[CONTRIBUTION FROM THE LABORATORIES OF SHARP AND DOHME, INC.]

Hydroxyphenyl Alkyl Sulfides[1]

BY ELLIS MILLER AND R. R. READ

In their study of the antiseptic properties of phenolic sulfur combinations, Hilbert and Johnson[2] discovered that *p*-hydroxydiphenyl sulfide possessed greater germicidal power than was then shown by the most active members of the alkylated phenol family. Since this unusual activity appeared to be due largely to the sulfur linkage, it was felt by the authors that even more striking results might be obtained by substituting an alkyl group for one of the phenyl groups in this compound. Accordingly, they undertook the synthesis of a series of hydroxy-phenyl alkyl sulfides of which a number are described in this paper.

Experimental

The procedure first used was an adaptation of the method of Hilbert and Johnson. It was found that diazotized phenetidine would couple with mercaptans as readily as with thiophenol. However, in order to simplify the process and, especially, to eliminate the dealkylation step, use was made of the Leuckart[3] reaction, which depends upon the greater reactivity of the sulfhydryl group in thiohydroquinone as compared with the hydroxyl group. Thiohydroquinone is prepared by coupling diazotized *p*-aminophenol with ethyl potassium xanthate. Leuckart prepared *p*-hydroxyphenyl ethyl sulfide by converting thiohydroquinone into the lead salt through lead acetate and heating it in alcoholic suspension with ethyl iodide. The authors found, in preparing the other members of the series, that the mono-sodium salt of thiohydroquinone in methyl alcohol solution was even more effective than the lead salt.

Since the methods of preparation are uniformly applicable to any member of the series, only one example, that of *p*-hydroxyphenyl butyl sulfide, will be given. The other members thus prepared, together with their physical constants and analyses, are shown in the accompanying table.

Preparation of Thiohydroquinone.—110 grams of *p*-aminophenol (1.0 mole) was dissolved in an excess of 10% hydrochloric acid (2.25 moles). The solution was cooled below 15° and was diazotized by the gradual addition of 70 g. of sodium nitrite (1.0 mole), the temperature being maintained at 15 to 20° by means of ice.

The diazo solution was then run slowly beneath the surface of a hot solution of 224 g. of potassium ethyl xanthate (1.4 moles) in 650 g. of water, the reaction mixture being stirred vigorously and kept at 70 to 75° to ensure complete decomposition of the intermediate diazo combination. When all the diazo was in, the temperature was raised to 90° and maintained for a half hour. The xanthate ester was then decomposed by adding 160 g. of solid sodium hydroxide (4 moles) and refluxing for several hours, the mixture being then strongly acidified with an excess of 50% sulfuric acid and further refluxed in the presence of zinc and benzene in order to reduce any disulfide which may have been formed. The crude thiohydroquinone was separated as an oil, washed with dilute hydrochloric acid and water, and distilled *in vacuo*. There was obtained 61 g. of a clear colorless liquid, boiling at 133–137° (11 mm.).

(1) *Cf.* Miller and Read, THIS JOURNAL, **54**, 4113 (1932).
(2) Hilbert and Johnson, *ibid.*, **51**, 1526 (1929).
(3) Leuckart, *J. prakt. Chem.*, [2] **41**, 193 (1890).

TABLE I

STRUCTURAL, PHYSICAL AND ANALYTICAL DATA

A number of chain-substituted derivatives of hydroxyphenyl alkyl sulfides have been prepared and will be described later.

Side chain on phenol	Position	Phenol coefficient[a]	M. p., °C.	B. p., °C.	Analyses, % S Calcd.	Found
—SCH_3	*p*	8	...	113 (6 mm.)		
—SCH_2CH_3[b]	*p*	10	41	153–155 (13 mm.)	...	...
—$SCH_2CH_2CH_3$	*p*	36	37	150–153 (5–6 mm.)	19.6	18.93
—$SCH_2CH_2CH_2CH_3$	*p*	77	49–50	166–168 (7 mm.)	17.6	17.4
—$SCH_2CH_2CH_2CH_2CH_3$[c]	*p*	120	59	175–180 (8–10 mm.) 164–168 (3–4 mm)	16.35	16.79
—$SCH_2CH_2CH_2CH_2CH_2CH_3$	*p*	0[d] 230[e]	60	194–196 (16 mm.) 178–180 (5 mm.)	15.2	15.64
—$SCH_2C_6H_5$	*p*	0[d] <20[e]	104	220–225 (15 mm.)	14.8	14.79
—$SCH(CH_3)_2$	*p*	20	...	150–152 (13 mm.)	19.1	19.38
—$SCH_2CH(CH_3)_2$	*p*	61	...	159–162 (10 mm.)	17.6	17.79
—$SCH_2CH_2CH(CH_3)_2$	*p*	30	...	150–152 (3 mm.)	16.35	16.44
—$SCH_2CH_2CH_2CH_3$	*o*	25	...	110–112 (5 mm.)	17.6	17.91
—$SCH_2CH_2CH_2CH_3$	*m*	40	...	127–140 (4 mm.)	17.6	17.1

[a] Phenol coefficients by the Hygienic Laboratory method, 20°, *Staph. aureus*.

[b] This product was reported by Leuckart, Ref. 3. No analysis was made, since its melting point checked that given in the literature.

[c] This product was recently reported by Moness, Braker and Christiansen [*J. Am. Pharm. Assoc.*, **21**, 565 (1932)], who describe it as an oil boiling at 123–130° (2–3 mm.).

[d] The coefficient measured by the usual procedure was 0, *i. e.*, a saturated solution was inert.

[e] When these products were dissolved 1:1000 in *N*/100 sodium hydroxide and further dilutions made with water, the values 230 and 20 were obtained. The solubility of the *n*-hexyl sulfide is apparently less than 1:10,000 in water.

I. ***p*-Hydroxyphenyl Butyl Sulfide by the Thiohydroquinone Method.**—Twenty grams of sodium hydroxide (0.5 mole) was partially dissolved in 50 g. of methyl alcohol and to this added a solution of 58.3 g. of thiohydroquinone (0.55 mole) in 50 g. of methyl alcohol. The mixture was stirred while 68 g. of *n*-butyl bromide (0.5 mole) was being added during the course of fifteen minutes. Reaction set in at once and proceeded vigorously with evolution of heat and formation of a voluminous precipitate of sodium bromide. The mass was refluxed for about an hour, allowed to cool and filtered. The filtrate was distilled to remove methyl alcohol, the residual oil washed with water, extracted with benzene and distilled *in vacuo*. A major fraction of *p*-hydroxyphenyl butyl sulfide was obtained, boiling at 165–8° (7 mm.). It solidified on standing to a white crystalline mass which was recrystallized from ligroin and melted at 49–50°. The yield was practically theoretical.

II. *p*-Hydroxyphenyl Butyl Sulfide by the Mercaptan Method.—68.5 grams of *p*-phenetidine (0.5 mole) was dissolved in an excess of 10% hydrochloric acid (1.25 moles); the solution was cooled below 15° and diazotized by the gradual addition of 35 g. of sodium nitrite (0.5 mole), the temperature being maintained at 15–20° by means of ice.

The diazo solution was then run slowly beneath the surface of a hot solution of 49.5 g. of *n*-butyl mercaptan (0.55 mole) in 400 g. of 20% caustic soda, care being taken to

stir the mixture vigorously and to maintain the temperature at 70–75°. When all the diazo was in, the temperature was raised to 90° and maintained until no further evolution of nitrogen could be observed. The solution was then allowed to cool down to room temperature and acidified with concentrated hydrochloric acid. A heavy black oil separated. The oil was washed with dilute hydrochloric acid and with water and then distilled *in vacuo*, yielding an intermediate product—*p*-ethoxyphenyl butyl sulfide (b. p. 150–60° (12 mm.)). This ether was de-ethylated by refluxing at 75–85° for six hours with an excess (3 moles) of 20% hydrobromic acid in glacial acetic acid and the excess hydrobromic: acetic acid mixture was removed by vacuum distillation. Ester present in the residual oil was hydrolyzed by refluxing with 10% caustic soda dissolved in 25% alcohol and the alcohol distilled off, leaving in solution the sodium salt of *p*-hydroxyphenyl butyl sulfide. This solution was extracted a number of times with benzene to remove any unchanged ether and the aqueous solution acidified with hydrochloric acid. The oil which separated was taken up with benzene, washed with water and distilled *in vacuo*. A white crystalline product resulted similar in all respects to the *p*-hydroxyphenyl butyl sulfide obtained by the first method.

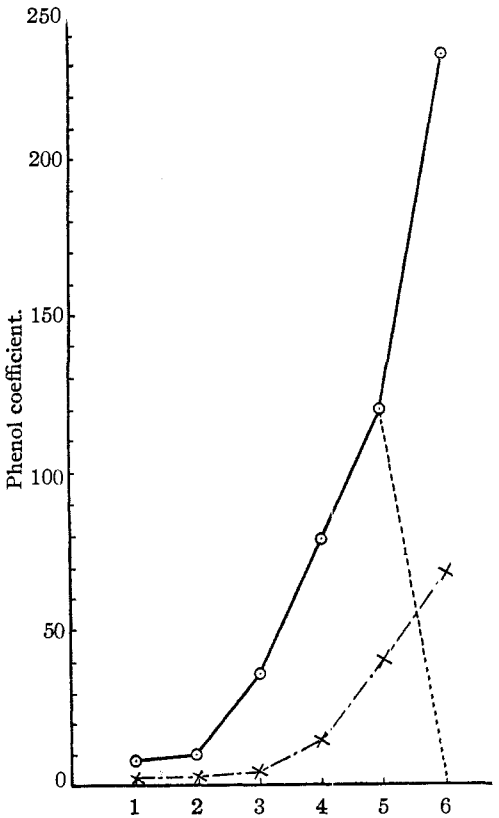

Fig. 1.—Curve ——, bactericidal activity of an homologous series of *p*-hydroxyphenyl *n*-alkyl sulfides. In the case of the hexyl derivative, it is necessary to use *N*/100 alkali, instead of water, to bring it into solution; otherwise no activity is observed, as is indicated by the broken line of the curve. Curve — · — · —, bactericidal activity of a corresponding series of *p*-hydroxyphenyl *n*-alkyl oxides. The oxygen linkage is thus seen to be far less effective than sulfur in augmenting germicidal activity.

In the foregoing examples, the *n*-butyl bromide of Example I may be replaced by any other alkyl halide and the *n*-butyl mercaptan of Example II may be replaced by any other alkyl mercaptan to give the corresponding *p*-hydroxyphenyl alkyl sulfide. Aralkyl halides and mercaptans may also be used to produce the corresponding products.

Preliminary values for the germicidal activity of this series indicates that, except for a higher level of activity, the same relation holds for thioalkyl phenols as for alkyl phenols, namely, that the phenol coefficient increases

with increase in the length of the side chain; and that the normal chain compound is more active than the corresponding branched chain derivatives. They differ, however, in the effect of position isomerism, as shown by the three isomeric hydroxyphenyl butyl sulfides. In marked contrast, the three isomeric butylphenols[4] show no variation whatever.

This phase of the subject will be dealt with more fully in a later paper.

Summary

1. A series of hydroxyphenyl alkyl sulfides has been prepared.

2. A preliminary bactericidal study of these compounds has been made, which indicates that they are more powerful than corresponding alkyl phenols.

3. The investigation of phenol alkyl sulfides is being continued in this Laboratory.

(4) Read and Miller, THIS JOURNAL, **54**, 1196 (1932).

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Capric Acid from the Seed Fat of the California Bay Tree

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In 1882 Stillman and O'Neill[1a] reported the isolation of an eleven carbon acid, which they called "umbellulic acid," from the seed fat of the California laurel or bay tree (*Umbellularia californica*). Lewkowitsch[2] states that "umbellulic acid" is really lauric acid, but the only other reference to work on this fat that we have been able to find is a further note by Stillman and O'Neill[1b] stating that their previous work was in error and that they were dealing with a mixture of fatty acids, one of which was lauric acid.

Because their original analyses indicated an eleven carbon acid, it seemed likely to us that they were dealing with a mixture of capric and lauric acids. Accordingly a quantity of the seeds was collected, shelled and ground through a food chopper, and the fat extracted with hot carbon tetrachloride. On evaporating the solvent, the fat to the extent of 58.5% of the ground nuts was obtained, a yield almost identical with the 59% previously reported.[1a] The physical and chemical constants of the fat were as follows: m. p. 28–30°; saponification number, 275.1; unsaponifiable material, 2.1%; iodine number, 5.7; acid number, 2.8. The fat showed no optical rotation in chloroform solution.

The methyl esters of the fatty acids were prepared by alcoholysis of 530 g. of fat and separated by four fractional distillations at a pressure of 17.5 mm. using a lagged 30-cm. column of the Vigreux type. There were obtained two main fractions boiling at 119–122° and 145–147°, which weighed 133 g. (28%) and 256 g. (54%), respectively. Saponification equivalents of 187 and 213 indicated that they consisted of pure methyl caprate and pure methyl laurate. The remainder of the material, 84 g. (18%), was almost uniformly distributed among eight other fractions distilling from below 115° to above 153°.

(1) (a) Stillman and O'Neill, *Am. Chem. J.*, **4**, 206 (1882); (b) *ibid.*, **28**, 327 (1902).

(2) Lewkowitsch, "Oils, Fats and Waxes," 6th ed., 1921, Vol. I, p. 158.