at 25° to remove MeOH. NaOH (100 ml, 0.5 *N*) was added to the residue and the mixture was extracted with C_6H_6. This extract furnished crude product, mp 102°, $[\alpha]^{21}D$ −17.3° (*c* 0.98, EtOH). A solution of 9 g (0.0393 mole) of this crude base and 7.58 g (0.0196 mole) of (+)-O,O-di-*p*-toluoyltartaric acid in 60 ml of MeOH and 45 ml of H_2O at 50° was cooled slowly to room temperature. The solid which separated was isolated and crystallized from aqueous 66% MeOH (by volume) until the rotation became constant. (−)-**1** (+)-O,O-di-*p*-toluoyltartrate trihydrate was obtained.

(αS,βR)-(+)-2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol and (αR,βR)-(−)-2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol.—$NaBH_4$ (5 g) was added during 30 min to a stirred solution of 2-naphthylglyoxal hydrate (21.5 g, 0.106 mole) and (*R*)-(−)-1-methyl-2-phenylethylamine (13.6 g, 0.101 mole) in MeOH (180 ml) at 0°. The mixture was stirred for 16 hr and then the solvent was evaporated. HCl (500 ml, 1 *N*) was added to the residue and the mixture was extracted with $CHCl_3$ (300 ml). The extract was washed (H_2O) and dried, and then the $CHCl_3$ was evaporated. The residual oil was dissolved in EtOAc (30 ml) and ethereal HCl was added until a slight excess of HCl was present. Et_2O was added and the solid which separated was isolated by filtration, the filtrate being retained for further examination. The solid, mp 167–168°, $[\alpha]^{21}D$ +23.1° (*c* 0.97, EtOH), was crystallized from MeOH–EtOAc and then from MeOH until the rotation became constant. (αS,βR)-(+)-**6** hydrochloride was obtained.

The Et_2O–EtOAc filtrate retained above and the MeOH–EtOAc mother liquors remaining after as much of the (αS,βR)-(+) isomer as possible had been removed were combined and evaporated to small volume. The solid, mp 145–146°, $[\alpha]^{21}D$ −40.6° (*c* 0.98, EtOH), which separated on cooling the solution was recrystallized from MeOH–EtOAc and then from MeOH until the rotation became constant. (αR,βR)-(−)-**6** hydrochloride was obtained.

(αR,βS)-(−)-2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol and (αS,βS)-(+)-2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol.—The previous experiment was repeated using (*S*)-(+)-1-methyl-2-phenylethylamine in place of (*R*)-(−)-1-methyl-2-phenylethylamine.

Racemic 2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)-ethanol.—Equal weights of (αS,βR)-(+)- and (αR,βS)-(−)-2-(1-methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol were mixed and the mixture was crystallized from EtOAc–petroleum ether (bp 40–60°). The racemate formed prisms, mp 93–94°, identical in melting point, mixture melting point, and ir spectrum with the racemate **51B**.[1]

Isopropyl-2-(2-naphthyl)ethylamine.—A solution of 2-(2-naphthyl)ethylamine (0.88 g) in EtOH (20 ml) and Me_2CO (5 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of PtO_2 (0.3 g). The organic base was isolated, dissolved in EtOAc, and converted to the hydrochloride by adding ethereal HCl. Isopropyl-2-(2-naphthyl)ethylamine hydrochloride formed plates, mp 206–207°, from MeOH–EtOAc. *Anal.* ($C_{15}H_{22}ClNO$) C, H, N.

1-(3-Isopropylaminopropoxy)naphthalene.—1-Naphthol (21.6 g) was added to a solution of Na (3.45 g) in absolute EtOH (120 ml). The resulting solution was added during 1 hr to a boiling solution of 1-bromo-3-chloropropane (30 ml) in absolute EtOH (60 ml). The mixture was refluxed overnight and then the EtOH was evaporated. The residue was shaken with a mixture of H_2O and Et_2O. The Et_2O extract was washed with 5% NaOH (400 ml) and then H_2O and dried. The Et_2O was evaporated and the 1-(3-chloropropoxy)naphthalene was distilled, bp 164–168° (2 mm). 1-(3-Chloropropoxy)naphthalene (3 g) and *i*-$PrNH_2$ (10 ml) were heated at 100° for 10 hr in a sealed tube. Excess *i*-$PrNH_2$ was evaporated, 2 *N* NaOH (25 ml) was added, and the mixture was extracted with Et_2O. The extract was dried and then a slight excess of ethereal HCl was added. 1-(3-Isopropylaminopropoxy)naphthalene hydrochloride was obtained; mp 185–186°, from MeOH–EtOAc. *Anal.* ($C_{16}H_{22}ClNO$) C, H, N.

Some Epinephrine Analogs

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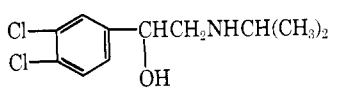
A number of epinephrine analogs and corresponding 1-aryl-2-alkylaminoethyl chloride hydrochlorides and bromide hydrobromides have been prepared. The central intermediates of the syntheses were the 5-aryl-3-alkyl-2-oxazolidones (IV), accessible by alkylation of the product obtained using the Reformatzky reaction of an aromatic aldehyde with ethyl bromoacetate. The results of a pharmacological study of the products obtained are summarized.

Based on the great variety of epinephrine analogs which have been studied, some theories have been advanced regarding the correlation between structure and activity, especially in the case of antiadrenergic activity.[1] The latter has been observed in halogen-substituted compounds carrying halogen either in the benzene ring of the 2-alkylamino-1-phenylethanol skeleton or instead of the hydroxyl group in this structure. An example of the former is dichloroisoproterenol (I), which blocks the β-adrenergic receptors;[2] examples for the second group, the α-adrenergic receptor blocking agents, have been described, *e.g.*, by Chapman and Triggle,[3] and investigated pharmacologically by Hunt,[4] Ferguson and Wescoe,[5] and Graham and Karrar.[6]

An additional stimulus for a further study of this series was the observation that epinephrine accelerates glycolysis in the liver and in the muscle.[7]



I

One of the aims of this investigation was to prepare and study the nuclear-fluorinated 2-amino- and 2-alkylamino-1-phenylethanols and the corresponding 1-

(1) *Cf.* (a) N. B. Chapman, K. Clarke, and R. D. Strickland, *Proc. Roy. Soc.* (London), **163B**, 116 (1965); (b) N. B. Chapman and G. D. P. Graham in "Drugs Affecting the Peripheral Nervous System," A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 473 ff; (c) B. Belleau, *Can. J. Biochem. Physiol.*, **36**, 731 (1958); (d) D. J. Triggle, *J. Theoret. Biol.*, **7**, 241 (1964); (e) B. Belleau, *Ann. N. Y. Acad. Sci.*, **139**, 580 (1967).

(2) B. Levy and R. P. Ahlquist, *J. Pharmacol. Exptl. Therap.*, **130**, 334 (1960); E. E. Vogin and W. W. Baker, *Am. J. Pharm.*, **133**, 314 (1961).

(3) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 1358 (1963).

(4) C. C. Hunt, *J. Pharmacol. Exptl. Therap.*, **95**, 177 (1949).

(5) F. C. Ferguson and W. C. Wescoe, *ibid.*, **100**, 100 (1950).

(6) G. D. P. Graham and M. A. Karrar, *J. Med. Chem.*, **6**, 103 (1963).

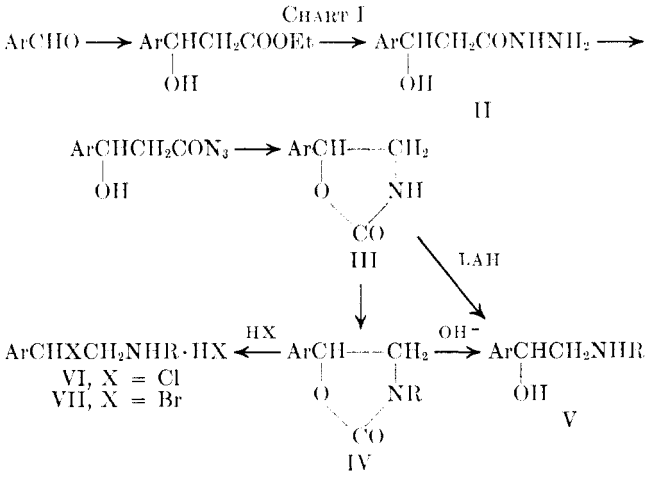
(7) *Cf.* A. Holzbauer and J. H. Gaddum, *Vitamins Hormones*, **15**, 151 (1957).

arylethyl chlorides and bromides, because of the well-known effect that fluorine substitution produces antimetabolites.[8]

Equally, we have prepared some analogs in which the aryl group was 2-thienyl, 3-thienyl, 2-furyl, and 1- and 2-naphthyl. Fluorine-substituted compounds of the phenethylamine series have been prepared before,[1a,9] among them also 1-(*p*-fluorophenyl)-2-methylaminoethanol. Some representatives of the β-thienyl-,[10a] β-furyl-,[10b] and β-naphthylethylamine[10c] series have been also described; 1-(2-naphthyl)-2-isopropylaminoethanol (propranolol) has found clinical application as a β-adrenergic receptor blocking agent.[11]

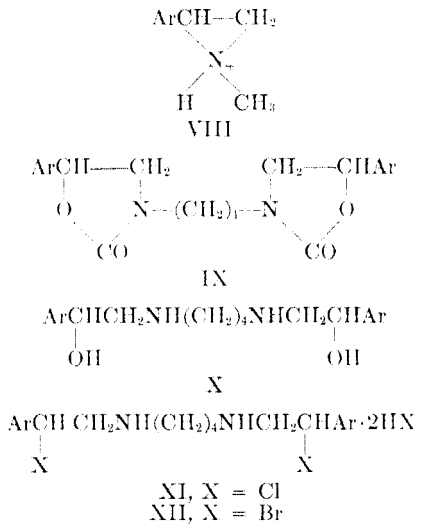
The method used in the synthesis of the desired compounds was one designed by Bergmann and Sulzbacher[12] which has since been employed for the preparation of labeled epinephrine.[13] This simple method (Chart I) involves the following steps: (1) Reformatzky con-

CHART I



densation of an aromatic aldehyde with ethyl bromoacetate, (2) transformation of the (crude) hydroxy ester obtained into the hydrazide II, (3) reaction of the hydrazide with sodium nitrite and Curtius rearrangement of the azide formed into 5-aryl-2-oxazolidone (III), (4) methylation (by successive treatment with NaH and MeI or Me_2SO_4) to a 5-aryl-3-methyl-2-oxazolidone (IV, R = CH_3). The latter is hydrolyzed by alkali to the 1-aryl-2-methylaminoethanol (V, R = CH_3) which is also obtained when oxazolidone III is reduced ($LiAlH_4$), the carbonyl group forming the methyl in the final product.[14] In addition to its simplicity, this method has the advantages that it can be used for the preparation of other monoalkyl derivatives, *e.g.*, by alkylation with isopropyl iodide or 1,4-dibromobutane, and that it permits the easy synthesis of 1-aryl-2-alkylaminoethyl chloride hydrochlorides (VI) or bromide hydrobromides (VII). They are obtained when the oxazolidone IV is treated with gaseous HCl or HBr in a suitable solvent. As examples of alkylation with radicals other than methyl, the preparation of 5-(2-naphthyl)-3-isopropyl-2-oxazolidone and of difunctional compounds of formula IX (*e.g.*, Ar = thienyl) may be cited, from which again substances such as X XII are accessible.[15]

Compounds of type VI and VII are stable in the form of their hydrohalides (with the exception of the thienyl derivatives which decompose very rapidly in the presence of even traces of moisture); in neutral or alkaline aqueous solution the side-chain halogen is eliminated probably *via* the cyclic intermediate VIII which is assumed to be the form in which these substances act on adrenergic receptors.[1]



Pharmacology.—A summary of the pharmacological testing is given in Table I. The tests in which some of the compounds in this series have shown activity are indicated. In addition, a notation is included showing which compounds were evaluated for these activities. None of the compounds described demonstrated marked activity. The activity was considered significant but quite weak. These compounds were not tested specifically for epinephrine antagonist activity. It is noted that compounds **1**, **4–10**, **13**, **15–18**, **22–24**, **26**, **27**, **34–37**, and **39** were screened for several other pharmacological activities such as hypotensive, hypoglycemic, antiinflammatory, antifertility, anorexic, diuretic, anticonvulsant, and antiparkinsonism activity. Since none of the compounds described in this report demonstrated activity in these areas, the details of the test models will not be described.

Experimental Section

Pharmacological Methods. Central Nervous System Activity.—All of the compounds in Table I were tested for general CNS activity in the mouse. The CNS testing includes determination of reflex depressant, behavioral depressant, muscular relaxation, motor stimulation, and antidepressant activities. The test compound treated animals were observed and compared to control animals employing a rigid scoring system. The mice were carefully observed for signs of behavioral depression or stimulation. Their reaction to auditory, painful, and tactile stimuli was also determined. Spontaneous motor activity was

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(9) (a) C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.*, **63**, 602 (1941); (b) G. Schiemann and W. Winkelmueller, *J. Prakt. Chem.*, [2] **135**, 101 (1932); (c) L. Fosdick, O. Fancher, and K. F. Urbach, *J. Am. Chem. Soc.*, **68**, 840 (1946); (d) N. B. Chapman, K. Clarke, R. M. Pinder, and S. N. Sawhney, *J. Chem. Soc., C*, 293 (1967).

(10) (a) C. F. Huebner, P. A. Diassi, and C. R. Scholz, *J. Org. Chem.*, **18**, 21 (1953); (b) S. Kanao, *J. Pharm. Soc. Japan*, **550**, 1019 (1927); *Chem. Abstr.*, **22**, 1588 (1928); (c) J. S. Stephenson, British Patent 909,357 (1962); *Chem. Abstr.*, **58**, 5597 (1963).

(11) S. E. Epstein and E. Braunwald, *New Engl. J. Med.*, **275**, 1106, 1175 (1966).

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(15) The unsubstituted oxazolidone has been used in this manner.[16]

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TABLE I
PHARMACOLOGICAL DATA

No.	Compd	Tests performed[a] CNS	Spinal depressant	Analgetic	Sm musc relax.	Local anesth	Antimicrobial	Significant act. obsd	MED[b]
1	III, Ar = C_6H_5	+[c]	+	+	+	+	+	Antidepressant	150
2	III, Ar = 3-FC_6H_4	+	+	+	−[d]	−	+	Analgetic	80
								Antidepressant	300
3	III, Ar = 3,4-$F_2C_6H_3$	+	+	+	−	−	+	Muscle relaxant	300
								Analgetic	150
4	III, Ar = 3,4-$Cl_2C_6H_3$	+	+	+	−	−	+	Antidepressant	300
								Analgetic	40
5	III, Ar = 1-$C_{10}H_7$	+	−	+	+	+	+	Antifungal[e]	12.5–25
6	III, Ar = 4-FC_6H_4	+	+	+	−	+	+	None	
7	III, Ar = 2-$C_{10}H_7$	+	−	+	+	−	+	None	
8	III, Ar = 2-thienyl	+	−	+	+	−	+	None	
9	III, Ar = 3-thienyl	+	−	+	+	−	+	None	
10	III, Ar = 2-furyl	+	−	+	+	+	+	None	
11	IV, Ar = C_6H_5, R = CH_3	+	+	+	−	−	+	Analgetic	150
12	IV, Ar = 3-FC_6H_4, R = CH_3	+	+	+	−	−	+	Analgetic	40
13	IV, Ar = 4-FC_6H_4, R = CH_3	+	+	+	+	+	+	Analgetic 150 Spinal depressant 150	May not represent analgetic activity in view of spinal depressant activity.
14	IV, Ar = 3,4-$F_2C_6H_3$, R = CH_3	+	+	+	−	−	+	Analgetic	80
15	IV, Ar = 3,4-$Cl_2C_6H_3$, R = CH_3	+	+	+	+	+	+	None	
16	IV, Ar = 1-$C_{10}H_7$, R = CH_3	+	+	+	+	−	+	Antifungal[e]	50
17	IV, Ar = 2-$C_{10}H_7$, R = CH_3	+	−	+	+	+	+	None	
18	IV, Ar = 2-$C_{10}H_7$, R = $CH(CH_3)_2$	+	−	+	+	+	+	Antifungal[e]	50
19	V, Ar = 3-FC_6H_5, R = CH_3	+	−	−	−	−	−	CNS stimulant	300
20	V, Ar = 3,4-$F_2C_6H_3$, R = CH_3	+	+	+	−	−	+	CNS stimulant	300
21	V, Ar = 3,4-$Cl_2C_6H_3$, R = CH_3	+	−	−	−	−	−	CNS stimulant	300
22	V, Ar = 2-$C_{10}H_7$, R = CH_3	+	−	+	+	+	+	Intestinal smooth muscle relaxant	10
23	V, Ar = 2-$C_{10}H_7$, R = $CH(CH_3)_2$	+	−	+	+	+	+	Intestinal smooth muscle relaxant Local anesthetic	10 0.5
24	V, Ar = 4-FC_6H_4, R = CH_3	+	+	+	+	+	+	None	
25	V, Ar − 3-thienyl, R = CH_3	+	+	+	−	−	+	None	
26	V, Ar = 2-thienyl, R = $CH(CH_3)_2$	+	+	+	+	−	−	None	
27	V, Ar = 2-furyl, R = CH_3	+	+	+	+	+	+	None	
28	VI, Ar = 3,4-$Cl_2C_6H_3$, R = CH_3	+	−	−	−	−	+	CNS stimulant	200–300
29	VI, Ar = 2-$C_{10}H_7$, R = $CH(CH_3)_2$	+	−	+	−	−	+	Muscle relaxant	300
30	VI, Ar = C_6H_5, R = CH_3	+	+	+	−	+	+	None	
31	VI, Ar = 3-FC_6H_4, R = CH_3	+	−	−	−	−	+	None	
32	VI, Ar = 3,4-$F_2C_6H_3$, R = CH_3	+	+	+	−	+	+	None	
33	VII, Ar = 3,4-$F_2C_6H_3$, R = CH_3	+	+	+	−	+	+	None	
34	VII, Ar = 1-$C_{10}H_7$, R = CH_3	+	+	+	+	−	+	Intestinal smooth muscle relaxant	10
35	VII, Ar = C_6H_5, R = CH_3	+	+	+	+	+	+	None	
36	VII, Ar = 3-FC_6H_4, R = CH_3	+	+	+	−	+	+	None	
37	VII, Ar = 4-FC_6H_4, R = CH_3	+	+	+	+	+	+	None	
38	VII, Ar = 3,4-$Cl_2C_6H_3$, R = CH_3	+	−	−	−	−	+	None	
39	VII, Ar = 2-$C_{10}H_7$, R = CH_3	+	−	+	+	−	+	None	

[a] In addition to the testing described, compounds **1**, **4–10**, **13**, **15–18**, **22–24**, **26**, **27**, **34–37**, and **39** were screened for several other general pharmacological activities. Since no activity was found, these tests will not be described. [b] Minimal effective dose for CNS, spinal depressant, and analgetic activity (mg/kg *po*), local anesthetic activity (%), and smooth muscle relaxation (μg/ml); minimal inhibitory concentration for microbiological activity (μg/ml). [c] Test performed. [d] Not tested for activity indicated. [e] *Microsporum canis*.

compared to that of control animals. The animals were observed for the presence or absence of the righting, pinna, and corneal reflexes. The status of muscle tone was determined by evaluation of the abdominal and limb tone. In addition, grip strength was checked by placing the mice on a vertical pole. Inability to climb the pole or to maintain themselves on the pole indicated a reduction of the parameter.

Testing for antidepressant activity was performed in mice by intravenous injection of reserpine (5 mg/kg) 3 hr after the oral administration of test compound. Reserpine normally induces ptosis and decreased motor activity in these animals. A "reserpine reversal" as indicated by one or more of the observations given below suggests antidepressant activity: (a) increased motor activity, (b) profuse salivation, (c) reversal of reserpine ptosis.

Spinal depressant activity was evaluated in mice according to the method of Bastian and Ridlon.[17] An increase of at least 30% over control in the latency between decapitation and onset of clonic convulsions was considered significant.

Smooth Muscle Relaxant Activity.—Test compounds were evaluated for intestinal smooth muscle relaxant activity employing guinea pig ileum strips *in vitro* according to the method of Magnus.[18] As another part of this test, the compounds were evaluated for antihistaminic and anticholinergic activity. In addition, the compounds also were evaluated for uterine smooth muscle relaxant activity employing isolated rat uterus.

Analgetic activity was determined employing a modification

(17) J. W. Bastian and S. A. Ridlon, *Fed. Proc.*, **17**, 1367 (1958).
(18) R. Magnus, *Arch. Ges. Physiol.*, **102**, 123 (1904).

of the phenylquinone method of Sigmund, Cadmus, and Lu.[19] The total number of writhes for a group of test compound phenylquinone-treated mice was compared to that of a group receiving only phenylquinone. Evaluation was 60 min after test compound administration. A reduction of 30% in the number of writhes was considered significant.

Anorexic acitivty was evaluated in mice which were trained to consume their daily food intake over an 8-hr period. The amount of food intake for a group of mice treated with a test compound was determined and compared to that of a nontreated control group. A reduction of 30% in the test group was considered significant.

Local anesthetic activity was evaluated by instilling a solution of the test compound into a rabbit eye and determining the presence or absence of the corneal reflex. Absence of the corneal reflex is taken as an indication of local anesthetic activity. The lowest concentration (per cent) preventing the corneal reflex is taken as the minimal effective dose for local anesthetic activity.

Microbiological Testing.—Test compounds were evaluated for antimicrobial activity employing a series of gram-negative and gram-positive organisms. In addition, these compounds are also tested for antitrichomonal and antifungal activity. All of these tests were performed *in vitro*.

Chemistry.—Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements are within 0.4% of the theoretical values.

3- and 4-fluorobenzaldehydes were prepared according to the literature method;[20] 3,4-difluorobenzaldehyde was prepared analogously from 3,4-difluorotoluene,[21] bp 82–84° (30 mm), yield 70%; 2,4-dinitrophenylhydrazone, mp 288° (from DMF–MeOH) [*Anal.* ($C_{13}H_8F_2N_4O_4$) C, H, F]; semicarbazone, mp 222° (from EtOH) [*Anal.* ($C_8H_7F_2N_3O$) C, H, F]. Also prepared according to the literature method were 2-thenaldehyde,[22] 3-thenaldehyde,[23] and 1- and 2-naphthaldehydes.[24]

General Procedures.—Ethyl β-arylhydracrylates[25] and β-arylhydracrylyl hydrazides (II) were prepared essentially by the method of Bergmann and Sulzbacher.[12] The former were used in their crude form for the preparation of the hydrazides, which are described in Table II.

TABLE II

β-ARYLHYDRACRYLYL HYDRAZIDES (II)

Aryl	Mp, °C	Yield, %[a]	Recrystn solvent	Formula	Analyses
p-FC_6H_4	180	57	Ethanol	$C_9H_{11}FN_2O_2$	C, H, F
m-FC_6H_4	183	50	Ethanol	$C_9H_{11}FN_2O_2$	C, H, F
3,4-$F_2C_6H_3$	167	65	Ethanol	$C_9H_{10}F_2N_2O_2$	C, H, F
3,4-$Cl_2C_6H_3$	186	70	Ethanol	$C_9H_{10}Cl_2N_2O_2$	C, H, Cl
1-Naphthyl	202	76	Cellosolve	$C_{13}H_{14}N_2O_2$	C, H
2-Naphthyl	207	64	Cellosolve	$C_{13}H_{14}N_2O_2$	C, H
2-Thienyl	138	54	Dimethoxyethane	$C_7H_{10}N_2O_2S$	C, H
3-Thienyl	146	70	Dimethoxyethane	$C_7H_{10}N_2O_2S$	C, H
2-Furyl	141	50	Dimethoxyethane	$C_7H_{10}N_2O_3$	C, H

[a] Calculated on the aldehyde.

5-Aryl-2-oxazolidones (III).—With stirring and a temperature not exceeding 15°, 2.1 g (0.03 mole) of $NaNO_2$ in 10 ml of H_2O was added to a mixture of 0.03 mole of the hydrazide and 40 ml of 0.1 *N* HCl (AcOH was used in the case of the thienyl and furyl derivatives). Stirring was continued for another 15 min and the suspension was extracted with three 50-ml portions of C_6H_6. This solution was dried quickly ($MgSO_4$) and heated to 50–60° when an exothermic reaction set in with vigorous evolution of N_2. After the reaction had subsided, the mixture was refluxed for 15 min and concentrated to 20 ml, whereupon the oxazolidone crystallized (sometimes hexane was added to complete the crystallization). The products were recrystallized from C_6H_6–hexane (Table III).

5-Aryl-3-alkyl-2-oxazolidones (IV).—A solution of 0.01 mole of the oxazolidone (III) in 20 ml of dry DMF was added to a well-stirred suspension of 0.3 g of hexane-washed NaH in the same solvent (50 ml). The mixture was stirred until H_2 evolution had ceased, treated with 0.015 mole of the alkyl iodide in 10 ml of DMF, stirred 1 hr, and gently refluxed for another 1 hr. It was then concentrated *in vacuo*, and the residue was dissolved in C_6H_6 (100 ml), washed (H_2O), and dried. The crude product which remained after removing the solvent was purified either by vacuum distillation or by recrystallization from C_6H_6–hexane (Table IV).

TABLE III

5-ARYL-2-OXAZOLIDONES (III)

Aryl	Mp, °C	Yield, %	Formula	Analyses
p-FC_6H_4	110	55	$C_9H_8FNO_2$	C, H, N
m-FC_6H_4	72	55	$C_9H_8FNO_2$	C, H, F, N
3,4-$F_2C_6H_3$	92–93	50	$C_9H_7F_2NO_2$	C, H, F
3,4-$Cl_2C_6H_3$	108–109	71	$C_9H_7Cl_2NO_2$	C, H, N
1-Naphthyl	147	70	$C_{13}H_{11}NO_2$	C, H, N
2-Naphthyl	173	62	$C_{13}H_{11}NO_2$	C, H, N
2-Thienyl	94–95	69	$C_7H_7NO_2S$	C, H, N
3-Thienyl	109–110	51	$C_7H_7NO_2S$	C, H, N
2-Furyl	90	75	$C_7H_7NO_3$	C, H, N

TABLE IV

Aryl	Alkyl	Mp or bp (mm), °C	Yield, %	Formula	Analyses
5-Aryl-3-alkyl-2-oxazolidones (IV)					
p-FC_6H_4	CH_3	58	70	$C_{10}H_{10}FNO_2$	C, H, F, N
m-FC_6H_4	CH_3	43	70	$C_{10}H_{10}FNO_2$	C, H, N
3,4-$F_2C_6H_3$	CH_3	70	82	$C_{10}H_9F_2NO_2$	C, H, F
3,4-$Cl_2C_6H_3$	CH_3	96–97	80	$C_{10}H_9Cl_2NO_2$	C, H, Cl
C_6H_5[a]	CH_3	53	70	$C_{10}H_{11}NO_2$	C, H, N
1-Naphthyl	CH_3	82	54	$C_{14}H_{13}NO_2$	C, H, N
2-Naphthyl	CH_3	112	62	$C_{14}H_{13}NO_2$	C, H, N
2-Naphthyl	$CH(CH_3)_2$	77	70	$C_{16}H_{17}NO_2$	C, H, N
2-Thienyl	CH_3	146–147 (0.5)	73	$C_8H_9NO_2S$	C, H, N
2-Thienyl	$CH(CH_3)_2$	160–162 (0.8)	63	$C_{10}H_{13}NO_2S$	C, H, N
3-Thienyl	CH_3	147–149 (0.2)	60	$C_8H_9NO_2S$	C, H, S
3-Thienyl	$CH(CH_3)_2$	150–152 (0.5)	50	$C_{10}H_{13}NO_2S$	C, H, S
3,3′-Tetramethylenebis(5-aryl-2-oxazolidones) (IX)					
2-Thienyl		144	51	$C_{18}H_{20}N_2O_4S_2$	C, H, N
3-Thienyl		118–120	56	$C_{18}H_{20}N_2O_4S_2$	C, H, N

[a] 5-Phenyl-2-oxazolidione has been described by M. S. Newman and A. Kutner, *J. Am. Chem. Soc.*, **73**, 4199 (1951).

The analogous procedure was carried out for the preparation of the **3,3′-tetramethylenebis(5-thienyl-2-oxazolidones) (IX)** using 0.005 mole of 1,4-dibromobutane.

1-Aryl-2-alkylaminoethanols (V).—A mixture of 0.5 g of the foregoing compound, 15 ml of 10% NaOH, and 5 ml of EtOH was refluxed 4 hr, cooled, and extracted with $CHCl_3$ (sometimes the product crystallized out directly). The solution was dried, the solvent evaporated, and the residue, after it had solidified, recrystallized from hexane (Table V). For the preparation of the **hydrochlorides,** the bases were dissolved in Et_2O, containing a little EtOH, and treated wih HCl gas. They could be recrystallized from *i*-PrOH by addition of Et_2O. The **benzoates** were prepared by mixing an ethereal solution of the bases with a solution of benzoic acid in Et_2O. They crystallized out immediately.

1-Aryl-2-methylaminoethanols (V, R = CH_3) (Reduction with $LiAlH_4$).—A solution of 0.01 mole of the oxazolidone III in 50 ml of C_6H_6 was slowly added to a stirred slurry of 1 g of LAH in 50 ml of Et_2O. The mixture was refluxed for 6 hr, cooled, and carefully decomposed with H_2O (*ca.* 5 ml). Then 5 g of $MgSO_4$ was added and the gelatinous mass was stirred for 10 min, filtered, washed several times with Et_2O, and concentrated *in vacuo*. The residue was recrystallized from hexane.

1-Aryl-2-alkylaminoethyl Chloride Hydrochlorides (VI). (a) Aryl ≠ Thienyl.—HCl gas was passed into a solution of 0.5 g of a 5-aryl-3-alkyl-2-oxazolidone (IV) in EtOH. The solution was refluxed for 3 hr and evaporated *in vacuo* to dryness and the residue was recrystallized from *i*-PrOH by addition of Et_2O (Table VI).

(b) Aryl = Thienyl.—A solution of 0.5 g of 5-thienyl-3-alkyl-2-oxazolidone in 25 ml of Et_2O was added to 50 ml of ether, saturated with HCl gas. After 24 hr the product, which crystal-

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(23) E. Campaigne, R. C. Bourgeois, and W. C. McCarthy, ref 22, p 918.

(24) S. J. Angyal, J. R. Tetaz, and J. G. Wilson, ref 22, p 690.

(25) Ethyl β-(2- and 3-thienyl)hydracrylates have been described by R. D. Schuetz and W. H. Houff, *J. Am. Chem. Soc.*, **77**, 1835 (1955).

TABLE V

Aryl	Alkyl	Mp, °C	Yield, %	Formula	Analyses	Salt	Mp, °C	Analyses
1-Aryl-2-alkylaminoethanols (V)								
p-FC_6H_4	CH_3	83	87	$C_9H_{12}FNO$	C, H, F, N	HCl	136–137[a]	Cl
m-FC_6H_4	CH_3	80	80	$C_9H_{12}FNO$	C, H, F, N			
3,4-$F_2C_6H_3$	CH_3	54	80	$C_9H_{11}F_2NO$	C, H, F, N	HCl	139[b]	F
3,4-$Cl_2C_6H_3$	CH_3	94–95	95	$C_9H_{11}Cl_2NO$	C, H, N	HCl	187	Cl
2-Naphthyl	CH_3	109	68	$C_{13}H_{15}NO$	C, H, N			
2-Naphthyl[c]	$CH(CH_3)_2$	106	67	$C_{15}H_{19}NO$	C, H, N			
2-Thienyl	CH_3	54–55	50	$C_7H_{11}NOS$	C, H, N	$C_6H_5CO_2H$	115	C, H
2-Thienyl	$CH(CH_3)_2$	58–59	64	$C_9H_{15}NOS$	C, H, N	$C_6H_5CO_2H$	114	C, H
3-Thienyl	CH_3	64	84	$C_7H_{11}NOS$	C, H, N	$C_6H_5CO_2H$	110	C, H
2-Furyl[d]	CH_3	122	70	$C_{14}H_{17}NO_2$	C, H, N			
N,N′-Tetramethylenebis(1-aryl-2-aminoethanols) (X)[e]								
2-Thienyl		173	67	$C_{16}H_{14}N_2O_2S_2$	C, H, N			
3-Thienyl		154	70	$C_{16}H_{24}N_2O_2S_2$	C, H			

[a] Lit.[9c] mp 118–121°. [b] Compound described by L. Villa and E. Grana, *Farmaco* (Pavia), *Sci. Ed.*, **18**, 871 (1963); *Chem. Abstr.*, **60**, 5370 (1964). [c] Hydrochloride was described in ref 10c. [d] Characterized as the benzoate. [e] Recrystallized from EtOH.

TABLE VI

Aryl	Alkyl	Mp, °C dec	Yield, %	Formula	Analyses
1-Aryl-2-alkylaminoethyl Chloride Hydrochlorides (VI)					
p-FC_6H_4	CH_3	164	87	$C_9H_{12}Cl_2FN$	C, H, F
m-FC_6H_4	CH_3	166	87	$C_9H_{12}Cl_2FN$	C, H, Cl, F
3,4-$F_2C_6H_3$	CH_3	164–165	70	$C_9H_{11}Cl_2F_2N$	Cl, N
3,4-$Cl_2C_6H_3$	CH_3	186–188	80	$C_9H_{11}Cl_4N$	C, H, N
Phenyl[a]	CH_3	164	69	$C_9H_{13}Cl_2N$	C, H
2-Naphthyl	$CH(CH_3)_2$	182	75	$C_{15}H_{19}Cl_2N$	C, H, N
2-Thienyl	CH_3	106	80	$C_7H_{11}Cl_2NS$	C, H, N
3-Thienyl	CH_3	139	55	$C_7H_{11}Cl_2NS$	C, H, Cl
3-Thienyl	$CH(CH_3)_2$	152	36	$C_9H_{15}Cl_2NS$	C, H, Cl
N,N′-Tetramethylenebis(1-aryl-2-aminoethyl Chloride) Hydrochlorides (XI)					
2-Thienyl		146	83	$C_{16}H_{24}Cl_4N_2S_2$	C, H, Cl

[a] Compound described (mp 177°) by H. Bretschneider, *Oesterr. Akad. Wiss. Math-Naturw. Kl. Sitzber. Ab. IIb*, **159**, 372 (1950); *Chem. Abstr.*, **47**, 6860 (1953).

lized out, was filtered and washed thoroughly with Et_2O. It is very sensitive to moisture and decomposes slowly, even if kept in a desiccator, with evolution of HCl.

Analogous treatment of 5-aryl-3-alkyl-2-oxazolidones (IV) with ethereal HBr gave a precipitate of **1-aryl-2-alkylaminoethyl bromide hydrobromides (VII)** (Table VII).

TABLE VII

Aryl	Alkyl	Mp, °C dec	Yield, %	Formula	Analyses
1-Aryl-2-alkylaminoethyl Bromide Hydrobromides (VII)					
p-FC_6H_4	CH_3	159–160	70	$C_9H_{12}Br_2FN$	C, H, Br, F
m-FC_6H_4	CH_3	167	70	$C_9H_{12}Br_2FN$	C, H, Br
3,4-$F_2C_6H_3$	CH_3	167–168	70	$C_9H_{11}Br_2F_2N$	C, H, F
3,4-$Cl_2C_6H_3$	CH_3	173–175	70	$C_9H_{11}Br_2Cl_2N$	C, H
C_6H_5[a]	CH_3	153	70	$C_9H_{13}Br_2N$	C, H, Br
1-Naphthyl	CH_3	163	90	$C_{13}H_{15}Br_2N$	C, H, N
2-Naphthyl	CH_3	160	66	$C_{13}H_{15}Br_2N$	C, H, N
2-Thienyl	CH_3	87	83	$C_7H_{11}Br_2NS$	C, H, Br, N
2-Thienyl	$CH(CH_3)_2$	107	82	$C_9H_{15}Br_2NS$	C, H, N
3-Thienyl	CH_3	126–127	80	$C_7H_{11}Br_2NS$	C, H
3-Thienyl	$CH(CH_3)_2$	140	90	$C_9H_{15}Br_2NS$	C, H, Br
N,N′-Tetramethylenebis(1-aryl-2-aminoethyl Bromide) Hydrobromides (XII)					
2-Thienyl		104	60	$C_{16}H_{24}Br_4N_2S_2$	C, H, N
3-Thienyl		136	80	$C_{16}H_{24}Br_4N_2S_2$	C, H, N

[a] Lit.[3] mp 142–143°.

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