

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

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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, antiarthritic 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 □ Antiarthritic 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 phen-

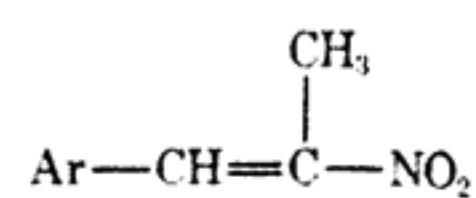
ethanolamines conferred either adrenergic stimulant or blocking activity (the latter generally appearing with an isopropyl or larger group on the aliphatic nitrogen) (4, 5).

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.

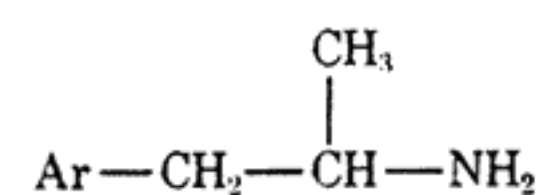
A series of heterocyclic analogs of amphetamine, including neutral or negatively substituted functions on the aliphatic nitrogen, was synthesized to determine if behavioral activity could be diminished and other useful effects retained. Corresponding derivatives of *p*-chloroamphetamine and the 1-naphthyl 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.


Table I—1-Aryl-2-nitropropenes

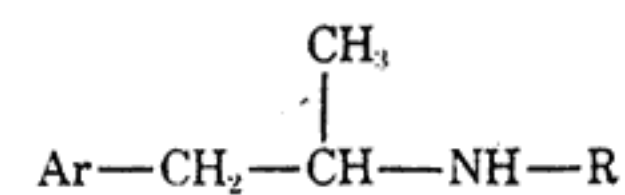
Ar	Formula	Yield, %	Melting Point	Analysis, %		
				Calc.	Found	
2-Furyl	C ₇ H ₇ NO ₃	65	47–48° ^a	—	—	
2-Thienyl	C ₇ H ₇ NO ₂ S	44	67–68°	C 49.69	49.55	
				H 4.17	4.42	
				N 8.27	8.02	
				S 18.95	18.68	
3-Methyl-2-thienyl	C ₈ H ₉ NO ₂ S	65.5	67–69°	C 52.46	52.52	
				H 4.92	5.34	
				N 7.65	7.51	
				S 17.47	17.33	
3-Pyridyl	C ₈ H ₈ N ₂ O ₂	18	61–63°	C 58.53	58.33	
				H 4.91	5.04	
				N 17.06	17.15	
6-Methyl-2-pyridyl	C ₉ H ₁₀ N ₂ O ₂	39	68–69°	C 60.67	60.54	
				H 5.61	5.71	
				N 15.73	15.72	
4-Chlorophenyl	C ₉ H ₈ ClNO 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 ₇ H ₁₁ NO	65	66–70° (20 mm) ^a	—	—	
II	2-Thienyl	C ₇ H ₁₁ NS	39	146–150° (20 mm)	—	—	
	2-Thienyl hydrochloride	C ₇ H 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 ₈ H ₁₃ NS	90	125–130° (20 mm)	—	—	
	3-Methyl-2-thienyl hydrochloride	C ₈ H 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 ₈ H ₁₂ N ₂	37	125–130° (20 mm)	—	—	
V	6-Methyl-2-pyridyl	C ₉ H ₁₄ N ₂	68	100–105° (20 mm)	—	—	
	6-Methyl-2-pyridyl hydrochloride	C ₉ H 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 ₉ H 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 ₂ H ₅) ₃ NH ⁺	C ₁₄ H ₂₅ N ₂ OS ₂ ·1½H ₂ O	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 ₂ CH ₃	C ₈ H ₁₃ NO ₂ S 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 ₉ H ₁₀ F ₃ NOS	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 ₂ CF ₃	C ₈ H ₁₀ F ₃ NO ₂ S 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	$\begin{array}{c} \text{S} \\ \\ \text{CNHCH}_3 \end{array}$	C ₉ H ₁₄ N ₂ S 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

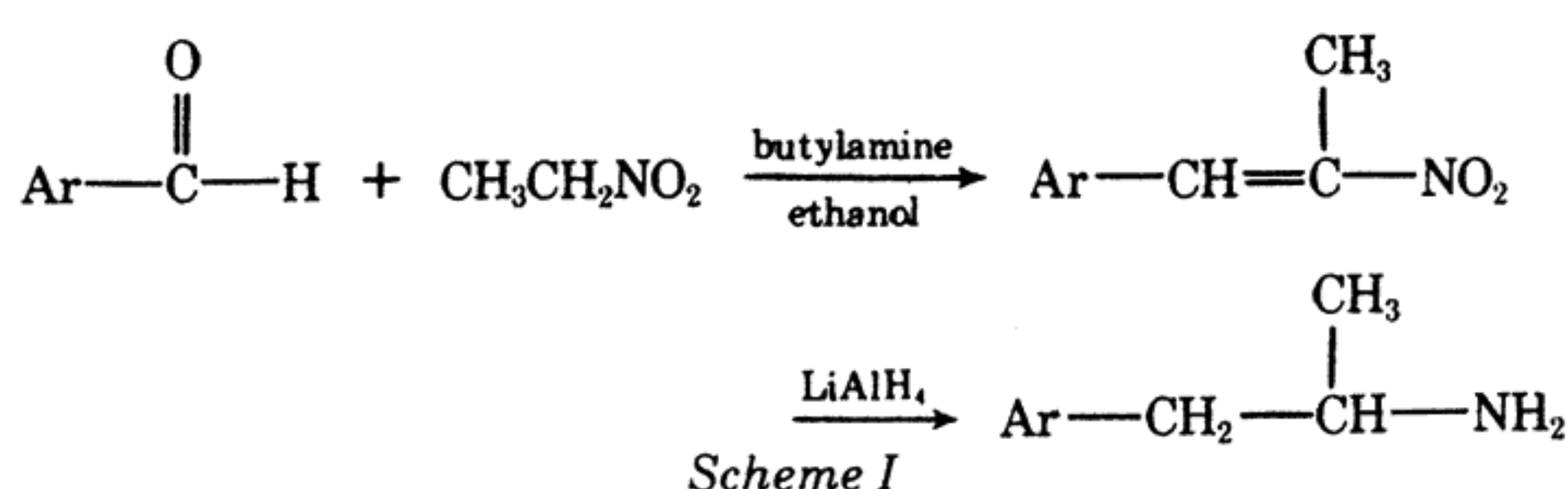
Compound	Ar	R	Formula	Yield, %	Melting Point	Analysis, %		
						Calc.	Found	
XIII	2-Thienyl	CS ₂ ⁻ (C ₂ H ₅) ₃ NH ⁺	C ₁₄ H ₂₆ N ₂ S ₃ ·1/2H ₂ O	64.5	Oil	C	51.38	51.62
						H	8.17	7.75
						N	8.56	8.34
XIV	3-Methyl-2-thienyl	SO ₂ CH ₃	C ₉ H ₁₅ NO ₂ S ₂	51.5	41–43°	S	29.35	29.11
						C	46.35	46.80
						H	6.43	6.34
						N	6.00	5.85
XV	3-Methyl-2-thienyl	COCF ₃	C ₁₀ H ₁₂ F ₃ NOS	82	57–58°	S	27.46	27.40
						C	47.81	47.44
						H	4.78	5.12
						N	5.58	5.69
						S	12.75	13.19
XVI	3-Methyl-2-thienyl	$\begin{array}{c} \text{S} \\ \parallel \\ \text{CNHCH}_3 \end{array}$	C ₁₀ H ₁₆ N ₂ S 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 ₂ H ₅) ₃ NH ⁺	C ₁₅ H ₂₈ N ₂ S ₃ ·1 1/2H ₂ O	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 ₂ CH ₃	C ₉ H ₁₄ N ₂ O ₂ S	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 ₃ N ₂ O·CF ₃ CO ₂ H	55	112–113°	C	41.76	41.83
						H	2.89	3.32
						N	8.09	8.10
XX	3-Pyridyl	$\begin{array}{c} \text{S} \\ \parallel \\ \text{CNHCH}_3 \end{array}$	C ₁₀ H ₁₅ N ₃ S	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 ₂ H ₅) ₃ NH ⁺	C ₁₅ H ₂₆ N ₃ S ₂ ·1 1/2H ₂ O	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 ₂ CH ₃	C ₁₀ H ₁₆ N ₂ O ₂ S	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 ₃ N ₂ O	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 ₂ H ₅) ₃ NH ⁺	C ₁₆ H ₂₉ N ₃ S ₂ ·H ₂ O	35	Oil	C	55.65	55.48
						H	8.98	8.91
						N	12.17	12.34
XXV	4-Chlorophenyl	SO ₂ CH ₃	C ₁₀ H ₁₅ ClNO ₂ S	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 ₃ NO	90	127–128°	C	49.71	49.92
						H	4.14	4.02
						N	5.27	5.40
XXVII	4-Chlorophenyl	$\begin{array}{c} \text{S} \\ \parallel \\ \text{CNHCH}_3 \end{array}$	C ₁₁ H ₁₅ ClN ₂ S	70	Oil	C	54.42	54.73
						H	6.23	6.56
						N	11.54	11.13
XXVIII	4-Chlorophenyl	CS ₂ ⁻ (C ₂ H ₅) ₃ NH ⁺	C ₁₆ H ₂₇ ClN ₂ S·2H ₂ O	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 ₂ CH ₃	C ₁₄ H ₁₇ NO ₂ S	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 ₃ NO	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 re-

spective 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



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).

EXPERIMENTAL¹

Melting points were determined in capillaries with a melting-point block² and are uncorrected. IR absorption spectra were obtained with a grating spectrophotometer³. Silica gel TLC was carried out, and products were detected by exposure to iodine vapor.

The aldehydes and nitroethane were commercially prepared⁴. Methanesulfonyl chloride⁵, trifluoromethanesulfonyl chloride⁵, trifluoroacetic anhydride⁵, methyl isothiocyanate⁵, carbon disulfide⁵, and lithium aluminum hydride in ether⁶ (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 (NO₂), and 1300 (NO₂) 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.

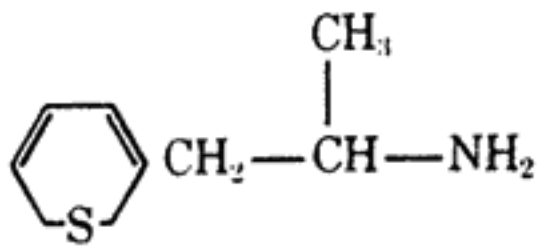
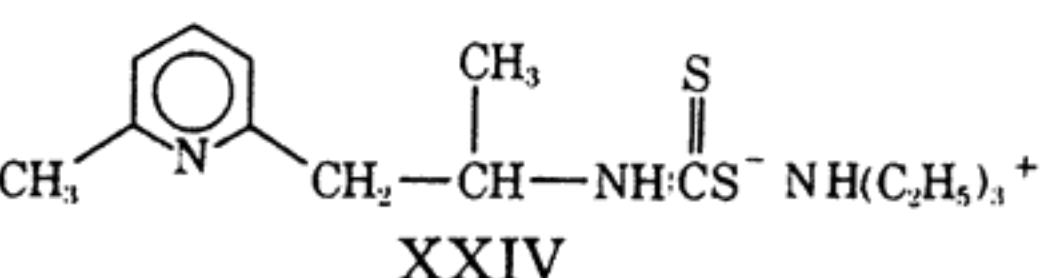
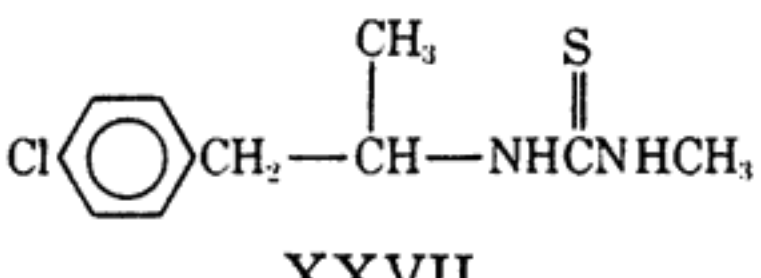
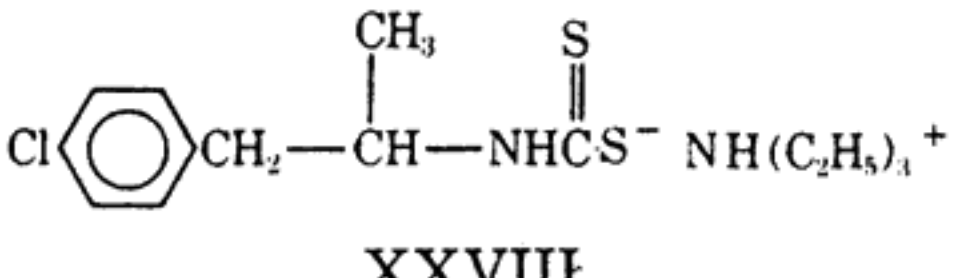
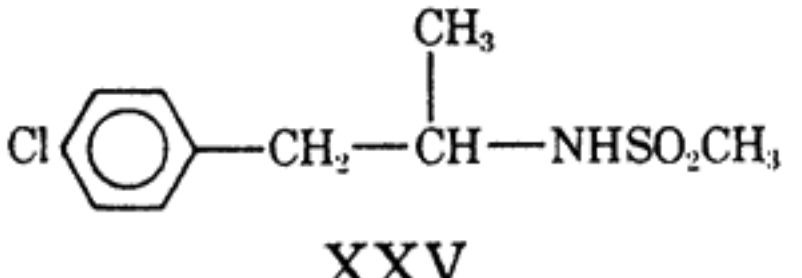
The ether layer was separated, the solvent was removed by flash evaporation, and the product was distilled at 146–150° (20 mm), giving 5.5 g (39% yield) of amber liquid. Addition of dry hydrogen chloride to an ethereal solution of the amine produced the hydrochloride, mp 149–152°; IR (KBr): 2900–3000 (NH₃⁺) 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 (SO₂), and 1125 (SO₂) 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 (CF₃) 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

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
 XXIV	200	Mydriasis
	25	Piloerection
	200	Placing reflex inhibition
	100	Prostration
	200	Respiratory distress
	200	Salivation, tremors
	200	Stereotyped behavior
	200	Bizarre behavior
	200	Curiosity increase
	200	Hyperthermia
 XXVII	200	Motor activity increase
	200	Mastication
	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
 XXVIII	200	Mydriasis
	200	Piloerection
	200	Placing reflex inhibition
	200	Prostration
	50	Salivation
	200	Semiprostration
	200	Stereotyped behavior
	200	Bizarre behavior
	200	Curiosity increase
	200	Hyperthermia
 XXV	200	Mastication
	200	Motor activity increase
	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	Ptoxis

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 (SO₂), 1190 (CF₃), and 1145 (SO₂) cm⁻¹.

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			
	<i>Staphylococcus aureus</i> ^a	<i>Escherichia coli</i> ^a	<i>Aspergillus niger</i> ^b	<i>Candida albicans</i> ^b
	(ATCC 6538)	(ATCC 1129)	(ATCC 16404)	(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.

RESULTS⁷

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 sig-

nificant 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).

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