4-Oxospiro[benzopyran-2,4'-piperidines] as Class III Antiarrhythmic Agents. Pharmacological Studies on 3,4-Dihydro-1'-[2-(benzofurazan-5-yl)-ethyl]-6-methanesulfonamidospiro[(2*H*)-1-benzopyran-2,4'-piperidin]-4-one (L-691,121)‡,[1]

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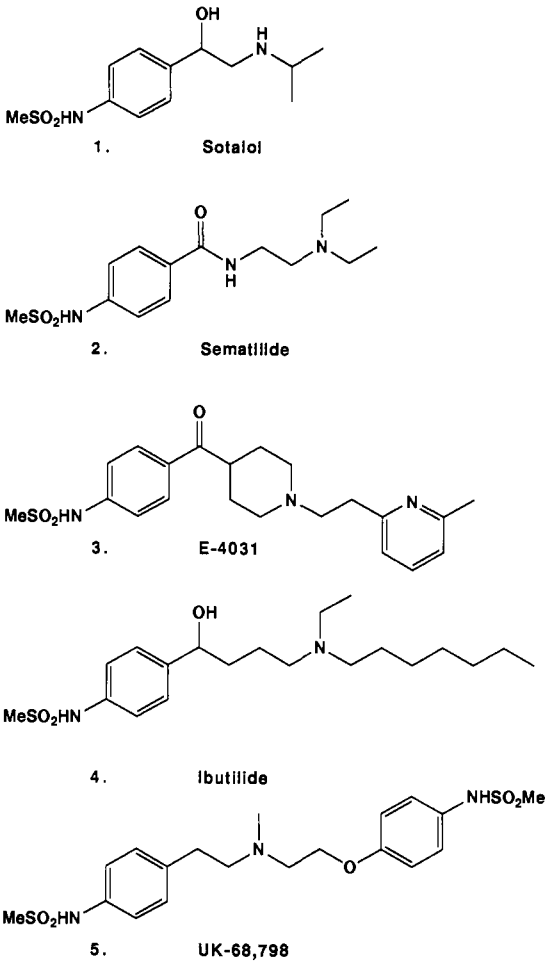
Received December 13, 1991

Sudden coronary death (SCD) is a major public health problem worldwide.[2] In the United States alone, over 400 000 people succumb to SCD each year.[3] It is generally accepted that the terminal event in the majority of SCD cases is a lethal ventricular arrhythmia such as ventricular tachycardia degenerating into ventricular fibrillation. The electrical instability of the myocardium that leads to these rhythm disturbances is usually due to some prior ischemic damage to the heart muscle. Therefore, persons who survive a myocardial infarction are at increased risk for SCD. These people form an identifiable population that would benefit from appropriate prophylactic antiarrhythmic therapy.

Conventional treatments primarily involve the use of class I antiarrhythmic agents.[4] These drugs exert their antiarrhythmic effects by modulating sodium ion transport, hence affecting impulse conduction. However, the results of the cardiac arrhythmia suppression trial (CAST)[5,6] suggest that class I agents are not effective at decreasing long-term mortality. It has been proposed that an agent that could selectively prolong the myocardial refractory period, having little or no effect on impulse conduction (a class III drug) would be useful against arrhythmias leading to SCD.[4,7]

Currently there is no selective class III agent available for clinical use; only amiodarone, a nonspecific agent, is approved for therapeutic applications.[8] Recently however, a number of reports have appeared describing the synthesis and biological activity of potent and selective class III antiarrhythmic agents. Several of these, notably **1** (Sotalol[9]), **2** (Sematilide[10]), **3** (E-4031[11]), **4** (Ibutilide[12]), and

Chart I



‡ This paper is dedicated to Professor Ralph Hirschmann on the occasion of his 70th birthday.

(1) This paper has been presented in part: Elliott, J. M.; Baldwin, J. J.; Buhrow, S. A.; Claremon, D. A.; Lynch, J. J.; Ponticello, G. S.; Radzilowski, E. M.; Remy, D. C.; Selnick, H. G.; Stein, R. B.; White, J. I.; Young, M. B. Benzopyranone Spiropiperidines as Novel, Potent and Selective Class III Antiarrhythmic Agents. Development of L-691,121. Fourth Chemical Congress of North America, New York, NY, August 25–30, 1991; Abstract No. MEDI 191.

(2) Newman, W. P., III; Tracy, R. E.; Strong, J. P.; Johnson, W. D.; Oalmann, M. C. Pathology of Sudden Coronary Death. *Ann. N. Y. Acad. Sci.*; 1982, *382*, 39–49 (Dwyer, E. M., Jr., Greenberg, H. M., Eds.).

(3) Kaplan, H. R. Advances in Antiarrhythmic Drug Therapy—Changing Concepts. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1986, *45*, 2184–2185.

(4) Vaughan Williams, E. M. A Classification of Antiarrhythmic Drugs Reassessed After a Decade of New Drugs. *J. Clin. Pharmacol.* 1984, *24*, 129–147.

(5) The Cardiac Arrhythmia Suppression Trial Investigators, Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression After Myocardial Infarction. *N. Engl. J. Med.* 1989, *321*, 406–412. Echt, D. S.; Liebson, M. D.; Mitchell, L. B. et al. Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo—The Cardiac Arrhythmia Suppression Trial. *N. Engl. J. Med.* 1991, *324*, 781–788.

(6) Woosley, R. L. CAST: Implications for Drug Development. *Clin. Pharmacol. Ther.* 1990, *47*, 553–556.

(7) Vaughan Williams, E. M. Delayed Ventricular Repolarization as an Anti-arrhythmic Principle. *Eur. Heart J.* 1985, *6* (Suppl D), 145–149.

(8) Zipes, D. P.; Prystowsky, E. N.; Heger, J. J. Amiodarone: Electrophysiologic Actions, Pharmacokinetics and Clinical Effects. *J. Am. Coll. Cardiol.* 1984, *3*, 1059–1071. Greene, H. L. The Efficacy of Amiodarone in the Treatment of Ventricular Tachycardia or Ventricular Fibrillation. *Prog. Cardiovasc. Dis.* 1989, *31*, 319–354.

(9) Sahar, D. I.; Reiffel, J. A.; Bigger, J. T., Jr.; Squatrito, A.; Kidwell, G. A. Efficacy, Safety, and Tolerance of d-Sotalol in Patients with Refractory Supraventricular Tachyarrhythmias. *Am. Heart J.* 1989, *117*, 562–568.

(10) Lumma, W. C., Jr.; Wohl, R. A.; Davey, D. D.; Argentieri, T. M.; DeVita, R. J.; Gomez, R. P.; Jain, V. K.; Marisca, A. J.; Morgan, T. K., Jr.; Reiser, H. J.; Sullivan, M. E.; Wiggins, J.; Wong, S. S. Rational Design of 4-[(Methylsulfonyl)amino]benzamides as Class III Antiarrhythmic Agents. *J. Med. Chem.* 1987, *30*, 755–758.

(11) Oinuma, H.; Miyake, K.; Yamanaka, M.; Nomoto, K.-I.; Katoh, H.; Sawada, K.; Shino, M.; Hamano, S. 4'-[(4-Piperidyl)carbonyl]methanesulfonanilides as Potent, Selective, Bioavailable Class III Antiarrhythmic Agents. *J. Med. Chem.* 1990, *33*, 903–905.

(12) Hester, J. B.; Gibson, J. K.; Cimini, M. G.; Emmert, D. E.; Locker, P. K.; Perricone, S. C.; Skaletsky, L. L.; Sykes, J. K.; West, B. E. N-[(ω-Amino-1-hydroxyalkyl)phenyl]methanesulfonamide Derivatives with Class III Antiarrhythmic Activity. *J. Med. Chem.* 1991, *34*, 308–315.

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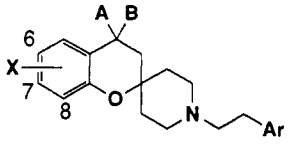
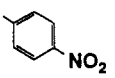
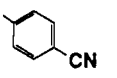
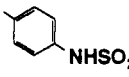
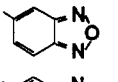
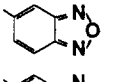
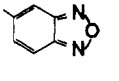
Table I. Effects of Spiro[benzopyran-2,4′-piperidines] on Refractory Period and α_1 Receptor Affinities



compd	X	A, B	Ar	formula[a]	mp, °C	ERP: EC_{25}, μM[b]	RRP: ED_{20ms}, $\mu g/kg$[c]	α_1 receptor affinity: IC_{50}, μM[d]
6	H	A,B = O		$C_{20}H_{22}N_2O_2 \cdot 2HCl$	229–230	0.16	500	
7	6-$MeSO_2NH$	A,B = O		$C_{21}H_{25}N_3O_4S \cdot 2HCl \cdot H_2O$	214–215	0.033	10	0.5
8	7-$MeSO_2NH$	A,B = O		$C_{21}H_{25}N_3O_4S \cdot 2HCl \cdot H_2O$	191–193	6.6		
9	8-$MeSO_2NH$	A,B = O		$C_{21}H_{25}N_3O_4S \cdot 2HCl \cdot H_2O$	188–190	7.4		
10	6-$MeSO_2NH$	A,B = O		$C_{22}H_{26}N_2O_4S \cdot HCl$	263–265	0.007	5	0.1
11	6-$MeSO_2NH$	A,B = O		$C_{22}H_{25}N_3O_6S \cdot HCl \cdot 0.33CH_3OH$	263–265	0.005		0.9
12	6-$MeSO_2NH$	A,B = O		$C_{23}H_{25}N_3O_4S \cdot HCl$	284–285	0.003	7	1.0
13	6-$MeSO_2NH$	A,B = O		$C_{23}H_{29}N_3O_6S_2 \cdot HCl$	285–288	0.074	3	15.0
14	6-$MeSO_2NH$	A,B = O		$C_{22}H_{24}N_4O_5S \cdot HCl$	287–289	0.013	2.8	1.5
15	6-$MeSO_2NH$	A = H, B = OH (±)		$C_{22}H_{26}N_4O_5S \cdot HCl$	242–244	0.9	200	2.3
16	6-$MeSO_2NH$	A = H, B = H		$C_{22}H_{26}N_4O_4S \cdot HCl$	257–259	0.054		3.0

[a] Satisfactory analyses (C, H, and N; ±0.4% of theoretical values) were obtained for all compounds. Spectral data was consistent with indicated structures. [b] Molar concentration of compound required to prolong effective refractory period (ERP) 25% above baseline in ferret isolated right ventricular papillary muscles using a paired pacing protocol.[15] EC_{25} value determined graphically from concentration–response relationships. [c] Intravenous dose required to prolong relative refractory period (RRP) 20 ms above baseline in chloralose anesthetized dogs using a paired pacing protocol.[16] ED_{20ms} value determined graphically from dose–response relationships. [d] Binding activity at bovine brain α_1 receptors determined in a filtration-based assay using [^{3}H]prazosin as the radioligand.

5 (UK-68,798[13]) (Chart I) are in clinical trials. All of the compounds listed exert their class III effect (prolonging myocardial refractoriness) by blocking outward repolarizing potassium current.[14]

We report here the results for a series of compounds based on the 4-oxospiro[benzopyran-2,4′-piperidine] ring system. Compounds were initially evaluated in vitro in an isolated ferret papillary muscle preparation using standard protocols.[15] The EC_{25} values are the concentrations required to increase effective refractory period (ERP) by 25% above baseline in tissue paced at 1 Hz. Promising compounds were further studied in vivo in chloralose anesthetized dogs to determine their cardiac electrophysiologic and hemodynamic profiles. The ED_{20ms} values are the concentrations required to increase ventricular relative refractory period by 20 ms above baseline.[16]

Compound 6 (Table I) containing the above spirocyclic ring system with a 2-pyridylethyl side chain (similar to the side chain found in 3) attached to the piperidine nitrogen showed an in vitro potency of 0.16 μM. Although this compound is less potent than 3 by a factor of 2–3, this result demonstrated the utility of this ring system for the preparation of class III antiarrhythmic agents.

The methanesulfonamide group attached to an aromatic ring is common to most published class III agents, and it has been speculated that its presence is essential for

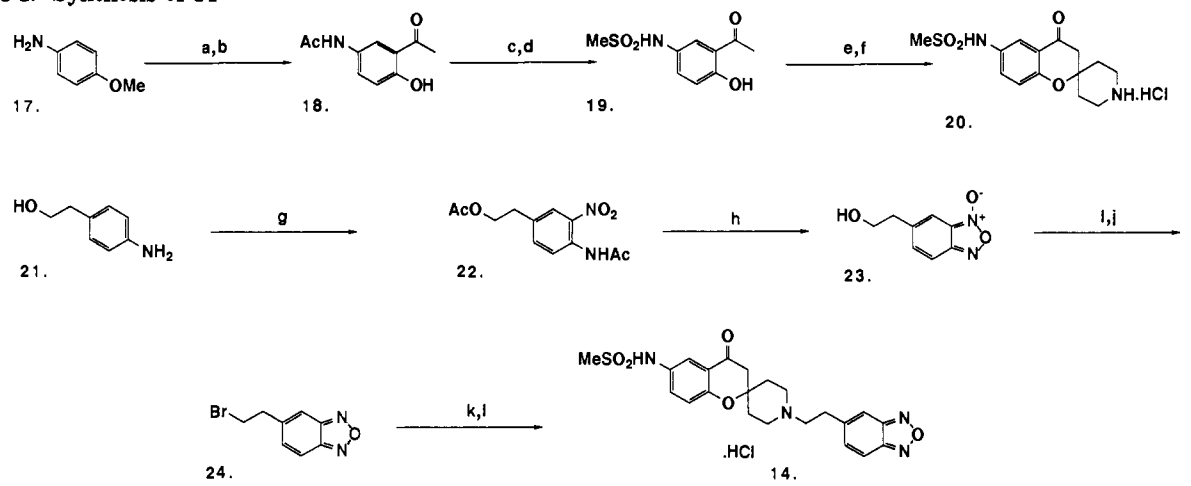
(13) Cross, P. E.; Arrowsmith, J. E.; Thomas, G. N.; Gwilt, M.; Burges, R. A.; Higgins, A. J. Selective Class III Antiarrhythmic Agents. 1. Bis(arylalkyl)amines. *J. Med. Chem.* **1990**, *33*, 1151–1155. *Drugs Future* **1991**, *16*, 521–526.

(14) Colatsky, T. J.; Follmer, C. H. K^+ Channel Blockers and Activators in Cardiac Arrhythmias. *Cardiovasc. Drug Rev.* **1989**, *7*, 199–209. E-4031 and Sotalol have been shown to block a single component of the delayed rectifier potassium current: Sanguinetti, M. C.; Jurkiewicz, N. K. Two Components of Cardiac Delayed Rectifier K^+ Current. Differential Sensitivity to Block by Class III Antiarrhythmic Agents. *J. Gen. Physiol.* **1990**, *96*, 195–215.

(15) Baskin, E. P.; Serik, C. M.; Wallace, A. A.; Brookes, L. M.; Selnick, H. G.; Claremon, D. A.; Lynch, J. J., Jr. Effects of New and Potent Methanesulfonanilide Class III Antiarrhythmic Agents on Myocardial Refractoriness and Contractility in Isolated Cardiac Muscle. *J. Cardiovasc. Pharmacol.* **1991**, *18*, 406–414.

(16) Wallace, A. A.; Stupienski, R. F.; Brookes, L. M.; Selnick, H. G.; Claremon, D. A.; Lynch, J. J., Jr. Cardiac Electrophysiologic and Inotropic Actions of New and Potent Methanesulfonanilide Class III Antiarrhythmic Agents in the Anesthetized Dog. *J. Cardiovasc. Pharmacol.* **1991**, *18*, 687–695.

Scheme I. Synthesis of 14[a]



[a] Reagents: a, Ac_2O, CH_2Cl_2 (90%); b, CH_3COCl, $AlCl_3$, CH_2Cl_2 (87%); c, HCl, H_2O (99%); d, CH_3SO_2Cl, pyridine, CH_2Cl_2 (69%); e, *N*-benzoyl-4-piperidone, pyrrolidine, MeOH (87%); f, HCl, H_2O, EtOH (59%); g, Ac_2O, 4-DMAP and then HNO_3 (72%); h, KOH, MeOH and then NaOCl–H_2O (98%); i, $(MeO)_3P$, MeOH (75%); j, CBr_4, PH_3P, CH_2Cl_2 (86%); k, **20**, $NaHCO_3$, EtOH; l, HCl, EtOH [41% from **20**].

Table II. Comparison of Class III Agents

compd	ERP: EC_{25}, μM[a]	RRP: ED_{20ms}, $\mu g/kg$[b]
14	0.013 (0.011–0.015)[c]	2.8 (2.10–3.55)[d]
5	0.018 (0.015–0.021)[e]	5.2 (4.2–6.6)[f]
3	0.058 (0.048–0.068)[g]	17.4 (12.9–23.3)[h]

[a] Molar concentration of compound required to prolong effective refractory period (ERP) 25% above baseline in ferret isolated right ventricular papillary muscles using a paired pacing protocol.[15] EC_{25} value ±95% confidence limits determined from concentration–response relationships using a parallel line bioassay technique. [b] Intravenous dose required to prolong relative refractory period (RRP) 20 ms above baseline in chloralose-anesthetized dogs using a paired pacing protocol.[16] ED_{20ms} value ± 95% confidence limits determined from dose–response relationships using a parallel line bioassay technique. [c] $n = 8$. [d] $n = 7$. [e] $n = 12$. [f] $n = 8$. [g] $n = 8$. [h] $n = 16$.

maximum potency.[10,11,17] Accordingly, a series of compounds with 2-pyridylethyl substitution on the piperidine nitrogen and a methanesulfonamide group attached to the benzopyranone ring in the 6-, 7- and 8-positions were synthesized (Table I, compounds **7–9**). Substitution in the 7- or 8-positions causes a loss in potency, compared to the unsubstituted compound. Only when the methanesulfonamide is introduced in the 6-position (compound **7**) is there an improvement in the EC_{25} value. This increases the in vitro potency to 0.033 μM to give a compound which is more potent than **3** ($EC_{25} = 0.058\ \mu M$[15]) and comparable to **5** ($EC_{25} = 0.018\ \mu M$[15]).

With the 6-methanesulfonamido-4-oxospiro[benzopyran-2,4′-piperidine] system fixed, a series of compounds with different aromatic or heteroaromatic rings attached via flexible chains to the piperidine nitrogen were examined (Table I, compounds **10–14**). It was found that the optimum length for the linking chain was two carbons. Although most of these compounds show excellent in vitro activity in the ferret papillary muscle assay, many of the monosubstituted aryl examples also had high affinities for α_1 receptors[18] which would be expected to introduce the complication of additional cardiovascular effects. The compound with a 4-nitrophenyl group **11** showed exceptional activity, and since the benzofurazanyl group was an effective replacement for nitrophenyl in calcium channel blockers,[19] compound **14** was synthesized. In vitro and in vivo evaluation established that **14** was both potent and essentially devoid of significant affinity for α_1 receptors.

Finally, the effect on potency of the benzopyranone carbonyl group was examined. The compound with a (benzofurazan-5-yl)ethyl group attached to the piperidine nitrogen **14** was reduced to give the racemic benzopyranol **15**. This change, however, led to a large loss of potency. Synthesis of the compound in which the carbonyl group is replaced by a methylene group gave **16** which, although more potent than the alcohol, was less potent than the ketone.

On the basis of its in vitro and in vivo properties, the compound with a (benzofurazan-5-yl)ethyl side chain attached to a 6-methanesulfonamido-4-oxospiro[benzopyran-2,4′-piperidine] **14** (L-691,121) was selected for further studies.

The preparation of **14** is shown in Scheme I. *p*-Anisidine (**17**) was converted to 5-acetamido-2-hydroxyacetophenone (**18**) by a modification of the published method.[20] Hydrolysis and treatment with methanesulfonyl chloride in the presence of pyridine gave 5-methanesulfonamido-2-hydroxyacetophenone (**19**). Spirocyclization of this compound with *N*-benzoyl-4-piperidone occurred in the presence of pyrrolidine[21] and acid hydrolysis gave the spirocyclic secondary amine as its hydrochloride **20**. 4-Aminophenethyl alcohol (**21**) was treated with acetic anhydride and then nitric acid[22] to give the nitroacetamide **22**. Base hydrolysis and oxidation with sodium hypochlorite gave the benzofuroxan **23**. Deoxygenation with trimethyl phosphite and bromination gave the benzofurazan ethyl bromide **24**. This was then used to alkylate the spirocyclic nucleus **20** to give **14**.

(17) Morgan, T. K., Jr.; Lis, R.; Lumma, W. C., Jr.; Nickisch, K.; Wohl, R. A.; Phillips, G. B.; Gomez, R. P.; Lampe, J. W.; Di Meo, S. V.; Marisca, A. J.; Forst, J. Synthesis and Cardiac Electrophysiological Activity of N-Substituted-4-(1H-imidazol-1-yl)benzamides—New Selective Class III Agents. *J. Med. Chem.* **1990**, *33*, 1091–1097.

(18) Buhrow, S. Unpublished results.

(19) Handler, C. E.; Rosenthal, E.; Tsagadopoulos, D.; Najm, Y. Comparison of Isradipine and Nifedipine in Chronic Stable Angina. *Intl. J. Cardiol.* **1988**, *18*, 15–26.

(20) Chang, C. T.; Chen, F. C.; Chen, T. S.; Hsu, K. K.; Ueng, T.; Hung, M. Synthesis of 6-Halogenoflavones and Related Compounds. *J. Chem. Soc.* **1961**, 3414–3417.

(21) Kabbe, H. J. Eine Einfache Synthese von 4-Chromanonen. *Synthesis* **1978**, 886–887.

(22) Modification of the procedure published in: Mazur, S.; Jayalekshmy, P. Chemistry of Polymer-Bound o-Benzyne. Frequency of Encounter between Substituents on Cross-Linked Polystyrenes. *J. Am. Chem. Soc.* **1979**, *101*, 677–683.

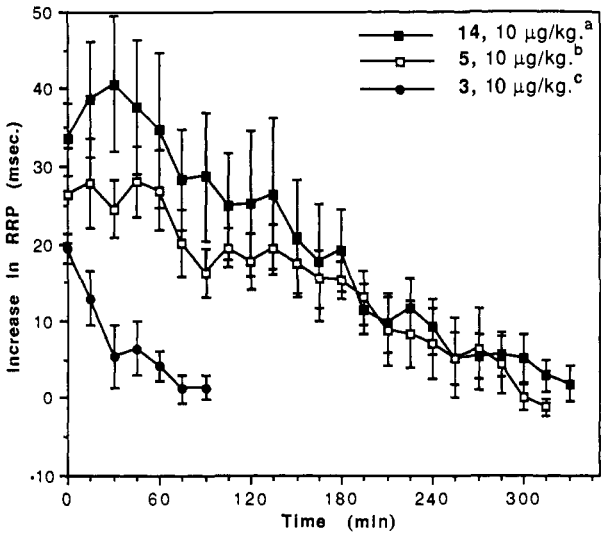


Figure 1. Comparison of durations of action of class III agents after iv dosing in chloralose anesthetized dogs. Test agents were administered intravenously over a period of 5 min in a solution of 5% dextrose in distilled water. Class III activity was monitored by the determination of ventricular refractory period (RRP) using a paired pacing protocol.[16] Values are mean ± SEM. [a]$n = 5$. [b]$n = 4$. [c]$n = 6$.

The full hemodynamic profile of **14** at 1–1000 μg/kg showed increases in paced QT and QT_c intervals and a modest increase in LV+dP/dt. Similar effects were found for **3** and **5** in this preparation.[23] Compound **14** did not cause any significant change in excitation threshold, electrocardiographic QRS interval, heart rate, or mean arterial pressure.

Isolated guinea pig ventricular myocytes were used to determine the effects of **14** on K^+ and Ca^{2+} currents. Similar to **3**,[14] **14** specifically blocks a rapidly activating component (I_{Kr}) of delayed rectifier K^+ current (I_K), while having no effect on the larger, slowly activating component (I_{Ks}) of I_K, inward rectifier K^+ current (I_{K1}), or L-type Ca^{2+} current.[24]

A comparison of the in vitro and in vivo effects on refractory period of **14**, **5**, and **3** (Table II) and a comparison of the durations of increases in refractory period after iv dosing in chloralose anesthetized dogs (Figure 1) are shown. These studies show that **14** is comparable to **5** and clearly more potent than **3**. Compound **14** was well absorbed and

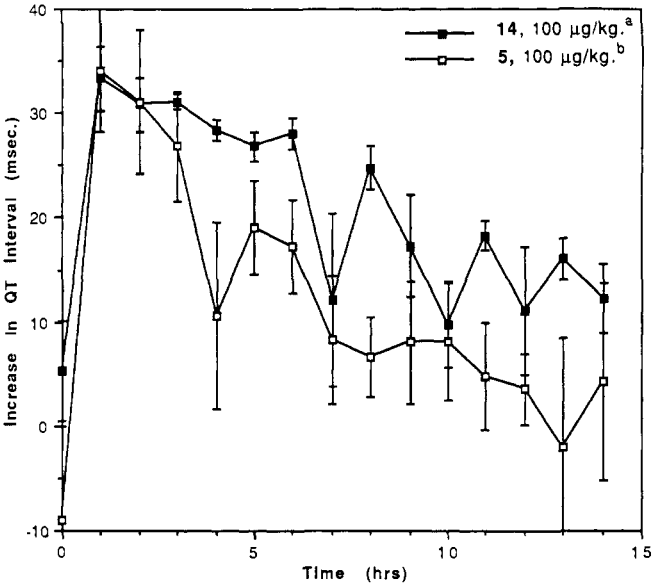


Figure 2. Comparison of durations of action of class III agents after po dosing in Holter-monitored conscious dogs. Test agents were administered orally by gastric lavage in a solution of 5% dextrose in distilled water. Class III activity was monitored by the determination of electrocardiographic QT interval prolongation, recorded on Holter monitors. Values are mean ± SEM. [a]$n = 4$. [b]$n = 4$.

a comparison of the increase in QT interval, measured in conscious dogs after oral dosing, is shown (Figure 2).

In conclusion, we have found that conformationally constrained compounds based on the 4-oxospiro[benzopyran-2,4′-piperidine] ring system with a 6-methanesulfonamide substituent are potent class III antiarrhythmic agents. One of these compounds, **14**, shows in vivo potency comparable to **5**, good absorption, and long duration of action in animal models and is being studied in man. Further investigations of the medicinal chemistry of compounds based on this spirocyclic ring system are being carried out and will be the subject of forthcoming publications.

Acknowledgment. We are indebted to S. McKee for preparation of synthetic intermediates, E. Mazack for determination of α_1 receptor binding affinities, E. Baskin and C. Serik for in vitro ERP determinations, R. Stupienski and A. Wallace for in vivo RRP determinations, and J. Moreau for analytical determinations.

Supplementary Material Available: Hemodynamic data for iv dosing of **14** in chloralose anesthetized dogs, elemental analyses for **6**–**16**, and full synthetic procedures for the preparation of **14** and **18**–**24** (6 pages). Ordering information is given on any current masthead page.

(23) Stupienski, R.; Wallace, A.; Brookes, L. M.; Claremon, D. A.; Selnick, H. G.; Stein, R. B.; Lynch, J. J., Jr. Cardiac Electrophysiologic and Hemodynamic Effects of Class III Antiarrhythmic Agents in Anesthetized Dogs. *FASEB J.* **1990**, *4*, A265.

(24) Sanguinetti, M. C.; Jurkiewicz, N. K. Personal communication.