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Naphthalimide hydroperoxides as photonucleases: substituent effects and structural basis

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Abstract

A variety of naphthalimide hydroperoxides as novel photochemical DNA cleavers were synthesized and evaluated. Their photochemical DNA-cleaving abilities depend on the substituents on the aromatic moiety. The DNA-cleaving differences of these hydroperoxides may result from the differences of the intercalating ability of the naphthalene moiety. X-ray single crystal structure of a representative compound **1** was determined, and showed that all endocyclic atoms were coplanar, indicating a structural basis for potential and efficient DNA intercalation by **1**. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: DNA cleaver; DNA intercalator; naphthalimide; Peroxides; X-ray single crystal structure; Hydroxyl radicals

1. Introduction

The development of artificial photonucleases has received considerable interest due to their significant importance in molecular biology and human medicine [1,2]. Such molecules are chemically stable and activable by photoirradiation, particularly by a pulse of light. The advantage of such photoactivable DNA-cleaving molecules is that their action can be controlled within time and space by choosing proper irradiation methods. While some strategies for photoinduced DNA cleavage have been investigated, hydroxyl radical-generating molecules, the so-called photo-Fenton reagents [3–7], are particularly attractive since hydroxyl radicals play a particularly important role in oxidation damage of biomolecules in cellar systems [8] and biochemical tools for the function and structure of nucleic acids [9–10]. Recently, we described a new class of intercalating DNA cleavers termed "naphthalimide hydroperoxide photonucleases" [11]. These molecules, designed to generate hydroxyl radicals, were shown to intercalate into the DNA duplex in the dark, and efficiently cleave DNA upon photochemical activation. We herein report the synthesis of a number of naphthalimide hydroperoxides with different substituents on the aromatic moiety as photochemical DNA cleavers, and an investigation of substituent effects on the DNA-cleaving efficiency. In order to more fully understand the mechanism of the interactions of naphthalimides with DNA, X-ray single crystal structure of a representative compound **1** was determined.

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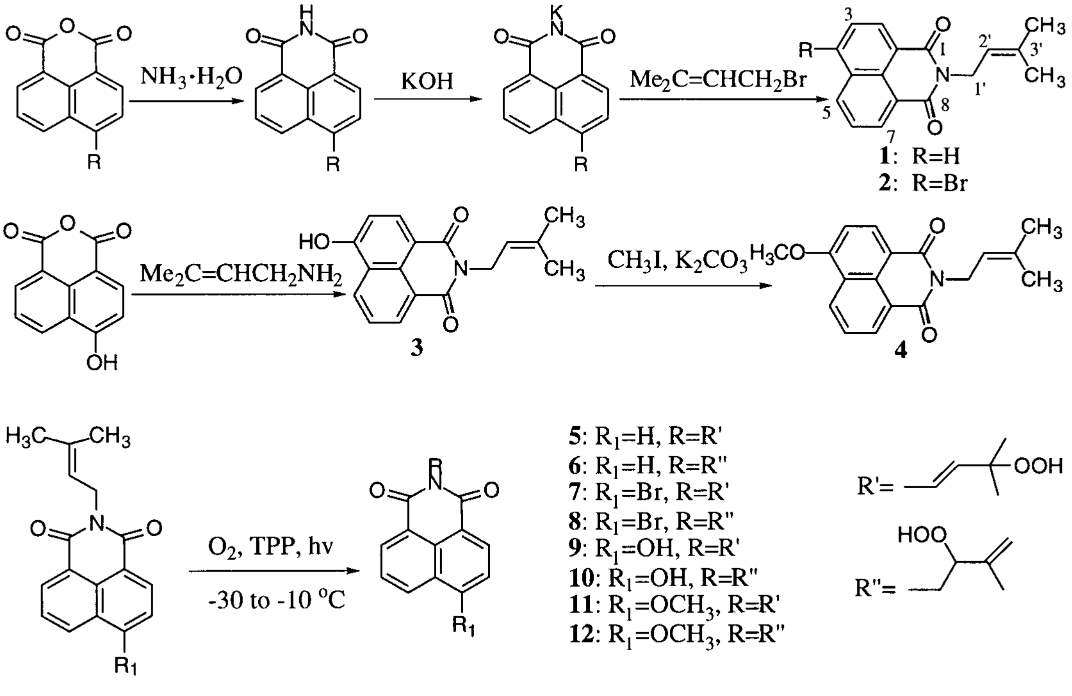
2. Results and discussion

To investigate substituent effects on the DNA-cleaving efficiency, several new naphthalimide hydroperoxide derivatives were synthesized, in addition to the previously reported **5** and **6** [11]. The synthetic methodology is shown in Scheme 1. Condensation of 3-methyl-2-butenyl bromide with potassium naphthalimide afforded the *N*-phenylated-1,8-naphthalimides **1** and **2** in good yield. 3-Methyl-2-butenylamine readily condensed with 4-hydroxynaphthalic anhydride to give **3**, which was methylated with iodomethane to produce **4** in excellent yield. The photooxygenation of **2** in methylene chloride and tetraphenylporphine (TPP) as sensitizer gave the regioisomeric allyl hydroperoxides **7** and **8** as minor and major products, respectively. From the two possible geometrical isomers of **7**, only the E isomer was formed, which showed two doublets at $\delta = 6.72$ and 7.02 ppm with a coupling constant of $J = 15.0$ Hz in the ^{1}H NMR spectrum. Similarly, the photooxygenation of **4** produced **12** as the major product. Another isomer was detected with TLC, which could be isomer **11** but this material was not characterized. However, the photooxygenation of **3**, only in low yield, gave a mixture of **9** and **10** as indicated by ^{1}H NMR, probably due to the low solubility of **3** in methylene chloride. The separation of **9** and **10** was not successful.

The DNA-cleaving activities of these newly-synthesized naphthalimide peroxides were tested and their reactivities compared with that of the previously reported analog **6**. As shown in Fig. 1, except for mixture **9** and **10** having comparable DNA-cleaving ability to **6**, other compounds had negative substituent effects on the DNA cleavage. The relative amounts of cleavage in Fig. 1 indicate that the DNA-cleaving activities are in the order: **6** > **9** + **10** > **8** ≈ **12**. These results suggest that the intercalating moieties could significantly affect the DNA-cleaving efficiencies of such types of peroxide photonucleases, and indicates that a new generation of peroxide photonucleases, through introduction of new intercalating moieties, would be obtained [12–15].



Scheme 1.

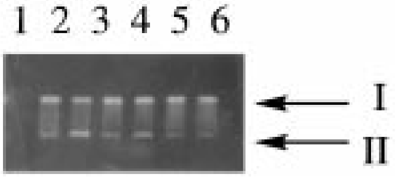


Fig. 1. Light-induced cleavage of DNA by naphthalimide hydroperoxides. Supercoiled DNA runs at position I, nicked DNA at position II. pUC19 DNA (1.0 μg) was incubated in 10 μl of 1×TBE with drugs (400 μM concentration) at room temperature in the dark for 2 h, and irradiation for 30 min. The samples were analysed by gel electrophoresis in 1% agarose and the gel was stained with ethidium bromide. Lane 1: DNA control, Lane 2: **6**, Lanes 3: **8**, 4: **9**:**10**≈1:1, 5: **12**, 6: **1**

In order to better understand the mechanism of the interactions of naphthalimides with DNA, the X-ray single crystal structure of a representative compound, 2-(3′,3′-dimethylallyl)-1H-benz[de]isoquindine-1,3(2H)-dione **1**, was determined. The crystal structure of **1**, including numbering of the atoms, is shown in Fig. 2. Selected valence angles and bond lengths are summarized in Tables 1 and 2. All the bond lengths and angles of **1** are normal compared with its ethyl analog [16]. All the endocyclic atoms are coplanar (as shown in Table 3); and the mean deviations from the least-square plane through the naphthalenediimide group is 0.057 ($x^2 = 291.6$).

Planarity of intercalators is generally suggested to be one of the important features needed for efficient intercalation into the DNA helix [17]. The planarity of the naphthalene moiety in **1** is consistent with the efficient DNA intercalation of **5** and **6** [11]. It is well known that naphthalimide type dyes have been used as electro-optically sensitive materials [18,19], singlet oxygen probes [20], DNA intercalators and human medicines [21,22]. The single crystal structural data will be very useful in the design of a new class of naphthalimide analogs with novel functions and properties.

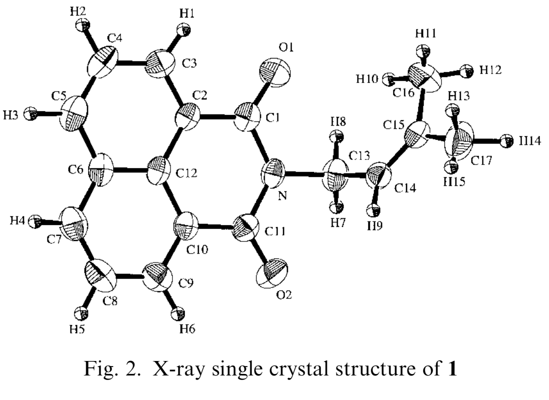


Fig. 2. X-ray single crystal structure of **1**

3. Experimental section

3.1. General

Melting points were taken on a digital melting point apparatus WRS-1 made in Shanghai and uncorrected. Infrared spectra were recorded on a Nicolet FT IR-20sx or a Spectrometer 7650 made in Shanghai, mass spectra on a Hitachi M 80 or HP5989A, and 1H NMR on a Bruker AM-300 or Brucker DRX-400 using $CDCl_3$ or 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 Shimadzu UV-265, and fluorescence spectra on a Perkin–Elmer LS 50. Commercial reagents and solvents were purchased from standard chemical suppliers and used without further purification.

3.1.1. N-*Prenyl-1,8-naphthalimide (**1**)*

To a solution of 0.495 g (3.3 mmol) of potassium naphthalimide in 15 ml of dry DMF was added 0.854 g (3.6 mmol) of 3-methyl-2-butenyl bromide and the mixture was then stirred at 0°C for 30 min. After further stirring at 55°C for 3 days, the mixture was cooled, poured onto ice-water, and extracted with $CHCl_3$ (3×10 ml). The organic layer was washed with 0.2 N NaOH and then with brine, before being dried with anhydrous K_2CO_3. After evaporation of the solvent, the crude product was obtained; this was purified by recrystallization from a mixture of petroleum and chloroform to afford colorless crystals of **1** in 54% yield. mp 110.8~111.3°C. ^1H NMR (Acetone-d_6, 100 MHz) δ 1.68 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 4.73 (d, $J=7.0$ Hz, 2H, NCH_2), 5.35 (t, $J=7.0$ Hz, 1H, –CH=C<), 7.68 (dd, $J_{AX}=7.4$

Table 1
Intramolecular bond angles involving the nonhydrogen atoms of **1**[a]

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(1)	N	C(11)	124.7(4)	C(7)	C(8)	C(9)	120.9(6)
C(1)	N	C(13)	117.7(5)	C(8)	C(9)	C(10)	120.8(6)
C(11)	N	C(13)	117.6(5)	C(9)	C(10)	C(11)	120.5(5)
O(1)	C(1)	N	119.5(5)	C(9)	C(10)	C(12)	119.7(5)
O(1)	C(1)	C(2)	123.9(5)	C(11)	C(10)	C(12)	119.8(5)
N	C(1)	C(2)	116.6(5)	O(2)	C(11)	N	119.2(4)
C(1)	C(2)	C(3)	120.2(5)	O(2)	C(11)	C(10)	123.3(5)
C(1)	C(2)	C(12)	120.6(5)	N	C(11)	C(10)	117.6(5)
C(3)	C(2)	C(12)	119.2(5)	C(2)	C(12)	C(6)	120.3(5)
C(2)	C(3)	C(4)	121.0(6)	C(2)	C(12)	C(10)	120.7(4)
C(3)	C(4)	C(5)	120.4(6)	C(6)	C(12)	C(10)	118.9(5)
C(4)	C(5)	C(6)	121.0(6)	N	C(13)	C(14)	111.6(4)
C(5)	C(6)	C(7)	122.7(5)	C(13)	C(14)	C(15)	127.1(5)
C(5)	C(6)	C(12)	118.0(5)	C(14)	C(15)	C(16)	123.3(6)
C(7)	C(6)	C(12)	119.3(5)	C(14)	C(15)	C(17)	121.7(5)
C(6)	C(7)	C(8)	120.4(6)	C(16)	C(15)	C(17)	114.9(6)

[a] Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Table 2
Intramolecular distances involving the nonhydrogen atoms of **1**[a]

Atom	Atom	Distance	Atom	Atom	Distance
O(1)	C(1)	1.222(5)	C(6)	C(7)	1.407(7)
O(2)	C(11)	1.220(5)	C(6)	C(12)	1.421(6)
N	C(1)	1.411(6)	C(7)	C(8)	1.351(8)
N	C(11)	1.402(6)	C(8)	C(9)	1.404(7)
N	C(13)	1.485(6)	C(9)	C(10)	1.367(7)
C(1)	C(2)	1.460(7)	C(10)	C(11)	1.457(6)
C(2)	C(3)	1.384(6)	C(10)	C(12)	1.419(6)
C(2)	C(12)	1.414(6)	C(13)	C(14)	1.498(7)
C(3)	C(4)	1.400(7)	C(14)	C(15)	1.301(7)
C(4)	C(5)	1.366(7)	C(15)	C(16)	1.521(8)
C(5)	C(6)	1.422(7)	C(15)	C(17)	1.507(9)

[a] Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Table 3
The least-squares plane of endocyclic atoms of **1**

Atoms defining plane	Distance	esd
N	0.0252	0.0034
C(1)	0.0041	0.0045
C(2)	−0.0167	0.0042
C(3)	0.0070	0.0051
C(4)	0.0037	0.0052
C(5)	0.0022	0.0050
C(6)	0.0039	0.0043
C(7)	0.0497	0.0053
C(8)	0.0196	0.0056
C(9)	−0.0240	0.0051
C(10)	−0.0275	0.0043
C(11)	0.0033	0.0046
C(12)	−0.0207	0.0040
Additional atoms	Distance	
O(1)	0.0262	
O(2)	0.0135	
C(13)	0.1574	
Mean deviation from plane is	0.0160 Å	

Hz, $J_{BX} = 8.0$ Hz, 2H, 3-H, 6-H), 8.40 (dd, $J_{XB} = 7.4$ Hz, $J_{AB} = 1.0$ Hz, 2H, 4-H, 5-H), 8.54 (dd, $J_{AX} = 8.0$ Hz, $J_{AB} = 1.0$ Hz, 2H, 2-H, 7-H). MS (EI, 70 eV): m/e = 266 (15.1) [M + 1], 265 (78.2) [M], 250 (20.8) [M–CH_3], 222 (78.6), 237 (27.3), 210 (33.2), 198 (100), 197 (63.8). IR (KBr): 2920, 2860, 1696, 1650, 1625, 1588, 1436, 1380, 1336, 1238, 1172, 1028, 948, 854, 840, 780 cm^{-1}. UV (ethanol): λ_{max} (lgε) = 212 nm (4.287), 236 (4.522), 332 (4.092), 343 (4.058). FL (ethanol): λ_{max} = 383.5 nm. Anal. for $C_{17}H_{15}O_2N$. Calc.: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.06; H, 5.69; N, 5.27.

3.1.2. *4-Bromo-*N*-prenyl-1,8-naphthalimide* (**2**)

A similar synthetic procedure to **1** was employed for preparation of **2**. Yield 62%, mp. 126.1∼128.5°C. ^{1}H NMR (CDCl$_3$, 100 MHz) δ 1.72 (s, 3H, 3′–CH$_3$), 1.91 (s, 3H, 3′-CH$_3$), 4.78 (d, $J=$ 7.0 Hz, 2H, –NCH$_2$–), 5.33 (t, $J=7.0$ Hz, 1H, –CH=C<), 7.84 (dd, $J_{XA}=7.5$ Hz, $J_{XB}=8.5$ Hz, 1H, 8-H), 8.04 (d, $J=7.9$ Hz, 1H, 5-H), 8.42 (d, $J=7.9$ Hz, 1H, 4-H), 8.56 (dd, $J_{BX}=8.5$ Hz, $J_{AB}=0.7$ Hz, 1H, 9-H), 8.66 (dd, $J_{AX}=7.5$ Hz, $J_{AB}=0.7$ Hz, 1H, 7-H). MS (EI, 70 eV) *m/z* (%): 345 (100) [M+2], 343 (99.9) [M], 344 (95.9), 346 (87.8), 300 (58.5), 278 (38). IR (KBr): 3060, 2960, 2900, 2840, 1700, 1650, 1580, 1564, 1496, 1470, 1372, 1344, 1314, 1230, 1174, 924, 854, 776 cm^{-1}. UV (ethanol): $\lambda_{\max}$ (lge) = 213 nm (4.304), 235 (4.542), 339 (4.176), 353 (4.112). Fluorescence (ethanol): $\lambda_{\max}=391.4$ nm. Anal. for C$_{17}$H$_{14}$BrNO$_2$. Calc.: C, 59.30; H, 4.10; N, 4.07. Found: C, 59.42; H, 4.10; N, 4.07.

3.1.3. *4-Hydroxyl-*N*-prenyl-1,8-naphthalimide* (**3**)

To a solution of 3.10 g (15 mmol) of 4-hydroxyl-1,8-naphthalic anhydride in 50 ml of anhydrous ethanol was added 1.2 g (14.1 mmol) of 3-methyl-2-butenyl amine. The mixture was refluxed for 12 h, cooled and filtered to give the crude product. After recrystallization from anhydrous ethanol, **3** was obtained in 42% yield. mp 237.0∼241.5°C. ^{1}H NMR (DMSO-d_6, 100 MHz) δ 1.77 (s, 3H, 3′-CH$_3$), 1.93 (s, 3H, 3′-CH$_3$), 4.73 (d, $J=6.2$ Hz, 2H, 1′-H), 5.35 (t, $J=6.2$ Hz, 1H, 2′-H), 7.26 (d, $J=9.0$ Hz, 1H, 3-H), 7.87 (t, $J=8.2$ Hz, 1H, 6-H), 8.46 (d, $J=9.0$ Hz, 1H, 2-H), 8.58 (d, $J=8.2$ Hz, 1H, 5-H), 8.65 (d, $J=8.2$ Hz, 1H, 7-H), 12.50 (br, 1H, OH). MS (EI, 70 eV), *m/z* (%): 282 (10.1) [M+1], 281 (35.3) [M], 266 (8.3) [M–CH$_3$], 238 (47.2), 213 (100), 196 (19.5). Anal. for C$_{17}$H$_{15}$NO$_3$. Calc.: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.30; H, 5.21; N, 4.90.

3.1.4. *4-Methoxyl-*N*-prenyl-1,8-naphthalimide* (**4**)

A mixture of 0.4 g (1.42 mmol) of 3, 1 g of anhydrous K$_2$CO$_3$ and 0.78 g (5.5 mmol) of methyl iodide in 2.0 ml of acetone was stirred at 40°C for 3 h, and cooled. After addition of 5% aq KOH, filtration and recrystallization from ethanol, the yellow product **4** was obtained in 85% yield. mp 133∼134°C. ^{1}H NMR (Acetone-d_6, 300 MHz) δ 1.66 (s, 3H, 3′-CH$_3$), 1.84 (s, 3H, 3′-CH$_3$), 4.17 (d, $J=2.1$ Hz, 3H, OCH$_3$), 4.68 (d, $J=6.7$ Hz, 2H, N–CH$_2$–), 5.28 (m, 1H, 2′-H), 7.29 (dd, $J=8.3$ and 2.1 Hz, 1H, 5-H), 7.80 (dd, $J_{XA}=7.3$ Hz, $J_{XB}=7.2$ Hz, 1H, 8-H), 8.47∼8.57 (m, 3H, 4-H, 9-H, 7-H). MS (EI, 70 eV), *m/z* (%): 296 (8.2) [M+1], 295 (39.6) [M], 252 (45.7), 240 (16.1), 227 (100), 184 (15.9). UV (ethanol): $\lambda_{\max}$ (lge) = 213 nm (4.333), 246 (4.538), 362 (4.194), 343 (4.058). FL (ethanol): $\kappa_{\max}=438.8$ nm. Anal. for C$_{18}$H$_{14}$NO$_3$. Calc.: C, 73.20; H, 5.80; N, 4.65. Found: C, 73.33; H, 5.80; N, 4.59.

3.1.5. *Naphthalimide hydroperoxides* **7** *and* **8**

A solution of 0.207 g (0.60 mmol) of **2** and 5 mg of tetraphenylporphine (TPP) in 40 ml of CH$_2$Cl$_2$ was irradiated externally by means of a sodium lamp (100 W) at −30∼−10°C for 7 h while passing a continuous slow stream of dry oxygen gas through the solution. After the removal of the solvent, the residue was subject to preparative TLC to afford **7** and **8** separately in 56% total yield.

Data for 7: ^{1}H NMR (Acetone-d$_3$, 300 MHz) δ 1.46 (s, 6H, 3′-CH$_3$), 6.72 (d, $J=15.0$ Hz, 1H, 2′-H), 7.02 (d, $J=15.0$ Hz, 1H, 1′-H), 8.06 (dd, $J_{XA}=8.4$ Hz, $J_{XB}=7.2$ Hz, 1H, 8-H), 8.26 (d, $J=7.9$ Hz, 1H, 5-H), 8.48 (d, $J=7.9$ Hz, 1H, 4-H), 8.67 (d, $J_{AX}=8.4$ Hz, 1H, 9-H), 8.69 (d, $J_{BX}=7.2$ Hz, 1H, 7-H). MS, *m/z* (%): 379 (0.54) [M+2], 377 (0.69) [M], 360 (1.2) [M–OH], 344 (41.2), 301 (100) [M-C(OOH) Me$_2$]. IR (Nujol): 3400 (OOH), 1710, 1650, 1462, 1378, 1238, 1050, 780, 720 cm^{-1}. HRFABMS for C$_{17}$H$_{14}$BrNO$_4$, Calc: 375.0107; Found: 375.0106.

Data for 8: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.88 (s, 3H, 3′-CH$_3$), 4.53 (m, 2H, 1′-H), 4.71 (m, 1H, 2′-H), 5.03 (d, $J=1.0$ Hz, 1H, =CH), 5.08 (d, $J=1.3$ Hz, 1H, =CH), 7.89 (dd, $J_{XA}=8.5$ Hz, $J_{XB}=7.3$ Hz, 1H, 8-H), 8.09 (d, $J=7.9$ Hz, 1H, 5-H), 8.46 (d, $J=7.9$ Hz, 1H, 4-H), 8.63 (dd, $J_{AX}=8.5$ Hz, $J_{AB}=1.1$ Hz, 1H, 9-H), 8.71 (dd, $J_{BX}=7.3$ Hz, 1H, 7-H), 9.95 (s, 1H, OOH). MS, *m/z* (%): 358 (3.4) [M–OH], 343 (3.61), 289 (100) [M–(HCOOH) C (CH$_3$)=CH$_2$]. IR (Nujol): 3380 (OOH), 3087, 1699, 1660, 1587, 1464, 1377, 1342, 1238, 1063, 1045, 906, 783 cm^{-1}. HRFABMS for C$_{17}$H$_{14}$BrNO$_4$, Calc: 375.0107; Found: 375.0108.

3.1.6. Naphthalimide hydroperoxide **12**

A similar synthetic procedure to that for **7** and **8** was employed for preparation of **12**. However, only isomer **12** was obtained after separation by preparative TLC.

Data for **12**: ^{1}H NMR ($CDCl_3$, 400 MHz) d 1.97 (s, 3H, 3′-CH_3), 4.16 (s, 3H, OCH_3), 4.53 (m, 2H, 1′-H), 4.70 (m, 1H, 2′-H), 5.04 (s, 1H, =CH), 5.08 (s, 1H, =CH), 7.08 (d, $J = 8.3$ Hz, 1H, 5-H), 7.74 (dd, $J_{XA} = 7.4$ Hz, $J_{XB} = 7.3$ Hz, 1H, 8-H), 8.60∼8.66 (m, 3H, 4-H, 9-H, 7-H), 10.23 (s, 1H, OOH). MS (EI, 70 eV), *m/z* (%): 327 (1.0) [M], 310 (3.28) [M–OH], 309 (5.3) [M–H_2O], 266 (23.3), 240 (100) [M–CH (OOH) C(CH_3)=CH_2], 227 (59.0), 210 (56.1). IR (Nujol): 3284 (OOH), 3080, 1693 (C=O), 1639 (C=O), 1618, 1602, 1579, 1458, 1385, 1277, 1240, 1182, 1088, 1055, 899, 779, 754, 580 cm^{-1}. HRFABMS for $C_{18}H_{16}NO_5$, Calc: 326.1028; Found: 326.1029.

Table 4
Crystal data and experimental details for **1**

Empirical formula	$C_{17}H_{15}NO_2$
Formula weight	265.31
Crystal dimensions	$0.20 \times 0.20 \times 0.30$ mm^3
Crystal system	Monoclinic
Space group	$P2_1/n$(#14)
a	8.8503(9) Å
b	12.453(3) Å
c	12.271(4) Å
β	93.59(2)°
V	1349.8(5) Å
Z value	4
D_{calc}	1.305 g cm^3
F_{000}	560.00
μ (MoK_α)	0.86 cm^{-1}
Radiation	MoK_α ($\lambda = 0.71069$ A) graphite monochromated
Take-off angle	6.0°
Detector aperture	9.0 mm horizontal. 13.0 mm vertical
Crystal to detector distance	235 mm
Scan type	ω-2θ
Scan rate 160°/min (in ω) up to 4 scans	
Scan widen	($1.26 + 0.30 \tan \theta$)
$2\theta_{max}$	50.0°
No. of reflections measured	Total: 2319. Unique: 2153 ($R_{int} = 0.071$)
No. observations ($I > 3.00\sigma(I)$)	972
R	0.051
R_w	0.058

3.2. X-ray data collection and structure determination of **1**

A colorless crystal of **1** having approximate dimensions of $C_{17}H_{15}NO_2$, 0.20×0.20×0.30 mm^3, obtained by recrystallization from a mixture of petroleum ether and chloroform, was mounted on a glass fiber. All measurements were made on a Regaku AFC7R diffractometer with graphite monochromated Mo–K_α radiation and a 12 kw rotating anode generator. The crystal data and experimental details were shown in Table 4. The structure was solved by direct methods [23] and expanded using Fourier techniques [24]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. Neutral atom scattering factors were taken from Crommer and Waker [25]. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

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