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THE CARBETHOXYLATION PRODUCTS OF p-AMINOACETOPHENONE
AND p-DIMETHYLAMINOACETOPHENONE

A THESIS
SUBMITTED TO THE
DEPARTMENT OF CHEMISTRY
OF
THE BRIGHAM YOUNG UNIVERSITY
In Partial Fulfillment of the Requirements
For the Degree
of
Master of Science

By
Chao-Yuan Chu (1)

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CHAPTER I

INTRODUCTION

Aldehydes, ketones, esters, anhydrides, and similar compounds containing active hydrogen atoms undergo many reactions involving the formation of carbon-carbon linkages; one of the various types is the so-called Claisen condensation.

The Claisen type of condensation may be represented by the following formula:

The electron-donating component is usually an ester or ketone, and the electron-accepting component (R-C=O) is

generally an ester, anhydride, or acid chloride. The Claisen condensation is frequently used to prepare a variety of β -ketoesters or diketones.

The Claisen condensation is usually effected by basic catalysts. The bases capable of effecting such reactions include sodium alkoxides, triphenylmethyl sodium and sodium amide. Some special Grignard reagents such as isopropyl magnesium bromide¹ and mesitylmagnesium

¹Conant and Blatt, J. Am. Chem. Soc., 51, 1227 (1929).

bromide² have proved to be effective in certain condensations. Metallic sodium also effects certain condensations; however, the sodium alkoxide formed in the reaction mixture probably serves as the active condensing agent³.

A number of Claisen-type reactions have been used for the preparation of β -ketoesters, but none appears to be an entirely satisfactory general method. The one most frequently used method is the acylation of ethyl acetate by other ethyl esters, (this type of condensation is frequently called the acetoacetic ester condensation). The condensation between two different ethyl esters may be expressed as follows:

The first ester may be designated as the acylating ester. This condensation is generally satisfactory only when one of the esters (the acylating ester) has no active hydrogen, or if the same ester serves the function of both electron-donor and electron-acceptor. The condensation of two esters each of which has active hydrogen atoms may result in the formation of a mixture of four different β -ketoesters, the two self-condensation products and the two mixed ester condensation products. Even the application of the special techniques has not been particularly successful thus far, as mixtures of β -ketoesters are still obtained⁴.

²Spielman and Schmidt, J. Am. Chem. Soc., 59, 2009 (1937).

³Snell and McElvain, ibid., 59, 1823 (1937).

⁴Hudson and Hauser, ibid., 63, 3156 (1941).

Another method which has been used in several cases is the acylation of ethyl acetoacetate with acid chlorides or anhydrides and the subsequent ammonolysis or alcoholysis of the product. This reaction may be represented as follows:

The acylation of ethyl acetoacetate is readily carried out with acid chlorides or anhydrides⁵, and the ammonolysis (or alcoholysis) of the acyl acetoacetate ester gives good yields of the desired acyl acetate in some cases⁶. However, certain ethyl acyl acetates such as ethyl propionylacetoacetate give a mixture of acyl acetates on ammonolysis which is difficult to separate⁶.

A third method which is coming into importance is the carbethoxylation of ketones with alkyl carbonates. This method consists in heating or digesting the ketone with certain bases, such as sodium alkoxides, in a large excess of alkyl carbonate. We may express this method as follows:

But they are not limited to methyl ketones and ethyl carbonate.

This direct carbethoxylation process is not entirely satisfactory for the synthesis of ethyl propionylacetate or

⁵Bouveault and Bongert, Bull. soc. chim., (3) 27, 1046 (1902).

⁶Bouveault and Bongert, ibid., (3) 27, 1089 (1902).

ethyl isobutyrylacetate; however, it appears to be very successful for the synthesis of the higher acylacetates⁷. The reactions carried out in this investigation belong to the third method but with somewhat different and interesting meanings.

The ketones employed in all the journal references cited in this thesis are those containing no active hydrogen in the molecule beside the α -methylene hydrogens. However, if another active functional group such as the amino group ($-\text{NH}_2$) is attached to the reacting ketone, either of the following reactions might take place, taking the reactants, *p*-aminoacetophenone and diethyl carbonate, as an example:

The product might be a β -ketoester, a carbamate, or even a mixture of both depending upon which functional group is more active toward carbethoxylation.

The base most commonly used for the Claisen type condensation is the sodium alkoxide that corresponds to the alcohol portion of the ester; for example, sodium ethoxide is used with ethyl esters. It usually produces no by-product

⁷Wallingford, Homeyer and Jones, J. Am. Chem. Soc., 63 2252 (1941).

except the corresponding alcohol, which is easily separated from the condensation product. Under the proper conditions, sodium alkoxides effect the condensation of most esters that have two hydrogens on the α -carbon atom; however, two such esters, ethyl isovalerate and ethyl t-butyl acetate⁸, as well as those having only one α -hydrogen, such as ethyl isobutyrate⁹, fail to condense in the presence of sodium ethoxide.

The second most widely used base is triphenylmethyl sodium, which condenses not only the esters that are condensed by sodium alkoxides, but also some of those that are not condensed by the latter bases⁴. However, the triphenylmethane produced is sometimes difficult to separate from the condensed product.

Sodium amide is comparatively the least used base in acetoacetic ester condensations, but it is superior to sodium ethoxide for the carbethoxylation of methyl ketones with aliphatic esters higher than ethyl acetate, and for certain acylations with the latter ester¹⁰. Even certain ketones, for example, methyl ethyl ketone, that failed to show carbethoxylation with ethyl carbonate by means of

⁸Roberts and McElvain, J. Am. Chem. Soc., 59, 2007 (1937).

⁹McElvain, ibid., 51, 3124 (1929).

¹⁰Baumgarten, Levine and Hauser, ibid., 66, 1230 (1944).

triphenylmethyl sodium, are effected by sodium amide¹¹. Sodium amide is also quite satisfactory for the cyclization of certain esters such as ethyl adipate¹², and especially for various ketone-ester condensations¹³.

The ketone originally used for carbethoxylation studies in this investigation was p-aminoacetophenone, which bears two functional groups having active hydrogen atoms, $-NH_2$ and $-COCH_3$. Either of these two attached groups of p-aminoacetophenone might conceivably undergo carbethoxylation by virtue of their active hydrogen atoms and thus lead to two entirely different products as mentioned above, a β -ketoester or a carbamate. The carbethoxylation of p-aminoacetophenone with diethyl carbonate was carried out by means of sodium amide as the basic catalyst. The product was then systematically identified.

After finding out that the product was a carbamate, which shows the amino group is more active than the methyl ketonic group toward carbethoxylation in this case, the active hydrogens of p-aminoacetophenone were then replaced by methylation by means of dimethyl sulfate yielding p-dimethylaminoacetophenone.

¹¹Abramovitch and Hauser, J. Am. Chem. Soc., 64, 2271 (1942).

¹²Haller and Cornubert, Bull. soc. chim., (4) 39, 1626 (1926).

¹³Bergstrom and Fernelius, Chem. Rev., 12, 142 (1933); ibid., 20, 459 (1937).

The carbethoxylation of p-dimethylaminoacetophenone was then carried out by using the same catalyst. The product was systematically identified and some derivatives were prepared. The product was a β -ketoester having amphoteric properties. Further investigations leading to the preparation of a new series of compounds would be interesting.

CHAPTER II

HISTORICAL REVIEW

The earliest attempt to condense ethyl carbonate with esters was made by Wislicenus in 1887¹⁴. He reported that all attempts to condense diethyl carbonate with ethyl acetate failed, and in a later report¹⁵ concluded that alkyl carbonates were not suitable for such Claisen type condensations.

In the same year Claisen¹⁶ condensed acetophenone with diethyl carbonate by adding alcohol-free sodium ethoxide slowly to the mixture without a solvent. Ethyl benzoyl-acetate was isolated in poor yield and was accompanied by high boiling by-products.

Koetz and Grethe¹⁷ appear to be the first investigators to condense camphor and some cyclic ketones with diethyl carbonate by using sodium amide as the effective base and

¹⁴Wislicenus, Ber., 20, 2930 (1887); Ann., 246, 313 (1888).

¹⁵Wislicenus, Ber., 27, 795 (1894).

¹⁶Claisen, Ber., 20, 656 (1887).

¹⁷Koetz and Grethe, J. prak. Chem., (2) 80, 473 (1909).

reported a successful result in 1910. The next year Gardner, Perkin, and Watson¹⁸ also described some satisfactory carbethoxylations of several cyclic ketones with diethyl carbonate.

In 1916 Schroeter¹⁹ obtained about a 25 per cent yield of methyl α,γ -diphenylacetoacetate by condensing dimethyl carbonate with dibenzylketone in ether by means of sodium. Then Bredt condensed another few cyclic ketones with diethyl carbonate in 1922²⁰ (also in 1932)²¹ by using sodium amide.

Kraus and Kahler began to prepare triphenylmethyl sodium in 1925²² and had success in 1933²³; however, no application has been made on carbethoxylation.

Lux²⁴ obtained ethyl acetoacetate in 40 per cent yield by slowly adding acetone to a refluxing mixture of diethyl carbonate with ether and sodium in 1929. Comparable results were obtained by Nelson and Cretcher²⁵,

¹⁸Gardner, Perkin and Watson, J. Chem. Soc., 97, 1756 (1910).

¹⁹Schroeter, Ber., 49, 2712 (1916).

²⁰Bredt, J. prak. Chem., (2) 104, 9 (1922).

²¹Bredt, ibid., (2) 131, 132 (1932).

²²Kraus and Kahler, J. Am. Chem. Soc., 47, 2739 (1925).

²³Kraus and Kahler, ibid., 55, 3538 (1933).

²⁴Lux, Ber., 62, 1826 (1929).

²⁵Nelson and Cretcher, J. Am. Chem. Soc., 50, 2758 (1928).

who tried the reaction of diethyl carbonate with ethyl phenylacetate under various conditions, in alcohol, ether, and benzene and with both sodium and sodium amide. Better yields in this same reaction were reported by Skinner²⁶ in 1937, who used potassium and sodium-potassium alloys as condensing agents in benzene.

Using metallic sodium or potassium in the presence of xylene or other solvent, Preobrashenski, Schtschukina and Lapina²⁷ condensed diethyl carbonate with tropinone.

In 1941 Wallingford, Homeyer and Jones⁷ described a general method for effecting the carbethoxylation using sodium or potassium alkoxides under forced conditions. Although their method is quite satisfactory with a number of ketones, it fails with relatively reactive ketones such as methyl ethyl ketone and benzalacetone, and with relatively unreactive ketones such as di-isobutyl ketone and camphor.

Certain of these ketones were converted to β -ketoesters by carbethoxylation with triphenylmethyl sodium and potassium as reported by Baumgarten, Levine and Hauser.^{10, 28} A general method for carbethoxylation by means of this useful base was also suggested.

²⁶Skinner, J. Am. Chem. Soc., 59, 322 (1937).

²⁷Preobrashenski, Schtschukina and Lapina, Ber., 69, 1615 (1936).

²⁸Baumgarten, Levine and Hauser, J. Am. Chem. Soc., 66, 862 (1944).

In the same year Adams and Hauser²⁹ reported a number of β -ketoesters prepared by carbethoxylation of a series of aliphatic methyl ketones with aliphatic esters using sodium amide as the catalyst. Then Levine and Hauser³⁰ described a number of β -ketoesters made by reactions of ketones with diethyl carbonate by means of sodium amide and also suggested a general procedure.

In 1945 Hauser, Shivers and Skell³¹ described the carbethoxylations of a series of high-molecular ketones with diethyl carbonate by means of potassium amide. Anderson, Halverstadt, Miller and Roblin, Jr.³² modified the method developed by Levine and Hauser by cooling the reactive mixture in an ice-bath; a better yield was reported.

In 1946 Walker, Levine, Kibler and Hauser³³ reported that higher acetates such as ethyl phenylacetate have been satisfactorily carbethoxylated with diethyl carbonate by means of sodium amide.

²⁹Adams and Hauser, J. Am. Chem. Soc., 66, 1220 (1944).

³⁰Levine and Hauser, ibid., 66, 1768 (1944),

³¹Hauser, Shivers and Skell, ibid., 67, 409 (1945).

³²Anderson, Halverstadt, Miller and Roblin, Jr., ibid., 67, 2197 (1945).

³³Walker, Levine, Kibler and Hauser, ibid., 68, 672 (1946).

In 1947 Shivers, Dillon and Hauser³⁴ described another series of β -ketoesters prepared by ester condensation by means of sodium amide. In the same year Soloway and La Forge³⁵ reported a synthesis of ethyl β -oxocaprylate from methyl ketone, 2-heptanone, and diethyl carbonate with a rarely used but stronger base, sodium hydride, as the condensing agent.

Apparently no report has been published concerning the carbethoxylation of ketones containing amino group or other functional group bearing active hydrogen atoms in addition to α -methylenic hydrogen atoms.

³⁴Shivers, Dillon and Hauser, J. Am. Chem. Soc., 69, 119 (1947).

³⁵Soloway and La Forge, ibid., 69, 2677 (1947).

CHAPTER III

EXPERIMENTAL PART

A. CARBETHOXYLATION OF p-AMINOACETOPHENONE

1. Procedure:

Our method of carbethoxylation consisted of first converting p-aminoacetophenone into its sodium derivative by means of sodium amide in liquid ammonia, then replacing the liquid ammonia by absolute ether and refluxing the ether suspension of the sodium ketone with diethyl carbonate. Due to the fact that excess of sodium amide has a favorable effect on the yield of the β -ketoester in the carbethoxylation of ketone,³⁰ two experiments were carried out, in the first case using one molecular equivalent of sodium amide and diethyl carbonate per mole of ketone, and another using three equivalents of both sodium amide and ethyl carbonate for comparison.

In a 500 cc. three-necked round-bottom flask equipped with a Hershberg stirrer, a separatory funnel and a water condenser (carrying a soda lime tube) was placed 400 cc. of commercial anhydrous liquid ammonia. To the stirred solution 4.6 g. (0.2 atom) of sodium was then added followed by a few crystals of ferric nitrate³⁶ to catalyze the conversion of blue solution of sodium in

³⁶Vaughn, Vogt and Nieuwland, J. Am. Chem. Soc., 56, 2120, (1934).

ammonia into sodium amide. The conversion was completed as indicated by the disappearance of the blue color and subsidence of the gray suspension of sodium amide. Then 27 g. (0.2 mole) of p-aminoacetophenone in 200 cc. of absolute ether was added over a period of five minutes; the reaction flask was then placed on a steam-bath. The ammonia was evaporated as rapidly as possible (during fifteen to twenty minutes) sufficient ether being added to maintain the volume at approximately 400 cc. When the ether began to reflux, indicating that all the liquid ammonia had evaporated, 20.3 g. (0.2 mole) of diethyl carbonate was added, and the mixture was vigorously stirred and refluxed for two hours. Finally the cooled mixture was slowly poured into 400 g. of cracked ice and 40 cc. of glacial acetic acid and allowed to stand in the hood until the ether had evaporated. The precipitate was filtered off, dried, and twice recrystallized from ethanol or benzene-ligroin mixtures.

Fifteen grams (36 per cent) of the straw colored crystals melting at 157-158°C. were obtained.

Another experiment was carried out by the above described procedure but using 13.8 g. (0.6 atom) sodium, 27 g. (0.2 mole) of p-aminoacetophenone and 71 g. (0.6 mole) of diethyl carbonate instead of the above quantities. Twenty three grams (56 per cent) of straw colored crystals melting at 157-158°C. were obtained in this way.

2. Identification of the Carbethoxylation Product:

As pointed out earlier the carbethoxylation product might be a ketoester, a carbamate, a mixture, polycondensation products, or even other side-products, depending on the relative activity of the active hydrogen atoms attached to the amino group and α -methylene group. A systematic identification was, therefore, carried out by determining the general physical properties, the molecular weight, nitrogen content, and degradation products and by preparing suitable derivatives. As a final check the proposed compound was synthesized by an independent process and compared with the original.

a) General physical properties:

- (1) Crystal form: Pale yellow needles from benzene; pale yellow crystalline powder from ethanol.
- (2) Melting point: 157-158°C.³⁷
- (3) Solubility: Insoluble in hot or cold water and ligroin. Sparingly soluble in cold benzene and alcohol. Quite soluble in acetone, dioxane, hot alcohol, and benzene. Soluble in concentrated sulfuric acid producing an orange-red color, but recovered unchanged on dilution.

b) Molecular weight and nitrogen content:

Two methods were carried out in this investigation for the determining the molecular weight of the unknown product; one was Rast's camphor method; the other was

³⁷Ethyl p-acetylaminoacetophenone as prepared by Raadsveld had a melting point of 159°C. Raadsveld, Rec. trav. chim., 54, 813 (1935).

the more accurate, Beckmann's freezing point depression method.

(1) Rast method:³⁸ About 50 mg. of the sample was weighed accurately into a pyrex test tube, then approximately 500 mg. of sublimed pure d-camphor was added and the mixture was weighed again to the nearest 0.1mg. The mixture was quickly melted in an oil-bath at 180°C., then cooled and powdered. A 1 mm. layer of the solid mixture was packed tightly into a melting-point tube, and the melting point was determined. The melting point was taken as the stage at which the last bit of solid disappeared. Meantime the melting point of the pure d-camphor was determined. The molecular weight of the sample was calculated by the following formula:

$$M = \frac{40 \times w \times 1,000}{t \times W}$$

in which w is the weight of the sample, W is the weight of camphor, t is the depression of the melting point in degrees centigrade, and 40 is the molecular melting point depression constant for camphor.

The results are summarized in Table 1.

TABLE 1
MOLECULAR WEIGHT OF THE CARBETHOXYLATION
PRODUCT OF p-AMINOACETOPHENONE (Rast Method)

W, g.	w g.	Melting point of		t °C.	M
		camphor °C.	mixture °C.		
0.5200	0.0520	177.0	157.6	19.4	206
0.4984	0.0484	177.0	157.9	19.1	202
0.4960	0.0480	177.0	157.8	19.2	201
Average molecular weight					203*

*The molecular weight calculated for both ethyl

³⁸Rast, Ber., 55, 1051, 3727 (1922).

p-aminobenzoylacetate and ethyl p-acetylphenylcarbamate, $C_{11}H_{13}O_3N$ is 207.

(2) Beckmann method:³⁹ Benzene was unsuitable as a solvent in this determination because it dissolved very little sample while cold. Purified dioxane, which is more suitable, was placed in a tube surrounded by an air jacket and a suitable freezing bath. The tube containing the solvent was fitted with a stirrer and a Beckmann thermometer graduated in hundredths of a degree. By gradually lowering the temperature of the liquid and stirring at the same time to avoid supercooling, the freezing point, the point at which the temperature remained stationary, could be observed. A known weight of the unknown product was then dissolved in 25.0* cc. of purified dioxane, and the freezing point was also determined. The molecular weight was calculated by the following formula:

$$M = \frac{4.63 \times w \times 1,000}{t \times W}$$

in which w is the weight of the unknown compound, W is the weight of dioxane, t is the depression of the melting point, and 4.63 is the molecular freezing point depression constant for dioxane. The results are listed in Table 2.

*25.0 cc. of purified dioxane with specific gravity of 1.0350 was used.

³⁹Weissburger, "Physical Methods of Organic Chemistry," Inter Science Publishers Inc., New York, 1, 37 (1945).

TABLE 2

MOLECULAR WEIGHT OF THE CARBETHOXYLATION
PRODUCT OF p-AMINOACETOPHENONE (Beckmann Method)

W g.	W g.	t °C:	M
25.8750	0.3300	0.283	207.3
25.8750	0.5200	0.452	205.8
25.8750	0.5002	0.430	208.1
Average molecular weight			207.1

The nitrogen content determination was carried out by the Dumas Method. The procedure is omitted here since a detailed description may be found in many organic chemistry manuals.⁴⁰

Anal. Calcd. for $C_{11}H_{13}O_3N$ (both ethyl p-aminobenzoyl-acetate and ethyl p-acetylphenylcarbamate): N, 6.76 per cent.

Found: N, 6.97 per cent and 6.82 per cent.

c) Degradation studies:

(1) Aqueous HCl:

The unknown product, 0.64 g., was dissolved in a little alcohol and refluxed with concentrated HCl for 24 hours. The original compound was recovered unchanged.

(2) Aqueous H_2SO_4 :

The unknown product, 0.05 g., was dissolved in concentrated H_2SO_4 ; an orange-red solution was obtained. The mixture was refluxed for 24 hours, but the original compound was again recovered un-

⁴⁰For example, Fisher, "Laboratory Manual of Organic Chemistry," John Willey and Sons, Inc., New York, 338-78 (1938).

changed.

(3) Alcoholic HCl:

Five-hundreth g. of the unknown product was dissolved in 5 cc. of alcohol saturated with anhydrous HCl while cooling in an ice-bath. The mixture was warmed up and refluxed for 5 hours. On cooling, long, pale yellow needles separated from the deep red solution. They were filtered off, washed and dried. The melting point of these long needles was 158°C . Hence, the product was unchanged.

(4) Alcoholic KOH, 3 per cent:

Five-hundreth g. of the unknown product was dissolved in 25 cc. of 0.56 N alcoholic KOH and refluxed for one hour. On cooling, long, pale yellow needles precipitated out. The precipitate was filtered off, washed, and dried. Long needles melting at 158°C . were obtained. Hence, the product was unchanged still.

(5) Alcoholic KOH, 5 per cent:

Five-hundreth g. of the unknown product was dissolved in 25 cc. of 5 per cent alcoholic KOH and refluxed for five hours. On cooling no precipitate appeared. The solution was neutralized with HCl and made slightly acid. The solution was extracted with ether for many times, or the solution was saturated with sodium chloride at first then extracted with ether. The ether extract was evaporated to a small

volume on a steam bath, whereupon, long needles with pale yellow color appeared. The product was insoluble in water. It was recrystallized from a benzene-ligroin mixture. The unknown product became almost colorless and melted at 105°C. This product had a melting point quite close to that of p-aminoacetophenone (105-106°C.).

The unknown was dissolved in ether, and a stream of anhydrous HCl gas was bubbled through the solution. A bright, white precipitate immediately appeared. The product, probably p-aminoacetophenone hydrochloride, had no definite melting point. It was quite soluble in water. This product was easily acylated.

Five-hundreth g. of this product was dissolved in 2 cc. of acetic anhydride; development of heat took place immediately, and the acetyl derivative soon separated from the solution. It was recrystallized from dilute alcohol. The product melting at 156°C. This proved this unknown product was really p-aminoacetophenone, because p-aminoacetophenone, has a melting point of 167°C.⁴¹

(6) Acylation:

Five-hundreth g. of the original unknown product was dissolved in 25 cc. of acetic anhydride and refluxed for five hours. The original compound was recovered unchanged. Moreover, it was dissolved in 25 cc. of

⁴¹Kliegel, Ber., 18, 2691 (1855).

acetyl chloride and refluxed for five hours. The original compound was still recovered unchanged. This indicated that the amino group of the original unknown occurred as part of some group incapable of acylation.

d) Preparation of derivatives:

(1) 2, 4-dinitrophenylhydrazone:

To 3 cc. of the 2, 4-dinitrophenylhydrazine reagent (prepared by adding a solution of 2 g. of 2, 4-dinitrophenylhydrazine in 15 cc. of concentrated sulfuric acid to 500 cc. of 30 per cent alcohol) was added a small amount of the unknown product. Then the resulting solution was heated to boiling and allowed to stand until a precipitate formed, which was filtered off and recrystallized from alcohol. The 2, 4-dinitrophenylhydrazone had an orange-red color and melted at 232-234°C.

Anal. Calcd. for $C_{17}H_{17}O_6N_5$ (2, 4-dinitrophenylhydrazone of ethyl p-acetylphenylcarbamate):
N, 18.08 per cent.

Calcd. for $C_{15}H_{11}O_5N_5$ (pyrazolone of ethyl p-aminobenzoylacetate): N, 20.52 per cent.

Found: N, 18.30 per cent and 18.19 per cent.

This proved not only the existence of the ketonic group, but also that the unknown product was a probably carbamate rather than a β -ketoester. Because a carbamate produces a hydrazone and a β -ketoester produces a pyrazolone upon reacting with phenylhydrazine. The result of the nitrogen determination in-

dicated the former product.

(2) Mononitro derivative:

At 0°C., 0.05 g. of the unknown product was dissolved in a little concentrated sulfuric acid; 0.25 cc. of fuming nitric acid was then slowly added. When the reaction was finished, a yellow product separated after pouring onto 100 g. of cracked ice. The nitro derivative was isolated from the starting material by extraction with carbon tetrachloride from which it was also recrystallized. Bright yellow crystals were thus obtained.

It was quite soluble in acetone, chloroform, hot alcohol and benzene. It was sparingly soluble in cold alcohol and benzene, and insoluble in water and ligroin. It melted at 110°C.

Anal. Calcd. for $C_{11}H_{12}O_5N_2$ (mononitro derivative of either ethyl p-aminobenzoylacetate or ethyl p-acetylphenylcarbamate): N, 11.11 per cent.

Found: N, 10.90 per cent.

The melting point of the mononitro derivative of the unknown product was very close to that of the mononitro derivative of ethyl p-acetylphenylcarbamate prepared by Raadsveld,⁴² which melted at 111°C.

e) Preparation of ethyl p-acetylphenylcarbamate:

In order to positively identify that the unknown was ethyl p-acetylphenylcarbamate, the latter was directly synthesized by the following procedure:

⁴²Raadsveld, Rec. trav. chim., 54, 813 (1935).

A mixture of 10 g. of ethyl chloroformate, 12 g. of p-aminoacetophenone and 10 g. of anhydrous sodium carbonate were refluxed in benzene for about four hours. The product, which separated on cooling, was washed with hot boiling water and then recrystallized from alcohol. Pale yellow, needle-like crystals melting at 158°C. were obtained. Yield: 50 per cent. A mixed melting point of the unknown, obtained by the sodamide catalyzed carbethoxylation of p-aminoacetophenone, and of the above synthesized ethyl p-acetylphenylcarbamate was found undepressed. This indicated strongly that both were the same compound.

3. Discussion:

From the data obtained above we could say that the carbethoxylation product of p-aminoacetophenone with sodamide catalyst was not ethyl p-aminobenzoylacetate, but definitely ethyl p-acetylphenylcarbamate. The proof, step by step, in resume, is as follows:

a. The molecular weight and nitrogen content of the unknown product indicated that both were possible.

b. It could not be acylated by either acetic anhydride or acetyl chloride. It formed no salt when dry hydrochloride gas bubbled through an ethanolic solution of it. These facts showed that the amino group was deactivated or altered by some group attached to it.

c. It hydrolyzed in 5 per cent alcoholic alkali

solution to form p-aminoacetophenone, the starting material, which was very easily acylated. This showed that the altered amino group was converted to the free amino group by hydrolysis.

d. It formed a phenylhydrazone with 2, 4-dinitrophenylhydrazine. This indicated not only the existence of a ketonic group, but also that a carbamate was more likely than a β -ketoester, the latter forming pyrazones with phenylhydrazines. The nitrogen determination showed that it was not a pyrazolone.

e. Its mononitro derivative had the same melting point as that of ethyl p-acetylmononitrophenylcarbamate prepared by Raadsvelde,⁴² by another method.

f. It had a melting point the same as that of ethyl p-acetylphenylcarbamate as prepared by Raadsvelde, by another method; moreover, a mixed melting point of the two substances showed no depression.

Thus the unknown product obtained by carbethoxylating p-aminoacetophenone with diethyl carbonate in the presence of sodamide has been shown to be ethyl p-acetylphenylcarbamate.

The following scheme represents the reactions described in this chapter:

SCHEME 1

REACTIONS INVOLVED IN THE CARBETHOXYLATION
OF p-AMINOACETOPHENONE

* Melting point.

4. Effect of Large Excesses of Sodium Amide and Ethyl Carbonate on the Carbethoxylation: An Attempt at Di-carbethoxylation.

The yield of ethyl p-acetylphenylcarbamate was greatly increased by using excess of sodium amide and ethyl carbonate. One mole of p-aminoacetophenone with

with one mole of sodium amide and one mole of ethyl carbonate gave a yield of 36 per cent while using one mole of p-aminoacetophenone with three moles of sodium amide and three moles of ethyl carbonate raised the yield to 56 per cent. The higher yield in the presence of excess sodium amide is understandable on the basis of the mechanism of the reaction, which may be represented as follows:

or

Although the p-aminoacetophenone is converted into its sodium derivative by an equivalent of sodium amide, one half of it could theoretically be regenerated in the third step. Two extra equivalents of sodium amide keep the p-aminoacetophenone in the form of its sodium derivative as in (1) and make possible the carbethoxylation of all the p-aminoacetophenone.

Conceivably still larger excesses of sodium and ethyl carbonate might lead to carbethoxylation at both positions in p-aminoacetophenone bearing active hydrogens, viz., the amino and acetyl groups.

An experiment designed to test this hypothesis was carried out by using 1 mole of p-aminoacetophenone with 6 mole of sodium amide and ethyl carbonate; further carbethoxylation on the ketonic group was hoped for. However, the product was still only ethyl p-acetylphenylcarbamate, not ethyl N-carbethoxy-p-aminobenzoylacetate. A little higher yield of 58 per cent of the former compound was realized, nevertheless.

Another experiment was carried out by using ethyl p-acetylphenylcarbamate as the starting material. The original material, however, was recovered unchanged. Stronger bases such as sodium hydride might be of some help in effecting further carbethoxylation, but no such experiment was performed.

B: CARBETHOXYLATION OF p-DIMETHYLAMINOACETOPHENONE

Since the amino group of p-aminoacetophenone is more active than the methyl ketonic group toward carbethoxylation, the product obtained by its carbethoxylation is ethyl p-acetylphenylcarbamate rather than ethyl p-aminobenzoylacetate. It was thought that by methylating the amino group to remove the active hydrogens a β -ketoester might be obtained. by carbethoxylation.

1. Preparation of p-dimethylaminoacetophenone:

Klingel⁴³ prepared p-dimethylaminoacetophenone by methylation of p-aminoacetophenone with methyl iodide. However, it was announced later by Weil⁴⁴ that the main product was p-monomethylaminoacetophenone. Weil prepared p-dimethylaminoacetophenone by reacting p-dimethylamino- α -bromostyrene with alcoholic potassium hydroxide, and also by treatment of p-aminoacetophenone with dimethyl sulfate; however, a detailed description of the procedure was not given. Staudinger and Kon⁴⁵ prepared p-dimethylaminoacetophenone by refluxing dimethyl aniline with acetic anhydride and zinc chloride; a poor yield was reported. The method used in this investigation was

⁴³Klingel, Ber., 18, 2694 (1885).

⁴⁴Weil, Monatsh., 29, 905.

⁴⁵Staudinger and Kon, Ann., 384, 111.

methylation of p-aminoacetophenone with dimethyl sulfate as follows:

Thirteen and five tenths g. of p-aminoacetophenone (0.1 mole) and 18 g. of dimethyl sulfate (0.15 mole) were mixed, stirred by a Hershberg stirrer, and heated by a steam bath. An aqueous solution of 8 g. of sodium hydroxide was slowly added to the mixture and boiled for two hours. On cooling, a mixture of p-aminoacetophenone and p-dimethylaminoacetophenone precipitated out. The precipitate was dissolved in acetic anhydride, and the acetyl derivative of p-aminoacetophenone soon separated from the solution after adding a few drops of conc. sulfuric acid and heating a little while. After filtering off the acetyl derivative and carefully neutralizing the solution with sodium hydroxide solution, p-dimethylaminoacetophenone reappeared as the precipitate. Upon recrystallizing from dilute alcohol, p-dimethylaminoacetophenone was obtained as white needle-like crystals melting at 103°C.* It failed to be acylated but formed an oxime with hydroxylamine with a melting point of 157°C.** Yield: 9 grams. (56 per cent).

Anal. Calcd. for $C_{10}H_{13}ON$: N, 8.59 per cent.

Found: N, 8.84 per cent.

* The melting point of p-monomethylaminoacetophenone is 59°C.

** The oxime of p-aminoacetophenone has a melting point of 147°C.

2. Carbethoxylation of p-dimethylaminoacetophenone:

The method of carbethoxylation was more or less the same as described in Chapter III, pp. 13-14. In a 1,000 cc. three necked round-bottom flask equipped with a Hershberg stirrer, a water reflux-condenser having a soda lime tube, and a separatory funnel, was placed 300 cc. of commercial liquid ammonia. To the stirred solution was added a few crystals of anhydrous ferric chloride and 6 g. (0.25 atom) of sodium. The formation of sodium amide was completed within an hour. The liquid ammonia was then evaporated while 16 g. (0.1 mole) of p-dimethylaminoacetophenone dissolved in 300 cc. of anhydrous ether was added and refluxed for two hours. Thirty g. of diethyl carbonate was then added and vigorously stirred and refluxed for about four hours. The reacting period was longer than that described in Chapter III, pp. 13-14 due to the comparatively lower activity of p-dimethylaminoacetophenone compared to p-aminoacetophenone. After the mixture was allowed to cool, 500 cc. of water was added. The ether phase was washed with saturated sodium bicarbonate, dried with sodium sulfate, and the solvent distilled. The residue was recrystallized from dilute alcohol. Pale yellow crystals melting at 64°C. were obtained. Yield: 2.5 g. (10.6 per cent).

3. Identification of the Carbethoxylation Product:

a) General physical properties:

- (1) Crystal form: Pale yellow needles from alcohol.
- (2) Melting point: 64°C .
- (3) Solubility: Hardly soluble in cold and hot water and ligroin. Quite soluble in 5 per cent aqueous hydrochloride. Soluble in warm 5 per cent aqueous sodium hydroxide. Quite soluble in ether, dioxane, acetone, hot alcohol, and hot benzene.

b) Molecular weight and nitrogen content:

(1) Molecular weight: Determination of the molecular weight of the product was carried out by the previously described Beckmann's freezing point depression method with dioxane as the solvent. The results are listed as follows:

TABLE 3

MOLECULAR WEIGHT OF THE CARBETHOXYLATION
PRODUCT OF p-DIMETHYLAMINOACETOPHENONE
(BECKMANN METHOD)

*Weight of dioxane g.	Weight of sample g.	Freezing point depression $^{\circ}\text{C}$.	Molecu- lar weight
25.8750	0.5140	0.393	234.0
25.8750	0.5250	0.402	233.6
Average molecular weight			233.8**

*Twenty five cc. of dioxane with a specific gravity of 1.0350 was used.

**The calculated molecular weight of $\text{C}_{13}\text{H}_{17}\text{O}_3\text{N}$, p-(CH_3) $_2$ N- C_6H_4 -COCH $_2$ COOC $_2\text{H}_5$, is 235.0.

(2) Nitrogen content: Determination of nitrogen was carried by the Dumas method. The results were as follows:

Anal. Calcd. for $C_{13}H_{17}O_3N$: N, 5.95 per cent.

Found: N, 6.17 per cent and 6.08 per cent.

The molecular weight and nitrogen content of the unknown product was quite close (within the experimental limits of error) to that of ethyl p-dimethylaminobenzoylacetate.

c) Degradation studies:

(1) Aqueous KOH, 5 per cent:

Twenty-five hundredth g. of the unknown product was dissolved in 25 cc. of 5 per cent aqueous potassium hydroxide solution and refluxed for two hours. On cooling, white needles precipitated. Recrystallized from benzene-ligroin mixture, the product had a melting point of $103^{\circ}C$. It failed to be acylated. It formed an oxime with hydroxylamine with a melting point of $157^{\circ}C$. The mixture of the hydrolyzed product with p-dimethylaminoacetophenone showed no depression of the melting point. It was, therefore, the starting material, p-dimethylaminoacetophenone.

(2) Dry hydrogen chloride gas:

Twenty five hundredth g. of the unknown product was dissolved in anhydrous ether and a stream of dry hydrogen chloride bubbled through. A white

precipitate immediately appeared. It was quite soluble and had no sharp melting point. It was very possibly the acid salt of ethyl p-dimethylaminobenzoylacetate, but it may also have been a cleaved product. Titration tests were, therefore, carried out for identification. The results are summarized as follows:

TABLE 4

TITRATION OF ACID SALT OF THE CARBETHOXYLATION
PRODUCT OF p-DIMETHYLAMINOACETOPHENONE

Weight of sample g.	Normality of NaOH N.	Volume of NaOH used cc.	Eq. wt. of sample
0.3520	0.1032	12.62	271.0
0.2038	0.1032	7.25	272.3

Average equivalent weight

271.7 *

*Calcd. eq. wt. of $\text{HCl} \cdot (\text{CH}_3)_2\text{N}-\text{C}_6\text{H}_4-\text{COCH}_2\text{COOC}_2\text{H}_5$:
270.5.

The conclusion is that it was the acid salt of the expected ϕ -ketoester.

d) Preparation of derivatives:

(1) 3-(p-dimethylaminophenyl)-1-(2,4-dinitrophenyl-)pyrazolone-5.

A solution of 0.5 g. of the unknown product in 15 cc. of alcohol was treated with 1 g. of 2,4-dinitrophenylhydrazine and 2 cc. of concentrated hydrochloric acid. An orange-red precipitate immediately formed, which changed instantly into dark purple-red color. It was recrystallized from methanol. The resulting pyrazolone melted at 243-244°C. Yield: 0.4 g. (52 per cent).

Anal. Calcd. for $C_{17}H_{15}O_5N_5$: N, 18.97 per cent.

Found: 18.62 per cent.

(2) 3-p-Dimethylaminophenylisoxazolone-5

Seven-tenth g. of the unknown product and 0.5 g. of hydroxylamine hydrochloride were dissolved in 10 cc. of dilute alcohol and refluxed for one hour. On cooling and scratching the inner wall of the container with a glass rod, white, needle-like crystals precipitated. Melting point: 164°C. Yield: 0.3 g. (50 per cent).

The product was acidic in aqueous solution, forming salt with ammonia, which is characteristic of isoxazolones. The ammonia salt of 3-p-dimethylaminophenylisoxazolone had no definite melting point.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: N, 13.72 per cent.

Found: 13.52 per cent.

4. Discussion:

The carbethoxylation product of p-dimethylaminoacetophenone was ethyl p-dimethylaminobenzoylacetate instead of a carbamate as concluded from the experiments described above.

The following points, in resume, confirmed the fact:

1. The molecular weight and nitrogen content of the product were identical with that expected within the experimental limits of error.

2. It was quite soluble in dilute acid solution and soluble in warm alkali solution.

3. The product of ketonic cleavage in 5 per cent alkali solution was p-dimethylaminoacetophenone, the starting material.

4. It formed a salt with dry hydrogen chloride, the equivalent weight of which was calculated by titration to be quite close to that of the expected acid salt.

5. It formed a pyrazolone with 2,4-dinitrophenylhydrazine.

6. It formed an isoxazolone with hydroxylamine.

The following scheme represents the reactions described in this Chapter:

[illegible]

Ethyl p-dimethylaminobenzoylacetate has a quite low melting point in spite of its amphoteric character because it does not possess either sufficient basic strength or acidic strength evidently to form a zwitter ion structure.⁴⁶

Ethyl p-dimethylaminobenzoylacetate is a very interesting compound because it is a β -ketoester but with amphoteric character. Many interesting derivatives might be prepared from this compound.

The yield of this compound was low (10.6 per cent) even though excess sodium amide was used in its preparation. This was possibly due to the relative inactivity of p-dimethylaminoacetophenone. Using a stronger basic agent such as sodium triphenylmethide and prolonging the reacting time might improve the yield.

⁴⁶McElvain, "The Characterization of Organic Compounds," The McMillan Co., New York, 1947, p. 60.

SUMMARY

The carbethoxylation product of p-aminoacetophenone with diethyl carbonate by means of sodium amide has been proved to be ethyl p-acetylphenylcarbamate instead of ethyl p-aminobenzoylacetate. Thus the amino group was shown to be more active than the methyl ketonic group toward carbethoxylation. Attempt at further carbethoxylation of this carbamate were unsuccessful.

After removing the active hydrogen atoms of the amino group of p-aminoacetophenone by methylation yielding p-dimethylaminoacetophenone, the carbethoxylation product was found to be ethyl p-dimethylaminobenzoylacetate. The last compound is an interesting β -ketoester especially because of its amphoteric character. Further investigation of this compound and its homologues and derivatives is suggested.

The following new compounds were prepared: 2,4-dinitrophenylhydrazone of ethyl p-acetylphenylcarbamate, oxime of p-dimethylaminoacetophenone, ethyl p-dimethylaminobenzoylacetate and its hydrochloride salt, 3-(p-dimethylaminophenyl)-1-(2,4-dinitrophenyl)-pyrazolone-5, and 3-(p-dimethylaminophenyl)-isoxazolone-5, and its ammonium salt.

BIBLIOGRAPHY

1. Abramovitch and Hauser, J. Am. Chem. Soc., 64, 2271 (1942).
2. Adams and Hauser, ibid., 66, 1220 (1944).
3. Anderson, Halverstadt, Miller and Roblin, Jr., ibid., 67, 2197 (1945).
4. Baumgarten, Levine and Hauser, ibid., 66, 862 (1944).
5. Baumgarten, Levine and Hauser, ibid., 66, 1230 (1944).
6. Bergstrom and Fernelius, Chem. Rev., 12, 142 (1933); ibid., 20, 459 (1937).
7. Bouveault and Bongert, Bull. soc. chim., (3) 27, 1046 (1902).
8. Bouveault and Bongert, ibid., (3) 27, 1089 (1902).
9. Bredt, J. prak. Chem., (2) 104, 9 (1922).
10. Bredt, ibid., 131, 132 (1932).
11. Claisen, Ber., 20, 656 (1887).
12. Conant and Blatt, J. Am. Chem. Soc., 51, 1227 (1929).
13. Fisher, "Laboratory Manual of Organic Chemistry," John Willey & Sons, Inc., New York, 1938, pp. 338-78.
14. Gardner, Perkin and Watson, J. Chem. Soc., 97, 1756 (1910).
15. Haller and Cornubert, Bull. soc. chim., (4) 39, 1626 (1926).
16. Hauser, Shivers and Skell, J. Am. Chem. Soc., 67, 409 (1945).

17. Hudson and Hauser, J. Am. Chem. Soc., 63, 3156 (1941).
18. Kliegel, Ber., 18, 2691 (1885).
19. Kliegel, Ber., 18, 2694 (1885).
20. Koetz and Grethe, J. prak. Chem., (2) 80, 473 (1909).
21. Kraus and Kahler, J. Am. Chem. Soc., 47, 2739 (1925).
22. Kraus and Kahler, ibid., 55, 3538 (1933).
23. Levine and Hauser, ibid., 66, 1768 (1944).
24. Lux, Ber., 62, 1826 (1929).
25. McElvain, J. Am. Chem. Soc., 51, 3124 (1929).
26. McElvain, "The Characterization of Organic Compounds," The McMillan Co., New York, 1947, p. 60.
27. Nelson and Cretcher, J. Am. Chem. Soc., 50, 2758 (1928).
28. Preobrashenski, Schtschukina and Lapina, Ber., 69, 1615 (1936).
29. Raadsveld, Rec. trav. chim., 54, 813 (1935).
30. Rast, Ber., 55, 1051, 3721 (1922).
31. Roberts and McElvain, J. Am. Chem. Soc., 59, 2007 (1937).
32. Schroeter, Ber., 49, 2712 (1916).
33. Shivers, Dillon and Hauser, J. Am. Chem. Soc., 69, 119 (1947).
34. Skinner, ibid., 59, 322 (1937).
35. Snell and McElvain, ibid., 1823 (1937).
36. Soloway and La Forge, ibid., 69, 2677 (1947).
37. Spielman and Schmidt, ibid., 59, 2009 (1937).

38. Staudinger and Kon, Ann., 384, 111.
39. Vaughn, Vogt and Nieuwland, J. Am. Chem. Soc., 56, 2120 (1934).
40. Wallingford, Homeyer and Jones, ibid., 63, 2252 (1941).
41. Walker, Levine, Kibler and Hauser, ibid., 68, 672 (1946).
42. Weil, Monatsh., 29, 905.
43. Weissburger, "Physical Methods of Organic Chemistry," Interscience Publishers Inc., New York, 1945, Vol. I., p. 37.
44. Wislicenus, Ber., 20, 2930 (1887); Ann., 246, 313 (1888).
45. Wislicenus, Ber., 27, 795 (1894).