

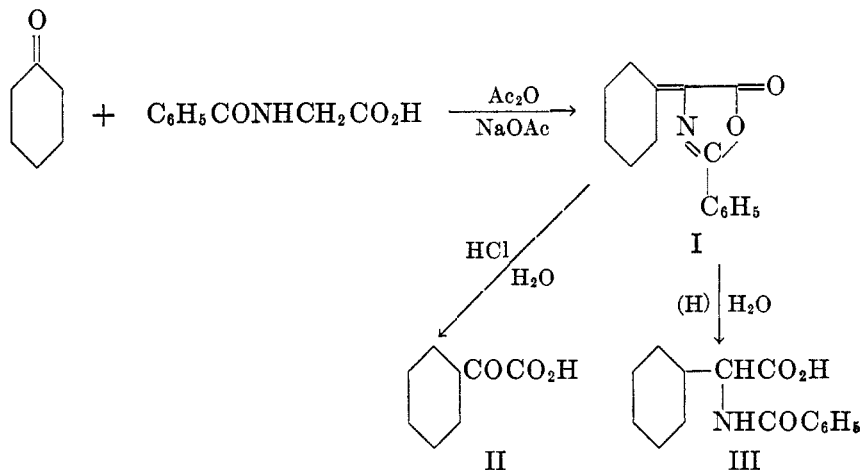
THE USE OF KETONES IN THE ERLENMEYER AZLACTONE SYNTHESIS

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In certain investigations in this laboratory, it became highly desirable to have a method which would be generally applicable for the conversion of ketones to α -amino acids of the type $R_1R_2CHCH(NH_2)CO_2H$. Although such excellent methods as the Erlenmeyer azlactone synthesis (1), the hydantoin synthesis (2), and the rhodanine synthesis (3) have been worked out for the conversion of aldehydes to the analogous α -amino acids, there are only a few cases in which ketones have been employed in these syntheses. Acenaphthenequinone (4), isatin (5), and alloxan (6) have been reported to undergo condensation with rhodanine. Also, Ramage and Simonsen (7) have reported that the condensation of acetone with hippuric acid gives a fair yield of 2-phenyl-4-isopropylidene-5-oxazolone. In the present investigation the use of ketones in the Erlenmeyer azlactone synthesis has been studied to determine the scope and applicability of the reaction.

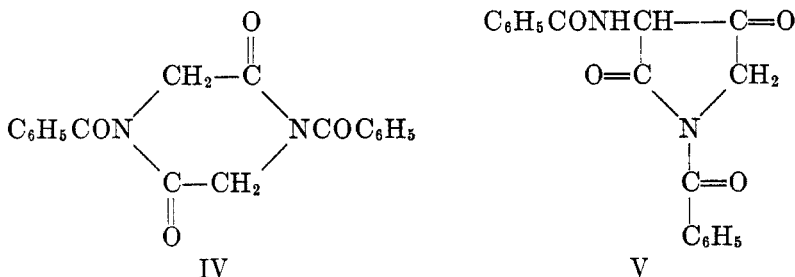
When cyclohexanone was treated with hippuric acid under the usual conditions of the Erlenmeyer azlactone synthesis, there was obtained in 49% yield the desired 2-phenyl-4-cyclohexylidene-5-oxazolone, I. The structure assigned to I was substantiated by hydrolysis and reduction experiments. Mild alkaline hydrolysis of I gave an excellent yield of a compound having the properties to be expected for α -cyclohexylidenehippuric acid. On the other hand, hydrolysis with concentrated hydrochloric acid gave a good yield of cyclohexyloxooacetic acid, II. Although the attempted reduction of I with platinum oxide as catalyst was unsuccessful, reduction accompanied by hydrolysis occurred, when Raney nickel was employed as catalyst, and a good yield of α -cyclohexylhippuric acid, III, was obtained.



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Although the formation of the azlactone of cyclohexanone occurred readily in the expected manner, the reaction took a different course with less active ketones. When the reaction was attempted using methyl ethyl ketone, mesityl oxide, acetophenone, or 2-methylcyclohexanone, there was obtained from each of the reaction mixtures a small yield of a white solid, which melted at 138°. The product was the same regardless of the ketone employed, since no depression of melting point was found for mixtures of samples from different runs. Combustion analysis of the product melting at 138° indicated an empirical formula of $(C_9H_7NO_2)_x$. Furthermore, the product gave a distinct purple ferric chloride test. These properties are in agreement with those which have been reported for a dimolecular product of hippuric acid. This dimolecular product has been obtained by Rugheimer (8) by the action of sodium ethoxide on sodium hippurate; by Curtius (9) from the reaction of hippurazide with alkali; by Scheiber and Reckleben (10) from the reaction of sodiomalonic ester and hippuryl chloride; and by Karrer, Wehrli, Biedermann, and dalla Vedova (11) from the reaction of hippuryl chloride, pyridine, and copper powder. The identity of our product with that obtained by Karrer and his co-workers was established by repeating their preparation and making a comparison of the two samples.

Although Karrer *et al.* assign structure IV to their product, this is probably not correct. Cornforth and Huang² (12) have obtained evidence indicating that the correct structure is V. In view of this recent evidence no further investigation of our product was made, and it was assumed to be V.



Since the reaction had not taken the desired course with ketones less active than cyclohexanone, the reaction was attempted with a more active ketone, cyclopentanone. However the only product to be isolated in this case, also, was V.

Several attempts were made to obtain the desired condensation of methyl ethyl ketone with hippuric acid by varying the reaction conditions and the length of time of reaction, but these attempts were without success.

EXPERIMENTAL³

2-Phenyl-4-cyclohexylidene-5-oxazolone, I. A mixture of finely divided, anhydrous sodium acetate (9.0 g., 0.1 mole), hippuric acid (18.0 g., 0.1 mole), cyclohexanone (30 g., 0.3 mole), and acetic anhydride (35 ml.) was heated with intermittent shaking until the mixture

² We should like to thank Dr. H. T. Huang for his kindness in allowing us to examine his doctoral dissertation.

³ Analyses by Mrs. G. L. Sauvage and the Micro-Tech Laboratories.

had gone from a pink, semi-solid mass to a deep orange liquid (ten to fifteen minutes). The mixture was then cooled to room temperature and the crystalline product, which separated, was removed by filtration. The crude product was recrystallized from ethanol, and there was obtained 11.3 g. (49%) of fine, white needles, m.p. 137-138°.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27.

Found: C, 74.56; H, 6.13.

α -Cyclohexylidenehippuric acid. A mixture of 1.0 g. of 2-phenyl-4-cyclohexylidene-5-oxazolone, 0.5 g. of potassium hydroxide, and 15 ml. of water was heated on the steam-bath until solution was complete. On acidification a white solid separated. After recrystallization from ethanol, there was obtained 0.9 g. (85%) of white needles, m.p. 244-246°.

Anal. Calc'd for $C_{15}H_{17}NO_3$: C, 69.47; H, 6.62.

Found: C, 69.35; H, 6.46.

Cyclohexyloxoacetic acid, II. A mixture of 8.0 g. of 2-phenyl-4-cyclohexylidene-5-oxazolone and 50 ml. of concentrated hydrochloric acid was heated on the steam-bath for twenty hours. The precipitated benzoic acid was separated by filtration, the filtrate was extracted with ether, and the ethereal solution was washed with a small amount of water and dried over sodium sulfate. After the ether had been removed, the residual oil was distilled yielding 3.1 g. (60%) of a colorless oil; b.p. 73-74° at 3.5 mm.

Anal. Calc'd for $C_8H_{10}O_2$: C, 61.52; H, 7.75.

Found: C, 61.65; H, 8.10.

α -Cyclohexylhippuric acid, III. A mixture of 8.0 g. of 2-phenyl-4-cyclohexylidene-5-oxazolone, 1 g. of Raney nickel catalyst, and 20 ml. of alcohol was shaken at 100° under a pressure of about 80 atm. of hydrogen. The theoretical amount of hydrogen was absorbed in about forty-five minutes. After separation of the catalyst and removal of the solvent, the crude product was warmed with a 5% potassium hydroxide solution. The material insoluble in potassium hydroxide was removed by filtration, and the filtrate was acidified. The crude acid was collected and recrystallized from alcohol. There was obtained 4.1 g. (55%) of white crystals, m.p. 197-199°.

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33.

Found: C, 68.96; H, 7.21.

The material, which was not soluble in potassium hydroxide solution, was recrystallized from methanol and obtained as white crystals, m.p. 179-180°. This material was not hydrolyzed by boiling with acid or base, and it was not further identified.

When the reduction of 2-phenyl-4-cyclohexylidene-5-oxazolone was attempted using acetic acid as solvent and platinum oxide as catalyst with a hydrogen pressure of 3 atm., no hydrogen uptake was observed and the starting material was recovered. In another attempt, the condensation of cyclohexanone and hippuric acid was carried out with acetic anhydride as solvent, platinum oxide as catalyst, and under a hydrogen atmosphere. It was hoped that condensation would be accompanied by reduction and in this way the reaction would go to completion. However, at temperatures of 80-100° condensation occurred to give I in the usual yield, but no reduced product was isolated.

Attempted condensations of hippuric acid with methyl ethyl ketone, mesityl oxide, acetophenone, 2-methylcyclohexanone, and cyclopentanone. For each of the aforementioned ketones the following procedure was employed. A mixture of anhydrous sodium acetate (9.0 g., 0.1 mole), hippuric acid (18.0 g., 0.1 mole), acetic anhydride (35 g., 0.3 mole), and freshly distilled ketone (0.3 mole) was heated with shaking until the mass became liquid (usually fifteen minutes). The mixture was then heated a few minutes longer, cooled, and poured into water. The insoluble, oily layer was removed and washed by decantation with water. After the oil had been heated *in vacuo* to remove volatile impurities, it set to a thick, red mass. The crude product was treated with charcoal in methanol several times and then recrystallized a number of times from methanol. In this way there was eventually obtained 3.0 g. (18%) of white crystals. The same product in approximately the same yield was obtained regardless of the ketone employed and mixtures of samples from different reaction mixtures showed no depression of melting point.

Anal. Calc'd for $(C_9H_7NO_2)_x$: C, 67.07; H, 4.38.

Found: C, 67.22, 66.88; H, 4.30, 4.27.

The condensation of methyl ethyl ketone with hippuric acid was also tried under conditions in which the reaction mixture was boiled under reflux for several hours, under conditions in which the reaction mixture was heated until it became liquid and was then allowed to stand 24 hours at room temperature, and under conditions in which the ratio of reactants was varied. The only product to be isolated in each case was the material melting at 138° and none of these measures improved the yield of this product.

Peculiarly enough, when the above reaction was carried out without ketone present, no dimolecular product was obtained but instead benzoic acid was isolated. The benzoic acid was probably derived from a transacetylation of the hippuric acid by acetic anhydride.

Identification of the material melting at 138°. The material melting at 138° gave a distinct purple ferric chloride test. This behavior in conjunction with the melting point and empirical formula corresponded to the product which Karrer *et al.* (11) had reported from the reaction of hippuryl chloride, pyridine, and copper powder. The preparation of their product was repeated, and it was found that a mixture of the two samples melted at 138°. As indicated by Cornforth and Huang (12), the material melting at 138° is probably N-benzoyl-2,4-diketo-3-benzamidopyrrolidine, V.

SUMMARY

Cyclohexanone has been found to condense with hippuric acid in the Erlenmeyer azlactone synthesis to give 2-phenyl-4-cyclohexylidene-5-oxazolone. However, with a number of other simple ketones the Erlenmeyer azlactone synthesis with hippuric acid did not give any condensation product but instead gave a dimolecular product which is probably N-benzoyl-2,4-diketo-3-benzamidopyrrolidine.

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