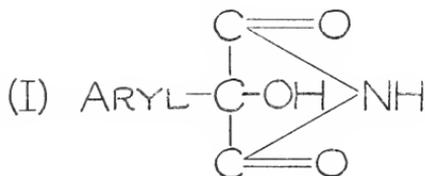


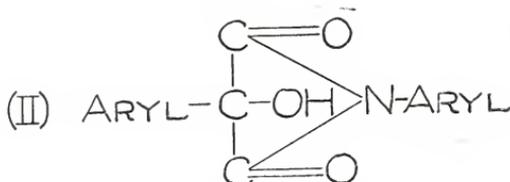
## An Attempted Synthesis of n-Aryl-2,4-Diketo-3-Hydroxy-3-Arylazetidines

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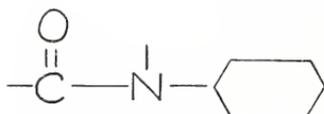
Recently we have described a method for the preparation of 2,4-diketo-3-hydroxy-3-arylazetidines,<sup>1</sup> (I) and reported certain pharma-



cological studies on these compounds. It was suggested to us that it would be of interest to prepare compounds of this same type in which the hydrogen atom attached to the nitrogen was replaced by an aryl group as indicated by formula (II).



This compound was suggested to us because it might prove to be useful as an antipyretic. This prediction was based on its structural relationship to acetanilide. In acetanilide we find the grouping

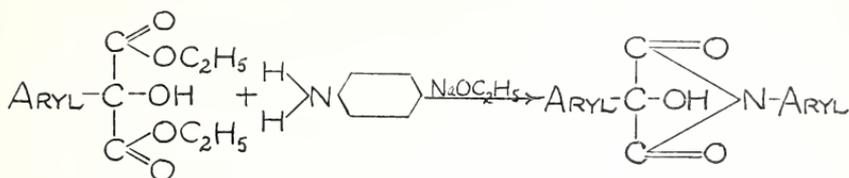


which also occurs in (II).

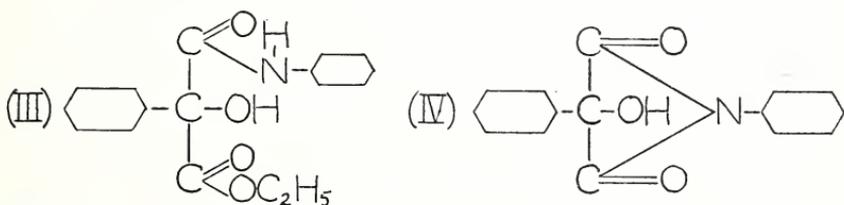
Our attempt to prepare compounds of this type was based on the experience in the preparation of type (I). The basic reaction for the preparation of type (I)<sup>1</sup> was to heat aryl hydroxy malonic esters with urea or ammonia gas and sodium ethylate and to follow the procedure for a typical barbituric acid synthesis.

<sup>1</sup>Riebsomer, Burkett, Hodgson and Senour, 1939. J. Amer. Chem. Soc., 61:3491.

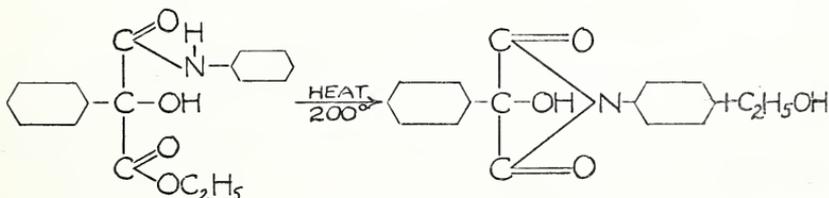
Accordingly it was predicted that if the same general procedure was followed except that aniline should be substituted for urea or ammonia that the following reactions should take place:



This reaction was carried out using phenyl hydroxy malonic ester and aniline. When the reaction product was worked up in the usual manner, a white solid was produced which crystallized readily from benzene, but which melted over a range of several degrees, usually about 145°. This indicated impurity. It seemed reasonable to suspect that the reaction had not gone to completion and that we probably had a mixture of (III) and (IV).



Accordingly the procedure of Tafel and Stern<sup>2</sup> and Dunlap<sup>3</sup> suggested itself for the closing of the ring by heating the mixture to 200° for 2-3 hours with the hope that (III) would react to produce (IV).



When this procedure was carried out the product was crystallized from benzene and melted sharply at 151°. But when the compound was analyzed the percentages of carbon, hydrogen and nitrogen were far too high to be the expected compound of type (II).

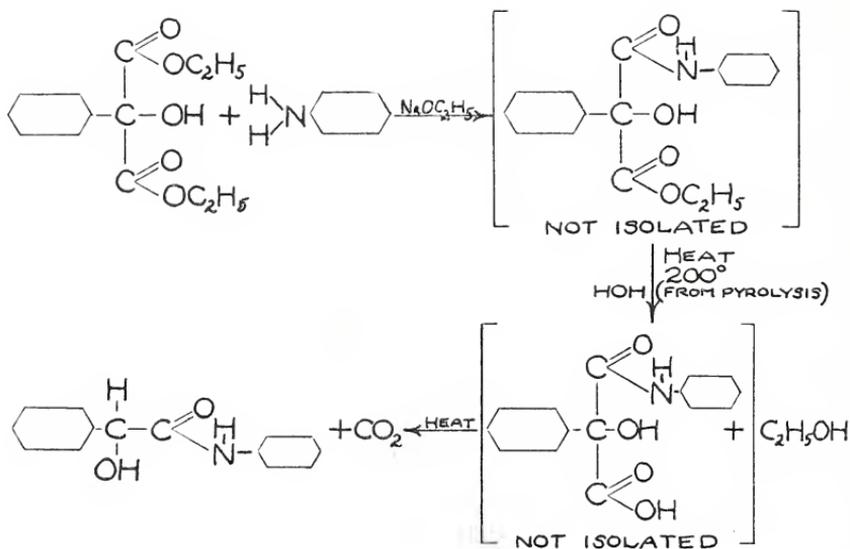
This compound was then saponified with potassium hydroxide. Mandelic acid and aniline were produced which would be expected from (IV) but which would also be produced from another compound, namely, the anilide of mandelic acid. The anilide of mandelic acid melts at 151°,

<sup>2</sup> Tafel and Stern, 1900. Ber., 33:2232.

<sup>3</sup> Dunlap, 1896. Amer. Chem. J. 18:332.

and its carbon, hydrogen and nitrogen composition checked with the analyses which we obtained for the unknown compound. A mixed melting point with the known anilide of mandelic acid showed no depression.

Therefore, the following equations are suggested to account for the reactions which actually took place:



Comparable results were obtained when p-toluidine and other aromatic amines were substituted for aniline and the same procedure was used.

It was also found that magnesium methylate when used instead of sodium ethylate as the condensing agent that the same results were produced.

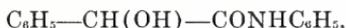
Furthermore when phenyl hydroxy malonic ester and aniline were mixed using no solvent or condensing agent and heated to 200° for eight to ten hours the anilide of mandelic acid was produced, in which case the course of the reaction may be the same as indicated in the suggested equations.

### Experimental Part

**Reaction of aromatic amines and phenyl hydroxy malonic ester.** In a typical synthesis 7.5 g. of sodium was dissolved in 100 ml. of absolute alcohol. To this sodium alcoholate was added 25 g. of phenyl hydroxy malonic ester and 14 g. of aniline. The mixture was heated to 115-120° and stirred for about 16 hours. The excess alcohol was evaporated, reducing the pressure with a water pump. To the dried solid remaining was added ice and water, and dilute hydrochloric acid was added with stirring until the mixture was faintly acid to litmus. The semi-solid mass remaining was extracted with ether, dried, the ether evaporated, and the

residue crystallized from benzene. The melting point at this stage was 140-145°.

This partially purified product was transferred to a small test tube and heated in a metal bath to 200° for about two hours. It was then crystallized from benzene until its melting point was unchanged at 151°. Yield from 1 to 3 g. of the highly purified product. Analysis: calcd. for



C, 74.0; H, 5.7; N, 6.1. Found: C, 74.2; H, 5.9; N, 5.84. A mixed melting point with known anilide of mandelic acid (m.p. 151°) showed no depression.

This compound was further shown to be the anilide of mandelic acid by boiling 0.5 g. of the compound in 20% aqueous potassium hydroxide for four to five hours. The alkaline solution was extracted with ether, dried and the ether evaporated. To the residue was added chloroform and dilute sodium hydroxide and the mixture was then heated. The typical amine odor was produced.

To the potassium hydroxide solution was added excess hydrochloric acid, and this acidified solution was warmed on a steam bath for three to four hours. The acid solution was evaporated to dryness and the residue was extracted with benzene. From this benzene solution a white solid crystallized (m.p. 116-118°). Mixed m.p. mandelic acid (m.p. 120°) was 118-119°. Thus aniline and mandelic acid were produced upon saponification with potassium hydroxide which would be expected from the anilide of mandelic acid.

A similar experiment was carried out using p-toluidine instead of aniline and the yield was 2 g. of



(m.p. 171°). o-Toluidine failed to produce any comparable product. Presumably steric hindrance would explain this difference. m-Toluidine gave results comparable to p-toluidine.

**Use of magnesium methylate-magnesium ethylate mixture as condensing agent.** Eight grams of magnesium turnings was added to 100 ml. of absolute methyl alcohol. After the magnesium had all reacted, 150 ml. of ethyl alcohol, 12.5 g. of phenyl hydroxy malonic ester and 7 g. of aniline were added and the mixture stirred at 115-120° for about 16 hours. From here on the procedure was the same as when sodium ethylate was used. Yield 1.5 g. of the anilide of mandelic acid, which indicates that magnesium is about as effective as sodium in this reaction.

**Reaction of phenyl hydroxy malonic ester and aniline without any condensing agent.** Ten grams of phenyl hydroxy malonic ester and 15 g. of aniline were heated eight hours at 200° in a test tube. The mixture was cooled and crystallized from benzene (m.p. 150°). Mixed m.p. with the anilide of mandelic acid showed no depression. Yield 1.2 g.

The authors wish to express their indebtedness to Dean William M. Blanchard, who was instrumental in securing a research grant from the Indiana Academy of Science to promote our research program,

### Summary

1. An attempt was made to synthesize N-aryl-2,4-diketo-3-hydroxy-3-arylazetidines using the procedure previously used to make 2,4-diketoazetidines. In each case amido derivatives of mandelic acid were formed.

2. It has been demonstrated that the same derivatives of mandelic acid can be made by heating directly phenyl hydroxy malonic ester and the aromatic amines.