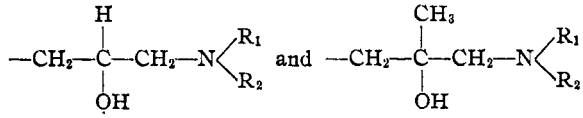
effected from ethanol-ether. The products form yellow or orange colored crystals.

Samples for analysis were dried at 100–120° *in vacuo* for one hour. Some of the compounds contained a molecule of water of crystallization which was lost with difficulty.

## Summary

Forty-four new disubstituted amino derivatives of 8-aminoquinolines have been prepared. These cover compounds having the groupings



in the side chain.

INDIANAPOLIS, INDIANA RECEIVED JUNE 14, 1944

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

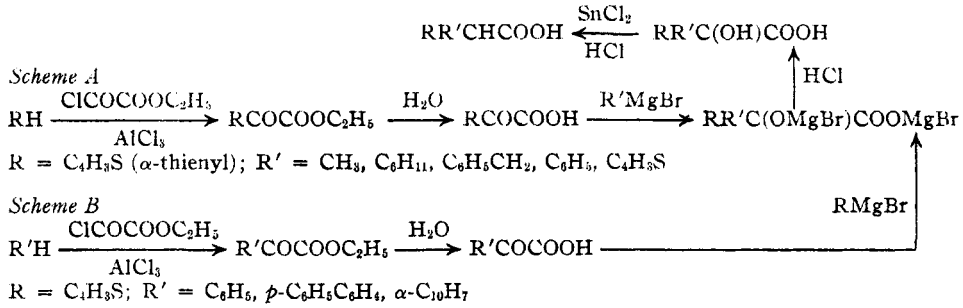
# Antispasmodics. VII[1]

BY F. F. BLICKE AND M. U. TSAO[2a,b]

The pharmacological equivalence of certain compounds which contain a benzene ring and corresponding α-thienyl derivatives has been demonstrated, at least in a qualitative sense, in a number of instances,[3] however, the literature contains little information with regard to quantitative comparisons or to the possible clinical merits of thiophene derivatives.

Basic-alkyl esters of diphenyl-, cyclohexylphenyl-, benzylphenyl-, α-naphthylphenyl- and *p*-xenylphenylacetic acid have been shown to be active antispasmodics.[4] During this investigation we have synthesized α-thienyl analogs of these types of esters, that is, basic-alkyl esters of di-α-thienyl-, phenyl-α-thienyl-, benzyl-α-thienyl-, α-naphthyl-α-thienyl- and *p*-xenyl-α-thienylacetic acid. We obtained the disubstituted acetic acids from the corresponding disubstituted hydroxyacetic acids, and in some instances the latter also were converted into basic-alkyl esters, and examined pharmacologically; esters of the following disubstituted hydroxyacetic acids were obtained: methyl-α-thienyl-, cyclohexyl-α-thienyl-, phenyl-α-thienyl-, α-naphthyl-α-thienyl- and *p*-xenyl-α-thienylhydroxyacetic acid. The basic-alkyl groups in the esters were represented by such radicals as β-diethylaminoethyl, β-morpholinoethyl, β-piperidinoethyl, γ-diethylaminopropyl and γ-dibutylaminopropyl. The esters were tested pharmacologically in the form of their water-soluble hydrochlorides, hydrobromides or methobromides.

The antispasmodic activity of our esters was determined by Dr. A. M. Lands and Miss V. L. Nash in the Frederick Stearns and Company Laboratories.[5] In general, the spasmolytic activity of the esters of hydroxyacetic acids on the isolated intestinal strip which had been stimulated with acetylcholine was found to be much greater than that of the esters of acetic acids. The remarkable effectiveness of some of these esters, especially those which contain a cyclohexyl group, is shown in Table V. Several of the esters are equal to, or exceed, atropine in activity, a potency seldom found hitherto in synthetic antispasmodics.




The required disubstituted hydroxyacetic and disubstituted acetic acids were prepared in the manner indicated above.

The acetic acids were converted into the basic-

(1) Presented before the Division of Medicinal Chemistry at the 108th Meeting of the American Chemical Society in New York, N. Y., Sept. 11–15, 1944.

(2) (a) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by M. U. Tsao in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan. (b) Frederick Stearns and Company Fellow.

(3) Finzi, *Gazz. chim. ital.*, **45**, 11, 280 (1915); Steinkopf and Wolfram, *Ann.*, **437**, 22 (1924); Erlenmeyer, Berger and Leo, *Helv. Chim. Acta*, **16**, 733 (1933); Blicke and Zienty, THIS JOURNAL, **63**, 2945 (1941); Rhodehamel and Degering, *J. Am. Pharm. Assoc.*, **31**, 281 (1942); Blicke and Burckhalter, THIS JOURNAL, **64**, 477 (1942); Warren, Marsh, Thompson, Shelton and Becker, *J. Pharmacol. Exptl. Therap.*, **79**, 187 (1943); and Dann, *Ber.*, **76**, 419 (1943).

(4) For a discussion of these compounds see Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

(5) See Lands and Nash, *Proc. Soc. Exptl. Biol. Med.*, (in press) 1944.

TABLE I

SUBSTITUTED α-THIENYLHYDROXYACETIC ACIDS, α-$C_4H_3S$—CR(OH)COOH

Compounds 1, 2 and 4 were recrystallized from benzene; 3, 5 and 6 from dilute acetic acid; 7 was not recrystallized.

| | R | M. p., °C. | Formula | Sulfur, % Calcd. | Sulfur, % Found | Color with conc. $H_2SO_4$ |
|---|---|---|---|---|---|---|
| 1 | $CH_3$ | 111–113 | $C_7H_8O_3S$ | 18.62 | 18.34 | Red |
| 2 | $C_6H_{11}$, cyclohexyl | 125–126 | $C_{12}H_{16}O_3S$ | 13.34 | 13.30 | Scarlet |
| 3 | $C_6H_5CH_2$ | 140–142 | $C_{13}H_{12}O_3S$ | 12.87 | 12.97 | Scarlet |
| 4 | $C_6H_5$ | 123 dec. | $C_{12}H_{10}O_3S$ | 13.68 | 13.56 | Red |
| 5 | $p$-$C_6H_5C_6H_4$ | 129–130 | $C_{18}H_{14}O_3S$ | 10.33 | 10.28 | Blue |
| 6 | α-$C_{10}H_7$ | 101–102 dec. | $C_{16}H_{12}O_3S$ | 11.27 | 11.33 | Purple |
| 7 | α-$C_4H_3S$ | 93 dec. | $C_{10}H_8O_3S_2$ | 26.68 | 26.72 | Purple |

alkyl ester hydrohalides when they were heated with a basic-alkyl halide in isopropyl alcohol.[6]

## Experimental Part

**Ethyl α-Thienylglyoxylate.**[7]—A mixture of 84 g. (1 mole) of thiophene, 137 g. (1 mole) of ethyl oxalyl chloride[8] and 1500 cc. of tetrachloroethane was poured into a 3-liter, 3-necked flask fitted with a stirrer and a thermometer. The mixture was cooled to −5–0°, stirred vigorously, and 147 g. (1.1 moles) of aluminum chloride added, portionwise, during a period of forty-five minutes. The material was stirred for three hours at room temperature, and after eight hours was treated with ice and hydrochloric acid. The organic layer was separated, shaken successively with 1:1 hydrochloric acid, five portions of water, dilute sodium carbonate solution and finally with water. The solution was dried with fused sodium sulfate, the solvent removed and the residue fractionated; b. p. 115–120° (3 mm.)[9]; yield 93 g. (50%).

**α-Thienylglyoxylic Acid.**—A mixture of 40 g. of ethyl α-thienylglyoxalate, 75 cc. of alcohol, 58 g. of sodium carbonate monohydrate and 450 cc. of water was refluxed for twelve hours, the solution boiled with Norite, filtered and the water and alcohol removed under reduced pressure. The residue was kept cold while it was acidified with 1:1 hydrochloric acid; it was then extracted with ether, the extract shaken with water, the ether removed and the acid recrystallized from benzene; yield 24 g. (70%); m. p. 89–91°.[10]

**Methyl-α-thienylhydroxyacetic Acid.**—Methylmagnesium iodide was prepared from 85.2 g. (0.60 mole) of methyl iodide, 14.4 g. (0.60 mole) of magnesium and 300 cc. of ether in a 500-cc. flask into which a siphon, with a stopcock attached to the lower end, had been inserted. The solution of the Grignard reagent was added, dropwise, to 31.2 g. (0.20 mole) of α-thienylglyoxylic acid dissolved in 300 cc. of ether. The latter had been placed in a 3-necked, 1000-cc. flask fitted with a stirrer and reflux condenser, and was cooled with an ice–salt mixture and stirred during the addition of the methylmagnesium iodide. A vigorous reaction took place, and a precipitate formed immediately. After complete addition the bath was removed, the mixture stirred for one hour at room temperature, refluxed for two hours, cooled, and the ether layer decanted and discarded. The colorless, granular precipitate was washed with ether, treated with dilute sulfuric acid, and extracted several times with ether. The product was then extracted from the ether extract with 100 cc. of 20% sodium carbonate solution. The alkaline solution was shaken with Norite, filtered, the filtrate acidified with dilute sulfuric acid, and the precipitated product extracted thoroughly with ether. After removal of the solvent the acid obtained weighed 30 g. (86%); m. p. 111–113° after recrystallization from benzene.

**Cyclohexyl-, Benzyl-, Phenyl-, p-Xenyl- and α-Naphthyl-α-thienylhydroxyacetic Acid.**—These compounds were prepared by the same general procedure described above except that an arylmagnesium bromide was employed. Usually the precipitate, formed by interaction of the solution of the Grignard reagent with the glyoxylic acid, was a granular material but this became gummy upon the addition of the last fourth of the solution. However, the gummy product became hard after exposure to air and could be pulverized and washed with ether.

Phenyl-α-thienylhydroxyacetic acid was obtained also by a second procedure. α-Thienylmagnesium bromide was prepared from 196 g. (1.2 moles) of α-thienyl bromide,[11] 29.2 g. (1.2 moles) of magnesium and 500 cc. of ether. It was added to 60 g. (0.4 mole) of phenylglyoxylic acid (benzoylformic acid)[12] dissolved in 400 cc. of ether. The gummy precipitate was treated in the manner described above. The thienylphenylhydroxyacetic acid synthesized by this procedure, as well as that obtained by the interaction of phenylmagnesium bromide with α-thienylglyoxylic acid, melted at 123° (dec.) after recrystallization from benzene; yield 64 g.

**Di-α-thienylhydroxyacetic Acid.**—A solution of α-thienylmagnesium bromide, prepared from 98 g. (0.6 mole) of α-thienyl bromide, 14.4 g. of magnesium and 300 cc. of ether, was allowed to react with 31.2 g. (0.2 mole) of α-thienylglyoxylic acid, dissolved in 300 cc. of ether, in the manner already described. The initial, yellow precipitate was transformed into a brown, gummy mass. After decantation of the ether layer and trituration of the material with anhydrous ether, it turned into a light brown powder. The latter was stirred with saturated ammonium chloride solution, whereupon considerable heat was evolved, and then filtered; yield 50.5 g. This brown material (A) was found to be water-soluble. Thirty-nine grams of the latter was triturated with three different portions of acetone, and then was ground in a mortar

TABLE II

SUBSTITUTED α-THIENYLACETIC ACIDS. α-$C_4H_3S$—CRHCOOH

All of these acids were recrystallized from dilute acetic acid.

| R | M. p., °C. | Formula | Sulfur, % Calcd. | Sulfur, % Found |
|---|---|---|---|---|
| $C_6H_{11}$[a] | 129–132 | $C_{12}H_{16}O_2S$ | 14.29 | 14.20 |
| $C_6H_5CH_2$ | 76–78 | $C_{13}H_{12}O_2S$ | 13.75 | 13.47 |
| $C_6H_5$ | 115–116 | $C_{12}H_{10}O_2S$ | 14.69 | 14.41 |
| $p$-$C_6H_5C_6H_4$ | 137–139 | $C_{18}H_{14}O_2S$ | 10.89 | 10.89 |
| α-$C_{10}H_7$ | 133–135 | $C_{16}H_{12}O_2S$ | 11.95 | 11.84 |
| α-$C_4H_3S$ | 91–94 | $C_{10}H_8O_2S_2$ | 28.59 | 28.36 |

[a] Cyclohexyl.

(6) Horenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

(7) Our procedure is a modification of that published by Steinkopf and Wolfram (*Ann.*, **437**, 22 (1924)).

(8) "Organisch-chemische Experimentier Kunst," Conrad Weygand, J. A. Barth, Leipzig, 1938, p. 231; Kindler, Metzendorf and Dschi-yin-Kwok, *Ber.*, **76**, 308 (1943).

(9) The reported boiling points are 263° and 138–140° (13 mm.) (ref. 7) and 264–265° (Bradley, *Ber.*, **19**, 2119 (1886)).

(10) Steinkopf and Wolfram (ref. 7), who obtained a small amount of the acid as a by-product, found the melting point to be 92°.

(11) Blicke and Burckhalter, THIS JOURNAL, **64**, 479 (1942).

(12) "Organic Syntheses," Coll. Vol. I, 1941, p. 244.

TABLE III

HYDROCHLORIDES AND METHOBROMIDES OF BASIC-ALKYL ESTERS OF SUBSTITUTED α-THIENYLHYDROXYACETIC ACIDS, $(C_4H_3S)CR(OH)COOR'\cdot HCl$ OR $CH_3Br$

Compounds 1, 2, 3, 5, 6 and 11 were recrystallized from absolute alcohol. All of the others were recrystallized from a mixture of absolute alcohol and dry ether.

| | R′ | R | M. p., °C. | Formula | Halogen, % Calcd. | Found |
|---|---|---|---|---|---|---|
| 1 | $CH_2CH_2N(C_2H_5)_2$ | $CH_3$ | 119–121 | $C_{13}H_{22}O_3SNCl$ | 11.52 | 11.64 |
| 2 | $CH_2CH_2N(C_2H_5)_2$ | $C_6H_{11}$ | Above 200 | $C_{18}H_{30}O_3SNCl$ | 9.43 | 9.56 |
| 3 | $CH_2CH_2NC_5H_{10}$ | $C_6H_{11}$ | 186–188 dec. | $C_{19}H_{30}O_3SNCl$ | 9.16 | 9.32 |
| 4 | $CH_2CH_2CH_2N(C_2H_5)_2$ | $C_6H_{11}$ | 152–154 | $C_{19}H_{32}O_3SNCl$ | 9.09 | 9.10 |
| 5 | $CH_2CH_2N(C_2H_5)_2$ | $C_6H_5$ | 181–182 | $C_{18}H_{24}O_3SNCl$ | 9.59 | 9.78 |
| 6 | $CH_2CH_2NC_5H_{10}$[a] | $C_6H_5$ | 177–178 dec. | $C_{19}H_{24}O_3SNCl$ | 9.28 | 9.29 |
| 7 | $CH_2CH\ CH_2N(C_2H_5)_2$ | $C_6H_5$ | 142–143 | $C_{19}H_{26}O_3SNCl$ | 9.24 | 9.35 |
| 8 | $CH_2CH_2CH_2N(C_4H_9)_2$[b] | $C_6H_5$ | 152–154 | $C_{24}H_{36}O_3SNBr$ | 16.03 | 16.31 |
| 9 | $CH_2CH_2N(C_2H_5)_2$ | α-$C_{10}H_7$ | 203 dec. | $C_{22}H_{26}O_3SNCl$ | 8.44 | 8.35 |
| 10 | $CH_2CH_2NC_5H_{10}$ | α-$C_{10}H_7$ | 127–129 dec. | $C_{23}H_{26}O_3SNCl$ | 8.21 | 8.20 |
| 11 | $CH_2CH_2N(C_2H_5)_2$ | p-$C_6H_5C_6H_4$ | 178–180 dec. | $C_{24}H_{28}O_3SNCl$ | 7.95 | 7.85 |
| 12 | $CH_2CH_2NC_5H_{10}$ | p-$C_6H_5C_6H_4$ | 189–191 dec. | $C_{25}H_{28}O_3SNCl$ | 7.74 | 7.70 |
| 13 | $CH_2CH_2NC_4H_8O$[c] | p-$C_6H_5C_6H_4$ | 225 dec. | $C_{24}H_{26}O_4SNCl$ | 7.69 | 7.93 |

[a] $NC_5H_{10}$ = Piperidino. [b] Methobromide. [c] $NC_4H_8O$ = Morpholino.

TABLE IV

HYDROCHLORIDES, HYDROBROMIDES AND METHOBROMIDES OF BASIC-ALKYL ESTERS OF SUBSTITUTED α-THIENYLACETIC ACIDS, $(C_4H_3S)CRHCOOR'\cdot HCl$ OR $CH_3Br$

All of the compounds were recrystallized from a mixture of absolute alcohol and dry ether except compound 5 which was recrystallized from absolute alcohol.

| | R′ | R | M. p. °C. | Formula | Halogen, % Calcd. | Found |
|---|---|---|---|---|---|---|
| 1 | $CH_2CH_2N(C_2H_5)_2$ | $C_6H_5$ | 98–100 | $C_{18}H_{24}O_2SNCl$ | 10.02 | 10.16 |
| 2 | $CH_2CH_2CH_2N(C_2H_5)_2$ | $C_6H_5$ | 87–89 | $C_{19}H_{26}O_2SNCl$ | 9.77 | 9.67 |
| 3 | $CH_2CH_2CH_2N(C_4H_9)_2$[a] | $C_6H_5$ | 129–132 | $C_{24}H_{36}O_2SNBr$ | 16.58 | 16.80 |
| 4 | $CH_2CH_2NC_5H_{10}$[a] | $C_6H_5$ | 153–155 | $C_{20}H_{28}O_2SNBr$ | 18.74 | 19.20 |
| 5 | $CH\ CH\ CH_2N(C_2H_5)_2$[a] | $C_6H_5CH_2$ | 134–136 | $C_{21}H_{30}O_2SNBr$ | 18.14 | 18.30 |
| 6 | $CH_2CH_2NC_5H_{10}$ | α-$C_{10}H_7$ | 169–172 | $C_{23}H_{26}O_2SNCl$ | 8.53 | 8.37 |
| 7 | $CH_2CH_2CH_2N(C_4H_9)_2$[a] | α-$C_{10}H_7$ | 162–164 | $C_{28}H_{38}O_2SNBr$ | 15.00 | 15.20 |
| 8 | $CH_2CH_2CH_2N(C_2H_5)_2$ | α-$C_{10}H_7$ | 151–153 | $C_{23}H_{28}O_2SNCl$ | 8.48 | 8.29 |
| 9 | $CH_2CH_2N(C_2H_5)_2$ | p-$C_6H_5C_6H_4$ | 101–103 | $C_{24}H_{28}O_2SNCl$ | 8.25 | 8.02 |
| 10 | $CH_2CH_2NC_5H_{10}$[b] | p-$C_6H_5C_6H_4$ | 163–165 | $C_{25}H_{28}O_2SNCl$ | 8.02 | 7.96 |
| 11 | $CH_2CH_2NC_4H_8O$[c] | p-$C_6H_5C_6H_4$ | 165–166 | $C_{24}H_{26}O_3SNCl$ | 7.97 | 8.05 |
| 12 | $CH_2CH_2N(C_2H_5)_2$[d] | α-$C_4H_3S$ | 90–92 | $C_{16}H_{22}O_2S_2NBr$ | 19.76 | 20.20 |
| 13 | $CH_2CH_2NC_5H_{10}$ | α-$C_4H_3S$ | 113–115 | $C_{17}H_{24}O_2S_2NCl$ | 9.53 | 9.35 |
| 14 | $CH_2CH_2CH_2N(C_4H_9)_2$[a] | α-$C_4H_3S$ | 131–133 | $C_{22}H_{34}O_2S_2NBr$ | 16.36 | 16.66 |
| 15 | $CH_2CH_2CH_2N(C_2H_5)_2$ | α-$C_4H_3S$ | 93–96 | $C_{17}H_{24}O_2S_2NCl$ | 9.48 | 9.50 |

[a] Methobromide. [b] $NC_5H_{10}$ = Piperidino. [c] $NC_4H_8O$ = Morpholino. [d] Hydrobromide.

with a mixture of 210 cc. of water and 11 cc. of hydrochloric acid, filtered, and the acid filtrate discarded. The material was triturated with 140 cc. of 5% sodium bicarbonate solution, filtered, and 1:4 hydrochloric acid added to the filtrate until it was only slightly alkaline. The solution was shaken with Norite at room temperature, filtered and the Norite treatment repeated. Upon acidification of the filtrate 20 g. of the hydroxy acid precipitated in crystalline form; m. p. 93° (dec.).

**Phenyl-, Cyclohexyl-, Benzyl-, *p*-Xenyl- and α-Naphthyl-α-thienylacetic Acid.**—The preparation of these acids is illustrated in the case of the phenyl compound.

A mixture of 12 g. (0.051 mole) of phenyl-α-thienylhydroxyacetic acid, 24 g. (0.106 mole) of stannous chloride dihydrate and 200 cc. of acetic acid was put into a 500-cc., 3-necked flask fitted with a stirrer and a tube through which hydrogen chloride could be led into the mixture. The latter was stirred and maintained at 15° while a stream of hydrogen chloride was passed into it until a drop of the mixture no longer became red when treated with a drop of concd. sulfuric acid.[13] The time required for complete reduction usually was about three hours.

The acetic acid was removed in a stream of air at room temperature, ice-water was added to the residue, and the solid material filtered. After the product had been washed thoroughly with water, it was recrystallized from 50% acetic acid; yield 7 g. (62%). The yields, in general, varied from 60–70%.

In the case of the cyclohexyl and the benzyl compound, the mixture was not cooled during the introduction of hydrogen chloride.

**Di-α-thienylacetic Acid.**—Twenty-five grams of the brown, water-soluble material, described under di-α-thienylhydroxyacetic acid, which seemed to contain magnesium, was mixed with 110 cc. of acetic acid and reduced

(13) The color produced by the hydroxy acid and sulfuric acid was not always red (see Table I). The disubstituted acetic acids remained colorless or became only slightly colored when brought into contact with concd. sulfuric acid.

with 50 g. of powdered stannous chloride dihydrate and hydrogen chloride in the described manner. After reduction, the material was poured into 1500 cc. of ice-water, kept cold for several hours, and the brown, crystalline product filtered. It was dissolved in 200 cc. of 10% sodium bicarbonate solution, treated with Norite at room temperature, filtered and the filtrate extracted with ether in order to remove colored impurities. The cold, aqueous solution was acidified with 1:1 hydrochloric acid and, after several hours in an ice-bath, the brown product was filtered. The material was dissolved again in bicarbonate solution, treated with Norite, filtered and the product precipitated with acid. It was then dissolved in the minimum amount of acetic acid required for solution. The solution was stirred with 4 g. of Norite for an hour, then filtered, whereupon a light yellow filtrate was obtained. Enough water was added to produce a turbidity, and the mixture cooled in a refrigerator for a day. The dithienylacetic acid separated in the form of large, glistening, colorless crystals; yield 12 g.; m. p. 91–94°.

TABLE V

ANTISPASMODIC ACTIVITY

| R | Average max. effective dilution: Acetylcholine | Barium chloride |
|---|---|---|
| $\alpha$-$C_4H_3S$—CR(OH)$COOCH_2CH_2N(C_2H_5)_2$·HCl | | |
| Methyl | 1,000,000 | Inactive |
| *p*-Xenyl | 1,000,000 | 200,000 |
| $\alpha$-Naphthyl | 20,000,000 | 500,000 |
| Phenyl | 60,000,000 | 200,000 |
| Cyclohexyl | 80,000,000 | 500,000 |
| $\alpha$-$C_4H_3S$—CRH$COOCH_2CH_2N(C_2H_5)_2$·HCl | | |
| *p*-Xenyl | 1,000,000 | 200,000 |
| $\alpha$-Thienyl[a] | 4,000,000 | 200,000 |
| Phenyl | 5,000,000 | 400,000 |
| $\alpha$-$C_4H_3S$—CR(OH)$COOCH_2CH_2NC_5H_{10}$·HCl | | |
| $\alpha$-Naphthyl | 4,000,000 | 400,000 |
| Phenyl | 20,000,000 | 400,000 |
| Cyclohexyl | 70,000,000 | 200,000 |
| $\alpha$-$C_4H_3S$—CRH$COOCH_2CH_2NC_5H_{10}$·HCl | | |
| $\alpha$-Naphthyl | 2,000,000 | 400,000 |
| Phenyl[b] | 4,000,000 | 200,000 |
| $\alpha$-Thienyl | 10,000,000 | 200,000 |
| $\alpha$-$C_4H_3S$—CR(OH)$CH_2CH_2CH_2N(C_2H_5)_2$·HCl | | |
| Phenyl | 50,000,000 | 200,000 |
| Cyclohexyl | 80,000,000 | 1,000,000 |
| $\alpha$-$C_4H_3S$—CRH$COOCH_2CH_2CH_2N(C_2H_5)_2$·HCl | | |
| $\alpha$-Naphthyl | 1,000,000 | 200,000 |
| $\alpha$-Thienyl | 5,000,000 | 200,000 |
| Benzyl[b] | 20,000,000 | 100,000 |
| Atropine | 50,000,000 | .... |
| Trasentin-6H | 3,000,000[c] | 500,000 |
| Trasentin | 1,000,000 | 200,000 |
| Papaverine | ..... | 200,000 |

[a] Hydrobromide. [b] Methobromide. [c] Since a sample of trasentin-6H was not available for test purposes, this value was taken from the literature. The activity of all of the other commercial antispasmodics was determined under the same conditions employed in the examination of the thienyl compounds.

**γ-Diethylaminopropyl Phenyl-α-thienylhydroxyacetate Hydrochloride.**—The general procedure employed for the preparation of the ester salts is illustrated in the case of this compound.

A mixture of 3.4 g. of phenyl-α-thienylhydroxyacetic acid, 2.2 g. of γ-diethylaminopropyl chloride and 50 cc. of dry isopropyl alcohol was refluxed for twelve hours. After 100 cc. of absolute alcohol had been added to the cold mixture, it was treated with Norite at room temperature, filtered, and the Norite treatment repeated several times. The solvents were removed under reduced pressure, and the residue rubbed under dry ether. The crude ester hydrochloride (4.6 g.) was dissolved in a small amount of warm, absolute alcohol, the solution shaken and absolute ether added until further addition just failed to produce a permanent turbidity. The mixture was placed in a refrigerator and, after some time, the ester salt separated in pure crystalline form.

Methobromides were obtained in the manner described previously.[14]

## Summary

Twenty-eight basic-alkyl esters of substituted α-thienylhydroxyacetic, $C_4H_3S$—CR(OH)COOR′ and substituted α-thienylacetic acids, $C_4H_3S$—CRHCOOR′, have been prepared in which the substituents, R, were represented by such groups as methyl, cyclohexyl, benzyl, phenyl, *p*-xenyl, α-naphthyl and α-thienyl; the basic-alkyl groups, R′, were β-diethylaminoethyl, β-morpholinoethyl, β-piperidinoethyl, γ-diethylaminopropyl and γ-dibutylaminopropyl. The antispasmodic activity of some of the esters was equal to, or exceeded, that of atropine.

ANN ARBOR, MICHIGAN RECEIVED JULY 20, 1944

(14) Blicke and Maxwell, THIS JOURNAL, **64**, 430 (1942).