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SYNTHESES AND ANTIMICROBIAL PROPERTIES OF SOME ARYL ESTERS OF METHANE- AND ETHANETHIOSULFONIC ACIDS

(Presented by Academician M. I. Kabachnik, December 29, 1959)

Aromatic esters (I) of alkanethiosulfonic acids have not hitherto been described in the literature. Meanwhile, they may be of practical interest because related compounds (II) often possess high antimicrobial activity, especially against phytopathogenic bacteria and fungi, and at the same time exhibit properties of plant-growth stimulants (^{1}).

For this reason, in the present work we decided to synthesize the first representatives of this group of compounds—aryl esters III and IV of methane- and ethanethiosulfonic acids—and to study their antimicrobial properties

$$\mathrm{Alk} - \mathrm{SO_2} - \mathrm{S} - \mathrm{Ar}, \qquad \mathrm{Alk} - \mathrm{SO_2} - \mathrm{S} - \mathrm{Alk}',$$

$$(\mathrm{I}) \qquad (\mathrm{II})$$

$$\mathrm{CH_3} - \mathrm{SO_2} - \mathrm{S} - \langle\ - \mathrm{X}, \qquad \mathrm{C_2H_5} - \mathrm{SO_2} - \mathrm{S} - \langle\ - \mathrm{X},$$

$$(\mathrm{III}) \qquad (\mathrm{IV})$$

$$\text{where } X = \mathrm{H},\ \mathrm{Cl},\ \mathrm{CH_3O},\ \mathrm{NO_2}.$$

The preparation of esters (I) was carried out by us through the reaction of sodium salts of alkanesulfinic acids with sulfenyl chlorides according to the reaction

$$\mathrm{Alk} - \mathrm{SO_2Na} + \mathrm{X} - \mathrm{C_6H_4} - \mathrm{S} - \mathrm{Cl} \rightarrow \mathrm{Alk} - \mathrm{SO_2} - \mathrm{S} - \mathrm{C_6H_4} - \mathrm{X} + \mathrm{NaCl}. \tag{1}$$

The sulfinates required for this were prepared by the known method (^{2}), by converting the corresponding sulfochlorides, under the action of zinc dust, first into zinc salts and then, by treating them with sodium carbonate, into sodium salts. The latter were thoroughly dried in vacuo before use; in the case of hygroscopic sodium methanesulfinate, the necessary precautions were taken against the ingress of moisture into the reaction mixture during preparation of the esters (grinding the salt under a layer of absolute carbon tetrachloride, etc.). The use of silver salts of sulfinic acids instead of the sodium salts did not give any noticeable effect, especially if one takes into account a certain loss of products when converting the sodium salts into silver salts; for this reason we abandoned the use of the latter immediately after the first experiments.

Arenesulfenyl chlorides were prepared in the usual way ($^{3-5}$)—by the action of gaseous chlorine on solutions of thiophenols or disulfides in absolute ether or carbon tetrachloride. When thiophenols were used for this purpose, a solution of the latter in carbon tetrachloride was added, with cooling, to carbon tetrachloride saturated with an equimolar amount of chlorine, followed by removal of the solvent and distillation of the residue in vacuo.

Benzenesulfenyl chloride and *p*-chlorobenzenesulfenyl chloride were isolated by us in pure form; *p*-methoxybenzenesulfenyl chloride was obtained by an analogous procedure as a reddish-brown oily liquid, not distillable

···distilled in vacuo at a residual pressure of 10^{-2} mm, which compelled us to use it without additional purification, immediately after distillation of carbon tetrachloride in vacuo. *p*-Nitrobenzenesulfenyl chloride was obtained by the action of gaseous chlorine on an ethereal suspension of p,p'-dinitrodiphenyl disulfide, with subsequent removal of excess chlorine and isolation of the crystalline product; this sulfenyl chloride likewise was not subjected to additional purification before use.

Our attempts to obtain *p*-acetylaminobenzenesulfenyl chloride have so far not been successful: the action of gaseous chlorine on p,p'-diacetyldiaminodiphenyl disulfide, as well as the action of chlorine on *p*-acetylaminothiophenol, gives insignificant yields of a highly contaminated sulfenyl chloride; use of the latter for the synthesis of esters does not subsequently permit isolation of the final products in pure form. As is known (^{6}), the action of bromine on the same disulfide gives similar results. The reaction for obtaining the esters was carried out in absolute benzene or carbon tetrachloride with simultaneous charging of the sulfinate and the sulfenyl chloride. At first the reaction often proceeded very vigorously, with considerable evolution of heat; the colored solution rapidly became decolorized. Then the reaction mass was heated on a water bath for 2–3 h and filtered from the precipitated salts. The solvent was distilled off in vacuo, and the residue was crystallized by cooling with an ice-salt mixture and purified by recrystallization from alcohol to constant melting point. Excessive, even slight, overheating, as well as prolonged heating both during distillation of the solvent from the sulfenyl chlorides and during its removal after formation of the final product, sharply affected the purity of the latter and often led to noncrystallizing residues, evidently owing to partial decomposition of the sulfenyl chlorides. When an excess of sulfinates relative to the sulfenyl chlorides was used (1.3 : 1.0 in moles), the yields of esters and their purity increased noticeably. The latter is especially important when the sulfenyl chlorides were not used in pure form, since the need for repeated purification of the final products sharply reduced their yields. The esters we obtained are presented in Table 1.

Table 1

Aryl esters of methanethiosulfonic and ethanethiosulfonic acids Alk—SO_2—S—Ar

Alkyl	Aryl	M.p., °C	Sulfur content, % calculated	Sulfur content, % found	Yields* from theory, %
CH_3	C_6H_5	85–86	34.06	34.12; 34.18	56.7
CH_3	*p*-ClC_6H_4	102–103	28.80	28.62; 28.96	46.1
CH_3	*p*-$CH_3OC_6H_4$	78–79	29.38	29.33; 29.46	50.0
CH_3	*p*-$NO_2C_6H_4$	148–149	27.49	27.35; 27.45	48.3
C_2H_5	C_6H_5	52	31.70	31.94; 31.90	40.9
C_2H_5	*p*-ClC_6H_4	55–56	27.09	27.15; 27.21	49.3
C_2H_5	*p*-$CH_3OC_6H_4$	38–39	27.60	27.45; 27.58	52.5
C_2H_5	*p*-$NO_2C_6H_4$	85	25.93	25.80	46.8

* The yields of the esters may be increased by extracting additional amounts of these compounds from the mother liquors.

All these compounds are colorless crystalline substances, and only the *p*-nitrophenyl esters have a pale-yellow color. They are readily soluble in benzene, alcohol, ether, acetone, and other organic solvents, and are very poorly soluble in water.

The results of the study of the antimicrobial activity of these compounds, presented in Table 2, showed*, that aryl esters of methane- and ethane–

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* The antimicrobial properties of the esters of thiosulfonic acids were studied by the D. K. Zabolotny Institute of Microbiology, Academy of Sciences of the Ukrainian SSR; we express our gratitude to V. G. Drobotko, B. E. Aizeman, and S. I. Zelenukhe for carrying out these studies.

thiosulfonic acids differ in their antimicrobial properties from the esters (II): they do not act on gram-negative bacteria, are somewhat more active than alkyl esters of alkanethiosulfonic acids with respect to gram-positive bacteria (*Staphylococcus aureus*), and are inferior to them in their action on *Mycobacterium* B_5. With respect to various fungi, aryl esters of methane- and ethanethiosulfonic acids differ little from the esters (II): they are not inferior, and more often surpass the latter, in their action on *Penicillium* and *Mucor*, show higher activity with respect to *Fusarium* and *Saccar. ellipsoid*, and exert a weaker action on *Aspergillus* and, in part, *Rhizopus*.

It should be noted that the esters of methanethiosulfonic acid presented in Table 2 are less active than the analogous esters of ethanethiosulfonic acid, both with respect to bacteria and to fungi.

Table 2

Antimicrobial activity of aryl esters of methane- and ethanethiosulfonic acids
(activity in dilutions in thousands*) Alk—SO_2—S—Ar

Alkyl	Aryl	*Staphylococcus aureus*	*B. coli*	*Mycobacterium* B_5	*Penicillium*	*Aspergillus*	*Fusarium*	*Rhizopus*	*Mucor*	*Saccar. ellipsoid*	*Candida albicans*
CH_3	C_6H_5	–	–	–	–	–	10	–	–	50	–
CH_3	*n*-ClC_6H_4	500	–	10	50	10	250	10	50	500	250
CH_3	*n*-$CH_3OC_6H_4$	40	–	50	50	–	250	50	10	50	50
CH_3	*n*-$NO_2C_6H_4$	500	–	–	10	–	50	–	50	500	500
C_2H_5	C_6H_5	500	–	50	50	50	500	10	10	50	50
C_2H_5	*n*-ClC_6H_4	500	–	50	250	50	250	50	250	500	500
C_2H_5	*n*-$CH_3OC_6H_4$	50	–	50	250	10	250	10	50	250	50
C_2H_5	*n*-$NO_2C_6H_4$	250	–	10	10	–	50	–	50	500	500

* A dash denotes absence of activity.

The phenyl ester of methanethiosulfonic acid generally exhibits no antibacterial action against the tested species of bacteria and is almost inactive against the tested species of fungi.

Of greater interest are aryl esters of methane- and ethanethiosulfonic acids in terms of their action on phytopathogenic fungi.

A study of the fungicidal activity of these compounds*, carried out by the Ya. V. Samoilov Scientific Institute for Fertilizers and Insectofungicides (NIUIF), showed that some of them are highly active fungicides and, in *in vitro* experiments, exert a fungistatic action on many fungi, in a number of cases surpassing such fungicides as zineb and captan (at the same concentrations), and at a higher concentration giving better results than figon.

For this reason we believe that aryl esters of alkanethiosulfonic acids are of great interest for further investigations; the synthesis and study of the antimicrobial activity of these compounds are being continued by us at the present time.

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Note: Figure translations are in progress. See original paper for figures.

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