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THE PREPARATION OF
2-ACETYL-3-NITROBENZOIC ACID

by

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A THESIS

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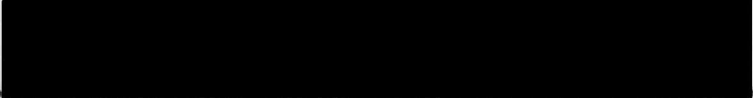
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TABLE OF CONTENTS

	Page
Discussion.....	1
Experimental.....	5
Summary.....	11
Bibliography.....	12

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THE PREPARATION OF
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DISCUSSION

In the course of the preparation of certain physiologically active compounds it became imperative to devise the synthesis of an amino diacetyl benzene or amino acetyl benzoic acid with amino groups in ortho position. Methods which appeared most promising involved the use of one of the phthalic acid chlorides or phthalic anhydride, which might possibly be converted by the use of organo-cadmium reagents to the diketone or the keto acid, respectively.

Because of its cost and availability, phthalyl chloride was first used as a precursor in the preparation of the ketones. Gilman and Nelson synthesized several ketones by use of organo-cadmium reagents but reported that attempts to prepare diketones from aliphatic dibasic acid chlorides were not successful. (5) In preliminary work it was found that phthalyl chloride would not produce the diketone. The reaction proceeded beyond the ketone to the tertiary alcohol in the same manner as reported for aliphatic acyl halides.

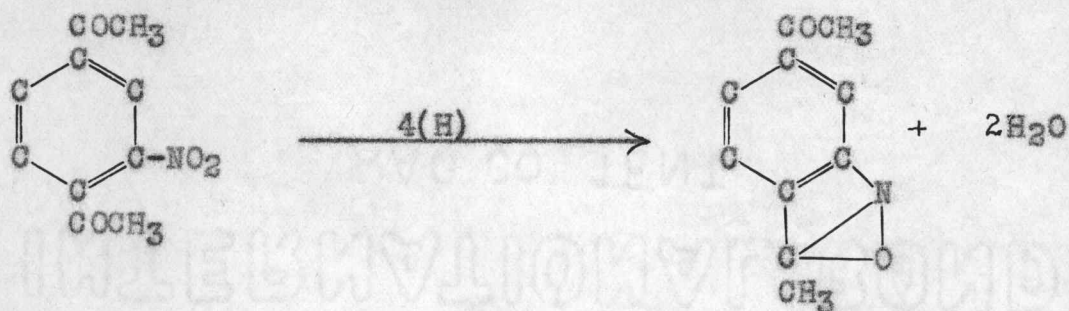
Since the course of the reaction might depend on the position of the acyl groups, the possibility of using terephthalyl chloride was investigated. Initial experiments with the organo-cadmium reagent using terephthalyl chloride were not promising. Attempts were then made to

condense terephthalyl chloride with malonic ester. Although the condensation was successful, the hydrolysis of this product to the diketone gave very low yields.

Behrend and Herms have reported the successful preparation of p-diacetyl benzene in low yields using an acetoacetic ester condensation followed by alkaline and acid hydrolyses. (1) This work was repeated and their results were confirmed in this laboratory.

Ruggli and Gassenmeier prepared 2-nitro-1,4-diacetyl benzene from p-diacetyl benzene by nitration with fuming nitric acid ($d=1.52$) in an acetic anhydride medium. (7) In this laboratory it was found that red fuming nitric acid ($d=1.60$) with the same procedure gave better yields of the nitro compound.

2-Nitro-1,4-diacetyl benzene was reduced at room temperature with a solution of stannous chloride in concentrated hydrochloric acid. However, the product which was isolated from the reducing medium was not an amine. Analysis confirmed the hypothesis that the compound was an anthranil resulting from partial reduction.



o-Nitroacetophenone and certain of its analogs readily form anthranils when treated with reducing agents. (6)

The complete reduction of the nitro groups was only achieved by using a reaction temperature of 100°C. The product obtained in this manner was 2-amino-1,4-diacetyl benzene.

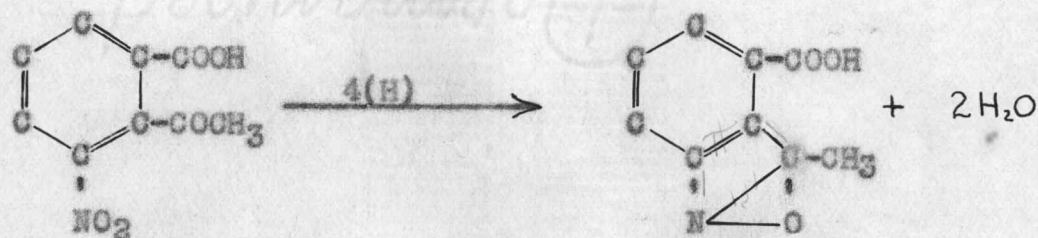
Since, in the preparation of amino diacetyl benzene, overall yields were small and intermediates costly, the possibility of using another starting material was investigated. 3-Nitrophthalic acid can easily be prepared from phthalic anhydride and nitric acid by direct nitration.

(3) Treatment of this acid with acetic anhydride yields the nitrophthalic anhydride. (4)

De Benneville has shown that acid anhydrides can be converted into ketones or keto acids in good yields by the use of cadmium alkyls. (2) In this investigation the use of 3-nitrophthalic anhydride was successful with the isolation of 2-acetyl-3-nitrobenzoic acid.

Catalytic reduction of the nitro acid with platinum and hydrogen at low pressures gave a product which was not completely reduced. The same product was obtained from reduction with a solution of stannous chloride in concentrated hydrochloric acid at room temperature. Maintaining the reaction mixture at 100°C. produced no further reduction as it did in the reduction of the nitro diacetyl benzene. This partial reduction product also turned out

to be an anthranil.



Although anthranils are known to form with carboxyl groups as well as with carbonyl groups, the fact that this product had a neutralization equivalent of 176 indicated that in this case the anthranil was formed with the carbonyl group.

During the catalytic reduction of the nitro acid, the measured amount of hydrogen absorbed corresponded to two-thirds of the amount necessary for conversion to the amine. This confirms the data obtained from the analysis.

EXPERIMENTAL

2-Nitro-1,4-diacetyl Benzene

p-Diacetyl benzene (155 g.) (0.96 mole) was added to 750 ml. of acetic anhydride in a 5-liter, three-neck flask equipped with stirrer, thermometer, and dropping funnel. The flask was surrounded by an ice bath, and red fuming nitric acid ($d=1.60$) (1500 ml.) was added as rapidly as possible while maintaining a temperature of 5°C . or below. Powdered dry ice was added periodically to maintain this reduced temperature. After the nitric acid was added, the solution was stirred for two hours at $2-5^{\circ}\text{C}$. The reaction mixture was then poured onto 3 kg. of ice, and the aqueous mixture was extracted with 4 liters of ether in 500 ml. portions. The ether was washed with sodium carbonate solution, then with water, and was finally dried with CaCl_2 . The ether extract yielded 147 g. of crude product, which was crystallized from 600 ml. of absolute alcohol, yielding 117 g. (59%) of large colorless needles melting at 63°C .

Reduction of 2-Nitro-1,4-diacetyl Benzene

2-Nitro-1,4-diacetyl benzene (2 g.) was added to a solution of 8.2 g. of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in 21 ml. of concentrated HCl . The reaction flask was maintained at $15-25^{\circ}\text{C}$. by a cold water bath. A few seconds after the addition of the

nitro compound, a white solid precipitated. This failed to dissolve even though the mixture was stirred for 3 hours. The mixture was diluted with 100 ml. of water and then extracted with ether, which removed the white solid. The ether was washed with dilute Na_2CO_3 solution, then with water, and was finally dried with CaCl_2 . The ether extract yielded 1.5 g. of white solid; m.p. $113-114^\circ\text{C}$. It was insoluble in HCl , indicating that it was not 2-amino-1,4-diacetyl benzene but rather an anthranil.

Analysis: Calcd. for $\text{C}_{10}\text{H}_9\text{NO}_2$: C, 68.55; H, 5.18;
N, 7.99

Found C, 68.40; H, 5.52;
N, 8.05

2-Amino-1,4-diacetyl Benzene

2-Nitro-1,4-diacetyl benzene (117 g.) was added to a solution of 500 g. of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in 1270 cc. of concentrated HCl . The flask was warmed to 90°C . on a water bath and maintained at this temperature for 2-5 hours with good stirring. During the reaction the solution became orange-colored. Cooling failed to produce any precipitation. The solution was then neutralized with Na_2CO_3 and NaOH . The resulting yellow precipitate was collected and the filtrate extracted with four liters of ether in one liter portions. The ether extract was washed with sodium carbonate solution, and then with water. After being dried with sodium sulfate, the ether was removed by distillation.

The residue from the ether extractions and the precipitate collected by filtration were combined and crystallized from water. Seventy-five grams (76%) of yellow crystals were obtained; m.p. 125°C. Further recrystallization from water did not change the melting point of the amino diacetyl benzene.

Analysis: Calcd. for $C_{10}H_{11}NO_2$:	C, 67.77; H, 6.26; N, 7.91
Found	C, 67.45; H, 6.18; N, 7.69

3-Acetyl-3-nitrobenzoic Acid

A 500 ml., three-necked, round-bottomed flask was fitted with a mechanical stirrer and a condenser with a soda-lime tube. The Grignard reagent was prepared in the apparatus from 7.3 g. (0.3 mole) Mg. and about 40 g. (0.4 mole) of methyl bromide in 300 ml. of dry ether. The cadmium alkyl was then prepared by the addition of 31.2 g. (0.17 mole) of anhyd. $CdCl_2$ by the method of Gilman and Nelson.

(5) When a Michler's ketone test showed the absence of Grignard reagent, the reaction flask was surrounded by an ice bath, and 33 g. (0.16 mole) of 3-nitro-phthalic anhydride was added in small portions with good stirring. When all of the anhydride had been added, the ice bath was replaced by a hot water bath and the reaction mixture was refluxed for an hour. Stirring during the period was prevented by the formation of a gummy precipitate soon after

the addition of all the anhydride.

The reaction-mixture was hydrolyzed by carefully adding a slight excess (350 ml.) of 10% H_2SO_4 while cooling the flask with an ice bath. Because of the nature of the reaction, a small amount (3-5 g.) of the anhydride could usually be recovered by filtering the ether-water mixture following hydrolysis. The ether layer was separated and combined with an ether washing of the water layer. The ether solution was shaken in a separatory funnel with slightly more than an equivalent (200 ml.) of 10% K_2CO_3 solution. The K_2CO_3 solution was filtered and carefully added to an excess of dilute sulfuric acid. The solid which was obtained from this solution was 2-acetyl-3-nitrobenzoic acid. Yield: 15 g. crystallized from water; m.p. 159°C . Neutral equivalent: Calcd. 209; Found 209.

Analysis: Calcd. for $\text{C}_9\text{H}_7\text{O}_5\text{N}$: C, 51.68; H, 3.37;
N, 6.70

Found C, 51.70; H, 3.30;
N, 6.58

The dark brown oil (8 g.) which separated along with the crystalline nitro-acetyl benzoic acid was not examined extensively. A sample which was washed with water and dried until it formed a dark brown solid had a neutral equivalent of 199.

Reduction of 2-Acetyl-3-nitrobenzoic Acid with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ Solution

The reduction was carried out in a manner similar to that used by Scott and Cohen for preparing 3-amino phthalic acid. (8) Seventeen grams of 2-acetyl-3-nitrobenzoic acid was added in small portions to a solution of 90 g. of stannous chloride in 225 cc. of concentrated hydrochloric acid in a flask fitted with a mechanical stirrer. After about two-thirds of the nitro compound had been added, a solid began to precipitate from the reaction mixture. After all of the nitro compound had been added, the reaction mixture was cooled. The precipitate was filtered off and washed with hydrochloric acid. The product weighed 13 g. and contained no ionizable chloride. This material had a neutralization equivalent of 176; m.p. 195°C .

The same product was obtained when the reduction was repeated at 100°C .

Reduction of 2-Acetyl-3-nitrobenzoic Acid by Catalytic Hydrogenation

Five grams (0.024 mole) of acetyl nitrobenzoic acid was dissolved in a solution of 100 ml. of alcohol and 25 ml. of water. Fifty milligrams of platinum black catalyst was added, and the solution was hydrogenated at 2.5-3.0 atm. pressure. Over a period of several hours 0.048 mole of hydrogen was absorbed. Continued treatment and the addition of fresh catalyst produced no further reduction.

The alcoholic solution was evaporated to dryness, and the product obtained melted at 195°C. This material had a neutralization equivalent of 176. A mixed melting point determination with the material obtained from the stannous chloride reduction produced no change in the melting point.

Analysis: Calcd. for $C_9H_7O_3N$: C, 61.01; H, 3.98;
N, 7.91

Found C, 60.80; H, 4.12;
N, 7.97

SUMMARY

2-Acetyl-3-nitrobenzoic acid was prepared from 3-nitrophthalic anhydride by the use of an organo-cadmium reagent.

Reduction of this acid and of 2-nitro-1,4-diacetyl benzene was studied. Both compounds formed anthranils when reduced with stannous chloride and hydrochloric acid at room temperature. However, 2-nitro-1,4-diacetyl benzene was reduced to the amine by raising the reaction temperature to 100°C.

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