3-(4-Hydroxyphenylthio)pyrrolidine-2,5-diones

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3-(4-Hydroxyphenylthio)pyrrolidine-2,5-diones were prepared by the conjugate addition of substituted 4-hydroxybenzenethiols to 1-alkyl-1*H*-pyrrole-2,5-diones. The analytical and spectral data are reported.

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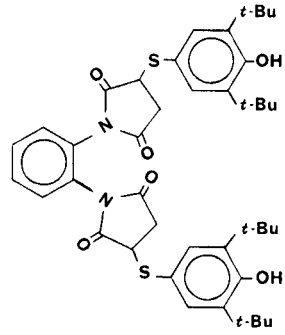
The addition of alkyl-substituted benzenethiols to 1-ethyl-1*H*-pyrrole-2,5-dione has been used to both model the reactivity of protein sulfhydryl groups [2] and to probe the thiol environment in the protein [3]. Despite the known hypocholesteremic activity of hydroxybenzenethiol derivatives [4-5], the reaction of 4-mercaptophenols with *N*-substituted 1*H*-pyrrole-2,5-diones has not been reported in the chemical literature [6].

Results and Discussion.

The reaction of alkanethiolate anions with 4-bromo-5-methoxy-3-pyrrolin-2-one was reported to give 3-(alkylthio)pyrrolidine-2,5-diones upon hydrolysis of the reaction product [7]. Based upon the known conjugate addition of thiols to both 1*H*-pyrrole-2,5-diones [2,8] and α,β-unsaturated esters [9], we anticipated that 3-(hydroxyphenylthio)-pyrrolidine-2,5-diones could be obtained directly by the base catalyzed reaction of mercaptophenols with *N*-substituted 1*H*-pyrrole-2,5-diones. In fact, the reaction of **1a** with **2a** catalyzed by triethylamine gave the pyrrolidine-2,5-dione **3a** in high yield (88% recrystallized).

The structure of **3a** rests on the following observations. A distinct ABX coupling pattern was observed in the ^{1}H nmr spectrum of **3a** with $^3J_{AX}$ = 4 Hz, $^3J_{BX}$ = 8 Hz, and $^2J_{AB}$ = 18 Hz. Two absorptions were observed in the ir spectrum of **3a** at 1790 cm^{-1} and 1710 cm^{-1}, which result from asymmetrical and symmetrical C=O stretching modes. A hindered phenolic absorption was observed at 3630 cm^{-1}. Both the spectral and elemental analysis are fully in accord with the proposed structure. The pyrrolidine-2,5-diones **3b-h** were prepared by the reaction of the



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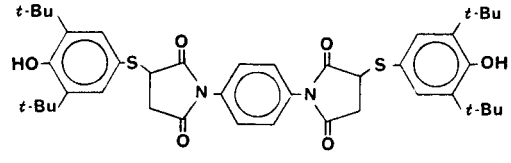

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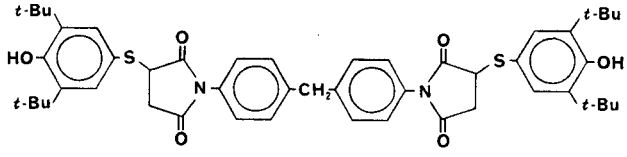

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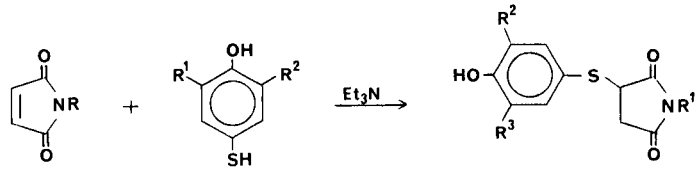

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a R = Methyl
b R = n-Butyl
c R = n-Dodecyl
d R = n-Octadecyl
e R = Cyclohexyl
f R = Phenyl

2

a $R^1 = R^2$ = t-Butyl
b R^1 = t-Butyl, R^2 = Methyl
c $R^1 = R^2$ = H

3

a R^1 = Methyl, $R^2 = R^3$ = t-Butyl
b R^1 = n-Butyl, $R^2 = R^3$ = t-Butyl
c R^1 = n-Dodecyl, $R^2 = R^3$ = t-Butyl
d R^1 = n-Octadecyl, R^2 = Methyl, R^3 = t-Butyl
e R^1 = Cyclohexyl, $R^2 = R^3$ = t-Butyl
f R^1 = Phenyl, $R^2 = R^3$ = t-Butyl
g R^1 = Phenyl, R^2 = Methyl, R^3 = t-Butyl
h R^1 = Phenyl, $R^2 = R^3$ = H

appropriate *N*-substituted 1*H*-pyrrole-2,5-dione with the corresponding mercaptophenol. Similarly, the bridged heterocycles **4-6** were prepared from the appropriate bispyrrole and mercaptophenol.

EXPERIMENTAL

All melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H nmr spectra were taken on a Varian Model CFT-20, XL-100 or XL-200 spectrometer. All ^{1}H shifts are reported relative to tetramethylsilane, where a positive sign is downfield from the standard. Infrared spectra (1% solution in sodium chloride cells) were recorded on a Perkin-Elmer Model 710 spectrometer, and reported peak absorptions are estimated to be accurate to ± 10 cm^{-1}. WOELM 04526 silica gel (ICN Pharmaceuticals GmbH & Co., West Germany) was used for dry-column chromatography. The hplc was done on a Waters Prep 500A HPLC. All solvents were dried prior to use. Reagents were purchased from Aldrich Chemical Company except where noted. Reactions were carried out in flame-dried apparatus under a dry-nitrogen atmosphere. Elemental analyses were performed by Analytical Research Services, CIBA-GEIGY Corporation.

3-(3,5-Di-*t*-butyl-4-hydroxyphenylthio)-1-methylpyrrolidine-2,5-dione (**3a**).

To a stirred solution of 11.92 g (50 mmoles) of **2a** [10] and 0.51 g (5 mmoles) of triethylamine in 50 ml of toluene was added dropwise a solution of 5.55 g (50 mmoles) of **1a** in a mixture of 15 ml of dichloromethane and 50 ml of toluene. The reaction mixture was stirred overnight at rt and then the solvent was removed *in vacuo*. The residue was recrystallized from a mixture of heptane and toluene to give 15.37 g (88%) of a white solid, mp 132-132.5°; ^{1}H nmr (deuteriochloroform): δ 1.44 (s, $(CH_3)_3C$, 18 H), 2.83 (s, CH_3, 3 H), 3.0 (m, H(4), 2 H), 3.90 (m, H(3), 1 H), 5.42 (s, OH, 1 H), 7.32 (s, ArH, 2 H); ir (carbon tetrachloride): ν 3630 (OH), 1780 (C=O), 1710 (C=O) cm^{-1}.

Anal. Calcd. for $C_{19}H_{27}NO_3S$: C, 65.3; H, 7.8; N, 4.0. Found: C, 65.1; H, 7.6; N, 4.4.

3-(3,5-Di-*t*-butyl-4-hydroxyphenylthio)-1-*n*-butylpyrrolidine-2,5-dione (**3b**).

By the procedure used to prepare **3a**, compound **3b** was prepared from 11.92 g (50 mmoles) of **2a**, 7.66 g (50 mmoles) of **1b** [11], and 0.51 g (5 mmoles) of triethylamine in toluene. The residue was purified by dry-column chromatography (1:1 toluene:heptane eluent) to give 10.73 (55%) of an oil which crystallized upon standing to a white solid, mp 80-85°; ^{1}H nmr (deuteriochloroform): δ 0.96 (t, CH_3, 3 H), 1.28 (m, 4 H), 1.44 (s, $(CH_3)_3C$, 18 H), 2.90 (m, H(4), 2 H), 3.32 (t, NCH_2, 2 H), 3.88 (m, H(3), 1 H), 5.40 (s, OH, 1H), 7.30 (s, ArH, 2 H); ir (carbon tetrachloride): ν 3620 (OH), 1770, 1700 (C=O) cm^{-1}.

Anal. Calcd. for $C_{22}H_{33}NO_3S$: C, 67.5; H, 8.5; N, 3.6; S, 8.2. Found: C, 67.2; H, 8.2; N, 3.6; S, 8.2.

3-(3,5-Di-*t*-butyl-4-hydroxyphenylthio)-1-*n*-dodecylpyrrolidine-2,5-dione (**3c**).

To a stirred mixture of 11.92 g (50 mmoles) of **2a** and 13.27 g (50 mmoles) of **1c** [12] in 100 ml of toluene was added 0.51 g (5 mmoles) of triethylamine [13]. The reaction mixture was stirred overnight at rt and then the solvent was removed *in vacuo*. The residue was purified by dry-column chromatography (1:1, toluene-heptane eluent) to give 17.1 g (68%) of a colorless viscous liquid, ^{1}H nmr (deuteriochloroform): δ 0.88 (t, CH_3, 3 H), 1.26 (m, 20 H), 1.44 (s, $(CH_3)_3C$, 18 H), 2.89 (m, H(4), 2 H), 3.30 (t, NCH_2, 2 H), 3.88 (m, H(3), 1 H), 5.38 (s, OH, 1 H), 7.30 (s, ArH, 2 H); ir (carbon tetrachloride): ν 3620 (OH), 1770, 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{30}H_{49}NO_3S$: C, 71.5; H, 9.8; N, 2.8. Found: C, 71.3; H, 9.8; N, 2.9.

3-(3-*t*-butyl-4-hydroxy-5-methylphenylthio)-1-*n*-octadecylpyrrolidine-2,5-dione (**3d**).

By the procedure used to prepare **3c**, compound **3d** was prepared from 9.81 g (50 mmoles) of **2b** [10], 17.48 g (50 mmoles) of **1d** [12], and 0.51 g (5 mmoles) of triethylamine. The residue was purified by dry-column chromatography (7:3 heptane:ethyl acetate eluent) to give 10.28 g (68%) of a white solid. The analytical sample was prepared by two recrystallizations from heptane, mp 160-162°; ^{1}H nmr (deuteriochloroform): δ 1.33 (br m, 35 H), 1.46 (s, $(CH_3)_3C$, 9 H), 2.27 (s, CH_3, 3 H), 2.93 (m, H(4), 2 H), 3.40 (t, NCH_2, 2 H), 3.93 (m, H(3), 1 H), 5.15 (s, OH, 1 H), 7.19 (d, ArH, 1 H), 7.27 (d, ArH, 1 H); ir (chloroform): ν 3600 (OH), 1780, 1710 (C=O) cm^{-1}.

Anal. Calcd. for $C_{33}H_{55}NO_3S$: C, 72.6; H, 10.2; N, 2.6. Found: C, 72.9; H, 10.2; N, 2.5.

3-(3,5-Di-*t*-butyl-4-hydroxyphenylthio)-1-cyclohexylpyrrolidine-2,5-dione (**3e**).

By the procedure used to prepare **3a**, compound **3e** was prepared from 11.92 g (50 mmoles) of **2a**, 8.96 g (50 mmoles) of **1e**, and 0.51 g (5 mmoles) of triethylamine [14]. The residue was recrystallized from a mixture of heptane and toluene to give 10.50 g (50%) of a white solid, mp 94-98°; ^{1}H nmr (deuteriochloroform): δ 1.13-2.0 (complex m, 10 H), 1.44 (s, $(CH_3)_3C$, 18 H), 2.94 (m, H(4), 2 H), 3.62 (m, NCH, 1 H), 3.81 (m, H(3), 1 H), 5.38 (s, OH, 1 H), 7.31 (s, ArH, 2 H); ir (chloroform): ν 3630 (OH), 1770, 1710 (C=O) cm^{-1}.

Anal. Calcd. for $C_{24}H_{35}NO_3S$: C, 69.0; H, 8.5; N, 3.4; S, 7.7. Found: C, 69.0; H, 8.3; N, 3.4; S, 7.7.

3-(3,5-Di-*t*-butyl-4-hydroxyphenylthio)-1-phenylpyrrolidine-2,5-dione (**3f**).

By the procedure used to prepare **3c**, compound **3f** was prepared from 10 g (42 mmoles) of **2a**, 7.26 g (42 mmoles) of **1f**, and 0.51 g (5 mmoles) of triethylamine. The residue was recrystallized sequentially from 2-propanol and a mixture of ethyl acetate and toluene to give 8.30 g (48%) of a white solid, mp 134-137°; ^{1}H nmr (d_6-dimethylsulfoxide): δ 1.30 (s, $(CH_3)_3C$, 18 H), 3.20 (m, H(4), 2 H), 4.30 (m, H(3), 1 H), 6.74-7.42 (complex m, ArH, 7 H); ir (carbon tetrachloride): ν 3630 (OH), 1780, 1710 (C=O) cm^{-1}.

Anal. Calcd. for $C_{24}H_{29}NO_3S$: C, 70.0; H, 7.1; N, 3.4; S, 7.8. Found: C, 69.8; H, 6.8; N, 3.4; S, 7.9.

3-(3-*t*-Butyl-4-hydroxy-5-methylphenylthio)-1-phenylpyrrolidine-2,5-dione, (**3g**).

By the procedure used to prepare **3a**, compound **3g** was prepared from 9.82 g (50 mmoles) of **2b**, 8.66 (50 mmoles) of **1f**, and 0.51 g (5 mmoles) of triethylamine. The residue was recrystallized from a mixture of heptane and toluene to give 16.44 g (89%) of a white solid, mp 158-160°; ^{1}H-nmr (deuteriochloroform): δ 1.30 (s, $(CH_3)_3C$, 9 H), 2.16 (s, CH_3, 3 H), 3.10 (m, H(4), 2 H), 3.95 (m, H(3), 1 H), 5.04 (s, OH, 1 H), 7.12 (m, ArH, 7 H); ir (dichloromethane): ν 3630 (OH), 1780, 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{21}H_{23}NO_3S$: C, 68.3; H, 6.3; N, 3.8. Found: C, 68.5; H, 6.3; N, 3.7.

3-(4-Hydroxyphenylthio)-1-phenylpyrrolidine-2,5-dione (**3h**).

By the procedure used to prepare **3a**, compound **3h** was prepared from 6.31 g (50 mmoles) of **2c** [15], 8.66 g (50 mmoles) of **1f**, and 0.51 g (5 mmoles) of triethylamine. The residue was recrystallized from acetonitrile to give 10.00 g (67%) of a white solid, mp 177.5-179.5°; ^{1}H nmr (d_6-dimethylsulfoxide): δ 3.11 (m, H(4), 2 H), 4.27 (m, H(5), 1 H), 6.47-7.68 (complex m, ArH, 9 H), 9.87 (s, OH, 1 H); ir (chloroform): ν 3590, 3300 (OH), 1780, 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}NO_3S$: C, 64.2; H, 4.4; N, 4.7. Found: C, 63.9; H, 4.1; N, 4.6.

1,2-Bis[3-(3,5-di-*t*-butyl-4-hydroxyphenylthio)-2,5-dioxopyrrolidin-1-yl]benzene (**4**).

By the procedure used to prepare **3a**, compound **4** was prepared from 11.92 g (50 mmoles) of **2a**, 6.71 g (25 mmoles) of *N,N-ortho*-phenylenedimaleimide, and 0.51 g (5 mmoles) of triethylamine. The residue was recrystallized twice from a mixture of toluene and heptane [16] to give 8.18 g (44%) of a white solid, mp 128-133°; ^{1}H nmr (deuteriochloroform): δ 1.42 (s, $(CH_3)_3C$, 36 H), 3.04 (m, H(4), 4 H), 4.00 (m, H(3), 2 H), 5.40 (s, OH,

2 H), 7.36 (m, ArH, 8 H); ir (carbon tetrachloride): ν 3620 (OH), 1780, 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{42}H_{52}N_2O_6S_2$: C, 67.7; H, 7.0; N, 3.8. Found: C, 67.5; H, 6.9; N, 3.7.

1,4-Bis[3-(3,5-di-*t*-butyl-4-hydroxyphenylthio)-2,5-dioxo-pyrrolidin-1-yl]-benzene (**5**).

By the procedure used to prepare **3c**, compound **5** was prepared from 17.8 g (75 mmoles) of **2a**, 10.0 g (37 mmoles) of *N,N-para*-phenylenedimaleimide, and 0.8 g (8 mmoles) of triethylamine. The residue was recrystallized from acetone to give 21.5 g (77%) of a white solid, mp 274-278°: ^1H nmr (d_6-dimethylsulfoxide): δ 1.30 (s, $(CH_3)_3C$, 36 H), 3.12 (m, H(4), 4 H), 4.24 (m, H(3), 2 H), 6.80-7.24 (complex m, ArH, 8 H); ir (carbon tetrachloride): ν 3625 (OH), 1780, 1720 (C=O) cm^{-1}.

Anal. Calcd. for $C_{42}H_{52}N_2O_6S_2$: C, 67.7; H, 7.0; N, 3.8; S, 8.6. Found: C, 67.8; H, 7.3; N, 3.7; S, 8.6.

4,4'-Bis[3-(3,5-Di-*t*-butyl-4-hydroxyphenylthio)-2,5-dioxo-pyrrolidin-1-yl]-diphenylmethane (**6**).

By procedure used to prepare **3a**, compound **6** was prepared from 23.84 g (100 mmoles) of **2a**, 17.90 g (50 mmoles) of 1,1'-(methylene-4,1-phenylene)bismaleimide, and 0.51 g (5 mmoles) of triethylamine. The residue was purified by preparative hplc (65:35 heptane:ethyl acetate eluent) to give 20.04 g (48%) of a white solid; mp 120-125°; ^1H nmr (deuteriochloroform): δ 1.40 (s, $(CH_3)_3C$, 36 H), 3.10 (m, H(4), 4 H), 3.94 (s, CH_2, 2 H), 4.00 (m, H(3), 2 H), 5.40 (s, OH, 2 H), 6.96-7.36 (complex m, ArH, 12 H); ir (carbon tetrachloride): ν 3650 (OH), 1790, 1730 (C=O) cm^{-1}.

Anal. Calcd. for $C_{49}H_{58}N_2O_6S_2$: C, 70.5; H, 7.0; N, 3.4. Found: C, 70.8; H, 6.9; N, 3.1.

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[13] The reaction temperature was observed to rise from 22° to 30° upon addition of the triethylamine.

[14] Compound **1e** was added as a solid.

[15] Compound **2c** was obtained from Polysciences, Inc., Warrington, Pennsylvania.

[16] A small amount of dark insoluble tar was removed by decantation of the hot solvent mixture.