[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

The Preparation of 3,3-Dimethylphthalide and Several of its Derivatives[1]

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Recently this Laboratory prepared the first reported acetyl derivatives of quinazoline.[2] The purpose of this synthesis was the preparation of an intermediate for the synthesis of amino alcohols. This was accomplished by utilizing acetamino-1,4-diacetylbenzene which was cyclized by amination to yield a quinazoline derivative with an acetyl substituent in the 7-position.

The extension of this study to the preparation of the 5-substituted isomer has now led to the investigation of phthalic acid as a starting material for synthesis of the proper intermediate.

De Benneville[3] has shown that acid anhydrides can be converted into keto acids in good yield by the use of cadmium alkyls. In the present work 3-nitrophthalic anhydride was successfully converted to 2-acetyl-3-nitrobenzoic acid. Increasing the ratio of dimethylcadmium to anhydride threefold, however, gave 1% yield of a neutral compound.

The reductions of 2-acetyl-3-nitrobenzoic acid with a solution of stannous chloride at both low and elevated temperatures were incomplete yielding instead 3-methyl-4-carboxyanthranil. The same product was obtained by catalytic reduction with platinum and hydrogen at low pressures. Since this reduced compound was acidic with a neutralization equivalent of 176, it appeared that the dimethylcadmium must have reacted with the carbonyl adjacent to the nitro group.

Bogert and Renshaw[4] employed zinc and alcoholic hydrogen chloride to reduce dimethyl-3-nitrophthalate. In this Laboratory a similar reduction was attempted with 2-acetyl-3-nitrobenzoic acid; however, both the nitro and acetyl groups were reduced resulting in the formation of 4-amino-3-methylphthalide. This compound was easily acylated to yield a mono and a diacylated derivative. Since the diacetate was not acidic, the acylation must have involved the amino nitrogen only.

The 2-acetyl-3-nitrobenzoic acid was converted to the acid chloride. Attempts to treat the acid chloride with dimethylcadmium using the Gilman and Nelson procedure[5] were unsuccessful. No diacetyl derivative was isolated from the reaction products.

3-Nitrophthalic anhydride was reduced to 3-aminophthalic acid in excellent yield using stannous chloride in hydrochloric acid solution. This method was found to be superior to the usual reduction of 3-nitrophthalic acid.[6] The product was then treated with acetic anhydride and converted directly to 3-acetaminophthalic anhydride.

Using the de Benneville procedure on this anhydride gave a very poor yield of a 3-acetamino-acetylbenzoic acid. However, increasing the cadmium alkyl reagent three-fold gave 22% yield of a neutral derivative. Since this might possibly be the desired intermediate it was subjected to cyclization experiments. Heating in alcoholic ammonia at 105° yielded only recovery products; heating at 180° resulted in ammonolysis of roughly half the starting material. No quinazoline compounds were isolated in these experiments.

Attempts to isolate quinazoline compounds from cyclization experiments using 3-acetamino-acetylbenzoic acid and its free base with both amination and formamide procedures were also unsuccessful.

Had a quinazoline compound been isolated it would have established the relative positions of the adjacent acetyl and carboxyl groups. In view of the low yield of this intermediate and the indefinite results of cyclization experiments no further attempts were made to establish the structure of the 3-acetamino-acetylbenzoic acid.

Since the neutral derivative isolated from the reaction of excess dimethylcadmium with 3-acetaminophthalic anhydride did not yield positive ketone tests or cyclize, a neutral derivative of phthalic anhydride itself was prepared in 60% yield by merely increasing the ratio of the dimethylcadmium to anhydride three fold. This compound was found to be identical with 3,3-dimethylphthalide described in Beilstein. This would indicate that these neutral compounds must all have a phthalide structure especially in view of the reported stability (toward hydrolysis) of the lactone ring in derivatives of phthalide.[7]

Experimental

2-Acetyl-3-nitrobenzoic Acid.—A Grignard reagent was prepared in the usual manner in a 500-ml., three-necked flask, fitted with a mechanical stirrer and a condenser with a soda lime tube, using 7.3 g. (0.3 mole) of magnesium and an excess of methyl bromide in 300 ml. of dry ether. Dimethylcadmium was then prepared from the Grignard by the addition of 31.2 g. (0.17 mole) of anhydrous cadmium chloride according to the method of Gilman and Nelson.[5] When a Michler ketone test showed the absence of Grignard reagent,[8] the reaction flask was surrounded by an ice-bath, and 33 g. (0.16 mole) of 3-nitrophthalic anhydride was added in small portions with good stirring.

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(2) Christensen, Graham and Griffith, THIS JOURNAL, **67**, 2001 (1945).

(3) De Benneville, *J. Org. Chem.*, **6**, 462 (1941).

(4) Bogert and Renshaw, THIS JOURNAL, **28**, 618 (1906).

(5) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

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After the addition of about four-fifths of the anhydride, the mixture became impossible to stir. After all of the anhydride had been added, the reaction mixture was refluxed for an hour. The contents of the flask were cooled in an ice-bath and hydrolyzed by carefully adding a slight excess (350 ml.) of 10% sulfuric acid. The ether–water mixture was then filtered yielding 5 g. of the starting material. 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% potassium carbonate solution. The carbonate solution was filtered and carefully added to an excess of dilute sulfuric acid. An oil separated. On cooling the mixture and then allowing it to rise to room temperature, there was obtained a light orange solid and a dark oil. The orange solid was soluble in hot water while the oil was not. On the basis of different water solubilities the two were separated and there were obtained 9 g. (29.7%) of the light orange solid; m. p. 159–160°.

Anal. Calcd. for $C_9H_7NO_5$: neut. equiv., 209; C, 51.68; H, 3.37; N, 6.70. Found: neut. equiv., 209; C, 51.70; H, 3.30; N, 6.58.

3,3-Dimethyl-4-nitrophthalide.—3-Nitrophthalic anhydride (11 g., 0.056 mole) was added in small portions to an ice cold, ethereal solution of dimethylcadmium prepared from 7.3 g. (0.3 mole) or magnesium, 40 g. (0.4 mole) of methyl bromide, 33 g. (0.18 mole) of cadmium chloride and 300 ml. of dry ether according to the method of Gilman and Nelson.[5] When all of the anhydride had been added, the reaction mixture was refluxed gently for two hours. A brownish gummy precipitate was formed during this period. The reaction mixture was cooled and hydrolyzed with 175 ml. of 20% sulfuric acid. The ether layer was separated and combined with an ether washing of the water layer. The combined ethereal solution was then extracted twice with 50 ml. of 10% potassium carbonate solution. Four and one-half grams (38%) of 2-acetyl-3-nitrobenzoic acid were obtained from the carbonate extract on acidification. The potassium carbonate extracted ethereal solution was evaporated and the residue recrystallized from water; 0.12 g. (1%) of 3,3-dimethyl-4-nitrophthalide was obtained in needles, m. p. 140°.

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.34; N, 6.77. Found: C, 58.31; H, 4.39; N, 6.68.

2-Acetyl-3-nitrobenzoyl Chloride.—2-Acetyl-3-nitrobenzoic acid (6 g.) was refluxed with 20 ml. of thionyl chloride for three hours. The crude acid chloride obtained after the evaporation of thionyl chloride was recrystallized from heptane and weighed 5.5 g. (85%); m. p. 108.5°.

Anal. Calcd. for $C_9H_6ClNO_4$: C, 47.50; H, 2.64; Cl, 15.65; N, 6.17. Found: C, 48.00; H, 2.90; Cl, 15.40; N, 6.13.

3-Methyl-4-carboxyanthranil.—2-Acetyl-3-nitrobenzoic acid (17 g.) was added in small portions to a solution of 90 g. of stannous chloride in 225 ml. of concentrated hydrochloric acid in a flask equipped with a mechanical stirrer. After 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 and the precipitate filtered off and washed with hydrochloric acid. There were obtained 12 g. (84%) of a light brown powdery solid; m. p. 195°.

Anal. Calcd. for $C_9H_7NO_3$: neut. equiv., 177; C, 61.01; H, 3.98; N, 7.91. Found: neut. equiv., 176; C, 60.80; H, 4.12; N, 7.97.

4-Amino-3-methylphthalide.—The reduction was carried out following procedure of Bogert and Renshaw.[4] 2-Acetyl-3-nitrobenzoic acid (5 g.) was added to a mixture of 35 ml. of 95% ethyl alcohol and 49 ml. of concentrated hydrochloride acid in a 500 ml. round-bottom flask. The mixture was placed in an ice-bath and mechanically stirred. Then zinc dust (7.5 g.) was added in small portions over a period of two hours. At the end of the addition of about 5 g., the nitroacetylbenzoic acid had dissolved. The solution was diluted with an equal volume of water and filtered through a sintered glass-funnel. It was then carefully neutralized by addition of 6 *N* sodium hydroxide solution. Cracked ice was added from time to time to keep the solution cold. When the solution was about neutral, 10% sodium carbonate solution was added until the solid which precipitated just failed to redissolve. Then 150 ml. of a saturated sodium acetate solution were added and the solution was placed in the refrigerator. Slightly brownish needle-like crystals (2.2 g.) precipitated. Recrystallization from water gave 1.8 g. (46%) of white needle-like crystals; m. p. 121–124°.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.26; H, 5.52; N, 8.58. Found: C, 66.10; H, 5.98; N, 8.53.

4-Acetamino-3-methylphthalide.—4-Amino-3-methylphthalide (1.6 g.) was added to a mixture of 5 ml. of acetic anhydride and 4 ml. of pyridine. The mixture was allowed to stand at 30–35° for sixty hours. It was then poured into 20 ml. of water and stirred and cooled until crystallization started and then placed in the refrigerator. The leaflet-like crystals obtained weighed 0.8 g. By concentrating the filtrate another 0.6 g. of slightly impure crystals were obtained. The crystals on recrystallization from water had a m. p. of 174–176°.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.39; H, 5.37; N, 6.82. Found: C, 63.93; H, 5.49; N, 6.67.

4-Diacetamino-3-methylphthalide.—4-Amino-3-methylphthalide (0.7 g.) was refluxed for about twenty hours with 6 ml. of dry pyridine and 3 ml. of acetic anhydride. The cool reaction mixture was then poured into 20 ml. of water and cooled in an ice-bath. There was thus obtained 0.45 g. of slightly impure crystals. Purification by recrystallization from water gave a product with a m. p. of 139–140°.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.16; H, 5.26; N, 5.67. Found: C, 62.64; H, 5.54; N, 5.60.

3-Acetamino-phthalic Anhydride.—3-Nitrophthalic acid (70 g.) was prepared and converted into the corresponding anhydride by refluxing with an equal amount of acetic anhydride. The anhydride (58 g.) was ground into fine powder and added in small portions to a filtered, ice cold solution of 240 g. of stannous chloride in 600 ml. of concentrated hydrochloric acid with good stirring, while maintaining the temperature of the reaction mixture below 10°. Soon after the addition of all the anhydride, the hydrochloride of 3-aminophthalic acid crystallized out. The mixture was stirred for two hours and set overnight. The crystals were filtered, sucked as dry as possible, washed with a small amount of concentrated hydrochloric acid and recrystallized once from hot concentrated hydrochloric acid. The product weighed 55 g. (84%); sintering at 178° and completely melting at 190° with gas evolution; resolidifying, then remelting around 225°.[9] Bogert[10] reported the melting point of 3-aminophthalic acid hydrochloride to be 227°.

Twenty-seven and one-half grams of the hydrochloride of 3-aminophthalic acid was refluxed with 55 ml. of acetic anhydride for an hour. The resulting clear solution was cooled overnight and filtered. Twenty-three and one-tenth grams of crystalline 3-acetaminophthalic anhydride (89%) was obtained; m. p. 181–182°. The substance after recrystallization from acetic anhydride gave a m. p. of 185–186° which is the same as that reported by Bogert and Jouard.[10]

4-Acetamino-3,3-dimethylphthalide.—Eleven grams (0.053 mole) of 3-acetaminophthalic anhydride was added to an ethereal solution of dimethylcadmium prepared from 7.3 g. (0.3 mole) of magnesium, 40 g. (0.4 mole) of methyl bromide, 33 g. (0.18 mole) of fused cadmium chloride and 300 ml. of dry ether according to the

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[9] Since the melting point of *m*-aminobenzoic acid hydrochloride was found in this Laboratory to be 224–227°, the authors believe the higher melting point to be that of the *m*-aminobenzoic acid hydrochloride—a probable decomposition product.

[10] Bogert and Jouard, This Journal, 31, 483 (1909).

method of Gilman and Nelson.[5] The reaction mixture was then refluxed gently for four hours during which time a grayish, sirupy precipitate was formed. The reaction mixture was cooled with an ice-bath and hydrolyzed carefully with 180 ml. of 20% sulfuric acid. The ether layer was separated and combined with an ether washing of the water layer. The ethereal solution was then extracted twice with 50 ml. of 10% potassium carbonate solution.

The carbonate solution was filtered and carefully acidified with dilute sulfuric acid. A 3-acetamino-acetylbenzoic acid was precipitated along with some brownish gummy substance. This was filtered and the filtrate extracted twice with a small amount of ether. Some more of the acid was obtained on evaporating the ether solution. The combined crude product thus obtained was recrystallized from a water-alcohol mixture, yield, 0.75 g. (6.5%) of colorless, transparent crystals; m. p. 142.5–144°.

Anal. Calcd. for $C_{11}H_{11}NO_4$: neut. equiv., 221; C, 59.70; H, 4.98; N, 6.33. Found: neut. equiv., 220; C, 59.80; H, 5.10; N, 6.13.

The potassium carbonate extracted ethereal solution was evaporated to dryness and a colorless solid was obtained. The substance after recrystallization from alcohol was identified as 4-acetamino-3,3-dimethylphthalide; yield, 2.60 g. (22%); m. p. 127.5°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.93; N, 6.40. Found: C, 65.68; H, 6.08; N, 6.19.

4-Amino-3,3-dimethylphthalide.—One gram of 4-acetamino-3,3-dimethylphthalide was refluxed with 15 ml. of 0.6 *N* alcoholic potash solution for an hour. The reaction mixture was evaporated, acidified with dilute hydrochloric acid and extracted with ether to remove any acidic substance. The water layer was then converted again to the alkaline side with dilute sodium hydroxide and extracted twice with a small amount of ether. The combined ether extract was evaporated and the residue recrystallized twice from alcohol. The colorless plates thus obtained were 4-amino-3,3-dimethylphthalide, m. p. 70°; yield, 0.7 g. (87%).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.22; N, 7.91. Found: C, 67.58; H, 6.18; N, 7.99.

3,3-Dimethylphthalide.—Phthalic anhydride (9.9 g., 0.067 mole) was treated with an ethereal solution of dimethylcadmium prepared from 8.9 g. (0.37 mole) of magnesium, 50 g. (0.53 mole) of methyl bromide, 39 g. (0.21 mole) of cadmium chloride and 300 ml. of dry ether according to the method of Gilman and Nelson.[5] The reaction mixture was refluxed for two hours, cooled and hydrolyzed with 215 ml. of 20% sulfuric acid. The ether layer was separated and combined with an ether washing of the water layer. The ethereal solution was extracted twice with 50 ml. of 10% potassium carbonate solution. The carbonate extracted ethereal solution was evaporated and the residue recrystallized from alcohol; 6.5 g. (60%) of 3,3-dimethylphthalide were obtained, m. p. 67.5°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17. Found: C, 74.26; H, 6.18.

The carbonate extract was acidified with dilute sulfuric acid. A very small amount of 2-acetylbenzoic acid was recovered.

Anal. Calcd. for $C_9H_7ClO_2$: Cl, 19.45. Found: Cl, 18.95.

Summary

3,3-Dimethylphthalide and its 4-amino-4-acetamino and 4-nitro derivatives were prepared from phthalic anhydride. Studies of the preparation and reduction of 2-acetyl-3-nitrobenzoic acid were made.

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Preparation of N,N-Dimethylacrylamide by Pyrolysis of N,N-Dimethyl-α-Acetoxypropionamide

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Acrylamides, which are similar to acrylic acid and acrylic esters[2] in being capable of addition polymerization,[3,4,5] have been made by the reaction of acrylyl chloride with ammonia or amines,[3,5,6,7] removal of hydrogen chloride from β-chloro-propionamides,[8,9] interaction of N,N-diethyl-α-bromopropionamide with Grignard reagents,[10] decomposition of β-dimethylaminopropionamide,[11] and the interaction of acetylene, carbon monoxide and amines.[12] Acrylamides cannot be made satisfactorily by treating methyl or ethyl acrylate with amines because primary and secondary amines add readily to the olefinic linkage of acrylic esters.[13]

The primary purpose of the present work was to develop a convenient and inexpensive method for transforming lactic acid into N,N-dimethylacryl-

$$\underset{\text{I}}{CH_3COOCH(CH_3)CON(CH_3)_2} \longrightarrow \underset{\text{II}}{CH_2{=}CHCON(CH_3)_2} + CH_3COOH$$

$$\underset{\text{III}}{CH_3COOCH(CH_3)COOCH_3} \longrightarrow \underset{\text{IV}}{CH_2{=}CHCOOCH_3} + CH_3COOH$$

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[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

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