The Synthesis of 5,8-Difluoronaphtho[2,3-*c*]thiophene-4,9-dione and its Facile Conversion to 2-[2-(Dimethylamino)ethyl]-5-[2-(dimethylamino)ethylamino]-8-fluoronaphtho[2,3-*c*]pyrrole-4,9-dione

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The synthesis of 5,8-difluoronaphtho[2,3-*c*]thiophene-4,9-dione (**2a**) has been accomplished. Treatment of **2a** with 2,2-dimethylaminoethylamine leads to 2-[2-(dimethylamino)ethyl]-5-[2-(dimethylamino)ethylamino]-8-fluoronaphtho[2,3-*c*]pyrrole-4,9-dione (**6**).

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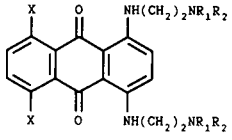
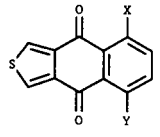
Anthracene-9,10-diones with specific 1,4-bis[aminoalkyl]amino substitutents (*e.g.*, **1a** and **1b**) have outstanding anticancer activities [1-5]. As part of a program dealing with structure-activity relationships of these chemotypes, we have been exploring the synthesis of heterocyclic analogues related to **1** [6].



1 a, X = R_1 = H, R_2 = $(CH_2)_2OH$
b, X = OH, R_1 = H, R_2 = $(CH_2)_2OH$
c, X = H, R_1 = R_2 = CH_3

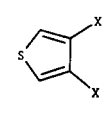


2 a, X = Y = F
b, X = Y = $NH(CH_2)_2N(CH_3)_2$
c, X = Cl, Y = H

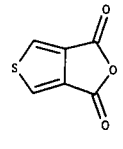
Our previous studies have shown that the fluorides in 1,4- and 1,8-difluoroanthracene-9,10-diones undergo facile stepwise room temperature displacements by amines to yield the corresponding 1,4-bis- and 1,8-bis-(aminoalkyl)-aminoanthracene-9,10-diones [7,8]. Based on these results, we have synthesized 5,8-difluoronaphtho[2,3-*c*]thiophene-4,9-dione (**2a**) and investigated the displacements of the fluorides by 2,2-dimethylaminoethylamine in an attempt to prepare the quinone **2b** for antitumor comparisons with the carbocyclic model **2c**. We wish to report the results of this displacement study.

Results and Discussion.

Commercial 3,4-dibromothiophene (**3a**) was treated with cuprous cyanide to obtain 3,4-dicyanothiophene (**3b**) which was hydrolyzed by potassium hydroxide in refluxing 1,2-ethanediol to the dicarboxylic acid **3c** [9]. Anhydride **4** was obtained on refluxing **3c** in acetic anhydride [10].



3 a, X = Br
b, X = CN
c, X = CO_2H



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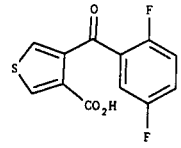

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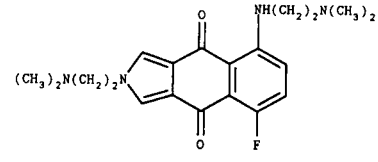
Treatment of anhydride **4** with excess 1,4-difluorobenzene in the presence of aluminum chloride gave the keto acid **5**. The crude **5** was cyclized to the desired quinone **2a** by treatment with hot polyphosphoric acid (32% overall conversion from **4**).



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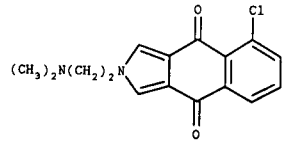
Treatment of **2a** with 2,2-dimethylaminoethylamine in DMSO as solvent at room temperature for several hours followed by tlc analysis (silica gel) showed the presence of a major reddish-orange compound. No further change in the reaction mixture could be detected after 20 hours at room temperature or at 60° for 48 hours. Workup of the reaction mixture led to the isolation of the pyrrole analogue **6** (25%) which was readily identifiable by ^1H nmr spectroscopy.

Of particular interest in this reaction is the fact that the fluoride displacement is competitive with the thiophene to pyrrole ring conversion. Attempts to establish the displacement sequence have been unsuccessful. The remaining fluoride on **6** is deactivated by the nitrogens and resists further substitution.



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One precedent exists for this thiophene to pyrrole conversion in that Marecki and Butke [11] have reported that the chloro analog **2c** on treatment with 2,2-dimethylaminoethylamine led to **7** (31%). Mechanisms for this transformation have been proposed.

The biological evaluations of **6** will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Proton and ^{13}C nmr were recorded on a Bruker WP-250 pulsed Fourier transform spectrometer. For thin layer chromatography precoated silica gel and alumina plates (Eastman Chromagram sheets) with fluorescent indicator were used. Baker analyzed 80-200 mesh silica gel was used for column chromatography. Mass spectra were run on a Finnigan MAT 4610 instrument. Microanalysis were performed by Robertson Laboratory, Madison, NJ.

3,4-Dicyanothiophene (**3b**):

This was prepared according to the procedure of McDowell and Wisowaty [9] in 67% yield, mp 165-166°, lit mp 169-170°.

3,4-Thiophenecarboxylic Acid (**3c**).

This was prepared by the method of McDowell and Wisowaty [9] in 51% yield, mp 226-228°, lit mp 227-229°.

3,4-Thiophenedicarboxylic Anhydride (**4**).

This was prepared by the method of Reinecke *et al.* [10] in a 72% yield, mp 143-144°, lit mp 144-146°.

5,8-Difluoronaphtho[2,3-c]thiophene-4,9-dione (**2a**).

A mixture of **4** (0.21 g, 1.36 mmoles), aluminum chloride (0.73 g, 5.50 mmoles) and 1,4-difluorobenzene (5 m*l*) was refluxed for 48 hours. Upon removal of the excess 1,4-difluorobenzene by distillation, the reaction mixture was cooled in an ice bath, hydrochloric acid (20 m*l*, 1*N*) was added and the product was filtered. The solid was dissolved in a minimum of chloroform and low-boiling petroleum ether was added to precipitate **5** (0.165 g, 45%). This crude product and polyphosphoric acid (1.5 g) were heated in an oil bath at 150° for 3 hours. The hot mixture was poured over ice (15 g) and the product was filtered. Purification by column chromatograhy on alumina, eluting with chloroform, followed by crystallization from chloroform/ligroin gave yellow crystals of **2a** (0.11 g, 32% based on the anhydride), mp 231-232°; ^1H nmr (deuteriochloroform): 8.37 (s, 2H), 7.47 (m, 2H); ^{13}C nmr (deuteriochloroform): 176.55, 158.59, 137.01, 132.74, 124.56, 123.36; ms: m/z (relative intensity) 250.0 (100, M^+), 222.0 (87.1), 193.9 (48.2).

Anal. Calcd. for $C_{12}H_4F_2O_2S$: C, 57.61; H, 1.61. Found: C, 57.33; H, 1.52.

2-[2-(Dimethylamino)ethyl]-5-[2-(dimethylamino)ethylamino]-8-fluoronaphtho[2,3-*c*]pyrrole-4,9-dione (**6**).

A solution of **2a** (92 mg, 0.37 mmole) and 2,2-dimethylaminoethylamine (195 mg, 2.2 mmoles) in dimethyl sulfoxide (2 m*l*) was heated in an oil bath to 50-60° for 48 hours. The DMSO was removed under reduced pressure and the product purified by column chromatography on silica gel eluting with 7% methanol in chloroform. Crystallization from a mixture of toluene/ligroin yielded reddish-orange needles (34 mg, 25%), mp 162-164°; ^1H nmr (deuteriochloroform): 9.93 (s, 1H), 7.39 (d, 1H), 7.35 (d, 1H), 7.24 (m, 1H), 6.95 (m, 1H), 4.03 (t, 2H), 3.35 (q, 2H), 2.66 (m, 4H), 2.34 (s, 6H), 2.23 (s, 6H); ms: m/z (relative intensity) 372.2 (0.72, M^+), 327.1 (1.02), 314.1 (2.24), 72.0 (9.03), 58.0 (100).

Anal. Calcd. for $C_{20}H_{25}FN_4O_2$: C, 64.49; H, 6.79; N, 15.03. Found: C, 64.23; H, 6.95; N, 14.79.

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