

James B. Kramer, Diane H. Boschelli* and David T. Connor

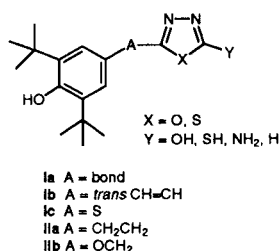
Department of Chemistry, Parke-Davis Pharmaceutical Research Division
Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105

Received June 1, 1994

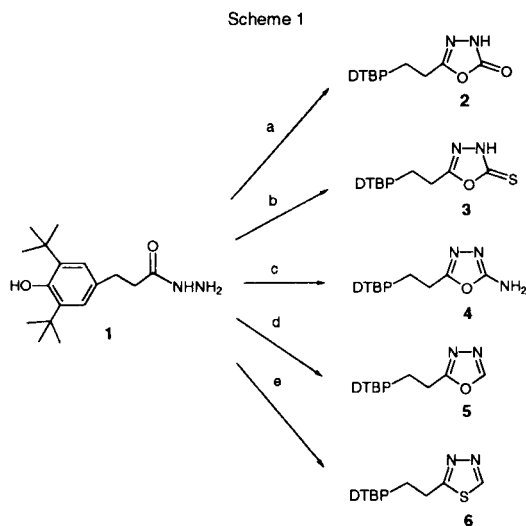
The preparation of a series of analogs of 2,6-di-*tert*-butylphenol linked to a 1,3,4-oxadiazole or 1,3,4-thiadiazole *via* an ethylene or methyleneoxy spacer is discussed.

J. Heterocyclic Chem., **31**, 1439 (1994).

We recently reported the preparation and biological activity of a series of 2,6-di-*tert*-butylphenols linked at C-4 to a 1,3,4-thiadiazole or a 1,3,4-oxadiazole either directly (**Ia**), *via* a double bond (**Ib**) [1] or a sulfur atom (**Ic**) [2]. We describe here the preparation of two related series where an ethylene or methyleneoxy group now links the two rings, providing compounds of general structure **IIa** and **IIb**.



We envisioned that several 1,3,4-oxadiazoles of type **IIa** would be accessible *via* hydrazide **1**. This key intermediate was prepared by reaction of the corresponding known ester [3] with hydrazine. As shown in Scheme 1,

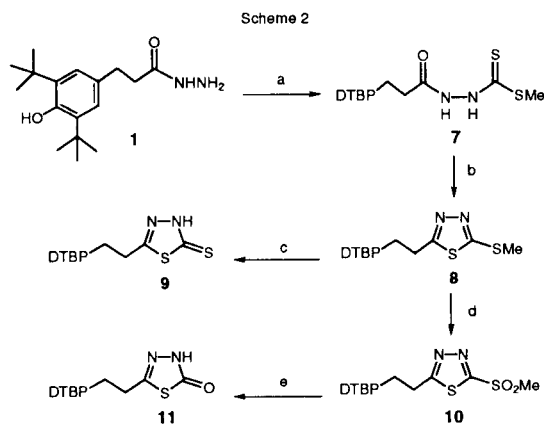


DTBP = 3,5-di-*t*-butyl-4-hydroxyphenyl

a) 12.5% COCl₂ in toluene/THF (74%); b) CSCl₂/THF (16%); c) BrCN/NaHCO₃/aqueous dioxane (59%); d) HC(OEt)₂ (67%); e) 1) HCOOH, 2) P₂S₅/dioxane (39%)

treatment of **1** with phosgene provided the 1,3,4-oxadiazol-2-one **2** [4]. Similar treatment of **1** with thiophosgene gave the 1,3,4-oxadiazole-2-thione **3**. The 2-amino-1,3,4-oxadiazole analog **4** was prepared by reaction of **1** with cyanogen bromide and sodium bicarbonate in aqueous dioxane [5]. Condensation of **1** with triethylorthoformate [6] provided the unsubstituted 1,3,4-oxadiazole **5**. The unsubstituted 1,3,4-thiadiazole **6** was obtained from **1** *via* a two step protocol of formylation followed by ring closure with phosphorus pentasulfide [7].

We planned to prepare additional 1,3,4-thiadiazoles from the thiohydrazide analog of **1**. Since all attempts to thionate **1** with Lawesson's reagent or phosphorus pentasulfide gave complex mixtures, the route depicted in Scheme 2 was utilized. Reaction of **1** with carbon disulfide and potassium hydroxide followed by the addition of



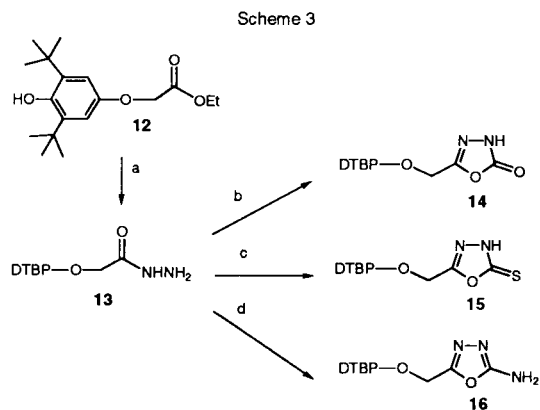
DTBP = 3,5-di-*t*-butyl-4-hydroxyphenyl

a) KOH/CS₂/MeOH/Mel; b) *p*-TsOH/toluene (25% from **1**); c) NaSMel/DMF (84%); d) *m*-CPBA/CH₂Cl₂; e) NaOH/aqueous dioxane (45% from **8**)

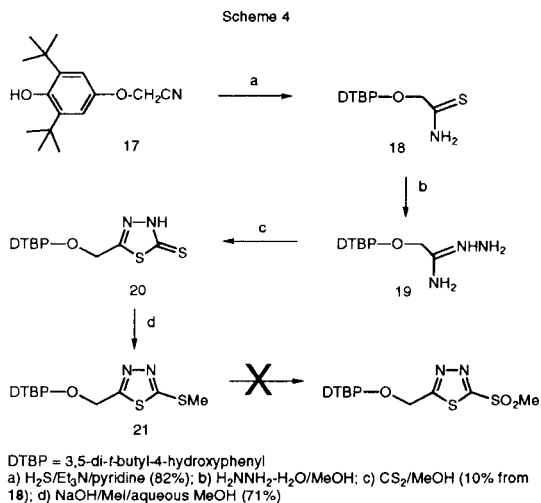
iodomethane gave the thiosemicarbazide intermediate **7** which was not purified. Cyclization to 1,3,4-thiadiazole **8** occurred upon heating of **7** with *p*-toluenesulfonic acid in toluene [8]. Cleavage of the exocyclic thioether with sodium thiomethoxide provided 1,3,4-thiadiazole-2-thione **9**. Alternatively, the exocyclic sulfur of **8** was selectively oxidized to the sulfone **10** with an excess of *m*-chloroperbenzoic acid. Basic hydrolysis of this labile sulfone group

[9] converted **10** to 1,3,4-thiadiazol-2-one **11**.

1,3,4-Oxadiazoles of type **IIb** were prepared from **13**, the methyleneoxy linked analog of **1** (see Scheme 3).



Addition of ethyl bromoacetate to 2,6-di-*tert*-butyl-1,4-dihydroquinone [**10**] in the presence of potassium carbonate gave **12** which upon treatment with hydrazine provided the key intermediate **13**. Hydrazide **13** was converted into the 1,3,4-oxadiazoles **14**, **15**, and **16** via reactions analogous to those depicted in Scheme 1. As in the case of **1**, the thiohydrazide corresponding to **13** could not be obtained via thionation. Preparation of a thiosemicarbazide intermediate analogous to **7** also failed, requiring the use of the alternate route shown in Scheme 4.



Reaction of 2,6-di-*tert*-butyl-1,4-dihydroquinone with bromoacetonitrile in the presence of potassium carbonate gave the nitrile **17**. Addition of hydrogen sulfide to **17** resulted in the thioamide **18**. Treatment of **18** with hydrazine hydrate yielded the unstable amidrazone **19**

which was directly cyclized with carbon disulfide [**11**] to provide the 1,3,4-thiadiazole-2-thione **20**. Alkylation of **20** with iodomethane gave thioether **21** with no evidence of reaction on nitrogen. All attempts to cleanly oxidize the exocyclic sulfur of **21** failed. The difference in reactivity observed in the two series is most likely a result of the labile ether functionality in the methyleneoxy linked vs. the ethylene linked compounds.

The initial *in vitro* testing results were promising for several of these compounds. Compounds **5** and **6** were potent inhibitors of both cyclooxygenase and 5-lipoxygenase, while the 1,3,4-thiadiazole-2-thiones **9** and **20** were selective inhibitors of 5-lipoxygenase. We are continuing to evaluate the biological activity of these and additional analogs.

EXPERIMENTAL

Melting points were recorded on a Uni-melt Thomas Hoover capillary melting point apparatus and are uncorrected. The ^1H nmr spectra were obtained on a Bruker AM 250 spectrometer, with chemical shifts reported in δ units relative to Tms. The ir spectra were recorded on a Nicolet MX-1 FTir spectrometer. Mass spectra were recorded on a Fisons TRIO-2A mass spectrometer. All new compounds yielded satisfactory ir and ms data. Elemental Analyses were performed by the Parke-Davis Analytical Chemistry staff and were within $\pm 0.4\%$ of the theoretical values. Reactions were run under an atmosphere of nitrogen or argon. Flash chromatography was performed with E. Merck silica gel 70-230 mesh.

3,5-Bis(1,1-dimethylethyl)-4-hydroxybenzenepropanoic Acid Hydrazide (**1**).

Hydrazine monohydrate (232 ml, 470 mmoles) was added to a room temperature solution of methyl 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]propanoate (11.4 g, 39 mmoles) in methanol (500 ml). The reaction mixture was heated at reflux for 2 hours, then cooled, diluted with ethyl acetate and washed 6 times with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation to 100 ml gave 9.25 g of colorless crystals. Further evaporation yielded 0.84 g providing a total of 10.1 g (88%) of compound **1**, mp 153.0-154.5°; ir: ν 3541, 3331, 2958, 1629, 1433, 1116 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 2.3-3.0 (m, 4H, CH_2CH_2), 3.90 (br s, 2H, NH_2), 5.10 (s, 1H, OH), 6.62 (br s, 1H, NH), 6.99 (s, 2H, ArH).

Anal. Calcd. for $\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_2$: C, 69.83; H, 9.65; N, 9.58. Found: C, 69.67; H, 9.47; N, 9.47.

5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethyl]-1,3,4-oxadiazol-2(3*H*)-one (**2**).

A 12.5% solution of phosgene in toluene (10.7 ml, 12.0 mmoles) was added dropwise to a -78° solution of compound **1** (2.00 g, 6.8 mmoles) in tetrahydrofuran (200 ml). The reaction mixture was stirred for 10 minutes then partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was washed 3 times with water and once with brine. Drying the organic phase over magnesium sulfate and evapora-

tion gave a crude product which was recrystallized from hexane to afford 1.6 g (74%) of compound **2**, mp 120.0-123.0°; ir: ν 2943, 1782, 1643, 1440, 956 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 2.7-3.0 (m, 4H, CH_2CH_2), 5.12 (s, 1H, OH), 6.99 (s, 2H, ArH), 8.58 (br s, 1H, het-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.58; H, 8.17; N, 8.68.

5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethyl]-1,3,4-oxadiazole-2(3*H*)-thione (**3**).

Thiophosgene (0.55 ml, 6.8 mmoles) was added dropwise to a -78° solution of compound **1** (2.00 g, 6.8 mmoles) in tetrahydrofuran (200 ml). The reaction mixture was stirred for 10 minutes then partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was washed 3 times with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave a heavy oil which was crystallized from ethyl acetate/hexane. The resultant solid was chromatographed on a 100 g column of silica eluting with ethyl acetate/dichloromethane (5/95) and then recrystallized from dichloromethane/hexane to afford 0.36 g (16%) of compound **3**, mp 164.5-165.5°; ir: ν 2971, 1614, 1520, 1179, 972 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 2.97 (s, 4H, CH_2CH_2), 5.14 (s, 1H, OH), 6.98 (s, 2H, ArH), 10.79 (br s, 1H, het-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$: C, 64.64; H, 7.83; N, 8.38. Found: C, 64.43; H, 7.69; N, 8.47.

4-[2-(5-Amino-1,3,4-oxadiazol-2-yl)ethyl]-2,6-bis(1,1-dimethylethyl)phenol (**4**).

A solution of compound **1** (0.50 g, 1.71 mmoles) in dioxane (15 ml) was added to a solution of sodium bicarbonate (0.16 g, 1.88 mmoles) in water (4 ml). Cyanogen bromide (0.20 g, 1.88 mmoles) was then added in four equal portions at 1 minute intervals, and stirring was continued for 5 hours. The reaction mixture was diluted with ethyl acetate and sequentially washed with aqueous sodium bicarbonate, water and brine. Drying the organic phase over magnesium sulfate and evaporation provided a solid which was recrystallized from ethyl acetate/hexane and then methanol/water to give 0.32 g (59%) of compound **4**, mp 220.0-221.0°; ir: ν 2950, 1655, 1583, 1435 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 2.97 (s, 4H, CH_2CH_2), 4.85 (s, 1H, OH), 5.12 (s, 2H, NH_2), 6.99 (s, 2H, ArH).

Anal. Calcd. for $\text{C}_{18}\text{H}_{27}\text{N}_3\text{O}_2$: C, 68.11; H, 8.57; N, 13.24. Found: C, 67.93; H, 8.43; N, 13.18.

2,6-Bis(1,1-dimethylethyl)-4-[2-(1,3,4-oxadiazol-2-yl)ethyl]phenol (**5**).

A catalytic amount of *p*-toluenesulfonic acid (25 mg) was added to a stirred solution of compound **1** (0.50 g, 1.71 mmoles) in triethylorthoformate (10 ml). After 30 minutes, 10 ml of 1*N* hydrochloric acid was added, and stirring was continued for 30 minutes. The reaction mixture was diluted with ethyl acetate and washed twice with saturated sodium bicarbonate, twice with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave a crude product which was chromatographed on a column of silica gel eluting with ethyl acetate/hexane (1/9 then 1/4) to afford 0.34 g (67%) of compound **5**, mp 100.0-101.0°; ir: ν 2960, 1583, 1434, 1234, 1089 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 3.0-3.2 (m, 4H, CH_2CH_2), 5.12 (s, 1H, OH), 7.00 (s, 2H, ArH), 8.35 (s, 1H, het-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.23; H, 8.53; N, 8.89.

2,6-Bis(1,1-dimethylethyl)-4-[2-(1,3,4-thiadiazol-2-yl)ethyl]phenol (**6**).

A solution of compound **1** (0.70 g, 2.39 mmoles) in 96% formic acid (5.6 ml) was stirred at room temperature overnight. The volatiles were removed *in vacuo* and the oily residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate, twice with water and once with brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to yield a white solid. Recrystallization from ethyl acetate/hexane gave 0.67 g of the intermediate formylhydrazide as white crystals. A portion (0.45 g, 1.40 mmoles) of this intermediate was treated with phosphorous pentasulfide (0.31 g, 1.40 mmoles) in 14 ml of dioxane. The reaction mixture was heated at 45° overnight. Volatiles were removed *in vacuo* and the residue was recrystallized from methanol/water. The remaining impurities were removed by dissolving the product in ethyl acetate and washing with 1 *N* sodium hydroxide, followed by water and brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give 0.20 g (39% from **1**) of compound **6** as a white crystalline solid, mp 98.5-100.5°; ir: ν 3578, 2958, 1433, 1234 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 3.0-3.6 (m, 4H, CH_2CH_2), 5.12 (s, 1H, OH), 7.00 (s, 2H, ArH), 9.01 (s, 1H, het-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{OS}$: C, 67.88; H, 8.23; N, 8.80; S, 10.07. Found: C, 68.03; H, 8.48; N, 8.65; S, 9.90.

2,6-Bis(1,1-dimethylethyl)-4-[2-[5-(methylthio)-1,3,4-thiadiazol-2-yl]ethyl]phenol (**8**).

Potassium hydroxide (0.22 g, 3.3 mmoles) was added to a 0° solution of compound **1** (1.00 g, 3.4 mmoles) and carbon disulfide (0.22 ml, 7.2 mmoles) in methanol (36 ml). The reaction mixture was stirred at 0° for 2 hours then at room temperature for 4 hours. Iodomethane (0.21 ml, 3.4 mmoles) was added and stirring was continued overnight. The reaction was diluted with ether and washed twice with water, once with saturated sodium bicarbonate, and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave 1.2 g of crude intermediate **7** which was dissolved in toluene (20 ml).

p-Toluenesulfonic acid (0.72 g, 3.8 mmoles) was added to the solution followed by heating at reflux for 1.5 hours. The reaction solution was cooled and filtered. The filtrate was diluted with ether and washed twice with water, once with saturated sodium bicarbonate, and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave a crude product which was chromatographed on silica gel eluting with ethyl acetate/hexane (1/9 then 1/4) yielding 0.29 g (25%) of compound **8** as white solid, mp 135-139°; ^1H nmr (deuteriochloroform): δ 1.4 (s, 18H, *t*-Bu), 2.78 (s, 3H, CH_3), 2.9-3.5 (m, 4H, CH_2CH_2), 5.13 (s, 1H, OH), 7.01 (s, 2H, ArH).

5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethyl]-1,3,4-thiadiazole-2(3*H*)-thione (**9**).

Sodium thiomethoxide (0.10 g, 1.35 mmoles) was added to a solution of compound **8** (0.10 g, 0.27 mmole) in dimethylformamide (2.7 ml). The reaction solution was heated at 80° for 4 hours then cooled, diluted with ethyl acetate and washed once with 1*N* hydrochloric acid, three times with water, and once with

brine. Drying the organic phase over magnesium sulfate and evaporation gave 0.10 g of a white solid which was recrystallized from ethyl acetate/hexane yielding 0.08 g (84%) of compound **9** as colorless crystals, mp 213.0-214.0°; ir: ν 2962, 2889, 1471, 1436, 1271, 1238, 1063, 736 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 2.8-3.2 (m, 4H, CH_2CH_2), 5.15 (s, 1H, OH), 6.97 (s, 2H, ArH), 10.70 (br s, 1H, het-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2$: C, 61.67; H, 7.48; N, 7.99. Found: C, 61.77; H, 7.40; N, 8.03.

5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethyl]-1,3,4-thiadiazol-2(3*H*)-one (**11**).

m-Chloroperbenzoic acid (80%) (0.05 g, 0.24 mmole) was added to a 0° solution of compound **8** (0.086 g, 0.24 mmole) in methylene chloride (4 ml). After 30 minutes an additional portion of 80% *m*-chloroperbenzoic acid (0.05 g, 0.24 mmole) was added. The reaction was allowed to warm slowly to room temperature and another portion of 80% *m*-chloroperbenzoic acid (0.05 g, 0.24 mmole) was added. The reaction solution was stirred for 5 hours then diluted with ethyl acetate and washed 5 times with saturated sodium bicarbonate, once with water, and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave 0.13 g of compound **10** as a brown oil.

Compound **10** was dissolved in dioxane (2 ml) and a solution of 50% sodium hydroxide (0.16 g, 2.0 mmoles) in water (0.7 ml) was added. Stirring was continued for 6 hours at room temperature. The dark red reaction solution was diluted with ethyl acetate and washed once with 1*N* hydrochloric acid, twice with water, and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave a brown solid which was chromatographed on silica gel eluting with ethyl acetate/hexane (1/4) followed by crystallization from ethyl acetate/hexane yielding 0.03 g (38% from **8**) of compound **11** as pale yellow crystals, mp 149.5-151.0°; ir: ν 3020, 1220, 1213, 787 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.44 (s, 18H, *t*-Bu), 2.8-3.1 (s, 4H, CH_2CH_2), 5.13 (s, 1H, OH), 7.00 (s, 2H, ArH), 9.25 (s, 1H, het-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$: C, 64.64; H, 7.84; N, 8.38. Found: C, 64.54; H, 7.79; N, 8.00.

Ethyl [3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenoxy]acetate (**12**).

A solution of 2,6-di-*tert*-butyl-1,4-dihydroquinone (5.0 g, 22.5 mmoles), ethyl bromoacetate (5.0 ml, 45.0 mmoles), and powdered potassium carbonate (9.3 g, 67.5 mmoles) in freshly distilled tetrahydrofuran (100 ml) was stirred vigorously at a gentle reflux for 26 hours. The reaction mixture was poured into water and acidified with 6*N* hydrochloric acid. The aqueous phase was extracted twice with ether. The combined organic phases were washed twice with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave an oil which was chromatographed on silica gel eluting with ethyl acetate/hexane (2/98 then 5/95). The resulting heavy oil crystallized to give 5.2 g (75%) of compound **12**. An analytically pure sample was obtained by recrystallization from ethanol/water, mp 54.5-56.0°; ir: ν 3604, 2959, 1722, 1434, 1315, 1095 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.31 (t, 3H, CH_3), 1.42 (s, 18H, *t*-Bu), 4.28 (q, 2H, CH_2), 4.56 (s, 2H, OCH_2), 4.84 (s, 1H, OH), 6.78 (s, 2H, ArH).

Anal. Calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_4$: C, 70.10; H, 9.15. Found: C, 69.99; H, 9.07.

3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenoxy acetic acid hydrazide (**13**).

A solution of compound **12** (2.5 g, 8.1 mmoles) and hydrazine monohydrate (1.2 ml, 24.3 mmoles) in ethanol (40 ml) was heated at 65-75° for 8 hours. The reaction mixture was cooled and poured into 500 ml of water. The solids were removed by filtration and washed twice with water and dried overnight at 50°C *in vacuo* to give 2.1 g (87%) of compound **13**, mp 141.0-142.5°; ir: ν 3338, 2964, 1666, 1634, 1428, 1119, 1070 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 3.8 (br s, 2H, NH_2), 4.53 (s, 2H, OCH_2), 4.91 (s, 1H, OH), 6.75 (s, 2H, ArH), 7.83 (br s, 1H, NH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.62; H, 8.99; N, 9.23.

5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenoxy]methyl]-1,3,4-oxadiazol-2(3*H*)-one (**14**).

A 12.5% solution of phosgene in toluene (2.4 ml, 2.7 mmoles) was added dropwise to a -78° solution of compound **13** (0.40 g, 1.36 mmoles) in tetrahydrofuran (25 ml). The reaction mixture was stirred for 30 minutes, diluted with ethyl acetate, and washed 3 times with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave a pale yellow oil which was crystallized from ethyl acetate/hexane yielding 0.34 g (79%) of compound **14**, mp 138.0-140.0°; ir: ν 1779, 1433, 1064 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 4.88 (s, 2H, OCH_2), 4.91 (s, 1H, OH), 6.83 (s, 2H, ArH), 9.14 (br s, 1H, het-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.99; H, 7.49; N, 8.62.

5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenoxy]methyl]-1,3,4-oxadiazole-2(3*H*)-thione (**15**).

Thiophosgene (0.10 ml, 1.36 mmoles) was added dropwise to a -78° solution of compound **13** (0.40 g, 1.36 mmoles) in tetrahydrofuran (25 ml). The reaction mixture was stirred for 30 minutes, diluted with ethyl acetate, and washed 3 times with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave a pale yellow oil which was crystallized from ethyl acetate/hexane yielding 0.36 g (78%) of compound **15**, mp 195.0-196.5°; ir: ν 3637, 2962, 1507, 1431, 1293, 1179, 1066, 947 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 4.94 (s, 1H, OH), 5.01 (s, 2H, OCH_2), 6.83 (s, 2H, ArH), 10.9 (br s, 1H, het-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$: C, 60.68; H, 7.19; N, 8.32; S, 9.53. Found: C, 60.86; H, 7.05; N, 7.96; S, 9.14.

4-[(5-Amino-1,3,4-oxadiazol-2-yl)methoxy]-2,6-bis(1,1-dimethylethyl)phenol (**16**).

A solution of compound **13** (0.15 g, 0.52 mmole) in dioxane (5 ml) was added to a solution of sodium carbonate (0.04 g, 0.52 mmole) in water (1.2 ml). After stirring for 10 minutes, cyanogen bromide (0.06 g, 0.52 mmole) was added and stirring was continued for 4 hours. The reaction solution was diluted with ethyl acetate and washed twice with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave a crude residue which was chromatographed on silica gel eluting with ethyl acetate/methylene chloride (3/7) yielding 0.14 g (84%) of compound **16**, mp 177.5-180.0°; ir: ν 3640, 2960, 1662, 1431, 1057 cm^{-1} ; ^1H nmr (deuteriochloro-

form): δ 1.42 (s, 18H, *t*-Bu), 4.89 (s, 1H, OH), 5.04 (s, 2H, OCH₂), 5.22 (br s, 2H, NH₂), 6.85 (s, 2H, ArH).

Anal. Calcd. for C₁₇H₂₅N₃O₃: C, 63.93; H, 7.89; N, 13.15. Found: C, 63.71; H, 7.81; N, 13.18.

3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenoxyacetonitrile (17).

A solution of 2,6-di-*tert*-butyl-1,4-dihydroquinone (3.5 g, 15.6 mmoles), bromoacetonitrile (5.4 ml, 77.8 mmoles), and powdered potassium carbonate (6.4 g, 46.7 mmoles) in freshly distilled tetrahydrofuran (70 ml) was stirred vigorously while heating at a gentle reflux for 72 hours. An additional amount of bromoacetonitrile (4.0 ml, 57.6 mmoles) was added and stirring and heating continued for 24 hours. The reaction mixture was cooled and diluted with ether and ethyl acetate and filtered. The filtrate was washed 3 times with water, once with 1*N* hydrochloric acid, twice with dilute aqueous sodium hydroxide, twice with water and once with brine. Drying the organic phase with magnesium sulfate and evaporation gave an oil which was chromatographed on silica gel solvent eluting with ethyl acetate/hexane (1/9) yielding 2.0 g (50%) of compound 17 as a pale yellow oil. An analytical sample was obtained by Kugelrohr distillation; ¹H nmr (deuteriochloroform): δ 1.44 (s, 18H, *t*-Bu), 4.71 (s, 2H, OCH₂), 4.99 (s, 1H, OH), 6.86 (s, 2H, ArH).

Anal. Calcd. for C₁₆H₂₃NO₂: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.66; H, 8.94; N, 5.17.

2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenoxy]ethanethioamide (18).

Hydrogen sulfide gas was bubbled for 30 minutes into a solution of compound 17 (1.16 g, 4.44 mmoles) and triethylamine (0.68 ml, 4.88 mmoles) in pyridine (4.5 ml). The reaction mixture was diluted with ether and washed once with dilute aqueous hydrochloric acid, 3 times with water, and once with brine. The organic phase was dried over magnesium sulfate and filtered. Argon was bubbled through the organic solution to remove residual hydrogen sulfide. The organic phase was concentrated *in vacuo*, and the solid residue crystallized from ether/hexane yielding 1.10 g (82%) of compound 18 as white crystals, mp 163.0-164.0°; ir: ν 3380, 2920, 1620, 1590, 1422, 1163, 1071 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.42 (s, 18H, *t*-Bu), 4.82 (s, 2H, OCH₂), 4.91 (s, 1H, OH), 6.76 (s, 2H, ArH), 7.6 (br s, 1H, NH), 8.0 (br s, 1H, NH).

Anal. Calcd. for C₁₆H₂₅NO₂S: C, 65.05; H, 8.53; N, 4.74; S, 10.85. Found: C, 64.95; H, 8.18; N, 4.77; S, 11.08.

5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenoxy]methyl]-1,3,4-thiadiazole-2(3*H*)-thione (20).

Hydrazine monohydrate (0.18 ml, 3.72 mmoles) was added to a solution of compound 18 (1.10 g, 3.72 mmoles) in methanol (37 ml). After stirring for 1 hour an additional amount of hydrazine monohydrate (0.18 ml, 3.73 mmoles) was added and stirring continued for 1 hour. The reaction mixture was diluted with ether and washed 4 times with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave 1.16 g of intermediate 19 as a pale yellow foam. This material was dissolved in methanol (40 ml). Carbon disulfide (2.4 ml, 40 mmoles) was added and stirring was continued overnight. The reaction solution was diluted with ether and

washed 3 times with water and once with brine. Drying the organic phase over magnesium sulfate and evaporation gave a solid which was crystallized from ether/hexane, followed by crystallization from methanol/water. Chromatography on silica gel eluting with acetone/methylene chloride/hexane (2/3/15) yielded 0.14 g (10%) of compound 20 as a white powder, mp 192-195°; ir: ν 2955, 2874, 1596, 1429, 1076 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 4.92 (s, 1H, OH), 5.09 (s, 2H, OCH₂), 6.79 (s, 2H, ArH), 10.4 (br s, 1H, het-H).

Anal. Calcd. for C₁₇H₂₄N₂O₂S₂: C, 57.92; H, 6.86; N, 7.95. Found: C, 58.12; H, 6.95; N, 7.82.

2,6-Bis(1,1-dimethylethyl)-4-[(5-methylthio-1,3,4-thiadiazol-2-yl)methoxy]phenol (21).

A solution of 1*N* sodium hydroxide (1.05 ml, 1.05 mmoles) was added over 5 minutes to a solution of compound 20 (0.37 g, 1.05 mmoles) and iodomethane (0.26 ml, 4.20 mmoles) in methanol (10 ml). The reaction was stirred for 30 minutes, the precipitate was filtered and washed with methanol/water. A second crop was collected and the combined precipitate recrystallized from methanol/water to give 0.27 g (71%) of compound 21 as pink platelets, mp 128.0-129.5°; ir: ν 2957, 1595, 1430, 1379, 1367, 1206, 1186, 1064 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.43 (s, 18H, *t*-Bu), 2.79 (s, 3H, CH₃), 4.89 (s, 1H, OH), 5.36 (s, 2H, OCH₂), 6.83 (s, 2H, ArH).

Anal. Calcd. for C₁₈H₂₆N₂O₂S₂: C, 58.98; H, 7.15; N, 7.64. Found: C, 59.08; H, 7.48; N, 7.65.

Acknowledgement.

We thank the Parke-Davis Analytical Chemistry Department for the spectral data and elemental analysis.

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