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S-OXIDATION PRODUCTS OF ALKYLTHIOAMPHETAMINES

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ABSTRACT

The preparation of the sulfoxides and the sulfones of two centrally active alkylthioamphetamine salts, (±)-1-(4-methylthiophenyl)-2-aminopropane hydrochloride (**2**) (MTA · HCl) and (±)-1-(2,5-dimethoxy-4-ethylthiophenyl)-2-aminopropane hydrochloride (**7**) (ALEPH-2 · HCl), is described.

Key Words: Alkylthioamphetamines; *S*-oxidation

Amphetamine analogues substituted at the 4-position with an alkylthio group constitute a pharmacologically interesting class of compounds exhibiting a wide range of activities in the central nervous system. The simplest member of the family, (±)-1-(4-methylthiophenyl)-2-amino-

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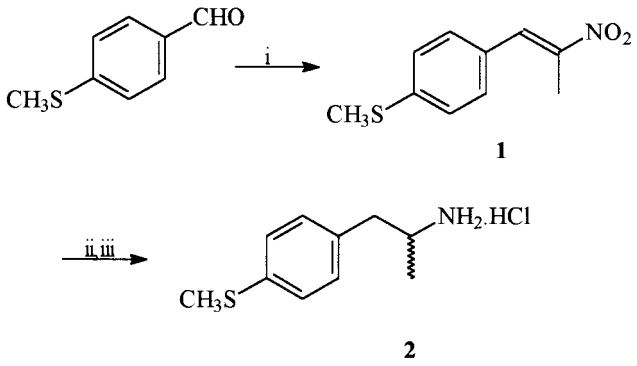
propane (methylthio-amphetamine, MTA) is a potent non-neurotoxic serotonin-releasing agent,[1–3] and a potent, selective and reversible monoamine oxidase-A (MAO-A) inhibitor.[4] Its use as a street drug has been reported recently,[5,6] and one case of fatal poisoning has been attributed to its ingestion.[7] (±)-1-(2,5-Dimethoxy-4-ethylthiophenyl)-2-aminopropane (ALEPH-2), on the other hand, is part of a series of 2,5-dimethoxy-4-alkylthioamphetamines (ALEPH's) possessing hallucinogenic properties in humans.[8] Evidence of its anxiolytic effects in rodents has been reported.[9] Both hallucinogenic and anxiolytic effects may be ascribed to interactions with serotonin receptors, and quite recently compound ALEPH-2 has been characterized as a partial 5-HT_{2A}, and a full 5-HT_{2c} receptor agonist.[10] ALEPH-2 is also a selective MAO-A inhibitor.[4]

There are good reasons for preparing derivatives of these alkylthioamphetamines with the sulfur atom oxidized. In the first place, a comparison of the MAO and serotonergic activities of these compounds with those of the parent amphetamines may shed more light on the role played by the 4-alkylthio substituent in these drugs. There are several structure-activity studies on psychotomimetic amphetamine analogues in the literature.[11–18] In the particular case of the 2,5-dimethoxy-4-X pattern of ring substitution, their activity has been associated with the lipophilicity of the X substituent. When this is an RS-group, its oxidation may be expected to lead to sulfoxides and sulfones with strongly reduced lipophilicities, and resulting changes in activity. Furthermore, the presence of *S*-oxygen atom(s) may be viewed as a branching of the substituent, and on the molecular scale as a site of high electron density which is absent in the parent substances. Examples of such changes in medicinal compounds, brought about by the oxidation of a sulfide group, have been reviewed.[19]

A second reason stems from the reportedly variable response to the psychotropic or behavioral action of the ALEPH series by different human subjects or laboratory rats.[8,9] This may be due to individual metabolic characteristics, leading to variations in metabolic inactivation or in the production of metabolites with increased or qualitatively different activities. Among these, the sulfoxides and sulfones are strong candidates, but there is as yet no study on the metabolic modification of any alkylthioamphetamines. The preparation of the *S*-oxidized derivatives of the better characterized MTA and ALEPH-2 is thus a necessary step towards understanding the somewhat bewildering activity of these compounds.

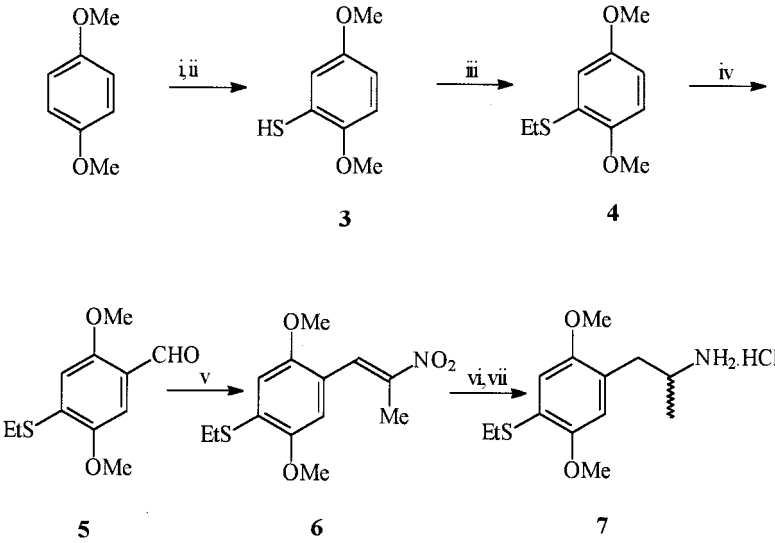
Phenylisopropylamine salts (**2**) and (**7**) were prepared from the corresponding substituted benzaldehydes, by condensation with nitroethane followed by reduction with $LiAlH_4$. The preparation of the hydrochloride (**2**), starting from 4-methylthiobenzaldehyde, is described in a patent,[20] with an

overall yield of 23%. We have obtained compound (**2**) in 72% yield, introducing some modifications to the reported procedure.

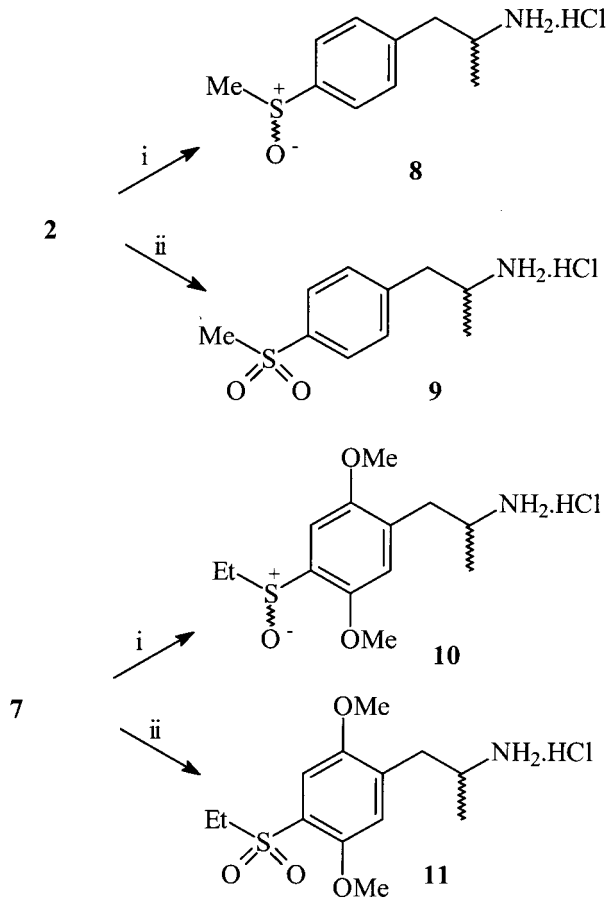


i)$EtNO_2$ / $AcONH_4$ / toluene ; ii) $LiAlH_4$; iii) HCl

The route to ALEPH-2 from 1,4-dimethoxybenzene was that described by Shulgin et al.,[8,21,22] and is shown in the scheme below.



i) HSO_3Cl ; ii) Zn/HCl ; iii) EtBr /NaOH ; iv) $POCl_3$ / DMF ;
v) $EtNO_2$ / $AcONH_4$; vi) $LiAlH_4$; vii) HCl

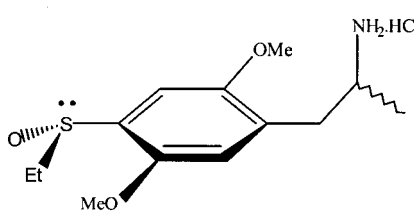


i) CF_3CO_3H, 0°C, 1:1; ii) CF_3CO_3H, 60°C, 2:1

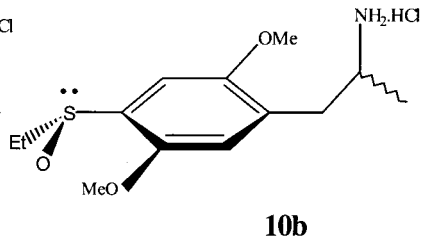
The oxidation of both alkylthioamphetamines was achieved with trifluoroperacetic acid,[23] which avoided the need of protecting the amino group and formed in a selective way the corresponding sulfoxides or sulfones.

Oxidation of (**2**) should in principle give a pair of diastereomeric sulfoxides, but this was not confirmed by the ^{1}H NMR spectrum of the product. The spectral evidence pointing to the apparent formation of essentially one sulfoxide might also be an indication that interconversion of the two diastereomers is too rapid to be detected at room temperature, or that their ^{1}H NMR spectra are indistinguishable. In contrast, oxidation

of (**7**) led to two diastereomeric sulfoxides (**10a**) and (**10b**), separated by fractional crystallization. Semiempirical calculations of the heats of formation of the two possible sulfoxide diastereomers at the AM1 level gave for the optimized structures of (**10a**), with the S-O bond *anti* to the adjacent MeO substituent, and (**10b**), where the S-O bond was *syn* to that group, a difference of ca 4 kcal/mol, suggesting the more stable *anti* configuration for this sulfoxide.



10a



10b

EXPERIMENTAL

Melting points were taken using a Kofler hot-stage apparatus, and were not corrected. IR spectra were recorded with a Perkin-Elmer 750B spectrometer, and NMR spectra with a Bruker AMX 300 instrument, employing tetramethylsilane as internal standard in $CDCl_3$ and referring the spectra to the HDO signal in D_2O.

1-(4-Methylthiophenyl)-2-nitropropene (1): A mixture of 4-methylthiobenzaldehyde (0.075 mol, 11.4 g, 10 mL), anhydrous ammonium acetate (6 g, 0.081 mol), nitroethane (55 mL) and toluene (100 mL) was refluxed for 12 h with elimination of water in a Dean-Stark apparatus. The mixture was concentrated to 70 mL and cooled to $-20^{\circ}C$. The nitropropene separated as a bright yellow precipitate, which weighed 8.5 g after drying. The mother liquor was rotary evaporated, and the dark reddish-brown oily residue was diluted with 80 mL of hot methanol. On cooling, a second crop (5.3 g) of the nitropropene precipitated, sufficiently pure for use in the next synthetic step. The methanol was removed, the residue was partitioned between water and chloroform, and the chloroform layer was dried with Na_2SO_4, concentrated and purified by column chromatography (silica gel, elution with chloroform). In this way, an additional amount of pure nitropropene was recovered (0.5 g). The overall yield of 1-(4-methylthiophenyl)-2-nitropropene was 14.3 g (91%), recrystallized from methanol, m.p. 67–68°C, m.p. lit.[20] 68.2–69.8°C. ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, SCH_3), 2.52 (s, 3H, ArCH=CHCH_3), 7.28 (2H, d, $J = 8$ Hz, ArH), 7.36 (2H, d, $J = 8$ Hz, ArH),

8.04 (s, 1H, ArC*H*=C); ^{13}C NMR ($CDCl_3$) δ 14.09 (SCH_3), 14.95 (C1), 125.81 (C2′ and C6′), 128.51 (C2), 130.44 (C3′ and C5′), 142.12 (C1′), 146.80 (C4′). Analysis, found: C, 57.61; H, 5.36; N, 6.89%. Calculated for $C_{10}H_{11}NO_2S$: C, 57.42; H, 5.26; N, 6.70%.

(±)-1-(4-Methylthiophenyl)-2-aminopropane Hydrochloride (2): A solution of 1-(4-methylthiophenyl)-2-nitropropene (13 g, 0.062 mol) in dry THF (100 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (13 g, 0.342 mol) in dry THF (200 mL). The reaction mixture was refluxed with stirring for 24 h and then cooled to 5–10°C in an ice bath and quenched by cautious addition of 15 mL of water, 13 mL of NaOH 40% and finally 45 mL of water. Filtration and evaporation of the filtrate under reduced pressure gave the crude product as light yellow oil, purified by bulb-to-bulb distillation. The pure, colorless (±)-1-(4-methylthiophenyl)-2-aminopropane weighed 10 g (81% yield). ^{1}H NMR ($CDCl_3$) δ 1.08 (d, 3, $J = 6.3$, CHCH_3), 2.44 (s, 3H, SCH_3), 2.47 (dd, 1H, $J = 13.4$ Hz, $J' = 8.0$ Hz), 2.64 (dd, 1, $J = 12.8$ Hz, $J' = 7.9$ Hz), 3.11 (m, 1H), 7.08 (2H, d, J = 8 Hz), 7.19 (2H, d, J = 8 Hz).

The (±)-1-(4-methylthiophenyl)-2-aminopropane hydrochloride (2) was prepared by adding one equivalent of conc. HCl to a solution of the aminopropane (10 g, 0.055 mol) in a minimal volume of 2-propanol. The hydrochloride (11.7 g, 98% yield) crystallized out by addition of ethyl ether, m.p. 190–192°C, m.p. lit.[20] 190–191°C. Analysis, found: C, 55.67; H, 7.46; N, 6.69%. Calculated for $C_{10}H_{12}ClNO_2S$: C, 55.19; H, 6.90; N, 6.44%. ^{1}H NMR (D_2O) δ 1.22 (3H, d, $J = 7$ Hz, C$\underline{H}_3$CH), 2.42 (3H, s, CH_3S), 2.85 (2H, d, $J = 7$ Hz, ArCH_2), 3.54 (1H, m, C$\underline{H}$CH_3), 7.22 (2H, d, $J = 8$ Hz, Ar-H *meta* to MeS), 7.81 (2H, d, $J = 8$ Hz, Ar-H). ^{13}C NMR ($CDCl_3$) δ 14.98 (SCH_3), 17.64 (C3), 39.74 (C1), 49.36 (C2), 127.13 (C2′/C6′), 130.35 (C3′/C5′), 133.41 (C1′), 136.73 (C4′).

2-Ethylthio-1,4-dimethoxybenzene (4): Prepared from the corresponding thiol (**3**) by the reported procedure,[22] in 86% yield. ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, $J = 7$ Hz, C$\underline{H}_3$CH$_2$), 2.87 (2H, q, $J = 7$ Hz, CH$_3$C$\underline{H}_2$), 3.70 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 6.65 (2H, s, ArH), 6.78 (1H, s, ArH).

2,5-Dimethoxy-4-ethylthiobenzaldehyde (5): Prepared by the reported procedure,[22] in 79% yield, m.p. 86–88°C, lit.[8] m.p. 87–88°C. IR (KBr) 1650 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, $J = 7$ Hz, C$\underline{H}_3$CH$_2$), 2.98 (2H, q, $J = 7$ Hz, CH$_3$C$\underline{H}_2$), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.74 (1H, s, ArH), 7.21 (1H, s, ArH), 10.34 (1H, s, CHO).

1-(2,5-Dimethoxy-4-ethylphenyl)-2-nitropropene (6): Prepared by the reported procedure,[22] in 73% yield, m.p. 110–111°C, lit.[8] m.p. 110–112°C. ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, $J = 7$ Hz, CH_3CH_2), 2.42 (3H, s, CH_3C=C), 2.98 (2H, q, $J = 7$ Hz, CH$_3$C$\underline{H}_2$), 3.88 (6H, s, OCH_3), 6.75 (1H, s, ArH), 6.78 (1H, s, ArH), 8.28 (1H, s, CH=C).

(±)-1-(2,5-Dimethoxy-4-ethylthiophenyl)-2-aminopropane hydrochloride (7): Prepared by $LiAlH_4$ reduction of the corresponding arylnitropropene and converted into the corresponding hydrochloride,[22] in 50% yield, m.p. 127–129°C, lit[8] m.p. 128–130°C. IR (KBr) 2900 (broad), 1600, 1500, 1210 and 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.31 (3H, t, $J = 7$ Hz, $C\underline{H_3}CH_2S$); 1.37 (3H, d, $J = 6$ Hz, $C\underline{H_3}CHNH_2$); 2.92–3.15 (4H, m, CH_2S and $ArCH_2$); 3.71 (1H, m, $C\underline{H}NH_2$); 3.81 (3H, s, OCH_3); 3.86 (3H, s, OCH_3); 6.76 (1H, s, ArH); 6.83 (1H, s, ArH).

(±)-1-(4-Methylsulfoxylphenyl)-2-aminopropane hydrochloride (8): A solution of the hydrochloride **2** (100 mg, 0.460 mmol) in trifluoroperacetic acid (0.115 mL, 0.460 mmol), prepared from hydrogen peroxide (30%) (8.6 mL) and trifluoroacetic acid (16.4 mL), was stirred for 5 h in an ice-bath (0°C) until the complete disappearance of the reacting sulfide, as shown by thin-layer chromatography. The resulting solution was then poured into cold water (10 mL) and the aqueous solution made basic (pH = 10) with a 15% NaOH solution. The free amine was then extracted with chloroform (3 × 5 mL), and the extracts concentrated to give an oily residue that was redissolved in 2-propanol (2 mL). To this solution were then added drops of concentrated HCl and diethyl ether (15 mL) to precipitate the crude hydrochloride. The product was purified through column chromatography (silica gel 60 G Merck, $CHCl_3$/MeOH 4:1 as eluent), to give 58 mg (55% yield) of (±)-1-(4-methylsulfoxylphenyl)-2-aminopropane hydrochloride, m.p. 236–237°C. Analysis, found: C, 50.92; H, 7.00; N, 6.05; S, 13.93%. Calculated for $C_{10}H_{16}ClNOS$: C, 51.39; H, 6.85; N, 6.00; S, 13.70%. IR (KBr) 1040 cm^{-1} (RSOAr). ^1H NMR (D_2O) δ 1.20 (3H, d, $J = 7$ Hz, $C\underline{H_3}CH$), 2.76 (3H, s, CH_3SO), 2.90 (2H, d, $J = 7$ Hz, $ArCH_2$), 3.55 (1H, m, $C\underline{H}CH_3$), 7.42 (2H, d, $J = 8$ Hz, Ar-H *meta* to MeS), 7.60 (2H, d, $J = 8$ Hz, Ar-H *ortho* to MeS).

(±)-1-(4-Methylsulfonylphenyl)-2-aminopropane hydrochloride (9): A solution of the hydrochloride **2** (100 mg, 0.460 mmol) in trifluoroperacetic acid (0.230 mL, 0.920 mmol), prepared from hydrogen peroxide and trifluoroacetic acid as described above, was allowed to react for 5 h in a water bath at 60°C until the complete disappearance of the reacting sulfide, as shown by thin-layer chromatography. The resulting solution was then poured into cold water and worked up as before. The precipitated product was purified through column chromatography as above to give 76 mg (67% yield) of (±)-1-(4-methylsulfonylphenyl)-2-aminopropane hydrochloride, m.p. 241–242°C. Analysis found: C, 46.51; H, 6.59; N, 5.98; S, 12.03%. Calculated for $C_{13}H_{16}ClNSO_3$. 1/2 H_2O: C, 46.42; H, 6.58; N, 5.42; S, 12.38%. IR (KBr) 1145 and 1300 cm^{-1} (RSO_2Ar). ^1H-NMR (D_2O) δ 1.25 (3H, d, $J = 7$ Hz, $C\underline{H_3}CH$), 3.01 (2H, d, $J = 7$ Hz, $ArCH_2$), 3.22 (3H, s, CH_3SO_2), 3.65 (1H, m, $C\underline{H}CH_3$), 7.52

(1H, d, $J = 8$ Hz, Ar-H *meta* to MeS), 7.88 (1H, d, $J = 8$ Hz, Ar-H *ortho* to MeS).

(±)-1-(2,5-Dimethoxy-4-ethylsulfoxylphenyl)-2-aminopropane hydrochloride (10): A cooled (0°C) solution of the hydrochloride **7** (100 mg, 0.343 mmol) in an equimolar amount of trifluoroperacetic acid, prepared as described above, was allowed to react for 6 h, until the complete disappearance of the reacting sulfide, as shown by thin-layer chromatography. The resulting solution was then poured into cold water and worked up as before. The precipitated crude hydrochloride was purified through column chromatography (silica gel 60 G Merck, $CHCl_3$/MeOH 4 : 1 as eluent), to give 51 mg of a mixture of two diastereomeric sulfoxides. The mixture was redissolved in 2-propanol (0.5 mL) and diethyl ether was added to precipitate the hydrochloride (**10a**) (23 mg, 21% yield), m.p. 199–201°C. Analysis, found: C, 50.45; H, 7.33; N, 4.64; S, 10.21%. Calculated for $C_{13}H_{22}ClNO_3S$: C, 50.73; H, 7.15; N, 4.55; S, 10.41%. IR (KBr) 2900, 1210, 1030 and 1040 cm^{-1}. ^1H NMR (D_2O) δ 1.18 (3H, t, $J = 6$ Hz, $C\underline{H_3}CH_2SO$), 1.22 (3H, d, $J = 6$ Hz, $C\underline{H_3}CH$), 2.95 (3H, m, $CH_3C\underline{H_2}SO$ and $ArC\underline{H_a}H_bCH$), 3.14 (1H, m, $ArCH_a\underline{H_b}CH$), 3.64 (1H, m, $C\underline{H}NH_3^+$), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.99 (1H, s, ArH *meta* to RSO), and 7.14 (1H, s, ArH *ortho* to RSO).

The filtrate was cooled to 0°C and the precipitate which separated was further purified by column chromatography (silica 60G, $CHCl_3$/MeOH 10:3 as eluent), to give sulfoxide (**10b**) (18 mg, 17% yield), m.p. 207–208°C. ^1H NMR (D_2O) δ 1.10 (3H, t, $J = 6$ Hz, $C\underline{H_3}CH_2SO$), 1.13 (3H, d, $J = 6$ Hz, $C\underline{H_3}CH$), 2.80 (3H, m, $CH_3C\underline{H_2}SO$ and $ArC\underline{H_a}H_bCH$), 3.01 (1H, m, $ArCH_a\underline{H_b}CH$), 3.52 (1H, m, $C\underline{H}\ NH_3^+$), 3.67 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 6.85 (1H, s, ArH *meta* to RSO), and 6.95 (1H, s, ArH *ortho* to RSO). ^{13}C NMR (D_2O) δ 5.05 ($\underline{C}H_3$-CS), 17.05 ($\underline{C}H_3$-CN), 34.80 (Ar-$\underline{C}H_2$), 46.15 ($\underline{C}H_2$-S), 47.85 ($\underline{C}$H-N), 55.99 (OCH_3), 107.05 (arom. C-3), 115.50 (arom. C-6), 126.05 (arom. C-4), 129.50 (arom. C-1), 149.50 (arom. C-5) and 152.80 (arom. C-2).

(±)-1-(2,5-Dimethoxy-4-ethylsulfonylphenyl)-2-aminopropane hydrochloride (11): A solution of the hydrochloride **7** (100 mg, 0.343 mmol) in trifluoroperacetic acid (0.255 mL, 1.209 mmol), prepared as described above, was allowed to react for 6 h in a water bath at 70°C until the complete disappearance of the reacting sulfide, as shown by thin-layer chromatography. The resulting solution was the poured into cold water and worked up as before. The hydrochloride (**11**) which separated was filtered to give 57 mg (52% yield) of the pure product, m.p. 201–203°C. Analysis, found: C, 48.03; H, 6.44; N, 4.86; S, 9.57%. Calculated for $C_{13}H_{22}ClNSO_4$: C 48.22; H, 6.80; N, 4.33; S, 9.89%. IR (KBr) 2900, 1300, 1140, 1210 and 1030 cm^{-1}. ^1H NMR (D_2O) δ 1.14 (3H, t, $J = 7$ Hz, $C\underline{H_3}CH_2SO_2$), 1.23 (3H, d, $J = 7$ Hz, $C\underline{H_3}CH$), 2.96 (2H, m, $ArC\underline{H_2}CH$), 3.46 (2H, q, $J = 7$ Hz, $CH_3C\underline{H_2}SO_2$),

3.64 (1H, m, C<u>H</u> NH_3^+), 3.81 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 7.11 (1H, s, ArH *meta* to RSO_2), and 7.34 (1H, s, ArH *ortho* to RSO_2).

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