

solution. After standing for the time specified, Solution 1b contained less of the anthrahydroquinone and more of the anthranol. The change in titer of the latter is approximately half that of the former.

A summary of the average values found for the normal potentials, or the potentials of the half-oxidized solutions against a hydrogen electrode in the same buffer solution at 25°, is given in Table III.

TABLE III
POTENTIALS (E_0) OF THE SYSTEMS FROM α -AROYLANTHRAQUINONES AND THE CORRESPONDING RADICALS

Aryl group	Quinone, v.	Radical, v.
Phenyl-	0.182	0.360
<i>m</i> -Xylyl-	.178	.361
<i>p</i> -Anisyl-	.178	.356

Summary

The free anthroxyl radicals discovered by R. Scholl form, with their reductants, fairly stable oxidation-reduction systems of definite, if not very accurately determinable, potential. In dilute acidic solution the reductant of the radical is formed by the intramolecular condensation of the corresponding α -aroylanthrahydroquinone.

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THE PREPARATION AND GERMICIDAL PROPERTIES OF PARA-HYDROXYPHENYL ALKYL SULFIDES

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RECEIVED JUNE 14, 1932

PUBLISHED OCTOBER 5, 1932

Although many investigations of the germicidal properties of alkylated phenolic compounds¹ have been made, the available systematic information demonstrating the influence of alkyl groups not directly attached to the aromatic nucleus has been limited to the recent^{1,2} work on the alkoxyphenols. The present communication describes a study of a series of *p*-hydroxyphenyl *n*-alkyl sulfides, the alkyl group varying from methyl to *n*-hexyl. Since it has been shown by other workers³ that the hydroxy-

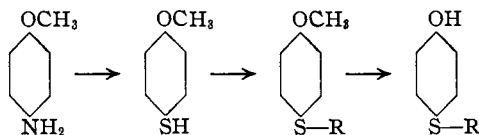
¹ Only some of the more recent articles can be listed here: (a) Johnson and Lane, *THIS JOURNAL*, **43**, 348 (1921); (b) Dohme, Cox and Miller, *ibid.*, **48**, 1688 (1926); (c) Talbot and Adams, *ibid.*, **49**, 2040 (1927); (d) Klarmann, *ibid.*, **48**, 791, 2358 (1926); (e) Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930); (f) Read and Miller, *THIS JOURNAL*, **54**, 1195 (1932).

² Klarmann, Gatyas and Shternov, *ibid.*, **53**, 3397 (1931); **54**, 298, 1204 (1932).

³ Hilbert and Johnson, *ibid.*, **51**, 1526 (1929); Dunning, Dunning and Drake, *ibid.*, **53**, 3466 (1931); Klarmann, Gates and Shternov, *ibid.*, **54**, 1204 (1932).

diphenyl sulfides are more potent germicides than the corresponding hydroxydiphenyl ethers, it was thought that the hydroxyphenyl alkyl sulfides would be more bactericidal than the corresponding oxygen compounds. The results have substantiated this surmise.

There are several procedures by which *p*-hydroxyphenyl alkyl sulfides have been synthesized.⁴ The method developed for this work is outlined below.



The last step is of interest as it illustrates the relative inertness of the sulfide linkage toward hydrobromic acid. No trace of a thiol was ever noted among the reaction products. In two cases *p*-ethoxyphenyl alkyl sulfides were deethylated but they gave somewhat lower yields of the desired phenols than the methoxy derivatives. An attempt to prepare *p*-hydroxyphenyl *n*-butyl sulfide by the action of diazotized *p*-amino-phenol upon the sodium salt of butanethiol-1 was not successful.

Since the *p*-alkoxyphenyl alkyl sulfides were prepared in a pure state, a study of the value for the atomic refraction of sulfur in these compounds was made. It has been shown recently⁵ that the value for thiol sulfur recommended by Price and Twiss⁶ gives good results for two series of aliphatic thiols. The corresponding value for sulfide sulfur (7.97 for Na_D) is in only fair agreement with the refractive index for phenyl methyl sulfide and the presence of a methoxy group results in an exaltation which increases somewhat irregularly with the size of the alkyl group attached to the sulfur. These results are shown in Table I together with the boiling points of the samples used in the determinations.

TABLE I

Compound	B. p., °C.	mm.	d_4^{25}	n_D^{25}	MR_D Found	Calcd.	EM_D
$C_6H_5SCH_3$	58–60	6	1.0533	1.5832	39.40 ⁷	38.85	0.55
<i>p</i> - $CH_3OC_6H_4SH$	89–90	5	1.1313	1.5801	41.23	39.46	1.77
<i>p</i> - $CH_3OC_6H_4SCH_3$	99	4	1.1069	1.5764	46.12	44.16	1.96
<i>p</i> - $CH_3OC_6H_4SC_2H_5$	103	5	1.0674	1.5600	50.95	48.58	2.37
<i>p</i> - $CH_3OC_6H_4SC_3H_7$	110	5	1.0424	1.5545	56.07	53.00	3.07
<i>p</i> - $CH_3OC_6H_4SC_4H_9$	120	5	1.0303	1.5445	60.17	57.42	2.75
<i>p</i> - $CH_3OC_6H_4SC_5H_{11}$	127	5	1.0149	1.5380	64.64	61.84	2.80
<i>p</i> - $CH_3OC_6H_4SC_6H_{13}$	142	5	0.9975	1.5315	69.61	66.26	3.35
<i>p</i> - $C_2H_5OC_6H_4SCH_3$	98–100	5	1.0693	1.5618	52.58	48.58	4.00

⁴ Leuckart, *J. prakt. Chem.*, [2] **41**, 192 (1890); Zincke and Ebel, *Ber.*, **47**, 1105 (1914).

⁵ Ellis and Reid, *THIS JOURNAL*, **54**, 1674 (1932).

⁶ Price and Twiss, *J. Chem. Soc.*, **101**, 1263 (1912).

The effect of the ethoxy group is very pronounced, the exaltation corresponding to a 50% increase in the value for the atomic refraction of sulfur. A study of the exaltations caused by a number of substituents in anisole and phenyl methyl sulfide has previously shown⁷ the great susceptibility of sulfur to influences which cause optical exaltation.

The germicidal properties⁸ of the *p*-hydroxyphenyl alkyl sulfides are at a maximum toward *B. typhosus* with the *n*-butyl and *n*-amyl compounds. The *n*-hexyl compound is probably the most effective in this series toward *Staph. aureus*, since its phenol coefficient is not much higher than that of the *n*-amyl derivative. In Table II is shown a summary of the results obtained together with the values for the corresponding oxygen compounds.⁹

TABLE II

Alkyl group	<i>B. typhosus</i>		<i>Staph. aureus</i>	
	Sulfide	Ether	Sulfide	Ether
Methyl	5	1.0	4	0.8
Ethyl	12	1.5	12	1.5
<i>n</i> -Propyl	25	5.4	25	4.1
<i>n</i> -Butyl	75	14	60	9.3
<i>n</i> -Amyl	75	29	150	30
<i>n</i> -Hexyl	<40	18	200	100

The determinations of the phenol coefficients were made by diluting with water a solution of the sulfide in 20% alcohol (except *n*-hexyl where a 50% alcohol solution was used) to obtain the desired concentrations. The tests using *B. typhosus* were made at 20° in accordance with the Hygienic Laboratory method while those with *Staph. aureus* were made at 37.5°. The *n*-hexyl compound was too insoluble to determine its phenol coefficient toward *B. typhosus* except to note its ineffectiveness at a concentration corresponding to the value 40.

The study of various types of hydroxyphenyl alkyl sulfides is being continued in this Laboratory.

Experimental

***p*-Methoxythiophenol.**—This was first prepared by Gattermann¹⁰ by reduction of the corresponding sulfinic acid. In the present work it was prepared from *p*-anisidine by the Leuckart¹¹ reaction. The following conditions were found to be the most satisfactory. In a 5-liter 3-necked flask equipped with a mechanical stirrer, dropping funnel and outlet tube to the hood, was placed a solution of 300 g. (1.9 moles) of potassium ethyl xanthate dissolved in 700 cc. of water. To this solution, kept at 70 to 80°, was

⁷ The value 39.44 is given by Brand and Kranz, *J. prakt. Chem.*, [2] **115**, 143 (1927).

⁸ We are very much indebted to Dr. Oliver Kamm, scientific director, and Mr. H. C. Hamilton, pharmacologist, of Parke, Davis and Company for permission to include a report of the results of the pharmacological study of these compounds made by them.

⁹ Klarmann, Gates and Shternov, *THIS JOURNAL*, **54**, 298 (1932).

¹⁰ Gattermann, *Ber.*, **32**, 1147 (1899).

¹¹ Leuckart, *J. prakt. Chem.*, [2] **41**, 186 (1890).

added slowly with vigorous stirring a cold solution containing 123 g. (1 mole) of diazotized *p*-anisidine to which had been added enough sodium acetate to neutralize the free acid. Stirring and heating were continued for about an hour after the addition of the diazonium solution to complete the decomposition of the intermediate diazonium ethyl xanthate. The dark oil was removed from the cooled solution and the aqueous layer extracted with ether, the product obtained being combined with that first removed; this material was then refluxed for three hours with a solution of 115 g. of potassium hydroxide in 2 liters of 95% ethyl alcohol to which had been added 20 g. of glucose. The alcohol was removed by distillation until the residual volume was about 300 cc. This was acidified with cold dilute sulfuric acid, a few grams of zinc dust added, and the oily thiol removed by distillation with steam. The distillate was extracted with ether, the ether dried over calcium chloride, and the oil remaining after distillation of the ether was distilled under reduced pressure. The yield was 100 to 110 g. or 71 to 79% of the calculated amount of material boiling at 88–90° at 5 mm. pressure. The physical constants in Table I were determined on a redistilled sample boiling at 89–90° at 5 mm. pressure. The brown amorphous lead salt was prepared and analyzed.

Anal. Calcd. for $C_{14}H_{14}O_2S_2Pb$: Pb, 42.68. Found: Pb, 42.47.

p-Ethoxythiophenol.—This has been made by Law and Johnson¹² by the Leuckart reaction. Following the procedure outlined for *p*-methoxythiophenol a 76% yield of material boiling at 102–104° under 4 mm. was obtained.

p-Alkoxyphenyl *n*-Alkyl Sulfides.—The *p*-methoxyphenyl methyl sulfide¹³ and *p*-ethoxyphenyl ethyl sulfide¹⁴ have been prepared previously. The methyl and ethyl aryl sulfides were prepared here by the method of Gilman and Beaber¹⁵ from the dialkyl sulfates and the thiol. For the other alkyl compounds the bromides were used. The following experiment is typical.

Preparation of *p*-Methoxyphenyl *n*-Propyl Sulfide.—To a solution of sodium ethylate made by dissolving 8 g. (0.35 mole) of sodium in 150 cc. of absolute ethyl alcohol, was added 42 g. (0.3 mole) of *p*-methoxythiophenol and 40 g. (excess) of *n*-propyl bromide. The mixture was refluxed for an hour, the alcohol removed by distillation and the residue poured into water. The yellow oil was extracted with ether, dried with sodium sulfate and distilled under reduced pressure. In Table III are given the yields obtained in the preparations and the boiling points and analyses of the sulfides prepared. The densities and refractive indices have been given in Table I.

TABLE III

Compound	Yield, %	B. p., °C.	Pressure, mm.	Sulfur, %	
				Calcd.	Found
<i>p</i> -CH ₃ OC ₆ H ₄ SCH ₃	90	99–100, m. p. 22–23	4
<i>p</i> -CH ₃ OC ₆ H ₄ SC ₂ H ₅	93	103	5	19.06	19.33
<i>p</i> -CH ₃ OC ₆ H ₄ SC ₃ H ₇	77	110–111	5	17.59	17.72
<i>p</i> -CH ₃ OC ₆ H ₄ SC ₄ H ₉	87	119–122	5	16.33	16.41
<i>p</i> -CH ₃ OC ₆ H ₄ SC ₅ H ₁₁	81	124–127	5	15.25	15.56
<i>p</i> -CH ₃ OC ₆ H ₄ SC ₆ H ₁₃	87	138–141	5	14.29	14.19
<i>p</i> -C ₂ H ₅ OC ₆ H ₄ SCH ₃	90	98–100, m. p. 19–20	5	19.06	19.30
<i>p</i> -C ₂ H ₅ OC ₆ H ₄ SC ₂ H ₅	96	110–112	6

¹² Law and Johnson, *THIS JOURNAL*, **52**, 3625 (1930).

¹³ Gattermann, *Ber.*, **32**, 1147 (1899).

¹⁴ Kehrman and Sava, *ibid.*, **45**, 2895 (1912).

¹⁵ Gilman and Beaber, *THIS JOURNAL*, **47**, 1449 (1925).

The boiling points of the compounds when refractionated have been given in Table I. Three of the sulfides were converted into the corresponding sulfones by oxidation with 30% hydrogen peroxide in glacial acetic acid solution.¹⁵ *p*-Methoxyphenyl methyl sulfone was recrystallized from hot water and melted at 119–120°.

Anal. Calcd. for C₈H₁₀O₃S: S, 17.22. Found: S, 17.23.

p-Methoxyphenyl ethyl sulfone, crystallized from dilute alcohol, melted at 55–56°.

Anal. Calcd. for C₉H₁₂O₃S: S, 16.01. Found: S, 16.18.

p-Ethoxyphenyl methyl sulfone crystallized from hot water in glistening white flakes which melted at 89–89.5°.

Anal. Calcd. for C₉H₁₂O₃S: S, 16.01. Found: S, 16.34.

Oxidation of *p*-ethoxyphenyl ethyl sulfide gave an oily material. Since the sulfones were prepared as convenient derivatives and this one was not suitable for identification purposes it was not further studied.

***p*-Hydroxyphenyl Alkyl Sulfides.**—The alkoxy compounds were all dealkylated by a procedure based in part upon the methods used by Stoermer¹⁶ and Semmler.¹⁷ Details are given for the preparation of *p*-hydroxyphenyl methyl sulfide. The results for the whole series are given in tabular form in Table IV.

In a round-bottomed flask attached to a reflux condenser and supplied with an inlet tube for carbon dioxide were placed 5 g. of *p*-methoxyphenyl methyl sulfide, 40 cc. of glacial acetic acid and 15 cc. of 48% hydrobromic acid. A slow stream of carbon dioxide was passed through the mixture while it was heated at 120–130° in an oil-bath for three and one-half hours. The reaction mixture was poured onto ice, the acid neutralized with sodium carbonate and the phenol extracted with ether. The product was treated with sodium hydroxide to separate the phenol from any unchanged material, the alkaline solution acidified and the precipitate twice crystallized from petroleum ether (b. p. 60–90°). Included in Table IV are the approximate solubilities of the sulfides in 20% ethyl alcohol solutions.

TABLE IV

<i>p</i> -Hydroxyphenyl <i>n</i> -alkyl sulfide	Yield, %	M. p., °C. corr.	Sulfur, %		Soly. in 20% g./100 cc.
			Calcd.	Found	
Methyl ¹⁸	55	83–84	22.87	23.00	1.0 (25°)
Ethyl ¹⁹	59	39–41	0.4 (26°)
<i>n</i> -Propyl	54	33–33.5	19.06	19.23	.15 (25°)
<i>n</i> -Butyl	37	36–37	17.59	17.81	.1 (26°)
<i>n</i> -Amyl	42	55–56	16.34	16.54	.05 (30°)
<i>n</i> -Hexyl	26	58–59	15.26	15.35	.013 (25°)

Summary

A considerable number of sulfides have been prepared by alkylation of *p*-methoxy- and *p*-ethoxythiophenol. The atomic refraction of sulfur in these compounds is abnormally great.

A series of *p*-hydroxyphenyl alkyl sulfides has been prepared and the germicidal properties of these compounds are reported.

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¹⁶ Stoermer, *Ber.*, **41**, 321 (1908).

¹⁷ Semmler, *ibid.*, **41**, 1773 (1908).

¹⁸ Zincke and Ebel, *Ber.*, **47**, 1105 (1914).

¹⁹ This has been previously prepared by Leuckart, *Chem. Centr.*, [II] 1, 758 (1890), by alkylation of *p*-hydroxythiophenol.