

A Chemical Study of a Mercurated Carvacrol

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In a desire to increase the therapeutic action of certain organic compounds, attempts have been made to introduce mercury into their nuclei, thereby creating a fertile field of research that has attracted the attention of many investigators who, as a result, have contributed to chemistry a good number of important organic mercury compounds. Many of the latter have found use in the treatment of diseases, while others present merely an interesting study of their chemical behavior. Because of their importance in medicine, the chemistry of organic mercury compounds has been studied to throw some light regarding the relationship between the chemical constitution and therapeutic effects of these substances.

The mercury derivatives of thymol, a phenol for instance, have been the subject of investigations. The mercury is introduced into the ring, according to Rupp (1), by reacting thymol with mercuric acetate. By nitrating the diacetoxymercuri-carvacrol, the positions occupied by the mercury complex groups have been determined. The nitrated product was found to be identical with the reported 2:6 dinitro-thymol, m. p. 55° C. From the diacetoxymercurithymol other mercury derivatives of thymol were formed.

Following Burt's (2) method of mercuriation, carvacrol and mercuric acetate in equimolecular proportion produced a diacetoxymercuri-carvacrol. When one-fifteenth of a mole of carvacrol was made to react with two-fifteenths of a mole of mercuric acetate, a greater percentage of the yield of diacetoxymercuri-carvacrol was obtained.

The carvacrol used in the experiment was obtained from Dr. Fränkel and Dr. Landau in Berlin and was purified by fractional distillation. It was identified by the phenyl urethane of carvacrol, m. p. 136-137°.

It would appear that the best possible positions for anchorage of the acetoxymercuri

radicals are the positions *ortho* and *para* to the hydroxyl group in carvacrol. We are at present engaged in the nitration of the mercurated carvacrol to determine the positions occupied by the mercury complex groups. The nitro compound of carvacrol has not yet been obtained in pure form, however.

From the results of our experiments, the mercury in the mercury derivatives of carvacrol seems to be in non-ionic form. These derivatives dissolve in sodium hydroxide solution without the precipitation of mercuric oxide. Hydrogen sulfide does not readily produce a blackening of the diacetoxymercuri-carvacrol held in aqueous suspension. Strong acids, like hydrochloric acid, cause a breakage of the mercury from the organic linking when the substance is heated. The liberated carvacrol becomes manifest by its characteristic odor. A saturated solution of sodium chloride precipitates a dichlormercuri-carvacrol from an alcoholic solution of diacetoxymercuri-carvacrol. From a warm sodium hydroxide solution of diacetoxymercuri-carvacrol a sodium compound of dihydroxymercuri-carvacrol crystallizes out on cooling. It seems that, due to its decreased solubility in alkali, the oxide of dihydroxymercuri-carvacrol with one molecule of water is precipitated as amorphous powder by passing a current of carbon dioxide into a sodium hydroxide solution of diacetoxymercuri-carvacrol. It appears that one of the two mercury atoms becomes linked with the oxygen of the phenolic hydroxyl group while the other is still attached to the ring and to the hydroxyl radical. The linking can possibly take place only with a hydroxymercuri group adjacent to the phenolic hydroxyl radical. Other derivatives of mercurated carvacrol are still under study.

The analyses of these compounds for the percentages of carbon and hydrogen were conducted according to the method of Pregl (3) in the micro-combustion apparatus. The mercury determinations were performed according to the methods of Rupp (1) and the U. S. P. XI.

A dichlormercuri-carvacrol has been reported by Burt (4) to be giving good results

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in the treatment of various skin diseases. Ointments of dichlormercuri-carvacrol in 2.5% and 5% strengths have been prepared in our laboratories and are being tried in treating cases of athlete's foot, ringworm, eczema and other skin diseases to determine the degree of success with which it can be used as a remedy for skin infections. Burt states that even a 10% ointment of the compound produces no untoward effects.

The 2.5% ointment has been tried in certain cases of burns and it was observed that there was almost instantaneous relief from the attendant pain and that the threatening blisters did not form.

EXPERIMENTAL

Diacetoxymmercuri-carvacrol.—In the presence of 12 cc. of glacial acetic acid, 10 Gm. of carvacrol with 42.4 Gm. of mercuric acetate dissolved in 125 cc. of alcohol were refluxed on a water-bath for two and a half hours. The white crystals of diacetoxymmercuri-carvacrol that appeared on cooling were filtered off by suction, washed with cold alcohol and water and then dried. The product weighed 29.9 Gm. corresponding to 67.2% of the theoretical yield. It melted at 192–195° C. with decomposition and evolution of gases. Analysis of the substance gave the following results:

5.380 mg. subs.: 4.964 mg. CO₂ and 1.254 mg. H₂O.
0.3030 Gm. subs.: 0.2112 Gm. HgS.

	C	H	Hg
Calcd.: C ₁₄ H ₁₈ O ₅ Hg ₂	(667.2)	25.19	2.7 60.12
C ₁₂ H ₁₆ O ₃ Hg	(408.6)	35.24	3.9 49.09
Found:		25.12	2.6 60.11

The white crystalline product obtained by using equimolecular quantities of carvacrol and mercuric acetate and following the same method of preparation melted also with decomposition and evolution of gases at 192–195° C. and gave the following results on analysis:

4.880 mg. subs.: 4.559 mg. CO₂ and 1.160 mg. H₂O.
0.2372 mg. subs.: 12.6 cc. 0.1119N NH₄CNS.

	C	H	Hg
Calcd.: C ₁₄ H ₁₈ O ₅ Hg ₂	25.19	2.7	60.12
C ₁₂ H ₁₆ O ₃ Hg	35.24	3.9	49.09
Found:	25.16	2.66	59.65

Dichlormercuri-carvacrol.—Ten grams of carvacrol with 42.4 Gm. of mercuric acetate in 200 cc. alcohol and 12 cc. acetic acid were refluxed on a water-bath for three hours and the reaction mixture was filtered while hot into a saturated solution of sodium chloride producing a fine white precipitate. This was filtered with suction, washed with alcohol

and water and dried. The yield of 34.22 Gm. was equivalent to 82.7% of the theoretical yield. It occurs as white powder with the property of clinging tenaciously to any surface it comes in contact with. It crystallizes out in needles when dried over sulfuric acid. It is decomposed without fusion at 216–218° C.

5.771 mg. subs.: 4.058 mg. CO₂ and 1.074 mg. H₂O.

	C	H
Calcd.: C ₁₄ H ₁₂ OHg ₂ Cl ₂	19.35	2.08
Found:	19.18	2.08

Sodium Compound of Dihydroxymmercuri-carvacrol.—Two grams of diacetoxymmercuri-carvacrol were dissolved in 10 cc. of 10% sodium hydroxide solution. The mixture is taken up with 10 cc. of boiling water and then filtered. On cooling possibly a sodium compound of dihydroxymmercuri-carvacrol crystallizes out. Only a small amount was isolated and it decomposed at 180° C. without fusion. It is insoluble in alcohol and other organic solvents, but dissolves readily in warm water.

Oxide of Dihydroxymmercuri-carvacrol.—Two grams of diacetoxymmercuri-carvacrol were treated with 10 cc. of 10% sodium hydroxide solution and to the mixture 20 cc. of boiling water were added. The solution was filtered while hot. A current of carbon dioxide was passed into the alkaline solution precipitating the oxide of dihydroxymmercuri-carvacrol. The precipitate was filtered off, washed with alcohol and water and then dried. The precipitate appeared as a fine, yellowish white amorphous powder which decomposed without fusion at 223–250° C.

Results of the analysis:

9.259 mg. subs.: 7.003 mg. CO₂ and 1.690 mg. H₂O.

	C	H
Calcd.: C ₁₀ H ₁₂ OHg ₂ ·H ₂ O	20.57	2.42
Found:	20.64	2.04

SUMMARY

From the results of the experiments, it can be concluded that a disubstituted product is produced when carvacrol is made to react with mercuric acetate. It appears that, following the method of Rupp, nitration may be used to determine the positions occupied by the acetoxymmercuri groups in the carvacrol molecule.

The curative effects of dichlormercuri-carvacrol in skin infections have been reported by Burt (4). Galenical preparations of this compound in the form of ointments are being tried here and indications point to some possibilities for the compound to find a place in medicine as a remedy for skin diseases and burns.

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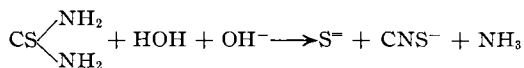
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Assay of Mercuric Chloride

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Much of the discussion which follows is applicable to other mercury compounds which are generally determined as the sulfide. Some of the work on ammoniated mercury already completed in this laboratory and which will be presented at some future time tends to confirm the conclusions of this study.

The study was prompted by an effort to avoid the use of hydrogen sulfide in the official assay of mercuric chloride. The use of organic compounds which evolve hydrogen sulfide vapors was also to be avoided. It was believed that thiourea would be suitable for this purpose, since thiourea hydrolyzes in an alkaline medium according to the following equation given by Taylor (1):



This reaction does not produce any perceptible odor of hydrogen sulfide.

The thiourea procedure was developed and the utilization of the method was found to be dependent on controlling the p_{H} of the solution during precipitation. If the solution was too alkaline, the results were low and failed to show any degree of reproducibility. The low results are due probably to the solution of mercuric sulfide, forming the complex ion, HgS_2^{--} . If the p_{H} of the solution is controlled so as to render it suffi-

ciently alkaline for hydrolysis according to the above equation, the thiourea method yields precise results, but invariably the results are high. In twenty-five determinations by the thiourea method all results ran over 100%. The precision of the series of determinations was about one per thousand.

Since the results were high by the thiourea method, the mercuric chloride was assayed according to the method of U. S. P. XI. The results, presented in Table I, indicate satisfactory precision, but, as in the thiourea method, exceed 100%. The high results, by both the thiourea method and the U. S. P. method, indicate a constant error in the sulfide precipitation of mercuric chloride. Bassett (2) states that the sulfide determination of mercuric chloride may be high by a few tenths of a per cent.

The U. S. P. directs that the precipitate of mercuric sulfide be treated with carbon tetrachloride for one-half hour, that the carbon tetrachloride be drained and that the precipitate of mercuric sulfide be treated with further portions of carbon tetrachloride, until on evaporating a 1-cc. portion of the filtrate, no visible residue remains. In spite of this treatment, the results are high. The treatment was, therefore, modified so that the precipitate of mercuric sulfide was treated with carbon disulfide from one to twenty-four hours in an arrangement described by Scott (3), whereby the precipitate is subjected to continuous extraction.

Table II shows that the average value was only slightly less when extracted with carbon disulfide than when extracted with carbon tetrachloride, although sulfur is considerably more soluble in the former. This would suggest that the amount of free sulfur present is quite small and that the amount is readily extracted by either carbon tetrachloride or carbon disulfide. If the amount of free sulfur is as small as is indicated, then treatment with either solvent may be unnecessary. A series of determinations was, therefore, made according to the U. S. P., except that the precipitated mercuric sulfide was not treated with carbon tetrachloride, nor was it treated with carbon disulfide. Table II includes the result of this series of nine determinations. The result was about

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