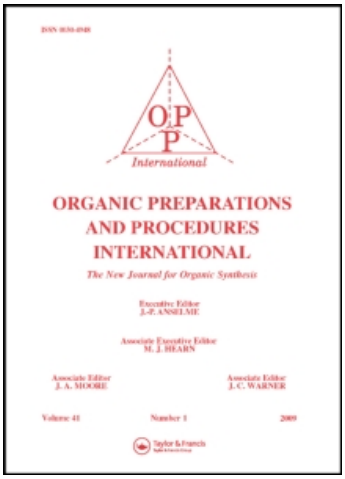

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SYNTHESIS OF SOME 3,4-DIHYDRO-2*H*-1-BENZOTHIOPYRAN-4-OLS

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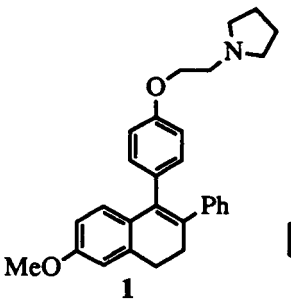
Breast cancer is believed to be the result of many variables.[1] Antiestrogens Nafoxidine (**1**) and Tamoxifen (**2**) have shown promise in the inhibition of growth of rat mammary tumors[2] and of human mammary tumors.[3-8] Antiestrogenic action may involve[9,10] binding of the anti-estrogen with estrogen receptors, a process which may retard cell growth as found with **1** and **2** and with relatives **3** and **4**.[11] We report herein the total synthesis of three sulfur-containing



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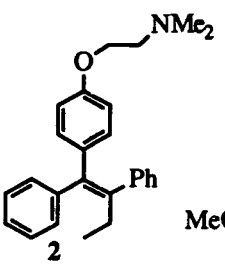

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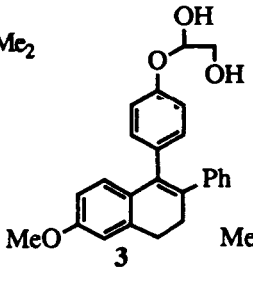

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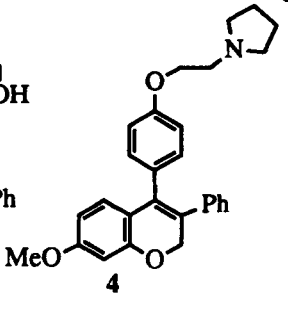

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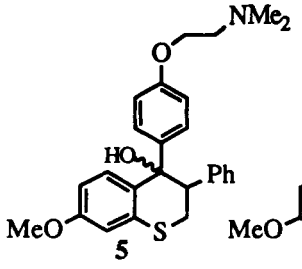
compounds **5-7** which also retain the hydroxyl group that could enhance receptor binding. Moreover, we have developed improved procedures[12] for key intermediates such as 3-(3-meth-



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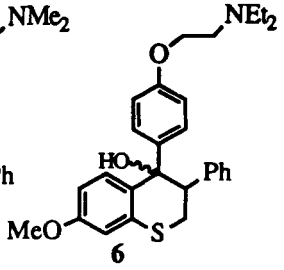

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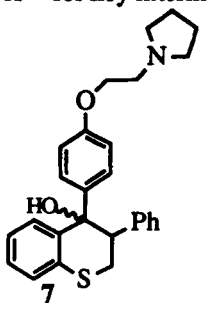

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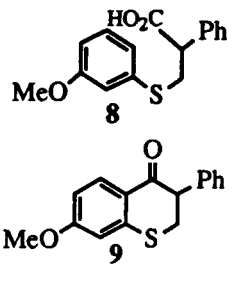


8 **9**

oxyphenylthio)-2-phenylpropanoic acid (**8**) [previously reported as an oil][13] and for 7-meth-oxy-3-phenyl-4-thiochromanaone (**9**), a potentially important synthon for thiasteroids.

Treatment of methyl phenylacetate with dimethyl oxalate and sodium methoxide in thiophene-free benzene gave crude dimethyl 2-oxo-3-phenylsuccinate. The use of thiophene-free benzene is mandatory for optimum yields. The addition of 37% formaldehyde/K_2CO_3 produced methyl phenylacrylate [**10** (R = Me), 76%] or the ethyl ester from ethyl phenylacetate (**10** R = Et). A small amount of contaminating methyl phenylacetate did not prove deleterious

$$MeO_2C\text{-}CO_2Me + PhCH_2CO_2R \longrightarrow PhCH(CO_2R)\text{-}C(O)CO_2CH_3$$

$$\xrightarrow[2.\ H_3O^+]{1.\ H_2C{=}O/K_2CO_3} H_2C{=}C(Ph)\text{-}CO_2R \quad (\mathbf{10},\ R = Me \text{ or } Et)$$

in the subsequent Michael reaction of **10** with 3-methoxybenzenethiol and triethylamine/$HCCl_3$ to produce previously unknown methyl 3-(3-methoxphenylthio)-2-phenylpropanoate (**11**, 88%, spectra were satisfactory).

$$\mathbf{10}\ (R = Me) + 3\text{-}MeOC_6H_4SH \xrightarrow[HCCl_3]{Et_3N} 3\text{-}MeOC_6H_4SCH_2CH(Ph)\text{-}CO_2Me \quad \mathbf{11}$$

$$\xrightarrow{Me_3SiI/HCCl_3} 3\text{-}MeOC_6H_4SCH_2CH(Ph)\text{-}CO_2H \quad \mathbf{8} \xrightarrow[2.\ SnCl_4]{1.\ PCl_5/H_2CCl_2} \mathbf{9}$$

Conversion of **11** to give acid **8** (94%) was best effected with iodotrimethylsilane. Vacuum drying and refrigeration induced oil **8** to crystallize as a low melting solid. With the ethyl ester of **10** (R = Et), the yield of acid **8** was sharply reduced. The conversion of pure **8** to the corresponding acid chloride, and subsequent cyclization thereof, gave ketone **9** (overall yield of 40%; 29% reported[13]); spectral data supported **9**.

Reagents to obtain the title compounds required the *O*-alkylation of phenol **12** to give ethers

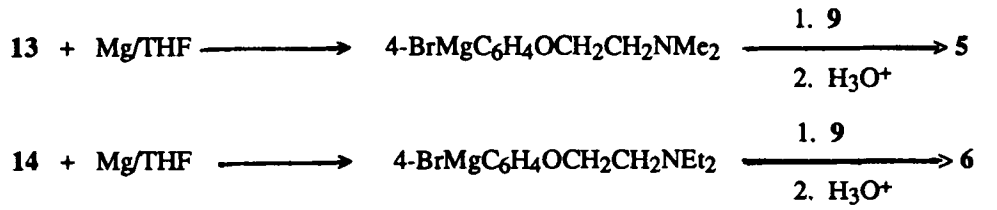
$$4\text{-}BrC_6H_4OH \quad \mathbf{12}$$

$$\xrightarrow[K_2CO_3/DMF]{ClCH_2CH_2NMe_2\cdot HCl} 4\text{-}BrC_6H_4OCH_2CH_2NMe_2 \quad \mathbf{13}$$

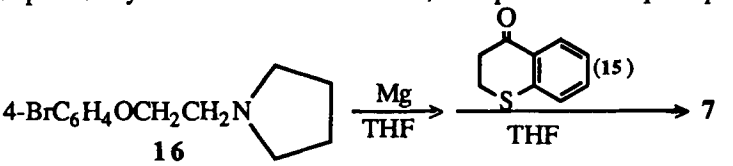
$$\xrightarrow[K_2CO_3/DMF]{ClCH_2CH_2NEt_2\cdot HCl} 4\text{-}BrC_6H_4OCH_2CH_2NEt_2 \quad \mathbf{14}$$

13 and **14**. Grignard reagents from **13** and **14** were prepared in THF and treated with **9** to yield alcohols **5** and **6**. A variety of conditions, including short reaction times, reactions at

room temperature, or reactions run at gentle reflux for long or short times, did not alter the yields significantly. Reactions run at the boiling point of the solvent for long periods (48 hrs)



resulted in the *lowest* yields of the alcohols. Molecular models imply the C=O in **9** is hindered [by the 2-phenyl group and the peri H(9)] and attack by bulky Grignard reagents may be retarded. Side reactions such as dehydration to isomeric alkenes, simple enolization, etc. are conceivable. The latter possibility is supported by the fact that ketone **15**, which lacks the 2-phenyl group, also proved resistant to attack by the Grignard reagent from **16**, and some starting material was recovered from a complex mixture. Variations in workup did not alter the modest yield of previously unknown alcohol **7**. Thus, we speculate that perhaps unusually



large and highly solvated Grignard reagents from **13**, **14**, and **16** may have difficulty in adding to the C=O in ketones **9** and **15**.

The ^{1}H and ^{13}C NMR signals were assigned by comparing shifts of protons with those in starting materials and by use of heteronuclear correlated 2-dimensional (HETCOR 2-D) NMR experiments.[14] The chirality of C(3) in ketone **9** (and its precusors **8** and **11**), makes protons alpha to S [C(2)] *nonequivalent*. Thus, each proton [two on C(2) and one on C(3)] signal appears as a doublet of doublets in the ^{1}H NMR spectrum. A HETCOR 2-D NMR experiment[14] was performed on ketone **9** and on the methyl ester **11**. From these data, the doublet of doublets at the lowest field was assigned to H(3) and the other signals in the aliphatic region were assigned to H(2) (see Experimental for details). The ^{1}H and ^{13}C NMR assignments for the alkyl protons and carbons in the aromatic bromides **13** and **14** were relatively simple from analysis of splitting patterns and chemical shifts. NMR data for bromides **13** and **14** are in the

Experimental. Spectral data for the alcohols **5** and **6** were compared with those of ketone **9** and bromides **13** and **14**. Both alcohols had ^1H NMR signals which correlated with those patterns in both starting materials. The aromatic methoxyl groups had large singlets in the ^1H NMR spectrum at δ 3.83, 3.80, and 3.80 for ketone **9** and alcohols **5** and **6**, respectively. The ^{13}C NMR spectrum had corresponding carbon signals at 55.57, 55.27, and 55.27 ppm for **9**, **5**, and **6**, respectively. Two doublets of doublets appeared for H(2) in ketone **9**, while H(3) was a broad doublet. Two triplets for H(16) and H(17) correspond with those in **13** and **14**. A broad singlet at δ 2.03 in the ^1H NMR spectrum of **6** was exchangeable with D_2O. The carbon attached to the hydroxy group [C(4)] appeared at 75.75 and 75.76 ppm for **5** and **6**, respectively. The corresponding resonance is at 75.8 ppm[15] in the model system benzhydrol. IR analyses showed a C=O stretching frequency at 1745 cm^{-1}, 1720 cm^{-1}, and 1665 cm^{-1} for the methyl ester **11**, the acid **8**, and the ketone **9**, respectively. Evidence that the O-H group remained intact in **5**, **6**, and **7** was clear from the stretching band at 3200 cm^{-1}.

In summary, these examples of benzothiopyran-4-ols constitute an interesting class of potential antiestrogenic agents. A good synthetic procedure was developed to obtain solid 3-(3-methoxyphenylthio)-2-phenylpropanoic acid (**8**), and a much improved method for 7-methoxy-3-phenyl-4-thiochromanone (**9**) was realized. Both compounds are potentially useful in the synthesis of heterosteroids and related systems.

EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere and used magnetic stirring unless otherwise specified. NMR spectra were taken on a Varian XL-300 spectrometer operating at 299.99 MHz and 75.4 MHz for ^1H and ^{13}C, respectivley. All ^1H and ^{13}C NMR signals are reported in δ values or in ppm downfield from tetramethylsilane (TMS) with $DCCl_3$ as the solvent. IR data were collected on a Perkin-Elmer 681 spectrophotometer. Melting points were obtained using a Thomas-Hoover apparatus or Fischer-John's unit and were uncorrected. Chromatography was accomplished with a Chromatotron, Model 7924 [Harrison Research, 840 Moana Court, Palo Alto, California 94306] with silica gel. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The following starting materials were purchased from Aldrich and were used without further purification: methyl phenylacetate, ethyl phenylacetate, dimethyl oxalate, diethyl oxalate, iodotrimethylsilane, 4-bromophenol, 2-dimethylaminoethyl chloride hydrochloride, 4-thiochromanone (**15**), [2-(*p*-bromophenoxy)ethyl]pyrrolidine (**16**), and 3-methoxybenzenethiol. Thiophene-free benzene was obtained by washing reagent-grade benzene with concentrated H_2SO_4 (until the yellow color was very faint), H_2O, $KMnO_4$ in 10% H_2SO_4, and with 10% NaOH. This purified benzene was then dried ($MgSO_4$) overnight, filtered, and then distilled from CaH_2. Dry tetrahydrofuran (THF) was distilled from sodium prior to use, while chloroform was dried over alumina. All other solvents were used without additional purification.

Preparation of Methyl 2-Phenylacrylate (**10**, R = CH_3).- Sodium methoxide was freshly prepared from sodium metal (5.8 g, 0.25 mol) and absolute methanol (100 mL) in the standard manner. Excess methanol was distilled and purified, thiophene-free benzene (100 mL) was added. To the stirred suspension was added dimethyl oxalate (29.8 g, 0.25 mol) and methyl phenylacetate (49.6 g, 0.33 mol). After stirring (30 min), the solution stood for 18 h. Filtration of the solid deposited and washing (benzene, 100 mL, and ether, 3 x 100 mL) gave a solid which was acidified (2 *N* H_2SO_4, 100 mL). The resulting mixture was stirred (30 min) and two layers separated. Extracts (ether, 3 x 100 mL) and the original small ether layer were combined and dried ($MgSO_4$). Filtration and concentration of the filtrate gave an oil which was treated with 37% aqueous formaldehyde (31 mL) and H_2O (100 mL). The mixure at 15° was treated (30 min) with K_2CO_3 (27 g, 0.20 mol) in H_2O (50 mL). After warming to room temperature with stirring (2 h), the solution was extracted (ether, 150 mL). Combined organics were dried ($MgSO_4$) and filtered. Concentration and distillation gave a colorless liquid; bp 62-66°/0.65 mm Hg (lit[16] 95-98°/6 mm). The ^1H NMR analysis of the liquid confirmed ester **10** along with a small amount of methyl phenylacetate. This liquid could be used satisfactorily in the next step. IR (film) cm^{-1} 1731 (C=O); ^1H NMR ($DCCl_3$): δ 3.84 (s, 3 H, OCH_3), 5.91 (s, 1 H, $=CH_2$) and 6.38 (s, 1 H, $=CH_2$), 7.3-7.45 (m, 5 H, Ar-*H*).

Preparation of Methyl 3-(3-Methoxyphenylthio)-2-phenylpropanoate (**11**).- Methyl 2-phenylacrylate [**10** (R=Me), 11.7 g, 0.039 mol], 3-methoxybenzenethiol (5.0 g, 0.034 mol), and 12 mL of $HCCl_3$ were combined and cooled (0°). Triethylamine (0.2 mL) was added (syringe). The solution was allowed to warm to room temperature and then was stirred (20 h). The final mixture was diluted (ether, 20 mL) and washed with 5% NaOH (2 x 15 mL), H_2O (45 mL), and saturated NaCl (2 x 15 mL). The ether layer was dried (Na_2SO_4), filtered, evaporated, and vacuum distilled to give colorless ester **11**; bp 143-160°/0.04 mm Hg (8.96 g, 0.03 mol, 88%). IR (film) cm^{-1}: 1745 (C=O); ^1H NMR ($DCCl_3$): δ 3.24 (dd, 1 H, -S-CH_2), 3.58 (dd, 1 H, -S-CH_2), 3.64 (s, 3 H, [C=O]-OCH_3), 3.81 (dd, 1 H, C_6H_5-CH-C=O), 6.7-7.3 (m, 9 H, Ar-*H*); ^{13}C NMR ($DCCl_3$): ppm 36.19 (t, -S-CH_2), 51.36 (d, C_6H_5-CH-C=O), 52.19 (q, [C=O]-OCH_3), 55.19 (q, -OCH_3), 172.84 (s, C=O).

Anal. Calcd. for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00; S, 10.60

Found: C, 67.74; H, 6.09; S, 10.55

Preparation of 3-(3-Methoxyphenythio)-2-phenylpropanoic Acid (**8**) from the Methyl Ester **11**.- Methyl ester **11** (5.0 g, 0.0166 mol) and spect. grade $HCCl_3$ (30 mL) were combined, and stirred (room temperature, 10 min). Iodotrimethylsilane (8.0 mL, 11.25 g, 0.056 mol) was added (syringe), and the solution was boiled (21.5 h) to produce a dark red solution which was cooled to room temperature (15 min) and diluted (ether, 50 mL). Extraction with 0.5 *N* NaOH (5 x 25 mL) gave two colorless layers, and the water layer was separated, cooled (ice), and acidified (10% HCl, pH ~1). At pH 7, a pale yellow oil appeared in the bottom of the flask. Extracts ($HCCl_3$, 200 mL) of the water layer (pH~l) were dried (Na_2SO_4), filtered, and concentrated to an oil which was dried under high vacuum (30 min). Refrigeration of the oil induced crystallization of **8** (4.45 g, 94%, mp 54-56°). IR (film) cm-^{1}: 1720 (C=O), 3010 (vb, O-H); ^{1}H NMR ($DCCl_3$): δ 3.24 (dd, 1 H, S-C*H*$_2$), 3.58 (dd, 1 H, S-C*H*$_2$), 3.80 (s, 3 H, S-CH_2-CH), 6.7-7.4 (m, 9 H, Ar-*H*), 8.6-8.9 (bs, 1 H, OH); ^{13}C NMR ($DCCl_3$): ppm 36.70 (S-*C*H$_2$), 51.46 (S-C-*C*H), 55.29 (O*C*H$_3$), 177.99 (*C*=O), Ar-*C*: 112.57, 115.54, 122.31, 127.83, 128.79, 129.78, 135.8, 136.78, 159.72 (Ar*C*-OCH$_3$).

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.67; H, 5.56; S, 11.11

Found: C, 66.46; H, 5.65; S, 11.24

Preparation of 7-Methoxy-3-phenyl-4-thiochromanone (**9**).- Acid **8** (2.0, 6.94 mmol) in H_2CCl_2 (30 mL)was stirred (ice/salt/water bath, 15 min). Solid PCl_5 (1.6 g, 7.68 mmol) was added, and the mixture was stirred (0°, 1 h). To the resulting light yellow solution was added (syringe) $SnCl_4$ [2.4 mL, 0.534 g, 2.0 mmol, mixture turned dark red]. After stirring (0°, 30 min), the mixture was allowed to warm to room temperature (stirring, 6 h). The red mixture was poured into ice water. A yellow suspension formed and was diluted (H_2CCl_2, 20 mL and 10% NaOH, 25 mL). The water layer was washed (H_2CCl_2, 300 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and evaporated to an orange oil to which was added absolute methanol (10 mL). Refrigeration produced an off-white ketone **9** (0.7557 g, 40%) which was recrystallized (H_3COH); 147-148° (lit[10] 151-152.5°). IR (KBr) cm-^{1}: 1665

(C=O); ^{1}H NMR ($DCCl_3$): δ 3.30 (dd, 1 H, S-C*H*$_2$-CH), 3.55 (dd, 1 H, S-C*H*$_2$-CH), 3.83 (s, 3 H, OC*H*$_3$), 4.05 (dd, 1 H, S-CH$_2$-C*H*), 5.7-8.2 (m, 8 H, Ar-*H*); ^{13}C NMR ($DCCl_3$): ppm 33.33 (S-*C*H$_2$-CH), 53.64 (S-CH$_2$-*C*H), 55.57 (O*C*H$_3$), 193.12 (*C*=O), Ar-C: 110.63, 112.76, 124.95, 127.46, 128.43, 128.68, 132.15, 138.23, 144.12, 163.25 (Ar*C*-OCH$_3$). Mass spectal analysis calcd for $C_{16}H_{14}O_2S$: M$^+$ 270.0714. Found: 270.0726.

Attempted preparations of ketone **9** using acid **8** and various concentrations of polyphosphoric acid produced impure **9** in yields less than 15%.

Preparation of 4-(2-*N,N*-Dimethylaminoethoxy)bromobenzene (**13**).- *p*-Bromophenol (**12**, 5.2 g, 0.03 mol), K_2CO_3 (10.4 g, 0.075 mol), and 150 mL of dimethylformamide were combined and boiled (45 min). After the mixture was cooled (30 min, *not* to room temperature), 2-(dimethylamino)ethyl chloride hydrochloride (3.6 g, 0.025 mol) was added. The resulting mixture was boiled (2 h) and cooled to room temperature (stirring, 12 h). The precipitate was filtered, and the solution was diluted with H_2O (50 mL) and ether (50 mL) and then extracted (10% HCl, 30 mL). The orange, aqueous layer was basified (10% NaOH, pH~12.5) and then extracted (ether, 250 mL). Combined extracts were dried ($MgSO_4$) and evaporated to an oil which was distilled to give 3.0 g (41%) of ester **13** as a light yellow oil; bp 80-84°/-0.075 mm Hg (lit[17] 152-153°/4 mm Hg). ^{1}H NMR ($DCCl_3$): δ 2.35 [s, 6 H, N(C*H*$_3$)$_2$], 2.72 (t, 2 H, OCH$_2$-C*H*$_2$-N), 4.05 (t, 2 H, OC*H*$_2$-CH$_2$-N), 6.85 (d, 2 H, Ar-*H*, ortho to Br), 7.40 (d, 2 H, Ar-*H*, ortho to O); ^{13}C NMR ($DCCl_3$): ppm 45.78 [N(*C*H$_3$)$_2$], 58.05 (OCH$_2$-*C*H$_2$-N), 66.13 (O*C*H$_2$-CH$_2$-N); Ar-*C*: 112.65, 115.15, 131.94, 157.65.

Preparation of 4-(2-*N,N*-Diethylaminoethoxy)bromobenzene (**14**).- *p*-Bromophenol (**12**, 10.4 g, 0.06 mol), K_2CO_3 (20.8 g, 0.15 mol), and 200 mL of dimethylformamide were boiled (30 min), and the resulting mixture was allowed to cool (15 min, *not* to room temperature). 2-(Diethylamino)ethyl chloride hydrochloride (8.6 g, 0.05 mol) was added, and the mixture was boiled (16 h). The solution was filtered and diluted with H_2O (100 mL) and ether (100 mL). After washing the aqueous layer with 10% HCl (3 x 100 mL), all aqueous phases were combined and basified (10% NaOH, pH ~ 12). Extracts (ether, 3 x 100 mL) of the water layer were combined, dried ($MgSO_4$), evaporated, and distilled to give ester **14** (1.5 g, 11%); bp

131-135°/0.26 mm Hg (lit[17] 174-178°/4 mm Hg); ^{1}H NMR ($DCCl_3$): δ 1.08 [t, 6 H, $N(CH_2$-$CH_3)_2$], 2.67 [q, 4 H, $N(CH_2$-$CH_3)_2$], 2.90 (t, 2 H, OCH_2-CH_2N), 4.04 (t, 2 H, OCH_2-CH_2N), 6.62-7.42 (m, 4 H, Ar-*H*); ^{13}C NMR ($DCCl_3$): ppm 11.47 [$N(CH_2$-$CH_3)_2$], 47.57 [$N(CH_2$-$CH_3)_2$], 51.46 (OCH_2-CH_2N), 66.45 ($O(CH_2$-CH_2N).

Preparation of 3,4-Dihydro-7-methoxy-3-phenyl-4-[4-{2-(*N,N*-dimethyl)ethoxy}phenyl]-2*H*-1-benzothiopyran-4-ol (**5**).- Magnesium (0.45 g, 0.018 mol) and dry THF(0.5 mL) were treated with 1-2 drops of 4-(2-*N,N*-dimethylaminoethoxy)bromobenzene (**13**, 1.5 g, 0.006 mol). A heat gun initiated the reaction. Addition of THF (10 mL) diluted the halide, and this new solution was added (30 min). After being boiled (2 h), the solution was allowed to cool to room temperature (15 min). Addition (60 min) of ketone **9** (1.0 g, 0.0037 mol, ice temperature) gave a red solution which was stirred (room temperature, 48 h). The mixture was diluted (THF), filtered and decomposed (H_2O). The organic phase was washed with water and with 15% NH_4Cl (3 x 15mL). The dried (Na_2SO_4) organic solution was evaporated to an oil which was chromatographed [neutral alumina in hexanes; ethyl acetate:hexanes (1:20)]. Alcohol **5** was a white solid (0.40 g, 25%), mp 151-152.5°. IR (KBr) cm^{-1}: 3200 (b, O-H); ^{1}H NMR ($DCCl_3$): δ 2.32 [s, 6 H, $N(CH_3)_2$], 2.70 (t, 2 H, OCH_2-CH_2-N), 2.90 (dd, 1 H, SCH_2-CH), 3.55 (s, 1 H, SCH_2-CH), 3.76 (bd, 1 H, SCH_2-CH), 3.80 (s, 3 H, OCH_3), 4.02 (t, 2 H, OCH_2-CH_2N), 6.5-7.3 (m, 12 H, Ar-*H*); ^{13}C NMR ($DCCl_3$): ppm 28.30 (t, SCH_2-CH), 45.88 [q, $N(CH_3)_2$], 53.22 (d, SCH_2-CH), 55.27 (q, OCH_3), 58.27 (t, OCH_2-CH_2-N), 65.84 (t, OCH_2-CH_2-N), 75.75 (s, *C*-OH).

Anal. Calcd. for $C_{26}H_{29}NO_3S$: C, 71.72; H, 6.67; N, 3.22; S, 7.36

Found: C, 71.59; H, 6.72; N, 3.21; S, 7.35

Preparation of 3,4-Dihydro-7-methoxy-3-phenyl-4[4-{2-(*N,N*-diethyl)ethoxy}phenyl]-2*H*-1-benzothiopyran-4-ol (**6**).- The conditions were the same as for **5** with the following changes. Magnesium metal (0.40 g, 0.015 mol) and 4-(2-*N,N*-diethylaminoethoxy)bromobenzene (**14**, 2.0 g, 0.007 mol) were employed. After ketone **9** (1.0 g, 0.0037 mol) was added to the Grignard reagent from **14**, the mixture was stirred (room temperature, 22.5 h) and then boiled (9.5 h). Alcohol **6** was a white solid (0.250 g, 15%); mp 102-104°. IR (KBr) cm^{-1}: 3200 (b,

O-H); ^{1}H NMR ($DCCl_3$): δ 1.05 [t, 6 H, $N(CH_2CH_3)_2$], 2.13 (bs, 1 H, OH), 2.72 [q, 4 H, $N(CH_2CH_3)_2$], 2.74 (d, 1 H,SCH_2-CH), 2.86 (t, 2 H, OCH_2-CH_2N), 2.92 (bd, 1 H, SCH_2-CH), 3.56 (bd, 1 H, SCH_2-CH), 3.80 (s, 3 H, OCH_3), 4.02 (t, 2 H, OCH_2-CH_2-N), 6.46-7.4 (m, 12 H, Ar-*H*); ^{13}C NMR ($DCCl_3$): ppm 11.83 [$N(CH_2CH_3)_2$], 28.29 (SCH_2-CH), 47.86 [$N(CH_2$-$CH_3)_2$], 51.67 (OCH_2-CH_2-N), 53.20 (SCH_2-CH), 55.27(OCH_3), 66.42 (OCH_2-CH_2-N), 75.76 (*C*-OH).

Anal. Calcd. for $C_{28}H_{33}NO_3S$: C, 72.57; H, 7.13; S, 6.91

Found: C, 72.58; H, 7.29; S, 6.84

Preparation of 3,4-Dihydro-4-[-{2-(*N*-pyrrolidinyl)ethoxy}phenyl]-2*H*-1-benzothiopyran-4-ol (7).- The reaction was performed as for **5** with some changes. Magnesium metal (0.9 g, 0.037 mol), 1-[2-*p*-bromophenoxy)ethyl]pyrrolidine (**16**, 5.0 g, 0.0185 mol) in 25 mL of dry THF, and thiochroman-4-one (**15**, 2.0 g, 0.012 mol) in dry THF (15 mL) were used. After **15** was added to the Grignard reagent from **16**, the mixture was stirred (room temperature, 4 h) and boiled (25 h). Alcohol **6** was a white solid (0.200 g, 5%); mp 129.5-131°. IR (KBr) cm-^{1}: (b, O-H); ^{1}H NMR ($DCCl_3$): δ 1.80 [bs, 4 H, $N(CH_2.CH_2)$], 2.40 (m, 2 H, SCH_2-CH), 2.50 (bs, 1 H, OH), 2.62 [bs, 4 H, $N(CH_2$-$CH_2)_2$], 2.75 (m, 1 H, SCH_2-CH_2), 2.94 (t, 2 H, OCH_2.CH_2-N), 3.2 (m, 1 H, SCH_2-CH_2), 4.10 (t, 2 H, OCH_2-CH_2-N), 6.7-7.4 (m, 8 H Ar-*H*); ^{13}C NMR ($DCCl_3$): ppm 23.20 (SCH_2-CH_2), 23.46 [$N(CH_2$-CH_2-$N)_2$], 39.54 (SCH_2-CH_2), 54.67 [$N(CH_2$-$CH_2)_2$], 55.04 (OCH_2-CH_2-N), 66.95 (OCH_2-CH_2N), 73.56 (*C*-OH).

Anal. Calcd. for $C_{21}H_{25}NO_2S$: C, 70.99; H, 7.04; S, 9.01

Found: C, 70.73; H, 7.01; S, 9.12

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