A New Series of Cardioselective Adrenergic β-Receptor Blocking Compounds. 1-(2-Acyl-4-acylaminophenoxy)-3-isopropylaminopropan-2-ols

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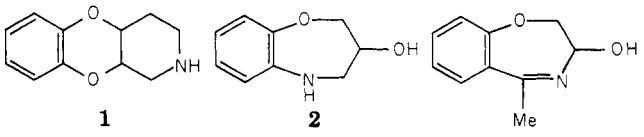
A series of 1-(2-acyl-4-acylaminophenoxy)-3-isopropylaminopropan-2-ols has been synthesized and examined for β-receptor blocking and antiarrhythmic activity. Several of these compounds are more than 20 times as active in blocking cardiac β-receptors than vascular β-receptors when given intravenously to anesthetized cats. The activities have been correlated quantitatively with partition and steric substitution constants. The observed relationships are consistent with a tentative proposal that the vascular receptor is situated in a more lipophilic environment than the cardiac receptor so that there is a differential transport effect between the two types of receptor.

Most adrenergic β-receptor blocking compounds affect the heart (β_1) and vascular (β_2) receptors to a similar degree. Practolol, however, is reported to inhibit the β_1 response at lower doses than those required to inhibit the β_2 response.[1] We became interested in the possibility of modifying known β-blocking compounds in order to enhance the selective blockade of the β_1 or β_2 responses. We first examined the possibility of achieving selectivity by partially immobilizing the hydroxyisopropylaminopropoxy side chain of conventional β-blockers by incorporating it into heterocyclic systems such as hexahydropyridobenzodioxane (1),[2] benzoxazepine (2),[3] and benzoxazocine (3).[4]



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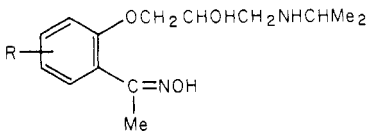
This work led us to examine some oximes (4) and subsequently the parent ketones (5) in which the relative β_1 and β_2 responses were observed to vary markedly according to the nature of the substituents in the aromatic ring.



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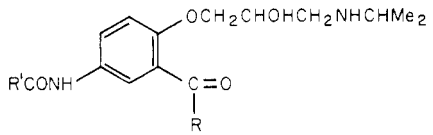

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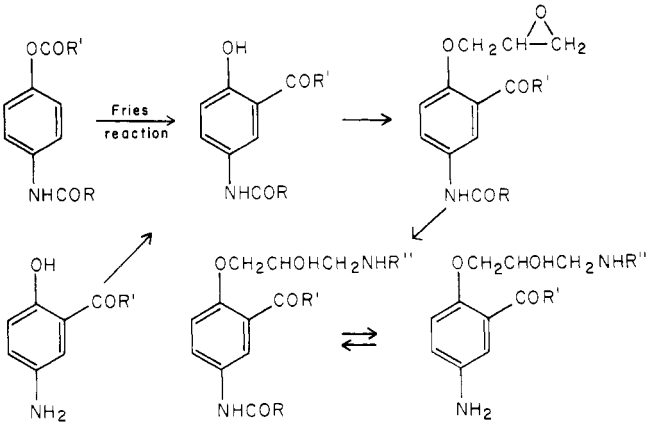
This paper describes the synthesis and structure–activity relationships of a series of acylamino compounds (5) in which a considerable degree of cardioselectivity was obtained.

Chemistry. The compounds were prepared by the routes indicated in Scheme I and are listed in Table I.

Pharmacological Evaluation. Doses of test compound to antagonize the effects of isoproterenol on the tachycardia and diastolic hypotensive response in anesthetized cats were measured by the technique described in the Experimental Section. The half-blocking doses and the confidence intervals are recorded in Table I.

The adrenergic β-receptor blocking action of a compound was expressed as the dose of that compound which desensitized the cat so that twice the dose of isoproterenol was required to maintain the response unchanged. The tachycardia response and the fall in diastolic blood pressure response to isoproterenol were both measured simultaneously in all experiments.

Scheme I



The doses of test compound required to revert ouabain-induced cardiac arrhythmia in the dog were measured by the method described by Lucchesi et al.[5] and are given in Table I.

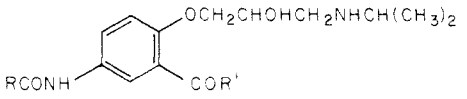
Results and Discussion

The vascular and cardiac half-blocking doses, their ratio (cardioselectivity), and the antiarrhythmic activity of the series were examined by the multiparameter extrathermodynamic approach developed by Hansch and others.[6]

Cardioselectivity. From the data on the compounds containing normal and branched alkyl substituents (compounds 1–12), a highly significant quadratic relationship was obtained between the cardioselectivity and the sum of the substituent partition constants for the two groups R and R'[7] (Table II, eq 1). This equation, accounting for 80% of the variance, is not significantly improved by addition of terms containing Taft's steric factor,[8] molar refraction,[9] or the Newman six-number.[10] The cardioselectivity of the benzyl-substituted compound 13 is inconsistent with the equation and the data for the phenyl-substituted compound 14 are unsuitable for quantitative treatment.

We also considered the effect of structural variation on the separate cardiac and vascular responses. Using the data on all the compounds (1–14), only a poor correlation was obtained between the cardiac half-blocking dose and the sum of the substituent partition constants (Table II, eq 2), but this was significantly improved by addition of a term containing Taft's steric factor for the group R (Table II, eq 3) although the π^2 coefficient is only significant at the 90% level. In fact, examination of the single parameter equations revealed E_s to be the dominant single variable accounting for 52% of the variance in the data (Table II, eq 4). There is no correlation between π and E_s (r = 0.184).

Table I



No.	R	R'	Mp, °C	Formula[a]	Cardiac half-blocking dose,[b,g] mg/kg iv	Vascular half-blocking dose,[b,g] mg/kg iv	Cardioselectivity[c]	Reverting dose, mg/kg iv	Yield, %
1	CH_3	CH_3	127-130	$C_{16}H_{24}N_2O_4$	0.089 (0.056-0.15)	0.32 (0.19-0.74)	3.59	>15.0	74
2	C_2H_5	CH_3	110-113	$C_{17}H_{26}N_2O_4$	0.063 (0.027-0.13)	0.52 (0.12-*)	8.25	22.5	14
3	n-C_3H_7	CH_3	141-143	$C_{18}H_{29}ClN_2O_4$[d]	0.13	2.6	20.00	8.1	29
4	n-C_4H_9	CH_3	130-132	$C_{19}H_{30}N_2O_4$	0.033 (0.021-0.051)	0.89 (0.29-*)	27.00	4.8	27
5	n-C_5H_{11}	CH_3	141-142	$C_{20}H_{32}N_2O_4$	0.029 (0.004-0.11)	0.85 (0.15-*)	29.31	3.2	18
6	n-C_6H_{13}	CH_3	119-121	$C_{21}H_{34}N_2O_4$	0.040 (0.026-0.067)	0.50 (0.11-*)	12.50	2.7	52
7	n-C_7H_{15}	CH_3	117-119	$C_{22}H_{36}N_2O_4$	0.05 (*-0.36)	0.692 (0.603-0.796)	13.84	3.9	14
8	C_2H_5	C_2H_5	89-92	$C_{18}H_{28}N_2O_4$	0.026 (0.013-0.042)	0.41 (0.27-0.71)	15.77	6.4	24
9	n-C_3H_7	C_2H_5	130-132	$C_{19}H_{30}N_2O_4$	0.079 (0.032-0.18)	1.12[e]	14.18	6.1	55
10	n-C_3H_7	n-C_3H_7	170-172	$C_{20}H_{33}ClN_2O_4$[d]	0.23	4.78	20.78	3.5	9
11	i-C_3H_7	CH_3	102-104	$C_{18}H_{28}N_2O_4$	0.10 (*-0.15)	1.85 (*-6.0)	18.50	17.2	12
12	i-C_4H_9	CH_3	115-117	$C_{19}H_{30}N_2O_4$	0.11 (0.068-0.16)	2.1[e]	19.09	3.8	22
13	$PhCH_2$	CH_3	117-119	$C_{22}H_{28}N_2O_4$	0.03 (0.002-0.11)	0.16 (0.064-5.2)	5.33	12.6	37
14	Ph	CH_3	144-146	$C_{21}H_{26}N_2O_4$	0.54 (0.14-*)	1.0[f]		5.8	20
Practolol					0.158 (0.073-0.46)	1.6 (0.54-18)	10.13	>35	

[a] All compounds were analyzed for C, H, and N. The figures were within ±0.4% of the theoretical values. [b] In the anesthetized cat. [c] Ratio of the vascular half-blocking dose/cardiac half-blocking dose determined in the same animal. [d] Hydrochloride. [e] Calculated by extrapolation. [f] Highest dose employed. [g] Figures in parentheses are 95% confidence intervals calculated using the standard error. An * indicates that the limit is remote.

Table II. Equations Relating Biological Responses to Physical Properties

Eq no.	Compd used in deriving regression	Equation[a]	n[b]	r[c]	s[d]	$F(n_1, n_2)$[e]	p[f]	π^0
1	1-12	Log $(v/c) = -0.463 + 1.296\ (5.75)\ \pi - 0.230\ (5.22)\ \pi^2$	12	0.900	0.118	19.22 (2, 9)	0.0006	2.82
2	1-14	Log $(mw/c) = 3.481 + 0.67\ (0.00)^*\ \pi + 0.009\ (0.07)^*\ \pi^2$	14	0.264	0.366	0.41 (2, 11)	0.677	
3	1-14	Log $(mw/c) = 2.754 + 0.849\ (2.21)\ \pi - 0.133\ (1.78)^*\ \pi^2 + 0.498\ (5.43)\ E_s$	14	0.874	0.193	10.83 (3, 10)	0.0018	3.19
4	1-14	Log $(mw/c) = 3.915 + 0.399\ (3.65)\ E_s$	14	0.726	0.250	13.37 (1, 12)	0.0032	
5	1-12	Log $(mw/v) = 2.897 + 0.704\ (2.61)\ E_s$	12	0.637	0.215	6.83 (1, 10)	0.025	
6	2-12	Log $(mw/RD) = -0.989 + 1.842\ (5.56)\ \pi - 0.272\ (4.55)\ \pi^2$	11	0.953	0.108	39.90 (2, 8)	0.0001	3.37

[a] v = vascular half-blocking dose (Table I), c = cardiac half-blocking dose (Table I), π = sum of partition substituent constants for R and R', mw = molecular weight of the compound, E_s = Taft's steric factor for the substituent R, RD = reverting dose (Table I), figures in parentheses refer to the t-test statistic of the individual coefficients, and * = not significant at 95% level. [b] n = number of compounds used to derive the regression. [c] r = correlation coefficient. [d] s = standard deviation. [e] F = variance ratio test statistic for the overall equation, n_1 = degrees of freedom for parameters fitted, and n_2 = degrees of freedom for residual error. [f] p = probability that the relationship occurred by chance.

We were unable to obtain good correlations between the vascular response and structural parameters but the results did suggest that the Taft substitutent parameter for R was involved (e.g., Table II, eq 5). However, additional partition terms failed to reach significant levels. Since the cardiac response is related to π and E_s, and the ratio between the vascular and cardiac responses is related to π, we should expect the vascular response also to be related to π and E_s. The failure to do so at a significant level could be due to the less reliable nature of the figures for the vascular response. The "between animal" variation is greater than that of the cardiac response as reflected in the wider confidence intervals for the experimental figures for most of the compounds in the series (Table I). However, we consider that the ratios of the cardiac to vascular responses are more reliable because these figures were determined simultaneously in the same animal.

Parabolic dependence of a biological response on partition has often been observed in in vivo systems[11] and this is usually associated with translocation by passive diffusion

Table III. Cardioselectivity and Cardiac Potency

No.	π^b	$E_s{}^c$	Log (v/c)[a] Obsd	Log (v/c)[a] Calcd[d]	Log (mw/c)[a] Obsd	Log (mw/c)[a] Calcd[e]
1	1.0	0.00	0.556	0.604	3.540	3.470
2	1.5	−0.07	0.917	0.965	3.709	3.694
3	2.0	−0.36	1.301	1.211	3.451	3.742
4	2.5	−0.39	1.431	1.342	4.026	3.854
5	3.0	−0.40	1.467	1.358	4.099	3.908
6	3.5	−0.40[f]	1.097	1.260	3.976	3.902
7	4.0	−0.40[f]	1.141	1.046	3.719	3.829
8	2.0	−0.07	1.198	1.211	4.112	3.887
9	2.5	−0.36	1.152	1.342	3.647	3.869
10	3.0	−0.36	1.318	1.358	3.700	3.928
11	1.8	−0.47	1.267	1.126	3.527	3.619
12	2.3	−0.93	1.281	1.303	3.503	3.542
13	3.13	−0.38			4.108	3.923
14	2.63	−2.58			2.836	2.786

[a] Defined in Table II. [b] π values for R and R' quoted in ref 6 (octanol-water). [c] Value for R: M. S. Newman, Ed., "Steric Effects in Organic Chemistry", Chapman and Hall, London, 1956, p 598. [d] Equation 1. [e] Equation 3. [f] Estimated value.

mechanisms through biological tissues.[12] The parabolic dependence of cardioselectivity on partition suggests that there are differences in tissue specificity between cardiac and vascular receptors, which would be reflected in different optimum π values for cardiac potency and vascular potency. Thus the optimum π value for cardiac-blocking activity is 3.19 and it may be estimated from eq 1 and 3 that the optimum π for vascular-blocking activity is ca. 2.3. The optimum π for cardioselectivity is 2.82 and is a value which allows selective accumulation at the cardiac receptor site at the price of a slight fall in potency.[6] This is consistent with the vascular receptor being associated with a more lipophilic environment than the cardiac receptor, possibly due to additional lipid membranes. Thus, the more lipophilic compounds would be absorbed strongly, and passage across the membrane to the receptor would be slowed down.

However, this proposal is necessarily tentative in view of the inherent uncertainties in the calculation of optimum π values using eq 3 in which one of the terms is only significant at the 90% level.

The occurrence of the steric term in the cardiovascular potency relationship suggests that bulky substituents may hinder interaction at the receptor site. The absence of the steric term in the cardioselectivity equation could mean that the cardiac and vascular receptors have similar steric contact requirements.

Antiarrhythmic Activity. The data on the ouabain reversal activity of the series revealed a good correlation between activity and the sum of the partition substituent constants for R and R', which was not significantly improved by steric terms (Table II, eq 6).

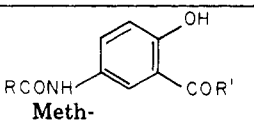
For possible clinical use, a balance of β-blocking potency, cardioselectivity, and antiarrhythmic properties is required. Compound **3** [Sectral (M&B 17803A)][13] was adjudged to have the requisite balance and has received detailed pharmacological[14] and clinical study[15] (Table III).

Experimental Section

The synthetic methods employed are illustrated by the following examples.

2'-Hydroxy-5'-propionamidoacetophenone (Example of Method A). *p*-Propionamidophenol (82 g), AcCl (40 g), and PhH (1000 ml) were heated under reflux until a clear solution was obtained (1 hr). Treatment with H_2O gave crude *p*-propionamidophenyl acetate (50 g), mp 100–105°, which was dried and then mixed with $AlCl_3$ (100 g) and heated to 170° for 5 hr. Excess of H_2O was added to the cooled mixture and the resulting solid was isolated and crystallized from EtOH to give 2'-hydroxy-5'-propionamidoacetophenone (16 g, 16%), mp 116–120°. Anal. ($C_{11}H_{13}NO_3$) C, H, N.

Table IV



R	R'	Method	Mp, °C	Formula	Yield, %
n-C_3H_7	CH_3	A	120–122	$C_{12}H_{15}NO_3$	85
n-C_3H_7	n-C_3H_7	A	80–82	$C_{14}H_{19}NO_3$	73
n-C_4H_9	CH_3	B	112–115	$C_{13}H_{17}NO_3$	46
n-C_5H_{11}	CH_3	B	120–121	$C_{14}H_{19}NO_3$	40
n-C_7H_{15}	CH_3	B	108–110	$C_{16}H_{23}NO_3$	35
i-C_4H_9	CH_3	B	119–120	$C_{13}H_{17}NO_3$	60
$PhCH_2$	CH_3	B	164–166	$C_{16}H_{15}NO_3$	41
n-C_3H_7	C_2H_5	B	104–105	$C_{13}H_{17}NO_3$	45
i-C_3H_7	CH_3	B	131–132	$C_{12}H_{15}NO_3$	55

2'-Hydroxy-5'-isobutyramidoacetophenone (Example of Method B). Isobutyric anhydride (17.5 g) was added during 0.5 hr to a mixture of 5'-amino-2'-hydroxyacetophenone (13.7 g), isobutyric acid (10 g), and H_2O (25 ml) at 100°. Heating and stirring were continued for a further 1 hr and then the reaction mixture was cooled. Addition of H_2O (25 ml) afforded 2'-hydroxy-5'-isobutyramidoacetophenone (14.15 g, 55%), mp 131–132°. Anal. ($C_{12}H_{15}NO_3$) C, H, N.

Other new compounds prepared similarly are listed in Table IV.

DL-1-(2-Acetyl-4-propionamidophenoxy)-3-isopropylaminopropan-2-ol (2). A solution of 2'-hydroxy-5'-propionamidoacetophenone (11.5 g) in EtOH (200 ml) was added to NaOEt in EtOH [from EtOH (200 ml) and Na (1.27 g)] and the reaction mixture concentrated to dryness under reduced pressure. DMF (100 ml) and epichlorohydrin (20 ml) were added and the solution was heated at 100° for 4 hr and then concentrated under reduced pressure to give a residue of crude 2'-(2,3-epoxypropoxy)-5'-propionamidoacetophenone. The crude epoxide and isopropylamine (40 g) and MeOH (200 ml) were heated under reflux for 1.5 hr. The reaction mixture was then concentrated under reduced pressure and the residual oil was treated with 1 *N* HCl and extracted with EtOAc. The acid solution was made alkaline and extracted with $CHCl_3$. The extract was concentrated to give the product (5.5 g), mp 110–113°. The hydrochloride, mp 141–143°, was formed on treatment with HCl in Et_2O. Compounds prepared similarly are listed in Table I.

DL-1-(2-Acetyl-4-aminophenoxy)-3-isopropylaminopropan-2-ol (15). Compound **3** (25 g) was refluxed for 2 hr with 2 *N* HCl (500 ml). The solution was then brought to pH 8 by the addition of $NaHCO_3$ and continuously extracted with $CHCl_3$ for 3 days. Evaporation of the extract afforded 17 g (90%) of crude amine which was crystallized from EtOAc to give the pure product (12.5 g, 66%) as yellow needles, mp 106–108°. Anal. ($C_{14}H_{22}N_2O_3$) C, H, N.

DL-1-(4-Amino-2-propionylphenoxy)-3-isopropylaminopropan-2-ol. This material, mp 110–112.5° (yellow needles from PhH), was obtained similarly (78%) by hydrolysis of compound **8**. Anal. ($C_{15}H_{24}N_2O_3$) C, H, N.

DL-1-(2-Acetyl-4-heptanamidophenoxy)-3-isopropylaminopropan-2-ol (7). Compound **15** (5 g), heptanoic anhydride (5.6 g), glacial AcOH (1.5 ml), and H_2O (100 ml) were stirred at 100° for 18 hr. The reaction mixture was extracted with $CHCl_3$, the extract was evaporated, and the residue was crystallized from EtOAc to give the product (3.95 g, 52%), mp 119–121°.

Compounds **1**, **3**, **7**, and **9** (Table I) were prepared by a similar method.

Biological. All compounds were dissolved in water or 0.1 *N* HCl immediately prior to use. The pH was adjusted to 5.0 with 0.1 *N* NaOH if necessary. A 0.1% solution of isoproterenol sulfate in 0.1% ascorbic acid stored at 4° was diluted to 2 μg/ml with normal physiological saline as required.

Estimation of the Intravenous Antagonism of the Tachycardia and Diastolic Hypotensive Response to Isoproterenol in Anesthetized Cats. Cats were deprived of food overnight. In the morning they were anesthetized with chloralose suspension (80 mg/kg) together with sodium pentobarbitone

solution (6 mg/kg) intraperitoneally. The carotid blood pressure was recorded with a Bell and Howell pressure transducer and the heart rate was recorded from the EKG or the pulse wave. Doses of 0.2 and 0.4 μg of isoproterenol intravenously were administered alternately at 7-min intervals. When the preparation had been shown to respond regularly, the test compound was administered 3.5 min after a 0.2-μg dose of isoproterenol. The next dose of isoproterenol 3.5 min later challenged the sensitivity of the preparation. The extent of the block produced was calculated

$$\% \text{ apparent isoproterenol} = \text{antilog } [2 - (I_2 - I_{2a})/(I_2 - I_1) \times 0.301]$$

where I_1 and I_2 are the responses to 0.2 and 0.4 μg of isoproterenol, respectively, before the dose of test compound and I_{2a} is the response to 0.4 μg of isoproterenol afterwards. By repeating the experiment with adjustment of the dose of test compound, a series of values of the above expression was obtained. From a graph of these values the dose was found by linear interpolation which reduced the sensitivity to isoproterenol to one-half. This dose is elsewhere referred to as the half-blocking dose. Both the tachycardia and diastolic hypotension responses to isoproterenol were considered separately, and in each case the dose found was called the half-blocking dose. The half-blocking doses refer only to the condition of the animal 3.5 min after dosing.

Statistics. Statistical calculations were carried out on a Wang 2200B computer using programs devised by the authors.

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Aminobenzoic Acid Diuretics. 8.[2] 3,4-Disubstituted 5-Methylsulfonylbenzoic Acids and Related Compounds

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Various 2,4- and 3,4-disubstituted 5-methylsulfonylbenzoic acids were synthesized as methylsulfonyl analogues of previously described 5-sulfamoylbenzoic acid diuretics. The results of the diuretic screening in dogs reveal that substitution of the sulfamoyl group by the spatially and sterically similar methylsulfonyl group does not affect the diuretic pattern but leads generally to somewhat decreased potency. For the highly potent 3-benzylamino-4-phenoxy-5-methylsulfonylbenzoic acid the corresponding 5-methylthio and 5-methylsulfinyl analogs were prepared and found still to exhibit diuretic activity. Internal aldol condensation and subsequent dehydration of 3-benzylamino- and 3-*n*-butylamino-4-benzoyl-5-methylsulfonylbenzoic acid provided the corresponding inactive 4-alkylamino-6-carboxy-2,3-dihydro-3-hydroxy-3-phenylbenzo[*b*]thiophene 1,1-dioxides and 4-alkylamino-6-carboxy-3-phenylbenzo[*b*]thiophene 1,1-dioxides.

Novello et al.[1] reported that replacement of the methylsulfonyl group for either sulfamoyl group in the diuretically active 5-chloro-2,4-disulfamoylaniline and for the 7-sulfamoyl group in both 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide (chlorothiazide) and its 3,4-dihydro compound (hydrochlorothiazide) leads to weakly or inactive compounds, respectively. The present paper deals with the effect of a similar replacement in a series of 2,4- and 3,4-disubstituted 5-sulfamoylbenzoic acids selected from the recently described class of high-ceiling diuretics.[2-6]

In addition we prepared one of the corresponding 5-methylthio- and one 5-methylsulfinylbenzoic acid derivative. Furthermore, in connection with our studies on the structural requirements for high-ceiling diuretic activity, we synthesized 4-benzylamino- and 4-*n*-butylamino-6-carboxy-3-phenylbenzo[*b*]thiophene 1,1-dioxide.

Chemistry. The preparation of the 3,4-disubstituted 5-methylsulfonylbenzoic acids **18**, **19**, and **22–29** (Table I) is outlined in Scheme I. The 5-methylthio- and 5-methylsulfinylbenzoic acids **20** and **21** were provided as given in Scheme II. For details see the Experimental Section.

The N-alkylated 4-substituted methylsulfonylanthranilic acids **30–33** (Table I) were obtained by successive replacement of the halogens in the methylsulfonylbenzoic acid derivative **14** as shown in Scheme III. **14** is easily available from 2-chloro-5-chlorosulfonyl-4-fluorobenzoic acid (**44**). The 4-benzoyl-5-methylsulfonylbenzoic acid derivatives readily undergo internal aldol condensation in aqueous alkaline solution to the corresponding 6-carboxy-2,3-dihydro-3-hydroxy-3-phenylbenzo[*b*]thiophene 1,1-dioxides. This reaction was utilized for the preparation of the 4-alkylamino-6-carboxy-3-phenylbenzo[*b*]thiophene