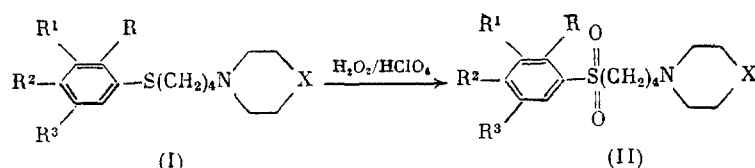


Two methods are proposed for the preparation of aryl aminoalkyl sulfones substituted in the aromatic ring: a method based on the oxidation of aryl aminoalkyl sulfides by hydrogen peroxide or of their bases in the presence of HClO_4 and a method based on the oxidation of aryl ω -chloroalkyl sulfides to chlorosulfones by hydrogen peroxide followed by their condensation with amines.

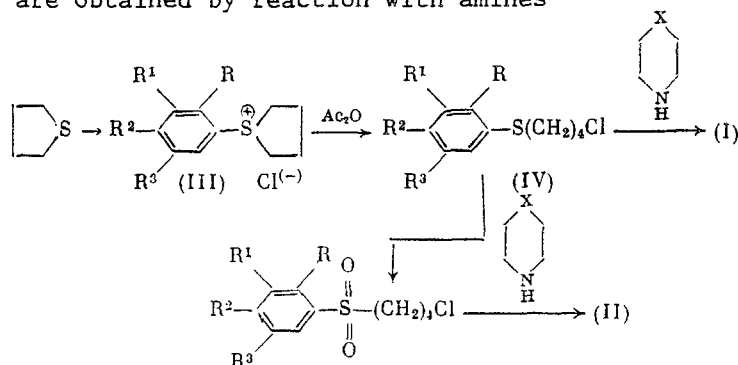
Continuing investigations of the chemistry of saturated sulfides [1], we developed a preparative method for obtaining aryl aminoalkyl sulfones by oxidation of appropriate amino sulfides in the presence of an equimolar amount of HClO_4 in the presence of excess 26-30% H_2O_2 in glacial AcOH .



(I), (II): $\text{R} = \text{Me}$, $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{OH}$, $\text{X} = \text{CH}_2$ (a); $\text{R} = \text{Me}$, $\text{R}^1 = \text{R}^3 = \text{H}$; $\text{R}^2 = \text{OH}$, $\text{X} = \text{O}$ (b); $\text{R} = \text{R}^3 = \text{H}$, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{OH}$, $\text{X} = \text{CH}_2$ (c); $\text{R} = \text{R}^3 = \text{H}$, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{OH}$, $\text{X} = \text{O}$ (d); $\text{R} = \text{R}^3 = \text{OH}$, $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{X} = \text{CH}_2$ (e); $\text{R} = \text{R}^3 = \text{OH}$, $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{X} = \text{O}$ (f).
 (I): $\text{R} = \text{R}^3 = \text{AcO}$, $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{X} = \text{CH}_2$ (g); $\text{R} = \text{R}^2 = \text{AcO}$, $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{X} = \text{CH}_2$ (h); $\text{R} = \text{R}^2 = \text{OH}$, $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{X} = \text{CH}_2$ (i); $\text{R} = \text{R}^2 = \text{OH}$, $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{X} = \text{O}$ (j). (II): $\text{R} = \text{OH}$, $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{AcO}$, $\text{X} = \text{CH}_2$ (g).

Perchloric acid, protonating the nitrogen atom of the amino sulfide, protects it from the action of the oxidizing agent and simultaneously catalyzes the oxidation reaction. Another variant of protection of the amino group from the action of the oxidizing agent consists in the use of amino sulfide hydrochlorides as the starting substances. The hydrochlorides of amino sulfides (I) were oxidized with excess H_2O_2 in glacial AcOH , and hydrochlorides of amino sulfides (IIe), (IIe), and (IIg) were obtained (Table 1). The hydrochlorides of (IIe) and (IIf) were converted into bases (IIe) and (IIf) by neutralization with KHCO_3 (Table 1).

In the present paper, we also propose a different method for functionalization of saturated sulfides, conversion of cyclic sulfonium salts to diacetoxy chloro sulfides, from which amino sulfides are obtained by reaction with amines



(III): $\text{R} = \text{Me}$, $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{OH}$ (a); $\text{R} = \text{R}^2 = \text{OH}$, $\text{R}^1 = \text{R}^3 = \text{H}$ (b); $\text{R} = \text{R}^1 = \text{R}^2 = \text{OH}$, $\text{R}^3 = \text{H}$ (c); $\text{R} = \text{Me}$, $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{OH}$ (perchlorate) (d); $\text{R} = \text{Me}$, $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{AcO}$ (perchlorate) (e). (IV): $\text{R} = \text{Me}$, $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{AcO}$ (a); $\text{R} = \text{R}^2 = \text{AcO}$, $\text{R}^1 = \text{R}^3 = \text{H}$ (b); $\text{R} = \text{R}^1 = \text{R}^2 = \text{AcO}$, $\text{R}^3 = \text{H}$ (c).

TABLE 1. Characteristics of Aryl 4-Aminobutyl Sulfones (II)

Compound	Yield, %	Mp, °C (solvent)	Found, %					Empirical formula	Calculated, %			
			C	H	N	S	N+ a		C	H	N	S
(IIa)	74	156-157 ^b	62.2	8.2	4.4	10.1	4.4	C ₁₆ H ₂₅ NO ₃ S	61.7	8.1	4.5	10.3
(IIb)	53 ^c	139-140 (benzene)	58.3	7.4	4.4	10.3		C ₁₅ H ₂₃ NO ₃ S	57.5	7.4	4.5	10.2
(IIb) hydrate	88	192.5-193.5 (alcohol)	54.2	7.3	3.9	10.3	4.2	C ₁₅ H ₂₃ NO ₃ S·H ₂ O	54.4	7.6	4.2	9.7
(IIc)	72	157.5-159.5 (alcohol:water = 1:4)	61.5	7.6	4.2	10.4	4.3	C ₁₆ H ₂₅ NO ₃ S	61.7	8.1	4.5	10.3
(IId)	64.5	141.5-143.5 (methanol:benzene = 1:6)	57.3	7.0	4.2	10.3	4.4	C ₁₅ H ₂₃ NO ₃ S	57.5	7.4	4.5	10.2
(IIe)		175-177	57.1	7.5	4.5			C ₁₅ H ₂₃ NO ₃ S	57.5	7.4	4.5	
(IIe) hydrate	68	Oil	46.8	7.5	4.2			C ₁₄ H ₂₁ NO ₃ S·2.5H ₂ O	46.6	7.3	3.9	
(IIe) hydrochloride hydrate	91	113-115 ^d	49.1 ^e	7.2		8.5	3.3	C ₁₅ H ₂₄ ClNO ₃ S·H ₂ O	48.9	7.1	3.8	8.7
(IIe) hydrochloride hydrate	93	Oil	40.9 ^f	6.6	3.8	8.9	3.1	C ₁₁ H ₂₂ ClNO ₃ S·3H ₂ O	41.4	7.0	3.5	8.9
(IIg) hydrochloride	100	125-127			3.5 ^g	8.3	3.2	C ₁₇ H ₂₆ ClNO ₃ S			3.6	8.2

a) Here and in what follows, N⁺ was determined by titration with HClO₄ in Ac₂O according to [2].

b) After precipitation by hexane from a mixture of alcohol with benzene.

c) The yield decreased because of dissolution of part of (IIb) when the precipitated KClO₄ was washed away.

d) It dehydrated during melting.

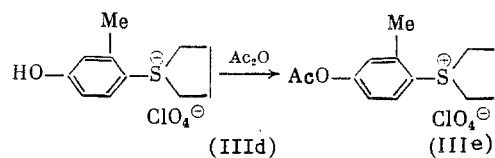
e) After precipitation with ether from a solution in an alcohol-benzene mixture (1:1). Found, %: Cl 10.13, Calculated, %: Cl 9.64.

f) Found, %: Cl 8.75; Calculated, %: Cl 8.74.

g) Found, %: Cl 8.86; Calculated, %: Cl 9.05.

$$\text{AcO}-\text{C}_6\text{H}_4(\text{Me})-\text{S}(\text{CH}_2)_4\text{Cl} \rightarrow \text{HO}-\text{C}_6\text{H}_4(\text{Me})-\text{S}(\text{CH}_2)_4\text{Cl} \xrightarrow{\text{Pyridine}} \text{(IIa)}$$

From a comparison of both methods for functionalization of sulfides using sulfonium salts, it is evident that the C-S bond of the heterocycle in hydroxyphenylthiolanium perchlorates (unlike in the case of chlorides) is cleaved only by the action of amines, and acylation of hydroxyl groups occurs in the presence of Ac₂O: (IIIId) is converted to (IIIe).



EXPERIMENTAL*

2-Methyl-4-hydroxyphenyl (4-Piperidinobutyl)Sulfone (IIa). To a solution of 0.84 g (3 mmoles) of (Ia) in 10 ml of glacial AcOH were added 0.27 ml (3 mmoles) of 67.5% HClO₄ and, after cooling, 3 ml of 28% H₂O₂, and the whole was kept at 32-37°C for 2 h, concentrated in vacuo at 35°C, neutralized with a saturated KHCO₃ solution, and extracted with chloroform. The residue after evaporation of the extract was treated in vacuo with 2 ml of acetone. We obtained 0.73 g of (IIa). The product gave no depression during melting of a mixed sample with the sulfone (mp 155-156.5°C) obtained by back-synthesis.

b. Under similar conditions (at 40-50°C for 3 h), 0.8 g (2.8 mmoles) of (Ib) was oxidized with excess H_2O_2 , the product was concentrated in vacuo, and the residue was dissolved in 3 ml of water and neutralized with solid KHCO_3 . The separated oil was extracted with chloroform, and the precipitate that resulted from the aqueous solution was washed with cold water. We obtained the hydrate of (IIb). Mass spectrum (m/z): 313 M^+ , 281.

3-Methyl-4-hydroxyphenyl 4-Morpholinobutyl Sulfone (IIId). We oxidized 1 g (3.5 mmol) of (Id) similarly to (IIc). We obtained 0.87 g (79%) of (IIId). Mass spectrum (m/z): 313 M^+ , 281 (227, 243, 198, 171/173, 155, 142, 98).

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2,5-Dihydroxyphenyl 4-Piperidinobutyl Sulfone (IIe) Hydrochloride Hydrate. We oxidized 1.17 g (2.9 mmol) of (Ie) hydrochloride in 15 ml of glacial AcOH with 26% H_2O_2 (at 20°C for 20 h and then at 40-50°C for 2 h) and concentrated the product in vacuo and washed it with ether and hexane. We obtained 0.92 g of (IIe) hydrochloride; it was soluble in water and alcohol and sparingly soluble in acetone. The precipitate was dissolved in an alcohol-benzene mixture (1:1) and reprecipitated with ether. The purified salt of (IIe) was dissolved in water and neutralized with KHCO_3 , and base (IIe) was recovered. Mass spectrum (m/z): 313 M^+ , 138/140, 98.

2,5-Dihydroxyphenyl 4-Morpholinobutyl Sulfone (IIIf) Hydrochloride Hydrate. We oxidized 2 g (6.25 mmol) of (If) hydrochloride with 28% H_2O_2 in 20 ml of glacial AcOH (at 70-80°C for 8 h), concentrated the product in vacuo, and washed the residue with ether and dried it in vacuo. We obtained 2 g of (IIIf) hydrochloride hydrate. The salt of (IIIf) was dissolved in water and neutralized with KHCO_3 , and 1.33 g of base (IIIf) hydrate was extracted with chloroform.

2-Hydroxy-5-acetoxyphenyl 4-Piperidinobutyl Sulfone (IIg) Hydrochloride. We oxidized 2 g (5 mmol) of (Ig) hydrochloride with H_2O_2 in AcOH (at 40-50°C for 1 h and then at 20°C for 20 h), evaporated the mixture in vacuo, washed the residue with ether, and dried it in vacuo. We obtained 1.86 g of (IIg) hydrochloride. Mass spectrum (m/z): 335 M^+ , 313 (M^+ , $\text{C}_2\text{H}_2\text{O}$), 140, 98.

2,4-Diacetoxyphenyl 4-Chlorobutyl Sulfide (IVb). A mixture of 3 g (12.9 mmol) of (IIIb) (obtained according to [3]) and 11 ml of Ac_2O was boiled for 1 h, concentrated in vacuo, dissolved in ether, and precipitated with hexane. The (IVb) was a yellow oil, and the yield was 89%. Found: C 53.5; H 5.4; Cl 11.1; S 10.4%. $\text{C}_{14}\text{H}_{17}\text{ClO}_4\text{S}$. Calculated: C 53.1; H 5.4; Cl 11.2; S 10.2%. Mass spectrum (m/z): 316/318 M^+ , 274/276, 232/234.

2-Methyl-4-acetoxyphenyl 4-Chlorobutyl Sulfide (IVa). A mixture of 6.06 g (26.2 mmol) of (IIIa) and 25 ml of Ac_2O was heated at 100°C for 6 h, the excess anhydride was driven off at low vacuum, the residue was treated with ether and filtered, and the filtrate was distilled. We obtained 5.71 g (79.9%) of (IVa), a colorless oil with bp 172-174°C (1 mm), n_D^{20} 1.5520. Found: C 57.3; H 6.3; Cl 13.0; S 12.1%. $\text{C}_{13}\text{H}_{17}\text{ClO}_2\text{S}$. Calculated: C 57.3; H 6.3; Cl 13.0; S 11.8%. Mass spectrum (m/z): 272/274 M^+ . PMR spectrum (CDCl_3 , δ , ppm): 1.8 multiplet (4H, CH_2CH_2), 2.2 singlet (3H, CH_3CO), 2.83 triplet (2H, CH_2S), 2.35 singlet (3H, $\alpha\text{-CH}_3$), 3.48 triplet (2H, CH_2Cl), 6.92 singlet (1H, aromatic H), 7.05 quartet (2H, $\text{H}_{\alpha,\beta}$ aromatic, $J_{\text{av}} = 9$ Hz).

2,3,4-Triacetoxyphenyl 4-Chlorobutyl Sulfide (IVc). From 0.5 g (2 mmol) of (IIIc) and 15 ml of Ac_2O (at 100°C for 2 h), we obtained 0.75 g (100%) of (IVc), light-yellow crystals with mp 52.5-55°C, soluble in ether, acetone, methanol, and alcohol. Found: C 51.8; H 5.1; Cl 9.5; S 8.7%. $\text{C}_{16}\text{H}_{19}\text{ClO}_6\text{S}$. Calculated: C 51.3; H 5.1; Cl 9.5; S 8.6%. PMR spectrum (CCl_4 , δ , ppm): 1.73 multiplet (4H, CH_2CH_2), 2.17 singlet (9H, CH_3CO), 2.77 triplet (2H, S-CH_2), 3.42 triplet (2H, CH_2Cl), 7.04-7.4 doublet (2H, $\text{H}_{\alpha,\beta}$ aromatic).

2-Methyl-3-acetoxyphenylthiolanium Perchlorate (IIIe). We heated 0.5 g (1.7 mmol) of perchlorate (IIIId) (obtained by the procedure of [1]) and 10 ml of Ac_2O at 100°C for 3 h, drove off the Ac_2O at low vacuum, treated the obtained oil with ether, separated the precipitate, and added water and benzene and drove them off. The mass of the residue was 0.51 g (74.2%), mp 146-148.5°C (from ethanol), colorless crystals soluble in acetone. Found: C 46.5; H 5.2%. $\text{C}_{13}\text{H}_{17}\text{ClO}_6\text{S} \cdot 2\text{H}_2\text{O}$. Calculated: C 46.4; H 5.2%.

2,4-Diacetoxyphenyl 4-Piperidinobutyl Sulfide (Ih) Hydrochloride. We boiled 1.95 g (6.1 mmol) of (IVb) and 5 ml of piperidine for 0.5 h, treated the mixture with 5 ml of Ac_2O (at 100°C for 45 min) and then with ether and hexane, dissolved the unextractable residue in acetone and treated it with active carbon, and kept the filtrate in vacuo. We obtained 2.42 g (100%) of (Ih) hydrochloride, a dark oil. Found: C 56.3; H 7.2; Cl 8.8; N 3.6; S 7.4; N^+ 3.5%. $\text{C}_{19}\text{H}_{28}\text{ClNO}_4\text{S}$. Calculated: C 56.8; H 7.0; Cl 8.8; N 3.5; S 8.0%.

2,4-Dihydroxyphenyl 4-Piperidinobutyl Sulfide (Ii) Hydrochloride. We hydrolyzed 0.9 g (2.24 mmol) of (Ih) hydrochloride with HCl in acetone at 20-23°C for 48 h, drove off the acetone in vacuo, and obtained 0.56 g (79%) of (Ii) hydrochloride, a yellow crystalline substance with mp 132-136°C. Found: Cl 10.7; N 4.3; N^+ 4.1%. $\text{C}_{15}\text{H}_{24}\text{ClNO}_2\text{S}$. Calculated: Cl 11.1; N 4.4%. Mass spectrum (m/z): 281 (M^+ , HCl). A sample from mixing of the obtained substance did not give depression with a known sample [4].

2,4-Dihydroxyphenyl 4-Morpholinobutyl Sulfide (Ij) Hydrochloride. A mixture of 1.14 g (3.6 mmol) of (IVb) and 3 ml (38 mmol) of morpholine was heated at 100°C for 0.5 h, cooled, and poured into ether, and the separated oil was extracted with ether and kept in vacuo. We obtained 1.07 g (93%) of (Ij) hydrochloride with mp 127-129°C. Found: C 52.7; H 6.7; Cl 11.0; N 4.7; S 9.7; N⁺ 4.4%. C₁₄H₂₂ClNO₃S. Calculated: C 52.6; H 6.9; Cl 11.1; N 4.4; S 10.0%. Mass spectrum (m/z): 283 (M⁺, HCl), 142, 100.

2-Methyl-4-hydroxyphenyl 4-Chlorobutyl Sulfone (Va). To 3 g (11 mmol) of (IVa) in 10 ml of glacial AcOH were added 2 drops (0.05 g) of 67.5% HClO₄ and a solution of 2.5 ml of 30% H₂O₂ in 5 ml of glacial AcOH. The mixture was heated at 100°C for 6 h, 0.5 ml of H₂O₂ was added, and the whole was kept at 100°C for 4 h. The degree of oxidation was monitored by thin-layer chromatography (Silufol plates, acetone-chloroform eluent (1:1), and detection with I₂ vapor). The mixture was concentrated in vacuo, 20 ml of water was added to the residue, and the precipitate was separated, dried, dissolved in acetone, and treated with active carbon. From the filtrate was recovered (Va) in 78% yield with mp 109-110.5°C (from benzene). Found: C 50.7; H 5.4; Cl 13.6; S 12.6%. C₁₁H₁₅ClO₃S. Calculated: C 50.3; H 5.8; Cl 13.5; S 12.2%.

Reaction of Sulfone (Va) with Piperidine. A mixture of 1.5 g (5.7 mmol) of (Va) and 6 ml of piperidine was boiled for 0.5 h, cooled, and treated with ether, and the precipitate of piperidine hydrochloride (0.62 g, 89%) was separated. The filtrate was concentrated in vacuo and treated with hexane. We obtained 1.36 g (76%) of (IIa) with mp 155-156.5°C (from acetone). Found: C 61.6; H 7.9; N 4.3; S 10.5%. C₁₆H₂₅NO₃S. Calculated: C 61.7; H 8.1; N 4.5; S 10.3%.

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