

of atropine and that +++ against barium chloride indicates an activity about equal to that of paverine.

Intravenous acute toxicities determined in mice for the most active compounds showed that, in general, the quaternary methiodides are approximately four times more toxic than the corresponding hydrochlorides. The LD<sub>50</sub> for the tertiary hydrochlorides ranged between 50–80 mg./kg., whereas the quaternaries showed LD<sub>50</sub> of 11–25 mg./kg.

Fast and complete mydriasis of relatively short duration was produced by several compounds following local application in the rabbit eye.

Anesthetic properties of short duration were also exhibited by several tertiary hydrochlorides on the rabbit cornea. Quaternary compounds were not effective.

A detailed discussion of the pharmacological investigation will be published elsewhere.

### Experimental

The examples below illustrate the procedures used for the preparation of the acid intermediates (see Table I) and of the hydrochlorides and methiodides of the esters (see Tables II and III).

**(1-Hydroxycyclohexyl)-phenylacetic Acid.**—To a Grignard reagent prepared from 2.4 g. (0.1 mole) of magnesium turnings and 12.3 g. (0.1 mole) of isopropyl bromide in 75 cc. of anhydrous ether, 9.1 g. (0.058 mole) of sodium phenyl acetate was added. The mixture was refluxed for one-half hour after the evolution of gas ceased. Then 5.7 g. (0.058 mole) of cyclohexanone in 50 cc. of anhydrous ether was added dropwise and the mixture refluxed for one hour. The reaction product was decomposed with ice-cold dilute hydro-

chloric acid solution, and the ether layer was separated and extracted with 200 cc. of 5% sodium hydroxide solution. The free acid which was obtained on acidification, was washed with hot water and recrystallized from dilute methanol. There was obtained 7.5 g. (60%) of product, m.p. 143–144°.

**β-Diethylaminoethyl (1-Hydroxycyclohexyl)-phenylacetate Hydrochloride.**—To a solution of 2.3 g. (0.1 mole) of sodium in 150 cc. of isopropyl alcohol, 23.4 g. (0.1 mole) of (1-hydroxycyclohexyl)-phenylacetic acid was added followed by 17.5 g. (0.1 mole) of β-chloroethyldiethylamine hydrochloride. The mixture was refluxed for 16 hours, filtered and the solvent removed under reduced pressure on the steam-bath. The residue was washed with anhydrous ether and recrystallized from an ethyl acetate-ethanol mixture. The white crystals obtained weighed 23.2 g. (63%) and melted at 136–137°.

It was often found necessary to purify the compounds by converting the hydrochlorides to the free bases with alkali. The hydrochlorides were then reobtained by passing a stream of hydrogen chloride through ethereal solutions of the free bases. The precipitates thus formed were filtered off and recrystallized from the proper solvents.

**β-Diethylaminoethyl (1-Hydroxycyclohexyl)-phenylacetate Methiodide.**—Five grams of β-diethylaminoethyl (1-hydroxycyclohexyl)-phenylacetate hydrochloride, 100 cc. of ether and 25 cc. of a concentrated solution of sodium bicarbonate were vigorously stirred for 15 minutes. The ether layer was separated, dried over anhydrous potassium carbonate and filtered. The ether solution was then evaporated to dryness, the residue dissolved in 25 cc. of ethanol and an excess of methyl iodide (3.7 g.) added. After allowing the solution to stand at room temperature for a few hours, the alcohol and excess methyl iodide were driven off on the steam-bath under reduced pressure. The residue was dissolved in a mixture of ethyl acetate and ethanol, from which 5.4 g. (83%) of crystalline material melting at 139–141° was obtained.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

## The Basic Isomerization of Allyl Aryl Sulfides to Propenyl Aryl Sulfides<sup>1a</sup>

By D. S. TARBELL AND M. A. MCCALL

A series of allyl aryl sulfides has been shown to isomerize readily on treatment with base to the corresponding propenyl aryl sulfides. The structures have been established in most cases by catalytic reduction of both isomers to the *n*-propyl aryl sulfides, as well as by consideration of the infrared and ultraviolet spectra. The compounds studied are the allyl derivatives of thiosalicylic and 3,5-dichlorothiosalicylic acids, allyl 2-pyridyl sulfide and allyl phenyl sulfide. The latter has been shown to isomerize to a mixture of *cis*- and *trans*-propenyl phenyl sulfides, which have been separated as the sulfilimines by chromatography. The usefulness of hydrogenolysis of sulfilimines to regenerate the parent sulfides has been demonstrated. The mechanism of the isomerization of the allyl sulfides is believed to involve a removal of a proton to form an anion stabilized by contributions from forms with a decet of electrons around sulfur.

The present work was undertaken as part of a general comparison of the cleavage of carbon-sulfur and carbon-oxygen bonds in analogous compounds.<sup>1b</sup> It seemed that a study of the behavior on heating of allyl aryl sulfides should yield results of value in this connection, because the thermal rearrangement of the allyl aryl ethers (Claisen rearrangement) has been studied intensively.<sup>2</sup> In the only previous study on allyl aryl sulfides, Hurd and Greengard<sup>3</sup> found that allyl phenyl and allyl *p*-tolyl sulfides rearranged very much more

slowly than the corresponding oxygen compounds to give small yields of the allylthiophenols. Since it is known<sup>4</sup> that compounds such as I undergo rearrangement (with loss of carbon dioxide) much more rapidly than the ethers which lack the carboxyl group, it appeared that compounds of the type II should be suitable for the purpose we had in mind. During the preparation of the allyl compound II, we observed that it was readily isomerized by base into the propenyl sulfide. This behavior, which appears to be general, forms the subject of the present paper.

3,5-Dichlorothiosalicylic acid (VIII) was obtained from methyl 3,5-dichloro-2-aminobenzoate<sup>5</sup> in 70% yield by the Leuckart xanthate reaction.<sup>6</sup>

(1) (a) Presented at the 118th Meeting of the American Chemical Society, Chicago, Ill., Sept. 7, 1950. (b) Earlier papers on this topic: Harnish and Tarbell, *THIS JOURNAL*, **70**, 4123 (1948); Rylander and Tarbell, *ibid.*, **72**, 3021 (1950); Wilson and Tarbell, *ibid.*, **72**, 5200 (1950). For a review of the cleavage of the carbon-sulfur bond, see D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, **49**, 1 (1951).

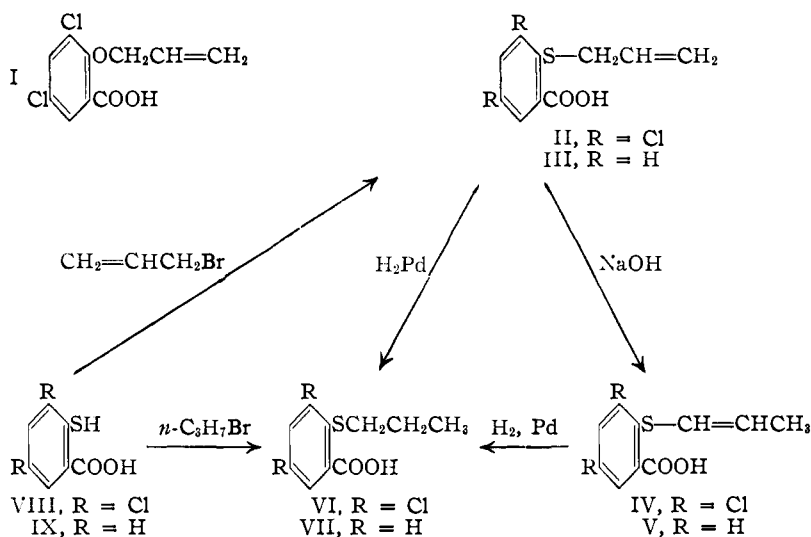
(2) For a review, see "Organic Reactions," Vol. 11, John Wiley and Sons, New York, N. Y., pp. 1–48.

(3) Hurd and Greengard, *THIS JOURNAL*, **52**, 3356 (1930).

(4) (a) Claisen and Eisleb, *Ann.*, **401**, 21 (1913); Claisen, *ibid.*, **418**, 69 (1918); (b) Tarbell and Wilson, *THIS JOURNAL*, **64**, 607 (1942).

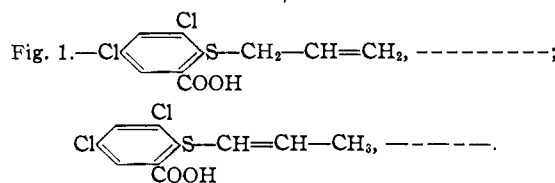
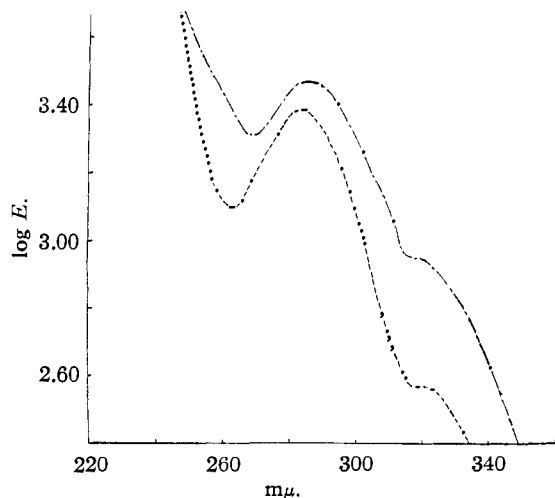
(5) Freudler, *Bull. soc. chim.*, **49**, 606 (1911).

(6) *Cf. Org. Syntheses*, **27**, 81 (1947).



Alkylation of this compound with allyl bromide and sodium hydroxide in aqueous acetone, followed by alkaline hydrolysis of the initially formed ester, led to a mixture of two readily separated isomeric compounds, melting at 85.5–87° and 73.5–74.5°. The 87° compound was converted to the 75° isomer by refluxing for 12 hours with 10% aqueous alkali, and hence the latter was believed to be the propenyl sulfide IV; its presence in the alkylation product of the thiosalicylic acid VIII was believed to be due to isomerization, by the alkaline hydrolysis, of the initially formed allyl sulfide II (the 87° compound).

Both compounds were shown to have the same carbon skeleton in the side-chain by catalytic reduction with palladium-charcoal catalyst<sup>7</sup> to yield the same *n*-propyl compound VI, which was identical with a sample prepared by alkylation of the dichlorothiosalicylic acid VIII with *n*-

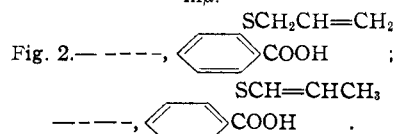
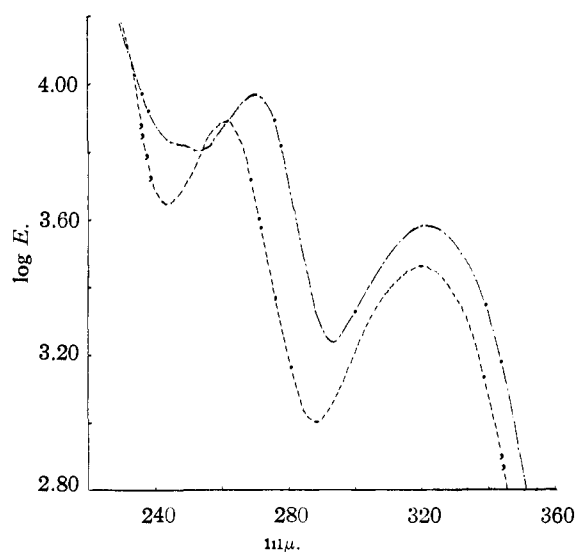


(7) Cf. Cope, Morrison and Field, *THIS JOURNAL*, **72**, 66 (1950).

propyl bromide. The hydrogenation of the allyl compound II was accompanied by a certain amount of hydrogenolysis of the carbon-sulfur bond, with the formation of the thiosalicylic acid VIII; this behavior was not shown by IV, and is in agreement with the structure assigned, because some allyl ethers have been found to undergo hydrogenolysis on catalytic reduction.<sup>8</sup>

The structures assigned to the two isomers are in agreement with the ultraviolet absorption curves (Fig. 1); the two curves are similar in shape, but that for the 75° isomer shows a bathochromic shift of about 8–10 mμ, compared to that of the 87° isomer. The interaction of the side-chain double bond with the aromatic ring through the sulfur atom should be stronger with the propenyl than with the allyl isomer, and hence the former should absorb at longer wave lengths.<sup>9</sup>

A study of the allyl derivative III of unchlorinated thiosalicylic acid IX showed that the presence of the nuclear chlorine atom was not necessary for the isomerization of the allyl group. The behavior of this series exactly paralleled that of the dichloro compounds, and the structures were established in the same way; the ultraviolet absorption curves (Fig. 2) showed a similar bathochromic shift for the propenyl compound.



Allyl 2-pyridyl sulfide (X) was prepared by the alkylation of 2-mercaptopyridine<sup>10</sup> with allyl bro-

(8) Cf. Mumm, Hornhardt and Diederichsen, *Ber.*, **72**, 100 (1939); Bergmann and Heimhold, *J. Chem. Soc.*, 1365 (1935).

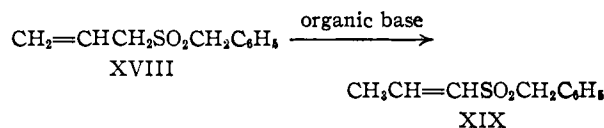
(9) Cf. (a) Bader, Cross, Heilbron and Jones, *ibid.*, 619 (1949); (b) Koch, *ibid.*, 387 (1949).

(10) Thirtle, *THIS JOURNAL*, **63**, 342 (1946).

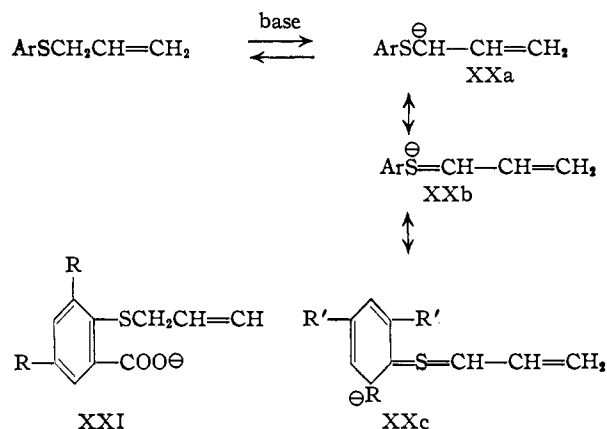


shown that artificial mixtures of the *cis* and *trans* forms of XVI containing 50–60% of the *trans* form showed the same melting point behavior as the mixture obtained from the isomerization product. It is possible that, in the isomerizations of II, III and X discussed above, *cis-trans* isomers were formed, and that only one of these was isolated pure. This may be the reason that the S-propenyl compound V required repeated crystallization before a sharp-melting product was obtained.

**Discussion.**—Base-catalyzed prototropic shifts are of course well known in which a carbon-carbon double bond is brought into conjugation with a carbonyl or other unsaturated group, a recent example involving sulfones being indicated below.<sup>19</sup>



The allyl sulfone XVIII in the presence of aqueous alkali yields the  $\beta$ -hydroxysulfone,  $\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{SO}_2\text{CH}_2\text{C}_6\text{H}_5$ , and none of the vinyl sulfone XIX.<sup>20</sup> The mechanism of such shifts doubtless involves removal of a proton with the formation of a resonance-stabilized anion, followed by addition of a proton on the  $\gamma$ -carbon atom. The occurrence of the shift in the cases described in this paper must involve the formation of the anion XX, which is stabilized significantly by contributions from resonance forms such as XXb and XXc, in which sulfur has a deficit of electrons. The effect of divalent sulfur in increasing the acidity of the hydrogen on



an adjacent carbon atom has been noted previously,<sup>21</sup> and this effect is emphasized in the cases of II and III in the present work, because in basic solution these acids would exist as the carboxylate ions, which nevertheless must readily undergo removal of a second proton from the methylene group, to allow the isomerization of the double bond to occur.<sup>22</sup>

The contrast between sulfur and oxygen in promoting prototropic change is shown by our observation that the oxygen analog of II, the dichloro-

salicylic acid derivative I, was recovered unchanged after treatment with base under conditions which isomerized the sulfur compound II. This is in line with the fact that oxygen, being in the first row of the periodic table, cannot expand its valence shell beyond eight electrons.

These observations support the conclusions of Koch,<sup>9b</sup> arrived at from a study of ultraviolet spectra of sulfides and ethers, that in sulfides of the type  $-\text{S}-\text{C}=\text{C}$ , there was interaction of the carbon-carbon double bond with the sulfur, through hyperconjugative forms in which the sulfur acted both as electron acceptor and donor.<sup>23</sup> Such interaction was completely lacking in the corresponding oxygen compounds.<sup>9b</sup>

### Experimental<sup>24</sup>

**3,5-Dichlorothiosalicylic Acid<sup>8</sup> (VIII).**—Methyl 3,5-dichloro-2-aminobenzoate<sup>8</sup> (43.8 g.) was added slowly with stirring to about 500 cc. of concentrated hydrochloric acid, the resulting slurry was heated until solution was nearly complete and was then cooled to 4° with vigorous stirring. A solution of 17.1 g. of sodium nitrite was added, and the mixture was stirred for an hour below 10°. The diazotization was assumed to be complete if a small sample of the diazotization mixture did not precipitate any solid when added to excess water.

Water (about 30 cc.) was added, the solution was cooled to 0° and neutralized with a slurry of about 350 g. of sodium bicarbonate, then back-titrated with a few cc. of concentrated hydrochloric acid until faintly acid to congo red paper. The cold diazonium solution thus prepared was added with good stirring to a solution of 64.1 g. of potassium ethyl xanthate in 85 cc. of water, keeping the temperature of the latter at 40–45°. The mixture was stirred for 30 minutes after the addition was complete; it was then cooled and the red, oily layer separated. The aqueous layer was extracted twice with small portions of ether, the combined oil and ether extracts were washed with aqueous alkali, then with water, the solution dried and the solvent removed. The residue was saponified by refluxing eight hours with a solution of 46.6 g. of potash in 150 cc. of 95% ethanol.

The alcohol was removed on the steam-bath, the residue was dissolved in a minimum of water and extracted with three 15-cc. portions of ether, the extracts being discarded. The aqueous solution was made strongly acidic with sulfuric acid, the precipitated product was collected, washed and dried, and was then refluxed overnight in glacial acetic acid with 25–30 g. of zinc dust to reduce any disulfide which might be present. The solid was collected, washed with cold water, digested with concentrated hydrochloric acid for about 30 minutes, then filtered again, washed with cold water and dried. The product, after crystallization from ethanol, weighed 31 g. (70%), and melted at 207–208°.

*Anal.* Calcd. for  $\text{C}_7\text{H}_4\text{Cl}_2\text{O}_2\text{S}$ : C, 37.68; H, 1.80; Cl, 31.79; S, 14.37. Found: C, 37.87; H, 1.80; Cl, 31.5; S, 14.3.

Oxidation of the compound with iodine yielded the known disulfide,<sup>26</sup> m.p. 262–263.5°.

**S-Allyl-3,5-dichlorothiosalicylic Acid (II) and S-Propenyl-3,5-dichlorothiosalicylic Acid (IV).**—Allyl bromide (72.6 g.) was added dropwise to a well stirred dispersion containing 13.2 g. of sodium hydroxide, 33.5 g. of 3,5-dichlorothiosalicylic acid in 550 cc. of acetone and 50 cc. of water. This reaction mixture was refluxed for eight hours. More water (100 cc.) and allyl bromide (72.6 g.) were then added, and the mixture was refluxed for another eight hours. The excess acetone and allyl bromide were distilled from the reaction mixture, and the resulting oil was separated from the water layer. The water layer was extracted with ether, the oil and ether extracts were combined and the ether was removed on the steam-bath. The resulting oil was then

(19) Backer and de Jonge, *Rec. trav. chim.*, **67**, 884 (1948).

(20) Rothstein, *J. Chem. Soc.*, 684 (1934).

(21) Rothstein, *ibid.*, 1550 (1940); Gilman and Webb, *This Journal*, **62**, 987 (1940); Woodward and Eastman, *ibid.*, **68**, 2229 (1946).

(22) A somewhat similar case involving removal of a proton from an anion is discussed by Teich and Curtin, *ibid.*, **72**, 2481 (1950).

(23) Cf. Fehnel and Carmack, *ibid.*, **71**, 2889 (1949).

(24) All m.ps. corrected; analyses by Miss Claire King and Micro-Tech Laboratories.

(25) The reported m.p. (Hart, McClellan and Fowkes, *J. Chem. Soc.*, 2117 (1938)) is 263°.

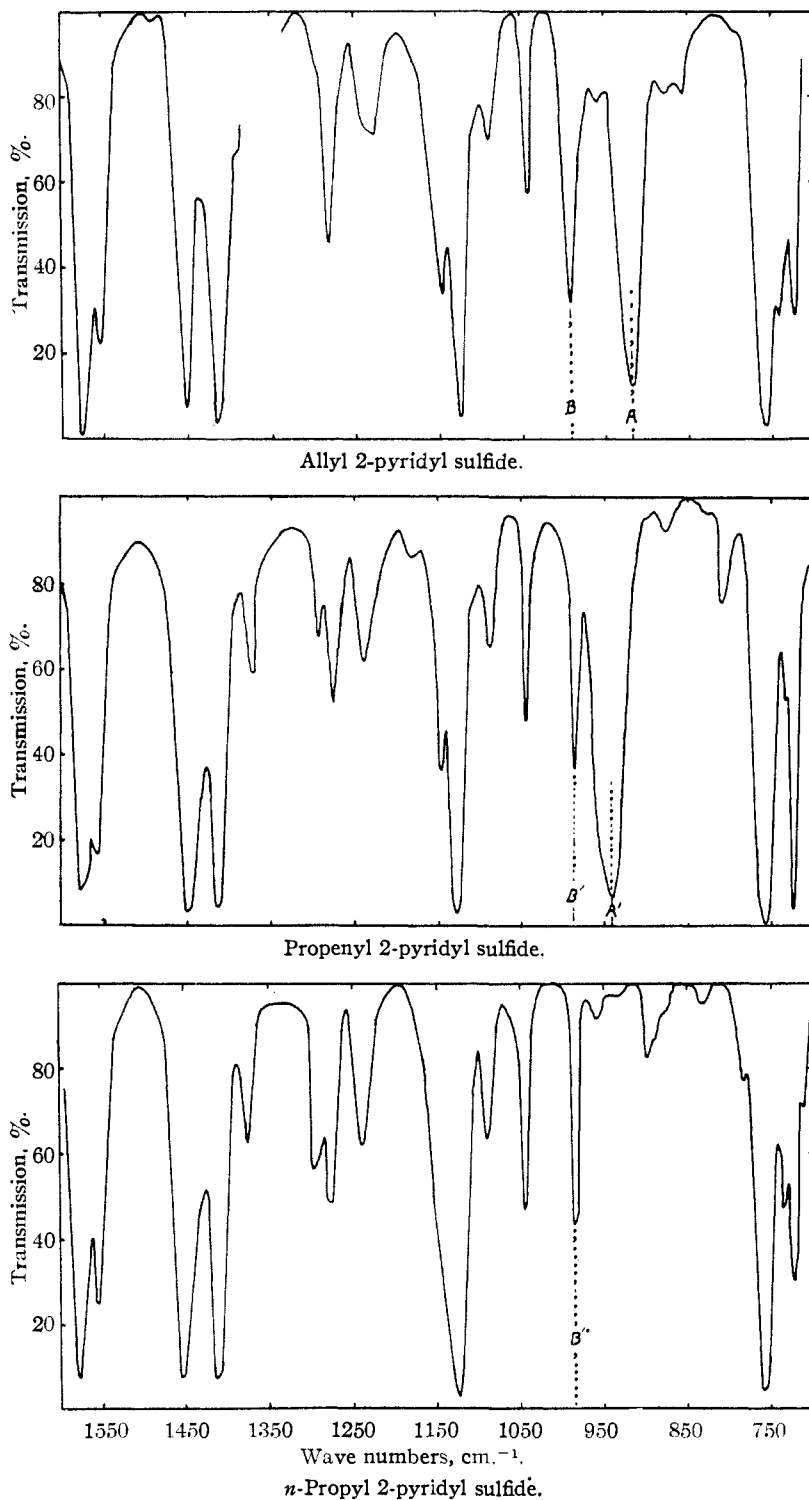


Fig. 3.—Infrared absorption spectra.

hydrolyzed by heating on steam-bath for 15 hours in 200 cc. of 10% sodium hydroxide solution containing 45 cc. of ethyl alcohol. The resulting solution was acidified and the oil layer separated. The water layer was extracted with ether, which was combined with the oil and the solvent was removed on the steam-bath. The oil was dissolved in 5% sodium bicarbonate solution, and extracted with two 50-cc. portions of ether, and the ether extracts were discarded. The bicarbonate solution was treated with Norite, filtered, diluted to 1.5 l. with ice and water, and acidified with concentrated hydrochloric acid. The product crystallized on

stirring, yielding 35.7 g. (91%) of material melting at 68.5–70.5°. This material was recrystallized from 200 cc. of heptane, which gave 25.1 g. of crystalline material melting at 80.5–82.5°, and 11.5 g. of material melting at 70.5–72.5°. These two samples were recrystallized separately three more times from heptane, and two distinct products with constant m.ps. of 85.5–87° and 73.5–74.5° were obtained.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_8\text{Cl}_2\text{O}_2\text{S}$ : C, 45.64; H, 3.06; Cl, 26.95; S, 12.18; neut. equiv., 263.1. Found (87° compound, the allyl isomer II): C, 45.88; H, 3.31; Cl, 26.6; S, 12.2; neut. equiv., 264.9. Found (75° compound, the propenyl isomer IV): C, 45.74; H, 3.10; Cl, 27.0; S, 12.3; neut. equiv., 265.8.

**Isomerization of the Allyl Sulfide II to the Propenyl Sulfide IV.**—Two grams of II (m.p. 85.5–87°) was dissolved in 50 cc. of 10% sodium hydroxide solution and refluxed for 12 hours, filtered, and then precipitated by making the solution acid with concentrated hydrochloric acid. The precipitated product was recrystallized from heptane. The yield was 1.0 g. (50%), m.p. 71–73°. A mixed melting point with II (85.5–87°) gave a melting range of 73–76.5°. A mixed m.p. with a sample of the propenyl compound (m.p. 73.5–74.5°) isolated from the alkylation reaction as above showed a m.p. of 73–73.5°.

**Attempted Isomerization of O-Allyl-3,5-dichlorosalicylic Acid (I).**—Compound I,<sup>4b</sup> the oxygen analog of II, was not isomerized when refluxed for fifteen hours with 10% sodium hydroxide solution. The solution turned dark and there appeared to be some decomposition, but over 50% of the starting material was recovered unchanged.

**S-*n*-Propyl-3,5-dichlorothiosalicylic Acid (VI).** A. **By Catalytic Reduction of the S-Propenyl Compound (IV).**—Palladium-on-Norite catalyst (5%) was suspended in 20 cc.<sup>26</sup> of 95% ethanol and stirred with hydrogen at atmospheric pressure until there was no further absorption. The catalyst was filtered by suction and washed with ethanol, returned to the reduction flask and stirred with hydrogen until absorption of hydrogen had again stopped. A solution of 1.21 g. of S-propenyl-3,5-dichlorothiosalicylic acid (IV) (m.p. 73.5–74.5°) in 25 cc. of ethanol was added, and the mixture stirred with hydrogen at atmospheric pressure for approximately five hours or until 100% of one molar equivalent of hydrogen was absorbed. The catalyst was removed by filtration and digested twice with 25 cc. of boiling ethanol. The solvent from the combined filtrates was removed under reduced pressure, and the residue was extracted with 5% sodium bicarbonate solution and the product was precipitated with concentrated hydrochloric acid. This product (0.54 g.) was recrystallized three times from hexane by cooling the hexane solution in Dry Ice-acetone-bath, and melted at 64–66°; the reduced product no longer absorbed bromine, and was shown to be identical by mixed m.p. with the S-*n*-propyl-3,5-dichlorothiosalicylic acid prepared by alkylation below.

B. **By Catalytic Reduction of the S-Allyl Compound (II).**—The S-allyl compound (II, 2.42 g.) was subjected to the

(26) Catalyst C. *Org. Syntheses*, **26**, 78 (1946).

same reductive procedure described above except that the time required for absorption of 106% of one molar equivalent of hydrogen was only 25 minutes. The product (0.71 g.) obtained from two extractions of the catalyst with boiling ethanol was in turn extracted with hexane. The hexane insoluble part (0.34 g.) and the material (0.30 g.) obtained from a 10% sodium hydroxide extract of the catalyst were combined and recrystallized from methyl alcohol, yielding a product (0.15 g.), m.p. 206–208°. A mixed m.p. with an authentic sample of 3,5-dichlorothiosalicylic acid (VIII, m.p. 206–207°) showed no depression. The hexane-extracted product (0.37 g.) was recrystallized twice from hexane containing a small amount of Darco. The purified product (0.2 g.) melted at 64.5–66.5°, and gave no depression on mixed m.p. with an authentic sample of the *S*-*n*-propyl compound.

C. By Alkylation of 3,5-Dichlorothiosalicylic Acid (VIII) with *n*-Propyl Bromide.—*n*-Propyl bromide (16.6 g.) was added dropwise to a well-stirred suspension of 3,5-dichlorothiosalicylic acid (10.0 g.) and powdered sodium hydroxide in 200 ml. of methyl ethyl ketone at approximately 75°. The addition of *n*-propyl bromide required about 45 minutes and the mixture was then stirred at reflux for approximately three hours. A second portion (10.0 g.) of *n*-propyl bromide was added dropwise to compensate for the loss of *n*-propyl bromide through evaporation. The mixture was refluxed for an additional hour, then stirred overnight without heat. Water (50 cc.) and acetone (50 cc.) were then added to the reaction mixture to dissolve the insoluble salts and a third portion (10.0 g.) of *n*-propyl bromide was added, and refluxed for four more hours. The methyl ethyl ketone was removed under reduced pressure and the remaining oily product was refluxed for four hours in a 10–15% sodium hydroxide solution to hydrolyze any ester present. The product was then precipitated with concentrated hydrochloric acid. The oil thus obtained was seeded with a crystal of the reduction product above and crystallization of the oil followed immediately. The crystals were dissolved in a 5% sodium bicarbonate solution, reprecipitated with concentrated hydrochloric acid, and were then recrystallized from hexane; the product (9.0 g., 75%) melted at 65–66.5°.

Anal. Calcd. for  $C_{10}H_{10}Cl_2O_2S$ : C, 45.31; H, 3.80. Found: C, 45.42; H, 3.76.

*S*-Allylthiosalicylic Acid (III).—Allyl bromide (53.2 g.) was added dropwise to a vigorously stirred suspension of 53.2 g. of potassium carbonate and 42.3 g. of thiosalicylic acid<sup>27</sup> in 300 cc. of methyl ethyl ketone and 100 cc. of acetone. This reaction mixture was allowed to stir for three hours, during which time it was gradually brought to reflux

(27) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., p. 580.

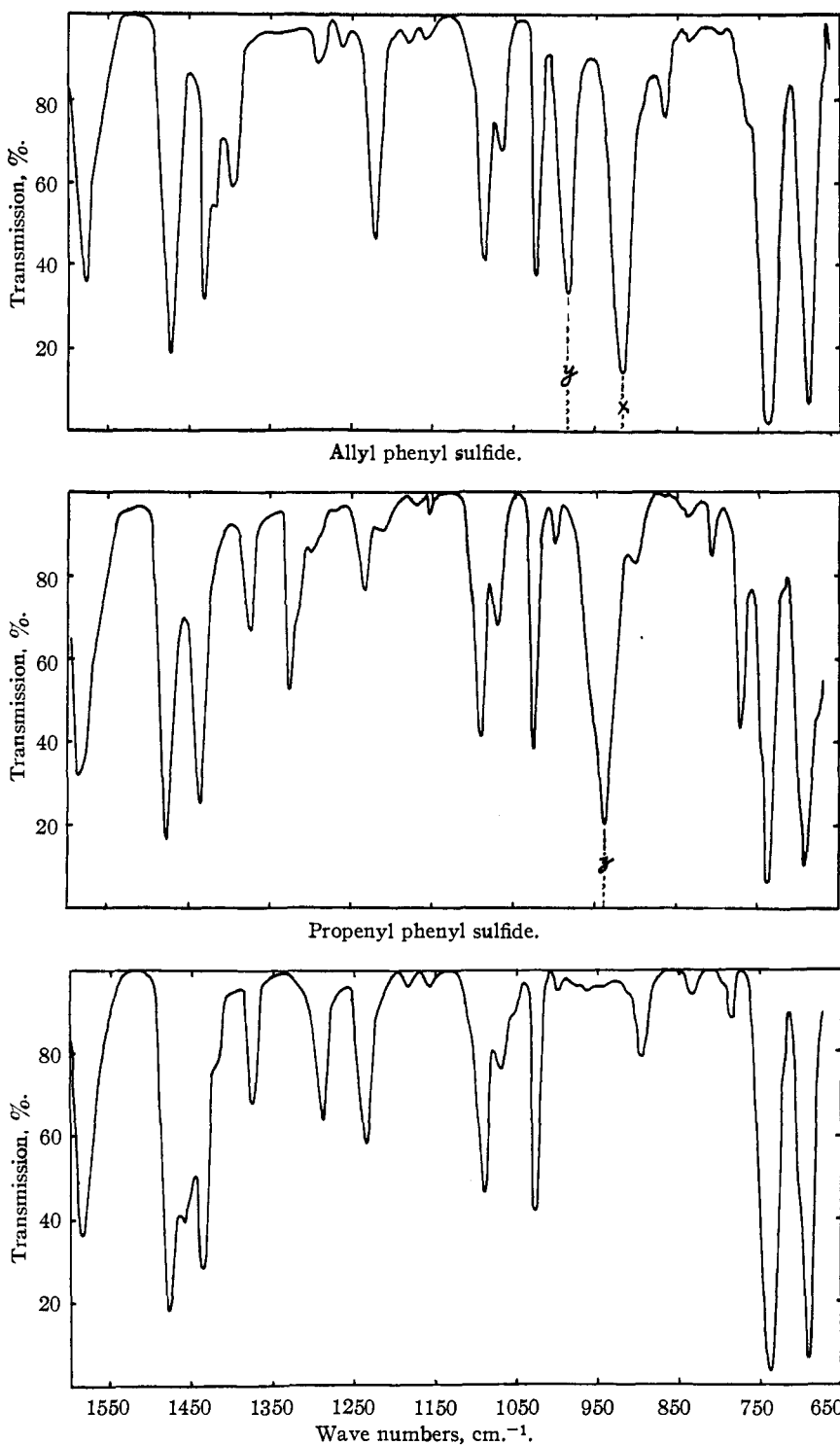


Fig. 4.—Infrared absorption spectra.

temperature. More allyl bromide (53.2 g.) and 25 cc. of water were then added and refluxing was continued for 16 hours. The reaction mixture was then concentrated under reduced pressure to approximately 50 cc. To this was added 200 cc. of 15% sodium hydroxide solution and the mixture was refluxed for one hour. It was allowed to stand overnight, was then diluted with water to approximately 750 cc., filtered and acidified with concentrated hydrochloric acid. The precipitated product was dissolved in 700 cc. of 5% sodium bicarbonate solution, treated with Norite, filtered, cooled and reprecipitated with concentrated hy-

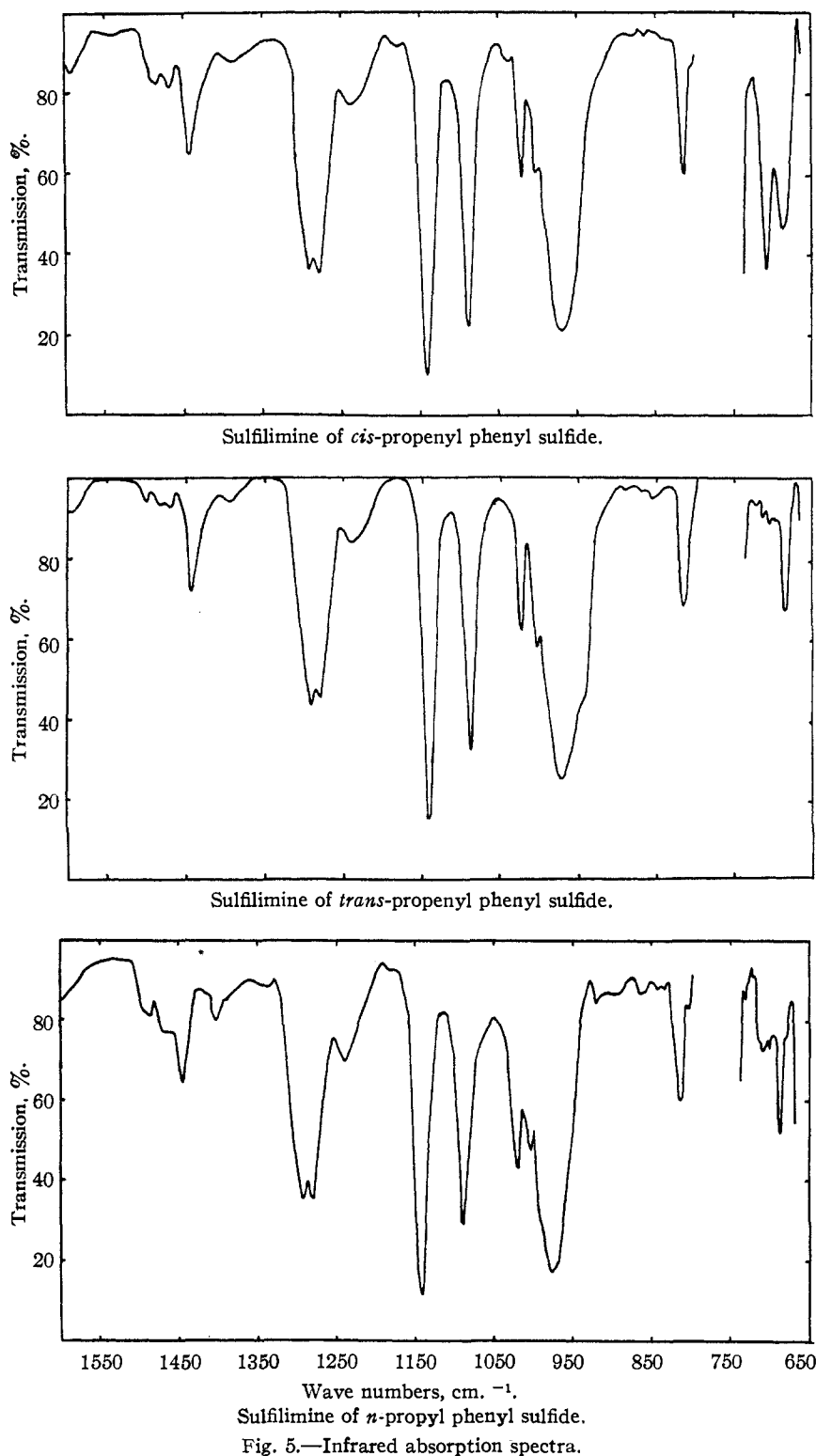


Fig. 5.—Infrared absorption spectra.

drochloric acid. The crude product (42.5 g., 93%) m.p. 106–110°, after repeated crystallization from heptane melted at 113–114° but, in spite of a careful search, an isomeric compound could not be isolated.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{10}\text{O}_2\text{S}$ : C, 61.83; H, 5.19; neut. equiv., 194.2. Found: C, 61.83; H, 5.17; neut. equiv., 194.9.

**Isomerization of S-Allylthiosalicylic Acid (III) to S-Propenylthiosalicylic Acid (V).**—S-Allylthiosalicylic acid (4 g.) was dissolved in 100 cc. of 10% sodium hydroxide solution

and refluxed for 15 hours under an atmosphere of nitrogen. The cooled mixture was then diluted to 200 cc., filtered and precipitated by making the solution acid with concentrated hydrochloric acid. The product was recrystallized once from heptane and once from ethyl alcohol. It was then dissolved in a 5% sodium bicarbonate solution and treated with Norite, reprecipitated with hydrochloric acid, and recrystallized a final time from heptane; the product (2 g., 50%) melted at 144–146°.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{10}\text{O}_2\text{S}$ : C, 61.83; H, 5.19; neut. equiv., 194.2. Found: C, 61.81; H, 5.24; neut. equiv., 195.2.

**S-*n*-Propylthiosalicylic Acid (VII).** A. **By Catalytic Reduction of the S-Allyl Compound (III).**—The procedure was essentially the same as described above for the reduction of II and IV. The absorption of one mole of hydrogen was complete within fifteen minutes. The yield after several recrystallizations from heptane was 1.38 g. (59%) of material melting at 122.5–124°, showing no depression on mixed m.p. with an authentic sample prepared by alkylation of thiosalicylic acid with *n*-propyl bromide.<sup>28</sup>

B. **By Catalytic Reduction of the S-Propenyl Compound (V).**—The S-propenyl compound was reduced by the procedure described above to the S-propylthiosalicylic acid in 57% yield; the identity of the compound was proved by a mixed m.p. with an authentic sample.

**Allyl 2-Pyridyl Sulfide (X).** A. **By Alkylation of 2-Mercaptopyridine.**—Powdered sodium hydroxide (24.0 g.) was added to a hot, vigorously stirred solution of 55.37 g. of 2-mercaptopyridine<sup>10</sup> in 500 cc. of methyl ethyl ketone. The mixture became very hot and some salt precipitated. To this mixture was added 61.5 g. of allyl bromide dropwise. The reaction mixture was cooled with ice-water from time to time. After the addition of the allyl bromide (ten minutes), the reaction mixture was stirred for three hours on the steam-bath, cooled, and the salt was filtered off. The filtrate was carefully neutralized with a few drops of acetic acid, and the methyl ethyl ketone was removed *in vacuo*. The crude material (87 g.) was added to 300 cc. of *n*-heptane and a small amount of precipitated dark oil (probably the disulfide) was removed by filtration.

The heptane filtrate was then washed with two 25-cc. portions of 10% sodium hydroxide. The 10% sodium hydroxide was then washed with 25 cc. of *n*-heptane and the heptane solutions combined. The heptane solution was then passed through a column of activated alumina, and the solvent was removed from the eluate *in vacuo*. Vacuum distillation of the residue yielded 53.4 g. (71%) of material with the following properties: b.p. 77–86° (3.5 mm.),  $n_D^{20}$

(28) Donlevy and English, *THIS JOURNAL*, **62**, 220 (1940), report the m.p. as 121°.

1.5716. The product was carefully fractionated three times through a 6-in. helix-packed column, and 30.8 g. of pure product (41%) obtained, with the following properties: b.p. 85–87° (3 mm.);  $n_D^{20}$  1.5811;  $d_4^{20}$  1.0778. More material (18 g.) was accounted for in slightly lower-boiling fractions, and all fractions gave picrates of the same m.p. (see below).

*Anal.* Calcd. for  $C_8H_9NS$ : C, 63.53; H, 5.99;  $M_D$  46.19. Found: C, 63.57; H, 6.06;  $M_D$ , 46.75.

The picrate was prepared in alcohol, and melted, after crystallization from alcohol, at 114–115.5°.

*Anal.* Calcd. for  $C_{14}H_{12}N_4O_7S$ : C, 44.21; H, 3.19. Found: C, 44.38; H, 3.32.

The pure picrate (5 g.) was decomposed by Burger's procedure<sup>13</sup> and after fractionation through a helix-packed column, 1.35 g. (68%) of the allyl 2-pyridyl sulfide,  $n_D^{20}$  1.5812, was obtained. This showed that the material described above was pure, because the refractive indices were identical.

**B. By Action of S-Allylthiouonium Bromide on 2-Bromopyridine.**<sup>12</sup>—A solution of 3.9 g. of potassium hydroxide was added to a hot solution of S-allylthiouonium bromide<sup>10</sup> (5.5 g.) and 2-bromopyridine (4.4 g.) containing a trace of potassium iodide. There was an immediate precipitate of potassium bromide. The reaction mixture was heated at reflux for an additional three hours and then allowed to stand overnight. The solid potassium bromide was removed by filtration and the alcohol by distillation. The residue was diluted with 250 cc. of water and then extracted with three 50-cc. portions of purified heptane. The heptane was then removed under slightly reduced pressure. The remaining oil (2.75 g.) was added to an alcohol solution of picric acid (4.12 g.) and heated on a steam-bath until the precipitate that first formed was completely dissolved. Upon cooling there was obtained 3.25 g. of picrate (m.p. 81–85°) which was recrystallized from ethyl alcohol. The yield of pure picrate melting 114–115° was 1.05 g. (10%). A mixed melting point with the picrate of allyl phenyl sulfide obtained by Method A showed that the two compounds were identical.

**Isomerization of Allyl 2-Pyridyl Sulfide (X) to Propenyl 2-Pyridyl Sulfide (XII).**—Allyl 2-pyridyl sulfide (5 g.,  $n_D^{20}$  1.5811) was refluxed for 12 hours with 75 cc. of Claisen alkali in a nitrogen atmosphere. The two layers were separated, the alkaline layer was extracted with ether, and the extract was combined with the oil layer. Fractionation of the residue from the ether solution through a 7-in. helix-packed column yielded 2.7 g. (54%) of material, b.p. 88–93° (4 mm.), with  $n_D^{20}$  varying from 1.5969 to 1.5974.

The picrate was prepared in good yield in alcohol, and melted, after two recrystallizations from the same solvent, at 154–155°.

*Anal.* Calcd. for  $C_{14}H_{12}N_4O_7S$  (picrate): C, 44.21; H, 3.19. Found: C, 44.42; H, 3.23.

This process of isomerization and preparation of the picrate was repeated several times on larger quantities of the allyl compound and the over-all yields were somewhat better. The average over-all yield of purified picrate (m.p. 154–155°) based on starting material before isomerization was 25%. The yield of a high melting picrate (145–150°) was always high (75–85%), but the purification by repeated recrystallization to a constant melting picrate was accompanied by great loss.

The purified picrate (6 g.) was converted to the free propenyl pyridyl sulfide XII by the lithium hydroxide method,<sup>13</sup> and 2.01 g. (84%) of pure product was obtained after two distillations; it had the following properties: b.p. 72° (0.6 mm.);  $n_D^{20}$  1.5970;  $d_4^{20}$  1.0842.

*Anal.* Calcd. for  $C_8H_9NS$ : C, 63.53; H, 5.99;  $M_D$  46.19. Found: C, 63.52; H, 6.18;  $M_D$ , 47.53 (exaltation 1.34).

***n*-Propyl 2-Pyridyl Sulfide.**—*n*-Propyl bromide (12.3 g.) was added dropwise to a warm, well-stirred solution of 2-mercaptopyridine (11.2 g.) in 150 cc. of methyl ethyl ketone containing 5.0 g. of powdered sodium hydroxide. The tem-

perature rose to reflux temperature during the addition and the flask was cooled externally from time to time. After the addition was complete, the reaction mixture was stirred at reflux temperature for one hour and allowed to stand overnight. The solid salt was filtered off, the filtrate was concentrated to one-third its original volume, filtered again and 100 cc. of purified *n*-heptane was added. A brown precipitate formed and was filtered off. The heptane solution was then purified further by passing it through a small column of activated alumina which removed most of the color. The heptane was then removed *in vacuo* and the residue yielded, after distillation, 9.4 g. (62%) of product of the following properties: b.p. 53–55° (1 mm.);  $n_D^{20}$  1.5595;  $d_4^{20}$  1.0466.

*Anal.* Calcd. for  $C_8H_{11}NS$ : C, 62.69; H, 7.23;  $M_D$ , 46.65. Found: C, 62.93; H, 7.17;  $M_D$ , 47.31.

The picrate, prepared in ethanol, melted, after several recrystallizations from that solvent, at 124–125.5°.

*Anal.* Calcd. for  $C_{14}H_{14}N_4O_7S$ : C, 43.97; H, 3.69. Found: C, 43.87; H, 3.76.

**Allyl Phenyl Sulfide (XIII).**—This compound was prepared in good yield by alkylation of thiophenol in alcoholic sodium ethoxide with allyl bromide,<sup>8</sup> and had the following properties, which agree well with those previously reported<sup>17</sup>: b.p. 59–60° (1.5 mm.);  $n_D^{20}$  1.5760;  $d_4^{20}$  1.0275; the exaltation ( $M_D$  calcd. 47.66; found, 48.38) was appreciable, in agreement with earlier work,<sup>7</sup> and suggested that there might have been some isomerization of the allyl to the propenyl isomer by the sodium ethoxide during synthesis. Therefore the allyl phenyl sulfide was also prepared using aqueous sodium hydroxide for the alkylation, with the idea that the smaller solubility of the sulfide in the aqueous solution should diminish the amount of isomerization by the base. However, material prepared in this way had the same refractive index as that from the first method, and the exaltation must be a property of allyl phenyl sulfide.

The allyl phenyl sulfide was reduced catalytically with hydrogen and palladium-charcoal to *n*-propyl phenyl sulfide, which was identified by conversion to the crystalline sulfilimine and comparison with an authentic sample, described later.

The sulfilimine of allyl phenyl sulfide was prepared by treating a solution of 5 g. of the sulfide in 10 cc. of acetone with a solution of 12.2 g. of chloramine-T in 25 cc. of ice-water; the mixture was shaken for one hour, then allowed to come to room temperature and was extracted with chloroform. The chloroform was removed on the steam-bath, and the viscous residue was diluted with benzene, which, on cooling, gave a precipitate of *p*-toluenesulfonamide, which was separated by filtration. The *p*-toluenesulfonamide was identified by a mixed m.p. with an authentic sample. The residue was dissolved in ether, treated with Darco, and was then cooled in a Dry Ice-acetone-bath. Crystals formed, which after several recrystallizations from ether, gave a constant melting point of 33–34°. The yield was 5.8 g. (58%).

*Anal.* Calcd. for  $C_{10}H_{11}O_2NS_2$ : C, 60.16; H, 5.36. Found: C, 60.00; H, 5.15.

**Isomerization of Allyl Phenyl Sulfide (XIII) to Propenyl Phenyl Sulfide (XIV).**—The allyl phenyl sulfide was unchanged (judging by the refractive index) after refluxing for eight hours with tributylamine. It was isomerized by refluxing two days with Claisen alkali, but the following procedure gave better results.

The sulfide (8.0 g.,  $n_D^{20}$  1.5760) was refluxed for 12 hours in a nitrogen atmosphere in a solution prepared from 3.5 g. of sodium and 100 cc. of absolute alcohol. The reaction mixture was diluted to 500 cc. with ice-water and extracted four times with 100-cc. portions of ether; the ether solution was washed with water, dried and the solvent was removed. The oily residue was distilled from a Claisen flask (b.p. 61–69° (1.3 mm.)). The distillate was collected as three separate fractions, which were later combined when the refractive indices were found to be the same ( $n_D^{20}$  1.5860); the yield was 7.61 g. (95%). Material of  $n_D^{20}$  1.5850, from an isomerization using Claisen alkali, was analyzed.

*Anal.* Calcd. for  $C_8H_{10}S$ : C, 71.95; H, 6.71. Found: C, 71.61; H, 6.56.

**Preparation and Separation of the Sulfilimines (XVIa and XVIb) from *cis*- and *trans*-Propenyl Phenyl Sulfides.**—Propenyl phenyl sulfide (21.6 g.) was dissolved in ethyl alcohol (150 cc.) and mixed with a cold solution (800 cc.) of chlora-

(29) Using the value of 7.97 for S (Price and Twiss, *J. Chem. Soc.*, 102, 1264 (1912)), the value of 3.77 for C—N=C (Eisenlohr, *Z. physik. Chem.*, 75, 146 (1912)), and other values from Eisenlohr, *ibid.*, 75, 605 (1911).

(30) Werner, *J. Chem. Soc.*, 57, 299 (1890).



mine-T (80.4 g.) in alcohol and water (50%). The resulting solution was heated gently on a steam-bath for one hour, and allowed to evaporate to approximately one-half of its original volume. More water was added until the hot solution just began to cloud, and it was set aside to crystallize. The crystals were collected, washed with water, and with ether; the yield was 35.8 g. (78.6%) of crude material. This product was dissolved in ethyl alcohol, treated with Darco, diluted with water until the hot solution became slightly cloudy, and was allowed to crystallize. The yield of pure material was 27.45 g. (62%), m.p. 94.5–99°.

*Anal.* Calcd. for  $C_{16}H_{17}O_2NS_2$ : C, 60.16; H, 5.36. Found: C, 59.95; H, 5.24.

Numerous attempts to obtain sharp-melting sulfilimines by recrystallization of the above mixture were unsuccessful. It was, however, separated into the pure *cis* and *trans* forms by chromatography, as follows.

The sulfilimine (20 g., m.p. 94.5–99°) prepared as above was dissolved in 2 l. of C.P. benzene and passed through a 3.5 × 90 cm. column packed with Florisil<sup>31</sup> (60–100 mesh). Elution with 2 l. of pure benzene followed by elution with 2 l. of benzene containing 1% of chloroform did not remove any product from the column. The chloroform content of the eluting mixture was increased to 5%, then to 50% chloroform–benzene, and finally to pure chloroform. A total of 40 l. of solvent was used in the eluting; the solvent was recovered and recycled. The course of the separation was followed by taking the m.p. of the solid obtained from 1-l. portions of the eluate.

The recovery of the material from the benzene and chloroform mixtures amounted to a crude yield of 13.3 g. The balance of the material (6.5 g.) was obtained from the column by eluting it with acetone. After combining and recrystallizing like samples, the over-all recovery was 15.71 g. (78%). The material that was obtained by eluting with 5% chloroform was almost pure *trans*-compound, m.p. 111–112.5°. After recrystallization from ethyl alcohol and water the yield of pure *trans*-compound was 3.55 g. (18%).

The material that was removed from the column by acetone was fairly pure *cis*-compound. The yield of *cis*-compound, m.p. 122–123.5° after several recrystallizations from benzene–pentane, and finally from water–alcohol, was 4.05 g. (20%). The material obtained from the intermediate fraction appeared, from the m.p., to be a mixture of the *cis* and *trans* forms and was not investigated further.

*Anal.* Calcd. for  $C_{16}H_{17}NO_2S_2$ : C, 60.16; H, 5.36. Found (*cis*, 123° compound, XVIa): C, 60.28; H, 5.24. Found (*trans*, 112° compound, XVIb): C, 60.07; H, 5.45.

A melting point–composition curve was prepared from known mixtures of the pure *cis* and *trans* isomers, and the sulfilimine mixture obtained above (m.p. 94.5–99°) was shown to contain about 60% of the *trans* and 40% of the *cis* form.

**Proof of Structure of the *cis*- and *trans*-Propenyl Phenyl Sulfides. Hydrogenolysis of the Sulfilimines.**—The mixed sulfilimines XVI (2 g.) were reduced in 95% alcohol at atmospheric pressure with 7.0 g. of 5% palladium–Norite catalyst.<sup>26</sup> The hydrogen uptake was very rapid with the absorption of 179 cc. (114%) of one mole within 20 minutes. The Norite catalyst was removed by filtration, and the alcohol by vacuum distillation. A white residue was washed with hexane to remove traces of propenyl phenyl sulfide;

the dried product (0.9 g.) (85%) melted at 135–136.5° and a mixed melting point with an authentic sample of *p*-toluenesulfonamide was not changed. It was noted by its odor that the alcohol distillate contained the propenyl phenyl sulfide and it was therefore returned to the reduction flask with the same catalyst. The absorption of the hydrogen was again rapid, 137 cc. (88% of one molar equivalent) was absorbed within 30 minutes and it then stopped. Stirring in an atmosphere of hydrogen was continued for one hour after absorption had stopped. The total uptake for the two steps was 306 cc. (calcd. for two moles 308 cc.). The catalyst was removed by filtration; the alcohol was removed at atmospheric pressure through a short column on a steam-bath, and the oily residue containing some alcohol was diluted with 10 cc. of water and 10 cc. of acetone. Two grams of chloramine-T dissolved in ice-water was next added and the mixture shaken vigorously for half an hour. After cooling in ice-bath for an additional ten minutes, the product was filtered and washed with cold water, ether and was dried; the product melted at 84.5–85.5°. A mixed m.p. with an authentic sample of the sulfilimine of *n*-propyl phenyl sulfide (see below) was 84.5–86°. The sulfilimines of propenyl phenyl sulfide (5.8 g.) (m.p. 97.5–102°) was subjected to hydrogenolysis with hydrogen using palladium–Norite catalyst. The hydrogenolysis was stopped when 90% of one mole equivalent of hydrogen had been absorbed. The liquid sulfide was obtained in the usual way and distilled twice. The yield was 0.71 g. b.p. 58–59° (0.8–1.0 mm.),  $n_D^{20}$  1.5690. The refractive index was much too low, showing that some of the propenyl phenyl sulfide had been reduced to propyl phenyl sulfide during the hydrogenolysis. The infrared spectrum was identical with a curve obtained from propenyl phenyl sulfide before the sulfilimine was formed, indicating that the amount of contaminating reduced product was small.

The purified sulfilimines of the *cis*- and *trans*-propenyl phenyl sulfides were each reduced, by essentially the above procedure, with the absorption of 2 moles of hydrogen, to *n*-propyl phenyl sulfide. This was characterized in each case by conversion to the sulfilimine, and followed by a mixed m.p. with an authentic sample.

**Sulfilimine of *n*-Propyl Phenyl Sulfide (XVII).**—*n*-Propyl phenyl sulfide was obtained in 63% yield by the action of *n*-propyl bromide on thiophenol in alcoholic potash; the properties were b.p. 89–90° (7 mm.),  $n_D^{20}$  1.5546.<sup>32</sup>

The sulfilimine was prepared in aqueous acetone, and the product, after recrystallization from benzene–ether, melted at 85–86°.

*Anal.* Calcd. for  $C_{16}H_{19}NO_2S_2$ : C, 59.78; H, 5.95. Found: C, 59.49; H, 5.88.

**Spectroscopic Measurements.**—The ultraviolet absorption curves were obtained with a Beckman spectrophotometer, using 95% alcohol as solvent.

The infrared curves were obtained with a Perkin–Elmer spectrometer, model 12 A-B, and were measured in Nujol suspension (for solid samples) and without solvent, for liquid samples; the sulfilimines were measured in chloroform. We are greatly indebted to Mr. Carl Whiteman for his work in obtaining the tracings.

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(31) Obtained from the Floridin Company, Warren, Pa.

(32) The reported value (Ipatieff, Pines and Friedman, THIS JOURNAL, 60, 2731 (1938)) is  $n_D^{20}$  1.5571.