

Synthesis and Antiarrhythmic Activity of Substituted (2-Pyrimidinylthio)acetamidoximes¹

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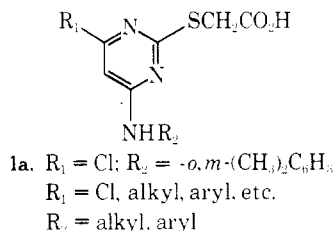
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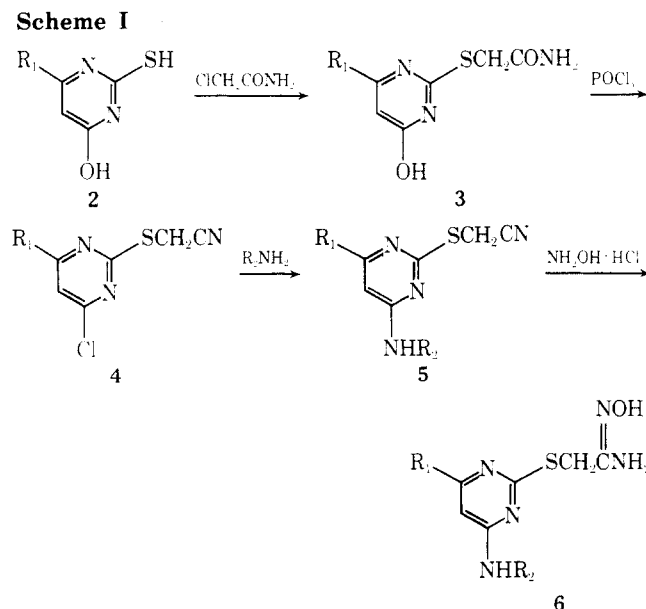
A series of (2-pyrimidinylthiomethyl)carbonitriles and -carboxamidoximes was synthesized and the antiarrhythmic effects were evaluated against ventricular arrhythmias as measured by the electrical fibrillatory threshold in the anesthetized dog. Structure-activity studies indicated 2-[4-(*p*-chlorobenzylamino)-6-methyl-2-pyrimidinylthio]acetamidoxime 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.



Results and Discussion

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



trile 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**.

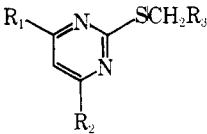
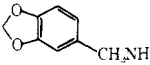
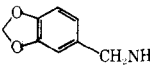
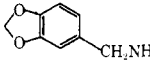
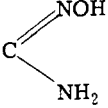
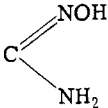
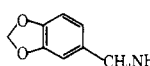
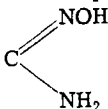
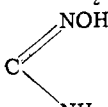
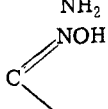
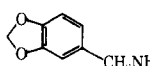
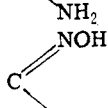
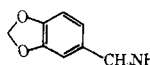
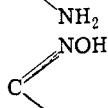
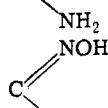
Most of the compounds, including intermediates, were screened as antiarrhythmic agents in the heart of the anesthetized dog. They were also examined for their effects on blood pressure in hypertensive rats as well as their ability to reduce serum cholesterol in hypercholesterolemic rats. None of the 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, propranolol,

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 ₇ H ₉ N ₃ SO ₂	C, H, N
3b	C ₆ H ₅	OH	CONH ₂	275 dec	DMF–EtOH	50	C ₁₂ H ₁₁ N ₃ SO ₂	C, H, N
3c ^c	CH ₃ CH ₂ CH ₂	OH	CONH ₂	200–203 dec	EtOH	25	C ₉ H ₁₃ N ₃ SO ₂	C, H, N
4a	Me	Cl	CN	62–65	Heptane	51	C ₇ H ₆ ClN ₃ S	C, H, N
4b	C ₆ H ₅	Cl	CN	136–141	Heptane–ethyl acetate	27	C ₁₂ H ₈ ClN ₃ S	C, H, N
4c	CH ₃ CH ₂ CH ₂	Cl	CN	Oil		50	C ₉ H ₁₀ ClN ₃ S	C, H, N
5a	Me	4-ClC ₆ H ₄ CH ₂ NH	CN	97–101	Ethyl acetate–petr ether	35	C ₁₄ H ₁₃ ClN ₄ S	C, H, N
5b	Me	4-CH ₃ OC ₆ H ₄ NH	CN	128–131	Benzene–petr ether	33	C ₁₄ H ₁₄ N ₄ OS	C, H, N
5c	Me		CN	115–118	EtOH	74	C ₁₅ H ₁₄ N ₄ O ₂ S	C, H, N
5d	C ₆ H ₅	4-ClC ₆ H ₄ CH ₂ NH	CN	146–149	EtOH	39	C ₁₉ H ₁₅ N ₄ ClS	C, H, N
5e	C ₆ H ₅	4-CH ₃ OC ₆ H ₄ NH	CN	128–131	Benzene–petr ether	32	C ₁₉ H ₁₆ N ₄ OS	C, H, N
5f	C ₆ H ₅		CN	140–142	EtOH	57	C ₂₀ H ₁₆ N ₄ SO ₂	C, H, N
5g	CH ₃ CH ₂ CH ₂	4-ClC ₆ H ₄ CH ₂ NH	CN	68–70	Benzene–heptane	19	C ₁₆ H ₁₇ ClN ₄ S	C, H, N
5h	CH ₃ CH ₂ CH ₂	4-CH ₃ OC ₆ H ₄ NH·HCl	CN	204–208	EtOH	15	C ₁₆ H ₁₉ ClN ₄ OS	C, H, N
5i	CH ₃ CH ₂ CH ₂		CN	92–94	EtOH–petr ether	15	C ₁₇ H ₁₈ N ₄ O ₂ S	C, H, N
6a	Me	4-ClC ₆ H ₄ CH ₂ NH·2HCl		230–232 dec	Ethyl acetate ^d	26	C ₁₄ H ₁₈ Cl ₃ -N ₅ OS	C, H, N
6b	Me	4-CH ₃ OC ₆ H ₄ NH		189–191 dec	EtOH–petr ether	30	C ₁₄ H ₁₇ N ₅ O ₂ S	C, H, N
6c	Me			190–192 dec	DMF–EtOH	52	C ₁₅ H ₁₇ N ₅ O ₃ S	C, H, N
6d	C ₆ H ₅	4-ClC ₆ H ₄ CH ₂ NH		196–198 dec	Ethyl acetate–petr ether	58	C ₁₉ H ₁₈ Cl-N ₅ OS	C, H, N
6e	C ₆ H ₅	4-CH ₃ OC ₆ H ₄ NH		190–192 dec	EtOH–petr ether	39	C ₁₉ H ₁₉ N ₅ O ₂ S	C, H, N
6f	C ₆ H ₅			160–163	Ethyl acetate–petr ether	40	C ₂₀ H ₁₉ N ₅ O ₃ S	C, H, N
6g	CH ₃ CH ₂ CH ₂			145–147 dec	Ethyl acetate	26	C ₁₇ H ₂₁ N ₅ O ₃ S	C, H, N
6h	CH ₃ CH ₂ CH ₂	4-CH ₃ OC ₆ H ₄ NH		175–178 dec	EtOH	20	C ₁₆ H ₂₁ N ₅ O ₂ S	C, H, N

^aMelting points were determined in capillary tubes and are uncorrected. ^bAnalytical results for these elements were within $\pm 0.4\%$ of the theoretical values. ^cCompound 3c was previously described.³ ^dThe 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

^aSee 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 crystallized 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.

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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-9 α - and - β -propyl-6,7-benzomorphans

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The 2,5-dimethyl-2'-hydroxy-9 α - 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 2,9 α - 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-