All five of the cholesteryl oxides prepared react with "pyridine hydrochloride" and benzoyl chloride to give 5-hydroxy-6-chlorocholestane derivatives.

β-Cholesterol oxide, as its acetate, has been converted to α-cholesterol oxide through the 5-hydroxy-6-chloro compound.

The stereochemical implications of these reactions have been pointed out.

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[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME, INC.]

Synthesis of *p*-Hydroxyphenyl Amyl Sulfide

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A previous publication from these Laboratories[1] confirmed the report[2] that the hydroxyphenyl alkyl sulfides were more powerful in their bactericidal activity than the corresponding alkylphenols. These results prompted us to seek a practical method for the preparation of *p*-hydroxyphenyl *n*-amyl sulfide, which had been shown to possess maximum activity for the compounds in this series.

The hydroxydiphenyl sulfides have been prepared by Hilbert and Johnson[3] by use of the Ziegler[4] reaction between diazotized anisidine and thiophenol. The diazothio ether thus formed breaks down at 70° to give a methoxydiphenyl sulfide which is converted into the desired product by dealkylation. They reported that an attempt to prepare *p*-hydroxydiphenyl sulfide by treating diazotized *p*-aminophenol with sodium thiophenate was unsuccessful. Suter and Hansen[2] treated diazotized anisidine with potassium ethyl xanthate and decomposed the intermediate diazonium ethyl xanthate to obtain *p*-methoxythiophenol which then reacted with amyl bromide and the product was dealkylated to give *p*-hydroxyphenyl *n*-amyl sulfide. They also reported an unsuccessful attempt to combine the sodium salt of butanethiol-1 with diazotized *p*-aminophenol.

In the previous publication,[1] a more satisfactory procedure was developed which involved the synthesis of thiohydroquinone and subsequent reaction of this with amyl bromide to give the desired *p*-hydroxyphenyl *n*-amyl sulfide. The success of the thiohydroquinone synthesis suggested that diazotized *p*-aminophenol should react with the sodium salt of *n*-amyl mercaptan, even though previous workers[2,3] had been unsuccessful with similar reactions. An extensive study of possible experimental conditions for the reaction has shown that it can be used to prepare the compound in yields of 25–30%.

The diazotization was carried out at a temperature of 0–10° and the diazothio ether decomposed by heating at 60°. The resulting product was distilled and gave a yield of 50–60% of a material which solidified at room temperature. However, on crystallizing the material from solvent naphtha the yield of *p*-hydroxyphenyl *n*-amyl sulfide dropped to 25–30%. Careful fractionation of the reaction mixture disclosed that two definite products were formed during the reaction and permitted the isolation of the second product with its purification. The product was identified by preparation of derivatives and synthesis as di-*n*-amyl disulfide. The reaction has been applied to *n*- and isoamyl mercaptan with comparable results.

Experimental Part

***p*-Hydroxyphenyl *n*-Amyl Sulfide.**—*p*-Aminophenol, 21.8 g. (0.2 mole), was dissolved in 110 cc. of 4 *N* hydrochloric acid (0.44 mole) and diazotized in the usual manner by the slow addition of a solution of 15 g. (0.23 mole) of sodium nitrite in 30 cc. of water. The mixture was stirred until the diazotization was complete (starch–iodide paper test) and the deep purple solution of *p*-hydroxyphenyldiazonium chloride rapidly filtered from a small amount of insoluble material. The solution was then added slowly to a cold (10°) sludge of 24 g. (0.23 mole) of *n*-amyl mercaptan in 75 cc. of water containing 37.5 g. (0.94 mole) of sodium hydroxide. The temperature was maintained at 10° throughout the addition and frothing was controlled by the addition of small amounts of *n*-butanol. After the reaction had subsided, the cooling bath was removed and stirring continued at room temperature until the diazonium salt disappeared (R-salt test). The mixture was then heated to 60° to complete the decomposition of the diazothio ether and allowed to stand overnight at room temperature, after which it was diluted with five volumes of water, acidified with concentrated hydrochloric acid and extracted with 500 cc. of toluene. The extract was washed three times with 500-cc. portions of water, dried over anhydrous

(1) Miller and Read, THIS JOURNAL, **55**, 1224 (1933).
(2) Suter and Hansen, *ibid.*, **54**, 4100 (1932).
(3) Hilbert and Johnson, *ibid.*, **51**, 1526 (1929).
(4) Ziegler, *Ber.*, **23**, 2469 (1890).

sodium sulfate, and the toluene removed by distillation at atmospheric pressure. The residue was distilled rapidly at about 2 mm. pressure to separate the distillable portion (20 g. of orange-yellow oil which solidified on standing) from a heavy tar. A slow redistillation of this product gave 16 g. of a light yellow oil, boiling over a range of 110–140° (1 mm.), which solidified immediately.

Material (120 g.) from several of the above runs was carefully fractionated, through a 12″ indented column, insulated with a glass air-jacket. into two main fractions:

Fraction A, 45 g., b. p. 89–91° (1 mm.), $n^{20}D$ 1.4876, d^{25}_{25} 0.9224, was identified as di-*n*-amyl disulfide.[5] Reduction with metallic sodium in anhydrous ethanol[6] gave a solid sodium salt of *n*-amyl mercaptan which reacted with 2,4-dinitrochlorobenzene on refluxing in anhydrous ethanol to give 2,4-dinitrophenyl *n*-amyl sulfide, m. p. 79.5–80°, identical with the product, m. p. 80°, prepared from *n*-amyl mercaptan,[7] and by the reduction of synthetic di-*n*-amyl disulfide. The material also readily formed a crystalline derivative, m. p. 134–136°, which resolidified and did not remelt up to 250°, when treated with mercuric chloride in an alcohol solution at room temperature for seven hours which was identical with the derivative from synthetic di-*n*-amyl disulfide.

Fraction B, 45 g., b. p. 142–145° (1 mm.), was recrystallized twice from solvent naphtha and gave 37 g. of *p*-hydroxyphenyl *n*-amyl sulfide, m. p. 62–62.5°.[1]

p-Hydroxyphenyl isoamyl sulfide,[1] a red oil, b. p. 134–136° (1 mm.), $n^{25}D$ 1.5523, was prepared by the above reaction using isoamyl mercaptan and di-isoamyl disulfide, b. p. 94–96° (1 mm.), isolated as the by-product.

Di-*n*-amyl Disulfide.—(A) This compound was prepared by the method described in "Organic Syntheses" for *p,p'*-dinitrodiphenyl disulfide.[8] To 180 g. (0.75 mole) of sodium sulfide, dissolved in 750 cc. of 95% ethanol with refluxing, was added 24 g. (0.75 atom) of sulfur and the mixture stirred until dissolved. *n*-Amyl bromide, 151 g. (1 mole), dissolved in 250 cc. of 95% ethanol, was placed in a two-liter, three-necked flask, and the hot sodium disulfide solution was added at such a rate as to maintain gentle refluxing.[9] The addition was complete in about twenty minutes and the mixture refluxed on the steam-bath for three hours, after which it was allowed to stand overnight at room temperature. Alcohol was removed to about one-third volume by distilling at reduced pressure (water pump), two volumes of water added and the mixture extracted with 500 cc. of benzene. The extract was washed several times with water, dried over anhydrous sodium sulfate, and, after removing the benzene, the di-*n*-amyl disulfide distilled through the 12″ column as a colorless liquid, b. p. 90–92° (1 mm.); yield 62 g., $n^{25}D$ 1.4875; d^{25}_{25} 0.9212.

(B) *n*-Amyl mercaptan, 52 g. (0.5 mole), was dissolved in a solution of 22 g. (0.55 mole) of sodium hydroxide in 125 cc. of water and oxidized by the addition of 60.3 g. (0.475 atom) of iodine in small portions over a period of twenty minutes according to the method of Kekulé and Linnemann[10] for the preparation of diethyl disulfide. The mixture was stirred until all of the iodine dissolved and then extracted with 200 cc. of benzene. The extract was washed three times with water, dried over anhydrous sodium sulfate and the benzene removed by distillation. The yield of di-*n*-amyl disulfide was 36 g.. b. p. 101–103° (2 mm.). $n^{25}D$ 1.4868.

Summary

p-Hydroxyphenyl *n*-amyl sulfide has been prepared in yields of 25–30% by the diazotization of *p*-aminophenol, coupling with sodium *n*-amyl mercaptide, and decomposition of the diazothio ether. A second product was obtained from this reaction in a yield of 25% and has been identified as di-*n*-amyl disulfide by preparation of derivatives and synthesis.

p-Hydroxyphenyl isoamyl sulfide was prepared in the same manner and di-isoamyl disulfide obtained as a second product.

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(5) (a) Rosser and Ritter, THIS JOURNAL, **59**, 2179 (1937); (b) Blackburn and Challenger, *J. Chem. Soc.*, 1872 (1938).

(6) Reid, *et al.*, THIS JOURNAL, **48**, 776 (1926).

(7) Bost, Turner and Norton, *ibid.*, **54**, 1985 (1932).

(8) "Organic Syntheses," Coll. Vol. I, p. 215.

(9) The reaction between the amyl halide and sodium disulfide was not as energetic as that between nitrochlorobenzene and sodium disulfide.

(10) Kekulé and Linnemann, *Ann.*, **123**, 277 (1862).