Sulfur-Containing Derivatives of β-Phenethylamine: Dithiocarbamates and Thioureas

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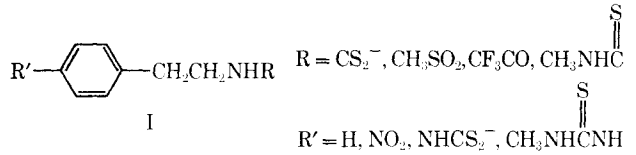
Abstract □ Dithiocarbamate and thiourea derivatives of β-phenethylamine, β-4-aminophenethylamine, and their *N*-substituted derivatives have been synthesized. 1-Methyl-3-phenethylthiourea was found to lower blood pressure significantly in both hypertensive dogs and rats, and the dithiocarbamate of β-phenethylamine showed hypotensive effects in the dog. Appreciable antifungal activity was also revealed for the latter compound.

Keyphrases □ β-Phenethylamine, sulfur derivatives—synthesis □ IR spectrophotometry—structure, identity □ Pharmacological screening—β-phenethylamine derivatives □ Antimicrobial activity—β-phenethylamine derivatives

Several dithiocarbamates, including disulfiram (1), diethyldithiocarbamate (2), and β-phenethyldithiocarbamate (3), have been found to be potent inhibitors of dopamine-β-hydroxylase both *in vitro* and *in vivo*. This causes an accumulation of dopamine and insufficient production of norepinephrine in a number of tissues and gives rise to several distinct pharmacological effects. Some that have been observed are an increase in hexobarbital sleeping time in mice (4), maintenance of the conditioned avoidance response in rats (5), and sedation (3) and diminished hypermotility in rats through CNS depression (4).

The enzyme dopamine-β-hydroxylase is subject to relatively complete noncompetitive inhibition by a number of common metal-binding agents, and evidence indicates it to be copper-containing (6). Although any metal-binding agent, theoretically, should inhibit the enzyme, those agents whose structures are related to the enzyme substrates, dopamine and tyramine, should function the most effectively *in vivo*. Of the dithiocarbamates investigated so far as *in vivo* inhibitors of this enzyme, β-phenethyldithiocarbamate has been stated to be the most potent (3).

Accordingly, other dithiocarbamates which contain the β-phenethylamine structure have been prepared for pharmacological evaluation. In addition, several thioureas of this structure, which should also be inhibitors of a copper-containing enzyme, have been prepared. These sulfur-containing functions have been included on both the aliphatic nitrogen and the aromatic ring (Structure I). Antimicrobial activity was also investigated for these compounds.



I

Both ammonium β-phenethyldithiocarbamate and β-phenethylammonium dithiocarbamate have been reported by Buck and Leonard (7). Their procedure failed for the preparation of the dithiocarbamate of 4-nitro-β-phenethylamine, but the method of Fairfull and Peak (8), involving the formation of triethylammonium salts of dithiocarbamates, was successful. This procedure was also used to prepare the dithiocarbamates of β-phenethylamine, 4-trifluoroacetamidoethylaniline, and 4-methylsulfonamidoethylaniline, as well as the bis-(dithiocarbamate) of 4-amino-β-phenethylamine. IR absorption attributable to C=S in these compounds was found at 950–1000 and near 1300 cm.$^{-1}$.

Thioureas were prepared by reaction of the amines with methyl isothiocyanate, either in the presence or absence of a solvent. *N*-Methylthioureas were thus obtained using β-phenethylamine, 4-nitro-β-phenethylamine, 4-methylsulfonamidoethylaniline, and 4-trifluoroacetamidoethylaniline, along with the bis-(methylthiourea) of 4-amino-β-phenethylamine. In both the dithiocarbamate and thiourea series, it was therefore possible to obtain examples of sulfur-containing functions on both aliphatic and aromatic nitrogens, as well as the bis-substituted products. IR absorption due to C=S in the thioureas was found near 1000 and 1300 cm.$^{-1}$.

PHARMACOLOGICAL RESULTS

Tests for blood pressure effects in unanesthetized neurogenic hypertensive dogs and in metacorticoid hypertensive rats were carried out.[1]

Ammonium β-phenethyldithiocarbamate produced a significant hypotensive effect in two dogs following administration of 40 mg./kg. No effect on heart rate was observed. Reduction of systolic blood pressure in rats was not biosignificant. No significant effects on blood pressures or heart rates were observed in either dogs or rats with the bis-(dithiocarbamate) of 4-amino-β-phenethylamine or with the dithiocarbamate of 4-methylsulfonamidoethylaniline. A significant reduction in heart rate with one of two dogs was observed with the dithiocarbamate of 4-trifluoroacetamidoethylaniline, however.

1-Methyl-3-phenethylthiourea exhibited a significant lowering of blood pressure in one of two dogs following a dose of 2.0 mg./kg. A significant lowering of systolic blood pressure in 4 rats was produced by a dose of 80 mg./kg. of this compound. The methylthiourea of 4-trifluoroacetamidoethylaniline and the bis-(methylthiourea) of 4-amino-β-phenethylamine showed no significant effects on blood pressure.

ANTIMICROBIAL ACTIVITY

Tests for antimicrobial activity were carried out by the *in vitro* serial dilution procedure; results are expressed in terms of the minimum inhibitory concentration ($1/M$) of compound for growth of the organism in a 24-hr. broth culture. Four organisms were selected which include Gram-positive and Gram-negative bacteria, a mold.

[1] Smith Kline & French Laboratories under the direction of Dr. J. Wilson. Results were made available through the courtesy of Dr. C. W. French.

Table I—Antimicrobial Activity

Compound	Minimum Inhibiting Concn., 1/*M*			
	S. aureus[a]	*E. coli*[a]	*A. niger*[b]	*C. albicans*[b]
β-Phenethylamine	>1000	>1000	>1000	>1000
4-Amino-β-phenethylamine	>1000	>1000	>1000	>1000
4-Nitro-β-phenethylamine	>1000	>1000	>1000	>1000
β-Phenethylammonium β-phenethyldithiocarbamate	>1000	>1000	100000	100000
Triethylammon. 4-methylsulfonamidoethylphenyldithiocarbamate	2000	2000	20000	20000
Triethylammon. 4-trifluoroacetamidoethylphenyl dithiocarbamate	2000	2000	20000	20000
Triethylammon. 4-amino-β-phenethylamine-*N*,*N*′-bis-(carbodithioate)	2000	2000	2000	2000
1-Methyl-3-phenethylthiourea	>1000	>1000	>1000	>1000
1-Methyl-3-(4-nitrophenethyl)-thiourea	2000	2000	2000	2000
1-Methyl-3-(4-methylsulfonamidoethylphenyl)-thiourea	2000	2000	2000	2000
1-Methyl-3-(4-trifluoroacetamidoethylphenyl)-thiourea	2000	2000	2000	2000
N,*N*′-Bis-(*N*-methylthiocarbamido)-4-amino-β-phenethylamine	2000	2000	2000	2000

[a] Determined in brain heart infusion broth after 24 hr. at 37°. [b] Determined in Sabouraud's broth after 72 hr. at 25°.

and a yeast. Results are listed in Table I, and it can be seen that appreciable activity was found against *A. niger* and *C. albicans* with the dithiocarbamate of β-phenethylamine.

EXPERIMENTAL

Analyses for carbon, hydrogen, and nitrogen were performed.[2] Sulfur analyses were done by the macro Parr bomb peroxide fusion method. Melting points were taken on a Mel-Temp block and are uncorrected. IR absorption spectra were obtained with a Perkin-Elmer model 137B spectrometer.

Triethylammonium β-Phenethyldithiocarbamate—To a cooled solution of 30 ml. (0.375 mole) of carbon disulfide and 50 ml. (0.375 mole) of triethylamine was added dropwise with stirring 3 ml. (0.025 mole) of β-phenethylamine. The mixture was stirred for 3 hr., allowing the temperature to reach 25°. The yellow product was collected, washed with ether, and dried *in vacuo*, giving a 93% yield; m.p. 68–69°. IR(KBr)960(C=S), 1315(C=S) cm.$^{-1}$.

Anal.—Calcd. for $C_{15}H_{26}N_2S_2$: C, 60.36; H, 8.78; N, 9.39. Found: C, 59.55; H, 8.35; N, 9.42.

Triethylammonium β-4-Nitrophenethyldithiocarbamate—To a cooled solution of 60 ml. (0.75 mole) of carbon disulfide and 100 ml. (0.75 mole) of triethylamine in 15 ml. of absolute ethanol was added dropwise with stirring, 8.30 g. (0.05 mole) of 4-nitro-β-phenethylamine (9). The mixture was stirred for 24 hr., allowing the temperature to reach 25°. The yellow product was filtered, washed with absolute ether, and dried *in vacuo*, giving a 77% yield; m.p. 112–114°.

Anal.—Calcd. for $C_{15}H_{25}N_3O_2S_2$: C, 52.50; H, 7.34; N, 12.23; S, 18.63. Found: C, 52.04; H, 7.04; N, 11.49; S, 19.30.

N-Trifluoroacetyl-β-4-nitrophenethylamine—To a cooled solution of 5 g. (0.03 mole) of 4-nitro-β-phenethylamine (9) in 40 ml. of benzene was added dropwise with stirring 6.7 g. (0.03 mole) of trifluoroacetic anhydride. A white precipitate appeared. The mixture was refluxed for 3 hr. and distilled under reduced pressure. The residue was washed with water and dilute hydrochloric acid, and recrystallized from ethanol, giving a 43% yield; m.p. 97–98°.

Anal.—Calcd. for $C_{10}H_9F_3N_2O_3$: C, 45.81; H, 3.46; N, 10.68. Found: C, 46.07; H, 3.30; N, 10.46.

4-Trifluoroacetamidoethylaniline—A solution of 2.0 g. (0.008 mole) of *N*-trifluoroacetyl-β-4-nitrophenethylamine in 15 ml. of tetrahydrofuran with 0.3 g. of 10% palladium-on-charcoal was hydrogenated at 2–3 atm. After the theoretical amount of hydrogen had been taken up, the catalyst was filtered, and the solvent was allowed to evaporate. The residue was washed with acetone, giving a 65% yield of white product, m.p. 83–86°.

Anal.—Calcd. for $C_{10}H_{11}F_3N_2O$: C, 51.72; H, 4.79; N, 12.06. Found: C, 51.60; H, 5.11; N, 12.11.

[2] Weiler and Strauss, Oxford, England.

Triethylammonium 4-Trifluoroacetamidoethylphenyldithiocarbamate—To a cooled solution of 6 ml. (0.075 mole) of carbon disulfide and 10 ml. (0.075 mole) of triethylamine was added dropwise with stirring 1.16 g. (0.005 mole) of 4-trifluoroacetamidoethylaniline in 15 ml. of absolute ethanol. The solution was stirred for 10 min., and a yellow solid precipitated. The suspension was stirred for 3 hr. at 25° and the solid was collected, washed with absolute ether, and dried *in vacuo*, giving a 50% yield; m.p. 203–205°. IR(KBr)980(C=S), 1295(C=S)cm.$^{-1}$.

Anal.—Calcd. for $C_{17}H_{26}F_3N_3OS_2$: C, 49.87; H, 6.40; N, 10.26. Found: C, 49.72; H, 6.10; N, 10.69.

N-Methylsulfonyl-β-4-nitrophenethylamine—To a cooled solution of 3.3 g. (0.02 mole) of 4-nitro-β-phenethylamine (9) in 25 ml. of benzene was added 1.67 ml. (0.022 mole) of methanesulfonyl chloride in 20 ml. of methylene chloride and 3 ml. of triethylamine in 20 ml. of methylene chloride. The solution was stirred for 15 hr. at 25°, was washed with *N* hydrochloric acid and water, and was distilled *in vacuo*. The residue was recrystallized from ethanol, giving a 63% yield; m.p. 120–121°.

Anal.—Calcd. for $C_9H_{12}N_2O_4S$: C, 44.26; H, 4.95; N, 11.46. Found: C, 44.46; H, 5.11; N, 11.73.

4-Methylsulfonamidoethylaniline—A solution of 2.88 g. (0.012 mole) of *N*-methylsulfonyl-β-4-nitrophenethylamine in 50 ml. of tetrahydrofuran with 0.6 g. of 10% palladium-on-charcoal was hydrogenated at 2–3 atm. After the theoretical amount of hydrogen had been taken up, the catalyst was filtered, and the solvent was allowed to evaporate. The residue was dried *in vacuo*, giving a 75% yield of white product; m.p. 91–93°.

Anal.—Calcd. for $C_9H_{14}N_2O_2S$: C, 50.47; H, 6.59; N, 13.08. Found: C, 50.69; H, 6.55; N, 12.95.

Triethylammonium 4-Methylsulfonamidoethylphenyldithiocarbamate—To a cooled solution of 6 ml. (0.075 mole) of carbon disulfide and 10 ml. (0.075 mole) of triethylamine was added dropwise with stirring 1.07 g. (0.005 mole) of 4-methylsulfonamidoethylaniline in 15 ml. of absolute ethanol. Precipitation of a yellow solid appeared, and the mixture was stirred at 25° for 3 hr. and allowed to stand for 12 hr. The solid was filtered, washed with absolute ether, and dried *in vacuo* giving a 92% yield; m.p. 95–97°. IR(KBr)975(C=S), 1315(C=S)cm.$^{-1}$.

Anal.—Calcd. for $C_{16}H_{29}N_3O_2S_3$: C, 49.11; H, 7.47; N, 10.73. Found: C, 49.46; H, 7.10; N, 10.52.

Bis-(triethylammonium) β-4-Aminophenethylamine-N,N′-bis(carbodithioate)—A solution of 1.36 g. (0.01 mole) of β-4-aminophenethylamine (Aldrich Chemical Co.) dissolved in 5 ml. of absolute ethanol was added dropwise with stirring to 12 ml. (0.15 mole) of carbon disulfide and 20 ml. (0.15 mole) of triethylamine at 0–5°. A yellow solid appeared which gradually became gummy. Stirring was continued for 24 hr. at room temperature, and the crystalline solid was filtered, washed with absolute ethanol and ether, and dried *in vacuo*, giving an 80% yield; m.p. 86–88°. IR(KBr)950(C=S), 1310(C=S)cm.$^{-1}$.

Anal.—Calcd. for $C_{22}H_{42}N_4S_4$: C, 53.81; H, 8.62; N, 11.41. S, 26.13. Found: C, 53.90; H, 8.45; N, 11.16; S, 26.35.

1-Methyl-3-phenethylthiourea—To a cooled solution of 1.21 g. (0.01 mole) of β-phenethylamine in 5 ml. of ethanol was added 0.73 g. (0.01 mole) of methyl isothiocyanate. After an evolution of heat, water was added dropwise to a lasting turbidity. The mixture was stored in the refrigerator overnight, and the precipitate was filtered, washed with ethanol, and air-dried, giving 69% of white product; m.p. 61–63°. IR(Nujol)975(C=S), 1300(C=S)cm.$^{-1}$.

Anal.—Calcd. for $C_{10}H_{14}N_2S$: C, 61.80; H, 7.26; N, 14.42. Found: C, 62.18; H, 7.19; N, 14.15.

1-Methyl-3-(4-nitrophenethyl)-thiourea—To a cooled solution of 1.66 g. (0.01 mole) of 4-nitro-β-phenethylamine (9) in 5 ml. of ethanol was added slowly with stirring 0.73 g. (0.01 mole) of methyl isothiocyanate in 2 ml. of ethanol. The solution was refluxed for one hr., cooled, and stored in the refrigerator overnight. The white solid was collected, washed with ethanol, and air-dried; giving a 75% yield m.p. 79–82°.

Anal.—Calcd. for $C_{10}H_{13}N_3O_2S$: C, 50.18; H, 5.48; N, 17.56. Found: C, 50.42; H, 5.48; N, 17.30.

1-Methyl-3-(4-methylsulfonamidoethylphenyl)-thiourea—A mixture of 0.530 g. (0.0025 mole) of 4-methylsulfonamidoethylaniline and 0.185 g. (0.0025 mole) of methyl isothiocyanate was heated on a steam bath until it became liquid. Absolute ethanol (10 ml.) was added, and the mixture was refluxed until it became homogeneous. After being cooled, the crystalline solid was collected, washed with ethanol, and dried *in vacuo*, giving an 83% yield; m.p. 179–181°.

Anal.—Calcd. for $C_{11}H_{17}N_3O_2S_2$: C, 45.95; H, 5.96; N, 14.62. Found: C, 46.04; H, 5.92, N, 14.27.

1-Methyl-3-(4-trifluoroacetamidoethylphenyl)-thiourea—A mixture of 1.16 g. (0.005 mole) of 4-trifluoroacetamidoethylaniline and 0.365 g. (0.005 mole) of methyl isothiocyanate in 10 ml. of ethanol was refluxed for 1 hr. The solution was cooled, and the white solid was collected, washed with ethanol, and dried *in vacuo*, giving an 86% yield; m.p. 167–170°.

Anal.—Calcd. for $C_{12}H_{14}F_3N_3OS$: C, 47.21; H, 4.62; N, 13.76. Found: C, 47.07; H, 4.90; N, 13.80.

N,N′-Bis(N-methylthiocarbamido)-β-4-aminophenethylamine—Methyl isothiocyanate (1.46 g., 0.02 mole) was added slowly to β-4-aminophenethylamine (1.36 g., 0.01 mole) (Aldrich Chemical Co.) with ice-cooling. After an evolution of heat, ethanol (25 ml.) was added, and the mixture was refluxed until a solution resulted. After being cooled, a white solid appeared which was collected, recrystallized from aqueous ethanol, and air-dried, giving an 80% yield; m.p. 185–190°.

Anal.—Calcd. for $C_{12}H_{18}N_4S_2$: C, 51.03; H, 6.42; N, 19.84. Found: C, 51.13; H, 6.55; N, 19.45.

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Biosynthesis of Rubrofusarin by *Fusarium graminearum*

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Abstract □ Using radioactively labeled acetate, evidence was obtained to support the hypothesis that the biosynthesis of rubrofusarin proceeds through a polyketide chain intermediate. It was shown that labeled acetate when diluted with nonlabeled malonate, is preferentially incorporated into the terminal acetate starting unit of the polyketide chain.

Keyphrases □ *Fusarium graminearum*—rubrofusarin biosynthesis □ Acetate-malonate condensation—rubrofusarin formation □ Rubrofusarin, biosynthesis—polyketide chain intermediate

Rubrofusarin is an orange-red pigment produced by the fungus, *Fusarium graminearum* Schwabe. This organism is the imperfect stage of *Gibberella zeae* (Schweinitz) Petch, a common plant pathogen. Rubrofusarin was first thought to be a xanthone derivative, as reported by Ashley *et al.* (1), but was later discovered by Tanaka and Tamura (2) to be a derivative of 2-methylnaphtho-γ-pyrone.

Several hypotheses can be proposed for the biosynthesis of rubrofusarin. One theory is that it is a product of a biosynthetic pathway involving shikimic acid and mevalonic acid, as are some of the anthraquinones found in higher plants (3). The most likely proposal, however, is that rubrofusarin is formed by an acetate-malonate condensation with the formation of a polyketide chain which cyclizes to give the tricyclic ring system (Scheme I). Shibata and Ikekawa (4) have shown that rugulosin, a fungal anthraquinone dimer, was biosynthetically formed by the head-to-tail linkage of 14 malonate units and two units of acetate with release of carbon dioxide from each malonate. In each of the tricyclic monomers one of the acetate units served as a terminal starting unit in building the polyketide chain.