

has been synthesized and it has been shown that the reduction of this compound with sodium and butyl alcohol results in the formation of 2-benzylamino-1-hexanol. An explanation of the replace-

ment of the  $\beta$ -methoxy group by hydrogen under the conditions of the Bouveault-Blanc reduction has been offered.

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

## Antispasmodics. VIII

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It has been found that basic-alkyl esters of certain substituted acetic acids, in which one of the substituents is a 2-thienyl group, are very potent antispasmodics.<sup>3</sup> Since Wagner-Jauregg, Arnold and Born<sup>4</sup> have shown that  $\beta$ -diethylaminoethyl esters of a number of aralkylacetic acids, for example those of benzylphenylacetic and benzylisopropylacetic acid, possess this activity to a high degree, we decided to synthesize a variety of  $\beta$ -diethylaminoethyl esters of substituted 2-thienylmethylacetic acids,  $C_6H_5SCH_2(R)CHCOOH$ , in which R was represented by such radicals as alkyl, cycloalkyl, aryl, cycloalkylalkyl and aralkyl.

In order to obtain the acetic acid esters, we prepared, first, the monosubstituted malonic esters (Table II) either by interaction of the required ethyl arylacetate, diethyl carbonate and sodium ethylate<sup>5</sup> or by the malonic ester synthesis. After conversion of the mono- into the disubstituted malonic esters (Table II), the latter compounds were hydrolyzed to the corresponding disubstituted malonic acids (Table III). In some instances the malonic acids lost carbon dioxide spontaneously with the formation of the acetic acids; in other cases it was necessary to heat the malonic acids in order to bring about this conversion. The acetic acids (Table III) were esterified by the use of  $\beta$ -diethylaminoethyl chloride according to the general procedure of Hörenstein and Pählicke.<sup>6</sup>

Incidentally, we prepared  $\beta$ -methylaminoethyl 2-thienylmethylbenzylacetate hydrochloride by interaction of 2-thienylmethylbenzylacetyl chloride with  $\beta$ -methylaminoethanol to form N-methyl-N-( $\beta$ -hydroxyethyl)-2-thienylmethylbenzylacetamide, and then heated the amide with hydrochloric acid, according to the general method of Reasenber and Goldberg,<sup>7</sup> in order to convert it into the ester hydrochloride.

(1) This paper represents part of a dissertation to be presented to the Horace H. Rackham School of Graduate Studies by Frederick Leonard in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Frederick Stearns and Company Fellow.

(3) Blicke and Tsao, *THIS JOURNAL*, **66**, 1645 (1944); Lands and Nash, *Proc. Soc. Exp. Biol. Med.*, **57**, 55 (1944); Lands, Nash and Hooper, *J. Pharmacol. Exp. Therap.*, **86**, 129 (1946); Abreu and Troeschler-Elam, *ibid.*, **86**, 205 (1946).

(4) Wagner-Jauregg, Arnold and Born, *Ber.*, **72**, 1551 (1939).

(5) Wallingford, Homeyer and Jones, *THIS JOURNAL*, **63**, 2056 (1941); Wallingford, Thorpe and Homeyer, *ibid.*, **64**, 580 (1942).

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

(7) Reasenber and Goldberg, *THIS JOURNAL*, **67**, 933 (1945).

Our esters (Table IV) were studied pharmacologically in the Frederick Stearns and Company laboratories, and we are indebted to Dr. A. M. Lands and Miss Harriet McCarthy for the report (Table I). It is evident from an examination of the table that, as far as the compounds which have been reported are concerned, the anticholinergic activity is decreased when a cyclic radical, such as phenyl, 2-thienyl or cyclohexyl, is separated from the rest of the molecule by one or more aliphatic carbon atoms.

TABLE I

ANTISPASMODIC ACTIVITY,  
 $C_6H_5SCH_2(R)CHCOOCH_2CH_2N(C_2H_5)_2 \cdot HCl$

R	Maximum effective dilution		
	Acetylcholine <sup>a</sup> $\times 10^4$	Barium chloride <sup>a</sup> $\times 10^4$	Histamine <sup>b</sup> $\times 10^4$
$C_6H_5$	100-200	10-20	10-20
$C_6H_5S^c$	200-400	20-40	20-40
$C_6H_{11}^d$	50-100	20-40	20-50
$C_6H_7$	100-200	100-200	20-50
$C_6H_5CH_2$	20-50	20-50	...
$C_6H_5SCH_2$	100-200	20-50	20-40
$C_6H_{11}CH_2$	20-50	10-20	50-100
$C_6H_5CH_2CH_2$	20-40	20-30	20-40
$C_6H_5SCH_2CH_2$	20-40	10-20	20-40
$C_6H_{11}CH_2CH_2$	4-8	4-10	4-8

<sup>a</sup> Rabbit jejunum. <sup>b</sup> Guinea pig ileum. <sup>c</sup> 2-Thienyl. <sup>d</sup> Cyclohexyl.

### Experimental Part

**2-Thienylmethyl Chloride.**—A rapid stream of hydrogen chloride was passed into a stirred mixture of 525 cc. of concentrated hydrochloric acid, 450 cc. of 40% aqueous formaldehyde and 465 cc. of thiophene while the temperature was maintained at 0-10°. After saturation with the gas, the material was poured into two liters of water, the oily precipitate separated, and the aqueous layer extracted several times with ether. The extracts and oil were combined, washed with water a number of times, and then dried over potassium carbonate. After removal of the ether, the product boiled at 78-82° (18 mm.); yield 373 g. (47%).

This procedure represents a variation of one described by Blicke and Burckhalter<sup>8</sup> who obtained the chloride in 40% yield.

The chloride should not be kept in a tightly closed container since it undergoes spontaneous decomposition, often with explosive violence. It remains undecomposed for some time if preserved in a refrigerator.

**2-Thienylacetoneitrile.**—A mixture of 133 g. of 2-thienylmethyl chloride, 60 cc. of acetone and 74 g. of sodium

(8) Blicke and Burckhalter, *ibid.*, **64**, 477 (1942).

cyanide, which had been dissolved in 100 cc. of water, was stirred and heated in a water-bath at 60–65° for four hours. Water was added, and the organic layer was separated and added to the ether extract of the aqueous layer. The ether was removed from the dried solution and the nitrile distilled; b. p. 115–120° (22 mm.); yield 100 g. (81%).<sup>9</sup>

**Ethyl 2-Thienylacetate.**—A mixture of 100 g. of 2-thienylacetonitrile, 225 cc. of 95% alcohol and 7 cc. of water was poured into a citrate bottle and saturated with hydrogen chloride at 0–5°. After twelve hours at room temperature the mixture was heated for two hours on a steam-bath, cooled, 150 cc. of water added, the oily layer separated and added to the ether extract of the aqueous layer. The solution was dried and the solvent removed; b. p. 119–121° (23 mm.); yield 93 g. (66%).<sup>10</sup>

**$\beta$ -(2-Thienyl)-ethyl Chloride.**—From 97.8 g. of 2-bromothiophene, 14.6 g. of magnesium, 375 cc. of ether and 280.0 g. of  $\beta$ -chloroethyl *p*-toluenesulfonate,<sup>11</sup> dissolved in 300 cc. of ether, we obtained 62.6 g. (71.4%) of the chloride<sup>12</sup>; b. p. 88–92° (20 mm.).

*Anal.* Calcd. for C<sub>8</sub>H<sub>7</sub>SCl: Cl, 24.19. Found: Cl, 24.06.

**Monosubstituted Malonic Esters.**—For the preparation of diethyl 2-thienylmalonate and diethyl phenylmalonate we used the procedure described by Wallingford, *et al.*,<sup>5</sup> for the latter compound. However, it was found that a simpler apparatus, which consisted merely of a three-necked, 500-cc. flask fitted with a dropping funnel, inclined condenser and a sealed stirrer, was satisfactory. Excess diethyl carbonate was used because of the unavoidable loss of this substance from the reaction mixture during the removal of the alcohol.

In order to obtain diethyl 2-thienylmalonate, a solution, prepared from 18.5 g. of sodium and 300 cc. of alcohol, was heated in an oil-bath, stirred and the alcohol removed under reduced pressure. The cake of sodium ethylate was broken into small pieces, and 650 cc. of diethyl carbonate added, followed by 132.4 g. of ethyl 2-thienylacetate. The mixture was stirred while the bath temperature was maintained at 80–85°, and the alcohol was removed, as fast as it was formed, under 300–320 mm. pressure. After five hours the distillate, a mixture of alcohol and diethyl carbonate, amounted to about 200 cc. The material was poured into a mixture of water and ice to which 90 cc. of concentrated hydrochloric acid had been added. The organic layer was separated, the aqueous layer extracted with benzene, the extract and organic layer were combined and shaken with water. After removal of the benzene and excess diethyl carbonate, the product boiled at 148–151° (6 mm.); yield 117 g.<sup>13</sup>

Diethyl phenylmalonate was obtained in 83% yield.

All other monosubstituted malonic esters were prepared by the procedure used for diethyl  $\beta$ -(2-thienyl)-ethylmalonate which is described below.

A solution of sodium ethylate, prepared from 7.8 g. of sodium and 135 cc. of alcohol, was warmed to 50° and 81.5 g. of diethyl malonate added. The mixture was heated to the boiling point and 50.5 g. of  $\beta$ -(2-thienyl)-ethyl chloride was added slowly. The mixture was refluxed for twenty hours, the alcohol removed under reduced pressure, water was added to the oily residue, and the mixture neutralized with dilute hydrochloric acid. The organic layer was separated and combined with the benzene extract of the aqueous layer. After removal of the solvent, the ester boiled at 150–154° (4 mm.); yield 46.7 g. (51%).

**Disubstituted Malonic Esters.**—Diethyl  $\beta$ -cyclohexylethyl-2-thienylmethylmalonate and diethyl cyclohexyl-2-thienylmethylmalonate were obtained by the method

(9) This procedure is an improvement over the one mentioned by Blicke and Zienty (THIS JOURNAL, 63, 2945 (1941)) who isolated the nitrile in 60% yield.

(10) Ref. 9, b. p. 124–129° (26 mm.).

(11) Clemo and Tenniswood, *J. Chem. Soc.*, 2549 (1931).

(12) The general procedure described by Rossander and Marvel (THIS JOURNAL, 50, 1493 (1928)) was employed.

(13) Ref. 9, b. p. 145–148° (5 mm.).

used for the latter ester which is described below. The use of diethyl carbonate as a solvent was recommended by Wallingford, *et al.*<sup>5</sup>

The alcohol was removed, under reduced pressure, from a solution of sodium ethylate prepared from 4.6 g. of sodium and 120 cc. of alcohol; then 200 cc. of diethyl carbonate and 48.4 g. of diethyl cyclohexylmalonate was added. The mixture was heated in a bath at 60–65° under 200 mm. pressure. After about 40 cc. of distillate, a mixture of alcohol and diethyl carbonate, had been obtained, 31.0 g. of 2-thienylmethyl chloride was added, the mixture heated at 100–105° for three hours, and the product isolated in the usual manner; yield 46.0 g. (68%).

The other disubstituted malonic esters were prepared by the method employed in the case of diethyl 2-thienylmethyl- $\beta$ -(2-thienyl)-ethylmalonate. A solution, obtained from 4.3 g. of sodium and 140 cc. of alcohol, was warmed to 50° and 37.8 g. of diethyl  $\beta$ -(2-thienyl)-ethylmalonate was added. After the mixture had been refluxed for a few minutes, 24.9 g. of 2-thienylmethyl chloride was added, dropwise, at such a rate that the mixture continued to reflux. After the material had been boiled for three hours, the product was isolated in the usual manner.

TABLE II

## MONO- AND DISUBSTITUTED MALONIC ESTERS

2-Thienylmethyl chloride was used to prepare all of the disubstituted malonic esters except 3', 4' and 6'; benzyl chloride was employed for 3',  $\beta$ -phenylethyl bromide for 4' and  $\beta$ -cyclohexylethyl bromide for 6'. Each disubstituted ester was obtained from the monosubstituted ester which is indicated by a corresponding number.

RCH(COOC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>		RR'(COOC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	
R	B. p. °C. mm.	R'	B. p. °C. mm.
1 C <sub>6</sub> H <sub>5</sub>	153–155 10 <sup>a</sup>	1' C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	174–178 2
2 C <sub>4</sub> H <sub>9</sub> S	148–151 6 <sup>b</sup>	2' C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	219–223 9
3 C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	149–152 6 <sup>c</sup>	3' C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	203–206 5
4 C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>		4' C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	226–228 8
5 C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>		5' C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	200–203 3
6 C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>		6' C <sub>6</sub> H <sub>11</sub> CH <sub>2</sub> CH <sub>2</sub>	213–214 6
7 C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub> CH <sub>2</sub>	150–154 4 <sup>d</sup>	7' C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	203–206 4
8 C <sub>6</sub> H <sub>11</sub>	158–159 21 <sup>e</sup>	8' C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	201–204 8
9 C <sub>6</sub> H <sub>11</sub> CH <sub>2</sub>	149–153 8 <sup>f</sup>	9' C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	204–206 6
10 C <sub>7</sub> H <sub>7</sub>	100–104 13 <sup>g</sup>	10' C <sub>4</sub> H <sub>9</sub> SCH <sub>2</sub>	153–156 4

<sup>a</sup> Wallingford, Homeyer and Jones (THIS JOURNAL, 63, 2056 (1941)) reported 118–119.5° (2 mm.). <sup>b</sup> Blicke and Zienty (*ibid.*, 63, 2945 (1941)) found 145–148° (5 mm.).

<sup>c</sup> When this compound was hydrolyzed with a mixture of water, alcohol and potassium hydroxide, it yielded 2-thienylmethylmalonic acid; m. p. 138–139° after recrystallization from a mixture of acetone and benzene. *Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>O<sub>4</sub>S: S, 16.01; Found: S, 15.77.

<sup>d</sup> This substance was converted by hydrolysis into  $\beta$ -(2-thienyl)-ethylmalonic acid; m. p. 130–131° after recrystallization from a mixture of acetone and benzene. *Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>4</sub>S: S, 14.97. Found: S, 14.90. <sup>e</sup> Hope and Perkin (*J. Chem. Soc.*, 95, 1363 (1909)) found 163–165° (20 mm.). <sup>f</sup> Katsnel'son and Brodskii (*Compt. rend. acad. sci. U. R. S. S.*, 17, 477 (1939)) reported 122–124° (4 mm.); *C. A.*, 32, 2912 (1938). <sup>g</sup> Volwiler (THIS JOURNAL, 47, 2239 (1925)) found 222–227° (750 mm.).

The preparation of the malonic acids, acetic acids and esters is illustrated by the following procedures.

**2-Thienylmethyl- $\beta$ -(2-thienyl)-ethylmalonic Acid.**—A mixture of 36.3 g. of diethyl 2-thienylmethyl- $\beta$ -(2-thienyl)-ethylmalonate and 19.6 g. of potassium hydroxide, which had been dissolved in 20 cc. of water and 78 cc. of alcohol, was refluxed for twenty hours. The water and alcohol were removed under reduced pressure, the residue dissolved in a small amount of water, the solution cooled to 5°, 50 cc. of ether added and the mixture acidified with concentrated hydrochloric acid. The ether layer was separated and mixed with the ether extract of the aqueous layer. After the ether solution had been washed with

TABLE III

## SUBSTITUTED 2-THIENYLMETHYLMALONIC AND SUBSTITUTED 2-THIENYLMETHYLACETIC ACIDS

The malonic acids 1, 4 and 7 lost carbon dioxide spontaneously with the formation of the corresponding acetic acid. The malonic acids 2 and 5 were recrystallized from water, 3 and 6 from a mixture of benzene and acetone, and 8, 9 and 10 from a mixture of benzene and petroleum ether (60–75°). The acetic acid 2 was recrystallized from a mixture of benzene and petroleum ether (60–75°); all of the other acetic acids were recrystallized from petroleum ether.

R	$C_4H_5SCH_2(R)C(COOH)_2$ M. p., °C.	Formula	Calcd. Sulfur, %	Found Sulfur, %	B. p., °C.	mm.	$C_4H_5SCH_2(R)CHCOOH$ M. p., °C.	Formula	Calcd. Sulfur, %	Found Sulfur, %
1	$C_6H_5$	...	...	...	196–197	5	73–74	$C_{13}H_{12}O_2S$	13.80	14.09
2	$C_6H_5CH_2$	$C_{15}H_{14}O_4S$	11.05	10.81	212–214	7	70–71	$C_{14}H_{12}O_2S$	13.02	12.99
3	$C_6H_5CH_2CH_2$	$C_{16}H_{16}O_4S$	10.53	10.30	224–226	8	oil	...	...	...
4	$C_4H_9S$	...	...	...	...	...	94–95	$C_{11}H_{10}O_2S_2$	26.90	26.48
5	$C_4H_9SCH_2$	$C_{13}H_{12}O_4S_2$	21.63	21.75	218–219	9	71–72	$C_{12}H_{12}O_2S_2$	25.42	25.64
6	$C_4H_9SCH_2CH_2$	$C_{14}H_{14}O_4S_2$	20.65	20.50	232–233	8	oil	...	...	...
7	$C_6H_{11}$	...	...	...	174–176	3	62–63	$C_{13}H_{18}O_2S$	13.45	13.28
8	$C_6H_{11}CH_2$	$C_{15}H_{20}O_4S$	10.82	10.79	205–206	6	54–56	$C_{14}H_{20}O_2S$	12.70	12.73
9	$C_6H_{11}CH_2CH_2$	$C_{16}H_{22}O_4S$	10.33	10.14	211–212	5	oil	...	...	...
10	$C_6H_7$	$C_{11}H_{14}O_4S$	13.23	13.21	159–162	6	oil	...	...	...

TABLE IV

HYDROCHLORIDES OF  $\beta$ -DIETHYLAMINOETHYL ESTERS OF SUBSTITUTED 2-THIENYLMETHYLACETIC ACIDS,  
 $C_4H_5SCH_2(R)CHCOOCH_2CH_2N(C_2H_5)_2 \cdot HCl$ 

Compound 1 was recrystallized from a mixture of acetone and ether, 8 from a mixture of benzene and ether, and all other compounds from a mixture of isopropyl alcohol and ether.

R	M. p., °C.	Formula	Halogen, %		Nitrogen, %	
			Calcd.	Found	Calcd.	Found
1	$C_6H_5$	$C_{16}H_{26}O_2SNBr$	19.37	19.23	3.39	3.54
2	$C_6H_5CH_2$	$C_{20}H_{28}O_2SNCl$	9.28	9.27	3.67	3.86
3	$C_6H_5CH_2CH_2$	$C_{21}H_{30}O_2SNCl$	8.95	8.99	3.54	3.64
4	$C_4H_9S$	$C_{17}H_{24}O_2S_2NCl$	9.48	9.57	3.75	3.85
5	$C_4H_9SCH_2$	$C_{18}H_{26}O_2S_2NCl$	9.15	9.29	3.61	3.76
6	$C_4H_9SCH_2CH_2$	$C_{19}H_{28}O_2S_2NCl$	8.82	8.82	3.49	3.52
7	$C_6H_{11}$	$C_{19}H_{32}O_2SNCl$	9.48	9.51	3.75	3.87
8	$C_6H_{11}CH_2$	$C_{20}H_{34}O_2SNCl$	9.14	9.02	3.61	3.62
9	$C_6H_{11}CH_2CH_2$	$C_{21}H_{36}O_2SNCl$	8.82	8.91	3.49	3.58
10	$C_6H_7$	$C_{16}H_{28}O_2SNCl$	10.55	10.67	4.20	4.25

water, it was dried over magnesium sulfate, and the solvent removed; yield 25.5 g. (82%).

**2-Thienylmethyl- $\beta$ -(2-thienyl)-ethylacetic Acid.**—Ten grams of the corresponding malonic acid was heated to 175–185° for one hour, and the material then distilled; yield 6.8 g. (77%).

**$\beta$ -Diethylaminoethyl 2-Thienylmethyl- $\beta$ -(2-thienyl)-ethylacetate Hydrochloride.**—2-Thienylmethyl- $\beta$ -(2-thienyl)-ethylacetic acid (6.8 g.), 3.5 g. of  $\beta$ -diethylaminoethyl chloride and 80 cc. of anhydrous isopropyl alcohol were refluxed for forty-eight hours, and the mixture then placed in a refrigerator. After several hours the precipitated ester hydrochloride was filtered; yield 5.2 g. (51%).

**2-Thienylmethylbenzylacetyl Chloride,  $(C_4H_5SCH_2)(C_6H_5CH_2)CHCOCl$ .**—A mixture of 24.6 g. of 2-thienylmethylbenzylacetic acid and 75 cc. of thienyl chloride was heated in a bath at 50–60° until the evolution of hydrogen chloride ceased. When the mixture was fractionated, there was obtained 22.0 g. (83%) of the acid chloride; b. p. 170–172° (5 mm.).

**N-Methyl-N-( $\beta$ -hydroxyethyl)-2-thienylmethylbenzylacetamide,  $(C_4H_5SCH_2)(C_6H_5CH_2)CHCON(CH_3)(CH_2CH_2OH)$ .**—To a mixture of 6.2 g. of  $\beta$ -methylaminoethanol, 165 cc. of water and 4.0 g. of sodium hydroxide, which was stirred and maintained at 10–15°, there was added, dropwise, 22.0 g. of 2-thienylmethylbenzylacetyl chloride, dissolved in 250 cc. of ether. The mixture was stirred for one hour at room temperature, the ether layer separated, washed with 100 cc. of 5% hydrochloric acid and then with water. After removal of the ether, a yellow oil (23 g.) was obtained; b. p. 185–190° (0.05 mm.); m. p. 55–57°; yield 17 g. (71%).

*Anal.* Calcd. for  $C_{17}H_{21}O_2S$ : N, 4.84. Found: N, 4.88.

**$\beta$ -Methylaminoethyl 2-Thienylmethylbenzylacetate Hydrochloride,  $(C_4H_5SCH_2)(C_6H_5CH_2)CHCOOCH_2CH_2NH(CH_3) \cdot HCl$ .**—A mixture of 7.5 g. of the amide and 2.5 g. of 36% hydrochloric acid was heated at 80° for one-half hour. Alcohol was added to the cold mixture and then removed by distillation in order to free the mixture from excess hydrochloric acid. The sirupy residue solidified when rubbed under ether; yield 5 g.; m. p. 130–131° after several recrystallizations from a mixture of alcohol and ether. The product was soluble in dilute hydrochloric acid.

*Anal.* Calcd. for  $C_{17}H_{22}O_2S \cdot Cl$ : Cl, 10.88. Found: Cl, 10.84.

## Summary

Ten  $\beta$ -diethylaminoethyl esters of substituted 2-thienylmethylacetic acids, in which the substituents are alkyl, cycloalkyl, aryl, cycloalkyl-alkyl or aralkyl, have been described.

The substituted 2-thienylmethylacetic acids were obtained by preparation of the required mono- and disubstituted malonic esters, hydrolysis of the latter compounds, and conversion of the malonic into the acetic acids. Interaction of the acetic acids with  $\beta$ -diethylaminoethyl chloride yielded the basic esters.

The effect of these esters against spasm induced by acetylcholine, barium chloride or histamine has been reported.