Nucleophilic Substitutions of 2-Chloronaphtho[2,3-*b*]furan-4,9-dione with Amines

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2-Chloronaphtho[2,3-*b*]furan-4,9-dione **4** was allowed to react with pyrrolidine to produce 2-(1-pyrrolidinyl)naphtho[2,3-*b*]furan-4,9-dione **8** in 64% yield. In a similar manner, the reaction of **4** with cyclic amines (piperidine, morpholine, 4-substituted piperazines, *etc.*) gave the desired compounds. 2-Dimethylaminonaphtho[2,3-*b*]furan-4,9-dione **20** and 2-propylaminonaphtho[2,3-*b*]furan-4,9-dione **23** were obtained from the reactions of **4** with amines in 67% and 48% yields, respectively. Furthermore, the reactions of **4** with acyclic amines (diethylamine, dipropylamine, isopropylamine, butylamine, *etc.*) gave the desired compound. Compound **4** was treated with sodium azide to give 2-azidonaphtho[2,3-*b*]furan-4,9-dione **28** in 42% yield. All these nucleophilic substitutions were carried out at room temperature. It was found that **4** showed high reactivity for amines. Unexpectedly, 2-morpholinonaphtho[2,3-*b*]furan-4,9-dione **13** was obtained from the reaction of **4** with 1-morpholino-1-cyclohexene.

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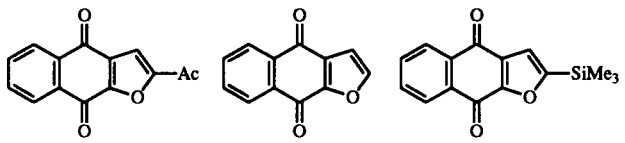
A number of naphtho[2,3-*b*]furan-4,9-diones, which have interesting biological activities, have been isolated from various plants [1]. For example, 2-acetylnaphtho-[2,3-*b*]furan-4,9-dione **1** isolated from *Tabebuia cassinoides* (Lam.) DC (*Bignoniaceae*) exhibits cytotoxic acivity [2]. Hayashi *et al.* [3] reported that the cytotoxic activity of 2-methylnaptho[2,3-*b*]furan-4,9-dione is three times that of **1**. As already mentioned, the activity of the 2-substituted naphtho[2,3-*b*]furan-4,9-diones varies with the type of substituent on the parent naphtho[2,3-*b*]furan-4,9-dione **2**. Therefore, organic chemists have an interest in the syntheses of these compounds. Up to now, a convenient method to directly introduce various substituents into the 2-position of **2** has not been reported. Recently, we also became interested in the syntheses of the 2-substituted compounds, and reported the preparations of the parent compound **2** [4], the natural product **1** [5,6], and 2-trimethylsilylnaphtho[2,3-*b*]furan-4,9-dione **3** [6]. The halodesilylations and nitrodesilylation of **3** have been reported in connection with studies to prepare the 2-substituted compound. 2-Chloronaphtho[2,3-*b*]furan-4,9-dione **4**, 2-bromonaphtho[2,3-*b*]furan-4,9-dione **5**, 2-iodonaphtho[2,3-*b*]furan-4,9-dione **6**, and 2-nitronaphtho-[2,3-*b*]furan-4,9-dione **7** were then obtained in good yield [6]. Furthermore, **4** was treated with oxygen, sulfur, and carbon nucleophiles to give the desired compound [7]. In the present paper, we report the nucleophilic substitutions of the 2-halo compounds **4-6** and a 2-nitro compound **7** with amines to prepare the 2-substituted compounds.



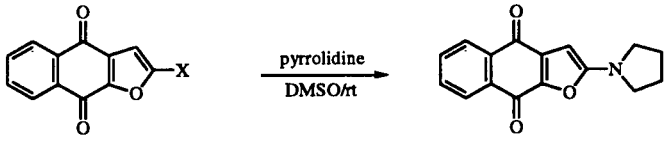
1 **2** **3**

Figure 1.

First, the reactions of a cyclic secondary amine with **4-7** were carried out to study the nucleophilic ability at the 2-position. Compound **4** was allowed to react with pyrrolidine (2.5 equivalents) in dimethyl sulfoxide at room temperature for 1 hour to give 2-(1-pyrrolidinyl)naphtho[2,3-*b*]furan-4,9-dione **8** in 64% yield. Compound **8** was purple needles, mp 231-233°. The ms of **8** showed a molecular ion peak at 267. The carbonyl group absorptions were observed at 1680 cm^{-1} and 1660 cm^{-1} in the ir spectrum. The pmr spectrum of **8** showed the benzene ring at δ 8.00 (2H, m) and δ 7.53 (2H, m), and the furan ring at δ 5.40 (1H, s). In the aliphatic region of the spectrum, the proton signals attributed to the pyrrolidine ring were observed at δ 3.50 (4H, m) and δ 2.03 (4H, m). Also, the structure was supported by elemental analyses.

In a similar manner, **5** was treated with pyrrolidine (2.5 equivalents) for 2.5 hours to give **8** in 63% yield. It was found that the leaving ability of the chloro group was slightly superior to the bromo group. Since the reactivity of **6** is considered to be lower than it of **4**, **6** was allowed to react with pyrrolidine (5 equivalents) for 20 hours to give **8** in 59% yield. On the other hand, when **7** was treated with pyrrolidine (2.5 equivalents) for 0.5 hour at room temperature, it gave only an intractable complex mixture. For this reason, it is thought that the decomposition of **7** proceeded in preference to the substitution, because **7** is susceptible to the base due to the influence of the nitro group. These results showed that the leaving ability of the chloro group was excellent. Compound **4** was then used as substrate in all the folowing substitutions. The reactions were carried out in dimethyl sulfoxide at room temperature.

Scheme 1



8

Compound	X	Pyrrolidine equivalents	Time (hours)	Yield (%)
4	Cl	2.5	1	64
5	Br	2.5	2.5	63
6	I	5	20	59
7	NO_2	2,5	0.5	–

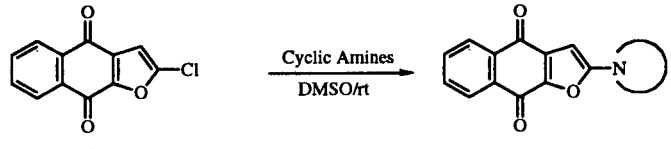
Next, in a similar manner, **4** was allowed to react with the cyclic amines as mentioned in Scheme 2 to give 2-substituted derivatives. However, in the case of 2-methylpiperidine and morpholine, the yields were very low. An improvement in the yields was accomplished by increasing the molar ratio of the amines.

Next, using acyclic amines, the reaction of **4** with diethylamine (2.5 equivalents) was also run in a similar manner, but the yield was very low. The amount of the amine was then largely increased to improve the yields. These results are shown in Scheme 3. However, when **4** was allowed to react with 70% ethylamine solution for 3.5 hour (the disappearance of **4** was confirmed by thin-layer chromatography), only an intractable complex was produced. The reactions of **4** with diisopropylamine and *tert*-butylamine were also attempted, but intractable complex mixtures were only obtained. It is thought that these results are due to the steric hindrance of the amines.

The reaction of **4** with sodium azide for 7 hours gave 2-azidonaphtho[2,3-*b*]furan-4,9-dione **28** in 42% yield. The structure was confirmed by various instrumental analyses.

Furthermore, the reaction of **4** with enamine as a carbanion was planned. Compound **4** was allowed to react

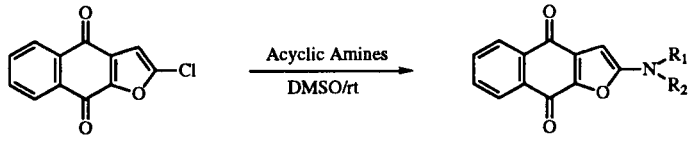
Scheme 2



4

Cyclic Amines	Equivalents	Time (hours)	Product	Substituent group	Yield (%)
piperidine	2.5	1	9	2-piperidino	65
2-methylpiperidine	20	20	10	2-(2-methylpiperidino)	55
3-methylpiperidine	2.5	2	11	2-(3-methylpiperidino)	41
4-methylpiperidine	2.5	2	12	2-(4-methylpiperidino)	75
morpholine	7.5	2	13	2-morpholino	71
4-methylpiperazine	2.5	7	14	2-(4-methyl-1-piperazinyl)	55
4-ethylpiperazine	2.5	7	15	2-(4-ethyl-1-piperazinyl)	65
4-(2-hydroxyethyl)piperazine	2.5	7	16	2-[4-(2-hydroxyethyl)-1-piperazinyl]	75
3-pyrroline	2.5	6	17	2-(3-pyrrolin-1-yl)	65
hexamethyleneimine	2.5	4	18	2-(perhydroxyazepin-1-yl)	79
heptamethyleneimine	2.5	6	19	2-(perhydroxyazocin-1-yl)	78

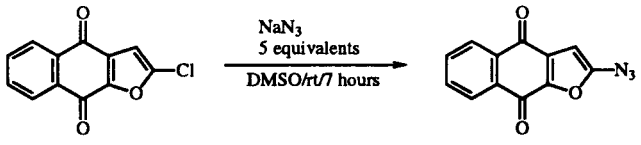
Scheme 3



4

Acyclic Amines	Equivalents	Time (hours)	Product	R_1	R_2	Yield (%)
$(Me)_2NH$ (50% in water)	60	0.5	20	Me	Me	67
$(Et)_2NH$	60	4	21	Et	Et	83
$(Pr)_2NH$	60	8	22	Pr	Pr	75
$(i\text{-}Pr)_2NH$	60	24	–	*i*-Pr	*i*-Pr	–
$EtNH_2$ (70% in water)	60	3.5	–	Et	H	–
$PrNH_2$	60	0.5	23	Pr	H	48
i-$PrNH_2$	60	4	24	*i*-Pr	H	24
$BuNH_2$	60	1	25	Bu	H	26
i-$BuNH_2$	60	5	26	*i*-Bu	H	49
s-$BuNH_2$	60	8	27	*s*-Bu	H	11
t-$BuNH_2$	60	55	–	*t*-Bu	H	–

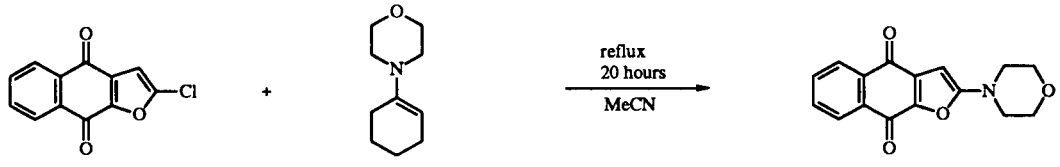
Scheme 4



4 **28**
Yield, 42%

with 1-morpholino-1-cyclohexene (12 equivalents) at room temperature for 24 hours in an atmosphere of argon, however, no product could be detected, and only **4** was recovered. The reaction mixture was then refluxed for 20 hours which produced purple needles, mp 241-242°. This compound was confirmed to be the 2-morpholino compound **13**, because the melting point and various spectral data were in acoordance with that of **13** [8]. This result showed that **4** was a more active compound against nucleophilic nitrogen than nucleophilic carbon.

Scheme 5



4 12 equivalents **13**
Yield, 39%

Therefore, **4** having a chloro group, has the highest leaving acivity of the substitutions of the 2-halo and 2-nitro compounds. Compound **4** was treated with cyclic secondary amines, acyclic secondary amines, and primary amines to produce the desired compounds. We found that the reactions were affected by steric factors. The yields of the substitution **4** with primary amines were not satisfactory, because primary amines have only low nucleophilic ability. Furthermore, a 2-azido compound **28** was obtained by the reaction of **4** with sodium azide. All these substitutions were carried out at room temperature. It was found that **4** has high reactivity aganst amines. However, the reaction of **4** with 1-morpholino-1-cyclohexene unexpectedly gave **13**. These results show that **4** was a convenient intermediate to produce 2-substituted naphthofuranquinones. Further studies on the nucleophilic substitutions of **4** with azoles are in progress. These results will be reported in due course.

EXPERIMENTAL

All melting points (open capillaries) were determined using a Yamato MP-21 and are uncorrected. The pmr spectra were determined at 60 MHz with a Nippon Denshi JNM PMX-60 SI spectrometer with tetramethylsilane as the internal reference. The pmr of **17** was also determined at 270 MHz using a Nippon Denshi JEOL GX270FT NMR spectrometer, because **17** was not completely dissolved in any solvent. The ir spectra were measured with a JASCO IR-810 spectrometer. The mass spectra were obtained using a Nippon Denshi JMS-700 spectrometer at 70 ev.

2-(1-Pyrrolidinyl)naphtho[2,3-*b*]furan-4,9-dione **8**.

Compound **4** (230 mg, 1 mmole) in dimethyl sulfoxide (20 ml) was added to pyrrolidine (180 mg, 2.5 mmoles) in dimethyl sulfoxide (4 ml) at room temperature. The mixture was stirred for 1 hour at the same temperature and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from ethanol-water to give 170 mg (64%) of **8** as purple needles, mp 231-233°; ir (potassium bromide): 1680, 1660 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.00 (2H, m, Ph), 7.53 (2H, m, Ph), 5.40 (1H, s, F-3), 3.50 (4H, m, pyrrolidine), 2.03 (4H, m, pyrrolidine); ms: m/z 268 (17), 267 (100), 184 (12), 183 (11), 127 (14).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.90: H, 5.05; N, 5.25.

In a simlar manner, **8** was obtained from the reaction of **5** and **6** with pyrrolidine in 63% and 59% yields, respectively.

General Reactions of **4** with Cyclic Secondary Amines.

Compound **4** (230 mg, 1 mmole) in dimethyl sulfoxide (20 ml) was added to cyclic secondary amines in dimethyl sulfoxide (4 ml) at room temperature. The mixture was stirred at the same temperature and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was purified by recrystallization to give corresponding compound. The quantity of amines and the reaction times were showed in Scheme 2.

2-Piperidinonaphtho[2,3-*b*]furan-4,9-dione **9**.

The yield was 65% as purple needles (ethanol-water), mp 162-163°; ir (potassium bromide): 1680, 1650 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.98 (2H, m, Ph), 7.52 (2H, m, Ph), 5.50 (1H, s, F-3), 3.43 (4H, m, piperidine), 1.67 (6H, m, piperidine); ms: m/z 282 (20), 281 (100), 184 (13).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.29; H, 5.46; N, 4.85.

2-(2-Methylpiperidino)naphtho[2,3-*b*]furan-4,9-dione **10**.

The yield was 55% as purple needles (ethanol-water), mp 143-144°; ir (potassium bromide): 1680, 1645 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.00 (2H, m, Ph), 7.57 (2H, m, Ph), 5.50

(1H, s, F-3), 4.32-4.13 (1H, m, piperidine), 3.88-3.67 (1H, m, piperidine), 3.38-2.90 (1H, m, piperidine), 1.70 (6H, bs, piperidine), 1.27 (3H, d, CH_3, 7 Hz); ms: m/z 296 (13), 295 (66), 281 (20), 280 (100).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.01; H, 5.96; N, 4.64.

2-(3-Methylpiperidino)naphtho[2,3-*b*]furan-4,9-dione **11**.

The yield was 41% as purple needles (ethanol-water), mp 212-213°; ir (potassium bromide): 1680, 1640 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.00 (2H, m, Ph), 7.53 (2H, m, Ph), 5.53 (1H, s, F-3), 3.93-3.70 (2H, m, piperidine), 3.45-3.17 (2H, m, piperidine), 1.97-1.15 (5H, m, piperidine), 0.95 (3H, d, CH_3, 7 Hz); ms: m/z 296 (20), 295 (100), 240 (12).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.04; H, 5.86; N, 4.65.

2-(4-Methylpiperidino)naphtho[2,3-*b*]furan-4,9-dione **12**.

The yield was 75% as purple needles (ethanol-water), mp 139-140°; ir (potassium bromide): 1680, 1650 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.95 (2H, m, Ph), 7.52 (2H, m, Ph), 5.52 (1H, s, F-3), 4.02-3.77 (2H, m, piperidine), 3.12-2.75 (2H, m, piperidine), 1.88-1.13 (5H, m, piperidine), 0.98 (3H, d, CH_3, 5 Hz); ms: m/z 296 (20), 295 (100), 210 (12).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.01; H, 6.00; N, 4.64.

2-Morpholinonaphtho[2,3-*b*]furan-4,9-dione **13**.

The yield was 71% as purplish red needles (acetonitrile), mp 242-243°; ir (potassium bromide): 1690, 1665 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.02 (2H, m, Ph), 7.58 (2H, m, Ph), 5.57 (1H, s, F-3), 3.78 (4H, t, morpholine, 5 Hz), 3.42 (4H, m, morpholine, 5 Hz); ms: m/z 284 (18), 283 (100), 225 (21), 197 (30), 157 (13).

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.63; H, 4.70; N, 4.98.

2-(4-Methyl-1-piperazinyl)naphtho[2,3-*b*]furan-4,9-dione **14**.

The yield was 55% as purple needles (ethanol-water), mp 151-152°; ir (potassium bromide): 1680, 1650 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.00 (2H, m, Ph), 7.51 (2H, m, Ph), 5.55 (1H, s, F-3), 3.48 (4H, t, piperazine, 5 Hz), 2.48 (4H, t, piperazine, 5 Hz), 2.33 (3H, s, CH_3); ms: m/z 297 (20), 296 (100), 295 (11), 211 (20), 71 (29), 70 (33).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.10; H, 5.56; N, 9.19.

2-(4-Ethyl-1-piperazinyl)naphtho[2,3-*b*]furan-4,9-dione **15**.

The yield was 65% as purple needles (ethanol-water), mp 146-147°; ir (potassium bromide): 1680, 1650 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.97 (2H, m, Ph), 7.55 (2H, m, Ph), 5.55 (1H, s, F-3), 3.47 (4H, t, piperazine, 5 Hz), 2.50 (4H, t, piperazine, 5 Hz), 2.43 (2H, q, CH_2CH_3, 7 Hz), 1.08 (3H, s, CH_2CH_3, 7 Hz); ms: m/z 311 (22), 310 (100), 309 (13), 295 (45), 211 (14), 84 (31), 57 (45), 56 (26).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.71; H, 5.92; N, 8.78.

2-[4-(2-Hydroxyethyl-1-piperazinyl]naphtho[2,3-*b*]furan-4,9-dione **16**.

The yield was 75% as purple needles (ethanol-water), mp 173-174°; ir (potassium bromide): 1680, 1645 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.00 (2H, m, Ph), 7.57 (2H, m, Ph), 5.55 (1H, s, F-3), 3.65 (2H, t, NCH_2CH_2OH, 6 Hz), 3.48 (4H, t, piperazine, 5 Hz), 2.62 (4H, t, piperazine, 5 Hz), 2.60 (2H, t, NCH_2CH_2OH, 6 Hz), 2.10 (1H, bs, OH, exchangeable proton); ms: m/z 326 (28), 296 (19), 295 (100), 70 (21), 56 (14).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.44; H, 5.62; N, 8.42.

2-(3-Pyrrolin-1-yl)naphtho[2,3-*b*]furan-4,9-dione **17**.

The yield was 65% as purple needles (acetonitrile), mp 247-248°; ir (potassium bromide): 1685, 1660 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.12 (2H, m, Ph), 7.65 (2H, m, Ph), 5.95 (2H, s, pyrroline), 5.52 (1H, s, F-3), 4.37 (4H, s, pyrroline); ms: m/z 266 (18), 265 (100), 264 (28), 183 (11), 127 (17), 76 (11), 54 (44).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.34; H, 4.42; N, 5.20.

2-(Perhydroazepin-1-yl)naphto[2,3-*b*]furan-4,9-dione **18**.

The yield was 79% as purple needles (ethanol-water), mp 177-178°; ir (potassium bromide): 1685, 1645 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.00 (2H, m, Ph), 7.53 (2H, m, Ph), 5.45 (1H, s, F-3), 3.88 (4H, t, perhydroazepine, 5 Hz), 1.67 (8H, m, perhydroazepine); ms: m/z 296 (21), 295 (100), 280 (11), 184 (12).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.00; H, 5.85; N, 4.57.

2-(Perhydroazocin-1-yl)naphtho[2,3-*b*]furan-4,9-dione **19**.

The yield was 78% as purple needles (ethanol-water), mp 195-196°; ir (potassium bromide): 1685, 1650 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.03 (2H, m, Ph), 7.57 (2H, m, Ph), 5.48 (1H, s, F-3), 3.57 (4H, t, perhydroazocine, 5 Hz), 2.03-1.57 (10H, m, perhydroazocine); ms: m/z 310 (21), 309 (100), 240 (12), 184 (11), 157 (13), 55 (15).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.63; H, 6.38; N, 4.43.

General Reaction of **4** with Secondary Amines and Primary Amines.

Compound **4** (230 mg, 1 mmole) in dimethyl sulfoxide (20 ml) was added to amines at room temperature. The mixture was stirred at the same temperature and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was purified by recrystallization to give corresponding compound. The quantity of amines and the reaction times were showed in Scheme 3 and Scheme 4.

2-Dimethylaminonaphtho[2,3-*b*]furan-4,9-dione **20**.

The yield was 67% as purple needles (ethanol), mp 243°; ir (potassium bromide): 1680, 1660 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.00 (2H, m, Ph), 7.50 (2H, m, Ph), 5.47 (1H, s, F-3), 3.10 (6H, s, CH_3); ms: m/z 242 (16), 241 (100), 199 (12), 198 (87), 157 (14), 129 (14), 101 (16).

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.57; H, 4.71; N, 5.80.

2-Diethylaminonaphtho[2,3-*b*]furan-4,9-dione **21**.

The yield was 83% as purple needles (ethanol-water), mp 158-160°; ir (potassium bromide): 1685, 1650 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 8.03 (2H, m, Ph), 7.53 (2H, m, Ph), 5.47 (1H, s, F-3), 3.47 (4H, q, CH_2 x 2, 7 Hz), 1.26 (6H, t, CH_3 x 2, 7

Hz); ms: m/z 270 (18), 269 (100), 255 (15), 254 (89), 226 (26), 184 (36), 157 (18).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.15; H, 5.73; N, 5.10.

2-Dipropylaminonaphtho[2,3-*b*]furan-4,9-dione **22**.

The yield was 75% as purple needles (ethanol-water), mp 163-164°; ir (potassium bromide): 1675, 1640 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.97 (2H, m, Ph), 7.52 (2H, m, Ph), 5.43 (1H, s, F-3), 3.35 (4H, t, $NCH_2CH_2CH_3$ x 2, 7 Hz), 1.68 (4H, m, $NCH_2CH_2CH_3$ x 2, 7 Hz), 0.95 (6H, t, $NCH_2CH_2CH_3$ x 2, 7 Hz); ms: m/z 298 (17), 297 (84), 269 (18), 268 (100), 227 (11), 226 (77), 184 (14), 157 (12).

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.43; H, 6.46; N, 4.77.

2-Propylaminonaphtho[2,3-*b*]furan-4,9-dione **23**.

The yield was 48% as purple needles (ethanol-water), mp 217-218°; ir (potassium bromide): 3240 (NH), 1680, 1650 (C=O) cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ 7.95 (2H, m, Ph), 7.62 (2H, m, Ph), 5.57 (1H, s, F-3), 3.22 (1H, s, NH, exchangeable proton), 3.17 (2H, dt, $NCH_2CH_2CH_3$, 3 and 7 Hz), 1.52 (2H, m, $NCH_2CH_2CH_3$), 0.93 (3H, t, $NCH_2CH_2CH_3$, 7 Hz); ms: m/z 256 (16), 255 (100), 227 (15), 226 (97), 213 (28), 185 (19), 157 (15), 101 (19).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.31; H, 5.21; N, 5.30.

2-Isopropylaminonaphtho[2,3-*b*]furan-4,9-dione **24**.

The yield was 24% as purple needles (ethanol-water), mp 205-206°; ir (potassium bromide): 3250 (NH), 1680, 1645 (C=O) cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ 7.98 (2H, m, Ph), 7.70 (2H, m, Ph), 5.60 (1H, s, F-3), 3.65 (1H, m, CH, 6 Hz), 3.28 (1H, s, NH, exchangeable proton), 1.23 (6H, d, CH_3 x 2, 6 Hz); ms: m/z 256 (13), 255 (81), 240 (15), 214 (14), 213 (100), 185 (21), 158 (17), 157 (13), 129 (13), 101 (13).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.46; H, 5.25; N, 5.44.

2-Butylaminonaphtho[2,3-*b*]furan-4,9-dione **25**.

The yield was 26% as purple needles (ethanol), mp 204-205°; ir (potassium bromide): 3230 (NH), 1675, 1650 (C=O) cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ 8.02 (2H, m, Ph), 7.72 (2H, m, Ph), 5.62 (1H, s, F-3), 3.30 (1H, s, NH, exchangeable proton), 3.27 (2H, m, $NHCH_2CH_2CH_2CH_3$), 1.70-1.13 (4H, m, $NHCH_2CH_2CH_2CH_3$), 0.90 (3H, m, $NHCH_2CH_2CH_2CH_3$); ms: m/z 270 (18), 269 (100), 227 (18), 226 (80), 213 (35), 185 (16), 157 (13), 129 (12), 101 (13).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.29; H, 5.73; N, 5.19.

2-Isobutylaminonaphtho[2,3-*b*]furan-4,9-dione **26**.

The yield was 49% as purple needles (ethanol), mp 228-229°; ir (potassium bromide): 3230 (NH), 1670, 1645 (C=O) cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ 7.95 (2H, m, Ph), 7.68 (2H, m, Ph), 5.63 (1H, s, F-3), 3.27 (1H, s, NH, exchangeable proton), 3.05 (2H, t, CH_2, 7 Hz), 1.85 (1H, m, CH), 0.93 (6H, d, CH_3 x 2, 7 Hz); ms: m/z 270 (14), 269 (74), 227 (16), 226 (100), 214 (11), 213 (38).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.38; H, 5.83; N, 5.19.

2-*sec*-Butylaminonaphtho[2,3-*b*]furan-4,9-dione **27**.

The yield was 11% as purple needles (ethanol-water), mp 167°; ir (potassium bromide): 3260 (NH), 1685, 1650 (C=O) cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ 7.95 (2H, m, Ph), 7.72 (2H, m, Ph), 5.62 (1H, s, F-3), 3.50 (1H, m, CH), 3.28 (1 H, s, NH, exchangeable proton), 1.48 (2H, q, CH_2CH_3, 7 Hz), 1.18 (3H, d, CH_3, 7 Hz), 0.92 (3H, t, CH_2CH_3, 7 Hz); ms: m/z 270 (11), 269 (64), 240 (38), 214 (14), 213 (100), 185 (18), 158 (14), 157 (11), 129 (12), 101 (11).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.14; H, 5.82; N, 5.08.

2-Azidonaphtho[2,3-*b*]furan-4,9-dione **28**.

Compound **4** (230 mg, 1 mmole) in dimethyl sulfoxide (20 ml) was added to the solution of sodium azide (320 mg, 5 mmoles) in dimethyl sulfoxide (8 ml) and water (2 ml) at room temperature. The mixture was stirred for 7 hours at the same temperature and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from ethanol to give 100 mg (42%) of **28** as yellow needles, mp 124-125° dec; ir (potassium bromide): 2160 (N_3), 1670 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 7.98 (2H, m, Ph), 7.55 (2H, m, Ph), 6.17 (1H, s, F-3); ms: m/z 239 (10), 232 (11), 211 (13), 184 (13), 183 (100), 127 (86), 104 (31), 76 (42); hrms; Calcd. for $C_{12}H_5N_3O_3$: 239.0331. Found: 239.0327.

The Reaction of **4** with 1-Morpholino-1-cyclohexene.

The mixture of **4** (230 mg, 1 mmole) and 1-morpholino-1-cyclohexene (2 g, 12 mmoles) in acetonitrile (30 ml) was refluxed for 20 hours in an atmosphere of argon, and poured into ice-cold water. The solution was extracted with dichloromethane. The organic layer was washed with brine, then dried over anhydrous sodium sulfate. The solution was evaporated and the residue was recrystallized from acetonitrile to give 110 mg (39%) of **13** as purple needles, mp 241-242° (mp 242-243° [8]).

REFERENCES AND NOTES

[1] M. Tisler, Advances in Heterocyclic Chemistry, Vol **45**, A. R. Katritzky, ed, Academic Press, Inc., San Diego, 1989, pp 56-63.

[2] M. M. Rao and D. G. I. Kingston, *J. Nat. Prod.*, **45**, 600 (1982).

[3] T. Hayashi, F. T. Smith and K. H. Lee, *J. Med. Chem.*, **30**, 2005 (1987).

[4] J. Koyanagi K. Yamamoto, K. Nakayama and A. Tanaka, *J. Heterocyclic Chem.*, **31**, 1030 (1994).

[5] J. Koyanagi, K. Yamamoto, K. Nakayama and A. Tanaka, *J. Heterocyclic Chem.*, **32**, 1289 (1995).

[6] J. Koyanagi, K. Yamamoto, K. Nakayama and A. Tanaka, *J. Heterocyclic Chem.*, **34**, 407 (1997).

[7] J. Koyanagi, K. Yamamoto, K. Nakayama and A. Tanaka, *Chem. Pharm. Bull.*, **45**, 1579 (1997).

[8] Compound **13** was obtained the nucleophilic substitution of **4** with morpholine.