

acetate undergo a partial deacetylation and a characteristic rearrangement. With these facts in mind, glycerophenylene enedioldiacetate was treated in the following way: a solution of 2 g. (0.0091 mole) of enedioldiacetate, 1 g. (0.0102 mole) of freshly fused potassium acetate and 10 cc. of acetic acid were refluxed for thirty minutes. Upon pouring the mixture into ice water a brown oil separated. The oil was dissolved in ether, decolorized with carboraffin, dried over anhydrous sodium sulfate and the solvent removed with a stream of dry air. The sirup was then dissolved in warm ligroin from which crystals appeared upon cooling; m. p. 49°, yield 0.26 g. (16%).

(b) **Conversion to *keto*-Glycerophenylene.**—Evans and Parkinson have shown that *aldo*-glycerophenylene, a possible rearrangement product of the free enediol, is unstable<sup>6b</sup> in aqueous solution and rearranges to *keto*-glycerophenylene. Thus, the reaction product of the deacetylation of this enediol diacetate should be *keto*-glycerophenylene, as borne out by the following experiment. To a mixture of 5 g. of calcium carbonate in 25 cc. of water was added 1 g. (0.0045 mole) of pure glycerophenylene enedioldiacetate. The reaction mixture was refluxed for four hours under a reverse condenser and filtered while hot. The precipitate was washed well with acetone and ethanol. The filtrate was extracted with ether, dried over anhydrous sodium sulfate and high-boiling petroleum ether was then added to turbidity. Upon standing in the ice chest a short time, bold, plate-like crystals of *keto*-glycerophenylene formed, m. p. 86.5°, yield 0.17 g. (27.5%).

(c) **Glycerophenylene Enedioldiacetate, Copper Sulfate and Sodium Hydroxide.**—To a mixture of 1.62 g. (0.0074 mole) of the diacetate and 3.62 g. (0.0227 mole) of copper sulfate in 80 cc. of water was added 1.60 g. of sodium

hydroxide in 5 cc. of water. The solution turned yellow almost immediately. The mixture was then heated for fifteen minutes on a steam-bath, filtered and filtrate evaporated to dryness at 100° under reduced pressure.<sup>9</sup> A few cc. of dilute hydrochloric acid was added and the solution extracted with ethyl ether. Upon addition of petroleum ether, white crystals formed. These crystals melted at 118.5° and with an authentic sample of *r*-mandelic acid no depression was noticed, yield 0.90 g.

### Summary

1. Glycerophenylene enedioldiacetate has been prepared from *o*-bromoacetophenone with acetic anhydride and potassium acetate.

2. The structure of this enediol has been proved by its hydrogenation to phenyl glycol diacetate and the conversion of this diacetate to phenyl glycol which was in turn shown to be identical with phenyl glycol prepared by an independent method.

3. The enedioldiacetate on deacetylation, partial and complete, rearranges to *keto*-glycerophenylene monoacetate and *keto*-glycerophenylene, respectively.

4. The enedioldiacetate in sodium hydroxide solution is oxidized to mandelic acid with cupric hydroxide, a reaction similar to that of *keto*-glycerophenylene with the same reagent.

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## Sulfur Studies. XVII. The Synthesis of Sulfathiophene, 2-Sulfanilamidothiophene

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Due to the extensive interest shown in sulfanilamide compounds and more particularly in sulfapyridine, sulfathiazole and sulfaguanidine, it seemed desirable to prepare and investigate the properties of their isolog, sulfathiophene. It was felt that sulfathiophene might offer certain therapeutic advantages over the aforementioned compounds or perhaps might even have a specificity for certain organisms which previous compounds have not hitherto shown.

In this paper are described the synthesis and physical properties of 2-sulfanilamidothiophene. Tests of the pharmacological properties have been carried out by the Wm. S. Merrell Company, through the courtesy of Dr. Robert S. Shelton, and will be reported elsewhere.

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Considerable difficulty was encountered at first in obtaining good yields in the synthesis of 2-sulfanilamidothiophene. The low yields in the preparation of this compound were largely due to improper decomposition of the stannic chloride salt of thiophenine hydrochloride. The decomposition of this salt was best accomplished by slow addition of alkali to the aqueous solution, under ether, while being stirred in a nitrogen atmosphere. The ether solution was then added to a slurry of *p*-acetamidobenzene sulfonyl chloride in ether, in the presence of pyridine, and allowed to stand ten to fourteen hours under nitrogen. Due to the amphoteric nature of 2-sulfanilamidothiophene, some difficulty was also experienced in the isolation of the compound after hydrolysis. Only small amounts of the compound

were obtained by neutralization of the acid solution with sodium or ammonium hydroxide. Hydrolysis with 16% hydrochloric acid takes place but the subsequent removal of the chloride ion by successive lead oxide and silver oxide treatment was unsuccessful. The low yield on hydrolysis may be partly explained by partial decomposition during hydrolysis as was indicated by the evolution of hydrogen sulfide.

### Experimental

**2-Nitrothiophene.**—This material was prepared by the nitration of thiophene as described in "Organic Syntheses."<sup>2</sup> The recrystallized material melted at 42.3–43°.

**Stannic Chloride Salt of 2-Thiophenine Hydrochloride.**—To 40 g. of 2-nitrothiophene and 680 ml. of concentrated hydrochloric acid in a three-liter, three-necked, round-bottom flask equipped with a mechanical stirrer and a T-tube connected to an aspirator to remove excess fumes was added, with constant stirring, 68 g. of finely granulated tin in the course of a half-hour. The temperature was maintained at 40–50°. The mixture was allowed to stir at 40–50° for an additional half-hour and then stood in the ice chest for several hours. Upon filtration, washing with 50 ml. of ethanol, then with 100 ml. of ether, 58 g. of light brown crystals was obtained, yield 70%. The material was not further purified. On exposure to strong light the salt gradually darkens. Using varying amounts of 2-nitrothiophene up to 63 g. and other materials in proportion, consistent yields of 68 to 70% were obtained.

**Acetyl-2-sulfanilamidothiophene.**—A solution of 30 g. (0.057 mole) of the stannic chloride salt of thiophenine hydrochloride in 300 ml. of water was put into a one-liter, three-necked, round-bottom flask having a separatory tube with stopcock attached to the bottom. The flask was equipped with a condenser, tube for passing in nitrogen, dropping funnel, and a mechanical stirrer; it was cooled by an ice-water bath. Two hundred ml. of ether was added and nitrogen was introduced. After the air in the apparatus was swept out, 50% sodium hydroxide was added dropwise, with stirring, until the first formed white

precipitate had completely dissolved. The aqueous layer was drawn off through the separatory tube and discarded.

The ether layer, after being passed through a tube packed with glass wool to remove polymerized material, was run into a liter round-bottom flask containing a slurry of 27.7 g. (0.114 mole) of *p*-acetamidobenzenesulfonyl chloride in 300 ml. of ether and 21 ml. of pyridine. The mixture was allowed to stand under nitrogen with occasional shaking for twelve hours. About 250 ml. of water was then added and the ether evaporated. To the residual product was added enough 95% ethanol to form a clear solution, it was boiled with charcoal, filtered and the filtrate concentrated. Upon cooling, there separated 15.2 g. of light brown crystals, yield 44%. The crude product was further purified by recrystallization from dilute ethanol (50% by volume) followed by one crystallization from a 5% acetic acid solution, giving fine, white, flaky crystals, m. p. 196°. The crystals are soluble in hot dilute ethanol, and hot 5% acetic acid; soluble in methanol, ethanol, glacial acetic acid, 1% sodium hydroxide solution; slightly soluble in cold dilute ethanol and 5% acetic acid. *Anal.* Calcd.: S, 21.65. Found: S, 21.81.

**2-Sulfanilamidothiophene.**—To 250 ml. of 10.4% sulfuric acid solution was added 15.2 g. of crude acetyl-2-sulfanilamidothiophene and the mixture gently refluxed for five minutes past the time at which all the material went into solution (twenty-five to forty minutes). The red solution was then poured cautiously into a hot suspension of 83 g. of Ba(OH)<sub>2</sub>·8H<sub>2</sub>O in 300 cc. of water, boiled a few minutes, and filtered. From the combined filtrates there separated on cooling 5.4 g. of white, needle-like crystals, yield 41%. After four recrystallizations from water, the melting point was constant at 156.5–157.5°. The compound is soluble in hot water, methanol, ethanol, 1% aqueous sodium hydroxide, 1% aqueous hydrochloric acid, and slightly soluble in ethyl ether. *Anal.* Calcd.: S, 25.22. Found: S, 25.07.

### Conclusion

1. A synthesis of sulfathiophene is described.
2. The solubility of acetyl-2-sulfanilamidothiophene and 2-sulfanilamidothiophene in certain solvents is given.

(2) "Organic Syntheses," Vol. XIV, John Wiley and Sons, Inc., New York, N. Y., 1934, pp. 76–77.