# SYNTHESIS OF 2-(ALKYLAMINO)-1-PHENYLETHANE-1-THIOSULFURIC ACIDS, POTENTIAL SCHISTOSOMICIDES

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**The total synthesis of seven here-to-fore unreported aromatic aminoalkanethiosulfuric acids, their physical properties and those of the aminoalcohol and bromoalkanamine intermediates are reported. All structures were established by including $^{1}H$ and $^{13}C$ NMR, IR and MS spectroscopy and elemental analysis.**

**Keywords: aminolkanethiosulfate; schistosomicide; β-aminoalcohol.**

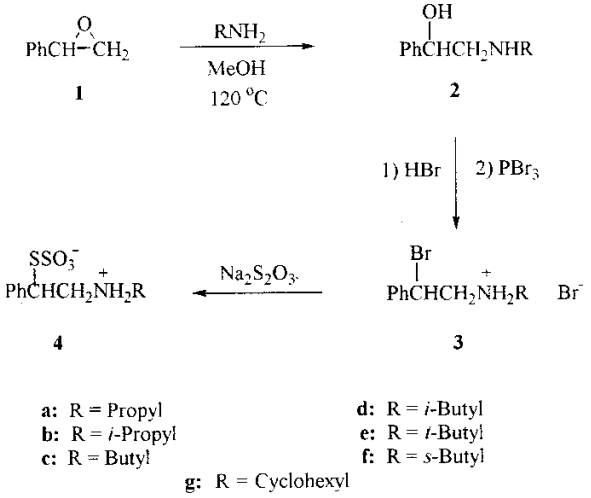
## INTRODUCTION

Schistosomiasis is an endemic disease which is caused by the parasite *Schistosoma mansoni* and which affects ten to twelve million persons in Brazil[1]. Drugs such as oxamniquine[2], preferred for mass treatment, may produce mutagenic effects and cause hepatic lesions; in addition, resistant strains of *S. mansoni* have been observed[3-5]. Thus, studies aimed at the production of new drugs active against this disease have been realized[6-10]. Several compounds which have demonstrated activity against this disease can be synthesized via the intermediate β–aminoalcohols and bromoalkanamines. These substances include the mercaptoalkanamines, the aminoalkanethiosulfuric acids and the corresponding aminoalkyl disulfides[6-8,11-14]. An alternate route to the aminoalkanethiosulfuric acids involves conversion of epoxides to thiiranes[15] and the reaction of thiiranes with primary amines to furnish the mercaptoalkanamines[16]. The disulfides may be obtained by oxidation of the amino-thiols[14], and they may be converted to the thiosulfuric acids by treatment with sodium sulfite[12]. However, because of the ease of polymerization of the thiiranes, the yields obtained in the reaction with the amines are frequently very low, especially when the amine bears a branched alkyl group. Also, the maximum yield obtainable in the reaction of the disulfide with sodium sulfite is necessarily only 50%, based on the thiol from which the disulfide is obtained. Therefore, the route via aminoalcohols is preferred. The aminoalcohols may also be converted to aziridines which can be opened with thiosulfuric acid[12], but the number of steps is the same as in the selected route and the probability of rearrangement is higher because of the acidic conditions employed. The preparation of aziridines using the method of Corey and Chaykovsky[17] has not proved fruitful when the imine bears an aliphatic group[18].

The activity of several aliphatic aminoalkanethiosulfuric acids against schistosomiasis has been demonstrated[6,8-10]. However, the effect of an alpha phenyl substituent on the activity of these compounds has never been studied. Therefore, seven new aromatic aminoalkanethiosulfuric acids (**4**) were synthesized with the objective of verifying their *in vivo* activities against schistosomiasis. These syntheses involved classical methods as shown in Scheme 1.

## RESULTS AND DISCUSSION

The literature describes various synthetic methods for the preparation of β-aminoalcohols, including the substitution reaction of primary and secondary amines with alkylene chlorohydrins[19-20]; the reduction of α-hydroxyamides[21] and the opening of 1,2-epoxyalkanes by primary and secondary amines[22]. This last method was chosen because of its simplicity and the availability of starting materials. According to the Kraussuski rule[23], the nucleophile attacks the less substituted carbon in a bimolecular substitution mechanism to form the aminoalcohol shown in Scheme 1.

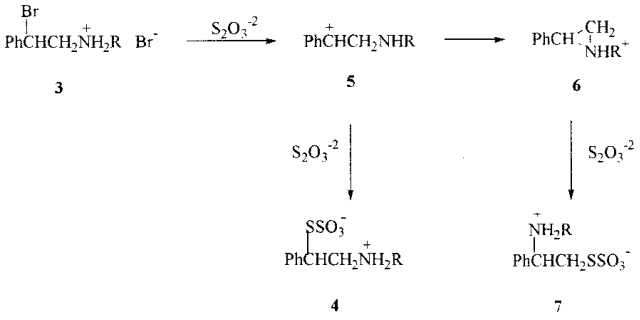



***Scheme 1.*** *Formation of 2-(alkylamino)-1-phenyl-1-thiosulfuric acids*

In the synthesis of β-aminoalcohols, Biel[24] obtained good yields by refluxing a mixture containing a secondary amine, epoxide and metanol in the molar ratio of 3:1:0.5. With the aim of improving the yields of these reactions, a modification of the procedure was used in which the reaction was carried out under pressure in a Parr reactor. This modification also resulted in a significant reduction in the reaction time. Even though an excess of amine was used, there was still the possibility of obtaining secondary products since primary amines were being used, as well as of polymerization of the epoxide and the products. These factors would be responsible for the relatively low yields for many of the aminoalcohols obtained even with the improvements in the method. No attempt was made to maximize the yields.

The amino groups of the β-aminoalcohols were protected by conversion to the hydrobromide salts and then the hydroxyl groups were substituted by bromide using excess phosphorous tribromide in refluxing benzene, in accord with the method of Leffler and coworkers[25]. With the present series of aminoalcohols, there was no possibility of rearrangement of the intermediate carbonium ion, as has been observed in previous syntheses[6].

The β-bromoalkanamines were converted to the Bunte salts by reaction with sodium thiosulfate[26-29]. Even under weakly acidic conditions (pH = 3.5), a rearrangement normally occurs in which the β-bromoalkanamines are converted to the intemediate aziridinium ions which then suffer attack on the least hindered carbon to yield the primary thiosulfates (Scheme 2)[8]. Because of the instability of thiosulfuric acid, a lower pH cannot be used. However, in the present case, because of the high stability of the intermediate benzilic carbocation, the preferred pathway involved attack on the benzilic carbon to yield the secondary thiossulfuric acid. HPLC analyses demonstrated the presence of approximately 10% of a secondary product which was no doubt the primary thiosulfuric acid although it was not isolated for identification. Relatively low yields of the final product were obtained when the alkyl group bound to the amine was branched, possibly in part because of a degree of steric hindrance, but chiefly because of difficulty in purifying the products.




***Scheme 2.*** *Mechanism of formation of **4** in the reaction of the N-alkyl-1-bromo-1-phenyl-2-ethanamine **3** with thiosulfate ion.*

The structures of the intermediates and products were confirmed by IR[30-32], NMR[32,33] and mass spectroscopy[32,34]. In the $^1$H NMR spectra of all the 2-(alkylamino)-1-phenyl-1-ethanols (**2**), the signal for the amino and hydroxyl hydrogens was observed in the region between δ = 3.4 and 3.9. The signal corresponding to the methinyl hydrogen appeared between δ = 4.5 and 4.8, whereas that corresponding to the aromatic hydrogens appeared as a sharp peak centered at δ = 7.2. The spectra were also determined in $CF_3CO_2D$ in order to observe the effect of protonation of the amino group on the chemical shifts of the neighboring hydrogens for later comparison with the spectra of the bromoalkanamine hydrobromides (**3**). In the case of **2f**, the double doublet expected for the methinyl hydrogen alpha to the hydroxyl group is complicated, probably because of superposition of the signals for the two diasteriomers which are formed in the reaction of the epoxide with the racemic *s*-butylamine.

The alterations observed in the $^1$H NMR spectra of **3**, when compared with those of the respective aminoalcohols, are the substitution of the hydroxyl group for a bromine atom and protonation of the amino group which appeared as a wide signal from δ = 8–10. The signal for the methinyl hydrogen is shifted to the δ = 5.7–5.8 region. Although one might expect to see a triplet, as in the case of **3b**, a double doublet was observed for the other bromoalkanamines, indicating that the methylenic hydrogens alpha to the ammonium group [$PhCH(Br)CH_2NH_2R^+$] are not equivalent.

In **3d**, with an 80 MHz instrument, the simple first order spectrum is observed. However, on a 400 MHz instrument, instead of a simple doublet for the gem methyl groups due to coupling with the methinyl proton, two doublets are observed because the two methyl groups are in different environments. Thus, rotation around the C1–C2 bond is not completely free. In **3e**, **3f** and **3g**, the two hydrogens bound to the nitrogen are in very different environments, leading to very different chemical shifts. This is no doubt due to the steric hindrance to rotation because of the more voluminous alkyl groups bound to the amino group and the large bromine atom. The remaining signals also presented a chemical shift to higher δ.

In the spectra of the 2-(alkylamino)-1-phenylethane-1-thiosulfuric acids, all the signals for the alkyl substituents are observed between δ = 1.0 and 4.0. The signal for the methinyl hydrogen is found near δ = 4.6 as a triplet, with the exception of **4b** and **4d**, which present a multiplet and a double doublet, respectively.

The signal corresponding to the methylenic hydrogens alpha to the ammonium group is observed as a doublet for **4d**, but appears as a multiplet (**4a, 4b, 4e** and **4f**) or two double doublets (**4c** and **4g**) in the case of the remaining compounds. The signal for the ammonium hydrogens appears near δ = 8.5 and the chemical shifts for the aromatic hydrogens are similar to those of **2** and **3.**

The infrared spectra of the aromatic β-aminoalcohols (**2**) are quite similar. The bond stretching absorptions of the NH and OH groups are observed between 3400 to 3100 $cm^{-1}$ and the angular deformation absorption of the NH group is observed at 1650 $cm^{-1}$, as well as the out of plane bending absorptions of the C–OH bond near 650 $cm^{-1}$. The absorption resulting from the C–O stretching vibration is found between 1180 and 1050 $cm^{-1}$.

The IR spectra of the bromoalkanamines (**3**) show the bands characteristic of the ammonium stretching vibrations between 2400 and 2550 $cm^{-1}$ and the bending vibration at 1580 $cm^{-1}$. Evidence for the C-Br bond is presented by a weak absorption beyond 500 $cm^{-1}$. The IR spectra of (**4**) present absorption bands between 510 and 550 $cm^{-1}$, attributed to the $SSO_3^-$ group and the symmetrical and unsymmetrical stretching bands of the $SO_3^-$ and S-S bonds are observed at 620, 1020 and 1180 $cm^{-1}$. In addition, they show one band between 2360 and 2462 $cm^{-1}$ which is not a fundamental band and is identified as a combination band associated with the zwitterion structure[31,32].

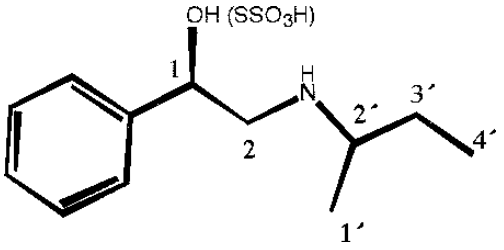
The decoupled $^{13}$C NMR spectra of **2** present signals characteristic of the aromatic carbons between δ = 125–144, a signal for CHOH in the region between δ = 71–72 and a signal for $CH_2NHR$ in the region between δ = 54–57. The signals attributed to the carbons of **2**, **3** and **4** were compared with those calculated using the ACD/CNMR version 1.0 simulation program and a good agreement was obtained. The signals for the benzilic carbons of **4** varied from δ = 47 to 49 and for the neighboring methylene carbons from δ = 50 to 53.

The mass spectra of **4** all showed similar fragmentation patterns: a peak resulting from fragmentation beta to the aromatic ring (*m/z* = 147 Thonson for R = $C_3H_7$; 161 Thonson for R = $C_4H_9$; 187 Thonson for R = $C_6H_{11}$) and a peak corresponding to the tropylium ion at *m/z* = 92 Thonson. As has been previously observed[15], since the thiosulfate decomposes when heated, the molecular ion and fragmentation peaks observed are chiefly those of the corresponding disulfides (*m/z* = 388, 416 and 468 Thonson) and thiols (*m/z* = 195, 209 and 235 Thonson) rather than those of the thiosulfuric acids.

## EXPERIMENTAL

**General Remarks:** Melting points were determined on a Mettler FP 80 HT melting point apparatus and are uncorrected. Infrared spectra were registered on Shimadzu IR 408 and

Mattson Instruments FTIR spectrophotometers in KBr disks. $^1$H and $^{13}$C NMR spectra were recorded on Bruker AC-80, Bruker DPX200 and Bruker DRX400 *AVANCE* spectrometers. Chemical shifts are reported in parts per million (δ units) relative to tetramethylsilane or $CDCl_3$ as internal standards. Coupling constants (*J*) are reported in Hertz. The numbering of the carbons of the alkyl groups in the assignment of the chemical shifts of the $^{13}$C NMR spectra of **2** and **4** was systematic, as illustrated below for the *sec*-butyl derivative (Structure **2f**/**4f**). Mass spectra of the β-aminoalcohols (**2**) were determined on a Hewlett-Packard Model HP-5989A GC-MS monoquadropole spectrometer equipped with an HP-5ME capillary column. Mass spectra of the aminoalkanethiosulfuric acids (**4**) were determined by introduction of solid via probe into a GCQ Finnigan GC-MS spectrometer equipped with an ion trap detector. The ionization energy used was 70 eV in all cases. Isobutane was used for chemical ionization. Elemental analyses were obtained on a Perkin-Elmer Model 2400 apparatus. All reagents were reagent grade. Amines were treated with KOH for 24 hr, filtered and distilled.




***Structure 2f/4f.*** *Illustrating the numbering of the alkylamino group according to normal systematic nomenclature.*

*General Procedure for the Synthesis of 2-Alkylamino-1-phenyl-1-ethanol* **2**: A mixture of 0.125 moles of styrene oxide, 0.6 moles of methanol and 0.376 moles of alkylamine were stirred in a Parr reactor for 6 hr at 120°C under a pressure of 60 psig. The reactor was cooled to room temperature, and the methanol and excess amine were removed on a rotary evaporator. The residue was recrystallized from petroleum ether.

**2a**: Yield = 11.2 g (50%); m.p.: 57–9°C; IR (KBr): $\nu_{max}$ 3300, 3100, 2950, 2850, 2750, 1650, 1450, 1430, 1400, 1350, 1110, 1070, 1050, 1030, 940, 860, 750, 700, 650, 550, 520, 450 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz): δ 0.91 (t, *J* = 7.3 Hz, 3 H, $CH_3$), 1.49 (sex, *J* = 7.3 Hz, 2 H, Me*C*$H_2$C$H_2$), 2.52–2.67 (m, 2 H, Et*C*$H_2$NH), 2.69 (dd, $J_{ab}$ = 9.0, 12.1 Hz, 1 H CHC$H_a$H$_b$N), 2.85 (dd, *J* = 3.8, 12.1 Hz, 1 H, CHCH$_a$$H_b$N), 4.71 (dd, *J* = 3.8, 9.0 Hz, 1 H, C*H*OH), 7.25–7.38 (m, 5 H, aromatic CH); $^{13}$C NMR ($CDCl_3$, 50 MHz): δ 142.8 ($C_{ipso}$), 128.3 (*o*-CH), 127.4 (*p*-CH), 125.8 (*m*-CH), 76.4 (CH-1), 56.9 ($CH_2$-2), 51.2 ($CH_2$-1´), 22.7 ($CH_2$-2´), 11.5 ($CH_3$-3´); MS *m/z* (%): 194 (4), 176 (2), 132 (6), 105 (5), 86 (100); 79 (7), 77 (11), 57 (16); $C_{11}H_{17}NO$ (179): calcd. C 73.70%, H 9.56%, N 7.81%; found C 73.63%, H 9.39%, N 7.64%.

**2b**: Yield = 9.2 g (41%); m.p.: 85–7°C; IR (KBr): $\nu_{max}$ 3300, 3050, 2950, 2800, 2750, 1605, 1230, 1180, 1140, 1000, 1060, 1030, 985, 955, 925, 915, 880, 800, 750, 700, 670 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz): δ 0.99 (d, *J* = 6.2 Hz, 6 H, $CH_3$), 2.61–2.91 (m, 3 H, Me$_2$C*H*, C$H_2$NH), 3.34 (broad, 2 H, NHR, OH), 4.70 (dd, *J* = 8.6, 4.2 Hz, 1 H, C*H*OH), 7.30 (s, 5 H, aromatic CH); $^{13}$C NMR ($CDCl_3$, 20 MHz): δ 143.1 ($C_{ipso}$), 128.2 (*o*-CH), 127.3 (*p*-CH), 125.8 (*m*-CH), 72.0 (CH-1), 54.7 ($CH_2$-2), 48.6 (CH-2´), 22.9 ($CH_3$-1´); MS *m/z* (%): 180 (7), 162 (2), 146 (3), 105 (2), 79 (6), 77 (10), 72 (100); $C_{11}H_{17}NO$ (179): calcd. C 73.70%, H 9.56%, N 7.81%; found C 73.71%, H 11.34%, N 7.82%.

**2c**: Yield = 10.1 g (42%); m.p: 59–60°C; IR (KBr): $\nu_{max}$ 3300, 3050, 2950, 2820, 1460, 1440, 1350, 1125, 1090, 1080, 1065, 1040, 960, 920, 870, 760, 700, 670 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz): δ 0.83 (t, *J* = 5.9 Hz, 3 H, $CH_3$), 1.09 – 1,30 (m, 4 H, Me*C*$H_2$C$H_2$CH$_2$), 2.47 (t, *J* = 6.9 Hz, 2 H, PrC$H_2$), 2.64 (d, *J* = 6.4 Hz, 2 H, CHC$H_2$N), 3.81(broad, 1 H, NHR), 4.74 (t, *J* = 6.4 Hz, 1 H, C*H*OH), 7.24 (s, 5 H, aromatic CH); $^{13}$C NMR ($CDCl_3$, 20 MHz): δ 143.1 ($C_{ipso}$), 128.2 (*o*-CH), 127.3 (*p*-CH), 125.8 (*m*-CH), 71.7 (CH-1), 57.2 ($CH_2$-2), 49.2 ($CH_2$-1´), 32.0 ($CH_2$-2´), 20.3 ($CH_2$-3´), 13.9 ($CH_3$-4´); MS *m/z* (%): 194 (47), 176 (8), 150 (1), 132 (3), 105 (4), 86 (100), 79 (11), 77 (13), 57 (6); $C_{12}H_{19}NO$ (193): calcd. C 74.57%, H 9.91%, N 7.25%; found C 74.72%, H 12.0%, N 7.27%.

**2d**: Yield = 8.9 g (37%); m.p.: 62–3°C; IR (KBr): $\nu_{max}$ 3330, 3100, 2980, 2820, 2730, 2560, 1650, 1450, 1430, 1125, 1100, 1060, 1050, 990, 940, 890, 820, 760, 700, 650, 550, 540, 470 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz): δ 0.83 (d, *J* = 6.5 Hz, 6 H, $CH_3$), 1.66 (hep, *J* = 6.5 Hz, 1 H, Me$_2$C*H*), 2.33 (d, *J* = 6.6 Hz, 2 H, *i*-PrC$H_2$N), 2.66 (d, *J* = 6.3 Hz, 2 H, CHC$H_2$N), 3.44 (broad, 1 H, NHR), 4.70 (t, *J* = 6.3 Hz, 1 H, C*H*OH), 7.27 (s, 5 H, aromatic CH); $^{13}$C NMR ($CDCl_3$, 20 MHz): δ 142.8 ($C_{ipso}$), 128.3 (*o*-CH), 127.3 (*p*-CH), 125.8 (*m*-CH), 71.6 (CH-1), 57.2 ($CH_2$-2), 57.2 ($CH_2$-1´), 28.3 (CH-2´), 20.5 ($CH_3$-3´); MS *m/z* (%): 194 (4), 176 (2), 132 (6), 105 (5), 86 (100), 79 (7), 77 (11), 57 (16); $C_{12}H_{19}NO$ (193): calcd. C 74.57%, H 9.91%, N, 7.25%; found C 74.68%, H 12.88%, N 7.21%.

**2e**: Yield = 20.5 g (85%); m.p.: 86–8°C; IR (KBr): $\nu_{max}$ 3330, 3100, 2980, 2850, 2550, 1600, 1450, 1360, 1340, 1240, 1090, 1050, 1020, 960, 920, 860, 750, 700, 630, 560, 520, 470, 440 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz): δ 1.04 [s, 9 H, C(CH$_3$)$_3$], 2.46–2.88 (m, 3 H, CH$_2$N), 4.66 [dd, *J* = 6.6, 4.4 Hz, 1 H, C*H*OH], 7.30 [s, 5 H, aromatic CH]; $^{13}$C NMR ($CDCl_3$, 20 MHz): δ 143.1 ($C_{ipso}$), 128.2 (*o*-CH), 127.3 (*p*-CH), 125.8 (*m*-CH), 72.3 (CH-1), 50.2 ($CH_2$-2), 50.2 (C-2´), 29.1 ($CH_3$); MS *m/z* (%): 194 (8), 178 (1), 160 (13), 86 (100), 77 (15), 57 (18); $C_{12}H_{19}NO$ (193): calcd. C 74.57%, H 9.91%; N 7.25%; found C 74.76%, H 11.47%, N 7.35%.

**2f**: Yield = 15.7 g (65%); p.e.: 150°C (1.5 mm Hg); IR.(KBr): $\nu_{max}$ 3300, 3100, 2970, 2390, 1660, 1450, 1400, 1360, 1220, 1100, 1070, 1030, 940, 870, 770, 700, 640 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz): δ 0.81 (t, *J* = 7.4 Hz, 3 H, CH$_2$C$H_3$), 0.95 [d, *J* = 6.3 Hz, 3 H, CHC$H_3$ (diasteriomer a)], 0.96 [d, *J* = 6.3 Hz, 3 H, CHC$H_3$ (diasteriomer b)], 1.10 – 1.56 (m, 2 H, C$H_2$Me), 2.44–2.84 (m, 3 H, C$H_2$NHC*H*), 3.70 (broad s, 2 H, NHR, OH), 4.66 – 4.78 (m, 1 H, CHOH), 7.31 (m, 5 H, ring CH); $^{13}$C NMR ($CDCl_3$, 50 MHz): δ 143.1 ($C_{ipso}$), 128.2 (*o*-CH), 127.2 (*p*-CH), 125.7 (*m*-CH), 71.8 (CH-1), 54.6 (CH-2´), 54.2 ($CH_2$-2), 29.5 ($CH_2$-3´), 19.6 ($CH_3$-1´), 10.1 ($CH_3$-4´); MS *m/z* (%): 194 (100), 176 (6), 146 (4), 107 (4), 79 (18), 77 (19), 57 (23); $C_{12}H_{19}NO$ (193): calcd. C 74.61%, H 9.85%, N 7.25%; found C 77.14%, H 11.49%, N 6.43%.

**2g**: Yield = 10.7 g (39%); m.p.: 91–2°C. IR (KBr): $\nu_{max}$ 3250, 3080, 2900, 2850, 2800, 1610, 1500, 1450, 1380, 1345, 1220, 1120, 1080, 1065, 1030, 980, 940, 890, 880, 750, 700, 665 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200 MHz): δ 0.90–1.35 (m, 5 H, ring $CH_2$), 1.50–1.80 (m, 3 H, ring $CH_2$), 1.80–1.93 (m, 2 H, ring $CH_2$), 2.42 (tt, *J* = 3.6, 10.1 Hz, 1 H, ring CHN], 2.66 [dd, *J* = 9.1, 12 Hz, 1 H, CHC$H_a$H$_b$NH], 2.94 [dd, *J* = 3.7, 12 Hz, 1 H, CHCH$_a$$H_b$N], 4.65 [dd, *J* = 3.7, 9.1, 1 H, C*H*OH], 7.22–7.37 [m, 5 H, aromatic CH]; $^{13}$C NMR ($CDCl_3$, 50 MHz): δ 143.0 ($C_{ipso}$), 128.3 (*o*-CH), 127.3 (*p*-CH), 125.8 (*m*-CH), 71.7 (CH-1), 56.5 (CH-1´), 54.3 ($CH_2$-2), 33.3 [$CH_2$-2´(6´)], 25.9 ($CH_2$-4´), 24.9 [$CH_2$-3´(5´)]; MS *m/z* (%): 220 (28), 202 (3), 112 (100), 79 (13), 55 (14); $C_{14}H_{21}NO$ (219): calcd. C 76.67%, H 9.65%, N 6.39%; found C 76.54%, H 9.81%, N 6.15%.

*General Procedure for the Synthesis of N-Alkyl-1-bromo-1-phenyl-2-ethanamine hydrobromide* **(3)**: To a stirred solution of 0.1 moles of 2-(alkylamino)-1-phenyl-1-ethanol (**2**) in 50 mL of ethanol, was added 0.11 moles of 48% hydrobromic acid over a one hour period at ice bath temperature. The ethanol and excess hydrobromic acid were removed on a rotary

evaporator and the crude product was dried under vacuum. Addition of dry ethanol to the yellow solid resulted in precipitation of a white solid which was dried in a desiccator.

To a stirred mixture of the β-aminoalcohol hydrobromide and 120 mL of dry benzene, 7.5 mL (0.15 moles) of redistilled $PBr_3$ was slowly added. The system was refluxed for 4 hr, the course of the reaction being accompanied by TLC. The mixture was allowed to stand for 24 hr and the benzene and excess $PBr_3$ were removed on a rotary evaporator. The residue was recrystallized from AcOEt:i-PrOH (9:1).

**3a**: Yield = 26.3 g (81.4%); m.p.: 194–5°C; IR (KBr): $\nu_{max}$ 3425, 2960, 2800, 2400, 1563, 1438, 1392, 1367, 1233, 1183, 1008, 983, 763, 700, 583, 517, 467 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz): δ 0.99 (t, *J* = 7.4 Hz, 3 H, $CH_3$), 1.95 (sex, *J* = 7.5 Hz, 2 H, $CH_2CH_2Me$), 2.93–3.20 (m, 2 H, $CH_2Et$), 3.61 (dd, *J* = 5.6, 13.5 Hz, 1 H, $CHCH_aH_bN$), 3.73 (dd, *J* = 9.0, 13.5 Hz, 1 H, $CHCH_aH_bN$), 5.73 (dd, *J* = 5.6, 9.0, 1 H, CHBr), 7.36–7.41 (m, 3 H, *m*- and *p*-aromatic CH), 7.44–7.53 (m, 2 H, *o*-aromatic CH), 8.98 – 9.30 (broad, 2 H, $NH_2^+$); $^{13}C$ NMR ($CDCl_3$, 50 MHz ): δ 137.4, 129.6, 129.2, 127.7, 54.0, 49.9, 47.1, 19.2, 11.2.

**3b**: Yield = 18 g (56%); m.p.: 172–4°C; IR (KBr,): $\nu_{max}$ 3425, 2930, 2750, 2375, 1575, 1475, 1450, 1400, 1375, 1290, 1150, 1000, 775, 705, 600, 538, 475 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.50 [dd, *J* = 6.6, 10.3 Hz, 3 H, $CH(CH_3)_2$], 1.55 [dd, *J* = 6.6, 10.3 Hz, 3H, $CH(CH_3)_2$], 3.57–3.71 [m, 3 H, $Me_2CH$, $CHCH_2N$], 5.78 (t, 1 H, 7.1, CHBr), 7.36-7.55 (m, 5 H, aromatic CH); $^{13}C$ NMR (MeOH, 50 MHz): δ 139.1, 130.7, 130.3, 128.9, 53.1, 52.5, 48.9, 19.3, 18.7.

**3c**: Yield = 22.6 g (67%); m.p.: 153–5°C; IR (KBr): $\nu_{max}$ 3475, 2950, 2790, 2450, 1605, 1450, 1400, 1250, 1188, 775, 700, 600, 525, 487 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 0.93 (t, *J* = 7.3 Hz, 3 H, $CH_3$), 1.40 (sex, *J* = 7.5 Hz, 2 H, $CH_2CH_2Me$), 1.90 (quin, *J* = 7.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.99–3.15 (m, 2 H, $PrCH_2N$), 3.62 (dd, *J* = 5.3, 13.5 Hz, 1 H, $CHCH_aH_bN$), 3.75 (dd, *J* = 9.3, 13.5 Hz, 1 H, $CHCH_aH_bN$), 5.75 (dd, *J* = 5.3, 9.3 Hz, 1 H, CHBr), 7.36 – 7.41 (m, 3 H, *m*- and *p*-aromatic CH), 7.50–7.53 (m, 2 H, *o*-aromatic CH ), 9.03–9.46 (broad, 2 H, $NH_2^+$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 137.6, 129.6, 129.3, 127.7, 54.0, 48.3, 47.2, 27.6, 20.0, 13.5.

**3d**: Yield = 21.9 g (65%); m.p.: 143–4°C; IR (KBr): $\nu_{max}$ 3400, 2960, 2775, 2330, 1538, 1475, 1437, 1413, 1213, 900, 763, 700, 575, 513, 488 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.05 [d, *J* = 6.7 Hz, 3 H, $(CH_3)_aCH(CH_3)_b$], 1.08 [d, *J* = 6.7 Hz, 3 H, $(CH_3)_aCH(CH_3)_b$], 2.24 (hep, *J* = 6.8 Hz, 1 H, $Me_2CH$), 2.80 (dd, *J* = 7.5, 12.4 Hz, 1 H, *i*-$PrCH_aH_bN$), 2.95 (dd, *J* = 6.8, 12.4 Hz, 1 H, *i*-$PrCH_aH_bN$), 3.68 (dd, *J* = 5.6, 13.6 Hz, 1 H, $CHCH_aH_bN$), 3.73 [dd, *J* = 9.0, 13.6 Hz, 1 H, $CHCH_aH_bN$), 5.82 [dd, *J* = 5.6, 9.0 Hz, 1H, CHBR], 7.27–7.41 [m, 3 H, *m*- and *p*-aromatic CH], 7.47–7.54 [m, 2 H, *o*-aromatic CH], 9.05 [broad, 2 H, $NH_2^+$]; $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 137.6, 129.7, 129.3, 127.8, 55.3, 54.3, 47.1, 25.6, 20.5.

**3e**: Yield = 21.9 g (65%); m.p.: 168–9°C; IR (KBr): $\nu_{max}$ 3425, 3025, 2775, 2380, 1562, 1488, 1475, 1375, 1250, 1200, 1169, 1063, 1000, 963, 769, 700, 575, 526, 431 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): δ 1.60 [s, 9 H, $C(CH_3)_3$], 3.48–3.72 (m, 2 H, $CHCH_2N$), 5.82 (dd, *J* = 4.0, 11.5 Hz, 1 H, CHBr), 7.35–7.43 (m, 3 H, *m*- and *p*-aromatic CH), 7.51 – 7.56 (m, 2 H, *o*-aromatic CH ), 7.80 and 9.95 (broad, 1 H each, $NH_aH_b^+$); $^{13}C$ NMR ($CDCl_3$, 100 MHz ): δ 137.5, 129.5, 129.2, 127.6, 59.4, 50.2, 48.4, 26.2.

**3f**: Yield = 4%; m.p.: 144–5°C; IR (KBr): $\nu_{max}$ 3460, 2961, 2756, 2420, 1577, 1456, 1412, 1387, 1281, 1244, 1113, 763, 699, 595, 507 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): Less abundant diasteriomer: δ 0.99 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_3$), 1.51 [d, *J* = 6.6 Hz, 3 H, $CH(CH_3)$], 1.68 – 1.83 (m, 2 H, $MeCH_2$), 3.42–3.48 [m, 1 H, C*H*(Me)Et], 3.59–3.72 (m, 2 H, $CHCH_2N$); More abundant diasteriomer: δ 1.0 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_3$), 1.45 [d, *J* = 6.7 Hz, 3 H, $CH(CH_3)$], 1.99–2.14 (m, 2 H, $MeCH_2$), 3.32–3.38 [m, 1 H, C*H*(Me)Et], 3.59–3.72 (m, 2 H, $CHBrCH_2$); Both isomers: δ = 5.81–5.87 (m, 1 H, CHBr), 7.33–7.40 (m, 3 H, *m*- and *p*-aromatic CH), 7.51–7.55 (m, 2 H, *o*-aromatic CH), 8.61–8.76 and 9.42–9.57 (broad, 1 H each, $NH_aH_b^+$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 137.5, 129.5, 129.1, 127.6, 56.3, 50.6, 47.3, 25.9, 15.3, 10.2.

**3g**: Yield = 23.6 g (65%); m.p.: 158–9°C; IR (KBr): $\nu_{max}$ 3425, 2950, 2719, 2425, 1588, 1463, 1238, 1050, 1013, 775, 700, 600, 538, 482 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz ): δ 1.10–1.31 (m, 3 H, ring $CH_2$ ), 1.55–1.86 (m, 6 H, ring $CH_2$), 2.17–2.35 (m, 2 H, ring $CH_2$), 3.15 (tt, *J* = 3.6, 11.6 Hz, 1 H, ring CH), 3.66 (dd, *J* = 8.8, 13.6 Hz, 1 H, $CHCH_aH_bN$), 3.73 (dd, *J* = 5.5, 13.6 Hz, 1 H, $CHCH_aH_bN$), 5.81 (dd, *J* = 5.5, 8.8 Hz, 1 H, CHBr), 7.36–7.38 (m, 3 H, *m*- and *p*-aromatic CH), 7.50–7.53 (m, 2 H, *o*-aromatic CH), 8.68 and 9.48 (broad, 1 H each, $NH_aH_b^+$); $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 139.9, 129.2, 128.7, 125.9, 68.9, 58.7, 51.0, 29.2, 24.5.

*General Procedure for the Synthesis of 2-(alkylamino)-1-phenylethane-1-thiosulfuric acid* **(4)**: A solution containing 0.02 moles of (**3**) dissolved in the minimum volume necessary of 50% ethanol was stirred with an equimolar quantity of a concentrated aqueous solution of sodium thiosulfate for 2 hr at room temperature. The reaction was monitored by TLC using ethyl acetate:chloroform:methanol [1:2:0.5] as eluent and its completion was determined by the lack of a precipitate of sulfur when sulfuric acid was added to an aliquot of the reaction mixture. After completion of the reaction, the mixture was filtered and the resulting white solid was recrystallized from chloroform and dried in a desiccator.

**4a**: Yield = 4.0 g (73%); m.p.: 198–9°C; IR (KBr): $\nu_{max}$ 3451, 3026, 2363, 1583, 1454, 1210, 1023, 630, 538 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 200 MHz): δ 0.88 [t, *J* = 7.1 Hz, 3H, $CH_3$], 1.54–1.65 [m, 2 H, $CH_2CH_2CH_3$], 2.86–2.93 [t, *J* = 7.3 Hz, 2 H, $CH_2Et$], 3.56 [dd, *J* = 6.9, 12.5, 1 H, $PhCHCH_aH_bNH_2^+$]; 3.77 [dd, *J* = 7.3, 12.5, 1 H, $PhCHCH_aH_bNH_2^+$] 4.65 [t, *J* = 7.2 Hz, 1 H, $PhCHSSO_3^-$], 7.35 [s, 5 H, aromatic CH], 8.47 [broad, 2 H, $NH_2R^+$]; $^{13}C$ NMR (DMSO-$d_6$, 50 MHz): δ 138.4 ($C_{ipso}$), 129.0 (*p*-CH), 128.0 (*o*-CH), 127.6 (*m*-CH), 52.2 ($CH_2$-2), 49.1 ($CH_2$-1´), 48.6 (CH-1), 18.9 ($CH_2$-2´), 10.8 ($CH_3$-3´); MS (EI) *m/z* (%): 39 (10), 41 (16), 43 (8), 55 (20), 56 (7), 57 (8), 67 (6), 69 (5), 70 (12), 71 (7), 82 (5), 83 (15), 84 (6), 100 (52) $[H_2SO_3 + H_2O]^+$, 101 (1), 111 (41) $[CH_3NHSO_2H]^+$, 112 (7), 128 (7), 129 (100) $[CH_3NHSO_2H + H_2O]^+$**,** 130 (7), 146 (5), 147 (52) $[PhCHCH_2NC_2H_5]^+$, 149 (6), 241 (10) $[PhCH(CH_2NHC_3H_7)SSH=CH_2]^+$, 259 (16) $[PhCH(CH_2N=CHCH_3)SSO_3]^+$, 386 (2) $[\{PhCH(CH=NHC_3H_7)S\}_2]^+$. MS (CI) *m/z* 137 (6), 162 (18), 192 (8), 194 (5), 196 (13), 233 (7), 236 (6), 293 (18), 294 (11), 295 (100), 296 (44), 297 (12), 298 (5), 324 (6), 327 (6), 328 (6), 389 (4) $[\{PhCH(CH_2NHC_3H_7)S\}_2 + H]^+$; $C_{11}H_{17}NO_3S_2$ (275.4): calcd. C 48.0%, H 6.18%, N 5.09%, S 23.27%; found C 48.07%, H 6.30%, N 4.77%, S 25.52%.

**4b**: Yield = 1.8 g (33%): m.p.: 175–7°C. IR (KBr): $\nu_{max}$ 3445, 3052, 2369, 1583, 1454, 1244, 1195, 1023, 759, 630, 538 $cm^{-1}$.; $^1H$ NMR (DMSO-$d_6$, 200 MHz): δ 1.58 [s, 6 H, $CH(CH_3)_2$], 3.36–3.81 (m, 3 H, $CH_2NH_2^+$, $Me_2CH$), 4.51–4.66 (m, 1 H, $PhCHSSO_3^-$), 7.39–7.41 (s, 5 H, aromatic CH), 8.43 (broad, 2 H, $NH_2R^+$).; $^{13}C$ NMR (DMSO-$d_6$, 50 MHz): δ = 138.3 ($C_{ipso}$), 128.9 (*p*-CH), 128.4 (*o*-CH), 127.9 (*m*-CH), 50.5 ($CH_2$-2), 48.8 (CH-2´), 46.6 (CH-1), 18.5 ($CH_3$-1´); MS (EI) *m/z* (%): 39 (29), 41 (35), 55 (21), 64 (30), 72 (40) $[CH_2=NHC_3H_7]^+$, 77 (42) $[Ph]^+$, 91 (93) $[C_7H_7]^+$, 104 (68), 118 (45), 121 (73), 135 (64), 146 (53) $[PhCHCH_2NC_2H_4]^+$, 161 (26) $[PhCHCH_2NC_3H_7]^+$, 162 (51) $[PhCHCH_2NHC_3H_7]^+$, 176 (100) $[PhThiazoleCH_3]^+$, 192 (36), 227 (28), 241 (16), 250 (47), 295 (34), 309 (33), 387 (6) $[\{PhCH(CH_2NHC_3H_7)S\}_2 - H]^+$. – MS (CI) *m/z* (%) 162 (49), 164 (11), 192 (15), 194 (11), 196 (22) $[PhCH(CH_2NHC_4H_9)SH + H]^+$, 293 (42), 294 (15), 296 (20), 387 (10), 389 (100) $[\{PhCH(CH_2NHC_3H_7)S\}_2 + H]^+$, 390 (22); $C_{11}H_{17}NO_3S_2$ (275.4): calcd. C 48.0%, H 6.18%, N 5.09%; S 23.27%; found C 46.57, H 6.26%, N 4.19%, S 25.52.

**4c**: Yield = 2.72 g (47%); m.p.: 175–6ºC; IR (KBr): $\nu_{max}$ 3438, 2955, 2363, 1461, 1223, 1023, 759, 630, 539 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 200 MHz): δ 0.87 (t, $J$ = 7.2 Hz, 3 H, $CH_3$), 1.21–1.39 (sex, $J$ = 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 1.49–1.63 (quin, $J$ = 7.4 Hz, 2 H, $CH_2CH_2Et$), 2.93 (t, $J$ = 7.3 Hz, 2 H, $PrCH_2N$), 3.56 (dd, $J$ = 6.8, 12.9 Hz, 1 H, $CH_aH_bNH_2^+$), 3.77 (dd, $J$ = 8.0, 12.9 Hz, 1 H, $CH_aH_bNH_2^+$), 4.64 (t, $J$ = 7.3 Hz, 1 H, $PhCHSSO_3^-$), 7.31 (s, 5 H, aromatic CH), 8.46 (broad, 2 H, $NH_2^+$); $^{13}C$ NMR (DMSO-$d_6$, 50 MHz): δ 138.5 ($C_{ipso}$), 128.9 (*p*-CH), 128.0 (*o*-CH), 127.6 (*m*-CH), 52.2 ($CH_2$-2), 48.6 (CH-1), 47.2 ($CH_2$-1´), 27.3 ($CH_2$-2´), 19.2 ($CH_2$-3´), 13.4 ($CH_3$-4´); MS (EI) *m/z* (%): 44 (55), 65 (22), 77 (27) $[Ph]^+$, 91 (47), 104 (40), 121 (43), 135 (32), 162 (99) $[PhCHCH_2\ NHC_3H_7]^+$, 176 (51) $[PhCHCH_2NHC_4H_9]^+$, 209 (25) $[PhCHSH(CH_2NHC_4H_9)]^+$, 218 (100) $[PhCHCH_3SSO_3H]^+$, 220 (76), 241 (23) $[PhCH(CH_2NHC_4H_9)SSH]^+$, 261 (22), 276 (41), 309 (81), 341 (63); MS (CI) *m/z* (%) 176 (13), 210 (10) $[PhCHSH(CH_2NHC_4H_9) + H]^+$, 261 (6), 262 (9), 306 (5), 308 (79), 309 (100), 310 (37), 311 (13), 312 (7), 341 (20), 342 (21), 343 (6), 344 (5), 346 (6), 415 (7), 417 (64) $[\{PhCH(CH_2NHC_4H_9)S\}_2 + H]^+$, 418 (16), 419 (7); $C_{12}H_{19}NO_3S_2$ (289.4): calcd. C 49.8%, H 6.57%, N 4.84%, S 22.15%; found C 49.33%, H 6.67%, N 4.63%, S 22.76%.

**4d**: Yield = 2.0 g (35%), m.p.: 220–1ºC; IR (KBr): $\nu_{max}$ 3432, 2968, 2385, 1583, 1454, 1203, 753, 624, 532 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 200 MHz): δ 0.92 [d, $J$ = 6.6 Hz, 6 H, $CH(CH_3)_2$], 1.96 [hep, $J$ = 6.7 Hz, 1 H, $Me_2CH$], 2.82 (d, $J$ = 5.6 Hz, 2 H, $i\text{-}PrCH_2N$), 3.53 (m, 2 H, $CH_2NH_2$), 4.70 (dd, $J$ = 5.9, 8.2 Hz, 1 H, $PhCHSSO_3^-$), 7.35 (s, 5 H, aromatic CH), 8.47 (broad, 2 H, $NH_2^+$); $^{13}C$ NMR (DMSO-$d_6$, 50 MHz): δ 138.6 ($C_{ipso}$), 130.0 (*p*-CH), 128.0 (*o*-CH), 127.5 (*m*-CH), 54.5 ($CH_2$-1´), 53.2 ($CH_2$-2), 48.6 (CH-1), 25.3 (CH-2´), 19.8 ($CH_3$-3´); MS (EI) *m/z* (%): 39 (41), 41 (60), 55 (51), 67 (32), 81 (30), 83 (28), 91 (26) $[C_7H_7]^+$, 98 (32), 100 (100) $[H_2SO_3 + H_2O]^+$, 129 (40), 132 (29), 178 (25), 185 (21), 256 (21); MS (EI) *m/z* (%) 162 (8), 176 (8), 210 (7) $[PhCHSH(CH_2NHC_4H_9) + H]^+$, 243 (12), 250 (23), 261 (11), 277 (17), 307 (23), 308 (24), 309 (100), 310 (45), 311 (12), 337 (10), 417 (2) $[\{PhCH(CH_2NHC_4H_9)S\}_2 + H]^+$; $C_{12}H_{19}NO_3S_2$ (289.4): calcd. C 49.8%, H 6.57%, N 4.84%; S 22.15%; found C 49.31%, H 6.54%, N 4.95%, S 22.47%.

**4e**: Yield = 4.2 g (73%); m.p.: 208–9ºC; IR (KBr): $\nu_{max}$ 3438, 3032, 2462, 1605, 1384, 1249, 1022, 758, 629, 537 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 200 MHz): δ 1.30 [s, 9 H, $C(CH_3)_3$], 3.40-3.60 (m, 1 H, $CH_aH_bNH_2^+$); 3.80-4.00 (m, 1 H, $CH_aH_bNH_2^+$); 4.57 (t, 1H, 7.0, $PhCHSSO_3^-$), 7.38 (s, 5 H, aromatic CH), 8.42 and 8.62 (broad, 1 H each, $NH_aH_b^+$); $^{13}C$ NMR (DMSO- $d_6$, 50 MHz): δ 138.2 ($C_{ipso}$), 129.0 (*o*-CH), 128.1 (*p*-CH), 127.7 (*m*-CH), 57.1 (C-2´), 49.5 ($CH_2$-2), 47.0 (CH-1), 25.1 ($CH_3$); MS (EI) *m/z* (%): 39 (77), 41 (100), 43 (69), 45 (40), 55 (85), 67 (65), 69 (44), 73 (41), 77 (39) $[Ph]^+$, 79 (49), 81 (64), 83 (47), 87 (46), 91 (96) $[C_7H_7]^+$, 95 (50), 96 (41), 98 (40), 100 (82) $[H_2SO_3 + H_2O]^+$, 118 (73), 121 (55), 129 (55), 134 (39), 149 (42), 157 (30), 161 (28), 162 (42), 171 (25), 174 (49), 195 (37), 199 (22), 207 (31), 213 (21), 258 (42); MS (CI) *m/z* (%) 120 (38), 137 (32), 161 (11), 162 (37), 175 (12), 176 (46) $[PhCHCH_2NHC_4H_9]^+$, 192 (12), 193 (12), 194 (16), 196 (25), 206 (17), 207 (16), 208 (25), 210 (42) $[PhCH(CH_2NHC_4H_9)\ SH + H]^+$, 236 (14), 250 (13), 252 (12), 253 (10), 276 (11), 293 (61), 294 (34), 295 (100), 296 (44), 297 (13), 307 (35), 308 (33), 309 (37), 310 (16), 316 (7), 338 (**7**), 389 (9), 417 (8) $[\{PhCH(CH_2NHC_4H_9)S\}_2 + H]^+$; $C_{12}H_{19}NO_3S_2$ (289.4): calcd. C 49.8%, H 6.57%, N 4.84%, S 22.15%; found C 50.34%, H 7.18%, N 9.46%, S 18.34%.

**4f**: Yield = 1.7 g (30%); m.p.: 173–6ºC; IR (KBr): $\nu_{max}$ 3412, 2981, 2363, 1615, 1454, 1244, 1182, 1022, 771, 633, 542 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 200 MHz): δ 0.89 (t, $J$ = 7.2 Hz, 3 H, $CH_3$), 1.21 [d, $J$ = 6.2 Hz, 3 H, $NCH(CH_3)Et$], 1.40–1.54 (m, 1 H, $CH_aH_bMe$), 1.67–1.73 (m, 1 H, $CH_aH_bMe$), 3.05-3.28 [m, 1 H, NCH(Me)Et], 3.50–3.68 (m, 1 H, $CH_aH_bNH_2^+$); 3.68-3.87 (m, 1 H, $CH_aH_bNH_2^+$); 4.63 [t, $J$ = 6.7 Hz, 1 H, $PhCHSSO_3^-$], 7.36 [s, 5 H, aromatic CH], 8.44 [broad, 2 H, $NH_2^+$]; $^{13}C$ NMR (DMSO-$d_6$, 50 MHz): δ 138.4 ($C_{ipso}$), 129.0 (*p*-CH), 128.1 (*o*-CH), 127.6 (*m*-CH), 55.7 (CH-2´), 49.9 ($CH_2$-2), 49.0 (CH-1), 25.2 ($CH_2$-3´), 15.3 ($CH_3$-1´), 9.5 ($CH_3$-4´); MS (EI) *m/z* (%): 41 (37), 43 (40), 55 (32), 57 (40), 65 (37), 77 (46) $[Ph]^+$, 78 (38), 86 (85), 88 (57), 91 (78) $[C_7H_7]^+$, 103 (57), 104 (57), 118 (39), 120 (78), 121 (61), 135 (60), 146 (41), 162 (38), 176 (100) $[PhCHCH_2NHC_4H_9]^+$, 205 (35), 209 (58), 241 (33), 253 (35), 309 (77), 331 (26), 387 (15); MS (CI) *m/z* (%) 137 (11), 175 (15), 176 (97), 177 (20), 205 (13), 206 (26), 207 (10), 208 (16), 210 (100) $[PhCH(NHC_4H_9)CH_2SH + H]^+$, 211 (14), 253 (16), 307 (30), 308 (18), 309 (34), 310 (17), 417 (19) $[\{PhCH(NHC_4H_9)CH_2S\}_2 + H]^+$; $C_{12}H_{19}NO_3S_2$ (289.4): calcd. C 49.8%, H 6.57%, N 4.84%, S 22.15%; found C 49.71%, H 6.77%, N 5.19%, S 21.99%.

**4g**: Yield = 4.4 g (70%); m.p.: 193–5ºC; IR (KBr): $\nu_{max}$ 3451, 3013, 2409, 1590, 1448, 1242, 1016, 761, 624, 532 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 200 MHz): δ 1.13–1.37 (m, 5 H, ring $CH_2$), 1.55–1.60 (m, 1 H, ring $CH_2$), 1.72–1.75 (m, 2 H, ring $CH_2$), 1.99–2.03 (m, 2 H, ring $CH_2$), 3.02 – 3.08 (m, 1 H, ring CH), 3.59 (dd, $J$ = 6.2, 12.6 Hz, 1 H, $CH_aH_bNH_2^+$), 3.82 (dd, $J$ = 8.1, 12.1 Hz, 1H $CH_aH_bNH_2^+$), 4.62 (t, $J$ = 7.2, 1 H $PhCHSSO_3^-$), 7.36 (s, 5 H, aromatic CH), 8.51 (broad, 2 H, $NH_2^+$); $^{13}C$ NMR (DMSO-$d_6$, 50 MHZ): δ 138.4 ($C_{ipso}$), 128.9 (*o*-CH), 128.0 (*p*-CH), 127.6 (*m*-CH), 56.8 (CH-1´), 49.6 ($CH_2$-2), 49.0 (CH-1), 28.5 [$CH_2$-2´(6´)], 24.7 ($CH_2$-4´), 23.8 [$CH_2$-3´(5´)]; MS (EI) *m/z* (%): 41 (41), 55 (33), 67 (23), 77 (43) $[Ph]^+$, 86 (87), 91 (98) $[C_7H_7]^+$, 103 (53), 104 (63), 118 (42), 120 (69), 121 (62), 135 (66), 146 (55), 162 (35), 175 (53), 176 (100) $[PhCHCH_2NHC_4H_9]^+$, 177 (40), 208 (38), 209 (42), 250 (39), 280 (30), 307 (40), 309 (71); MS (CI) *m/z* (%) 100 (16), 112 (41), 120 (19), 137 (26), 179 (13), 201 (17), 202 (80), 203 (14), 230 (10), 231 (49), 232 (82), 233 (28), 234 (45), 235 (18), 236 (100) $[PhCHSH(CH_2NHC_6H_{11}) + H]^+$, 237 (16), 274 (13), 278 (12), 292 (14), 333 (55), 334 (29), 335 (59), 336 (26), 363 (16), 398 (15), 469 (22) $[\{PhCH(CH_2NHC_6H_{11})S\}_2 + H]^+$; $C_{14}H_{21}NO_3S_2$ (315.4): calcd. C 53.3%, H 6.67, N 4.44%, S 20.25%; found C 53.37%, H 6.91%, N 5.21%, S 20.25%.

## CONCLUSION

Seven new aminoalkanethiosulfuric acids were synthesized which differed in the alkyl group bound to the amine. The structures of the intermediates and products were verified by IR, NMR and mass spectroscopy and elemental analyses. Contrary to results previously observed[17], a rearrangement via the aziridinium ion does not occur in the last step of the synthesis and the final product bears the thiosulfate group bound to the benzilic carbon. This series of compounds has been submitted for biological testing for activity against schistosomiasis in mice, as well as antitumorigenic, anti-fungal and radioprotective activities. Preliminary results in the tests for activity against schistosomiasis were very promising. Future studies will include analogs bearing substituents on the aromatic ring.

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## REFERENCES


1. Pessoa, F. S.; Martins, A. V. P.; *Parasitologia Médica*, 10th ed., Ed. Guanabara Koogan, Rio de Janeiro, 1977.
2. Pellegrino, J.; Katz, N.; Dias, P. E.; *Rev. Inst. Med. Trop. Sao Paulo* **1973**, *15*, 25.
3. Katz, N.; Dias, P. E.; Araujo, N.; Souza, C. P.; *Rev. Soc. Bras. Med. Trop*. **1973,** *7*, 381.
4. Dias, L. C. S.; Bruce, J. I.; Coles, G. C.; *Rev. Inst. Med. Trop. São Paulo* **1988**, *30*, 81.
5. Araújo, N.; Katz, N.; Dias, E. P.; Souza, C. P.; *Amer. J. Trop. Med. Hyg*. **1980,** *29*, 890.
6. W. Y. Liu; *M. Sc*., Univ. Fed. Minas Gerais, 1981.
7. Vieira Filho, S. A.; Nelson, D. L.; Piló-Veloso, D.; *An. Acad. Bras. Cien.* **1986**, *58*, 547.
8. Penido, M. L. O.; Piló-Veloso, D.; Nelson, D. L.; *J. Braz. Chem. Soc*. **1990**, *1*, 35.
9. Penido, M. L. O.; Nelson, D. L.; Vieira, L. Q.; Coelho, P. M. Z.; *Mem. Inst. Oswaldo Cruz.* **1994**, *89*, 595.
10. Penido, M. L. O.; Nelson, D. L.; Vieira, L. Q.; Watson D. G.; Kusel, J. R.; *Parasitol.* **1995**, *111*, 177.
11. Fuchs, R.; *J. Org.Chem*. **1958**, *23*, 902.
12. Oae, S.; *Organic Chemistry of Sulfur*, Plenum Press, New York, 1977, p.317.
13. Kice, J. L.; *J. Org. Chem.* **1963**, *28*, 957.
14. Harnish, D. P.; Tarbell, D. S.; *Anal. Chem*. **1949**, *21*, 968.
15. Price, C. C.; Kirk, P. F.; *J. Am. Chem. Soc*. **1953**, *75*, 2396.
16. Snyder, H. R.; et al.; *J. Am. Chem. Soc*. **1947**, *69*, 2672.
17. Corey, E. J.; Chaykovsky, M.; *J. Am. Chem. Soc*. **1965,** *87*, 1345.
18. Unpublished results.
19. Knorr, L.; *Chem. Ber*. **1889**, *18*, 2088.
20. Elderfield, R. C.; Craig, L. C.; Lauer, W. M.; Arnold, R. T.; Gensler, W. J.; Head, J. D.; Bembry, T. H.; Mighton, H. R.; Tinker, J.; Galbreath, J.; Holley, A. D.; Goldman, L.; Maynard, J. T.; Picus, N.; *J. Am. Chem. Soc.* **1946**, *68*, 1518.
21. Dukes, M.; Smith, L. A.; *J. Med. Chem*. **1971**, *14*, 326.
22. Nichols, P. L.; Ingham, J. D.; *J. Am. Chem. Soc*. **1955**, *77*, 6547.
23. Kraussuski, K. J.; *J. Pract Chem*. **1907**, *75*, 238, apud Parker, R. E.; Isaacs, N. S.; *Chem. Rev*. **1959**, *9*, 731.
24. Biel, J. H.; *J. Am. Chem. Soc*. **1949**, *71*, 1306.
25. Leffer, M. T.; Adams, R.; *J. Am. Chem. Soc*. **1947**, *59*, 2252.
26. Bunte, H.; *Chem. Ber*. **1874**, *7*, 646.
27. Klayman, D. L.; Gilmore, W. F.; *J. Med. Chem*. **1964,** *7*, 823.
28. Klayman, D. L.; Lown, J. W.; Sweeney, T. R.; *J. Org. Chem*. **1965**, *30*, 2275.
29. Klayman, D. L.; Grenan, M. M.; Jacobus, D. P.; *J. Med. Chem*. **1969**, *12*, 510.
30. Nakanishi, K.; Solomon, P. H.; *Infrared Absorption Spectroscopy*, 2nd ed., Holden-Day, San Francisco, 1977.
31. Cross, A. D.; Jones, R. A.; *An Introduction to Pratical Infrared Spectroscopy*, 3rd ed., Plenum Press, New York, 1969.
32. Silverstein, R. M.; Bassler, G. C.; Morril, T. C.; *Spectrometric Identification of Organic Compounds*, Guanabara Dois, Rio de Janeiro, 1994.
33. Breitmaier, E.; Voelter, W.; *Carbon-13 NMR Spectroscopy*, 3rd Ed., VCH, Weinheim, 1987.
34. Gottlieb, O. R.; *Introdução a Espectrometria de Massa*, Univ. Fed. Rural de Rio de Janeiro, Rio de Janeiro, 1970.