AN ABSTRACT OF THE THESIS OF
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Date Thesis Presented, May 17, 1948
Title: The Synthesis of 3-Chloro-3-Methylphthalide.
Abstract Approved

It has been discovered in this laboratory that the treatment of 2-acetylbenzoic acid with thionyl chloride yields a compound which is not an acid chloride and shows anomalous properties.

Attempts to convert this chloride to 1,2-diacetylbenzene by means of dimethyl cadmium have been unsuccessful. It was also impossible to isolate a diazoketone from an Arndt-Eistert reaction. When the chloride was treated with aluminum chloride and benzene the resulting compound was identified as 3-methyl-3-phenylphthalide; no ketonic product was isolated.

When the acid chloride of 2-acetylbenzoic acid was treated with dithiocarbamic acid salts there was no development of the intensely colored dithioureas which are characteristic of normal acid chlorides.

In view of these results and the existence of similar compounds the acid chloride of 2-acetylbenzoic acid is presumed to exist in the pseudo or phthalide structure.

The pseudo amide, anilide and ester were prepared.
A SYNTHESIS
OF
3-CHLORO-3-METHYLPHTHALIDE

by
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A THESIS
submitted to
OREGON STATE COLLEGE

in partial fulfillment of
the requirements for the
degree of
MASTER OF SCIENCE

June 1948
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ACKNOWLEDGEMENT

The author wishes to express his thanks to Dr. B. E. Christensen for his helpful suggestions pertaining to this work.
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THE SYNTHESIS 
OF 
3-CHLORO-3-METHYLPHTHALIDE

De Benneville (2) reported that phthalic anhydride when treated with molar quantities of dimethyl cadmium gave a good yield of 2-acetylbenzoic acid. Recently Wang (11) discovered that the application of a three-fold excess of this reagent to 3-nitrophthalic anhydride gave appreciable yields of by-products which were later identified as the corresponding phthalide derivatives.

Because of the unusual by-products, experiments were undertaken in this laboratory to study the synthesis of 1,2-diacylbenzene from 2-acetylbenzoic acid.

The acid chloride has frequently been used as an intermediate in the preparation of methyl ketones. This is usually accomplished by the reaction with diazomethane, dimethyl cadmium or the acetoacetic ester condensation. The diazomethane reagent yields a diazoketone which is readily converted to the bromomethyl ketone by the method of Haberland (3) and then reduced to the acetyl derivative by the procedures described by Isensee (5). Both the p- and the m-diacetylbenzenes have been prepared in good yields using this reaction.

The preparation of the acid chloride of 2-acetylbenzoic acid has been reported and the compound is described
as an oily liquid; no analytical data are given. This work has been repeated by Wang using thionyl chloride as the chlorinating agent. The product obtained however, was a low melting solid which on analysis gave the theoretical chlorine content. This compound was not stable but appeared to slowly decompose on standing.

When this chloride was treated with diazomethane no diazoketone was isolated and there was no evidence that it had been formed although the original products were not recovered; furthermore, there was no reaction with dimethyl cadmium. In view of these results and the tendency of o-phthalic acid derivatives to form phthalalides it appeared that the chlorination product may exist in some form other than the acid chloride.

Lutz has studied the structures of the cis and trans forms of the acid chlorides of dimethylfumaric acid (9), b-p-bromobenzoylcrotonic acid (7,8,10) and b-benzoyl dibromoacrylic acid (6). He reports the acid chlorides of the trans forms to exist in the normal structures and to exhibit the usual properties of an acid chloride. These compounds gave usual ketonic products in a Friedel-Crafts reaction with aluminum chloride and benzene, as well as the typical esterification and hydrolysis reactions.
The behavior of the cis forms of the acid chlorides on esterification and hydrolysis were slow and not characteristic of an acyl halide. Furthermore, the acid chlorides of this form failed to give ketonic derivatives in Friedel-Crafts reaction. For this reason Lutz postulated pseudo structures for these compounds (Fig. 1). Cyclic amides (7) have also been produced using aniline and methylaniline with the pseudo 3-(p-bromobenzoyl)-3-methylacrylic acid chloride (Fig. 2).

Other examples of pseudo acid chlorides have been described in the literature. Hantzch and Schweite (4) have studied the acid chloride of o-benzilbenzoic acid and from adsorption data they are able to establish the existence of both the normal and pseudo forms. Auwers and Heintzs (1) on the basis of refractive index measurements have confirmed the pseudo form of the acid chloride of phthalaldehydeic acid.

It has long been known that normal acid chlorides will react with dithiocarbamic acid salts to yield intensely colored dithiourethanes. Phthalyl chloride for example yields the colored intermediate in contrast to the pseudo form which gives a colorless product. When the acid chloride of 2-acetylbenzoic acid was tested with this reagent no colored products were found.

On the basis of the color tests and the Friedel-Crafts
reactions it appears that the acid chloride of 2-acetylbenzoic acid must also exist in the pseudo (or phthalide) structure. The behavior of this compound appears to be typical of the cis forms of the acid chlorides reported by Lutz.

Attempts to confirm this structure by synthesis from 3-methyleneephthalide failed; chlorination experiments of 3-methylphthalide were also unsuccessful.

The pseudo amide, anilide and ester were prepared in the usual manner.
Dimethylfumaric acid chlorides

B-p-Bromobenzoylcrotonic acid chlorides

b-Benzoyldibromocrotonic acid chlorides

3-(p-Bromobenzoyl)-3-Methylacrylic acid anilides
3-Chloro-3-methylphthalide -- 2-Acetylbenzoic acid
(2 g. - 0.01 mole) and 15 ml. of thionyl chloride were refluxed on a water bath for twenty minutes or until all the acid had gone into solution; prolonged heating resulted in decomposition of the product. The excess thionyl chloride was removed under reduced pressure leaving a crude crystalline product. This was dissolved in hot n-heptane, treated with decolorizing carbon and filtered. On cooling 4.4 g. (80%) of colorless crystals were obtained, m.p. 58.5-59°. Anal. Calc. for C₉H₇ClO₂: Cl, 19.4. Found: Cl, 19.3.

3-Methyl-3-phenylphthalide -- 3-Chloro-3-methylphthalide
(3 g. - 0.016 mole) and 50 ml. of thiophene-free benzene were placed in a round-bottom flask and cooled in an icebath. Aluminum chloride (7 g.) was then added portion-wise with vigorous stirring. The solution was allowed to warm to room temperature and stand until the mass became dark. The mixture was then refluxed for thirty minutes and the reaction mass decomposed with ice-water and hydrochloric acid. The benzene layer was washed with very dilute hydrochloric acid and the benzene evaporated. A viscous oil remained which was treated with dilute sodium carbonate solution to remove any acidic fraction.
The insoluble material after recrystallizing from n-heptane gave 2.3 g. (62%) of white leaflets, m.p. 77.5-78°. A mixed melting point with 3-methyl-3-phenylphthalide gave no depression which fact confirmed the identity of the product.

3-Amino-3-methylphthalide -- 3-Chloro-3-methylphthalide (2. g. - 0.011 mole) was added to 50 ml. of concentrated aqueous ammonium hydroxide and shaken until dissolved. The excess ammonia was removed and the solution evaporated to a volume of 10 ml. On standing several hours slightly colored needle-like crystals were formed. These were recrystallized from water to yield 0.75 g. (32%) of white needles. The melting point behavior was not normal; with slow heating the crystals decomposed without melting, but when dropped on a hot block they melted above 120°. Anal. Calc. for C₉H₇NO₂: C, 66.2; H, 5.56; N, 8.58. Found: C, 66.5; H, 5.71; N, 8.60.

3-Anilino-3-methylphthalide -- 3-Chloro-3-methylphthalide (3.3 g. - 0.018 mole) and aniline (3.76 g. - 0.036 mole) were dissolved in 20 ml. of dry ether. After standing overnight, the crystalline mass was removed by filtration and then extracted with water to remove the aniline hydrochloride. The remaining crystals were finally triturated with dry ether and filtered, yielding 1.5 g. (35%) of white crystals, m.p. 112.5-114.0°. Anal: Calc.
for C\textsubscript{15}H\textsubscript{13}NO\textsubscript{2}; C, 75.3; H, 5.47; N, 5.85.  Found: C, 75.3; H, 5.61; N, 6.15.

3-Ethoxy-3-methylphthalide -- 3-Chloro-3-methylphthalide (8.6 g. - 0.047 mole) and 50 ml. of absolute ethanol were refluxed for three hours. The mixture was washed with sodium carbonate solution and then extracted with ether to remove the ester. The ether was evaporated and the residue distilled under reduced pressure yielding 3.8 g. (42%) of a colorless oil, b.p. 108°/1mm.

**Anal.:** Calc. for C\textsubscript{11}H\textsubscript{12}O\textsubscript{3}: C, 68.7; H, 6.30. Found: C, 68.4; H, 6.57.

**SUMMARY**

The chlorination of 2-acetylbenzoic acid with thionyl chloride yields the pseudo form of the acid chloride. This was confirmed by the Friedel-Crafts reaction with benzene which gave the product 3-methyl-3-phenylphthalide. The pseudo amide, anilide and ester were prepared.
BIBLIOGRAPHY


