_{XA} = 8·1 Hz, J_{XB} = 7·5 Hz, 8.53, 1H, 10-H, t, J_{XB} = 7·5 Hz, J_{BA} = 1·0 Hz, 8·62, 1H, 8-H, t, J_{XA} = 8·10 Hz, J_{AB} = 1·0 Hz, 8·70 1H, 4-H, s. UV (ethanol): λ_{max} (log ϵ) = 207 nm (4·31),

240 (4·48), 273 (4·51), 345 (4·01); Fluorescence (ethanol):λ^{fl} = 482·5 nm; ϕ^{fl} = 0·099. MS(El 70eV): m/e(%) 334(11·5)[M^+ + 1], 333(44·8)[M^+], 265(100), 290(50·5) $C_{21}H_{19}NO_3$: Calcd C,75·66, H,5·74, N,4·20. Found, C,75·37, H,5·79, N,4·01.

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