2,2-Dimethyl-5-butylsulfonyl-1,3-thiazane Hydrochloride (XIVb). This was prepared analogously; yield 80%, mp 176-178°C (from methanol—ether). Found: C 41.58; H 7.52; Cl 12.58; S 22.36%. $C_{10}H_{22}ClNO_2S_2$. Calculated: C 41.71; H 7.70; Cl 12.31; S 22.27%.

2,2-Dimethyl-5-butylsulfonyl-1,3-thiazane Hydrobromide (XIVb). A solution of 0.005 mole of (XIb) in 20 ml of 48% HBr was boiled for 3 h, cooled, the phthalic acid separated, and the filtrate evaporated to dryness under vacuum. The residue was reprecipitated several times from ethanol with ether, and the oily (XIIIb) (66%) dissolved in 6 ml of methanol. The mixture was treated with 10 ml of acetone, kept at $\sim$20°C for 24 h, and the product separated and recrystallized to give a 90% yield of (XIVb), mp 184-186°C (from methanol—ether). Found: C 35.95; H 6.40; N 4.11%. $C_{10}H_{22}BrNO_2S_2$. Calculated: C 36.14; H 6.67; N 4.21%.

CONCLUSIONS

1. Novel 3-amino(or phthalimido)-2-alkylsulfonylpropanethiols, their disulfides, and S-sulfate, S-phosphate and isothiuronium derivatives have been synthesized by reacting alkyl 3-amino(or phthalimido)-1-chloro-2-propyl sulfones with thiosulfate, thiourea, trilithium thiophosphate, and potassium thioacetate.

2. Reaction of 3-amino-2-alkylsulfonylpropanethiols with acetone gives 2,2-dimethyl-1,3-thiazanes, and S-(3-amino-2-alkylsulfonylpropyl)isothioureas cyclize to 2-amino-5-alkylsulfonyl-5,6-dihydro-1,3-thiazines.

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2-(3-AMINO-2-ALKYLSULFONYLPROPYLAMINO)-ETHANETHIOLS AND SOME OF THEIR S-DERIVATIVES

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The present paper describes the synthesis of alkyl 3-phthalimidopropen-2-yl sulfones (Ia, b, c), their reaction with ethyleneimine (EI), and some reactions of the N-substituted EIs formed. A series of S-derivatives of 2-(3-amino-2-alkylsulfonylpropylamino)ethanethiols has also been synthesized.

Compounds (Ia, b, c) were obtained by the dehydrochlorination with triethylamine of the previously described [1] alkyl 3-phthalimido-1-chloroprop-2-yl sulfones (IIa, b, c). By dephthalylation under the action of HBr, compounds (Ia, b, c) were converted into the hydrobromides of the alkyl 3-aminopropen-2-yl sulfones (IIIa, b, c). Prolonged boiling of (IIa, b, c) with HBr led not only to the elimination of the phthalyl group but also to the splitting out of HCl with the formation of the unsaturated amino sulfones (IIIa, b).

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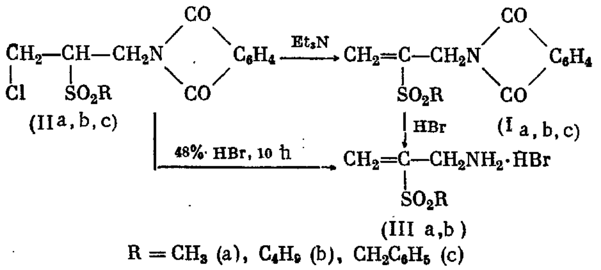
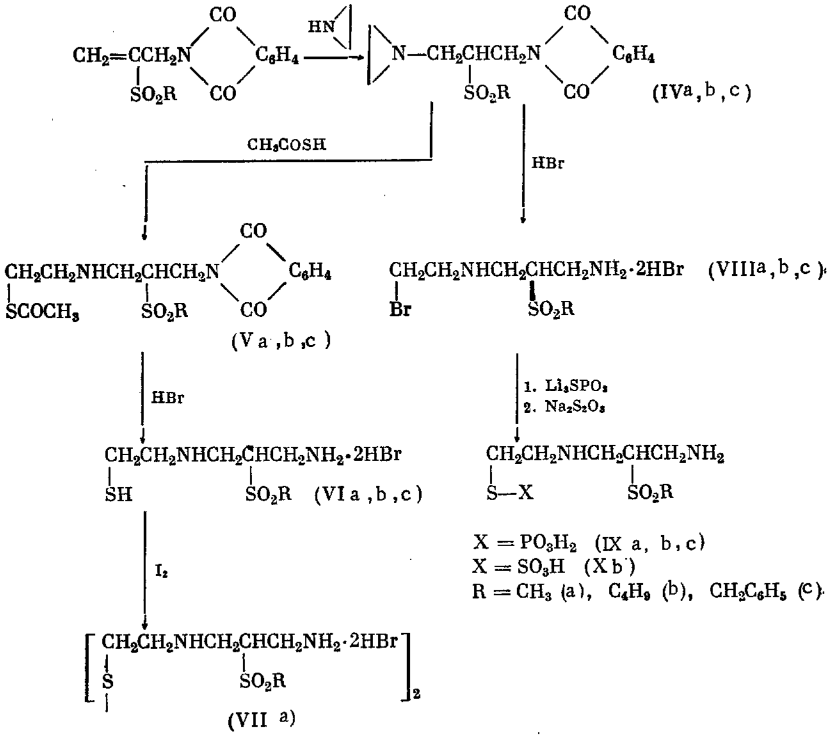


The reaction of EI with α,β-unsaturated systems has been well studied [2-4]. However, the addition of EI to unsaturated amino sulfones has not previously been investigated. The most suitable conditions for this reaction with (Ia, b, c) proved to be boiling the reactants in benzene, using a threefold excess of EI. The N-(3-phthalimido-2-alkylsulfonylpropyl)ethyleneimines (IVa, b, c) so obtained readily react with thioacetic acid to form 1-acetylthio-2-(3-phthalimido-2-alkylsulfonylpropylamino)ethanes (Va, b, c). By boiling the latter with HBr, the phthalyl and S-acetyl groups were eliminated simultaneously, giving the dihydrobromides of the 2-(3-amino-2-alkylsulfonylpropylamino)ethanethiols (VIa, b, c), which were oxidized by iodine to the corresponding disulfides (VIIa, b, c). When compounds (IVa, b, c) were boiled with 48% HBr, dephthalylation and the opening of the ethyleneimine ring took place with the formation of the 1-(3-amino-2-alkylsulfonylpropylamino)-2-bromoethanes (VIIIa, b, c).



With trilithium phosphorothioate under the conditions given by Akerfeldt [5], the latter forms S-[2-(3-amino-2-alkylsulfonylpropylamino)ethyl] phosphorothioates (IXa, b, c). By reaction of the bromides (VIIIa, b, c) with sodium thiosulfate in the presence of an acetate buffer, the thiosulfates (Xa, b, c) were obtained. It was possible to isolate only (Xb) in the crystalline state; the thiosulfates (Xa, c) were obtained in the form of syrups contaminated with sodium salts (see above Scheme).

EXPERIMENTAL

Methyl 3-Phthalimidopropen-2-yl Sulfone (Ia). A solution of 0.1 mole of methyl 1-chloro-3-phthalimidoprop-2-yl sulfone [1] and 0.01 mole of Et_3N in 120 ml of absolute dioxane (or in 50 ml of absolute $CHCl_3$) was stirred at ~20°C for 5 h, the $Et_3N \cdot HCl$ (90%) was separated off by filtration, and the filtrate was diluted with 200 ml of water. The resulting precipitate (Ia) was separated off, dried in the air, and recrystallized; yield 90%, mp 156-158°C ($CHCl_3$—ether). Found: C 54.72; H 4.30; N 5.56; S 12.22%. $C_{12}H_{11}NO_4S$. Calculated: C 54.34; H 4.18; N 5.28; S 12.09%.

Butyl and Benzyl 3-Phthalimidopropen-2-yl Sulfones (Ib and c). The sulfones (Ib and c) were obtained similarly. (Ib), yield 85%, mp 95-96°C ($CHCl_3$—ether). Found: C 58.74; H 5.82; N 4.83; S 10.50%. $C_{15}H_{17}NO_4S$. Calculated: C 58.61; H 5.57; N 4.56; S 10.42%. (Ic), yield 85%, mp 158-159°C ($CHCl_3$—ether). Found: C 63.45; H 4.74; N 3.94; S 9.48%. $C_{18}H_{15}NO_4S$. Calculated: C 63.33; H 4.43; N 4.10; S 9.39%.

Hydrobromide of 3-Aminopropen-2-yl Methyl Sulfone (IIIa). a) A mixture of 0.01 mole of (Ia) and 25 ml of 48% HBr was boiled until dissolution was complete (~2 h). Then the solution was cooled, the precipitate of phthalic acid was precipitated off, and the filtrate was evaporated in vacuum to dryness. This gave 1.72 g (80%) of (IIIa), mp 177-178°C (ethanol—ether). Found: C 22.03; H 4.84; N 6.60%. $C_4H_{10}BrNO_2S$. Calculated: C 22.23; H 4.66; N 6.48%.

b) A mixture of 0.016 mole of (IIa) and 60 ml of 48% HBr was boiled for 10 h, the phthalic acid was separated off, and the filtrate was evaporated in vacuum to dryness. Fractional crystallization of the residue from ethanol with the addition of ether yielded 2.28 g (60%) of (IIIa), mp 176-177°C, and 0.8 g (18%) of the hydrobromide of 1-amino-3-chloro-2-methylsulfonylpropane [1].

Hydrobromide of 3-Aminopropen-2-yl Butyl Sulfone (IIIb). The sulfone (IIIb) was obtained similarly: a) yield 60%, mp 125-126°C (ethanol—ether). Found: C 32.68; H 6.10; N 5.31%. $C_7H_{16}BrNO_2S$. Calculated:C 32.57; H 6.24; N 5.42%. b) Yield 30%, mp 124-126°C (ethanol—ether).

N-(2-Methylsulfonyl-3-phthalimidopropyl)ethyleneimine (IVa). A mixture of 0.01 mole of (Ia) and 0.3 mole of ethyleneimine in 50 ml of absolute benzene was boiled for 3 h, the solvent was driven off in vacuum, and the residue was recrystallized. Yield of (IVa) 70%, mp 101-102°C (ethanol). Found: 54.58; H 5.55; N 9.15; S 12.31%. $C_{14}H_{16}N_2O_4S$. Calculated: C 54.54; H 5.23; N 9.08; S 12.61%.

N-(2-Butylsulfonyl-3-phthalimidopropyl)ethyleneimine (IVb). This was obtained similarly; yield 86%, mp 96-98°C (ethanol). Found: C 58.20; H 6.21; N 8.09; S 8.97%. $C_{17}H_{22}N_2O_4S$. Calculated: C 58.26; H 6.33; N 7.99; S 9.15%.

N-(2-Benzylsulfonyl-3-phthalimidopropyl)ethyleneimine (IVc). This was obtained similarly; yield 95%, mp 133-134°C (ethanol). Found: C 62.18; H 5.31; N 7.31; S 8.33%. $C_{20}H_{20}N_2O_4S$. Calculated: C 62.48; H 5.24; N 7.29; S 8.34%.

1-Acetylthio-2-(2-methylsulfonyl-3-phthalimidopropylamino)ethane (Va). A mixture of 0.01 mole of (IVa) and 0.01 mole of CH_3COSH in 40 ml of absolute benzene was kept at ~20°C for 2 h, the reaction being followed by TLC on Al_2O_3. After the solvent had been driven off in vacuum, a colorless noncrystallizing syrup was obtained which was used without further purification.

1-Acetylthio-2-(2-butylsulfonyl-3-phthalimidopropylamino)ethane (Vb). Obtained similarly in the form of an oil.

1-Acetylthio-2-(2-benzylsulfonyl-3-phthalimidopropylamino)ethane (Vc). Obtained similarly; yield 90%, mp 123-124°C (ethanol). Found: 57.22; H 5.34; N 6.01; S 14.18%. $C_{22}H_{24}N_2O_5S_2$. Calculated: C 57.36; H 5.25; N 6.08; S 13.92%.

Dihydrobromide of 2-(3-Amino-2-methylsulfonylpropylamino)ethanethiol (VIa). A mixture of 0.01 mole of (Va) and 50 ml of 48% HBr was boiled for 3 h. The solution was cooled, the phthalic acid was separated off, and the filtrate was evaporated in vacuum to dryness. The residue was dried over P_2O_5 and recrystallized. The yield of (VIa) was 60%, mp 165-166°C (ethanol). Found: C 19.52; H 5.11; N 7.44%. $C_6H_{18}Br_2N_2O_2S_2$. Calculated: C 19.26; H 4.85; N 7.47%.

Dihydrobromide of 2-(3-Amino-2-butylsulfonylpropylamino)ethanethiol (VIb). Compound (VIb) was obtained similarly with a yield of 95%, mp 165-167°C (48% HBr—ethanol). Found: C 25.90; H 5.55; N 6.88%. $C_9H_{24}Br_2N_2O_2S_2$. Calculated: C 25.96; H 5.81; N 6.73%.

Dihydrobromide of 2-(3-Amino-2-benzylsulfonylpropylamino)ethanethiol (VIc). This was obtained similarly; yield of (VIc) 77%, mp 139-140°C (ethanol—ether). Found: C 32.20; H 4.80; N 6.12%. $C_{12}H_{22}Br_2N_2O_2S_2$. Calculated: C 32.02; H 4.92; N 6.22%.

Tetrahydrobromide of Bis[2-(3-amino-2-methylsulfonylpropylamino)ethyl] Disulfide (VIIa). A solution of 0.0025 mole of (VIa) in the minimum amount of ethanol was titrated with a 0.1 N methanolic solution of iodine until a faint yellow color appeared. The disulfide (VIIa) was precipitated with ether, dried in vacuum over P_2O_5, and recrystallized. The yield of (VIIa) was 55%; hygroscopic powder, mp 95°C (decomp.) (48% HBr—ethanol). Found: C 19.76; H 4.91; N 7.36%. $C_{12}H_{34}Br_4N_4O_4S_4$. Calculated: C 19.32; H 4.59; N 7.51%.

Dihydrobromide of 1-(3-Amino-2-methylsulfonylpropylamino)-2-bromoethane (VIIIa). A mixture of 0.01 mole of (IVa) and 30 ml of 48% HBr was boiled for 3 h, the phthalic acid was separated off, and the filtrate was evaporated in vacuum to dryness. Yield of (VIIIa) 70%, mp 198-199°C (85% ethanol—ether). Found: C 17.38; H 3.92; N 6.80%. $C_6H_{17}Br_3N_2O_2S$. Calculated: C 17.12; H 4.07; N 6.65%.

Dihydrobromide of 1-(3-Amino-2-butylsulfonylpropylamino)-2-bromoethane (VIIIb). Obtained similarly; yield 80%, mp 201-203°C (ethanol—ether). Found: C 23.60; H 5.22; N 6.27%. $C_9H_{23}Br_3N_2O_2S$. Calculated: C 23.34; H 5.01; N 6.05%.

Dihydrobromide of 1-(3-Amino-2-benzylsulfonylpropylamino)-2-bromoethane (VIIIc). Obtained similarly; yield 70%, mp 139-140°C (ethanol—ether). Found: C 29.15; H 4.56; N 5.51%. $C_{12}H_{21}Br_3N_2O_2S$. Calculated: C 28.99; H 4.26; N 5.63%.

S-[2-(3-Amino-2-methylsulfonylpropylamino)ethyl Phosphorothioate (IXa). At ~20°C, 0.0015 mole of (VIIIa) was added in small portions to a stirred suspension of 0.0015 mole of $Li_3SPO_3 \cdot 6H_2O$ in 2 ml of water. Stirring was continued until the test for SPO_3^{3-} with $AgNO_3$ was negative (~1 h). The product was precipitated with methanol (50 ml) and dried in the air. Yield of (IXa) 95%. Found: C 20.63; H 6.63; N 7.89%. $C_6H_{17}N_2O_5S_2P \cdot 3H_2O$. Calculated: C 20.80; H 6.69; N 8.08%.

S-[2-(3-Amino-2-butylsulfonylpropylamino)ethyl] Phosphorothioate (IXb). Obtained similarly; yield 30%. Found: C 28.90; H 7.47; S + P 24.95%. $C_9H_{23}N_2O_5S_2P \cdot 2H_2O$. Calculated: C 29.18; H 7.34; S + P 25.68%.

S-[2-(3-Amino-2-benzylsulfonylpropylamino)ethyl] Phosphorothioate (IXc). Obtained similarly; yield 60%. Found: C 37.98; H 5.73; N 7.52%. $C_{12}H_{21}N_2O_5S_2P \cdot 0.5\ H_2O$. Calculated: C 38.19; H 5.87; N 7.42%.

S-[2-(3-Amino-2-butylsulfonylpropylamino)ethyl] Thiosulfate (Xb). A mixture of 0.002 mole of (VIIIb), 0.002 mole of $Na_2S_2O_3 \cdot 5H_2O$, and 0.002 mole of CH_3COONa in 6 ml of water was boiled for 1 h. After evaporation in vacuum, the residue was extracted with hot ethanol. The product crystallized on cooling; yield of (Xb) 43%, mp 205-207°C (ethanol). Found: C 31.18; H 7.02; N 8.01%. $C_9H_{22}N_2O_5S_3 \cdot H_2O$. Calculated: C 31.37; H 7.02; N 8.13%.

SUMMARY

1. Alkyl 1,3-diaminoprop-2-yl sulfones have been synthesized from alkyl 3-phthalimidopropen-2-yl sulfones.

By the addition of ethylene imine to these propenyl sulfones N-(3-phthalimido-2-alkylsulfonylpropyl)-ethyleneimines were obtained. The cleavage of the ethyleneimine rings of the latter by the action of HBr gave 1-(3-amino-2-alkylsulfonylpropylamino)-2-bromoethanes, from which S-[2-(3-amino-2-alkylsulfonylpropylamino)ethyl] thiosulfates and phosphorothioates were obtained.

2. 2-(3-Amino-2-alkylsulfonylpropylamino)ethanethiols have been synthesized.

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