

corresponding hydrochloride, were prepared in concentrations of 10, 20, and 40 mg/ml. Acute intravenous or intraperitoneal toxicities were determined in female albino mice (Charles River CD random-bred). The results are estimates and should only be regarded as approximate LD<sub>50</sub> values (Table VI).

**Local Tissue Irritation (9)**—Solutions were prepared containing 20 and 40 mg of the hydrochloride/ml (or equivalent amounts of other salts) in isotonic saline. Injections were made intradermally in female New Zealand White rabbits, and the effects were estimated from gross examination of the sites 24 hr after injection (Table VI).

## REFERENCES

- (1) B. H. Takman, G. Camougis, and N. M. Löfgren, *Acta Pharm. Suec.*, **6**, 373 (1969); *Chem. Abstr.*, **71**, 47999p (1969).
- (2) N. Löfgren, "Studies on Local Anesthetics, Xylocaine®, A New Synthetic Drug," Haeggströms, Stockholm, Sweden, 1948, p. 25.
- (3) G. H. Kronberg, R. S. Leard, and B. H. Takman, *J. Med. Chem.*, **16**, 739 (1973).
- (4) L. I. Smith and W. W. Prichard, *J. Am. Chem. Soc.*, **62**, 778 (1940).
- (5) B. Dofek and Č. Vrba, *Acta Fac. Pharm. Brun. Bratisl.*, **2**, 141 (1959).
- (6) A. Brändström, *Acta Chem. Scand.*, **17**, 1218 (1963).
- (7) N. Löfgren, "Studies on Local Anesthetics, Xylocaine®, A New Synthetic Drug," Haeggströms, Stockholm, Sweden, 1948, p. 95.
- (8) G. Camougis and B. H. Takman, in "Methods in Pharmacology," vol. 1, A. Schwartz, Ed., Appleton-Century-Crofts, New York, N.Y., 1971, pp. 1-40.
- (9) A. P. Truant, *Arch. Int. Pharmacodyn. Ther.*, **115**, 483 (1958).
- (10) T. P. Carney, in "Medicinal Chemistry," vol. 1, C. M. Suter, Ed.,

Wiley, New York, N.Y., 1951, pp. 280-389.

- (11) S. M. McElvain, *J. Am. Chem. Soc.*, **49**, 2835 (1927).
- (12) P. P. Koelzer and K. H. Wehr, *Arzneim.-Forsch.*, **8**, 181 (1958).
- (13) T. L. Jacobs, S. Winstein, R. B. Henderson, and E. C. Spaeth, *J. Am. Chem. Soc.*, **68**, 1310 (1946).
- (14) J. B. Shoesmith and A. Mackie, *J. Chem. Soc.*, **1928**, 2334.
- (15) W. E. Parham, E. L. Wheeler, R. M. Dodson, and S. W. Fenton, *J. Am. Chem. Soc.*, **76**, 5380 (1954).
- (16) N. Löfgren, *Ark. Kemi Mineral. Geol.*, **22A** (18), 1 (1946).
- (17) N. Löfgren and C. Tegnér, *Acta Chem. Scand.*, **9**, 493 (1955).
- (18) A. Tigerstedt, *Chem. Ber.*, **25**, 2919 (1892).
- (19) N. Löfgren and B. Lundqvist, *Sv. Kem. Tidskr.*, **58**, 206 (1946).
- (20) D. M. Hall and E. E. Turner, *J. Chem. Soc.*, **1948**, 1909.
- (21) L. Wessely, *Monatsh. Chem.*, **22**, 66 (1901).
- (22) J. L. Green, Jr., and H. J. Hagemeyer, Jr., *J. Am. Chem. Soc.*, **77**, 3016 (1955).
- (23) F. Nerdel, P. Weyerstahl, and U. Kretschmar, *Chem. Ber.*, **92**, 1329 (1959).
- (24) E. Hofstetter and A. E. Wilder Smith, *Helv. Chim. Acta*, **36**, 1698 (1953).
- (25) O. H. Wheeler, *J. Am. Chem. Soc.*, **78**, 3216 (1956).
- (26) D. Gagnaire, *Bull. Soc. Chim. Fr.*, **1960**, 1813.
- (27) E. Hultin, *Acta Chem. Scand.*, **15**, 879 (1961).
- (28) *Ibid.*, **15**, 1130 (1961).

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# Syntheses and Pharmacological Activity of N-Acyl-substituted Imidazolidinethiones and Thioimidazolines

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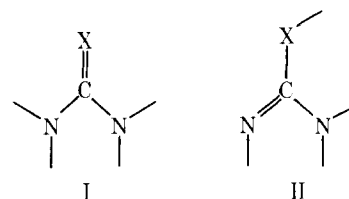
**Abstract** □ A series of imidazolidinethiones and thioimidazolines was synthesized and tested for their effects on both forced and spontaneous motor activities as well as their ability to raise the convulsion threshold. The N-acyl-substituted 2-p-fluorobenzylthioimidazolines were the most active compounds, producing protection against maximal electroshock seizures and tonic convulsions induced by pentylenetetrazol. Both compounds had high LD<sub>50</sub> values and safety indexes.

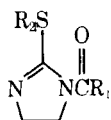
**Keyphrases** □ Imidazolidinethiones, substituted—synthesized, evaluated for CNS depressant and anticonvulsant activity □ Thioimidazolines, various—synthesized, evaluated for CNS depressant and anticonvulsant activity □ CNS depressant activity—evaluated in substituted imidazolidinethiones and various thioimidazolines □ Anticonvulsant activity—evaluated in substituted imidazolidinethiones and various thioimidazolines □ Structure-activity relationships—substituted imidazolidinethiones and various thioimidazolines evaluated for CNS depressant and anticonvulsant activity

An increasingly larger number of medicinal agents containing either the ureido (I) or the isoureido (II) moiety as part of their molecular framework have been developed recently (1-3). The syntheses and CNS depressant and anticonvulsant properties of a series of isomeric acyl-

substituted imidazolidinethiones and thioimidazolines were described previously (4). Based on a limited number of compounds, the thioimidazolines examined all significantly prolonged the time for the onset of convulsions induced by maximal electroshock in male Swiss-Webster mice when compared to the isomeric imidazolidinethiones. To provide additional insight into the pharmacological properties of these two types of compounds, the thioimidazolines III-VI (5) and the imidazolidinethione VII were synthesized. In general, these compounds contain substituents that are more lipophilic in nature than those previously investigated (4).

The pharmacological data in the present report indicate





- III:  $R_1 = \text{OCH}_3$ ,  $R_2 = \text{CH}_2\text{CH}=\text{CH}_2$   
 IV:  $R_1 = \text{CH}_3$ ,  $R_2 = \text{CH}_2\text{CH}=\text{CH}_2$   
 V:  $R_1 = \text{OCH}_3$ ,  $R_2 = \text{CH}_2\text{C}_6\text{H}_4\text{-}p\text{-F}$   
 VI:  $R_1 = \text{CH}_3$ ,  $R_2 = \text{CH}_2\text{C}_6\text{H}_4\text{-}p\text{-F}$

that V and VI afforded significant protection against maximal electroshock seizures and clonic convulsions induced by pentylenetetrazol in male Swiss-Webster mice.

## EXPERIMENTAL

Melting points were determined with a melting-point apparatus<sup>1</sup> and are uncorrected. IR spectra<sup>2</sup> were calibrated against the 1601-cm<sup>-1</sup> band of polystyrene. Proton NMR<sup>3</sup> spectra were taken in deuteriochloroform, and values are reported in parts per million ( $\delta$ ) downfield from tetramethylsilane as the internal standard.

**Preparation of *N*-Methoxycarbonyl-*N'*-phenylcarbamoylimidazolidinethione (VII)**—To a stirred dimethoxyethane solution (50 ml) containing *N*-methoxycarbonylimidazolidinethione (VIII) (6) (1.00 g, 6 mmoles), 0.7 ml of phenyl isocyanate (6 mmoles) was slowly added (Scheme I). The solution was refluxed (120 hr) and then concentrated *in vacuo*. The white solid was reprecipitated from carbon tetrachloride-hexane in a yield of 1.60 g (96%), mp 164–165°; IR (KBr): 1740, 1690, and 1600 cm<sup>-1</sup>; PMR:  $\delta$  3.94 (s, 3H), 3.95–4.20 (m, 4H), 7.05–7.66 (m, 5H), and 12.15–12.50 (broad s, 1H); mass spectrum<sup>4</sup>: *m/e* (relative intensity) 279 (22), 160 (98), 119 (100), 102 (26), and 72 (32).

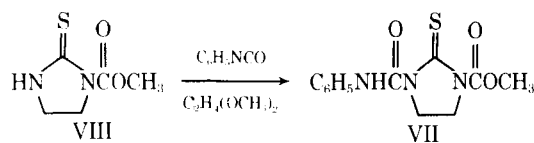
*Anal.*<sup>5</sup>—Calc. for C<sub>12</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>S: C, 51.60; H, 4.96; N, 15.04. Found: C, 51.45; H, 4.68; N, 15.00.

**Pharmacology**—Male rats<sup>6</sup>, Wistar descendant, 150–200 g, were utilized for the gross observation studies. White male Swiss-Webster mice, 20–25 g, were used to investigate the effects of the compounds on forced and spontaneous motor activities and for anticonvulsant activity studies. The animals were initially acclimated to laboratory conditions for 3–4 days. The compounds were freshly prepared in a 5% polysorbate 80 suspension in 95% isotonic saline, and the volumes administered were 1 ml/kg ip for rats and 10 ml/kg ip for mice. The results that differed from control values at the  $p < 0.05$  level (Student *t* test) were considered statistically significant.

The acute 24-hr intraperitoneal lethal dose was determined in mice using three dose levels, and the LD<sub>50</sub> value was calculated using the method of Litchfield and Wilcoxon (7).

The effects of the compound on the gross behavior in rats were evaluated using a gross observation rating scale described by Watzman *et al.* (8) (Table I). The time course of drug effect was ascertained by checking items on the scale at 15 min prior to and 30, 60, 120, and 180 min following drug administration, with special emphasis on behavioral and autonomic effects. The effects of the compounds on forced and spontaneous motor activities were evaluated in mice utilizing a wooden rod (16-cm circumference), which was rotated at 4 rpm for the first 30 sec, at 6 rpm during the next 30 sec, and at progressively increasing speeds thereafter at 30-sec intervals (maximum 50 rpm) until the mouse fell off the rod.

Six animals were tested simultaneously and were given four trials, with two spaced 4–6 hr apart, on each of 2 consecutive days. The fourth trial was preceded by an interval of 50 min for the administration of the vehicle or one experimental compound. The drug or placebo effect for each animal



Scheme I

Table I—Effect of Selected Imidazolidinethiones and Thioimidazolines on Gross Observation in Rats

| Compound | Dose, mg/kg ip | Body Temperature | Pupil Size, mm | Respiration, breaths/min | Heart Rate, beats/min |
|----------|----------------|------------------|----------------|--------------------------|-----------------------|
| III      | Control        | 37.0°            | 5.0            | 120.0                    | 440                   |
|          | 40             | 36.4°            | 5.8            | 90.8                     | 345                   |
| IV       | Control        | 38.5°            | 6.0            | 144.0                    | 440                   |
|          | 40             | 37.0°            | 4.0            | 77.0                     | 328                   |
| V        | Control        | 39.0°            | 5.0            | 134.3                    | 440                   |
|          | 400            | 37.8°            | 4.5            | 111.6                    | 387                   |
| VI       | Control        | 39.0°            | 5.0            | 171.4                    | 512                   |
|          | 120            | 37.3°            | 3.4            | 92.7                     | 350                   |
| VII      | Control        | 39.0°            | 5.0            | 150.0                    | 440                   |
|          | 400            | 38.9°            | 4.3            | 125.3                    | 420                   |

Table II—Effects of Selected Imidazolidinethiones and Thioimidazolines on Spontaneous and Forced Motor Activities in Mice

| Compound  | Dose, mg/kg ip | Spontaneous Motor Activity               |                    | Forced Motor Activity            |                    |
|-----------|----------------|--|--------------------|----------------------------------|--------------------|
|           |                | Drug Treated, Mean $\pm$ SE (for 15 min) | Percent of Control | Drug Treated, Mean, sec $\pm$ SE | Percent of Control |
| III       | 5              | 277.3 $\pm$ 32.83                        | 81                 | 203.3 $\pm$ 13.84                | 121                |
|           | 10             | 410.0 $\pm$ 89.03                        | 69                 | 152.8 $\pm$ 28.87                | 91                 |
|           | 20             | 204.3 $\pm$ 76.20                        | 34 <sup>a</sup>    | 143.1 $\pm$ 22.60                | 70                 |
| IV        | 5              | 687.0 $\pm$ 110.94                       | 81                 | 157.4 $\pm$ 18.27                | 93                 |
|           | 10             | 574.3 $\pm$ 53.00                        | 68                 | 132.4 $\pm$ 19.24                | 79                 |
|           | 20             | 387.3 $\pm$ 63.43                        | 46 <sup>a</sup>    | 117.4 $\pm$ 21.15                | 70                 |
| V         | 100            | 175.0 $\pm$ 26.46                        | 50 <sup>a</sup>    | 161.8 $\pm$ 13.41                | 90                 |
|           | 200            | 40.3 $\pm$ 12.39                         | 12 <sup>a</sup>    | 114.9 $\pm$ 18.73                | 64 <sup>a</sup>    |
|           | 400            | 29.0 $\pm$ 6.66                          | 8 <sup>a</sup>     | 49.2 $\pm$ 31.43                 | 27 <sup>a</sup>    |
| VI        | 30             | 110.0 $\pm$ 53.36                        | 57                 | 117.2 $\pm$ 21.98                | 57 <sup>a</sup>    |
|           | 60             | 77.7 $\pm$ 21.67                         | 40 <sup>a</sup>    | 58.5 $\pm$ 13.13                 | 28 <sup>a</sup>    |
|           | 120            | 28.0 $\pm$ 6.11                          | 15 <sup>a</sup>    | 23.9 $\pm$ 9.50                  | 12 <sup>a</sup>    |
| VII       | 100            | 476.3 $\pm$ 119.27                       | 92                 | 129.8 $\pm$ 23.83                | 67 <sup>a</sup>    |
|           | 200            | 229.0 $\pm$ 62.07                        | 44                 | 84.4 $\pm$ 22.79                 | 43 <sup>a</sup>    |
|           | 400            | 64.0 $\pm$ 19.66                         | 12 <sup>a</sup>    | 113.8 $\pm$ 28.54                | 58 <sup>a</sup>    |
| Phenytoin | 5              | 679.0 $\pm$ 133.27                       | 62                 | 148.8 $\pm$ 11.62                | 68                 |
|           | 10             | 560.0 $\pm$ 32.58                        | 51 <sup>a</sup>    | 147.0 $\pm$ 6.84                 | 67                 |
|           | 20             | 426.7 $\pm$ 57.51                        | 39 <sup>a</sup>    | 118.0 $\pm$ 21.87                | 54 <sup>a</sup>    |

<sup>a</sup>  $p < 0.05$ .

was computed as a ratio of performance time on the fourth trial divided by performance time on the third trial.

The effects of the compounds on spontaneous motor activity in mice were determined using three photocell cages<sup>7</sup> (Table II). Two animals, treated with identical doses of the same compound, were placed in each of two photocell cages 50 min after drug administration; a 15-min count was initiated 5 min after the animals were placed in the cages. To negate the differences in sensitivity among units, each dose was tested in a factorial design in each of the three activity cages. Control animals were tested simultaneously at the same time intervals after administration of an equal volume of vehicle, and the ED<sub>50</sub> value of each compound (defined as the dose that decreased the level of performance to 50% of the control scores) was calculated.

Anticonvulsant activity was investigated in mice. The effects of the compounds on convulsions and death produced by pentylenetetrazol (100 mg/kg sc) and strychnine sulfate (2 mg/kg ip) were investigated as described by Watzman *et al.* (8); the effects on maximal electroshock seizure were investigated as described by Swinyard *et al.* (9).

## RESULTS AND DISCUSSION

**Chemistry**—The syntheses and spectral properties of the thioimidazolines III–VI were described previously (5). The molecular structure assigned to VII was the *N,N'*-disubstituted product rather than the isomeric *N,S*-disubstituted thioimidazoline. Support for this assignment is based on a satisfactory correlation of the spectral properties (NMR and IR) observed for VII with those absorptions previously identified as characteristic peaks for the imidazolidinethione ring system (5). In addition, a significant feature was noted in the mass spectral fragmentation pattern (ionization voltage = 70 ev) for VII. A discernible parent peak

<sup>1</sup> Thomas-Hoover.

<sup>2</sup> Perkin-Elmer models 700 and 237B.

<sup>3</sup> Varian T-60.

<sup>4</sup> Hitachi Perkin-Elmer RMU-5H.

<sup>5</sup> Spang Microanalytical Laboratories.

<sup>6</sup> Texas Inbred, Houston, Tex.

<sup>7</sup> Woodard Research Corp.

**Table III—LD<sub>50</sub>, ED<sub>50</sub>, and Safety Index Values for Selected Imidazolidinethiones and Thioimidazolines**

| Compound               | LD <sub>50</sub> <sup>a</sup> ,<br>mg/kg ip | ED <sub>50</sub> <sup>a</sup> ,<br>mg/kg ip | Safety Index<br>(LD <sub>50</sub> /ED <sub>50</sub> ) |
|------------------------|---|---|---|
| III                    | 88  | 14.8  | 5.9   |
| IV                     | 96  | 13.9  | 6.9   |
| V                      | >1000                                       | 95.1  | >10.5   |
| VI                     | 658   | 45.7  | 14.4  |
| VII                    | >1000                                       | 190.1                                       | >5.3  |
| Phenytoin <sup>b</sup> | 200   | 10.7  | 18.7  |

<sup>a</sup> Calculated from spontaneous motor activity, Table II. <sup>b</sup> Reference 4.

at *m/e* 279 was detected along with two characteristic fragments at P - 119 and P - 177. This pattern can be rationalized in terms of two successive McLafferty-type rearrangements of the starting molecular ion (5).

**Pharmacological Evaluation**—Male Wistar rats were utilized for the gross observation studies. White male Swiss-Webster mice were used to investigate the effects of III-VII on forced and spontaneous motor activities, as well as their ability to alter the threshold for convulsive seizures. The acute 24-hr intraperitoneal lethal dose effects were also determined in mice. The intraperitoneal doses used in the spontaneous and forced motor activity studies were: III and IV, 5, 10, and 20 mg/kg; V and VII, 100, 200, and 400 mg/kg; and VI, 30, 60, and 120 mg/kg. The doses used in the anticonvulsant studies were: V-VII, the same as in the activity studies; and III and IV, 10, 20, and 40 mg/kg. The highest doses indicated were used for the gross observation studies in rats.

All five compounds investigated in the gross observation studies did produce ptosis and decrease the startle response and grip strength. As Table I shows, the compounds also decreased body temperature, respiration, and heart rate. Compound VI was the most effective of the five compounds, producing a 78-breaths/min decrease in respiration, a 1.7° decrease in body temperature, a 162-beats/min decrease in heart rate, and a 1.6-mm decrease in pupil size. Compound VII was the least active of the five compounds.

The most toxic compounds examined were III and IV (Table III). Compounds V and VII had LD<sub>50</sub> values greater than 1000 mg/kg ip, whereas III, IV, and VI had LD<sub>50</sub> values of 88, 96, and 6.6 mg/kg ip, respectively (Table III). The ED<sub>50</sub> value (calculated from spontaneous motor activity data) was highest for VII and lowest for IV (Table III). The safety indexes (LD<sub>50</sub>/ED<sub>50</sub>) determined were: III, 14.8; IV, 13.9; and VI, 14.4. Since V and VII had LD<sub>50</sub> values greater than 1000 mg/kg, the precise safety index could not be determined.

All five compounds decreased both spontaneous and forced motor activities (Table II). The effects of III-VI were dose dependent in both tests; the effects of VII were dose dependent only in the spontaneous motor activity studies. Compounds III and IV, however, did have their maximum effect at 20 mg/kg; when the dose was increased to 40 mg/kg, the decrease in activity was less than the one produced by 20 mg/kg.

**Table IV—Effects of Selected Thioimidazolines and Phenytoin on Convulsion Induced by Pentylene-tetrazol (100 mg/kg sc)**

| Compound  | Dose,<br>mg/kg ip | Onset of<br>Convulsion,<br>sec ± SE | Percent<br>Protected |
|-----------|-------------------|-------------------------------------|----------------------|
| V         | 0                 | 747.2 ± 19.69 <sup>a</sup>          | 0                    |
|           | 100               | 871.0 ± 88.98                       | 0                    |
|           | 200               | 1390.3 ± 281.11 <sup>b</sup>        | 0                    |
|           | 400               | 3710.0 ± 656.43 <sup>b</sup>        | 70                   |
| VI        | 0                 | 657.5 ± 36.11 <sup>a</sup>          | 0                    |
|           | 30                | 750.1 ± 46.13 <sup>b</sup>          | 0                    |
|           | 60                | 844.0 ± 28.35 <sup>b</sup>          | 0                    |
|           | 120               | 969.0 ± 47.71 <sup>b</sup>          | 0                    |
|           | 240               | 3565.0 ± 1820.00 <sup>b</sup>       | 80                   |
| Phenytoin | 0                 | 475.09 ± 28.70 <sup>a</sup>         | 0                    |
|           | 5                 | 581.0 ± 46.33                       | 0                    |
|           | 10                | 440.4 ± 24.24                       | 0                    |
|           | 20                | 554.6 ± 13.90                       | 0                    |

<sup>a</sup> Timed for clonic convulsion, since drug-treated animals did not go into tonic convulsion. <sup>b</sup> *p* < 0.05.

**Table V—Effects of Selected Thioimidazolines and Phenytoin on Convulsion Induced by Electroshock (60 mamp, 0.2 sec)**

| Compound  | Dose,<br>mg/kg ip | Onset of<br>Convulsion,<br>sec ± SE | Percent<br>Protected |
|-----------|-------------------|-------------------------------------|----------------------|
| V         | 0                 | 1.92 ± 0.17                         | 0                    |
|           | 100               | 1.96 ± 0.17                         | 0                    |
|           | 200               | 2.42 ± 0.14                         | 0                    |
|           | 400               | 3.32 ± 0.20 <sup>a</sup>            | 60                   |
| VI        | 0                 | 1.18 ± 0.05                         | 0                    |
|           | 30                | 2.01 ± 0.10                         | 0                    |
|           | 60                | 2.10 ± 0.12 <sup>a</sup>            | 0                    |
|           | 120               | 3.03 ± 0.19 <sup>a</sup>            | 30                   |
|           | 240               | 4.53 ± 0.24 <sup>a</sup>            | 70                   |
| Phenytoin | 0                 | 1.17 ± 0.06                         | 0                    |
|           | 5                 | 2.64 ± 0.17 <sup>a</sup>            | 0                    |
|           | 10                | 5.00 ± 0.00 <sup>a</sup>            | 80                   |
|           | 20                | —                                   | 100                  |

<sup>a</sup> *p* < 0.05.

The anticonvulsant studies showed that none of the compounds protected against strychnine convulsions. Table IV shows that at 400 mg/kg ip, V protected 70% of the mice from tonic convulsions and death induced by pentylenetetrazol; at 200 mg/kg ip, V did not protect the animals from death, but the onset of time of convulsion was significantly prolonged. Compound VI produced almost the same results as V; 120 mg/kg ip did not protect the animals, but the onset of time of convulsion was significantly prolonged; 240 mg/kg protected 80% of the animals from convulsion and death. Only V and VI produced protection against maximal electroshock seizures (Table V).

Phenytoin was tested for its effect on convulsions induced by strychnine, pentylenetetrazol, and maximal electroshock seizures to compare the effect of a known anticonvulsant with the five compounds investigated. Although a previous investigation (4) demonstrated that phenytoin decreased spontaneous motor activity without affecting forced motor activity, it decreased both spontaneous and forced motor activities by 61 and 46%, respectively, in the present study. The LD<sub>50</sub>, ED<sub>50</sub>, and safety index values are recorded in Table III.

Phenytoin (Table V) protected against maximal electroshock seizures at 10 and 20 mg/kg ip but did not show any protection against convulsions induced by strychnine or pentylenetetrazol (Table IV).

Compounds V and VI were the most active compounds with high LD<sub>50</sub> and safety index values; both produced protection against maximal electroshock seizures and pentylenetetrazol. Both compounds are thioimidazolines with a *p*-fluorophenylmethylene substituent not found in any other compound, suggesting the importance of this link on a thioimidazoline for producing anticonvulsant activity.

## REFERENCES

- (1) W. T. Comer and A. W. Gomoll, in "Medicinal Chemistry," 3rd ed., part II, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, chap. 39, p. 1019.
- (2) J. N. Delgado and E. I. Isaacson, in *ibid.*, chap. 52, p. 1386.
- (3) A. Krentzberger, *Prog. Drug Res.*, **11**, 356 (1968).
- (4) H. Kohn, B. A. Kohn, M. L. Steenberg, and J. P. Buckley, *J. Med. Chem.*, **20**, 158 (1977).
- (5) H. Kohn, M. J. Cravey, J. H. Arceneaux, R. L. Cravey, and M. R. Willcott, III, *J. Org. Chem.*, **42**, 941 (1977).
- (6) H. Kohn, *J. Am. Chem. Soc.*, **98**, 3690 (1976).
- (7) J. T. Litchfield and F. J. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
- (8) N. Watzman, A. A. Manian, H. Barry, III, and J. P. Buckley, *J. Pharm. Sci.*, **57**, 2089 (1968).
- (9) E. Swinyard, W. Brown, and L. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).

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