A New Synthesis of Naphtho[2,3-*c*]pyrroles. Conversion of Naphtho[2,3-*c*]thiophene-4,9-diones to Naphtho[2,3-*c*]pyrrole-4,9-diones.

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A series of 2-substituted-4,9-dihydronaphtho[2,3-*c*]pyrrole-4,9-diones was prepared by the reaction of 4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-diones with primary amines under mild conditions. The presence of halogen in the naphtho[2,3-*c*]thiophene-4,9-dione and the presence of hydroxyl, ether, or tertiary amine functions in the amine reagent do not interfere with the course of the reaction.

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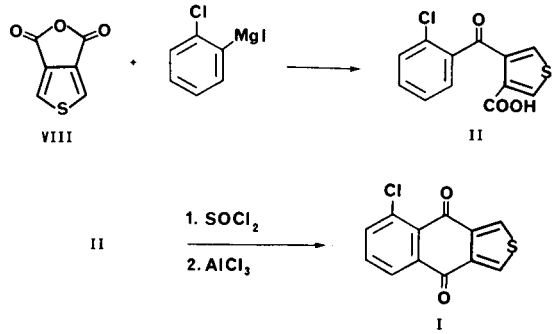
The conversion of thiophenes to pyrroles is an unusual reaction requiring special catalysts, conditions, or substituent patterns and which usually affords the pyrrole in very low yield. Pyrolysis of thiophene in the presence of ammonia over aluminum oxide at 350-450° gives 3% yields of pyrrole [1]. Middleton, *et al.* [2] were able to convert 2,5-diamino-3,4-dicyanothiophene to 2-amino-3,4-dicyano-5-mercaptopyrrole under basic aqueous conditions. This reaction required that the pyrrole nitrogen be present as a substituent at the two or five position of the starting thiophene. More recently it has been shown that dilute solutions of thiophene and methylthiophenes in propylamine or in cyclohexylamine undergo a photochemical conversion to *N*-substituted pyrroles in 5-8% yields [3,4], while benzo[*b*]thiophene does not [5]. This reaction is thought to involve formation of a cyclopropenyl thioketone or thioaldehyde [6] by analogy to a similar photochemical process exhibited by furans [7] but remains under investigation [8]. Colburn and coworkers have reported that *N*-(2-nitrothiophene-3-ylidene)aniline reacts with triethyl phosphite to give 1-phenyl-3-cyanopyrrole while the 3-nitro-2-ylidene isomer led to 5-phenylthieno[3,2-*c*]-pyrazole [9,10].

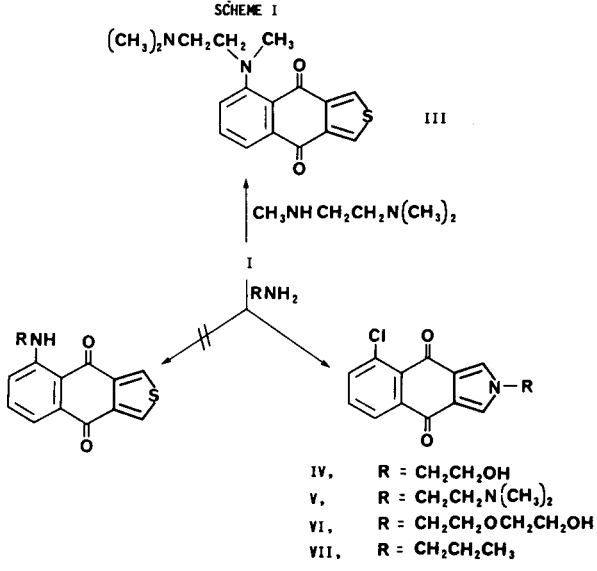
In the course of our studies of the displacement of halogen from various aromatic systems we examined the reactions of 5-chloro-4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-dione (I) with amines. This compound was prepared by intramolecular Friedel-Crafts acylation of 4-(2-chlorobenzoyl)thiophene-3-carboxylic acid (II) which was in turn prepared by reaction of 2-chlorophenylmagnesium iodide [11] with 3,4-thiophenedicarboxylic anhydride [12] (eq. 1).

When I was allowed to react with methyl 2-dimethylaminoethylamine in refluxing dioxane the product of halogen displacement III was obtained. When the reaction was attempted with ethanolamine (Scheme I) the product obtained initially appeared to be the expected product of halogen displacement, however, elemental analyses revealed the absence of sulfur and the presence of chlorine. The spectroscopic data for this material were consistent with an *N*-substituted pyrrole and suggested IV as the product. In the nmr spectrum of I the protons at C1 and C3 appear at 8.55 ppm and this peak would be expected to remain close to this position had the thiophene ring remained intact. For IV-VII and XI these signals appear near 7.7 ppm. This upfield shift is consistent with conversion of the thiophene moiety to a pyrrole and is observed for the parent heterocycles where the difference is 0.7 ppm.

Similar results were obtained when I was allowed to react with dimethylaminoethylamine and with 2-(2-hydroxyethoxy)ethylamine to give V and VI, respectively. As both



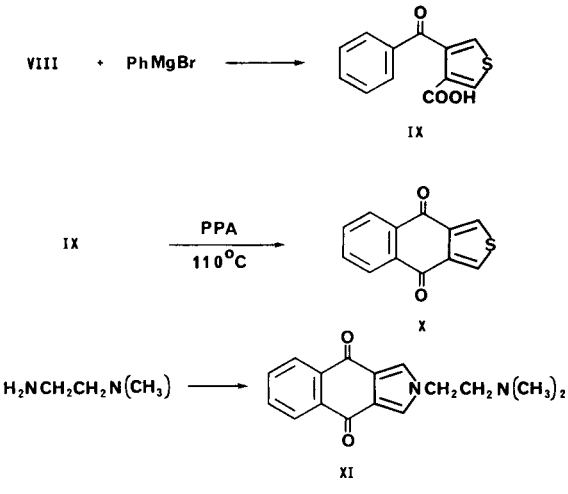
SCHEME I



of these amines bear functional groups apparently not involved in the reaction it was of interest to determine if a simple primary amine was sufficient for the conversion. Accordingly, reaction of I with *n*-propylamine was carried out and the product was identified as pyrrole VII. This result demonstrates that the reaction requires only a simple primary amine and does not depend on any unusual intramolecular effect arising from other functional groups present in the amine.

It was also of interest to determine if the halogen in I exerted an effect, perhaps through the quinone system, which made pyrrole formation possible. The unsubstituted naphtho[2,3-*c*]thiophene (X) required to test this possibility was prepared by ring closure of the benzoylthiophene IX under acidic conditions (Scheme II). Compound IX was

SCHEME II



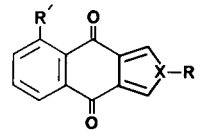
prepared by reaction of anhydride VIII [12] with phenylmagnesium bromide. When X was allowed to react with 2-dimethylaminoethylamine, pyrrole XI was obtained in 40% purified yield. This result supports the hypothesis that this thiophene to pyrrole conversion is a function of the amine and the naphtho[2,3-*c*]thiophene system alone and is not due to the presence of other substituents on either reactant.

If the reaction takes place as described hydrogen sulfide should be evolved. During the synthesis of XI a gentle stream of argon was passed through the reaction solution then into a trap containing aqueous lead acetate solution. A black precipitate gradually formed in the trap as the reaction progressed. This solid was collected and identified as lead sulfide by X-ray powder diffraction [14] and accounted for 37% of the theoretical yield of hydrogen sulfide.

It is reasonable to suggest that this reaction is assisted by the strongly electron withdrawing quinone function. A possible mechanism is illustrated in Scheme III. Nucleophilic attack of the amines on C1 or C3 of I or X assisted by the quinone system in a Michael sense should lead to thioaminal XII which can revert to X or undergo yet another quinone assisted addition at C3 or C1 leading to XIII. A ring opening route may also be envisioned where formation of XIV from XII would avoid any ring strain associated with XIII. Return to the quinone state from either XIII or XIV would enhance expulsion of hydrogen sulfide to give the observed pyrroles. This mechanism is consistent with the observed formation of hydrogen sulfide and of the pyrroles. It also explains the reaction of the secondary amine exclusively by halogen displacement since this reagent could undergo initial attack but could not continue to a stable pyrrole. It is also possible that a mechanism similar to that suggested by Couture, *et al.* [6] operates wherein the naphtho[2,3-*c*]thiophene would contract to a naphtho[2,3-*c*]cyclopropene thioaldehyde. Imine formation from the thioaldehyde followed by ring expan-

TABLE I

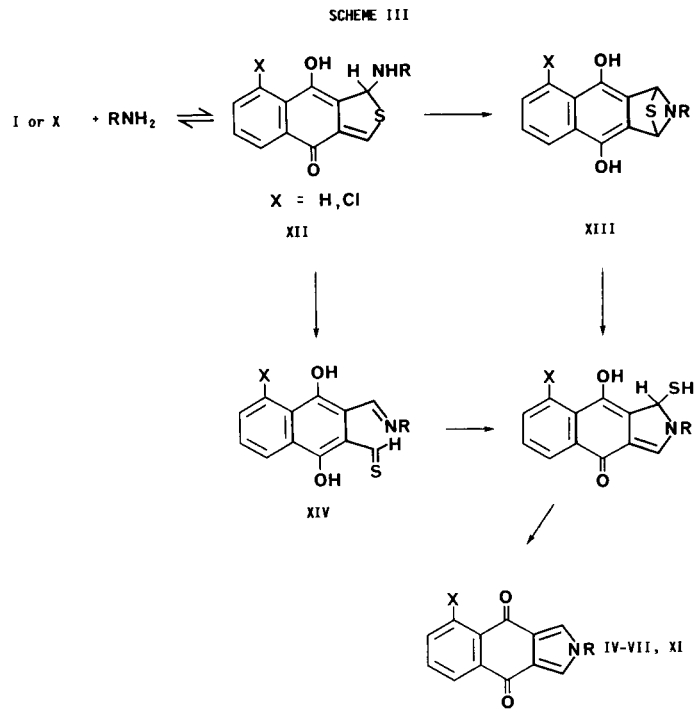
2-Substituted 4,9-Dihydronaphtho[2,3-*c*]pyrrole-4,9-diones and 4,9-Dihydronaphtho[2,3-*c*]thiophene-4,9-diones



Compound	R'	X-R	mp (°C)	Crude Yield (%)	Recrystallization Solvent
IV	Cl	NCH_2CH_2OH	233-235	21	Ethyl Acetate
V	Cl	$NCH_2CH_2N(CH_3)_2$	212-215	31	Ethyl Acetate/Ether (1/9)
VI	Cl	$NCH_2CH_2OCH_2CH_2OH$	161.5-162.5	52	Ethyl Acetate
VII	Cl	$NCH_2CH_2CH_3$	178-179	67	Ethanol
XI	H	$NCH_2CH_2N(CH_3)_2$	191-193	72	Ether
III [a]	$CH_3NCH_2CH_2N(CH_3)_2$	S	272-275	38	Ethanol
I	Cl	S	190-192	31	Methanol

[a] The free base was obtained as a red oil which was converted to the dihydrochloride salt for ease of handling.

SCHEME III



sion would lead to a pyrrole. No data is available to distinguish among these possibilities although it should be noted that thiophene isomerizations to cyclopropene thioaldehydes are photochemically induced processes.

A search of the literature showed that the compounds described here are new and that this method of thiophene to pyrrole conversion has not been reported. A list of the compounds prepared by this method and their properties is shown in Table I. Although the reaction conditions were not optimized, synthetically useful yields of the naphtho[2,3-*c*]pyrroles were prepared, and these yields can undoubtedly be improved. This method differs from the few reports of thiophene to pyrrole conversions in that catalysts or photochemical stimulation are not needed, the yields are usually higher, and it is not necessary for the pyrrole nitrogen to be present initially as a substituent on the thiophene ring. Experiments are in progress to further define the scope and limitations of this unique reaction.

EXPERIMENTAL

Melting points are uncorrected and were measured with a Thomas-Hoover Meltemp apparatus. Infrared spectra were measured with a Perkin Elmer Model 297 infrared spectrophotometer. Nmr spectra were measured in the stated solvent with a Hitachi-Perkin Elmer Model R-24B nmr spectrometer using tetramethylsilane as internal reference. Microanalyses were performed by the Analytical Research Department, Diamond Shamrock Corporation.

3,4-Thiophenedicarboxylic Anhydride (VIII).

This compound was prepared according to the method of Reinecke, *et al.* [12] in 83% yield, mp 143-146°, lit [12] mp 144-146°.

3-Benzoylthiophene-4-carboxylic Acid (IX).

A solution of phenylmagnesium bromide (prepared from 5.75 mmoles of bromobenzene) in 15 ml of ether was added in one portion to a solution of 0.75 g (4.9 mmoles) of VIII in 25 ml of toluene warmed to 40°. The reaction mixture was stirred at room temperature for 17 hours then extracted with 5% sodium hydroxide solution (2 × 100 ml). The alkaline extracts were washed with toluene (100 ml) then adjusted to *p*H 1 with 1 *N* hydrochloric acid solution. The resulting suspension was extracted with ethyl acetate (2 × 100 ml) and the extracts were dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 2.70 g of off-white solid which was recrystallized from toluene-hexane (70-30) to give 0.39 g of IX, mp 125-129°, lit [15] ml 132°.

4,9-Dihydronaphtho[2,3-*c*]thiophene-4,9-dione (X).

A mixture of 1.20 g (5.1 mmoles) of IX and 100 g of polyphosporic acid was stirred and heated at 110° for 45 minutes, cooled briefly, and poured into 400 ml of water. The resulting mixture was extracted with ethyl acetate (2 × 100 ml). The combined extracts were washed with water (100 ml), 5% sodium carbonate solution (100 ml), and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a brown powder which was sublimed (110°, 0.01 mm Hg) to give 180 mg of X as a tan powder, mp 258-267°, lit [13] mp 277°. All spectral data agreed with that reported [13].

4-(2-Chlorobenzoyl)thiophene-3-carboxylic Acid (II).

To a solution of 1.0 g (6.5 mmoles) of 3,4-thiophenedicarboxylic anhydride in 40 ml of toluene at 40° was added a suspension of 2-chlorophenylmagnesium iodide (prepared from 1.43 g of 2-chloroiodobenzene) in 7 ml of ether. Following the addition the reaction mixture was stirred at room temperature for 2 hours then extracted with 5% sodium hydroxide solution (3 × 50 ml). The aqueous extracts were washed with toluene (50 ml), adjusted to *p*H 1 with concentrated hydrochloric acid solution then filtered to give 0.87 g of white solid. Recrystallization from toluene-cyclohexane afforded II as a white solid, mp 139-142°; ir (potassium bromide): 1692 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 8.17 (d, 1H, C5-H), 7.88 (d, 1H, C1-H), and 7.23-7.76 (m, 4H, aromatic).

Anal. Calcd. for $C_{12}H_7ClO_3S$: C, 54.04; H, 2.65; Cl, 13.29; S, 12.02. Found: C, 54.23; H, 2.52; Cl, 13.6; S, 12.0.

5-Chloro-4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-dione (I).

A solution of 17.5 g (5.9 mmoles) of II in 75 g of thionyl chloride was stirred at room temperature for 18 hours then the excess thionyl chloride was removed under reduced pressure. The residue was dissolved in 150 ml of carbon disulfide then 30 g (0.11 mole) of aluminum chloride was slowly added. The mixture was stirred at room temperature for 72 hours, the solvent was decanted, and the residue was cautiously poured onto ice-10% hydrochloric solution. The mixture was extracted with ethyl acetate (500 ml) then the organic phase was washed with 5% sodium carbonate solution (3 × 100 ml) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 4.6 g of yellow powder. Sublimation (180°, 0.1 mm Hg) followed by recrystallization from methanol gave I as yellow plates, mp 190-192°; ir (chloroform): 1680 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 8.55 (m, 2H, C1 and C3 H), 8.16 (m, 1H, C7 H) and 7.86 (m, 2H, C6 and C8 H).

Anal. Calcd. for $C_{12}H_5ClO_2S$: C, 57.96; H, 2.03; Cl, 14.26; S, 12.87. Found: C, 57.68; H, 1.75; Cl, 14.4; S, 13.0.

5-[2-(Dimethylamino)ethyl methylamino]-4,9-dihydronaphtho[2,3-*c*]thiophene-4,9-dione (III).

A solution of 2.25 g (9.0 mmoles) of I and 4.6 g (45 mmoles) of *N,N,N'*-trimethylethylenediamine in 75 ml of dioxane was stirred and heated at reflux for 16 hours then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (200 ml) and extracted with 10% hydrochloric acid solution (250 ml). The acidic aqueous phase was washed with ethyl acetate (200 ml), adjusted to *p*H 10 with sodium carbonate, and extracted with ethyl acetate (2 × 200 ml). The extracts were combined, dried over anhydrous sodium sulfate and the sol-

vent was removed under reduced pressure to give a red oil. The oil was dissolved in ether-hexane (1/1) and hydrogen chloride gas was passed through the solution. The resulting mixture was filtered and the solid was recrystallized from ethanol to give 0.6 g of III as hygroscopic orange powder, mp 272-275° dec; ir (potassium bromide): 1630 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 8.48 (m, C7 H, 1H), 8.10 (broad, C1 and C3 H, 2H), 7.68 (broad, C6 and C8 H, 2H), 3.83 (m, NCH_2, 2H), 3.40 (m, NCH_2, 2H), 2.95 (s, NCH_3, 3H), and 2.81 (s, $N(CH_3)_2$, 6H).

Anal. Calcd. for $C_{17}H_{18}N_2O_2S{\cdot}HCl$: C, 58.2; H. 5.5; N, 8.0. Found: C, 57.8; H, 5.5; N, 8.1.

5-Chloro-2-(2-hydroxyethyl)-4,9-dihydronaphtho[2,3-*c*]pyrrole-4,9-dione (IV).

A solution of 2.25 g (9.0 mmoles) of I and 2.75 g (45 mmoles) of ethanolamine in 75 ml of dioxane was stirred and heated at reflux for 18 hours, the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The resulting solution was washed with 10% hydrochloric acid solution (2 × 250 ml), water (250 ml), dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was chromatographed on silica gel (ethyl acetate) to give 0.52 g of yellow solid. Two recrystallizations from ethyl acetate afforded 60 mg of IV as a yellow powder, mp 233-235°; ir (potassium bromide): 3350 cm^{-1} (OH) and 1650 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 8.12 (m, C7 H, 1H), 7.76 (m, aromatic, 4H), 5.00 (m, OH, 1H), 4.17 (m, OCH_2, 2H), 3.80 (m, NCH_2, 2H).

Anal. Calcd. for $C_{14}H_{10}ClNO_3$: C, 60.98; H, 3.65; N, 5.08. Found: C, 60.59; H, 3.46; N, 5.05.

5-Chloro-2-(2-hydroxyethoxyethyl)-4,9-dihydronaphtho[2,3-*c*]pyrrole-4,9-dione (VI).

This compound was prepared in the same manner as described for IV to give VI as yellow needles, mp 161.5-162.5°; ir (potassium bromide): 3250 cm^{-1} (OH) and 1650 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 8.12 (m, C7 H, 1H), 7.78 (m, aromatic, 4H), 4.61 (m, OH, 1H), 4.32 (m, NCH_2, 2H), 3.82 (m, CH_2OH, 2H), and 3.55 (m, CH_2OCH_2, 4H).

Anal. Calcd. for $C_{16}H_{14}ClNO_4$: C, 60.09; H, 4.41; Cl, 11.09; N, 4.38. Found: C, 60.04; H, 4.17; Cl, 11.4; N, 4.34.

5-Chloro-2-*n*-propyl-4,9-dihydronaphtho[2,3-*c*]pyrrole-4,9-dione (VII).

A solution of 1.70 g (6.8 mmoles) of I and 2.02 g (34 mmoles) of *n*-propylamine in 50 ml of dioxane was stirred and heated at reflux for 45 hours then concentrated under reduced pressure. The residue was slurried with ethyl acetate (150 ml), filtered and dried to give 1.25 g of brown powder. Recrystallization from ethanol afforded 280 mg of VII as tan needles, mp 178-179°; ir (chloroform): 1670 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 8.10 (m, C7 H, 1H), 7.73 (m, aromatic, 4H), 4.07 (t, NCH_2, 2H, J = 7 Hz), 1.83 (m, CH_2, 2H), and 0.87 (t, CH_3, 3H, J = 7 Hz).

Anal. Calcd. for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; Cl, 12.95; N, 5.12. Found: C, 65.47; H, 4.47; Cl, 12.6; N, 5.30.

2-(2-Dimethylaminoethyl)-4,9-dihydronaphtho[2,3-*c*]pyrrole-4,9-dione (XI).

A solution of 300 mg (1.4 mmoles) of X and 620 mg (7.0 mmoles) of dimethylaminoethylamine in 25 ml of dioxane was stirred and heated at reflux for 7 days then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 ml) and extracted with 10% hydrochloric acid solution (100 ml). The acidic aqueous phase was washed with ethyl acetate (100 ml) then adjusted to *p*H 10 with sodium carbonate and extracted with ethyl acetate (2 × 100 ml). The combined extracts were dried over anhydrous sodium sulfate and concentrated to dryness to give 270 mg of yellow powder. Recrystallization from ether afforded 150 mg of XI as yellow needles, mp 191-193°; ir (chloroform): 1655 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 7.92 (m, aromatic, 6H), 4.18 (t, pyrrole NCH_2, 2H, J = 6 Hz), 2.63 (t, NCH_2, 2H, J = 6 Hz), and 2.22 (s, CH_3, 6H).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.0; N, 10.4. Found: C, 71.6; H, 6.2; N, 10.5.

5-Chloro-2-(2-dimethylaminoethyl)-4, 9-dihydronaphtho[2,3-*c*]pyrrole-4,9-dione (V).

This compound was prepared in the manner described for XI. The crude product was purified by chromatography on silica gel (toluene/methanol; 87/13) and recrystallized from ethyl acetate to give V as yellow prisms, mp 212-215°; ir (chloroform): 1665 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 8.08 (m, C7 H, 1H), 7.73 (m, aromatic, 4H), 4.15 (t, NCH_2, 2H, J = 6 Hz), 2.62 (t, CH_2, 2H, J = 6 Hz), and 2.18 (s, $N(CH_3)_2$, 6H).

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; Cl, 11.71; N, 9.25. Found: C, 63.82; H, 5.15; Cl, 11.4; N, 9.17.

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