SHORT-STEP SYNTHESIS OF 1,3-DISUBSTITUTED NAPHTHO[2,3-*c*]FURAN-4,9-DIONE AND NAPHTHO[2,3-*b*]FURAN-4,9-DIONE BY THE FRIEDEL-CRAFTS REACTION

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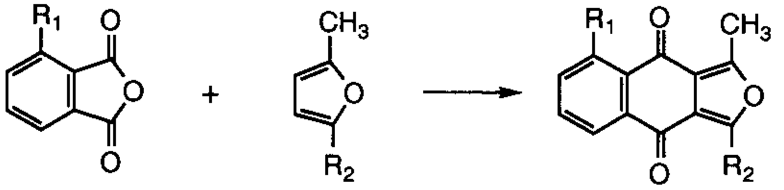
Abstract - 1,3-Dialkylnaphtho[2,3-*c*]furan-4,9-diones were obtained by the Friedel-Crafts reaction of phthalic anhydride with 2,5-dialkylfurans. The reaction of phthalic anhydride with 2-acetyl-5-methylfuran, instead of 2,5-dialkylfurans, produced 2-methylnaphtho[2,3-*b*]furan-4,9-dione. The application of this method to the synthesis of 8-hydroxynaphtho[2,3-*b*]furan-4,9-dione [isodiodantunezone] is also described.

Several naphtho[2,3-*c*]furan-4,9-dione derivatives that exhibit antimicrobial activity have been isolated from fungi[1] and plants.[2] Many naphtho[2,3-*b*]furan-4,9-diones with interesting biological activities have also been isolated from various plants.[3] However, there have been a few reports[4,5] on the synthesis of the furanoquinones, which have relatively simple structures. In addition, in some of the previous reports the yields were low and numerous steps were required to synthesize furanoquinones. In a continuation of our work on the



(**1A**) $R_1 = H$
(**1B**) $R_1 = OH$

(**2a**) $R_2 = CH_3$
(**2b**) $R_2 = CH_2CH_3$

(**3A-a**) $R_1 = H, R_2 = CH_3$
(**3A-b**) $R_1 = H, R_2 = CH_2CH_3$
(**3B-a**) $R_1 = OH, R_2 = CH_3$

constituents of plants, we have found that anthraquinones and azaanthraquinones have inhibitory activities on Epstein-Barr virus early antigen activation[6] and studied the connection with their electronic properties[7] and the correlation with the redox potentials of the anthraquinones.[8] We therefore synthesized several furanoquinones to compare their biological activities with those of anthraquinones and azaanthraquinones.

This report describes the short-step synthesis of naphtho[2,3-*c*]furan-4,9-dione and naphtho[2,3-*b*]furan-4,9-dione derivatives by the Friedel-Crafts reaction of phthalic anhydride and substituted furans.

In addition, by applying the results, the synthesis of 8-hydroxy-naphtho[2,3-*b*]furan-4,9-dione, isodiodantunezone, which was isolated from *Lantana achyrantifolia*,[9] is reported.

After a mixture of phthalic anhydride (**1A**) and Lewis acid ($AlCl_3$) in *o*-dichlorobenzene was stirred for 30 min in a glass tube, a solution of 2,5-dimethylfuran (**2a**) in *o*-dichlorobenzene was added. The glass tube was sealed and the mixture was heated at 120°C to produce 1,3-dimethylnaphtho[2,3-*c*]furan-4,9-dione (**3A-a**). The yields and reaction time are summarized in Table I.

We investigated the effect of Lewis acids on this reaction and found that $AlCl_3$ gave the best result (BF_3· etherate [yield 3%]; $FeCl_3$, $ZnBr_2$, $TiCl_4$, Et_2AlCl, Nafion [trace-0%]). We also tried the reaction in several other solvents, of which *o*-dichlorobenzene gave the best

Table **I.** Yields of (**3A-a**)

$AlCl_3$	reaction time	yield (%)
2.5 eq.	20 h[a]	26
"	5 h[a]	30
4.5 eq.	5 h[a]	0
2.5 eq.	20 h[b]	30
"	10 h[b]	26
"	6 h[b]	45
"	2 h[b]	32

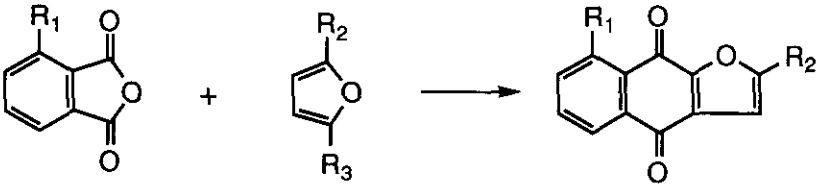
a: in an open tube
b: in a sealed tube

result (nitrobenzene [2.5%]; benzene, $CHCl_3$ [0%]).

Treatment of 2-ethyl-5-methylfuran (**2b**) with **1A** under the same conditions produced 1-ethyl-3-methylnaphtho[2,3-*c*]furan-4,9-dione (**3A-b**) in 21% yield. The Friedel-Crafts reaction of 3-hydroxyphthalic anhydride (**1B**) with **2a** produced 1,3-dimethyl-5-hydroxynaphtho[2,3-*c*]furan-4,9-dione (**3B-a**) in 18% yield.

The reaction of **1A** with other 2,5-disubstituted furans (R_2=CH_3, R_3= $COCH_3$, CHO, $COOCH_3$, CH_2OH, or CH_2OCH_3) in *o*-dichlorobenzene and in nitrobenzene afforded no naphtho[2,3-*c*]furan-4,9-dione derivative under the present conditions. In the case of the reaction of **1A** with 2-acetyl-5-methylfuran (**2C**) in nitrobenzene, 2-methylnaphtho[2,3-*b*]furan-4,9-dione (**4A**) was obtained in 4% yield. The reaction of **1B** with **2c** in nitrobenzene for 2 h produced 8-hydroxy-2-methylnaphtho[2,3-*b*]furan-4,9-dione (**4B**) in 9% yield. The structure of **4B** was confirmed by comparison with an authentic sample, which was synthesized by the cyclization of 2,8-dihydroxy-3-(2-propenyl)-1,4-naphthoquinone (**6**) prepared from 3,5-dihydroxynaphthoquinone (**5**)[10] and propionaldehyde.[11,12]

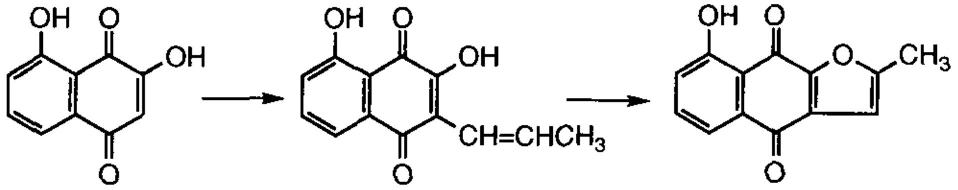
On the basis of the above results, we carried out the synthesis of isodiodantunezone, 8-hydroxynaphtho[2,3-*b*]furan-4,9-dione. The Friedel-Crafts reaction of **1B** with 2-acetylfuran (**2d**) in nitrobenzene in the presence of $AlCl_3$ at 120°C for 2 h produced 8-hydroxynaphtho[2,3-*b*]furan-4,9-dione (**7**) in 9.8% yield. Its spectroscopic data coincided with those described in the literature.[9]



(**1A**) R_1= H
(**1B**) R_1= OH

(**2c**) R_2= CH_3
R_3= $COCH_3$
(**2d**) R_2= H
R_3= $COCH_3$

(**4A**) R_1= H, R_2= CH_3
(**4B**) R_1= OH, R_2= CH_3
(**7**) R_1= OH, R_2= H



(**5**) (**6**) (**4B**)

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. ^1H-NMR spectra were determined in $CDCl_3$ with Me_4Si as an internal reference on a NEVA NV-21 instrument. MS spectra were recorded on a JEOL JMS-01SG spectrometer. IR spectra were measured on a Perkin Elmer 1600 FTIR spectrophotometer. Column chromatography was carried out on silica gel (Kieselgel 60, 70-230 mesh, Merck) with appropriate solvents.

General method for the Friedel-Crafts reaction:

1,3-Dimethylnaphtho[2,3-c]furan-4,9-dione (**3A-a**)

A solution of 2,5-dimethylfuran (0.32 g, 3.3 mmol) in *o*-dichlorobenzene (0.5 mL) was added dropwise to the mixture of phthalic anhydride (0.5 g, 3.4 mmol) and $AlCl_3$ (1.15 g, 8.6 mmol) in *o*-dichlorobenzene (4 mL) in a glass tube, and the mixture was stirred for 30 min at rt. After the glass tube was sealed, the mixture was heated for 6 h at 120°C. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over $MgSO_4$, and then evaporated to dryness to give a residue. The residue was separated by column chromatography with benzene. The first yellow eluate from benzene was evaporated to dryness and the residue was recrystallized from methanol to give 1,3-dimethylnaphtho[2,3-*c*]furan-4,9-dione in the form of yellow crystals. Yield: 338 mg (45.3%). mp: 168-170°C (MeOH) (lit.,[5b]: 171-172°C).

1-Ethyl-3-methylnaphtho[2,3-c]furan-4,9-dione (**3A-b**)

mp: 105-108°C (MeOH). IR ($CHCl_3$) cm^{-1}: 1672, 1596, 1523. ^1H-NMR ($CDCl_3$) δ: 1.34 (3H, t, *J*=7.5 Hz, CH_2CH_3), 2.73 (3H, s, CH_3), 3.14 (2H, q, *J*=7.5 Hz, CH_2), 7.75 (2H, m, 6,7-H), 8.27 (2H, m, 5,8-H). MS *m/z*: 240.0786 (M^+, calcd for $C_{15}H_{12}O_3$, 240.0786). *Anal*. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.11; H, 5.07.

1,3-Dimethyl-5-hydroxynaphtho[2,3-c]furan-4,9-dione (**3B-a**)

mp: 168-172°C (MeOH). IR ($CHCl_3$) cm^{-1}: 1669, 1636, 1603. ^1H-NMR ($CDCl_3$) δ: 2.71, 2.73 (3H each, s, 1,3-CH_3), 7.24 (1H, dd, *J*=8, 1.5 Hz, 6-H), 7.62 (1H, dd, *J*=7, 8 Hz, 7-H), 7.78 (1H, dd, *J*=7, 1.5 Hz, 8-H), 12.92 (1H, s, OH). MS *m/z*: 242.0578 (M^+, calcd for $C_{14}H_{10}O_4$, 242.0578). *Anal*. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.21; H, 4.46.

2-Methylnaphtho[2,3-b]furan-4,9-dione (**4A**)

mp: 245-246°C (MeOH) (lit.,[12]: 245-246°C). IR ($CHCl_3$) cm^{-1}: 1670, 1595. ^1H-NMR ($CDCl_3$) δ: 2.56 (3H, s, CH_3), 6.64 (1H, s, 3-H), 7.78 (2H, m, 6,7-H), 8.18 (2H, m, 5,8-H). MS *m/z*: 212.0470 (M^+, calcd for

$C_{13}H_8O_3$, 212.0473).

8-Hydroxy-2-methylnaphtho[2,3-b]furan-4,9-dione (**4B**)

mp: 183-184°C (MeOH). IR ($CHCl_3$) cm^{-1}: 1676, 1644, 1583, 1539. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s, CH_3), 6.62 (1H, s, 3-H), 7.25 (1H, d, *J*=8 Hz, 7-H), 7.58 (1H, t, *J*=8 Hz, 6-H), 7.70 (1H, d, *J*= 8 Hz, 5-H), 12.09 (1H, s, OH). MS *m/z*: 228.0420 (M^+, calcd for $C_{13}H_8O_4$, 228.0422). *Anal.* Calcd for $C_{13}H_8O_4$ + 0.1XH_2O: C, 67.88; H, 3.57. Found: C, 67.74; H, 3.59.

Another method: 3,5-Dihydroxynaphthoquinone (**5**) (1 g, 5.3 mmol) was dissolved in acetic acid (15 mL) and concentrated hydrochloric acid (1 mL) was added, followed immediately by the addition of propionaldehyde (2.5 mL, 34 mmol). The mixture was stirred at 75°C for 30 min and then poured into water (150 mL). After cooling, the mixture was extracted with benzene. The benzene solution was washed with water, dried over $MgSO_4$, and evaporated to dryness to give a residue. The residue was purified by column chromatography with benzene to yield 2,8-dihydroxy-3-(2-propenyl)-1,4-naphthoquinone (**6**) as an oil (0.75 g, 62%). (**6** is unstable, and therefore it was used immediately in the subsequent reaction.) ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, d, *J*=6 Hz, CH_3), 6.62 (1H, d, *J*=14 Hz, -CH=), 7.10 (1H, m, =C$\underline{H}$-CH_3), 7.20 (1H, dd, *J*=7, 1.5 Hz, 7-H), 7.54 (1H, t, *J*=7 Hz, 6-H), 7.64 (1H, dd, *J*=7, 1.5 Hz, 5-H), 11.14 (1H, s, OH). EIMS *m/z*: 230 (M^+).

A mixture of **6** (100 mg, 0.43 mmol) and DDQ (150 mg, 0.66 mmol) in benzene (10 mL) was refluxed for 2 h. After cooling, the reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by column chromatography with benzene to give **4B** in the form of yellow crystals (30 mg, 30.3%).

8-Hydroxynaphtho[2,3-b]furan-4,9-dione (**7**)

mp: 167-168°C (MeOH) (lit.,[9]: 167-168°C).

REFERENCES

1. D. Parisot, M. Devys, J. P. Ferezou, and M. Barbier, *Phytochemistry*, 1983, **22**, 1301; J. H. Tatum, R. A. Baker, and R. E. Berry, *Phytochemistry*, 1987, **26**, 2499; H. Fujimoto, H. Okuyama, Y. Motohashi, E. Yoshida, and M. Yamazaki, *Maikotokishin*, 1995, **41**, 61.
2. T. Hanumaiah, G. S. R. Rao, C. P. Rao, K. V. J. Rao, H. J. Cowe, P. J. Cox, R. A. Howie, D. S. Marshall, and R. H. Thomson, *Tetrahedron*, 1985, **41**, 635; J. Koyama, T. Ogura, and K. Tagahara, *Phytochemistry*, 1994, **37**, 1147.
3. M. Tisler, '*Advances in Heterocyclic Chemistry* ,' vol. 45, ed. by A. R. Katritzky, Academic Press, Inc., San Diego, 1989, pp. 56-63.
4. M. M. Rao and D. G. I. Kingston, *J. Nat. Prod.*, 1982, **45**, 600; A. V. Pinto, M. Do C. Pinto, M. A. Aguiar, and R. S. Capella, *Ann. Acad. Bras. Cienc.*, 1982, **54**, 115 (*Chem. Abstr.*, 1982, **97**, 162672a); C. C. Lopes, R. S. C. Lopes, A. V. Pinto, and P. R. R. Costa, *J. Heterocycl. Chem.*, 1984, **21**, 621; V. F. Ferrira, A. V. Pinto. M. C. F. R. Pinto M. C. Da Cruz, and A. Clarino, *Synth. Commun.*, 1989, **19**, 1061.
5. a) L. M. Gomes, *C. R. Acad. Sci., Ser. C*, 1974, **278**, 1055;
   b) D. V. Nightingale and B. Sukornick, *J. Org. Chem.*, 1959, **24**, 497;
   c) M. Davys, M. Barbier, and D. Rarisot, *Heterocycles*, 1990, **31**, 1485.
6. T. Konoshima, M. Kozuka, J. Koyama, T. Okatani, K. Tagahara, and H. Tokuda, *J. Nat. Prod.*, 1989, **52**, 987.
7. K. Tagahara, J. Koyama, T. Ogura, T. Konoshima, M. Kozuka, H. Tokuda, H. Nishino, and A. Iwashima, *Chem. Express*, 1992, **7**, 557.
8. J. Koyama, K. Tagahara, T. Osakai, Y. Tsujino, S. Tsurumi, H. Nishino, and H. Tokuda, *Cancer Lett.*, 1997, **115**, 179.
9. C. Abeygunawardena, V. Kumar, D. S. Marshall, R. H. Thomson, and D.

B. M. Wickramaratne, *Phytochemistry*, 1991, **30**, 941.

10. A. Closse and H. P. Sigg, *Helv. Chim. Acta*, 1973, **56**, 619.
11. S. C. Hooker, *J. Am. Chem. Soc.*, 1936, **58**, 1163.
12. T. Hayashi, F. T. Smith, and K. H. Lee, *J. Med. Chem.*, 1987, **30**, 2005.

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