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New products

β-Methylsulfonylamino phenethylamines and aryloxypropylamines as potential β-adrenergic agents

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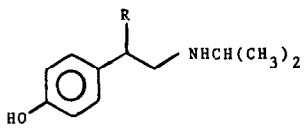
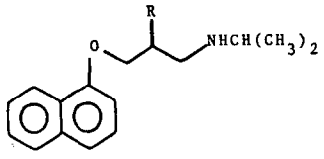
To see if a methylsulfonylamino function, CH_3SO_2NH, could serve as a pharmacophoric replacement for the β-hydroxy group present in typical β-adrenergic drugs, we prepared compounds **2** and **4** and compared them to standards **1** (*N*-isopropyloctopamine is a potent agonist [1] which was prepared from d,l-octopamine by hydrogenation in ethanol—acetone according to [2]) and **3** (propranolol is a potent antagonist [3]) in several β-adrenergic screens.



1, R = OH
2, R = CH_3SO_2NH

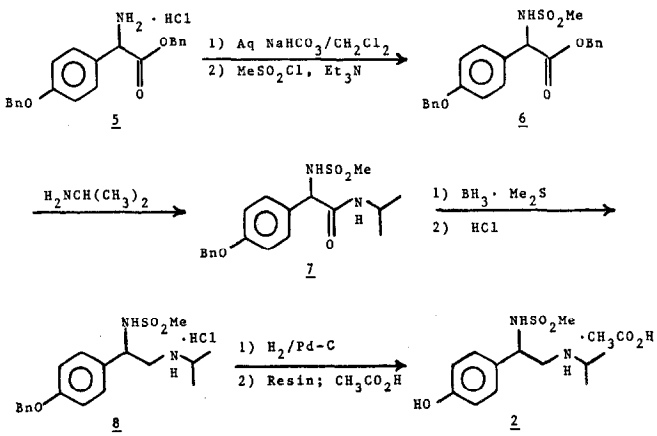


3, R = OH
4, R = CH_3SO_2NH

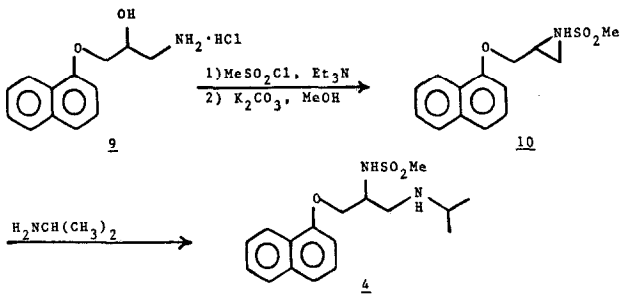
Chemistry

The potential agonist target **2** was synthesized as shown in Scheme 1. α-Amino-4-hydroxybenzeneacetic acid was protected as its *t*-butylcarbamate [4] to inactivate the amino function followed by simultaneous benzyl ether and benzyl ester formation [5]. Acidification provided amino ester **5** as crystals (known compound [5]: mp 160—164°C. Our compound: mp 187—189°C; NMR (DMSO-d_6) δ 5.16 (s, 2H); 5.25(s, 3H); 7.00—7.70(m, 14H); 9.26(br s, 3H); Anal. ($C_{22}H_{22}ClNO_3$) C, H, N). Compound **5** was mesylated [6] and reacted with isopropylamine to give amide **7** which underwent borane reduction [7,8] to **8**. Catalytic hydrogenolysis provided target **2**.

The synthesis of the potential antagonist target **4** is shown in Scheme 2.



Scheme 1 (Bn = $C_6H_5CH_2$—)



Scheme 2

Preparation of **9** followed literature methods [9]. Treatment of **9** with methanesulfonyl chloride gave the dimesylate which when stirred in a methanolic solution containing potassium carbonate [10] afforded aziridine **10**. The aziridine was reacted with isopropylamine to provide **4**.

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Pharmacology

Compounds **1**—**4** were tested in guinea pig papillary muscle. The results are shown in Table I. While *N*-isopropyloctopamine, **1**, showed positive inotropic effects, its methylsulfonamino analogue **2** was essentially inactive. In addition, the positive inotropic effects of **1** were not altered when **2** was administered simultaneously. This suggests a lack of interaction of **2** with β-receptors either as an agonist or as an antagonist. When **1** and **2** were studied in guinea pig right atria the same pattern was found: **1** possesses potent positive chronotropic activity, while **2** was inactive and did not alter the increase in rate obtained for **1**.

Table I. Inotropic[a] activity and β-adrenergic receptor binding[b] activity.

No.	GPPM	Binding IC_{50}
1	(+) 0.01[c]	12.4 ± 6.0
2	NR[d]	2,150 ± 700
3	7[e]	0.004 ± 0.001[f]
4	4	64.3 ± 17.4

[a] Concentrations in μM which cause a 20% decrease in the force of guinea pig papillary muscle (GPPM) contraction (C_{-20}) except for **1** which is a positive inotropic agent (value for **1** represents μM concentration effecting a 20% increase in the contractile force). Values represent the mean of at least two separate three dose experiments. Values obtained for any single compound were within the range ± 25%.
[b] Concentration in μM which is effective in displacing 50% of [^{3}H]-dihydroalprenolol from canine ventricular tissue expressed as the mean ± SEM from at least three experiments.
[c] Similar to literature [1].
[d] C_{-20} not reached at 100 μM.
[e] Similar to literature value [3].
[f] Similar to literature value [11].

While the decrease in inotropy obtained for the methylsulfonylamino analogue **4** was comparable to propranolol, **3**, **4** did not show competitive antagonism of the response from epinephrine. Furthermore, studies in guinea pig right atria revealed that while 0.1 μM propranolol essentially abolished the positive chronotropic activity obtained from 0.1 μM isoproterenol, 10 μM concentrations of **4** had essentially no effect. Since negative inotropy can also result from general membrane depression [12], **4** was tested in isolated canine ventricular muscle to determine its electrophysiological profile. **4** was found to have significant membrane depressant activity in the high μM range suggesting that the negative inotropy observed for **4** is the result of general membrane depression.

1—**4** were also examined for their ability to displace [^{3}H]dihydroalprenolol from canine cardiac tissue (Table I). In both cases the CH_3SO_2NH analogue had greatly reduced affinity for β-receptors. For pairs, **1** and **2**, and, **3** and **4**, this reduction is by approximately two and four orders of magnitude, respectively.

In vascular screens sensitive to β_2-blocking properties, **4** was found to be essentially inactive at doses up to 100 mg/kg in the spontaneously hypertensive rat [13] and showed only very weak activity at 100 μM in an isolated circumflex artery preparation [14].

Taken together, these studies show that the methylsulfonylamino analogues do not interact significantly with β_1- or β_2-adrenergic receptors. However, **4** did retain some apparent membrane depressant properties.

Theoretical studies

Hartree—Fock level 3-21G(*) calculations using the GAUSSIAN 82 system of programs (J. Binkley, M. Frisch, D. DeFrees, K. Raghavachari, R. Whiteside, H. Schlegel, E. Fluder and J. Pople, Carnegie—Mellon University) [15—17], showed that the proton affinities of NH_3, H_2O and $CH_3SO_2NH_2$ are in kcal/mol: 227 [18], 192 [18], and 204, respectively. These values suggest that methylsulfonylamino, like a hydroxyl group, would not be preferentially protonated over the side chain amine. As a proton donor, the $CH_3SO_2NH_2$ group formed a stronger complex with a hydroxyl anion than H_2O (97.6 *vs* 54.8 kcal/mol), suggesting that it is as good a proton donator as an OH group. Finally, MNDO [19] and MINDO/3 [20] calculations as implemented through MOPAC (M. Dewar's group, University of Texas at Austin) showed that the lowest energy conformations of the hydroxyl and methylsulfonylamino compounds are essentially the same and were similar to those determined previously using x-ray and other theoretical methods [21—25]. Possibly the spatial requirements of the methylsulfonylamino group are simply too great for the β-receptor. Similar steric limitations to substitution along the central chain of dopaminergic neurotransmittors have been proposed previously [26].

Experimental protocols

Chemistry

Melting points were taken on a Thomas Hoover apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 or XL-300 spectrometer. Microanalyses were performed on a Perkin—Elmer instrument and were within 0.4% of the theoretical values. In cases where an asymmetric center was present, all compounds existed as racemic mixtures.

α-[(Methylsulfonyl)amino]-4-(phenylmethoxy)benzeneacetic acid phenylmethyl ester, 6

23.23 g (0.060 mol) of α-amino-4-(phenylmethoxy)benzeneacetic acid phenylmethyl ester HCl, **5**, in 200 ml of water was neutralized with $NaHCO_3$ and extracted with 3 × 100 ml of CH_2Cl_2. The extracts were dried and evaporated to give an oil which was dissolved in 250 ml of CH_2Cl_2 and 12.5 ml (0.09 mol) of triethylamine. The solution was cooled to 0°C and 5.20 ml (0.067 mol) of methanesulfonyl chloride in 50 ml of CH_2Cl_2 were added dropwise. After stirring for 1 h, cooling was removed and the mixture stirred overnight. The mixture was diluted with 200 ml of water and made acidic (pH *ca.* 2) with 2 N HCl. The layers were separated and the aqueous layer extracted with 3 × 200 ml of CH_2Cl_2. The extracts were dried and evaporated to give 25.10 g (97.6%) of a solid suitable for subsequent reactions. An analytical sample was obtained by recrystallization from ethyl acetate: hexane (2:1): mp 121—124°C; NMR (DMSO-d_6) δ 2.80(s,3H); 5.04—5.22(m,5H); 7.01(d,2H); 7.18—7.50(m,12H); 8.24(d,1H); Anal. ($C_{23}H_{23}NO_5S$) C,H,N.

N-(1-Methylethyl)-α-(methylsulfonyl)amino-4-(phenylmethoxy)-benzeneacetamide, 7

5.55 g (0.013 mol) of **6** in 30 ml of isopropylamine was stirred at room temp. for 4 days. The volatiles were removed and the resulting solid

recrystallized from methanol to give 3.00 g (61%) of crystals: mp 194—195°C; NMR (DMSO-d_6) δ 1.00(dd,6H); 2.68(s,3H); 3.70—3.80 (m,1H); 4.97(s,1H); 5.12(s,2H); 7.00—7.60(m,9H); 7.84(s,1H); 8.18 (d, 1H); Anal. ($C_{19}H_{24}N_2O_4S$) C, H, N.

N-[2-[(1-Methylethyl)amino]-1-[4-(phenylmethoxy)phenyl]ethyl]methanesulfonamide hydrochloride hydrate, 8

To a suspension of 13.83 g (0.037 mol) of **7** in 200 ml of anhydrous THF under nitrogen at 0°C was added dropwise 50.0 ml (0.100 mol) of a 2 M solution of borane—methyl sulfide complex in THF. The mixture was stirred for 1 h at 0°C, 30 min at room temp. and heated to reflux for 6 h during which the dimethylsulfide was removed by distillation [27]. After cooling to room temp., 100 ml of methanolic HCl was added and the mixture was refluxed for 30 min, then cooled and evaporated. The resulting material was taken up in 100 ml of ethyl acetate and 100 ml of 1 N HCl. The ethyl acetate was removed *in vacuo* leaving a solid which was recrystallized twice from water to give 6.64 g (44.8%) of crystals: mp 208—210°C; NMR (DMSO-d_6) δ 1.30(dd,6H); 2.80(s,3H); 2.83—3.70(m,3H); 4.63—5.33(m,1H); 5.16(s,2H); 7.30(q,4H); 7.47(s,5H); 8.10(d,1H); 8.93(br s,1H); 9.48 (br s,1H); Anal. ($C_{19}H_{26}N_2O_3S$ HCl 0.25 H_2O) C, H, N.

N-[1-(4-Hydroxyphenyl)-2-[(1-methylethyl)amino]ethylmethanesulfonamide acetic acid salt, 2

4.04 g (0.010 mol) of **8** and 0.50 g of 10% Pd/C in 100 ml of methanol was hydrogenated (50 psi) for 4 h. The catalyst and solvent were removed to give a clear oil. The oil in *ca.* 15 ml of H_2O was applied to a Bio-Rex 70 weak acid resin column. Elution with 100 ml of 0.1 N acetic acid gave the acetate which when evaporated and triturated with $CHCl_3$ provided 0.98 g (30%) of crystals: mp 158—161°C; NMR (D_2O) δ 1.36(dd,6H); 1.92(s,3H); 2.74(s,3H); 3.28—3.49(m,2H); 3.49—3.62(m,1H); 4.66—4.80(m,1H); 7.00(d,2H); 7.39(d,2H); Anal. ($C_{14}H_{24}N_2O_5S$) C,H,N.

1-Methylsulfonyl-2-[(1-naphthalenyloxy)methyl]aziridine 10

To a suspension of 29.47 g (0.116 mol) of **9** [9] in 235 ml of CH_2Cl_2 and 64.6 ml (0.465 mol) of triethylamine at 0°C was added a solution of 18.2 ml (0.232 mol) of methanesulfonylchloride in 15 ml of CH_2Cl_2. The mixture was stirred at room temp. for 1.5 h, diluted with 200 ml of 1 N HCl, the layers separated and the aqueous layer extracted with 3 × 200 ml of CH_2Cl_2. The organic layers were dried and evaporated to yield 38.27 g of crude dimesylate as a viscous oil (its NMR in $CDCl_3$ showed two singlets at δ 2.98 and 3.12 for the methanesulfonamide and methanesulfonate methyls). To 38.27 g (0.103 mol) of the dimesylate in 250 ml of methanol was added 27.6 g (0.20 mol) of anhydrous K_2CO_3. After stirring for 3 h, the methanol was evaporated and the residue taken up in 250 ml of ethyl acetate and 250 ml of water. The layers were separated and the aqueous layer extracted with 2 × 250 ml of ethyl acetate. The organic extracts were dried and evaporated to give 25 g of crude **10** as an oil which was chromatographed on silica gel using CH_2Cl_2 as the eluent. Evaporation of the desired fractions gave an oil which then crystallized from hexane to provide 20 g (67% overall) of needles; mp 89—90°C; NMR ($CDCl_3$) δ 2.43 (d,1H); 2.80 (d,1H); 3.00—3.50(m,1H); 3.10(s,3H); 3.87—4.60(m,2H); 6.72—6.92(m,1H); 7.20—7.68(m,4H); 7.68—8.00(m,1H); 8.08—8.43 (m,1H); Anal. ($C_{14}H_{15}NO_3S$) C,H,N.

N-[2-[(1-Methylethyl)amino]-1-[(1-naphthalenyloxy)methyl]ethyl]methanesulfonamide, 4

25.71 g (0.093 mol) of **10** and 25 ml (0.294 mol) of isopropylamine in 100 ml of methanol were heated to reflux for 5 h. The volatiles were removed and the residue taken up in 250 ml of ethyl acetate and 250 ml of 3 N HCl. The layers were separated and the organic layer extracted with 2 × 250 ml of 3 N HCl. The aqueous extracts were basified with $NaHCO_3$. The alkaline mixture was extracted with 3 × 250 ml of ethyl acetate. The organic extracts were dried and evaporated. Recrystallization from toluene:hexane (4:1) gave 2.95 g (9%) of crystals; mp 90—92°C; NMR ($CDCl_3$) δ 1.06(d,6H); 2.60—3.13(m,3H); 3.03 (s,3H); 3.50(br s,2H); 3.73—4.16(m,1H); 4.16—4.43(m,2H); 6.80—7.00(m,1H); 7.13—7.73(m,4H); 7.73—8.07(m,1H); 8.13—8.40(m,1H); Anal. ($C_{17}H_{24}N_2O_3S$) C,H,N.

Pharmacology studies

The papillary muscle and electrophysiological studies were conducted according to published methods [28].

β-Adrenergic receptor binding studies

Membrane from canine ventricular tissue [12] was homogenized in 5 vol. of a solution containing 0.25 M sucrose, 1 mM $MgCl_2$, and 5 mM Tris, pH 7.5. After removal of the nuclear (700 × *g*) and mitochondrial (10 000 × *g* for 15 min) fractions, a microsomal fraction was collected by centrifugation at 100 000 × *g* for 30 min. The pellet was resuspended in 50 mM Tris, pH 7.5, at a protein concentration of 4 mg/ml and stored at — 80°C until used. Binding of [^{3}H]dihydroalprenolol, DHA, performed according to Cantor *et al.* [29], was measured in 4.5 nM [^{3}H]DHA, 0.1 mg of protein and 50 mM Tris, pH 7.5, in a total volume of 0.25 ml after 15 min at 37°C. Bound complexes were separated by vacuum filtration over glass fiber filters (Whatman, GF/C). The filters were washed with 15 ml of cold 50 mM Tris, pH 7.5, and counted in 5 ml of Aquasol in a liquid scintillation spectrometer. Nonspecific binding was determined in parallel in the presence of 10 μM *d*,1-propranolol. Test compounds were added from 0.1 nM to 10 mM.

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