

ORIGINAL PAPERS

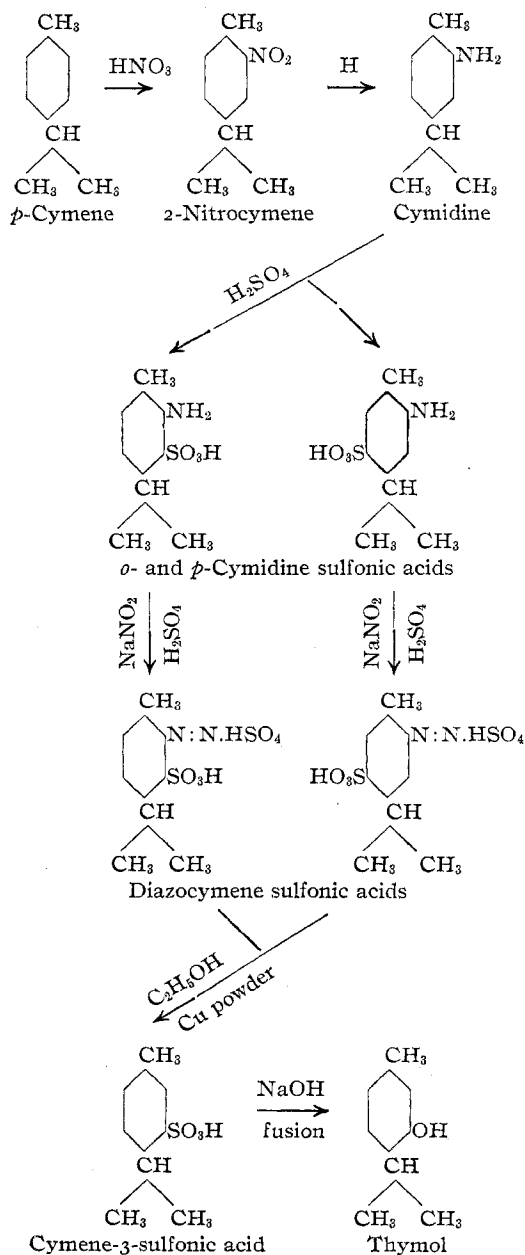
A SYNTHESIS OF THYMOL FROM *p*-CYMENE

By Max Phillips and H. D. Gibbs

COLOR LABORATORY, BUREAU OF CHEMISTRY, WASHINGTON, D. C.

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When *p*-cymene, 1-methyl-4-isopropyl benzene, is sulfonated or nitrated, substitution takes place very largely in the position ortho to the methyl group.



Although it has been reported that the second isomer also forms during the sulfonation or nitration, its relative amount is too small to be of any practical value. Hence the two common methods of making phenols from their corresponding hydrocarbons, *viz.*, (1) decomposition of the diazo derivative, especially the sulfate, with boiling water and

(2) fusion of the sulfonic acid with potassium or sodium hydroxide, cannot be used in making thymol from *p*-cymene. In order to bring about this synthesis an indirect method must be adopted, and of the several possible methods the one outlined herewith was used.¹

As indicated above, both the *o*- and *p*-cymidine sulfonic acids may be formed by sulfonating cymidine. However, so far as the synthesis of thymol is concerned, it is immaterial which is formed, since both give one and the same cymene sulfonic acid.

HISTORICAL REVIEW

Thymol was first synthesized by Widman² in 1882. This classical synthesis very well illustrates the rather indirect method that has to be used. Starting with cuminal, nitro-cuminal was prepared, the nitro group entering the position meta to the aldehyde group. This compound when treated with phosphorus pentachloride was converted into nitro-cymyline chloride, which on reduction with zinc and hydrochloric acid gave 3-aminocymene, and upon diazotization and subsequent hydrolysis thymol resulted.

Thymol has since been synthesized by a number of chemists,³ but only two of these syntheses need be considered in this connection because of their close relationship to the present method.

Dinesmann⁴ obtained a patent on a process of making thymol from 2-brom-*p*-cymene. This process consists in sulfonating 2-brom-*p*-cymene, obtaining 2-brom-3- or 5-sulfonic acid, which when heated with zinc dust and ammonia in an autoclave at 170° gives cymene 3-sulfonic acid. This compound on fusion with potassium hydroxide gives thymol.

Recently a patent has been granted to Andrews⁵ on a process of making thymol from cymidine (2-aminocymene). Cymidine is first acetylated, then nitrated, whereupon the nitro group enters meta to the methyl group. The acetyl group is hydrolyzed off and the amino group removed through diazotization and subsequent reduction of the diazo compound with alkaline stannous chloride or with boiling alcohol. The nitro compound thus obtained is then reduced to the corresponding amino compound, which on diazotization and subsequent hydrolysis gives thymol.

EXPERIMENTAL

ISOLATION OF *p*-CYMENE FROM CRUDE OIL—The starting material for this work was *p*-cymene isolated from a crude oil obtained from a sulfite spruce pulp mill. The oil after standing over lime for about a week was subjected to steam distillation. To the distillate about one-fourth its volume of sulfuric acid was added, and the mixture stirred in the cold by means of a mechanical stirrer. After 2 hrs. stirring the dark acid was separated from the oil, a fresh

¹ Phillips, U. S. Patent 1,332,680 (1920).² *Ber.*, **15** (1882), 166.³ *Ibid.*, **29** (1896), 420; *Nachr. kgl. Ges. Göttingen*, **1903**, 223; *Ber.*, **39** (1906), 1163; **41** (1908), 3993.⁴ D. R. P., 125,097 (1900).⁵ U. S. Patent 1,306,512 (1919).

quantity of sulfuric acid added and the stirring continued. This operation was carried on until a sample of the oil after being washed with water gave a very slight yellowish color when shaken with sulfuric acid. The oil was then washed with water, dried over calcium chloride, and distilled over sodium, using a Glinsky still head. Practically all of the material came over from 174° to 175° (759.6 mm. pressure), leaving only a small amount of dark-colored oil in the flask.

PREPARATION OF NITROCYMENE AND CYMIDINE—For the preparation of nitrocymene the method developed in this laboratory¹ was used. The nitro group enters in the ortho position with respect to the methyl group. The reduction of this compound to aminocymene or cymidine was accomplished by means of iron powder and hydrochloric acid in exactly the same way as nitrobenzene is reduced to aniline.

CONVERSION OF CYMIDINE TO CYMIDINE SULFONIC ACID—Cymidine sulfonic acid was first prepared by Widman² in 1886. Starting with cymidine sulfate, he prepared the sulfonic acid by heating one part of the sulfate with two parts of fuming sulfuric acid at 160° to 165° until a test portion, when made alkaline with sodium hydroxide solution, showed the complete absence of globules of cymidine. Using his method, only small quantities of the sulfonic acid could be obtained, the yield being in the neighborhood of 4 to 5 per cent of the theory. A considerable amount of material decomposed during the process of heating with the fuming acid. The method adopted was essentially the same as that used in the preparation of sulfanilic acid by the so-called "baking process."³ The process was carried out as follows: To 61 cc. of concentrated sulfuric acid 160 g. of cymidine were added in small quantities at a time, stirring after each addition of the cymidine. The cymidine sulfate was placed in an oven and heated for 6 hrs. at about 200°. The mass on cooling was ground and dissolved in hot water. Upon making the solution distinctly alkaline with sodium hydroxide the cymidine which had escaped sulfonation separated as an oil and was recovered by steam distillation. The residue in the flask was concentrated, if necessary, boiled with animal charcoal, filtered, and acidified with hydrochloric acid. Cymidine sulfonic acid separated out as a crystalline mass. The yield of cymidine sulfonic acid was about 30 g. (32 per cent yield calculated on the 60 g. of cymidine actually used up) and the unused cymidine recovered amounted to 100 g. An analysis of the cymidine sulfonic acid for sulfur gave the following results:

Per cent S Found	Per cent S Calculated for $C_{10}H_{12}NH_2SO_3H$
14.12	13.98
14.16	...

DIAZOTIZATION OF CYMIDINE SULFONIC ACID AND ITS CONVERSION INTO CYMENE 3-SULFONIC ACID—Widman⁴ in 1886 prepared diazocymene sulfonic acid

by suspending cymidine sulfonic acid in dilute alcohol and diazotizing in the cold with nitrous acid. However, his attempt to convert this compound into cymene 3-sulfonic acid was not successful, as an ethoxy derivative of it was obtained. That the diazo group of certain compounds, when boiled with alcohol, is replaced by the ethoxy group instead of hydrogen, has been observed by a number of chemists.¹ It has been found, however, that when certain substances such as copper powder, zinc dust, sodium ethylate, sodium hydroxide, potassium carbonate, or sodium methylate are added to the diazo compound, complete reduction takes place without the formation of the ethoxy derivative.² For the preparation of cymene 3-sulfonic acid from cymidine sulfonic acid, the following modification of Widman's method was used: One-tenth of a mole (22.9 g.) of the cymidine sulfonic acid was suspended in about 400 cc. of 95 per cent alcohol, 20 cc. concentrated sulfuric acid added, and diazotized in the cold in the usual manner. After diazotization the solution was allowed to stand in the cold for an hour, and then 10 g. of copper powder were added in small quantities at a time, allowing the rapid evolution of nitrogen to subside before making any further additions. The mixture was filtered and the filtrate distilled on the water bath. The residue in the flask was diluted with water, boiled with barium carbonate, filtered, and the filtrate containing the barium salt of cymene 3-sulfonic acid was treated with sodium carbonate and the sodium salt of the sulfonic acid obtained. This sodium salt was converted into thymol, as follows: Thirty grams of 98 per cent sodium hydroxide were treated with a little water and heated in a nickel crucible, with stirring, to 280°. To this 10 g. of the sulfonate were added, with stirring. After all the salt had been added the temperature was raised to 310° and kept there for about 15 min., when the reaction was complete. The melt on cooling was dissolved in water, acidified with hydrochloric acid, and steam distilled. The distillate was extracted with ether, dried over anhydrous sodium sulfate and fractionated after distilling off the ether. Nearly all of the product distilled over at the boiling temperature of thymol. From one-tenth of a mole of cymidine sulfonic acid about 6 g. of thymol oil could be obtained (a 40 per cent yield calculated on the cymidine sulfonic acid used). The thymol obtained was identified by its phenylurethane derivative (m. p. 107°).

SUMMARY

Thymol has been synthesized from *p*-cymene. The process consists in nitrating *p*-cymene; reducing this 2-nitrocymene to 2-aminocymene or cymidine; sulfonating the cymidine by the "baking process" used in the preparation of sulfanilic acid; diazotizing the cymidine sulfonic acid; reducing this to cymene 3-sulfonic acid, and finally fusing the sodium salt of this acid with sodium hydroxide.

¹ THIS JOURNAL, 10 (1918), 453.

² Ber., 19 (1886), 246.

³ Z. angew. Chem., 9 (1896), 685

⁴ Loc. cit.

¹ Ann., 172 (1874), 215; 198 (1879), 25; Ber., 17 (1884), 1887; 17 (1884), 1917; 17 (1884), 2703; Ann., 230 (1884), 286; Ber., 18 (1885), 65.

² Am. Chem. J., 16 (1894), 235; 19 (1897), 163; 20 (1898), 298.