Preparation of New Dihydrofuro[2,3-*f*]indole Derivatives

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The preparation of new dihydrofuro[2,3-*f*]indole derivatives and their fully aromatic counterparts is described. Key steps in the synthesis include a Claisen rearrangement/*m*-chloroperoxybenzoic acid oxidation sequence to form a dihydrobenzofuran intermediate and an iron/acetic acid reductive cyclization to generate the dihydrofuro[2,3-*f*]indole nucleus. Introduction of a 5-phenyl substituent on the indole nitrogen was effected by a modified Ullmann reaction. Fully aromatic furo[2,3-*f*]indoles were obtained from the dihydro congeners by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

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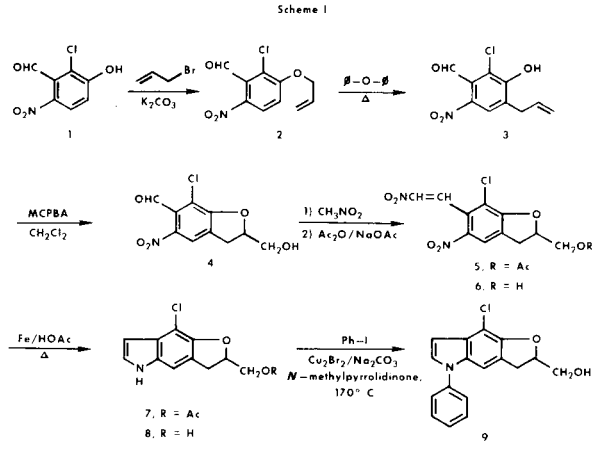
In connection with our studies directed towards the discovery of novel therapeutic agents, we required derivatives of 3,5-dihydro-2*H*-furo[2,3-*f*]indole for biological evaluation. A search of the literature reveals a multistep entry into 5-acyl-6,7-dialkyl-3,5-dihydro-2*H*-furo[2,3-*f*]indoles [1] as well as a synthesis of fully aromatic 5,6-dimethyl-5*H*-furo[2,3-*d*]indole-7-carboxylic acid derivatives [2]. Aside from these two reports, the chemistry of the furo[2,3-*f*]indole ring system has remained unexplored. Our requirements for compounds lacking substituents on the pyrrole ring carbon atoms precluded the use of the known routes and led us to develop a new synthesis affording both dihydro- and fully aromatic furo[2,3-*f*]indoles. Herein we wish to report our results.

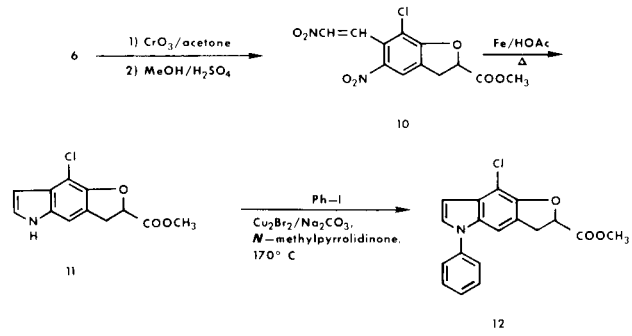
In view of the known susceptibility of the indole nucleus to undergo oxidative and electrophilic reactions, our synthetic pathway to the desired compounds was designed so that formation of the indole ring occurred near the end of the synthesis. The first objective thus became the synthesis of an appropriately functionalized dihydrobenzofuran intermediate from which a fused pyrrole ring could be annulated (Scheme I). Starting with 3-hydroxybenzaldehyde, the nitrophenol **1** was prepared as described in the literature by chlorination with chlorine in acetic acid [3] followed by nitration [4]. Alkylation of **1** with allyl bromide/potassium carbonate in methyl ethyl ketone gave the allyl ether **2** in 87% yield. This compound underwent a Claisen rearrangement when heated in diphenyl ether at 225° to give the rearranged phenol **3**. Ring closure of **3** to the dihydrobenzofuran **4** was effected with *m*-chloroperoxybenzoic acid in methylene chloride in 64% yield. To set the stage for the final ring closure and generation of the requisite dihydrofuro[2,3-*f*]indole nucleus, aldehyde **4** was converted to the corresponding nitrostyrene derivative **5** by treatment with nitromethane and alcoholic sodium hydroxide followed by dehydration in hot acetic anhydride/sodium acetate. Reductive cyclization of **5** with iron and acetic acid afforded dihydrofuro[2,3-*f*]indole **7**, from which the corresponding alcohol **8** was obtained by deacylation with potassium carbonate in anhydrous methanol. Formation of the *N*-phenyl derivative **9** was achieved in 58% yield by a modified Ullmann reaction [5] which involved heating **8**, iodobenzene, sodium carbonate and cuprous bromide in *N*-methyl-2-pyrrolidinone at 170°.

Scheme I



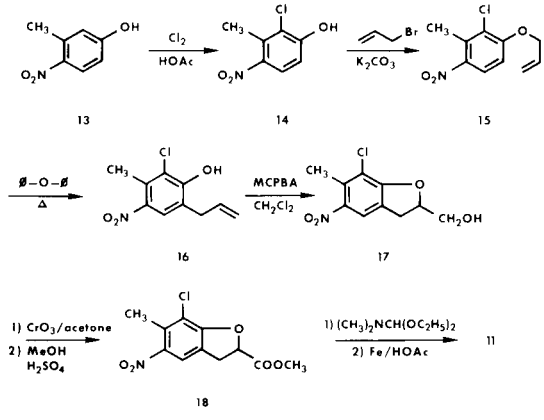
In an attempt to obtain the corresponding carboxyl derivative in this series, alcohol **9** was subjected to a number of mild oxidative procedures, including the Jones [6] and Pfitzner-Moffatt [7] conditions. In all cases, no useful quantities of carboxylic acid were obtained, presumably due to the extreme oxidative sensitivity of the indole nucleus. Attention was therefore directed to the precursor intermediate **5**. Deacetylation of this compound to alcohol **6** was readily effected in 90% yield by reaction with ethanol and catalytic sulfuric acid at room temperature. Jones oxidation of **6** was followed by esterification to afford the carbomethoxy intermediate **10**. Ring closure and phenylation as described above then gave the dihydrofuro[2,3-*f*]indoles **11** and **12**, respectively.

An alternative pathway to methyl ester **11** was also developed starting with 3-methyl-4-nitrophenol **13** (Scheme II). The allyl ether **15** was prepared *via* the known [8] chloro derivative **14** and converted to dihydrobenzofuran **18** in an analogous manner and in comparable yields as described in the first route. In order to annulate a fused pyrrole ring onto compound **18**, several attempts were made to functionalize the 6-methyl group. A reaction with *N*-bromosuccinimide in carbon tetrachloride led to a com-

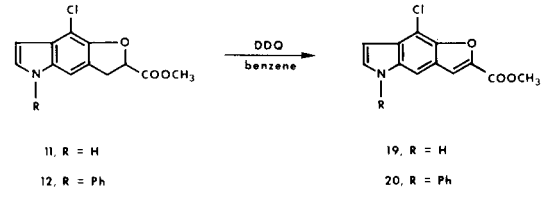


plex mixture of products including the aromatized benzofuran derivative of **18**. The Thiele reagent [9], which has been widely used for oxidation of arylmethyl compounds, gave the aromatized derivative as the sole reaction product. Successful ring closure to **11** was finally achieved by utilizing a recently described indole synthesis [10]. This involved heating **18** with dimethylformamide diethyl acetal in hot DMF to form the corresponding dimethylaminostyrene derivative which was reductively cyclized with iron/acetic acid.

Scheme II



To obtain the fully aromatic furo[2,3-*f*]indoles in this series, intermediates **11** and **12** were exposed to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in the benzene solution. This led to compounds **19** and **20**, respectively, in virtually quantitative yield. The determination of the pharmacological activity of the new furo[2,3-*f*]indole derivatives described in this paper is in progress.



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. The nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane and an internal standard. Mass spectra were recorded on a Kratos MS-50 mass spectrometer. Microanalyses were performed by the Abbott Analytical Department. The uv spectra were recorded on a Varian-Cary 219 visible spectrophotometer.

2-Chloro-3-hydroxy-6-nitro-4-(propenyloxy)benzaldehyde (**2**).

To a stirred mixture of 53 g (0.26 mole) of 2-chloro-6-nitro-3-hydroxybenzaldehyde [4] and 65 g (0.47 mole) of potassium carbonate in 350 ml of dry dimethylformamide was added 97 g (0.8 mole) of allyl bromide all at once. After stirring for 6 hours at 60°, the reaction mixture was cooled and poured into 1000 ml of water. The resulting precipitate was filtered, dried and triturated with hexane to give 55 g (87%) of light tan solid, mp 75-76°; nmr (deuteriochloroform): δ 4.8 (multiplet, OCH_2, 2H), 5.2-6.5 (multiplet, $CH{=}CH_2$, 3H), 7.1 (d, aromatic, 1H, J = 9 Hz), 8.1 (d, aromatic, 1H, J = 9 Hz), 10.3 (s, 1H, CHO).

Anal. Calcd. for $C_{10}H_8ClNO_4$: C, 49.71; H, 3.34; N, 5.80. Found: C, 49.85; H, 3.38; N, 5.73.

2-Chloro-3-hydroxy-6-nitro-4-propenylbenzaldehyde (**3**).

A stirred solution of **2** (50 g, 0.21 mole) in 550 ml of diphenyl ether was heated under a nitrogen atmosphere at 225-230° for 1 hour. After cooling, the reaction mixture was diluted with 650 ml of ether and the resulting solution extracted several times with aqueous sodium bicarbonate. The organic phase was discarded and the aqueous layer was acidified by dropwise addition of concentrated hydrochloric acid. The resulting precipitate was filtered and dried to give 23.5 g (47%) of a brown solid which was used in the next step without purification. An analytical sample was prepared by filtering a small portion through a short plug of silica gel eluting with methylene chloride to give white crystals, mp 110-111°; nmr (deuteriochloroform): δ 3.55 (d, $ArCH_2$, 2H, J = 7 Hz), 5.0-6.4 (multiplet, $CH{=}CH_2$, 3H), 8.01 (s, aromatic, 1H), 10.2 (s, CHO, 1H).

Anal. Calcd. for $C_{10}H_8ClNO_4$: C, 49.71; H, 3.34; N, 5.80. Found: C, 49.73; H, 3.43; N, 5.75.

7-Chloro-2,3-dihydro-2-(hydroxymethyl)-5-nitro-6-benzofurancarboxaldehyde (**4**).

To a stirred solution of 24 g (0.1 mole) of **3** in 230 ml of methylene chloride was added 22.6 g (0.11 mole) of 85% *m*-chloroperoxybenzoic acid. After stirring for 20 hours in the dark at room temperature, the *m*-chlorobenzoic acid was filtered and the filtrate was washed with aqueous sodium bicarbonate. The methylene chloride layer was dried over anhydrous magnesium sulfate and evaporated to a residue which crystallized from hexane-ethanol giving 16.5 g (64%) of pale yellow crystals, mp 108-109°; nmr (deuteriochloroform): δ 3.41 (d, CH_2OH, 2H, J = 8 Hz), 3.6-4.3 (multiplet, $ArCH_2$, 2H), 5.0-5.6 (multiplet, ArOCH, 1H), 8.0 (s, aromatic, 1H), 10.3 (s, CHO, 1H).

Anal. Calcd. for $C_{10}H_8ClNO_5$: C, 46.62; H, 3.13; N, 5.44. Found: C, 46.46; H, 3.12; N, 5.39.

2-(Acetoxymethyl)-7-chloro-2,3-dihydro-5-nitro-6-(β-nitrovinyl)benzofuran (**5**).

To a stirred solution of 12.6 g (0.05 mole) of **4** in 50 ml of methanol and 30 ml of tetrahydrofuran was added 6.0 g (0.098 mole) of nitromethane. After cooling to −5°, a solution of 2.3 g (0.058 mole) of sodium hydroxide in 6 ml of water was added over a period of 10 minutes. The temperature was allowed to rise to 10°, stirred for 1 hour and then poured into dilute hydrochloric acid. The resulting mixture was extracted with methylene chloride, and the organic layer was washed with brine solution and dried over magnesium sulfate. Removal of the solvent left a residue which was mixed with 19 g of anhydrous sodium acetate and 65 ml of acetic anhydride. Heating this mixture at 140° for 30 minutes was followed by evaporation under reduced pressure. The residue was distributed between water and methylene chloride. The organic layer was separated, washed with brine solution, and dried over magnesium sulfate. After removal of the methylene chloride, the residual oil was chromatographed on silica gel eluting with benzene-ethyl acetate (5/1) to give

15.1 g (90%) of a viscous liquid; nmr (deuteriochloroform): δ 2.1 (s, $COCH_3$, 3H), 3.45 (multiplet, $ArCH_2$, 2H); 4.4 (d, CH_2O, 2H, J = 6 Hz), 5.4 (multiplet, ArOCH, 1H), 7.3 (d, ArCH=C, 1H, J = 13 Hz), 8.1 (s, aromatic, 1H), 8.2 (d, C=$CHNO_2$, 1H, J = 13 Hz); molecular weight (HRMS), Calcd. for $C_{13}H_{11}N_2O_7$: C, 342.0255. Found: C, 342.0254.

Anal. Calcd. for $C_{13}H_{11}N_2O_7$: C, 45.56; H, 3.24; N, 8.17. Found: C, 44.96; H, 3.22; N, 7.95.

2-(Acetoxymethyl)-8-chloro-3,5-dihydro-2*H*-furo[2,3-*f*]indole (**7**).

To a mechanically stirred solution of 3.5 g (0.0102 mole) of **5** in 16 ml of ethanol and 24 ml of acetic acid was added 18 g of iron powder. The mixture was placed in an oil bath pre-heated to 90°, at which time an exothermic reaction began. The heating bath was removed and the reaction stirred for an additional 25 minutes. After the addition of ethyl acetate (175 ml), the resulting mixture was then filtered through Celite and the filtrate treated with solid sodium bicarbonate to neutralize the acetic acid. Extraction of this mixture successively with aqueous sodium bicarbonate and brine solution was followed by drying of the organic layer over magnesium sulfate and evaporation. There was obtained a dark solid which was chromatographed on silica gel eluting with benzene-ethyl acetate (4/1) to give 2.3 g (85%) of crystalline product, mp 106-108°; nmr (DMSO-d_6): δ 2.05 (s, $COCH_3$, 3H), 2.8-3.8 (multiplet, $ArCH_2$, 2H), 4.4 (d, CH_2O, 2H), 5.1 (multiplet, ArOCH, 1H), 6.6 (multiplet, H-7, 1H), 7.1 (s, aromatic, 1H), 7.2 (multiplet, H-6, 1H).

Anal. Calcd. for $C_{13}H_{12}NO_3$: C, 58.77; H, 4.55; N, 5.27. Found: C, 58.56; H, 4.46; N, 5.16.

8-Chloro-3,5-dihydro-2*H*-furo[2,3-*f*]indole-2-methanol (**8**).

The acetate **7** (6.0 g, 0.023 mole) was dissolved in 75 ml of dry methanol under nitrogen and treated all at once with 6.5 g (0.047 mole) of anhydrous potassium carbonate. After stirring for 35 minutes at room temperature, the reaction mixture was added to 100 ml of methylene chloride and filtered through Celite. The filtrate was evaporated to dryness and the residue dissolved in ethyl acetate. The organic solution was washed with aqueous sodium chloride, dried over magnesium sulfate, and evaporated under reduced pressure. There was obtained 5 g (99%) of a light tan solid after trituration with hexane, mp 136-137°; nmr (DMSO-d_6): δ 3.31 (d, CH_2OH, 2H, J = 9 Hz), 3.72 (multiplet, $ArCH_2$, 2H), 5.0 (multiplet, ArOCH, 1H), 6.4 (multiplet, H-7, 1H), 7.3 (s, aromatic, 1H), 7.35 (multiplet, H-6, 1H).

Anal. Calcd. for $C_{11}H_{10}ClNO$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.89; H, 4.56; N, 6.32.

8-Chloro-3,5-dihydro-5-phenyl-2*H*-furo[2,3-*f*]indole-2-methanol (**9**).

A mixture of **8** (3.4 g, 0.015 mole), iodobenzene (13.1 g, 0.064 mole), cuprous bromide (4.76 g, 0.0166 mole), and sodium carbonate (1.77 g, 0.0166 mole) in 32 ml of dry *N*-methyl-2-pyrrolidinone was heated with vigorous stirring at 170° for 3 hours under a nitrogen atmosphere. After cooling, the reaction mixture was poured into 75 ml of water and 10 ml of ethylenediamine. Ethyl acetate (25 ml) was added, and the resulting mixture was filtered through Celite. The filtrate was then extracted several times with ethyl acetate, and the combined extracts were washed with aqueous sodium chloride, dried and evaporated to a dark oil. Chromatography on silica gel eluting with benzene-ethyl acetate (4/1) gave 2.6 g (58%) of white solid. An analytical sample was prepared by recrystallization from toluene-cyclohexane, mp 105-106°; nmr (deuteriochloroform): 3.2 (d, CH_2OH, 2H, J = 8 Hz), 3.8 (multiplet, $ArCH_2$, 2H), 5.0 (multiplet, ArOCH, 1H), 6.7 (d, H-7, 1H, J = 3 Hz), 7.3 (multiplet, H-4 and H-6, 2H), 7.5 (s, aromatic, 5H).

Anal. Calcd. for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.17; N, 4.67. Found: C, 68.11; H, 5.01; N, 4.32.

7-Chloro-2,3-dihydro-2-(hydroxymethyl)-5-nitro-6-(β-nitrovinyl)benzofuran (**6**).

A solution of 23 g of **5** in 400 ml of absolute methanol containing 0.5 ml of concentrated sulfuric acid was stirred for 24 hours at room temperature. The methanol was evaporated to about 1/5 the original volume and the residue distributed between methylene chloride and brine solution. The organic layer was dried over magnesium sulfate and evaporated to give 18.2 g (90%) of a viscous liquid. This compound was used without purification in the next step; nmr (deuteriochloroform): 3.4 (d, CH_2OH, 2H, J = 9 Hz), 3.9 (multiplet, $ArCH_2$, 2H), 5.2 (multiplet, ArOCH, 1H), 7.3 (d, Ar CH=C, 1H, J = 13 H_3), 8.0 (s, aromatic, 1H), 8.2 (d, C=$CHNO_2$, 1H, J = 13 Hz).

Molecular weight (HRMS), Calcd. for $C_{11}H_9ClN_2O_6$: C, 300.0149. Found: C, 300.0150.

7-Chloro-2,3-dihydro-5-nitro-6-(β-nitrovinyl)benzofuran-2-carboxylic Acid Methyl Ester (**10**).

To a stirred solution of 23 g (0.077 mole) of alcohol **6** in 1000 ml of acetone was added 50 ml of Jones reagent [11] dropwise over a period of 4 hours. At this time the chromium salts were removed by filtration and the filtrate evaporated to 1/4 the original volume. The residue was distributed between methylene chloride and brine solution and the organic layer dried and evaporated. The residual crude acid was esterified by stirring with 500 ml of methanol and 0.75 ml of concentrated sulfuric acid at room temperature overnight. Partial evaporation of the methanol was followed by extractive work up with methylene chloride and aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate and evaporated to give a brown oil. Chromatography on silica gel eluting with methylene chloride furnished 2.5 g (11%) of recovered alcohol and 11 g (44%) of methyl ester, mp 113-114°; nmr (deuteriochloroform): δ 3.8 (multiplet, $ArCH_2$, 2H), 3.9 (s, OCH_3, 3H), 5.55 (multiplet, ArOCHCO, 1H), 7.3 (d, ArCH=C, 1H, J = 13 Hz), 8.1 (s, H-4, 1H), 8.2 (d, C=$CHNO_2$, 1H, J = 13 Hz).

Anal. Calcd. for $C_{12}H_9ClN_2O_7$: C, 43.85; H, 2.76; N, 8.52. Found: C, 43.61; H, 2.77; N, 8.41.

8-Chloro-3,5-dihydro-2*H*-furo[2,3-*f*]indole-2-carboxylic Acid Methyl Ester (**11**).

Method A.

The procedure described above for **7** was used to reduce 5.5 g (0.017 mole) of **10** giving 2.8 g (65%) of pure product after trituration with ether, mp 143-144°; nmr (DMSO-d_6): δ 3.6 (multiplet, $ArCH_2$, 2H), 3.8 (s, OCH_3, 3H), 5.5 (multiplet, ArOCHCO, 1H), 6.4 (multiplet, H-7, 1H), 7.3 (s, H-4, 1H), 7.4 (multiplet, H-6, 1H).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; N, 5.57. Found: C, 57.06; H, 3.99; N, 5.51.

Method B.

A solution of 6.98 g (25.7 mmoles) of **18** (*vide infra*) and 6.9 ml (40 mmoles) of dimethylformamide diethyl acetal in 25 ml of dimethylformamide was heated under an argon atmosphere at 160-163° for 9 hours. The solvent was evaporated *in vacuo* to give the corresponding dimethylaminostyrene derivative as a dark red oil. A 2.0 g (5.9 mmoles) sample of this material was dissolved in a mixture of acetic acid (6 ml) and absolute ethanol (6 ml) and treated all at once with 2.37 g (42.4 mmoles) of iron powder. The mixture was vigorously stirred at 80-85° for 30 minutes and then cooled to room temperature. The resulting thick brown paste was diluted with ethyl acetate, filtered through Celite, and the filtrate treated with solid sodium bicarbonate. Extraction of this mixture successively with aqueous sodium bicarbonate, 0.5 *N* sulfuric acid and brine solution was followed by drying of the organic layer over magnesium sulfate and evaporation. Purification of the residue by column chromatography eluting with methylene chloride gave 220 mg (14%) of product, identical in all respects to the sample prepared by Method A.

8-Chloro-3,5-dihydro-5-phenyl-2*H*-furo[2,3-*f*]indole-2-carboxylic Acid Methyl Ester (**12**).

Methyl ester **12** was prepared following the procedure described above for **9** from 4.0 g (0.016 mole) of **11**, 6.8 ml (0.054 mole) of iodobenzene, 5.0 g (0.017 mole) of cuprous bromide, 1.85 g (0.017 mole) of sodium carbonate and 33 ml of *N*-methyl-2-pyrrolidinone at 170° for 5 ½ hours.

The work up was modified as follows. After cooling to room temperature, the reaction mixture was distributed between ethyl acetate and 0.5 *N*

hydrochloric acid. Both layers were filtered through Celite and the organic phase was washed with brine solution, dried over magnesium sulfate and evaporated. The residue contained both methyl ester and carboxylic acid as indicated by thin layer chromatography and was therefore esterified in 100 ml of methanol containing 0.4 ml of concentrated sulfuric acid as described above for ester **10**. Chromatography of the crude product on silica gel eluting with methylene chloride gave 3.52 g (68%) of white crystals. Recrystallization from methanol provided an analytical sample, mp 144-145°; nmr (deuteriochloroform); δ 3.6 (multiplet, $ArCH_2$, 2H), 3.8 (s, OCH_3, 3H), 5.3 (multiplet, ArOCHCO, 1H), 6.7 (d, H-7, 1H, J = 4 Hz), 7.2 (s, H-4, 1H), 7.3 (d, H-6, 1H, J = 4 Hz), 7.5 (s, aromatic, 5H).

Anal. Calcd. for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.30; N, 4.27. Found: C, 65.58; H, 4.15; N, 4.25.

2-Chloro-6-nitro-3-(propenyloxy)toluene (**15**).

Allyl ether **15** was prepared following the same procedure as described for **2** from 77 g (0.5 mole) of **14** [9], 80 g (0.95 mole) of sodium bicarbonate, 100 ml (1.16 mole) of allyl bromide, and 400 ml of dimethylformamide for 12 hours at 60°, yield 103 g (91%), mp 51-52°; nmr (deuteriochloroform): δ 2.6 (s, $ArCH_3$, 3H), 4.7 (multiplet, OCH_2, 2H), 5.2-6.5 (multiplet, $CH=CH_2$, 3H), 6.9 (d, aromatic, 1H, J = 9 Hz), 7.9 (d, aromatic, 1H, J = 9 Hz).

Anal. Calcd. for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.96; H, 4.48; N, 6.17.

2-Chloro-3-hydroxy-6-nitro-4-propenyltoluene (**16**).

Claisen product **16** was prepared following the same procedure described above for **3** except that 0.5 *N* sodium hydroxide rather than aqueous sodium bicarbonate was used for the extraction. From 25 g (0.11 mole) of **15** and 125 ml of diphenyl ether there was obtained 13 g (52%) of product, mp 72-73°; nmr (deuteriochloroform): δ 2.6 (s, $ArCH_3$, 3H), 3.5 (d, $ArCH_2$, 2H, J = 6 Hz), 4.8-6.3 (multiplet, $CH=CH_2$, 3H), 7.8 (s, aromatic, 1H).

Anal. Calcd. for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.86; H, 4.52; N, 6.19.

7-Chloro-2,3-dihydro-6-methyl-5-nitrobenzofuran-2-methanol (**17**).

Dihydrobenzofuran **17** was prepared following the procedure used above for **4** with the exception that 0.5 *N* sodium hydroxide was used in place of aqueous sodium bicarbonate for the extraction. From 37.5 g (0.0165 mole) of **16** and 0.195 mole of *m*-chloroperoxybenzoic acid in 350 ml of methylene chloride there was obtained 29 g (72%) of alcohol **17** after recrystallization from benzene-hexane, mp 102-104°; nmr (deuteriochloroform): δ 2.5 (s, $ArCH_3$, 3H), 3.3 (d, CH_2OH, 2H,J = 9 Hz), 3.9 (multiplet, $ArCH_2$, 2H), 5.1 (multiplet, ArOCH, 1H), 7.8 (s, H-4, 1H).

Anal. Calcd. for $C_{10}H_{10}ClNO_4$: C, 49.30; H, 4.14; N, 5.75. Found: C, 49.19; H, 4.12; N, 5.72.

7-Chloro-2,3-dihydro-6-methyl-5-nitrobenzofuran-2-carboxylic Acid Methyl Ester (**18**).

To a stirred solution of 12 g (0.049 mole) of alcohol **17** in 500 ml of acetone was added by dropwise addition 23.5 ml of Jones reagent [11] over a period of 1 hour. The reaction was then stirred for an additional 2 hours at which time the chromium salts were removed by filtration and the filtrate evaporated to *ca.* 1/5 the original volume. The residue was distributed between ethyl acetate and aqueous sodium bicarbonate. After extraction the organic layer was discarded and the aqueous phase was acidified with 6 *N* hydrochloric acid. Extraction of the acidified mixture with ethyl acetate was followed by drying and evaporation to give 5.2 g (41%) of 8-chloro-2,3-dihydro-6-methyl-5-nitrobenzofuran-2-carboxylic acid, mp 160-163°. A 7.0 g (0.027 mole) sample of acid was esterified by heating at reflux in 50 ml of 1,2-dichloroethane, 10 ml of methanol and 0.5 ml of concentrated sulfuric acid for 1.5 hours. The cooled reaction mixture was diluted with methylene chloride, washed with brine solution and dried over magnesium sulfate. Removal of the solvent left methyl ester **18** which was recrystallized from cyclohexane-methylene chloride to give 7.0 g (95%) of pale yellow crystals, mp 83-84°; nmr (deuteriochloroform): 2.6 (s, $ArCH_3$, 3H), 3.6 (multiplet, $ArCH_2$, 2H), 3.9 (s, OCH_3, 3H), 5.4 (multiplet,ArOCHO, 1H), 7.75 (s, aromatic, 1H).

Anal. Calcd. for $C_{11}H_{10}ClNO_5$: C, 48.63; H, 3.71; N, 5.16. Found: C, 48.45; H, 3.85; N, 4.99.

8-Chloro-5*H*-furo[2,3-*f*]indole-2-carboxylic Acid Methyl Ester (**19**).

A stirred solution of **11** (880 mg, 3.50 mmoles) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.1 g, 4.85 mmoles) in 30 ml of benzene was stirred at room temperature for 16 hours. The reaction mixture was filtered and the filtrate evaporated. The residue was chromatographed on silica gel eluting with 1,2-dichloroethane to give 410 mg (47%) of crystalline product, mp 180-183°; uv (methylene chloride): absorption max 316 nm (ε 18,029), 306 nm (ε 14,423).

Molecular weight (HRMS), Calcd. for $C_{12}H_8ClNO_3$: C, 249.0193. Found: C, 429.0199.

8-Chloro-5-phenyl-5*H*-furo[2,3-*f*]indole-2-carboxylic Acid Methyl Ester (**20**).

A stirred solution of **12** (250 mg, 0.77 mmole) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (180 mg, 0.79 mmole) in 10 ml of benzene was heated at reflux for 6 hours. After cooling, the reaction mixture was filtered and the filtrate evaporated. The residue was chromatographed on silica gel eluting with methylene chloride to give 200 mg (81%) of crystalline product, mp 193-194°; nmr (DMSO-d_6): δ 3.9 (s, OCH_3, 3H), 6.9 (d, H-7, 1H, J = 3 Hz), 7.6 (multiplet, aromatic, 5H), 7.9 (multiplet, aromatic, 3H); uv (methylene chloride): absorption max 352 nm (ε 11,890), 318 nm (ε 28,200), 272 nm (ε 22,930), 228 nm (ε 15,920).

Anal. Calcd. for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30. Found: C, 66.15; H, 3.70; N, 4.69.

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[11] Jones reagent was prepared by dissolving 26.72 g of chromic trioxide in 23 ml of concentrated sulfuric acid and diluting with water to a volume of 100 ml.