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Synthesis and evaluation of novel lidocaine sulfur analogs

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Summary

In order to test whether the structural requirement for basic or quaternary nitrogen in antiarrhythmic drugs is essential, several sulfur-containing lidocaine analogs were synthesized and their metabolism investigated in human plasma, various esterase preparations, bovine liver microsomes, and in vivo in rats. Skin diffusion was measured through hairless mouse skin.

Two of the compounds were found to have long-lasting antiarrhythmic activity in dogs, and in the case of the ethylthio analog, activity equivalent to that of lidocaine persisted without the presence of an ionized group to interact with the proposed anionic portion of membrane polypeptides. Thus, non-specific antiarrhythmic activity is possible when only the myocardial membrane phospholipids interact with the drug and charge attractions between the drug and membrane peptide groups are not necessary.

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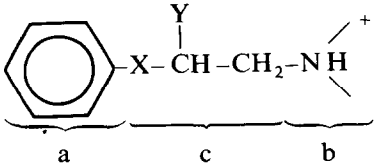
Introduction

Antiarrhythmic drugs often differ greatly in their chemical structure, pharmacokinetic characteristics, and electrophysiological effects. Also, because many drugs have more than one possible mode of action, their classification into distinct categories is difficult.

Apart from diphenyl hydantoin which is a weak acid, all antiarrhythmic drugs used contain a basic or quaternary nitrogen group and are therefore capable of existing mainly as cations under physiological conditions. In order to check if this structural requirement for nitrogen is essential for the activity, several sulfur analogs of lidocaine were synthesized. Some of these analogs were tested under various enzymatic conditions in vitro as well as in vivo in rats and in dogs, using lidocaine as a reference substance.

The local anesthetic and antiarrhythmic agent lidocaine is considered one of the most useful drugs in treatment of ventricular arrhythmias. Despite rapid and relatively complete absorption, oral administration of lidocaine is not clinically useful due to extensive first-pass metabolism and short biological half-life (Keenaghan and Boyes, 1972). Following intravenous administration, it is rapidly taken up by highly perfused organs, such as liver (which is considered the prime site of its metabolism), heart, brain, lungs, and kidney, leaving only about 15% of the dose in blood (Sung and Truant, 1954; Hollunger, 1960; Rowland et al., 1981). In humans and most other species studied, the major pathway of lidocaine biotransformation appears to be N-dealkylation followed by secondary hydrolysis, oxidations, and conjugations (Keenaghan and Boyes, 1972; Nelson et al., 1977). Two of its metabolites, the mono- and didesethyl lidocaine, have been shown to have 83% and 10% of the antiarrhythmic activity of lidocaine, respectively (Burney et al., 1974). There is some indication that these metabolites of lidocaine may be responsible for its CNS toxicity. Because of this toxicity and the facile formation of these metabolites during first pass through the liver, lidocaine is generally administered intravenously.

Antiarrhythmic drugs can be divided into two broad groups: (a) those that act specifically by interacting with a receptor (e.g. β-adrenergic blocking agents such as propranolol); and (b) those that act non-specifically by accumulating in membranes (e.g. local anesthetic agents such as lidocaine). The molecular structure which appears to be essential for non-specific antiarrhythmic activity consists of three moieties: (a) a lipophilic aromatic group connected to (b) an animo group (ionized at biological pH), via (c) a hydroxyl-substituted alkyl chain, ester, or amide group capable of hydrogen bonding (Szekeres and Papp, 1971; Morgan and Mathison, 1976b).



It has been observed that more potent non-specific antiarrhythmic agents can be

produced by increasing the lipophilicity and agents of low CNS toxicity can be produced by increasing the pK_a of the amine (Tenthorey et al., 1981). In fact, quaternization of the amino group seems to abolish toxic effects on the CNS and diminish local anesthetic activity without reducing antiarrhythmic activity. These changes are thought to be due to changes in distribution. Thus, quaternization of the compounds prevents them from penetrating the blood–brain barrier, whereas the plasma membrane of the myocardial cells is a part of the central compartment and therefore is readily accessible. A number of quaternary antiarrhythmic drugs have been clinically evaluated and appear to have rapid onset and long duration of action, as well as reduced incidence of side effects (Kniffen et al., 1975). The observation that the mono- and didesethyl metabolites have antiarrhythmic activity has prompted a further investigation of compounds with similar structures (Tenthorey et al., 1981; Byrnes et al., 1979).

Materials and Methods

2-Methylthio-N-(2,6-dimethylphenyl)acetamide (II)

To a chilled solution containing 1.21 g (10 mmol) of 2,6-dimethylaniline in 10 ml chloroform was added, in portions over 10 min with stirring, 1.25 g (10 mmol) of methylthioacetyl chloride. After 20 min 0.79 g (10 mmol) of pyridine was added to the solution, and the temperature was allowed to rise to room temperature under stirring for 25 min. The reaction mixture was washed once with 5% aqueous hydrochloric acid and twice with water. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford a white crystalline compound, which was purified further by recrystallization from isopropyl alcohol (87% yield), m.p. 116–117°C, IR (KBr): 3200, 3030, 2980, 2930, 2820, 1650, 1590, 1530, 1470, 1310, 1140, 774 and 710 cm^{-1}; NMR ($CDCl_3$): δ 2.20 (s, 9H), 3.30 (s, 2H), 6.97 (s, 3H), and 8.23 (br s, 1H).

Anal.—Calc. for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69; S, 15.32. Found: C, 63.19; H, 7.24; N, 6.69; S, 15.25.

2-Dimethylsulfonic-N-(2,6-dimethylphenyl)acetamide iodide (III)

To a stirred solution of 2.09 g (10 mmol) II in a mixed solvent of 20 ml acetonitrile and 30 ml diethyl ether was added 10 ml of methyl iodide. The reaction mixture was stirred at room temperature for 23 h. The pale yellow crystals formed were washed twice with diethyl ether and dried in vacuo (31% yield), m.p. 123–124°C; IR (KBr): 3470, 3210, 3000, 2920, 2890, 1675, 1645, 1600, 1545, 1530, 1475, 1435, 1420, 1375, 1230 and 765 cm^{-1}; NMR (DMSO-d_6): δ 2.15 (s, 6H), 3.00 (s, 6H), 4.72 (s, 2H), and 6.95 (s, 3H).

Anal.—Calc. for $C_{12}H_{18}INOS$: C, 41.03; H, 5.17; N, 3.99; S, 9.13. Found: C, 40.97; H, 5.21; N, 3.97; S, 9.09.

2-Methylsulfinyl-N-(2,6-dimethylphenyl)acetamide (IV)

To a methylene chloride solution containing 2.09 g (10 mmol) of II was added, in

portions over 30 min with stirring at 5°C, 2.16 g (10 mmol) of *m*-chloroperbenzoic acid (80% solution). The reaction mixture was kept at 5°C for an additional 1.25 h. The precipitate formed was filtered and washed twice with methylene chloride. The filtrate and washings were combined, washed once with saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to afford a white crystalline compound (88% yield), m.p. 112–114°C; IR (KBr): 3300, 2990, 2930, 1640, 1600, 1520, 1475, 1420, 1385, 1315, 1220, 1055, 970 and 785 cm^{-1}; NMR (DMSO-d_6): δ 2.12 (s, 6H), 2.67 (s, 3H), 3.77 (br s, 2H), 6.93 (s, 3H), and 9.60 (br s, 1H).

Anal.—Calc. for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.70; N, 6.22; S, 14.23. Found: C, 58.65; H, 6.72; N, 6.19; S, 14.12.

2-Methylsulfonyl-N-(2,6-dimethylphenyl)acetamide (V)

Use of the method described for IV, but with 2 equivalents of *m*-chloroperbenzoic acid, afforded the desired product (78% yield), m.p. 193–196°C; IR (KBr): 3220, 3040, 2940, 1665, 1545, 1310, 1160 and 1110 cm^{-1}; NMR (DMSO-d_6): δ 2.12 (s, 6H), 3.08 (s, 3H), 4.22 (s, 2H), 6.92 (s, 3H), and 9.67 (br s, 1H).

Anal.—Calc. for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80; S, 13.29. Found: C, 54.89; H, 6.32; N, 5.72; S, 13.21.

2-Ethylthio-N-(2,6-dimethylphenyl)acetamide (VI)

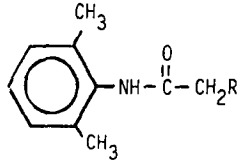
To a chilled chloroform solution containing 12.1 g (0.1 mol) of 2,6-dimethylaniline was added, in portions over 20 min with stirring, 15.0 g (0.1 mol) of ethylthioacetyl chloride. After 10 min 8.50 g (0.1 mol) of pyridine was added to the solution and the temperature was allowed to rise to room temperature under stirring for 2 h. The reaction mixture was washed once with 3% aqueous hydrochloric acid and twice with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was recrystallized from isopropyl alcohol and diethyl ether to afford a crystalline compound (84% yield), m.p. 96–98°C; IR (KBr): 3250, 3030, 2980, 2930, 1645, 1590, 1525, 1470, 1320, 1225, 1160 and 770 cm^{-1}; NMR (CDCl): δ 1.33 (t, 3H, J = 7Hz), 2.20 (s, 6H), 2.68 (q, 2H, J = 7Hz), 3.38 (s, 2H), 7.02 (s, 3H), and 8.20 (br s, 1H).

Anal.—Calc. for $C_{12}H_{17}NOS$: C, 64.54; H, 7.67; N, 6.27; s, 14.63. Found: C, 64.45; H, 7.71; N, 6.26; S, 14.31.

2-Ethylsulfinyl-N-(2,6-dimethylphenyl)acetamide (VII)

The method described for synthesis of IV was used, starting with 2.23 g (10 mmol) of VI. Recrystallization from ethyl acetate resulted in pure crystalline compound (83% yield), m.p. 114–115°C; IR (KBr): 3240, 3040, 2980, 2930, 1650, 1600, 1530, 1480, 1325, 1225, 1170, 1140, 1050, 1025, 985 and 770 cm^{-1}; NMR (DMSO-d_6): δ 1.23 (t, 3H, J = 8Hz), 2.13 (s, 6H), 2.83 and 2.88 (each q, 1H, J = 8Hz), 3.73 and 3.83 (each ABq, 1H, J = 14Hz), 7.02 (s, 3H), and 9.53 (br s, 1H).

Anal.—Calc. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85; S, 13.40. Found: C, 60.27; H, 7.16; N, 5.80; S, 13.36.



Compound	R
I	$-N(C_2H_5)_2 \cdot HCl \cdot H_2O$
II	$-S-CH_3$
III	$-S^+(CH_3)_2 \cdot I^-$
IV	$-\overset{\uparrow}{S}(O)-CH_3$
V	$-SO_2CH_3$
VI	$-S-C_2H_5$
VII	$-\overset{\uparrow}{S}(O)-C_2H_5$
VIII	$-SO_2C_2H_5$

2-Ethylsulfonyl-N-(2,6-dimethylphenyl)acetamide (VIII)

By using the method described for the preparation of IV and VII, but with two equivalents of *m*-chloroperbenzoic acid, compound VI was transformed into the desired product in a 75% yield, m.p. 128–130°C; IR (KBr): 3220, 3180, 3040, 3000, 2960, 1670, 1635, 1595, 1545, 1480, 1400, 1340, 1235, 1150 and 1105 cm^{-1}; NMR (DMSO-d_6): δ 1.27 (t, 3H, J = 8Hz), 2.13 (s, 6H), 3.23 (q, 2H, J = 8Hz), 4.20 (s, 2H), 6.95 (s, 3H), and 9.73 (br s, 1H).

Anal.—Calc. for $C_{12}H_{17}NO_3S$: C, 56.45; N, 6.71; N, 5.49; S, 12.56. Found: C, 56.48; H, 6.72; N, 5.44; S, 12.50.

Chromatography

The chromatographic analyses were performed in a system consisting of Waters Associates Model 600A solvent delivery system, Model U-6K injector and Model 440 dual channel absorbance detector operated at 254 nm. A Z-Module system containing reverse phase 10 μm, 10 cm × 8 nm i.d. Radial-PAK C_{18} cartridge (Water Associates), operated at ambient temperature, was used for all separations. The mobile phase used for separation of I [1], II, III, IV, V and 2,6-dimethylaniline consisted of methanol and water (2 : 5). At a flow rate of 2.0 ml/min, the retention times of I, II, III, IV, V and 2,6 dimethylaniline were 11.6, 16.6, 14.1, 7.1, 10.2 and

[1] Lidocaine hydrochloride monohydrate (I) was obtained from Astra Pharmaceutical Products, Worcester, MA 06106, U.S.A.

15.0 min, respectively. The mobile phase used for separation of VI, VII, VIII and 2,6-dimethylaniline consisted of methanol, water and glacial acetic acid (700 : 300 : 1). At a flow rate of 2.0 ml/min, the retention times of VI, VII, VIII and 2,6-dimethylaniline were 5.6, 2.7, 3.1, and 3.6 min, respectively. The degradation products were identified by HPLC.

Influence of human plasma on compounds III and VI

Freshly collected human plasma [2] was stored in a refrigerator and used within 1 week from the date it was collected. Fifty μl of a standard methanol solution of the compound to be tested was mixed with 7.0 ml of plasma, previously equilibrated to 37.0°C, to give an initial concentration of 0.2 mg/ml. Samples of 1.0 ml were withdrawn from the test medium, mixed immediately with 5.0 ml of ice cold 95% ethanol, and placed in a freezer. When all the samples had been collected, they were centrifuged and the supernatant analyzed by HPLC.

Influence of purified esterases on compound III

The influences of esterase (carboxylic-ester hydrolase EC 3.1.1.1 [3] and butyryl cholinesterase EC 3.1.1.8) [3] isolated from porcine liver and horse serum, respectively, on compound III were tested. The enzymes and 30 μl of a standard solution of the compound in methanol were added to 2.5 ml of 0.05 M Tris buffer, pH 8.0, previously equilibrated to 37°C, to give solutions containing 5.2 units of enzyme and 0.4 mg of III in one ml. Aliquots (50 μl) were injected into the column at various intervals.

Evaluation of the metabolism in bovine liver microsomal preparations

Two kg of minced bovine liver were mixed with 4 liters of homogenization medium (0.34 M sucrose, 1 mM EDTA, and 5 mM Tris-HCl buffer, pH 7.5) and sieved through a screen. The sieved tissue was homogenized for 2 min in a Tekmar grinder. The homogenate was centrifuged successively at $980 \times g$ for 10 min and $10{,}960 \times g$ for 10 min. The resulting supernatant was then centrifuged at $31{,}300 \times g$ for 45 min. All procedures were carried out at 4°C. The microsomal pellet was suspended in an equal volume of 20 mM Tris-HCl buffer at pH 8.0 containing 1 mM EDTA. Centrifugation of this suspension at $123{,}000 \times g$ for 90 min produced the washed microsomes. The resulting pellet could be stored frozen for months with little loss of activity.

The washed microsomes were mixed in a ratio of 1 : 2 (v/v) with 50 mM Tris-HCl buffer, pH 8.0. To 3.0 ml of this solution, previously equilibrated to 37.0°C, was added 0.2 ml of standard solution of the compound to be tested resulting in an initial concentration of 1 mg/ml. Samples of 0.50 ml were withdrawn from the test

[2] The plasma was obtained from the Civitan Regional Blood Center, Gainesville, and contained 80% plasma diluted with anticoagulant citrate phosphate dextrose solution USP.

[3] Sigma Chemicals.

medium, mixed immediately with 1.0 ml of ice-cold 95% ethanol and placed in a freezer. When all samples had been collected, they were centrifuged and the supernatant analyzed by HPLC.

In vivo evaluation in rats

A solution of I, II, III or VI in DMSO was injected slowly through the jugular vein (65 mg/kg) to a group of female Sprague–Dawley rats (150–200 g) [4]. 1.00 ml blood samples were taken at various time intervals (from 15 min to 2 h following administration), mixed with 2.00 ml of ice-cold acetonitrile, and placed in a freezer. When all samples had been collected, they were centrifuged for 5 min at 2500 rpm and stored on ice. The supernatants were then analyzed by HPLC using a Beckman 160 detector at 254 nm and 0.002 sensitivity. In a separate experiment urine samples were collected at 24 and 48 h following i.v. administration of III and VI and analyzed by HPLC. A solution of III and VI in polyethylene glycol was also given p.o. to a group of rats (0.25 g/kg) and blood samples were analyzed as before. In addition, 24 h urine and feces samples were analyzed after the p.o. administration of III and VI.

Determination of the permeability through hairless mouse skin in vitro

The novel lidocaine analogs were also investigated for topical application. Their transdermal absorption was studied in several skin diffusion experiments. Skins from HRS/J hairless mice [5] were fitted over circular teflon holders and held in place with O-rings. The holders were attached to Plexiglas reservoirs with the underside of the skin in contact with pH 7.4 isotonic phosphate-buffered saline solution. The drugs were administered as solutions ('donor phase') containing iso-propyl myristate in methanol, acetone or diethyl toluamide (Table 3). Twenty to 100 μl of the donor phase were applied to the outside of the skin. In those cases where the applied solution contained methanol or acetone, these solvents were evaporated immediately after each application to the skin by blowing warm air on the surface. Each cell was placed on a magnetic stirrer in a 33°C incubator in which a pan of water was kept to maintain a high constant humidity. If the compound formed a suspension in the donor phase, its solubility at 33°C in the non-volatile medium was determined. For analysis, samples of 1 ml were removed from the receptor phase and replaced with fresh buffer.

Evaluation of antiarrhythmic activity of compounds III and VI

Dogs of either sex were anesthetized with pentabarbital sodium, 30 mg/kg i.v. A lead II EKG was recorded and heart rate monitored on a Grass polygraph with appropriate signal treatment modules. A venous catheter was introduced into the inferior vena cava via a femoral vein. After a 20-min stabilization period during which fast paper speed record segments (100 mm/s) were taken to assess EKG

[4] Animal Resources Department, J. Hillis Miller Health Center, University of Florida.
[5] Female hairless mice were obtained from Jackson Laboratories, Bar Harbor, ME 04609.

profile, a 40 mg/kg dose of ouabain was injected i.v. as a bolus. This was followed by 5 mg/kg doses of ouabain, i.v., every 10 min until ventricular arrhythmias occurred—at least 50% ventricular or septal ectopic beats. This usually occurred after a total dose of about 60 mg/kg. After 10 min of sustained arrhythmias, the compound to be tested was given by i.v. infusion at a rate of 0.5 mg/kg/min (2 ml/min flow-rate). The infusion was maintained until a normal sinus node heart rhythm was noted. The infusion was stopped and the total dose of compound administered was determined. The length of time that the normal sinus rhythm persisted after the end of infusion of the compound was also determined.

Results and Discussion

The lidocaine sulfur analogs (II–VIII) were well-defined, stable compounds, which were stable towards hydrolytic enzymes in vitro. Thus, both III and VI were stable towards human plasma and compound III showed no hydrolysis in esterase or butyryl cholinesterase preparations. On the other hand, the amide bond in I, II, and VI was hydrolyzed rapidly by the microsomes, 2,6-dimethylaniline being the main product (Table 1). When II and VI were degraded only small amounts of IV and V, and VII and VIII could be detected, respectively. In a separate experiment compounds IV and V were shown to be essentially stable in the microsomal preparation. Compound III was hydrolyzed very slowly, most likely due to the permanent positive charge (Junge and Krisch, 1975).

In rats, lidocaine hydrochloride (I) and III have comparable rates of disappearance from the general circulatory system, (Table 2), whereas the uncharged compounds (II and VI) disappear much faster from the blood. After intravenous injection of I, III or VI to rats, some 2,6-dimethylaniline could be detected in the blood. The biological half-life of I in rats is comparable to what can be estimated from data available in the literature (Sung and Truant, 1954). Others have estimated the half-life to be less than 30 min in rats after intravenous administration (Keenaghan and Boyes, 1972), compared to 45–60 min in dogs (Boyes et al., 1970), and 90 min in man (Boyes et al., 1971). These same authors found that after oral administration to rats only 0.2% of I was recovered unchanged in the urine, compared to 2.0% and 3.8% in dogs and man, respectively. Compound III was

TABLE 1

OBSERVED PSEUDO-FIRST-ORDER RATE CONSTANTS AND CORRESPONDING HALF-LIVES FOR DISAPPEARANCE OF I, II, III, AND VI IN BOVINE LIVER MICROSOMES

Compound	$k_{obs} \pm$ S.E. (min^{-1})	$t_{1/2}$ (min)
I	0.267 ± 0.008	2.60
II	0.136 ± 0.001	5.07
III	–	~ 500
VI	1.58 ± 0.05	0.44

absorbed slowly after oral administration to rats. The unchanged compound could be detected in the blood but not in the urine. About 7% appeared unchanged in the feces. Compound VI also appeared to have good oral bioavailability. No unchanged compound could be detected in the feces or the urine. Only very small amounts (0.1%) of III or VI could be detected in the urine after intravenous injection into rats.

The skin permeability of lidocaine hydrochloride (I) was remarkably enhanced by adding N,N-diethyl-*m*-toluamide to the donor phase as compared to isopropylmyristate alone, but its permeability coefficient remained significantly smaller than either that of II or VI (Table 3). No hydrolysis of the amide bond could be detected after skin diffusion, but very small amounts of the thioether were oxidized to the corresponding sulfonyl derivative.

In dogs compounds III and VI showed considerable antiarrhythmic activity (Table 4). Although the dose required to produce reversion to normal rhythm was comparable to that of I, the duration of the effect was much longer.

TABLE 2

THE BIOLOGICAL HALF-LIVES OF I, II, III, AND VI IN RATS AFTER SLOW INTRAVENOUS INJECTIONS

Compound	Number of animals	$t_{1/2} \pm$ S.E. (min)
I	5	16.1 ± 2.6
II	7	7.7 ± 0.4
III	5	17.3 ± 1.8
IV	4	6.9 ± 1.7

TABLE 3

PERMEABILITY COEFFICIENT AND TOTAL FLUX THROUGH EXCISED HAIRLESS MOUSE SKIN AT 33° OF COMPOUNDS I, II AND VI UNDER VARIOUS EXPERIMENTAL CONDITIONS

Compound	Donor phase	T lag (h)	V_d (μl) [a]	C_d (mol/l) [b]	Permeability coefficient $\pm$ S.E. (cm/h)	Flux (mg/h·cm^2)
I	1	~ 0	20	1.52	$6.58 \pm 0.04 \times 10^{-9}$	3×10^{-6}
I	3	2.9	100	3.0	$6.46 \pm 0.04 \times 10^{-6}$	5.6×10^{-2}
II	2	0.8	20	1.06	$1.70 \pm 0.03 \times 10^{-4}$	3.7×10^{-2}
VI	1	0.6	20	1.11	$1.19 \pm 0.03 \times 10^{-4}$	3.0×10^{-2}
VI	2	0.6	20	1.08	$9.62 \pm 0.28 \times 10^{-5}$	2.3×10^{-2}
VI	3	0.7	100	0.30	$1.89 \pm 0.03 \times 10^{-3}$	0.13
VI	4	0.9	100	1.68	$1.41 \pm 0.01 \times 10^{-4}$	5.3×10^{-2}

[a] Volume of donor phase applied.

[b] Concentration of the donor phase.

Donor phase: 1 = 10% isopropyl myristate in methanol; 2 = 10% isopropyl myristate in acetone; 3 = suspension in isopropyl myristate and N,N-diethyl-*m*-toluamide (2:1); 4 = suspension in isopropyl myristate.

TABLE 4

ANTIARRHYTHMIC ACTIVITY OF I, III, AND VI IN DOGS

Compound	n [1]	Dose ± S.D. [2] (mg/kg)	Duration ± S.D. [3] (min)
I	4	2.98 ± 1.60	1.92 ± 0.99
III	4	3.82 ± 0.85	15.3 ± 4.1
VI	4	4.0 ± 1.8	24.9 ± 14.11

[1] n is the number of animals in each experiment.

[2] Dose of compound producing reversion to normal rhythm.

[3] Duration of normal synus rhythm after the end of drug infusion.

Some sulfonium analogs of dopamine have been tested for dopaminergic activity and their potency found to be approximately one-tenth that of dopamine (Anderson et al., 1981). This is not the case for the lidocaine analogs where similar doses were needed to obtain the same effect, which, however, lasted much longer. According to the physical membrane occupancy theory of nonspecific antiarrhythmic action (Morgan and Mathison, 1976a and b) the molecules interact with three regions of the myocardial cell membrane: (a) the aromatic portion of the molecule interacts with the alkyl chains of the membrane phospholipids; (b) the ionized amino group interacts with anionic groups of the membrane polypeptides; and (c) the polar substituents on the interconnecting alkyl chain associate with polar groups in the head of the membrane phospholipid molecule. Compound III possesses all of these three criteria, but compound VI, on the other hand, only fulfills two and, thus, should not possess antiarrhythmic activity. The thio group is not able to interact with anionic groups in the same manner as the ionized amino group or the sulfonium group and, hence, this theory does not explain the antiarrhythmic activity of VI. The possibility, although it is not very likely, that VI forms a highly active metabolite in vivo cannot be excluded. If this is the case then significant amounts of this metabolite have to be formed in dogs after intravenous infusion. At present there is no indication that an active metabolite is produced; the main degradation product of VI in the washed microsomal preparation was the inactive 2,6-dimethylaniline and small amounts of this same product could also be detected in in vivo studies in rats.

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