Isolation of *l*-Ephedrine.—The material obtained on exhaustive ether extraction of the mother liquors (II) could be shown to contain neoline and a small amount of napelline. The mother liquors were made strongly alkaline and steam distilled until the distillate no longer reacted alkaline. The distillate was neutralized carefully with hydrochloric acid, concentrated to a small volume, filtered and evaporated to dryness. The residue was taken up in the minimum volume of boiling alcohol and 5 to 6 volumes of acetone was then added with good shaking. In a few seconds needles began to appear. After several hours of standing in the ice box the material was filtered off and recrystallized in the same way; yield 0.68 g. The filtrate from the first crystallization was saved for the isolation of sparteine. The substance melted at 217–218°; $[\alpha]^{23}\mathrm{D}$ −33.0° (H_2O, c = 6.0).

Anal. Calcd. for $C_{10}H_{15}NO \cdot HCl$: C, 59.61; H, 8.00; N, 6.95; Cl, 17.61. Found: C, 59.59, 59.98; H, 7.84, 8.27; N, 6.97, 7.05; Cl, 17.57, 17.59.

The derivatives described below were prepared by standard methods, using the hydrochloride as starting material. They all appeared identical with the corresponding derivatives prepared from synthetic *l*-ephedrine (Merck).

Ephedrine Hydrobromide.—Needles, m. p. 206°, $[\alpha]^{21}\mathrm{D}$ −28.1° (H_2O, c = 4.0).

Anal. Calcd. for $C_{10}H_{15}NO \cdot HBr$: C, 48.80; H, 6.55; N, 5.68; Br, 32.46; (N)CH_3, 6.09. Found: C, 49.01, 48.82; H, 6.20, 6.21; N, 5.59, 5.64; Br, 31.91; (N)CH_3, 5.66, 5.50.

Ephedrine Oxalate.—Needles, m. p. 245°.

Anal. Calcd. for $(C_{10}H_{15}NO)_2 \cdot H_2C_2O_4$: N, 6.66. Found: N, 6.67.

Ephedrine *p*-Toluenesulfonate.—M. p. 126°.

Anal. Calcd. for $C_{10}H_{14}NOSO_2C_7H_7$: N, 4.38. Found: N, 4.40.

Isolation of Sparteine.—The mother liquor from the first crystallization of ephedrine hydrochloride was evaporated to dryness. The residue was taken up in water, an excess of sodium hydroxide was added and the basic material extracted with ether. The dried and filtered ether extract was evaporated in a small centrifuge tube. On complete removal of the ether about 200 mg. of yellow-brown oil remained. In order to remove the ephedrine present, the filtrate was shaken with four successive 2-cc. portions of water. After each treatment the mixture was centrifuged and the water drawn off. The base was then dissolved in ether and the solution dried. The filtered solution was transferred to a Craig micro-still and, after removal of the ether, distilled at 1 mm. The fraction distilling between 120–130° (bath temp.) was examined. This was a clear yellow oil which became brown on standing. The odor resembled that of authentic sparteine: b. p. above 250°, $[\alpha]^{23}\mathrm{D}$ −14.4° (EtOH, c = 5.5); $n^{24}\mathrm{D}$ 1.528.

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 76.87; H, 11.18; N, 11.95. Found: C, 77.06; H, 11.05; N, 12.07.

Sparteine Picrate.—M. p. 208°.

Anal. Calcd. for $C_{15}H_{26}N_2(C_6H_2(OH)(NO_2)_3)_2$: N, 16.17. Found: N, 16.24.

Acknowledgments.—The authors desire to express their appreciation to E. Merck for the starting material, to Merck and Co., Inc., Rahway, N. J., for a grant to one of us (E. F. R.).

The micro-analyses were carried out in this Laboratory by Mr. J. F. Alicino.

Summary

The fractionation of the ether soluble alkaloids contained in the residual bases of *aconitum napellus* yielded two new alkaloids, neoline, $C_{24}H_{41}NO_6$, and napelline, $C_{22}H_{33}NO_3$, as the main constituents together with traces of *l*-ephedrine and sparteine. All four alkaloids must be considered as genuine aconitum alkaloids.

NEW YORK, N. Y. RECEIVED OCTOBER 15, 1937

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Some Derivatives of Monothiophloroglucinol

BY C. M. SUTER AND GEORGE A. HARRINGTON

Previous investigations in this Laboratory[1] and elsewhere[2] have shown that hydroxyaryl alkyl sulfides exhibit strong germicidal properties. In the present paper are reported the synthesis and phenol coefficients of a series of alkyl sulfides derived from monothiophloroglucinol.

Synthesis of Sulfides

The starting material for the preparation of the sulfides was *sym*-benzenetrisulfonic acid. This was obtained in good yields by sulfonating sodium *m*-benzenedisulfonate in the presence of a mercury catalyst by a modification of the procedure of Behrend and Mertelsmann.[3] Fusion of sodium *sym*-benzenetrisulfonate with six times its weight of sodium hydroxide at 240–250° gave a 77% yield of sodium 3,5-dihydroxybenzenesulfonate.[4] When less alkali was employed a mixture of products was obtained from which none of the dihydroxysulfonate could be isolated.

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(1) Suter and Hansen, THIS JOURNAL, **54**, 4100 (1932); Suter and McKenzie, *ibid.*, **56**, 2470 (1934).

(2) Miller and Read, *ibid.*, **55**, 1244 (1933).

(3) Behrend and Mertelsmann, *Ann.*, **378**, 352 (1910).

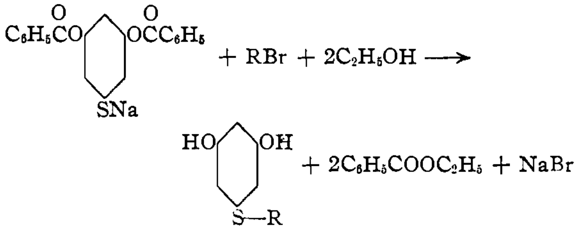
(4) Senhofer, *Sitzber. K. Akad. Wiss. Wien*, **78**, II, 678 (1879).

When the fusion was carried out in a copper container the yield was not as satisfactory as when a nickel crucible was used.

Since Barth and Schreder[5] reported that fusion of sodium *sym*-benzenetrisulfonate with sodium hydroxide for ten minutes gives a 25–30% yield of phloroglucinol while Barth and Schmidt[6] found it not possible to prepare this compound from potassium 3,5-dihydroxybenzenesulfonate and potassium hydroxide the sodium hydroxide fusion was repeated. Barth and Schreder[5] did not report the ratio of alkali to sulfonate or the temperature of the fusion so it is not possible to duplicate their reaction conditions exactly. However, in previous work in this Laboratory[7] it was observed that at 310° the second sulfonate group is removed slowly from potassium *sym*-chlorobenzenedisulfonate (the chlorine hydrolyzes at a much lower temperature); hence for a short fusion a somewhat higher temperature is required. The amount of ether-soluble phenolic material obtained from 0.1 mole of the sodium trisulfonate was 2.8 g. when the fusion was effected at 335° for ten minutes. No phloroglucinol could be isolated from this product or from the trace of phenolic material obtained when the fusion was run for one hour at 335–340°. Apparently any phloroglucinol produced is destroyed by the fused alkali under the conditions employed.

The diacetate of sodium or potassium[8] 3,5-dihydroxybenzenesulfonate is hygroscopic and the corresponding sulfonyl chloride is difficult to purify. The dibenzoate is obtained readily, however, and the sulfonyl chloride from this is more tractable. After investigating various methods for converting this into the thiol the action of zinc in glacial acetic acid was found to be most suitable. After four hours at 50° the reduction had not gone beyond the sulfinate stage but by refluxing the reaction mixture a satisfactory yield of the thiol resulted. This method of reduction is recommended for sulfonyl chlorides containing groups that would be hydrolyzed by the usual procedure involving zinc and dilute acid.

The 3,5-dihydroxyphenyl alkyl sulfides were prepared from the thiol in one operation; the reactions occurring are indicated in the equation. The alcoholysis was catalyzed by the presence of a trace of sodium ethoxide. Alcoholysis alone gave monothiophloroglucinol. The properties of the compounds prepared are listed in the experimental part.



Phenol Coefficients[9]

The phenol coefficients of the 3,5-dihydroxyphenyl alkyl sulfides could not be determined in aqueous solution because their solubilities were too small. Since a 40% solution of propylene glycol in water was found to be without action on the test organisms this solvent was employed in making up the stock solutions. Saturated solutions of the *n*-amyl and *n*-hexyl sulfides showed no activity even in this solvent. In Table I are listed the results obtained using the F. D. A. method for the organisms *Eberthella typhi* and *Staphylococcus aureus*.

TABLE I

3,5-Dihydroxyphenyl alkyl sulfide	Phenyl coefficients, 37° *Staph. aureus*	*E. typhi*
Methyl	5.9	4.3
Ethyl	8.3	5.2
n-Propyl	16	11
n-Butyl	17	14
n-Amyl	<16	<11
n-Hexyl	<34	<23

It will be necessary to investigate other derivatives of resorcinol containing substituents in the 5-position and also the 2,4-dihydroxyphenyl alkyl sulfides before any conclusions can be drawn regarding the relationship between structure and bactericidal properties in this series.

Experimental

Sodium *sym*-Benzenetrisulfonate.—After investigating the various methods of preparation outlined in the literature the following procedure, based on that of Behrend and Mertelsmann,[3] was found to be most satisfactory. To 50 g. of crude sodium *m*-benzenedisulfonate in a 300-cc. Kjeldahl flask were added 50 cc. of 15% oleum and 2 g. of mercury. The mixture was heated in a salt-bath at 275° for twelve hours with occasional vigorous shaking, cooled and dissolved in 1 liter of water. Solid calcium

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(5) Barth and Schreder, *Sitzber. K. Akad. Wiss. Wien*, **79**, II, 294 (1879).

(6) Barth and Schmidt, *ibid.*, **79**, II, 633 (1879).

(7) Suter and Scrutchfield, *J. Org. Chem.*, **1**, 192 (1936).

(8) Scrutchfield, Ph.D. Thesis, Northwestern University, 1935.

(9) The phenol coefficients were determined in the Bacteriology Laboratory of the Northwestern University Medical School. We are grateful to Professor A. A. Day for his helpful suggestions and interest in the work.

carbonate was added to the hot solution until neutral to litmus, the calcium sulfate was filtered off and washed with three 200-cc. portions of boiling water. A saturated solution of sodium carbonate was added to the combined filtrate and washings until just alkaline to phenolphthalein. The mixture was digested on a steam-bath, filtered through a norite pad and the filtrate evaporated to dryness. The residue which was practically pure sodium *sym*-benzenetrisulfonate was dried in an oven at 140° for four hours. The yield was 50 g. or 73% of the theoretical amount. Treating a sample with phosphorus pentachloride gave the trisulfonyl chloride, m. p. 187° (corr.). Jackson and Wing[10] report 184° as the melting point of the pure sulfonyl chloride. No appreciable amount of any other sulfonyl chloride was noted, indicating the substantial purity of the sodium sulfonate.

Sodium 3,5-Dihydroxybenzenesulfonate.—Two hundred and thirty grams of sodium hydroxide was fused in a nickel crucible at 240–250° by adding just enough water to keep the mixture fluid. To this was added 38.5 g. (0.1 mole) of sodium *sym*-benzenetrisulfonate over a period of twenty minutes. After three hours the melt was dissolved in 1 liter of water, cooled, and neutralized with 33% sulfuric acid. Evolution of sulfur dioxide was vigorous. The solution was filtered and evaporated to dryness under reduced pressure. The residue was extracted repeatedly with 95% ethyl alcohol and the alcohol solution evaporated to a thick sirup on the water-bath. Upon cooling the residue in the refrigerator is solidified. The pasty mass was filtered and the product air dried. The yield was 19 g. or 77% of the theoretical amount. The sodium dihydroxysulfonate was found to crystallize with two molecules of water of hydration instead of the one reported by Barth and Schmidt.[6]

Anal. Calcd. for $C_6H_5O_5SNa \cdot 2H_2O$: Na, 9.27. Found: Na, 9.20.

Analysis of the salt after drying under reduced pressure gave correct results for the anhydrous material.

Anal. Calcd. for $C_6H_5O_5SNa$: Na, 10.84. Found: Na, 10.80.

Senhofer[4] reports the potassium salt as containing two molecules of water while Barth and Schmidt[6] report it without water of hydration.

Attempted Preparation of Phloroglucinol.—To 117 g. of fused sodium hydroxide in a nickel crucible was added 38.4 g. (0.1 mole) of sodium benzenetrisulfonate. The mixture was kept at 335° for ten minutes with frequent stirring, cooled rapidly by holding under the cold water tap, dissolved in water and the solution neutralized with dilute sulfuric acid. This solution (1500 cc.) was extracted three times with ether, the ether solution dried and the ether distilled off. The residue was treated with water, which dissolved most of it. Evaporation of the water solution at room temperature gave 2.8 g. of dark brown crystals. Redissolving this product in 28 cc. of water according to the "Organic Syntheses" procedure[11] for purifying phloroglucinol and allowing the solution to stand for several days in the refrigerator gave none of the desired material. The solution gave a greenish-purple color with ferric chloride. Heating the fusion mixture for one hour likewise gave no detectable amount of phloroglucinol.

Sodium Dibenzoylresorcinol-5-sulfonate.—To 50 cc. of water was added 10.6 g. (0.05 mole) of the sodium dihydroxybenzenesulfonate and 4 g. (0.1 mole) of sodium hydroxide. Fifteen grams (0.1 mole) of benzoyl chloride was then added, the mixture stirred for fifteen minutes and cooled in the refrigerator. The yield of dry product was 10.5 g. or 50% of the theoretical amount.

Anal. Calcd. for $C_{20}H_{13}O_7SNa$: Na, 5.47. Found: Na, 5.37.

Dibenzoylresorcinol-5-sulfonylchloride.—Ten grams of the sodium sulfonate was refluxed with 50 cc. of phosphorus oxychloride for three hours. The excess oxychloride was removed under reduced pressure, the residue extracted with decalin and the solution cooled in dry ice and acetone. A second crystallization gave a stable pure product, m. p. 105°.[12]

Anal. Calcd. for $C_{20}H_{13}O_6SCl$: Cl, 8.51. Found: Cl, 8.39.

Dibenzoylresorcinol-5-thiol.—A solution containing 10 g. (0.024 mole) of the sulfonyl chloride in 75 cc. of glacial acetic acid was stirred vigorously for four hours at 50° with 10 g. of zinc dust. The mixture was then refluxed for six hours, cooled, filtered, and diluted with three times its volume of water. The thiol precipitated as a gum which gradually crystallized. Recrystallization from ethyl alcohol gave 4.2 g. (a 50% yield) of material melting at 110°. It was analyzed by iodine titration according to the method of Klason and Carlson.[13]

Anal. Calcd. for $C_{20}H_{14}O_4S$: S, 9.16. Found: S, 9.01.

The alcoholic solution from the iodine titration was cooled and the pure disulfide filtered off. It melted at 146°. This was analyzed by the usual Parr bomb method.

Anal. Calcd. for $C_{40}H_{26}O_8S_2$: S, 9.17. Found: S, 9.20.

Monothiophloroglucinol.—To 3.5 g. of dibenzoylresorcinol-5-thiol in 50 cc. of absolute alcohol was added enough alcoholic sodium ethoxide to make the solution just alkaline to phenolphthalein. The mixture was refluxed for three hours, cooled and acidified with dilute acetic acid, and the alcohol and ethyl benzoate distilled off. The ether extract of the aqueous residue gave the usual tests for a thiol with iodine and lead acetate. Evaporation of the ether left a light brown viscous oil from which a white solid was sublimed by heating in an oil-bath at 140° and 1 mm. pressure. The majority of the product did not distil even at 180° and gave no test for a thiol group. The white solid melted at 88–89° and gave a precipitate with lead acetate.

Anal. Calcd. for $C_6H_6O_2S$: S, 22.56. Found: S, 22.0.

3,5-Dihydroxyphenyl Alkyl Sulfides.—The alkylation and removal of the benzoyl groups from dibenzoylresorcinol-5-thiol were effected in one operation. The procedure for the *n*-butyl compound is typical.

A solution containing 3.5 g. (0.01 mole) of thiol in 50 cc. of absolute alcohol was made just alkaline with sodium ethoxide, 1.4 g. (0.01 mole) of *n*-butyl bromide was added, and the mixture refluxed for three hours. It was then dis-

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[10] Jackson and Wing, *Am. Chem. J.*, **9**, 329 (1887).

[11] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, 1932, p. 444.

[12] All melting points are corrected.

[13] Klason and Carlson, *Ber.*, **39**, 738 (1906).

tilled with steam to remove the alcohol and ethyl benzoate, the residue extracted with ether, and the ether-soluble oil distilled in a small Hickman type still. This gave a solid which was recrystallized from carbon tetrachloride. The properties of this and other sulfides are given in Table II. The solubilities are approximate values.

Table II

3,5-Dihydroxyphenyl alkyl sulfide	M. p., °C.	Sulfur, % Found	Sulfur, % Calcd.	So!y. in H_2O g./100 g. soln., 20°
Methyl	78–78.5	20.48	20.53	0.25
Ethyl	71–72	18.82	18.69	.14
n-Propyl	67–68	16.98	17.31	.08
n-Butyl	66	15.78	16.18	.06
n-Amyl	66	14.97	15.11	.01
n-Hexyl	Oil[a]	13.85	14.17	< .01

[a] All attempts to obtain this as a solid failed. It distilled from a bath kept at 250° at 1 mm. pressure.

The methyl and ethyl sulfides gave a red color with ferric chloride, the *n*-propyl a purple color and the *n*-butyl and *n*-amyl a green color.

Summary

1. Sodium *sym*-benzenetrisulfonate was found to be convertible into 3,5-dihydroxybenzenesulfonate in satisfactory yields but the reported preparation of phloroglucinol has not been confirmed.

2. A series of *n*-alkyl 3,5-dihydroxyphenyl sulfides has been synthesized and the phenol coefficients of these compounds are tabulated.

3. Monothiophloroglucinol has been prepared for the first time.

Evanston, Illinois Received September 5, 1937

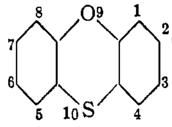
[Contribution from the Chemical Laboratory of Northwestern University]

Phenoxthin. II. Extension of the Ferrario Reaction

By C. M. Suter and Frank O. Green

Earlier[1] work in this Laboratory has shown that under the proper conditions the action of sulfur and aluminum chloride upon phenyl ether gives a good yield[2] of phenoxthin. This reaction which was first reported almost simultaneously by Ferrario[3] and Ackerman[4] for convenience may be referred to as the "Ferrario reaction."

The report of Ackerman[4] that *p*-chloro- and *p*-methylphenyl phenyl ethers are readily converted into the corresponding phenoxthins while *p*-bromophenyl phenyl ether and di-(*p*-bromophenyl) ether give only tarry products[1] made desirable an investigation of the behavior of other substituted aryl ethers toward sulfur and aluminum chloride. It has been found that the isomeric phenyl tolyl ethers and phenyl chlorophenyl ethers all give the corresponding phenoxthin derivatives in fair yields. With the chloro ethers the reaction is complete in about thirty minutes at 100° while the tolyl ethers require several hours. Long heating of the reaction mixtures containing the chloro ethers leads to decomposition with evolution of hydrogen chloride. The yield of the phenoxthin is higher when the directive influences of the ether oxygen and the methyl or chloro group coincide, *i. e.*, in the meta substituted ethers. It is assumed for the present that this reaction yields 2-substituted phenoxthins as in I rather than the 4-isomers (II) which are possible but not probable.



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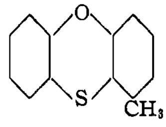

II

Additional attempts to convert 4-bromophenyl phenyl ether into the bromophenoxthin were unsuccessful. Reaction with sulfur and aluminum chloride is violent at 100° but the product was a mixture with an indefinite melting point from which no pure compound was isolated.

o-Methoxyphenyl phenyl ether gave no evidence of undergoing the Ferrario reaction at 100°. It is probable that the *m*-methoxy compound would react satisfactorily but this was not investigated. 3-Phenoxyphenoxthin was found to evolve hydrogen sulfide slowly when heated at 40° with sulfur and aluminum chloride. At higher temperatures decomposition set in with evolution of hydrogen chloride. No "diphenoxthin" was isolated.

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[1] Suter, McKenzie and Maxwell, This Journal, **58**, 717 (1936).

[2] A slight modification of the directions given in ref. 1 improves the yield. By fractionating the reaction mixture containing unchanged phenyl ether and phenoxthin at 4 mm. through a 50-cm. punched-in lagged column 87% yields of crude material are obtained consistently. The approximate boiling point of phenoxthin at atmospheric pressure given in ref. 1 is low. Pure phenoxthin distils at 311° (745 mm., corr.) with slight decomposition.

[3] Ferrario, *Bull. soc. chim.*, **9**, 536 (1911).

[4] Ackerman, German Patent 234,743, *Frdl.*, **10**, 153 (1913).