Synthesis of 5,8-Dihydroxynaphtho[2,3-*c*][1,2,5]thiadiazole-6,9-dione and 6,9-Dihydroxybenzo[*g*]quinoxaline-5,10-dione

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The synthesis of 5,8-dihydroxynaphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione **3**, 6,9-dihydroxybenzo[*g*]quinoxaline-5,10-dione **4**, and their lesser oxygenated analogs *via* Friedel-Crafts and Diels-Alder synthesis is reported.

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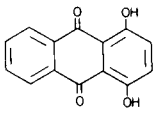
Quinizarin, 1,4-dihydroxyanthracene-9,10-dione, **1**, and chinizarin, 6,9-dihydroxybenzo[*g*]quinoline-5,10-dione, **2**, are versatile synthons utilized in the synthesis of many dyestuffs (1) and cytotoxic compounds (2).



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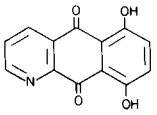

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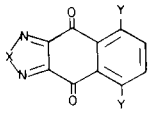
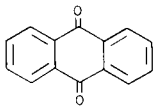


3, X = S; Y = OH

4, X = CH=CH; Y = OH

5, X = S; Y = H

6, X = CH=CH; Y = H



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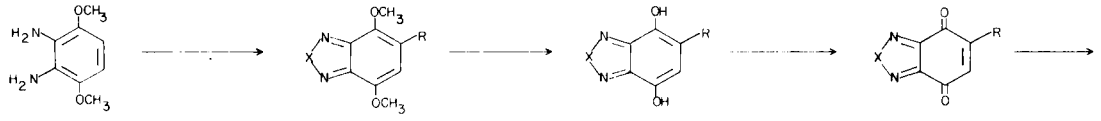
For these reasons we were interested in the synthesis of novel heterocyclic analogs of **1** and **2** that would possess similar stereoelectronic characteristics and chemical reactivity. We hypothesized that the quinone diols **3** and **4** would be such compounds on the basis of literature reports that their respective unsubstituted parent quinones **5** (3) and **6** (4) were chemically similar to their carbocyclic analog, anthraquinone **7**.

Results and Discussion.

Our strategy was to construct **3** and **4** by patterning the synthesis after the classical syntheses of substituted anthraquinones. Quinones **3** and **4**, for example, might be prepared by utilizing the appropriate heterocyclic intermediates and the Diels-Alder reaction route (Scheme I) or the Friedel-Crafts reaction route (Schemes II and III).

The Diels-Alder approach to **3** and **4** *via* **23** and **24** was studied as a general entry to functionalized heterotricyclic

Scheme I



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9, X = CH=CH; R = H

10, X = S; R = H

11, X = S; R = Cl

12, X = CH=CH; R = H

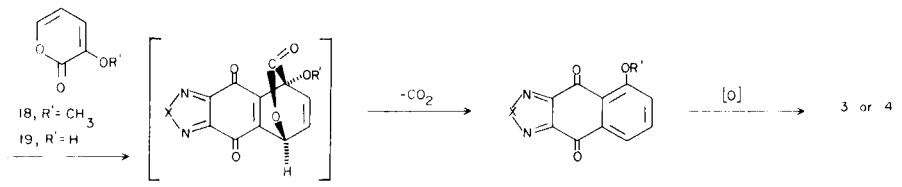
13, X = S; R = H

14, X = S; R = Cl

15, X = CH=CH; R = H

16, X = S; R = H

17, X = S; R = Cl



18, R' = CH_3

19, R' = H

20

21, X = CH=CH; R' = CH_3

22, X = S; R' = CH_3

23, X = CH=CH; R' = H

24, X = S; R' = H

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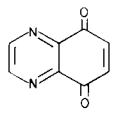
quinones. Joullié and coworkers have reported that in the Diels-Alder reaction, quinoxaline-5,8-dione, **25**, possesses dienophilicity greater than that of 1,4-naphthoquinone, **26** (5). On the basis of this report, we hypothesized that quinones **15** and **16** should react with either 3-methoxy-2-pyrone **18** (6) or 3-hydroxy-2-pyrone **19** (7) to yield the unstable intermediates **20**. Elimination of carbon dioxide from **20** by a retro-Diels-Alder reaction would yield **21**, **22**, **23** or **24**, respectively. Selective oxidative transformation of **21**, **22**, **23**, or **24** to **3** or **4** might then be effected.



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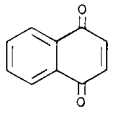

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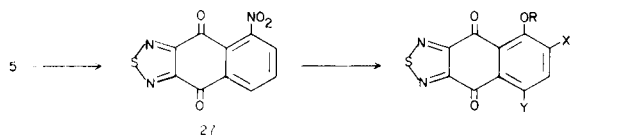
Treatment of 2,3-diamino-1,4-dimethoxybenzene **8** (8) with either glyoxal sodium bisulfite adduct or *N*-thionylaniline/pyridine yielded 5,8-dimethoxyquinoxaline **9** or 4,7-dimethoxy-2,1,3-benzothiadiazole **10**, respectively, in approximately 60% yield. However, when thionyl chloride/pyridine was used instead of *N*-thionylaniline (according to Sandri and coworkers (9)) a mixture of **10** and **11** was obtained in which **11** was the major product. Interestingly, **10** does not react with neat thionyl chloride, neither at ambient temperature nor when heated under reflux for two hours. Demethylation of **9**, **10**, and **11** with anhydrous aluminum chloride afforded **12**, **13** and **14**, respectively, in over 80% yield. Oxidation of **12**, **13** and **14** with silver(I) oxide cleanly gave quinones **15**, **16** and **17** in greater than 90% yield. The reaction of **15** and **16** with methoxypyrone **18** in the presence of one equivalent of silver(I) oxide did indeed afford the desired heterotricyclic quinones **21** and **22** in 60-65% yield. However, the analogous reaction utilizing hydroxypyrone **19** did not yield any detectable amounts of **23** or **24**.

A more efficient large-scale preparation of **22** was accomplished by the synthetic route described below.

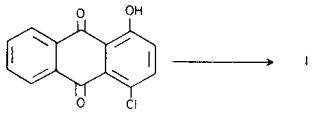


27

22, R = CH_3, X = Y = H
24, R = H, X = Y = H
28, R = CH_3, X = H, Y = NO_2
29, R = CH_3, X = Y = NO_2
30, R = CH_3, X = H, Y = OCH_3
31, R = H, X = H, Y = Br
32, R = H, X = Br, Y = Br

Nitration of **5** with excess 90% red fuming nitric acid in 20-23% fuming sulfuric acid at steam bath temperature consistently gave **27** in 50-55% yield on a 0.5 mole scale. Attempted nitration of **5** under milder conditions (70% nitric acid in acetic acid or 70% nitric acid in sulfuric acid) gave either no reaction or incomplete conversion of the starting material even after prolonged heating of the respective reaction solutions at steam bath temperature. In contrast, attempted nitration of analogous quinoxaline **6** (or **21**) resulted in decomposition of the molecule irrespective of the reaction conditions. Reaction of the nitronaphthothiadiazole **27** with sodium methoxide in methanol under reflux conditions afforded analytically pure **22** in 75-90% yield from the chilled reaction solution. This substance was identical in all aspects to that obtained by the Diels-Alder route (Scheme I).

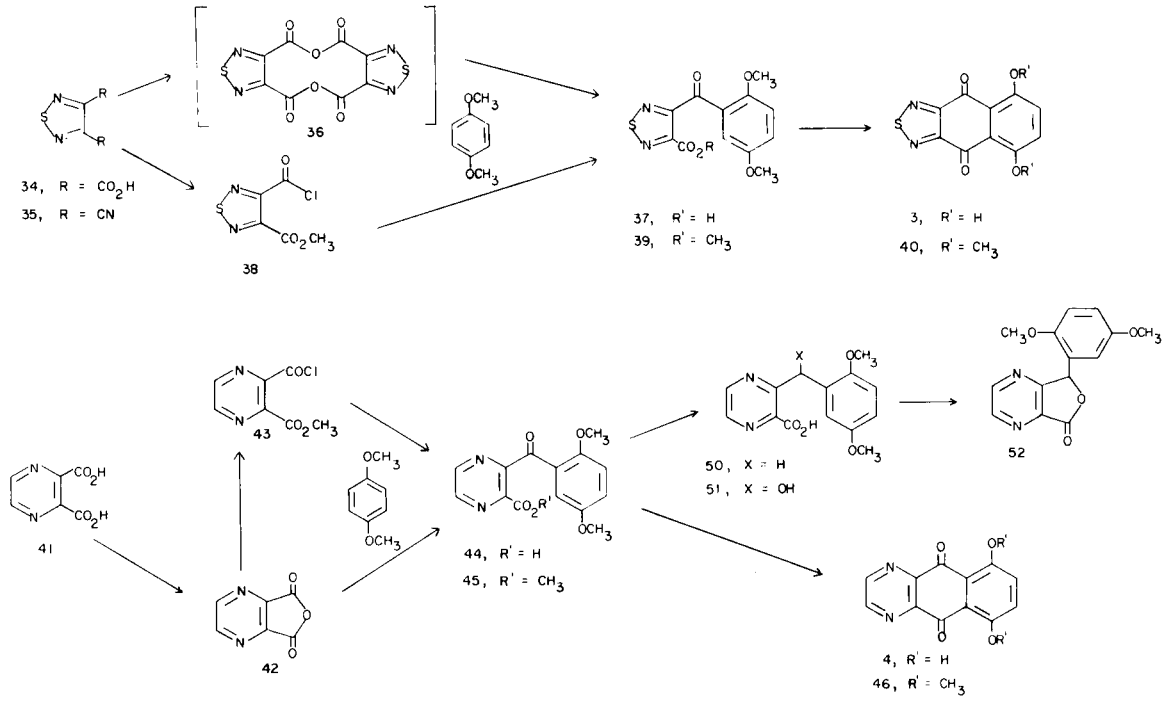
With this convenient preparation of **22** available, we studied the possibility of selective oxidative transformation of **22** to **3** by the nitration or bromination route described below. Methyl ether **22** was nitrated with 90% red fuming nitric acid at ambient temperature to give **28** in 77% yield. Nitration of **22** with 70% nitric acid in concentrated sulfuric acid yielded the dinitro derivative **29** in 88% yield. Reaction of **28** with sodium methoxide, as described above for **27**, repeatedly yielded a small amount of a complex mixture of solids which contained some of the desired dimethyl ether **30** by mass spectral analysis. Attempts to improve thie procedure were futile. Demethylation of **22** with 30-33% hydrogen bromide in acetic acid by heating under reflux for 24 hours gave a 97% yield of **24**. Attempted nitration of **24**, under conditions described above for **5** and **22** gave either no reaction or complex mixtures of mono- and poly-nitrated products. Reaction of **24** with one equivalent of bromine in acetic acid cleanly yielded the mono-bromo derivative **31** in 85% yield. The use of two equivalents of bromine in this reaction gave the dibromo derivative **32** in 64% yield. Hydrolysis of **31** with 88% sulfuric acid yielded no isolable solid products. However, it has been reported that these conditions convert the anthraquinone analog **33** to **1** in 88% yield (10). This route was then abandoned in favor of the Friedel-Crafts reactions routes (Schemes II and III).



33

An efficient synthesis of 1,2,5-thiadiazole-3,4-dicarboxylic acid **34** (from diaminomaleonitrile) was accomplished by modification of Shew's original two-step procedure (11). Thus, reaction of diaminomaleonitrile with thionyl chloride at 0° in THF/pyridine solution cleanly afforded **35** in 44% yield on a 2.25 mole scale. Base hydrolysis of **35** followed by acidification of the cool solution to *p*H 1 with concentrated sulfuric acid yielded **34** in 91% yield. Surprisingly, acidification of the basic reaction solution to *p*H 2 with concentrated hydrochloric acid yielded only the monosodium salt of **34**. The reaction of **34** with trifluoroacetic anhydride did not yield the expected intramolecular

Scheme II

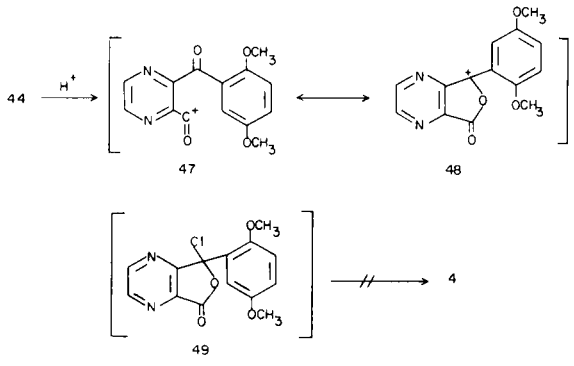


anhydride, but rather, the unstable bicyclic anhydride **36** (12). Anhydride **36** did react with 1,4-dimethoxybenzene in the presence of anhydrous aluminum chloride to give **37** in low and variable yield (~20%). A more consistent procedure was the conversion of **34** to **37** *via* **38** and **39**. The half-ester, half-acid chloride **38** was prepared by monomethylation of the silver salt of **34** with methyl iodide followed by reaction of the intermediate half-ester, half-acid with thionyl chloride (11). Reaction of **38** with 1,4-dimethoxybenzene using anhydrous aluminum chloride consistently gave 35-40% yields of **39**. Hydrolysis of **39** with dilute sodium hydroxide followed by acidification afforded **37** in 50% yield.

Cycliacylation of **37** to **40** did not proceed in either liquid hydrogen fluoride, concentrated sulfuric acid, trifluoromethesulfonic acid at ambient temperature, or in polyphosphoric acid at reaction temperatures of up to 160°. Reaction of **37** with concentrated sulfuric acid or trifluoromethanesulfonic acid at 80-84° gave low and variable yields (~5%) of **3**. However, treatment of **39** with trifluoromethanesulfonic acid at 80-84° consistently gave **3** in 35-40% yield. The use of reaction temperatures lower than 80° gave either no reaction or complex mixtures of products while reaction temperatures greater than 84° effected decomposition of **37**. A more convenient synthesis of **3** is described below (Scheme III).

The synthesis of **4** began with pyrazine-2,3-dicarboxylic acid **41** which was converted to the cyclic anhydride **42** and the half-methyl ester, half-acid chloride **43** (13). Reaction of anhydride **42** with 1,4-dimethoxybenzene in the presence of aluminum chloride in dichloromethane resulted in the decomposition of **42**.

Repetition of this reaction in the presence of stannic chloride in dichloromethane gave **44** in ~5% yield. However, the preferred method of synthesis for **44** was the reaction of **43** with 1,4-dimethoxybenzene employing one equivalent of stannic chloride to yield, after workup, 41% of the methyl ester **45**. Base hydrolysis of **45** followed by acidification afforded **44** in 94% yield. Cycliacylation of **44** with concentrated sulfuric acid at 80-84° gave **4** in 6% yield. A study of several different cycliacylation catalysts (as described above for **37, 39 → 3, 40**) did not yield any **4** or **44** or **45**. Presumably, the acylium ion intermediate **47** can stabilize itself *via* the pseudo-lactone **48**. Newman and co-workers have reported that the analogous thiopheno pseudo-lactones are poor cycliacylation agents (14).

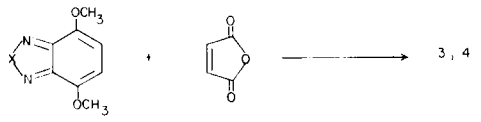


The ketoacid **44** was converted to the intermediate chlorolactone **49** by treatment with thionyl chloride (15). Reaction of **49** with a variety of Lewis acids (for example, aluminum chloride, stannic chloride or boron trifluoride) resulted in the decomposition of **49**.

Another approach to **4** and **46** was the selective reduction of the keto acid **44** to the bisaryl methane acid **50**, followed by cycliacylation and oxidation to the tricyclic quinone. This procedure has been successful in an analogous thiophene system (16). However, reduction of **44** with the standard reagents (zinc in ammonium hydroxide or in dilute sodium hydroxide) (16,17) yielded complex mixtures from which only small amounts of **51** were isolated. Reduction of **44** with hydrazine/potassium hydroxide/ethylene glycol or hydrogen gas over platinum or palladium/carbon catalyst gave gross mixtures of products. However, sodium borohydride in dilute sodium hydroxide smoothly reduced **44** to hydroxy acid **51** in 86% yield. Hydroxy acid **51** was cyclized to lactone **52** in 85% yield by heating it with acetic anhydride. Attempted cycliacylation of **51** and **52** to **4** with a variety of catalysts and conditions failed.

Our final approach to the hetero-tricyclic quinones **3** and **4** was the Friedel-Crafts type sodium aluminum chloride fusion of either the diacids **34** or **41**, or anhydride **42** (Scheme II) with hydroquinone or 1,4-dimethoxybenzene; or of maleic anhydride with the hetero-bicyclic ethers **9** and **10** (Scheme III).

Scheme III



9, X = CH=CH
10, X = S

Reaction of pyridine-2,3-dicarboxylic acid anhydride with hydroquinone in a sodium aluminum chloride melt at 150-180° has been reported to give a 44% yield of **2** (18). However, the analogous reaction using **34**, **41**, or **42** resulted in decomposition of the starting materials. Similarly, sodium aluminum chloride fusion of **9** with maleic anhydride resulted in decomposition of the starting materials. However, the same reaction with **10** cleanly afforded **3** in 76% yield.

Conclusions.

In conclusion, our results have shown that both **3** and **4** can be synthesized *via* the Freidel-Crafts reaction (albeit in low yield for compound **4**). In addition, our results indicate hetero-tricyclic quinones of type **21** and **22** can be prepared *via* the Diels-Alder reaction.

EXPERIMENTAL

General Remarks.

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were obtained at 70 eV on an AEI Model MS-9 double-focusing spectrometer. Infrared spectra were recorded on a Nicolet Model 7199 FT-IR. All ^{1}H nmr chemical shifts are given as δ (ppm) from internal tetramethylsilane and were recorded on a Varian HA-100 or EM-360 spectrometer. All ^{13}C nmr chemical shifts are given as δ (ppm) from internal tetramethylsilane and were recorded on a Varian CFT-20 spectrometer. Ultraviolet spectra were obtained on a Cary Model 16 spectrometer. All chemicals were reagent grade. The term "workup" implies dilution of the reaction mixture with water followed by exhaustive extraction into an organic solvent. The combined organic extracts were washed with either dilute hydrochloric acid, dilute sodium bicarbonate, or saturated sodium chloride (where appropriate) followed by drying over a filter cone of either sodium or magnesium sulfate.

5,8-Dihydroxynaphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione (**3**).

Procedure A.

A burgundy colored solution of 100 mg. (0.32 mmole) of **39** in 3.0 ml. of trifluoromethanesulfonic acid was heated at 80-84° for 2 hours then poured onto 30 g. of chipped ice and allowed to stand for 1 hour. The orange-brown colored solid was isolated by filtration, washed well with water, and dried to afford 30 mg. (37%) of **3**, which was purified by trituration of the crude material with hot toluene, followed by evaporation of the triturate to yield an orange-red solid which, when crystallized from acetic acid, afforded shiny orange-red crystals, m.p. 296-298°. Calcd: m/e 247.9892. Found: m/e 247.9877, ir (potassium bromide): 1630, 1580, 1460, 1360, 1340, 1320, 1250, 1220, 1180, 1100, 978, 800 cm^{-1}; uv (methanol): λ 230, 281, 470, 500; nm; m/e (relative intensity): 248 (M$^+$, 100).

Anal. Calcd. for $C_{10}H_4N_2O_4S$: C, 48.39; H, 1.62; N, 11.29; S, 12.92. Found: C, 48.09; H, 1.53; N, 11.20; S, 13.07.

Procedure B.

A mixture of 1.15 g. of **10** and 1.15 g. (11.7 mmoles) of maleic anhydride was added to a sodium aluminum chloride melt at 130°. The mixture was stirred with a glass rod occasionally and heated from 130° to 180° over a period of 1 hour. After heating at 180° for an additional hour, the mixture was cooled to 25° and 60 g. of chipped ice and 25 ml. of concentrated hydrochloric acid was added. The mixture was heated on the steam bath for 1.0 hour and then filtered. The dark colored precipitate was washed well with water and dried *in vacuo* to yield 1.1 g. (75%) of **3**, m.p. >300°.

6,9-Dihydroxybenzo[*g*]quinoxaline-5,10-dione (**4**).

A solution of 0.5 g. (1.74 mmoles) of **44** in 12 ml. of concentrated sulfuric acid was heated on the steam bath for 20 minutes and then poured onto 100 g. of chipped ice. The resultant solution was extracted well with chloroform. The combined organic layer was washed with saturated sodium bicarbonate solution and then dried over magnesium sulfate, filtered, and the filtrate evaporated to yield 0.08 g. (19%) of **4** as a red solid. An analytical sample prepared by recrystallization from acetone had m.p. 249-250°; ir (potassium bromide): 1639, 1458, 1391, 1362, 1325, 1266, 1163, 990, and 794 cm^{-1}.

Anal. Calcd. for $C_{12}H_6N_2O_4$: C, 59.51; H, 2.50; N, 11.57. Found: C, 59.30; H, 2.81; N, 11.28.

5,8-Dimethoxyquinoxaline (**9**).

1,4-Dimethoxy-2,3-dinitrobenzene (91.2 g., 400 mmoles) was hydrogenated over platinum oxide in ethanol (Paar apparatus) and the mixture diluted with water and filtered through a Celite bed. The dark brown colored filtrate, containing **8**,was diluted with water to *ca* 900 ml. volume and treated with a warm saturated aqueous solution of 119.7 g.

(450 mmoles) of glyoxal sodium bisulfite adduct. The mixture was kept at 26° for 1 hour, cooled to 0-4°, and made alkaline (*ca* pH 9) with potassium hydroxide pellets. Methylene chloride extraction afforded a dark colored residue which was percolated through a column of Woehlm neutral alumina (Activity I) with methylene chloride (*ca* 2½ ℓ.). The light brown colored eluent was concentrated and the residue recrystallized (2x) from acetone-ether to afford 51.5 g. (68%) of **9** as yellow crystals, m.p. 148-149° (lit (19) m.p. 150-150.5°); ir (potassium bromide): 1612, 1490, 1270, 1110, 824, and 725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.04 (s, 6H, OCH_3) 7.00 (s, 2H, CH=), and 8.86 (s, 2H, N-CH=); m/e (relative intensity): 191 (M+1, 14), 190 (M^+, 96), 175 (100), and 161 (70).

4,7-Dimethoxy-2,1,3-benzothiadiazole (**10**).

A mixture of *N*-thionylaniline (200 g., 1.42 moles), crude **8** (115.0 g., *ca* 680 mmoles), and 450 ml. of pyridine was refluxed for 18 hours, cooled, and poured onto cold 3 *N* hydrochloric acid. The dark colored suspension was filtered and the filtrate extracted with methylene chloride (3x) and ethyl acetate (2x). The combined extract was worked up and the resultant dark colored solid was percolated through a silica gel column (60 mm × 200 mm) with 2.5 ℓ. of methylene chloride. Concentration of the eluate and trituration of the resultant brown colored solid with ether afforded orange colored crystals. Crystallization (3x) from methanol afforded 70.0 g. (52.5%) of **10** as yellow needles, m.p. 125.5-127° (lit. (9) m.p. 125-126°); uv (ethanol): λ 226, 248, 295, 307, and 395 nm; ir (potassium bromide): 1605, 1500, 1340, 1265, and 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.02 (s, 6H, OCH_3) and 6.65 (s, 2H, CH=); m/e (relative intensity): 196 (M+, 88 and 181 (100).

5-Chloro-4,7-dimethoxy-2,1,3-benzothiadiazole (**11**).

Thionyl chloride (*ca.* 100 ml.) was added dropwise with cooling (0°) to crude **8** (*via* hydrogenation of 68.5 g. of 1,4-dimethoxy-2,3-dinitrobenzene over platinum oxide in ethanol) and kept at reflux for 2 hours. After standing at 25° for two days, the dark colored solution was carefully poured onto ice-water and the dark colored precipitate (m.p. 70-95°) collected and air-dried. This material was dissolved in methylene chloride, and percolated through a column of Merck alumina (60 mm × 200 mm) with 1.5 ℓ. of methylene chloride. The yellowish-orange eluate was collected, concentrated, and the residue crystallized (2x) from hexane affording 19.5 g. (28.1%) of yellow needles, of **11**, m.p. 126.5-127.5°. Methanol recrystallization afforded an analytical sample melting at 124.5-125.5°; uv (ethanol): λ 245, 302, 315, and 380; ir (potassium bromide): 1592, 1504, 1340, 1274, 1157, 1082, 985, 973, 890, and 831 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.03 (s, 3H, OCH_3), 4.20 (s, 3H, OCH_3), and 6.72 (s, 1H, CH=); m/e (relative intensity): 232 (M+2, 20), 230 (M^+, 50), and 217 (32), and 215 (100).

Anal. Calcd. for $C_8H_7ClN_2O_2S$: C, 41.65; H, 3.06; Cl, 15.41; N, 12.14; S, 13.87. Found: C, 41.44; H, 2.95; Cl, 15.77; N, 12.12; S, 14.11.

Quinoxaline-5,8-diol (**12**).

A vigorously stirred mixture of 14.3 g. (75 mmoles) of **9**, 75.0 g. (5.65 mmoles) of anhydrous aluminum chloride, and 250 ml. of toluene was heated at *ca.* 80° for 4 hours and poured onto cold 2 *N* hydrochloric acid. The tan colored precipitate was collected, washed well with water, and dried. Ethyl acetate extraction of the filtrate afforded a brown colored solid whose ir spectrum was identical to the filter cake material. The combined product was dissolved in dioxane, decolorized, and concentrated to a small volume. Dilution of the resultant slurry with 2/1-ether/acetone afforded, after filtration, 9.8 g. (80%) of tan colored product, **12**, m.p. 238-239° (lit. (19) m.p. 236-237°); ir (potassium bromide): 3333, 1629, 1495, 1418, 1266, 1170, 1075, 865, 829, and 762 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.96 (s, 2H, CH=) 8.80 (s, 2H, N-CH=), and 9.34 (bs, 2H, OH); m/e (relative intensity): 162 (M^+, 100) and 134 (28).

2,1,3-Benzothiadiazole-4,7-diol (**13**).

A vigorously stirred mixture of 19.69 g. (100 mmoles) of **10**, 44.6 g. (333 mmoles) of anhydrous aluminum chloride, and 350 ml. of toluene was refluxed for 45 minutes and poured onto cold 3 *N* hydrochloric acid. The reaction mixture was extracted with ethyl acetate (3x) and ether (2x) and the combined extracts worked up. The crude product was recrystallized (2x) from toluene to afford 16.3 g. (97%) of crimson red colored crystals **13**, m.p. 194-195° (lit. (20) m.p. 195-196°); ir (potassium bromide): 3360, 1500, 1378, 1230, 1055, 895, 847, and 610 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.74 (s, 2H, CH=), and 9.78 (bs, 2H, OH); m/e (relative intensity): 170 (M + 2, 27), 169 (M + 1, 45), and 168 (M+, 100).

5-Chloro-2,13-benzothiadiazole-4,7-diol (**14**).

A stirred mixture of 9.8 g. (42.6 mmoles) of **11**, 30.0 g. (225 mmoles) of anhydrous aluminum chloride, and 250 ml. of toluene was refluxed for 45 minutes and poured onto cold 3 *N* hydrochloric acid. The mixture was extracted with ether (4x) and the combined organic extracts were worked up to afford after recrystallization from toluene (2x) 8.0 g. (93%) of maroon-colored spars of demethylated product, **14**, m.p. 173.5-174°; ir (potassium bromide): 3360, 1620, 1493, 1440, 1368, 1302, 1267, 1208, 1125, 909, and 843 cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): δ 6.82 (s, 1H, CH=), and 9.75 and 10.12 (s, 2H, OH); m/e (relative intensity): 204 (M+2, 35) and 202 (M^+, 100).

Anal. Calcd. for $C_6H_3ClN_2O_2S$: C, 35.56; H, 1.49; Cl, 17.54; N, 13.82; S, 15.79. Found: C, 35.98; H, 1.59; Cl, 17.43; N, 13.86; S, 15.32.

5,8-Quinoxalinedione (**15**).

A stirred mixture of 9.2 g. (56 mmoles) of **12**, 16.2 g. (70 mmoles) of silver(I) oxide, and 300 ml. of dioxane was refluxed for 6 hours and filtered. The concentrated residue was recrystallized from acetone (2x) to yield 8.0 g. (89%) of quinone **15**, m.p. 172-173° (lit. (19) m.p. 171-172°); ir (potassium bromide): 1683, 1325, 1198, 1180, 1096, and 840 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.24 (s, 2H, CH=), and 9.04 (s, 2H, N-*CH*=), and 9.04 (s, 2H, N-*CH*=); m/e (relative intensity): 160 (M^+, 100), 132 (54), 104 (37), and 82 (79).

2,1,3-Benzothiadiazole-4,7-dione (**16**).

A mixture of 12.6 g. (75 mmoles) of **13**, 23.1 g. l(100 mmoles) of silver(I) oxide, 5 g. of anhydrous sodium sulfate, and 125 ml. of dioxane was stirred overnight at 24° and filtered through a Celite pad. The filter cake was washed with additional solvent and the filtrates concentrated under reduced pressure. Recrystallization of the residue from chloroform-carbon tetrachloride (2:8) afforded 11.2 g. (90%) of yellow colored quinone **16**, m.p. 163.5-165°, darkening *ca.* 155° (lit. (20) m.p. 156-157°); ir (potassium bromide): 1690, 1592, 1475, 1408, 1358, 1074, 850, and 833 cm^{-1}; ^1H nmr (deuteriochloroform/DMSO-d_6): δ 7.21 (s); m/e (relative intensity): 166 (M^+, 100).

5-Chloro-2,1,3-benzothiadiazole-4,7-dione (**17**).

A mixture of 1.68 g. (8.3 mmoles) of **14**, 5.0 g. of silver(I) oxide, 2.0 g. of anhydrous sodium sulfate, and 100 ml. of dioxane was stirred overnight at 24° and filtered through a Celite pad. The filter cake was washed with methylene chloride and the filtrates concentrated under reduced pressure. Recrystallization of the residue from carbon tetrachloride-chloroform (8:1) afforded needles of **17** which disintegrated into a yellow amorphous powder on drying, 1.10 g. (66%); m.p. 157.5-158°; uv (ethanol): λ 225, 295, 305, 318, and 420 nm; ir (potassium bromide): 1700, 1675, 1570, 1360, 1285, 1220, 1140, 1045, 900, and 815 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.41 (s); m/e (relative intensity): 202 (M + 2, 35) and 200 (M^+, 100).

3-Methoxy-2*H*-pyran-2-one (**18**).

A solution of excess ethereal diazomethane was treated with 8.40 g. (75 mmoles) of **19**, in 1/1-methanol/ether (*ca.* 200 ml.). After standing overnight at 5°, excess diazomethane was destroyed with glacial acetic acid, filtered, and the solvent removed under reduced pressure to afford 9.0 g. (95.6%) of **18** as a yellow hygroscopic solid, m.p. 57-59°, (lit. (7) m.p. 60°); ir (potassium bromide): 1730, 1628, 1265, 1124, 1081, and 760 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.86 (s, 3H, OCH_3), 6.20 (dd, 1H, J = 6.0; 8.0 Hz; CH=*CH*-CH), 6.55 (dd, 1H, J = 2.0; 8.0 Hz, *CH*=C-OH), and 7.20 (dd, 1H, O-*CH*=); m/e (relative intensity) 126 (M^+, 100).

3-Hydroxy-2*H*-pyran-2-one (**19**).

An intimate mixture of 210.0 g. (1.0 mole) of mucic acid and 200.0 g.

(1.50 moles) of anhydrous potassium bisulfate, in a 2.0 ℓ. round bottom flask equipped with a distillation head, was gradually heated with a Meker burner for *ca.* 2 hours. The yellow colored smelly distillate (b.p. 145-165°) was collected, adjusted to *p*H 6 with 10 *N* sodium hydroxide, and extracted continuously with ether for 18 hours. Drying (magnesium sulfate) of the extracts, sublimation (*ca* 2.0 mm) and crystallization (2x) from petroleum ether (30-60°)-ether afforded 12.5 g. (11%) of pyrone **19**, m.p. 89.0-89.5°C (lit. (6) m.p. 92°); ir (potassium bromide): 1695, 1640, 1294, 1219, 1130, 1063, and 763 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.05 (bs, 1H, -OH), 6.18 (dd, 1H, J = 5.5; 8.0 Hz, CH=*CH*-CH), 6.65 (dd, 1H, J = 2.0; 8.0 Hz, *CH*=C-OH), 7.12 (dd, 1H, =*CH*-O); m/e (relative intensity): 113 (M+1, 23), 112 (M^+, 89), 84 (91), 55 (78), 54 (100).

6-Methoxybenzo[*g*]quinoxaline-5,10-dione (**21**).

A stirred mixture of 9.50 g. (75.0 mmoles) of **18**, 10.1 g. (63.0 mmoles) of **15**, 23.0 g. (99.0 mmoles) of silver(I) oxide, and 250 ml. of dioxane was refluxed for 18 hours under nitrogen. The hot mixture was filtered and the filter cake washed well with dioxane, and hot glacial acetic acid. The filtrates were concentrated *in vacuo* to a small volume, diluted with ether, and the tan-colored precipitate collected. Recrystallization of the product from hot glacial acetic acid afforded 12.0 g. (80%) of **21** as golden yellow platelets, m.p. 255-257°; ir (potassium bromide): 1675, 1582, 1322, 1269, 1202, 1175, 1048, 972, 802, and 732 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 4.12 (s, 3H, OCH_3), 7.60 (d, 1H, J = 8 Hz, CH=), 7.94 (t, 1H, J = 8 Hz, CH=), 8.10 (d, 1H, CH=), and 9.32 (s, 2H, N-CH=); m/e (relative intensity): 241 (M+1, 20), and 240 (M^+, 100).

Anal. Calcd. for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 64.73; H, 3.52; N, 11.52.

5-Methoxynaphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione (**22**).

Procedure A.

A mixture of 4.98 g. (30 mmoles) of **16**, 3.60 g. (30 mmoles) of **18**, and 14.0 g. (64 mmoles) of silver(I) oxide (Ag_2O) in 75 ml. of dioxane was heated at reflux for 28 hours. On cooling, the mixture was filtered and the filter cake washed well with dioxane, methylene chloride, and ethyl acetate. The concentrated filtrate was suspended in acetone and filtered to afford a yellow solid. Recrystallization from glacial acetic acid afforded 4.50 g. (60%) of tricyclic dione **22**, m.p. 206.5-208°; uv (methanol): λ 222, 274 and 368 nm; ir (potassium bromide): 1680, 1590, 1475, 1360, 1280, 1205, and 1000 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.02 (s, 3H, OCH_3), 7.55 (dd, 1H, J = 5.0 Hz; 2.0 Hz), and 7.85 (m, 2H).

Anal. Calcd. for $C_{11}H_6N_2O_3S$: C, 53.65; H, 2.46; N, 11.37; S, 13.02. Found: C, 53.46; H, 2.53; N, 11.23; S, 12.99.

Procedure B.

A stirred mixture of 15.3 g. (58.6 mmoles) of **27** in 940 ml. of absolute methanol was treated at room temperature with 12.67 g. (234 mmoles) of sodium methoxide. The resultant dark brown solution was heated at reflux for 3.0 hours and cooled at 0°. The crystalline product **22**, was isolated by filtration, washed well with cold methanol and dried affording 11.5 g. (80%) of greenish-yellow product, m.p. 205-206.5°.

5-Hydroxynaphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione (**24**).

A solution of 10.0 g. (40.6 mmoles) of **22** in 500 g. of 30-33% hydrogen bromide in acetic acid was heated under reflux for 24 hours then poured onto 1 kg. of chipped ice and allowed to stand 2 hours. The yellow precipitate was isolated by filtration, washed well with water, dried and yielded 9.1 g. (97%) of **24**, m.p. 201-203°. An analytical sample prepared by recrystallization from glacial acetic acid had m.p. 204-206°; ir (potassium bromide): 1690, 1640, 1453, 1418, 1360, 1312, 1240, 1210, 1080, 1042, 935, 888, 840, 785, and 717 cm^{-1}; uv (methanol): λ 222, 275, 400 nm; ^1H nmr (DMSO-d_6): δ 7.4 (dd, 1H, J = 12 Hz; 4.0 Hz), 7.81 (m, 2H), 11.96 (s, 1H).

Anal. Calcd. for $C_{10}H_4N_2O_3S$: C, 51.72; H, 1.74; N, 12.06; S, 13.81. Found: C, 51.45; H, 1.98; N, 11.85; S, 13.57.

5-Nitronaphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione (**27**).

A stirred solution of 50 g. (0.232 mole) of **5** in 0.5 ℓ. of 90% red fuming HNO_3 was treated dropwise over 1.5 hours with 0.5 ℓ. of 20-25% fuming sulfuric acid. The resultant solution was heated on the steam bath for 18.0 hours, then poured onto 6 kg. of cracked ice and the mixture let stand 4 hours. The yellow precipitate was isolated by filtration, washed well with water, dried, to give 31.5 g. (52%) m.p. 201-203°. An analytical sample of **27** prepared by recrystallization from acetic acid had m.p. 205.5-207°; ir (potassium bromide): 1695, 1590, 1545, 1418, 1387, 1353, 1221, 1020, 839, and 711 cm^{-1}; uv (methanol): λ 254 and 272 nm; ^1H nmr (DMSO-d_6): δ 8.14 (m, 2H) and 8.43 (dd, 1H, J = 12 Hz; 4 Hz).

Anal. Calcd. for $C_{10}H_3N_3O_4S$: C, 45.98; H, 1.16; N, 16.09; S, 12.28. Found: C, 45.70; H, 1.22; N, 15.96; S, 12.18.

5-Methoxy-8-nitronaphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione (**28**).

A solution of 2.32 g. (10 mmoles) of **22** in 50 ml. of 90% nitric acid was allowed to stand at room temperature for 20 minutes, then poured onto 400 g. of chipped ice and then allowed to stand for 1 hour. The mixture was extracted well with dichloromethane, the combined dichloromethane layer washed with brine, dried over magnesium sulfate, filtered, and the filtrate evaporated to yield 2.1 g. (77%) of **28** as a yellow powder, m.p. 219-222°. An analytical sample prepared by recrystallization from glacial acetic acid had m.p. 228.5-230°; ir (potassium bromide): 1695, 1585, 1538, 1351, 1290, 1190, 1006, 837, and 718 cm^{-1}; uv (methanol): λ 220, 255, 270, and 380 nm; ^1H nmr (DMSO-d_6): δ 4.04 (s, 3H) 7.70 (d, 2H, J = 10 Hz), and 8.10 (d, 2H).

Anal. Calcd. for $C_{11}H_5N_3O_5S$: C, 45.36; H, 1.73; N, 14.43; S, 11.01; Found: C, 45.21; H, 1.84; N, 14.22; S, 10.89.

5,7-Dinitro-8-methoxynaphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione (**29**).

A solution of 2.0 g. (8.1 mmoles) of **22** in 50 ml. of 70% nitric acid and 50 ml. of concentrated sulfuric acid was heated at 57° for 5.0 hours and then poured onto 500 g. of chipped ice. The yellow precipitate was isolated by filtration, washed well with water, and then dried to yield 2.4 g. (88%) of yellow powder, m.p. 183-185°. An analytical sample of **29** prepared by recrystallization from glacial acetic acid had m.p. 199.5-200.5°; ir (potassium bromide): 1695, 1605, 1538, 1361, 1212, 1093, 1005, 858, and 717 cm^{-1}; uv (methanol): λ 250, 275, and 340 nm; ^1H nmr (DMSO-d_6): δ 4.02 (s, 3H) and 8.96 (s, 1H).

Anal. Calcd. for $C_{11}H_4N_4O_7S$: C, 39.29; H, 1.20; N, 16.66; S, 9.54. Found: C, 39.12; H, 1.24; N, 16.50; S, 9.61.

5-Bromo-8-hydroxynaphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione (**31**).

A solution of 2.32 g. (10 mmoles) of **24**, 1.62 g. (10.13 mmoles) of bromine, 0.82 g. (10 mmoles) of anhydrous sodium acetate, and 50 ml. of glacial acetic acid was heated at reflux for 5 minutes then cooled at 25°. The dark colored crystalline material was collected, washed with water and ethanol, and dried *in vacuo* to yield 2.65 g. (85%) of **31**, m.p. 223-224.5°. An analytical sample prepared by recrystallization from glacial acetic acid had m.p. 223-225°C: ir (potassium bromide): 1690, 1642, 1577, 1408, 1351, 1222, 1115, 1050, and 769 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.08 (AB quartet) (2H, J = 14.0 Hz) and 12.8 (s, 1H).

Anal. Calcd. for $C_{10}H_3BrN_2O_3S$: C, 38.60; H, 0.97; Br, 25.69; N, 9.00; S, 10.31. Found: C, 38.82; H, 1.30; Br, 25.34; N, 8.84. S, 9.96.

5,7-Dibromo-8-hydroxynaphtho[2,2-*c*][1,2,5]thiadiazole-4,9-dione (**32**).

A solution of 2.32 g. (10 mmoles) of **24**, 6.4 g. (40 mmoles) of bromine and 3.28 g. (40 mmoles) of sodium acetate, in 50 ml. of acetic acid was heated under reflux for 0.75 hour, filtered while hot and the filtrate allowed to cool to room temperature. The red-orange crystalline precipitate was collected, washed with water then ethanol, and then dried to yield 2.5 g. (64%) of **32**, m.p. 209.5-211.5°. An analytical sample prepared by recrystallization from acetic acid had m.p. 208.5-210°; ir (potassium bromide): 1692, 1639, 1290, 1167, 1136, 1067, 830, 821 and 707 cm^{-1}; uv (methanol): λ 230, 283, 420 nm; ^1H nmr (DMSO-d_6): δ 8.52 (s, 1H) and 13.46 (s, 1H).

Anal. Calcd. for $C_{10}H_2Br_2N_2O_3S$: C, 30.79; H, 0.52; Br, 40.98; N, 7.18; S, 8.22. For C, 31.17; H, 0.74; Br, 40.66; N, 7.22; S, 8.27.

1,2,5-Thiadiazole-3,4-dicarboxylic Acid (**34**).

To a stirred ice-cold solution of 0.44 ℓ. 2.5 *N* sodium hydroxide and 50 ml. of ethanol was added 37.4 g. (0.275 mole) of **35**. The resultant solution was heated slowly to a mild reflux and maintained there for 24 hours, then cooled to 5° and cautiously acidified to *p*H 1 with concentrated sulfuric acid. The solution was exhaustively extracted with ether, the combined ethereal solution dried over magnesium sulfate, filtered, and the filtrate evaporated to yield 43.6 g. (91%) of **34** as a white powder, m.p. 178-180° dec. (lit (11) m.p. 181° dec.). An analytical sample prepared by sublimation had m.p. 178.5-179° dec.; ir (potassium bromide): 3390, 3077-2353, 1724, 1626, 1504, 1460, 1242, 1075, 926, 866, 803, 763, 727, and 704 cm^{-1}; uv (methanol): λ 215, 275 nm; ^{13}C nmr (deuterium oxide): 154.8 (-C=N), 164.0 ($-CO_2H$) ppm.

Anal. Calcd. for $C_4H_2N_2O_4S$: C, 27.59; H, 1.16; N, 16.08; S, 18.41. Found: C, 27.64; H, 1.28; N, 15.99; S, 18.31.

Acidification of the above cold basic solution to *p*H 2 with concentrated hydrochloric acid afforded the monosodium salt, m.p. > 300°. An analytical sample prepared by recrystallization from aqueous methanol had m.p. >325°.

Anal. Calcd. for $C_4H_5N_2O_4SNa$: C, 24.49; H, 0.51; N, 14.30; S, 16.35; Na, 11.72. Found: C, 24.51; H, 0.74; N, 14.19; S, 16.48; Na, 11.68.

3,4-Dicyano-1,2,5-thiadiazole (**35**).

A stirred solution of 250 g. (2.31 moles) of diaminomaleonitrile in 2.8 ℓ. of acetonitrile and 0.46 ℓ. of pyridine maintained at 0-2° by an ice-salt slurry was treated with a solution of 302 g. (2.54 moles) of thionyl chloride in 1.4 ℓ. of acetonitrile, the rate of addition being regulated as to maintain a reaction temperature of 5-15°. The reaction solution was stirred for another hour after completion of addition. The solution was then concentrated under reduced pressure at 35-40° on a rotary evaporator to yield a dark oil. The oil was dissolved in 4.75 ℓ. of methylene chloride and washed well with 1.5 *N* hydrochloric acid solution, then brine, dried over magnesium sulfate, filtered, and the filtrate evaporated to yield 138.6 g. (44%) of **35** as a yellow solid, m.p. 48-50° (lit. (11) m.p. 48-49°). An analytical sample obtained by recrystallization from hexane had m.p. 49.5-50.5°; ir (potassium bromide): 2247, 1395, 1136, 850, and 769 cm^{-1}; uv (methanol): λ 225, 272 nm.

Anal. Calcd. for C_4N_4S: C, 35.29; N, 41.16; S, 23.55. Found: C, 35.01; N, 40.87; S, 23.31.

4-(2,5-Dimethoxybenzoyl)-1,2,5-thiadiazole-3-carboxylic Acid (**37**).

To a solution of 1.74 g. (10 mmoles) of **34** in 25 ml. of anhydrous THF was added dropwsie a solution of 3.15 g. of trifluoroacetic anhydride in 25 ml. of THF over a period of 10 minutes. The resultant solution was heated under reflux for 0.5 hour, cooled to room temperature and the solvent evaporated under reduced pressure to yield a colorless white solid. To a solution of this solid in 25 ml. of dichloromethane was added 2.67 g. (20 mmoles) of anhydrous aluminum chloride the mixture was then stirred at room temperature for 10 minutes, followed by addition of a solution of 2.78 g. (20 mmoles) of 1,4-dimethoxybenzene in 25 ml. dichloromethane. The reaction mixture rapidly became burgundy colored and was stirred for 20 minutes at room temperature, then poured onto a slurry of concentrated hydrochloric acid and ice. The mixture was extracted well with ether, and then the combined ethereal solution was extracted with saturated sodium bicarbonate solution. The bicarbonate layer was extracted with ether, the layers separated, and the bicarbonate layer was acidified with dilute hydrochloric acid then extracted well with ether. The latter ethereal solution was dried over magnesium sulfate filtered, and the filtrate evaporated to yield 0.58 g. (20%) of yellow powder **37**, m.p. 142-146°. An analytical sample prepared by recrystallization from ethyl acetate-cyclohexane had m.p. 154.5-156°: ir (potassium bromide): 1695, 1661, 1499, 1482, 1282, 1227, 1176, 1044, 855, 833, and 784 cm^{-1}; uv (ethanol): λ 222m 264, 352 nm; ^{13}C nmr (DMSO-d_6): 55.6, 56.6, 112.9, 115.0, 122.9 124.7, 153.25, 154.1, 160.3, 187.0 ppm; ^1H nmr (DMSO-d_6): δ 3.48 (s, 3H), 3.83 (s, 3H), 7.18 (m, 2H), and 7.47 (d, 1H, J = 4.5 Hz).

Anal. Calcd. for $C_{12}H_{10}N_2O_5S$: C, 48.98; H, 3.43; N, 9.52; S, 10.90. Found: C, 48.83; H, 3.48; N, 9.52; S, 10.84.

Alternatively, **37** was synthesized by heating under reflux for 4.5 hours 1.1 g. (3.57 mmoles) of **39** in solution with 10 ml. of 20% potassium hydroxide and 25 ml. of ethanol, which after cooling and acidification with 30 ml. of 6 *N* sulfuric acid afforded 0.52 g. (50%) of **37** by ether extraction.

4-(2,5-Dimethoxybenzoyl)-1,2,5-thiadiazole-3-carboxylic Acid Methyl Ester (**39**).

To a solution of 5.73 (28 mmoles) of **38** in 50 ml. was added 4.0 g. (30 mmoles) of anhydrous aluminum chloride in one portion. The mixture was stirred at room temperature for 10 minutes and then 2.8 g. (20 mmoles) of 1,4-dimethoxybenzene was added and the burgundy colored solution stirred at room temperature for 24 hours. The reaction solution was then poured onto an ice-concentrated hydrochloric acid slurry, stirred, allowed to stand 0.5 hour, then extracted well with dichloromethane. The combined dichloromethane was washed successively with saturated sodium bicarbonate solution, brine, dried over magnesium sulfate; filtered and the filtrate evaporated to yield 4.0 g. of dark brown oil. Chromatography on 250 g. of silica gel with CH_2Cl_2 afforded 3.0 g. (35%) of **39** as light yellow crystals, m.p. 54-57°. An analytical sample prepared by recrystallization from xylenes-isooctane had m.p. 57.5-59.5°; ir (potassium bromide): 1724, 1647, 1499, 1333, 1290, 1047, 844, 839, and 741 cm^{-1}; uv (methanol): λ 220, 264, 355 nm; ^{13}C nmr (deuteriochloroform): 53.0, 55.9, 56.5, 113.4, 114.0, 123.6, 154.0, 154.5 ppm; ^1H nmr (deuteriochloroform): δ 3.42 (s, 3H), 3.82, 3.83 (two overlapping singlets, 6H), 6.83 (d, 1H, J = 10 Hz), 7.12 (dd, 10 Hz; 4 Hz) and 7.52 (d, 1H, J = 4.0 Hz).

Anal. Calcd. for $C_{13}H_{12}N_2O_5S$: C, 50.64; H, 3.92; N, 9.09; S, 10.40. Found: C, 50.85; H, 3.90; N, 9.08; S, 10.55.

3-(2,5-Dimethoxybenzoyl)-2-pyrazinecarboxylic Acid (**44**).

A stirred solution of 6.05 g. (20 mmoles) of **45** and 1.2 g. (30 mmoles) of sodium hydroxide in 50 ml. of water and 150 ml. of methanol was heated under reflux for 22 hours and then concentrated under water aspirator pressure at 50°. The colorless residue was dissolved in 50 ml. of concentrated hydrochloric acid and the solution stored at 5° for 1.5 hours. The yellow crystalline precipitate was isolated by filtration, washed well with water, and then dried to yield 5.4 g. (94%) of **44**, m.p. 140-141°. An analytical sample prepared by recrystallization from ethyl acetate had m.p. 141.5-142.5°; ir (potassium bromide): 1695, 1664, 1497, 1333, 1227, 1166, 1045, 877, 833, and 714 cm^{-1}; uv (methanol): λ 223, 264, 350 nm; ^1H nmr (DMSO-d_6): δ 3.34 (s, 3H), 3.80 (s, 3H), 7.3 (d, 1H, J = 8 Hz; J = 4 Hz), 7.41 (d, 1H, J = 4.0 Hz), and 8.78 (s, 2H).

Anal. Calcd. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.45; H, 4.22; N, 9.76.

3-(2,5-Dimethoxybenzoyl)-2-pyrazinecarboxylic Acid Methyl Ester (**45**).

To a stirred solution of 27.0 g. (0.135 mole) of **43** and 19.32 g. (0.14 mole) of 1,4-dimethoxybenzene in 250 ml. of dichloromethane at 5° was added a solution of 36.5 g. (0.14 mole) of anhydrous stannic chloride in 50 ml. of dichloromethane over a 0.5 hour period. The stirred mixture was allowed to warm to room temperature and then heated to a gentle reflux and maintained there for 22 hours. The dark brown solution was then poured onto 300 g. of chipped ice and allowed to stand 1 hour. The layers were separated and the aqueous layer extracted well with dichloromethane. The combined dichloromethane layer was washed successively with water, saturated sodium bicarbonate solution, then dried over magnesium sulfate, filtered, and the filtrate evaporated to yield 33 g. of dark viscous oil. This oil was column chromatographed on 300 g. of silica gel packed in toluene. Elution with ethyl acetate afforded 16.6 g. (41%) of pure **45** as a yellow solid. An analytical sample prepared by recrystallization from toluene-hexanes had m.p. 86.5-87.5°; ir (potassium bromide): 1724, 1661, 1562, 1504, 1333, 1312, 1295, 1096, 1043, 991, 870, 830, 772, 767, and 720 cm^{-1}; uv (methanol): λ 225, 265, 335 nm; ^1H nmr (DMSO-d_6): δ 3.38 (s, 3H), 3.85 (s, 6H), 6.97 (d, 1H, J = 9 Hz), 7.18 (dd, 1H, J = 10 Hz; J = 4 Hz), 7.50 (d, 1H, J = 4 Hz), and 8.74 (s, 2H).

Anal. Calcd. for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.60; H, 4.73; N, 9.14.

3-(α-Hydroxy-2,5-dimethoxybenzyl)-2-pyrazinecarboxylic Acid (**51**).

To a solution of 4.18 g. (14.5 mmoles) of **44** and 1.16 g. (29.0 mmoles) of sodium hydroxide in 100 ml. of water at room temperature was added 1.1 g. (29.0 mmoles) of sodium borohydride. The resultant solution was stirred at room temperature for 22 hours, then poured onto 200 g. of cracked ice and then cautiously acidified with dilute hydrochloric acid. The solution was exhaustively extracted with dichloromethane. The combined organic extract was dried over magnesium sulfate, filtered, and the filtrate evaporated to yield 3.6 g. (86%) of **51** m.p. 145-146.5°. An analytical sample prepared by recrystallization from ethyl acetate-hexane had m.p. 149-149.5°; ir (potassium bromide): 3572, 2941, 2500, 1698, 1497, 1468, 1427, 1221, 1100, 1050, 872, and 788 cm^{-1}; uv (methanol): λ 274 nm, ^1H nmr (DMSO-d_6):δ 3.62 (s, 3H), 3.78 (s, 3H), 6.70 (m, 3H), 7.20 (s, 1H), and 8.53 (AB quartet, 2H, J = 12 Hz).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 57.93; H, 5.13; N, 9.50. Found: C, 58.28; H, 5.13; N, 9.50.

7-(2,5-Dimethoxyphenyl)furo[3,4-*b*]pyrazin-5(7*H*)one (**52**).

A solution of 3.45 g. (11.9 mmoles) of **51** in 50 ml. of acetic anhydride was heated under reflux for 1 hour and then allowed to cool to room temperature. Excess acetic anhydride was removed under water aspirator vacuum to yield 3.9 g. (85%) of **52** as a light yellow solid. An analytical sample prepared by recrystallization from ethyl acetate had m.p. 166-167°; ir (potassium bromide): 1786, 1504, 1282, 1266, 1235, 1093, 1047, 977, 803, and 733 cm^{-1}; uv (methanol): λ 280, 285 and 300 nm; ^1H nmr (DMSO-d_6): δ 3.46 (s, 3H), 3.72 (s, 3H), 6.72 (s, 1H), 7.0 (m, 3H), and 8.90 (dd, 2H, J = 10 Hz, J = 2 Hz).

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.58; H, 4.60; N, 10.35.

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