

### Summary

Phenyl-*p*-tolylacetophenone could not be prepared from phenyl-*p*-tolylacetyl chloride and benzene, but it was obtained from desyl chloride and toluene. It reacted normally with phenylmagnesium bromide, and it gave a sodium salt which oxygen cleaved into phenyl *p*-tolyl ketone and sodium benzoate.

The work of McKenzie, Mills and Myles on the dehydration of  $\alpha,\beta$ -diphenyl- $\alpha$ -*p*-tolylethylene glycol has been repeated and confirmed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

## THE HYDROGEN CHLORIDE ADDITION PRODUCTS OF TYROSINE N-PHENYLACETIC ACID AND OF THE CORRESPONDING METHYL AND ETHYL ESTERS

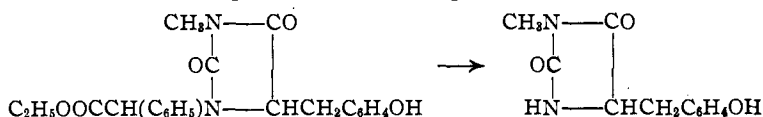
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The following account of certain transformations of the N-phenylacetic acid derivative of tyrosine,  $\text{NH}(\text{CHC}_6\text{H}_5\text{COOH})\text{CH}(\text{CH}_2\text{C}_6\text{H}_4\text{OH})\text{COOH}$ , represents a continuation of work previously reported.<sup>2</sup> The imino dibasic acid was prepared by the same general method that has already been described,<sup>3</sup> but due to the fact that larger quantities of material were used in the reactions, a few additional facts in regard to this preparation need to be noted.

It was found, for example, during the process of digesting 50 g. of ethyl N-3-methyl-5-anisalhydantoin-N-1-phenylacetate<sup>4</sup> with hydrogen iodide and then hydrolyzing the product with barium hydroxide, that a slight amount of decomposition had taken place in the sense



The decomposition product, N-3-methyl-5-*p*-hydroxybenzylhydantoin, was found mixed with the imino dibasic acid in the filtrate from the barium sulfate. Both substances separated in crystalline condition on concentrating the solution and were readily separated due to the fact that the hydantoin is very soluble in hot water while the imino acid is relatively insoluble. After several recrystallizations from water the hydantoin was

<sup>1</sup> This work was offered in partial fulfillment of the requirements for the degree of Master of Arts at Mount Holyoke College.

<sup>2</sup> Hahn and Dyer, *THIS JOURNAL*, **52**, 2494 (1930).

<sup>3</sup> Hahn and Dyer, *ibid.*, p. 2503.

<sup>4</sup> Hahn and Dyer, *ibid.*, p. 2497.

analyzed and finally identified by comparison with a specimen of N-3-methyl-5-*p*-hydroxybenzylhydantoin which had been synthesized according to the method described by Johnson and Nicolet.<sup>5</sup>

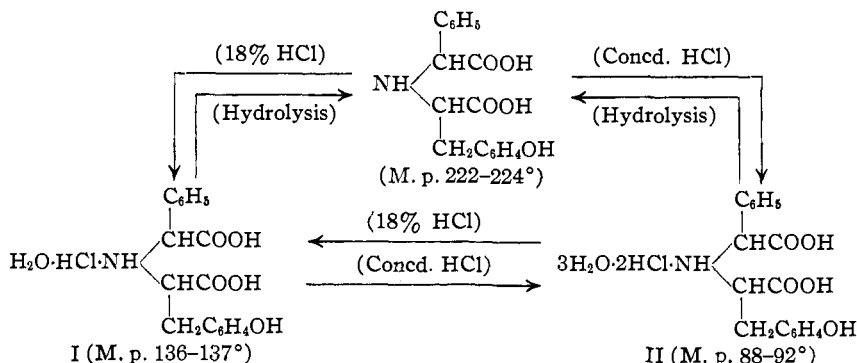
Due to the relatively great insolubility of the imino dibasic acid in boiling water, considerable difficulty was experienced at first in attempting to prepare it in quantity. For example, when starting with 50 g. of ethyl N-3-methyl-5-anisalhydantoin-N-1-phenylacetate and proceeding in the usual way,<sup>6</sup> it was found convenient to precipitate the barium sulfate in approximately one liter of boiling solution. The filtrate under these conditions when concentrated was found to yield only about 2-3 g. of the imino acid, the bulk of the product being retained along with barium sulfate as an insoluble white precipitate. The fact that one gram of imino acid requires about 500 cc. of boiling water for solution made the matter of separating it from the barium sulfate extremely difficult. The problem was finally solved by extracting the barium sulfate with small quantities of boiling aqueous hydrochloric acid (18%). Under these conditions the imino acid reacted to form the corresponding hydrochloride, which is very soluble in boiling acid of this concentration and only slightly soluble in the cold solution. The hydrochloride, which separates in well-defined crystals and is readily purified by recrystallization from aqueous hydrochloric acid, is further characterized by the fact that it dissociates hydrogen chloride when boiled with water, passing quantitatively into the free imino dibasic acid. If the precaution is taken of first extracting the barium sulfate precipitate with boiling alcohol to remove all traces of organic coloring matter, approximately 65% of the amount of imino acid required by theory may be obtained in exceptionally pure condition by then extracting the barium sulfate precipitate with aqueous hydrochloric acid in the manner just described.

The N-phenylacetic acid derivative of tyrosine reacts with aqueous hydrochloric acid to form two different addition products melting at 136-137° and 88-92°, respectively, with the evolution of a gas. They represent the addition of one and two molecules of hydrochloric acid to one molecule of imino acid, and separate, respectively, from dilute and concentrated solutions of hydrochloric acid. Of the two the first represents the more stable form but each may be readily transformed into the other and also be hydrolyzed to the free imino acid. These relationships are shown by means of the chart.

The hydrochloride, I,  $C_{17}H_{17}O_5N \cdot HCl \cdot H_2O$ , m. p. 136-137°, was prepared by dissolving 7.0 g. of imino acid, m. p. 222-224°, in 15 cc. of boiling 18% aqueous hydrochloric acid. The clear solution on cooling deposited 6.9 g. of fine white crystals which melted at 136-137°. An additional 0.8 g. was obtained by concentrating the mother liquor, thus bringing the yield up to approximately the amount required by theory.

<sup>5</sup> Johnson and Nicolet, *Am. Chem. J.*, **47**, 470 (1912).

<sup>6</sup> Hahn and Dyer, *ibid.*, **52**, 2503 (1930).



The substance was purified by recrystallization from hot 18% aqueous hydrochloric acid in which it is extremely soluble (1 g. in 1.5 cc.) and from which it separates on cooling in clusters of small hard white crystals which form on the bottom of the beaker.

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{17}\text{O}_5\text{N}\cdot\text{HCl}\cdot\text{H}_2\text{O}$ : N, 3.79; Cl, 9.61. Found: N, 3.79, 3.85; Cl, 9.53, 9.57.

Although the analyses indicate the presence of water of crystallization, it was impossible to determine this separately because of the fact that the substance dissociates hydrochloric acid on heating. Solution in alcohol or water produces the same effect but under these conditions quantitative yields of the free imino dibasic acid are obtained as a result of the hydrolysis. When concentrated hydrochloric acid, sp. gr. 1.18, is added to solutions of this hydrochloride in hot aqueous 18% hydrochloric acid, the mixture on cooling deposits a white crystalline precipitate which melts at 88–92° and which represents the second modification referred to above.

The hydrochloride, II,  $\text{C}_{17}\text{H}_{17}\text{O}_5\text{N}\cdot\text{2HCl}\cdot\text{3H}_2\text{O}$ , m. p. 88–92°, was prepared by adding 4.5 cc. of concentrated hydrochloric acid, sp. gr. 1.18, to a solution of 2.0 g. of imino acid, m. p. 222–224°, in 9 cc. of hot 18% aqueous hydrochloric acid. Under these conditions a substance crystallizing in long soft white needles and filling the entire space occupied by the solution separated on cooling. The product consisted of 1.8 g., m. p. 88–92°, and corresponded to a yield of 64% of the theoretical. On concentrating the mother liquor, 0.25 g. of the hydrochloride, I, m. p. 136–137°, was deposited.

In order to recrystallize the hydrochloride, II, m. p. 88–92°, it was always necessary to dissolve it in hot 18% aqueous hydrochloric acid and treat the solution with twice its volume of concentrated hydrochloric acid, sp. gr. 1.18. After purification by several recrystallizations, the melting point was found to remain constant, 88–92°, with the evolution of a gas.

Here again it was found to be impossible to dehydrate the substance before making the analyses since decomposition begins at about 90°. The results of analysis would seem to indicate, however, that three molecules of water are held in the form of water of crystallization.

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{17}\text{O}_5\text{N}\cdot\text{2HCl}\cdot\text{3H}_2\text{O}$ : N, 3.17; Cl, 16.07. Found: N, 3.18, 3.20; Cl, 16.05, 15.93.

The hydrochloride, m. p. 88–92°, is extremely soluble in alcohol but cannot be obtained from this solvent in crystalline form since it separates as a gummy mass on concentrating the solution. The substance is also very soluble in water but hydrolyzes immediately to give the free imino acid, which separates as a flocculent precipitate. The transformation to the free acid may be carried out almost quantitatively by boiling 4.0 g. of the hydrochloride with 50 cc. of water for an hour. The substance is very

soluble in hot 18% aqueous hydrochloric acid (1 g. in 1.8 cc.) and less soluble in hot concentrated hydrochloric acid, sp. gr. 1.18 (1 g. in 10 cc.).

This hydrochloride is of interest because of the fact that it is extremely unstable, tending to dissociate hydrochloric acid under a variety of different conditions. For example, when a sample of the substance was dissolved in 18% aqueous hydrochloric acid and the solution allowed to cool, the product was found to lose one molecule of hydrochloric acid, passing quantitatively into the hydrochloride, I, m. p. 136–137°. The same general effect was produced by heating the dry crystals, m. p. 88–92°, in a test-tube at a temperature of 80°. In this case the evolution of hydrogen chloride gas was demonstrated by collecting the gas in water and testing the solution with silver nitrate. That the substance dissociates hydrochloric acid even on standing in the air at ordinary temperatures has also been demonstrated, the change having been followed by means of melting point determinations and analyses for chlorine. For example, a sample, m. p. 88–92°, was allowed to stand in a stoppered bottle for five months. At the end of this time the melting point had changed from 88–92° to 93–138°, approaching the melting point of the hydrochloride I. In analyzing for halogen it was found that a freshly prepared sample showed 15.93 and 16.05% of chlorine while a specimen that had stood in a stoppered bottle for two months gave 15.88% and 15.82%. The same specimen was then allowed to stand in an open bottle in a desiccator and was analyzed three days later, when the percentage of chlorine was found to have dropped to 15.74 and 15.70%.

The diethyl ester hydrochloride of the imino acid<sup>7</sup> was readily prepared by dissolving 7.7 g. of imino acid, m. p. 222–224°, in 100 cc. of absolute alcohol which had been saturated with dry hydrogen chloride gas. The mixture, after heating on a steam-bath for five hours, with a reflux condenser, was concentrated to one-third its original volume and allowed to cool. Since no precipitate formed under these conditions, 60 cc. of dry ether was added, when a gum separated out which gradually became crystalline on standing. The product, which was filtered and washed with a little alcohol-ether mixture, weighed 2.2 g. and melted at 160–162° with the evolution of a gas. Purified by recrystallization from absolute alcohol-ether mixtures (1:3), the melting point changed to 161–162° with the evolution of a gas.

*Anal.* Calcd. for  $C_{21}H_{25}O_5N \cdot HCl$ : N, 3.44. Found: N, 3.44, 3.43.

This substance is extremely soluble in alcohol, dissolving in less than its own volume of the solvent. It is insoluble in ether and may be precipitated from alcohol solution by the addition of about three volumes of ether.

When treated with water it undergoes hydrolysis and an oil separates at once. The aqueous solution, when decanted, was found to contain hydrochloric acid.

The corresponding dimethyl ester hydrochloride, m. p. 180–180.5°, was prepared according to Fischer's esterification method.

For example, 10 g. of imino acid, m. p. 222–224°, was dissolved by warming with 50 cc. of a saturated absolute methyl alcohol solution of hydrogen chloride. After heating the mixture with a reflux condenser, the alcohol was distilled off under reduced pressure and the process repeated until the gummy residue remaining in the flask after the distillation of alcohol finally changed into a hard brittle mass. This was then dissolved in 30 cc. of a saturated absolute methyl alcohol solution of hydrogen chloride and 30 cc. of ether added. Under these conditions the solution became cloudy and on standing a crystalline precipitate was formed. The product obtained in this way when filtered and washed with a small quantity of an absolute methyl alcohol-ether mixture (1:1) weighed 6.0 g. and melted at 177–180°. Additional quantities of this substance were obtained on concentrating the mother liquor and then adding ether. When purified by recrystallization

<sup>7</sup> Acknowledgment is made to Elizabeth Dyer for preparation of this substance.

tallization from absolute methyl alcohol-ether mixtures, it separates in the form of very fine white needles which melt at 180-180.5° with the evolution of a gas.

*Anal.* Calcd. for  $C_{13}H_{21}O_5N \cdot HCl$ : N, 3.69; Cl, 9.37. Found: N, 3.67, 3.68; Cl, 9.32, 9.29.

The dimethyl ester hydrochloride is extremely soluble in absolute methyl alcohol, dissolving in less than its own volume, and is insoluble in ether. While stable in alcohol-ether mixtures, it readily dissociates hydrochloric acid when dissolved in water. Solution in this solvent is accompanied by the immediate separation of an oil and the water layer when decanted gives a precipitate of silver chloride when tested in the usual way.

### Summary

An improved method for separating and purifying tyrosine-N-phenylacetic acid is described. Two distinct hydrogen chloride addition products of this acid have been prepared, together with the hydrochlorides of the corresponding methyl and ethyl esters.

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## RESEARCHES ON PYRIMIDINES. CXXVIII. THE REARRANGEMENT OF 2-ETHYLMERCAPTO-4-METHYL-6-THIOCYANOPYRIMIDINE INTO ITS ISOTHIOCYANATE MODIFICATION<sup>1,2</sup>

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Since Wheeler, Johnson and their co-workers began the study of the chemistry of thiocyanopyrimidine compounds,<sup>3</sup> no specific change has proved to be more interesting to the writers than the rearrangement of 2-ethylmercapto-5-carbethoxy-6-thiocyanopyrimidine into its isomeric isothiocyanate modification, a transformation which was described recently in a paper by Johnson and Chi.<sup>4</sup> They found that this thiocyanate could be distilled without decomposition and without molecular conversion to the isothiocyanate form, while its molecular rearrangement into the isothiocyanate form could be accomplished easily, under specific experimental conditions, at a temperature much below that of its boiling point.

<sup>1</sup> This publication is a report of one phase of a research program dealing with the chemistry of certain pyrimidine thiocyanates, which was started originally in the Sterling Chemistry Laboratory of Yale University under the direction of Professor Treat B. Johnson.

<sup>2</sup> This research has been accomplished and arranged for publication through the support of a grant of \$750 from the Rockefeller Foundation. The authors desire to express here their appreciation and heartiest thanks for this liberal assistance.

<sup>3</sup> Wheeler and Bristol, *Am. Chem. J.*, **33**, 450 (1905); Johnson and McCollum, *ibid.*, **36**, 143 (1906); Johnson and Storey, *ibid.*, **40**, 131 (1908).

<sup>4</sup> Johnson and Chi, *THIS JOURNAL*, **52**, 1580 (1930).