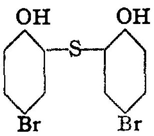
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GIVAUDAN-DELAWANNA, INC.]

2-Hydroxyphenyl Sulfoxides and 2-Hydroxyphenyl Sulfones

BY WILLIAM S. GUMP AND JAMES C. VITUCCI

The literature contains several references to 2-hydroxyphenyl sulfoxides[1,2] and sulfones.[3,4,5,6] However, our knowledge in this field is quite fragmentary and the purpose of this investigation was to prepare a series of compounds in each group. Of particular interest is the synthesis of the yet unknown 2-hydroxyphenyl sulfoxide and 2-hydroxyphenyl sulfones containing halogen substituents.

2-Hydroxyphenyl sulfone itself was synthesized by Tassinari[3] who thought, however, that he had prepared the 3-isomer. By the reaction of 4-bromophenol with sulfur dichloride, Tassinari obtained 5-bromo-2-hydroxyphenyl sulfide (I) which he debrominated with zinc dust in alkaline solution. The resulting 2-hydroxyphenyl sulfide (II) was acetylated, oxidized by means of potassium permanganate and saponified to the sulfone (III) of the m. p. 186–187°.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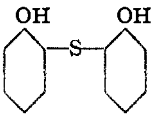
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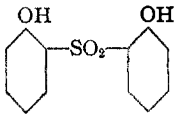
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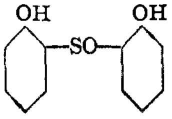
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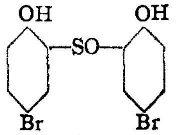
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Mauthner[4] synthesized 2-hydroxyphenyl sulfide by a different method, but proceeded from the sulfide to the sulfone in the same manner as Tassinari. However, Mauthner's melting points were wrong and Machek and Haas[6] correcting his data stated that Mauthner had apparently obtained mixtures on account of incomplete oxidation and that 2-hydroxyphenylsulfone and 2-acetoxyphenyl sulfone melt at 191° and 186–188°, respectively, instead of 164–165° and 147–148° which Mauthner reported. We prepared the sulfone in good yield and purity by direct oxidation of 2-hydroxyphenyl sulfide with hydrogen peroxide in acetic acid solution; our melting points (cor.) 190–191° both for the sulfone and its diacetate, are in general agreement with Machek and Haas and with Tassinari.

Attention might also be called to discrepancies in the literature concerning 5-methyl-2-hydroxyphenyl sulfide. Tassinari[3a] obtained this sulfide from *p*-cresol and sulfur dichloride, believing, as in similar condensations, that he had the 3-isomer, and reporting a m. p. of 117–118°. Gazdar and Smiles[2] reduced 5-methyl-2-hydroxyphenyl sulfoxide to the sulfide and reported a m. p. of 143°. We found a m. p. of 114–115° for 5-methyl-2-hydroxyphenyl sulfide, prepared by either Tassinari's or Gazdar and Smiles' methods. Tassinari[3b] had also prepared 5-methyl-2-acetoxyphenyl sulfide, melting at 83–84°, whereas we found a m. p. of 126–127°. Oxidation of this substance gave 5-methyl-2-acetoxyphenyl sulfone, m. p. 212–213° (Tassinari, 206–208°; Heppenstall and Smiles,[7] 211°).

2-Hydroxyphenyl sulfoxide (IV) has not been previously described. One might conjecture that Mauthner's substances of the m. p. 164–165° and 147–148° represented the sulfoxide and its diacetate, but such is not the case. The direct oxidation of 2-hydroxyphenyl sulfide (II) with the theoretical amount of hydrogen peroxide or of the diacetate by means of potassium permanganate or chromic acid resulted in mixtures from which the pure sulfoxide could not be isolated. Therefore, an indirect method was sought. Condensation of 4-bromophenol with thionyl chloride to 5-bromo-2-hydroxyphenyl sulfoxide (V) and debromination of the latter substance to 2-hydroxyphenyl sulfoxide (IV) with zinc dust in potassium hydroxide solution proved satisfactory. It is interesting to note that zinc and alkali remove the bromine and leave the sulfoxide group unchanged, whereas zinc and acetic acid act just in the opposite manner, the bromine being retained and the sulfoxide (V) reduced to the sulfide (I).

2-Hydroxyphenyl sulfoxide (IV) can be reduced readily with zinc and acetic acid to the corresponding sulfide (II), and oxidized to the sulfone (III) with hydrogen peroxide.

It may be mentioned that 2-hydroxyphenyl sulfoxide dissolves in concd. sulfuric acid with a deep-blue color which is characteristic for sulfoxides.[2]

Substituted 2-hydroxyphenyl sulfoxides were synthesized by the reaction of *p*-substituted phenols having at least one free *o*-position with thionyl chloride in the presence of aluminum chloride or by careful oxidation of the substituted sulfides by means of one mole of hydrogen peroxide. 2,4,5-Trichlorophenol did not condense with thionyl chloride; however, 3,5,6-trichloro-2-hydroxyphenyl sulfoxide was obtained readily by hydrogen peroxide oxidation of the corresponding sulfide. No further oxidation of the sulfoxide

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[1] S. Smiles and R. LeRossignol, *J. Chem. Soc.*, **93**, 745 (1908).

[2] M. Gazdar and S. Smiles, *ibid.*, **97**, 2248 (1910).

[3] G. Tassinari, *Gazz. chim. ital.*, (a) **17**, 90 (1887); (b) **19**, 343 (1889).

[4] F. Mauthner, *Ber.*, **39**, 1351 (1906).

[5] J. Zehenter and O. Ripl, *J. prakt. Chem.*, **139**, 309 (1934).

[6] G. Machek and H. Haas, *ibid.*, **160**, 41 (1942).

[7] M. Heppenstall and S. Smiles, *J. Chem. Soc.*, 903 (1938).

TABLE I

2-HYDROXYPHENYL SULFOXIDES AND 2-HYDROXYPHENYL SULFONES

Compound	M. p., °C., cor.	Formula	Sulfur, % Calcd.	Sulfur, % Found	Halogen, % Calcd.	Halogen, % Found
2-Hydroxyphenyl sulfoxide	172–173	$C_{12}H_{10}O_3S$	13.7	13.9		
5-methyl[3]	191–192	$C_{14}H_{14}O_3S$	12.2	12.0		
5-chloro[3]	204–205	$C_{12}H_8O_3SCl_2$	10.6	10.8	Cl, 23.4	23.2
5-bromo	203–204	$C_{12}H_8O_3SBr_2$			Br, 40.8	40.7
3,5-dichloro	221–223	$C_{12}H_6O_3SCl_4$	8.6	8.5	Cl, 38.1	37.8
3,5,6-trichloro	224–225	$C_{12}H_4O_3SCl_6$	7.3	7.4	Cl, 48.3	48.5
2-Hydroxyphenyl sulfone[3,6]	190–191	$C_{12}H_{10}O_4S$	12.8	12.8		
5-methyl[3b]	208–209	$C_{14}H_{14}O_4S$	11.5	11.7		
5-chloro	190–191	$C_{12}H_8O_4SCl_2$	10.0	10.2	Cl, 22.2	22.0
5-bromo	208–210	$C_{12}H_8O_4SBr_2$			Br, 39.2	38.9
3,5-dichloro	169–170	$C_{12}H_6O_4SCl_4$	8.6	8.4	Cl, 36.6	36.5

TABLE II

2-ACETOXYPHENYL SULFOXIDES AND 2-ACETOXYPHENYL SULFONES

Compound	M. p., °C., cor.	Formula	Sulfur, % Calcd.	Sulfur, % Found	Halogen, % Calcd.	Halogen, % Found
2-Acetoxyphenyl sulfoxide	129–130	$C_{16}H_{14}O_5S$	10.0	9.8		
5-methyl	120–120.5	$C_{18}H_{18}O_5S$	9.2	8.9		
5-chloro	159.5–160.5	$C_{16}H_{12}O_5SCl_2$			Cl, 18.4	18.5
5-bromo	162–163.5	$C_{16}H_{12}O_5SBr_2$			Br, 33.7	33.6
3,5-dichloro	170–171	$C_{16}H_{10}O_5SCl_4$			Cl, 31.1	31.1
3,5,6-trichloro	170.5–171	$C_{16}H_8O_5SCl_6$			Cl, 40.6	40.3
2-Acetoxyphenyl sulfone[3,6]	190–191	$C_{16}H_{14}O_6S$	9.4	9.6		
5-methyl[3b,7]	212–213	$C_{18}H_{18}O_6S$	8.8	8.6		
5-chloro	158.5–159	$C_{16}H_{12}O_6SCl_2$			Cl, 17.6	17.3
5-bromo	169.5–170	$C_{16}H_{12}O_6SBr_2$			Br, 32.5	32.1
3,5-dichloro	206.5–207.5	$C_{16}H_{10}O_6SCl_4$			Cl, 30.1	30.2

to the sulfone could be realized. All the sulfones were prepared by oxidation of the sulfides or sulfoxides with an excess of hydrogen peroxide.

The 2-hydroxyphenyl sulfoxides and sulfones and their diacetates are well-crystallized, colorless and odorless substances. They are soluble to varying degrees in alcohols, ketones and aromatic hydrocarbons, but are practically insoluble in petroleum solvents.

The series of compounds studied are tabulated in Tables I and II.

Experimental Part

2-Hydroxyphenyl Sulfide (II)

(a) **From 5-Bromo-2-hydroxyphenyl Sulfide.**—5-Bromo-2-hydroxyphenyl sulfide[8] (100 g.) was dissolved in 1500 g. of 20% potassium hydroxide solution and heated to 90°. Under stirring, 200 g. of zinc dust was added slowly. After the addition of the zinc dust, stirring was continued at 90° for three hours. The solution was filtered, cooled and acidified with hydrochloric acid. The crude product was filtered off, washed thoroughly with water and dried (45 g.). Crystallization from benzene yielded the pure 2-hydroxyphenyl sulfide (28 g.), m. p. 136–137°.

Anal. Calcd. for $C_{12}H_{10}O_2S$: S, 14.7. Found: S, 14.6.

Applying Schwenk's[9] method of dehalogenation of 5-chloro-2-hydroxyphenyl sulfide,[8] using nickel–aluminum alloy and aqueous alkali, 2-hydroxyphenyl sulfide was also obtained; however, the yield was poor (about 30%), as apparently the sulfur linkages are not too resistant to this reducing agent. In the case of bis-(2-hydroxy-5-chlorophenyl)-methane, nickel–aluminum alloy gave a 90% yield of bis-(2-hydroxyphenyl)-methane.

(b) **From 2-Hydroxyphenyl Sulfoxide.**—2-Hydroxyphenyl sulfoxide (2.5 g.), glacial acetic acid (10 cc.) and zinc dust (2.5 g.) were refluxed for one hour. After filtration, water was added until crystals appeared. The precipitate which formed on cooling was filtered, washed with water and dried (2.2 g.). Crystallization from benzene resulted in pure 2-hydroxyphenyl sulfide, m. p. 137°; mixed with sulfide obtained by debromination of 5-bromo-2-hydroxyphenyl sulfide, m. p. 137°.

2-Hydroxyphenyl Sulfoxide (IV).—5-Bromo-2-hydroxyphenyl sulfoxide (30 g.) was dissolved in 300 g. of 20% potassium hydroxide solution and heated to 90°. At that temperature, 40 g. of zinc dust was added slowly under stirring. After two hours of heating at 90°, the mixture was cooled and about 100 g. of crushed ice added. Acidification was carried out with 62% sulfuric acid; the brownish precipitate was filtered, washed with water and dried (23 g.). The powder was then treated with 100 g. of alcohol; 8 g. which did not dissolve was removed by filtration and the filtrate was diluted with 300 cc. of water. The precipitate was filtered, washed with water and dried (13 g.). Crystallization from a mixture of 500 cc. of toluene and 20 cc. of acetone yielded the pure 2-hydroxyphenyl sulfoxide (9 g.), m. p. 172–173°. A second crystallization from a small amount of dioxane gave white, small crystals of the same melting point.

2-Acetoxyphenyl sulfoxide, prepared in the usual manner and crystallized from alcohol, formed fine needles, m. p. 129–130°.

2-Hydroxyphenyl Sulfone (III).—2-Hydroxyphenyl sulfide (20 g.) was dissolved in 200 g. of glacial acetic acid and 60 g. of 30% hydrogen peroxide were added. The mixture was refluxed for one hour and poured into 500 cc. of water. The precipitated sulfone was filtered, washed with water and dried (20.5 g.), m. p. 188–190°. Crystalli-

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(8) F. Dunning, B. Dunning, Jr., and W. E. Drake, THIS JOURNAL, **53**, 3466 (1931).

(9) E. Schwenk, D. Papa, B. Whitman and H. Ginsberg, *J. Org. Chem.*, **9**, 1 (1943).

zation from benzene yielded the pure 2-hydroxyphenyl sulfone, m. p. 190–191°. In a similar manner, 2-hydroxyphenyl sulfoxide was oxidized to the sulfone.

3,5,6-Trichloro-2-hydroxyphenyl Sulfide.—To a mixture of 70 g. of anhydrous aluminum chloride and 500 cc. of ethylene dichloride was added slowly, under stirring, a warm solution of 100 g. of 2,4,5-trichlorophenol in 100 g. of ethylene dichloride, whereby hydrogen chloride gas was evolved. A solution of 30 g. of sulfur dichloride in 50 g. of ethylene dichloride was dropped in during one hour. The mixture was then heated to 45° for another hour, allowed to stand overnight and quenched with ice. The solvent and unchanged trichlorophenol were removed by steam distillation. The solid residue was dissolved in hot 10% sodium hydroxide solution, the solution filtered and reprecipitated with hydrochloric acid. After filtering, washing and drying, 85 g. of a brownish powder was obtained. Crystallizations from acetic acid with the addition of a small amount of decolorizing carbon and from toluene yielded 35 g. of 3,5,6-trichloro-2-hydroxyphenyl sulfide in form of feathery needles, m. p. 156–157°.

Anal. Calcd. for $C_{12}H_4O_2SCl_6$: Cl, 50.1. Found: Cl, 49.8.

The diacetate formed colorless, thin needles, m. p. 174–175°.

Anal. Calcd. for $C_{16}H_8O_4SCl_6$: Cl, 41.8. Found: Cl, 41.6.

5-Bromo-2-hydroxyphenyl Sulfoxide (V).—Anhydrous aluminum chloride (100 g.) was added under stirring to 800 cc. of ethylene dichloride kept in an ice-bath. After that, 240 g. of 4-bromophenol was added in small portions, and then a solution of 120 g. of thionyl chloride in 100 cc. of ethylene dichloride dropped in during one hour. The ice-bath was removed and stirring continued for four hours. The mixture was allowed to stand overnight and was then quenched with ice. Steam distillation removed the ethylene dichloride and the unreacted 4-bromophenol. After cooling, the crystalline product obtained was filtered, washed with water and dried (75 g., m. p. 198–200°). Crystallization from alcohol yielded the pure 5-bromo-2-hydroxyphenyl sulfoxide in the form of colorless, thin platelets, m. p. 203–204°.

3,5-Tetrachloro-2-hydroxyphenyl Sulfoxide.—3,5-Tetrachloro-2-hydroxyphenyl sulfoxide was prepared in a similar manner from 2,4-dichlorophenol and thionyl chloride. Crystallizations of the crude product (m. p. 210–212°) from toluene containing 10% of alcohol and from alcohol alone yielded white, fine needles of 3,5-dichloro-2-hydroxyphenyl sulfoxide, m. p. 221–223°.

3,5,6-Trichloro-2-hydroxyphenyl Sulfoxide.—3,5,6-Trichloro-2-hydroxyphenyl sulfide (20 g.), glacial acetic acid (200 cc.) and 30% hydrogen peroxide (12 g.) were refluxed for one hour. After cooling, the formed crystals were filtered, washed with 50% acetic acid and water and dried (17 g.; m. p. 222–224°). Crystallization from toluene yielded the pure 3,5,6-trichloro-2-hydroxyphenyl sulfoxide (14 g., m. p. 224–225°).

5-Chloro-2-hydroxyphenyl Sulfone.—A mixture of 20 g. of 5-chloro-2-hydroxyphenyl sulfide,[8] 150 cc. of glacial acetic acid and 35 g. of 30% hydrogen peroxide was refluxed for two hours and water added until precipitate started to form and the mixture allowed to cool. The obtained crystals were filtered, washed with 50% acetic acid and water and dried (17 g.; m. p. 189–190°). Crystallization from 70% acetic acid yielded pure 5-chloro-2-hydroxyphenyl sulfone of the m. p. 190–191°. The other substituted sulfones were prepared in the same way from the corresponding sulfides or sulfoxides.

5-Methyl-2-hydroxyphenyl Sulfide

(a) From *p*-Cresol and Sulfur Dichloride.—*p*-Cresol (108 g.) was dissolved in 500 cc. of petroleum ether. A solution of 55 g. of sulfur dichloride in 60 cc. of petroleum ether was dropped in during one hour. The mixture was allowed to stand overnight. The petroleum ether layer was then poured off from the brown, semi-solid mass which was crystallized from 100 g. of toluene; 27 g. of a white, crystalline powder was obtained. Crystallizations from toluene (100 cc.) and glacial acetic acid (100 cc.) yielded colorless crystals of 5-methyl-2-hydroxyphenyl sulfide, melting at 114–115°.

(b) By Reduction of 5-Methyl-2-hydroxyphenyl Sulfoxide.—5-Methyl-2-hydroxyphenyl sulfide was obtained by reduction of the sulfoxide by means of zinc dust in acetic acid solution (Gazdar and Smiles[2]) and melted at 114–115°; mixed with sulfide prepared by method a, m. p. 114–115°.

Anal. Calcd. for $C_{14}H_{14}O_2S$: S, 13.0. Found: S, 12.8.

5-Methyl-5-acetoxyphenyl sulfide, prepared in the usual manner and crystallized from alcohol, formed thin, large platelets of the m. p. 125–126°.

Anal. Calcd. for $C_{18}H_{18}O_4S$: S, 9.7. Found: S, 9.5.

Summary

1. 2-Hydroxyphenyl sulfoxide has been synthesized.

2. A series of halogenated 2-hydroxyphenyl sulfoxides and sulfones has been prepared.

Delawanna, New Jersey Received July 17, 1944

[Contribution from the College of Pharmacy, University of Michigan]

Ethyl- and Propylamines which Contain the 2-(1,5-Diphenyl)-pyrryl or the 2-(1-Methyl-5-phenyl)-pyrryl Nucleus[1]

By F. F. Blicke, J. E. Gearien, R. J. Warzynski and J. A. Faust

Our interest in amines which contain phenylpyrryl nuclei was aroused by the fact that tryptamine (I, β-(3-indolyl)-ethylamine) exhibits oxytocic activity to some degree,[2] an effect which was demonstrated by Chen and Chen[3] on the isolated guinea pig uterus.

Since it is of general interest to know the extent to which a phenylpyrryl radical might replace an indolyl group in a pharmacologically-active product, we decided to prepare amines such as those represented by general formula II. In these compounds the basic-alkyl side chain is attached to a 2 carbon atom of the pyrrole ring instead of a 3 carbon atom as in the case of tryptamine.

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(1) We wish to express our indebtedness to Eli Lilly and Company, the Board of Governors of the Horace H. Rackham School of Graduate Studies, and Park, Davis and Company for their joint support of this project.

(2) Barger ("Some Applications of Organic Chemistry to Biology and Medicine," page 99 (1930)) stated that tyramine has been manufactured in Japan for medicinal use. See also Guggenheim, "Die biogenen Amine," page 541 (1940).

(3) Chen and Chen, *J. Am. Pharm. Assoc.*, **22**, 813 (1933).