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# Notes

## Syntheses and Pharmacological Activity of Substituted Imidazolidinethiones and Thioimidazolines

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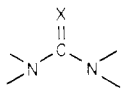
A series of imidazolidinethiones and thioimidazolines was synthesized and tested for their effects on both forced and spontaneous motor activity as well as for their ability to raise the convulsion threshold. The proton NMR spectra for the thioimidazolines synthesized were unusual in that they showed a sharp singlet for the ring ethylene unit rather than the expected $A_2B_2$ pattern. The thioimidazolines, **5** and **7**, were the most active CNS depressants and had the highest safety index. Significantly, the isomeric imidazolidinethiones, **8** and **9**, were comparatively much less effective while being considerably more toxic.

In recent years an increasingly larger number of pharmacologically active agents have appeared which contain either the ureido, **1**, or the corresponding isoureido, **2**, moiety.[2] Many of these compounds possess potent



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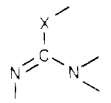

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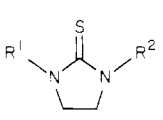
central nervous system (CNS) depressant and anticonvulsant properties.[2] There have been few studies, however, which compare the pharmacological properties of simple compounds which contain the ureido group with those which contain the isoureido group. Two classes of compounds, potentially isomeric to each other and containing one or the other of these functional groups, are the imidazolidinethiones, **3**, and thioimidazolines, **4**. It is worthwhile to note that provided both $R^1$ and $R^2$ are either alkyl or aryl groups, tautomerism between **3** and **4** is unlikely and, therefore, the distinction between **3** and **4**



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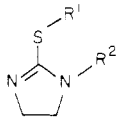

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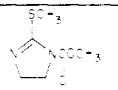
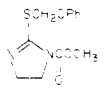
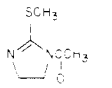
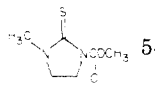
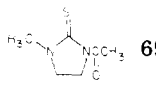
becomes less difficult.[3]

In relation to a current project dealing with the mechanism of biotin catalysis, a series of imidazolidinethiones, **3**, and thioimidazolines, **4**, was synthesized as model substrates.[4] In addition to our mechanistic studies, we felt that it would be desirable to evaluate some of these substrates for biological activity in male Swiss–Webster mice and male Wistar descendant rats. In this communication we report our preliminary findings which indicate that the thioimidazolines, **4**, exhibit more pronounced CNS depressant activity than the corresponding isomeric imidazolidinethiones, **3**.

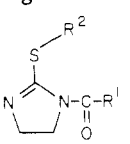
**Chemistry.** The five compounds, **5–9**, that were initially chosen for pharmacological evaluation are listed in Table I.

Table I

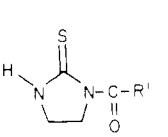
| No. | Substrate | % yield | Mp, °C | ν max[a] | δ[b] $-CH_2CH_2-$ |
|---|---|---|---|---|---|
| 5 |  | 61 | 103.5-105.5 | 1715 | 3.92 |
| 6 |  | 68 | 153.5-155.5 | 1715 | 3.87 |
| 7 |  | 38 | 112-113.5 | 1670 | 3.97 |
| 8 |  | 54 | 111-112.5 | 1745 | 3.44-4.23 |
| 9 |  | 69 | 81-82 | 1665 | 3.40-4.25 |

[a] C=O infrared absorption of carbomethoxy or acetyl group. [b] $^1H$ NMR chemical shift value for imidazoline ring protons.

Synthesis of **5–7** was accomplished by alkylation of either *N*-carbomethoxyimidazolidinethione (**10**) or *N*-acetylimidazolidinethione (**11**). *N*-Carbomethoxyimidazolidinethione (**10**) was prepared by the addition of methyl chloroformate to a $CH_2Cl_2$ solution of imidazolidinethione and pyridine. Subsequent alkylation of **10** with either MeI or α-bromoacetophenone in the presence of $Et_3N$ gave **5** and **6**, respectively. Correspondingly, *N*-



**5**, $R^1 = OCH_3$; $R^2 = CH_3$
**6**, $R^1 = OCH_3$, $R^2 = CH_2C(=O)Ph$
**7**, $R^1 = CH_3$; $R^2 = CH_3$

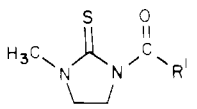


**10**, $R^1 = OCH_3$
**11**, $R^1 = CH_3$

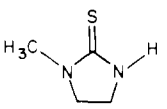
acetyl-2-methylthioimidazoline (**7**) was prepared by al-

kylation of 11[5] with MeI. Under comparable reaction conditions the yield of **5** (61%) was higher than that of **7** (38%). This observation appeared to be general for other related pairs of *N*-carbomethoxy- and *N*-acetylthioimidazolines[6] and may well be a reflection of the enhanced nucleophilicity of the thione group in the former series of compounds. The proton NMR spectra for all three thioimidazolines, **5–7**, were unusual in that they each showed a sharp singlet for the ring ethylene unit rather than the expected $A_2B_2$ pattern. On the other hand, the $^1H$ decoupled carbon-13 NMR spectrum for **6** revealed four carbon resonances (40.3, 47.9, 53.6, and 54.2 ppm) in the 40–55-ppm region. In the $^1H$ coupled carbon-13 spectrum, three of these resonances gave rise to triplets [40.3 ($J_{^{13}C-H}$ = 140 Hz), 47.9 ($J_{^{13}C-H}$ = 150 Hz), and 54.2 ($J_{^{13}C-H}$ = 145 Hz)], indicating the presence of three methylene carbons. The fourth resonance at 53.6 ppm (a quartet, $J_{^{13}C-H}$ = 145 Hz) was assigned to the methoxy carbon. From the above results it appears that the singlet observed in the proton spectrum for **6** and analogously for **5** and **7** can be ascribed to accidental equivalence of the protons within the ethylene unit.

Treatment of a $CH_2Cl_2$ solution of *N*-methylimidazolidinethione (**12**)[7] and pyridine with methyl chloroformate provided imidazolidinethione, **8**, while treatment of the same solution with acetyl chloride gave the corresponding acetyl derivative, **9**. The proton NMR spectrum for both



**8**, $R^1 = OCH_3$
**9**, $R^1 = CH_3$



**12**

of these molecules showed the expected $A_2B_2$ multiplet for the ethylene unit of the imidazolidinethione ring.

**Pharmacological Evaluation.** Male Wistar rats (Texas Inbred, Houston, Texas) were utilized for the gross observation studies. White male Swiss–Webster mice (Texas Inbred) were used to investigate the effects of compounds **5–9** on both forced and spontaneous motor activity, as well as their ability to alter the convulsion threshold. The acute 24-h intraperitoneal lethal dose effects were also determined on mice. The ip doses used in the spontaneous and forced motor activity and anticonvulsant studies were compounds **5–7**, 50, 100, and 200 mg/kg; compound **8**, 5, 10, and 15 mg/kg; and compound **9**, 8, 16, and 24 mg/kg. The highest doses indicated were used for the gross observation studies.

All five compounds investigated decreased respiration and body temperature and produced ptosis in rats used in the gross observation studies. Compound **7** was the most effective of the five compounds, producing a 50% decrease in respiration, a 3 °C decrease in body temperature, marked ptosis, and a decrease in heart rate of approximately 25 beats per minute. Compound **8** was the least active, producing only a slight decrease in respiration of 20%, a slight decrease in heart rate of eight beats per minute, no ptosis, and only a 1 °C decrease in body temperature.

The most toxic compounds examined in this study were the imidazolidinethiones, **8** and **9**. Compounds **5–7** had $LD_{50}$'s greater than 1000 mg/kg ip, whereas compounds **8** and **9** had $LD_{50}$'s of 25 and 40 mg/kg ip, respectively. The $ED_{50}$ (calculated from the spontaneous motor activity data) was highest for compound **7** (150 mg/kg) and lowest for compound **8**, being 18 mg/kg ip. The safety index ($LD_{50}/ED_{50}$) for compound **5** was 16.1, whereas the safety index of compound **9** was only 0.5.

All five compounds produced a decrease in both spontaneous and forced motor activity and the effects were dose dependent except for compound **6** which decreased spontaneous motor activity to 85% of control for the three doses given (50, 100, and 200 mg/kg ip) and decreased forced motor activity to 40% of control.

None of the compounds protected the mice from convulsions induced by maximal electroshock, strychnine, or pentylenetetrazole; however, compounds **5–7** all significantly prolonged the time for the onset of convulsions induced by electric shock. Compound **5** prolonged the time for onset of convulsion by 106%, compound **6** by 75%, and compound **7** by 90%. Compounds **5–7** also significantly prolonged the time for onset of convulsions induced by pentylenetetrazole. Compound **6** was the most effective by prolonging the time for onset of convulsions by 134% over a control. Compound **7** was the only compound which prolonged the time for onset of convulsions induced by strychnine, which was 48% over the control period.

Diphenylhydantoin (5, 10, and 20 mg/kg ip) was tested for its effects on spontaneous and forced motor activity and on convulsions induced by strychnine, pentylenetetrazole, and maximal electroshock seizures in order to compare the effect of a known anticonvulsant with the five compounds investigated. Diphenylhydantoin did decrease spontaneous motor activity but did not affect forced motor activity. The $ED_{50}$ for diphenylhydantoin was calculated to be 10.7 mg/kg ip and the $LD_{50}$ was 200 mg/kg ip, with the safety index calculated to be 18.7. Diphenylhydantoin protected the animals against electroshock seizures at 10 and 20 mg/kg but did not show any protection or extension of the time for onset of convulsions induced by strychnine or pentylenetetrazole.

Compounds **5** and **7** were the two most active of the experimental compounds and had the highest safety index, suggesting that the thiomethyl group is important for central activity. The studies also indicate that compounds **8** and **9**, both substituted imidazolidinethiones, are more toxic and less effective than compounds **5–7**, which are all members of the thioimidazoline class of compounds.

## Experimental Section

**General.** Melting points (mp) were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (ir) were run on a Perkin-Elmer Model 700 and 237B spectrometer and calibrated against the 1601-$cm^{-1}$ band of polystyrene. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates Model T-60 instrument. Carbon-13 nuclear magnetic resonance ($^{13}C$ NMR) spectra were determined at the Baylor College of Medicine on a Varian Associates Model XL100-15 spectrometer, equipped with a Nicolet Technology Corp. TT-100 data system through the courtesy of Dr. Roger Knapp. Chemical shifts are expressed in parts per million relative to $Me_4Si$, and coupling constants (*J* values) in hertz (Hz). Spin multiplicities are indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectral (MS) data were obtained at an ionizing voltage of 70 eV on a Hitachi Perkin-Elmer Model RMU-6H mass spectrometer. Elemental analyses were obtained at Spang Microanalytical Laboratories, Ann Arbor, Mich.

The solvents and reactants were of the best commercial grade available and were used without further purification. All reactions were run under nitrogen, and all glassware was dried before use.

***N*-Carbomethoxyimidazolidinethione (10).** To a mixture of 2-imidazolidinethione (22.5 g, 0.22 mol) and pyridine (18.2 g, 0.23 mol) in $CH_2Cl_2$ (500 ml), methyl chloroformate (17.1 ml, 0.22 mol) was added dropwise. The solution was gently refluxed overnight and then washed with $H_2O$ (2 × 100 ml). The organic layer was dried ($Na_2SO_4$) and then concentrated in vacuo. Purification of **10** was accomplished by reprecipitation from chloroform–hexanes: yield 11.13 g (32%); mp 156–158 °C. Anal. ($C_5H_8N_2O_2S$) C, H, N.

*N*-**Carbomethoxy-2-methylthioimidazoline (5).** MeI (6.3 ml, 0.10 mol) was added to a stirred solution of **10** (8.0 g, 0.05 mol) in $CH_2Cl_2$ (250 ml). The solution was heated at gentle reflux for 72 h, during which time the *N*-carbomethoxy-2-methylthioimidazolinium hydroiodide salt partially precipitated out as a white solid. After heating for the specified time, the mixture was cooled to room temperature and then treated with 100 ml of aqueous 5% $NaHCO_3$. The $CH_2Cl_2$ layer was collected, consecutively washed with aqueous 5% $NaHCO_3$ (100 ml) and $H_2O$ (100 ml), dried ($Na_2SO_4$), and evaporated in vacuo. The desired product was purified by reprecipitation from carbon tetrachloride–hexanes: yield 5.32 g (61%); mp 103.5–105.5 °C. Anal. ($C_6H_{10}N_2O_2S$) C, H, N.

*N*-**Carbomethoxy-2-phenacylthioimidazoline (6).** To a stirred $CH_2Cl_2$ solution (250 ml) containing **10** (6.40 g, 0.04 mol) and $Et_3N$ (7.12 g, 0.08 mol), 9.56 g of $\alpha$-bromoacetophenone (0.048 mol) was added all at once. After stirring for 72 h at room temperature, the solution was consecutively washed with aqueous 5% $NaHCO_3$ (2 × 100 ml) and $H_2O$ (100 ml). The $CH_2Cl_2$ solution was dried ($Na_2SO_4$) and then evaporated in vacuo. Purification of **6** was accomplished by reprecipitation from chloroform–hexanes: yield 7.57 g (68%); mp 153.5–155.5 °C; ir (KBr) 1715, 1670, 1580 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.78 (s, 3 H), 3.87 (s, 4 H), 4.54 (s, 2 H), 7.31–8.12 (m, 5 H); $^{13}C$ NMR (ppm) 40.3 (t, $J_{^{13}C-H}$ = 140 Hz), 47.9 (t, $J_{^{13}C-H}$ = 150 Hz), 53.6 (q, $J_{^{13}C-H}$ = 145 Hz), 54.2 (t, $J_{^{13}C-H}$ = 145 Hz), 128.7, 128.9, 133.8, 136.4, 152.4. The remaining quaternary carbons were not detected under the experimental conditions used. MS: *m/e* (rel %) 278 (14), 134 (47), 105 (100), 77 (75). Anal. ($C_{13}H_{14}N_2O_3S$) C, H, N.

*N*-**Acetyl-2-methylthioimidazoline (7).** To a stirred $CH_2Cl_2$ solution (400 ml) containing **11** (5.76 g, 0.04 mol), 5.0 ml of MeI (0.08 mol) was added all at once. The solution was gently refluxed for 72 h during which time the *N*-acetyl-2-methylthioimidazolinium hydroiodide salt precipitated out. The white crystalline salt was collected, placed in a beaker containing 150 ml of $CH_2Cl_2$, and then treated with 100 ml of aqueous 5% $NaHCO_3$. The $CH_2Cl_2$ layer was collected, consecutively washed with aqueous 5% sodium bicarbonate (100 ml) and $H_2O$ (100 ml), dried ($Na_2SO_4$), and then evaporated in vacuo leaving the desired product. Purification was accomplished by reprecipitation from carbon tetrachloride–hexanes: yield 2.43 g (38%); mp 112–113.5 °C. Anal. ($C_6H_{10}N_2OS$) C, H, N.

*N*-**Carbomethoxy-*N'*-methylimidazolidinethione (8).** To a $CH_2Cl_2$ solution (100 ml) containing **12**[7] (4.64 g, 0.04 mol) and pyridine (6.32 g, 0.08 mol), methyl chloroformate (73.4 g, 0.78 mol) was added. The exothermic reaction was kept under control (moderate $CH_2Cl_2$ reflux) by adjusting the rate of addition of methyl chloroformate. The solution was gently refluxed for 72 h, and then the organic layer washed with $H_2O$ (2 × 60 ml), dried ($Na_2SO_4$), and evaporated in vacuo. Recrystallization from $CCl_4$ afforded 3.75 g (54%) of **8**, mp 111–112.5 °C. Anal. ($C_6H_{10}N_2O_2S$) C, H, N.

*N*-**Acetyl-*N'*-methylimidazolidinethione (9).** To a stirred $CH_2Cl_2$ solution (100 ml) containing **12**[7] (4.64 g, 0.04 mol) and pyridine (3.32 g, 0.04 mol), acetyl chloride (3.32 g, 0.04 mol) was slowly added. The solution was gently refluxed overnight and then the organic layer washed with $H_2O$ (2 × 60 ml), dried ($Na_2SO_4$), and evaporated in vacuo. Purification of **9** was accomplished by reprecipitation from carbon tetrachloride–hexanes: yield 4.35 g (69%); mp 81–82 °C. Anal. ($C_6H_{10}N_2OS$) C, H, N.

**Pharmacology.** Male rats, Wistar descendant, weighing between 150 and 200 g were utilized for the gross observation studies and white male Swiss–Webster mice, 20–25 g, were used to investigate the effects of the compounds on forced and spontaneous motor activity and for anticonvulsant activity. The animals were initially acclimated to laboratory conditions for a period of 3–4 days. The suspensions of the compounds were freshly prepared in a 5% Tween 80 suspension in 95% isotonic saline solution 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's *t* test) were considered statistically significant.

The acute 24-h ip lethal dose was determined in mice using three dose levels and the $LD_{50}$ calculated using the method of Litchfield and Wilcoxon.[8]

The effects of the compound on the gross behavior in rats was evaluated using a gross-observation rating scale described by Watzman et al.[9] 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 activity were evaluated in mice utilizing a Rotarod in which the wooden rod rotated at 4 rpm for the first 30 s, at 6 rpm during the next 30 s, and progressively increasing speeds thereafter at 30-s 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 h 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 of the experimental compounds. The drug or placebo effect for each animal was computed on 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 (Woodard, Research Corp.). Two animals, treated with identical doses of the same compound, were placed in each of two photocell cages 50 min after drug administration and a 15-min count initiated 5 min after the animals were placed in the cages. In order 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 $ED_{50}$ 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 pentylenetetrazole (100 mg/kg subcutaneously) and strychnine sulfate (2 mg/kg ip) were investigated in mice, as described by Watzman et al.,[9] and on maximal electroshock seizure, as described by Swinyard et al.[10]

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## References and Notes

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