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Sulfur-Containing Derivatives of β-Phenethylamine: Methanesulfonamides

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Abstract □ *N*-Methanesulfonyl derivatives of β-phenethylamine, (+)-amphetamine, β-4-aminophenethylamine, and 4-(2-trifluoroacetamidoethyl)aniline have been prepared. *N*-Trifluoroacetyl-1-(4-methanesulfonamidophenyl)-2-ethylamine significantly lowered blood pressure in hypertensive rats, and the methanesulfonamide of (+)-amphetamine lowered blood pressure in the dog.

Keyphrases □ Methanesulfonamides—synthesis, pharmacological screening as antihypertensives □ β-Phenethylamine, sulfur-containing derivatives—synthesis, pharmacological evaluation □ Antihypertensive agents, potential—synthesis, evaluation of *N*-methanesulfonyl derivatives of β-phenethylamine

In continuation of a study of the effects of sulfur-containing functional groups on the biological activity of β-phenethylamine, it was desired to observe the effects of including the alkanesulfonamide function in the molecule. Larsen and Lish (1) already pointed out that incorporation of the alkanesulfonamide group into the ring of phenethanolamines gives compounds having similar acidities to phenolic structures. Their phenethanolamine sulfonamides either showed the same biological profile or were antagonists to the catecholamines. According to the list of compounds subsequently reported from their laboratory, numerous alkanesulfonamides and arenesulfonamides of the phenethanolamines were synthesized (2, 3), but no alkanesulfonamides of β-phenethylamine itself were prepared. Previously, the *N*-benzenesulfonyl derivatives of β-phenethylamine (4) and β-4-nitrophenethylamine (5), and the 4-methanesulfonamido derivative (6) of 1-phenyl-2-propylamine, were described. 1- and 2-*p*-Methanesulfonylphenethylamines were synthesized and found to have some antibacterial activity *in vitro* (7).

The *N*-methanesulfonyl derivative of β-phenethylamine was readily prepared from the sulfonyl chloride. To introduce the methanesulfonamido group into the 4-position of the ring, β-phenethylamine was first nitrated in the 4-position by the method of Ehrlich and Pistschimuka (8). The amino group was converted to the trifluoroacetamido group, and the nitro group was reduced to give the 4-amino derivative. This was sulfonated by methanesulfonyl chloride, giving *N*-trifluoroacetyl-1-(4-methanesulfonamidophenyl)-2-ethylamine. An attempt to obtain the corresponding molecule having a free aliphatic amino group by lithium aluminum hydride reduction of 4-methanesulfonamidobenzyl cyanide failed to give the desired 1-(4-methanesulfonamidophenyl)-2-ethylamine.

The methanesulfonamide derivatives of (+)-amphetamine and β-4-nitrophenethylamine (9) and the bismethanesulfonamide of β-4-aminophenethylamine were readily obtained. This series of compounds thus provides examples of β-phenethylamines having methanesulfonyl groups on the aliphatic nitrogen, on the 4-amino group of the ring, and on both the aliphatic and aromatic nitrogens. Examples of β-phenethylamines containing methanesulfonamide in addition to dithiocarbamate and thiourea groups were reported in a previous paper (9).

Pharmacological tests for effects on blood pressure in rats and dogs revealed that *N*-trifluoroacetyl-1-(4-methanesulfonamidophenyl)-2-ethylamine caused significant and consistent reductions in the blood pressure when administered orally to rats. The methanesulfonamide of (+)-amphetamine also produced a significant lowering of blood pressure after intravenous injection in a dog. Whereas the previous results of Uloth *et al.* (2) and Larsen *et al.* (3) showed that inclusion of the alkanesulfonamide group in the aromatic ring of phenethanolamines conferred either adrenergic stimulant or adrenergic-blocking activity (the latter generally in conjunction with an isopropyl or larger group on the aliphatic nitrogen), it is apparent from the results reported here that conversion of the aliphatic amino group to an acidic methanesulfonamide or even trifluoroacetamide group can lead to a depressor response from the simpler phenethylamine structure.

PHARMACOLOGICAL RESULTS

Tests for blood pressure effects in unanesthetized neurogenic hypertensive dogs (10) and in metacorticoid hypertensive rats (11) were performed[1].

[1] At Smith Kline and French Laboratories under the direction of Dr. R. A. McLean. Results were made available through the courtesy of Dr. C. W. French and Dr. J. W. Wilson.

N-Trifluoroacetyl-1-(4-methanesulfonamidophenyl)-2-ethylamine produced significant reductions in the mean systolic blood pressure of four test rats following oral administration of 80 mg./kg. The test animals were dosed on 2 consecutive days; significant reductions were seen on Day 1, 5 hr. postdrug, and on Day 2, both 5 and 24 hr. postdrug. Three dogs were administered oral doses of 5, 10, and 20 mg./kg. on Days 1, 2, and 3, respectively, and a fourth dog received doses of 10, 20, and 40 mg./kg. over the 3-day period. A significant hypotensive effect was seen on Days 2 and 3 in only one dog receiving the lower dose.

N-Methanesulfonyl-1-methyl-2-phenethylamine produced a significant reduction in blood pressure when a dose of 0.5 mg./kg. i.v. was administered to a normotensive dog[2]. *N,N'*-Bis(methanesulfonyl)-1-(4-aminophenyl)-2-ethylamine exerted no significant effect on blood pressure of either dogs or rats.

ANTIMICROBIAL RESULTS

Tests for antimicrobial activity (9) revealed that *N*-trifluoroacetyl-1-(4-methanesulfonamidophenyl)-2-ethylamine and the bis(methanesulfonyl) derivative of β-4-aminophenethylamine have some activity with minimum inhibitory concentrations of <1/2000 *M versus Staphylococcus aureus*, *Escherichia coli*, *Aspergillus niger*, and *Candida albicans*.

EXPERIMENTAL[3]

Melting points were taken on a Mel-Temp block and are uncorrected. IR absorption spectra were obtained with a Perkin-Elmer model 137 B spectrometer.

N-Methanesulfonyl-2-phenethylamine—To a cooled solution of 2.42 g. (0.02 mole) of β-phenethylamine[4] in 30 ml. of methylene chloride were added dropwise, with stirring, 1.67 ml. (0.022 mole) of methanesulfonyl chloride in 20 ml. of methylene chloride and 3 ml. (0.022 mole) of triethylamine in 20 ml. of methylene chloride. The mixture was allowed to come to 25° and was stirred for 15 hr. The resulting solution was washed with 1 *N* hydrochloric acid and water, and the solvent was distilled *in vacuo*. The product was air-dried and recrystallized from aqueous ethanol, giving a 55% yield; m.p. 50–52°. IR(KBr) 1160 (SO_2), 1325 (SO_2), 1600 (NH), and 3300 (NH) $cm.^{-1}$.

Anal.—Calc. for $C_9H_{13}NO_2S$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.51; H, 6.40; N, 7.20.

N-Methanesulfonyl-1-methyl-2-phenethylamine—To a cooled solution of 2.45 g. (0.02 mole) of (+)-amphetamine[4] in 10 ml. of methylene chloride were added dropwise, with stirring, 1.67 ml. (0.022 mole) of methanesulfonyl chloride in 30 ml. of methylene chloride and 3 ml. (0.022 mole) of triethylamine in 30 ml. of methylene chloride. The mixture was allowed to come to 25° and was stirred for 15 hr. The resulting solution was washed with 1 *N* hydrochloric acid and water, dried over Na_2SO_4, and evaporated in a rotary evaporator. The residue was distilled, and 2.10 g. was collected at 190–195°/1.9 mm.; IR(film) 1150(SO_2), 1315 (SO_2), 1600 (NH), and 3300 (NH) $cm.^{-1}$; $[\alpha]_D^{20} + 51°$(CH_2Cl_2).

Anal.—Calc. for $C_{10}H_{15}NO_2S$: C, 56.33; H, 7.04; N, 6.54. Found: C, 56.45; H, 7.40; N, 6.38.

N-Trifluoroacetyl-1-(4-methanesulfonamidophenyl)-2-ethylamine—To a cooled solution of 0.696 g. (0.003 mole) of 4-(2-trifluoroacetamidoethyl)aniline (9) in 5 ml. of methylene chloride were added dropwise, with stirring, 0.3 ml. (0.0035 mole) of methanesulfonyl chloride in 5 ml. of methylene chloride and 0.5 ml. of triethylamine in 5 ml. of methylene chloride. The mixture was allowed to reach 25°, was stirred for 3 hr., and was washed with 1 *N* hydrochloric acid and water. The solvent was distilled *in vacuo*, and a 70% yield of product remained; m.p. 155–160°. IR(KBr) 1160 (SO_2), 1325 (SO_2), 1700 (C=O), and 3250 (NH) $cm.^{-1}$.

Anal.—Calc. for $C_{11}H_{13}F_3N_2O_3S$: C, 42.58; H, 4.22; N, 9.03. Found: C, 42.70; H, 4.34; N, 9.04.

***N,N'*-Bis(methanesulfonyl)-1-(4-aminophenyl)-2-ethylamine**—To a cooled solution of 2.71 g. (0.02 mole) of β-(4-aminophenyl)-ethylamine[4] in 25 ml. of benzene were added dropwise, with stirring, 3.4 ml. (0.041 mole) of methanesulfonyl chloride in 30 ml. of methylene chloride and 6 ml. (0.044 mole) of triethylamine in 30 ml. of methylene chloride. The mixture was allowed to reach 25° and was stirred for 3 hr. The precipitate was collected, washed with 1 *N* hydrochloric acid and water, and dried *in vacuo*. Additional product was obtained from the filtrate, and the combined product was recrystallized from ethanol, giving a 92% yield; m.p. 190–192°. IR(KBr) 1150 (SO_2), 1320 (SO_2), 1600 (NH), and 3250 (NH) $cm.^{-1}$.

Anal.—Calc. for $C_{10}H_{16}N_2O_4S_2$: C, 41.09; H, 5.52; N, 9.58. Found: C, 41.06; H, 5.59; N, 9.70.

4-Methanesulfonamidobenzyl Cyanide—To a cooled solution of 2.64 g. (0.02 mole) of 4-aminobenzyl cyanide[4] in 25 ml. of benzene were added 1.67 ml. (0.022 mole) of methanesulfonyl chloride in 15 ml. of methylene chloride and 3 ml. (0.022 mole) of triethylamine in 15 ml. of methylene chloride. The mixture was allowed to reach 25° and was stirred for 4 hr. Precipitated triethylamine hydrochloride was removed, and the filtrate was washed with dilute hydrochloric acid and water and dried (Na_2SO_4). The solvent was distilled under reduced pressure, and the residue was dried *in vacuo* and recrystallized from ethanol, giving a 93% yield of product; m.p. 113–114°.

Anal.—Calc. for $C_9H_{10}N_2O_2S$: C, 51.42; H, 4.79; N, 13.32. Found: C, 51.35; H, 4.84; N, 12.99.

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[2] The authors are indebted to Mr. V. K. Sharma for this result.

[3] Analyses for carbon, hydrogen, and nitrogen were done by Weiler and Strauss, Oxford, England.

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