REACTION OF ARYLTHIACYCLANYLSULFONIUM SALTS WITH NITROGEN BASES. SYNTHESIS OF AMINOALKYL ARYL SULFIDES

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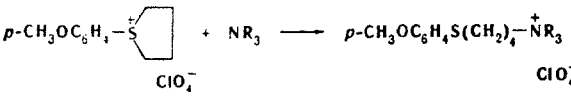
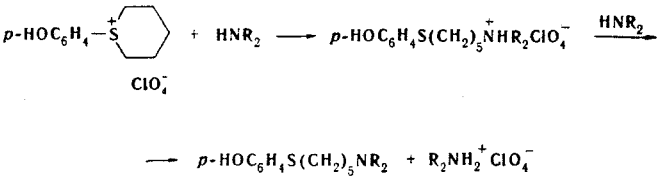
When arylthiacyclanylsulfonium salts are heated with nitrogen bases the C—S bond of the heteroring undergoes quantitative cleavage and the base adds to form a C—N bond. These sulfonium salts react with ammonia or pyridine to give ammonioalkyl sulfides; amino sulfides and secondary amine salts are obtained with excess secondary amines. The described reaction is a new preparative method for the synthesis of amino sulfides and ammonioalkyl aryl sulfides.

When alkyl- or arylthiacylanylsulfonium salts are heated with potassium hydroxide, potassium ethoxide, or potassium tert-butoxide the heteroring is cleaved to give, depending on the reaction conditions, unsaturated sulfides or alkoxy sulfides [1, 2]. When dialkylarylsulfonium chlorides are heated with pyridine an alkyl group is split out to give alkyl aryl sulfides and N-alkylpyridinium chloride [3].

We found [4] that when arylthiacyclanylsulfonium salts are heated with liquid ammonia or with pyridine the C—S bond of the heteroring is cleaved and the base adds to form a C—N bond.



The final products in the reaction of arylthiacyclanylsulfonium salts with secondary amines are aryl aminoalkyl sulfides and the salt of the corresponding amine:



A mixture of approximately equal amounts of p-hydroxyphenyl 5-piperidinoamyl sulfide and its perchlorate was obtained only in the reaction of piperidine with p-hydroxyphenylthiacyclohexylsulfonium perchlorate. The corresponding free amino sulfide can be obtained by heating the perchlorate with excess piperidine. Small amounts of the perchlorate of the amino sulfide were also obtained along with the amino sulfide in the reaction of p-hydroxyphenylthiophanylsulfonium perchlorate with dibutylamine.

The reactions between arylthiacyclanylsulfonium salts and nitrogen bases proceed quantitatively. These reactions open up a new method for the synthesis of amino sulfides (in the case of secondary amines) and ammonioalkyl aryl sulfides (in the case of ammonia or pyridine). We have previously proposed [5] practical methods for the synthesis of the starting arylthiacyclanylsulfonium salts. In the present research one of these methods

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(preparation of arylthiacyclanylsulfonium perchlorates by condensation of thiacyclane sulfoxides with phenol derivatives in the presence of perchloric acid and phosphorus oxychloride) was modified — the amount of perchloric acid was reduced by a factor of more than five and the amount of phosphorus oxychloride was reduced by a factor of almost two as compared with the investigations in [5].

The structures of the amino sulfides obtained were established by means of PMR and mass spectroscopy.

The amino sulfide and ammonium salts based on them have a wide range of application: in particular, they are used as physiologically active substances [6, 7]. p-Hydroxyphenyl 4-dialkylaminobutyl sulfide hydrochlorides (Table 2) have weak bacteriostatic activity.

EXPERIMENTAL METHOD

The PMR spectra of 10% solutions of the compounds in CCl_4 were recorded with a Varian T-60 spectrometer with hexaemthyldisiloxane as the internal standard. The mass spectra were recorded with an MI 1309 spectrometer with a system for direct introduction of the sample into the ion source; the ionizing-electron energy was 70 eV, the emission current was 0.25 mA, the vaporization temperature was 20-30°, and the ionization-chamber temperature was 150°.

Starting Arylthiacyclanylsulfonium Salts (Table 1). These compounds were obtained by the method in [5] from thiacyclane sulfoxide and phenol or anisole in the presence of perchloric acid and phosphorus oxychloride, but the sulfoxide—perchloric acid—phosphorus oxychloride molar ratio was 1:1:1. For example, 2.6 g (0.025 mole) of the thiophane sulfoxide was added at 0-5° in the course of 1.5 h to 2.7 g (0.025 mole) of anisole, 9.6 g (0.025 mole) of phosphorus oxychloride, and 2.52 g (0.025 mole) of 65% perchloric acid, after which the mixture was held at 20° for 24 h. It was then poured over ice, and the precipitated p-methoxyphenylthiophanylsulfonium perchlorate was separated to give a product with mp 104-106° in 94% yield. Recrystallization from alcohol or water gave a product with mp 107.5-108.5° (mp 108° [8]) in 85% yield.

The relative amounts of reagents described in [5] were optimal in the synthesis of arylthiacyclanylsulfonium perchlorate from thiacyclane and hydrogen peroxide; the sulfonium chloride and picrates were obtained by the method in [5].

Reaction of Arylthiacyclanylsulfonium Salts with Ammonia. A) A 4.33-g (0.02 mole) sample of p-hydroxyphenylthiophanyl sulfonium chloride and 15 ml of alcohol were placed in a 170-ml autoclave, the mixture was cooled, and 10 ml (0.48 mole) of liquid ammonia was added. The mixture was then heated at 70-72° for 3 h, after which the alcohol was removed by distillation to give 4.55 g of ether-insoluble p-hydroxyphenyl 4-aminobutyl sulfide hydrochloride (Table 1).

B) A solution of 0.02 mole of p-methoxyphenylthiophanylsulfonium perchlorate in 15 ml of alcohol and 4.2 ml of liquid ammonia was heated at 50-52° for 3 h, after which the mixture was worked up as in experiment A to give 3.35 g of p-methoxyphenyl 4-aminobutyl sulfide perchlorate (Table 1).

Reaction of Arylthiacyclanylsulfonium Salts with Pyridine. A) A mixture of 3.32 g (0.012 mole) of p-hydroxyphenylthiophanylsulfonium perchlorate and 22 ml of pyridine was refluxed for 6 h, after which the excess pyridine was removed by distillation, and the residue was washed with ether. On cooling to −30°, the reaction product — 1-[4-(p-hydroxyphenylthio)butyl]pyridinium perchlorate — began to crystallize to give 4.22 g of a product with mp 64-65° (Table 1).

B) 1-[4-(p-Hydroxyphenylthio)butyl]pyridinium chloride was obtained as in experiment A (except the reaction time was 8 h) from 2.58 g (0.012 mole) of p-hydroxyphenylthiophanyl sulfonium chloride (Table 1); the reaction product was converted to the picrate (Table 2).

C) A 1.47-g (0.005 mole) sample of p-hydroxyphenylthiacyclohexylsulfonium perchlorate was heated with pyridine, as in experiment A, for 4 h to give 1-[5-(p-hydroxyphenylthio)-pentyl]pyridinium perchlorate (Table 1).

Reaction of Arylthiacyclanylsulfonium Salts with Secondary Amines. A) A mixture of 2.8 g (0.01 mole) of p-hydroxyphenylthiophanylsulfonium perchlorate and 15 ml of diethyl-

amine was refluxed for 4.5 h, after which the excess amine was removed by distillation, the residue was treated repeatedly with warm ether, and the ether was decanted. Workup of the ether extract yielded 2.48 g of p-hydroxyphenyl 4-diethylaminobutyl sulfide (Table 1).

B) As in the preceding experiment, 4.82 g of p-methoxyphenyl 4-diethylaminobutyl sulfide (Table 1) was obtained from 5.89 g (0.02 mole) of p-methoxyphenylthiophanylsulfonium perchlorate and diethylamine. PMR spectrum: δ 0.93 (6H, triplet, J = 7 Hz, CH_3), 1.53 (4H, quintet, C—CH_2CH_2C), 2.42 [6H, multiplet, J = 7 Hz, $N(CH_2)_3$], 2.75 (2H, triplet, J = 7 Hz, S—CH_2), 3.72 (3H, singlet, CH_3O), and 6.75-7.25 ppm (4H, AB quartet, J = 9 Hz, p-C_6H_4). Mass spectrum, m/e (relative intensity, %): 267 (6.4), 252 (0.8), 195 (7.9), 153 (2.1), 139 (5.6), 128 (11.0), 124 (0.9), 86 (100.0), 58 (6.2).

C) A 5.6-g (0.02 mole) sample of p-hydroxyphenylthiophanylsulfonium perchlorate was dissolved in 10 ml of alcohol, and a solution of 5.16 g (0.02 mole) of dibutylamine in 5 ml of alcohol was added. The resulting mixture was refluxed for 4 h, after which the alcohol was removed by distillation and the residue was extracted with hexane to give 5.32 g of p-hydroxyphenyl 4-dibutylaminobutyl sulfide (Table 1).

D) A 0.01-mole sample of p-hydroxyphenylthiophanylsulfonium perchlorate was heated with piperidine as described in experiment A, after which the excess piperidine was removed by distillation. Extraction of the residue with ether gave 2.67 g of p-hydroxyphenyl 4-piperidinobutyl sulfide (Table 1). Mass spectrum, m/e (relative intensity, %): 265 (6.1), 181 (1.6), 140 (13.3), 139 (1.9), 125 (2.9), 98 (100.0), 84 (3.7), and 56 (2.7). The material that was not extracted by ether was dissolved in chloroform, and ether was added to precipitate piperidine perchlorate (Table 1). The reaction of p-hydroxyphenylthiophenylsulfonium perchlorate with a stoichiometric amount of piperidine in alcohol proceeded similarly (as in method C).

A 2-ml sample of 57% perchloric acid and ether were added successively to a cooled solution of 1 g of piperidine in 2 ml of alcohol, after which the mixture was worked up to give 0.25 g (11%) of piperidine perchlorate with mp 153-155°. No melting-point depression was observed for a mixture of this product with the piperidine perchlorate obtained in experiment D.

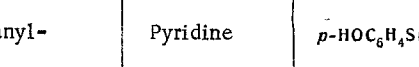
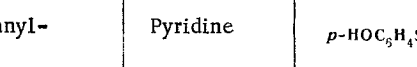
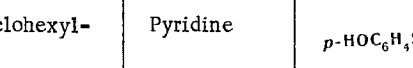
E) A solution of 5.89 g (0.02 mole) of p-methoxyphenylthiophanylsulfonium perchlorate in alcohol was heated with 3.4 g (0.04 mole) of piperidine as in experiment C to give 5.08 g of p-methoxyphenyl 4-piperidinobutyl sulfide (Table 1). PMR spectrum, δ: 1.5 (10H, multiplet, CH_2), 2.2 [6H, multiplet, $(CH_2)_3N$], 2.73 (2H, triplet, J = 7 Hz, SCH_2), 3.73 (3H, singlet, OCH_3), and 6.72-7.22 ppm (4H, AB quartet, J = 9 Hz, p-C_6H_4). Mass spectrum, m/e (relative intensity, %): 279 (9.0), 195 (2.1), 153 (1.5), 140 (23.7), 139 (4.6), 98 (100.0), and 84 (2.9).

F) A 2.94-g (0.01 mole) sample of p-hydroxyphenylthiacyclohexylsulfonium perchlorate was heated with piperidine as described in experiment D, after which the piperidine was removed by distillation, and the residue was extracted with benzene (with heating) to give p-hydroxyphenyl 5-piperidinoamyl sulfide (Table 1). The benzene-insoluble residue was dissolved in water by heating, the hot solution was treated with activated charcoal and filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from water to give p-hydroxyphenyl 5-piperidinoamyl sulfide perchlorate (Table 1). Piperidine perchlorate (0.08 g) was isolated from the mother liquor. A 0.2-g sample of the amino sulfide perchlorate was refluxed with 10 ml of piperidine for 10 h, and the mixture was worked up as described in the preceding experiment to give the free amino sulfide and piperidine perchlorate.

G) A 0.26-g (0.0006 mole) sample of p-hydroxyphenyl(2-methylthiacyclohexyl)sulfonium picrate was heated with piperidine as described in experiment D, after which the precipitated piperidine picrate was removed by filtration, and the piperidine was removed from the filtrate by distillation. The residue was extracted with benzene to give 0.08 g of the amino sulfide (Table 1).

H) The reactions of p-hydroxyphenyl- and p-methoxyphenylthiophanylsulfonium perchlorates with hexamethyleneimine and p-hydroxyphenylthiophanylsulfonium perchlorate with morpholine were carried out as described in experiment C (Table 1). Mass spectrum of p-methoxyphenyl 4-hexamethyleneiminobutyl sulfide, m/e (relative intensity, %): 293 (5.8), 195 (2.1), 154 (9.5), 153 (1.8), 139 (4.7), 112 (100.0), 98 (3.1), 84 (3.8), and 70 (2.5).

TABLE 1. Products of the Reaction of Thiacyclanylsulfonium Salts with Nitrogen Bases

Starting salt	Nitrogen base	Reaction product	mp or bp, °C (mm); n_D^{20}	Empirical formula	Found, %				Calc., %				Yield, %[a]
					C	H	N	S	C	H	N	S	
p-Hydroxyphenylthiophanyl-sulfonium chloride	Liquid NH_3	p-$HOC_6H_4S(CH_2)_4NH_2 \cdot HCl$	Viscous liquid	$C_{10}H_{15}NOS \cdot HCl$			6,0				5,0		(100)
p-Methoxyphenylthiophanyl-sulfonium perchlorate	Liquid NH_3	p-$CH_3OC_6H_4S(CH_2)_4NH_2 \cdot HClO_4$	Viscous liquid	$C_{11}H_{17}NOS \cdot HClO_4$			4,3				4,5		(100)
p-Hydroxyphenylthiophanyl-sulfonium perchlorate	Pyridine		65,5—66,5 [b]	$C_{15}H_{18}ClNO_5S$ [c]			4,2				3,9		(100)
p-Hydroxyphenylthiophanyl-sulfonium chloride	Pyridine		128—131 [d]	$C_{15}H_{18}ClNOS$ [e]			4,7				4,7		(100) 31
p-Hydroxyphenylthiacyclohexyl-sulfonium perchlorate	Pyridine		109—111 [f]	$C_{16}H_{20}ClNO_5S$ [g]	51,9	5,7	4,1	9,0	51,5	5,4	3,8	8,6	(96) 52
p-Hydroxyphenylthiophanyl-sulfonium perchlorate	Diethylamine	p-$HOC_6H_4S(CH_2)_4N(C_2H_5)_2$ (I)	208—210(6); 1,5698	$C_{14}H_{23}NOS$			6,0	12,7			5,5	12,7	(98)
p-Methoxyphenylthiophanyl-sulfonium perchlorate	Diethylamine	p-$CH_3OC_6H_4S(CH_2)_4N(C_2H_5)_2$ (II)	150—152(0,5); 1,5331	$C_{15}H_{25}NOS$			4,6	12,3			5,3	12,0	(91) 54
p-Hydroxyphenylthiophanyl-sulfonium perchlorate	Dibutylamine	p-$HOC_6H_4S(CH_2)_4N(C_4H_9)_2$ (III)	Oil	$C_{18}H_{31}NOS$	70,2	10,1	4,3	9,4	70,0	10,0	4,5	10,4	86
p-Hydroxyphenylthiophanyl-sulfonium perchlorate	Piperidine	p-$HOC_6H_4S(CH_2)_4NC_5H_{10}$ (IV) [i]	106—108 [j]	$C_{15}H_{23}NOS$	67,3	9,2	5,3	12,6	67,8	8,7	5,3	12,1	(100) 66
		Piperidine perchlorate	153 [l]	$C_5H_{11}NO_4 \cdot HClO_4$ [m]			7,1				7,6		30
p-Methoxyphenylthiophanyl-sulfonium perchlorate	Piperidine	p-$CH_3OC_6H_4S(CH_2)_4NC_5H_{10}$ [i]	191—192(2); 1,5475	$C_{16}H_{25}NOS$	67,7	8,5	4,5	11,3	68,8	9,0	5,0	11,5	(91) 83
p-Hydroxyphenylthiacyclohexyl-sulfonium perchlorate	Piperidine	p-$HOC_6H_4S(CH_2)_5NC_5H_{10}$ [i]	116—117 [j]	$C_{16}H_{25}NOS$			4,6				5,0		43
		p-$HOC_6H_4S(CH_2)_5NC_5H_{10} \cdot HClO_4$ [i]	129—130 [f]	$C_{16}H_{26}HO_5SCl$	50,8	6,9			50,7	6,9			37
p-Hydroxyphenyl(2-methylthia-cyclohexyl)sulfonium picrate	Piperidine	p-$HOC_6H_4SCH(CH_2)_4NC_5H_{10}$ (V) [i] and/or p-$HOC_6H_4S(CH_2)_4CHNC_5H_{10}$ (VI) [i]	101—102 [n]	$C_{17}H_{27}NOS$	70,0	9,2	4,8		69,7	9,2	4,8		46
p-Hydroxyphenylthiophanyl-sulfonium perchlorate	Hexamethyl-eneimine	p-$HOC_6H_4S(CH_2)_4NC_6H_{12}$ (V) [o]	216(2); 1,5756	$C_{16}H_{25}NOS$			4,9				5,0		45
p-Methoxyphenylthiophanyl-sulfonium perchlorate	Hexamethyl-eneimine	p-$CH_3OC_6H_4S(CH_2)_4NC_6H_{12}$ [o]	175—178(0,5); 1,5511	$C_{17}H_{27}NOS$	67,9	8,9	4,7		69,8	9,2	4,8		47
p-Hydroxyphenylthiophanyl-sulfonium perchlorate	Morpholine	p-$HOC_6H_4S(CH_2)_4NC_4H_8O$ (VI) [p]	96—99	$C_{14}H_{21}NO_2S$	63,0	8,2	4,9		63,0	7,9	4,9		95

a) The yield of crude product is indicated in parentheses; b) from methanol; c) found: Cl 9.5%. Calculated: Cl 9.8%; d) from alcohol—acetone (1:2); e) found: Cl 11.3%. Calculated: Cl 12.0%; f) from water; g) found: Cl 9.4%. Calculated: Cl 9.5%; h) along with the amino sulfide; i) the piperidino group is indicated by NC_5H_{10}; j) from benzene; k) from the appropriate sulfonium chloride in 68% yield; in addition, piperidine hydrochloride (84%) was isolated; l) from alcohol—ether; m) found: Cl 19.3%. Calculated: Cl 19.2%; n) from hexane; o) the hexamethyleneimino group is indicated by NC_6H_{12}; p) the morpholino group is indicated by NC_4H_8O.

TABLE 2. Amino Sulfide Derivatives

Starting compound (see Table 1)	Derivative	mp, °C	Empirical formula	Found, %					Calc., %					Yield, %
				C	H	N	S	halogen	C	H	N	S	halogen	
I	Hydrochloride[a]	110—111[b]	$C_{14}H_{23}NOS \cdot HCl$	57,8	7,6	5,4		12,4	58,0	8,3	4,8		12,3	51
	Methiodide	93—95[c]	$C_{15}H_{26}INOS$			2,8		32,0			3,5		32,2	62
	Methiodide	Viscous oil	$C_{30}H_{56}INOS$	58,0	8,7	2,3	5,6	21,4	59,5	9,3	2,3	5,3	21,0	100
II	Hydrochloride	87—88[d]	$C_{15}H_{25}NOS \cdot HCl$	59,5	8,6	4,2	10,5	11,6	59,4	8,5	4,6	10,5	11,7	72
III	Hydrochloride	125—126[d]	$C_{18}H_{32}NOS \cdot HCl$	62,9	9,6	5,0		10,2	62,5	9,3	4,1		10,3	47
IV	Hydrochloride	151—152[d]	$C_{15}H_{24}NOS \cdot HCl$	60,1	7,5	5,2		11,2	59,7	8,0	4,6		11,8	96
	Methiodide	108—109[c]	$C_{16}H_{26}INOS$			2,9		30,7			3,4		31,2	61
V	Hydrochloride	125—129[e]	$C_{16}H_{26}NOS \cdot HCl$	60,7	8,4	4,2		11,4	60,9	8,3	4,4		11,3	42
VI	Hydrochloride	148—149	$C_{14}H_{22}NO_2S \cdot HCl$	55,2	7,1	4,9		11,3	55,4	7,3	4,6		11,7	91

a) Obtained in alcohol solution; b) from alcohol—acetone; c) from alcohol—ethyl acetate; d) from acetone; e) from methanol—acetone.

Mass spectrum of p-hydroxyphenyl 4-morpholinobutyl sulfide: 267 (6.5), 181 (1.1), 142 (26.9), 139 (2.4), 125 (3.1), 100 (100.0), and 84 (5.0).

Aryl Aminoalkyl Sulfide Derivatives (Table 2). Hydrochlorides. A 3.31-g (0.0125 mole) sample of amino sulfide IV (Table 1) was dissolved in a mixture of 6 ml of acetone and 0.5 ml of alcohol, and 1.3 ml (0.0148 mole) of concentrated hydrochloric acid was added gradually. The hydrochloride was separated, washed with acetone and ether, and recrystallized. The hydrochlorides of the other amino sulfides were similarly obtained with variation of the amounts of acetone and alcohol as a function of the solubility of the amino sulfide.

Alkiodides. A 1-g (0.0038 mole) sample of amino sulfide IV was dissolved in a mixture of 3 ml of nitromethane and 1 ml of alcohol, and a solution of 0.6 g (0.0042 mole) of methyl iodide in 3 ml of nitromethane was added. The mixture was then held at room temperature for 12 h, after which it was heated at 90° for 2 h. The solvent was removed by distillation, and the residue was recrystallized. The methiodide of amino sulfide I and the ethiodide of amino sulfide I were similarly obtained.

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