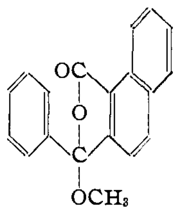
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

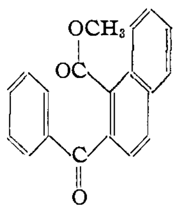
# Normal and Pseudo Esters of 2-Benzoylbenzoic Acid Types[1,2]

BY MELVIN S. NEWMAN AND CHARLES D. MCCLEARY

In connection with the synthesis of certain 1,2-benzanthracene derivatives[3] it was noted that upon treatment with methanol containing hydrogen chloride, 2-benzoyl-1-naphthoic acid, m. p. 143°, yielded a compound, m. p. 156°, in 90% yield. On alkaline hydrolysis the original acid was regenerated. Analysis gave values consistent with those to be expected from the methyl ester. However, the high melting point and the failure to react in the expected manner with methylmagnesium iodide led to the formulation of this compound as the lactone of a hemi-ketol, or pseudo ester,[4] I. The normal methyl ester, II, m. p. 73°, was obtained by treatment of the acid with diazomethane.



I

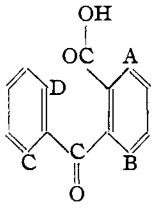


II

This behavior stands in marked contrast to that of 2-benzoylbenzoic acid, which has been shown to form only the normal methyl ester on Fischer esterification.[5] Indeed, pseudo methyl 2-benzoylbenzoate was only isolated some years later by treating the acid chloride (prepared with thionyl chloride) with methanol followed shortly by sodium carbonate solution.[5c] Furthermore, the pseudo ester was easily isomerized to the normal ester by short refluxing with mineral acids or. with thionyl chloride. Several other substituted 2-benzoylbenzoic acids were found to give rise to two types of esters upon similar treatment.[6]

Because of this marked difference in behavior of the similarly constituted 2-benzoyl-1-naphthoic acids, we became interested in possible explanations. It seemed likely that 2-benzoyl-1-naphthoic acid formed a pseudo ester on Fischer esterification because of some feature which militated against the formation of the normal ester. This feature was believed to be the hindering effect of two substituents ortho to the carboxyl group: the fused aromatic ring, and the benzoyl group. This effect, known as "steric hindrance," has been used with advantage to explain the difficulty with which diortho-substituted benzoic acids give esters on Fischer esterification, and also to explain many other cases of subnormal reactivity in addition reactions involving carbonyl groups.[7]

In order to obtain more evidence on this point we proposed to prepare all of the 2-benzoylbenzoic acids, III, having one or more methyl groups at positions A, B, C, and D, and to study their behavior on esterification.



III

Although this program has not yet been completed, we are presenting the results obtained to date because of several interesting features which have been noted. Of the twelve possibilities (including 2-benzoylbenzoic acid) six have been prepared and their behavior on Fischer esterification determined. The acids include the following: IV, 2-benzoylbenzoic; V, 2-(2-methylbenzoyl)-

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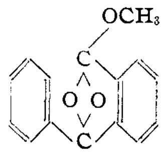
[1] The subject matter herein presented is contained in the thesis presented by C. D. McCleary to The Ohio State University in partial fulfillment of the requirements for the Ph.D. degree, June, 1940.

[2] Presented before the Organic Division at the Detroit meeting of the American Chemical Society, September, 1940. At this time the suggestion was made by Dr. H. S. Isbell of the National Bureau of Standards, Washington, D. C., that possibly the pseudo esters of 2-benzoyl-benzoic acids may possess an ortho ester form such as



We believe this structure unlikely since it requires a four-membered ring containing alternate carbon and oxygen atoms. We have been unable to find a well established example of such a ring system in the literature. See Arndt and Partale, *Ber.*, **60**, 446 (1927).

[3] Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).

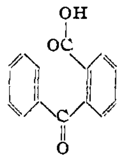
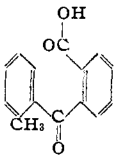
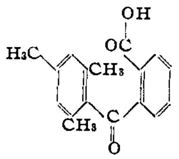
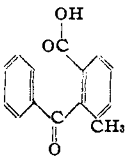
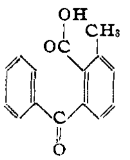
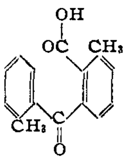
[4] For an example of similar pseudo esters in the aliphatic series see Lutz and Winne, *ibid.*, **56**, 445 (1934), and later papers.

[5] (a) Plaskuda, *Ber.*, **7**, 987 (1874); (b) Haller and Guyot, *Bull. soc. chim.*, (3) **25**, 54 (1901); (c) H. Meyer, *Monatsh.*, **25**, 475 (1904).

[6] A list of these compounds together with others culled from the literature may be found in the thesis of C. D. McCleary, at The Ohio State University.

[7] For a discussion of "steric hindrance," or "ortho effect" see H. B. Watson, "Modern Theories of Organic Chemistry," Oxford, England, 1937, pp. 207-212.

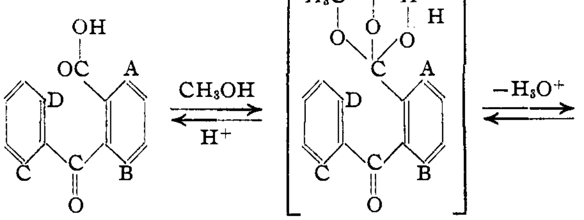
TABLE I

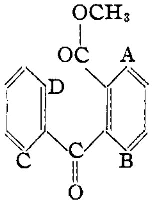
| No. | | IV | V | VI | VII | VIII | IX |
|---|---|---|---|---|---|---|---|
| Formula | |  |  |  |  |  |  |
| M. p., °C. | | 127.2–128.6° | 130.2–132.2° | 214.0–216.2° | 172.0–173.5° | 126.0–127.0° | 116.4–117.8° |
| A(Fischer) | Yield, % | 91 | 85 | 94 | 85 | 30 | 24 |
| | M. p., °C. | (51.0–51.8°) | 41.0–43.5° | 86.8–87.8° | 103.8–105.0° | 120.0–121.5° | 39.0–40.2° |
| B(Normal) | Yield, % | 96 | 94 | 94 | 94 | 90 | 89 |
| | M. p., °C. | (51.0–51.8°) | (41.5–43.5°) | (86.8–88.2°) | (104.6–105.6°) | liquid | (41.2–42.3°) |
| C(Pseudo) | Yield, % | 95 | 96 | 91 | 44 | 86 | 75 |
| | M. p., °C. | (81.4–82.4°) | (69.6–70.6°) | 85.0–87.8° | (124.4–125.4°) | (120.6–121.6°) | (96.4–97.8°) |

The percentages indicate yields. The figures in parentheses indicate melting points of the pure substances, except in column A where they represent the melting point of the unrecrystallized solids separating under the given conditions. See the experimental part for details as to preparation of the esters.

benzoic; VI, 2-(2,4,6-trimethylbenzoyl)-benzoic; VII, 2-benzoyl-3-methylbenzoic; VIII, 2-benzoyl-6-methylbenzoic; and IX, 2-(2-methylbenzoyl)-6-methylbenzoic. In order to secure samples of the normal and pseudo esters for comparison, it was necessary to prepare these esters by reliable methods. The reaction of the acid in methanol with ethereal diazomethane was considered as reliable for the production of the normal ester. Reaction of the acid chloride (prepared with thionyl chloride) with methanol in pyridine gave in all but one case (VI) a higher melting isomeric compound, considered as pseudo ester.[8] This method of preparing pseudo esters is to be preferred to that of Meyer.[5c] The behavior of these acids on Fischer esterification and the properties of the esters are indicated in Table I.

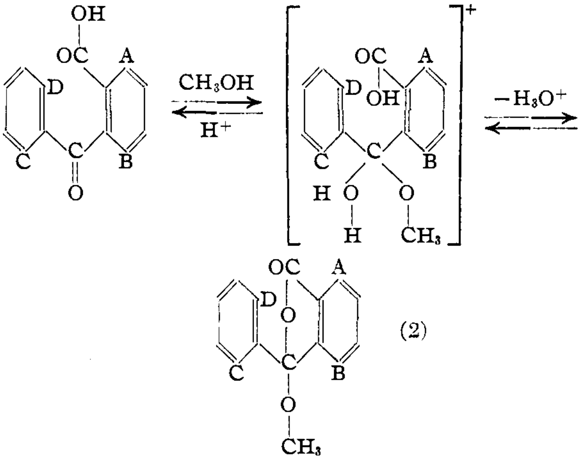
In order to facilitate discussion of these results we believe it desirable to attempt to picture possible mechanisms for the formation of normal and pseudo esters. The mechanisms for acid catalyzed esterifications have been reviewed recently by Roberts and Urey.[9] Of those mechanisms discussed we prefer that originally proposed by Lowry[10] and indicate the formation of normal methyl esters as





(1)

The formation of pseudo esters may be thought of as taking place through a similar mechanism



(2)

As may be seen, the first step in the formation of pseudo esters is represented as an acid catalyzed hemi-ketol formation. This representation perhaps needs support, as ketones are not generally considered to react to a large extent with alcohols to form hemi-ketols. In the present instance, however, the initially-formed hemi-ketol is stabilized by cyclization to form a lactone, the pseudo ester. Attention may here be drawn to the acid catalyzed formation of cyclic ketols in the sugar series (acetone sugars). Here also it is suggested that the initially-formed hemi-ketol is stabilized by ring formation.

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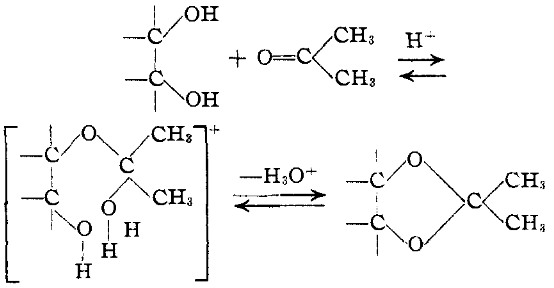
[8] The structures assigned are being checked by absorption spectra measurements.

[9] Roberts and Urey, THIS JOURNAL, **61**, 2584 (1939).

[10] Lowry, *J. Chem. Soc.*, 1381 (1925).



Since mechanisms (1) and (2) are of the type that would be expected to be subject to steric hindrance,[7] the nature of the product formed should be considerably affected by the groups at positions A, B, C, and D.

By referring to column A in Table I, it can be seen that the results are consistent with those to be expected on the basis of the proposed mechanisms, bearing in mind the so called "steric" effect of methyl groups. Thus acids IV, V, VI, and VII (none of which bears a methyl ortho to the carboxyl group) all formed the normal methyl ester in high yield on Fischer esterification. Acids VIII and IX gave mixtures of both types of ester on Fischer esterification, VIII yielding a larger amount of pseudo ester than IX. It should be noted here that in VIII only the carboxyl group has a methyl group ortho to it whereas in IX both carbonyl and carboxyl groups have ortho methyl groups. The result obtained with VIII is unexpected when one recalls that 2-benzoyl-1-naphthoic acid gave a 90% yield of the pseudo methyl ester.[3] Since one would expect approximately the same "steric" effect from a methyl group as from a fused aromatic ring, the low yield of pseudo ester in the case of VIII shows that substituents exert a considerable "chemical" effect in addition to the "steric" effect on the nature of the ester formed in Fischer esterification of 2-benzoylbenzoic acid types.

**Assignment of Structure of Isomeric Esters.**—A search of the literature revealed quite a few instances where aldehydo and keto acids form normal and pseudo methyl esters.[6] The assignment of structure in the case of the isomeric esters of aldehydo acids was in general facilitated by the characteristic aldehyde reactions of the normal ester. However, with keto acids, the structures were not easily assigned on the basis of chemical properties. In the case of 2-benzoylbenzoic acid the structures of the isomeric esters were correctly assigned on the basis of chemical reactions[11] and later confirmed by absorption spectra measurements,[12] and by calculations based on refractive indices.[13] In the majority of cases, the assignment of structure was not rigidly established but based on certain generalizations. For example, the pseudo esters were generally believed to be higher melting, less soluble in methanol, more easily hydrolyzed by aqueous alkali, and more intensely colored in concentrated sulfuric acid.[14] As assignment of structure on the basis of melting point or solubility is seldom trustworthy, we were more interested in testing the latter two generalizations. Our findings in regard to alkaline hydrolysis are to be reported in a separate publication.

**Sulfuric Acid Hydrolysis of Esters.**—The rapid hydrolysis of pseudo esters by means of concentrated sulfuric acid to give highly colored solutions, in contrast to slow hydrolysis and a weaker color in the case of normal esters, has been used most generally as a means of identifying the esters.[14] There are indications in the literature that this reaction may be unreliable. For example it is reported that the two esters of 2-benzoyl-3,4,5,6-tetrachlorobenzoic acid give the same color[15] and that the normal ester of fluorenone-1-carboxylic acid is immediately hydrolyzed by sulfuric acid to a bordeaux-red solution.[16]

A comparative study of the sulfuric acid hydrolysis of the esters prepared in this work has shown not only that the color test is unreliable, but also that certain types of normal esters are hydrolyzed quite rapidly. Thus both the normal and pseudo esters of 2-benzoyl-3-methylbenzoic acid, VII, gave identical light yellow colors although the pseudo ester was hydrolyzed to the extent of 90% while the normal ester was recovered unchanged. Furthermore, the normal esters of VIII and IX gave highly colored solutions and were both hydrolyzed in about 80% yields. It is interesting to note that these two esters are of the hindered type, usually resistant to hydrolysis with aqueous base or acid. An analogy for this behavior was found in the conversion of methyl 2,4,6-trimethylbenzoate to 2,4,6-trimethylbenzoic acid by solution in concentrated sulfuric acid followed by quenching in ice water.[17] The reactions of the esters with concentrated sulfuric acid are summarized in Table II.

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(11) H. Meyer, *Monatsh.*, **28**, 1231 (1907).

(12) Hantzsch and Schweite, *Ber.*, **49**, 213 (1916).

(13) Von Auwers and Heinze, *ibid.*, **52**, 584 (1919).

(14) Egerer and Meyer, *Monatsh.*, **34**, 69 (1913).

(15) H. Meyer, *ibid*, **25**, 1177 (1904).

(16) Goldschmidt and Lipschitz, *ibid.*, **25**, 1164 (1904).

(17) Treffers and Hammett, THIS JOURNAL, **59**, 1708 (1937).

TABLE II

| | Ester | Wt. ester, g. | $H_2SO_4$, cc. | Color in $H_2SO_4$ | Grams recovered | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Ester | M. p., °C. | Acid | M. p., °C. |
| IV | Normal | 1.10 | 10 | Light yellow | 0.993 | 49.8–52.0 | ..... | ........ |
| | Pseudo | 1.00 | 10 | Dichromate | ..... | ....... | 0.899 | 129–129.5 |
| V | Normal | 1.00 | 10 | Light orange | 0.924 | 39–42 | ..... | ........ |
| | Pseudo | 1.00 | 10 | Red | ..... | ....... | 0.896 | 132–132.8 |
| VI | Normal | 1.00 | 10 | Light orange | 0.794 | 86.8–87.8 | 0.019 | 210–214 |
| VII | Normal | 1.00 | 10 | Light yellow | 0.91 | 104–105.6 | ..... | ........ |
| | Pseudo | 0.35 | 5 | Light yellow | ..... | ....... | 0.298 | 172.2–173.5 |
| VIII | Normal | 1.00 | 10 | Deep orange | ..... | ....... | 0.741 | 125.4–127.0 |
| | Pseudo | 0.50 | 5 | Light orange | ..... | ....... | 0.437 | 126–127 |
| IX | Normal | 0.45 | 5 | Red | ..... | ....... | 0.36 | 115–117 |
| | Pseudo | 0.51 | 5 | Red | ..... | ....... | 0.43 | 115.8–117 |

## Experimental[18]

### Preparation of Keto Acids

**2-Benzoylbenzoic Acid, IV, and 2-(2,4,6-Trimethylbenzoyl)-benzoic Acid, VI.**—These acids were prepared by condensation of phthalic anhydride with benzene and mesitylene[19] (in *s*-tetrachloroethane) using standard procedures.[20] The yields were almost quantitative.

**2-(2-Methylbenzoyl)-benzoic Acid, V.**—To a well-stirred solution of 50 g. of phthalic anhydride in 750 cc. of benzene and 250 cc. of dry ether was added slowly 205 cc. of 1.125 *M* *o*-tolylmagnesium bromide, a pink solid complex being formed immediately. The reaction mixture was refluxed with stirring for twelve hours. On recrystallization of the acidic portion of the reaction products from 150 cc. of benzene there was obtained in several crops 47.0 g. of faintly colored acid V contaminated with a small amount of phthalic acid. The purified acid used for further work melted at 130.2–132.2°.[21] When first prepared, this acid was obtained in a polymorphic modification, m. p. 113.8–115.0°. Recrystallization from water, methanol, or xylene did not change the melting point, nor did heating for one hour at 100 and 130°. After standing several months the melting point had risen to 130° and thereafter only the higher melting form was obtained.

**2-Benzoyl-3-methylbenzoic Acid, VII, and 2-Benzoyl-6-methylbenzoic Acid, VIII.**—These acids were prepared from 3-methylphthalic anhydride by condensation with phenylmagnesium bromide and with benzene using aluminum chloride. Details of these reactions are presented in the following paper.[22]

**2-(2-Methylbenzoyl)-6-methylbenzoic Acid, IX.**—To a well-stirred solution of 16 g. (0.097 mole) of 3-methylphthalic anhydride in 90 cc. of ether and 100 cc. of benzene was added rapidly 100 cc. of 0.98 *M* *o*-tolylmagnesium bromide. The reaction was vigorous and a pink solid complex separated at once. After refluxing for three hours and stirring for twelve hours, the reaction mixture was treated with dilute acid and separated into acid and neutral fractions. On concentration of a benzene solution of the acids formed, there were obtained three crops of crystals: 13.49 g., m. p. 107–118°; 3.1 g., 72–145°; and 3.04 g. m. p. 70–90°. This represents a 79.2% yield. By fractional crystallization and separation by hand, there were isolated 11.57 g. (46.9%) of IX, m. p. 116–118°, and 1.31 g. (5.3%) of 2-(2-methylbenzoyl)-3-methylbenzoic acid, m. p. 158–161.4°. Further work with the latter acid is being delayed until more is prepared.

*Anal.*[18b] Calcd. for $C_{16}H_{14}O_3$: C, 75.6: H, 5.6. Found: C, 75.6: H, 5.6.

**Proof of Structure of Keto Acids.**—The structures of VII, VIII, and IX were proved by decarboxylation to the substituted benzophenones by heating in the presence of a small amount of copper salt.[23] Since the resulting benzophenones were liquids comparison with authentic synthetic samples of the benzophenones was effected through the crystalline 2,4-dinitrophenylhydrazones. From VII, VIII, and IX were obtained 2-methylbenzophenone, 3-methylbenzophenone, and 2,3′-dimethylbenzophenone. These ketones were converted into their 2,4-dinitrophenylhydrazones[24] which melted at 184–190°,[25] 220.4–221.4°, and 204–207°,[25] respectively, and formed thin red flat needles, small spherical orange rosets, and orange needles, respectively. The three ketones were prepared by condensation of *o*-tolylmagnesium bromide and benzonitrile, phenylmagnesium bromide and *m*-tolunitrile, and *o*-tolylmagnesium bromide and *m*-tolunitrile. The latter ketone, 2,3′-dimethylbenzophenone, b. p. 228–231 at 24 mm., is a new compound.

*Anal.*[18b] Calcd. for $C_{15}H_{14}O$: C, 85.7; H, 6.7. Found: C, 85.1, 85.1; H, 6.6, 6.7.

The analyses of the three 2,4-dinitrophenylhydrazones follow: *Anal.*[18b] Calcd. for $C_{20}H_6O_4N_4$: C, 63.8; H, 4.3; N, 14.9. Found for 2-methylbenzophenone 2,4-dinitrophenylhydrazone: C, 64.3; H, 4.3. Found[18c] for 3-methylbenzophenone 2,4-dinitrophenylhydrazone: N, 14.5. Calcd.[18b] for $C_{21}H_{18}O_4N_4$: C, 64.6; H, 4.7. Found for 2,3′-dimethylbenzophenone 2,4-dinitrophenylhydrazone; C, 64.9; H, 4.7.

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[18] All melting points corrected. All benzene used in Friedel–Crafts and Grignard reactions was freed of thiophene by stirring with concentrated sulfuric acid followed by distillation. Analyses marked a by J. H. Walker, Ohio State W. P. A. Project No. 65-1-42-89; b by D. Lester, Yale University; c through the courtesy of Dr. W. MacNevin.

[19] The authors are indebted to Mr. E. O. Woolfolk for the mesitylene used. Mr. Woolfolk's assistance was made possible by the Ohio State W. P. A. project No. 65-1-42-89.

[20] See Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1937, pp. 184–186. Pure VI, recrystallized from acetic acid, melted at 214–216° after sintering at 213°; compare Greasley and Meyer, *Ber.*, **15**, 639 (1882).

[21] Compare Scholl and Donat, *ibid*, **64**, 318 (1931).

[22] Newman and McCleary, THIS JOURNAL, **63**, 1542 (1941).

[23] L. F. Fieser, "Experiments in Organic Chemistry," Heath and Co., New York, N. Y., 1935, p. 197.

[24] Cahn, Jones and Simonsen, *J. Chem. Soc.*, 444 (1933).

[25] The wide melting ranges of these two derivatives are probably due to the presence of stereoisomers. These melting ranges were not changed by several recrystallizations.

### Preparation of Methyl Esters

**Column A. Table I.**—A weighed amount of the acid was dissolved in pure dry methanol, the resulting solution saturated with hydrogen chloride and refluxed for three hours. The ester was isolated by ether extraction, washed with saturated sodium bicarbonate solution, and transferred to a small amount of dry methanol. The crystals which separated at 0° were collected, washed with a small amount of ice cold methanol, and dried. The melting points recorded in parentheses in column A represent the melting range of this product. In calculating the yields recorded, second crops of crystals were included whenever the melting range was almost that of the first crop. In the case of VIII and IX only small yields of crystalline esters were obtained, the remainder consisting of a mixture of both types of esters which did not crystallize even on prolonged standing in the ice box and seeding. All esters obtained by this procedure were checked against authentic samples by mixed melting point determinations.

**Column C. Table I.**—A weighed amount of the acid was added to an excess of pure thionyl chloride, with or without benzene, and warmed until the reaction was complete. The excess of thionyl chloride (and solvent) was removed under reduced pressure. To the cooled acid chloride was added a cold solution of equal parts of pure dry pyridine and methanol. After standing for two days the mixture was poured into water and the ester taken into ether. The ether layer was well washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution, and was filtered through anhydrous calcium sulfate, "Drierite." The ether was evaporated and the remaining oil taken up in a small volume of methanol containing a drop of pyridine and allowed to crystallize. The trace of pyridine in the alcohol was added to ensure against any isomerization of the esters due to possible traces of acid in the flask. If no pyridine was used, the flask was thoroughly steamed before using. We were unable to prepare a pseudo ester from VI by this method.

**Column B. Table I.**—A weighed amount of the acid in dry methanol was titrated with ethereal diazomethane. The ester was then obtained by concentrating the reaction mixture and cooling.

The new esters prepared and their analyses are listed below:

**Methyl 2-(2-Methylbenzoyl)-benzoate, Pseudo Form.**—*Anal.*[18b] Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.6. Found: C, 75.3; H, 5.6.

**Methyl 2-(2-Methylbenzoyl)-6-methylbenzoate.**—*Anal.*[18b] Calcd. for $C_{16}H_{14}O_3$: C, 76.1; H, 6.0. Found: normal, C, 76.2; H, 5.9; cyclic, C, 76.2: H, 6.2.

**Methyl 2-Benzoyl-3-methylbenzoate, Pseudo Form.**—*Anal.*[18b] Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.6. Found: C, 75.7; H, 5.6.

**Methyl 2-(2,4,6-Trimethylbenzoyl)-benzoate.**—*Anal.*[18a] Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.6; H, 6.4.

**Treatment of the Esters with Sulfuric Acid.**—The results recorded in Table II were obtained by the following procedure. The ester was finely ground and covered with concentrated sulfuric acid. The esters dissolved rapidly and, after five minutes at room temperature (20–25°), the color was noted and the solution quenched with 100 cc. of water. The mixture was rapidly extracted with ether and the product separated into acid and neutral fractions by extraction with sodium bicarbonate solution. The neutral fraction was crystallized from a small amount of methanol after removing the ether. The acid fraction was obtained by acidifying the bicarbonate extract. The melting point and weights of these fractions are recorded in Table II.

## Summary

The behavior on esterification of five 2-benzoylbenzoic acids containing methyl groups adjacent to ketonic or carboxylic groups is described and compared to that of 2-benzoylbenzoic acid. The preparation and properties of the normal and pseudo methyl esters of these acids are described. Mechanisms for the formation of normal and pseudo esters are proposed and the effect of steric hindrance on those mechanisms is discussed. The behavior of the normal and pseudo methyl esters on treatment with concentrated sulfuric acid indicates that neither the formation of highly colored solutions nor rapid hydrolysis to the free acid is necessarily characteristic of pseudo ester structure.

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