# Synthesis and Antiarrhythmic Activity of Substituted (2-Pyrimidinylthio)acetamidoximes[1]

Anthony C. Scotese,* Arthur A. Santilli,

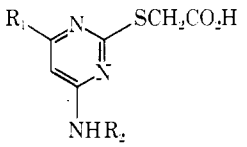
*Research and Development Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania 19087*

and George L. Nelson

*Department of Chemistry, Saint Joseph's College, Philadelphia, Pennsylvania 19131.* *Received February 24, 1975*

A series of (2-pyrimidinylthiomethyl)carbonitriles and -carboxamidoximes was synthesized and the antiarrhythmic effects were evaluated against ventricular arrhythmias as measured by the electrical fibrillatory threshold in the anesthetized dog. Structure–activity studies indicated 2-[4-(*p*-chlorobenzylamino)-6-methyl-2-pyrimidinylthio]acetamidoxime dihydrochloride (**6a**) and 2-[4-(1,3-benzodioxol-5-ylmethylamino)-6-propyl-2-pyrimidinylthio]acetamidoxime (**6g**) to be the most potent members of the series.

Previous reports from these laboratories described the preparation and potent antihypercholesterolemic activity of a series of variously substituted (2-pyrimidinylthio)acetic acid derivatives,[2] typified by **1a**. The results of this earlier study suggested further structural modifications which have led to the synthesis of novel (2-pyrimidinylthio)acetamidoximes (Table I). Although none of the compounds of this new series exhibited antihypercholesterolemic activity, several showed significant antagonism to ventricular arrhythmias as measured by the electrical fibrillatory threshold in the anesthetized dog. The synthesis and antiarrhythmic effects of these compounds are herein described.

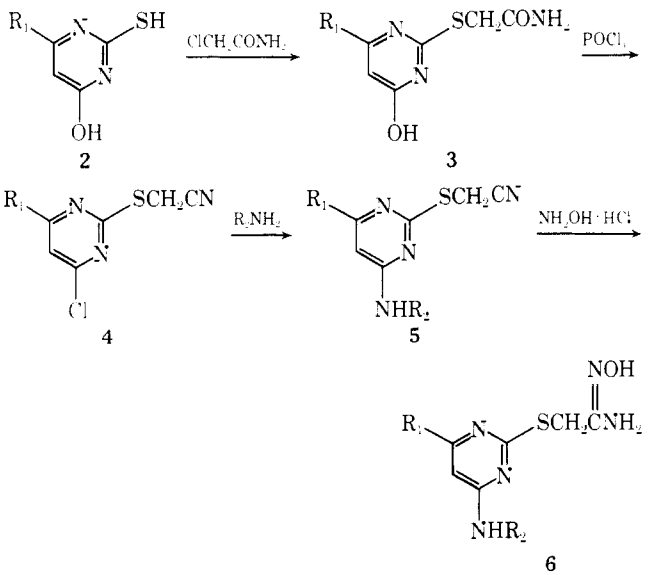


**1a.** $R_1$ = Cl; $R_2$ = *o,m*-$(CH_3)_2C_6H_3$
$R_1$ = Cl, alkyl, aryl, etc.
$R_2$ = alkyl, aryl

## Results and Discussion

The syntheses of the substitued (2-pyrimidinylthio)acetamidoximes (**6**) were carried out according to the steps outlined in Scheme I. Alkylation of the sodium salt of the

**Scheme I**



6-substituted 2-thiouracils (**2**) with 2-chloroacetamide gave the corresponding (2-pyrimidinylthio)acetamides (**3**). Treatment of **3** with boiling phosphorus oxychloride resulted in dehydration of the carbamoyl group to a carbonitrile moiety and simultaneous replacement of the 4-hydroxy group with a chloro group, affording **4**. Displacement of the chloro group in **4** by various amines gave **5**, which upon treatment with hydroxylamine afforded the desired acetamidoximes **6**.

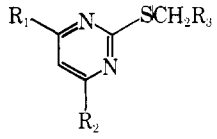
Most of the compounds, including intermediates, were screened as antiarrhythmic agents in the heart of the anesthetized dog. They were also examined for their effects on blood pressure in hypertensive rats as well as their ability to reduce serum cholesterol in hypercholesterolemic rats. None of the compounds screened had any significant effect on blood pressure or on serum cholesterol. Several of the acetamidoximes, however, were shown to have significant activity in the antiarrhythmic screen. The results are summarized in Table II.

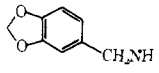
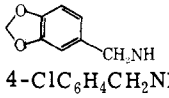
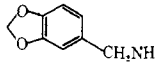
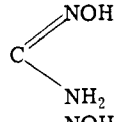
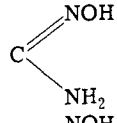
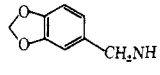
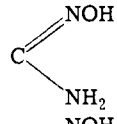
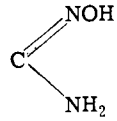
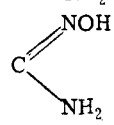
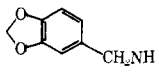
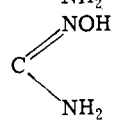
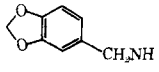
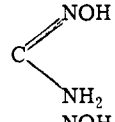
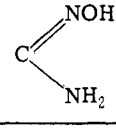
Compounds **6a** and **6g** were shown to be the most potent antiarrhythmic agents of this series, eliciting a marked and a moderate increase in fibrillatory threshold, respectively. Although an extensive structure–activity study was not carried out, the following observations were made relevant to the pharmacological data in Table II. The fact that compounds **5a** and **5i**, the carbonitrile precursors of **6a** and **6g**, showed no activity suggests that the acetamidoxime moiety in **6a** and **6g** must be an essential structural feature for activity. The substituent $R_2$ of the pyrimidine ring can be varied to some extent, because activity was retained when the 4-chlorobenzylamino group in **6a** was replaced by other amines such as the *p*-anisylamino group (compound **6b**) or the piperonylamino group (compound **6c**). Also, the substituent at position 4 ($R_1$) of the pyrimidine ring can be varied to some degree without loss of activity, since replacement of the propyl group in **6g** by either a phenyl group as in compound **6f** or a methyl group as in compound **6c** resulted in compounds that were active although less potent than **6g**. Further expansion of this work will be needed to establish the exact structural limitations for activity.

## Experimental Section

**Pharmacology.** In the electrical fibrillatory threshold screen the heart of an anesthetized dog is exposed by a left thoracotomy. Bipolar electrodes are sutured to the epicardial surface of the left ventricle. The heart is stimulated with square wave pulses of 2–3-msec duration and frequency of 60 Hz for periods of 5 sec. The voltage is increased until fibrillation ensues. The heart is then defibrillated by dc countershock and the procedure repeated at 10-min intervals. Drugs are administered intravenously over periods of 3 min and the fibrillatory threshold is examined at 10 min after the start of the injection of each dose. Effective antiarrhythmic agents elevate the fibrillatory threshold. The screen was performed on a minimum of two dogs. Useful new antiarrhythmic substances should exert only minimal depressant activity on systemic blood pressure, myocardial contractility, and conduction. Standard clinical compounds are quinidine, procainamide, lidocaine, propanolol,

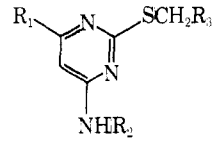
**Table I.** (2-Pyrimidinylthiomethyl)carboxamides, -carbonitriles, and -carboxamidoximes



| Compd | $R_1$ | $R_2$ | $R_3$ | Mp, °C[a] | Recrystn solvent | Yield, % | Formula | Analyses[b] |
|---|---|---|---|---|---|---|---|---|
| 3a | Me | OH | $CONH_2$ | 238–240 | DMF–EtOH | 20 | $C_7H_9N_3SO_2$ | C, H, N |
| 3b | $C_6H_5$ | OH | $CONH_2$ | 275 dec | DMF–EtOH | 50 | $C_{12}H_{11}N_3SO_2$ | C, H, N |
| 3c[c] | $CH_3CH_2CH_2$ | OH | $CONH_2$ | 200–203 dec | EtOH | 25 | $C_9H_{13}N_3SO_2$ | C, H, N |
| 4a | Me | Cl | CN | 62–65 | Heptane | 51 | $C_7H_6ClN_3S$ | C, H, N |
| 4b | $C_6H_5$ | Cl | CN | 136–141 | Heptane–ethyl acetate | 27 | $C_{12}H_8ClN_3S$ | C, H, N |
| 4c | $CH_3CH_2CH_2$ | Cl | CN | Oil | | 50 | $C_9H_{10}ClN_3S$ | C, H, N |
| 5a | Me | 4-$ClC_6H_4CH_2NH$ | CN | 97–101 | Ethyl acetate–petr ether | 35 | $C_{14}H_{13}ClN_4S$ | C, H, N |
| 5b | Me | 4-$CH_3OC_6H_4NH$ | CN | 128–131 | Benzene–petr ether | 33 | $C_{14}H_{14}N_4OS$ | C, H, N |
| 5c | Me |  | CN | 115–118 | EtOH | 74 | $C_{15}H_{14}N_4O_2S$ | C, H, N |
| 5d | $C_6H_5$ | 4-$ClC_6H_4CH_2NH$ | CN | 146–149 | EtOH | 39 | $C_{19}H_{15}N_4ClS$ | C, H, N |
| 5e | $C_6H_5$ | 4-$CH_3OC_6H_4NH$ | CN | 128–131 | Benzene–petr ether | 32 | $C_{19}H_{16}N_4OS$ | C, H, N |
| 5f | $C_6H_5$ |  | CN | 140–142 | EtOH | 57 | $C_{20}H_{16}N_4SO_2$ | C, H, N |
| 5g | $CH_3CH_2CH_2$ | 4-$ClC_6H_4CH_2NH$ | CN | 68–70 | Benzene–heptane | 19 | $C_{16}H_{17}ClN_4S$ | C, H, N |
| 5h | $CH_3CH_2CH_2$ | 4-$CH_3OC_6H_4NH$·HCl | CN | 204–208 | EtOH | 15 | $C_{16}H_{19}ClN_4OS$ | C, H, N |
| 5i | $CH_3CH_2CH_2$ |  | CN | 92–94 | EtOH–petr ether | 15 | $C_{17}H_{18}N_4O_2S$ | C, H, N |
| 6a | Me | 4-$ClC_6H_4CH_2NH$· 2HCl |  | 230–232 dec | Ethyl acetate[d] | 26 | $C_{14}H_{18}Cl_3N_5OS$ | C, H, N |
| 6b | Me | 4-$CH_3OC_6H_4NH$ |  | 189–191 dec | EtOH–petr ether | 30 | $C_{14}H_{17}N_5O_2S$ | C, H, N |
| 6c | Me |  |  | 190–192 dec | DMF–EtOH | 52 | $C_{15}H_{17}N_5O_3S$ | C, H, N |
| 6d | $C_6H_5$ | 4-$ClC_6H_4CH_2NH$ |  | 196–198 dec | Ethyl acetate–petr ether | 58 | $C_{19}H_{18}ClN_5OS$ | C, H, N |
| 6e | $C_6H_5$ | 4-$CH_3OC_6H_4NH$ |  | 190–192 dec | EtOH–petr ether | 39 | $C_{19}H_{19}N_5O_2S$ | C, H, N |
| 6f | $C_6H_5$ |  |  | 160–163 | Ethyl acetate–petr ether | 40 | $C_{20}H_{19}N_5O_3S$ | C, H, N |
| 6g | $CH_3CH_2CH_2$ |  |  | 145–147 dec | Ethyl acetate | 26 | $C_{17}H_{21}N_5O_3S$ | C, H, N |
| 6h | $CH_3CH_2CH_2$ | 4-$CH_3OC_6H_4NH$ |  | 175–178 dec | EtOH | 20 | $C_{16}H_{21}N_5O_2S$ | C, H, N |

[a]Melting points were determined in capillary tubes and are uncorrected. [b]Analytical results for these elements were within ±0.4% of the theoretical values. [c]Compound 3c was previously described.[3] [d]The free base was recrystallized from ethyl acetate.

Table II. Antiarrhythmic Activity in the Anesthetized Dog



| Compd | Dose (iv), mg/kg | Increase in fibrillatory threshold[a] |
|---|---|---|
| 5a | 20 | 0 |
| 5i | 20 | 0 |
| 6a | 20 | +++ |
| 6b | 20 | + |
| 6c | 10 | + |
| 6d | 20 | 0 |
| 6e | 20 | 0 |
| 6f | 20 | + |
| 6g | 20 | ++ |
| 6h | 20 | 0 |

[a] See the Experimental Section for explanation of terms.

and diphenylhydantoin. The fibrillatory threshold is measured in volts and the activity of the drug administered is determined according to Chart I.

**Chart I**

| Increase in fibrillatory threshold | Voltage increase |
|---|---|
| no significant effect (0) | 0-0.75 V |
| slight (+) | 0.75-1.0 V |
| moderate (++) | 1.0-2.0 V |
| marked (+++) | >2.0 V |

In the screening procedure described above, a standard clinical compound such as quinidine elevated the fibrillatory threshold greater than 2.0 V with a dose of 20 mg/kg.[4] Diphenylhydantoin and procainamide elevated the fibrillatory threshold less than 2.0 V with doses of 20 and 25 mg/kg, respectively.

**Chemistry.** Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in either potassium bromide disks or pyridine, dimethyl sulfoxide, or chloroform solutions using a Perkin-Elmer (Model 21) spectrophotometer. Nuclear magnetic resonance spectra were obtained either with a Varian A-60 or JEOLC60-HL spectrometer. Elemental analyses of the compounds were obtained with a Perkin-Elmer (Model 24) elemental analyzer. The examples given are illustrative of the preparative procedures used for all the members of a series.

**2-(4-Hydroxy-6-methyl-2-pyrimidinylthio)acetamide (3a).** To a solution of 16.8 g (0.02 mol) of sodium bicarbonate in 300 ml of water was added 22.8 g (0.02 mol) of 6-methyl-2-thiouracil. The mixture was heated on a steam bath for 10 min. To this mixture was then added 18.6 g (0.02 mol) of 2-chloroacetamide, followed by 100 ml of absolute ethanol. The mixture was heated on a steam bath for 2 hr. The solution was cooled in an ice bath and the precipitate which formed was collected and recrystallized from a mixture of dimethylformamide and ethanol, affording 8 g of **3a**.

**(4-Chloro-6-methyl-2-pyrimidinylthio)acetonitrile (4a).** To a solution of 19.4 g (0.13 mol) of *N, N*-dimethylaniline in 250 ml of phosphorus oxychloride was added 25.8 g (0.13 mol) of **3a**. The mixture was heated under reflux for 1 hr. The phosphorus oxychloride was removed in a rotary evaporator and the residue was poured onto 1 l. of cracked ice. The precipitate which resulted was collected, dried, and recrystallized from heptane, giving 13.0 g of **4a**.

**[4-(*p*-Chlorobenzylamino)-6-methyl-2-pyrimidinylthio]acetonitrile (5a).** A stirred mixture of 5.97 g (0.03 mol) of **4a**, 4.2 g (0.03 mol) of 4-chlorobenzylamine, and 3.15 g (0.03 mol) of sodium carbonate in 150 ml of absolute ethanol was heated under reflux for 6 hr. The mixture was filtered and the filtrate was evaporated in a rotary evaporator. The residue was triturated with petroleum ether containing a little ethanol. The solid which crystallized was collected and recrystallized from ethyl acetate (petroleum ether was added to initiate precipitation), giving 3.2 g of **5a**.

**2-[4-Methyl-6-(*p*-chlorobenzylamino)-2-pyrimidinylthio]acetamidoxime Dihydrochloride (6a).** A mixture of 10.6 g (0.035 mol) of **5a**, 4.83 g (0.07 mol) of hydroxylamine hydrochloride, and 14.7 g (0.14 mol) of sodium carbonate in 10.0 ml of DMF was heated on a steam bath for 3 hr. The mixture was filtered and the filtrate was evaporated in a rotary evaporator. The residue was triturated with petroleum ether containing a little ethyl acetate. The solid which crystalized was collected and recrystallized from ethyl acetate, giving pure free base, mp 113–116°. This free base was dissolved in absolute ethanol and acidified with an ethereal hydrochloric acid solution, giving 3.5 g of **6a**.

**Acknowledgments.** The authors wish to thank Drs. T. Baum and R. Tomarelli for performing the pharmacological screening procedures and Mr. B. Hofmann for the microanalyses and infrared and nuclear magnetic resonance spectral determinations.

## References and Notes

(1) Taken in part from the M.S. Thesis of one of the authors (A.C.S.), St. Joseph's College, Philadelphia, Pa., 1974.
(2) (a) A. A. Santilli, A. C. Scotese, and R. M. Tomarelli, *Experientia*, **30**, 1110 (1974). (b) Presented before the Division of Medicinal Chemistry, 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974.
(3) J. Druey, U.S. Patent 2,530,570 (1950) [*Chem. Abstr.*, **45**, 3428 (1951)].
(4) T. Baum, D. K. Eckfeld, A. T. Skropshire, G. Rowles, and L. L. Varner, *Arch. Int. Pharmacodyn.*, **193**, 149 (1971).

# Synthesis and Analgesic Activities of 2,5-Dimethyl-2′-hydroxy-9α- and -β-propyl-6,7-benzomorphans

Kenner C. Rice, Arthur E. Jacobson,* and Everette L. May

*Section on Medicinal Chemistry, Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Maryland 20014.* *Received January 29, 1975*

The 2,5-dimethyl-2′-hydroxy-9α- and -β-propyl-6,7-benzomorphans were synthesized from 4-methyl-3-propylpyridine in five steps, in an overall yield of 14 and 5%, respectively. The required 4-methyl-3-propylpyridine was prepared in an overall yield of 34% by a four-step sequence. The benzomorphans were about as potent as, or more potent than, morphine in vivo.

Although 2,9α- and -β-dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphans have been synthesized,[1,2] the isomeric 5-methyl-9-propyl compounds have not been prepared due to the commercial unavailability of 4-methyl-3-propylpyri-