

Studies in the Friedel-Crafts Reaction

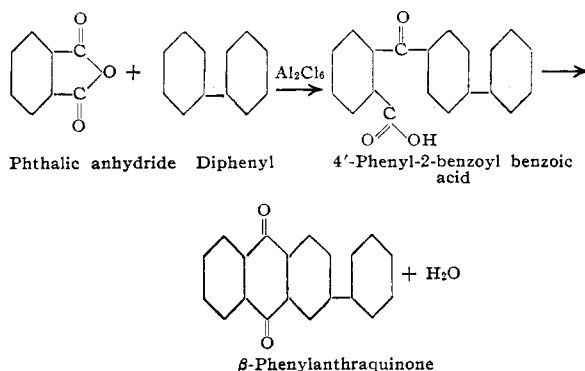
Diphenyl Series.¹ I—Preparation of 4'-Phenyl-2-Benzoyl Benzoic Acid and Its Derivatives²

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THE recent introduction in commercial quantities of diphenyl and its derivatives, at comparatively reasonable prices, has made possible the consideration of their employment in the syntheses of new dye intermediates. The utilization of these compounds for the preparation of intermediates for vat dyes opens up a new field of investigation. The products which are obtained offer possibilities of greatly increasing the number of anthraquinoid vat colors. This paper of necessity is in the nature of an introductory report covering the preparation of a number of such new compounds. The investigation relates to the preparation of the 4'-phenyl-2-benzoyl benzoic acids which are derived by treating diphenyl and its monohalogen derivatives with phthalic anhydride according to the Friedel-Crafts reaction. Consideration is also given to the formation of the hydroxy and amino compounds which are derived from the halogen keto acids. The preparation of β -phenylanthraquinone and its derivatives from these keto acids is discussed in a separate paper.

The principal reactions that occur in the preparation of β -phenylanthraquinone from diphenyl and phthalic anhydride may be represented by the following structural formulas:



The synthesis of 4'-phenyl-2-benzoyl benzoic acid by means of the Friedel-Crafts reaction has been previously reported. Elbs (1), using ligroin as a solvent at 90–100° C., obtained a yield of 30 to 40 per cent of impure resinous product. Kaiser (6), employing a 100 per cent excess of diphenyl, obtained a low yield of brown materials. Scholl and Novius (13) pre-

A practical and economic procedure for preparing 4'-phenyl-2-benzoyl benzoic acid and its chloro derivatives according to the Friedel-Crafts reactions has been developed. Amino and hydroxy derivatives were prepared from the chloro-keto acids. The melting point of 4'-phenyl-2-benzoyl benzoic acid was found to be 231.5° C., instead of 226° C. as previously reported. Physical constants have been established for the six new derivatives of 4'-phenyl-2-benzoyl benzoic acid.

This report must be interpreted as being merely a preliminary survey showing the possibilities of using diphenyl and its halogen derivatives for making new dye intermediates. Experience shows that the preparation of such derivatives is not so simple as the syntheses involving similar benzenoid compounds. The chemistry of these intermediates, which is of great interest, is discussed at considerable length in the following paper dealing with β -phenylanthraquinone.

pared a colorless crystalline product of satisfactory purity by using an excess of about 150 per cent phthalic anhydride and an excess of 100 per cent aluminum chloride, along with a large quantity of carbon disulfide as a solvent for the reacting materials.

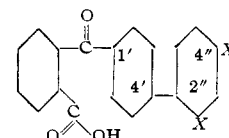
Nomenclature

An examination of the literature shows that the phenylbenzoyl benzoic acid under consideration has been variously designated by the previous investigators. Furthermore, the nomencla-

ture in the current patent literature differs from that suggested by E. J. Crane. Despite the fact that six names have already been set forth for the unsubstituted keto acid, it was believed that the previous nomenclature was either inadequate or confusing, particularly when substituents were introduced into the phenyl nucleus of 4'-phenyl-2-benzoyl benzoic acid. The system adopted is in accord with the present tendency towards the use of the logical nomenclature, wherein primed or unprimed numerals are used to designate or identify the position of the nuclei and radicals making up the compound. Below are listed the various names for the keto acid along with the nomenclature adopted for some of the compounds discussed in this paper:

NAME	AUTHOR
Phenylbenzoylbenzoic acid	Elbs (1)
Diphenyl-phthaloylic acid	Kaiser (6)
Diphenyl-4-monophthaloylic acid	Scholl (13)
4-Phenyl-benzophenone-2-carboxylic acid	
<i>o</i> -(<i>p</i> -Phenyl-benzoyl) benzoic acid	Suggested by E. J. Crane
<i>p</i> -Phenyl- <i>o</i> -benzoyl benzoic acid	According to current patents
4'-Phenyl-2-benzoyl benzoic acid	Used in this paper
4'-Chloro-4'-phenyl-2-benzoyl benzoic acid	
2'-Amino-4'-phenyl-2-benzoyl benzoic acid	

The structural formula of the keto acids may be depicted as follows:



where X represents either an ortho, 2'', or para, 4'', substituent. Proof of this structure is submitted later in this paper, as it was not established by the previous investigators.

Preparation of Keto Acids—General Discussion

Since an effort was made to render the results of this investigation susceptible to commercial exploitation, the Friedel-Crafts reactions were carried out by using approximately the

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molecular combining proportions of diphenyl and phthalic anhydride. Solvents were employed to insure homogeneity of the reaction mass only in preliminary small-scale laboratory experiments to determine the characteristics of the reaction. When a refined anhydrous aluminum chloride was used, a 10 per cent excess was taken for the reaction. An excess of 12 per cent was required, however, when a technical product of 94 to 95 per cent purity and containing small amounts of the chlorides of iron and silicon served as condensing agent.

Two major problems were present in the preparation of 4'-phenyl-2-benzoyl benzoic acid—namely, (1) to produce homogeneity of the reaction mass, and (2) to study the effect of time and temperature in the Friedel-Crafts condensation. The treatment of the anhydrous aluminum intermediate compound to obtain the keto acid followed the procedures described in previous papers (2, 3).

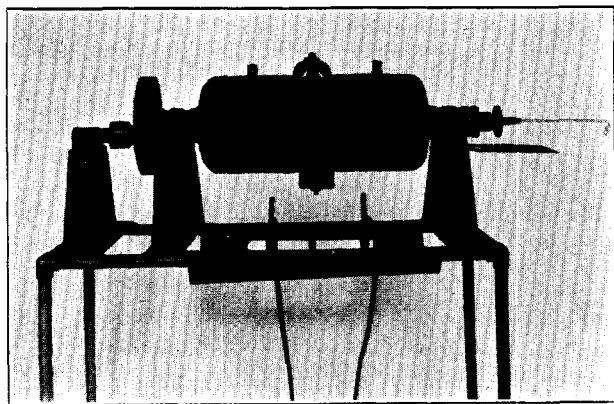
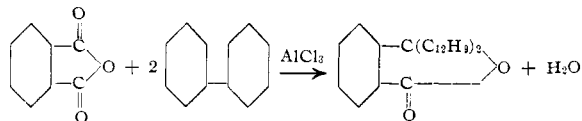


Figure 1—Iron Mill for Friedel-Crafts Synthesis

Preliminary experiments, in which the three solid reactants, diphenyl, phthalic anhydride, and aluminum chloride, were treated on the steam bath, showed conclusively that satisfactory results could not be obtained unless the charge was thoroughly stirred. In such experiments it was found necessary to use carbon disulfide to insure homogeneity. A number of runs then were made in an enamel-lined kettle provided with an anchor-type agitator. The desired temperature was obtained through the medium of a heated sand bath in which the apparatus was set. When in the course of operations the temperature rose to 35–45° C. the charge reached the intermediate liquid phase and resolved into a brown gummy mass. It was difficult, and at times impossible, to keep the stirrer in motion because the load became too great. As soon as the solid stage was reached the charge became powdery and the mass agitated easily. At the conclusion of a run an examination showed that the stirrer had compressed a dense film of the resinous material on the walls of the vessel. This portion of the charge was consequently overheated. The greatest fault of the system was its failure to provide homogeneity, particularly during the liquid phase of the reaction. The yields obtained with this equipment never exceeded 84 per cent of the theory, and the quality of the crude product was affected adversely by the presence of unconverted diphenyl and other impurities which presumably were phthalides.

The formation of phthalides (10, 11, 12, 13) is a characteristic side reaction of the Friedel-Crafts synthesis. The following factors contribute to their formation: excessive heating, particularly during the early stages, poor mixing, and an excess of the aromatic compound being condensed with phthalic anhydride. The basic reaction may be represented as follows:



The Friedel-Crafts synthesis finally was carried out in a horizontal, rotating iron mill (Figure 1) which was heated externally either with gas or by means of an electric resistance heater. The mill was supplied with iron blocks of various sizes and shapes. Suitable openings were provided for charging and discharging the mill and for venting the hydrogen chloride given off during the reaction. A thermometer well extending horizontally into the center of the mill afforded a practical method of obtaining the temperature of the charge. No deleterious effects on the quality of the keto acids were observed as a result of working in iron apparatus. It was found, however, that when insufficient iron blocks were provided the yields dropped off.

Preparation of 4'-Phenyl-2-Benzoyl Benzoic Acid

Molecular proportions of phthalic anhydride and diphenyl were ground together and to these was added the anhydrous aluminum chloride. The charge was then put into the mill and the contents were mixed for 1 hour before heat was applied. The temperature then was brought up slowly so that the desired point was reached after 2 hours. At 35–45° C. the batch became gummy, and the noise of the iron blocks was temporarily deadened. As the hydrogen chloride was given off, the fine green dust of the anhydrous aluminum intermediate compound became apparent at the vent. The heating was continued until the hydrogen chloride test at the vent became faint. The green aluminum compound was then discharged and slowly delivered into 2 liters of ice and water containing 350 grams of 95 per cent sulfuric acid. Thorough agitation, to prevent local overheating, was required during the hydrolysis. The crude 4'-phenyl-2-benzoyl benzoic acid thus obtained was finely divided and almost colorless. Live steam was then passed into the suspension to insure solution of the aluminum as sulfate and to remove traces of diphenyl. The batch was filtered hot and washed with 3 liters of hot water. The crude keto acid was dissolved in 10 liters of water containing 50 grams of sodium hydroxide. The sodium salt solution was boiled with live steam for about 1 hour. The solution showed only a slight cloudiness with very small quantities of insoluble material. The addition of decolorizing carbon to the solution during the final stages of heating was helpful in removing impurities and in the production of a colorless product of high purity. The sodium salt solution was cooled and filtered. The filtrate was added slowly to cold dilute sulfuric acid to precipitate out 4'-phenyl-2-benzoyl benzoic acid. When the material was quite pure, a colorless granular product was obtained, whereas the presence of impurities resulted in the formation of a very finely divided, white, creamy suspension. The keto acid then was filtered, washed with hot water, and dried.

Table I—Effect of Type of Agitation in Preparation of 4'-Phenyl-2-Benzoyl Benzoic Acid

TYPE OF AGITATION	TEMPERATURE ° C.	TIME Hours	CRUDE YIELD Grams	PURITY Per cent
EXPERIMENT 1				
Agitated kettle	55–60	18	244	97.4
Mill with insufficient agitation	55–60	20	278	97.6
Mill with efficient agitation	55–60	18	290	97.8
EXPERIMENT 2				
Agitated kettle	60–65	12	208	97.5
Mill with insufficient agitation	60–65	12	239	97.8
Mill with efficient agitation	60–65	12	292	98.0
Phthalic anhydride, 1 mol = 148 grams.				
Diphenyl, 1 mol = 154 grams.				
Aluminum chloride sublimed, 10 per cent excess = 293 grams.				
Yield, theory = 302 grams.				

Table I shows the effects of type of agitation in the production of 4'-phenyl-2-benzoyl benzoic acid. The experiments are divided into three groups as follows: (1) the yields obtained in the enamel-lined vessel; (2) the results in horizontal mill with insufficient iron blocks; and (3) results obtained with final equipment after adding more blocks to the mill.

The effects of time and temperature on the yield and purity of 4'-phenyl-2-benzoyl benzoic acid were found to be similar to those prevailing in the preparation of a large number of other keto acids. When too low a temperature was used, a much longer time was required to complete the reaction. Alkali-insoluble phthalides were found to accompany the product when the heating was excessive. In Table II are shown the effects of time and temperature in the preparation of 4'-phenyl-2-benzoyl benzoic acid. Of considerable interest was the fact that the yields and purity of the product obtained by the use of technical aluminum chloride were practically the same as those obtained with the better quality material.

When recrystallized from toluene and glacial acetic acid, 4'-phenyl-2-benzoyl benzoic acid is obtained as beautiful colorless rosettes of short rods. When examined individually, the rods exhibit a rectangular configuration at the end broken from the rosette, while the other end tapers to a fine point. These crystals melted at 231.5° C. (cor.), whereas the best melting point previously reported was 226° C. by Scholl and Novius. Titration with standard alkali showed that the product was 100 per cent pure. A combustion gave the following results:

Analysis of substance, 0.0603; CO₂, 0.1756; H₂O, 0.0252. Calculated for C₂₀H₁₄O₃: C, 79.44; H, 4.67. Found: C, 79.42; H, 4.67.

4'-Phenyl-2-benzoyl benzoic acid is readily soluble in glacial acetic acid, chlorobenzene, and toluene. It is best recrystallized from glacial acetic acid. A moderate purification may be obtained by making the soluble ammonium salt in the presence of decolorizing carbon and then precipitating the free keto acid by slowly adding the filtered ammonium salt solution to dilute, cold, mineral acid.

Table II—Effect of Time and Temperature in Preparation of 4'-Phenyl-2-Benzoyl Benzoic Acid

EXPT.	TEMPERATURE ° C.	TIME Hours	YIELD Per cent	PURITY Per cent	MELTING POINTS ° C.
1	45-50	24	76.0	97.3	222-224
2	50-55	24	83.7	97.4	222-225
3	55-60	24	92.8	97.8	223-226
4	60-65	9	79.9	96.9	220-223
5 ^a	60-65	12	94.4	97.8	223-227
6 ^b	60-65	12	94.1	97.7	223-226
7 ^c	60-65	15	94.6	97.6	222-225
8	70-75	12	93.9	96.8	218-222
9	75-80	6	67.9	95.8	218-220

Phthalic anhydride, 1 mol = 148 grams.

Diphenyl, 1 mol = 154 grams.

Aluminum chloride, white sublimed = 293 grams.

Aluminum chloride, brown technical = 300 grams.

Purity determined by titration with standard alkali in alcoholic solution.

^a Average 12 runs, white sublimed aluminum chloride.

^b Average 3 runs, technical aluminum chloride.

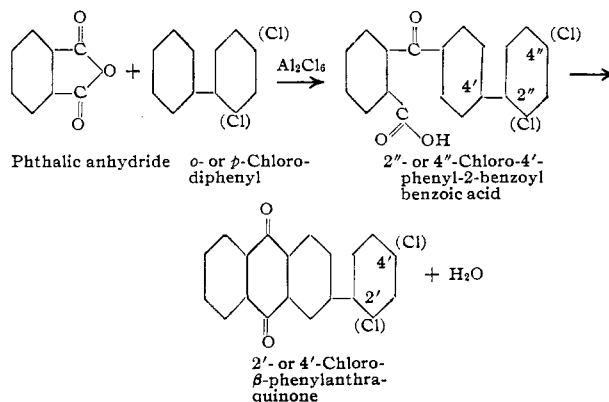
^c Average 3 runs, white sublimed aluminum chloride.

^d Melting point of pure product, 231.5° C. (cor.).

Preparation of Halogen Keto Acids

When diphenyl is chlorinated, two principal isomeric monochloro compounds are obtained. The technical para- or 4-chlorodiphenyl is a white flaky substance which melts at 74.6-74.9° C. (5) and is readily obtained in a comparatively pure state. Technical *o*-chlorodiphenyl contains small amounts of impurities and appears on the market as a faintly yellow, oily product. When recrystallized from alcohol, it is obtained as colorless needles, giving a solidification point of 30.5-31.0° C. These two compounds were found to be suitable for the preparation of chloro-4'-phenyl-2-benzoyl benzoic acids according to the Friedel-Crafts reaction. From these keto acids it was possible to obtain chloro- β -phenylanthra-

quinones. The principal reactions that take place in the syntheses of these compounds are shown by the following structural formulas:



Both halogen derivatives formed a green anhydrous aluminum intermediate compound when condensed with phthalic anhydride. When carbon disulfide was used as a solvent, the ortho compound formed a red reaction mass. The time and temperature functions in their preparation were similar to those which governed the preparation of 4'-phenyl-2-benzoyl benzoic acid. They did not, however, probably on account of the formation of isomers, respond to purification as readily as the unsubstituted compound.

4'-CHLORO-4'-PHENYL-2-BENZOYL BENZOIC ACID—Molecular proportions of 4-chlorodiphenyl and phthalic anhydride were condensed with a 10 per cent excess of anhydrous aluminum chloride. At the conclusion of the reaction, the anhydrous, green aluminum compound of 4'-chloro-4'-phenyl-2-benzoyl benzoic acid was added slowly to iced dilute sulfuric acid to precipitate the free keto acid. After hydrolyzing, a nicely granulated and almost colorless product was obtained. The suspension was boiled with live steam and filtered hot. The crude keto acid was purified by preparing the soluble ammonium salt in 15 liters of water, cooling and filtering, and adding the filtrate to dilute cold sulfuric acid. Efforts at purification by making the sodium salt were unsatisfactory, as the sodium salt of the crude 4'-chloro-4'-phenyl-2-benzoyl benzoic acid was only slightly soluble in boiling water. A test showed that approximately 50 liters of hot water were required to dissolve the alkali metal salt for filtration.

4'-Chloro-4'-phenyl-2-benzoyl benzoic acid is readily soluble in toluene, chlorobenzene, and glacial acetic acid. It is only sparingly soluble in alcohol and benzene. It is best recrystallized from glacial acetic acid. After recrystallizing from toluene and acetic acid, the colorless rectangular rods melted at 251° C. (cor.). A titration with standard alkali in alcoholic solution and chlorine determinations according to Parr's method showed that the product was pure. The crystal structure is similar to that of the unsubstituted keto acid.

Data concerning the preparation of this acid are summarized in Table III.

Table III—Preparation of 4'-Chloro-4'-Phenyl-2-Benzoyl Benzoic Acid

EXPT.	TEMPERATURE ° C.	TIME Hours	YIELD ^b Per cent
a	95	12	90.6
1	80-85	12	74.3
2	70-75	6	71.2
3	65-70	12	90.3
4	65-70	14	93.4
5	60-65	12	89.2
6	55-60	14	87.4

4-Chlorodiphenyl, 1 mol = 188.5 grams.

Phthalic anhydride sublimed, 1 mol = 148 grams.

Aluminum chloride, either 293 grams pure or 300 grams technical.

^a Laboratory control with carbon disulfide as solvent, heated on steam bath.

^b The purity of the crude product ranged from 97 to 98 per cent.

2''-CHLORO-4'-PHENYL-2-BENZOYL BENZOIC ACID—Phthalic anhydride and 2-chlorodiphenyl in molecular proportions were intimately mixed and put into the mill. The requisite quantity of anhydrous aluminum chloride was then added and the charge agitated for one or more hours before heat was applied. The reaction proceeded rapidly even at room temperature, and the charge became gummy. After several hours of heating the mass began to break up. The anhydrous aluminum intermediate compound obtained by heating, at the temperatures shown in Table IV, was hydrolyzed with iced dilute sulfuric acid. When live steam was introduced, the mass became gummy but granulated after several hours of vigorous steaming. The keto acid was filtered hot and then washed. When washed with hot water, the charge again became gummy as soon as the mineral acid was removed. This phenomenon was characteristic only of the charges made in the mill. The laboratory controls with 500 grams of carbon disulfide gave a colorless crystalline keto acid. Purification was effected by warming the keto acid in a large quantity of glacial acetic acid, a yellow color being imparted to the solvent by the impurities.

2''-Chloro-4'-phenyl-2-benzoyl benzoic acid is a colorless crystalline product which melts at 190.0° C. (cor.). The crude product melted at 177–183° C. It is best purified by recrystallizing from glacial acetic acid, from which it is obtained as rosettes of short rectangular rods. Titrations with standard alkali in alcoholic solution and chlorine determinations showed that the product was a pure halogen keto acid.

Calculated for $C_{20}H_{13}O_3Cl$: Cl, 10.53. Found: Cl, 10.48, 10.50.

Table IV—Preparation of 2''-Chloro-4'-Phenyl-2-Benzoyl Benzoic Acid

EXPT.	TEMPERATURE ° C.	TIME Hours	YIELD CRUDE Grams	YIELD ^a Per cent	REMARKS
1	55–60	12	250	74.3	
2	65–70	12	277	82.3	
3	65–70	15	283	84.1	Average of 6 runs
3a	65–70	15	281	83.5	Average of 4 runs 294 grams refined $AlCl_3$
4	70–80	12	250	74.3	Average of 4 runs
5	80–90	12	245	72.8	Considerable phthalide formation
6	90–100	12	221	65.7	Considerable resinous impurities
0	Steam bath	15	284	84.4	Lab. controls with CS_2

2-Chlorodiphenyl, 1 mol = 188.5 grams.
Phthalic anhydride, 1 mol = 148 grams.
Aluminum chloride, technical, 300 grams.

^a Average purity of keto acid, Expts. 2, 3, and 3a = 97.2 per cent.

Preparation of Hydroxy-4'-Phenyl-2-Benzoyl Benzoic Acids

When the chloro-4'-phenyl-2-benzoyl benzoic acids or their alkali metal salts were treated with caustic potash solutions, the corresponding hydroxy keto acids were obtained. The hydrolysis may be carried out with a 40 per cent solution of potassium hydroxide in an autoclave under pressure at 300° C. or in an open fusion pot starting with a 25 per cent caustic solution.

2''-HYDROXY-4'-PHENYL-2-BENZOYL BENZOIC ACID—The open-pot fusion was carried out in the following manner: One-tenth mol (33.6 grams) of 2''-chloro-4'-phenyl-2-benzoyl benzoic acid was added to 200 grams of 25 per cent caustic potash. On warming to 125° C. the solution became clear and at 180° C. a yellow oily layer separated out. On further heating to 210° C. the yellow layer became quite granular. The reaction was completed by slowly heating up to 250° C., when the charge lost its fluid character.

The contents of the fusion pot were washed out with warm water and diluted to 3 liters. Dilute sulfuric acid was carefully added until neutrality was reached and then until a faint

acidity to litmus was obtained, in order to precipitate out any unconverted chloro derivative or other less soluble condensation impurities. The addition of acid was accompanied by vigorous stirring and was continued until a colorless and flocculent, rather than a gummy or granular, precipitate formed. The suspension was filtered warm and the precipitate rejected. The filtrate was added slowly to dilute sulfuric acid to complete the precipitation of 2''-hydroxy-4'-phenyl-2-benzoyl benzoic acid. The keto acid was boiled until thoroughly granulated and then filtered hot. The crude 2''-hydroxy-4'-phenyl-2-benzoyl benzoic acid thus produced was faintly yellow and melted at 225° C. By recrystallizing from its ammonium salt and then twice from glacial acetic acid, colorless rods melting at 255–258° C. were obtained.

Note—When 2''-hydroxy-4'-phenyl-2-benzoyl benzoic acid was prepared by condensing *o*-phenylphenol (*o*-hydroxydiphenyl) with phthalic anhydride according to the Friedel-Crafts reaction, the melting point of the purified product was 262° C. (cor.). This is a more suitable method for synthesizing this keto acid.

2''-Hydroxy-4'-phenyl-2-benzoyl benzoic acid is a colorless crystalline compound melting at 262° C. (cor.). It is very soluble in dilute alkali and faintly soluble in boiling acidulated water. It is very soluble in alcohol and glacial acetic acid and to a lesser degree in chlorobenzene and toluene.

Analysis of substance: 0.0544, 0.0409; CO_2 , 0.1505, 0.1130; H_2O , 0.0220, 0.0163.

Calculated for $C_{20}H_{14}O_4$: C, 75.45; H, 4.44. Found: C, 75.45, 75.35; H, 4.52, 4.46.

4''-HYDROXY-4'-PHENYL-2-BENZOYL BENZOIC ACID—The open-pot fusion of 4''-chloro-4'-phenyl-2-benzoyl benzoic acid with caustic potash was carried out in a manner similar to that described for the ortho isomeride. Of particular interest is the fact that the reaction requires a higher temperature and progresses more slowly on account of the limited solubility of the 4''-chloro derivatives in caustic potash or soda. At no time during the hydrolysis was the charge free of suspended matter. Up to 190° C. the charge turned faintly yellow and gradually lost its fluid character. At 220° C. the contents became quite yellow and began to soften. By heating at 300° C. the yellow particles disappeared and a soft brown, homogeneous mass was obtained.

The alkaline reaction mass was washed out and diluted to 3 liters. A clear brown solution was obtained, indicating complete conversion, since the presence of considerable of the slightly soluble sodium salt of the chloro derivative would produce a flocculent suspension. Dilute sulfuric acid was added cautiously until a faint acidity to litmus was obtained. This precipitated any unconverted 4''-chloro-4'-phenyl-2-benzoyl benzoic acid and other less soluble condensation impurities. The suspension thus obtained by fractional precipitation was filtered, and the residue was rejected. The filtrate was added slowly to dilute sulfuric acid to complete the precipitation of 4''-hydroxy-4'-phenyl-2-benzoyl benzoic acid. The suspension was boiled to granulate the keto acid prior to filtering. The crude acid, which possessed a faint yellow coloration, melted at 225–235° C.

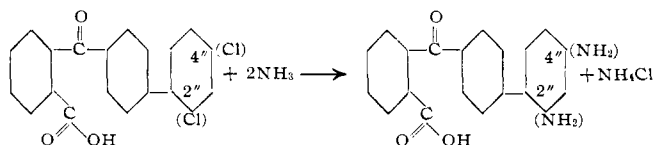
By recrystallizing from alcohol, making the ammonium salt and reprecipitating the keto acid, and finally recrystallizing three times from glacial acetic acid, 4''-hydroxy-4'-phenyl-2-benzoyl benzoic acid was obtained as colorless rectangular, rodlike crystals, m. p. 245–246° C. An identical product was synthesized by condensing *p*-hydroxydiphenyl with phthalic anhydride according to the Friedel-Crafts reaction. The ammonium and alkali metal salts are very soluble in water. The keto acid is very soluble in alcohol and glacial acetic acid and only moderately so in chlorobenzene and toluene.

Analysis of substance: 0.0358; CO₂, 0.0988; H₂O, 0.0142. Calculated for C₂₀H₁₄O₄: C, 75.44; H, 4.44. Found: C, 75.27; H, 4.44.

When the hydroxy-4'-phenyl-2-benzoyl benzoic acids were made in an autoclave under pressure at 300° C., the crude product was of a higher purity than that obtained by open-pot fusion. Considerable purification was required, however, before the product was comparable with that obtained by the Friedel-Crafts condensation of the *o*- and *p*-hydroxydiphenyls with phthalic anhydride.

Preparation of Amino-4'-Phenyl-2-Benzoyl Benzoic Acids

When the chloro-4'-phenyl-2-benzoyl benzoic acids were treated with ammonia under pressure, the corresponding amino keto acids were produced. The presence of a copper catalyst was found to be essential. A large number of experiments were performed in which the following variables were introduced. The ammonia ratio was varied from 10 to 25 mols, the temperature from 175° to 220° C., copper in the form of its salts as catalyst from 0.5 to 10 per cent. Although the crude acid often showed a purity in excess of 98 per cent by titration with sodium nitrite solution, it was most difficult to obtain a pure product on account of the presence of the usual by-products of reaction. The criterion of purity was the solubility of the amino keto acid in both dilute acids and alkalies. The impurities, chloro and hydroxy derivatives and imino condensation products, do not meet these tests. Purification with organic solvents was found to be unsatisfactory, as the impurities showed a more or less similar solubility coefficient. The principal reactions involved are shown by the following graphic formulas:



4''-AMINO-4'-PHENYL-2-BENZOYL BENZOIC ACID—The 4''-amino keto acid was prepared by treating 16.8 grams (0.05 mol) of 4'-chloro-4'-phenyl-2-benzoyl benzoic acid with 250 grams of ammonia in the presence of 1.68 grams of cuprous chloride and 0.5 gram of copper turnings. The charge was heated 16 hours at 210° C. and then cooled by immersing the autoclaves in cold water. The ammonium salt of 4''-amino-4'-phenyl-2-benzoyl benzoic acid was obtained as a bright yellow crystalline compound. The charge was filtered cold and washed with cold water. The mother liquor was distilled with steam to remove the excess of ammonia and then treated with caustic soda to precipitate the copper. A yellow solution over a black precipitate of copper oxide was obtained. This was filtered hot and to the filtrate was then added the main precipitate previously obtained. The suspension was warmed and then neutralized with hydrochloric acid. The yield on this crude product was 94.8 per cent of theory, and titration showed that it was 97.4 per cent pure.

The crude product was boiled with 2 liters of 2 per cent sodium hydroxide and filtered. Only about half of the amino keto acid went into solution. The filtrate containing the sodium salt of the keto acid was then neutralized with hydrochloric acid, and a flocculent yellow precipitate of 4''-amino-4'-phenyl-2-benzoyl benzoic acid was thrown out. Upon the addition of more acid most of the amino keto acid went into solution as the hydrochloride. The suspension was filtered and the filtrate neutralized with sodium bicarbonate. The purified material was then recrystallized from alcohol.

4''-Amino-4'-phenyl-2-benzoyl benzoic acid when pure is a

yellow crystalline compound which melts above 300° C. Its salts are slightly soluble in hot dilute acids and alkalies.

2''-AMINO-4'-PHENYL-2-BENZOYL BENZOIC ACID—This acid was prepared in a manner similar to that described for the 4-amino compounds, but with less satisfactory results. The ammonium salt obtained from the cooled autoclave was yellow, but this was turned to a brown resinous mass by the warm water used to wash out the charge. When the ammonolysis was incomplete or overdone this material in the autoclave was obtained as a solid, brown, gummy mass. In Table V are shown the results of aminating the ammonium salt of 2''-chloro-4'-phenyl-2-benzoyl benzoic acid under various conditions. In order to obtain a pure product for physical constants the autoclave product was purified by effecting a partial solution in dilute hydrochloric acid, and then making the filtrate alkaline. Only the portion soluble in acid and alkali was used. The product was finally recrystallized twice from alcohol.

Table V—Preparation of 2''-Amino-4'-Phenyl-2-Benzoyl Benzoic Acid

EXPT.	TIME Hours	TEMPERATURE ° C.	YIELD PPT. Grams	PURITY Per cent	Cu ₂ Cl ₂ Grams
1	18	175	11.6	53.0	1.5
2	18	175	14.2	63.8	3.0
3	18	175	15.7	82.2	5.0
4	18	175	16.4	88.0	20.0
5	18	215	19.4	78.9	1.0
6	18	215	18.1	92.7	3.0
7	15	215	15.3	98.5	5.8
8	18	215	16.0	98.5	5.0 ^a
9	18	215	14.5	98.0	10.0
10	36	215	9.8	92.1	5.0
11	12	215	16.7	91.9	3.0
12	12	215	16.9	95.4	1.4 copper oxide 0.5 copper

Ammonium salt, 2''-chloro-4'-phenyl-2-benzoyl benzoic acid, 23.6 grams. Ammonia, 28.5 per cent = 250 grams.

^a Average of 5 runs.

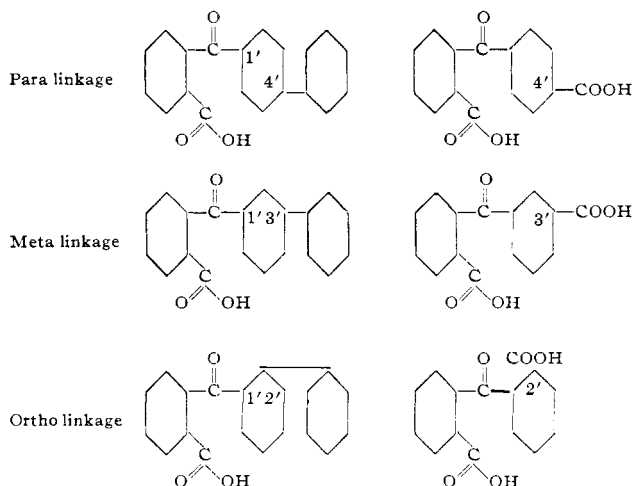
2''-Amino-4'-phenyl-2-benzoyl benzoic acid is a faint yellow, crystalline substance melting at 280–282° C. The sodium salt and the hydrochloride of the amino keto acid are slightly soluble in hot water. It is very soluble in glacial acetic acid and *o*-dichlorobenzene. Organic solvents, however, were not found effective in making the preliminary purification of the amino keto acid.

Structure of the Keto Acids

The previous investigators of phenylbenzoyl benzoic acid did not establish the structure of the keto acid. Scholl assumed that the phenyl linkage was para to the carbonyl group, this assumption being justified by the known behavior of similar mono-substituted benzene compounds in the Friedel-Crafts reaction. Thus, chlorobenzene and toluene form as the principal product of condensation 4'-chloro- and 4'-methyl-2-benzoyl benzoic acids.

It is also known that when attempts are made to condense a para-disubstituted benzenoid product—for example, *p*-dichlorobenzene—the reaction does not proceed satisfactorily as it necessitates an arrangement of halogen ortho and meta to the carbonyl group. It would therefore be permissible to infer that phenylbenzene (diphenyl) would react in a similar manner to form 4'-phenyl-2-benzoyl benzoic acid when condensed with phthalic anhydride in the presence of anhydrous aluminum chloride.

The Friedel-Crafts condensation of phthalic anhydride with diphenyl may result in the formation of three isomers. An effort was made, therefore, to establish the structure of the purified phenyl-2-benzoyl benzoic acid which gave a melting point of 231.5° C. (cor.). The three isomerides together with the respective carboxy-2-benzoyl benzoic acids which may be obtained as the principal products of oxidation are shown by the following graphic formulas:



No reference to β' -carboxy-2-benzoyl benzoic acid (meta linkage) was found in the literature.

The proof of structure involved the comparison of the physical constants of various products derived from phenylbenzoyl benzoic acid with similar known products derived from other sources, particularly from 4'-methyl-2-benzoyl benzoic acid. The methyl keto acid used was prepared in this laboratory according to the procedure outlined in a previous paper on the preparation of 4'-chloro-2-benzoyl benzoic acid (2). The product was purified by recrystallizations from acetic acid and toluene and gave a maximum melting point of 139° C., which is in agreement with the best results reported in the literature (4, 7). The keto acid was converted to β -methylantraquinone by treating it with 95 per cent sulfuric acid at 130° C. The purified product gave a sharp melting point of 176.3° C. (cor.) which, although 1 degree higher, is also in agreement with the known constant for this material (4, 9). The β -methylantraquinone was finally oxidized with alkaline permanganate, and the anthraquinone- β -carboxylic acid obtained melted at 290.5° C. (cor.). These tests indicate that the 4'-methyl-2-benzoyl benzoic acid used for comparison was quite pure and could be depended on for accurate controls.

Ten grams of phenylbenzoyl benzoic acid were oxidized by treating with 40 grams of chromium trioxide and 100 grams of 75 per cent acetic acid. The solution was refluxed for 2 hours, after which the reaction mass was diluted to 1 liter. A clear green solution was obtained, indicating the absence of unconverted phenylbenzoyl benzoic acid, which is practically insoluble in dilute acids. The solution was filtered and the filtrate made alkaline with sodium hydroxide. The suspension was warmed to coagulate the chromium hydroxide and the green precipitate filtered off. The filtrate was acidified with hydrochloric acid and a colorless precipitate obtained. This was recovered by filtration, washed with cold water, and dried. The melting point of this product was 237–238° C. After recrystallizing from alcohol, short, colorless needles, which melted sharply at 241° C. (cor.), were obtained. Further purification did not alter the melting point, which is appreciably higher than the constant reported in the literature for 4'-carboxy-2-benzoyl benzoic acid. (Melting point 234–235° C., *Ann.*, **309**, 99, 116; also Beilstein, Vol. X, p. 883.)

When pure 4'-methyl-2-benzoyl benzoic acid, melting point 139° C., was oxidized with 3.5 parts of potassium permanganate and 40 parts of 4 per cent sodium hydroxide, the resultant crude 4'-carboxy-2-benzoyl benzoic acid melted at 238–239° C. After recrystallizing from alcohol it melted at 241° C. (cor.), this constant being identical with that obtained for the oxidation product of phenyl-2-benzoyl benzoic

acid. The melting point of a mixture of the two oxidation products was also 241° C. (cor.). It appears, therefore, that the keto acid under consideration is principally 4'-phenyl-2-benzoyl benzoic acid and that the previously reported melting point for 4'-carboxy-2-benzoyl benzoic acid is too low.

To confirm the identity of the 4'-carboxy-2-benzoyl benzoic acid two sets of experiments were performed.

(1) Dimethyl esters were made from the oxidation products of 4'-methyl-2-benzoyl benzoic acid and phenyl-2-benzoyl benzoic acid, by refluxing the carboxy keto acids with methanol in the presence of phosphorus pentachloride. The dimethyl esters were precipitated out as colorless crystals by cooling and diluting. After recrystallizing from methanol the products melted at 107° C., which is in agreement with the constant obtained by Limpricht (8). The 2,2' dimethyl ester melts at 85–86° C.

(2) Anthraquinone carboxylic acids were made by treating both of the carboxy-2-benzoyl benzoic acids with 6 parts of 95 per cent sulfuric acid for 3 hours at 130° C. The crude products were purified by making the soluble sodium salt and reprecipitating with acid and finally recrystallizing from toluene. The anthraquinone-carboxylic acid derived from phenyl-2-benzoyl benzoic acid melted at 290° C. (cor.), whereas the anthraquinone- β -carboxylic acid derived from 4'-methyl-2-benzoyl benzoic acid melted at 290.5° C. (cor.).

From these experiments it was concluded that the keto acid under investigation was principally 4'-phenyl-2-benzoyl benzoic acid.

When the chlorophenyl-2-benzoyl benzoic acids were oxidized, the same principal end product—namely, 4'-carboxy-2-benzoyl benzoic acid—was obtained. This proves the presence of the chloro substituent in the attached phenyl nucleus. Since the relative position of the halogen in the diphenyl is unaltered by the Friedel-Crafts condensation, the chloro-keto acids reported in the paper must be principally 4''-chloro-4'-phenyl-2-benzoyl benzoic acid and 2''-chloro-4'-phenyl-2-benzoyl benzoic acid. The amino and hydroxy derivatives from these chloro derivatives will undoubtedly be compounds carrying similar nomenclature.

When the 2''-chloro-4'-phenyl-2-benzoyl benzoic acid was oxidized and diluted, the solution was not clear and contained some dark gummy material. This characteristic was found to prevail in the preparation of the keto acid, and has previously been mentioned. Since 2-chlorodiphenyl has both para positions open, the formation of isomers appears inevitable. This situation unquestionably accounts for the lower yields of crude products, the difficulties in purification, and the fact that the best crude products melted at 177–183° C., whereas 190° C. was obtained as the melting point of the purified material.

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