

Fig. 4.

Curve 2 when the solution was practically neutral, and Curve 3 when the hydrogen ion was about  $10^{-6.7}$  to  $10^{-6.1}$ .

#### Summary.

A method has been devised to follow the rate of enzyme action when oxynitrilase acts on benzaldehyde and hydrogen cyanide.

The enzyme does not have the same temperature coefficient as the spontaneous action. At  $0^\circ$  the enzyme is more efficient, at  $35^\circ$  the spontaneous action.

A new explanation has been offered for the phenomenon noticed by Rosenthaler, that the optical activity of the nitrile rises to a maximum and then falls to zero.

The hydrogen-ion concentration has a very marked effect on the ratio of spontaneous to enzyme action. When the solutions are neutral, practically all the benzaldehyde and hydrogen cyanide combine spontaneously and almost instantaneously. As the hydrogen-ion concentration is increased, the spontaneous action is repressed, and at  $10^{-5}$  to  $10^{-6}$  the enzyme exhibits its maximum activity.

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### 4-METHYL-BENZOPHENONE CHLORIDE AND ITS CONDENSATION WITH PHENOL.

By F. C. HAHN.

Received October 5, 1920.

The reaction between 4,4'-dimethyl-benzophenone chloride and phenol has been studied by Gomberg and Todd,<sup>1</sup> and the existence of the corresponding tautomeric carbinols has been indicated. In this work the condensation of 4-methyl-benzophenone chloride with phenol has been followed, and evidence obtained that the corresponding carbinol exists in 2 tautomeric forms.

<sup>1</sup> Gomberg and Todd. *THIS JOURNAL*, 39, 2392 (1917).

**4-Methyl-benzophenone Chloride.**—*p*-Tolyl-phenyl ketone was prepared by condensing toluene with benzoyl chloride in the presence of aluminum chloride.<sup>1</sup> In this manner a mixture of the *ortho* and *para* isomers was obtained. The *ortho* ketone being an oil, the *para* isomer can readily be purified by crystallization from alcohol. The keto-chloride was prepared by treating the pure ketone with a slight excess of phosphorus pentachloride, and heating the mixture for 1 to 2 hours at 110°–120°. It was found impossible to distil the mixture because of decomposition,<sup>2</sup> so the phosphorus oxychloride and pentachloride were removed under vacuum at 120°. The last traces were removed by passing dry air through the liquid at the same temperature under vacuum, and the residue used as 4-methyl-benzophenone chloride. It is a light yellow oil, and is very easily hydrolyzed to the ketone.

**Condensation with Phenol.**—The existence of 2 desmotropic forms in the case of *p*-hydroxy-triphenyl-carbinol and a series of *ortho*-substituted *p*-hydroxy-triphenyl-carbinols has been shown by Gomberg and Van Stone.<sup>3</sup> This work was taken up with the idea to determine the influence toward tautomerization of substitution in rings other than that containing the hydroxyl group. The condensation of benzophenone chloride with phenol proceeds in 3 stages as shown by Gomberg and Jickling.<sup>4</sup> Analogous results have been obtained in the condensation of 4-methyl-benzophenone chloride with phenol.

***p*-Tolyl-phenyl-diphenoxy-methane, (CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>)(C<sub>6</sub>H<sub>5</sub>):C:(OC<sub>6</sub>H<sub>5</sub>)<sub>2</sub>.**—The formation of this compound constitutes the first stage in the condensation reaction between 4-methyl-benzophenone chloride and phenol. 12.6 g. of the keto-chloride was dissolved in 150 cc. of dry benzene, and 12 g. of freshly distilled phenol added. The solution was warmed very gently on a water-bath for 3 to 4 hours under a reflux condenser, protected from moisture. It was then cooled and 1/2 of the benzene distilled off under reduced pressure. Enough ammonium hydroxide was added to give an alkaline reaction, and the resulting mixture steam distilled to remove excess phenol. After cooling, the supernatant liquid was decanted, the residue extracted with 100 cc. of 5% sodium hydroxide solution, to remove any carbinol, and washed with water. In extracting and washing it is necessary to warm the mixture so that the diphenoxy-methane becomes molten. The viscous red mass was dried and on standing became brittle.

The diphenoxy-methane is very soluble in most organic solvents except

<sup>1</sup> Elbs, *J. prakt. Chem.*, **35**, 466 (1887).

<sup>2</sup> Boeseken, *Rec. trav. chim.*, **24**, 1 (1905); *THIS JOURNAL*, **39**, 2392 (1917).

<sup>3</sup> Gomberg and Van Stone, *THIS JOURNAL*, **35**, 1035 (1913); *ibid.*, **38**, 1577 (1916).

<sup>4</sup> Gomberg and Jickling, *ibid.*, **37**, 2575 (1915).

alcohol and petroleum ether. For purification it was crystallized from alcohol; the first extraction being discarded as it contains any of the unchanged tolyl-phenyl ketone. By final crystallization from 95% alcohol by the addition of a little water, a white crystalline product is obtained which melts at 134°. On refluxing with 10% hydrochloric acid, it is decomposed into phenol and tolyl-phenyl ketone. Even on long standing this decomposition takes place, as some of the carefully purified product on standing several weeks possesses a strong odor of phenol. The product can also be crystallized from ether by the addition of a little petroleum ether. The yield of crystallized material is 60–65%.

Calc. for  $C_{26}H_{22}O_2$ : C, 85.35; H, 6.07. Found: C, 85.21; H, 6.11.

***p*-Methyl-*p*-hydroxy-triphenyl-carbinol**,  $(CH_3C_6H_4)(C_6H_5):C:(OH)-C_6H_4OH$ .—11 g. of phenol and 11 g. of 4-methyl-benzophenone chloride were mixed, protected from moisture, and left to stand for 1 to 2 days at room temperature with frequent agitation. Fifty cc. of water was added and the mixture steam distilled to remove excess of phenol. The residue, after steam distillation, was digested in 5% sodium hydroxide solution by slight warming, filtered, extracted with ether to remove all traces of tolyl-phenyl ketone, giving a clear red solution. After separating the ethereal layer, air was passed through the alkaline solution to remove the dissolved ether. The solution was then diluted with water several times, and the carbinol precipitated with carbon dioxide. After standing for a few hours it can be filtered and dried, giving a yellow powder. The yield is 80–85%. The carbinol is very soluble in all ordinary organic solvents except petroleum ether. No solvent or combination of solvents seemed to be suitable as crystallizing agent. Each time it came out of solution as an oil. Acetyl and benzoyl derivatives of the carbinol were prepared, but could not be crystallized.

In order to insure that the method of preparation of the carbinol was not responsible for its resistance to crystallization, it was prepared, as follows, by another method. The hydroxyl group of *p*-hydroxy-benzoic acid was protected by the carbo-ethoxy group, as given by Fischer.<sup>1</sup> The resulting *p*-carbo-ethoxy-*p*-oxy-benzoic acid was converted into the acid chloride, and then condensed with benzene by means of aluminum chloride. By saponification of the *p*-carbo-ethoxy-*p*-oxy-benzophenone, *p*-hydroxy-benzophenone was obtained. A Grignard reaction of *p*-tolyl-magnesium bromide with hydroxy-benzophenone gave *p*-methyl-*p*-hydroxy-triphenyl carbinol. The carbinol thus obtained was found to be identical in properties to the carbinol prepared by the condensation of 4-methyl-benzophenone chloride with phenol. It could not be crystallized. The presence of *p*-methyl groups in *p*-hydroxy-triphenyl-carbin-

<sup>1</sup> Ber., 42, 1015–22 (1909); Ann., 372, 32 (1910).

ols seems to give resistance to crystallization. The benzenoid form constitutes the carbinol as reprecipitated from dilute alkaline solution, and dried to constant weight in a desiccator containing soda-lime.

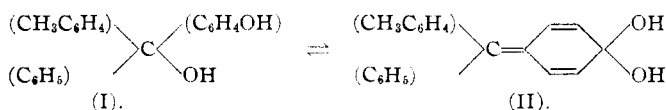
Because of the difficulty in crystallizing the carbinol, the usual methods for the preparation of the 2 desmotropic forms were of no avail. However, an amorphous form of the carbinol, resembling, to a greater degree, the quinoid modification, was obtained in the following manner. Five g. of the benzenoid carbinol was dissolved in a small amount of glacial acetic acid, and, after standing for half an hour, was poured into 200 cc. of ice-water with stirring. The carbinol precipitates as a red-orange powder. Its solubilities are identical with those of the benzenoid form. No distinct melting point could be obtained for either form, the benzenoid being 77°–83°, and the quinoid being several degrees lower.

Calc. for  $C_{20}H_{18}O_2$ : C, 82.74; H, 6.25. Found: Benzenoid—C, 82.63; H, 6.29. Quinoid—C, 82.47; H, 6.53.

**Dehydration of the Two Forms of Carbinol.**—Evidence of the existence of 2 tautomeric carbinols in the present case is indicated by the different rates in loss of water on heating. Equal weights of the benzenoid and quinoid modifications were heated in a glycerol bath as described by Gomberg and Van Stone.<sup>1</sup> The quinoid desmotope (II) loses water more rapidly than the benzenoid (I), as can be seen from the following data. The temperature was 95°–100°.

Time of Heating. Days.	Loss.	
	Benzenoid. %.	Quinoid. %.
1	1.51	3.48
2	2.40	4.47
3	3.18	5.15
4	3.78	5.78
5	4.01	5.90

Both carbinols are probably mixtures, the benzenoid containing the lesser proportion of actual quinoid form. Above the percentages given, the loss of water is about the same for both forms, and on prolonged heating, slightly more than the theoretical amount is lost due to decomposition of the resulting fuchsones. Attempts to crystallize the latter were unsuccessful.



The third product of the condensation, *p*-methyl-di-*p*-hydroxy-tetraphenyl methane, was obtained in crude form only by heating a mixture

<sup>1</sup> Gomberg and Van Stone, THIS JOURNAL, 38, 1577 (1916).

of phenol and 4-methyl-benzophenone chloride on the steam-bath. It is a wine-red amorphous powder, soluble in most organic solvents except carbon tetrachloride and petroleum ether. It can be precipitated from its alkaline solutions by either carbon dioxide or acetic acid. It could not be crystallized.

### Summary.

The results of this work show that the condensation of 4-methyl-benzophenone chloride with phenol is analogous to that between benzophenone chloride and phenol, and indicate that the corresponding carbinol exists in 2 tautomeric forms.

The author wishes to express his indebtedness to Professor M. Gomberg, under whose guidance this work was pursued.

ANN ARBOR, MICH.

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[CONTRIBUTION FROM THE HYGIENIC LABORATORY, U. S. PUBLIC HEALTH SERVICE, AND THE KENT CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO.]<sup>1</sup>

### PHENYLACETIC-PARA-ARSONIC ACID.

BY GEORGE ROSS ROBERTSON AND JULIUS STIEGLITZ.

Received September 7, 1920.

While arsphenamine<sup>2</sup> and neo-arsphenamine<sup>3</sup> have been found to be probably the best arsenical preparations for the treatment of disease involving infections by the spirochetes, and have been proved a great boon to mankind, they are nevertheless without question dangerous drugs, demanding extraordinary care in manufacture and skill in administration. That there is ample room for improvement is universally recognized. While engaged in investigation of arsenicals for the Hygienic Laboratory of the U. S. Public Health Service, we have started work on the study of preparation of other arsenicals which might lead to an equally efficient and less dangerous drug than the preparations now used.

As a first series in this direction it is the intention to use the carboxyl group of phenyl-acetic acid as the salt-forming group instead of the phenol group of arsphenamine in order to avoid the sensitiveness of the aromatic nucleus<sup>4</sup> to oxidation which makes the arsphenamine so liable to decomposition. Whether the availability of the arsenic in the body will thereby be also reduced in such a way as to make the derivatives of no therapeutic value, the event must tell.

<sup>1</sup> This work was carried out by Mr. Robertson, chemist in the employ of the U. S. Public Health Service, under the direction of Mr. Stieglitz in his capacity of Expert Advisor to the Hygienic Laboratory of the U. S. P. H. S. and is published with the consent of the Surgeon-General. The work was done at the University of Chicago.

<sup>2</sup> The official American name for the drug introduced as "salvarsan," or known scientifically as the hydrochloride of 3,3'-diamino-4,4'-dihydroxy-1,1'-arsenobenzene.

<sup>3</sup> The American name for the drug introduced as "neo-salvarsan" and known as sodium 3,3'-diamino-4,4'-dihydroxy-1,1'-arsenobenzene methanal-sulphoxylate.

<sup>4</sup> As distinguished from the arsenic atoms.