[p-[(Thienylcarbonyl)amino]phenoxy]propanolamines Derivatives as Diuretic and β-Adrenergic Receptor Blocking Agents

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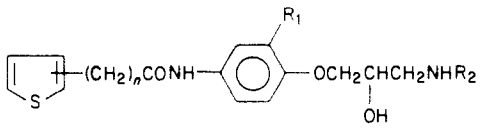
The synthesis of [[(thienylcarbonyl)amino]phenoxy]propanolamines and their β-adrenergic blocking and diuretic activity are described. Structure–activity relationships demonstrated that ortho substitution of the phenoxy ring with an hydrogen or an ester function leads to compounds possessing both activities. Ethyl 2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-5-[(2-thienylcarbonyl)amino]benzoate (**3d**) was selected as the most active compound for further investigation.

Combining a diuretic with a β-adrenoreceptor antagonist is a common therapeutic approach for hypertension management. It was therefore of interest to combine both properties in a single molecule. An unsuccessful attempt to achieve this goal by preparing a hybrid molecule combining the structures of a diuretic and of a β-adrenoreceptor antagonist was recently described.[1]

Our approach was different and was based on the observation that propranolol[2,3] has diuretic properties in the rat while atenolol, pindolol, nadolol, acebutolol, practolol, and metoprolol did not.

Propranolol's lack of diuretic properties in man (although some transient diuresis and effect on urinary osmolality were described by Imbs et al.[4] in a clinical study) was not considered a deterrent: we reasoned that molecules with a more potent diuretic effect in animals were needed to evidence a measurable effect in man. In any case, we were intrigued by the peculiar diuretic activity of propranolol in the rat and wanted to know more about structure and diuretic properties of other β-adrenergic antagonists in that species.

A diuretic screening program involving several potential β-adrenergic antagonists resulted in the finding that certain compounds of the general formula showed diuretic and



saluretic properties exceeding that of propranolol and hydrochlorothiazide, our reference drugs.

Chemistry. The compounds tested in this study are listed in Tables I and II. Standard procedures used for their synthesis are summarized in Scheme I.

As described in Scheme II, the starting phenols were prepared by two different ways.

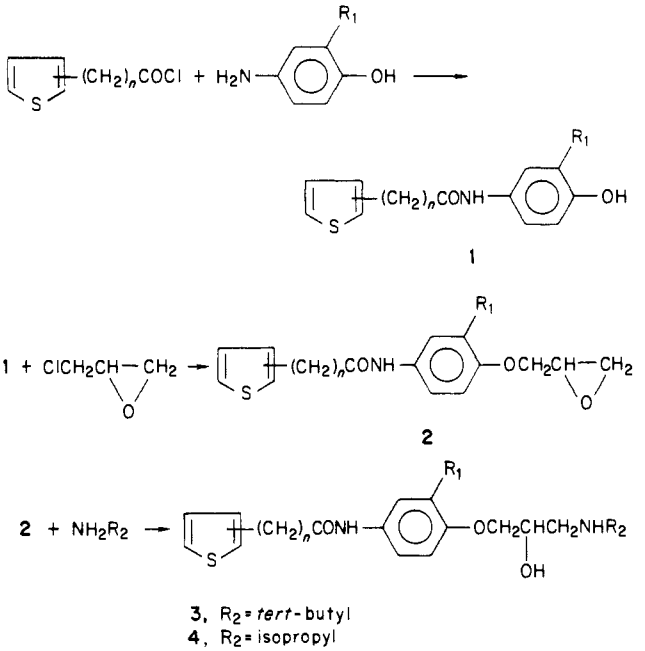
The epoxide intermediates **2** were easily obtained through reaction of the phenols with epichlorohydrin by using benzyltrimethylammonium chloride as a catalyst.

Results and Discussion

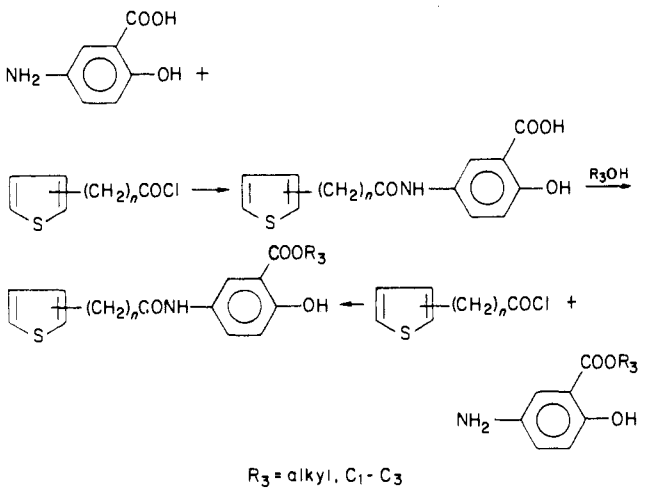
Biological data reported in Tables I and II allowed us to define a structure–activity relationship regarding both diuretic and β-adrenergic blocking activity.

Diuretic Activity. Previous studies (unreported data) showed that the substitution of the nitrogen in the aminopropanol chain by various groups (4-phenylpiperidine, 1-phenylpiperazine, 2-phenyl-1,1-dimethylethylamine, cyclopropylamine, and [2-(1*H*-indol-3-yl)-1,1-dimethylethyl]amine) led to compounds devoid of diuretic activity or less active than the *tert*-butyl (series **3**) and isopropyl (series **4**) derivatives described in the present work.

Scheme I



Scheme II



Lengthening the thienylcarbonylamino chain to form thienylacetamides caused a loss of diuretic activity (com-

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(1) Willard, A. K.; Smith, R. L.; Cragoe, E. J. *J. Org. Chem.* **1981**, *46*, 3846.
(2) Carrara, M. C.; Baines, A. D. *Can. J. Physiol. Pharmacol.* **1976**, *54*, 683.
(3) Smits, J. F. M.; Coleman, T. G.; Smith, J. L.; Kasbergen, C. M.; Van Essen, H.; Struyker Boudier, M. A. J. *J. Cardiovas. Pharmacol.* **1982**, *4*, 903.
(4) Imbs, J. L.; Spach, M. O.; Schmidt, M.; Schwartz, *Thérapie* **1977**, *32*, 329.

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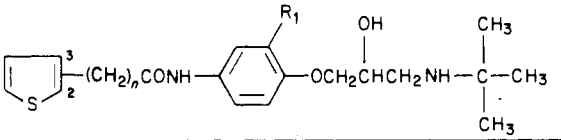
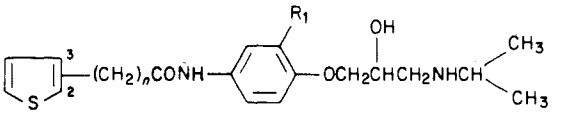
Table I. Salidiuretic and β-Adrenergic Blocking Activity of Compounds 3a–n



compd		n	R_1	yield, %	mp, °C	compd formula[a]	oral salidiuretic act.: control/drug treatment value: dosage, mg/kg	Na^+,[b] mequiv/6 h	urinary output,[b] mL	β-adrenergic blocking activity: β_1 ID50,[c] mg/kg iv	β_2 ID50,[c] mg/kg iv
3a	2	0	H	35	143–146	$C_{18}H_{24}N_2O_3S$	16	0.181/0.242	7.67/8.78	0.075	>1.000
							32	0.181/0.230	7.67/10.00		
							64	0.181/0.512**[d]	7.67/12.42**		
							128	0.181/0.607**	7.67/14.18**		
3b	2	0	CN	73	167–169	$C_{19}H_{23}N_3O_3S$	128	0.102/0.380	6.27/9.67	0.022	0.550
3c	2	0	$COOCH_3$	50	150–152	$C_{20}H_{26}N_2O_5S$	128	0.306/0.786*	6.83/10.83*	0.042	>1.000
3d	2	0	$COOCH_2CH_3$	45	127–128	$C_{21}H_{28}N_2O_5S$	16	0.207/0.554*	6.42/9.00*	0.065	>1.000
							32	0.207/0.626*	6.42/9.83**		
							64	0.207/0.766**	6.42/11.25***		
							128	0.207/1.364***	6.42/15.08***		
3e	2	1	$COOCH_2CH_3$	25	118–120	$C_{22}H_{30}N_2O_5S$	128	0.186/0.179	8.42/6.25	0.004	0.600
3f	2	0	$COOCH_2CH_2CH_3$	38	130–132	$C_{22}H_{30}N_2O_5S$	128	0.202/0.961***	7.17/11.25***	0.270	>1.000
3g	2	0	$COOCH(CH_3)_2$	59	138–141	$C_{22}H_{30}N_2O_5S$	128	0.210/1.197***	7.33/13.83***	0.320	>1.000
3h	2	0	$CONH_2$	35	170–172	$C_{19}H_{25}N_3O_4S$	128	0.301/0.148	7.67/6.97	0.120	>1.000
3i	3	0	$COOCH_2CH_3$	51	125–127	$C_{21}H_{28}N_2O_5S$	128	0.186/0.853**	8.42/10.18	0.060	>1.000
3j	3	1	$COOCH_2CH_3$	14	117–119	$C_{22}H_{30}N_2O_5S$	128	0.186/0.243	8.42/6.75	0.015	0.380
3k	2	0	COOH	40	>200	$C_{19}H_{24}N_2O_5S \cdot {}^3/_2H_2O$	128	0.229/0.172	4.88/5.32	>8.000	>8.000
3l	2	0	Cl	39	157–158	$C_{18}H_{23}ClN_2O_3S$	64	0.140/0.355*	10.33/9.33	0.014	0.400
3m	2	0	CH_3	40	143–145	$C_{19}H_{26}N_2O_3S$	32	0.140/0.416**	10.33/10.75	0.030	>1.000
3n	2	0	$COCH_3$	58	155–156	$C_{20}H_{26}N_2O_4S$	32	0.177/0.305	7.87/8.10	0.022	>1.000

[a] All compounds gave satisfactory C, H, Cl, N, and S analyses. [b] Mean value of $n = 3 \times 2$ animals per dosage. [c] n = two dogs. [d] *, **, and *** indicate a significant difference from control group respectively at $p < 0.05$, 0.01, and 0.001 (two-tailed Student's t-test).

Table II. Salidiuretic and β-Adrenergic Blocking Activity of Compounds **4a–n**



compd		n	R_1	yield, %	mp, °C	compd formula[a]	oral salidiuretic act.: control/drug treatment value: dosage, mg/kg	Na^+,[b] mequiv/6 h	urinary output,[b] mL	β-adrenergic blocking activity: β^1 ID50,[c] mg/kg iv	β_2 ID50,[c] mg/kg iv
4a	2	0	H	24	145–146	$C_{17}H_{22}N_2O_3S$	128	0.114/0.707***[f]	7.70/12.75***	0.045	>1.000
4c	2	0	$COOCH_3$	32	126–127	$C_{19}H_{24}N_2O_5S$	128	0.198/0.885***	8.17/12.83*	0.250	>1.000
4d	2	0	$COOCH_2CH_3$	44	107–108	$C_{20}H_{26}N_2O_5S$	16	0.205/0.350	7.33/9.75	0.300	0.450
							32	0.205/0.358	7.33/9.17		
							64	0.205/0.514*	7.33/10.00		
							128	0.205/0.712***	7.33/11.50**		
4e	2	1	$COOCH_2CH_3$	18	132–133	$C_{21}H_{28}N_2O_5S$	128	0.163/0.139	8.72/8.15	*d*	*d*
4f	2	0	$COOCH_2CH_2CH_3$	30	123–128	$C_{21}H_{28}N_2O_5S$	128	0.210/0.796**	7.33/10.83**	*d*	*d*
4g	2	0	$COOCH(CH_3)_2$	49	129–130	$C_{21}H_{28}N_2O_5S$	128	0.112/0.407**	7.25/9.43**	0.170	0.250
4i	3	0	$COOCH_2CH_3$	58	130–132	$C_{20}H_{26}N_2O_5S$	128	0.144/0.470**	6.50/8.47*	0.190	>1.000
4j	3	1	$COOCH_2CH_3$	24	129–130	$C_{21}H_{28}N_2O_5S$	128	0.163/0.133	8.72/8.02	0.020	>1.000
4l	2	0	Cl	44	132–133	$C_{17}H_{21}ClN_2O_3S$	32	0.140/0.417	10.33/10.08	0.170	>1.000
4m	2	0	CH_3	52	147–148	$C_{18}H_{24}N_2O_3S$	64	0.140/0.606	10.33/12.42*	0.020	>1.000
4n	2	0	$COCH_3$	57	133–134	$C_{19}H_{24}N_2O_4S$	128	0.177/0.304	7.87/8.70	0.450	>1.000
HCT[g]							14	0.261/0.695*	7.17/9.08	*d*	*d*
							27	0.261/0.742**	7.17/9.75*		
							55	0.261/0.745**	7.17/9.58*		
							110	0.261/0.735*	7.17/11.20**		
Prop[h]							16	0.216/0.178	9.05/9.87	0.069	0.038
							32	0.216/0.207	9.05/10.98		
							64	0.216/0.097	9.05/11.67*		
							128	0.216/0.263	9.05/12.83**		

[a] All compounds gave satisfactory C, H, Cl, N, and S analysis. [b] Mean value of $n = 3 \times 2$ animals per dosage. [c] n = two dogs. [d] These compounds have not been tested for their β-adrenergic blocking activity. [f] *, **, and *** indicate a significant difference from control group respectively at $p < 0.05$, 0.01, and 0.001 (two-tailed Student's t test). [g] HCT = hydrochlorothiazide. [h] Prop = propranolol.

pare **3d,3i/3e,3j**; **4d,4i/4e,4j**).

A decrease in efficacy was observed when the thienylcarbonylamino moiety was attached in the 3-position of the thienyl ring instead of the 2-position (**3d/3i,4d/4i**).

As far as 4-[(thienylcarbonyl)amino]phenoxy derivatives are concerned, the introduction of a substituent in the

ortho position lowered diuretic activity notably when R was a cyano (**3b**), a chloro (**3l**, **4l**), a carbamoyl (**3h**), or an acetyl (**3n**, **4n**). The one exception to this rule was the alkyl salicylates, some of which were as active or more than the parent compound (**3a**, **4a**).

The acid form (**3k**) was inactive when administered either by the oral or intraperitoneal route; thus the potency of the esters could be affected by in vivo enzymatic hydrolysis. Studies are currently underway to test this hypothesis, but it had already been demonstrated that the rate of chemical hydrolysis in vitro was greater for the methyl ester than for the ethyl ester; this is in good agreement with in vivo relative activity of both compounds.

β-Adrenergic Blocking Activity. All compounds (**3** and **4**) except for the acid derivative (**3k**) possessed cardioselective β-adrenergic blocking activity.

This activity was enhanced when the (thienylcarbonyl)amino side chain (**3d**, **3i**, **4i**) was substituted for a thienylacetamido moiety (**3e**, **3j**, **4j**).

In the carboxamido derivatives of series **3**, introduction of a cyano, chloro, acetyl, or methyl substituent on the phenyl group in the ortho position resulted in compounds with increased activity. Substitution with ester groups maintained β-adrenergic blocking potency for the methyl and ethyl esters but not for the propyl and isopropyl esters.

Changing the compound's terminal nitrogen from a *tert*-butyl group (series **3**) to an isopropyl (series **4**) modulated the β-adrenergic blocking effectiveness depending on the nature of the ortho substituent.

Finally, attachment of the thiophene ring in either the 2- or 3-position did not modify the activity (**3d**/**3i**,**4d**/**4i**).

In summary, a number of [*p*-[(thienylcarbonyl)amino]phenoxy]propanolamine derivatives, and specifically the compound **3d**, were found to possess diuretic and β-adrenergic blocking activity[5] in the same species and at the same dosage after oral administration (see Table III). This compound was selected for further pharmacological investigation.

Experimental Section

Biological Evaluation. Diuretic activity in rats was determined as follows. Fasted male rats (Sprague–Dawley, Iffa Credo, 130–140 g) with free access to water were used. At the time of test, the animals were given 2.5 mL of water/100 g of body weight and then were administred the vehicle or test substance in suspension by the oral route. The rats were housed in groups of two in metabolism cages. Urine was collected for the 0–6-h interval in volumetric graduated cylinders and was analyzed for sodium, potassium, and chloride content by using standard methods. Results that are geometric means for three cages for each dose level are expressed in milliliters of urine for the 6-h period and in milliequivalents for the electrolytes. Potassium and chloride elimination were omitted for clarity in Tables I–III.

β-Adrenergic blocking activity was measured in the dog as follows. Mongrel dogs of either sex in the weight range of 10–18 kg were anesthetized with a 30 mg/kg iv bolus of sodium pentobarbital followed by a 3 mg kg^{-1} h^{-1} slow perfusion. All dogs were artificially ventilated and supplied with oxygen by a RPP volumetric pump.

The carotid artery was cannulated and connected to a Statham P23 Db pressure transducer for blood pressure recording. Myocardium contractile force was recorded by a Walton-Brodie strain gauge sutured to the left ventricule. All signals were amplified and recorded continuously on a polygraph (Beckman R 411).

All injections were made into a cannulated saphenous vein. Contractile force and diastolic arterial pressure control effects

Table III. Salidiuretic and β-Adrenergic Activity of Compound **3d** on the Conscious Rat after Oral Administration

dosage, mg/kg vo	salidiuretic act.: control/treatment drug value				β_1 blocking act.: IPR ED50, μg/kg				β_2 blocking act.: IPR ED50, μg/kg			
	urinary output, mL			Na^+, mequiv/6 h	control value	treatment drug value			control value	treatment drug value		
	0–2 h	0–4 h	0–6 h			1 h	5 h			1 h	5 h	
32	7.42/9.64	9.02/11.67	9.99/13.01	0.259/.680	0.06 (0.04–0.09)	1.76 (1.29–2.43)	1.79 (1.29–2.48)		0.18 (0.12–0.27)	1.33 (0.95–1.86)	0.45 (0.27–0.75)	
	***[d]	***	***	***		***	***			***	***	
a	b			c								

[a] Compound **3d** used as the chlorhydrate; dosage expressed as equivalent base. [b] Mean value of $n = 3 \times 2$ animals per dosage. [c] ED50 of IPR with confidence limits, n = six to eight animals. [d] *** indicate a significant difference in comparison with control values at $p < 0.001$ (two-tailed Student's t test).

(5) Cloarec, A.; Cazes, M.; Provost, D.; Delchambre, C.; Deghenghi, R. In "Diuretics—Chemistry, Pharmacology, and Clinical Applications"; Puschett, J. B., Greenberg, A., Ed.; Elsevier: New York, 1984; pp 163–165.

were obtained by iv injection of a submaximal dose of isoprenaline (isoproterenol). Animals were used only once for each tested substance. The different intravenous doses of the same drug were injected every 30 min.

Isoproterenol hemodynamic effects after each test substance injection were compared to isoproterenol control values, and the blockage percentage of isoproterenol response for each dose level was calculated. A dose–response curve was constructed on the basis of these results and an estimated dose (ID50) producing a 50% inhibition of hemodynamic changes on contractile force or diastolic arterial pressure was determined.

β-Adrenergic blocking activity in the conscious rat was measured as follows. Chronically implanted[3] Sprague–Dawley rats were used. Before and after oral administration of test compounds (1 h, 5 h), β-adrenergic blockage was assessed by serial construction of dose response curves for iv isoproterenol induced tachycardia or hypotension. From the curves ED50 values were determined by linear regression and were defined as the dose of isoproterenol eliciting 50% of the maximal effects observed. They were considered as a measure of β-adrenergic blocking activity.

Synthesis. Melting points were determined on a Kofler apparatus and were uncorrected.

NMR spectra were recorded on a Perkin-Elmer R 12 A with $(CH_3)_4$ Si, as the internal reference. The various splitting patterns were designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet or quintuplet; m, multiplet. When the proton chemical shift was dependent on the dilution, it was indicated as V.

Where elemental analyses were given only symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

The compound's purity was checked by TLC analysis on silica gel GF 254 plates, and components were visualized by UV fluorescence inhibition properties.

HPLC assays were performed on a Varian 5060 analytical pump coupled with a Varian UV 100 detector set at 282 nm. The HPLC column was a prepacked 5-μm octadecyl-bonded column (150 × 4 mm). Elution was carried out at a flow rate of 1 mL/min with a mixture acetonitrile–0.1 M potassium dihydrogenophosphate aqueous solution (50/50).

Synthesis of epoxide **2d** is given as an example. The various epoxides **2** were prepared according to this procedure from corresponding phenols **1**.

Ethyl 2-(2,3-Epoxypropoxy)-5-[(2-thienylcarbonyl)amino]benzoate (2d). Ethyl 2-hydroxy-5-[(2-thienylcarbonyl)amino]benzoate (**1d**; 64 g, 0.22 mol) was heated to 110 °C in a flask with shaking with epichlorhydrin (340 mL). Benzyltrimethylammonium chloride (6.4 g) was then added and the reaction mixture was heated for 30 min to reflux. After cooling, water (300 mL) was added and the mixture vigorously shaken. After extraction with methylene chloride (600 mL), the organic phase was washed with water and dried on magnesium sulfate. The residual oil solidified upon concentration followed by trituration with diethyl ether. The solid was washed with isopropyl acetate (100 mL) and gave **2d** (60%): mp 124–126 °C; ^{1}H NMR ($CDCl_3$), δ 1.3 (3 H, t), 2.9 (2 H, d), 3.3 (1 H, m), 3.5–4.5 (4 H, m), 6.8–8 (6 H, m), 8 (1 H, V).

Ethyl 2-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-5-[(2-thienylcarbonyl)amino]benzoate (3d). Epoxide **2d** (22.6 g, 0.065 mol), dissolved in *tert*-butylamine (50 mL), was heated to 50 °C for 8 h in a flask. After vacuum evaporation of organic solution, the thick residue was added to a water (100 mL), acetic acid (6 mL), and ethyl acetate (50 mL) mixture. Once a clear mixture was obtained under vigorous shaking, the organic phase was removed and washed with a very diluted aqueous acetic acid solution. The aqueous phase was neutralized by ammonia and then extracted with methylene chloride (2 × 50 mL). The organic phase was vacuum concentrated. The residue obtained hardened in diethyl ether and gave **3d** which was recrystallized from isopropyl acetate: yield 45%; mp 127–128 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (12 H, s and t), 2.9–3.4 (2 H, m and 2 H, V), 3.9 (3 H, br s), 4.2 (2 H, q), 6.9–8 (6 H, m and 1 H, V). Anal. ($C_{21}H_{28}N_2O_5S$) C, H, N, S.

The various compounds **3** listed in Table I were prepared according to this procedure.

2-[3-[(1,1-Dimethylethyl)amino]-2-hydroxypropoxy]-5-[(2-thienylcarbonyl)amino]benzoic Acid (3k). Compound **3d** (8.2 g, 0.0195 mol) was refluxed with NaOH solution (0.8 g, 0.02 mol) in water (60 mL) for 2 h. After cooling, the aqueous solution was washed with chloroform (2 × 30 mL) and then acidified with CO_2. A precipitate was formed and collected by filtration washed with water (20 mL) and with ethanol (20 mL). After recrystallization from ethanol, **3k** was obtained, hydrated with $^3/_2H_2O$: yield 40%; mp >200 °C; ^{1}H NMR (Me_2SO-d_6/$CDCl_3$) δ 1.3 (9 H, s), 3.1 (2 H, m), 4.1 (3 H, m), 5.7 (6 H, V), 6.9–7.3 (2 H, m), 7.7–8.3 (4 H, m), 10.4 (1 H, V). Anal. ($C_{19}H_{24}N_2O_5S \cdot {}^3/_2H_2O$) C, H, N, O, S.

Ethyl 2-[3-[(1-Methylethyl)amino]-2-hydroxypropoxy]-5-[(2-thienylcarbonyl)amino]benzoate (4d). A solution of epoxide **2d** (17 g, 0.049 mol) in isopropylamine (25 mL) and ethanol (50 mL) was heated to 50 °C for 8 h. The solution was vacuum concentrated and the residue was added to a water (200 mL), acetic acid (6 mL), and isopropyl acetate (100 mL) mixture. The organic phase was separated by decanting. The aqueous phase was neutralized by ammonia and then extracted with chloroform (2 × 50 mL). The chloroform solution was dried, filtered, and vacuum concentrated. The residue crystallized in diethyl ether to give **4d**: yield 44%; mp 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 1 (6 H, d), 1.3 (3 H, t), 2.8 (3 H, m), 2.8–4 (2 H, V), 4.1 (3 H, br s), 4.3 (2 H, q), 6.8–8 (6 H, m), 7.5–8.5 (1 H, V). Anal. ($C_{20}H_{26}N_2O_5S$) C, H, N, S.

Other compounds **4** listed in Table II were prepared according to this procedure.

Registry No. **1a**, 98902-53-5; **1b**, 98902-54-6; **1c**, 90056-07-8; **1d**, 90055-92-8; **1e**, 90056-00-1; **1f**, 98902-55-7; **1g**, 98902-56-8; **1h**, 98902-57-9; **1i**, 90055-94-0; **1j**, 90056-03-4; **1k**, 98902-52-4; **1l**, 98902-58-0; **1m**, 98902-59-1; **1n**, 98902-60-4; **2a**, 98902-61-5; **2b**, 98921-41-6; **2c**, 90056-08-9; **2d**, 90055-93-9; **2e**, 90056-01-2; **2f**, 98902-62-6; **2g**, 98902-63-7; **2h**, 98902-64-8; **2i**, 90055-95-1; **2j**, 90056-04-5; **2l**, 98902-65-9; **2m**, 98902-66-0; **2n**, 98902-67-1; **3a**, 98902-68-2; **3b**, 98902-69-3; **3c**, 90056-09-0; **3d**, 90055-97-3; **3e**, 90056-02-3; **3f**, 98902-70-6; **3g**, 98902-71-7; **3h**, 98902-72-8; **3i**, 90055-99-5; **3j**, 90056-05-6; **3k**, 98902-73-9; **3l**, 98902-74-0; **3m**, 98902-75-1; **3n**, 98902-76-2; **4a**, 98902-77-3; **4c**, 98902-78-4; **4d**, 90055-96-2; **4e**, 98902-79-5; **4f**, 98902-80-8; **4g**, 98902-81-9; **4i**, 90055-98-4; **4j**, 90056-06-7; **4l**, 98902-82-0; **4m**, 98902-83-1; **4n**, 98902-84-2; $4\text{-}HOC_6H_4NH_2$, 123-30-8; 5-amino-2-hydroxybenzonitrile, 87029-84-3; methyl 5-amino-2-hydroxybenzoate, 42753-75-3; ethyl 5-amino-2-hydroxybenzoate, 62773-65-3; 5-amino-2-hydroxybenzoate, 59393-77-0; 4-amino-2-chlorophenol, 3964-52-1; 4-amino-2-methylphenol, 2835-96-3; 2′-hydroxy-4′-aminoacetophenone, 50-80-6; 5-amino-2-hydroxybenzoic acid, 89-57-6; 2-thiophenecarbonyl chloride, 5271-67-0; 2-thiopheneacetyl chloride, 39098-97-0; 3-thiophenecarbonyl chloride, 41507-35-1; 3-thiopheneacetyl chloride, 13781-65-2.