orated at 70–80°. The residual mixture was suspended in 100 ml of H_2O. The suspension was made basic (pH >10) with 50% aqueous KOH and the nonacidic matter removed by two washings with CH_2Cl_2. Acidification of the aqueous layer with HCl to about pH 1, followed by standing for 1 hr, yielded a yellow amorphous solid: 6.33 g, mp 269–271° dec. After recrystallization from DMF–H_2O, 5.20 g (82%) of yellow prisms were obtained, mp 278–280° dec (darkened above 245°). Further recrystallizations did not change the melting point. *Anal.* ($C_{17}H_{14}N_6O$) C, H, N.

1,3-Dihydro-1-methyl-7-(2-methyltetrazol-5-yl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (12) and 1,3-Dihydro-1-methyl-7-(1-methyltetrazol-5-yl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (13). To a solution of 318 mg (1.0 mmol) of 11 and 0.154 ml (1.1 mmol) of Et_3N in 5 ml of Me_2CO was added 0.069 ml (1.1 mmol) of CH_3I. The mixture was allowed to stand at 20° under N_2 for 6 hr. The solvent was evaporated and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer containing the nonacidic reaction products (292 mg of gum) was evaporated and the isomeric N-methylated products 12 and 13 (tlc R_f values 0.47 and 0.22, respectively, silica gel, EtOAc) were separated by preparative tlc (three silica gel plates, 20 cm × 20 cm × 1.5 mm; EtOAc as eluent). Pure 12 initially obtained as a gum (206 mg) crystallized from C_6H_6–hexane as light yellow flakes (154 mg; 46%), mp 201–202.5°. *Anal.* ($C_{18}H_{16}N_6O$) C, H, N. Pure 13 also obtained initially as a gum (36 mg) crystallized from C_6H_6–hexane as light yellow needles (28 mg; 8%), mp 212–214°. Larger amounts of 12 and 13 were prepared in similar yields following essentially the same procedure, but using column chromatography (silica gel, EtOAc followed by 5% MeOH in EtOAc as eluents) for the separation of the isomers.

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N-Substituted 2-Amino-1-(2-thienyl)ethanols as β-Adrenergic Blocking Agents

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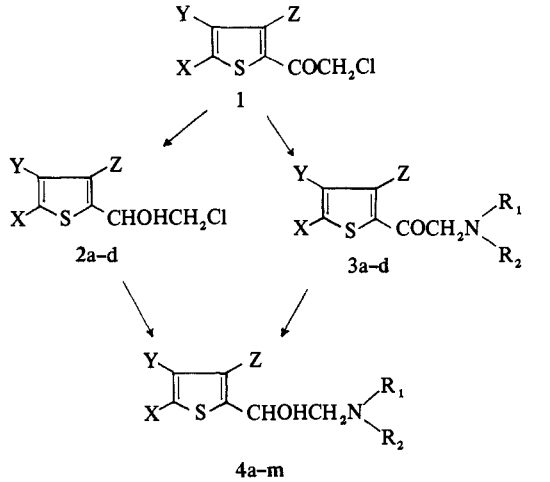
The synthesis and pharmacological properties of a series of N-substituted 2-amino-1-(2-thienyl)ethanols are described. A strong β-adrenergic blocking activity has been observed in *N*-isopropyl- or *N-tert*-butyl-substituted ring-chlorinated compounds.

Elucidation of the structure of the neurotransmitters of the sympathetic nervous system, epinephrine and norepinephrine, provided the impetus for extensive molecular modifications of these catecholamines in search of adrenergic stimulant or adrenergic blocking activity. The benzenoid hydroxyl group of the catecholamines has been replaced by a variety of substituents including chlorine,[1] fluorine,[2] iodine,[3] alkyl,[4] nitro,[5] amino,[6] alkoxy,[7] and alkyl- or arylsulfonamide.[8] The 2-hydroxyethylamino side chain and the N substituent have also been modified.[9] It appears, however, that the bioisosteric replacement of the benzene ring by thiophene has not received much attention, in spite of the extensive demonstration of the equivalence of these two rings in many therapeutics fields.[10]

A series of thienylethanolamine derivatives, some of which contain one or two chlorine atoms on the thiophene ring, has been prepared and the pharmacological activity of the new compounds has been tested. Since some of them, especially those with branched *N*-alkyl substituents, seem to fulfill the structural requirements for β-adrenergic blocking activity,[11] this pharmacological property was especially considered in the screening tests.

Chemical Synthesis. All the thienyl ethanolamine derivatives 4 (Table III) reported in this work are racemic modifications and were prepared from the appropriate chloroacetylthiophenes 1 by two alternate routes (Scheme I).

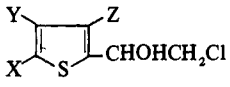
Scheme I



In route A, the chloroacetylthiophene 1 was reduced by the Meerwein-Ponndorf method to the corresponding 2-chloro-1-(2-thienyl)ethanol 2 (Table I) and the latter upon treatment with an amine yielded the corresponding thienylethanolamine derivative 4.

In route B, 1 was allowed to react with an amine and the obtained amino ketone 3 (Table II) was reduced to 4 by $NaBH_4$.

Table I. 2-Chloro-1-(2-thienyl)ethanols



Compd	X	Y	Z	Yield, %	Bp, °C (mm)	Formula	Analyses
2a	H	H	H	78	115 (4.5)	C_6H_7ClOS	C, H; Cl[a]
2b	Cl	H	H	67	110 (2)	$C_6H_6Cl_2OS$	C, H, Cl
2c	Cl	Cl	H	65	113 (0.25)	$C_6H_5Cl_3OS$	C, H, Cl
2d	H	Cl	Cl	80	96-98 (0.2)	$C_6H_5Cl_3OS$	H, Cl; C[b]

[a]Cl: calcd, 21.84; found, 21.42. [b]C: calcd, 31.10; found, 30.65.

Pharmacological Results and Discussion. The results of the pharmacological testing of the thienylethanolamine derivatives are presented in Table IV. All the dichlorinated compounds **4j-m**, especially compound **4j**, showed moderate to strong nonspecific spasmolytic activity in the guinea-pig ileum. The tachycardic response to isoproterenol in the anesthetized rat was inhibited by compounds **4f-m**. These compounds also antagonized to different degrees the hypotensive response to isoproterenol. Blood pressure being, however, a too fluctuant parameter in the rat as to allow an accurate evaluation of these antagonistic effects on vascular β-adrenergic receptors, the results obtained were not recorded in Table IV. All the compounds, with the exception of **4f**, provided a decrease in the resting heart rate of the animals but to a much lesser extent than propranolol. None of the tested products antagonized the β-adrenoceptor mediated effects of norepinephrine in the rat vas deferens at doses below 10^{-5} g/ml. It was also possible to observe in some pilot experiments that the most potent β-blocking compounds of this series either did not modify or potentiated the pressor effect induced by epinephrine in anesthetized rats.

These compounds appear to be one of the few examples in the literature in which a clear β-adrenergic blocking activity is observed when the ethanolamine side chain is attached to a single heterocyclic ring. Other β-blocking substances in which the propanolamine side chain is attached to a thiadiazole ring have been recently described.[12] In the new compounds described herein, chlorination of the thiophene ring seems to be a necessary requisite for this activity and chlorine atoms in positions 4 and 5 seem to favor predominantly the blockade of β-adrenergic receptors. As expected, the nature of the substituent on the terminal amino group is also important in this respect. Thus, the β-blocking activity of compounds **4h** and **4i** with a tetra- or pentamethylene group attached to the nitrogen is much weaker than that of compounds with the conventional *N*-isopropyl or *tert*-butyl substitution (compounds **4f** and **4g**). Depression of heart rate is, on the other hand, preferably observed with *N*-*tert*-butyl derivatives. Isopropyl derivatives resemble more closely isoproterenol and a partial agonist activity was observed with these compounds in supersensitized preparations (reserpinized rats) especially in the case of compound **4j**, which can be regarded as the bioisosteric analog of dichloroisoproterenol, the first β-blocking drug described.[13] Dichloroisoproterenol was withdrawn from clinical use because of its excessive sympathomimetic effect. Chlorinated thiophene derivatives with *N*-isopropyl or *tert*-butyl substituents were selected for a more extensive study of their β-adrenergic blocking activity and other pharmacological effects in cats and guinea pigs. Results obtained will be described in a forthcoming paper.

Experimental Section†

I. Chemical Methods. Chlorothiophenes. 2-Chlorothiophene was a commercial product from Fluka A. G., 2,3-dichlorothiophene was prepared according to Profft and coworkers[14-17] from tetrahydrothiophene, and 3,4-dichlorothiophene was made by the method of Coonradt, *et al.*,[18] from α-1,2,3,4-tetrachlorothiolane.

Chloroacetylthiophenes. 2-(Chloroacetyl)thiophene,[19] 2-(chloroacetyl)-5-chlorothiophene,[6] 2-(chloroacetyl)-4,5-dichlorothiophene,[17] and 2-(chloroacetyl)-3,4-dichlorothiophene[17] were prepared from thiophene and the above-mentioned chlorothiophenes according literature procedures.

2-Chloro-1-(2-thienyl)ethanols (Table I) were prepared by Meerwein-Ponndorf reduction of the corresponding 2-(chloroacetyl)thiophene following a standard procedure.[20] They are rather unstable colorless liquids that must be used soon after distillation.

2-Alkylaminoacetylthiophene Hydrochlorides (Table II). To a stirred solution cooled externally by ice of the corresponding 2-(chloroacetyl)thiophene (0.03 mol) in dry benzene (30 ml) was added the appropriate amine (0.075 mol) and the solution was kept at room temperature overnight. The produced solid (starting amine hydrochloride in nearly theoretical amount) was removed by filtration and washed with dry benzene. Benzene and excess amine were eliminated from the filtrate at room temperature under reduced pressure. The liquid residue was dissolved in dry Et_2O and treated with dry ethereal HCl. The hydrochloride was filtered, washed with dry Et_2O, and recrystallized (twice) from EtOH.

2-Dialkylamino-1-(2-thienyl)ethanols (Tables III and IV). Method A. The corresponding 2-chloro-1-(2-thienyl)ethanol (0.03 mol) and the appropriate amine (0.075 mol) were heated at 100° for 24 hr (in a sealed tube when the amine is volatile). The cooled mixture was treated with Et_2O and H_2O. Drying (Na_2SO_4) and concentration of the ethereal extracts gave the crude product which was purified by recrystallization (decoloring charcoal if necessary).

Method B. A stirred suspension of the corresponding 2-alkylaminoacetylthiophene hydrochloride (0.005 mol) in EtOH (10 ml) was neutralized with 1 *N* NaOH and treated with $NaBH_4$ (0.2 g, 0.005 mol). Stirring was continued for 2 hr and the solution was allowed to stand at room temperature overnight. After acidification with 1 *N* HCl, most of the ethanol was removed under reduced pressure. The solution was made basic and extracted with Et_2O. Drying (Na_2SO_4) and evaporation of the ethereal solution left the crude product which was purified by recrystallization (decoloring charcoal if necessary).

II. Pharmacological Methods. Compounds for pharmacological testing were dissolved in 0.05 *N* HCl and neutralized to pH 7 with $NaHCO_3$. Further dilutions were made with the bath solutions or with physiological saline.

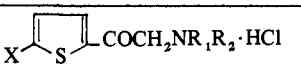
Studies on Isolated Preparations. Strips of guinea-pig ileum were suspended in a Tyrode's bath at 37°. Spasmogens and doses used were: acetycholine chloride (ACh, 0.01 μg/ml); histamine dihydrochloride (H, 0.02 μg/ml); 5-hydroxytryptamine creatinine sulfate (5 HT, serotonin, 0.5 μg/ml); and nicotine bitartrate (Nic, 0.2 μg/ml). Test compounds were added to the bath 2 min before adding each spasmogen. The approximate concentration causing a 50% reduction in the size of the isotonic ileal contraction (ID_{50}) was calculated.

Rat vas deferens was suspended in a Krebs bath at 30°. Contractions were induced by DL-norephinephrine hydrochloride NE, 1 μg/ml) and test compounds were added to the bath 2 min before. ID_{50}'s were calculated as above.

β-Adrenergic Blocking Activity in Rats. Male Wistar rats were anesthetized with urethane (1.5 g/kg ip). Blood pressure was recorded from the carotid artery using a Statham transducer and a Grass polygraph. Heart rate was measured by integration of ECG (lead II). Injections were made into the jugular vein. The effects of standard submaximal doses of isoproterenol (0.25 μg/kg) were determined three times before administering the test compounds at the same high dose of 4 mg/kg and repeated another three times after injections of compounds. The time interval between injections was 10 min. Blockade of the tachycardic response to isoproternol was expressed as the per cent mean inhibition of the mean control response. The per cent change in resting heart rate after the test

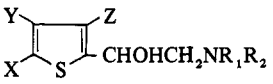
†All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra were recorded for all compounds and are consistent with assigned structures.

Table II. 2-Alkylaminoacetylthiophene Hydrochlorides



Compd	X	R_1	R_2	Yield, %	Mp, °C	Formula	Analyses
3a	H	H	*i*-C_3H_7	38	214–216 dec	$C_9H_{14}ClNOS$	C, H, N
3b	H	H	*t*-C_4H_9	50	233–235 dec	$C_{10}H_{16}ClNOS$	C, H, N
3c	Cl	H	*i*-C_3H_7	23	202–205 dec	$C_9H_{13}Cl_2NOS$	C, H, N
3b	Cl	H	*t*-C_4H_9	20	231 dec	$C_{10}H_{15}Cl_2NOS$	C, H, N

Table III. 2-Dialkylamino-1-(2-thienyl)ethanols



Compd	X	Y	Z	$-NR_1R_2$	% yield (method)	Mp, °C	Recrystn solvent[a]	Formula	Analyses
4a	H	H	H		50 (B)	66–68	Pe	$C_9H_{15}NOS$	C, H, N
4b	H	H	H		73 (B)	76–78	Pe	$C_{10}H_{17}NOS$	C, H, N[b]
4c	H	H	H	-c-NC_5H_{10}	40 (A)	80–81	Pe	$C_{11}H_{17}NOS$	C, H, N, S
4d	H	H	H	-c-$N(CH_2CH_2)_2O$	40 (A)	97–99	Cy	$C_{10}H_{15}NO_2S$	C, H, N, S
4e	H	H	H	-c-$N(CH_2CH_2)_2$-NC_6H_5	50 (A)	136–138	EtOH	$C_{16}H_{20}N_2OS$	C, H, N, S
4f	H	H	H		32 (A), 72 (B)	75–76	Pe	$C_9H_{14}ClNOS$	C, H, Cl, N, S
4g	Cl	H	H		50 (A), 75 (B)	95–97	Pe	$C_{10}H_{16}ClNOS$	C, H, Cl, N, S
4h	Cl	H	H	-c-NC_4H_8	50 (A)	104–106	Pe	$C_{10}H_{14}ClNOS$	C, H, Cl, N, S
4i	Cl	H	H	-c-NC_5H_{10}	50 (A)	77–79	Pe	$C_{11}H_{16}ClNOS$	C, H, Cl, N, S
4j	Cl	Cl	H		70 (A)	87–89	Pe	$C_9H_{13}Cl_2NOS$	C, H, N
4k	Cl	Cl	H		60 (A)	98–100	Pe	$C_{10}H_{15}Cl_2NOS$	C, H, N
4l	H	Cl	Cl		57 (A)	109-110	Pe	$C_9H_{13}Cl_2NOS$	C, H, N
4m	H	Cl	Cl		50 (A)	111–112	Pe	$C_{10}H_{15}Cl_2NOS$	C, H, N

[a]Cy, cyclohexane; Pe, petroleum ether, bp 50–70°. [b]N: calcd, 7.03; found, 7.45.

Table IV

Compd no.	*In vitro* activity: approximate ID_{50}, g/ml[a]					Cardiac effects on rats[b]	
	Guinea-pig ileum				Rat vas deferens,	% inhib of isoproterenol-induced	
	ACh	H	5-HT	Nic	NE	tachycardia	% change in heart rate
4a	10^{-5}	5.10^{-6}	3.10^{-5}	5.10^{-6}	10^{-5}	0	−13.7
4b	10^{-5}	5.10^{-6}	3.10^{-5}	5.10^{-6}	10^{-5}	0	−6.4
4c	10^{-5}	5.10^{-6}	10^{-5}	5.10^{-6}	10^{-5}	0	−6.0
4d	2.10^{-4}	10^{-4}	2.10^{-4}	10^{-4}	10^{-4}	0	−1.0
4e	3.10^{-5}	10^{-6}	10^{-5}	5.10^{-6}	5.10^{-6}	0	−3.8
4f	5.10^{-6}	3.10^{-6}	10^{-6}	3.10^{-6}	10^{-5}	84.7	+7.7
4g	10^{-5}	3.10^{-6}	10^{-5}	3.10^{-6}	10^{-5}	60.8	−14.6
4h	4.10^{-6}	2.10^{-7}	5.10^{-6}	4.10^{-6}	$>10^{-4}$	32.0	−14.8
4i	3.10^{-6}	10^{-6}	10^{-5}	2.10^{-6}	$>10^{-4}$	35.5	−12.4
4j	10^{-7}	10^{-8}	10^{-7}	10^{-7}	10^{-5}	90.1	−8.7
4k	7.10^{-7}	3.10^{-7}	5.10^{-7}	2.10^{-7}	10^{-5}	81.6	−16.3
4l	5.10^{-6}	6.10^{-7}	5.10^{-6}	10^{-6}	10^{-4}	69.9	−16.4
4m	10^{-6}	10^{-6}	5.10^{-7}	10^{-6}	10^{-4}	73.8	−23.4
Propranolol	*c*	*c*	*c*	*c*	*c*	81.0	−37.1

[a]Compounds were added to the bath at increasing concentrations from 10^{-8} to 10^{-4} g/ml. Each concentration was tested at least three times. [b]All compounds were iv administered at a single dose of 4 mg/kg. Each value is the mean of at least six experiments. [c]Not tested.

compounds was also calculated. Each compound was studied at least in six animals.

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Benzhydryl and Fluorenyl Lactamimides with Hypoglycemic, Diuretic, Blood Platelet Aggregation Inhibitory, and Antiinflammatory Activities

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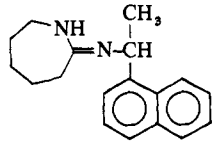
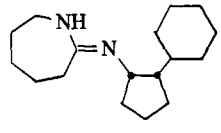
2-[(Diphenylmethyl)imino]piperidine hydrochloride (**2**) and 2-(9-fluorenylimino)hexahydroazepine hydrochloride (**45**) were found to have hypoglycemic properties in rats at 5–10 mg/kg po. These benzhydryl lactamimides were selected after extensive exploration of structural parameters including variation of lactam ring size, N and C substitution, aromatic substituents, and preparation of tricyclic fluorenyl and dihydrodibenzocycloheptenyl analogs. These compounds also showed potent diuretic properties in rats but not in dogs. Compounds **20** and **49** were the most potent diuretics in rats. While most benzhydryl lactamimides inhibited ADP-induced aggregation of human blood platelets only weakly, compounds **34**, **39**, and **41** were comparable to the naphthylalkyl lactamimide **1**. Several benzhydryl lactamimides showed antiinflammatory activity in rats (carrageenin-induced abcess method) at 100 mg/kg po but did not protect against uv-induced erythrema in guinea pigs. Compound **2** showed antihistaminic activity. Compounds **2** and **45** were selected for pathologic-toxicologic evaluation in preparation for clinical trial as hypoglycemic agents.

We recently reported on the effects of the naphthylalkyl lactamimide I† on adenosine diphosphate (ADP) and collagen-induced aggregation of human blood platelets.[1]



I



II

Extended evaluation of I led to the discovery of its hypoglycemic activity. Evaluation of other lactamimides then led us to follow a rationale according to which lactamimides derived from sterically hindered primary amines were pursued as potential hypoglycemic agents. This led to the development of II.†,[2] At the same time we found that the benzhydryl lactamimide **3** (Table I) had strong hypoglycemic activity. We now wish to report on the synthesis and biological evaluation of related benzhydryl, fluorenyl, and dibenzocycloheptenyl lactamimides.

Hypoglycemic Effects. The compounds listed in Table I were prepared and evaluated for hypoglycemic activity in fasted, glucose-primed rats by the method of Gerritsen and Dulin.[3] With compounds **1–6** the effect of the lactam ring size was explored. The five- and six-membered congeners **1** and **2**† were more potent than **3** while the larger eight-, nine-, and 13-membered ring congeners were less active. In the fluorene series **43–47**, on the other hand, the seven-membered ring congener **45**† was the most active, while the smaller ring congeners were inactive. Lactam ring *N*-methyl substitution (**7–9**) showed very similar, though somewhat reduced, potency while the *N*-benzyl congener **10** was inactive. A chlorine or *tert*-butyl substituent in the lactam ring (**11**, **12**, **47**) gave inactive compounds.

A large number of aromatic substituents were explored (**13–35**). In respect to hypoglycemic activity, however, all of these had less or no activity with the exception of the methoxy derivatives **22–25**. Of compounds in which the two benzene rings were tied into a tricyclic fluorene moiety (**43–47**), **45** showed highest activity, but the dihydrodibenzocycloheptene derivatives **48–50** had no hypoglycemic activity. Compounds **13**, **20**,† **21**, **33**, and **49**† had a hyperglycemic effect, as shown in Table II.

Diuretic Effects. In the course of the hypoglycemic evaluation, diuresis was observed. Diuretic activity was evaluated in saline-loaded rats by a modification of the

†The following code numbers were assigned: I, RMI 7822; II, RMI 11894; **2**, RMI 11943; **20**, RMI 11842; **41**, RMI 12366; **45**, RMI 10026; **49**, RMI 11749.