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Synthesis, Crystal Structure, and Properties of 2*H*-4,8-Dimethylfuro[2′,3′:5,6]naphtho[1,2-*b*]pyran-2-one, a Novel DNA Intercalator

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Summary. The furonaphthopyrone **6**, a novel DNA intercalator, was synthesized in two steps (*ca.* 56% overall yield) starting from naphthopyrone **3**. The new naphthopyrone derivatives **4** and **6** were fully characterized and the absorption and fluorescence spectroscopic properties of **6** were determined. The dark interactions of furonaphthopyrone **1** and **6** with DNA have been investigated by a fluorescence quenching technique and their apparent *Scatchard* binding constants were calculated. The crystal structure of **6** was determined. The planarity of **6** and the geometry of the active double bond between the α-pyrone and the furan moieties of **6** suggest that furonaphthopyrones are efficient monofunctional DNA intercalators.

Keywords. Furonaphthopyrone; DNA intercalator; X-ray crystal structure; Synthesis.

Synthese, Kristallstruktur und Eigenschaften von 2*H*-4,8-Dimethylfuro[2′,3′:5,6]naphtho[1,2-*b*]pyran-2-on, einem neuen DNA-Intercalator

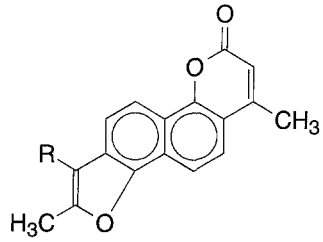
Zusammenfassung. Der neue DNA-Intercalator **6** wurde, ausgehend vom Naphthopyron **3**, in zwei Stufen mit einer Gesamtausbeute von *ca.* 56% hergestellt. Die neuen Naphthopyronderivate **4** und **6** wurden vollständig charakterisiert; die Absorptions- und Fluoreszenzeigenschaften von **6** wurden bestimmt. Die Dunkelwechselwirkungen von **1** und **6** mit DNA wurden mittels einer Fluoreszenzquenchtechnik untersucht; ihre *Scatchard*-Bindungskonstanten wurden berechnet. Die Kristallstruktur von **6** wurde bestimmt. Die Planarität von **6** und die Geometrie der aktiven Doppelbindung zwischen dem α-Pyron- und dem Furanteil von **6** lassen erwarten, daß Furonaphthopyrone effiziente monofunktionelle DNA-Intercalatoren sind.

Introduction

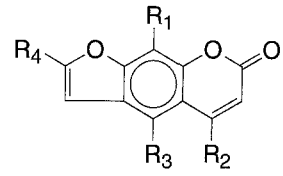
Furocoumarims such as psoralens are active photosensitizers which show interesting features and are widely employed as effective drugs in the photochemotherapy of various skin diseases such as psoriasis and vitiligo [1, 2], in extracorporal photochemotherapy [3, 4], as effective virucidal agents against HIV-1 [5], and as reagents

for the biophysical study of nucleic acids [6, 7]. They are also known to be phototoxic to insects, viruses, fungi, and bacteria [8]. A great attention has been paid to their intercalating with DNA [9] to their ability of undergoing [2 + 2] photocycloadditions to adjacent pyrimidine bases [10], and to their carcinogenic and mutagenic effects [11] which may be due to their interstrand crosslinks with DNA [6, 12], a consequence of their bifunctional nature (photoactive α-pyrone and furan sites).

In an attempt to develop new ways in diminishing undesirable side effects, new furocoumarins capable of producing only monofunctional photobinding with DNA have been prepared and studied [13–18]. Recently, we have suggested a novel strategy for enlarging the space between the photoactive double bonds of the α-pyrone and the furan moieties by an additional benzene ring, and reported the synthesis and photooxygenation of 2*H*-4,8,9-trimethylfuro[2′,3′:5,6]naphtho[1,2-*b*]pyran-2-one **1** [19]. Since compounds like 8-methoxypsoralen (**2b**), 5-methoxypsoralen (**2c**), and trimethylpsoralen (**2d**), which have no substituent or only one methyl group in their furan sites, are successfully employed in photochemotherapy, we here report the synthesis and crystal structure of the new furonaphthopyrone **6** which has a similar structure as the three psoralens mentioned above (Scheme 1). We have also investigated the interactions of **1** and **6** with DNA in the dark by fluorescence quenching techniques.



1: R = CH_3
6: R = H

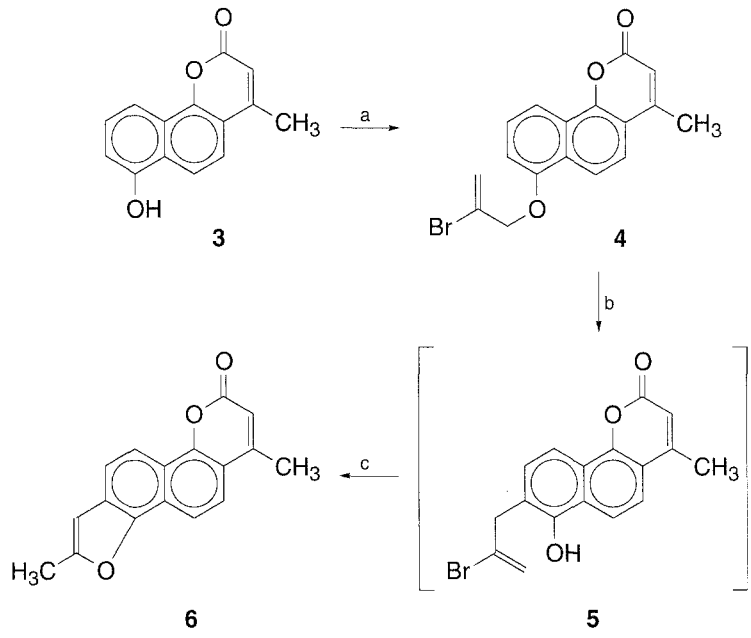


2a: R_1, R_2, R_3, R_4 = H
2b: R_1 =OMe; R_2, R_3, R_4 = H
2c: R_3 =OMe; R_1, R_2, R_4 = H
2d: R_1, R_2, R_4 = CH_3; R_3 = H

Scheme 1

Results and Discussion

The synthesis of furonaphthopyrone **6** is displayed in Scheme 2. 4-Methyl-7-hydroxynaphtho[1,2-*b*]pyran-2-one (**3**) was prepared by a *Pechmann* condensation of the commercially available 1,5-naphthalenediol with ethyl acetoacetate in H_2SO_4 according to the reported procedure [19]. The reaction of **3** with 2,3-dibromopropene in acetone in the presence of K_2CO_3 gave **4** in 80% isolated yield. The absence of the HO group absorption in IR spectrum and the presence of the proton resonances at 5.03 (s), 5.98 (t, $J = 1.10$ Hz), and 6.27 (t, $J = 1.0$ Hz) ppm for 1′-H and 3′-H confirm the presence of the bromoallyl group in **4**. **4** was heated in N,N-diethylaniline at 214 °C to give **6** in 71% isolated yield. According to the result of a related mechanistic study [20], **4** was probably produced by the dehydrobromination of the intermediate **5** formed *via* a rearrangement reaction of **4** as shown in



a: 2,3-dibromopropene, K_2CO_3, CH_3COCH_3, reflux, 15 h
b: N,N-diethylaniline, reflux, 24 h

Scheme 2

Scheme 2. Up to date, our two-step synthesis displayed in Scheme 2 is the most efficient synthesis of furonaphthopyrones from naphthopyrones as starting material [19, 21].

The UV/Vis and fluorescence spectroscopic data of furonaphthopyrone **6** are given in the experimental section; **1** and **6** exhibit almost the same absorption and fluorescence spectroscopic properties [19].

The dark interactions of furonaphthopyrones **1** and **6** with calf thymus DNA were studied in *Tris*-HCl (*pH* 7.4) containing 10% *DMSO* (v/v) by a fluorescence quenching technique. The intrinsic fluorescence of **1** and **6** was quenched to an appreciable extent due to their noncovalent binding to DNA molecules. The change in emission intensity may be attributed to environmental changes when intercalating with the base pairs of *ct*-DNA [22]. The emission data were analyzed using the *Scatchard* equation (Eq. 1, [23]) where $r_b = c_b/c_N$ and c_N is the concentration of DNA (in base pairs).

$$r_b/c_f = ka(n - r_b) \tag{1}$$

By assuming that the amount of fluorescence quenching is proportional to the amount of drug bound to DNA [24], the values of c_f and c_b can be calculated (c_b and c_f are the concentrations of bound and free drug, respectively). The apparent association constant, K_a, for each drug was computed from the slope of the straight line drawn in the *Scatchard* plot. The K_a values for **1** and **6** were found to be $1.51 \times 10^6\ M^{-1}$ and $4.74 \times 10^5\ M^{-1}$, respectively. A measure of the number of

apparent binding sites of DNA for drugs, n, was calculated from the intercept of the straight line with the r_b axis. The presence of an electron donating moiety in an intercalating drug facilitates the interaction of the latter with DNA [23]. As expected, furonaphthopyrone **1**, which contains three methyl groups (electron-donating groups), interacts with DNA more strongly than **6**, containing only two methyl groups. Since it is a general assumption that the formation of non-covalent complexes of DNA and an interacting drugs is the first step leading to the production of their covalent photoadduct in the presence of UV light, we presume that the relative interaction of the above two compounds with DNA in the presence of UV light and their capacity of form photoadducts are in the order **1** > **6**.

Knowledge of their accurate geometry is essential for understanding the structure-DNA binding activity relationships of compound like **6**. X-ray crystallographic analysis is the most useful technique for the structural studies in the solid state. An X-ray crystal structure analysis of compound **6** was performed. The crystal structure of **6** including numbering of the atoms and the molecular packing diagram are shown in Figs. 1 and 2, respectively. Final atomic coordinates, bond lengths, and valence angles are summarized in Tables 1, 2 and 3. The bond lengths and angles of the coumarin and furan moieties are normal [25]. The distances between carbon atoms of the a-pyrone and furan part of **6** (C_1-C_2:7.82, C_1-C_{14}: 8.57, C_2-C_{13}: 7.80, C_2-C_{14}: 8.36 Å) are much larger than those in psoralens [25] which exibit strong bifunctional activity. Such differences in distances of active double bonds suggest that furonaphthopyrone **6** no longer permits a proper geometry for [2 + 2] photocycloaddition of both its α-pyrone and furan double bonds with thymines on the two opposite DNA strands. Thus, **6** may serve as new monofunctional analogue of psoralens. All endocyclic atoms of **6** are coplanar (mean deviation: 0.0152, x^2: 954.3). Planarity of intercalators was generally suggested to be one of the important features needed for efficient intercalation into the DNA helix [26]. The planarity of **6** predicts that it will be an efficient DNA intercalator.

The photobiological activities of furonaphthopyrone **6** with respect to DNA are now being studied in our laboratory.

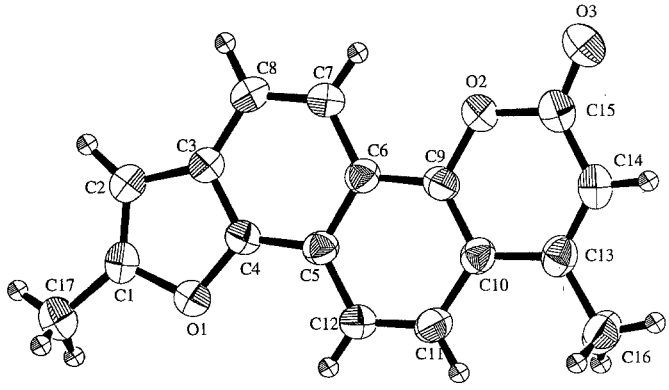


Fig. 1. ORTEP drawing (50% probility ellipsoids) of compound **6**

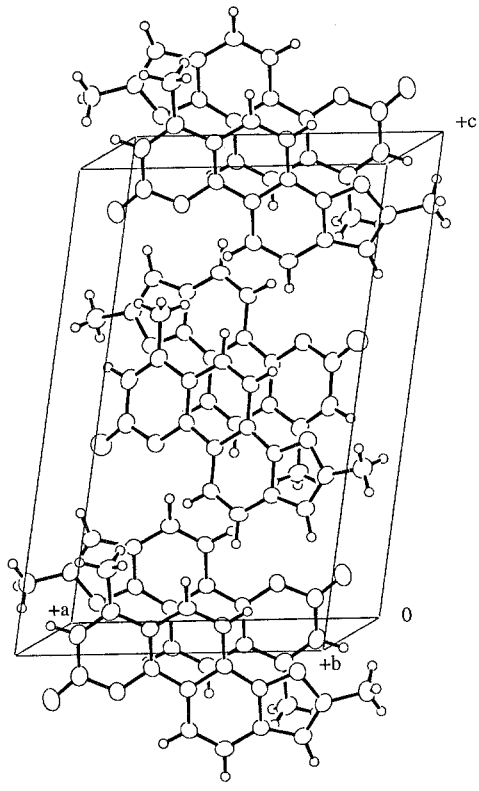


Fig. 2. Molecular packing of compound **6** in the unit cell

Experimental

Melting points were determined on a digital melting point apparatus made in Shanghai. Infrared spectra were recorded on a Niclet FT IR-20sx, spectrometer mass spectra on a Hitachi M 80 apparatus, and ^{1}H NMR spectra on a Bruker WP-100sy(100 MHz) or a Bruker AM (300 MHz) NMR spectrometer using $CDCl_3$ as solvent and *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 spectrometer, fluorescence spectra on a Perkin Elmer LS 50 fluorimeter with quinine sulfate in sulfuric acid as the quantum yield standard. Commercial reagents and solvents were purchased from standard chemical suppliers and used without further purification. 2,3-Dibromopropene was prepared according to the literature [27] and calf thymus DNA was purchased from Sigma (USA).

4-Methyl-7-(2'-bromoallyloxy)-naphtho[1,2-b]pyran-2-one (**4**)

A mixture of 1.135 g (5.02 mmol) of **3**, 2.720 g (13.60 mmol) of freshly distilled 2,3-dibromopropene, and 1.526 g (11.06 mmol) of anhydrous potassium carbonate in 50 ml of acetone were refluxed for 15 h. Inorganic salts were filtered from the cooled solution and washed with acetone. Evaporation of the combined filtrate and washing under reduced pressure left a brownish residue. After recrystallization from methanol, 1.392 g (80%) of **4** were obtained as white solid. M.p.: 125.8–127.0 °C; IR(KBr): $\nu = 2900$, 1718, 1610, 1560, 1495, 1428, 1386, 1260, 1166, 1056, 848, 800, 756 cm^{-1}; ^{1}H NMR (CD_3COCD_3): $\delta = 2.60$ (d, $J = 1.1$ Hz, 3 H, 4-CH_3), 5.03 (s, 2 H, 1'-CH_2), 5.98 (t, $J = 1.10$ Hz, 1 H, =CH), 6.27 (t, $J = 1.0$ Hz, 1 H, =CH), 6.46 (d, $J = 1.2$ Hz, 1 H, 3-H), 7.59 (d, $J = 7.84$ Hz, 1 H, 8-H), 7.64 (dd, $J = 7.84$ and 9.26 Hz, 1 H, 9-H), 7.84 (d, $J = 8.84$ Hz, 1 H, 6-H), 8.09 (d, $J = 8.84$ Hz, 1 H, 5-H), 8.23 (t,

Table 1. Atomic coordinates and B_{iso}/B_{eq} for compound **6**

atom	x	y	z	B_{eq}
O(1)	0.8513(2)	0.0569(3)	0.5707(1)	3.84(5)
O(2)	0.3141(2)	0.3052(3)	0.5881(1)	3.90(5)
O(3)	0.1210(2)	0.4060(3)	0.5956(1)	6.43(6)
C(1)	0.9371(2)	−0.0118(4)	0.6389(2)	3.98(7)
C(2)	0.8843(3)	−0.0102(4)	0.7066(2)	3.89(7)
C(3)	0.7560(2)	0.0608(4)	0.6826(1)	3.30(6)
C(4)	0.7410(2)	0.1000(4)	0.5994(2)	3.27(6)
C(5)	0.6292(2)	0.1706(3)	0.5498(1)	3.01(6)
C(6)	0.5258(2)	0.2017(3)	0.5924(2)	3.08(6)
C(7)	0.5396(3)	0.1608(4)	0.6786(2)	3.65(7)
C(8)	0.6514(3)	0.0919(4)	0.7229(2)	3.93(7)
C(9)	0.4112(2)	0.2745(3)	0.5449(2)	3.10(6)
C(10)	0.3958(2)	0.3138(3)	0.4614(2)	3.11(6)
C(11)	0.5017(2)	0.2784(4)	0.4219(2)	3.41(7)
C(12)	0.6141(3)	0.2105(4)	0.4640(2)	3.36(7)
C(13)	0.2738(2)	0.3889(4)	0.4194(2)	3.58(7)
C(14)	0.1813(3)	0.4199(4)	0.4636(2)	4.18(8)
C(15)	0.1972(3)	0.3804(4)	0.5507(2)	4.33(7)
C(16)	0.2524(4)	0.4330(6)	0.3287(2)	4.56(9)
C(17)	1.0632(3)	−0.0729(7)	0.6212(2)	5.18(10)

Table 2. Bond lengths (Å) for compound **6**

atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.394(3)	O(1)	C(4)	1.376(3)
O(2)	C(9)	1.373(3)	O(2)	C(15)	1.387(3)
O(3)	C(15)	1.206(3)	C(1)	C(2)	1.335(4)
C(1)	C(17)	1.488(4)	C(2)	C(3)	1.437(4)
C(3)	C(4)	1.374(3)	C(3)	C(8)	1.410(3)
C(4)	C(5)	1.401(3)	C(5)	C(6)	1.423(3)
C(5)	C(12)	1.418(3)	C(6)	C(7)	1.426(3)
C(6)	C(9)	1.416(3)	C(7)	C(8)	1.361(4)
C(9)	C(10)	1.378(3)	C(10)	C(11)	1.421(3)
C(10)	C(13)	1.451(3)	C(11)	C(12)	1.351(4)
C(13)	C(14)	1.342(4)	C(13)	C(16)	1.498(4)
C(14)	C(15)	1.435(4)			

Table 3. Bond angles (°) for compound **6**

Structural fragment			angle	Structural fragment			angle
C(1)	O(1)	C(4)	105.8(2)	C(9)	O(2)	C(15)	121.8(2)
O(1)	C(1)	C(2)	110.7(2)	O(1)	C(1)	C(17)	115.0(2)
C(2)	C(1)	C(17)	134.3(3)	C(1)	C(2)	C(3)	107.3(2)
C(2)	C(3)	C(4)	105.8(2)	C(2)	C(3)	C(8)	135.6(2)
C(4)	C(3)	C(8)	118.6(2)	O(1)	C(4)	C(3)	110.3(2)
O(1)	C(4)	C(5)	124.2(2)	C(3)	C(4)	C(5)	125.4(2)
C(4)	C(5)	C(6)	114.6(2)	C(4)	C(5)	C(12)	125.2(2)
C(6)	C(5)	C(12)	120.2(2)	C(5)	C(6)	C(7)	120.6(2)
C(5)	C(6)	C(9)	116.6(2)	C(7)	C(6)	C(9)	122.8(2)
C(6)	C(7)	C(8)	121.5(2)	C(3)	C(8)	C(7)	119.3(3)
O(2)	C(9)	C(6)	115.0(2)	O(2)	C(9)	C(10)	121.4(2)
C(6)	C(9)	C(10)	123.6(2)	C(9)	C(10)	C(11)	117.4(2)
C(9)	C(10)	C(13)	118.5(2)	C(11)	C(10)	C(13)	124.1(2)
C(10)	C(11)	C(12)	121.9(3)	C(5)	C(12)	C(11)	120.4(3)
C(10)	C(13)	C(14)	118.8(3)	C(10)	C(13)	C(16)	120.4(3)
C(14)	C(13)	C(16)	120.8(3)	C(13)	C(14)	C(15)	122.9(3)
O(2)	C(15)	O(3)	115.8(3)	O(2)	C(15)	C(14)	116.5(2)
O(3)	C(15)	C(14)	127.7(3)				

$J = 9.26$ Hz, $J = 0.7$ Hz, 1 H, 10-H) ppm; MS (EI, 70ev): *m/e* (%) = 347 (5.4) [$M^+ + 2$], 345 (5.7) [M^+], 225 (100) [M^+-C_3H_4Br]; found: C, 59.12; H, 5.33%; calcd. for $C_{17}H_{13}BrO_3$: C, 59.15; H, 5.26%.

2H-4,8-Dimethylfuro[2',3':5,6]naphtho[1,2-b]pyran-2-one (**6**)

A mixture of 0.505 g (1.46 mmol) of **4** and 15 ml of freshly distilled N, N-diethylaniline was refluxed for 24 h under a nitrogen atmosphere. An ether solution of the reaction mixture was filtered and the filtrate was washed with 5% aq. NaOH and two portions of 10% hydrochloric acid. After drying over $MgSO_4$, evaporation of the ether solution afforded a yellow solid which was washed with a little amount of acetone. Recrystallization from a mixture of petroleum ether and chloroform afforded 0.272 g (71%) **6**. M.p.: 212.0–212.5 °C; IR (KBr): $\nu = 2900$, 1710, 1635, 1590, 1565, 1465, 1370, 1050, 960, 860, 810, 720 cm^{-1}; ^1H NMR (CD_3COCD_3): $\delta = 2.62$ (s, 6 H, 4-CH_3, 8-CH_3), 6.42 (s, 1 H, 3-H), 6.75 (s, 1 H, 9-H), 7.86 (d, $J = 8.3$ Hz, 1 H, 11-H), 7.90 (d, $J = 8.2$ Hz, 1 H, 6-H), 8.13 (d, $J = 8.3$ Hz, 1 H, 10-H), 8.27 (d, $J = 8.2$ Hz, 1 H, 5-H) ppm; MS (EI, 70ev): *m/e* (%) = 265 (19.4) [$M^+ + 1$], 264 (100) [M^+], 238 (83.7) [M^+-CO]; UV (ethanol): $\lambda_{max}(\lg\varepsilon) = 250$ (4.457), 2.77 (4.259), 284 (4.393), 338 (3.938), 361 (3.899), 375 (3.853) nm; fluorescence (ethanol): $\lambda_{max} = 424$ nm; $\Phi_{fl} = 0.24$; found: C, 77.23; H, 4.52%; calcd for $C_{17}H_{12}O_3$: C, 77.27; H, 4.55%.

Interactions of furonaphthopyrones **1** *and* **6** *with DNA* [23, 28]

Compounds **1** or **6** were dissolved in *DMSO* and calf thymus DNA in 0.1 *M Tris*-HCl buffer (*pH* 7.4) was added to give a bulk solution. Then, two groups of samples were prepared in *Tris*-HCl (*pH* 7.4) containing 10% (v/v) *DMSO*. In one group of solutions, the concentration of DNA was constant (3×10^{-6} *M*) and that of the drug was gradiently changed ($10^{-6} \sim 10^{-8}$ *M*); the other group contained no DNA but had the same concentration of drug as above and was used as control. All the above

Table 4. Crystal data and experimental details for compound **6**

Empirical formula	$C_{17}H_{12}O_3$
Formula weight	264.28
Crystal dimensions	$0.20 \times 0.20 \times 0.40\,mm^3$
Crystal system	monoclinic
Space group	$P2_1/c$(#14)
a	10.557(2) Å
b	7.451(2) Å
c	16.398(2) Å
	$\beta = 101.10(1)^0$
V	1265.8(4) Å^3
Z	4
D_{calc}	$1.387\,g/cm^3$
F(000)	552.00
μ(MoKα)	$0.95\,cm^{-1}$
Radiation	MoKα($\lambda = 0.71069$ Å), graphite monochromated
Take-off angle	6.0^0
Detector aperture	9.0 mm horizontal, 13.0 mm vertical
Crystal to detector distance	235 mm
Scan type	ω-2θ
Scan rate	16.0^0(in ω)-up to 5 scans
Scan width	$(1.63 + 0.30 \tan\theta)^0$
$2\theta_{max}$	45.0^0
No. of reflections measured	Total: 1923, Unique: 1810 ($R_{int} = 0.013$)
No. observations ($I > 3.00\,\sigma(I)$)	1140
R	0.036
R_w	0.043

solutions were shaken for 3 days at 25 °C in the dark. Fluorescence spectra of samples were measured at following conditions: excitment wavelength: 365 nm, emission fluorescence range: 390–520 nm.

X-ray data collection and structure determination of **6**

A yellow prismatic crystal of **6** having approximate dimensions of $0.20 \times 0.20 \times 0.40\,m^3$, obtained by recrystallization from ethyl acetoacetate, was mounted on a glass fiber. All measurements were made on a Regaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a 12 kw rotating anode generator. Crystallographic data and experimental details are given in Table 4. The structure was solved by direct methods [29] and expanded using *Fourier* techniques [30]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. Neutral atom scattering factors were taken from *Crommer* and *Waker* [31]. All calculations were performed using the *teXsan* crystallographic software package of Molecular Structure Corporation.

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