Monatshefte für Chemie 130, 1109–1116 (1999)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Synthesis of Novel *DNA*-Intercalating Naphthopyrone Derivatives with Improved Water Solubility and Photophysical Properties

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Summary. The efficient synthesis of several novel *DNA*-intercalating furonaphthopyrone derivatives with improved water solubility or photophysical properties are described. As expected, all new compounds can efficiently intercalate into *DNA* with higher or comparable binding affinity relative to the parent naphthopyranone. The highest binding affinity is found for the aminomethyl derivative and may result from its good water solubility and the electrostatic interaction between the amino group and the *DNA* phosphate backbone. The described synthetic methodology could be utilized in the preparations of other analogs with different skeletons.

Keywords. *DNA* intercalator; Furonaphthopyrone; Photosensitizer; Photophysical property; X-Ray crystal structure.

Zur Synthese neuer *DNA*-interkalierender Naphthopyronderivate mit verbesserter Wasserlöslichkeit und verbesserten photophysikalischen Eigenschaften

Zusammenfassung. Die effiziente Synthese einiger neuer *DNA*-interkalierender Furonaphthopyrone mit verbesserter Wasserlöslichkeit und verbesserten photophysikalischen Eigenschaften wird beschrieben. Wie erwartet, interkalieren alle neuen Verbindungen effizient mit *DNA*, wobei die Bindungaffinitäten gleich oder höher als jene der Stammverbindung sind. Die höchste Bindungsaffinität wurde für das Aminomethylderivat beobachtet; sie könnte von der verbesserten Wasserlöslichkeit und der elektrostatischen Wechselwirkung zwischen Aminogruppe und *DNA*-Phosphatrückgrat herrühren. Die beschriebene Synthesemethodik kann auch für die Darstellung anderer Analoga mit unterschiedlichen Skeletten genützt werden.

Introduction

Since *Lerman* proposed the intercalation concept in 1961 [1], *DNA* intercalating agents have been extensively studied [2]. They usually have coplanar extended aromatic chromophores and intercalate into *DNA* primarily by stacking and electrostatic interactions. While some *DNA* intercalators have been used in human medicine [3] and as biophysical and biochemical tools [4, 5], there is much current

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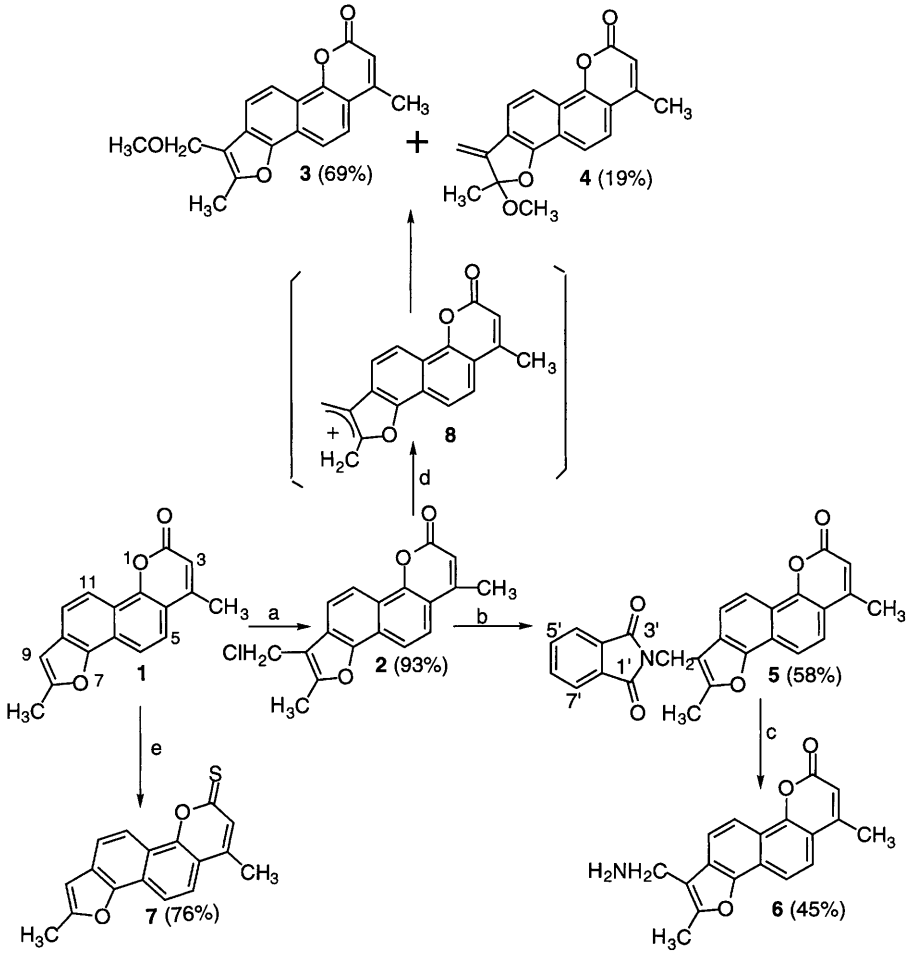
interest focusing on the development of *DNA* intercalating agents with novel structures and functions [6–10]. Furocoumarins are a typical class of *DNA* intercalators which have been widely used in the photochemotherapy of skin diseases [11] and as photochemical reagents for investigating nucleic acid structure and function [12]. We recently developed furonaphthopyrones as novel *DNA* intercalators which were expected to have photophysical and photobiological properties superior to furocoumarins [13–15]. Recent investigations on the photoreactivity of furonaphthopyrone towards *DNA* showed that this drug was capable of generating *DNA* strand breaks and/or alkali labile sites within the *DNA* without introduction of mutagenicity into cells [16]. These results suggest that furonaphthopyrones may be utilized as photodynamic sensitizers, photophores for the study of one-electron oxidation of *DNA*, and that a considerable variety of photoreactions are available for furonaphthopyrones in cells [17]. However, this drug suffers from low water solubility, absorption in the long wavelength region, and other shortcomings. Therefore, structural optimization seems highly desirable.



Scheme 1. a: chloromethyl ether, dry CH_3COOH; b: potassium phthalimide, *DMF*, 100–110°C; c: 85% aq. hydrazine, 95% ethanol; d: CH_3OH, reflux, 8 h; e: *Lawesson*'s reagent, toluene, reflux, 2 h

In this paper, we describe the synthesis of several naphthopyrone derivatives based on the following strategies: (1) introduction of an amino group to improve water solubility and to enhance electrostatic interaction with *DNA*; (2) introduction of a thiocarbonyl moiety to improve the photophysical properties; (3) the chloromethyl group in **2** and the amino group in **6** can be easily attached to other reactive *DNA* binding functionalities.

Results and Discussion

The synthetic methodology is displayed in Scheme 1. The starting material **1** was prepared according to a previously reported procedure [14]. Chloromethylation of **1** at position 9 was achieved in the presence of chloromethyl ether and afforded **2** in 93% yield. A solution of **2** in methanol was refluxed to give the regioisomers **3** and **4** in 69% and 19% yield. These two isomers probably result from the same intermediate allylic cation **8** which is stabilized by the aromatic moiety. The structure of **4** was fully characterized by spectroscopic and X-ray diffraction methods. The single crystal structure of **4** is shown in Fig. 1. Final atomic coordinates, bond lenghts, and valence angles are summarized in Tables 1, 2, and 3.

Condensation of **2** with potassium phthalimide gave **5** which reacted with hydrazine to afford the target water soluble amine **6** in 45% yield. The thiocarbonyl furonaphthopyrone analog **7** was directly obtained in 76% yield *via* reaction of **1** with *Lawesson*'s reagent [18]. The efficient synthesis of these new naphthopyrone derivatives also provided general methods for the preparation of other analogs with different skeletons [15].

The UV/Vis and fluorescence spectroscopic data of the new compunds are shown in Table 4. As expected, the thiocarbonyl analog **7** exhibits a large red shift (*ca*. 60 nm) in its absorption spectrum as compared with the naphthopyrones.

The interactions of these new compounds with calf thymus *DNA* in the dark were studied by a fluorescence quenching technique according to Ref. [19]. The intrinsic fluorescence of the drugs was quenched to a considerable extent due to their noncovalent binding to *DNA* molecules. These changes in emission intensity

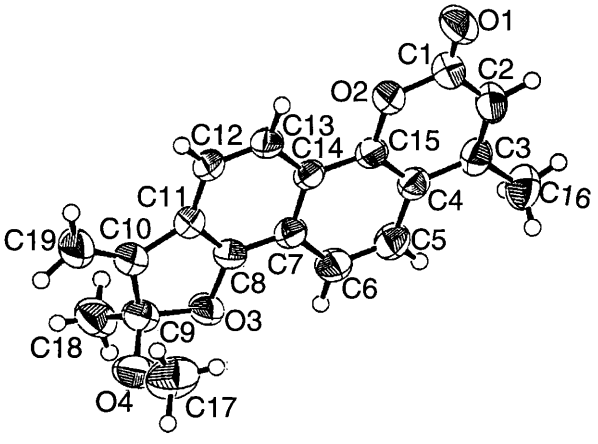


Fig. 1. X-Ray single crystal structure of compound **4**

Table 1. Atomic coordinates and B_{iso}/B_{eq} for compound **4**

O1	0.1531	1.0758	0.3407	0.0857
O2	0.3099(2)	0.9579(2)	0.3448(3)	0.0570
O3	0.7217	0.6119	0.3326	0.0678
O4	0.8289(3)	0.4780(2)	0.0855(5)	0.0865
C1	0.2009(3)	1.0018(3)	0.4200(6)	0.0644
C2	0.1576(3)	0.9532(4)	0.5782(6)	0.0663
C3	0.2160(3)	0.8666(3)	0.6493(5)	0.0574
C4	0.3276(3)	0.8207(3)	0.5635(5)	0.0518
C5	0.3963(3)	0.7269(3)	0.6215(6)	0.0614
C6	0.4993(3)	0.6873(3)	0.5350(5)	0.0601
C7	0.5444(3)	0.7379(3)	0.3823(5)	0.0508
C8	0.6500(3)	0.7018(3)	0.2844(5)	0.0529
C9	0.8261(3)	0.5995(3)	0.2018(6)	0.0672
C10	0.8040(3)	0.6908(3)	0.0735(6)	0.0620
C11	0.6922(3)	0.7512(3)	0.1369(5)	0.0524
C12	0.6270(3)	0.8445(3)	0.0763.(4)	0.0534
C13	0.5236(3)	0.8827(3)	0.1655(5)	0.0523
C14	0.4797(3)	0.8324(3)	0.3187(5)	0.0472
C15	0.3714(3)	0.8698(3)	0.4142(5)	0.0492
C16	0.1671(5)	0.8202(6)	0.8184(8)	0.0809
C17	0.7278(5)	0.4344(5)	−0.0728(9)	0.1008
C18	0.9416(5)	0.6284(5)	0.3537(9)	0.0806
C19	0.8780(4)	0.7071(4)	−0.0638(8)	0.0869

Table 2. Bond lengths (Å) for compound **4**

Atom	Atom	Distance	Atom	Atom	Distance
O(1)	C(1)	1.215(4)	C(5)	C(6)	1.343(5)
O(2)	C(1)	1.386(4)	C(6)	C(7)	1.420(4)
O(2)	C(15)	1.377(3)	C(7)	C(8)	1.393(4)
O(3)	C(8)	1.389(3)	C(7)	C(14)	1.435(4)
O(3)	C(9)	1.487(4)	C(8)	C(11)	1.369(4)
O(4)	C(9)	1.363(4)	C(9)	C(10)	1.526(5)
O(4)	C(17)	1.446(6)	C(9)	C(18)	1.532(6)
C(1)	C(2)	1.431(5)	C(10)	C(11)	1.455(4)
C(2)	C(3)	1.353(5)	C(10)	C(19)	1.324(5)
C(3)	C(4)	1.443(4)	C(11)	C(12)	1.418(4)
C(3)	C(16)	1.505(5)	C(12)	C(13)	1.351(4)
C(4)	C(5)	1.434(5)	C(13)	C(14)	1.416(4)
C(4)	C(15)	1.385(4)	C(14)	C(15)	1.415(4)

may be attributed to environmental changes when intercalating into the base pair of *DNA*. The *Scatchard* apparent association constants (*Ka*) are shown in Table 4. All new derivatives have comparable or higher binding affinities to *DNA* relative to the parent compund **1**; in particular, **6** shows the highest *Ka* value, probably due to

Table 3. Bond angles (°) for compound **4**

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(1)	O(2)	C(15)	121.9(3)	O(3)	C(9)	O(4)	108.0(3)
C(8)	O(3)	C(9)	106.4(2)	O(3)	C(9)	C(10)	105.0(2)
C(9)	O(4)	C(17)	114.8(3)	O(3)	C(9)	C(18)	106.9(3)
O(1)	C(1)	O(2)	115.7(3)	O(4)	C(9)	C(10)	114.9(3)
O(1)	C(1)	C(2)	128.0(3)	O(4)	C(9)	C(18)	106.8(3)
O(2)	C(1)	C(2)	116.3(3)	C(10)	C(9)	C(18)	114.7(3)
C(1)	C(2)	C(3)	123.1(3)	C(9)	C(10)	C(11)	106.4(3)
C(2)	C(3)	C(4)	119.0(3)	C(9)	C(10)	C(19)	123.4(3)
C(2)	C(3)	C(16)	120.8(4)	C(11)	C(10)	C(19)	130.1(3)
C(4)	C(3)	C(16)	120.2(4)	C(8)	C(11)	C(10)	107.5(3)
C(3)	C(4)	C(5)	124.4(3)	C(8)	C(11)	C(12)	119.7(3)
C(3)	C(4)	C(15)	118.1(3)	C(10)	C(11)	C(12)	132.8(3)
C(5)	C(4)	C(15)	117.5(3)	C(11)	C(12)	C(13)	119.0(3)
C(4)	C(5)	C(6)	121.7(3)	C(12)	C(13)	C(14)	121.5(3)
C(5)	C(6)	C(7)	120.7(3)	C(7)	C(14)	C(13)	120.4(3)
C(6)	C(7)	C(8)	124.4(3)	C(7)	C(14)	C(15)	116.7(3)
C(6)	C(7)	C(14)	120.0(3)	C(13)	C(14)	C(15)	122.9(3)
C(8)	C(7)	C(14)	115.6(3)	O(2)	C(15)	C(4)	121.6(3)
O(3)	C(8)	C(7)	121.5(2)	O(2)	C(15)	C(14)	115.1(3)
O(3)	C(8)	C(11)	114.7(3)	C(4)	C(15)	C(14)	123.3(3)
C(7)	C(8)	C(11)	123.8(3)				

Table 4. Photophysical properties and CT *DNA*-binding apparent association constant (*Ka*)

	UV (λ_{max} (nm)) (logε))	FL (λ_{max} (nm))	*Stoke*'s Shift	$Ka\times10^{-6}$ M^{-1}
1	375 (3.853)	424	49	0.48
3	375 (3.893)	424	49	1.18
4	403 (3.799)	453	50	1.28
6	375 (3.967)	424	49	1.39
7	430 (3.757)	469	39	1.37

electrostatic interactions between its amino group and the phosphate backbone of the *DNA*.

Experimental

Melting points were measured on a digital melting point apparatus WRS-1 made in Shanghai and are uncorrected. Infrared spectra were recorded on a Nicolet FT IR-20sx or a Spectrometor 7650 made in Shanghai, mass spectra on a Hitachi M 80 or HP5989A, ^{1}H NMR Spectra on Bruker AM 300 or DRX 400 Spectrometers (*TMS* as internal standard). Combustion analyses were carried out on an Italy MOD.1106 analyzer at the Analysis Center of the East China University of Science and Technology (C$\pm$0.34, H $\pm$0.09, N$\pm$0.03%); the results agreed favourably with the calculated values.

Absorption spectra were measured in absolute ethanol on a Shimadzu UV-265 Spectrometer, fluorescence spectra on a Perkin Elmer LS 50 instrument. Commercial reagents and solvents were purchased from standard chemical suppliers and used without further purification.

2H-4,8-Dimethyl-9-chloromethylfuro[2′3′:5,6]naphtho[1,2-b]pyran-2-one (**2**; $C_{18}H_{13}ClO_3$)

To a solution of 0.500 g (1.89 mmol) of **1** in 50 cm^3 dry acetic acid, 2.0 cm^3 (26.35 mmol) chloromethyl ether were added. The reaction mixture was stirred for 5 h and kept at 0°C for 5 min. The precipitate was collected by filtration, washed with a small amount of dry acetic acid, and dried to afford 0.550 g of **2** as white needles (93%).

M.p.: > 290°C; IR (KBr): $\nu = 2930, 1730, 1718, 1645, 1605, 1590, 1475, 1392, 1370, 1180, 980, 870, 818, 720, 700\ cm^{-1}$; ^{1}H NMR ($CD_3COCD_3$, δ, 300 MHz): 2.56 (d, $J = 1.1$ Hz, 3H, 4-CH_3), 2.56 (s, 3H, 8-CH_3, 5.10 (s, 2H, 9-CH_2-), 6.51 (d, $J = 1.1$ Hz, 1H, 3-H), 7.94 (d, $J = 8.8$ Hz, 1H, 11-H), 7.98 (d, $J = 8.8$ Hz, 1H, 10-H), 8.12 (d, $J = 8.7$ Hz, 1H, 6-H), 8.28 (d, $J = 8.7$ Hz, 1H, 5-H) ppm; MS (EI, 70 eV): *m/z* (%) = 314 (32.7) [M+2], 312 (94.1) [M], 277 (100) [M-C1].

2H-4,8-Dimethyl-9-methoxymethylfuro[2′,3′:5,6]naphtho[1,2-b]pyran-2-one (**3**; $C_{19}H_{16}O_4$) and *2H-4,8-Dimethyl-8-methoxy-9-methylenefuro[2′,3′:5,6]naphtho[1,2-b]pyran-2-one* (**4**; $C_{19}H_{16}O_4$)

A solution of 0.200 g (0.64 mmol) of **2** in 30 cm^{-3} of methanol was refluxed for 8 h. After removal of the solvent, the residue was subjected to flash chromatography using a mixture of petroleum ether and dichloromethane as eluent to give 0.136 g of yellow needles of **3** (69%) and 0.037 g of yellow crystals of **4** (19%).

3. M.p.: 213.4–214.4°C; IR (KBr): $\nu = 2917, 2850, 1737, 1716, 1643, 1607, 1568, 1473, 1447, 1435, 1385, 1373, 1231, 1180, 1091, 1073, 1028, 948, 845, 810, 728\ cm^{-1}$; ^{1}H NMR ($CD_3COCD_3$, δ, 400 MHz): 2.55 (d, $J = 1.1$Hz, 3H, 4-CH_3), 2.61 (s, 3H, 8-CH_3), 3.44 (s, 3H, 9-OCH_3), 4.65 (s, 2H, 9-CH_2-), 6.36 (d, $J = 1.1$Hz, 1H, 3-H), 7.70 (d, $J = 8.8$Hz, 1H, 11-H), 7.82 (d, $J = 8.8$ Hz, 1H, 10-H), 8.12 (d, $J = 8.7$ Hz, 1H, 6-H), 8.41 (d, $J = 8.7$ Hz, 1H, 5-H) ppm; MS (EI, 70 eV): *m/z* (%) = 308 (21.9) [M], 307 (100) [M-1], 277 (91.2), 276 (60.5), 248 (32.1).

4. M.p.: 234.0–235.0°C; IR (KBr): $\nu = 3093, 2989, 2937, 2825, 1726, 1571, 1471, 1419, 1384, 1348, 1311, 1229, 1186, 1175, 1085, 1051, 1032, 996, 950, 939, 913, 844, 825, 816, 744, 582\ cm^{-1}$; ^{1}H NMR ($CD_3COCD_3$, δ, 400 MHz):1.74 (s, 3H, 8-CH_3, 2.54 (d, $J = 1.2$ Hz, 3H, 4-CH_3), 3.20 (s, 3H, 8-OCH_3), 5.29 (d, $J = 0.5$ Hz, 1H, 9- = CH), 5.78 (d, $J = 0.5$ Hz, 1H, 9-=CH), 6.40 (d, $J = 1.2$ Hz, 1H, 3-H), 7.62 (d, $J = 8.8$ Hz, 1H, 5-H), 7.64 (d = 8.7 Hz, 1H, 10-H), 7.96 (dd, $J = 8.8$ and 0.8 Hz, 1H, 6-H), 8.16 (dd, $J = 8.7$ and 0.8 Hz, 1H, 11-H) ppm; MS (EI, 70 eV): *m/z* (%) = 309 (16.4) [M+1], 308 (76.8) [M], 277 (16.5), 251 (100).

9-(Phthalimidylmethyl)-4,8-dimethylfuro[2′,3′:5,6]naphtho[1,2-b]pyran-2-one (**5**; $C_{26}H_{17}NO_5$)

A mixture of 0.300 g (0.96 mmol) of **2** and 0.200 g (1.08 mmol) of potasssium phthalimide in 25 cm^3 of *DMF* was stirred at 100–110°C for 1 h, cooled, filtered and dried. After recrystallization from acetone, 0.350 g of **5** were obtained as white needles (86%).

M.p.: > 290°C; ^{1}H NMR (CD_3COCD_3, δ, 400 MHz): 2.67 (s, 3H, 4-CH_3), 2.74 (s, 3H, 4-CH_3), 2.74 (s, 3H, 8-CH_3), 4.94 (s, 2H, 9-CH_2-), 6.49 (s, 1H, 3-H), 7.84 (d, 2H, 4′-H, 7′-H), 7.90 (t, 2H, 5′-H, 6′-H), 7.93 (d, 1H, 5-H), 7.99 (d, 1H, 10-H), 8.10 (d, 1H, 6-H), 8.20 (d, 1H, 11-H) ppm; MS (EI, 70 eV): *m/z* (%) = 424 (29.2) [M+1], 423 (100) [M], 277 (19.7), 276 (75.7), 263 (47.0).

2H-4,8-Dimethyl-9-aminomethylfuro[2′,3′:5,6]naphtho[1,2-b]pyran-2-one (**6**; $C_{18}H_{15}NO_3$)

A mixture of 0.300 g (0.71 mmol) of **5** and 0.5 cm^3 of 85% aqueous hydrazine in 50 cm^3 of 95% ethanol was refluxed for 1.5 h, cooled, and filtered. The filtrate was evaporated, and the residue was

mixed with 100 cm^3 0.1*N* aq. NaOH. The precipitate was collected by filtration and washed with water to give the crude product. After recrystallization from a mixture of petroleum ether and dichloromethane, 94 mg (45.2%) **6** were obtained as yellow needles.

M.p.: 204.1–204.8°C; IR (KBr): $\nu = 3382$–3265 (NH_2), 2940, 2922, 2860, 1734, 1720, 1600, 1588, 1565, 1470, 1392, 1260, 1030, 990, 972, 935, 860, 808, 738, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.52 (s, br, 2H, 9-NH_2), 2.54 (s, 3H, 4-CH_3), 2.60 (s, 3H, 8-CH_3), 4.02 (s, 2H, 9-CH_2-), 6.35 (s, 1H, 3-H), 7.67 (d, $J = 8.8$ Hz, 1H, 5-H), 7.82 (d, $J = 8.7$ Hz, 1H, 10-H), 8.10 (d, $J = 8.8$ Hz, 1H, 6-H), 8.38 (d $J = 8.7$ Hz, 1H, 11-H) ppm; MS (EI, 70 eV): *m/z* (%) = 294 (22.8) [M+1], 293 (100) [M], 291 (16.0) 278 (11.3), 277 (62.6), 276 (25.2), 248 (56.3).

2H-4,8-Dimethylfuro [2′, 3′:5,6]naphtho[1,2-b]pyran-2-thione (**7**; $C_{18}H_{15}NO_3$)

To a solution of 0.450 g (1.02 mmol) of *Lawesson*'s reagent in 30 cm^3 of tolune, 0.500 g (1.89 mmol) of **1** were added. The mixture was refluxed for 2 h, and cooled. After evaporation of the solvent and recrystallization from a mixture of petroleum ether and dichloromethane, 0.402 g of **5** were obtained as yellow needles (76%).

M.p.: 288.4−289.2°C; IR (KBr): $\nu = 2920$, 1640, 1605, 1582, 1548, 1470, 1434, 1414, 1378, 1320, 1296, 1170, 1090, 1036, 952, 915, 864, 820, 808, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 2.50 (s, 3H, 4-CH_3), 2.62 (s, 3H, 8-CH_3), 6.60 (s, 1H, 9-H), 7.31 (s, 1H, 3-H), 7.72 (d, $J = 8.9$ Hz, 1H, 5-H), 7.77 (d, $J = 8.7$ Hz, 1H, 1H, 10-H), 8.19 (d, $J = 8.9$ Hz, 1H, 6-H), 8.53 (d, $J = 8.7$ Hz, 1H, 11-H) ppm; MS (EI, 70 eV): *m/z* (%) = 282 (6.2) [M+2], 280 (100) [M], 236 (91.1) [M-CS], 235 (20.5).

X-Ray data collection and structure determination of **4**

A yellow prismatic crystal of **4** with approximate dimensions of $0.20 \times 0.20 \times 0.30$ mm^3, obtained by recrystallization from ethyl acetate, was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo$K\alpha$ radiation and a 12 kW rotating anode generator. Compound **4** crystallizes in the triclinic crystal system with $a = 11.059$, $b = 11.248$, $c = 6.661$ Å, $\alpha = 106.89$, $\beta = 94.69$, $\gamma = 90.99°$ $V = 789.5A^3$, space group P1, formula $C_{19}H_{16}O_4$. The structure was solved by direct methods [20] and expanded using *Fourier* techniques [21]. Non-hydrogen atoms were refined anisotropically, hydrogen atoms isotropically. Neutral atom scattering factors were taken from Ref. [22]. All calculations were performed using the *teXsan* crystallographic software package of Molecular Structure Corporation. The coordinates were deposited at the Cambridge Structural Data Center (No. 125054).

Acknowledgments

We are grateful to the *National Natural Science Foundation* and the *Ministry of Education of China* for financial support.

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Received November 16, 1998. Accepted (revised) March 15, 1999