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FOOD AND DRUG LABORATORY,  
COLLEGE OF PHARMACY,  
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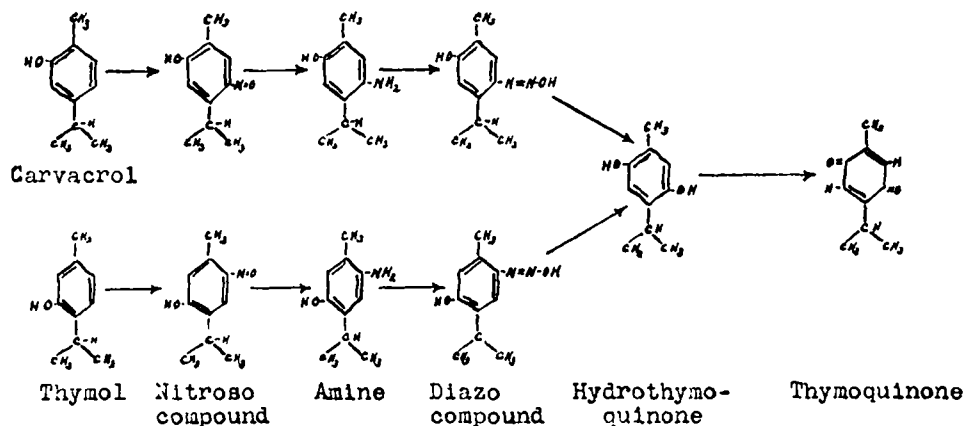
### MISCELLANEOUS CHEMICAL PAPERS.\*

#### PRODUCTION OF THYMOQUINONE ON A SEMI-COMMERCIAL SCALE IN THE LABORATORY.\*\*

BY RALPH M. HIXON.\*\*\*

A modification of the Liebermann-Illinski method<sup>1</sup> of preparing thymoquinone was developed in this laboratory,<sup>2</sup> whereby a yield of 90-93% of the theoretical amount of thymoquinone could be obtained from thymol. This reaction has now been tried on a larger scale (500-Gm. batches) with the object of ascertaining the feasibility of these proportions for the commercial production of thymoquinone from thymol or carvacrol.

The reaction can be expressed by the following series of intermediate products of which only the nitroso compound and the amine are actually isolated in the process:



The details of the method for the preparation of thymoquinone as originally developed in this laboratory were given as follows:<sup>2</sup>

"Dissolve 5 grams of thymol in 25 cc of 95 p. c. alcohol and add 25 cc of concentrated hydrochloric acid. Place this solution in a freezing mixture and add gradually, with constant stirring, crystals of sodium nitrite till 5 grams have been added. The solution at first becomes light green, then dark green, and, after a few minutes, solidifies to a bluish mass. Transfer this to a beaker containing about a liter of cold water and stir until the product becomes light yellow and fluffy in appearance. Wash this product with cold water and use it for the preparation of thymoquinone while still moist. Yield of nitrosothymol about 6 grams.

\* From the Laboratory of Edward Kremers.

\*\* This communication is a portion of a thesis submitted at the University of Wisconsin in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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"It is very necessary that the bluish mass be added to a correspondingly large volume of cold water and stirred till soft and light, and pale yellow in color, especially when large quantities (50 grams or more) of thymol are used; otherwise brownish lumps will form that will not go into solution and the yield of thymoquinone will be materially lessened. A soft, pale yellow nitroso compound means almost invariably a good yield of thymoquinone.

"Dissolve the nitroso compound in about 300 cc of 10 p. c. ammonia, with constant stirring, allowing each part to dissolve before more is added. Filter and pass in sulphuretted hydrogen until the amino compound is all precipitated. Filter rapidly on a force filter, keeping a layer of water above the precipitate while filtering and washing to prevent oxidation by contact with the air.

"Dissolve the amino compound quickly in an excess of 5 p. c. sulphuric acid (about 200 cc). Add gradually crystals of sodium nitrite till about 8 grams have been added, shaking vigorously after each addition. Heat on a water-bath, to about 60°, shaking occasionally till most of the gas has passed off. Distil with steam and separate out the thymoquinone.

"It requires several hours to prepare thymoquinone by this method. When necessary to allow it to stand over night, it was found that the best results were obtained by leaving it either in the ammonia solution or just before distilling, after adding the sodium nitrite. If proper precautions are observed an excellent yield and a pure product are obtained."

In working with thymoquinone derivatives this year, a large supply of the quinone was desired. It was found, however, that the supply of thymol was practically exhausted whereas considerable carvacrol<sup>3</sup> had accumulated in the laboratory. Carvacrol had been substituted for thymol in the production of small quantities of thymoquinone according to the above process and had been found to give satisfactory yields although no figures were available as to the exact percentage. It was accordingly used in a 200-Gm. batch and was found to yield 163 grams of thymoquinone which represents 75% of the theoretical.

In a later experiment (see p. 698 for technic), 500 grams of carvacrol yielded 560 grams of nitrosocarvacrol, which was converted into 390 grams of thymoquinone. This represents 93% of the theoretical yield of nitrosocarvacrol and 71% of the theoretical for thymoquinone. If the calculation of the percentage yield of thymoquinone is based on the yield of nitroso compound, it is only increased to 77% of the theoretical. Since no tar is encountered at any step of this reaction, we are obliged to attribute the decreased yield to greater solubility of the amine or else to incomplete reduction of the nitroso compound under the conditions used. It should be pointed out that the details of this method were worked out for thymol, not for carvacrol, and such a possibility is not unlikely. The aminocarvacrol is apparently more stable than the aminothymol. It seems probable that carvacrol would be a more suitable substance for the production of thymoquinone on a commercial scale than would thymol when the exact proportions were worked out for maximum yield. It may be added that, although carvacrol prices are not quoted on the open market and when these prices are given they range above those of thymol in value, it can be obtained from *Monarda fistulosa* quite as easily and cheaply as thymol can be obtained from *Monarda punctata*.

It was indicated above that 90-93% of the theoretical amount of thymoquinone has been obtained from thymol when working on a small scale. In working on a larger scale the yield was only 80% (500 Gm. thymol giving 430 Gm. of thymoquinone), but a part of this loss can be directly ascribed to the unexpected difficulty encountered in handling the nitroso reaction mixture on this scale. This reaction was carried out in a 10-kilo calcium chloride jar (see step 1); as the reaction approaches completion a thick mush of nitrosothymol is formed. (The nitroso-

thymol reaction mixture is more solid than is the nitrosocarvacrol reaction mixture.) The evolution of oxides of nitrogen from the nitrous acid causes the volume of this reaction mixture to increase 2 to 3 times. The jar used was not large enough for this increase in volume and it was necessary to stop the reaction by dumping into water before all of the sodium nitrite had been added. The skill gained by repetition of this reaction would undoubtedly enable the operator to at least equal the percentage yield obtained in the laboratory.



Fig. 1.

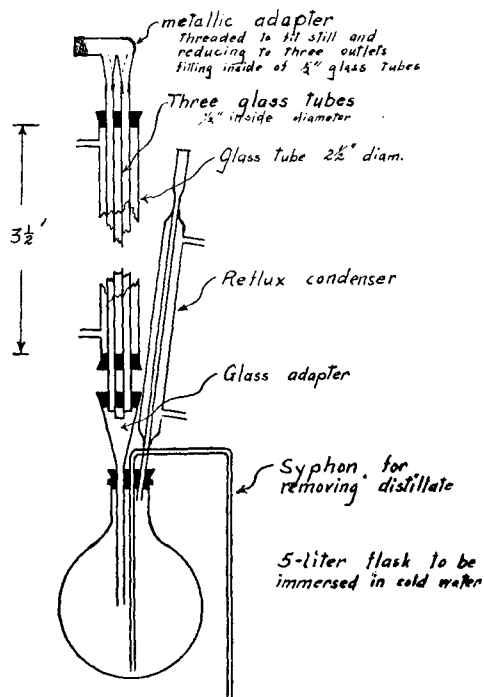


Fig. 2.—Structure of condenser recommended for the distillation of thymoquinone in the 60-liter still shown in Fig. 1.

The following details for the handling of these quantities of materials and the time required for each step are included for the convenience of laboratory workers:

1. Dissolve 500 grams thymol or carvacrol in 2.5 liters alcohol; add 2.5 liters concentrated hydrochloric acid; keep the temperature between 0–10° and add powdered sodium nitrite, slowly stirring with a stout wooden paddle. A 10-kilo calcium chloride jar surrounded by a salt-ice mixture in a 10-gallon crock was used in the experiments described above. (These two earthenware vessels with the paddle used for stirring the reaction mixture are shown in the background of the photograph, Fig. 1). This jar is too small for the thymol reaction mixture but is of convenient size for the carvacrol reaction. Time required for the addition of the sodium nitrite was approximately 1 hour; allow reaction mixture to stand 1/2 hour with frequent stirring in order to complete reaction.

2. Pour the reaction mixture slowly into 100 liters of water with brisk stirring. This step is very important for, unless the nitroso compound is washed carefully, it will separate as hard brown lumps which will form a brown tar with the ammonium hydroxide used in the next step. For this operation, three 10-gallon jars will be found convenient utensils. Time, 3/4 hour; allow to stand 1/2 hour to facilitate filtration.

3. Filter off the nitroso compound. This step involves the handling of 100 liters of liquor from which a flocculent precipitate is obtained which reduces to a volume of about 2 liters. This was accomplished quite rapidly with a water pump by fitting a 10-inch Büchner funnel by means of Gooch crucible tubing to the mouth of an aspirating bottle from which a large tube led to a carboy which in turn was connected to the water pump. (See Fig. 1.) The mouth of a carboy will be found to be too small to allow the direct insertion of a Büchner funnel and exhaust tubing. Time required,  $\frac{3}{4}$  hour.

4. Mix nitroso compound with enough water, about 5 liters, to give a thick paste and pour slowly, with frequent shaking, into a carboy containing 10 liters of concentrated ammonia plus 15 liters of water. This gives a total of 30 liters of approximately 10% ammonia containing the nitroso compound in solution from which a small amount of tar separates. The tar must be filtered off; this can be rapidly accomplished with the filter described in step 3, but the precaution of a strong draft of fresh air must be supplied to eliminate the fumes. Time required, 1 hour.

5. Pass  $H_2S$  gas into the ammoniacal solution until the nitroso compound is completely reduced to the amine. The end of the reaction can be easily detected by the change in color of the solution (solution changes from a non-transparent brownish red to a clear yellow) and by the fact that no more amine precipitates with additional gas. A large Kipp was used to generate the hydrogen sulfide. The gas was allowed to flow as rapidly as it could be generated, the precaution being taken to insert a combined wash bottle and safety valve to prevent sucking back or mechanical contamination. Time required, about 3 hours.

6. Filter off amine and wash, keeping level of water always above the precipitate to prevent decomposition. Operation same as step 4. Time required,  $\frac{1}{2}$  hour.

7. Dissolve the amine as quickly as possible in 20 liters of 5%  $H_2SO_4$ . Filter. Time required,  $\frac{1}{2}$  hour.

8. Diazotize in a carboy, by adding slowly with frequent shaking, about 800 grams sodium nitrite. Allow reaction mixture to stand over night so that the greater portion of the gases have been evolved before the distillation. It will be observed that diazotization gives the hydrothymoquinone, but an excess of sodium nitrite has been used which oxidizes the hydrothymoquinone to thymoquinone.

9. Drive off the thymoquinone by steam distillation. This operation requires careful control of the temperature of the condenser for thymoquinone solidifies at  $45^\circ$ , while the molten substance is highly volatile. The condensing system shown in the photograph (Fig. 1) was found to give satisfactory results for a 60-liter still if the operator carefully controlled the rate of volatilization by means of the steam valve. This condensing system has the disadvantage of inefficiency due to the high velocity of the vapors but offers the advantage of ease of construction for small production. For any extended work, the condenser (sketched in Fig. 2) would be more desirable. It should be pointed out that this condenser will have to be constructed so that the operator can actually watch the rate of condensation to prevent undue loss by volatilization or accident by plugging. Time required, 3 hours. This time could be greatly reduced by a more efficient condensing system. This distillation could be carried out in five 5-liter flasks.

10. The volume of distillate required for the volatilization of 430 grams of thymoquinone was only 7 liters. By cohobation this distillate yielded 0.7 gram thymoquinone per liter. The yield, therefore, can be increased about 1% by cohobation. The solid thymoquinone can be powdered, dried between filter paper in the air and used without further purification.

The condensing system consists of a 4-foot condenser leading to a 5-liter balloon flask in the large funnel. The distillate runs into this flask at a temperature of about  $60^\circ$  and is chilled by a rapid current of water kept flowing through the funnel. The flask is provided with a reflux condenser; the quinone should be occasionally pushed back into the flask from this condenser with a long glass rod to prevent plugging. A syphon tube is also provided to draw off the distillate. The stone jars used for the reaction and the filter connected to a carboy by means of an aspirating bottle can be seen in the background.

DETAILS NECESSARY FOR FIGURING COST OF PRODUCTION PER POUND OF  
THYMOQUINONE.

Total time required for the completion of the operation.....	30 hours
Actual time of one operator required during this period.....	10 hours
Apparatus—The 60-liter still was the only apparatus used which is not found in any average laboratory. This can easily be dispensed with and the distillation carried out in five 5-liter balloon flasks.	
Cost of reagents at current prices: <sup>4</sup>	
500 Gm. Thymol — \$5.00 per lb. <sup>5</sup> .....	\$5.50
500 Gm. Carvacrol — \$5.00 per lb. <sup>5</sup> .....	\$5.50
1.300 Gm. Sodium Nitrite — \$1.20 per kg.....	1.56
2½ liters Alcohol — \$0.75 per gal. <sup>6</sup> .....	.50
2½ liters Hydrochloric Acid — .07 per lb.....	.38
1 liter Sulphuric Acid — .09 per lb.....	.37
10 liters Ammonium Hydroxide — .09 per lb.....	1.80
Total.....	\$10.11
Grand total per lb. thymoquinone	
Chemicals.....	\$10
Labor.....	\$7
Overhead.....	?

SUMMARY.

The modified Liebermann-Illinski method of preparing thymoquinone from thymol or carvacrol, as developed in this laboratory, has been used in 500 Gm. batches to test the feasibility of these proportions for production on a commercial scale.

The yield of thymoquinone from carvacrol was 71% of the theoretical or practically as good as the 75% yield on a laboratory scale for this substance. The yield from thymol was 80% of the theoretical whereas 90–93% yields have been obtained in the laboratory. With increased experience, this percent yield on a large scale can be made to equal that of the laboratory. Details are given for handling these materials in the laboratory on this semi-commercial scale.

Details are given so that the cost of production can be easily calculated.

REFERENCES.

1. *Ber.*, 18, 3194, 1895.
2. *Ph. Rev.*, 26, p. 333. A historical résumé of the methods of preparation will be found in this publication.
3. The isomeric phenols thymol and carvacrol make up about 50% of the volatile oils of *Monarda punctata* and *M. fistulosa*, respectively. The thymol and carvacrol used in this laboratory have been obtained as a by-product in the experimental phyto-chemical studies of these plants.
4. The values in this table are for C. P. reagents and in many cases can be reduced by the use of commercial grades.
5. These figures are approximately the jobber's prices for 10-lb. lots at this time. The price on the open market would be higher.
6. This is the price of duty-free ethyl alcohol. Denatured alcohol is quoted at \$0.40 per gallon.