with each dose administered to at least eight animals.

Acknowledgment. We acknowledge the contributions of the following individuals and their staffs: Raymond Everett and Jon Kimball for the toxicology, Frank Santillo and Jeffrey Hane for the optical purity determinations, and Stephen Clemens for the spectroscopy support.

Registry No. **1a**, 92-43-3; (±)-**1b**, 133043-49-9; (±)-**1c**, 133043-50-2; (±)-**1d**, 133043-51-3; (±)-**1e**, 133043-52-4; (±)-**1f**, 133043-53-5; (+)-**1f**, 133043-34-2; (−)-**1f**, 133043-35-3; (±)-**1g**, 133043-54-6; (±)-**1h**, 133043-55-7; (±)-**1i**, 133043-56-8; (±)-**1j**, 133043-57-9; (±)-**1k**, 133043-58-0; (±)-**1l**, 133043-59-1; (±)-**1m**, 133071-03-1; (±)-**1n**, 133043-60-4; (±)-**1o**, 133043-61-5; (±)-**1p**, 133043-62-6; **2a**, 7190-52-5; (±)-**2f**, 133043-63-7; **3**, 38604-68-1; **4b**, 133043-64-8; **4f**, 133043-65-9; (±)-**5**, 133043-36-4; (±)-**6**, 133043-37-5; (±)-**7**, 133043-38-6; (±)-**8**, 133043-39-7; (±)-**9**, 133043-40-0; (±)-**10**, 133043-41-1; (±)-**11**, 133043-42-2; (±)-**12**, 133043-43-3; (±)-**13**, 133043-44-4; (±)-**14**, 133043-45-5; (±)-**15**, 133043-46-6; (±)-**16**, 133043-47-7; (±)-**17**, 133043-48-8; **19** (R_3 = H, X = 4-OCH_2Ph), 6080-54-2; **20** (R_3 = H, X = 4-OCH_2Ph), 133043-66-0; **22**, 61446-43-3; HMPA, 680-31-9; 5-LO, 80619-02-9; (*R*)-(+)-$PhCH(CH_3)NCO$, 33375-06-3; $PhNH_2$, 62-53-3; $Br(CH_2)_2OCH_3$, 6482-24-2; TBDMS-Cl, 18162-48-6; Pd, 7440-05-3; $PhNHNH_2$, 100-63-0; $(CH_3)_2C{=}C(COOEt)_2$, 6802-75-1.

Supplementary Material Available: Tables listing crystal data, atomic coordinates, thermal parameters, bond lengths and angles, and a stereoview of **1f** (5 pages). Ordering information is given on any current masthead page.

The Synthesis and Potassium Channel Blocking Activity of Some (4-Methanesulfonamidophenoxy)propanolamines as Potential Class III Antiarrhythmic Agents

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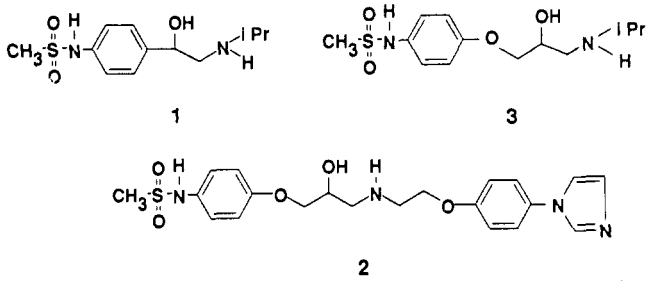
The synthesis of 22 (4-methanesulfonamidophenoxy)propanolamines and their testing on isolated guinea pig cardiac myocytes, on isolated preparations from guinea pig atria, and on rat blood pressure are described. Secondary amines in the series (**11a–f**) showed residual β-blocking activity, whereas incorporation of *N*-methyl phenylalkyl and 4-phenyl alicyclic amine groups abolished β-blocking activity but led to enhanced ability to block the channel conducting the delayed rectified potassium current, and hence produced an increase in the cardiac action potential duration (APD). Incorporation of hydrophobic Cl and CF_3 groups further enhanced potassium channel blocking activity. Compounds **8l** and **8m** produced a significant increase in APD at nanomolar concentrations, with no effect on cardiac muscle conduction velocity, and hence merit further investigation as Class III antiarrhythmic agents. Methylation of the methanesulfonamido group abolished channel-blocking activity; 4-carboxy and 3-methanesulfonamido analogues retained activity but at a reduced level.

Several years after its introduction as a β-blocking agent it was observed[1] that sotalol, **1**, produced a concentration-dependent increase of the cardiac action potential duration (APD) in a wide range of tissues, and it was this observation that prompted Vaughan Williams to designate a third category (class III) of antiarrhythmic agents.[2] This observation was not followed up immediately, but a resurgence of interest in sotalol (see ref 3 for a report on a recent symposium) occurred as a consequence of the increasing use of amiodarone (a compound that also increased cardiac APD) as an antiarrhythmic agent, and groups at Lilley,[4] Pfizer,[5] and Eisai[6] have recently reported results of searches for more potent class III agents.



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3

2

Recently a report has been published[7] by another group describing the development of a mixed function class II and class III antiarrhythmic agent **2** which, like ours, is based on an oxypropanolamine analogue of sotalol. The Berlex group sought to develop a mixed function compound on the grounds that a β-blocking (class II) action would reduce the possibility of a sympathetically mediated triggering of an arrhythmia, and that the increased cardiac refractory period produced by a class III agent would prevent a reentrant rhythm from becoming established. Our approach was quite different. There is a clinical need for a drug to reduce the likelihood of an arrhythmia developing in the recovery period immediately following a myocardial infarction. Chamberlain[8] has shown that during the 4 or 5 days following an infarction the risk of mortality is increased by the use of a β-blocking agent, as a consequence of an increased risk of heart failure. Under these circumstances the requirement is for a rapidly acting selective class III agent, devoid of class I or II actions. In general, as far as clinical use is concerned, the difficulty

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0022-2623/91/1834-1570$02.50/0

with a mixed-function compound is that the doses for the two independent activities cannot be optimized. As a research tool it will be much easier to analyze and exploit the effects of a compound with a potent and specific effect on only one component of the complex of events that make up the cardiac action potential. We also had it in mind to produce a compound that could be prepared in a radioactive form for use in tissue-binding studies. We therefore sought a compound with enhanced but selective class III properties.

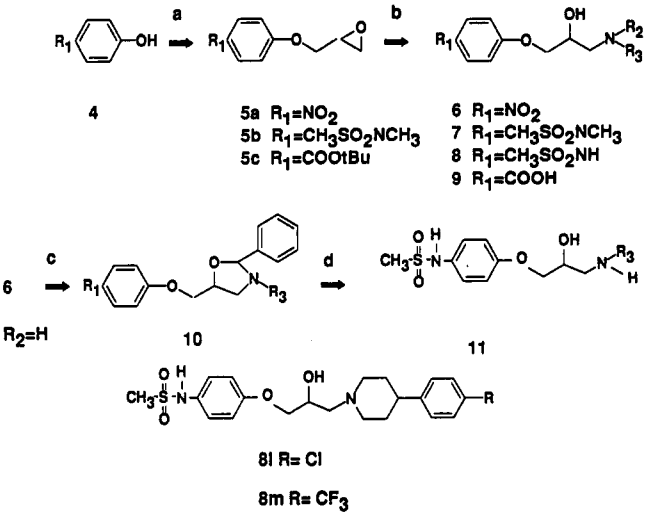
A major component of sotalol's ability to prolong cardiac APD has been shown to be due to a blockade of one particular potassium channel, that carrying the delayed rectifier potassium current,[9] an effect that appears to be independent of its antiadrenergic properties. For example, the two enantiomeric forms of sotalol are equiactive in their effect on the APD, whereas the *l* enantiomer is some 20 times more potent than the *d* as a β-blocker.[10] This observation, and others (see 4 for a discussion of clofilium, a quaternary ammonium compound with class III activity, and related compounds), lends support to the notion that potassium channel and β-adrenoceptor blocking activity are separable, and that a specific class III antiarrhythmic agent, devoid of class I (membrane stabilizing) or class II (β-adrenoceptor blocking) activity, could be derived from sotalol. This report describes the development of such a compound.

Sotalol is one of the ethanolamine group of β-blockers. The first step in our study was to determine whether its oxypropanolamine analogue, **3**, also possessed APD-prolonging activity. Such a compound would provide a more convenient starting point for synthetic variation. Compound **3** was first synthesized in the laboratories of I.C.I. as part of the program of work that led to practolol. The synthesis was described[11] as "not trivial" and, apart from a brief report of its cardioselective β-blocking activity,[12] no further details concerning this compound appear to have been published. We resynthesized **3**, confirmed that it was indeed a β-blocker and, more significantly, that it also possessed the ability to prolong cardiac APD, with a potency similar to that of sotalol. The compounds described in this report are therefore all oxypropanolamines, and in varying the structure of **3** attention has been focused on the methanesulfonamide substituent in the aromatic ring, the conformational flexibility of the side chain, and, because of its well-known determinant effect on adrenergic selectivity, the nature of the substituents on the side chain nitrogen atom.

Chemistry

Most phenoxypropanolamines in the β-blocking series have been prepared by routes utilizing the first steps shown in Scheme I. A suitably substituted phenol was reacted with epichlorhydrin, under basic conditions, and the side chain was elaborated by opening the epoxide ring in **5** with an appropriate primary or secondary amine. This route, using 4-acetamidophenol as the starting material, was successfully used for the synthesis of practolol, but an attempt to repeat it with 4-methanesulfonamidophenol (**4a**, $R_1 = CH_3SO_2NH$) was quickly abandoned. The methanesulfonamido group is significantly more acidic

Scheme I[a]

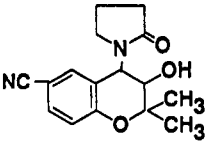


[a] (a) epichlorhydrin, NaOH; (b) primary or secondary amine; (c) benzaldehyde, Δ, H_2O; (d) H_2, Pd–C; CH_3SO_2Cl; HCl, H_2O.

than an acetamido group and in strongly basic conditions **4a** becomes bifunctional, with the phenolic and sulfonamido groups equally likely to ionize. Reaction with epichlorhydrin led only to a complex polymeric mixture. On the other hand, the corresponding *N*-methyl compounds (**4b**, $R = CH_3SO_2NCH_3$), which can only form a phenoxy anion, reacted smoothly with epichlorhydrin and, on opening the epoxide ring with a suitable amine, gave **7**. In order to obtain the secondary sulfonamides the more extended route shown in Scheme I was followed.

Nitrophenol was reacted with epichlorhydrin to give **5a**, which was reacted with an appropriate amine to yield a series of oxypropanolamines; when a secondary amine was used, reduction of the aromatic nitro group followed by mesylation gave the desired tertiary amines **8**. In the secondary amine series protection of the side-chain secondary amino group was necessary before the final mesylation stage, and this was achieved by condensing propanolamine **8** ($R_2 = H$) with benzaldehyde to form oxazolidine **10**. The presence of both diastereoisomers, with the 2-phenyl substituent cis or trans to the phenoxymethyl substituent, could be detected by the splitting of the NMR signal of the C2 proton, but both isomers were carried forward together. Reduction of the nitro group followed by selective mesylation of the aromatic amino group and subsequent acid hydrolysis of the oxazolidine ring proceeded smoothly to give the desired products **11**. Formation of carboxyl analogue **9** was effected by starting with the *tert*-butyl ester of 4-hydroxy benzoic acid, with cleavage of the *tert*-butyl ester with trifluoroacetic acid as the final step.

Cromakalim (BRL-34915, **12**) is one of a group of potent potassium channel openers[13] that are finding increasing use as vasodilators. Although described as dihydro-



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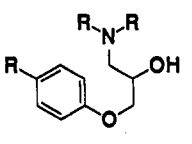

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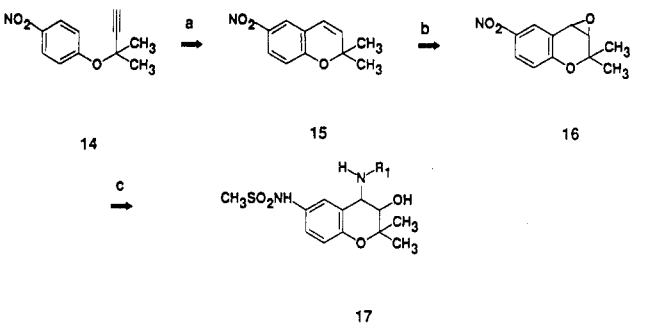
Scheme II[a]



[a] (a) heat; (b) *N*-bromosuccinimide, NaOH; (c) R_1NH_2; H_2, Pd–C; CH_3SO_2Cl.

benzpyran derivatives, they may also be regarded as oxypropanolamines that are folded in a cyclic conformation **13**, with the side chain pinned back to the aromatic ring. Although cromakalim itself contains a nonbasic pyrrolidone group, earlier members of the series had 4-amino substituents,[14] and it seemed worthwhile to explore the consequences of incorporating the methanesulfonamido group, which appears to be characteristic for potassium channel blocking activity, into the dihydrobenzpyran system. This approach culminated in the synthesis of **17a** (R = isopropyl) and **17b** (R = phenethyl). The synthesis of these compounds (Scheme II) was modeled on that for cromakalim.[14] A Claisen rearrangement of the 4-nitro propargyl ether **14** generated benzpyran system **15**, which was converted to epoxide **16**, via a bromohydrin. This latter stage was the only one that caused any difficulty. In our hands reaction of the pyran with *N*-bromosuccinimide only gave consistent yields of bromhydrin if the amount of water in the reaction system was very carefully controlled. Trans opening of the epoxide ring with primary amines proceeded regio- and stereoselectively, to give *trans*-4-amino 3-alcohols because of occlusion of the 3-position by the *gem*-dimethyl group in the pyran ring. The rigidity of the benzpyran ring imposes a fixed dihedral angle of 74° between the C–N and C–O bonds of the propanolamine system, which precludes the formation of an oxazolidine ring. However, protection of the 3-hydroxyl and 4-amino groups proved unnecessary; mesylation of the unprotected compound occurred exclusively on the aromatic amino group, possibly due to the steric congestion on the periphery of the pyran ring.

Pharmacological Testing. Pharmacological activity was assessed by the ability to prolong the action potential in stimulated isolated guinea pig ventricular myocytes using an intracellular recording microelectrode.[15] Response was measured as the prolongation of the action potential at the 90% repolarization level (APD_{90}). An increase of ca. 33% in APD_{90} was maximal in most cells and this increase was elicited by drug concentrations that also caused almost complete inhibition of the delayed rectifier current, I_K. The responses shown in Table I are expressed as a percentage of this maximal prolongation produced by the concentration(s) indicated; a typical response is shown in Figure 2. These preparations of isolated ventricular myocytes are characteristically less sensitive to the effects of class III agents than are Purkinje cells[16] but are more representative of the in vivo target for these compounds.

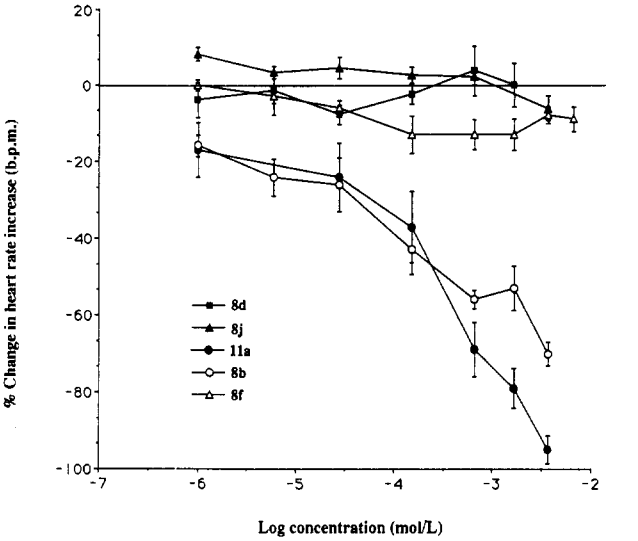


Figure 1. Dose–response relationship showing the effect of test compounds on the change in heart rate induced by 250 ng/kg isoprenaline in the pithed rat preparation. Compounds **8j**, **8d**, and **8f** are tertiary amines; **8b** and **11a** are secondary amines. Data are from three to five preparations for each compound.

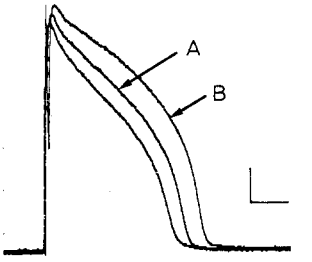


Figure 2. Records from an isolated guinea pig ventricular cell stimulated at 1 Hz at 37 °C. The effects of compound **8m** and Pfizer UK 68,798 are shown in the same cell. The control action potential was stable over 3 min; 100 nM UK 68,798 was then added and allowed to equilibrate for 4 min, during which time an increase in action-potential duration was seen (trace A). Subsequently, compound **8m** was added at a concentration of 10 nM, producing a further increase in action-potential duration (trace B).

The outcome of a typical experiment to show that these compounds block the delayed rectified potassium current channel is shown in Figure 3. The delayed rectifier potassium current, I_K, was recorded by applying step depolarizations under voltage-clamp conditions, e.g. to +40 mV from a holding potential of −50 mV for 300 ms, and was measured as the size of the outward tail current on repolarization to the holding potential.[17] The effect of the present compounds on I_K was assessed from the extent of reduction of the outward tail current (Figure 3).

Results

Class III antiarrhythmics, by definition, prolong cardiac APD and this was the primary parameter used to survey the compounds reported here. An early report[12] indicated that extending the side chain of sotalol to an oxypropanolamine group doubled its potency is a β-blocking agent, and we found that class III activity increased in about the same ratio. However, development of the sub-

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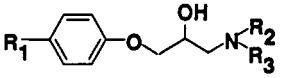
Table I. Physical and Biological Properties of (4-Sulfonamidophenoxy)propanolamines



compd[a]	R_1	R_2	R_3	mp,[b] °C	concn, nM	ΔAPD_{90}[c]
			Tertiary Amines			
8c[d]	CH_3SO_2NH	CH_3	$C_6H_5(CH_2)_2$	glass	100	48
					1000	88
8d	CH_3SO_2NH	CH_3	$C_6H_5(CH_2)_3$	glass	100	70
8e[e]	CH_3SO_2NH	CH_3	$C_6H_5CH{=}CHCH_2$	glass	50	50
					100	100
8f[f]	CH_3SO_2NH	CH_3	$3,4\text{-}Cl_2C_6H_3(CH_2)_2$	glass	1	20
					10	42
					100	85
8g	CH_3SO_2NH	CH_3	$3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_2$	glass	100	40
					1000	100
8g[g]	CH_3SO_2NH	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_2$	glass	100	65
					1000	100
8i	CH_3SO_2NH	C_2H_5	C_2H_5		1000	25
					10000	85
			Secondary Amines			
8a	$CH_3SO_2NCH_3$	H	$i\text{-}C_3H_7$	glass	10000	*h*
					33000	*h*
8b	$CH_3SO_2NCH_3$	H	$C_6H_5(CH_2)_2$	156–158	10000	*h*
					33000	*h*
11a	CH_3SO_2NH	H	$i\text{-}C_3H_7$	126–128[i]	10000	*h*
					33000	33
11b	CH_3SO_2NH	H	CH_3	glass	10000	*h*
					50000	*h*
11c	CH_3SO_2NH	H	$t\text{-}C_4H_9$	146–147[i]	33000	40
					50000	75
					75000	75
11d	CH_3SO_2NH	H	$C_6H_5(CH_2)_2$	213	10000	80
11e	CH_3SO_2NH	H	$4\text{-}ClC_6H_4(CH_2)_2$	206	10000	90
11f	CH_3SO_2NH	H	$3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_2$	101–103[i]	1000	15
					10000	80
1, sotalol					100000	75
					50000	30
19, Pfizer UK68798					50	23
					100	63
					250	100

compd	R_1	NR_2R_3	mp,[b] °C	concn, nM	ΔAPD_{90}[c]
		Alicyclic Amines			
8j	CH_3SO_2NH	4-phenylpiperidine	220–221	100	48
				1000	100
8k	CH_3SO_2NH	4-phenylpiperazine	237	1000	78
				10000	100
8l	CH_3SO_2NH	4-(4-chlorophenyl)piperidine	215	1	50
				10	100
8m	CH_3SO_2NH	$4\text{-}(4\text{-}CF_3\text{-phenyl})$piperidine	115	1	40
				10	100
				50	100
8n	CH_3SO_2NH	tetrahydroisoquinoline	glass	100	60
8o	COOH	4-phenylpiperidine	212–214[j]	1000	36
8p[k]	$(3)CH_3SO_2NH$	4-phenylpiperidine	glass	1000	48

[a] Analyses of hydrochloride salts (except where indicated) for C, H, N, and S were 0.4% of the expected values. [b] Hydrochloride salt, except where indicated. [c] Increase in duration or cardiac APD at 90% repolarization, as a percentage of the maximum increase observed. Each result is the mean of at least four sets of measurements; SE ± 3%. [d] Calcd for $C_{19}H_{26}N_2O_4S\cdot HCl\cdot 2H_2O$: C, 50.6; H, 6.95; N, 6.21; S, 7.1. Found: C, 50.1; H, 6.75; N, 6.35; S, 7.4. [e] ($C_{20}H_{26}N_2O_4S$) C, H, N; S: calcd 7.50; found 7.0. [f] ($C_{19}H_{24}N_2O_4S$) C, N, S; H: calcd 5.44; found 5.9. [g] ($C_{23}H_{34}N_2O_6S$) C, H, N; S: calcd 6.14; found 6.6. [h] No detectable change. [i] Free base. [j] Trifluoroacetate salt. [k] Calcd for $C_{21}H_{28}N_2O_4S\cdot HCl$: C, 57.2; H, 6.65; N, 6.35; S, 7.26. Found: C, 56.6; H, 7.0; N, 6.5; S, 7.0.

stituents on the side chain amino group showed that these two properties do not march together. Within the secondary amine series, increasing the size of the nitrogen substituent from isopropyl (**11a**, Table I) to phenylethyl (**11d**), for example, increased class III activity while diminishing but not abolishing β-blocking activity. This effect was also observed by the Berlex group,[7] and it may be noted that the optimum compound in their series (**2**) is a phenoxyethyl secondary amine, albeit with a hydrophilic 4-imidazolyl substituent on the benzene ring.

It is well-known, however, that within the alkanolamine series significant β-blocking activity is shown only by secondary amines (Figure 1). The incorporation of tertiary amino groups into the side chain sustained or increased class III activity but, as expected, abolished β-blocking activity (Figure 1); for example, the *N*-methyl derivative **8c** was 10 times more effective in prolonging APD than the corresponding secondary amine **11d**, but was devoid of β-blocking activity. Attention thereafter was concentrated on tertiary amines.

Increasing the size of one of the nitrogen substituents to phenylalkyl produced compounds (e.g. **8c** and **8d**, Table I) that were active at submicromolar concentrations (Figure 2). Incorporating the nitrogen atom into a ring, which has the effect of reducing the conformational flexibility of the terminal section of the side chain, did not

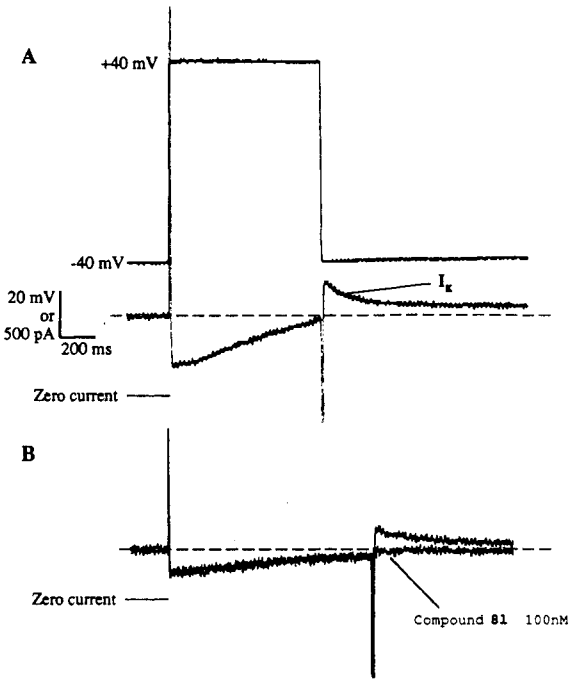
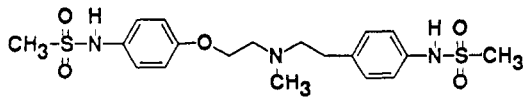


Figure 3. (A) This figure is an example of the measurement of I_k as a deactivating tail current upon repolarization. The cell was depolarized for 700 ms to +40 mV and then repolarized to −40 mV. The tail current was measured relative to the holding current at −40 mV. Nisoldipine (2 μM) was employed to block the calcium current in this example. (B) In this figure current traces, recorded before and after the addition of compound **81** (100 nM), under the same protocol as panel A for a depolarization duration of 1 s, are superimposed. It can be seen that the decaying outward tail current is completely suppressed.

greatly alter APD-prolonging potency compared to that of the corresponding phenylalkyl derivatives (compare **8j** and **8c**, Table I) but had the incidental advantage of producing compounds that crystallized readily. Attention has already been drawn to the hydrophilic imidazolyl substituent in **2**. We found that incorporating two weakly hydrophilic methoxy groups, with a combined π value of −0.04,[18] had no significant effect on activity (compare **8g** and **8c**). By contrast, introducing hydrophobic chlorine or trifluoromethyl groups greatly enhanced activity, and the optimum members of this series, in terms of potency and ease of handling, were **8l** and **8m**. These compounds produced significant prolongation of APD at nanomolar concentrations and are devoid of β-blocking activity. By direct comparison compound **8m** was some 15-fold more potent than the Pfizer compound UD 68798[5] (18), which is a good representative of the new generation of potent, selective class III agents (see Figure 2).



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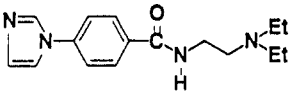
The more active members of this series were studied in greater detail and a full account of their pharmacological properties will be published elsewhere. A prolongation of the cardiac APD can be elicited by several mechanisms, and it is thought that sotalol produces its effect by an inhibition of the delayed rectifier potassium current.[13] This is one of the currents evoked in the later stages of the cardiac-action potential and causes the membrane to repolarize. Inhibition of this current, therefore, has the effect of delaying repolarization and hence of prolonging the action potential. This current can be measured as the size of the outward "tail" current after a step depolarization under voltage-clamp conditions.[16] Figure 3 shows that this current is abolished by, for example, compound **8l** at concentrations that also cause maximal prolongation of APD. This suggests that these more potent analogues of sotalol exert their effect by blocking the same potassium channel. Compounds **8l** and **8m** had no effect on atrial conduction velocity (diagnostic for the absence of a class I effect) at concentrations (100 μM) 10-fold higher than that required to produce maximum APD prolongation. Under the same recording conditions lignocaine (20 μM), a well-known class I compound, gave a readily detectable 17% change.

Other groups[4-6] have drawn attention to the significance of the sulfonamido group in sotalol as a determinant of class III activity, and our results reinforce this view. Relocation of the sulfonamido group to the 3-position (compound **8p**) diminishes but does not abolish activity. On the other hand, methylation of the sulfonamide nitrogen (**8a,b**, Table I) abolishes activity completely. The methanesulfonamido group is weakly acidic,[19] with pK_a of about 8.5. Exchange of the ionizable proton of the sulfonamide group for methyl abolishes acidic properties, but the extent to which the ionization of this group is a relevant factor in this context is difficult to establish. The pK_a of the side-chain amino group would also be in the range 9–10 and, assuming that these two ionizable groups are sufficiently widely separated to have a negligible interaction with one another, it would be expected that some 10% would be in the zwitterionic form. The 4-carboxylic acid derivative (compound **8o**) would be a stronger acid than the analogous sulfonamide and would have a larger fraction with both functional groups ionized at physiological pH. Compound **8o** is active but is some 10 times less so than the analogous methanesulfonamide **8j**. This poor correlation of activity with pK_a does not rule out the possibility that it is the zwitterionic form of these molecules that is the active species, but an alternative explanation could be that as with the classical sulfonamide antibacterials,[20] the relevant structural feature is a strongly solvated but not necessarily ionized group at the opposite end of the molecule to the cationic nitrogen. Methylation of the sulfonamide group would be expected to disrupt this solvation sphere. This view is consistent with the recent report[4] by the Berlex group of a derivative (**19**) of procainamide with class III activity where a strongly solvated[21] but cationic imidazole group was substituted for methanesulfonamide.



19

The sulfonamide derivatives of cromakalim were devoid of any potassium channel blocking activity, and increasing the bulk of the N substituent from isopropyl (**17a**) to phenylethyl (**17b**) produced no effect. At high concentrations (50–100 μM) they produced, if anything, a slight shortening of the APD, suggesting that they might retain some vestigial channel opening ability. There are several

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families of membrane potassium channels (see ref 22 for a recent review) and cromakalim is thought to act on the ATP-dependent channel, which is distinct from the channel conducting the delayed rectifier current. Compounds **17a** and **17b** were either without effect on the latter or whatever effect they did have was compensated by the opening of another channel. The characteristic blocking agents for the ATP-dependent channel are aryl sulfonyl ureas, and so not unrelated to sulfonamides, and this fact, together with the observation that cromakalim could be formulated as a folded phenoxypropanolamine, made the synthesis of **17a** and **17b** worthwhile. It would be disingenuous to suppose that the combination in one molecule of functional groups conferring activity on two distinct potassium channels would necessarily result in an active compound: the lack of blocking activity by **17a** or **17b** is of limited evidential value, but is not inconsistent with the view that cromakalim and sotalol act on different channel systems.

To summarize, we have shown that the two characteristic actions of sotalol can be developed independently. The oxypropanolamine side chain, which is characteristic of β-blocking agents, when combined with a bulky hydrophobic tertiary amino group also confers selectivity for the channel carrying the delayed rectifier potassium current. The most active members of this series produce a significant prolongation of the cardiac action potential at nanomolar concentrations and warrant further investigation as potential class III antiarrhythmic agents.[23]

Experimental Section

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected.

Infrared spectra (IR) were recorded on a Perkin-Elmer 298 spectrophotometer. Samples were run as KCl disks or thin films. Nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz on a Hitachi/Perkin-Elmer R-24B high-resolution spectrometer. Thin-layer chromatography (TLC) was carried out on glass plates coated with fluorescent silica gel (Kieselgel 60 PF_{254}, Merck). Elutants were chloroform (90)/methanol (10) v/v unless otherwise indicated and detection was with a UV lamp as well as iodine.

Microanalyses were carried out by Mr. M. Hart at the Micro Analytical Laboratory, University of Manchester. All values were within 0.4% of calculated values, unless otherwise noted.

1-[4-(*N*-Methylmethanesulfonamido)phenoxy]-2,3-propylene Oxide (4b). *N*-Methanesulfonamido-*N*-methyl-4-hydroxyaniline (2 g, 10 mmol) was dissolved in 12 mL of 1 N NaOH with stirring. Epichlorohydrin (1.17 mL, 15 mmol) was then added. After 10 h the solution was extracted with $CHCl_3$ and washed with 30 mL of 1 N NaOH. The $CHCl_3$ was dried over $MgSO_4$(s) and removed under reduced pressure, giving a white solid. Recrystallized from EtOAc/ether. Yield: 1.9 g (7.4 mmol, 74%). Mp: 92–94 °C.

(4-Nitrophenoxy)propanolamines were all prepared by the same procedure, and a typical preparation is given below. The secondary and tertiary amines used were either obtained from the Aldrich Chemical Co. or were prepared following published procedures. Physical constants for all (nitrophenoxy)propanolamines are given in Tables II and III. Several nitrophenoxy compounds were obtained as yellow oils, which decomposed on distillation under reduced pressure (Table II). They gave a single spot on TLC, and NMR and IR spectra consistant with the assigned structures were obtained in all cases. These compounds were carried forward without further purification. Elemental analyses for all crystalline solids were within 0.4% of the expected values.

(22) Cook, N. S. (Ed.) *Potassium Channels*. Ellis Horwood Ltd.: Chichester, 1990.

(23) The compounds described in this paper are the subject of provisional U.K. patent no. 9005318.2.

Table II. Physical Characteristics of Intermediate (4-Nitrophenoxy)propanolamines **6**

no.	R_2	R_3	mp,[a] °C
6a	H	CH_3	93–94
6b	H	i-C_3H_7	*b*
6c	H	t-C_4H_9	88–90[c]
6d	H	$C_6H_5(CH_2)_2$	104
6e	H	4-$ClC_6H_4(CH_2)_2$	91
6f	H	3,4-$(CH_3O)_2C_6H_3(CH_2)_2$	201–205
6g	CH_3	$C_6H_5(CH_2)_2$	*b*
6h	CH_3	$C_6H_5(CH_2)_3$	*b*
6i	CH_3	$C_6H_5CH{=}CHCH_2$	*b*
6j	CH_3	3,4-$Cl_2C_6H_3(CH_2)_2$	*b*
6k	CH_3	3,4-$(CH_3O)_2C_6H_3(CH_2)_2$	*b*
6l	i-C_3H_7	3,4-$(CH_3O)_2C_6H_3(CH_2)_2$	*d*
6m	C_2H_5	C_2H_5	*d*

[a] Except where indicated all solids were recrystallized from ethyl acetate. [b] Yellow oil. Single spot on TLC. [c] Ether/40–60 petroleum ether.

Table III. Physical Characteristics of Intermediate Alicyclic (4-Nitrophenoxy)propanolamines

compd[a]	NR_2R_3	mp,[b] °C
6n	4-phenylpiperidine	106–108
6o	4-phenylpiperazine	150–151
6p	4-(4-chlorophenyl)piperidine	112
6q	4-(4-CF_3-phenyl)piperidine	125
6r	1,2,3,4-tetrahydroisoquinoline	*c*

[a] Analyses for C, H, N were all ±0.4% of the expected values. NMR and IR spectra consistent with the assigned structures were obtained in all cases. [b] Solids were recrystallized from ethanol. [c] Yellow oil. Single spot on TLC.

1-(4-Nitrophenoxy)-3-(*N*-4-phenylpiperidine)-2-propanol (6n). 4-Phenylpiperidine (4.2 g, 26 mmol) was dissolved in 25 mL of ethanol along with 5.0 g (26 mmol) of 1-(4-nitrophenoxy)-2,3-epoxypropane. The mixture was then refluxed for 4 h. On cooling, 3 mL of concentrated HCl was added and the ethanol was removed under reduced pressure, giving a yellow oil which was redissolved in 150 mL of hot ethyl acetate. The hydrochloride salt precipitated as fine white needles on cooling of the ethyl acetate solution. Yield: 8.5 g (22 mmol, 83%). Mp: >300 °C. Free base mp: 106–108 °C. Open chain tertiary amino (nitrophenoxy)propanolamines (**6g–l**) were obtained as yellow oils that could not be induced to crystallize, and which decomposed on distillation. They ran as single spots on TLC, gave satisfactory spectra, and were carried forward to the next stage without further purification.

Typical reduction and mesylation procedures were as follows.

1-(4-Aminophenoxy)-3-(*N*-4-phenylpiperidine)-2-propanol (19). **6n** (2.0 g, 5.6 mmol) was added to 25 mL of ethanol along with 100 mg of 10% Pd/C. After shaking for 1 h under 1 atm of H_2(g) a quantitative uptake of H_2(g) was seen. The charcoal was removed by centrifugation and the ethanol was removed under reduced pressure, yielding a white solid. The amine was pure by TLC and used directly in the next stage. Yield: 1.8 g (5.4 mmol, 96%).

1-(4-Methanesulfonamidophenoxy)-3-(*N*-4-phenylpiperidine)-2-propanol (8j). **19** (1.0 g, 3.1 mmol) was dissolved in 5 mL of dimethylformamide, cooled in an ice bath, and treated with 0.23 mL (3.1 mmol) of methanesulfonyl chloride for 1 h at 0 °C. After this time the solution was left to warm slowly to room temperature over 2 h, after which 200 mL of ether was added. An oil separated which was taken up in 2 N NaOH, extracted with ethyl acetate, and reprecipitated by careful neutralization of the aqueous solution. The amine was converted to the hydrochloride by treatment with 1 equiv of concentrated HCl in ethanol and was obtained as a white solid which was recrystallized from ethanol/ether. Yield: 0.50 g (1.1 mmol, 35%). Mp: 220–222 °C. Free base mp: 165–166 °C.

A typical procedure for the preparation of oxazolidine derivatives of secondary phenoxy propanolamines is as follows. Physical constants for related compounds are given in Table IV.

2-Phenyl-3-phenethyl-5-[(4-nitrophenoxy)methyl]oxazolidine (10c). **6d** (5 g, 15.8 mmol) was dissolved in 75 mL of toluene

Table IV. Physical Characteristics of N-Substituted 2-Phenyl-5-(4-nitrophenoxymethyl)oxazolidines

compd[a]	R_3	mp,[b] °C
10a	CH_3	57–59, 79[d]
10b	i-C_3H_7	106–108
10c	$C_6H_5(CH_2)_2$	64, 90–91[d]
10d	4-$ClC_6H_4(CH_2)_2$	75–85[e]
10e	3,4-$(CH_3O)_2C_6H_3(CH_2)_2$	*c*

[a] Analyses for C, H, N were all ±0.4% of the expected values. NMR and IR spectra consistent with the assigned structures were obtained in all cases. [b] Solids were recrystallized from 40–60 petroleum ether. [c] Yellow oil. Single spot on TLC. [d] Diastereoisomers; structures not assigned. [e] Mixture of diastereoisomers.

along with 1.8 mL (17.7 mmol) of freshly distilled benzaldehyde and 50 mg of *p*-toluenesulfonic acid. The mixture was then refluxed in a Dean–Stark apparatus for 16 h, cooled, and washed with 2 × 50 mL of 1 N sodium bicarbonate. The organic layer was dried over magnesium sulfate and removed under reduced pressure, yielding a yellow oil. The oil was washed with 3 × 50 mL of 40–60 °C petroleum ether, and the combined extracts on cooling produced a white crystalline material. Yield: 4.6 g (11 mmol, 72%). There was a partial separation of the stereoisomers on crystallization, giving rise to two different melting points: 64 °C, 90–91 °C. NMR ($CDCl_3$, ppm): 8.17 (d, 2 H, J = 9 Hz, Ar-NO_2), 7.38 (m, 5 H, Ar), 7.20 (m, 5 H, Ar), 6.97 (d, 2 H, J = 9 Hz, Ar-NO_2), 4.98, 4.92 (both singlets of diff isomers, OCHN), 4.0–4.8 (m, 3 H), 2.5–3.0 (m, 6 H).

2-Phenyl-3-(phenylethylamino)-5-[(4-aminophenoxy)methyl]oxazolidine (20). **10c** (1 g, 2.5 mmol) was dissolved in 30 mL of ethanol along with 1 mL of 2 N NaOH and 100 mg of 10% Pd/C. On shaking in 1 atm of H_2(g), there was a quantitative uptake of hydrogen within 15 min. The reaction mixture was then centrifuged and the solvent was decanted and evaporated under reduced pressure, leaving a colorless opaque oil. This was then extracted with ether, washed with 2 × 50 mL of water, dried over magnesium sulfate, and the solvent was removed, yielding a colorless oil (0.90 g, 2.4 mmol, 97%). The amine was pure enough to use directly in the mesylation stage.

1-(4-Methanesulfonamidophenoxy)-3-(*N*-phenylethylamino)-2-propanol (11d). **20** (0.90 g, 2.4 mmol) was dissolved in 10 mL of sodium-dried ether and cooled to 5–10 °C. A solution of 0.20 mL (2.6 mmol) of methanesulfonyl chloride in 10 mL of sodium-dried ether was then added slowly and the solution was left for 12 h, warming to room temperature. The ether was decanted and 50 mL of 1 N HCl was added, stirred for 1 h, and then washed with 2 × 50 mL of ether. The water was removed under reduced pressure, giving a yellow solid which was recrystallized from ethanol/ether, giving the hydrochloride as fine white crystals (0.50 g, 1.2 mmol, 52%). Mp: 212–213 °C.

3-Methyl-3-(4-nitrophenoxy)but-1-yne (14). 4-nitrophenol (0.44 mol) and NaOH (0.66 mol) were added to a stirred suspension of water (400 mL) and methylene chloride (400 mL) followed by the phase-transfer catalyst benzyltrimethylammonium hydroxide (0.0825 mol, 40% MeOH solution) and 3-chloro-3-methylbutyne (1.1 mol). The solution was stirred for 4 days, at which point most of the 4-nitrophenol had dissolved. The reaction was then stopped, the layers were separated, and the aqueous layer was further extracted with $CHCl_3$. The solvent was removed from the combined organic extracts and the residue was taken up in ether and washed with 1 × 75 mL of water and 3 × 50 mL of 2 N NaOH. Drying with $MgSO_4$ and solvent removal gave the propargyl ether which was used without further purification (40.5 g, 45.2% yield).

2,2-Dimethyl-6-nitro-2*H*-1-benzopyran (15). **14** (40.5 g, 198 mmol) was heated under N_2 in *N*,*N*-diethylaniline (200 mL) at reflux for 8 h. The reaction mixture was then treated with an excess of cold concentrated HCl and the product was collected in ether. Solvent removal gave a crude solid which was recrystallized from petroleum ether (bp 80–100 °C). Yield: 32 g (158 mmol, 80%). Mp: 71–71.5 °C (lit.[14c] mp: 71–72 °C).

***trans*-3-Bromo-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1-benzopyran-4-ol.** *N*-Bromosuccinimide (25.6 g, 144 mmol) was added in one portion to a vigourously stirred solution of 28 g (137 mmol) of the benzopyran in dry dimethylsulfoxide (55 mL) and water (5.0 mL, 277 mmol). After the exothermic reaction, stirring was continued for 0.5 h. The reaction solution was then poured into water and extracted with ethyl acetate. The organic phase was then washed with water and dried over $MgSO_4$(s). Removal of the solvent left the crude bromohydrin which was recrystallized from 60–80 petroleum ether. Yield: 8.3 g (27 mmol, 20%). Mp: 112–113 °C. (lit.[14a] mp: 114–116 °C).

3,4-Epoxy-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1-benzopyran (16). **16** was prepared by using the procedure described by Evans et al.[14a] Yield: 95% (lit.[14a] yield: 75–95%). Mp: 91–92 °C lit.[14a] mp: 91–93 °C.

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(phenethylamino)-6-nitro-2*H*-1-benzopyran (21).** **16** (0.60 g, 2.7 mmol) was refluxed in ethanol with 0.34 g (2.7 mmol) of phenylethylamine for 18 h. The solvent was removed under reduced pressure, yielding an oil which was washed with 40–60 °C petroleum ether, giving a pale yellow solid. The compound was recrystallized from ether. Yield: 0.80 g (2.3 mmol, 86%). Mp: 94–95 °C.

***trans*-6-Amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-4-(phenethylamino)-2*H*-1-benzopyran (22).** **21** (0.60 g, 1.75 mmol) was dissolved in 20 mL of ethanol, and 100 mg of 10% Pd/C was added. The mixture was shaken under 1 atm of H_2(g) for 3 h, after which 117 mL of gas was taken up. Centrifugation of the charcoal and removal of the solvent left a clear oil which was used without further purification. Yield: 0.52 g (1.67 mmol, 95%).

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(phenethylamino)-6-methanesulfonamido-2*H*-1-benzopyran (17b).** A solution of 0.52 g (1.67 mmol) of **22** in 3 mL of dry dimethylformamide was cooled to 0 °C, 0.13 mL (1.67 mmol) of methanesulfonyl chloride was then added, and the mixture was left for 1 h at 0 °C and then allowed to warm slowly to room temperature over 2 h, after which 100 mL of ether was added. An oil precipitated which was resuspended in 75 mL of ethyl acetate, and addition of ether to the organic layer yielded a white solid. Yield: 0.47 g (1.21 mmol, 72%). This was then dissolved in 20 mL of ethanol to which 1 equiv of concentrated HCl was added; removal of the solvent yielded an oil which crystallized on addition of 1 mL of water. Mp: 152–153 °C (free base).

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(isopropylamino)-6-methanesulfonamido-2*H*-1-benzopyran hydrochloride (17a)** was prepared by using the same procedure. Mp: 145 °C.

1,2-Epoxy-3-[4-(*tert*-butoxycarbonyl)phenoxy]propane (5c). *tert*-Butyl-4-hydroxy benzoate (1.94 g) was dissolved in 10 mL of 1 N sodium methoxide in methanol. The solution was evaporated and the solid residue was dissolved in dry dimethylformamide (10 mL); epichlorohydrin (3 mL) was added and the mixture was maintained at 75 °C for 18 h. The reaction mixture was cooled, poured into 10% citric acid solution (40 mL), and extracted with ethyl acetate. The organic layer was washed with water and saturated salt solution and dried (magnesium sulfate). The solvent was removed and the residue was fractionated by flash chromatography on silica gel, eluting with methylene dichloride/toluene 1:1 v/v. The epoxy propane derivative was the first compound to elute and crystallized on removal of the solvent. Yield: 1.4 g (56%). Mp: 39 °C.

***N*-[3-[4-(*tert*-Butoxycarbonyl)phenoxy]-2-hydroxypropyl]-4-phenylpiperidine.** The above epoxypropane derivative (1.0 g) and 4-phenylpiperidine (0.65 g) were dissolved in ethanol (6 mL), and the mixture was refluxed for 2 h. On cooling, the product crystallized. It was collected and recrystallized from ethanol. Yield: 1.37 g. Mp: 105 °C.

***N*-[3-(4-Carboxyphenoxy)-2-hydroxypropyl]-4-phenylpiperidine Trifluoroacetate (8o).** The above *tert*-butyl ester (0.82 g) was dissolved in trifluoroacetic acid (5 mL) and stood at room temperature for 1 h. Dry ether (50 mL) was added and the white crystalline precipitate was collected. Yield: 0.76 g. Mp: 212–214 °C.

Pharmacological Testing. Action-potential duration was measured with microelectrodes inserted into isolated guinea pig ventricular myocytes stimulated with 2 ms rectangular current pulses, at a frequency of 1 Hz. All measurements were made at 37 °C. The response of cells to applied drug solutions stabilized within 1 min and measurements were made after 2 min. Ac-

tion-potential duration at the 90% repolarization level could be measured with a standard error of ±1%, as the mean of at least four (usually six to eight) cell samples. An increase of about 33% in APD was maximal for most cells, and hence estimates of the change in APD are reliable to ±3%. A single electrode voltage clamp[15] (using electrodes containing 0.5 M K_2SO_4) was used for the measurement of membrane currents. In some cases nisoldipine (2 μM) was present in the external solution to block currents carried by calcium, and in others cells were injected[15] with the calcium chelator BAPTA (1,2-bis(2-aminophenoxy)ethane-*N*,*N*,*N*',*N*'-tetraacetic acid) to suppress currents activated by increases in cytosolic calcium.

Conduction velocity in isolated guinea pig atrial preparations was measured by placing stimulating and recording electrodes at a fixed distance of ca. 20 mm and measuring the time interval between the delivery of the stimulus pulse and the recording of the first action potential.

β-Blocking activity was determined from the extent of reduction of the rise in heart rate elicited in pithed rat preparations in response to doses of 0.25 μg/kg isoprenaline.

Acknowledgment. We thank Dr. K. J. Blackburn, Pfizer Central Research, Sandwich, Kent, U. K., for the gift of a sample of Pfizer UK-68,798.

Phosphonate-Containing Inhibitors of Tyrosine-Specific Protein Kinases†

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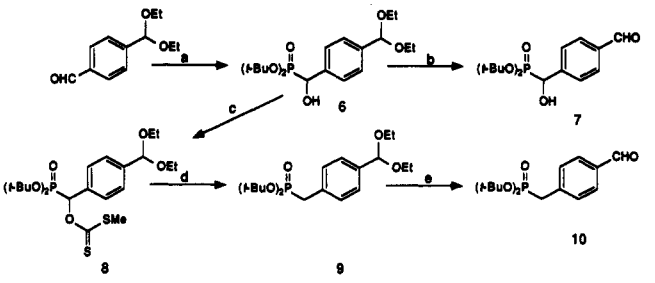
Tyrosine-specific protein kinases (TPK) are important signal transducing enzymes involved in normal cellular growth and differentiation and have been implicated in the etiology of a number of human neoplastic processes. Efforts to develop agents which inhibit the function of these enzymes by interfering with the binding of substrate have been limited by the lack of detailed three-dimensional structural data. Many inhibitors of substrate binding share a common styrene nucleus 1 which has been postulated to function as a conformationally constrained analogue of tyrosine. In an effort to develop high-affinity compounds based on this hypothesis, a number of derivatives were synthesized in which either methylphosphonate (**4a–c**) or (hydroxymethyl)phosphonate (**3a–c**) were appended to the aromatic 4-position of styrene-containing moieties. The intent of this approach was to prepare hydrolytically stable analogues which expressed additional enzyme recognition features present during the phosphorylation of tyrosine itself. None of the analogues showed inhibitory activity up to the maximum concentration tested (1000 μM) when assayed against autophosphorylation of A-431-derived epidermal growth factor receptor (EGFR) or $p56^{lck}$ (autophosphorylation and transphosphorylation of rabbit muscle enolase). Additionally, a series of naphthalene-based inhibitors including (1-naphthalenylhydroxymethyl)phosphonic acid (**14**), its known 2-positional isomer **16**, and sulfonate (**19**, **20**) and phosphate derivatives (**17**, **18**) were also tested under similar conditions. Only (2-naphthalenylhydroxymethyl)phosphonic acid (**16**) showed activity (IC_{50} = 250 μM in EGFR, in agreement with the reported literature value). These results suggest that the interaction of styrene-based inhibitors with the substrate binding domain of TPKS may not occur in a manner analogous to the interaction of tyrosine with this domain.

Tyrosine-specific protein kinases (TPK) constitute an important class of cyclic AMP-independent enzymes which transfer the γ-phosphate of either ATP or GTP to the 4-hydroxyl group of specific tyrosine residues within either peptide or protein substrates.[1] In normal cellular function TPKs are involved in the modulation of growth and differentiation[2] with ca. 50% of them functioning as the cytoplasmic signal-transducing domains of growth factor receptors.[3] A significant number of TPKs are the products of protooncogenes,[4] and their association with the etiology of a number of human cancers[5] makes them attractive targets for the development of new anticancer chemotherapeutics.[6] Since TPKs bind an appropriate nucleoside triphosphate along with a tyrosine-containing substrate, and catalyze the transfer of a phosphate group from one molecule to the other,[7] a possible approach in the design of agents which inhibit their function could involve (1) inhibition of nucleoside triphosphate binding or (2) inhibition of substrate binding to the enzyme.[8] While several potent inhibitors of nucleoside triphosphate binding are known[9] and active research continues in this area,[10] the homology of nucleoside triphosphate binding sites among a variety of different kinases[11] decreases the likelyhood of specificity for this class of inhibitors and makes them less desirable as therapeutic targets. Because

Scheme I[a]



[a] (a) $(t\text{-BuO})_2POH$, basic alumina; (b) HCl(aq)/$CHCl_3$; (c) NaH, CS_2, MeI; (d) $n\text{-Bu}_3SnH$, AIBN; (e) HCl(aq)/$CHCl_3$.

† A preliminary account of this work was presented at the 200th National Meeting of the American Chemical Society, Washington, DC, MEDI 138.

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§ Medicine Branch.

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