1,3-DIPOLAR CYCLOADDITION OF NITRILE OXIDES TO 1,4-NAPHTHOQUINONE DERIVATIVES

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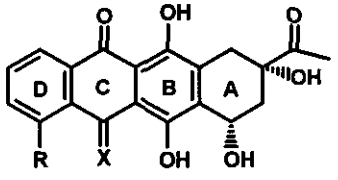
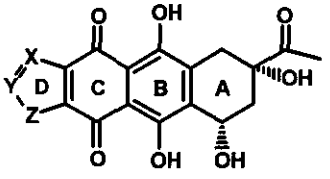
Abstract- The 1,3-dipolar cycloadditions of benzonitrile and bromoformonitrile oxides (**4** and **5**) to naphthoquinone derivatives (**3**) proceed across the C=C double bond to afford naphthoisoxazolinediones. In the reaction with benzonitrile oxide (**4**) the initial cycloadducts (**6** and **7**) were isolated in good yields. However, the cycloaddition of bromoformonitrile oxide (**5**) affords directly the corresponding aromatized naphthoisoxazolediones (**10** and **11**) in good yields.

INTRODUCTION

Anthracycline antibiotics[1a] are powerful antitumor agents,[1b,c] but their utilization in cancer chemotherapy is limited by undesired effects such as accumulative cardiotoxicity.[2] In the last decade considerable efforts have been devoted to develop new structurally modified anthracyclines with an improved antineoplastic activity and a low cardiotoxicity. 5-Iminodaunomycin, a quinone-modified analog, shows significantly less cardiotoxicity than daunomycin.[3] The lower cardiotoxicity has been credited to its poor redox capability for catalytic production of reactive oxygen species.[4] As part of our studies on the synthesis of anthracyclinones, the aglycones of anthracyclines, such as **1a**, we have reported recently[5] the first total synthesis of 5-iminodaunomycinone (**1b**), based on a BCD→ABCD approach. It would be of interest to synthesize heterocyclic anthracycline analogues,[6] since the heteroaromatic ring provides a useful bioisosteric replacement of the benzene ring D and it would be expected to change the redox potential. Moreover, numerous nitrogen-containing heterocyclic quinones also exhibit antitumor activity.[7]



1a: X=O, R=OMe
1b: X=NH, R=OMe



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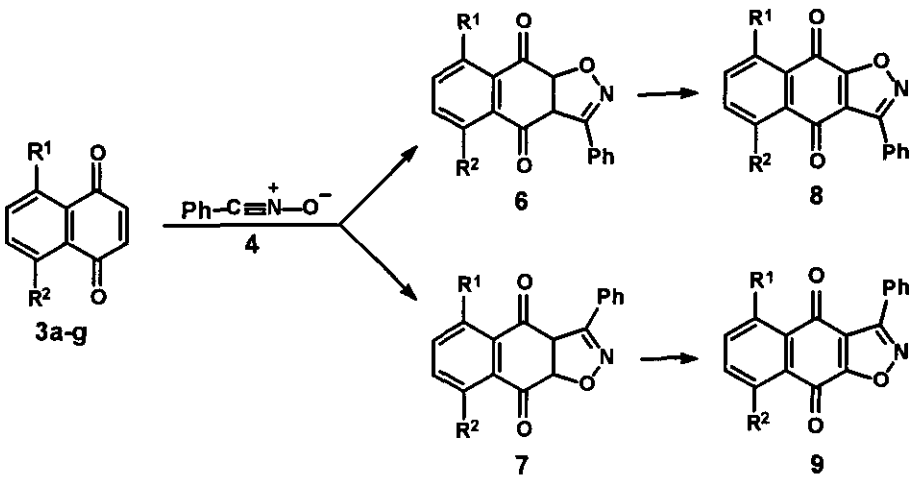
Some years ago we have described[8a] the construction of the tetracyclic system of anthracyclinones *via* two successive Diels-Alder reactions, starting from dihydroxynaphthoquinone derivatives as BC synthons. In a similar manner, their heterocyclic analogues of type (**2**), in which ring D is a 5-membered heterocycle, could be elaborated *via* 1,3-dipolar cycloaddition starting from naphthoquinone derivatives and subsequent Diels-Alder reaction. It is well known that 1,3-dipolar cycloaddition reactions provide a versatile entry to fused heterocyclic quinones.[7a,9] There are many examples of reactions between *p*-benzoquinones and several dipoles, such as nitrile ylides,[10] azomethine ylides,[11] nitrile imines,[12] nitrones,[13] diazoalkanes,[7c,14] and nitrile oxides.[7c,15] However, the cycloaddition to naphthoquinone derivatives has only been studied with few types of 1,3-dipoles, such as nitrile ylides,[10] nitrile imines,[16] diazoalkanes,[14b,17] and nitrile oxides.[18]

This paper describes the 1,3-dipolar cycloaddition reactions of benzonitrile and bromoformonitrile oxides to naphthoquinone derivatives of type (**3**). The results obtained would provide information on the reactivity and regioselectivity of the cycloaddition and offer a possible quick entry into the relatively unknown naphthoisoxazole ring system. The naphthoisoxazolediones reported herein, as such or after transformation to diquinones,[8b] diquinone monoimines[8c] or quinone monoimines,[8d] may allow the annelation through Diels-Alder reactions with suitable dienes. Therefore these compounds could be used as BCD synthons for the construction of heterocyclic analogues of anthracyclinones.

RESULTS AND DISCUSSION

As dipolarophiles, naphthoquinones have two kinds of potential reactive sites, the C=C and C=O bonds, that would originate fused isoxazoline derivatives or spiroderivatives, respectively. The reported selectivity for cycloadditions to *p*-benzoquinones[15] and naphthoquinones[18] depends on the nature of the substituents, as well as on the reaction conditions.

Scheme I



The cycloaddition of nitrile oxides (**4**, **5**) to naphthoquinone derivatives (**3a-g**) occurs selectively across the C=C double bond to give fused isoxazolines in good yield. The initial cycloadducts were readily aromatized to the corresponding naphthoisoxazoles under the reaction conditions or by chromatography on silica gel.

The 1,3-dipolar cycloaddition of benzonitrile oxide (**4**) to naphthoquinone derivatives (**3a-g**) was effected by treatment of the naphthoquinone (**3**) with 3 equivalents of dipole at room temperature (Scheme I). The results of the reactions are summarized in Table I.

Table I. Cycloadditions of benzonitrile oxide (**4**) to naphthoquinone derivatives (**3a-g**)

Quinone	R^1	R^2	Time (h)	Products	Ratio	Yield (%)
3a	OH	OH	24	**6a** + **8a**	70:30	80
3b	OMe	OMe	1	**6b**	-	90
3c	OH	OMe	24	**6c** + **7c**	90:10	85
3d	OAc	OAc	24	**6d**	95:5[a]	80
3e	OH	NH_2	72	**6e** + **7e**	75:25	75
3f	OH	NHAc	5	**6f** + **7f**	50:50	90
3g	OAc	NHAc	30	**6g** + **7g**	10:90	90

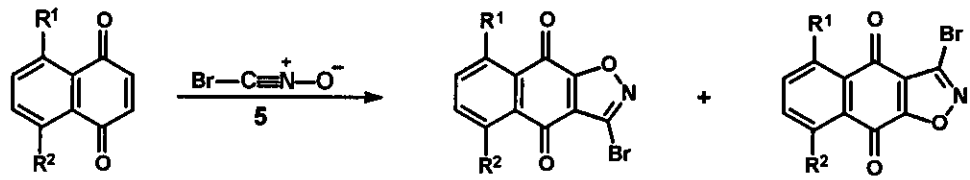
[a]A minor amount (*ca.* 5%) of another product, presumably a bisadduct, was detected in the ^{1}H-nmr of the crude reaction mixture.[19]

The reaction with the unsymmetrically substituted naphthoquinones (**3c,e-g**) afforded mixtures of the regioisomeric isoxazolines (**6c,e-g**) and (**7c,e-g**), and the ratios of the two regioisomers have been determined by integration of the well resolved chelated OH and NH protons. The cycloaddition to naphthoquinones (**3c,e**) proceeded with high regioselectivity to afford the isoxazolines (**6c,e**) as the major regioisomers. However, the cycloaddition to **3g**, in which the OH is blocked by acylation, proceeded with the reverse orientation to give the isoxazoline (**7g**) with high regioselectivity.

The structure of the cycloadducts was supported by the spectral data, particularly the ^{1}H-nmr spectra, in which there were no signals assignable to the quinonoid protons of the starting naphthoquinone derivative (**3**). Moreover, the presence of an AB system (δ 4.91-5.07 and δ 5.20-5.27, J=10 Hz) confirmed the presence of a *cis* ring-junction at the C-3a and C-9a.

The initial isoxazoline (**6a**) under the reaction conditions underwent in part oxidation to the fully aromatic naphthoisoxazole (**8a**). Naphthoisoxazoles (**8**, **9**) were obtained in good yields after chromatography on silica gel of the corresponding isoxazolines (**6**, **7**). However, chromatography of **6d** yielded a mixture of the isoxazole (**8d**) and 5-acetoxy-8-hydroxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione (**8h**) formed by selective hydrolysis of the C-8 acetoxy group. The regioisomeric assignment of compounds of type (**8**) and (**9**) will be discussed below.

Scheme II



Cycloaddition of bromoformonitrile oxide (**5**) to naphthoquinones (**3a-g**) proceeds at room temperature to afford the corresponding naphthoisoxazoles (**10**) and/or (**11**) in very good yields (Scheme II). The results obtained and the experimental conditions employed are summarized in Table II.

Table II. Cycloaddditions of bromoformonitrile oxide (**5**) to naphthoquinone derivatives (**3a-g**)

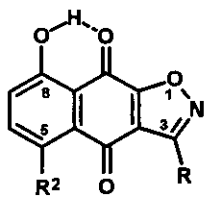
Quinone	R^1	R^2	Quinone/ Dipole	Time (h)	Products	Ratio	Yield (%)
3a	OH	OH	1:2	24	**10a**	-	80
3b	OMe	OMe	1:2	0.5	**10b**	-	95
3c	OH	OMe	1:3	20	**10c + 11c**	70:30	90
3d	OAc	OAc	1:2	1	**10d**	-	95
3e	OH	NH_2	1:4	24	**10e + 11e**	75:25	80
3f	OH	NHAc	1:2	1	**10f + 11f**	45:55	80
3g	OAc	NHAc	1:2	1	**10g + 11g**	30:70	90

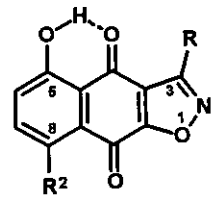
The predominant formation of isoxazoles of type (**8,10**) from naphthoquinones (**3c,e**) and nitrile oxides (**4, 5**) may be explained in terms of the enhanced activation of the C-1 carbonyl of the quinone by the strong intramolecular hydrogen bonding with the *peri*-OH group. This effect has been previously reported by Laatsch[17f] and by us[17g] for the cycloaddition of diazomethane to hydroxy- and aminonaphthoquinone derivatives. However, the low regioselectivity observed in the cycloaddition of nitrile oxides (**4** and **5**) to 5-acetylamino-8-hydroxy-1,4-naphthoquinone (**3f**) disagrees with the above results, and would be interpreted in terms of a competition between C-1 and C-4 carbonyl. Moreover, the regiochemical reversal observed with quinone (**3g**), can be attributed to the presence of the hydrogen bonding of the NHAc group with the C-4 carbonyl, which in this case is the dominant director of the cycloaddition.

The structural determination of the naphthoisoxazoles was made on the basis of the ^{1}H-nmr data. Differentiation between isomers (**8c**) and (**9c**) was based on the fact[20] that the signals at δ 12.40 of the 5-OH

proton in 5-hydroxy-8-methoxy-1,4-naphthoquinone (**3c**) is shifted to higher field (δ 12.22) by a 3-OCH_3 and to lower field (δ 12.86) by a 2-OCH_3 group. This allowed the assignment of structure (**9c**) to the compound in which the *peri*-OH signal resonates at lower field (δ 12.77) and **8c** to the isomer which shows the OH signal at higher field (δ 12.25). These regioisomeric assignment has been corroborated by an independent and regiospecific synthesis of **9c**, which will be reported in due course.[21]

Table III. ^{1}H Chemical shifts of OH and NH protons in isoxazoles (**8-10**) and (**9-11**)





Compd	8-OH	5-OH (NH)	R	R^2	Compd	5-OH	8-OH (NH)
8a	12.40	12.83	Ph	OH			
8c	12.25	-	Ph	OMe	**9c**	12.77	-
8e	13.22	(7.26)	Ph	NH_2	**9e**	13.62	(7.22)
8f	12.73	(12.17)	Ph	NHAc	**9f**	13.10	(12.14)
8h	12.23	-	Ph	OAc			
10a	12.32	12.59	Br	OH			
10c	12.13	-	Br	OMe	**11c**	12.44	-
10e	13.21	(7.20)	Br	NH_2	**11e**	13.45	(7.22)
10f	12.66	(12.15)	Br	NHAc	**11f**	12.92	(12.01)

Similarly, the assignment of the regiochemistry of isoxazoles (**8**, **10**) and (**9**, **11**) could be made on the basis of a study of the observed chemical shifts of the hydrogen bonded hydroxyl protons in their ^{1}H-nmr spectra. In fact, as shown in Table III, the sharp singlet of the chelated OH proton of isoxazoles of types (**8**, **10**), resonates at higher field (δ 12.2-13.2) than the more strong chelated OH signal of the regioisomers of type (**9**, **11**) (δ 12.6-13.6).

The comparison between the chemical shifts of the chelated NH protons of naphthoisoxazoles (**8f**, **10f** and **9f**, **11f**) (Table III) allows to assign tentatively the structure (**11g**) to the regioisomer which shows the NH proton at higher field (δ 11.95) and the structure (**10g**) to the isomer in which the NH proton resonates at lower field (δ 12.10).

In summary, the nitrile oxides (**4** and **5**) undergo selectively 1,3-dipolar cycloadditions to the C=C double bond of naphthoquinone derivatives (**3**) to afford fused isoxazolines. The addition of bromoformonitrile oxide (**5**) proceeds at a rate faster than that of the benzonitrile oxide (**4**) and the primary cycloadducts are converted directly into the corresponding naphthoisoxazoles.

EXPERIMENTAL

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed with a Heraeus analyzer. Ir spectra were recorded on a Perkin-Elmer model 681 grating spectrophotometer as nujol mulls, ν values in cm^{-1}. ^{1}H-Nmr spectra were determined with either a Varian Gemini 200, a Bruker AM-200 or a Varian XL-300 spectrometer, in $CDCl_3$ solution, unless otherwise stated. ^{13}C-Nmr were determined with either a Varian XL-300 or a Bruker AM-200 in $CDCl_3$ solution, unless otherwise stated. Chemical shifts were reported in ppm (δ) downfield from Me_4Si. Mass spectra were determined on a VG-12-250 spectrometer. Silica gel Merck 60 (70- 230 mesh) and DC-alufolien $60F_{254}$ were used for flash column chromatography and analytical tlc, respectively.

Benzonitrile oxide (BNO) (**4**) and bromoformonitrile oxide (**5**) were prepared by dehydrohalogenation of the corresponding hydroximic acid halides.

Cycloaddition of Benzonitrile Oxide (4) to Naphthoquinone Derivatives (3a-g). General Procedure

To a stirred mixture of 10% sodium hydroxide solution (5 ml) and ether (5 ml) was added portionwise during 10 min at 0 °C α-benzaldehyde chloroxime (467 mg, 3 mmol). The ethereal layer was separated, quickly dried over magnesium sulfate and added to a solution of the naphthoquinone (**3**) (1 mmol) in dry ether (5 ml) and the mixture was stirred at room temperature during the period indicated in Table I (disappearance of **3** was monitored by tlc). The solvent was removed and the residue was analyzed by ^{1}H-nmr. The isoxazolines were isolated by filtration.

Addition to 5,8-dihydroxy-1,4-naphthoquinone (**3a**).[22] Afforded a 70:30 mixture of the isoxazoline (**6a**) and the isoxazole (**8a**) (246 mg, 80%). ^{1}H-Nmr: 4.99 (d, 0.7H, H-3a, J=10.0 Hz, **6a**), 5.27 (d, 0.7H, H-9a, J=10.0 Hz, **6a**), 7.56-7.33 (m, 5H, H-6, H-7, 3 arom, **6a**, **8a**), 7.99 (m, 1.4H, arom, **6a**), 8.10 (m, 0.6 H, arom, **8a**), 11.87 (s, 0.7H, OH, **6a**), 11.96 (s, 0.7H, OH, **6a**) , 12.40 (s, 0.3H, OH, **8a**), 12.83 (s, 0.3 H, OH, **8a**). The crude mixture by column chromatography (chloroform) afforded **5,8-dihydroxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione** (**8a**) (230 mg, 75%), mp 176-179 °C (from chloroform/*n*-hexane). Anal. Calcd for $C_{17}H_9NO_5$: C, 66.46, H, 2.93, N, 4.56. Found: C, 66.21, H, 3.18, N, 4.60. Ir: 1625, 1570. ^{1}H-Nmr: 7.33, 7.38 (AB syst., 2H, H-6, H-7, J= 9.4 Hz), 7.56 (m, 3H, arom), 8.10 (m, 2H, arom), 12.40 (s, 1H, OH), 12.83 (s, 1H, OH). ^{13}C-Nmr: 112.4, 112.5, 120.1, 125.9, 128.7, 129.5, 130.1, 131.4, 132.4, 159.2, 160.1, 161.1, 166.3, 175.7, 182.7. Ms, *m/z*: 307 (M^+)(85), 279 (100), 176, 117, 108, 77.

Addition to 5,8-dimethoxy-1,4-naphthoquinone (**3b**). Afforded the isoxazoline (**6b**) (303 mg, 90%), mp 219-220 °C (from chloroform/*n*-hexane). Ir: 1710, 1590, 1580. ^{1}H-Nmr: 3.62 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.92 (d, 1H, H-3a, J=10.2 Hz), 5.24 (d, 1 H, H-9a, J=10.2 Hz), 7.08, 7.15 (AB syst., 2H, H-6, H-7, J= 9.3 Hz), 7.37-7.42 (m, 3H, arom), 7.82-7.86 (m, 2H, arom). ^{13}C-Nmr: 56.6, 62.3, 84.5, 118.5, 118.7, 127.0, 127.7, 128.6, 130.6, 151.5, 152.0, 153.7, 186.6. Ms, *m/z*: 337 (M^+)(27), 322, 278, 234, 203, 163 (100), 134, 106, 77. The isoxazoline by column chromatography (chloroform) afforded **5,8-dimethoxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione** (**8b**) (268 mg, 80%), mp 227-229 °C (from chloroform/*n*-hexane). Anal. Calcd for $C_{19}H_{13}NO_5$: C, 68.06, H, 3.88, N, 4.18. Found: C, 67.97, H, 3.60, N, 4.19. Ir: 1670, 1610, 1580. ^{1}H-Nmr: 3.97 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.36, 7.44 (AB syst., 2H, H-6, H-7, J= 9.6 Hz), 7.48-7.52 (m, 3H, arom), 8.09-8.14 (m, 2H, arom). ^{13}C-Nmr: 56.9, 57.2, 120.7, 122.7, 123.0, 128.5, 129.5, 130.9, 155.0, 155.6, 160.9, 165.2, 172.5, 178.3. Ms, *m/z* : 335 (M^+)(4), 278, 203, 163, 134, 105, 77 (100).

Addition to 5-hydroxy-8-methoxy-1,4-naphthoquinone (**3c**). The crude residue was a 90:10 mixture of the isoxazolines (**6c**) (δ 3.73, 2.7H, OCH_3) and (**7c**) (δ 3.70, 0.3H, OCH_3). The isoxazoline (**6c**) was isolated by filtration (200 mg, 65%), mp 135 °C (from chloroform/*n*-hexane). Ir: 1685, 1650, 1580. ^{1}H-Nmr: 3.73 (s, 3H, OCH_3), 4.91 (d, 1H, H-3a, J=10.3 Hz), 5.34 (d, 1H, H-9a, J=10.3 Hz), 7.31, 7.23 (AB syst., 2H, H-6, H-7, J=9.4 Hz), 7.38- 7.43 (m, 3H, arom), 7.78-7.83 (m, 2H, arom), 11.47 (s, 1H, OH). ^{13}C-Nmr: 57.3, 60.2, 82.4, 116.8, 121.8, 124.8, 125.2, 127.9, 128.7, 130.8, 152.4, 155.4, 156.1, 187.3, 194.1. Ms, *m/z*: 323 (M^+)(6), 321, 294, 266, 264, 249, 191, 163, 149, 119, 104, 92, 77 (100), 51. The isoxazoline (**6c**) after column chromatography (chloroform) afforded **8-hydroxy-5-methoxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione** (**8c**) (197 mg, 62%), mp 205-206 °C (from chloroform/*n*-hexane). Anal. Calcd for $C_{18}H_{11}NO_5$: C, 67.29, H, 3.43, N, 4.36. Found: C, 66.79, H, 3.71 N, 4.39. Ir: 1670, 1600, 1580. ^{1}H-Nmr: 3.95 (s, 3H, OCH_3), 7.30, 7.43 (AB syst., 2H, H-6, H-7, J= 9.5 Hz), 7.40-7.49 (m, 3H, arom), 8.09-8.08 (m, 2H, arom), 12.25 (s, 1H, OH). ^{13}C-Nmr: 57.1, 115.1, 121.1, 125.9, 126.2, 127.4, 128.5, 129.5, 131.1, 155.4, 156.5, 161.4, 163.4, 177.0, 177.7. Ms, *m/z* : 321 (M^+)(100), 292, 264, 248, 236, 220, 189. The mother liquor was concentrated and the residue by column chromatography (chloroform) afforded a 1:1 mixture of **8c** and **5-hydroxy-8-methoxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione(9c)**. ^{1}H-Nmr: 4.04 (s, 3H, OCH_3), 7.38, 7.42 (AB syst., 2H, H-6, H-7, J= 9.3 Hz), 7.48-7.59 (m, 3H, arom), 8.07-8.11 (m, 2H, arom), 12.77 (s, 1H, OH).

Addition to 5,8-diacetoxy-1,4-naphthoquinone (**3d**). Afforded the isoxazoline (**6d**) (317 mg, 80%). Ir: 1780, 1770, 1720, 1670, 1590. ^{1}H-Nmr: 2.07 (s, 3H, $OCOCH_3$), 2.37 (s, 3H, $OCOCH_3$), 4.97 (d, 1H, H-3a, J=10.5 Hz), 5.25 (d, 1 H, H-9a, J=10.5 Hz), 7.31, 7.38 (AB syst., 2H, H-6, H-7, J= 8.8 Hz), 7.40-7.44 (m, 3H, arom), 7.78-7.83 (m, 2H, arom.). ^{13}C-Nmr: 20.4, 20.7, 60.7, 83.5, 127.9, 128.0, 128.5, 129.0, 130.0, 130.4, 130.8, 146.4, 146,9, 154,0, 168.8, 185.5, 185.9. Ms, *m/z*: 349 (M^+- 44)(0.1), 307, 291, 276,

232, 190, 43 (100). The crude mixture by column chromatography (chloroform) afforded **5,8-diacetoxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione (8d)** (86 mg, 22%), mp 184-185 °C (from chloroform/*n*-hexane). Ir: 1775, 1680, 1610, 1580. ^{1}H-Nmr: 2.43 (s, 3H, $OCOCH_3$), 2.48 (s, 3H, $OCOCH_3$), 7.45 (AB syst., 2H, H-6, H-7, J= 9.4 Hz), 7.50-7.54 (m, 3H, arom), 7.98-8.04 (m, 2H, arom). Ms, *m/z*: 307(M^+- 84)(4), 279, 202, 184, 168, 141, 115, 77, 43 (100), and **5-acetoxy-8-hydroxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione (8h)** (118 mg, 34%), mp 203-204 °C (from chloroform/*n*-hexane). Anal. Calcd for $C_{19}H_{11}NO_6$: C, 65.33, H, 3.15, N, 4.01. Found: C, 65.48, H, 2.97, N, 3.92. Ir: 1770, 1660, 1600, 1580. ^{1}H-Nmr: 2.41 (s, 3H, $OCOCH_3$), 7.36 (s, 2H, H-6, H-7), 7.54 (m, 3H, arom), 8.03 (m, 2H, arom), 12.23 (s, 1H, OH). Ms, *m/z*: 349 (M^+)(0.4), 307, 279, 176, 117, 108, 77, 43 (100).

***Addition to 5-amino-8-hydroxy-1,4-naphthoquinone* (3e).**[23] Afforded a 75:25 mixture of the isoxazolines (**6e**) and (**7e**) (231 mg, 75%). ^{1}H-Nmr: 4.91 (d, 0.75H, H-3a, J=9.8 Hz, **6e**), 4.93 (d, 0.25H, H-3a, J=9.8 Hz, **7e**), 5.20 (d, 0.25H, H-9a, J=9.8 Hz, **7e**), 5.24 (d, 0.75H, H-9a, J=9.8 Hz, **6e**), 6.94-7.18 (AB systm., 2H, H-6, H-7, J=9.2 Hz, **6e**, **7e**), 7.06 (br s, 2H, NH_2, **6e**, **7e**), 7.39-8.18 (m, 5H, arom, **6e**, **7e**), 12.20 (s, 0.75H, OH, **6e**), 12.26 (s, 0.25H, OH, **7e**). The mixture of isoxazolines by column chromatography (chloroform) afforded **5-amino-8-hydroxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione(8e)** (168 mg, 55%), mp 254-255 °C (from ethanol). Anal. Calcd for $C_{17}H_{10}N_2O_4$: C, 66.60, H, 3.29, N, 9.15. Found : C, 66.36, H, 3.50, N, 9.08. Ir: 3400, 3280, 1620, 1610, 1570. ^{1}H-Nmr: 7.04, 7.19 (AB syst., 2H, H-6, H-7, J=9.4 Hz), 7.26 (br s, 2H, NH_2), 7.55 (m, 3H, arom), 8.09 (m, 2H, arom), 13.22 (s, 1H, OH). Ms, *m/z*: 306 (M^+)(20), 278, 229, 201, 77 (100) and **8-amino-5-hydroxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione(9e)** (46 mg, 15%), mp 261°C (from ethanol). Anal. Calcd for $C_{17}H_{10}N_2O_4$: C, 66.60, H, 3.29, N, 9.15. Found: C, 66.73, H, 3.49, N, 9.05. Ir: 3340, 3250, 3160, 1620, 1610, 1580. ^{1}H-Nmr: 6.99, 7.22 (AB syst., 2H, H-6, H-7, J= 9.12 Hz), 7.22 (br s, 2H, NH_2), 7.52 (m, 3H, arom), 8.13 (m, 2H, arom), 13.62 (s, 1H, OH). Ms, *m/z*: 306 (M^+)(2), 278, 249, 107, 77 (100).

***Addition to 5-acetylamino-8-hydroxy-1,4-naphthoquinone* (3f).**[23] Afforded a 50:50 mixture of the isoxazolines (**6f**) and (**7f**) (313 mg, 90%). Ir: 1695, 1650, 1640, 1590. ^{1}H-Nmr: 2.13 (s, 1.5H, $NCOCH_3$, **7f**), 2.25 (s, 1.5H, $NCOCH_3$, **6f**), 4.98 (d, 0.5H, H-3a, J=9.8 Hz, **7f**), 5.01 (d, 0.5H, H-3a, J=9.8 Hz, **6f**), 5.23 (d, 0.5H, H-9a, J=9.8 Hz, **6f**), 5.27 (d, 0.5H, H-9a, J=9.8 Hz, **7f**), 7.30 (d, 0.5H, H-7, J= 9.5 Hz, **6f**), 7.33 (d, 0.5H, H-6, J= 9.5 Hz, **7f**), 7.38- 7.48 (m, 3H, arom, **6f**, **7f**), 7.78-7.87 (m, 2H, arom, **6f**, **7f**), 8.99 (d, 0.5H, H-7, J= 9.5 Hz, **7f**), 9.04 (d, 0.5H, H-6, J= 9.5 Hz, **6f**), 11.19 (br s, 0.5H, NH, **6f**), 11.39 (br s, 0.5H, NH, **7f**), 12.10 (s, 0.5H, OH, **7f**), 12.21 (s, 0.5H, OH, **6f**). ^{13}C-Nmr: 25.4, 57.3, 58.4, 81.1, 82.1, 114.4, 114.9, 115.7, 116.4, 127.2, 127.6, 127.8, 128.3, 128.5, 128.7, 131.0, 131.1, 131.7, 132.0, 135.3, 135.8, 156.0, 156.3, 158.7, 158.9, 169.5, 169.7, 191.9, 192.0, 193.7, 193.9. Ms, *m/z*: 350 (M^+)(2), 348, 307, 278, 177, 119, 103, 77, 43 (100). The mixture of isoxazolines by column chromatography (chloroform) afforded **5-acetylamino-8-hydroxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione(8f)** (139 mg, 40%), mp 263-

264 °C (from ethanol). Anal. Calcd for $C_{19}H_{12}N_2O_5$: C, 65.58, H, 3.47, N, 8.05. Found: C, 65.31, H, 3.65, N, 8.03. Ir: 1695, 1630, 1580. ^{1}H-Nmr: 2.29 (s, 3H, $NCOCH_3$), 7.37 (d, 1H, H-7, J= 9.6 Hz), 7.55 (m, 3H, arom), 8.02 (m, 2H, arom), 9.20 (d, 1H, H-6, J= 9.6 Hz), 12.17 (br s, 1H, NH), 12.73 (s,1H, OH). ^{13}C-Nmr: 25.8, 113.5, 114.7, 120.6, 125.9, 128.4, 128.7, 129.6, 131.4, 133.2, 138.4, 161.4, 164.8, 170.2, 176.9, 181.9. Ms, *m/z*: 348 (M^+)(91), 306, 277 (100), 107, 77, 43 and **8-acetylamino-5-hydroxy-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione (9f)** (139 mg, 40%), mp 206.5-207.5°C (from ethanol). Anal. Calcd for $C_{19}H_{12}N_2O_5$: C, 65.58, H, 3.47, N, 8.05. Found: C, 65.31 , H, 3.65 , N, 8.03. Ir: 1710, 1695, 1630, 1580. ^{1}H-Nmr: 2.33 (s, 3H, $NCOCH_3$), 7.40 (d, 1H, H-6, J= 9.6 Hz), 7.57 (m, 3H, arom), 8.11 (m, 2H, arom), 9.13 (d, 1H, H-7, J= 9.6 Hz), 12.14 (br s, 1H, NH), 13.10 (s, 1H, OH). ^{13}C-Nmr: 25.7, 113.6, 114.0, 118.8, 125.9, 128.7, 129.5, 130.8, 130.9, 131.5, 139.2, 160.5, 160.9, 166.3, 170.2, 175.2, 183.7. Ms, *m/z*: 348 (M^+)(9), 306, 278, 249, 107, 77, 43 (100).

***Addition to 8-acetoxy-5-acetylamino-1,4-naphthoquinone* (3g).**[23] Afforded a 10:90 mixture of the isoxazolines (**6g**) and (**7g**) (351 mg, 90%). Ir: 1760, 1700, 1670, 1590. ^{1}H-Nmr: 2.08 (s, 0.1H, $NCOCH_3$, **6g**), 2.13 (s, 2.7H, $NCOCH_3$, **7g**), 2.30 (s, 2.7H, $OCOCH_3$, **7g**), 2.38 (s, 0.3H, $OCOCH_3$, **6g**), 5.07 (d, 0.9H, H-3a, J= 10.3 Hz, **7g**), 5.20 (d, 0.1H, H-3a, J= 10.3 Hz, **6g**), 5.30 (d, 0.1H, H-9a, J= 10.3 Hz, **6g**), 5.32 (d, 0.9H, H-9a, J= 10.3 Hz, **7g**), 7.33 (d, 1H, H-6, H-7, J=9.2 Hz, **6g**, **7g**), 7.38-7.57 (m, 3H, arom, **6g**, **7g**), 7.76-7.78 (m, 2H, arom, **6g**, **7g**), 8.97 (d, 0.1H, H-6, J=9.2 Hz, **6g**), 9.0 (d, 0.9H, H-7, J=9.2 Hz, **7g**), 10.86 (br s, 0.1H, NH, **6g**), 11.04 (br s, 0.9H, NH, **7g**). Ms, *m/z*: 392 (M^+)(2), 390, 350, 349, 348, 306, 280, 279, 278 (100), 249, 107, 43. The mixture of isoxazolines by column chromatography (chloroform) afforded **5-acetoxy-8-acetylamino-3-phenylnaphtho[2,3-*d*]isoxazole-4,9-dione (9g)** (242 mg, 62%), mp 259-261°C (from ethanol). Anal. Calcd for $C_{21}H_{14}N_2O_6$: C, 64.67, H, 3.62, N, 7.18. Found: C, 64.97, H, 3.90, N, 7.40. Ir: 1765, 1700, 1680, 1660, 1590. ^{1}H-Nmr: 2.34 (s, 3H, $NCOCH_3$), 2.44 (s, 3H, $OCOCH_3$), 7.46 (d, 1H, H-6, J= 9.4 Hz), 7.56 (m, 3H, arom.), 8.09 (m, 2H, arom), 9.19 (d, 1H, H-7, J= 9.4 Hz), 12.01 (br s, 1H, NH). ^{13}C-Nmr: 21.2, 25.9, 116.4, 124.9, 125.9, 128.0, 128.7, 129.4, 129.6, 131.4, 134.5, 142.1, 146.3, 161.1, 165.2, 169.6, 170.2, 176.7, 176.9. Ms, *m/z*: 390 (M^+) (1), 348, 306, 278, 249, 221, 77, 43 (100). The isoxazoles (**9f**) (17 mg, 5%) and (**8f**) (28 mg, 8%) formed by selective hydrolysis of OAc, were also isolated as minor components.

Cycladdition of Bromoformonitrile Oxide (5) to Naphthoquinone Derivatives (3a-g). General Procedure. Dibromoformaldoxime (406 mg, 2 mmol, unless otherwise stated) was added portionwise at room temperature to a stirred mixture of the naphthoquinone (**3**) (1 mmol) and potassium bicarbonate (200 mg, 2 mmol) in ethyl acetate (10 ml) and water (1 ml). The reaction was stirred during the period indicated in Table II (disappearance of **3** was monitored by tlc). Then chloroform was added and the organic layer was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The ratio of the isoxazoles was estimated by ^{1}H-nmr. The product was purified by crystallization from chloroform/*n*-hexane.

3-Bromo-5,8-dihydroxynaphtho[2,3-*d*]isoxazole-4,9-dione(10a). From naphthoquinone (**3a**) (248 mg, 80%), mp 205-206 °C. Anal. Calcd for $C_{11}H_4NO_5Br$: C, 42.58, H, 1.29, N, 4.52, Br, 25.81. Found: C, 42.80, H, 1.48, N,4.52, Br, 26.18. Ir: 1620, 1590, 1570. ^{1}H-Nmr: 7.33, 7.40 (AB syst., 2H, H-6, H-7, J= 9.5 Hz), 12.32 (s, 1H, OH), 12.59 (s, 1H, OH). ^{13}C-Nmr: 112.1, 112.6, 120.9, 130.6, 132.7, 138.3, 159.4, 160.7, 165.7, 174.4, 180.8. Ms, *m/z*: 311, 309 (M^+)(52), 230 (100), 202, 176, 163.

3-Bromo-5,8-dimethoxynaphtho[2,3-*d*]isoxazole-4,9-dione (10b). From naphthoquinone (**3b**) (321 mg, 95%), mp 211-213 °C. Anal. Calcd for $C_{13}H_8NO_5Br$: C, 46.15, H, 2.37, N, 4.14, Br, 23.67. Found: C, 46.41, H, 2.49, N, 4.30, Br 23.26. Ir: 1680, 1610, 1580. ^{1}H-Nmr: 4.00 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.38, 7.46 (AB syst., 2H, H-6, H-7, J= 9.6 Hz). ^{13}C-Nmr: 56.9, 57.0, 119.4, 120.5, 121.2, 121.5, 123.1, 138.4, 155.1, 155.9, 164.3 , 171.4, 176.6. Ms, *m/z*: 339, 337 (M^+)(20), 258, 243, 230, 228, 215, 212, 200, 172, 144, 133, 106, 89, 88, 76 (100).

3-Bromo-8-hydroxy-5-methoxynaphtho[2,3-*d*]isoxazole-4,9-dione (10c) and **3-Bromo-5-hydroxy-8-methoxy-naphtho[2,3-*d*]isoxazole-4,9-dione (11c)**. From naphthoquinone (**3c**) a 70:30 mixture (292 mg, 90%) of **10c** and **11c**, that could not be separated. Anal. Calcd for $C_{12}H_6NO_5Br$: C, 44.45 , H, 1.85, N, 4.32, Br, 24.69. Found: C, 44.25, H, 2.10, N, 4.07, Br, 24.41. Ir: 1660, 1650, 1600, 1580, 1570. ^{1}H-Nmr: 3.93 (s, 2.1H, OCH_3, **10c**), 3.95 (s, 0.9H, OCH_3, **11c**), 7.27, 7.40 (AB syst., 1.4H, H-6, H-7, J= 9.6 Hz, **10c**), 7.30, 7.35 (AB syst., 0.6H, H-6, H-7, J= 9.7 Hz, **11c**), 12.13 (s, 0.7H, OH, **10c**), 12.44 (s, 0.3H, OH, **11c**). Ms, *m/z*: 325, 323 (M^+)(30), 244 (100), 216, 188, 177.

3-Bromo-5,8-diacetoxynaphtho[2,3-*d*]isoxazole-4,9-dione (10d). From naphthoquinone (**3d**) (374 mg, 95%), mp 196-197 °C. Anal. Calcd for $C_{15}H_8NO_7Br$: C, 45.69, H, 2.03, N, 3.55, Br, 20.30. Found: C, 45.42, H, 1.84, N, 3.79, Br 20.42. Ir: 1770, 1690, 1680, 1610, 1570. ^{1}H-Nmr: 2.46 (s, 3H, $OCOCH_3$), 2.47 (s, 3H, $OCOCH_3$), 7.45, 7.50 (AB syst., 2H, H-6, H-7, J= 8.9 Hz). ^{13}C-Nmr: 20.9, 21.0, 119.9, 124.8, 125.8, 132.0, 133.4, 138.3, 148.9, 149.3, 164.1, 169.0, 169.1, 170.4, 175.2. Ms, *m/z*: 395, 393 (M^+)(0.1), 353, 351, 311, 309, 230, 202, 163, 94, 57, 43 (100).

5-Amino-3-bromo-8-hydroxynaphtho[2,3-*d*]isoxazole-4,9-dione(10e) and **8-Amino-3-bromo-5-hydroxy-3-naphtho[2,3-*d*]isoxazole-4,9-dione (11e)**. From naphthoquinone (**3e**) (247 mg, 80%). The crude mixture was separated by preparative tlc (chloroform). Isoxazole (**10e**) (164 mg, 53%), mp 260 °C. Anal. Calcd for $C_{11}H_5N_2O_4Br$: C, 42.72, H, 1.62, N, 9.06, Br, 25.81. Found: C, 42.79, H, 1.36, N, 8.80, Br, 25.88. Ir: 3390, 3260, 1625, 1610, 1570. ^{1}H-Nmr: 7.20 (br s, 2H, NH_2), 7.12, 7.20 (AB syst., 2H, H-6, H-7, J=9.4 Hz), 13.21 (br s, 1H, OH). Ms, *m/z*: 310,308 (M^+)(19), 230, 229, 202 (100), 201, 173, 162, 145, 107, 106, 81, 80, 79, 78, 53, 52. Isoxazole (**11e**) (46 mg, 15%). Ir: 3340, 3260, 3215, 1620, 1600. ^{1}H-Nmr: 7.22 (br s, 2H, NH_2), 7.10, 7.20 (AB system., 2H, H-6, H-7, J= 9.5 Hz), 13.45 (s, 1H, OH). Ms, *m/z*: 310, 308 (M^+)(3), 229, 202, 201, 173, 162, 107, 106, 78, 79, 53, 52 (100).

5-Acetylamino-3-bromo-8-hydroxy-3-naphtho[2,3-*d*]isoxazole-4,9-dione (10f) and **8-Acetylamino-3-bromo-**

5-hydroxy-3-naphtho[2,3-*d*]isoxazole-4,9-dione (11f). From naphthoquinone (**3f**) a 45:55 mixture (280 mg, 80%) of **10f** and **11f**, that could not be separated. Anal. Calcd for $C_{13}H_7N_2O_5Br$: C, 44.48, H, 2.01, N, 7.98, Br, 22.76. Found: C, 44.41, H, 2.03, N, 7.90, Br, 22.56. Ir: 1700, 1640, 1580. ^{1}H-Nmr: 2.32 (s, 1.65H, $NCOCH_3$, **11f**), 2.31 (s, 1.35H, $NCOCH_3$, **10f**), 7.38 (d, 0.45H, H-7, *J*=9.7 Hz, **10f**), 7.42 (d, 0.55H, H-6, *J*=9.7 Hz, **11f**), 9.14 (d, 0.55H, H-7, *J*=9.7 Hz, **11f**), 9.21 (d, 0.45H, H-6, *J*=9.7 Hz, **10f**), 12.01 (br s, 0.55H, NH, **11f**), 12.15 (br s, 0.45H, NH, **10f**), 12.66 (s, 0.45H, OH, **10f**), 12.92 (s, 0.55H, OH, **11f**). Ms, *m/z*: 352, 350 (M^+)(2), 310, 308, 229, 201, 173, 162, 106, 80, 79, 78, 77, 53, 52, 43 (100).

8-Acetoxy-5-acetylamino-3-bromo-3-naphtho[2,3-*d*]isoxazole-4,9-dione (10g) and **5-Acetoxy-8-acetylamino-3-bromo-3-naphtho[2,3-*d*]isoxazole-4,9-dione (11g)**. From naphthoquinone (**3g**) a 30:70 mixture (353 mg, 90%) of **10g** and **11g**. Anal. Calcd for $C_{15}H_9N_2O_6Br$: C, 45.80, H, 2.29, N, 7.12, Br, 20.36. Found: C, 45.69, H, 1.99, N, 7.36, Br, 20.58. Ir: 1770, 1700, 1680, 1665, 1610, 1590. ^{1}H-Nmr: 2.33 (s, 3H, $NCOCH_3$, **10g**, **11g**), 2.44 (s, 0.9H, $OCOCH_3$, **10g**), 2.45 (s, 2.1H, $OCOCH_3$, **11g**), 7.42 (d, 0.3H, H-7, *J*=9.4 Hz, **10g**), 7.45 (d, 0.7H, H-6, *J*=9.4 Hz, **11g**), 9.22 (d, 0.7H, H-7, *J*=9.4 Hz, **11g**), 9.26 (d, 0.3H, H-6, *J*=9.4 Hz, **10g**), 11.95 (br s, 0.7H, NH, **11g**), 12.10 (br s, 0.3H, NH, **10g**). The mixture by crystallization from chloroform/*n*-hexane afforded the isoxazole (**11g**) (216 mg, 55 %), mp 191.5° C. Anal. Calcd for $C_{15}H_9N_2O_6Br$: C, 45.80, H, 2.29, N, 7.12, Br, 20.36. Found: C, 45.65, H, 2.25, N, 7.00, Br, 20.58. Ir: 1770, 1700, 1680, 1660, 1610, 1585. ^{1}H-Nmr: 2.33 (s, 3H, $NCOCH_3$), 2.45 (s, 3H, $OCOCH_3$), 7.45 (d, 1H, H-6, *J*= 9.4 Hz), 9.22 (d, 1H, H-7, *J*= 9.4 Hz), 11.95 (br s, 1H, NH). ^{13}C-Nmr: 21.04, 25.78, 116.47, 124.19, 124.40, 128.55, 134.80, 138.42, 142.52, 146.46, 164.43, 169.29, 170.03, 175.19, 175.60. Ms, *m/z*: 394, 392 (M^+)(3), 352, 350, 310, 308, 229,78, 79, 80, 53, 52, 43 (100).

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