nique. This technique requires no reference to external standards since the molecular weight is obtained from a simple linear extrapolation to zero concentration of the light-scattering data obtained at a single angle from two or more solutions of different solute concentrations (13–16). The results (Table V) show that the HPLC molecular weight determinations were in fair agreement with those of the light-scattering technique. The average of the three samples agreed within 100 daltons, although there was considerable sample-to-sample variation. Both the HPLC and spectroscopic results showed a good correlation between molecular weight and anticoagulant activity.

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# Heterocyclic Analogs of Amphetamine: Thioureas, Dithiocarbamates, and Negatively Substituted Amides


**WILLIAM O. FOYE ˣ and SUCHINTA TOVIVICH**



Received September 1, 1978, from the *Samuel M. Best Research Laboratory, Massachusetts College of Pharmacy, Boston, MA 02115.* Accepted for publication October 20, 1978.



**Abstract** □ A series of heterocyclic analogs of amphetamine was synthesized. The heterocycles employed included the 2-furyl, 2-thienyl, 3-methyl-2-thienyl, 3-pyridyl, and 6-methyl-2-pyridyl rings. The aliphatic amine group was converted to the *N*-methylthiourea, dithiocarbamate, methanesulfonyl, trifluoromethanesulfonyl, and trifluoroacetyl functions since similar conversions of the β-phenethylamine structure had shown blood pressure-lowering effects and some loss of behavioral effects. *p*-Chlorophenyl and 1-naphthyl analogs were also converted to these derivatives. Behavioral and other biological effects, including antiarthritic, passive cutaneous anaphylactic, and antimicrobial, were observed. The 3-methyl-2-thienyl analog of amphetamine significantly increased papillary muscle contractile force without producing arrhythmias.



**Keyphrases** □ Amphetamine analogs—thioureas, dithiocarbamates, negatively substituted amides, synthesis, behavioral effects, antiarthritis effects, cutaneous anaphylaxis, antimicrobial effects, blood pressure, rats □ Structure–activity relationships—amphetamine analogs, thioureas, dithiocarbamates, negatively substituted amides, synthesis, behavioral and biological effects, rats □ Motor activity—effects of amphetamine analogs, rats □ Antiarthritis agents—amphetamine analogs, rats □ Blood pressure—effects of amphetamine analogs, rats


Formation of negatively substituted amides on the aliphatic nitrogen of amphetamine and related structures has produced compounds with blood pressure-lowering effects (1). This result occurred also with negatively substituted amides of the β-phenethylamine structure as well as dithiocarbamate and thiourea derivatives (2, 3). Conversion of the aliphatic nitrogen to a neutral or acidic function thus led to a depressor response from a basic structure having motor stimulant activity. Previously, inclusion of the alkanesulfonamide group in the aromatic ring of phenethanolamines conferred either adrenergic stimulant or blocking activity (the latter generally appearing with an isopropyl or larger group on the aliphatic nitrogen) (4, 5).

## DISCUSSION

A number of dithiocarbamates of the β-phenethylamine structure showed varying degrees of amphetamine-like behavioral effects (6). The presence of heterocyclic rings, in place of the phenyl, generally resulted in a loss of amphetamine behavioral effects. Diethyldithiocarbamate had previously been shown to deplete brain norepinephrine and to maintain the conditioned avoidance response of the rat (7). The dithiocarbamates of the heterocyclic ethylamines failed to alter this response (6). Antiobesity manifestations were observed in rats with some negatively substituted amides, dithiocarbamates, and thioureas of the β-phenethylamines and amphetamine derivatives. The possibility existed, therefore, of removing many or all of the behavioral attributes of the basic amphetamine structure while retaining depressor and antiobesity effects by appropriate substitutions on the nitrogen and inclusion of heterocyclic rings.

A series of heterocyclic analogs of amphetamine, including neutral or negatively substituted functions on the aliphatic nitrogen, was synthesized to determine if behavioral activity could be diminished and other useful effects retained. Corresponding derivatives of *p*-chloroamphetamine and the 1-naphthyl analog were prepared for similar observations. Negatively substituted amides prepared included the methanesulfonamide, trifluoromethanesulfonamide, and trifluoroacetyl as well as dithiocarbamates and methylthioureas. Both thioureas and dithiocarbamates have shown inhibitory activity against dopamine-β-hydroxylase (8, 9), so these derivatives were expected to produce depressor effects.

Previously, the furyl and thienyl analogs of amphetamine were obtained, and their motor effects were compared to those of amphetamine (10). Amphetamine and its thienyl analog were more active motor stimulants than the furyl analog, but both the heterocyclic analogs were less toxic than amphetamine.


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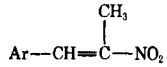
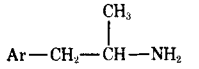
**Table I—1-Aryl-2-nitropropenes**



| Ar | Formula | Yield, % | Melting Point | Analysis, % | Calc. | Found |
|---|---|---|---|---|---|---|
| 2-Furyl | $C_7H_7NO_3$ | 65 | 47–48°[a] | | — | — |
| 2-Thienyl | $C_7H_7NO_2S$ | 44 | 67–68° | C | 49.69 | 49.55 |
| | | | | H | 4.17 | 4.42 |
| | | | | N | 8.27 | 8.02 |
| | | | | S | 18.95 | 18.68 |
| 3-Methyl-2-thienyl | $C_8H_9NO_2S$ | 65.5 | 67–69° | C | 52.46 | 52.52 |
| | | | | H | 4.92 | 5.34 |
| | | | | N | 7.65 | 7.51 |
| | | | | S | 17.47 | 17.33 |
| 3-Pyridyl | $C_8H_8N_2O_2$ | 18 | 61–63° | C | 58.53 | 58.33 |
| | | | | H | 4.91 | 5.04 |
| | | | | N | 17.06 | 17.15 |
| 6-Methyl-2-pyridyl | $C_9H_{10}N_2O_2$ | 39 | 68–69° | C | 60.67 | 60.54 |
| | | | | H | 5.61 | 5.71 |
| | | | | N | 15.73 | 15.72 |
| 4-Chlorophenyl | $C_9H_8ClNO_2$ | 64 | 86–87°[b] | | — | — |
| 1-Naphthyl | $C_{13}H_{11}NO_2$ | 81 | 64–65° | C | 73.23 | 73.02 |
| | | | | H | 5.11 | 5.49 |
| | | | | N | 6.57 | 6.60 |

[a] Lit. (12) mp 50–51°. [b] Lit. (13) mp 88–89°.

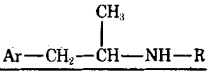
**Table II—1-Aryl-2-aminopropanes**



| Compound | Ar | Formula | Yield, % | Boiling Point or Melting Point | Analysis, % | Calc. | Found |
|---|---|---|---|---|---|---|---|
| I | 2-Furyl | $C_7H_{11}NO$ | 65 | 66–70° (20 mm)[a] | | — | — |
| II | 2-Thienyl | $C_7H_{11}NS$ | 39 | 146–150° (20 mm) | | — | — |
| | 2-Thienyl hydrochloride | $C_7H_{12}ClNS$ | — | 149–152° | C | 47.32 | 47.50 |
| | | | | | H | 6.81 | 6.85 |
| | | | | | N | 7.88 | 7.62 |
| | | | | | S | 18.04 | 17.76 |
| III | 3-Methyl-2-thienyl | $C_8H_{13}NS$ | 90 | 125–130° (20 mm) | | — | — |
| | 3-Methyl-2-thienyl hydrochloride | $C_8H_{14}ClNS$ | — | 148–150° | C | 50.13 | 49.69 |
| | | | | | H | 7.31 | 7.28 |
| | | | | | N | 7.31 | 7.12 |
| | | | | | S | 16.71 | 16.60 |
| IV | 3-Pyridyl | $C_8H_{12}N_2$ | 37 | 125–130° (20 mm) | | — | — |
| V | 6-Methyl-2-pyridyl | $C_9H_{14}N_2$ | 68 | 100–105° (20 mm) | | — | — |
| | 6-Methyl-2-pyridyl hydrochloride | $C_9H_{15}ClN_2$ | — | 160–161° | C | 57.90 | 57.73 |
| | | | | | H | 8.04 | 8.45 |
| | | | | | N | 15.01 | 14.89 |
| VI | 4-Chlorophenyl hydrochloride | $C_9H_{12}ClN$ | — | 166–168°[b] | | — | — |
| VII | 1-Naphthyl | $C_{13}H_{15}N$ | 81 | 160–165° (20 mm) | | — | — |
| | 1-Naphthyl hydrochloride | $C_{13}H_{16}ClN$ | — | 212–215° | C | 70.43 | 70.27 |
| | | | | | H | 7.22 | 7.21 |
| | | | | | N | 6.32 | 6.29 |

[a] Lit. (12) bp 68–75° (20 mm). [b] Lit. (14) mp 163–169°.

**Table III—Amide, Thiourea, and Dithiocarbamate Derivatives**



| Compound | Ar | R | Formula | Yield, % | Melting Point | Analysis, % | Calc. | Found |
|---|---|---|---|---|---|---|---|---|
| VIII | 2-Furyl | $CS_2^-(C_2H_5)_3NH^+$ | $C_{14}H_{25}N_2OS_2 \cdot 1\frac{1}{2}H_2O$ | 94 | Oil | C | 51.06 | 50.74 |
| | | | | | | H | 7.60 | 7.73 |
| | | | | | | N | 8.51 | 8.22 |
| | | | | | | S | 19.45 | 18.96 |
| IX | 2-Thienyl | $SO_2CH_3$ | $C_8H_{13}NO_2S_2$ | 70.5 | 63–64° | C | 43.83 | 43.80 |
| | | | | | | H | 5.93 | 5.78 |
| | | | | | | N | 6.39 | 6.33 |
| | | | | | | S | 29.20 | 28.88 |
| X | 2-Thienyl | $COCF_3$ | $C_9H_{10}F_3NOS$ | 16 | 59–61° | C | 45.56 | 45.76 |
| | | | | | | H | 4.24 | 4.16 |
| | | | | | | N | 5.90 | 5.73 |
| | | | | | | S | 13.50 | 14.00 |
| XI | 2-Thienyl | $SO_2CF_3$ | $C_8H_{10}F_3NO_2S_2$ | 22 | 35–37° | C | 35.16 | 35.11 |
| | | | | | | H | 3.66 | 3.95 |
| | | | | | | N | 5.12 | 5.06 |
| | | | | | | S | 23.44 | 23.70 |
| XII | 2-Thienyl | $CNHCH_3$ (S above C) | $C_9H_{14}N_2S_2$ | 75.5 | Oil | C | 50.46 | 50.18 |
| | | | | | | H | 6.54 | 6.76 |
| | | | | | | N | 13.08 | 12.92 |
| | | | | | | S | 29.90 | 29.51 |

**Table III—*Continued***

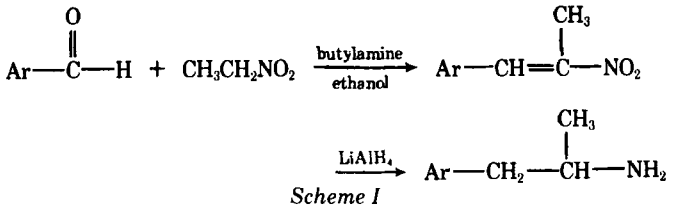
Ar—CH(CH₃)—CH—NH—R

| Compound | Ar | R | Formula | Yield, % | Melting Point | Analysis, % | Calc. | Found |
|---|---|---|---|---|---|---|---|---|
| XIII | 2-Thienyl | $CS_2^-(C_2H_5)_3NH^+$ | $C_{14}H_{26}N_2S_3 \cdot 1/2H_2O$ | 64.5 | Oil | C | 51.38 | 51.62 |
| | | | | | | H | 8.17 | 7.75 |
| | | | | | | N | 8.56 | 8.34 |
| | | | | | | S | 29.35 | 29.11 |
| XIV | 3-Methyl-2-thienyl | $SO_2CH_3$ | $C_9H_{15}NO_2S_2$ | 51.5 | 41–43° | C | 46.35 | 46.80 |
| | | | | | | H | 6.43 | 6.34 |
| | | | | | | N | 6.00 | 5.85 |
| | | | | | | S | 27.46 | 27.40 |
| XV | 3-Methyl-2-thienyl | $COCF_3$ | $C_{10}H_{12}F_3NOS$ | 82 | 57–58° | C | 47.81 | 47.44 |
| | | | | | | H | 4.78 | 5.12 |
| | | S ‖ | | | | N | 5.58 | 5.69 |
| | | | | | | S | 12.75 | 13.19 |
| XVI | 3-Methyl-2-thienyl | $CNHCH_3$ | $C_{10}H_{16}N_2S_2$ | 74.5 | Oil | C | 52.63 | 53.02 |
| | | | | | | H | 7.02 | 7.13 |
| | | | | | | S | 24.56 | 24.69 |
| XVII | 3-Methyl-2-thienyl | $CS_2^-(C_2H_5)_3NH^+$ | $C_{15}H_{28}N_2S_3 \cdot 1\frac{1}{2}H_2O$ | 34.5 | Oil | C | 50.14 | 49.80 |
| | | | | | | H | 7.80 | 7.55 |
| | | | | | | N | 7.80 | 7.50 |
| | | | | | | S | 26.74 | 27.01 |
| XVIII | 3-Pyridyl | $SO_2CH_3$ | $C_9H_{14}N_2O_2S$ | 30.5 | 114–115° | C | 50.46 | 50.72 |
| | | | | | | H | 6.54 | 6.56 |
| | | | | | | N | 13.08 | 12.93 |
| | | | | | | S | 14.95 | 15.20 |
| XIX | 3-Pyridyl | $COCF_3$ | $C_{10}H_{11}F_3N_2O \cdot CF_3CO_2H$ | 55 | 112–113° | C | 41.76 | 41.83 |
| | | | | | | H | 2.89 | 3.32 |
| | | S ‖ | | | | N | 8.09 | 8.10 |
| XX | 3-Pyridyl | $CNHCH_3$ | $C_{10}H_{15}N_3S$ | 72 | Oil | C | 57.41 | 57.01 |
| | | | | | | H | 7.18 | 7.40 |
| | | | | | | N | 20.09 | 19.64 |
| | | | | | | S | 15.30 | 14.92 |
| XXI | 3-Pyridyl | $CS_2^-(C_2H_5)_3NH^+$ | $C_{15}H_{26}N_3S_2 \cdot 1\frac{1}{2}H_2O$ | 75 | Oil | C | 53.09 | 53.54 |
| | | | | | | H | 7.66 | 7.72 |
| | | | | | | N | 12.39 | 12.70 |
| | | | | | | S | 18.87 | 18.66 |
| XXII | 6-Methyl-2-pyridyl | $SO_2CH_3$ | $C_{10}H_{16}N_2O_2S$ | 59 | Oil | C | 52.63 | 53.03 |
| | | | | | | H | 7.02 | 7.17 |
| | | | | | | N | 12.28 | 12.41 |
| | | | | | | S | 14.03 | 13.86 |
| XXIII | 6-Methyl-2-pyridyl | $COCF_3$ | $C_{11}H_{13}F_3N_2O$ | 71 | 43–44° | C | 53.66 | 53.73 |
| | | | | | | H | 5.28 | 5.35 |
| | | | | | | N | 11.38 | 11.15 |
| XXIV | 6-Methyl-2-pyridyl | $CS_2^-(C_2H_5)_3NH^+$ | $C_{16}H_{29}N_3S_2 \cdot H_2O$ | 35 | Oil | C | 55.65 | 55.48 |
| | | | | | | H | 8.98 | 8.91 |
| | | | | | | N | 12.17 | 12.34 |
| XXV | 4-Chlorophenyl | $SO_2CH_3$ | $C_{10}H_{15}ClNO_2S$ | 36 | 55–57° | C | 48.48 | 48.57 |
| | | | | | | H | 5.66 | 5.70 |
| | | | | | | N | 5.66 | 5.77 |
| | | | | | | S | 12.93 | 13.21 |
| XXVI | 4-Chlorophenyl | $COCF_3$ | $C_{11}H_{11}ClF_3NO$ | 90 | 127–128° | C | 49.71 | 49.92 |
| | | | | | | H | 4.14 | 4.02 |
| | | S ‖ | | | | N | 5.27 | 5.40 |
| XXVII | 4-Chlorophenyl | $CNHCH_3$ | $C_{11}H_{15}ClN_2S$ | 70 | Oil | C | 54.42 | 54.73 |
| | | | | | | H | 6.23 | 6.56 |
| | | | | | | N | 11.54 | 11.13 |
| XXVIII | 4-Chlorophenyl | $CS_2^-(C_2H_5)_3NH^+$ | $C_{16}H_{27}ClN_2S \cdot 2H_2O$ | 53 | 66–68° | C | 50.20 | 50.47 |
| | | | | | | H | 7.06 | 6.80 |
| | | | | | | N | 7.32 | 7.39 |
| | | | | | | S | 16.73 | 17.20 |
| XXIX | 1-Naphthyl | $SO_2CH_3$ | $C_{14}H_{17}NO_2S$ | 97 | 63–65° | C | 63.88 | 63.65 |
| | | | | | | H | 6.46 | 6.56 |
| | | | | | | N | 5.32 | 5.19 |
| | | | | | | S | 12.16 | 12.03 |
| XXX | 1-Naphthyl | $COCF_3$ | $C_{15}H_{14}F_3NO$ | 73 | 106–107° | C | 64.06 | 63.84 |
| | | | | | | H | 4.98 | 5.10 |
| | | | | | | N | 4.98 | 5.01 |

The heterocyclic analogs of amphetamine were synthesized by reduction of the intermediate nitropropenes. The nitropropenes were obtained by a base-catalyzed condensation of aromatic aldehyde and nitroethane (11). Physical constants of the nitropropenes are listed in Table I. The nitropropenes were reduced to amphetamines with lithium aluminum hydride (12) (Scheme I). The amines were generally isolated as the hydrochlorides. Physical constants of the amines are listed in Table II.

The methanesulfonamides were prepared from reaction of the respective amines with methanesulfonyl chloride and triethylamine, giving up to 97% yields. The trifluoroacetamides were obtained from reaction with trifluoroacetic anhydride, with yields up to 90%. The trifluoromethanesulfonamides were obtained from reaction with trifluoromethanesulfonyl chloride and triethylamine. Dark, sticky liquids were usually obtained, and they could not be purified by distillation; prolonged refrigeration generally produced semisolids that could be recrystallized.

The methylthioureas were prepared by reaction of the amine with



*Scheme I*

methyl isothiocyanate. The resulting liquids could not be distilled without decomposition. Therefore, the crude products were washed with petroleum ether and thoroughly dried, giving yields of analytically acceptable products of about 70%.

The dithiocarbamates were prepared as the triethylammonium salts on reaction of the amines with carbon disulfide and triethylamine. Generally, yellow liquids were obtained, and they gave hygroscopic solids on washing with anhydrous ether. The compounds were isolated as hydrates, as verified by the IR spectra (Table III).

## EXPERIMENTAL[1]

Melting points were determined in capillaries with a melting-point block[2] and are uncorrected. IR absorption spectra were obtained with a grating spectrophotometer[3]. Silica gel TLC was carried out, and products were detected by exposure to iodine vapor.

The aldehydes and nitroethane were commercially prepared[4]. Methanesulfonyl chloride[5], trifluoromethanesulfonyl chloride[5], trifluoroacetic anhydride[5], methyl isothiocyanate[5], carbon disulfide[5], and lithium aluminum hydride in ether[6] (1 *M*) were used as received.

The following procedures are representative.

**1-(2-Thienyl)-2-nitropropene**—A mixture of 56.0 g (0.5 mole) of 2-thiophenecarboxaldehyde, 37.5 g (0.5 mole) of nitroethane, 90 ml of absolute ethanol, and 10 ml of *n*-butylamine was stirred in the dark at room temperature for 5 days. The resulting yellow crystalline mass was filtered and recrystallized from absolute ethanol, giving 37.5 g (44.4% yield) of yellow needles, mp 67–68°; IR (KBr): 1640 (C=C), 1510 ($NO_2$), and 1300 ($NO_2$) $cm^{-1}$.

**1-(2-Thienyl)-2-aminopropane Hydrochloride**—To 300 ml of anhydrous ether was added 7.6 g (0.2 mole) of lithium aluminum hydride, and the mixture was stirred until the hydride dissolved. A solution of 16.8 g (0.1 mole) of 1-(2-thienyl)-2-nitropropene in 100 ml of anhydrous ether was added dropwise at such a rate that the capacity of the condenser was not exceeded, requiring 30–60 min. The mixture was stirred for 3 hr after the addition, the reaction flask was placed in an ice bath, and water was added dropwise until hydrogen evolution ceased.

The ether layer was separated, the solvent was removed by flash evaporation, and the product was distilled at 146–150° (20 mm), giving 5.5 g (39% yield) of amber liquid. Addition of dry hydrogen chloride to an ethereal solution of the amine produced the hydrochloride, mp 149–152°; IR (KBr): 2900–3000 ($NH_3^+$) and 720 (ring CH) $cm^{-1}$.

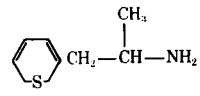
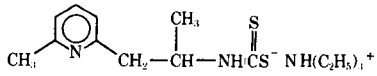
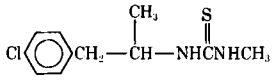
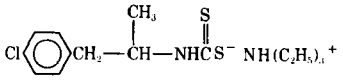
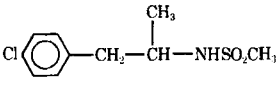
***N*-Methanesulfonyl-1-(2-thienyl)-2-aminopropane**—To a cooled solution of 2.8 g (0.02 mole) of 1-(2-thienyl)-2-aminopropane in 25 ml of benzene were added dropwise, with stirring, 1.67 ml (0.022 mole) of methanesulfonyl chloride in 20 ml of methylene chloride and 3 ml (0.022 mole) of triethylamine in 20 ml of methylene chloride. The mixture was stirred at 25° for 15 hr, and the resulting solution was washed with dilute hydrochloric acid and water and distilled *in vacuo*. The residue was recrystallized from ethanol, giving 3.1 g (70.5% yield) of colorless needles, mp 63–64°; IR (KBr): 3320 (NH), 1310 ($SO_2$), and 1125 ($SO_2$) $cm^{-1}$.

***N*-Trifluoroacetyl-1-(2-thienyl)-2-aminopropane**—To a cooled solution of 4.2 g (0.03 mole) of 1-(2-thienyl)-2-aminopropane in 50 ml of benzene was added dropwise, with stirring, 6.7 g (0.03 mole) of trifluoroacetic anhydride. The mixture was stirred for 3 hr and refrigerated overnight. The solvent was removed under reduced pressure, and the resulting semisolid was refrigerated. The solid obtained was washed with dilute hydrochloric acid and water and recrystallized from dilute ethanol, giving 1.1 g (16.4% yield) of colorless needles, mp 59–61°; IR (KBr): 3310 (NH), 1690 (C=O), and 1160–1180 ($CF_3$) $cm^{-1}$.

***N*-Trifluoromethanesulfonyl-1-(2-thienyl)-2-aminopropane**—To a cooled solution of 2.2 g (0.02 mole) of 1-(2-thienyl)-2-aminopropane in 25 ml of methylene chloride were added, with stirring, 3.36 g (0.02 mole) of trifluoromethanesulfonyl chloride in 20 ml of methylene chloride and 3 ml (0.022 mole) of triethylamine in 20 ml of methylene chloride. The mixture was stirred at room temperature for 12 hr, and the resulting solution was washed with dilute hydrochloric acid and water.

The solvent was removed under reduced pressure, and the residue was dissolved in anhydrous ether and decolorized with charcoal. The solvent was removed in a rotary evaporator, and the residue was refrigerated for 1 week. The resulting semisolid was recrystallized from petroleum ether, giving 1.2 g (22% yield) of colorless crystals, mp 35–37°; IR (KBr): 3300 (NH), 1375 ($SO_2$), 1190 ($CF_3$), and 1145 ($SO_2$) $cm^{-1}$.

**Table IV—Behavioral Effects in Rats**

| Compound | Dose, mg/kg po | Observations |
|---|---|---|
|  II | 100 | Ataxia |
| | 200 | Bizarre behavior |
| | 25 | High body posture |
| | 25 | Curiosity increase |
| | 200 | Cyanosis |
| | 25 | Exophthalmos |
| | 50 | Hypersensitivity |
| | 50 | Hyperthermia |
| | 100 | Motor activity decrease |
| | 50 | Motor activity increase |
| | 25 | Mydriasis |
| | 25 | Piloerection |
| | 200 | Placing reflex inhibition |
| | 100 | Prostration |
| | 200 | Respiratory distress |
| | 200 | Salivation, tremors |
| | 200 | Stereotyped behavior |
|  XXIV | 200 | Bizarre behavior |
| | 200 | Curiosity increase |
| | 200 | Hyperthermia |
| | 200 | Motor activity increase |
| | 200 | Mastication |
|  XXVII | 200 | High body posture |
| | 50 | Low body posture |
| | 200 | Curiosity increase |
| | 50 | Hypersensitivity |
| | 200 | Hyperthermia |
| | 200 | Lacrimation |
| | 100 | Motor activity decrease |
| | 50 | Motor activity increase |
| | 200 | Mydriasis |
| | 200 | Piloerection |
| | 200 | Placing reflex inhibition |
| | 200 | Prostration |
| | 50 | Salivation |
| | 200 | Semiprostration |
| | 200 | Stereotyped behavior |
|  XXVIII | 200 | Bizarre behavior |
| | 200 | Curiosity increase |
| | 200 | Hyperthermia |
| | 200 | Mastication |
| | 200 | Motor activity increase |
|  XXV | 200 | Ataxia |
| | 200 | Low body posture |
| | 200 | Grasp reflex inhibition |
| | 200 | Hypotonia |
| | 200 | Motor activity decrease |
| | 200 | Myotactic reflex inhibition |
| | 200 | Myotatic reflex inhibition |
| | 200 | Ptosis |

[1] Elemental analyses were performed by Strauss Microanalytical Laboratory, Oxford, England.
[2] Mel-Temp.
[3] Model 457A, Perkin-Elmer.
[4] Aldrich Chemical Co.
[5] Fisher Scientific Co.
[6] Ventron Corp.

**Table V—Antimicrobial Activity**

| Compound | Minimum Inhibitory Concentration, 1/*M*: *Staphylococcus aureus*[a] (ATCC 6538) | *Escherichia coli*[a] (ATCC 1129) | *Aspergillus niger*[b] (ATCC 16404) | *Candida albicans*[b] (ATCC 10231) |
|---|---|---|---|---|
| IX | <10,000 | <10,000 | <10,000 | <100,000 |
| XI | <10,000 | <10,000 | <10,000 | <100,000 |
| XIII | <1,000 | <10,000 | <100,000 | <100,000 |
| XIV | <10,000 | <10,000 | <10,000 | <10,000 |
| XVII | <1,000 | — | <100,000 | <100,000 |
| XVIII | <10,000 | <10,000 | <10,000 | <100,000 |
| XXI | <1,000 | <100 | <10,000 | <100,000 |
| XXV | <10,000 | <10,000 | <10,000 | <10,000 |
| XXVIII | <10,000 | <1,000 | <100,000 | <100,000 |
| Sulfathiazole | <2,000[c] | | | |

[a] Determined in brain heart infusion broth after 24–48 hr at 37°. [b] Determined in Sabouraud broth after 48–78 hr at 25°. [c] Reference 15.

**1-Methyl-3-[1-methyl-2-(2-thienyl)-ethyl]thiourea**—A solution of 1.125 g (0.025 mole) of methyl isothiocyanate in 10 ml of absolute ethanol was added dropwise, with stirring, to a cooled solution of 2.8 g (0.02 mole) of 1-(2-thienyl)-2-aminopropane in 25 ml of absolute ethanol. The mixture was refluxed for 12 hr and allowed to cool. The solvent was removed in a rotary evaporator under reduced pressure, and the residue was washed several times with petroleum ether and dried *in vacuo*. A yield of 3.23 g (75.5%) of viscous oil was obtained; IR (film): 3260 (NH) and 1340 (C=S) $cm^{-1}$.

**Triethylammonium 1-Methyl-2-(2-thienyl)-ethyldithiocarbamate**—Triethylamine (3.03 g, 0.03 mole) was added, with stirring, to a cooled solution of 2.2 g (0.02 mole) of 1-(2-thienyl)-2-aminopropane in 25 ml of absolute ethanol. To this mixture was added dropwise 2.28 g (0.03 mole) of carbon disulfide, and stirring was continued for 24 hr. The solvent was removed in a rotary evaporator, and the yellow residue was washed with anhydrous ether and dried *in vacuo*, giving 4.1 g (64.5% yield); IR (film): 2960–2990 ($NH^+$), 1290 (C=S), and 965 (C=S) $cm^{-1}$.

## RESULTS[7]

Rats were observed continuously for 6 hr and daily for 7 days after dosing (Table IV). The 2-thienyl analog of amphetamine (II) produced a behavior pattern similar to that of amphetamine. The dithiocarbamate of the 6-methyl-2-pyridyl analog (XXIV) showed few behavioral effects. The methylthiourea of the *p*-chloro analog (XXVII) also showed many behavioral effects of amphetamine, whereas the methanesulfonamide (XXV) and the dithiocarbamate (XXVIII) showed fewer of these effects.

Passive cutaneous anaphylaxis tests were conducted for XIV, XVII, XXII, and XXV. No inhibition was seen except for XVII, which gave 31% inhibition at a 5.0-mg/kg dose. Antiarthritic activity of X, XV, XVIII, and XXVI was observed *via* the adjuvant-induced arthritis test. A significant decrease in the inflamed hindleg volume of the treated rat was found for XXVI at a 50-mg/kg dose.

Blood pressure effects have not been determined yet for these compounds, but III gave a significant increase (42%) in papillary muscle contractile force *in vitro* at a 1.10-μg/ml dose. No arrhythmia was produced.

Tests for antimicrobial activity were also carried out by both the agar plate method and *in vitro* serial dilution (Table V). Results are expressed in terms of the minimum inhibitory concentration (1/*M*) of compound for inhibition of 24-hr broth cultures of Gram-positive and Gram-negative bacteria, a mold, and a yeast. Appreciable activity was observed against *Candida albicans* for most of the compounds tested and against *Aspergillus niger* for the dithiocarbamates. Previously, thiourea and dithiocarbamate derivatives of β-phenethylamine and 4-substituted β-phenethylamines showed significant antimicrobial activity against these organisms (2).

[7] Behavioral observations, antiarthritic tests, passive cutaneous anaphylaxis tests, and papillary muscle contractile force measurements were carried out at Smith Kline and French Laboratories through the courtesy of Dr. Blaine Sutton.

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