HETEROCYCLES. 11. SULFUR ANALOGS OF 3-(3-HYDROXYPHENYL)-N-n-PROPYLPIPERIDINE[1]

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Abstract - Analogs of 3-(3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP) and 3-(3-hydroxyphenyl)-N-(2-phenylethyl)piperidine (phenethyl 3-PP) in which carbon 4 was replaced by sulfur were synthesized and tested for dopamine autoreceptor activity.

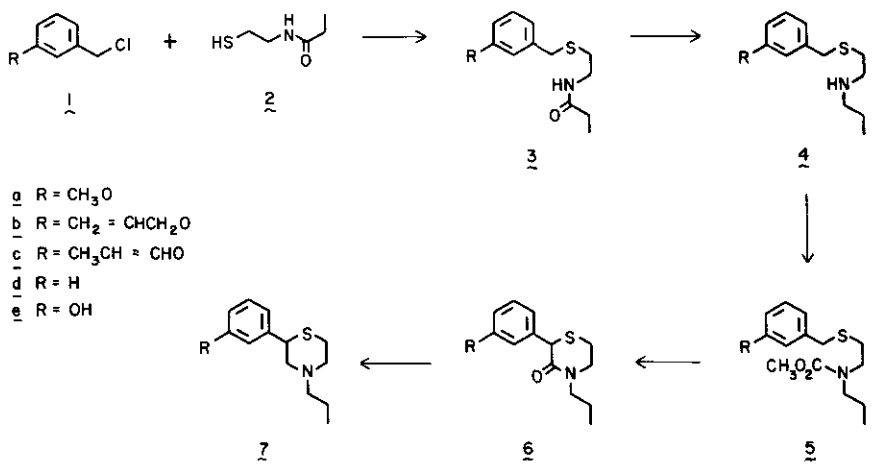
Compounds that have selective specificity for dopamine (DA) receptors in the brain have been sought after as an approach to new therapy for schizophrenia and parkinsonism. An autoreceptor for DA has been recently identified and pharmacologically characterized.[2] Compounds that preferentially activate the DA autoreceptor in the brain reduce impulse flow, transmitter synthesis rate and release of DA in the central nervous system.[2,3] The paradoxical improvement in schizophrenic[4] and in choreic[5] patients after treatment with low doses of apomorphine is thought to be mediated by preferential activation of the DA autoreceptor.[6]

A series of hydroxyphenylpiperidines has been described and one of these, 3-(3-hydroxyphenyl-N-n-propylpiperidine (3-PPP), was demonstrated to be a selective, centrally-acting DA autoreceptor agonist.[7-12] Recently the N-phenethyl analog of 3-PPP was shown to be 10-30 times more potent as a dopamine agonist.[8,13,14] This paper describes the preparation of analogs 7e and 8 of these two compounds in which carbon 4 has been replaced with a sulfur. This structural modification was made as an attempt to give increased potency or a longer duration of action.

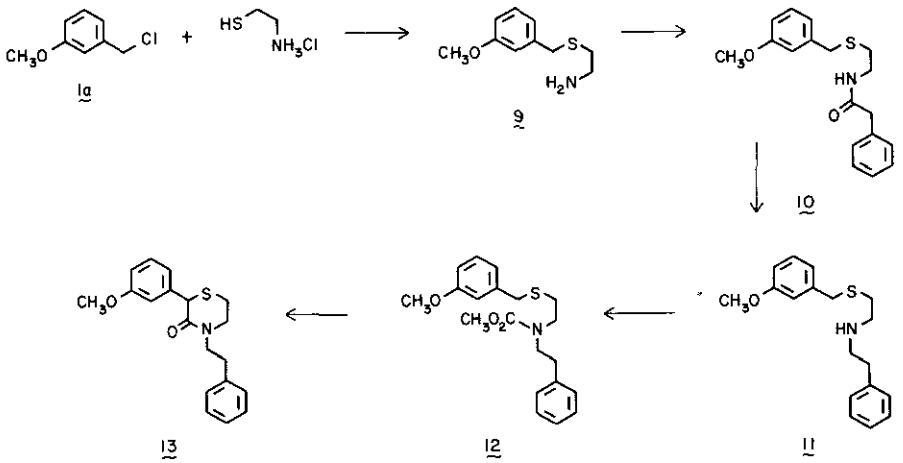
CHEMISTRY

Thioether 3a was obtained by reacting benzyl chloride 1a with thiol 2. Reduction of the amide group followed by reaction of the resulting amine 4a with methyl chloroformate gave urethane 5a. The key step in the sequence, base catalyzed cyclization of 5a, was successfully effected in tetrahydrofuran using three equivalents of lithium diisopropylamide (LDA).[15] Reduction of the resulting lactam 6a readily gave thiomorpholine 7a which was demethylated with trimethylsilyl iodide[17] in modest yield affording the target compound 7e. The free phenol could be more conveniently prepared using an allyl ether protecting group. We envisioned removal of this group using palladium catalyzed cleavage;[18] however, during the cyclization of 5b to 6b, a base induced

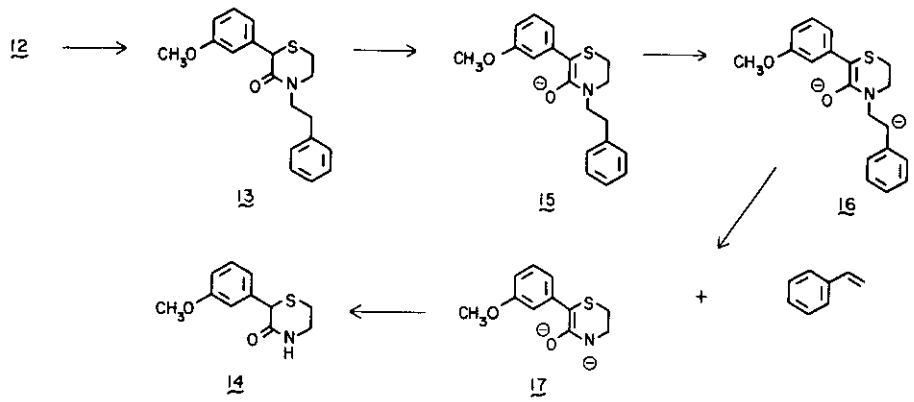
isomerization of the allylic double bond occurred which yielded 6c directly. Subsequent reduction and mild acid hydrolysis gave 7e in good yield.



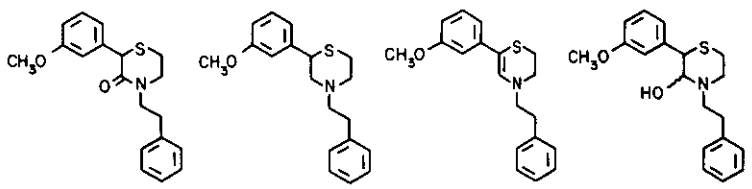
We reacted benzyl chloride 1a with 2-mercaptoethylamine hydrochloride according to Rydon et al.[19] to give amine 9. Reaction of the amine with phenacetyl chloride yielded amide 10 which was reduced with borane-dimethylsulfide[20] to amine 11. Amine 11 was then converted to urethane 12 by reaction with methyl chloroformate. Treatment of 12 with 3 equivalents of LDA as previously described gave some of the expected product (22%) and an amide (57%) which was shown by spectral and elemental analyses to be the N-dealkylated amide 14. The NMR spectrum of the crude product has signals corresponding to ethylenic protons suggesting that the phenethyl group has been lost as styrene.



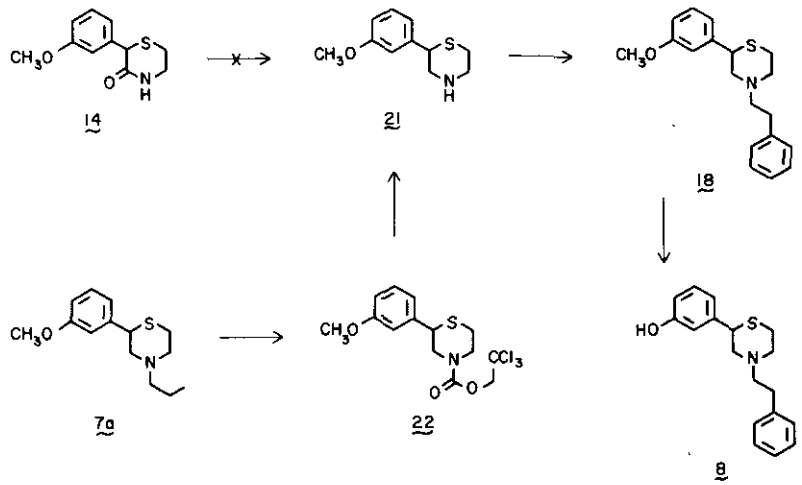
At first, it was not clear whether the dealkylation occurred from 12 or from 13. When 12 was treated with 2 equivalents of LDA we were able to isolate, in good yield, the amide 13. Furthermore, treatment of the latter with 3 equivalents of LDA gave amide 14 in good yield. It seems fairly clear, therefore, that N-dealkylation occurs from amide 13. The mechanism for the reaction has yet to be demonstrated, but we propose that amide 13 is formed with the first equivalent of LDA. The second equivalent then removes the relatively acidic methine proton in 13 to give 15. The third equivalent of LDA removes a second proton to form the dianion 16 which collapses as shown to give the dianion 17 and styrene.



Lithium aluminum hydride reduction of compound 13 in tetrahydrofuran resulted in a 1:1 mixture of amine 18 and the enamine 19. However, if the reaction is run in diethyl ether only 18 is obtained. Presumably, 19 is formed by partial reduction of the lactam to carbinolamine 20 and dehydration of 20 during the workup.[21]



The amine 18 could also be prepared via alkylation of 21. Amide 14, which can be readily obtained,[22,23] could not be reduced with lithium aluminum hydride despite reports to the contrary,[23] nor with diborane.[24] However, dealkylation of 7a with trichloroethyl chloroformate[25] followed by reductive cleavage of the resulting urethane 22 with zinc in acetic acid[25] gave 21. This reacted smoothly with phenethyl bromide to give 18. Removal of the methyl group with excess trimethylsilyl iodide in refluxing chloroform[15] yielded 8 as a crystalline solid.



PHARMACOLOGY

The target compounds were tested in mice in a spontaneous motor activity model similar in principle to that previously used to examine dopamine autoreceptor agonists.[4] Since dopamine autoreceptor agonists are known to inhibit the accumulation of DOPA in rats treated with γ-butyrolactone (GBL),[26] the target compounds were tested in this model as well. None of the compounds were active in either test. Thus, substitution of sulfur for carbon 4 of the piperidine ring resulted in *compounds which neither effected mouse spontaneous motor activity nor* altered DOPA synthesis in GBL-treated rats.

EXPERIMENTAL

All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer as a neat film unless otherwise noted. Nuclear magnetic resonance spectra ($CDCl_3$ with tetramethylsilane as internal standard) were run on a Varian FT80A spectrometer. The standard drying agent was magnesium sulfate and solvents were removed in vacuo on a rotary evaporator. All distillations were performed on a Kugelrohr apparatus purchased from Aldrich Chemical Company. Flash chromatography was effected as described in the literature[27] using 230-400 mesh, E. Merck silica gel.

N-[2-[[(3-Methoxyphenyl)methyl]thio]ethyl]propanamide (3a). A solution of 3-methoxyphenylmethyl chloride (1a, 25.0 g, 0.16 M) and thiol 2 (21.3 g, 0.16 M) in ethanol (150 ml) was treated with triethylamine (32.2 g, 0.32 M) and stirred at room temperature for 24 h. The solvent was removed and the residue diluted with water (400 ml) and extracted with diethyl ether (3 X 250 ml). The combined organic layers were backwashed with 10% aq hydrochloric acid (2 X 150 ml), with sat sodium

bicarbonate (2 X 100 ml), dried and concentrated to a yellow liquid which was distilled to give 3a (30.4 g, 75.2%), bp 210-215°C/0.3 T. IR ν: 3300, 1645, 1260 cm^{-1}. ^{1}H-NMR δ: 1.12 (3H, t), 2.11 (2H, quintet), 2.56 (2H, t), 3.34 (2H, q), 3.66 (2H, s), 3.75 (3H, s), 5.80 (1H, br s), 6.62-6.94 (3H, m), 7.17 (1H, t). Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53; S, 12.66. Found: C, 61.56; H, 7.79; N, 5.31; S, 12.55.

N-[2-[[(2-Propenyloxy)phenyl]methyl]thio]ethyl]propanamide (3b) was prepared as above and purified by flash chromatography. IR ν: 3300, 1650, 1600, 1580, 1545 cm^{-1}. ^{1}H-NMR δ: 1.10 (3H, t), 1.72 (1H, s), 2.16 (2H, q), 2.53 (2H, t), 3.34 (2H, q), 3.62 (2H, s), 4.41-4.59 (2H, m) 5.09-5.50 (2H, m), 5.69 + 5.75-6.28 (2H, br s + m), 6.62-6.94 (3H, m), 7.19 (1H, t). Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01; S, 11.48. Found: C, 63.80; H, 7.55; N, 4.84; S, 11.99.

N-[2-[(Phenylmethyl)thio]ethyl]propanamide (3d) was prepared as above in 72.2%, mp 50-51°C (ether-hexane). IR ν(KBr): 3300, 1645, 1545 cm^{-1}. ^{1}H-NMR δ: 1.12 (3H, t), 2.14 (2H, q), 2.55 (2H, t), 3.35 (2H, q), 3.66 (2H, s), 8.88 (1H, br s), 7.23 (5H, s). Calcd for $C_{12}H_{17}NOS$: C, 64.54; H, 7.67; N, 6.27; S, 14.36. Found: C, 64.69; H, 7.65; N, 6.05; S, 14.36.

N-[2-[[(3-Methoxyphenyl)methyl]thio]ethyl]-1-propanamine (4a). A stirred suspension of lithium aluminum hydride (4.0 g; 0.14 M) in dry ether (500 ml) was treated dropwise with a solution of amide 3a (29.3 g, 0.12 M) in dry ether (150 ml). After 24 h the excess reagent was decomposed by cautious addition of water then dilute aq sodium hydroxide. Magnesium sulfate was added. The solids were removed by filtration and washed with ether. The combined filtrate and wash was concentrated to a yellow liquid which was distilled to give 4a (23.7 g, 85.6%), bp 160-167°C/0.3 T. IR ν: 3300, 1670, 1600, 1260 cm^{-1}. ^{1}H-NMR δ: 0.90 (3H, t), 1.31-1.66 (4H, m, has an exchangeable proton), 2.34-2.81 (6H, m), 3.66 (2H, s), 3.77 (3H, s), 6.63-6.94 (3H, m), 7.16 (1H, t). Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84; N, 5.85; S, 13.39. Found: C, 64.53; H, 8.87; N, 5.57; S, 13.31.

N-[2-[[[3-(2-Propenyloxy)phenyl]methyl]thio]ethyl]-1-propanamine (4b). This was prepared as above, purified by flash chromatography and isolated as a liquid in 81.7%. IR ν: 1600, 1580 cm^{-1}. ^{1}H-NMR δ: 0.91 (3H, t), 1.22-1.75 (3H, m), 2.34-2.84 (6H, m), 3.62 (2H, s), 4.34-4.56 (2H, m), 5.09-5.50 (2H, m), 5.75-6.28 (1H, m), 6.62-6.94 (3H, m), 7.17 (1H, t). Calcd for $C_{15}H_{23}NOS$: C, 67.88; H, 8.73; N, 5.28; S, 12.08. Found: C, 67.51; H, 8.82; N, 5.14; S, 12.09.

N-[2-[(Phenylmethyl)thio]ethyl]-1-propanamine (4d). This was prepared as above in 95.1%, bp 120°C/0.3 T. IR ν: 1605, 1455 cm^{-1}. ^{1}H-NMR δ: 0.90 (3H, t), 1.42 + 1.45 (3H, s + hextet, has 1 exchangeable proton) 2.38-2.81 (6H, m), 3.66 (2H, s), 7.55 (5H, s). Calcd for $C_{12}H_{19}NS$: C, 68.85; H, 9.15; N, 6.99; S, 15.32. Found: C, 68.86; N, 9.35; N, 6.41; S, 15.00.

Methyl [2-[[[(3-Methylphenyl)methyl]thio]ethyl]propyl] carbamate (5a). A solution of 4a (22.8 g, 95.2 mM) and triethylamine (19.2 g, 0.19 M) in dry ether (750 ml) was treated slowly with a solution of methyl chloroformate (9.0 g, 95.2 mM) in dry ether (50 ml). (Exothermic!) After 90 min

the mixture was extracted with water (2 X 500 ml), with 5% aq hydrochloric acid (1 X 500 ml), dried and concentrated to a liquid which was distilled to give 5a (26.5 g, 93.6%), bp 180-186°C/0.25 T. IR ν: 1700 cm^{-1}. ^{1}H-NMR δ: 1.18 (3H, t), 1.74 (2H, hextet), 3.01 (2H, t), 2.97-3.44 (4H, m), 4.30-4.34 (5H, pr s), 4.47 (3H, s), 7.79-8.18 (3H, m), 8.66 (1H, t). Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71; S, 10.78. Found: C, 60.34; H, 7.47; N, 4.52; S, 10.58.

Methyl [2-[[[3-(2-Propenloxy)phenyl]methyl]thio]ethyl]propylcarbamate (5b). This was prepared as above and purified by flash chromatography to give 5b (79.6%) as a pale yellow liquid. IR ν: 1700, 1600, 1580 cm^{-1}. ^{1}H-NMR δ: 0.84 (3H, t), 1.47 (2H, hextet), 2.53 (2H, q), 2.66-3.44 (4H, m), 3.63 + 3.66 (5H, pr s), 4.41-4.56 (2H, m), 5.12-5.52 (2H, m), 5.75-6.28 (1H, m), 6.66-6.97 (3H, m), 7.19 (1H, t). Calcd for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 63.19; H, 8.03; N, 4.12; S, 9.84.

Methyl [2-[(Phenylmethyl)thio]ethyl]propylcarbamate (5d). This was prepared as above to give 5d (92.4%), bp 180-185°C/0.5 T. IR ν: 1700 cm^{-1}. ^{1}H-NMR δ: 0.84 (2H, t), 1.41 (2H, d of hextets), 2.52 (2H, d of d), 2.94-3.41 (4H, m), 3.63 + 3.69 (5H, pr s), 7.30 (5H, s). Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.95; H, 7.89; N, 5.03; S, 12.19.

2-(3-Methoxyphenyl)-4-propyl-3-thiomorpholinone (6a). A stirred solution of diisopropylamine (28.2 g, 0.28 M) in dry tetrahydrofuran (500 ml) cooled to -78°C under an argon atmosphere, was treated slowly with 2.1 M butyl lithium (133 ml, 0.28 M). After 15 min a solution of 5a (27.7 g, 93.1 mM) in dry tetrahydrofuran (100 ml) was added. The reaction was allowed to warm slowly to room temperature. After 3 h the reaction mixture was poured into sat ammonium chloride (300 ml). The organic layer was separated, dried and concentrated to a liquid which was distilled to give 6a (21.8 g, 88.2%), bp 195-202°C/0.25 T as a greenish-yellow liquid. The color was removed by a flash chromatography giving 6a (21.5 g, 87.0%). IR ν: 1655, 1640, 1595, 1260 cm^{-1}. ^{1}H-NMR δ: 0.99 (3H, t), 1.67 (2H, hextet), 2.89 (2H, t), 3.12-3.69 (4H, m), 3.81 (3H, s), 4.62 (1H, s), 6.67-7.06 (3H, m), 7.22 (1H, t). Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28; S, 12.08. Found: C, 63.28; H, 7.28; N, 5.23; S, 11.88.

2-[3-(1-Propenloxy)phenyl]-4-propyl-3-thiomorpholinone (6c). This was prepared as above and purified by flash chromatography to give 6c (79.4%). IR ν: 1655, 1635, 1600, 1565 cm^{-1}. ^{1}H-NMR δ: 0.96 (3H, t), 1.36-1.80 (5H, m), 2.84 (2H, t), 3.06-4.03 (4H, m), 4.59 (1H, s), 4.83 (1H, quintet), 6.22-6.47 (2H, m), 6.75-7.38 (4H, m). Calcd. for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81; S, 11.00. Found: C, 65.96; H, 7.29; N, 4.80; S, 10.77.

2-Phenyl-4-propyl-3-thiomorpholinone (6d). This was prepared as above to give 6d (80.8%) bp 170-180°C/0.05 T. IR ν: 1655, 1635 cm^{-1}. ^{1}H-NMR δ: 0.94 (3H, t), 1.62 (2H, hextet), 2.84 (2H, t), 3.12-3.75 (4H, m), 4.65 (1H, s), 7.00-7.50 (5H, m). Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95; S, 13.62. Found: C, 66.29; H, 7.47; N, 5.89; S, 13.29.

2-(3-Methoxyphenyl)-4-propylthiomorpholine (7a). A stirred suspension of lithium aluminum hydride (0.9 g) in dry ether (100 ml) was treated dropwise with a solution of 6a (5.1 g, 19.2 mM) in dry ether (50 ml) and stirred overnight. The excess reagent was decomposed by cautious addition of water and dilute aq sodium hydroxide. Magnesium sulfate was added. The solids were filtered off and washed with ether. The combined filtrate and wash was concentrated to a liquid which was distilled to give 7a (4.4 g, 91.1%), bp 160-162°C/0.05 T. IR ν: 1600, 1580 cm^{-1}. ^{1}H-NMR δ: 0.88 (3H, t), 1.50 (2H, sextet), 2.19-2.72 (5H, m), 2.83-3.28 (3H, m), 3.78 (3H, s), 4.00 (1H, d of d), 6.62-6.97 (3H, m), 7.19 (1H, t). Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57; S, 12.75. Found: C, 67.06; H, 8.48; N, 5.72; S, 12.83.

2-[3-(1-Propenloxy)phenyl]-4-propylthiomorpholine (7c). This was prepared as above and purified by flash chromatography to give 7c (95.1%) as a liquid. IR ν: 1665, 1660, 1585 cm^{-1}. ^{1}H-NMR δ: 0.88 (3H, t), 1.19-1.81 (5H, m), 2.16-2.73 (5H, m), 2.84-3.28 (3H, m), 4.00 (1H, d of d), 4.85 (1H, d of q), 6.25-6.53 (2H, m), 6.78-7.38 (4H, m). Calcd for $C_{16}H_{23}NOS$: C, 69.27; H, 8.36; N, 5.05; S, 11.56. Found: C, 69.41; H, 8.29; N, 4.87; S, 11.43.

2-Phenyl-4-propylthiomorpholine (7d). This was prepared as above to give 7d (72.1%), bp 120-125°C/0.1 T. IR ν: 1600 cm^{-1}. ^{1}H-NMR δ: 0.89 (3H, t), 1.31 (2H, hextet), 2.11-2.73 (5H, m), 2.81-3.28 (3H, m), 3.95 + 4.08 (1H, pr d), 7.12-7.44 (5H, m). Calcd for $C_{13}H_{19}NS$: C, 70.54; H, 8.65; N, 6.33; S, 14.48. Found: C, 70.84; H, 8.89; N, 6.59; S, 14.09.

2-(3-Hydroxyphenyl)-4-propylthiomorpholine (7e). From 7a. A solution of 7a (3.1 g, 12.3 mM) in chloroform (100 ml) was treated with trimethylsilyl iodide (9.0 ml, 63.1 mM) and kept under argon. After 15 days more trimethylsilyl iodide (4.0 ml) was added. After 9 days the volatiles were removed. The residue was partitioned between 5% aq hydrochloric acid and ether. The aqueous layer was separated and made basic with sat sodium bicarbonate. This milky mixture was extracted with ether (300 ml) which was dried and concentrated to a liquid which was purified by flash chromatography to an oil 7e (0.91 g, 31.4%) which crystallized on standing. IR ν: 3100-2500, 1595, 1450 cm^{-1}. ^{1}H-NMR δ: 0.84 (3H, t), 1.53 (2H, hextet), 2.15-2.75 (5H, m), 2.84-3.41 (3H, m), 4.00 (1H, d of d), 6.59-6.97 (3H, m), 7.19 (1H, t). Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90; S, 13.51. Found: C, 65.78; H, 8.06; N, 5.96; S, 13.42.

From 7c. A solution of 6c (15.5 g, 55.9 mM), acetone (100 ml), 10% aq hydrochloric acid (75 ml) and water (300 ml) was heated on a steam bath until the starting material was gone (by TLC, ca. 1 h). The solution was cooled, made basic with sat sodium bicarbonate and extracted with ether (1 X 750 ml then 2 X 250 ml). The combined ether extract was washed with brine, dried and concentrated to a liquid which was purified as above and crystallized from ether to give 7e (10.8 g, 81.4%), mp 115-116°C in two crops.

N-2-[[(3-Methoxyphenyl)methyl]thio]ethanamine (9). Sodium (12.0 g) was added in small portions to a solution of 2-mercaptoethylamine hydrochloride (24.8 g, 0.218 M) in liquid ammonia (700 ml) until the blue color persisted. A small quantity of ammonium chloride was added to discharge the color and 3-methoxyphenylmethyl chloride (34.1 g, 0.218 M) was added dropwise. After 1 h the ammonia was allowed to evaporate. The residue was treated with ether (250 ml) and water (350 ml). The organic layer was dried, treated with charcoal, filtered and concentrated to a liquid which was distilled to give amine 9 (34.1 g, 79.1%), bp 120-125°C/0.1 T, as a colorless liquid. IR ν: 3360, 3290, 1600, 1585 cm^{-1}. ^{1}H-NMR δ: 1.33 (2H, s), 2.52 (2H,t), 2.81 (2H,t), 3.67 (2H, s), 3.79 (3H, s), 6.76-6.81 (1H, m), 6.86-6.92 (2H, m), 7.22 (1H, t). Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10; S, 16.25. Found: C, 61.22; H, 7.56; N, 6.87; S, 15.81.

N-[2-[[(3-Methoxyphenyl)methyl]thio]ethyl]benzeneacetamide (10). A stirred solution of 9 (34.0 g, 0.17 M) and triethylamine (26.1 g, 0.26 M) in dry ether was treated dropwise with a solution of phenacetyl chloride (26.6 g, 0.17 M) in dry ether (75 ml). After 2 h the mixture was extracted with water (1 x 500 ml), with 10% aq hydrochloric acid (1 x 250 ml), dried and concentrated to a liquid which was distilled to give 10 (41.9 g, 77.0%), bp 215-220°C/0.15 T. IR ν: 3300, 1650, 1265 cm^{-1}. ^{1}H-NMR δ: 2.52 (2H, T), 3.33 (2H, q), 3.56 (2H, s), 3.36 (2H, s), 3.78 (3H, s), 5.75 (1H, br s), 6.66-6.97 (3H, m), 7.08-7.41 (6H, m). Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44; S, 10.16. Found: C, 68.82; H, 6.57; N, 4.36; S, 10.00.

N-[2-[[(3-Methoxyphenyl)methyl]thio]ethyl]benzeneethanamine (11). A stirred solution of 10 (40.2 g, 127 mM) in dry tetrahydrofuran (370 ml) was treated dropwise with borane-dimethylsulfide (32 ml, 0.32 M). After 24 h, methanol (65 ml) was added dropwise. After 24 h the solvent was removed by rotary evaporation and the residue was dissolved in methanol (400 ml) and concentrated. The residue was dissolved again in methanol (100 ml), treated with 20% aq hydrochloric acid (300 ml) and stirred 1 h at room temperature and 30 min on the steam bath. The cooled mixture was made basic with concentrated ammonium hydroxide (200 ml) and heated briefly on the steam bath. The mixture was extracted with dichloromethane (3 x 250 ml). The extract was dried and concentrated to a liquid which was distilled to give 11 (32.2 g, 83.8%). IR ν: 1600, 1580, 1260 cm^{-1}. ^{1}H-NMR δ: 1.53 (1H, br s, exchangeable), 2.41-2.84 (8H, m), 3.58 (2H, s), 3.72 (3H, s), 6.63-6.91 (3H, m), 7.03-7.31 (6H, m). Calcd for $C_{18}H_{23}NOS$: C, 71.72; H, 7.69; N, 4.65; S, 10.64. Found: C, 71.25; H, 7.67; N, 4.51; S, 10.57.

[2-[[(3-Methoxyphenyl)methyl]thio]ethyl][2-phenylethyl]carbamic Acid (12). A stirred solution of 11 (16.5 g, 54.7 mM), triethylamine (11.1 g, 0.11 M) and ether (500 ml) was cooled in an ice bath and treated dropwise with a solution of methyl chloroformate (5.17 g, 54.7 mM) in ether (100 ml). After 1 h the mixture was extracted with water (2 X 500 ml), with 5% aq hydrochloric acid (1 X 500 ml), dried and concentrated to a liquid which was purified by flash chromatography to give a yellow

liquid 12 (17.9 g, 90.9%). IR ν: 1700, 1600, 1580 cm^{-1}. ^{1}H-NMR δ: 2.31-2.91 (4H, m), 3.09-3.53 (4H, m), 3.66 (5H, s), 3.78 (3H, s), 6.66-6.94 (3H, m), 7.03-7.34 (6H, m). Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90; S, 8.92. Found: C, 67.04; H, 7.13; N, 3.94; S, 8.84.

2-(3-Methoxyphenyl)-4-(2-phenylethyl)-3-thiomorpholinone (13). A solution of urethane 12 (17.9 g, 49.8 mM) in tetrahydrofuran (1 L) under an argon atmosphere was cooled to -78°C and treated with a solution of 1.87 M lithium diisopropylamide in cyclohexane (from Lithco Corp., 53.3 ml, 99.6 mM). The cooling bath was removed and the solution stirred 2.5 h longer. Sat ammonium chloride (400 ml) was added. The organic layer was separated, dried and concentrated to a yellow liquid which was purified by flash chromatography to give 12 (2.6 g, 14.5%) and 13 (12.3 g, 75.5%). IR ν: 1700 (w), 1660, 1630, 1580, 1480 cm^{-1}. ^{1}H-NMR δ: 2.70-2.84 (4H, d of t + pr d), 3.40 (2H, d of q), 3.64 (2H, d of t), 3.83 (3H, s), 4.59 (1H, s), 6.69-7.38 (9H, m). Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.46; H, 6.49; N, 4.06; S, 9.54.

2-(3-Methoxyphenyl)-3-thiomorpholinone (14). From α-Chloro-3-methoxybenzeneacetyl Chloride. A magnetically stirred mixture of α-chloro-3-methoxyphenacetyl chloride (35.6 g, 0.163 M) and 2-mercaptoethylamine S-acetate hydrochloride (25.3 g, 0.163 M) and chloroform (400 ml) was treated slowly with a solution of triethylamine (32.8 g, 0.326 M) in chloroform (500 ml). After 6 h the mixture was extracted with water (2 X 200 ml), with 10% aq hydrochloric acid (2 X 200 ml), with sat bicarbonate (1 X 250 ml), dried and concentrated to a red-brown liquid (ca. 48 g) which was used without purification.

The above product (ca. 0.159 M) in tetrahydrofuran (100 ml) was diluted with methanol (200 ml) then treated with sodium methoxide (8.59 g, 0.159 M). After 18 h the solid was filtered off and washed with methanol. The combined filtrate and wash was concentrated. The residue was dissolved in dichloromethane (250 ml), washed with water (2 X 100 ml), dried, treated with charcoal, filtered and concentrated to a liquid which was purified by flash chromatography to give amide 14 (5.79 g, 16.3%), mp 116-117°C. IR ν: 3200, 1650, 1610, 1585 cm^{-1}. ^{1}H-NMR δ: 2.80 (2H, d of d), 3.44-3.69 (2H, m, collapses to d of d with D_2O), 3.75 (3H, s), 4.56 (1H, s), 6.66-7.00 (3H, m), 7.11 + 7.19 (2H, br s + d of d, has 1 exchangeable proton at 7.11). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.06; H, 5.90; N, 6.17; S, 14.40.

From 12. A solution of urethane 12 (4.26g, 11.8 mM) in tetrahydrofuran (15 ml) was added to a solution of lithium diisopropylamide (35.4 mM, from 3.59 g of diiospropylamine and 15.5 ml of 2.3 M butyl lithium) in tetrahydrofuran (150 ml) cooled to -78°C. After 0.5 h, the cold bath was removed and the reaction stirred 2.5 h more. Sat ammonium chloride (60 ml) was added. The organic layer was separated, dried and concentrated to a yellow liquid which was purified by flash chromatography to give 13 (0.9 g, 22.5%) and 14 (1.5 g, 56.6%).

When the reaction was repeated using 4.1 g (11.4 mM) of 12 in 150 ml of tetrahydrofuran and 3.5 equivalents of lithium diisopropylamide solution (from Lithco Corp), amide 14 (1.3 g, 51%) was obtained as the sole product.

From 13. A solution of amide 13 (3.25 g, 9.92 mM) in tetrahydrofuran (50 ml) under an argon atmosphere was cooled to 0°C and treated with 1.87 M lithium diisopropylamide (15.9 ml, 29.8 mm). the cooling bath was removed and the solution stirred for 2.5 h and the reaction worked up as above to give a yellow liquid which on flash chromatography gave recovered amide 13 (0.5 g, 15.4%) and dealkylated amide 14 (1.6 g, 72.2%) identical with authentic 14 (see below).

6-(3-Methoxyphenyl)-4-(2-phenylethyl-3,4-dihydro-2H-1,4-thiazine (19). A stirred suspension of lithium aluminum hydride (2.0 g, 52.6 mM) in tetrahydrofuran (100 ml) was treated with a solution of amide 13 (3.05 g, 9.34 mM) in tetrahydrofuran (25 ml) and stirred overnight at room temperature. Usual work up afforded a mixture of products which was separated by flash chromatography to give in order of elution: enamine 19 (0.8 g, 27.6%). IR ν: 1615, 1590 cm^{-1}. ^{1}H-NMR δ: 1.42 (1H, s), 2.66-3.03 (4H, m), 3.13-3.58 (4H, m), 3.75 (3H, s), 6.50 (1H, s), 6.58-7.35 (9H, m). Calcd for $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50; S, 10.30. Found: C,73.38; H, 7.02; N, 4.29; S, 9.76.
Amine 18 (1.0 g, 34.5%) identical with authentic sample (see below).

2-(3-Methoxyphenyl)-4-(2-phenylethyl)thiomorpholine (18). When the reduction was run as above using the same quantities of reagents but substituting ether as the solvent the reaction gave amine 18 (2.4 g, 81.6%) identical with authentic sample (see below).

2,2,2-Trichloroethyl 2-(3-methoxyphenyl)-4-thiomorpholinecarboxylate (22). A stirred solution of 7a (25.1 g, 0.10 M) and trichloroethyl chloroformate (26.3 g, 0.12 M) in toluene (950 ml) was heated at reflux temperature under an argon atmosphere. After 48 h the cooled reaction mixture was extracted with 10% aq hydrochloric acid, (2 X 125 ml), with water (1 X 150 ml), dried, treated with charcoal and concentrated to a yellow-brown liquid 22 which could be used directly in the next step. An analytical sample of 22 was prepared by flash chromatography. IR ν: 1720 cm^{-1}. ^{1}H-NMR δ: 2.41-3.22 (4H, m), 3.42 (3H, s), 3.92 (1H, d of d), 4.34-4.88 (4H, m), 6.66-7.00 (3H, m), 7.22 (1H, t). MS m/z (E I): 383 cluster (parent, appropriate cluster for 3 chlorines). Calcd for $C_{14}H_{16}Cl_3NO_3S$: C, 43.71; H, 4.19; N, 3.64; S, 8.33. Found: C, 43.64; H, 4.34; N, 3.43; S, 8.02.

2-(3-Methoxyphenyl)thiomorpholine (21). A solution of crude urethane 22 (38.3 g) in acetic acid (200 ml) was treated in portions with zinc dust (55.8 g). The reaction is exothermic. After 3.5 h the reaction was diluted with water (1 L) and filtered. The filtrate was made basic with ammonium hydroxide and then extracted with dichloromethane (4 X 250 ml). The combined organic extract was washed with dilute ammonium hydroxide, dried, treated with charcoal and concentrated to a liquid which was distilled to give 21 (12.8 g, 61.2% from 7a, bp 135-138°C/0.025 T. IR ν: 3310, 1600,

1580 cm^{-1}. ^{1}H-NMR ν: 1.73 (1H, s, exchangeable), 2.59 (1H, d of t), 2.84-3.50 (5H, m), 3.81-3.91 (4H, s + d of d), 6.66-6.98 (3H, m), 7.22 (1H, q). Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 62.80; H, 7.30; N, 6.32; S, 14.50.

2-(3-Methoxyphenyl)-4-(2-phenylethyl)thiomorpholine (18). A stirred mixture of 21 (12.8 g, 61.1 mM), 2-bromoethylbenzene (11.9 g, 64.3 mM) and potassium carbonate (8.88 g, 64.3 mM) in dimethylformamide (100 ml) was heated at 80 ± 1°C. After 18 h the solvent was distilled off under high vacuum. The residue was partitioned between water (100 ml) and dichloromethane (250 ml). The organic layer was washed with water (100 ml) and extracted wih 10% aq hydrochloric acid (2 X 100 ml). The combined acidic extract was made basic with ammonium hydroxide and extracted with dichloromethane. The organic layer was dried and concentrated to a liquid which was purified by flash chromatography to give 18 (13.8 g, 85.2%) as a liquid. IR ν: 1600, 1580, 1270 cm^{-1}. ^{1}H-NMR δ: 2.25-2.94 (8H, m), 3.00-3.34 (2H, m), 3.75 (3H, s), 3.98 (1H, d of d), 6.62-7.34 (9H, m). Anal. Calcd for $C_{19}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47; S, 10.23. Found: C, 72.87; H, 7.42; N, 4.38; S, 9.94.

2-(3-Hydroxyphenyl)-4-(2-phenylethyl)thiomorpholine (8). A stirred solution of 18 (12.4 g, 39.6 mM) in chloroform (300 ml) under argon was treated with trimethylsilyl iodide (28.9 ml) and heated under reflux for 72 h. More trimethylsilyl iodide (14 ml) was added and refluxing continued 72 h more. The volatiles were removed and the residue dissolved in dichloromethane (300 ml) and extracted with sat sodium bicarbonate (500 ml). The aqueous layer was backwashed with dichloromethane (2 X 250 ml). The combined organic layer and wash was dried, treated with charcoal and concentrated to a liquid which was purified by flash chromatography and crystallization to give 8 (3.55 g, 30.1%), mp 136-137°C (acetone-hexane). IR ν(KBr): 3100, 2500, 1600, 1455 cm^{-1}. ^{1}H-NMR δ: 2.25-3.47 (10H, m), 4.02 (1H, d of d), 6.59-7.34 (10H, m). Anal. Calcd for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N, 4.68; S, 10.71. Found: C, 72.00; H, 7.09; N, 4.59; S, 10.69.

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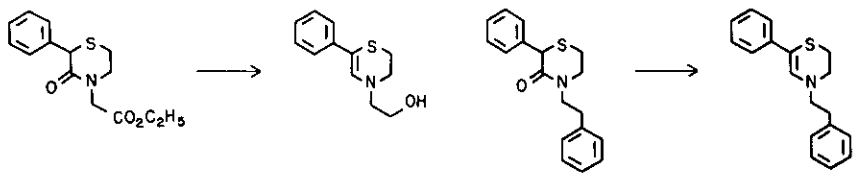

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